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Following in the footsteps of acute myeloid leukemia: Are we witnessing the start of a therapeutic revolution for higher-risk myelodysplastic syndromes?

Jan Philipp Bewersdorf, MD¹, Amer M. Zeidan, MBBS, MHS^{1,#}

¹Department of Internal Medicine, Section of Hematology, Yale University School of Medicine, New Haven, CT

Abstract

For most patients with higher-risk myelodysplastic syndromes (HR-MDS) the hypomethylating agents (HMA) azacitidine and decitabine remain the mainstay of therapy. However, the prognosis mostly remains poor and aside from allogeneic hematopoietic stem cell transplantation no curative treatment options exist.

Unlike acute myeloid leukemia, which has seen a dramatic expansion of available therapies recently, no new agents have been approved for MDS in the United States since 2006. However, various novel HMAs, HMA in combination with venetoclax, immune checkpoint inhibitors, and targeted therapies for genetically defined patient subgroups such as APR-246 or IDH inhibitors, have shown promising results in early stages of clinical testing. Furthermore, the wider availability of genetic testing is going to allow for a more individualized treatment of MDS patients. Herein, we review the current treatment approach for HR-MDS and discuss recent therapeutic advances and the implications of genetic testing on management of HR-MDS.

Keywords

Myelodysplastic syndrome; MDS; hypomethylating agent; combination therapy; immune checkpoint inhibition

1.) Introduction

Myelodysplastic syndromes (MDS) are a group of clonal hematopoietic disorders due to the impaired differentiation of hematopoietic cells that present with characteristic dysplastic cell morphologies, peripheral blood cytopenias, and a variable increase in peripheral blood and bone marrow blast percentage and risk of transformation to acute myeloid leukemia (AML).
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MDS is primarily a disease of elderly patients with a median age of 71 to 76 years and 86.4% of patients being older than 60 years at the time of diagnosis.³ Therefore, only a minority of patients are eligible for the only potentially curative therapy, allogeneic

[#]Corresponding Author: Amer M. Zeidan, MBBS, MHS. Section of Hematology, Department of Medicine, Yale University, 333 Cedar Street, PO Box 208028, New Haven, CT 06520-8028. amer.zeidan@yale.edu, Phone: 203-737-7103. Fax: 203-785-7232.

hematopoietic stem cell transplantation (allo-HSCT), due to the significant treatment-associated morbidity and mortality.^{3,4} Unlike AML, which has seen the approval of various novel treatments in recent years, the hypomethylating agent (HMA) azacitidine (AZA) remains the only agent with a survival benefit in higher-risk MDS (HR-MDS) patients.^{5–7} However, several novel agents in mono- or combination therapy are currently undergoing advanced stages of clinical testing and have yielded promising preliminary results. Furthermore, the wider availability of genetic testing is expected to lead to a greater individualization of treatments for MDS patients and has paved the way for molecularly targeted therapies.^{8,9} Herein, we briefly review the currently available treatment options for patients with HR-MDS and discuss recent developments of novel agents and the implications of the greater availability of genetic testing.

2.) Overview of current treatment options

Given the heterogeneity of MDS-associated symptoms and the variable risk of progression to AML, patients should be risk-stratified using a validated risk stratification tool such as the international prognostic scoring system (IPSS) or its revised version IPSS-R. However, each of those scores has certain limitations, and due to the advanced age and often relevant comorbidities, an individualized treatment concept should be discussed with patients.^{10–12} Traditionally, HR-MDS has been defined as a score of >4.5 points by IPSS-R or 1.5 points by IPSS.^{1,13} However, it is important to be aware of the distinct differences between IPSS and IPSS-R when comparing trials using those two scoring systems as this may limit comparability of included patient populations. This is especially important for patients with IPSS-R intermediate risk (score of 3.5–4.5 points) that fall in the grey zone between the higher or lower risk groups from a management point of view. Compared to IPSS, IPSS-R contains 5 instead of 3 prognostic cytogenetic risk groups with more extensive cytogenetic aberrations, splits bone marrow blast percentage into 4 subcategories, and considers the depth of cytopenias leading to upstaging of 27% of IPSS lower-risk and downstaging of 18% of IPSS higher-risk patients by IPSS-R.^{14,15} This could potentially lead to the enrollment of more previously lower-risk patients in trials using IPSS-R as an inclusion criterion especially if bone marrow blast counts are low or cytogenetics are normal.^{14,15} One group attempted to solve this issue by further dividing the IPSS-R intermediate risk group into intermediate-favorable and intermediate-adverse risk based on patient age ≥ 66 years, peripheral blood blasts ≥ 2%, and history of RBC transfusions into intermediate-favorable and intermediate-adverse risk.^{3,13,16,17}

In patients with HR-MDS progression to AML is a serious concern and patients should be evaluated for transplant eligibility early on especially in patients with high risk cytogenetic features (e.g. *TP53*, *JAK2* or *RAS* pathway mutations) or patients who are refractory to other therapies and those who have profound cytopenias.^{18,19} For HSCT-ineligible patients or patients without a suitable donor, non-transplant strategies such as HMA, chemotherapy (especially after progression to AML) or clinical trial enrollment are available.²⁰

Thanks to the greater availability of genetic testing, it has been shown that the majority of MDS patients harbors somatic mutations that provide additional prognostic information, which are not captured by clinical-pathologic scoring systems.^{8,21–23} Although some studies

have suggested that the presence of somatic mutations might predict response to certain treatments (e.g. higher response rates to HMA with *TET2* mutations), the role of genetic testing in the workup of HR-MDS continues to evolve and current guidelines do not recommend genetic testing as part of routine clinical practice and to guide individual treatment strategies.^{1,24}

2.1) Allogeneic HSCT

Allo-HSCT remains the only treatment modality with curative potential for MDS. Rigorous patient selection based on patient (age, performance status, comorbidities) and disease factors (IPSS/IPSS-R, presence of specific mutations, blast percentage) is essential to optimize outcomes.^{19,25–29} Recent data from 6434 MDS patients from the European Society for Bone Marrow Transplant registry showed 5-year and 10-year OS rates of 35% (95% CI: 34–37%) and 32% (95% CI: 30–33%), respectively, with 10-year non-relapse mortality (NRM) of 34% (95% CI: 33–35%).³⁰ Myeloablative conditioning regimens have been shown to have favorable outcomes with regard to relapse-related mortality but procedure-related toxicity can be prohibitive especially in older (generally defined as >60–65 years) patients.^{31,32} A recent multicenter, retrospective registry study showed that allo-HSCT can be safely performed even in patients older than 70 years (median age: 72 years, range 70–78 years). 3-year OS in the entire cohort was 34% with no effect of conditioning intensity on OS. CMV seronegativity and a good pre-transplant Karnofsky performance status were the only factors associated with an improved survival.³³ Another study demonstrated that patients 65 years or older did not have a higher rate of 3-year NRM (28% vs 25%; hazard ratio [HR]: 1.19; 95% CI: 0.93–1.52; p=0.16) or inferior 3-year OS (37% vs 42%; HR 1.09; 95% CI: 0.94–1.27; p=0.23) compared to MDS patients who were 55–64 years of age.³⁴ Similar results have been reported from a recent retrospective analysis of 125 consecutive MDS patients undergoing allo-HSCT with 2-year OS and NRM of 39% (95% CI: 30–48%) and 41.6% (95% CI: 31–52%) with transfusion dependence, cytogenetic risk group, and serum ferritin levels but not patient age as predictors for death in multivariable analyses.³⁵ Based on these results, allo-HSCT should be considered for all young and fit patients with HR-MDS and selected older patients.

Defining the optimal time point for allo-HSCT is difficult. Expert consensus guidelines recommend transplant after failure of non-transplant treatment strategies and if high-risk genetic features are present.¹⁹ However, the implications of high-risk genetic mutations (*TP53*, *DNMT3A*, *TET2*, *JAK2*, and *RAS* pathway) on timing and selection of conditioning regimen need to be further defined by clinical trials.^{27–29}

The burden of disease at the time of transplant is one of the most important predictors of disease relapse and the presence of minimal residual disease (MRD) among responding patients has been associated with inferior outcomes in both MDS and AML in various studies.^{36–40} However, whether pre-emptive MRD-guided treatment with HMA or immunotherapies such as donor-lymphocyte infusion is effective to prevent relapse or improves outcomes is an area of ongoing research.^{41,42} In the RELAZA-2 trial MRD-positive AML (n=48) and MDS (n=5) patients who were in CR after intensive chemotherapy or allo-HSCT were treated with AZA for relapse prevention for up to 24 cycles.⁴² Among

those 53 patients 1-year relapse-free survival (RFS) was 46% (95% CI: 32-59%) compared to 88% (95% CI 82-94%; HR: 6.6 [95% CI 3.7-11.8], $p < 0.0001$) in MRD-negative patients.⁴² Additionally, among MRD-positive patients, patients with higher levels of MRD had inferior OS and RFS compared to patients with lower levels of MRD.⁴² However, further studies to evaluate the impact of pre-emptive treatment following allo-HSCT are needed (e.g. [NCT01995578](#)).

2.2) Intensive chemotherapy

Especially in younger and fit patients with higher bone marrow blast percentage, intensive chemotherapy (e.g. anthracycline-cytarabine combination, high-dose cytarabine, etc.) can be a viable treatment option mainly to reduce leukemic burden prior to allo-HSCT.^{1,43}

However, rates of CR have been reported to be lower and duration of remission shorter in MDS compared to AML with frontline intensive chemotherapy (IC) but high-quality evidence is lacking.⁴⁴⁻⁴⁶ In a recent retrospective analysis comparing frontline treatment with HMA and IC in 106 young (<60 years) patients with MDS and 10% bone marrow blast percentage treated at MD Anderson Cancer Center between 1993 and 2017, patients treated with IC had a higher overall response (82% vs 60%, $p = 0.02$) and CR rate (63% vs 30%, $p < 0.001$).⁴⁷ Of note, rates of subsequent HSCT were similar in both groups (29% vs 34%, $p = 0.68$).⁴⁷ Unlike other studies that showed a higher response rate in patients with unfavorable karyotype and *TP53* mutations to HMAs and decitabine, respectively, baseline karyotype and *TP53* status did not influence response rates in this study.^{5,47,48}

CPX-351 is a liposomal formulation of cytarabine and daunorubicin that has recently been approved for the treatment of newly-diagnosed therapy-related AML and AML with myelodysplasia-related changes (AML-MRC) in patients 60-75 years of age.⁴⁹ Although there are no results from clinical trials of CPX-351 for treatment of HR-MDS available thus far, about 50% of patients in the phase III trial by Lancet et al. had preceding MDS. Several clinical trials investigating CPX-351 in untreated HR-MDS patients are currently active (e.g. [NCT03572764](#), [NCT01804101](#)).

2.3) Lower intensity treatment – hypomethylating agents

As the majority of MDS patients are older and ineligible for intensive treatment (allo-HSCT and IC), frontline HMAs are the mainstay of therapy in HR-MDS. In the respective landmark clinical trials, only AZA but not decitabine (DEC) showed survival benefits compared to standard of care leading to the approval of both AZA and DEC for MDS in the US (independent of disease risk) and Europe (only AZA for HR-MDS).^{5,20,50,51} In the landmark AZA-001 trial, a continuous schedule of AZA 75 mg/m² per day for 7 days every 28 days led to a 9.5 month OS (24.5 months vs 15 months; $p = 0.0001$) benefit compared to conventional care (supportive care, IC, low-dose cytarabine [LDAC]) with peripheral blood cytopenias being the most common adverse events.⁵ However, subsequent real-world and clinical trial data have nuanced these results compared to the original studies with median OS ranging from 10 to 17 months.^{11,52-55} This discrepancy might be due to differences in adherence to dosing schedules, treatment duration, less rigorous patient selection compared to the landmark clinical trials, or an inherently lower clinical effectiveness with HMA than initially thought.^{53,56}

In two large randomized phase III clinical trials DEC was shown to be superior to supportive care in terms of ORR and CR rate in HR-MDS patients.^{50,51} Kantarjian et al. randomized 170 MDS patients to receive either DEC at a dose of 15 mg/m² given intravenously every 8 hours for 3 days and repeated every 6 weeks, or best supportive care. In this study DEC was significantly superior in terms of ORR (17% vs 0%, $p<0.001$), and CR rate (9% vs 0%, $p<0.001$) but did not prolong median time to AML progression or death (12.1 months vs 7.8 months, $p=0.16$). However, in patients with intermediate-2 or high-risk disease by IPSS this difference reached statistical significance (12.0 months vs 6.8 months, $p=0.03$).⁵⁰ Of note, there was no difference in median OS in the intention to treat analysis for DEC compared to supportive care (14.0 months vs 14.9 months, $p=0.636$).⁵⁰ Similarly, in a subsequent German study of 237 older (60-90 years) HR-MDS patients, decitabine achieved significant improvements in progression-free survival, AML transformation, and quality of life parameters but not in OS.⁵¹

Unlike standard chemotherapy, response to HMAs takes several cycles to occur and the National Comprehensive Cancer Network (NCCN) is recommending to complete at least 6 cycles of AZA in the absence of unacceptable toxicity or disease progression prior to discontinuing therapy due to a lack of response.^{18,57} For patients responding to HMAs treatment should be continued until disease progression since responses may continue to improve over time⁵⁸ and treatment interruptions can lead to rapid relapses which are often resistant to resumption of HMA therapy.⁵⁹ However, HMAs are not a curative treatment modality and responses are often only transient. Given that the prognosis after HMA failure is poor with median OS of 14-17 months and 4-5.6 months for lower risk (LR)- and HR-MDS patients, respectively, novel treatments to prevent HMA failure in the first place or to improve outcomes after disease progression are desperately needed.⁶⁰⁻⁶²

3.) Novel treatment modalities for HR-MDS

Over the last several years multiple novel agents have been successfully tested either as monotherapy or in combination with HMA. Figure 1 illustrates the mechanism of action of selected novel agents for HR-MDS.

3.1) Next generation HMAs

Table 1 provides an overview of selected clinical trials of novel agents including HMAs in both the frontline and HMA-refractory setting. Guadecitabine (SGI-110) is a DEC analogue with an extended half-life due to its resistance to deamination by cytidine deaminase, which offers both greater ease of administration and the potential for greater efficacy as it may affect more cells undergoing S-phase of the cell cycle than AZA and DEC.⁶³ Although head-to-head comparisons with older HMAs are not available, guadecitabine may have some additional benefits based on results from single arm phase I/II studies in both first-line and relapsed/refractory (R/R) AML and MDS even in pretreated and HMA-refractory patients (pretreated setting: ORRs of 8.6% [2 CR, 3 CRi, 1 PR in 74 AML patients, 2 CRs in 19 MDS patients]; frontline setting: ORR 30-50%).⁶³⁻⁶⁶ In a dose-finding phase I/II study (NCT01261312) in 105 MDS patients (51 frontline and 54 HMA-refractory patients) guadecitabine yielded ORRs of 40% and 55% in the combined frontline and HMA-

refractory cohort when used at 60 mg/m² and 90 mg/m², respectively.⁶³ Median OS was 611 days (95% CI: 408-771) for the 60 mg/m² group and 399 days (95% CI: 303-663) for the 90 mg/m² group, with 1-year and 2-year OS rates of 67% (95% CI: 52-78%) and 39% (95% CI: 26-52%) for the 60 mg/m² group compared to 60% (95% CI: 45-72%) and 30% (95% CI: 18-43%) for the 90 mg/m² group, respectively.⁶³ Outcomes in the frontline and HMA-failure setting appeared numerically comparable with ORR of 51% (95% CI: 36-66%; 22% CR) and 43% (95% CI: 30-58%; 4% CR).⁶³ However, adverse events in this trial are a concern with 7 out of 102 patients (7%) dying due to adverse events with 2 deaths deemed to be treatment-related (septic shock with 60 mg/m²; pneumonia with 90 mg/m²).⁶³ Otherwise, the side effect profile was similar to other HMAs with hematologic side effects and pneumonia being most common (thrombocytopenia 41-57%, anemia 47-49%, febrile neutropenia 32-43%, and pneumonia 25-31%).⁶³ This led to a phase III clinical trial comparing 60 mg/m² guadecitabine with treatment choice (LDAC, standard induction chemotherapy, or best supportive care) in HMA-refractory patients with MDS or CMML, which is currently recruiting ([NCT02907359](#); ASTRAL-3).

Although, extrapolating results from AML trials to MDS patients is limited, sobering results have recently been presented from the randomized phase III ASTRAL-1 trial ([NCT02348489](#)) of guadecitabine vs treatment choice (AZA, DEC, LDAC) in elderly, treatment-naïve AML patients which failed to meet its primary endpoint of improved survival with guadecitabine with median OS of 7.1 months vs 8.5 months with treatment of choice in the intention to treat analysis (HR: 0.97 [95% CI: 0.83-1.14]; p=0.73; CR rate 19.4% for guadecitabine vs 17.4% for physician choice, p=0.48).⁶⁷ Subsequent analysis in R/R-AML patients have identified cytogenetic parameters (high *DNMT3B* and low *CDKN2B*, *CTCF*, and *CDA* expression, *RAS/NRAS* mutations, frequent CpG island hypermethylation) and high peripheral blood blast percentage and low hemoglobin as predictors for a low response rate to guadecitabine.⁶⁸

CC-486, an oral formulation of AZA, has shown response rates of up to 46% and a comparable toxicity profile (grade 3–4 adverse events in up to 83%, most commonly GI toxicity, 42% febrile neutropenia) when given on a 21 out of 28-day schedule.^{69–71} In a small trial of 30 patients with MDS (4 patients) or AML (26 patients) following allo-HSCT ([NCT01835587](#)), maintenance therapy with CC-486 has been shown to be safe with 1-year estimated survival rates of 86% and 81% for the 7-day and 14-day administration schedule, respectively, which compares favorably with prior trials of AZA maintenance.^{72,73}

Currently, there is only one active clinical trial of CC-486 as monotherapy for HMA-refractory MDS patients ([NCT02281084](#)). In AML, CC-486 has recently been studied in the phase III QUAZAR AML-001 trial ([NCT01757535](#)) for maintenance therapy in AML patients ≥55 years of age in CR/CRi following induction chemotherapy and who were not intended to proceed to allo-HSCT.⁷⁴ In the QUAZAR AML-001 trial, CC-486 led to a 9.9 months survival benefit compared to placebo (CC-486: 24.7 months [95% CI, 18.7-30.5] vs 14.8 months for placebo [95% CI, 11.7-17.6]; p=0.0009).⁷⁴ However, according to [clinicaltrials.gov](#) the combination arm of a trial studying the addition of the PD-L1 inhibitor durvalumab to CC-486 had to be closed due to dose finding difficulties ([NCT02281084](#)).⁷⁵

Since DEC is being deactivated by cytidine deaminase,⁷⁶ ASTX727, which combines DEC with the cytidine deaminase inhibitor cedazuridine, has been developed. In a recent open-label phase I, dose escalation study ([NCT02103478](#)) of 44 patients with MDS or CMML combination treatment with DEC and cedazuridine was shown to be safe and effective with ORR of 30% (11% CR) and 16% proceeded to allo-HSCT.⁷⁷ The most common grade 3 or higher adverse events were thrombocytopenia (41%), neutropenia (30%), and anemia (25%).⁷⁷ Phase II abstract data from 50 HR-MDS or CMML patients (94% HMA-naïve) showed rates of CR and hematologic improvement (HI) of 16% and 18%, respectively. Serious adverse events were comparable to other HMA trials (grade 3 neutropenia 48%, thrombocytopenia 38%, febrile neutropenia 38%, and pneumonia 20%).⁷⁸ ASTX727 is currently being studied in a phase III, open-label crossover study vs IV DEC in MDS and CMML patients ([NCT03306264](#), ASCERTAIN trial), as well as a phase I/II trial of low dose ASTX727 in LR-MDS ([NCT03502668](#)). In the ASCERTAIN trial patients are randomized 1:1 to receive either oral ASTX727 in cycle 1 followed by IV decitabine in cycle 2, or the converse order to establish pharmacokinetic equivalence between both agents. From cycle 3 onwards patients continue to receive ASTX727 until disease progression or unacceptable toxicity. Abstract data from the randomized phase of the ASCERTAIN trial showed that the trial met its primary endpoint of pharmacokinetic equivalence of ASTX727 and IV DEC, and the objective response rate for ASTX727 was 64% (12% CR, 46% mCR, 7% HI) with a safety profile comparable to IV DEC.⁷⁹

3.2.) Combination of HMAs with venetoclax

While the combination of HMAs or LDAC with the BCL-2 inhibitor venetoclax has been a major advancement in the treatment of older (age ≥ 75 years) or IC-ineligible AML patients, ^{80,81} data in MDS are eagerly awaited. Current retrospective analyses are only including few MDS patients. While highly effective, the combination of venetoclax with HMA can cause significant cytopenias including febrile neutropenia in up to 72% of relapsed/refractory patients, which may limit its use in elderly and frail patients.⁸² However, recent in vitro data showed that venetoclax in combination with lower dose AZA is effective in eliminating malignant cells while preserving healthy hematopoietic cells.⁸³ Multiple clinical trials in both the frontline ([NCT02942290](#)), as well as salvage setting ([NCT02966782](#)) of venetoclax + AZA in HR-MDS are currently recruiting. Data from phase I studies combining venetoclax and AZA in both the frontline and relapsed/refractory setting have recently been published in abstract form.^{84,85} In the R/R trial ([NCT02966782](#)), Zeidan and colleagues presented data from 22 patients who were treated with venetoclax monotherapy and 24 patients received venetoclax + AZA. Among the 40 evaluable patients, response rates, PFS, and OS appeared to be superior in the combination arm compared with venetoclax monotherapy (venetoclax monotherapy: mCR 7% (1/16 patients), median PFS 3.4 months (95% CI: 1.9-5.2 months) and 6-month OS estimate 57% (95% CI: 22%-81%); venetoclax + AZA: 13% CR (3/24 patients), 38% mCR (9/24 patients); median PFS and OS not reached).⁸⁵ In previously untreated MDS patients ([NCT02942290](#)), response rates appeared higher than in the R/R setting with 18 out of 57 patients achieving CR and 22 out of 57 with mCR and an 18-month OS estimate of 74% (95% CI: 50-87%).⁸⁴ Side effect profiles were similar in both trials with hematologic toxicities (neutropenia [including febrile neutropenia] up to 31%), thrombocytopenia [30-39%], and anemia [15-20%]) being the most common grade 3

or 4 treatment-emergent adverse events.^{84,85} However, additional and larger trials directly comparing venetoclax + AZA to AZA alone are needed.

3.3) Combination of HMAs with immune checkpoint inhibitors

While immune checkpoint blockade (ICB) has only limited efficacy if given as monotherapy in the HMA-refractory setting,^{86–88} combination of ICB with HMA has shown significant synergistic effects in abstract data.⁸⁹ However, subgroup analysis of the 28 MDS (57% HR-MDS) patients treated with the PD-1 inhibitor pembrolizumab in the phase Ib KEYNOTE-013 ([NCT01953692](#)) trial showed an ORR of only 4% (no CR, 1 PR) and treatment discontinuation due to adverse events in 2 patients (1 patient each with grade 4 tumor-lysis syndrome and musculoskeletal symptoms).⁹⁰

Zeidan et al. reported the results of a phase Ib study of 29 HMA-refractory HR-MDS patients treated with the CTLA-4 inhibitor ipilimumab that showed a mCR in 1 patient (3.4%), a prolonged stable disease >46 weeks in 24% of patients and 17% of patients were able to undergo HSCT without excess toxicity.⁸⁷ Of note, 20.7% of patients in this study developed immune-related adverse events (IRAE) grade 2 that required discontinuation of ipilimumab but resolved with corticosteroids.⁸⁷ However, preliminary data of a phase II study of the anti-PD1 antibody nivolumab or the anti-CTLA4 antibody ipilimumab alone or in combination with AZA in 76 patients with MDS (54% frontline and 46% HMA-refractory) showed encouraging results in terms of ORR and median OS for the two combination arms (ORR in 15/20 (75%), 15/21 (71%), 2/15 (13%), and 7/20 (35%) of patients with median OS of 12 months, not reached, 8 months, and 8 months treated with AZA + nivolumab, AZA + ipilimumab, nivolumab alone, or ipilimumab alone respectively) with an acceptable safety profile.⁸⁹

Several additional trials combining AZA with nivolumab and ipilimumab ([NCT02530463](#)), AZA + pembrolizumab ([NCT03094637](#)), AZA + durvalumab ([NCT02775903](#)), or combination with conventional chemotherapy ([NCT03094637](#), [NCT02464657](#)) are ongoing. Furthermore, additional inhibitory immune checkpoints besides PD-1/PD-L1 and CTLA-4 such as T-cell immunoglobulin mucin (TIM)-3 and lymphocyte activation gene (LAG)-3 can serve as promising targets for combination therapy.⁹¹ Co-expression of TIM-3 and PD-1 by T-cells in bone marrow aspirates from AML and MDS patients has been associated with a state of immune exhaustion and higher rates of relapse after HSCT.⁹² The combination of the anti-TIM-3 antibody MBG453 and the PD-1 inhibitor PDR001 is currently being tested in a phase I study ([NCT03066648](#)). A conceptually similar arm of the same study is combining the PDR001 +/- MBG453 with DEC. Abstract data from the combination of MBG453 with DEC appear promising (50% CR/mCR with no disease relapses during the study period).⁹³ Additional clinical trials are combining HMAs with MBG453 in HR-MDS (STIMULUS-MDS1; [NCT03946670](#)) or with HDM201, an oral HDM2 inhibitor that prevents the degradation of TP53 ([NCT03940352](#)).

While available data are scarce, abstract data from a phase Ib trial testing the anti-CD47 antibody magrolimab, a macrophage immune checkpoint inhibitor, in combination with AZA have recently been presented. Among 24 untreated MDS patients, 92% (22 out of 24 patients) had an objective response (50% CR) with 23% (5 out of 22) of responders being

MRD negative by multiparameter flow cytometry, which may translate into durable responses.⁹⁴ Table 2 provides an overview of clinical trials that are currently recruiting patients using ICB in MDS.

3.4) Rigosertib

Rigosertib is an oral multikinase inhibitor that causes mitotic arrest and apoptosis mainly by interference with the Ras pathway, while preserving healthy hematopoietic cells.^{95–97} In phase I trials in patients with MDS, objective responses were seen in up to 53% of patients with a substantial survival benefit in responders in one study (15.7 months for responders vs 2.0 months in non-responders).^{95,97,98}

However, in a large, randomized phase III trial ([NCT01241500](#); ONTIME) of 299 HR-MDS patients refractory to HMA, rigosertib did not provide a significant OS benefit compared to best supportive care (8.2 months [95% CI: 6.1–10.1] for rigosertib vs 5.9 months [95% CI: 4.1–9.3] for best supportive care [HR: 0.87, 95% CI: 0.67–1.14; p=0.33]).⁹⁹ While these lackluster results question the efficacy of rigosertib in this setting, subgroup analysis may lead to the identification of specific patient subsets that benefit from rigosertib ([NCT02562443](#)). Especially in HR-MDS and in the HMA-refractory setting rigosertib might provide additional benefits based on subsequent, single arm phase I/II studies with a median OS of 15.7 months reported in responding patients.^{97,98} However, these results need to be replicated in larger, randomized trials, especially in light of the negative results from the previous randomized, phase III ONTIME trial.

Since preclinical models have shown synergistic effects of HMA and Ras pathway inhibitors, the combination of AZA and rigosertib has been tested in both phase I and II clinical trials.^{100,101} Abstract data from a phase II study of 40 MDS patients (17 HMA-refractory patients) showed responses in 85% and 62% of HMA-treatment-naïve and HMA-refractory patients, respectively.¹⁰¹

3.5) APR-246

TP53 mutations have been associated with adverse outcomes and higher rates of resistance to standard treatments in MDS.^{22,28,102} While being less common in de novo MDS, *TP53* mutations are more frequently encountered in therapy-related MDS and in patients with complex or monosomal karyotypes.¹⁰³ With the greater availability of genetic testing and increasingly personalized treatment strategies, targeting *TP53*-mutated cells with the small molecule inhibitor APR-246 has been successfully tested both as a single agent as well as in combination with AZA.^{104,105} In a multicenter phase Ib/II study of APR-246 in combination with AZA in HMA-naïve patients with *TP53*-mutated higher-risk MDS, MDS/MPN overlap or AML with <30% blasts ([NCT03072043](#)), ORR among 45 evaluable patients was 87% with 53% CR and a median OS of 11.6 months (95% CI: 9.2–14 months).¹⁰⁶ In a similar study of APR-246 + AZA from France ([NCT03588078](#)), ORR was 75% (12 out of 16 evaluable patients) with 56% CR (100% MRD-negativity among patients who achieved CR).¹⁰⁷ The safety profile in both studies appeared acceptable with febrile neutropenia and neurologic adverse events being seen most frequently.^{106,107} These positive results have led

to a phase III trial comparing AZA+APR-246 with AZA monotherapy, which is currently recruiting ([NCT03745716](#)).

3.6) Additional combination partners for HMA - histone deacetylase (HDAC) and NEDD-8 activating enzyme inhibitors

Apart from DNA methylation, gene transcription is also regulated by the competing activity of histone lysine acetyltransferases and histone deacetylases (HDAC).^{108,109} Generally speaking, histone acetylation leads to a more accessible chromatin structure promoting gene transcription.¹⁰⁸ While HDAC inhibitors have only limited activity if used as monotherapy, the combination of HDAC inhibitors and HMA has shown synergistic effects in-vitro but had mixed results in clinical trials in both AML and MDS.^{110–113} In the SWOG1117 trial the combination of AZA and vorinostat did not provide a survival benefit compared to AZA monotherapy.¹¹² Furthermore, the combination of pracinostat and AZA did not improve OS with a higher rate of treatment discontinuation due to adverse effects in a randomized phase II trial of 102 HR-MDS patients.¹¹³ Optimization of treatment schedules, the development of more potent and specific HDAC inhibitors and better patient selection (e.g. patients with mutations in *EZH2* and *ASXL1*) might lead to higher response rates.¹⁰⁹

Pevonedistat (MLN4924) is a NEDD8-activating enzyme (NAE) inhibitor that impairs proteosomal destruction of intracellular proteins leading to their cytotoxic accumulation.¹¹⁴ Phase I studies have established the safety of pevonedistat in AML and MDS patients with hepatotoxicity and multiorgan failure being the most common dose-limiting adverse events.^{115,116} Since in vitro experiments suggested synergistic effects of pevonedistat and the HDAC inhibitor belinostat and AZA, a subsequent phase Ib trial ([NCT01814826](#)) showed an ORR of 50% in R/R-AML patients treated with AZA + pevonedistat.^{117,118} Interestingly, 4 out of 5 patients with *TP53* mutation had an objective response in this trial while no other predictive genetic or clinical markers were identified.¹¹⁷ Data from MDS patients are very limited but a recently published abstract ([NCT03238248](#)), showed ORR of 43% and CR rate of 24% in a cohort of 23 HMA-refractory patients with MDS or MDS/MPN.¹¹⁹ Given the poor prognosis of HMA-refractory patients, this combination could be an important addition to the treatment armamentarium in this setting. Furthermore, pevonedistat + AZA is currently tested against AZA in the phase III PANTHER trial for frontline treatment in HR-MDS, CMML, and AML ([NCT03268954](#)).

4.) Future directions

Thanks to the development of novel diagnostic techniques such as Next Generation Sequencing (NGS), our understanding of the genetic landscape of MDS continues to expand.^{8,21,120} Various studies have identified specific high-risk mutations in various genes such as *TP53*, *ASXL1*, and *EZH2* that provide additional prognostic information, which might enable a more individualized approach to patient care beyond traditional clinical-pathologic scoring systems such as IPSS-R.^{21,22,28,121} This prognostic effect is also seen for patients proceeding to allo-HSCT and may be used to guide selection of conditioning regimens, monitoring for disease recurrence or strategies for maintenance therapy to reduce risk of relapse.^{28,29}

Potentially more clinically relevant than the prognostic implications of somatic mutations, is the potential for treatment selection based on the presence of specific mutations. Although MDS is lagging behind AML with regards to other genetically targeted therapies, early data exist for the use of specific inhibitors in *IDH1/2*-mutated cases.⁷ Unlike AML, *IDH1/2* and *FLT3* mutations are much rarer in MDS and are encountered in less than 5% of MDS patients.^{21,122} However, in the minority of patients who harbor such mutations the *IDH1* inhibitor ivosidenib and the *IDH2* inhibitor enasidenib might be effective therapeutic options. Enasidenib showed ORR of 53% (8 out of 15 evaluable patients) in 16 *IDH2*-mutated MDS patients (11 HMA-refractory patients, 50% response rate).¹²³ Preliminary data from a phase II study of enasidenib for *IDH2*-mutated HR-MDS showed an ORR of 67% (12 out of 18 evaluable patients) with 100% response rate in HMA-naïve patients.¹²⁴ Phase I data from 12 *IDH1*-mutated MDS patients (9 HMA-refractory) treated with ivosidenib reported an ORR of 91.7% (11/12 patients) with 5 patients (41.7%) achieving CR.¹²⁵ Finally, novel *IDH* inhibitors such as olutasidenib (FT-2102) continue to be developed.¹²⁶ In an ongoing phase I/II study of 20 patients with *IDH1*-mutated MDS, olutasidenib was either given as a single agent or in combination with AZA. Response rates were higher in the combination arm compared to monotherapy (73% vs 33%) with neutropenia (30%) and thrombocytopenia (25%) being the most common grade 3/4 treatment emergent adverse events (NCT02719574).¹²⁷

Beyond those targeted agents, prior studies used genetic testing to identify predictive markers for a higher response to HMA. Although far from being used in routine clinical practice, data exist that showed higher response rates to HMA in patients with *TET2* and *DNMT3A* mutations.^{24,128,129} Conversely, the presence of 4 mutations or of *ASXL1* mutations were associated with a lower likelihood of response to HMAs and adverse OS, while *TP53* mutations were predictive of a lower response to lenalidomide even in patients with del(5q).¹²⁸

Multiple novel immunotherapies such as bispecific antibodies and chimeric antigen receptor (CAR) T-cells have been tested mainly in R/R-AML but are being increasingly studied in MDS as well.¹³⁰ However, none of these agents is ready for use outside of clinical trials and further studies to evaluate their safety and efficacy are needed.

Finally, treatment responses have traditionally been assessed using the International Working Group (IWG) response criteria, which included CR, PR, and HI as well as mCR with and without HI.¹³¹ However, some studies have suggested that mCR might not be a clinically beneficial response, and OS in patients with mCR was similar to patients with stable disease.¹³² It remains to be seen whether the high ORR for several novel agents that were driven by a high proportion of mCRs also translate into OS benefit with longer follow up.^{85,93,94} Nonetheless, while mCR might therefore be an inferior outcome compared to CR or PR, it might enable more patients to proceed to allo-HSCT, which remains the only curative therapeutic modality.^{85,93} As MRD-positivity prior to allo-HSCT is associated with adverse outcomes and treatment with HMA alone rarely leads to MRD-negativity, novel agents such as magrolimab and APR-246 might lead to MRD-negativity in a subset of patients and therefore might improve outcomes among patients undergoing allo-HSCT, but this remains to be seen.^{94,106} Lastly, revisiting the traditional IWG response criteria (and endpoints used

in clinical trials) is likely needed to better define and capture the full benefits of novel therapies beyond mCR.

5.) Conclusions

The therapeutic landscape for the wide spectrum of MDS patients has evolved substantially over the last decade. While HMA monotherapy has been the mainstay of treatment for several years, treatment concepts for the individual MDS patient will become more personalized and driven by genetic testing that has the potential to provide prognostic and predictive information. Novel HMAs, combinations of HMAs with immune therapies such as anti-CD47, venetoclax, or molecularly targeted agents such as APR-246 or IDH inhibitors may become first-line agents if longer follow-up of more patients and/or larger randomized trials confirm the promising preliminary results. Beyond the objective responses, it will be interesting to see if any of those agents has disease-modifying potential in terms of prolonging survival or reducing progression to AML. Although additional data are needed, the expansion of therapeutic options seen in AML recently, may hopefully expand to MDS soon and improve the dismal prognosis of HR-MDS patients.

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Figure 1: Selected novel agents in clinical trials for higher-risk MDS

For HR-MDS patients, novel HMAs (guadecitabine, ASTX727, CC-486), histone deacetylase inhibitors (HDAC; e.g. vorinostat, pracinostat, entinostat, and belinostat), small molecules targeting specific genetically defined subpopulations (e.g. APR-246 in *TP53*-mutated patients), and combinations with HMAs are potential new therapeutic approaches. Rigosertib is a multikinase inhibitor targeting Ras signaling, which has shown efficacy in phase I trials but less impressive phase III trial results. *IDH* mutations lead to the accumulation of the oncometabolite 2-hydroxyglutarate (2-HG) which alters gene transcription by DNA hydroxymethylation. In patients with *IDH* mutations targeted therapy with the *IDH1* and *IDH2* inhibitors ivosidenib and enasidenib may be an effective option. Additionally, the combination of HMA with various different immune checkpoint inhibitors targeting PD-1 (e.g. pembrolizumab, nivolumab), PD-L1 (e.g. durvalumab, atezolizumab), CTLA-4 (e.g. ipilimumab), or TIM-3 (e.g. MBG453) are ongoing. The anti-CD47 antibody Hu5F9-G4 (also known as magrolimab) is also being tested in HR-MDS and AML patients to enhance phagocytosis of leukemic cells. Pevonedistat inhibits proteosomal degradation of proteins leading to the accumulation of cytotoxic proteins. APR-246 is an inhibitor of mutant *TP53* and has been shown to be effective in combination with AZA in MDS patients with *TP53* mutations. Finally, venetoclax has been shown to trigger apoptosis in leukemic blasts and has been recently approved in combination with HMA or low-dose cytarabine in AML. Trials evaluating those combinations in MDS are ongoing.

Table 1:

Selected ongoing trials of novel agents in higher-risk MDS

Drug	Phase	NCT	Patient characteristics	Intervention	Results	Current status
Guadecitabine	I/II	NCT02935361	R/R MDS or CMML	Guadecitabine + atezolizumab	Preliminary results at ASH 2018: ¹³³ Efficacy: 9 patients included; 2 HI and 1 CR; median OS not reached Toxicity: 17 grade 3/4 TEAEs neutropenia, thrombocytopenia, and leukopenia most common (4 each)	Recruiting
	II	NCT02684162	AML and MDS relapsed after allogeneic HSCT	Guadecitabine and donor lymphocyte infusion	Not reported	Recruiting
	II	NCT03454984	HR-MDS following allo-HSCT	Guadecitabine + donor lymphocyte infusion for relapse prevention	Not reported	Not yet recruiting
	II	NCT02131597	HR-MDS	Guadecitabine	Not reported	Active, not recruiting
CC-486	III	NCT02907359 (ASTRAL-3 trial)	HMA-refractory MDS or CMML	Guadecitabine vs treatment choice (low-dose cytarabine, BSC, 7+3)	Not reported	Active, not recruiting
	II	NCT02281084	HMA-refractory MDS	CC-486 + durvalumab vs CC-486 alone	Not reported: combination arm of CC-486 and durvalumab closed	Active, not recruiting
	III	NCT04173553	AML or HR-MDS in CR following allogeneic HSCT	CC-486 vs placebo for maintenance after allo-HSCT	Not reported	Recruiting
	III	NCT03306264	Newly-diagnosed and R/R HR-MDS, CMML, or AML	ASTX727 vs IV decitabine	Preliminary results at ASH 2019: ⁷⁹ Efficacy: ORR: 65 patients (64%); CR: 12 patients (11.9%), mCR: 46 (45.5%) HI: 7 (6.9%) Toxicity: similar safety of ASTX727 and decitabine, only hematologic grade 3/4 TEAEs	Recruiting
Ipilimumab	I/II	NCT04013880	IDH1-mutated R/R-AML or MDS	ASTX727 + FT-2102	Not reported	Recruiting
	I	NCT02890329	RR MDS/AML	Ipilimumab + decitabine	Not reported	Recruiting
	I/II	NCT02464657	AML and HR-MDS eligible for intensive therapy	Nivolumab + idarubicin + cytarabine	Preliminary results at ASH 2018: ¹³⁴ Efficacy: (42 AML and 2 HR-MDS patients): 34 CR/CRi (77%), 53% MRD-negative Toxicity: 6 IRAsEs; 72% of patients developed GVHD after allo-HSCT	Active, not recruiting
	I	NCT04128020	AML and MDS following reduced-intensity allo-HSCT	Nivolumab alone or in combination with AZA	Not reported	Recruiting
Nivolumab	I	NCT03358719	HR-MDS, AML with 30% blasts	Nivolumab + NY-ESO-1 vaccination + decitabine	Not reported	Recruiting

Drug	Phase	NCT	Patient characteristics	Intervention	Results	Current status
Pembrolizumab	I	NCT03969446	Frontline and R/R HR-MDS and AML	Pembrolizumab + decitabine	Not reported	Not yet recruiting
	I	NCT03286114	AML, MDS and ALL with relapse after allo-HSCT	Pembrolizumab	Not reported	Recruiting
Hu5F9-G4	I	NCT03248479	RR MDS/AML or unfit ND-AML/MDS	Hu5F9-G4 + 5-AZA	Preliminary results at ASH 2019: ⁹⁴ Efficacy: MDS: ORR 92% (50% CR, 39% mCR); AML: 64% (CR: 41%; CRi: 14%) Toxicity: comparable to AZA monotherapy, anemia (37%), neutropenia (26%), and thrombocytopenia (26%)	Recruiting
TTI-621 (SIRPaFc)	I	NCT02663518	Hematologic and solid tumors	TTI-621 +/- rituximab or nivolumab	Results for AML/MDS cohort not reported	Recruiting
MBG453	I	NCT03066648	AML, HR-MDS	MBG453 + Decitabine or PDR001 (anti-PD-1 antibody)	Preliminary results at ASH 2019: ⁹³ Efficacy: MDS (17 patients): 50% CR or mCR; AML (14 patients): 14% CR, 14% PR Toxicity: most common TEAEs grade 3/4: febrile neutropenia (39%), neutropenia (34%), thrombocytopenia (31%), and anemia (29%). 8 patients (14%) with grade 2 IRAE	Recruiting
Rigosertib	II	NCT03946670	HR-MDS; no prior HMA	MBG453 + HMA vs placebo + HMA	Study design presented at ASH 2019 but no results available ¹³⁵	Recruiting
	III	NCT04266301 (STIMULUS-MDS2)	HR-MDS or CMML-2; no prior HMA	MBG453 or placebo + AZA	Not reported	Not yet recruiting
APR-246	III	NCT02562443 (INSPIRE trial)	HMA-refractory HR-MDS	Rigosertib vs treatment choice	Study design and baseline genetic profile of patients presented at ASH 2019 but no results available ¹³⁶	Recruiting
	III	NCT03745716	Newly-diagnosed <i>TP53</i> -mutated MDS	APR-246 + AZA vs AZA alone	Not reported	Recruiting
Pevonedistat	II	NCT03931291	<i>TP53</i> -mutated MDS and AML following allo-HSCT	APR-246 + AZA maintenance therapy after allo-HSCT	Not reported	Recruiting
	I	NCT03459859	R/R-AML, HMA-refractory MDS	Pevonedistat + low-dose cytarabine	Not reported	Recruiting
	II	NCT03238248	HMA-refractory MDS or MDS/MPN	Pevonedistat + AZA	Preliminary results at ASH 2019: ¹¹⁹ Efficacy: 21 patients evaluable: 1 CR, 4 mCR Toxicity: most common TEAEs grade 3/4: thrombocytopenia (39%), anemia (35%), leukopenia (26%)	Recruiting
	III	NCT03268954 (PANTHER trial)	Newly-diagnosed HR-MDS, CMML, or Low-Blast AML	Pevonedistat + AZA vs AZA alone	Not reported	Recruiting
	I	NCT03772925	R/R-AML, HMA-refractory MDS	Pevonedistat + belinostat	Not reported	Recruiting

Drug	Phase	NCT	Patient characteristics	Intervention	Results	Current status
Venetoclax	I	NCT02942290	Frontline HR-MDS	Venetoclax + AZA	Preliminary results at ASH 2019: ⁸⁴ Efficacy: 57 patients evaluable (18 CR, 22 mCR), 18-month OS: 74% Toxicity: most common TEAEs grade 3/4: neutropenia (61%), thrombocytopenia (39%), leukopenia (31%)	Active, not recruiting
	I	NCT02966782	HMA-refractory MDS	Venetoclax alone or in combination with AZA	Preliminary results at ASH 2019: ⁸⁵ Efficacy: VEN monotherapy: ORR 7% (1 out of 16), 75% (12 out of 16) with SD; VEN + AZA: ORR 50% (12 out of 24; 13% CR, 38% mCR) Toxicity: most common TEAEs grade 3/4: neutropenia (41%), thrombocytopenia (30%), leukopenia (24%)	Active, not recruiting
	I/II	NCT04160052	Frontline and R/R HR-MDS	Venetoclax + AZA	Not reported	Recruiting

Allo-HSCT – allogeneic hematopoietic stem cell transplantation; *AML* – acute myeloid leukemia; *AZA* – azacitidine; *CMML* – chronic myelomonocytic leukemia; *CR* – complete remission; *HMA* – hypomethylating agent; *IRAE* – immune-related adverse event; *mCR* – marrow complete remission; *MDS* – myelodysplastic syndrome; *ORR* – overall response rate; *OS* – overall survival; *PR* – partial remission; *R/R* – relapsed/refractory; *TEAE* – treatment emergent adverse event; *VEN* – venetoclax

Table 2:

Selected ongoing trials of immune checkpoint inhibitors in MDS

Drug	Target/mechanism	Phase	NCT	Patient characteristics	Intervention	Outcomes
Nivolumab	Anti-PD-1 antibody	I	NCT02530463	MDS	Nivolumab + ipilimumab + AZA	Only toxicity reported: Immune-mediated toxicity for common in nivolumab + ipilimumab combination arm (dermatologic, hepatic, and cardiovascular) requiring systemic steroids ¹³⁷
		II	NCT04044209	IDH-1 mutated MDS and AML	Nivolumab + ivosidenib	Not available
		II	NCT02397720	AML and MDS	Nivolumab +AZA +/- ipilimumab	Results available for AZA + nivolumab in 70 R/R-AML patients Toxicity: grade 3/4 IRAEs in 11% Efficacy: 33% ORR (22% CR) combined; 58% ORR in HMA-naïve and 22% in HMA pre-treated patients ¹³⁸
		I	NCT03600155	AML and MDS relapsed after allogeneic HSCT	Nivolumab + ipilimumab	Not available
Pembrolizumab	Anti-PD-1 antibody	I	NCT01953692	MDS, multiple myeloma, Hodgkin's and Non-Hodgkin's lymphoma	Pembrolizumab	MDS cohort (27 HMA-refractory patients) Toxicity: grade 3/4 IRAEs in 7% Efficacy: 0% CR, 4% PR, 11% mCR, 11% HI ⁹⁰
		I	NCT02981914	MDS, AML, Hodgkin's and Non-Hodgkin's lymphoma relapsed after allogeneic HSCT	Pembrolizumab	Not available
		I	NCT03286114	MDS, AML, ALL relapsed after allogeneic HSCT	Pembrolizumab	Not available
		I	NCT03969446	Frontline or R/R MDS/AML	Decitabine + pembrolizumab	Not available
		I	NCT02936752	HMA-refractory MDS	Entinostat + pembrolizumab	Not available
		II	NCT03094637	HR-MDS	Pembrolizumab + AZA	Toxicity: most common TEAEs neutropenia (37%), myalgias/artralgias (20%), constipation (17%) Efficacy: HMA-naïve (10 patients): 70% ORR (20% CR, 20% mCR without HI, 20% mCR with HI), median OS 12.9 months; HMA-refractory (20 patients): ORR 30% (10% CR, 10% mCR, 10% HI), median OS 5.9 months ¹³⁹
		I	NCT02890329	R/R MDS/AML	Ipilimumab + decitabine	Not available
Ipilimumab	Anti-CTLA-4 Antibody	I	NCT02890329	R/R MDS/AML	Ipilimumab + decitabine	Not available
Hu5F9-G4	Anti-CD47 antibody	I	NCT03248479	R/R MDS/AML or unfit frontline AML/MDS	Hu5F9-G4 + 5-AZA	Toxicity: comparable to AZA monotherapy, anemia (37%), neutropenia (26%), and thrombocytopenia (26%) Efficacy: MDS: ORR 92% (50% CR, 39% mCR); AML: 64% (CR: 41%; CRi: 14%) ⁹⁴
MBG453	Anti-TIM-3 antibody	I	NCT03066648	AML, HR-MDS	MBG453 + Decitabine or PDR001 (anti-PD-1 antibody)	Toxicity: most common TEAEs grade 3/4: febrile neutropenia (39%), neutropenia (34%), thrombocytopenia (31%), and anemia (29%); 8 patients (14%) with grade 2

Drug	Target/mechanism	Phase	NCT	Patient characteristics	Intervention	Outcomes
						IRAE Efficacy: MDS (17 patients): 50% CR or mCR; AML (14 patients): 14% CR; 14% PR ²⁵
		II	NCT03946670	HR-MDS; no prior HMA	MBG453 + HMA vs placebo + HMA	Not available ¹³⁵
		III	NCT04266301	HR-MDS or CMML-2; no prior HMA	MBG453 or placebo + AZA	Not available

Allo-HSCT – allogeneic hematopoietic stem cell transplantation; *AML* - acute myeloid leukemia; *AZA* – azacitidine; *CMML* – chronic myelomonocytic leukemia; *CR* - complete remission; *HMA* - hypomethylating agent; *IRAE* – immune-related adverse event; *MDS* - myelodysplastic syndrome; *ORR* – overall response rate; *PR* – partial remission; *R/R* – relapsed/refractory; *TEAE* – treatment emergent adverse event