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INVITED REVIEW – OPEN ACCESS

Immunotherapies for Myelodysplastic Syndromes: Current State and Future Developments

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ABSTRACT

Myelodysplastic syndromes (MDS) encompass a heterogeneous set of myeloid neoplasms characterized by ineffective hematopoiesis. Treatment remains challenging, especially for patients with unfavorable disease features. Hypomethylating agents have remained the standard of care for higher-risk MDS for almost 2 decades. A plethora of clinical trials utilizing different approaches ranging from small molecule inhibitors to antibodies are underway. In this mini review, we describe recent developments in treatment approaches that incorporate antibodies in the therapeutic context of MDS apart from immune checkpoint inhibitors.

Keywords: Antibody, immunotherapy, MDS, myelodysplastic, treatment

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INTRODUCTION

Myelodysplastic syndromes (MDS) affect 60,000–170,000 patients in the United States of America, and the prevalence increases with advancing age (1). The presentation can vary, ranging from mild cytopenias, to transfusion dependency and frequent infections, to evolution into acute myeloid leukemia (AML).

Risk factors for the development of *de novo* MDS include exposure to toxic chemicals, such as benzene and other chemicals in tobacco products, and predisposing germline genetic abnormalities. Risk factors for therapy-related MDS include exposure to cytotoxic chemotherapy and/or external beam radiotherapy.

The therapeutic options for patients with high-risk MDS are limited; the hypomethylating agents have been the therapeutic standard for more than 2 decades. Recently, targeted therapeutic approaches utilizing small molecule inhibitors and antibodies against certain antigens expressed by the neoplastic cells have been developed and are being investigated in several clinical trials.

The aim of this mini review is to discuss most of the currently available antibody-mediated therapy options for MDS. The PubMed database, the ClinicalTrials.gov registry, and abstracts from recent conferences were examined in this review.

Biology of MDS

MDS are clonal hematopoietic stem cell neoplasms that retain the capability of maturation and result in short-lived progenies with apoptotic propensity, which cause peripheral cytopenias, a hallmark of this disease. The increased apoptotic rate of the MDS hematopoietic cells is associated with proliferative hypercellular bone marrow, ineffective hematopoiesis, and intramedullary apoptosis. Although the exact MDS-initiating events and the biological pathways involved are not fully understood, it is accepted that the acquisition of driver mutations by MDS pluripotent stem cells confers a survival advantage and boosts cellular proliferation compared with wild-type cells. The propagation of the mutated clone is not initially coupled by blockage of differentiation; however, the acquisition of additional genetic drivers results in decreased apoptosis and blocking of differentiation that culminate in increased blasts, and thereafter transformation to AML, the final adverse outcome of this neoplasm. The pathobiology of MDS is complicated and determined by the interaction of various players within the bone marrow milieu. The defective genetic make-up of the MDS cells, per se, and likely of other hematologic and mesenchymal lineages in the marrow affects the intracellular, cell-cell, and cell-matrix biological interaction pathways, induces epigenetic changes, impairs paracrine communication and cytokine secretion, stimulates angiogenesis, and modulates the immune response. Theoretically, any of these pathogenic components or various combinations of them could be a potential therapeutic target for MDS.

MDS Risk Stratification

Historically, upon diagnosis of MDS, patients are stratified using prognostic scores. Many systems have been developed in recent years, but the most extensively used are the International Prognostic Score System (IPSS) and the revised IPSS (R-IPSS) (2).

The 2 prognostic scores weigh variables differently; the R-IPSS includes more granularity in the degree of cytopenia and blast burden. Patients are grouped into low-high risk categories.

Therapeutic approaches in MDS

Lower-risk MDS patients may be followed with count monitoring or treated with erythropoietin-stimulating agents or lenalidomide, although a sizable percentage will not respond or will lose response to these modalities. In some cases, outside of clinical trials, hypomethylating agents (HMA), such as azacitidine and decitabine, may be offered.

MDS patients falling in the higher-risk groups are usually afflicted by cytopenias that can lead to transfusion requirements and infectious complications and affect the quality of life. In addition, the propensity to develop AML is higher in this group. Higher-risk MDS patients are typically offered treatment with HMA outside clinical trials and/or referred for allogeneic bone marrow stem cell transplant (alloHSCT) evaluation, which is the only potentially curative modality. However, many patients are not candidates or decline alloHSCT treatment. Moreover, relapse can occur after alloHSCT, and non-relapse mortality after alloHSCT can be significant, depending on the regimen used. HMA may be used prior to alloHSCT, and data from retrospective studies suggest that HMA may have a beneficial impact on patients who proceed with alloHSCT.

Hypomethylating Agents

The backbone of treatment for higher-risk MDS is based on HMA, although the mode of action is not yet completely understood. The prevalent theory of the mechanism involves modulation of the methylation profile of key genes. Other proposed mechanisms include direct cytotoxic effect (at high doses) and modulation of the immune system.

The currently approved treatments include azacitidine, decitabine, and oral formulation of decitabine/cedazuridine. Azacitidine has shown efficacy in a phase III, open-label clinical trial with a median survival of 24 months (3). Real-world studies have indicated that the prognosis with azacitidine is less favorable, with a median overall survival (OS) of 13–16 months (4).

Another option is decitabine. The outcomes of patients with MDS in a phase III clinical trial were not as favorable as those reported for azacytidine (5). Oral decitabine/cedazuridine was approved for use in the USA and Canada in 2020.

It should be noted that responses such as complete remission (CR) are infrequent (3, 5, 6), but patients benefit from hematological improvement (HI) in terms of neutrophil, hemoglobin, and platelet count. Patients treated with HMA relapse, even if they initially respond. The mechanisms leading to relapse are not well understood. Attempts to obtain CR with novel agents may be associated with better outcomes both in patients who are candidates for alloHSCT and those who cannot proceed with this approach.

There are no approved treatments for patients with MDS who have failed or relapsed after HMA use. Therefore, a key objective for treatment-naïve, higher-risk MDS patients is to maximize and maintain the CR rates. A more difficult task is to overcome the resistance to treatment.

MDS Clinical Trial Landscape

Many clinical trials have combined HMA with other compounds in higher-risk MDS. So far, these trials have not resulted in conclusively better outcomes when compared with HMA alone. Cytopenias and additive toxicities have limited the application of these combinations. Current clinical trials include combinations of HMA with various agents, such as venetoclax, pevonedistat, isocitrate dehydrogenase and poly-ADP-ribose polymerase inhibitors, and molecules that target mutated TP53 protein. Chimeric antigen receptor (CAR) T-cell therapy approaches are also gaining momentum. Furthermore, another important component of MDS clinical trials is antibody-directed therapies, including immune checkpoint inhibitors, alone or in combination with HMA.

Targeting CD33

Gemtuzumab ozogomycin (GO) targets the CD33 epitope that is found in the majority of myeloid blasts. Upon internalization, the attached toxin is released and inflicts DNA damage. Daver et al. (7) reported on a phase II clinical trial that used decitabine 20 mg/m^2 IV for 5 days with a single 3 mg/m^2 dose of GO at day 5. Further cycles of this combination were administered depending on the response to treatment (7). The study was focused mainly on patients with AML.

Among 15 patients with untreated MDS, the CR/complete remission with incomplete count recovery (CRi) rate was 33% and the 2-month mortality was 20%. The median OS was only 5.7 months, significantly less than that of the historical cohort of the institution treated with HMA alone or in combination with histone deacetylase (HDAC) inhibitors.

Infections were prevalent in the study and may have impacted the administration of the combination of GO/HMA (median number of cycles: 3). Moreover, the 5 patients with relapsed/refractory (R/R) MDS were not reported to have evidence of greater OS.

Arsenic trioxide (ATO) was combined with GO in another study, which included patients with MDS, chronic myelomonocytic leukemia (CMML) and AML (8). Fifteen patients with MDS were enrolled. The majority had higher-risk MDS and had not previously had remission induction chemotherapy. Few patients had exposure to HMA. No cases of complete remission were noted, however, the overwhelming majority of patients had stable disease (8). Toxicities were not reported separately, though cytopenias were very common. Grade 3 pneumonia and dyspnea were reported in 17% and 13% of patients.

A phase II clinical trial explored the use of GO with intensive chemotherapy in patients with MDS or secondary AML (sAML) arising from MDS (9). Thirty patients were included. Only 13 patients had strictly defined MDS according to World Health Organization criteria (refractory anemia with excess blasts [RAEB] 1/2), 14 patients had RAEB in transformation/sAML, and the remainder had CMML. The chemotherapy program included

a cytarabine continuous infusion of 100 mg/m^2 for 10 days in combination with idarubicin 12 mg/m^2 on days 1, 3, and 5, as well as GO at a dose of 5 mg/m^2 on day 7. Patients could receive another cycle of the regimen if partial remission (PR) was achieved. Patients who attained CR/CRi received a consolidation therapy of cytarabine and idarubicin without GO. Forty-three percent of all of the patients achieved CR/CRi. Infections and pulmonary and liver toxicity were seen in some patients. Seventeen percent of the patients died within 40 days of starting treatment. Of note, patients with poor-risk cytogenetics per the IPSS had a particularly poor prognosis and all of those patients died within a year of the study initiation.

Vadastuximab talirine is a humanized IgG1 antibody that recognizes the CD33 epitope conjugated to pyrrolobenzodiazepine dimer. The immunoconjugate was tested in AML and MDS patients. A review of data from a randomized clinical trial of vadastuximab talirine plus HMA versus HMA alone revealed increased mortality in the vadastuximab talirine arm. These findings led to termination of clinical trials (NCT02706899). It is difficult to draw conclusions regarding toxicities and efficacy in this patient population, given that few patients were enrolled and none completed the study.

Targeting CD47

CD47 (integrin associated protein) is expressed in various malignancies, including MDS. Of note, CD47 has a wide expression repertoire in normal tissues (10). The role of CD47 is being explored, as it interacts with key proteins that regulate angiogenesis and FAS-mediated apoptosis as well as with integrins (10). In normal cells, the CD47 pathway prevents phagocytosis of cells by macrophages through interaction with signal regulatory protein alpha (SIRPα) (11). Experiments with mice have indicated that red blood cells lacking CD47 were rapidly phagocytized by macrophages in the spleen (12). In the context of MDS, data indicate that CD47 interacts with SIRPα on macrophages, inhibiting phagocytosis (13). The expression of CD47 in MDS is variable, with higher expression noted in high-risk MDS patients (RAEB) (14). Intriguingly, progenitor cells in low-risk MDS demonstrate increased expression of calreticulin, a pro-phagocytic signal, and CD47 is not increased when compared with normal progenitors (14).

Antibodies targeting the CD47 pathway have been engineered not only to block the interaction of CD47 with SIRPα but also to engage macrophages through their Fc component. The mechanism of anti-CD47 strategies involves inhibiting the phagocytic activity of macrophages. HMA can enhance the expression of molecules and increase phagocytosis, and anti-CD47 antibodies can also promote phagocytosis.

An early-stage clinical trial [NCT02641002] evaluated use of a humanized anti-CD47 antibody [CC-90002] in patients with R/R AML (24 patients) including 4 high-risk MDS patients (15). CC-90002 was administered once weekly for 4 weeks in a 6-week cycle. After cycle 4, CC-90002 was administered once every 4 weeks. The best overall response was a stable disease assessment in 2 MDS patients. CC-90002 did not reduce transfusion requirements. The most common adverse events were diarrhea, thrombocytopenia, transaminitis, and infections. Dose-limiting toxicities (DLT) included cerebral hemorrhage, acute respiratory failure, and congestive heart failure. The study results did not indicate a strong enough response to proceed with further testing (15).

TTI-621, a humanized antibody consisting of the CD47-binding domain of human SIRPα and the Fc region of human IgG1, was evaluated in a clinical trial that included MDS patients (16). The study used weekly infusions of TTI-621 for 3 weeks in a dose-escalation group to assess DLT. A dose-expansion group included TTI-621 as monotherapy or in combination with rituximab or nivolumab. The study included 6 patients with MDS in the dose-expansion group, representing 4% of patients in that cohort. Treatment-emergent adverse events were noted in 98% of patients. Infusion-related reactions were noted in 43% of patients, thrombocytopenia in 26%. One of the MDS patients had grade 3 bleeding (epistaxis). None of the MDS patients achieved complete or partial remission (16).

ALX148 is a humanized antibody that contains part of the D1 domain of SIRPα with amino acid modifications that increase affinity for CD47 to the picomolar range (17). Moreover, the Fc portion has been engineered to prevent interaction with C1q protein and Fc gamma receptor (17). ALX148 is devoid of antibody-dependent cellular cytotoxicity (ADCC) activity and does not cause hemagglutination *in vitro* (17).

The combination of ALX148 with azacitidine is being tested in an ongoing phase I/II clinical trial in patients with higher-risk MDS (NCT04417517). The provided estimated enrollment is 173 participants. The first patient received treatment in late 2020.

IBI188 is a humanized IgG4 antibody also engineered to interfere with CD47 signaling (18). IBI188 is being tested in clinical trials in combination with azacitidine in patients newly diagnosed with MDS (NCT04511975 and NCT04485065).

Other molecules that target the CD47 pathway, such as SRF231 and TTI-622, have not been tested in clinical trials that included patients with MDS.

Magrolimab is a humanized IgG1 antibody targeting CD47 and is in the most advanced phase of testing in comparison with other antibodies targeting CD47. Early clinical trials of magrolimab with azacitidine have been promising (19), and a phase III clinical trial is underway to explore the impact of azacitidine with magrolimab versus azacitidine monotherapy. Magrolimab is administered in a stepwise "priming" approach to avoid hemolysis of red blood cells.

An important phase Ib clinical trial (19) utilizing magrolimab included 39 MDS patients with at least intermediate-risk based on the R-IPSS. Thirty-one percent of patients had therapy-related MDS, and 64% had poor cytogenetics. Thirty of the 33 evaluable MDS patients had a response; 66% had CR or marrow CR, 3% demonstrated PR, and hematological improvement alone was noted in 21% of the patients. Minimal residual disease (MRD) negativity was achieved in 22% of the patients with CR/marrow CR. Seventy-five percent of the patients with TP53 mutations had an overall response. Reported toxicities among both MDS and AML patients included cytopenias, fatigue, and infusion reactions.

Importantly, responses were lasting, and 58% of the MDS patients became transfusion independent.

Targeting CD70

Seminal studies have demonstrated that CD70 and its receptor CD27 are expressed in AML cells and may play a role in the pathogenesis of AML (20). Cusatuzumab is a monoclonal antibody with augmented ADCC targeting the CD70 epitope. Two studies of MDS are recruiting (NCT04150887) or active but not recruiting (NCT03030612). Another antibody targeting CD70 is Sea-CD70 (SGNS70-101). A clinical trial enrolling patients with R/R MDS is underway (NCT04227847).

Targeting CD123

The interleukin 3 (IL-3) receptor alpha chain (CD123) is an attractive target, as it has low expression in cells involved in hematopoiesis, but is found in MDS and AML leukemic stem cells (21). SL-401 is an antibody immunoconjugate that has a truncated diphtheria toxin linked to IL-3 to allow targeting of CD123 (22). The internalized diphtheria toxin exerts an antineoplastic effect by interfering with protein synthesis (23). Blasts derived from MDS patients have been reported to express CD123, and SL-401 depleted CD123+ MDS blasts *ex-vivo* (24). A phase I clinical trial included 5 patients with MDS (25). The majority of the patients (3/5) had prior exposure to HMA and were elderly (all but 1 patient were at least 71 years old). The patients were treated with 6 doses at 1 of 5 dose levels (range: 4–12.5 microgram/kg) every other day. One of the MDS patients with prior exposure to HMA and unfavorable cytogenetics had PR that lasted 4 months. Patients enrolled in the study experienced transaminitis, hypoalbuminemia, hypotension, febrile episodes, and vascular leak syndrome.

SL-401 has been approved for the treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN). A clinical trial (NCT03113643) is ongoing and is recruiting patients with high-risk MDS who will be treated with SL-401 and azacitidine.

Talacotuzumab is an IgG1 monoclonal antibody that recruits natural killer cells to induce ADCC and interferes with CD123 signaling. Results of a phase II clinical trial using talacotuzumab in patients with AML and MDS who had relapsed or were resistant to HMA were recently published (21). Five MDS patients with an intermediate or high IPSS score were included. Talacotuzumab was given every 2 weeks over 3 months. The toxicities recorded were significant, with frequent infections and cytopenias observed, and 1 patient developed reversible Guillain-Barre syndrome. The 4-week mortality was 20%. Only 2 of 24 patients had a response: CRi and HI-erythroid, respectively. None of the MDS patients demonstrated a response.

KHK2823 is a non-fucosylated human monoclonal antibody targeting CD123. A phase I clinical trial (NCT02181699) recruited AML and R/R MDS patients; however, the study was terminated and results are not available.

Targeting TIM3

T cell immunoglobulin and mucin domain 3 (TIM3) has attracted attention in the context of MDS therapies. TIM3, a type I transmembrane glycoprotein with a repertoire of expression mainly in cells with a role in immunity (26), has been associated with inhibition of the cytotoxic CD8 T-cell function. The expression of TIM3 is increased in T-regulatory cells of MDS patients compared with controls and appears to be greater in patients with high-risk MDS (26). Importantly, the frequency of T-regulatory cells and T-helper type 2 cells is greater in high-risk MDS patients than in control or low-risk MDS samples (26). In contrast, the same study reported that the number of T-helper 1 cells was lower in high-risk MDS patients when compared with control and low-risk MDS patients.

TIM3 expression was reported to be higher in CD8-positive T cells derived from patients with MDS compared with controls (27). Moreover, TIM3-positive CD8-positive T cells derived from MDS had less granzyme B/perforin but greater Fas expression than TIM3-negative CD8-positive T cells (27).

Expression of TIM3 has also been detected in stem cells (defined as CD34+ CD38− Lin-cells) of untreated patients with MDS, while expression in healthy patients was low (28). The expression of TIM3 was higher in patients with increased blasts, those harboring cells with abnormal karyotype, or patients with cytopenia (neutropenia and anemia) (28). TIM3 is expressed in AML blasts, and a provocative hypothesis is that TIM3 upregulation may be beneficial to AML blast proliferation (29). It is unclear if a similar role can be postulated for MDS stem cells.

Clinical trials involving TIM3 antibodies (e.g., MBG453 [Sabatolimab]) and MDS are ongoing. Sabatolimab is a humanized IgG4 antibody targeting TIM3 and has been tested in clinical trials including both higher- and lower-risk MDS patients.

A phase Ib open-label study recruited patients with AML and high-risk MDS (30). Sabatolimab was combined with HMA. Thirty-nine patients with high-risk MDS were included (R-IPSS category at least high). Sabatolimab was used at a dose of 240 mg or 400 mg (days 8 and 22) or 800 mg every 4 weeks (administrated on day 8). Among 35 patients with MDS who were evaluable, the overall response rate (ORR) was 62.9%: 8 patients achieved CR, 8 marrow CR, and 6 stable disease with HI. Eight patients with MDS proceeded to alloHSCT. Notably, in the very high-risk MDS subgroup, the ORR was relatively high (11/13 patients).

The ORR was 61.1% in patients for whom sabatolimab was combined with decitabine (n=18), and 64.7% when combined with azacitidine (n=17). Toxicities were common, and patients with MDS experienced at least grade 3 neutropenia (46.1%), thrombocytopenia (51.2%), febrile neutropenia (41%), or anemia (28.2%). One patient with MDS died from septic shock and enterocolitis. None of the MDS patients discontinued treatment secondary to adverse events. Immune-mediated adverse events were noted in patients with AML, and included arthritis, possible hemophagocytic lymphohistiocytosis, increase in alanine aminotransferase, and hypothyroidism. A phase III trial comparing the combination of TIM3 antibody with azacitidine versus placebo and azacitidine (NCT04266301) is ongoing.

Targeting C-Type Lectin-Like Molecule-1

The C-type lectin-like molecule 1 (CLL-1) is encoded by a gene located on chromosome 12p13.31. It has a limited repertoire of expression, and myeloid cells appear to lose CLL-1 expression when migrating to tissues. CLL-1 expression was detected in spleen cells and leukocytes (monocytes, dendritic cells, and granulocytes) in an important study (31). However, dendritic cells and macrophages did not express CLL-1 in tissue-sample testing. CLL-1 detection was noted only in a small fraction of the CD34+ cells in bone mar-

Table 1. Select antibody studies in the context of MDS

Trial	Phase	Patients included	Outcome	Reference
Decitabine+GO	II	AML, MDS (HMA naïve)	CR/CRi: 33%	(7)
Arsenic trioxide+GO	II	Secondary AML, MDS	3/15 MDS patients with hematological improvement.	(8)
Intensive chemotherapy+GO	II	Treatment naïve MDS, secondary AML arising from MDS, CMML	Overall CR/CRi: 43%	(9)
Talacotuzumab	II	AML, MDS relapsed or refractory to HMA.	MDS patients did not respond.	(21)
Magrolimab+ azacitidine	I	MDS, AML	ORR for MDS: 90%, CR: 42%	(19)
Sabatolimab+HMA	I	MDS, AML	ORR for 35 patients with MDS: 62.9%	(30)
SL-401	I	AML, MDS	MDS-PR: 20%	(25)
Alemtuzumab	I/II	*De novo* MDS	HI: 51%	
			CR (per protocol definition): 31%	(33)
Rhenium 188-labeled anti-CD66	I/II	AML, MDS	Trial involved patients receiving alloHSCT. No reports of ORR	(36)

MDS: Myelodysplastic syndromes; AML: Acute myeloid leukemia; HMA: Hypomethylating agents; ORR: Overall response rate; CMML: Chronic myelomonocytic leukemia; HI: Hematological improvement; CR: Complete remission

row samples. AML blasts were found to have high CLL-1 expression in 68 of 74 samples. Expression in MDS samples was variable and not consistent with AML results.

Currently, clinical trials using monoclonal antibodies against CLL-1 in patients with MDS have not been reported. An antibody conjugate targeting CLL-1 was tested in patients with R/R AML (32). However, toxicities were significant, and further development is not anticipated.

Targeting CD52

Aletuzumab is a monoclonal antibody targeting CD52. Long-term outcomes of a clinical trial that enrolled MDS patients were recently reported (33). The trial enrolled *de novo* MDS patients with transfusion dependence or significant cytopenias, and there was a likelihood of response based on a model incorporating HLA-DR15 status, age, and months that the patient had been transfusion dependent. The patients received alemtuzumab 10 mg daily for 10 days. Thirty-nine evaluable patients were included. The majority of patients had an R-IPSS categorization at least intermediate (72%). Fifty-one percent of the patients demonstrated hematological improvement with a median duration of 1.5 years. Moreover, 31% of the patients had CR with a median response duration of 30 months. The median OS for responders was 7 years (range: 1.5–10 years). Toxicities included liver enzyme elevations, cytomegalovirus/Epstein-Barr virus re-activation, and infusion reactions, but the authors reported that the alemtuzumab was well tolerated overall.

Radioimmunoconjugates

The study of antibodies that are linked to radioactive isotopes spans several decades (34). Radioimmunoconjugates have some advantages, at least in theory, compared with immunoconjugates employing toxins. The radioimmunoconjugates can affect tumor cells in the vicinity of the target even if those tumor cells have limited expression of the targeted epitope, and the activity may persist over time. The enthusiasm for radioimmunoconjugates is hampered by the potential for myelosuppression, and the experience in clinical trials indicates potential for fatigue or asthenia (34), which may already affect patients with MDS. Currently, there is no approved radioimmunoconjugate for the treatment of MDS.

Rhenium-188, a Beta emitter, was conjugated with a murine IgG1 antibody and used in alloHSCT clinical trials with AML and MDS patients (35). One study of AML patients that included 4 MDS patients revealed a disease-free survival of 18 months with treatment-related mortality of 22%; renal toxicity was noted in 17% of patients (36). One MDS patient died from toxicity, and another due to relapse. However, some authors have reported a high incidence of graft-versus-host disease (as high as ~80%) and treatment-related mortality of ~50% in a predominantly lymphoid disease population (37). The varied results may be related to the different disease populations and manipulation of the graft.

Other radioimmunoconjugates that have been tested in clinical trials include iodine linked to BC8 or anti-CD33 antibodies (38). However, further development of radioimmunoconjugates for MDS has not been robust.

Checkpoint Inhibitors

Immune checkpoint inhibitors have attracted attention for use in hematological malignancies after practice-changing results in solid malignancies, especially melanoma. The research on immune checkpoint inhibitors in MDS was recently reviewed (39). Monotherapies have not resulted in high response rates, and combinations with HMA are being tested (40).

CONCLUSIONS

MDS comprise a spectrum of hematological malignancies that are difficult to treat. The standard of care remains HMAs. The experience accumulated with HMAs has led to a better understanding of the MDS pathophysiology and novel approaches are being tested. Furthermore, a plethora of antibody-based clinical trials are underway and the results are eagerly awaited. This review highlighted existing published studies (Table 1) and outlined some ongoing studies.

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