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# Emerging Immuno-Oncology Targets in Myelodysplastic Syndromes (MDS)

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## Introduction

In solid malignant tumors, immunotherapy has emerged as a successful therapy to achieve long-term remissions where traditional chemotherapies have failed – specifically with the use of therapies targeting the immune checkpoints, CTLA-4 and PD-1/PD-L1. In contrast, to date, attempts to utilize these therapies in myeloid neoplasms has shown limited activity, with some concerns around adverse event profile. Nonetheless, immune-mediated control of malignant progenitors remains an appealing option across a number of myeloid neoplasms, which is illustrated by the role of allogeneic transplantation and graft-versus-leukemia as the only curative option for many of these malignancies. Newer strategies with novel immune targets or dosing strategies are underway, and have the promise to change the treatment landscape in MDS. Here we will review the existing strategies for immunological targets in MDS, as well as new targets that are currently being investigated.

In general there are several ways to utilize the immune system in the treatment of MDS, with an common goal of augmenting immune recognition and clearance of malignant MDS precursors. The rationale driving many of these approaches is based in part on the observation of a “graft versus leukemia” or GvL concept in allogeneic transplantation.[1,2] Although allogeneic transplant in MDS is beyond the scope of this review, our understanding of how donor engraftment may maintain immunologic control of myeloid neoplasia, as well as features seen at disease relapse, may inform therapeutic approaches outside of transplantation as well. For instance, at relapse, donor T-cells appear to harbor a T-cell “exhaustion” phenotype, with increased PD-1 and TIM-3 surface expression.[3]

To date, approaches to immunologic therapies in MDS have generally fallen into two categories: therapies that target immune effector cells and enhance or direct an anti-leukemic effect, and therapies which target immunological markers on MDS progenitors themselves.

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Examples of the former include immune checkpoint inhibitors, immunomodulatory therapies, and vaccines, among others, while examples of the latter include antibody-drug conjugate therapies and naked antibodies; while bispecific antibodies and modified T-cells (such as CAR-T therapies) bridge both therapeutic modalities. In this review, we will discuss the rationale for the above therapies, clinical results to date, and potential future directions for investigation.

## Preclinical Rationale

Myelodysplastic syndromes are heterogeneous in clinical presentation, disease severity, and molecular and cytogenetic drivers of disease; nonetheless, varying degrees of immune dysregulation has been seen in many subtypes of MDS.[4] Efforts to fully characterize the immunologic landscape of MDS may be limited by this heterogeneity; previous studies have examined features according to higher or lower risk disease classification, or according to molecular subgroups of MDS. Lower risk MDS is associated with an expansion of Th17 cells, which are associated with autoimmune complications,[5] and in general associated with higher levels of pro-inflammatory cytokines,[6] although it is not clear if such are part of MDS pathogenesis or if they instead stem from the abnormal marrow. Patients with lower-risk MDS also exhibit increased levels of apoptosis in the marrow, potentially related to ineffective hematopoiesis. There is also data showing increased activity in the *TGFB/SMAD2/3* signaling pathway in MDS, which contributes to ineffective hematopoiesis and cellular maturation.[7] These alterations may also contribute to NK cell immune surveillance and the expansion/persistence of MDS progenitors.[8]

In higher risk MDS, in contrast, there is an increase in myeloid derived suppressor cells (MDSCs) which are distinct from the MDS clone and may play a role in suppressing hematopoiesis and contributing to an immunosuppressed state. [9,10] There is evidence of diminished T-cell function in higher risk MDS patients compared to healthy controls,[11] and some data suggests this could be related to altered expression of CD-80 or HLA-DR.[12] There is also emerging data to suggest that inflammatory profiles in MDS may also vary according to the mutation profile of the disease. For instance, in MDS with del5q, there is haploinsufficiency of *rps14*, and this disease has an associated increase in the expression of danger associated molecular pattern (DAMP) proteins S100A8 and S100A9.[13,14] Other evidence of immune dysregulation and an altered inflammatory state include data showing altered IL-6 and IL-1B levels in *TET2* deficient clonal hematopoiesis.[15,16] Hypomethylating agent therapy may increase the expression of endogeneous retroviruses,[17,18] which may serve as targets when combining IO therapies with HMA, and result in enhanced antitumor activity.

The sum of this data suggests that there are altered immune responses present in patients with MDS, although it remains unclear how best to target this therapeutically. Evasion of immune mediator cells appears to be a common finding across the various alterations noted above.

## Clinical Studies

More recently, a number of clinical trials have sought to evaluate the role of targeting various immunological targets in MDS. There are several putative outcomes of interest in these studies; for lower risk MDS, the goals are generally to restore better balance to the microenvironment and allow improvement in hematopoiesis. In higher risk disease, MDS remains incurable without transplantation, and immune targets seek to either improve the response rates to current therapies, or to prolong responses and improve overall survival. Here we will review clinical trials evaluating immunological targets in MDS (Table 1).

### Immune Checkpoint Inhibitors

Immune checkpoint inhibitors target an immune cell or an immune cell ligand/receptor that would otherwise inhibit the activation of the immune system. Numerous malignancies, hematologic included, have been shown to upregulate these markers that downregulate the activity of immune cells that interact with them. Checkpoint inhibitors prevent this negative stimulus and allow recruitment of T cells to kill cancerous cells. Their use in MDS treatment is currently being studied in conjunction with existing therapies and/or with other checkpoint inhibitors (Table 1).

**PD-1 and PD-L1—**Programed cell death 1 (PD-1) is expressed on immune cells such as T-cells; when the PD-1 receptor on a T-cell interacts with PD-L1 on another cell, this causes an inhibitory signal. When tumor cells express PD-1, this prevents cell-mediated destruction by anti-tumor T-cells. Monotherapy blocking activation of these receptors (e.g., pembrolizumab, nivolumab, and durvalumab) has been groundbreaking improvement in the improvement patient of patient outcomes in many malignancies, first notably in melanoma.

Several studies have evaluated PD-1/PD-L1 inhibition in the treatment of MDS. These studies have evaluated such agents both as monotherapy and in combination with HMA therapy, the use of PD-1 or PD-L1 inhibitors is currently being researched in conjunction with traditional therapies. Initial studies evaluated nivolumab monotherapy to patients with MDS progressing after HMA, dosed at 3mg/kg on days 1 and 15 of a 28 day cycle. A total of 15 patients received nivolumab monotherapy (6 with INT-1 disease and 9 INT-2). There were no responses seen with monotherapy; 3 patients had stable disease and 5 had progressive disease; median OS was 8 months.[19] Nivolumab was also combined with azacitidine in HMA-naïve patients with MDS, at 3mg/m2 on days 6 and 20 of every 28 day cycle, A total of 20 patients were treated with this combination

Another arm of this study combined azacitidine, nivolumab, and ipilumumab,[20] for patients with MDS either in the front line setting (n=6) or at progression after HMA (n=9). A total of 3/6 patients had a CR in the front line setting, while 2 of 7 patients had a response after HMA progression (CR=1, HI=1).

That said, the toxicity profile may be challenging. The combination of atezolizumab with azacitidine was explored in a phase I study and encountered significant toxicity including a high rate of early death in the frontline setting; although the safety profile was perhaps more acceptable among relapsed/refractory patients.[21]

## CTLA-4

CTLA-4 is expressed on the surface of regulatory T cells, and its activation leads to the down regulation of immune destruction of target cells. Initial interest in CTLA-4 inhibition stemmed from post-HCT studies showing activity in relapsed myeloid neoplasms, particularly in leukemia cutis.[22] This has led to further exploration of CTLA-4 blockade both as monotherapy and in combination with HMA. There may be some activity of ipilimumab monotherapy in higher risk MDS; of 9 patients with r/r MDS treated with ipilimumab monotherapy, 2 patients achieved marrow CR with associated hematologic improvement.[19]

Similar to studies evaluating PD-1/PD-L1 inhibition in combination with HMA therapy, there is rationale to combine CTLA-4 inhibition with HMA based on the idea of upregulated expression of neoepitopes. One trial compared several combinations of these agents, including azacitidine with ipilimumab (in addition to other arms noted above). The overall response rate for this combination was 71%, with a CR/CRp rate of 38% (8/21 patients) and a one-year survival rate of 68% alive at one year.[19] Decitabine and ipilimumab combinations have also been explored in AML and MDS, both in post-transplant relapse and transplant-naïve patient populations.[23] There were several responses seen in this overall higher risk group and further follow up is anticipated. Given the setting, close attention was paid to immune related AEs; post-HCT, 7 of 16 patients had grade 2 or higher immune AEs, 6 of which responded to steroids, while in the transplant naïve cohort 6 of 16 had immune AEs all steroid responsive.

## TIM-3

TIM-3 (T cell immunoglobulin and mucin domain-containing-3) is a cell surface molecule marker specific to CD4+ T helper 1 *Th1) and CD8+ cytotoxic T cells. TIM-3 blockade in a murine model was originally noted to exacerbate the clinical features of autoimmune encephalomyelitis, as well as increase the number and activity of macrophages[24]. CD8+ cytotoxic T cells with increased expression of Tim-3 have been noted to have increased dysfunction (“exhaustion”) in advanced melanoma patients, and blockade of TIM-3 resulted in an increased production of inflammatory cytokines[25]. This exhaustion phenotype has since been observed in myeloid malignancies as well, and similarly in conjunction with the increased expression of Tim-3. Tim-3 is preferentially expressed on leukemic progenitor cells, and may be associated with pathogenesis and disease progression in MDS.[26]

Preclinical research has identified TIM-3 as a potential therapeutic target. Tan et al. demonstrated in 15 newly-diagnosed AML cases that upregulation of PD-1 and TIM-3 was associated with increased amounts of “exhausted” T cell phenotypes, suggesting it may affect clinical outcomes.[27] Dual blockade of PD-1 and TIM-3 showed reduction of both tumor burden and mortality in mice with AML.[28] Similarly, Sakuishi et al. demonstrated that dual blockade of TIM-3 and PD-L1 led to decreased proliferation of injected solid tumor cells as well as increased expression of IFN-γ, as compared with either TIM-3 or PD-1L inhibition alone.[29] There may also be a role of TIM-3 blockade related to leukemic progenitor renewal; inhibiting TIM-3 may interrupt a feedback loop involving galectin-9.[30]

Moreover, administration of an anti-TIM-3 antibody in a mouse leukemia model resulted in the inability to serially transplant leukemia cells, suggesting again a role in leukemic persistence.[31,32]

To date, clinical trial data on TIM-3 inhibition in MDS is limited. Early data from a clinical trial were reported in 2019 (NCT03066648) in an open label, phase 1b dose-escalation study of MBG453, a humanized high-affinity monoclonal antibody targeting Tim-3, in combination with decitabine.[33] At the time of publication, 17 HR-MDS patients had received MBG453 (sabatolimab) at doses of either 240mg q2w, 400mg q2w, or 800mg q4w. 16 HR-MDS patients had post-baseline disease response assessments: 8 of 16 HR-MDS patients had complete remission or marrow complete remission, and none of these responders had disease recurrence at time of publication. Exposure durations for these subjects ranged from 3.4 to 18.6 months. The most common adverse events from this trial were febrile neutropenia, neutropenia, thrombocytopenia, and anemia.

Another trial is underway evaluating patients with AML or high-risk MDS and administering an MDM2 inhibitor, HDM201, in combination with MBG453 or venetoclax (NCT03940352). Further studies are also evaluating azacitidine combined with MBG453 for HR-MDS in a randomized fashion: STIMULUS-MDS1 (Phase 2) and STIMULUS-MDS2 (Phase 3), both multi-center, double-blinded, placebo-controlled studies. An additional phase 2 study is exploring MBG453 monotherapy to study TIM-3 inhibition in lower-risk MDS patients (NCT04823).

## Antibody and Antibody-Drug Conjugate Therapies

**CD47—**In addition to evasion of T-cell mediated immunity, evasion of phagocytosis by macrophages is increasingly seen as another mechanism of tumor cell immune evasion. Cells interact with macrophages in several ways; upregulated calreticulin serves as a marker for destruction by macrophages, while increased expression of CD47 downregulates the activity of macrophages and acts as a homeostatic mechanism.[34] Macrophages interact with the CD47 surface protein via its SIRPα receptor.

Malignant cells are able to negate the pro-phagocytic signal by the expression of CD47, which inhibits macrophage targeting, effectively functioning as a “do not eat me” signal.[34] This behavior has been observed in breast cancer,[35] pancreatic cancer,[36] ovarian cancer,[37] among others. These findings make the CD47 interaction with its ligand SIRPα a reasonable approach for targeted therapeutic strategies.

Azacitidine has been shown to increase expression of both calreticulin and CD47 in myeloid malignancies. Preclinical data showed that AML cells treated in vitro with azacitidine and CD47 blockade were more likely to undergo macrophage-mediated phagocytic elimination than treatment with CD47 blockade alone.[38] Similarly, in vivo with a murine AML model, greater phagocytosis was achieved with combination AZA and CD47 blockade than with either treatment alone.[38] These results formed the rationale for current ongoing clinical trials.

Magrolimab, an anti-CD47 antibody, is currently under investigation in the treatment of multiple solid and liquid tumors. A phase 1b trial from 2019 treated previously untreated MDS patients with a priming/intrapatient dose escalation regimen 1–30 mg/kg weekly, combined with azacitidine 75 mg/m$^2$ days 1–7 on a 28 day cycle.[39] 13 out of 13 MDS patients had on objective response, with 7 (54%) achieving CR, with 5 of these with marrow CR. Median time to response was 1.9 months in the treatment group. The ENHANCE study is a multi-center, double-blinded, multicenter study with and without azacitadine in treatment-naïve patients with MDS, and recruitment is ongoing (NCT04313881).

**CD70—**CD70, or CD27 ligand, is a member of the tumor necrosis factor superfamily and is expressed both on innate and adaptive immune effector cells. These immune cells constitutively express CD27; however, when there is immune activation, activated lymphocytes and dendritic cells express CD70 which binds CD27 and promotes lymphocyte survival.[40] Tumor cell expression of CD70 may result in local immunosuppression and tumor survival. However, similar to TIM-3, aberrant expression of CD70 has been detected on leukemic progenitor cells, suggesting a putative role for this therapy both as an immune-oncologic agent and as a direct leukemic therapy.[41]

Preclinical studies have evaluated CD70 blockade both for its immune-oncologic properties as well as its role in leukemic stem cell survival. One study evaluated an AML PDX model and showed that LSCs upregulate CD70 after exposure to hypomethylating agent therapy; while administering cusatuzumab, a human anti-CD70 monoclonal antibody, diminished the LSC population.[42]

There are several agents under investigation which target the CD70/CD27 axis. As noted above, cusatuzumab is an anti-CD70 monoclonal antibody and has been explored in patients with MDS and AML both as monotherapy, and also in combination with hypomethylating agents. In MDS, it has primarily been explored in combination with azacitidine; however, response data in MDS are not yet reported.[42]

Another agent targeting CD70 is SEA-CD70, a humanized non-fucosylated antibody to CD70 which may act through antibody-dependent cellular cytotoxicity (ADCC) or antibody-dependent cellular phagocytosis (ADCP). It is being studied in a phase I, dose escalation study of SEACD70 in patients with relapsed or refractory myeloid neoplasms, including post-HMA MDS (NCT04227847).

**CD123—**Another cell surface marker that is associated with leukemic progenitors, CD123 (IL3-R alpha chain) is expressed on the surface of most myeloid malignancies,[43] and in MDS expression has been noted to increase during progressing toward AML.[44] Several studies have explored therapeutic targeting of CD123 in MDS with antibody based therapies. Talacotuzumab is a humanized anti-CD123 monoclonal antibody that has been evaluated in combination with decitabine for AML and MDS; however, it did not add significantly to treatment response rates, and resulted in excess toxicity and is no longer under development.[45] Monotherapy with Talacotuzumab was also explored in the SAMBA trial (NCT02992860) but was prematurely terminated after 24 patients were enrolled and experienced excess toxicity with limited response.[46]

Other CD123 directed therapies incorporate a cytotoxic payload after binding to malignant cells. Tagraxofusp-erzs (SL-401) is a recombinant human fusion protein of the diphtheria toxin and IL-3, which binds to the IL-3 receptor (CD123) and results in selective toxicity. This agent is being studied in combination with azacitidine for AML, MDS, and BPDCN (NCT03113643) awaiting publication of the results of the MDS cohort. However, there have been studies of tagraxofusp erzs in CMML, which can have overlapping features with MDS, resulting in spleen reduction of 50% or greater in 8 of 10 patients with splenomegaly.[47]

**CD33—**Another cell surface target in myeloid neoplasms is CD33; gemtuzumab ozogamicin, an antibody-drug-conjugate targeting CD33, has been FDA approved both as monotherapy and in combination therapy for the treatment of AML in various settings. CD33 expression is similarly present in MDS and studies have evaluated targeting this in higher-risk MDS. CD33 is also expressed on myeloid derived suppressor cells (MDSCs) which may contribute to an inflammatory microenvironment in MDS.[48]

Combination therapy with gemtuzumab ozogamicin and decitabine has been studied, based on the preclinical rationale that HMA therapy may result in progenitor maturation and increased CD33 expression, and it may also enhance the expression of *Syk* which is necessary to respond to gemtuzumab.[49] in one such trial, patients received decitabine 20mg/m2 days 1–5 of a 28 day cycle and a single dose of gemtuzumab 3mg/m2 on day 5 of each cycle. A total of 22 patients with MDS were treated with this regimen, with 5 of 15 evaluable patients achieving a CR or marrow CR, and a survival of 5.7mo which was unfavorable compared to institutional controls.[50] Another study combined azacitidine 75mg/m2 days 1–7 with GO 3mg/m2 administered on day 8; of 56 patients, most had AML but 11 had higher risk MDS, and the CR/CRi rate was 27%.[51]

Other agents have also been evaluated in higher-risk MDS. Vadastuxumab talirine (SGN CD33) is an anti-CD33 antibody-drug-conjugate, somewhat similar in concept to gemtuzmab ozogamicin, and has been studied in combination with azacitidine; however, a phase III study comparing azacitidine monotherapy to the combination in AML showed an increase in early deaths with this combination,[52] underscoring the considerations around myelosuppression with CD33 directed therapies.

Other approaches have looked instead to antibodies against CD33 but lacking a chemotherapy payload. BI 836858 is a fully human anti-CD33 unconjugated antibody and has been explored in MDS, intending to result in antibody dependent cellular cytotoxicity (ADCC). Models using human MDS samples suggest that the administration of BI 836858 results in depletion of CD33+ MDSCs.[53] This led to it being studied in a phase I/II design for patients with symptomatic anemia and low or intermediate-1 risk MDS (NCT02240706) although terminated early by the company.

## Cellular Therapies

Another approach relies less on passive immunologic therapies and instead on more direct engagement of cellular immunity for the treatment of MDS. This can be done by enhancing cellular immunity such as through bispecific antibody therapy, which colocalize immune cells and tumor cells, or by administering modified cellular therapies such as chimeric

antigen receptor (CAR) T-cells. These strategies seek the generate an anti-tumor effect; some of the rationale stems from the graft-vs-leukemia effect described in allogeneic transplantation.

**Chimeric Antigen Receptor (CAR) T-cells—**Following their success in lymphoid neoplasia, a number of trials have assessed CAR-T cells in MDS and other advanced myeloid neoplasms. CAR-T constructs target a number of the same cell surface markers explored in antibody or ADC therapies as enumerated above. In contrast to humanized antibodies, however, cellular therapies may persist and require different processes for manufacturing. Each CAR-T construct can vary according to an increasing number of variables: identifying a MDS (or leukemia) specific target, modifications that alter the initial T-cell activation, and questions around CAR T-cell persistence. Particularly in myeloid neoplasms, such as MDS, the CAR-T needs to have a certain degree of specificity for malignant cells compared to healthy progenitors; eliminating all myeloid hematopoiesis would result in severe neutropenia and thus often requires the option of allogeneic salvage. Novel CAR products may provide such specificity, incorporating multiple neoantigens to activate CAR-T expansion; for instance, bispecific and split CAR T-cells targeting CD13 and TIM3.[54] An unanswered question in MDS, in contrast to acute leukemias, is around residual healthy hematopoietic reserve. By the time a patient has an MDS diagnosis, their blood is largely malignant clonal hematopoiesis.[55] If a modified cellular product eliminates all malignant progenitors, will enough healthy stem cells repopulate the marrow in a timely fashion to avoid complication?

Targets for CAR-T cells vary and are largely selected based on similar rationale as noted previously in this review. Several CAR products have been developed and are directed toward CD123, which may delineate higher risk MDS stem cells from normal progenitors[56] (e.g. NCT04109482). There are also CAR-T constructs targeting CD33, which has been explored as noted above, as well as trials evaluating combinatorial targets such as CD123-CD33 cCAR T-cells (NCT04156256), CLL1-CD33 (NCT03795779), or CD33-IL15 constructs (NCT03927261). To date, clinical data from such studies in MDS is limited.

Other approaches seek targets that are less prevalent on hematopoietic progenitors. One such approach is demonstrated by a CAR T-cell that employs a full length natural killer group 2D (NKG2D) gene, which is costimulated in response to DAP10.[57,58] Again, limited human data is available, though one NKG2D CAR T-cell study that included patients with relapsed or refractory AML and MDS did report some evidence of stable disease after CAR T-cell administration.[59] Another study of autologous anti-NKG2D CAR T-cells did not yield significant clinical activity although in AML and MM.[60] CD70 may provide another target for CAR T-cells that has more limited suppression of healthy HSCs,[61,62] with clinical studies in relapsed hematologic neoplasms planned (NCT04662294).

**Bispecific Antibodies—**Alternatively, other therapies may engage and activate the endogenous cellular immune system, such as those which employ bispecific antibody therapies. Generally, such constructs include a tumor-specific component, with similar targets as noted (CD123, CD33, etc), and a T-cell activating component, typically targeting CD3. This has also been primarily studied in acute leukemias to date, including the approved

therapeutic blinatumomab for the treatment of B-ALL, but increasingly is being explored in MDS as well.

Flotetuzumab is a bispecific dual-affinity re-targeting protein (DART) that engages with CD123 and CD3; it has activity against CD123+ blasts *in vivo*.[63] A total of 45 patients with R/R AML or MDS – 5 of which had MDS – received flotetuzumab in a phase 1 dose escalation study, with responses seen in 8 of 14 patients treated at a dose of 500 ng/kg/day (3 CR, 1 CRi, 1 MLFS, and 1 PR).[64] Another compound with a similar target, APVO436, a bispecific CD123-CD3 molecule, is being studied in patients with R/R AML and MDS; 28 patients received this agent at escalating doses, including 6 patients with higher risk MDS.[65] One of the MDS patients reported a durable response lasting over 11 cycles of therapy.

As the range of MDS targets expands, further constructs continue to be explored that impact other aspects of MDS hematopoietic dysfunction. For instance, natural killer (NK) cells play important roles in tumor immunosurveillance and are impaired in MDS; CD16 binding induces NK cell activation. Based on this, CD16xCD33 bispecific killer cell engager (BiKE) therapy has been explored as a possible way to activate an NK-cell based response toward the MDS progenitors.[66] Such a concept has been taken further to evaluate a tri-specific killer cell engager (TriKE) targeting CD16/IL-15/CD33 in patients with AML and MDS, although results remain preliminary.[67]

**Vaccines—**Antitumor vaccines also play a role in engaging the endogenous immune system to elicit and initial and ongoing anti-tumor response. This may have an appeal in MDS given there are a number of recurrently mutated genes in this blood cancer and these may provide neoepitopes for a tumor specific immune response. Hypomethylating agent therapy as well may induce expression of tumor antigens, suggesting that combination therapy may have some appeal.[18]

In one study, patients with MDS were treated with decitabine and also received an HLA-unrestricted NY-ESO-1 vaccine, which acts as a highly immunogenic tumor antigen.[68] The authors identified NY-ESO-1 specific T-cell responses in most of the 7 treated patients, suggesting the potential to further explore such a combination. Other approaches may take tumor cells to develop a vaccine and then administer; for instance, DCP-001, an allogeneic leukemia-derived dendritic cell vaccine. Of 12 patients with AML or MDS receiving this vaccine, seven responses were noted, including two MDS patients with mCR responses.[69]

## Targeting Immunological Dysfunction in MDS

As noted, a number of immunological pathways are disrupted in MDS, the impacts of which are yet to be fully characterized. In practice, a number of active therapies target some of these inflammatory pathways, particularly in lower risk MDS. An area of particular interest in related to inflammation, although still early in our understanding, is that of clonal hematopoiesis, particularly among patients with clonal cytopenias and higher risk features, a group that may have a number of overlapping features with lower risk MDS.[70,71]

Lenalidomide belongs to a class of drugs commonly referred to as immunomodulatory drugs or IMiDs, which encompass thalidomide analogues with various immune and inflammatory

effects, and may also be described as cereblon modulators.[72] Of this class, lenalidomide is particularly active in the subset of MDS patient with 5q deletion (MDS with del5q), where it is most effective in treating RBC transfusion dependence.[73] In MDS with del5q, the mechanism of lenalidomide has been described in part related to cereblon mediated degradation of CK1a.[72,74] That said, lenalidomide is also effective in a subset of patients with MDS but without del5q,[75] although the exact mechanism here is less clear. It is possible that the immunomodulatory properties of lenalidomide play a role in these non del5q responses; some data suggests inflammation and pyroptosis predicts these responses.[76] Understanding any role that inflammation or immune-modulation plays may become increasingly important as lenalidomide is explored in different settings; for instance, a recent study suggested that early initiation of lenalidomide may significantly prolong the time until transfusion dependence.[77]

Similarly, the TGF-beta signaling pathway has emerged as a potential therapeutic target in MDS.[78] When TGF-beta signaling is activated, there is downstream activation of smad2 in MDS progenitors; blocking this pathway results in improved late stage erythropoiesis. Inhibition of this pathway results improved hematopoiesis in pre-clinical MDS models.[7,79] One method to improve hematopoiesis may thus be through therapies that limit TGF-beta signaling, for instance by the activin receptor ligand “traps” sotatercept and luspatercept.[7] Luspatercept was approved for the treatment of transfusion dependent MDS with ring sideroblasts based on an improvement in transfusion independence compared to placebo in the MEDALIST trail.[80] It is being evaluated in other settings, including in a phase 3 randomized, open-label clinical trial comparing luspatercept versus epoeitin alfa in patients with very low to intermediate MDS (COMMANDS trial, NCT03682536). Other agents are also under investigation which may influence TGF-beta signaling, including agents that interact with downstream smad signaling such as TP-0184 (NCT04623996) or KER-050 (NCT04419649).

Adding to the complexity of this space is the fact that immune dysregulation appears to vary according to the disease stage, molecular profile, and other factors remaining unclear. Clonal hematopoiesis, for instance, may arise in the setting of dysregulated immune signaling, allowing mutant subclones to expand and dominate overall hematopoiesis.[78] There is some early evidence that treatment of patients with clonal myeloid processes may be able to alleviate cytopenias,[71] or may have impact on cardiac complications.[81] While preliminary, and beyond the scope of this review, these will drive studies in MDS, clonal hematopoiesis, and inflammation in the future.

## Conclusions

MDS represents a spectrum of malignant clonal myeloid neoplasms, and it is perhaps no surprise that immunologic dysfunction is frequent and varied across this malignancy. A number of efforts are underway to identify ways to use the immune system therapeutically; whether by awakening otherwise dormant immune effector cells, or by abrogating an altered inflammatory microenvironment. While early, there are already encouraging signals that in time may lead to new approaches to this malignancy.

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**Table 1.**

Checkpoint Inhibitors Currently Under Evaluation for the Treatment of MDS.

| Target | Population | Comments | Phase | n | Status | Clinicaltrials.org *Trial Number* |
|---|---|---|---|---|---|---|
| **PD-1 or PD-L1** | HR-MDS | Pembrolizumab + HMA | Phase Ib | 54 | Recruiting | NCT03969446 |
| | IR-MDS or HR-MDS | Atezolizumab + HMA | Phase I/II | | Recruiting | NCT04214249 |
| | Myeloid malignancies | Pembrolizumab | Phase I | 197 | Completed | NCT01953692 |
| **CTLA-4** | HR-MDS + AML | Ipilimumab | Phase I | 42 | Completed | NCT01757639 |
| | Pre- and post- HCT allograft, MDS and AML | Ipilimumab + decitabine | Phase I | 48 | Recruiting | NCT02890329 |
| **CTLA-4 + PD-1** | Myeloid malignancies post-allogeneic HSCT | Ipilimumab + nivolumab | Phase I | 71 | Completed | NCT01822509 |
| | AML or HR-MDS | Ipilimumab + nivolumab | Phase I | 8 | Active, not recruiting | NCT02846376 |
| | HR-MDS + AML s/p allogeneic HSCT | Ipilimumab + nivolumab | Phase I | 55 | Recruiting | NCT03600155 |
| | Myeloid malignancies | Nivolumab + AZA ± ipilimumab | Phase II | 182 | Recruiting | NCT02397720 |
| | All-risk MDS | Ipilimumab ± nivolumab ± AZA | Phase II | 160 | Recruiting | NCT02530463 |
| **TIM-3** | LR-MDS | MBG-453 | Phase II | 20 | Not yet recruiting | NCT04823624 |
| | LR to IR-MDS | MBG-453, canakinumab, NIS793 (Anti-TGF-β) | Phase I | 90 | Recruiting | NCT04823624 |
| | AML + HR-MDS | MBG453+ HDM201 (MDM2 inhibitor) | Phase Ib | 80 | Recruiting | NCT03940352 |
| | HR-MDS | MBG453 + AZA or HMA | Phase II | 90 | Not yet recruiting | NCT04878432 |
| | HR-MDS | MBG453 + AZA + venetoclax | Phase II | 76 | Recruiting | NCT04812548 |
| | IR-HR MDS | MBG453 versus placebo with HMA | Phase II | 127 | Active, not yet recruiting | NCT03946670 |
| | Myeloid malignancies | MBG453 ± PDR001 (anti-PD-1) ± HMA | Phase I | 243 | Active, not yet recruiting | NCT03066648 |
| | IR-HR MDS | MBG453 | Phase III | 500 | Recruiting | NCT04266301 |
| **CD47** | HR-MDS | AK117 (monoclonal Ab targeting CD47) + AZA | Phase I/II | 190 | Recruiting | NCT04900350 |
| | HR-MDS | Evorpacept (soluble CD47 inhibitor) + AZA | Phase I/II | 173 | Recruiting | NCT04417517 |

Abbreviations: allo-HSCT = allogeneic hematopoietic cell transplantation; AML = acute myeloid leukemia; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; HMA = hypomethylating agent; HR = higher-risk; IR = intermediate risk; LR = lower risk; MDS = myelodysplastic syndrome; PD-1 = programmed cell death 1; PD-L1 = programmed death ligand 1.