

Recent Advances in the Cellular and Molecular Understanding of Myelodysplastic Syndromes: Implications for New Therapeutic Approaches

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Abstract: It has been more than 10 years since any new disease-modifying therapies have received regulatory approval for indications related to myelodysplastic syndromes (MDS). Advances in our collective biological understanding of MDS in the last decade, however, have made it possible to hope that effective therapeutics can be designed to improve MDS-associated cytopenias and patients' quality of life, and perhaps even delay clonal progression and extend survival. Classes of MDS-associated mutations and disordered biological pathways targeted by developmental therapeutics include the following: aberrant messenger RNA splicing, neomorphic enzymes in the citric acid cycle with oncogenic activity, overactivated tyrosine and serine-threonine kinases, epigenetic and chromatin remodeling alterations, abnormal telomere dynamics, and failed protection of DNA integrity. At present, treatments for MDS are usually administered as sequential monotherapy, but there is a trend toward clinical trials of combination therapies—in which new agents are added to a DNA hypomethylating agent backbone—for both upfront treatment and the treatment of relapsed/refractory disease. Agents in clinical trials for subsets of MDS include luspatercept, antibodies targeting CD33, isocitrate dehydrogenase inhibitors, deacetylase inhibitors, venetoclax, and immunotherapies designed to overcome immune checkpoint inhibition. These biologically based therapeutics, as well as the encouraging precedent of 7 new approvals by the US Food and Drug Administration in 2017 for the treatment of acute leukemia, offer the prospect that 10 more years will not elapse before another new therapy is approved for MDS.

Introduction and Epidemiology of Myelodysplastic Syndromes

Myelodysplastic syndromes (MDS) encompass a spectrum of bone marrow malignancies characterized by cytopenias and ineffective clonal hematopoiesis, as well as a risk for evolution to acute myeloid leukemia (AML) in up to 30% of cases. It has long been recognized

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that the natural history of MDS varies widely according to the pathologic and molecular characteristics of the disease, with some patients having an indolent course that stretches over many years and others rapidly progressive disease with a survival measured in months.^{1,2}

Estimates of the incidence of MDS vary, but it is thought that at least 4 to 7 new cases of MDS occur per 100,000 persons per year in the United States and Western Europe, with a median age at diagnosis of approximately 70 years.³⁻⁶ The true incidence and prevalence of MDS have been difficult to estimate owing to the incomplete capture of cases by cancer registries, and estimates also vary based on the methodology employed. For example, incidence figures are lower when stringent pathologic confirmation of an MDS diagnosis is required and higher when criteria are expanded to include factors such as billing codes.⁷ Clinical practice patterns may also influence case ascertainment. For instance, older patients with isolated mild cytopenias, who may have low-grade MDS, may be less likely to undergo an evaluation that includes referral to a hematology specialist and marrow biopsy.⁸

MDS are characterized by the World Health Organization (WHO) according to specific morphologic, karyotypic, and cytogenetic abnormalities identified in a diagnostic bone marrow specimen. Bone marrow studies in patients with unexplained cytopenias and suspected MDS should include the following: a full cytogenetic analysis to assess the metaphase karyotype, iron staining of an adequate aspirate sample to evaluate for the presence of ring sideroblasts, a core biopsy, and a peripheral blood smear for morphologic evaluation. Fluorescence in situ hybridization (FISH) analysis may also be of use in identifying recurrent abnormalities, such as del(5q), del(7), and 20q-, among others. FISH is not needed if at least 20 metaphases can be examined, however, and it remains unclear whether the addition of FISH alters cytogenetic risk category assignment.⁹ Increasingly, next-generation sequencing with panels of multiple putative leukemic driver genes that are recurrently mutated in MDS is being employed in the clinic, as molecular testing results are of diagnostic and prognostic value.^{1,10,11} In 2016, the WHO updated its MDS classification to incorporate a DNA sequencing parameter for the first time: the presence of a mutation in the gene encoding splicing factor component SF3B1.

Risk Stratification and Disease Classification

The risk for death or leukemic transformation among patients with MDS can be characterized by using any of a number of risk stratification algorithms; the 1997 International Prognostic Scoring System (IPSS) and the

2012 Revised International Prognostic Scoring System (IPSS-R) are most commonly employed in clinical practice.¹²⁻¹⁵ Although the factors that are assessed in each of these scoring systems vary slightly, all incorporate the depth and number of cytopenias present, the burden of myeloid blast cells found in the bone marrow or blood, and the genetic composition of MDS, primarily through cytogenetic analysis. Patient risk groups are based on historical cohorts of individuals who were either untreated or received growth factor support alone, which may provide insight into the “natural history” of MDS following diagnosis and can then be used to guide treatment decisions.

Morphology and type of cytopenias have been used to subclassify MDS since the 1982 French-American-British (FAB) classification and are associated with differences in overall survival as well as varying risk for transformation to AML.¹² Subsequent modifications of MDS subgroup classifications^{16,17} have reflected the evolving understanding of certain cytogenetic and molecular features and their effect on prognosis and response to therapy.

A challenge in using cytogenetic analysis for defining risk is that approximately one-half of patients will have a normal karyotype. In addition, MDS may be challenging to diagnose in patients with mild cytopenias and minimal dysplasia, particularly when other medical conditions may be contributing to cytopenias or dysplasia. In this setting, rapid-sequencing platforms that can detect recurrent somatic mutations have emerged as an increasingly important diagnostic tool.^{1,18}

MDS that are associated with the chromosomal lesion del(5q), specifically losses that span 5q31-q33 and occur in isolation from other cytogenetic lesions (particularly chromosome 7 abnormalities), often exhibit a specific clinical presentation characterized by macrocytic anemia, thrombocytosis, hypolobated micromegakaryocytes, and a relatively indolent clinical course.^{19,20} Patients with MDS who have isolated del(5q) and lower-risk transfusion-dependent disease tend to respond favorably to lenalidomide (Revlimid, Celgene) therapy.²¹ As such, these patients represent a distinct subgroup within the WHO classification.

Similarly, more recent studies have identified mutations in *SF3B1* to be common among patients who have MDS with ring sideroblasts. Patients with MDS who have *SF3B1* mutations tend to have a more indolent clinical course.²²⁻²⁴ The identification of a somatic mutation in *SF3B1* can be useful to confirm a diagnosis of MDS, particularly when other causes of sideroblastic anemia are being considered.²⁵

The heterogeneity of MDS across subtypes, as well as variation in outcomes according to clinicopathologic characteristics, introduces several challenges in the management of these patients. As the median age of patients

at diagnosis of MDS is older than 70 years, many of them have comorbid conditions that can limit treatment options and present competing risks to their survival. The symptoms of these conditions, such as underlying cardiovascular disease and chronic obstructive pulmonary disease, may be exacerbated by MDS-associated cytopenias, so that patients' ability to tolerate infectious complications or transfusional iron overload is reduced. Although many deaths in MDS may be attributed to complications of the disease, such as infections or bleeding,^{26,27} a high burden of cardiovascular disease has also been noted in this population.^{6,28} Comorbidities should be considered when survival is estimated and a treatment strategy is developed for these patients.

Current Treatment of Myelodysplastic Syndromes

When therapeutic strategies for patients with MDS are determined, an evaluation of comorbidities and life expectancy is important. However, decisions regarding the initiation of therapies specific to MDS are largely predicated on the symptomatic burden of disease, the severity of cytopenias, and the risk for progression (Figure). Patients with MDS are typically categorized as having either higher- or lower-risk disease, most commonly by using a binary split of the 4-category IPSS¹² or 5-category IPSS-R.¹³

In addition, the incorporation of somatic mutations into the risk assessment is becoming increasingly important, which may be especially helpful for patients with IPSS-R intermediate-risk disease.²⁹ Patients with MDS who harbor mutations in certain genes may have higher-risk disease features that "upgrade" their risk from a lower- to a higher-risk category.³⁰ For instance, in one series of 435 patients, those with a mutation in *ASXL1*, *RUNX1*, *ETV6*, *EZH2*, or *TP53* had a disease risk consistent with a higher category than would otherwise have been estimated by using the IPSS.³¹ Moreover, an increase in the total number of somatic mutations may be associated with an increased risk for disease progression or death.³² Although heterogeneity is still found within lower- and higher-risk categories,^{14,33,34} therapies for lower-risk disease generally focus on mitigation of cytopenia and symptoms, whereas those employed for higher-risk disease seek to modify the natural history.

Lower-Risk Myelodysplastic Syndromes

In many patients with lower-risk MDS, disease may be diagnosed in the setting of relatively mild cytopenias before they have received any directed treatment—including transfusion support. For patients with indolent disease who do not have transfusional needs and have

minimal symptoms, prospective monitoring may be the most appropriate treatment approach. In addition, any non-MDS comorbidities, such as cardiovascular disease, should be addressed. Certain characteristics at diagnosis, such as the presence of an *SF3B1* mutation without other adverse risk features,²⁴ may help to identify patients who will benefit from this watchful waiting approach.

Once severe cytopenias or transfusion needs develop in patients with lower-risk MDS, therapies are focused on attaining transfusion independence and reducing associated risks, such as transfusional iron overload. The most frequently employed therapy for moderate-to-severe anemia is the off-label use of erythropoiesis-stimulating agents (ESAs), such as epoetin alfa (Epogen, Amgen; Procrit, Janssen Biotech) or darbepoetin alfa (Aranesp, Amgen).³⁵⁻³⁸ Several factors may help to predict those patients most likely to benefit from ESA use; on the basis of an analysis of 996 patients, the recently validated Italian and Canadian ITACA score identified a pretreatment serum erythropoietin (EPO) level of less than 100 U/L, IPSS low-risk disease, and a low number of required transfusions (defined here as <1 U of packed red cells over an 8-week period) as predictors of the greatest chance of response.³⁹ Clinically, the decision to initiate ESA therapy may depend on the convenience of ESA administration, the interval between transfusions, and the symptomatic burden of anemia. Some characteristics, such as a serum EPO level above 500 U/L,³⁸ portend a very low likelihood of response and merit consideration of an alternative therapy.

The approach to patients who have lower-risk MDS with thrombocytopenia or neutropenia is more challenging, given the limited number of effective therapies. Patients with isolated neutropenia present a particular clinical challenge. Some patients may have uncomplicated neutropenia for long periods without needing intervention; moreover, as regards the use of granulocyte colony-stimulating factor (G-CSF) in MDS, although it may improve neutrophil counts,⁴⁰ it is not clear that prophylactic dosing of G-CSF has any effect on MDS progression or infection risk.⁴¹ More recently, the role of thrombopoietin (TPO) agonists has been explored in the treatment of thrombocytopenia associated with MDS. Both romiplostim (Nplate, Amgen) and eltrombopag (Promacta, Novartis) can reduce platelet transfusion needs, improve counts, and modestly reduce clinically significant bleeding events.⁴²⁻⁴⁴ However, given that myeloid blasts occasionally have functional TPO receptors, there has been some concern about potential increases in the percentage of bone marrow blasts during administration, which occurred in fewer than 10% of patients in clinical trials and resolved in most patients after the cessation of TPO-mimetic therapy. The timing of the administration

of TPO agents with respect to other therapies is likely also an important consideration in MDS; the concurrent use of eltrombopag and azacitidine delayed platelet recovery and increased transfusion requirements compared with placebo.⁴⁵

There are several settings in which alternatives to ESA therapy should be considered in lower-risk MDS—most notably, patients with endogenous EPO levels above 200 to 500 U/L and patients with MDS who are harboring del(5q) and are transfusion-dependent. In this latter subset of patients, lenalidomide, an immunomodulatory drug (IMiD) that is a derivative of thalidomide, results in transfusion independence in approximately 3 of 4 patients, as well as temporary clearance of the cytogenetically abnormal clone in nearly half of patients.^{21,46} It was this impressive response that led to the US Food and Drug Administration (FDA) approval of lenalidomide for the lower-risk del(5q) subset of patients in 2005. Lenalidomide also appears to reduce transfusion requirements in approximately one-quarter of patients without del(5q),^{47,48} although responses are generally of shorter duration than those achieved with hypomethylating agents. Despite not being approved for this population, lenalidomide is still widely used off label in the clinic.

Another consideration in lower-risk MDS is the use of immunosuppressive therapy. A subset of patients with MDS may have disease that includes T-cell-mediated myelosuppression with features that overlap those of aplastic anemia, and immunosuppressive therapy, which consists of antithymocyte globulin (ATG) plus either cyclosporine or tacrolimus, can be considered for them. Identifying this subset of patients may be challenging, but factors that have correlated with favorable responses include lower-risk disease, with fewer than 5% bone marrow blasts, and patient age younger than 60 years.⁴⁹⁻⁵¹ The presence of hypoplastic disease and of HLA antigen HLA-DR15 also has been reported in some series (but not others) to predict a higher likelihood of responses to this therapy, and in some series, the presence of trisomy 8 or a paroxysmal nocturnal hemoglobinuria clone.^{51,52} In lieu of attractive alternative therapies, immunosuppressive therapy can be considered for patients with predictors of response to therapy after their disease fails to respond to ESA treatment.

The treatment design of patients whose MDS is a consequence of a germline disorder may require special consideration. For instance, patients with Fanconi anemia are extremely sensitive to cytotoxic agents and require dose adjustment if treated with such drugs. Inherited telomeropathies can present as MDS, and the treatment of these patients with danazol, a synthetic androgen, may be considered, given data showing telomere elongation and reduced transfusion requirements.⁵³

Danzol may also be considered in other patients with lower-risk disease, and several reports suggest efficacy among patients with predominant thrombocytopenia.⁵⁴

For patients whose disease fails to respond to the above approaches, a DNA hypomethylating agent or allogeneic transplant may be considered, as described below for those with higher-risk disease.

Higher-Risk Myelodysplastic Syndromes

Patients with higher-risk disease generally face a more imminent risk for complications, owing to either progressive cytopenias and associated complications or transformation to secondary AML, which is especially challenging to treat. For this subset of patients, the clinical approach is generally focused on disease-modifying therapies—that is, those that will prolong life, preferably without major impairment to quality of life.

Most patients with higher-risk disease will be treated with either azacitidine or decitabine. These are cytosine analogues that inhibit DNA methyltransferase, thereby decreasing global methylation with consequent alteration in gene expression and epitope presentation; they are therefore typically referred to as hypomethylating agents (HMAs) or DNA-methyl transferase inhibitors (DNMTIs). These drugs were approved by the FDA in 2004 (azacitidine) and 2006 (decitabine). The efficacy of HMA therapy in MDS was first shown in a study conducted by the Cancer and Leukemia Group B (CALGB 9221). This study, which began in the mid-1990s, compared HMA treatment vs standard of care and showed a trend toward improved survival in the arm receiving azacitidine.⁵⁵ A subsequent phase 3 study of patients with higher-risk MDS, published 5 years after the US marketing approval of azacitidine, confirmed a survival benefit among patients receiving azacitidine at 75 mg/m² on days 1 to 7 of a 28-day cycle in comparison with those receiving conventional care regimens (supportive care or cytarabine-based therapy).⁵⁶ Decitabine has delayed disease progression when dosed at 20 mg/m² on days 1 to 5 of a 28-day cycle,⁵⁷ and it is widely considered comparable with azacitidine, although direct comparisons between the 2 agents are lacking. It is not yet known whether the high response rate reported with decitabine in *TP53*-mutant AML also applies to MDS.⁵⁸ Patients who have *TP53*-mutant MDS treated with azacitidine also have relatively high response rates.⁵⁹

More recently, orally bioavailable HMA therapies (CC-486 and ASTX727, the latter representing decitabine co-administered with an inhibitor of cytidine deaminase) have been under development, with pharmacokinetic profiles mirroring those of parenteral azacitidine and decitabine.^{60,61} Although it is unclear whether these will improve efficacy, they will allow more flexible dosing and

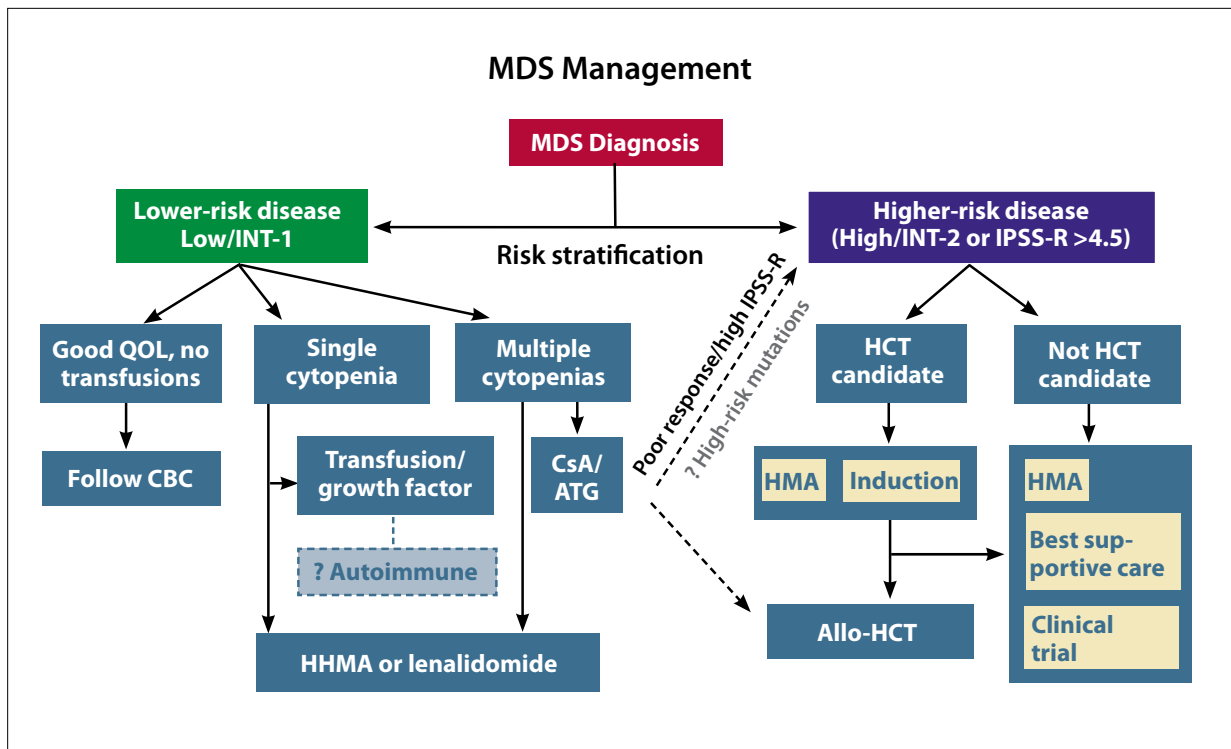


Figure. Approach to therapeutics in myelodysplastic syndromes. Clinical trial enrollment should be considered at all stages. Patients should be risk stratified with a tool such as the IPSS-R. Some patients with lower-risk disease who have mild cytopenias and are minimally symptomatic may just be observed with serial CBCs. Patients who have anemia alone can be administered an erythropoiesis-stimulating agent if their serum erythropoietin level is less than 500 U/L, or can receive lenalidomide if they have del(5q). The approach for other patients is challenging and may involve immunosuppressive therapy with CsA and ATG, a combination growth factor approach, lenalidomide despite the absence of del(5q), or a hypomethylating agent. For patients with higher-risk disease, the key decision is whether the patient is an allogeneic stem cell transplant candidate. If the patient is a transplant candidate, the transplant should be performed as soon as possible, potentially with a hypomethylating agent as a bridge. If not, the patient should receive therapy with a hypomethylating agent; in this setting, azacitidine has improved survival compared with conventional care. “Induction” might include CPX-351 instead of the conventional cytarabine-anthracycline “3&7” combination.

Allo-HCT, allogeneic hematopoietic stem cell transplant; ATG, antithymocyte globulin; CBC, complete blood cell count; CsA, cyclosporine-A; HCT, hematopoietic stem cell transplant; HMA, hypomethylating agent; INT, intermediate risk; IPSS, International Prognostic Scoring System; IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplastic syndromes; QOL, quality of life.

possibly improvements in quality of life. Newer parenteral HMAs, such as guadecitabine (SGI-110), are undergoing phase 3 trials in AML and MDS, as described below.

Another important consideration at the time of diagnosing higher-risk MDS is to determine whether a patient is a candidate for allogeneic hematopoietic stem cell transplant (allo-HCT), the only potentially curative therapy for MDS (in approximately 30%-40% of cases). Indeed, although historically many patients with MDS may not have been considered transplant candidates because of their age at diagnosis, this is a moving target because a number of studies have shown that allo-HCT may be pursued effectively in patients with higher-risk disease, including selected patients older than 70 years.⁶²⁻⁶⁴ A study is currently underway to compare the effect of HCT

in the older, Medicare population with intermediate-2 or high-risk MDS on the IPSS with that of other standard treatments (NCT02016781).

Transplant options for both older and younger patients have evolved over the last decade, with donor options expanding and transplant-related toxicity diminishing. The advent of reduced-intensity conditioning in the 1990s expanded the use of this treatment modality to older patients who were not considered candidates for myeloablative therapy.⁶⁴⁻⁶⁶ Transplant following pre-transplant reduced-intensity conditioning relies more on a graft-versus-leukemia (GvL) effect than does transplant with a myeloablative chemotherapy approach.⁶⁷ This approach may be effective in MDS but not in more proliferative diseases, such as AML, because

the GvL effect may take time to develop. Nonetheless, a recent study comparing reduced-intensity conditioning with myeloablative chemotherapy conditioning favored myeloablative chemotherapy in otherwise eligible patients, a finding driven largely by those with AML.⁶⁸ Other considerations, such as graft donor source, have also changed with expanded alternative donor options, such as haploidentical transplant.^{69,70} There has also been conflicting evidence about the use of older matched sibling donors, such as the siblings of most patients with MDS, compared with younger matched unrelated donors.^{71,72} Clonal hematopoiesis of indeterminate potential (CHIP), described in further detail below, is common in older donors—more than 10% of patients older than 60 years—and may lead to cytopenias and worse outcomes after transplant, including rare cases of donor-derived leukemia.⁷³

The Evolving Molecular Landscape of Myelodysplastic Syndromes

Expanded understanding of the molecular pathophysiology of MDS has provided insight into the biology of this disease while also raising new questions, particularly about the role of somatic mutations in MDS and other hematologic conditions.^{18,20,29} As previously noted, the diagnosis of MDS relies on demonstrating a clonal marrow process with resultant ineffective hematopoiesis. Particularly when comorbid conditions may contribute to a cytopenia or the appearance of dysplastic forms, establishing clonality can be useful to support the diagnosis of MDS in lieu of excess blasts. Although cytogenetic abnormalities are identified in only half of patients with MDS, somatic mutations may increase the percentage of patients with MDS who have a characteristic mutation to more than 90%.³² In a patient with other clear features of MDS, genetic mutations can thus enhance the certainty of a diagnosis; however, the presence of these mutations in patients without dysplasia, or even without cytopenias, has introduced new challenges to our understanding of their specificity in disease.^{74,75}

Increased use of genomic sequencing has also led to the development of a new vernacular to describe disease states associated with somatic mutations when patients do not otherwise meet criteria for MDS. The presence of a mutation at a variant allele frequency of at least 2% without concurrent malignancy or cytopenia represents CHIP and is common in the general population, seen in approximately 10% of those in their eighth decade of life.^{74,75} Most patients with CHIP have a single mutation, usually a *DNMT3A* or *TET2* point mutation. Similarly, patients who have a somatic mutation in a leukemia-associated driver gene and a cytopenia but who otherwise

do not meet WHO diagnostic criteria for MDS may be characterized as having clonal cytopenias of undetermined significance.¹⁸ Patients who have persistent cytopenias without mutations or evidence of MDS are said to have idiopathic cytopenias of undetermined significance and have a lower risk for progression to WHO-diagnosable MDS or AML.

Although these definitions may help to identify patients at risk for the development of a subsequent hematologic malignancy, the absolute rate of transformation of idiopathic cytopenias of undetermined significance and CHIP to MDS or other cancers is relatively low,⁷⁴⁻⁷⁶ primarily adding to the challenge of interpreting marrow results and sequencing reports. Indeed, an evolving clinical challenge has emerged in which patients who would not previously have fulfilled criteria for a hematologic malignancy may have an identified clonal process, and it is unclear when and how clinicians should intervene.

Although the evolving molecular landscape of MDS has introduced new challenges, it is also leading to improvements in risk assessment and treatment adaptation. The identification of frequent recurrent mutations in splicing factors in MDS, seen in approximately 50% to 60% of patients with MDS but uncommon in those with CHIP,^{77,78} may improve diagnostic and prognostic certainty^{22,24} and potentially lead to novel therapeutic targets. Patients who harbor a mutation in the splicing factor gene *SF3B1*, for instance, may have a more indolent course and tend to have better overall survival, particularly when the mutation occurs in isolation. Other mutations may provide insight into particularly aggressive forms of disease, as noted previously.³¹ Subclones that harbor or acquire mutations in *RAS* may expand during disease progression,^{79,80} presenting a potential target for therapeutic development. Mutations in *TP53*, recognized as predicting poor prognosis across many malignancies,⁸¹ are also associated with adverse outcomes in MDS. Those patients who harbor a mutation in *TP53* and undergo transplant have limited long-term survival (<20%),¹¹ underscoring the need for novel therapies in this subset of patients.

Emerging Therapeutic Strategies in Myelodysplastic Syndromes

Despite a burst of new therapies for MDS approximately 10 years ago, no new therapies have achieved regulatory approval since decitabine was approved in 2006,⁸² and patients whose disease does not respond or progresses on currently available therapies represent an unmet medical need. Current therapy options, excluding transplant, may prolong and improve the quality of life but are

not curative. Insight into the molecular pathogenesis of MDS may provide new therapeutic targets in this group of malignancies. Several ongoing studies are outlined below; this roster is only a selected list of new therapies in development, with the hope for significant improvements in MDS care in the next years (see the eTable at www.hematologyandoncology.net).

Luspatercept (ACE-536)

Patients with lower-risk MDS, whose disease is often characterized by red blood cell transfusion dependence, have limited effective treatment options once their disease stops responding to frontline therapy with an ESA, or if their pre-treatment EPO levels were above 500 U/L. Luspatercept is a modified activin receptor IIB–immunoglobulin G (IgG) Fc fusion protein; it targets transforming growth factor beta (TGF- β) signaling via Smad2/3 and growth and differentiation factor 11 (GDF-11), thereby enhancing erythropoiesis.⁸³ Certain ESA-resistant anemias may be related to ineffective late erythropoiesis and be responsive to targeting of the TGF- β superfamily.^{84,85} Luspatercept has achieved responses, including durable freedom from transfusions, in some patients with MDS, especially those with ring sideroblasts or elevated baseline EPO levels, and a phase 3 study comparing the efficacy of luspatercept with best supportive care in patients who have lower-risk MDS with ring sideroblasts has met accrual and will report in 2018 (MEDALIST; NCT02631070).^{86,87}

Spliceosome Modulation

Given the prevalence of splicing factor mutations in MDS, which are thought to be early events in the pathogenesis of this malignancy, the spliceosome complex is an appealing target for new therapies under development. Patients with MDS that harbors a splicing factor mutation, particularly *SF3B1*, have evidence of alternative splicing, especially the use of alternate 3' exons; targeted agents that bind the spliceosome complex may further perturb splicing by disrupting the remaining wild-type allele.^{78,88} On the basis of xenograft models showing selective pressure against splicing factor–mutated cells when exposed to splicing factor modulators, as well as absolute dependence on wild-type splicing even in mutant cells, a phase 1 study to evaluate an orally bioavailable splicing factor modulator, H3B-8800, that targets *SF3B1* is currently underway (NCT02841540).⁸⁹

Immune Checkpoint Inhibition

Immunologic dysregulation, including minor alterations of T-cell subsets, immunoglobulin level abnormalities, and paraneoplastic manifestations, is relatively common in patients with MDS, although the link to MDS

pathogenesis is still under investigation. HMA therapy may increase the expression of antigens associated with endogenous retroviruses, which are typically suppressed owing to promoter hypermethylation, potentially revealing novel immunologic targets that may be part of the mechanism of clinical efficacy of these agents.⁹⁰ Checkpoint inhibition with agents that block programmed death 1, programmed death ligand 1, and cytotoxic T-lymphocyte–associated antigen 4 are under investigation, both as monotherapy and in combination with azacitidine or decitabine^{91,92}; to date, these therapies, including nivolumab (Opdivo, Bristol-Myers Squibb) and ipilimumab (Yervoy, Bristol-Myers Squibb), appear to have quite limited activity as single agents.

DNA Hypomethylation

Given the success of azacitidine and decitabine in MDS, DNA methylation and epigenetic modulation remain targets of interest. Guadecitabine (SGI-110) is a dinucleotide of decitabine and deoxyguanosine that undergoes less degradation by cytidine deaminase; as such, it has been explored as a novel hypomethylating agent for the treatment of MDS.⁹³ In a phase 1 study of guadecitabine in progressive MDS and AML, a proportion of patients responded to therapy, including approximately one-third of the enrolled patients with MDS.⁹⁴ Guadecitabine is currently being explored in patients who have MDS previously treated with azacitidine or decitabine (NCT02907359).

(Histone) Deacetylase Inhibition

Epigenetic alterations are a hallmark of MDS, and much interest has focused on whether histone acetylation may be a viable target in the disease, given the significance of DNA methylation. That said, deacetylase inhibitors that target histones and other proteins (HDAC inhibitors) have achieved limited clinical success in MDS and AML, despite compelling preclinical rationale.⁹⁵ A number of studies have failed to show significant efficacy of HDAC inhibitors as monotherapy,⁹⁶⁻⁹⁸ and in combination with HMA therapy they have consistently increased toxicity (especially fatigue and thrombocytopenia) without improving response.⁹⁹⁻¹⁰² Most recently, a randomized study (North American Intergroup Study SWOG S1117) of azacitidine with or without lenalidomide or vorinostat (Zolinza, Merck) showed no significant survival benefit for azacitidine alone compared with azacitidine in combination with vorinostat.¹⁰³ A limitation to this study may have been the rate of dose modification owing to toxicity on the combination arms, and the overall challenges of treatment intensification in the general MDS population. Nonetheless, to date, combining HDAC inhibition with HMA therapy has not yielded significant gains in outcomes.

Antibody-Drug Conjugates

MDS with excess blasts that progress to AML are associated with resistance to chemotherapy and a median survival of less than 6 months. Agents that target progenitor cells or excess blasts in MDS, such as those directed at the cell surface marker CD33, remain of interest in higher-risk disease. The antibody-cytotoxin conjugate gemtuzumab ozogamicin (GO; Mylotarg, Pfizer) has been explored in patients with high-risk MDS and AML, both as monotherapy and in combination with HMA therapy; response rates have been encouraging, although coupled with significant myelosuppression.^{104,105} GO was reapproved by the FDA for relapsed/refractory CD33-positive AML in 2017 and is now available for use. Vadastuximab talirine, an antibody-drug conjugate that has a linker and a structure different from those of GO, was also being evaluated in patients with higher-risk MDS (NCT02706899) before unexpected adverse events led to trial cessation; bispecific antibodies directed against CD33 are now in development. For these and other agents targeting cell surface markers on progenitors, such as CD123/interleukin 3 receptor subunit alpha (IL3RA), proactive strategies to manage myelosuppression appear to be important because deaths from prolonged cytopenias have occurred.

Inhibition of Activated Cell Signaling Pathways

Several cell signaling pathways are upregulated in MDS cells, particularly as they progress or evolve into AML, and targeted small molecules may have a role in certain subsets of patients with MDS. With recognition of the role of the RAS signaling pathway in MDS, rigosertib has been explored for patients whose disease progresses on HMA therapy. Rigosertib is a small molecule that inhibits polo-like kinase 1 (PLK1) and also acts as a RAS mimetic, competing with RAS for binding to the phosphoinositide-3 kinase (PI3K) family; this results in RAS/MEK/ERK pathway inhibition.¹⁰⁶ In a phase 3 study of patients with MDS progressing on HMA that compared rigosertib vs best supportive care with or without low-dose cytarabine, rigosertib failed to show a survival benefit, and although there were more responses in the rigosertib group, many of these were related to an increase in bone marrow complete remissions without hematologic improvement.¹⁰⁷ A subset of patients with higher-risk disease appeared to respond, and a phase 3 study is ongoing to explore rigosertib in this population (NCT02562443).

Additional small-molecule inhibitors are of interest in MDS, such as inhibitors of mutant *IDH1* and *IDH2*, which encode enzymes in the citric acid cycle that have oncogenic neomorphic activity. Although *IDH1/2* mutations are present in only a small subset of patients with

MDS (<15%), early results with the oral chemotherapy agents enasidenib (AG-221; Idhifa, Celgene) and ivosidenib (AG-120) have been encouraging in MDS.¹⁰⁸

Targeting Anti-apoptotic Proteins

Dysregulated apoptosis is commonly seen in MDS; interestingly, in early, lower-risk MDS, background apoptosis appears to be increased,¹⁰⁹ whereas in advanced MDS, anti-apoptotic proteins are upregulated.¹¹⁰ A number of members of the Bcl-2 superfamily may present therapeutic targets in MDS at various stages of treatment, and therapies targeting Bcl-2 and Mcl-1 are currently in early therapeutic development. Of these, venetoclax (Venclexta, AbbVie/Genentech), a BH3 mimetic that inhibits Bcl-2 and is approved for 17p-mutated chronic lymphocytic leukemia, is farthest in development and seems to augment responses in combination with azacitidine¹¹¹; several studies are currently underway exploring both combination and monotherapy (NCT02966782 and NCT02942290). Preliminary results from the MD Anderson Cancer Center have indicated a response rate above 75% with a venetoclax/HMA strategy, including in patients with *TP53* mutations whose disease is resistant to other therapies.¹¹²

Conclusion

MDS, which are hematologic malignancies characterized by ineffective clonal hematopoiesis and a risk for progression to AML, are challenging to treat. Allogeneic transplant is the only curative treatment, and other therapies help only a minority of patients. Progress in the treatment of MDS has been limited during the last decade; however, advances in molecular genomics that have increased our understanding of the pathogenesis of MDS, evolving diagnostic criteria for these malignancies, improved risk stratification tools, and new therapeutic targets have led to the emerging strategies previously described and give hope that outcomes for patients will improve soon.

Disclosures

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Supporting Online Material for “Recent Advances in the Cellular and Molecular Understanding of Myelodysplastic Syndromes: Implications for New Therapeutic Approaches”

This eTable accompanies a review article by Andrew M. Brunner, MD, and David P. Steensma, MD, in the January 2018 issue of *Clinical Advances in Hematology & Oncology*.

eTable. Emerging Therapies in Myelodysplastic Syndromes^a

Drug Classes and Drugs	Mechanism of Action	Identifier
Kinase inhibitors		
LGH447	Pim kinase inhibitor	NCT02078609
Quizartinib (AC220)	FLT3 inhibitor	NCT02272478
Rigosertib (SyB C-1101, SyB L-1101, ON 01910.Na)	Inhibits PLK1, RAS mimetic that inhibits PI3K family, RAS/MEK/ERK signaling	NCT01926587 NCT02562443
Ruxolitinib (INCB18424)	JAK inhibitor	NCT01787487
Sorafenib	Inhibition of Raf, VEGFR, PDGFR, FLT3, and other kinases	NCT02196857 NCT02728050 NCT02530476
Tipifarnib	Nonpeptidomimetic quinolinone that binds to and inhibits the enzyme farnesyl protein transferase, preventing the activation of <i>RAS</i> genes	NCT02779777
TEW-7197	ALK5 inhibitor that inhibits the activity of TGFBR1 and prevents TGF- β /TGFBR1-mediated signaling	NCT03074006
ONC201	Akt/ERK inhibitor, blocks PI3K/MAPK/ERK signaling	NCT02392572
Ibrutinib	Small molecular inhibitor of BTK	NCT02553941
sEphB4-HAS	sEphB4 fused to HSA	NCT03146871
OTS167	Inhibitor of MELK, a serine/threonine kinase involved in survival	NCT02795520
BGB324	Inhibitor of AXL receptor tyrosine kinase, enhances chemosensitivity	NCT02488408
Regorafenib	Inhibits VEGFR2/3, Ret, Kit, PDGFR, Raf kinase	NCT03042689
DCC-3014	Inhibitor of the tyrosine kinase receptor CSF1R	NCT03069469
INCB053914	Pim kinase inhibitor	NCT02587598
Deacetylase inhibitors and DNA methyltransferase inhibitors		
Oral azacitidine (CC-486)	DNA methyltransferase inhibitor	NCT02281084 NCT02223052
Guadecitabine (SGI-110)	Nucleoside analogue with DNA methyltransferase inhibitory activity	NCT02907359 NCT02935361
Panobinostat (LBH-589)	Deacetylase inhibitor	NCT02676323
Pracinostat (SB939)	Deacetylase inhibitor	NCT03151304
Entinostat (SNDX-275)	Deacetylase inhibitor	NCT02936752
GSK2879552	LSD1 inhibitor, enhances H3K4 methylation	NCT02929498
Tranlycypromine sulfate	LSD1 inhibitor, enhances H3K4 methylation	NCT02717884 NCT02273102
IMG-7289	LSD1 inhibitor, enhances H3K4 methylation	NCT02842827
ASTX727	DNA methyltransferase inhibitor (decitabine) combined with cytidine deaminase inhibitor (E7727)	NCT02103478
Drugs that alter cell metabolism		
Enasidenib (AG-221) and ivosidenib (AG-120)	Small-molecule inhibitors of mutant <i>IDH1</i> (AG-120) and <i>IDH2</i> (AG-221)	NCT02577406 NCT03173248

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eTable. (Continued) Emerging Therapies in Myelodysplastic Syndromes^a

Drug Classes and Drugs	Mechanism of Action	Identifier
Drugs that alter cell metabolism (Continued)		
CPI-613 (6, 8-bis[benzylthio] octanoic acid)	Inhibitor of pyruvate dehydrogenase and ketoglutarate dehydrogenase	NCT01902381
CB-839	Glutaminase inhibitor	NCT03047993
AEB1102	Co-Argl-PEG–modified human arginase 1; degrades arginine levels	NCT02732184
Tosedostat (CHR-2797)	Inhibits M1 family of aminopeptidases, resulting in amino acid deprivation	NCT02452346
Cytotoxic agents/cell cycle inhibitors		
Cladribine (2-CDA)	Nucleoside analogue	NCT02115295 NCT01515527 NCT02044796 NCT02921061 NCT02728050 NCT02272478
Cytarabine/daunorubicin liposome injection (CPX-351)	Liposomal daunorubicin and cytarabine in a fixed 1:5 ratio	NCT02533115
Vosaroxin (SNS-595)	Quinolone derivative; replication-dependent DNA damage agent	NCT02658487
CFI-400945 fumarate	PLK4 inhibitor, disrupts mitosis and cell division	NCT03187288
AZD2811	AURKB inhibitor; disrupts mitosis and cell division	NCT03217838
OXi4503 (combretastatin A1 diphosphate)	Promotes microtubule depolymerization, mitotic arrest; disrupts tumor blood flow	NCT02576301
FF-10501-01 (inosine 5'-mono-phosphate dehydrogenase inhibitor)	Inhibits synthesis of guanine nucleotides and GTP; disrupts DNA and RNA synthesis	NCT02193958
AZD4573	CDK9 inhibitor	NCT03263637
Cell surface marker-directed therapies		
Daratumumab	Anti-CD38 human monoclonal antibody	NCT03067571 NCT03011034
BI 836858	Anti-CD33 human monoclonal antibody	NCT02240706
OPN-305	Anti-TLR2 humanized IgG4 monoclonal antibody	NCT02363491
Talacotuzumab (CSL362)	Anti-CD123 (IL3RA) antibody	NCT03011034
SL-401	Recombinant protein consisting of human IL3 fused to diphtheria toxin, binds to IL3RA (CD123)	NCT03113643
CC-90002	Anti-CD47 monoclonal antibody	NCT02641002 NCT02367196
Hu5F9-G4	Anti-CD47 monoclonal antibody	NCT03248479 NCT02678338
Hu8F4	Antibody against PR1/HLA-A2 (epitope expressed on leukemic blasts)	NCT02530034
TTI-621	Antibody fusion protein of the CD47 binding domain linked to human IgG1	NCT02663518
Gemtuzumab ozogamicin	Anti-CD33 antibody conjugated to a cytotoxin	NCT02221310 NCT02117297 NCT02272478
Immunosuppressive and immunomodulatory agents		
ALT-803	IL-15 superagonist mutant and a dimeric IL-15 receptor α Su/Fc fusion protein	NCT02989844 NCT01898793 NCT01885897

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eTable. (Continued) Emerging Therapies in Myelodysplastic Syndromes^a

Drug Classes and Drugs	Mechanism of Action	Identifier
Immunosuppressive and immunomodulatory agents (Continued)		
Equine anti-thymocyte globulin	T-cell inhibition by polyclonal antibodies raised in animals	NCT01624805 NCT02462252
Ipilimumab (MDX-101)	CTLA-4 inhibitor	NCT02530463 NCT02890329 NCT01822509
Pembrolizumab (MK-3475)	Anti-PD-1 antibody	NCT03094637 NCT02936752
Durvalumab (MEDI4736)	Anti-PD-L1 antibody	NCT02775903 NCT02117219 NCT02281084
Atezolizumab (MPDL3280A)	Anti-PD-L1 antibody	NCT02508870 NCT02935361
Nivolumab (BMS-936558)	Anti-PD-1 antibody	NCT02530463 NCT02599649 NCT02464657 NCT03259516 NCT03092674 NCT01822509
Pomalidomide (CC4047)	Immunomodulatory agent; modulates cereblon E3 ubiquitin ligase activity	NCT02029950
Sirolimus	mTOR inhibitor	NCT01869114
Lirilumab (BMS-986015)	Antibody against KIRs, activating NK cells	NCT02599649 NCT02399917
PDR001	Anti-PD-1 antibody	NCT03066648
MBG453	Anti-TIM-3 antibody	NCT03066648
ARGX-110	Antibody against CD70, which is the ligand for the costimulatory receptor CD27	NCT03030612
Apoptosis modulation		
Luspatercept (ACE-536)	Modified activin receptor IIB-IgG Fc fusion protein that targets TGF- β signaling via Smad2/3 and GDF-11	NCT02268383 NCT01749514
Venetoclax (ABT-199)	BH3 mimetic that inhibits Bcl-2	NCT02942290 NCT02966782
LY2606368	CHK1 inhibitor; interferes with DNA repair and cell cycle checkpoint control	NCT02649764
ALRN-6924	MDM2/MDMX inhibitor; restores p53 activity	NCT02909972
AZD1775	WEE1 inhibitor; impairs G2 DNA damage checkpoint	NCT02666950
S 64315 (MIK665)	Inhibitor of Mcl-1	NCT02979366
S 055746	Inhibitor of Bcl-2	NCT02920541
DS-3032b	MDM2 antagonist; inhibits p53 degradation	NCT02319369
APR-246	PRIMA-1 analogue; restores wild-type function to mutant p53	
Vaccines and cellular therapies (excluding transplant)		
Cellular immunotherapy	Autologous dendritic cells that have undergone electroporation with WT1 mRNA	NCT03083054
DSP-7888	WT1 protein-derived peptide vaccine	NCT02498665 NCT02436252
BPX-701	Autologous T cells genetically modified to express α/β T-cell receptor reacting with PRAME peptide/HLA*A2.01 and containing the suicide switch	NCT02743611

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eTable. (Continued) Emerging Therapies in Myelodysplastic Syndromes^a

Drug Classes and Drugs	Mechanism of Action	Identifier
Vaccines and cellular therapies (excluding transplant) (Continued)		
CD16/IL-15/CD33 tri-specific killer engagers (TriKes)	Cellular therapy directed toward CD33+ malignancies	NCT03214666
CAR-T cells	CAR T cells directed toward several targets, including CD33, CD39, CD56, CD117, CD123, CD34, and MUC1	NCT03291444 NCT03018405
Growth factors		
Eltrombopag	Small molecule agonist of TPO receptor c-Mpl (ie, thrombopoiesis-stimulating agent)	NCT02912208 NCT02928419 NCT01772420 NCT02446145
Romiplostim	Recombinant mimetic of TPO	NCT02335268
Epoetin beta	Recombinant protein similar to human EPO	NCT02145026
Pegol simecatide	Synthetic EPO peptide linked to PEG to increase circulation time	NCT02619097
Drugs that regulate transcription		
GSK525762	BET family inhibitor	NCT01943851
TEN-010 (RO6870810)	BET family inhibitor	NCT02308761
FT-1101	BET family inhibitor	NCT02543879
INCB057643	BET family inhibitor	NCT02711137
CPI-0610	BET family inhibitor	NCT02158858
PLX51107	BRD4 inhibitor, part of the BET family	NCT02683395
Miscellaneous		
H3B-8800	Orally bioavailable splicing factor modulator targeting SF3B1	NCT02841540
Bortezomib	Proteasome inhibition	NCT02312102 NCT02211755
Ganetespib (STA-9090)	Hsp90 inhibitor	NCT02272478
Omacetaxine mepesuccinate (homoharringtonine)	Protein translation inhibitor	NCT02159872
BL-8040	Inhibition of CXCR4	NCT02462252
CX-01 (2-0, 3-0 desulfated heparin)	Binds SDF-1 and CXCR4, as well as platelet factor 4	NCT02995655
Sertraline	Selective serotonin reuptake inhibitor, inflammatory cytokine modulator	NCT02452983
Selinexor (SINE KPT-330)	SINE that restores tumor-suppressing processes	
KPT-8602	Inhibitor of XPO-1 (SINE) that restores tumor-suppressing processes	NCT02228525 NCT02485535
Tamibarotene (SY-1425)	Orally active synthetic retinoid, approximately 10 times more potent than ATRA	NCT02807558
IRX5183	Retinoic acid receptor alpha agonist	NCT02749708
765IGF-MTX	IGF-1 conjugated to methotrexate	NCT03175978
Pevonedistat (MLN4924)	Small-molecule inhibitor of Nedd8-activating enzyme	NCT03268954 NCT03238248
Roxadustat (FG-4592)	HIF prolyl hydroxylase inhibitor	NCT03263091 NCT03303066
Nerofe	Novel tumor cell apoptosis factor, binds T1/ST2 receptor and activates apoptosis	NCT03059615
VSV-hIFNbeta-NIS	Vesicular stomatitis virus carrying the human <i>NIS</i> and <i>IFNB</i> genes (VSV-hIFN-beta-NIS), which may preferentially target cancer cells	NCT03017820

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eTable. (Continued) Emerging Therapies in Myelodysplastic Syndromes^a

Drug Classes and Drugs	Mechanism of Action	Identifier
Miscellaneous (Continued)		
Veliparib (ABT-888)	PARP-1/2 inhibitor	NCT03289910
Imetelstat (JNJ-63935937)	Competitive enzyme inhibitor of telomerase	NCT02598661
Nandrolone decanoate	Androgen therapy for telomeropathies	NCT02055456

Note: The trials in this table include those identified on the clinicaltrials.gov website on September 27, 2017, with the search term “myelodysplastic syndrome”; the search was restricted to “Open” trials. Agents have been included if the study in which they were being tested was in either “Recruiting” or “Not Yet Recruiting” status and excluded if the study was “Completed,” “Unknown,” or “Terminated.” Agents also have been included if they were not already approved by the US Food and Drug Administration for myelodysplastic syndromes (lenalidomide, azacitidine, and decitabine), for acute myeloid leukemia, or for an iron chelation indication. Excluded agents are those for stem cell transplant conditioning, cellular product manipulation, and graft-versus-host disease prevention or treatment.

ATRA, all-trans-retinoic acid; AURKB, Aurora B kinase; BET, bromodomain and extraterminal; BTK, Bruton tyrosine kinase; CAR, chimeric antigen receptor; CDK9, cyclin-dependent kinase 9; CHK1, checkpoint kinase 1; CSF1R, colony-stimulating factor 1 receptor; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; CXCR4, C-X-C chemokine receptor type 4; EPO, erythropoietin; ERK, extracellular signal-regulated protein; FLT3, Fms-like tyrosine kinase 3; GDF, growth and differentiation factor; GTP, guanosine triphosphate; HSA, human serum albumin; HIF, hypoxia-inducible factor; Hsp90, heat shock protein 90; IDH, isocitrate dehydrogenase; IFN, interferon; IGF-1, insulin-like growth factor 1; IgG, immunoglobulin G; IL, interleukin; IL3RA, interleukin 3 receptor subunit alpha; JAK, Janus-associated kinase; KIRs, killer cell immunoglobulin-like receptors; LSD1, lysine-specific histone demethylase 1; MAPK, mitogen-activated protein; MELK, maternal embryonic leucine zipper kinase; mTOR, mammalian target of rapamycin; NIS, sodium iodide symporter; NK, natural killer; PARP, poly(ADP-ribose) polymerase; PD-1, programmed death 1; PD-L1, programmed death 1–ligand 1; PDGFR, platelet-derived growth factor receptor; PEG, polyethylene glycol; PI3K, phosphoinositide-3 kinase; PLK4, polo-like kinase 4; sEphB4, soluble extracellular domain of EphB4; SINE, selective inhibitor of nuclear export; TGFBR1, transforming growth factor beta receptor 1; TIM-3, T-cell immunoglobulin and mucin domain-containing protein 3; TPO, thrombopoietin; VEGFR, vascular endothelial growth factor receptor.

^a Updated and based in part on Bejar R, Steensma DP. Recent developments in myelodysplastic syndromes. *Blood*. 2014;124(18):2793-2803.