An Agenda to Advance Research in Myelodysplastic Syndromes: A TOP 10 Priority List From the First International Workshop in MDS

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Myelodysplastic syndromes (MDS) are neoplasms with high molecular, biological, and clinical heterogeneity.1,2 Consequently, conducting basic, translational, and clinical research on MDS has historically been challenging and the field has lagged behind in terms of achieving significant therapeutic advances.

To advance research in MDS and translate those advances into clinical benefits for patients, the first international workshop for MDS (iwMDS) was conducted in Miami, Florida. Workshop participants represented a wide variety of international stakeholders in MDS across multiple disciplines. The workshop participants concluded that there is an overarching need for international and interdisciplinary collaboration and the coordination of research efforts. Here, we outline 10 critical areas that would benefit from broad collaborations (Table 1) and propose some concrete steps for future efforts (Table 2).
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Table 1. Top 10 list of MDS collaborative priority research goals

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<th>Action steps</th>
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<td>- Development of new frontline treatment of MDS: Several large, randomized trials, including azacitidine in combination with the BCL-2 inhibitor venetoclax, the anti CD47 antibody magrolimab and the anti TIM3 antibody sabatolimab are ongoing</td>
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<td>2. To develop better treatment options for DNA methyltransferase inhibitor (DNMTi)-refractory MDS</td>
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<td>3. To develop effective strategies for TP53-mutated MDS</td>
<td>- Develop trials with broad inclusion of both TP53 mutated MDS and AML</td>
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<td>4. To advance novel treatment strategies to impact the underlying pathophysiology of lower-risk MDS</td>
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<td>5. To conduct clinical trials in a collaborative international effort with emphasis on equal access and on PROs</td>
<td>- Utilize platform-based approaches to conduct multiple randomized phase II trials to establish a promising approach for phase III testing early (eg, NCI myeloMATCH)</td>
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<td>6. To formulate unified diagnostic criteria and classification subgroups for MDS</td>
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<td>7. To establish and systematically validate clinically meaningful response criteria for MDS therapy</td>
<td>- One promising area of investigation is targeting immune dysregulation in MDS clones and the BM microenvironment (eg, targeting IRAK1/4 and/or the NLRP3 inflamasome)</td>
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<td>8. To establish tools to predict, and ultimately reduce, risk of progression of CH to MDS and other hematological malignancies in clinical practice</td>
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Table 2. Potential steps to achieve MDS priority research goals

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DNA methyltransferase inhibitor (DNMTi) monotherapy remains the standard of care therapy for higher-risk MDS.2 Despite the established role of DNMTi therapeutics in MDS, several trials and real-world registry analyses have failed to replicate the survival benefit initially described with azacitidine in the AZA-001 trial.4,5 To improve outcomes, multiple clinical trials have tested azacitidine (or DNMTi backbone) combination therapy approaches, but to date, none have improved overall survival (OS) compared with azacitidine monotherapy.6-8 Hence, establishing a DNMTi backbone combination therapy for the frontline treatment of MDS is the top priority that has been identified by the faculty.

To develop better treatment options for DNMTi-refractory MDS

Outcomes for patients with DNMTi resistance are unfortunately dismal, with a median survival of <6 months and a 2-year survival probability of only 15% for patients with higher-risk MDS.9 Outcomes for lower-risk patients with DNMTi resistance are also poor with a median survival of 17 months.10 There is currently no standard
To develop effective strategies for TP53-mutated MDS

TP53 alterations (deletions and mutations) are associated with extremely poor prognosis, with lower response to all established therapies, higher rates of progression to AML, and significantly shortened OS.11 Even with allogeneic stem cell transplant outcomes remain poor.12 Hence, international efforts should be focused on dedicated trials for this patient population as a holistic platform to also include TP53-mutated AML, which shares similar features with TP53-mutated MDS.13 During the iwMDS, the NCI myeloMATCH program was presented which will include a multiam phase II trial platform entirely dedicated to patients with TP53 mutated MDS. Working groups developing directed algorithms for all TP53-mutated myeloid neoplasms should be considered given the dismal outcome for these disorders irrespective of blast percentage.13

To advance novel treatment strategies to impact the underlying pathophysiology of lower-risk MDS

In lower-risk MDS, the goal of treatment is to improve cytopenia, most commonly anemia. The standard of care remains supportive treatment with red blood cell transfusions, erythropoiesis-stimulating agents, luspatercept, lenalidomide for certain subtypes of LR-MDS, and DNMTis. However, “lower-risk” MDS is a misconception: while temporary benefit can be derived, these approaches do not have a significant disease-modifying effect, and therefore responses are of limited durability.10 Future efforts should focus on attempting to reverse the underlying pathophysiology of MDS.14,15

To conduct clinical trials in a collaborative international effort with emphasis on equal access and on patient-reported outcomes (PROs)

Clinical trials should be conducted jointly in different countries to achieve rapid study completion. Trials should also promote health care equity for patients with MDS and focus on the inclusion of PROs. Collaboration among research groups worldwide will facilitate these research goals. In addition, the focus should be on optimizing the inclusivity of patients concerning eligibility criteria to encompass the older population of patients (eg, limited eligibility due to creatinine and/or cardiac functions) that are currently frequently excluded, thereby hampering the investigation (and enrollment) of the population most afflicted with MDS.

To formulate unified diagnostic criteria for MDS

Recently the World Health Organization and the International Consensus Classification of myeloid neoplasms have published separate diagnostic criteria for AML and MDS.16,17 Several important differences between the 2 classifications exist, especially in how patients with 10% to 19% blasts are classified.18 There is a significant concern that having 2 separate classification systems could have a negative impact on clinical care and research and have the potential to create confusion among patients and providers, as well as in the design, conduct, and interpretation of clinical trials. The need to establish a unified consensus classification for MDS has been emphasized.

To establish and systematically validate clinically meaningful response criteria for MDS therapy

The current response MDS criteria suffer from significant limitations.19,20 First, there is a clear inconsistency in how complete remission (CR) is defined for MDS based on the International Working Group 200620 compared with the definition of CR for AML in the ELN 201721 and ELN 202222 criteria. While no hemoglobin threshold is used for CR in AML, for MDS, CR requires a hemoglobin value ≥11 g/Dl, which has not been validated. These differences in CR definition can lead to different outcomes depending on which definition is used.23 There is a need to develop and validate new response criteria for higher-risk MDS that capture meaningful clinical benefits, similar to the introduction of CR with partial hematological recovery in ELN 2022 AML criteria.24,25 Conversely, the elimination of responses with doubtful clinical benefits (eg, marrow CR without meaningful count recovery) should be considered.26

To establish tools to predict, and ultimately reduce, risk of progression of clonal hematopoiesis (CH) to MDS and other hematological malignancies in clinical practice

The advent and widespread availability of next generation sequencing has led to the discovery of CH, which, in some cases, is associated with higher risks of cardiovascular disease27 and hematologic malignancies.28-30 Therefore, early intervention should be monitored and considered, especially among patients with solid tumors where high-risk CH clones can dramatically expand under the selective pressure of chemotherapy, increasing the risk of subsequent therapy-related myeloid neoplasms. We need to learn more about the genotypic and phenotypic characteristics of CH evolution to accurately predict which patients with CH will develop MDS and other blood cancers. Ultimately, the goal is to develop effective secondary preventive/therapeutic strategies that reduce the risk of aggressive hematologic malignancies and/or other CH-related diseases in patients with higher-risk CH lesions. The identification of CH before exposure to intensive chemotherapy or radiation therapy is not frequently covered by insurance companies, which is a barrier to obtaining adequate informed consent and poses risks to patients when deciding to embark on potentially toxic therapies. Lastly, how best to identify and classify patients with a germ line predisposition to develop myeloid malignancies such as MDS and AML will be a significant future focus of genetic counseling and risk prevention efforts.31
To establish linked clinical databases and biobanks allowing sharing of data

Several large MDS registries have recently been developed to better understand the natural history of MDS and to establish large biorepositories. The global MDS community should establish a common minimum data set to enable data sharing across platforms. Achieving international alignment is essential for identifying and characterizing risk factors, clinical outcomes, and particularly drug responsiveness for subgroups of this rare disease, which are likely to be increasingly subdivided into more defined molecular subtypes.

To improve the development and dissemination of reliable preclinical models of MDS

Comprehensive in vivo preclinical studies of MDS have historically suffered from the limited ability of MDS stem cells to engraft in immunodeficient murine hosts. Recently, a patient-derived xenotransplantation model in cytokine-humanized immunodeficient "MISTRG" mice has been established, allowing disease modeling across MDS subtypes. A broader availability of improved preclinical models and wider dissemination of these resources to laboratories around the world is critical to maximize the efficient evaluation of novel drugs and therapeutics in MDS.

We conclude that, given that MDS are rare and biologically heterogeneous blood cancers, there is an overarching dire need for international and interdisciplinary collaboration and coordination of research efforts. What became clear from this first international workshop meeting was the necessity for the frequent continued exchange of ideas in a smaller informal setting that is more conducive to the creation of new collaborative efforts.

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Contribution: M.S. and A.M.Z wrote the initial draft of the manuscript; M.S., A.M.Z., R.B., M.A.S., D.P.S., U.P., S.L., A.H.W., and V.S. were involved with the conception and design of the study; and all authors were involved in writing, reviewing, and editing the manuscript, and approved the final version for submission.

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Jazz Pharmaceuticals. M.M.P. received research funding from Kura Oncology and StemLine Pharmaceuticals. A.M.B. received consulting or advisory board honoraria from Novartis, Acceleron, Agios, AbbVie, Takeda, Celgene/Bristol Myers Squibb, Keros Therapeutics, Taiho, and Gilead, and has research support from NIH SPORE in Myeloid Malignancies and the Edward P. Evans Foundation. E.P. receives research funding from Incyte and Bristol Myers Squibb, and honoraria from Stemline, Taiho, Blueprint, and Bristol Myers Squibb. T.K.K. received research funding from Nextcure and is a consultant for the Agensu. R.S.K. served on the speaker bureau of Jazz Pharmaceuticals, Servio, CTI, and PharmEssentia, and served on advisory boards and received honoraria from Bristol Myers Squibb, Novartis, AbbVie, Jazz Pharmaceuticals, Servio, PharmEssentia, Taiho, Geron, and CTI. M.S.A. has served on advisory boards for Bristol Myers Squibb, Novartis, Kurome, and Gilead. R.B. is employed by and has equity in Aptose Biosciences, and serves on independent drug monitoring committees for Gilead and Epizyme. R.P.H. has a consultancy agreement with Bluebird Bio. G.J.R. has a consultancy agreement and/or serves on the advisory board or data and safety monitoring committee for AbbVie, Amgen, Astellas, AstraZeneca, Bristol Myers Squibb, Blueprint Medicines, Bluebird Bio, Celgene, Glaxo SmithKline, Janssen, Jasper Therapeutics, Jazz Pharmaceuticals, Mesoblast, Novartis, Pfizer, Syndax, and Takeda, and received research support from Janssen. S.H. received honoraria from Forma Therapeutics. A.H.W. has served on advisory boards for Novartis, AstraZeneca, Astellas, Janssen, Amgen, Roche, Pfizer, AbbVie, Servier, Gilead, Bristol Myers Squibb, Shoreline, Macrogenics, and Agios; receives research funding (to institution) from Novartis, AbbVie, Servier, Janssen, Bristol Myers Squibb, Syndax, Astex, AstraZeneca, and Amgen; serves on speakers’ bureaus for AbbVie, Novartis, Bristol Myers Squibb, Servier, and Astellas; is an employee of the Walter and Eliza Hall Institute (WEHI); and is eligible for financial benefits associated with payments that WEHI receives in relation to venetoclax. A.F.L. is employed by and has equity in Precision Biosciences, and has served as a consultant for Halia Therapeutics, CTI Biopharma, and Aileron. M.X. participated in advisory boards and/or had a consultancy agreement with and received honoraria from Seattle Genetics, Pure Marrow and Blueprint Medicines. N.G.D. has received research funding from Daiichi-Sankyo, Bristol Myers Squibb, Pfizer, Gilead, Sevier, Genentech, Astellas, Daichi-Sankyo, AbbVie, Hanmi, Trovagene, Fate Therapeutics, Amgen, Novimmune, Glycomimetics, Trillium, and ImmunoGen, and has served in a consulting or advisory role for Daiichi-Sankyo, Bristol Myers Squibb, Aroa, Pfizer, Novartis, Jazz, Celgene, AbbVie, Astellas, Genentech, ImmunoGen, Servier, Syndax, Trillium, Gilead, Amgen, Shattuck Labs, and Agios. S.L. received research support from Astellas and Amgen; owns stock from AbbVie; and has received consultancy fees/honoraria from AbbVie, Gerson Lehrman Group, QualWorld, and Guidepoint. E.A.G. received honoraria from AbbVie, Alexion Pharmaceuticals, Genentech, Novartis, CTI Biopharma, Apellis, Celgene/Bristol Myers Squibb, Takeda Oncology, Taiho Oncology, Physician Educational Resource, MediCom Worldwide, American Society of Hematology, Picnic Health, and AAMDSIF, and research support (institutional) from Astex Pharmaceuticals, Genentech, Blueprint Medicine, Alexion Pharmaceuticals, Apellis, Bristol Myers Squibb/Celgene, and Celldex Therapeutics. M.R.S. serves on a board or advisory committee for AbbVie, Bristol Myers Squibb, CTI, Forma, Geron, Kar-yopharm, Novartis, Ryyu, Sierra Oncology, Taiho, Takeda, and TG Therapeutics; receives research funding from ALX Oncology, Astex, Incyte, Takeda, and TG Therapeutics; and has equity ownership in Karyopharm and Ryvu. O.A.W. has served as a consultant for H3B Biomedicine, Foundation Medicine Inc., Merck, Prelude Therapeutics, and Janssen; is on the scientific advisory board of Envisagenics Inc., AlChem, Harmonic Discovery Inc., and Pfizer Boulder; and has received prior research funding from H3B Biomedicine and LOXO Oncology, unrelated to the manuscript. The remaining authors declare no competing financial interests.

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**References**


