ABOUT THE AUTHOR

Mohamed Elemary, MD
Dr Mohamed Elemary is a hematologist and the Director of the Stem Cell Transplant Program at the Saskatoon Cancer Centre. He is also a Professor at the College of Medicine and an Adjunct Professor at the College of Graduate Studies and Research, University of Saskatchewan. Dr Elemary graduated from the School of Medicine, Cairo University in 1993 and completed his residency training in internal medicine followed by a residency in hematology and a fellowship in bone marrow transplant at Princess Margaret Hospital in Toronto. He joined the Saskatoon Cancer Centre in 2010. His main interest is in the treatment of malignant hematology, mainly leukemia, MDS, multiple myeloma, and lymphoma in addition to stem cell transplant. He has more than 60 publications in peer-reviewed journals, conference abstracts, and has also authored numerous book chapters.

The evolving treatment landscape of higher-risk MDS

Introduction
Myelodysplastic neoplasms (MDS) are a group of clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis, cytopenia, and morphologic dysplasia.[1] Most cases of MDS are de novo, and a minority are post cytotoxic therapy About 30% of the cases will eventually progress to acute myeloid leukemia (AML), with a higher incidence among the higher-risk MDS group. MDS is a rare disorder with an overall incidence of 3.7-4.8/100,000; the rate increases with age.[2,3]

Diagnosis and risk stratification
Bone marrow examination is needed to confirm the diagnosis of MDS after exclusion of other causes of cytopenia and morphological changes. Cytogenetics and molecular genetics are used to refine the diagnosis and risk stratification, which affects the management plan.[4]

Different risk stratification approaches can be used for MDS patients. The most commonly used is the International Prognostic Scoring System (IPSS), which uses three variables—blast percentages, cytogenetics, and the number of cytopenia—to define 4 risk categories—low, intermediate 1, intermediate 2, and high risk.[5] **(Tables 1 & 2)** The Revised International Prognostic Scoring System (IPSS-R) also considers degree of cytopenia in addition to blast percentages and cytogenetics, creating 5 risk categories: very low, low, intermediate, high, and very high.[6] **(Tables 3 & 4)**

Patients may be divided into lower-risk MDS (low and intermediate 1 on the IPSS and up to 3.5 in score on the IPSS-R) and higher-risk MDS (intermediate 2 and high on the IPSS or above 3.5 on the IPSS-R).

Molecular International Prognostic Scoring System (IPSS-M): Given the widespread availability of next-generation sequencing (NGS) as a diagnostic tool, researchers have investigated the utility of somatic gene mutations for risk stratification of MDS.[7] Diagnostic samples from 2,957 patients with less than 20% blasts and a white blood cell count below 13 X 10^9/L were profiled for mutations in 152 driver genes (discovery cohort). This was validated in an independent external cohort of 754 Japanese patients.

Candidate target risk variables included hematologic parameters (blood counts and blasts), cytogenetics, IPSS-R category, and both the type and number of mutations in 31 genes, resulting in 6 risk categories: very low, low, moderate-low, moderate-high, high and very high. The IPSS-M model improved prognostic discrimination across all clinical end points, restratifying 46% of patients as compared to the IPSS-R risk categories.[7]

Current and novel therapies
Goals of therapy: The goals of therapy for higher-risk MDS include altering the disease's natural history by delaying transformation to acute myeloid leukemia and prolongation of overall survival.[8]

Patients are usually divided into non-transplant candidates or transplant candidates based on several factors, including age, performance status, and co-morbidities, which are

	Score				
	0	0.5	1	1.5	2.0
Medullary blasts, %	0-4	5-10	-	11-20	21-29
Number of cytopenias*	0-1	2-3	-	-	-
Cytogenetic risk group†	Low	Intermediate	High	-	-

Table 1: *International Prognostic Scoring System (IPSS)[5]*
*† Low risk = normal karyotype, 5q,-20q -Y; intermediate risk = all other aberrations; High risk = complex karyotype (≥3 anomalies), chromosome 7 anomalies. * Platelets <100 000/μL; hemoglobin <10 g/dL, absolute neutrophil count <1 800/μL.*

Score	Risk Groups
0	Low risk
0.5-1	Intermediate risk 1
1.5-2	Intermediate risk 2
≥2.5	High risk

Table 2*: IPSS prognostic risk categories[5]*

	Score						
	0	0.5	1	1.5	2	3	4
Cytogenic group*	Very good	-	Good	-	Intermediate	Poor	Very Poor
Medullary blasts, %	≤2	-	>2 to <5	-	5-10	>10	-
Hemoglobin	≥10	-	8 to <10	<8	-	-	-
Platelets	≥100	50 to <100	<50	-	-	-	-
ANC	≥0.8	<0.8	-	-	-	-	-

Table 3: *Revised International Prognostic Scoring System (IPSS-R)[6]*
*ANC, absoulte neutrophil count. * Very good = del(11q), -Y;good = normal karyotype, del(20q), del(5q), del(12p), double including del(5q); intermediate = +8, del(7q), i(17q), +19, any other single or double independent clone, poor = -7 inv(3)/t(3q), double including -7/del(7q), complex: abnormalities; very poor = complex >3 abnormalitites.*

Score	Risk Groups	Median Survival, y	Median time to 25% evolution, y
0-1.5	Very low risk	8.8	Not reached
1.5-3	Low	5.3	10.8
>3-4.5	Intermediate	3.0	3.2
4.5-6	High	1.6	1.4
>6	Very High	0.8	0.73

Table 4: *IPSS-R prognostic risk categories[6]*

usually determined by individual institutional' policy. Treatments for non-transplant candidates usually involve hypomethylating agents (HMA) until disease progression or intolerance. For transplant candidate patients, hypomethylating agents are usually used as a bridge to allogeneic stem cell transplant.[9]

otherwise rapidly degrades decitabine in the gut and liver. A fixed-dose combination (oral tablet cedazuridine 100mg and decitabine 35mg) was used in the phase 3 ASCERTAIN trial for patients with higher-risk MDS, CMML and AML 20-30% blasts.[12] Patients were randomized to receive oral decitabine versus intravenous decitabine. The primary end point of this trial was mean

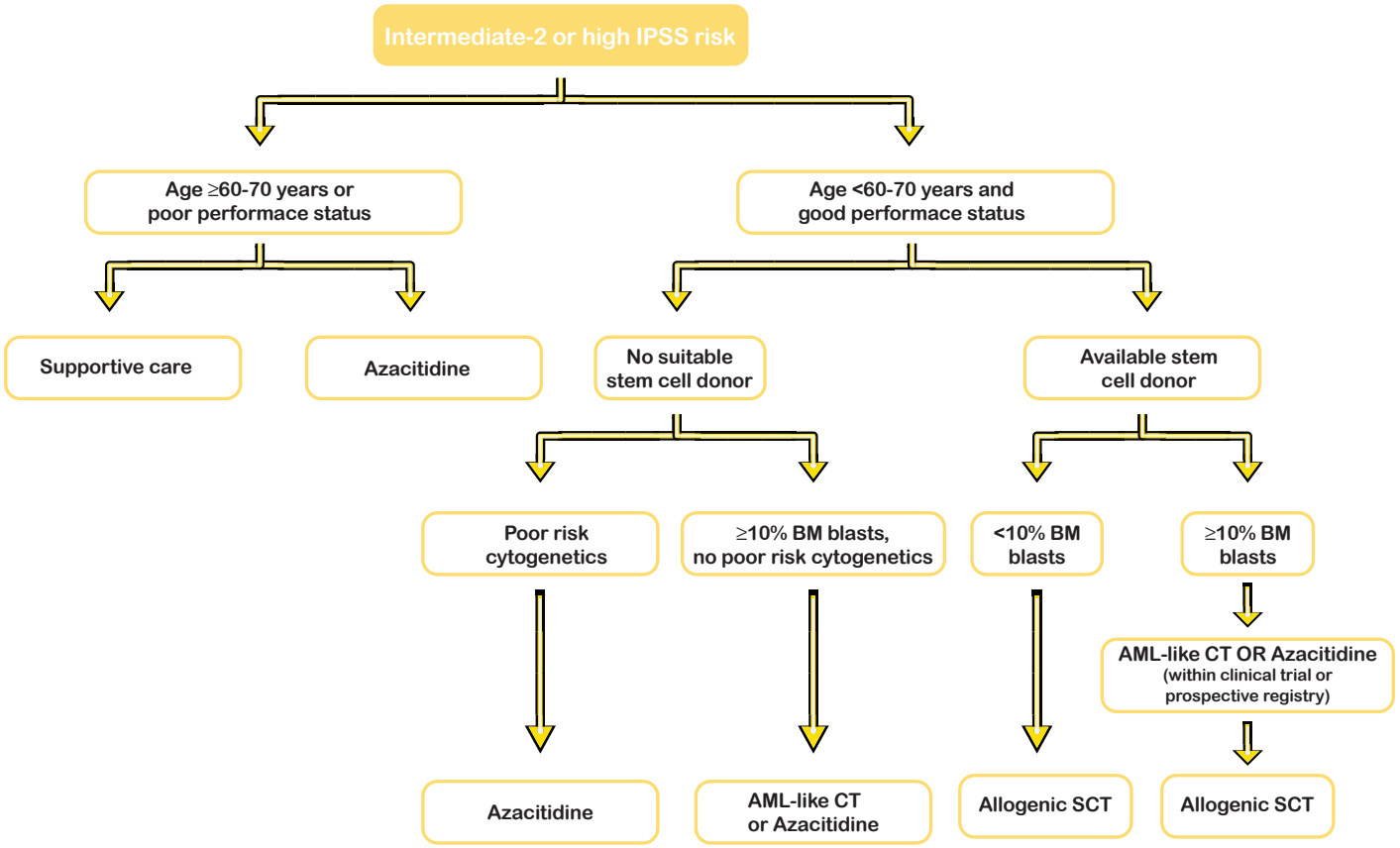

Figure 1. *Therapeutic algorithm for adult patients with primary MDS and intermediate-2 or high IPSS score. CT, chemotherapy; Adapted from Malcovati et al.*[10]

Available options for treatment

Azacitidine is currently the standard of care for higher-risk MDS and is used as monotherapy at the standard dose of 75 mg/m^2 daily for 7 days every 4 weeks until disease progression or intolerance. The AZA-001 phase 3 trial compared azacitidine to conventional care regimens, including intensive chemotherapy, low dose cytarabine, and best supportive care.[11] The study showed that azacitidine significantly improved outcomes versus conventional care regimens, with an overall response rate (ORR) of 29% and a complete response (CR) rate of 17%, as compared to 12% and 8% respectively in the conventional care group. After a median follow-up of 21.1 months, median overall survival was 24.5 months for the azacitidine group versus 15.0 months for the conventional care group (hazard ratio 0.58; 95% CI 0.43-0.77; stratified log-rank p=0.0001).[11]

Oral decitabine (Cedazuridine/Decitabine): When given in combination, cedazuridine enables the efficient oral bioavailability of decitabine. Cedazuridine is a novel, potent and safe inhibitor of cytidine deaminase, which

decitabine systemic exposure of oral/IV 5-day area under curve from time 0 to last measurable concentration. The trial demonstrated that oral cedazuridine/decitabine (100/35 mg) produced a similar systemic decitabine exposure, DNA demethylation, and safety vs decitabine 20 mg/m^2 IV in the first 2 cycles, with similar efficacy. Results also showed an objective response rate of 64% (65 patients), with CR or marrow CR (mCR) with hematological improvement in 26% of patients.[12]

Intensive chemotherapy: Intensive chemotherapy is a reasonable option for younger patients without unfavorable cytogenetics. It can yield a high complete response rate of 45 to 60%.[13,14]

Induction chemotherapy versus HMA in specific patients with higher-risk MDS: In a retrospective study, patients with higher-risk MDS and nucleophosmin (*NPM1*) mutations with more than 10 blasts treated with chemotherapy had higher complete response rates (90% vs 28%, P = .004), longer median progression-free survival

(not reached vs 7.5 months, P = .023), and overall survival (not reached vs 16 months, P = .047) as compared with patients receiving HMA or lenalidomide.[15] According to the new 2022 WHO classification, those patients are now considered acute myeloid leukemia cases.[16]

Allogeneic hematopoietic stem cell transplant (HSCT) is the only curative approach for higher-risk MDS. A patient's disease risk can be considered based on the IPSS or IPSS-R and the presence of underlying comorbidities may be graded according to the HCT Comorbidity Index (HCT-CI) which will help determine HSCT eligibility. Generally speaking, fit patients within higher-risk categories and those with lower-risk, with profound cytopenias, or high transfusion burden are candidates for HSCT. A retrospective analysis compared reduced-intensity SCT to HMA or best supportive care in patients aged 50-75 with intermediate 2 or high-risk de novo MDS.[17] The cohort was divided based on the availability of a matched donor within 90 days of study registration. The donor arm showed significant improvement versus the no-donor arm, with leukemia-free survival of 35.8% vs 20.6% and overall survival rate of 47.9% vs 26.6% at 3 years.[17]

Allogeneic stem cell transplant outcomes are affected by genetic mutations as well as the patient's risk profile. For example, research has demonstrated that *TP53* mutations confer poor outcomes in the range of 15-20% survival rates, even with HSCT.[18]

Investigational therapies

Different targeted therapies are emerging for the treatment of MDS.

1- *Venetoclax plus Azacitidine:* Abnormal overexpression of BCL-2 has been found in patients with higher-risk MDS. Venetoclax is a highly selective, orally bioavailable small-molecule BCL-2 inhibitor. Azacitidine treatment indirectly increases sensitivity to BCL-2 inhibition in higher-risk MDS by modifying the relative levels of BCL-2 family members, thus increasing sensitivity to BCL-2 inhibition by Venetoclax.[19]

A phase 1b dose escalation study of venetoclax plus azacitidine in treatment-naïve patients with higher-risk MDS showed a combined CR and mCR rate of 77%, with a median time to mCR of 0.9 months and a median time to CR of 2.6 months.[20] In addition, molecular responses were noted in patients who achieved CR or marrow CR. Venetoclax was used only for 14 days in addition to the standard doses of azacitidine until disease progression or intolerance.[20]

The phase 3 VERONA trial, a randomized, double-blind, phase 3 study of patients with treatment-naïve HR-MDS, comparing venetoclax plus azacitidine to azacitidine alone is currently ongoing.[21]

In July 2021, the FDA granted breakthrough therapy designation to the combination of venetoclax plus azacitidine as a potential systemic therapy for patients with treatment-naive higher-risk MDS.

2- *Magrolimab plus Azacitidine:* Magrolimab is a first-in-class anti-CD47 macrophage immune checkpoint inhibitor that promotes tumor cell elimination via phagocytosis. It has been observed to have synergistic effects in combination with azacitidine both in vitro and in-vivo.[22]

A phase 1b study showed an overall response rate to magrolimab plus azacytidine of 91% with a CR rate of 42%, with high response in patients with MDS and TP53 mutations, with an overall response rate of 75% and a CR rate of 42%.[23]

3- *Pevonedistat plus Azacitidine:* Pevonedistat is a first-in-class, selective inhibitor of NEDD8-activating enzyme, that causes cancer cell death by disrupting protein homeostasis. The phase 3 PANTHER trial randomized patients with higher-risk MDS, CMML or AML with 20-30% blasts to receive upfront treatment with a combination of pevonedistat plus azacitidine versus azacitidine alone. This trial did not meet the primary endpoint of event-free survival; however, in a post-hoc analysis, median overall survival(OS) for patients receiving >3 cycles was 23.8 vs 20.6 months (P = 0.021) and for >6 cycles was 27.1 vs 22.5 months (P = 0.008).[24]

4- *Sabatolimab plus Azacitidine:* Sabatolimab is a humanized IgG4 antibody targeting T-cell immunoglobulin and mucin domain-3 (TIM-3), a co-inhibitory receptor involved in regulating adaptive and innate immune responses. TIM-3 is highly expressed on immune cells in MDS and leukemic blasts and not on healthy cells. The combination with azacitidine showed promising antileukemic activity with an overall response rate of 64.7% and combined CR and mCR of 41.2%.[25]

Sabatolimab showed a high and durable response in patients with TP53, with an overall response rate of 71.4% and a median duration of response of 21.5 months.[26]

This combination received FDA Fast Track designation for the treatment of high-risk MDS in May of 2021.

5- *CPX-351 as first-line treatment for higher-risk MDS:* CPX-351 is a liposomal formulation of daunorubicin and cytarabine at a fixed 1:5 ratio that has shown synergistic activity, preferential uptake by leukemic cells, and prolonged delivery with a longer half-life than traditional chemotherapy. The Groupe Francophone des Myélodysplasies (GFM) carried out a phase 2 trial of CPX-351 in higher-risk MDS patients. Treatment included an induction phase and up to 4 cycles of consolidation with the option of allogeneic stem cell transplant after 1-4 cycles. The study included 31 patients; overall response

rate was 87% with a combined CR/Cri of 65% and mCR rate of 28%. Twenty-two patients (94%) proceeded to allogeneic stem cell transplants.[27]

Approaches to MDS patients who failed HMA: Patients who fail or relapse post-azacitidine therapy have a very poor prognosis, with median overall survival from a few months up to 1 year. Allogeneic stem cell transplant patients post HMA failure has a better median overall survival than other conventional or investigational therapies.[28]

There is no widely agreed upon standard of care for most patients who fail HMA therapy. However, newer targeted therapies for patients with certain genetic mutations, such as *IDH-1/2, BCL-2, CD47, NPM1, TP53, or FLT3*, may provide benefit.

Conclusions

MDS continues to pose a diagnostic and therapeutic challenge. Risk stratification for better assessment of prognosis and to guide therapy is essential and should be performed at diagnosis. Hypomethylating agents continue to represent first-line therapy for higher-risk MDS patients. Several ongoing frontline trials exploring combination therapies suggest synergies with HMA. There is no consensus approach to the management of patients who relapse or have refractory higher-risk MDS after HMA failure; however, several novel agents are being investigated. Participation in clinical trials is highly encouraged for higher-risk MDS patients.

References:

1. *Khoury J.D., Solary E., Abla O, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia 2022; 36, 1703–1719*
2. *Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2016, National Cancer Institute. Based on November 2018 SEER data submission, posted to the SEER web site, April 2019.*
3. *Zeidan AM, Shallis R, Wang R, et al. Blood Rev. 2019;34:1-15.*
4. *Valent P, Orazi A, Steensma D, et al. Oncotarget. 2017 Sep 26; 8 (43): 73483-73500.*
5. *Greenberg P, Cox C, LeBeau M et al. International Scoring System for evaluating prognosis in myelodysplastic syndromes. Blood 1997;89:2079-2088.*
6. *Greenberg P, Tuechler H, Schanz J et al. Revised International Prognostic Scoring System for Myelodysplastic Syndromes. Blood 2012;120 9120 (12):2454; 2465.*
7. *Bernard E, Tuechler H, Greenberg PL, et al. Molecular International Prognosis Scoring system for myelodysplastic syndromes. Blood. 2021;138 (supplement 1):61.*
8. *Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood. 2006 Jul 15;108(2):419-25.*
9. *Steensma DP. Myelodysplastic syndromes current treatment algorithm 2018. Blood Cancer J. 2018 May 24;8(5):47.*
10. *Malcovati L, Hellström-Lindberg E, Bowen D, Adès L, et al. Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. Blood. 2013 Oct 24;122(17):2943-64.*
11. *Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol. 2009 Mar;10(3):223-32.*
12. *Garcia-Manero G, McCloskey J, Griffiths EA, et al. Pharmacokinetic exposure equivalence and preliminary efficacy and safety from a randomized cross over phase 3 study (ASCERTAIN study) of an oral hypomethylating agent ASTX727 (cedazuridine/decitabine) compared to IV decitabine [ASH abstract 846]. Blood. 2019;134(suppl 1).*
13. *Kantarjian H, O'Brien S, Cortes J, et al. Results of intensive chemotherapy in 998 patients age 65 years or older with acute myeloid leukemia or high-risk myelodysplastic syndrome: predictive prognostic models for outcome. Cancer. 2006 Mar 1;106(5):1090-8.*
14. *Knipp S, Hildebrand B, Kündgen A, et al. Intensive chemotherapy is not recommended for patients aged >60 years who have myelodysplastic syndromes or acute myeloid leukemia with high-risk karyotypes. Cancer. 2007 Jul 15;110(2):345-52.*
15. *Montalban-Bravo, Kanagal-Shamanna R, Sasaki K, et al. NPM1 mutations define a specific subgroup of MDS and MDS/MPN patients with favorable outcomes with intensive chemotherapy. Blood Adv. 2019; 3 (6): 922–933.*
16. *Khoury, J.D., Solary, E., Abla, O. et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia. 2022; 36, 1703–1719*
17. *Nakamura R, Saber W, Martens M, et al. A Multi-Center Biologic Assignment Trial Comparing Reduced Intensity Allogeneic Hematopoietic Cell Transplantation to Hypomethylating Therapy or Best Supportive Care in Patients Aged 50-75 with Advanced Myelodysplastic Syndrome: Blood and Marrow Transplant Clinical Trials Network Study 1102. Blood. 2020; 136 (Supplement 1):75; 19-21.*
18. *Lindsley R, Saber W, Mar B et al. Prognostic Mutations in Myelodysplastic Syndrome after Stem Cell Transplantation. N Engl J Med. 2017; 376:536-547.*
19. *Stomper, J., Rotondo, J.C., Greve, G. et al. Hypomethylating agents (HMA) for the treatment of acute myeloid leukemia and myelodysplastic syndromes: mechanisms of resistance and novel HMA-based therapies. Leukemia 2021; 35, 1873-1889.*
20. *Garcia JS, Wei AH, Jacoby MA, et al. Molecular Responses Are Observed across Mutational Spectrum in Treatment-Naïve Higher-Risk Myelodysplastic Syndrome Patients Treated with Venetoclax Plus Azacitidine. Blood 2021; 138 (Supplement 1):241.*
21. *Zeidan AM, Garcia JS, Fenaux P, et al. Phase 3 VERONA study of venetoclax with azacitidine to assess change in complete remission and overall survival in treatment-naïve higher-risk myelodysplastic syndromes. J Clin Oncol. 2021, 39:15 Suppl.*
22. *Feng D et al. Combination treatment with 5F9 and azacitidine enhances phagocytic elimination of acute myeloid leukemia. Blood. 2018;132(Suppl 1):2729.*
23. *Sallman DA, Al Malki M, Asch AS, etal. Tolerability and efficacy of the first-in-class anti-CD47 antibody magrolimab combined with azacitidine in MDS and AML patients: Phase Ib results. J Clin Oncol. 2020;38 (Supplement 15) 7507.*
24. *Sekeres M, Girshova L, Doronin V et al. Pevonedistat (PEV) + Azacitidine (AZA) Versus AZA Alone As First-Line Treatment for Patients with Higher-Risk Myelodysplastic Syndromes (MDS)/Chronic Myelomonocytic Leukemia (CMML) or Acute Myeloid Leukemia (AML) with 20-30% Marrow Blasts: The Randomized Phase 3 PANTHER Trial. Blood. 2021 ; 138 (Supplement 1):242.*
25. *Brunner AM, Esteve J, Porkka K, et al. Efficacy and Safety of Sabatolimab (MBG453) in Combination with Hypomethylating Agents (HMAs) in Patients (Pts) with Very High/High-Risk Myelodysplastic Syndrome (vHR/HR-MDS) and Acute Myeloid Leukemia (AML): Final Analysis from a Phase Ib Study. Blood. 2021; 138 (supplement1):244.*
26. *Garcia-Manero G, Wei A, Porkka K et al. MDS-420: Sabatolimab Plus Hypomethylating Agents (HMAs) in Patients with High-/Very High-risk Myelodysplastic Syndrome (HR/vHR-MDS) and Newly Diagnosed Acute Myeloid Leukemia (ND-AML): Subgroup Analysis of a Phase 1 Study. Clinical Lymphoma, Myeloma and Leukemia. 2021; Volume 21, Supplement 1: S350.*
27. *Peterlin P, Turlure P, Chevallier P, et al. CPX 351 As First Line Treatment in Higher Risk MDS, a Phase II Trial By the GFM. Blood 2021; 138 (Supplement 1): 243.*
28. *Prébet T, Gore SD, Esterni B, et al. Outcome of high-risk myelodysplastic syndrome after azacitidine treatment failure. J Clin Oncol. 2011 Aug 20;29(24):3322-7.*