# About the author

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Rena Buckstein is a clinician investigator at the Odette Cancer Centre, Sunnybrook Health Sciences who specializes in malignant hematology. She is an associate professor in the department of medicine at University of Toronto. She completed her medical school training at Boston University and Internal Medicine/Hematology specialty and subspecialty training in Toronto, followed by a fellowship in lymphoma and high dose therapy at Sunnybrook Hospital. She also completed a diploma in clinical epidemiology. She chaired the hematology site group for 15 years and currently leads the hematology clinical trials program at the Odette Cancer Center. Dr. Buckstein founded and chairs a national registry for myelodysplastic syndromes (MDS-CAN) of more than 1400 patients and is an affiliate scientist of Sunnybrook Research Institute. She is a member of the International MDS Foundation scientific advisory board, the Canadian Cancer Society hematology clinical trials sub-committee, a co-chair of an international MDS Guidelines panel for MDS-RIGHT and has chaired national clinical trials in lymphoma and MDS. She has authored and co-authored 144 publications and holds peer reviewed grants from Canadian Cancer Society Research Institute (CCSRI), Canadian Institute of Health Research (CIHR), Ontario Institute for Cancer Research (OICR), and the Leukemia Lymphoma Society of Canada (LLSC) that fund investigator-initiated research in MDS and lymphoma. She is a recipient of the LLSC/UFCW award for leukemia research in Canada. She enjoys teaching and mentoring undergraduate and graduate students. Her interventional research focuses on novel targeted biologic and immunologic therapies for hematologic malignancies focusing on myelodysplastic syndromes and acute myelogenous leukemia and improving the transfusion experience for MDS patients. Her non-interventional research focuses on documenting QOL longitudinally and its predictors and the impact of patient-related factors like frailty and disability on quality of life, and clinical outcomes independent of disease-related prognostic factors. She collaborates on health services research pertaining to ‘real-life’ experience of approved therapies in MDS and the cost/predictors of health care resource utilization. Currently, she is evaluating the impact of age-related clonal hematopoiesis (ARCH) on chemotherapy outcomes in older adults with lymphoid cancers, the association of specific mutations with occult coronary artery disease in MDS patients.

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# Therapy for myelodysplastic syndromes beyond the front line in 2024 in Canada

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## Introduction

Management of anemia and/or transfusion dependence (TD) after failure of erythropoietic-stimulating agents (ESA) and therapeutic options after hypomethylating agent (HMA) failures remain the biggest challenges for physicians treating lower and higher-risk myelodysplastic syndromes (MDS), respectively. Fortunately, new therapies are available (or soon to be approved), and innovations in prognostic refinement using next-generation sequencing may also facilitate more precision medicine. This review highlights commercially available (or soon to be) options for the amelioration of anemia and transfusion dependence when ESA's fail and the management of higher-risk MDS when hypomethylating agents fail or cease working. While not all of these agents are currently funded or approved in Canada, some are available for off-label access or purchase.

## ESA background

The use of ESAs is the front-line treatment recommended by most guidelines for patients with low transfusion burden and lower endogenous serum erythropoietin (EPO) levels. Response rates vary between 20 to 60%, with median response durations ranging from 12 to 24 months.[1] In a large multinational series comprised of 1,698 patients, primary failure was observed in 34% of patients and 29% of patients experienced secondary failure (after an initial response) of therapy. Primary failure was associated with a higher risk of acute myeloid leukemia (AML) progression at 5 years than secondary failure (13.4% vs. 8.1%; p=0.001), but median survival did not differ between these groups (52.2 vs. 60 months; p=0.12). Prognostic factors after ESA failure were age >75 years, and intermediate revised international prognostic scoring system (IPSS-R) risk score.[2] Recently, evidence has emerged showing that a higher genetic complexity (>3 mutated genes) is a negative prognostic factor for ESA response.[3]

## Second-line options after ESA failure

### *Lenalidomide for del5q MDS*

Lenalidomide is an effective therapy for patients with del5q TD lower-risk MDS who lose response to or are refractory to ESAs **(Table 1)**. In a randomized phase 3 trial comparing placebo with two lenalidomide doses, lenalidomide at a dose of 10 mg daily for 21 out of 28 days was associated with the achievement of red blood cell transfusion independence (RBC-TI) in 56% of patients and had a cytogenetic response rate of 50%. For the lenalidomide groups combined, the 3-year overall survival (OS) and AML risk were 56.5% and 25.1%, respectively. RBC-TI for ≥8 weeks was associated with 47% and 42% reductions in the relative risks of death and AML progression or death, respectively (P = .021 and .048).[4] The median response duration in this study was two years. In a pooled analysis of all lenalidomide trials in patients with del5q and non-del5q MDS, the achievement of RBC-TI was associated with improved OS. In addition to advanced age and lower platelet count, elevated ferritin (>1,600 µg/L) and the transfusion of >6 units/8 weeks were associated with inferior OS.[5] The OS was 23 months following lenalidomide failure with longer survival for patients with relapsed disease or secondary loss of hematologic improvement (HI) (39 months) and in those that subsequently received HMAs (median OS 39 months).[6] The Spanish randomized controlled trial (RCT) SINTRA-REV demonstrated that the initiation of lenalidomide at 5 mg po daily for 24 months before TD significantly delayed time to TD compared with placebo (66 vs. 11.6 months) and achieved high rates of cytogenetic remissions (87.5%).[7] Up to 20% of patients will harbour *TP53* mutations. These patients are less likely

to achieve cytogenetic remissions and have a 5-year cumulative risk for leukemia development of 77% (compared with 24% for those without these mutations). These patients also have lower rates of RBC-TI (50% vs. 75%).[8] If detected, these patients need close surveillance and consideration for HMAs or allogeneic stem cell transplant (ASCT) when responses are lost or not achieved.

### *Lenalidomide for non del5q MDS*

For the 90-95% of patients with lower-risk MDS without del5q, lenalidomide has activity at reversing TI, albeit at greatly reduced rates and duration **(Table 1)**. In addition, there is no anti-clonal activity, as observed in those with del5q. In the MDS-005 study, RBC-TI lasting ≥8 weeks was observed in 27% of the patients treated with lenalidomide. As 90% of patients responded within 16 weeks, drug exposure should not exceed this in non-responders. The median duration of RBC-TI with lenalidomide was 30.9 weeks, and the median OS was 617 days. Higher response rates were observed in patients with lower baseline endogenous erythropoietin ≤500 mU/mL (34.0% vs. 15.5% for >500 mU/mL). The most common treatment-emergent adverse events were neutropenia and thrombocytopenia.[9] Lenalidomide did not adversely affect health-related quality of life (HrQOL), which improved in responding patients.[10] Baseline somatic mutations may predict response since the proportion of patients achieving RBC-TI ≥8 weeks was significantly lower in those with *ASXL1* mutations than in those without (10.3% vs. 31.7%; p=0.031). Furthermore, the proportion of patients achieving RBC-TI ≥8 weeks was nominally higher in those with *DNMT3A* mutations (43.8%), *SF3B1* mutations (42.9%) and *EZH2* mutations (44%).[11]

### *Luspatercept for MDS with ring sideroblasts (RS) or SF3B1 mutations*

Patients with MDS and RS have shorter response durations to ESAs.[12] Luspatercept is a recombinant fusion protein that binds select transforming growth factor β (TGF-β) superfamily ligands to decrease SMAD2 and SMAD3 signalling, thereby enabling erythroid maturation by means of late-stage erythroblast differentiation.[13] Based on promising results from the phase 2 PACE study[14], in particular, in the patients with RS, luspatercept was evaluated in a randomized, double-blind placebo-controlled trial (MEDALIST) in patients who had relapsed or refractory disease or were unsuitable for ESA **(Table 1)**. RBC-TI for ≥ 8 weeks was observed in 38% of patients in the luspatercept group compared with 13% of patients receiving a placebo, and over the course of 48 weeks, 33% (vs. 12% in the placebo group) achieved and maintained RBC-TI for ≥12 weeks. Patients who were more likely to achieve TI were those with a lower transfusion burden (TI 80% vs. 37% with low [<4 units/8weeks] vs. intermediate [4-<6 units/8 weeks]. Luspatercept had a very low (9%) likelihood of response in patients with high transfusion burden (6+ units/8 weeks). Contrary to low response rates to ESA observed when the endogenous EPO level exceeds 200 U/L, luspatercept achieved RBC-TI rates of 40%. Unfortunately, some patients treated with luspatercept still required intermittent RBC transfusions and the median duration of the longest single period of TI was 30.6 weeks (vs. 13.6 weeks in the placebo group). Another lesson from this study was that most patients ultimately required the highest dose of luspatercept (1.75 mg/kg) to achieve or maintain response. In patients with moderate transfusion burden or with EPO levels >200 U/L, it is reasonable to commence luspatercept at 1.33 mg/kg and dose escalate quickly, given the lower expected response rates in these patients.[15] A front-line open-label phase 3b trial of luspatercept at this maximum dose of 1.75 mg/kg is underway (MAXILLUS NCT06045689). In some instances, luspatercept achieved RBC-TI or a meaningful reduction in transfusion burden from baseline that was subsequently lost. In a study from the Moffitt Cancer Center in the US, 5/7 (71%) patients who lost response to luspatercept responded to the addition of ESA (2nd failure), but the response rate was only 17% (3/18) in those with primary failures to luspatercept.[16] Luspatercept in combination with roxadustat (NCT06006949) and lenalidomide (NCT04539236) is being evaluated in prospective clinical trials for patients in whom therapy with ESAs failed.

### *Imetelstat*

Imetelstat, which is not currently available in Canada, is an oligonucleotide that binds the RNA template of human telomerase and acts as a potent competitive inhibitor of enzymatic telomerase activity. By targeting cells with increased telomerase activity, imetelstat selectively induces apoptosis of malignant haematopoietic progenitor cells, facilitating bone marrow recovery and improved erythropoiesis.[17,18] The IMerge study evaluated imetelstat

| Agent | Study | Design | TI | Details |
|---|---|---|---|---|
| Lenalidomide del5q | Phase 3 MDS-003 MDS-004 | Lenalidomide vs. placebo | 56% | • Achieving RBC-TI is associated with improved OS<br>• Median TI duration: 2 years<br>• HMA may be effective after lenalidomide<br>• 10-20% harbor *TP53* mutations: lower responses and duration; worse LFS<br>• Starting before TD associated with improved TFS |
| Lenalidomide non-del5q | Phase 3 MDS-005 | Lenalidomide vs. placebo | 27% | • Not very durable<br>• Myelosuppressive<br>• QoL improved in responding patients<br>• Higher responses with lower baseline EPO levels and non-*ASXL1* mutations |
| Luspatercept | Phase 3 Medalist | Luspatercept vs. placebo | 38% | • Only for MDS-RS who are TD<br>• Response associated with lower transfusion burden, lower EPO levels<br>• Longest period of TI: 31 weeks<br>• Response agnostic to somatic mutations<br>• Highest doses often needed (1.75 mg/kg) |
| Imetelstat | Phase 3 IMerge | Imetelstat vs. placebo | 40% | • Patients enrolled had higher transfusion burden than Medalist<br>• Median duration of TI: 52 weeks<br>• Active with non-RS subtypes and high transfusion burden<br>• Anti-clonal activity appreciated |
| Decitabine-cedazuridine | Phase 3 Ascertain | Oral vs. IV decitabine | 48% | • Comprised 69/133 patients of larger trial including higher risk<br>• Myelosuppressive: neutropenia (59%) and thrombocytopenia (58%)<br>• Median OS and LFS not reached |

**Table 1.** Clinical trials for treatment after ESA failure in lower risk disease. *Courtesy of Rena Buckstein, MD, FRCPC*
**Abbreviations: EPO:** erythropoietin; **ESA:** erythropoietic-stimulating agents; **HMA:** hypomethylating agent; **LFS:** leukemia-free survival; **MDS-RS:** myelodysplastic syndromes ring sideroblasts; **OS:** overall survival; **QoL:** quality of life; **RBC-TI:** red blood cell transfusion independence; **TD:** transfusion dependence; **TFS:** transformation free survival; **TI:** transfusion independence

| Agent | Study | Design | Response or OS | Details |
|---|---|---|---|---|
| Induction CHEMO | Many | | 9-11 months | • As a bridge to transplant |
| Venetoclax | Phase 1-2 | Open-Label | 36% TI; CR 7%;<br>OS: 12.6 months | • As a bridge to transplant<br>• ++ myelosuppressive |
| Ivosidenib | Phase 1 | Open-Label | 83% ORR<br>39% CR<br>OS: 36 months<br>67% TI | • For the 3.6% with *IDH1* mutations<br>• Not funded<br>• Differentiation syndrome and QTc prolongation |
| Enasidenib | Phase 1 | Open-Label | 43% ORR<br>35% CR<br>OS: 20 months<br>30% TI | • For the 5% with IDH2 mutations<br>• Not Funded |

**Table 2.** Clinical trials for therapy after HMA failure. *Courtesy of Rena Buckstein, MD, FRCPC*
**Abbreviations: CR:** complete remission; **HMA:** hypomethylating agents; **ORR:** objective response rate; **OS:** overall survival; **TI:** transfusion independence

versus placebo in a double-blind study (2:1 randomization) including a lower risk TD patient population similar to that of MEDALIST albeit in all World Health Organization (WHO) subtypes of MDS, all EPO levels and in a population that was more heavily TD (median of 6 units/8 weeks) **(Table 1)**. The drug was intravenously (IV) administered as a fixed dose of 7.5 mg/kg every 3 weeks. RS was observed in 62% of patients. An RBC-TI of ≥8 weeks was reached in 40% of patients in the imetelstat group versus 15% of patients in the placebo group. The objective response rate (ORR) was higher in patients with RS (45%) but still quite respectable in MDS patients who were non-RS (32%). In addition, the ORR was quite impressive for patients who were heavily TD, defined as >6 units/8 weeks at 34% and higher in those with 4-6 units/8 weeks (ORR: 45%). The median duration of RBC-TI in the imetelstat group was 51.6 weeks vs. 13 weeks for those receiving placebo. The median increase in blood hemoglobin was 35.5 g/L. Anti-clonal activity was also observed, as supported by the achievement of cytogenetic responses in 35% of patients in the imetelstat arm. In addition, the reduction in variant allele frequency (VAF) of *SF3B1*, *TET2*, *DNMT3A*, and *ASXL1* was numerically greater with imetelstat than placebo and correlated with RBC-TI. Improvements in fatigue were observed faster with imetelstat, and a higher proportion of imetelstat responders showed a sustained, meaningful improvement in fatigue scores compared to non-responders. However, imetelstat was complicated by reversible grade 3-4 thrombocytopenia (62%) and neutropenia (68%). This agent was just granted approval by the US Food and Drug Administration (FDA) and will hopefully undergo Health Canada approval following that.[19]

### *Hypomethylating agents*

Despite the survival benefit observed with HMAs for higher-risk disease, the HMAs azacitidine and decitabine have single-agent activity in lower-risk MDS. In the ASCERTAIN study, 69 of 133 enrolled patients had lower-risk disease (93% Int-1, 7% low). The ORR to oral decitabine-cedazuridine (complete remission [CR], partial remission [PR], or marrow CR+ HI) was 57%, and 48% of patients achieved RBC-TI. This agent was associated with neutropenia (59%) and thrombocytopenia (58%). With approximately 32 months of median follow-up, the median leukemia-free survival (LFS) or OS had not been reached.[20] Subcutaneous azacitidine and IV decitabine for 3 days also have single-agent activity in lower-risk MDS[21], but are less convenient to administer than oral decitabine-cedazuridine, which is pharmacokinetically identical to IV decitabine. In a recent retrospective study from the MD Anderson Cancer Center and the Moffitt Cancer Center, the ORR to HMAs in lower-risk MDS was 36%. The median number of cycles administered was 6 (range 1-64 cycles), and the median response duration was 7 months (range 1-73 months). At the time of HMA failure, the majority (54-77%) of patients continued to have lower-risk disease, as assessed by the IPSS-R and IPSS. The median transformation-free survival and OS were 15 and 17 months, respectively, with no differences observed between the two types of HMAs administered. Patients who remained lower risk at the time of HMA failure had longer OS (3 years). Those who received salvage therapy (compared with best supportive care) also lived longer.[22]

### *Second-line therapy in higher-risk disease*

The median OS of patients with higher-risk MDS treated with HMAs is 17.5 months[23], and median response durations are 9-15 months. Patients who relapse or are refractory to HMAs as front-line therapy have a short survival of 4-6 months[24], and less than a third survive for one year.[25] A post-HMA prognostic model comprised of age, performance status, complex karyotype, marrow blast >20%, platelet count, and RBC-TD, separates MDS patients evaluated after HMA failure into two risk categories: lower-risk with a median OS of 11 months, and higher-risk with a median OS of 4.5 months.[26] HMA resistance can be defined as primary resistance comprised of any of the following: stable disease without any of the following: HI, CR or PR, hypoplastic marrow and pancytopenia or progression to higher-risk MDS or AML after 4-6 cycles. Secondary resistance occurs when, after initial response (CR, PR, or HI), the patient experiences any of the primary resistance scenarios.[27] Revised consensus International Working Group (IWG) response and progression criteria for higher-risk disease should be applied.[28] What are the current treatment options for these patients? Unfortunately, in the absence of ASCT or a clinical trial, treatment options are currently limited.

### *Intensive chemotherapy*

Induction AML-type chemotherapy may be considered in selected patients with good performance status MDS as a bridge to transplant,

which has been shown to result in a median OS of 8.9[24]-10.8 months[29] and an ORR of 41% **(Table 2)**. In patients who progress to AML, CPX-351 may be another treatment option in patients being considered for ASCT[30] and this strategy is being evaluated in the context of clinical trials for patients with higher-risk MDS.

### *Venetoclax*

Following HMA treatment, an increase in BCL-2 and a decrease in MCL-1 levels have been described. Venetoclax may restore responsiveness to HMA-resistant cells **(Table 2)**.[31] In an open-label multicenter study in 44 patients with R/R MDS, venetoclax in escalating doses (100-400 mg x 14 days) was tested in combination with azacitidine at usual doses. The recommended phase 2 dose was determined to be 400 mg po daily x 14 days. In the 37 patients evaluable for response, the CR rate was 7%, and the marrow CR rate was 32%, with a median time to response of 1.2 months and a median duration of response of 8.6 months. Out of those who achieved marrow CR, 43% also achieved HI, with 36% of patients achieving post-baseline TI for RBC and platelets lasting 4.3 months. The median OS was 12.6 months, the median PFS 8.6 months, and 21% of patients were able to proceed to ASCT. Therefore, this is a treatment option for blast count reduction in patients who are candidates for ASCT. This regimen is highly myelosuppressive, with febrile neutropenia observed in 34% and pneumonia in 23% of patients. Furthermore, in 9% of cases, possibly-related deaths occur within 30 days of the last study treatment. In the six patients with *IDH2* mutations in this study, the ORR was 83%.[32] Other studies of this combination are ongoing (NCT04160052).

### *IDH1 and IDH2 inhibitors*

While *IDH* mutations are uncommon in MDS (3.6% *IDH1*, 5% *IDH2*), the FDA has approved the IDH1 inhibitor ivosidenib based on a phase 1 study in 18 adults aged 61-82 with *IDH1*-mutated R/R MDS **(Table 2)**. At a dose of 500 mg po daily, 83% had an objective response, and 39% had a CR after a median of two months of treatment. The median treatment duration was 9.3 months and the OS was 36 months. Among the nine patients who had RBC or platelet TD at baseline, 67% achieved TI. Toxicities may include differentiation syndrome and QTc prolongation.[33] The ongoing GFM IDIOME study confirms the high response rates (50%) in R/R *IDH1*-mutated MDS treated with ivosidenib (n=7/13) and even in EPO-refractory lower-risk disease.[34] Similarly, the IDH2 inhibitor enasidenib is active as a monotherapy in 48% of patients with HMA-refractory MDS with *IDH2* mutations (CR 35%, mCR + HI 13%, RBC-TI 30%) **(Table 2)**.[35] The median OS was 20 months in this study, but was not yet reached in the 8 patients achieving CR or mCR. Ivosedinib, enasidenib, and newer IDH inhibitors are being evaluated in combination with HMAs in the front-line and relapsed setting in numerous clinical trials. There are a plethora of ongoing clinical trials of experimental agents and combinations in R/R MDS combined with AML. Furthermore, chimeric antigen receptor CAR T-cell therapy against myeloid antigens including CD33, CD123, CLL-1, CD70, and TIM-3[36] is under investigation in the R/R scenario.[37]

## Conclusion

Despite almost a decade of stagnation, newer agents for second-line use in both lower and higher-risk MDS are emerging. Clinical trials remain critical for progress to be made and serial next-generation sequencing is of paramount importance to help guide precision therapies, such as luspatercept for *SF3B1*-mutated, lenalidomide in del5q, and ivosidenib and enasidenib in *IDH1* and *IDH2*-mutated disease. Newer erythroid maturation agents are on the horizon, and we await the results of the VERONA study for higher-risk disease that may establish a new standard of care for higher-risk disease.

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