Impact of the Updated CTCAE Version 6.0 on Grading of Cytopenias Associated With Imetelstat in Lower-Risk Myelodysplastic Syndromes

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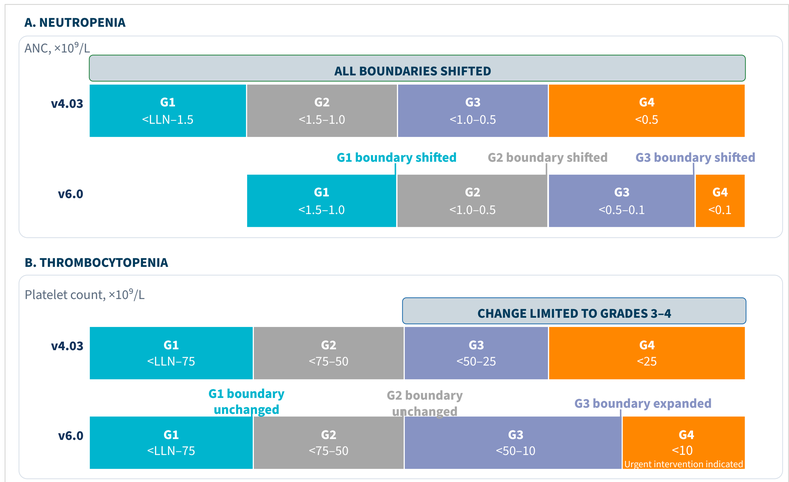
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Introduction

- The Common Terminology Criteria for Adverse Events (CTCAE) v6.0 was released in July 2025 to ensure that adverse event (AE) reporting remains aligned with current practice[1]
  - Key updates to hematologic AE grading criteria included **a general downward shift in grading thresholds**, so that **many laboratory abnormalities are assigned a lower grade compared with CTCAE v4.03** (**Figure 1**)[2,3]
    - **Neutropenia:** Under CTCAE v6.0, grade 1 neutropenia below the lower limit of normal (LLN) is no longer reportable and absolute neutrophil count (ANC) of 1.5 × 10^9/L to 1.0 × 10^9/L is now grade 1 (this was formerly grade 2); grade 4 is stricter with a cutoff of <0.1 × 10^9/L (previously <0.5 × 10^9/L)
    - **Thrombocytopenia:** There are no changes to grade 1 and grade 2 criteria per v6.0, but the grade 3 threshold is broader and grade 4 more stringent; urgent intervention was incorporated into grade 4 criteria
- Imetelstat is a first-in-class telomerase inhibitor approved for select patients with lower-risk myelodysplastic syndromes (LR-MDS) and red blood cell (RBC) transfusion-dependent (TD) anemia based on the results of the Phase 3 IMerge study (NCT02598661), in which imetelstat demonstrated clinically meaningful efficacy and a favorable safety profile[4]
- In Phase 3 IMerge, using CTCAE v4.03 criteria, the most common grade 3 or 4 treatment-emergent adverse events with imetelstat were neutropenia (68%) and thrombocytopenia (62%), which were expected on-target effects[4,5]
  - Cytopenias occurred predominantly during the first 3 cycles and were transient
  - They were not associated with an increased risk of serious clinical sequelae (bleeding, infection, or febrile neutropenia)

We hypothesized that implementation of CTCAE v6.0 would alter the classification of imetelstat-associated cytopenias, thereby affecting the interpretation of reported hematologic AEs

Figure 1. Updated CTCAE Criteria for Cytopenia Grading: Neutropenia (A) and Thrombocytopenia (B)[4,5]

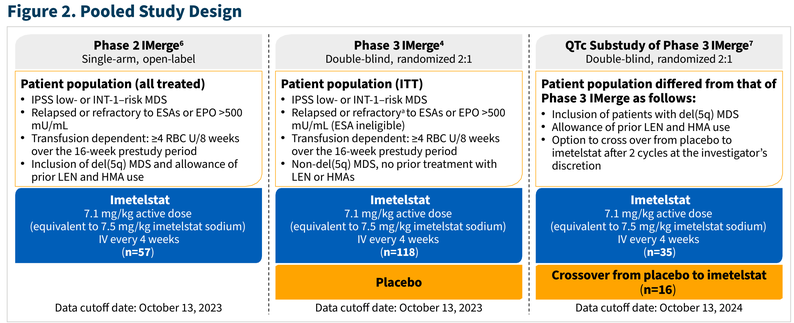


CTCAE, Common Terminology Criteria for Adverse Events; LLN, lower limit of normal.
LLN is displayed as a schematic endpoint, since CTCAE does not specify a numeric LLN.

Methods

- This post hoc analysis evaluated neutropenia and thrombocytopenia occurrence according to CTCAE v4.03 versus v6.0 in patients who received 7.1 mg/kg imetelstat administered as an intravenous infusion every 4 weeks
- Analyses were conducted in the pooled IMerge population (Phase 2, Phase 3, and QTc substudy) and the randomized, placebo-controlled IMerge Phase 3 population (**Figure 2**)

Figure 2. Pooled Study Design



EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HMA, hypomethylating agent; INT, intermediate; IPSS, International Prognostic Scoring System; ITT, intention-to-treat; IV, intravenous; LEN, lenalidomide; MDS, myelodysplastic syndromes; QTc, QT correction; RBC, red blood cell.
[a]Received ≥8 weeks of ESA treatment (EPO alfa ≥40,000 U, EPO beta ≥30,000 U, or darbepoetin alfa 150 µg or equivalent per week) without Hb rise ≥1.5 g/dL or decreased RBC transfusion requirement ≥4 U every 8 weeks or transfusion dependence or reduction in Hb by ≥1.5 g/dL after hematologic improvement from ≥8 weeks of ESA treatment.

Results

- The analysis comprised 226 imetelstat-treated patients from the pooled IMerge population, including 118 from the Phase 3 population
- Baseline characteristics are shown in **Table 1**
- The median duration of imetelstat treatment was 33.6 weeks, with 40% of patients receiving ≥13 treatment cycles (**Table 2**)

Table 1. Baseline Characteristics in the Pooled Patient Population

Baseline patient and disease characteristics	Imetelstat (N=226)
Age, median (range), years	71.0 (43-87)
≥65 years, n (%)	174 (77)
WHO classification, n (%)	
RS+	147 (65)
RS–	78 (35)
Missing	1 (<1)
IPSS risk category, n (%)	
Low	151 (67)
Intermediate-1	75 (33)
Prior RBC transfusion burden, n (%)	
≤6 U/8 weeks	112 (50)
>6 U/8 weeks	114 (50)
Serum EPO level, n (%)	
≤500 mU/mL	155 (69)
>500 mU/mL	64 (28)
Missing	7 (3)
Transfusion burden per IWG 2018, n (%)	
LTB[a]	38 (17)
HTB[b]	188 (83)

Table 2. Imetelstat Exposure in the Pooled Patient Population

Imetelstat treatment exposure	Imetelstat (N=226)
Imetelstat treatment duration, median (range), weeks	33.6 (0.1-260.1)
Number of imetelstat treatment cycles, n (%)	
1-3 cycles	34 (15)
4-6 cycles	56 (25)
7-12 cycles	46 (20)
≥13 cycles	90 (40)

EPO, erythropoietin; HTB, high transfusion burden; IPSS, International Prognostic Scoring System; IWG, International Working Group; LTB, low transfusion burden; RBC, red blood cell; RS, ring sideroblast; WHO, World Health Organization.
[a]LTB defined as 3-7 RBC U in 16 weeks in ≥2 transfusion episodes and a maximum of 3 in 8 weeks. [b]HTB defined as ≥8 RBC U in 16 weeks or ≥4 RBC U in 8 weeks.

- In the pooled IMerge population, grade 3 and 4 neutropenia were reported in 39.8% and 29.6% of patients, respectively, using CTCAE v4.03, compared with 26.1% and 3.5% using v6.0 (**Figure 3**)
  - Grade 3 and 4 thrombocytopenia occurred in 39.8% and 21.2% of patients, respectively, using v4.03, versus 56.6% and 4.0% using v6.0
- Similar cytopenia grading shifts were observed in the Phase 3 population (**Figure 3**)
- Across both populations, grade ≥3 neutropenia and thrombocytopenia generally occurred early during imetelstat treatment and were transient (**Figure 4**)
  - Cytopenias were associated with low rates of infection and bleeding compared with placebo[2]

Figure 3. Maximum Postbaseline CTCAE Grade and Worsening Since Baseline in IMerge: Pooled Population (A) and Phase 3 Population (B)

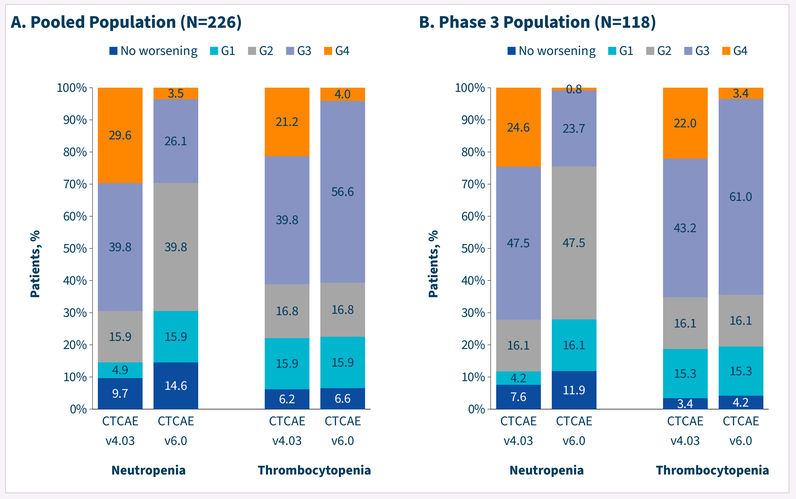
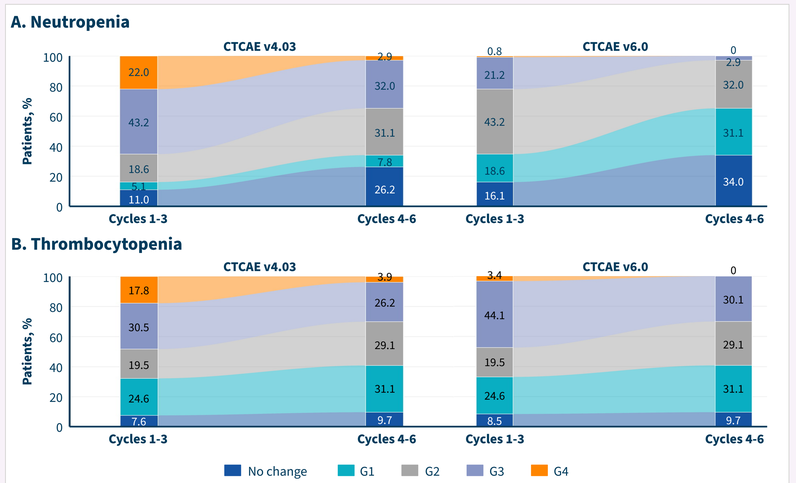


Figure 4. Maximum Postbaseline CTCAE Grade and Worsening Since Baseline by Cycle in IMerge Phase 3 Population (N=118): Neutropenia (A) and Thrombocytopenia (B)



Conclusions

- Compared with CTCAE v4.03, the use of v6.0 substantially reduced reported grade 3 and 4 neutropenia and shifted thrombocytopenia grading toward more grade 3 events and fewer grade 4 events in the IMerge study
- Although CTCAE v6.0 may offer advantages for future clinical studies, cytopenia assessment and management for imetelstat should remain consistent with the current prescribing information based on CTCAE v4.03

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