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Abstract S1557

Imetelstat in RBC Transfusion-Dependent Lower Risk MDS Relapsed/Refractory to Erythropoiesis-Stimulating Agents (IMerge): Updated Efficacy and Safety

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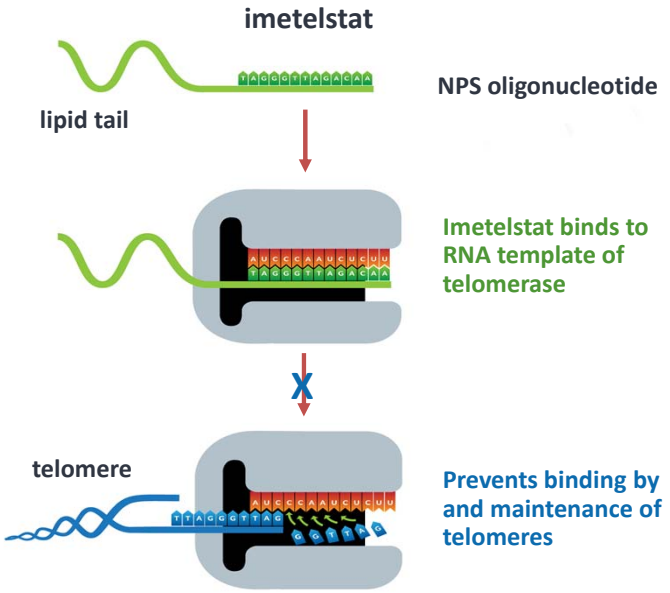
Kura	√						
Novartis						√	
Onconova			√				
Otsuka						√	
Syros	√						
Takeda			√				

Myelodysplastic Syndromes (MDS) and Imetelstat

- MDS are associated with multiple somatic genetic abnormalities and on average shorter telomeres than age-matched controls
- Limited treatment options are available for anemia in lower risk MDS relapsed or refractory to ESA therapy
- Higher telomerase activity, expression of hTERT and shorter telomeres predict for shorter overall survival in lower risk MDS
- Imetelstat is a first-in-class telomerase inhibitor, targets cells with short telomere lengths and active telomerase, and has clinical activity in myeloid malignancies[1-3]

ESA, erythropoiesis-stimulating agent; hTERT, human telomerase reverse transcriptase.



1. Baerlocher GM, et al. N Engl J Med 2015;373:920-928
2. Tefferi A, et al. N Engl J Med 2015;373:908-919
3. Tefferi A, et al. Blood Cancer J 2016;6:e405

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IMerge Study Design: Part 1

Patients with MDS (N=32)

- IPSS Low or Int-1
- Relapsed / refractory to ESA or ineligible for ESA
- Transfusion dependent (≥4u RBC/8 wks)
- Prior therapy with lenalidomide or HMA permitted
- Del(5q) karyotype permitted

single arm

open label

Imetelstat Treatment

7.5 mg/kg IV q4w
(2-hr infusion)

increase to 9.4 mg/kg
allowed after 3 cycles

1º Endpoint: 8-Week RBC TI

2º Endpoints: 24-Week RBC TI / Time to TI / TI duration / TR (HI-E: Transfusion Reduction by ≥ 4 RBC units over 8 weeks) / MDS response per IWG / OS / Incidence of AML / Safety

Pre-medication: diphenhydramine, hydrocortisone 100-200 mg (or equivalent)

Supportive care: RBC transfusions, myeloid growth factors per local guidelines

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IMerge: Baseline Characteristics and Prior Treatment

Parameters	N=32
Median age (range), year	68.5 (46-83)
Male, n (%)	16 (50)
ECOG PS 0-1, n (%)	29 (91)
IPSS risk, n (%) Low / intermediate-1	 19 (59) / 13 (41)
Baseline median (range) RBC transfusion burden, units/8 weeks	6 (4–14)
Karyotype[a], n (%) Normal Any abnormality / del(5q)	 17 (53) 11 (34) / 7 (22)
WHO 2001 category, n (%) RARS or RCMD-RS / All others	 16 (50) / 16 (50)
sEPO > 500 mU/mL, n (%)	13[b] (43)
Prior ESA / lenalidomide / decitabine or azacitidine, n (%)	28 (88) / 12 (38) / 8 (25)
Naïve to lenalidomide and HMA and non-del(5q), n (%)	13 (41)

[a]Results were missing from the central laboratory for 4 patients. [b]Of the 30 patients with sEPO levels reported.

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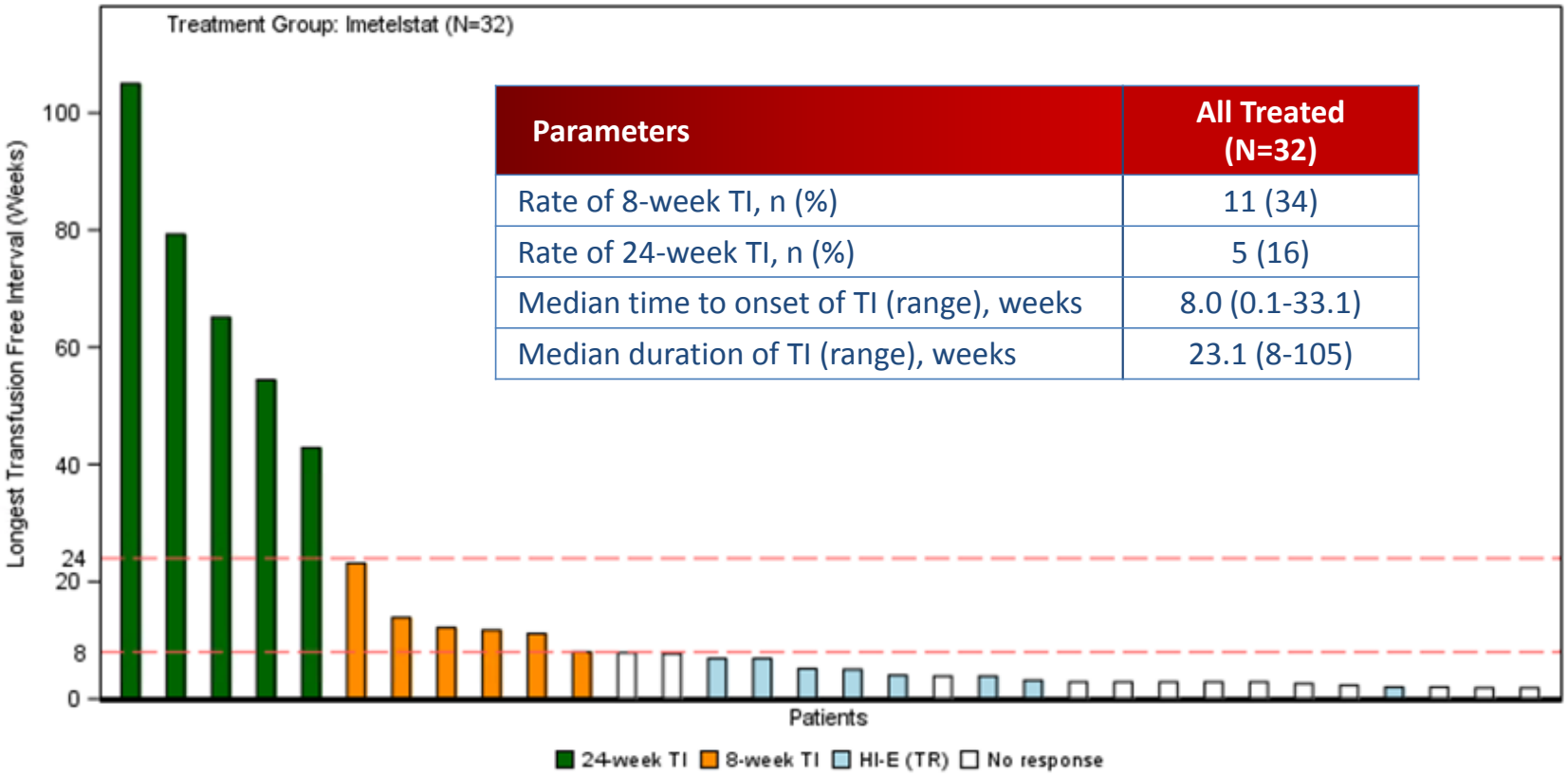
IMerge: Treatment Exposure

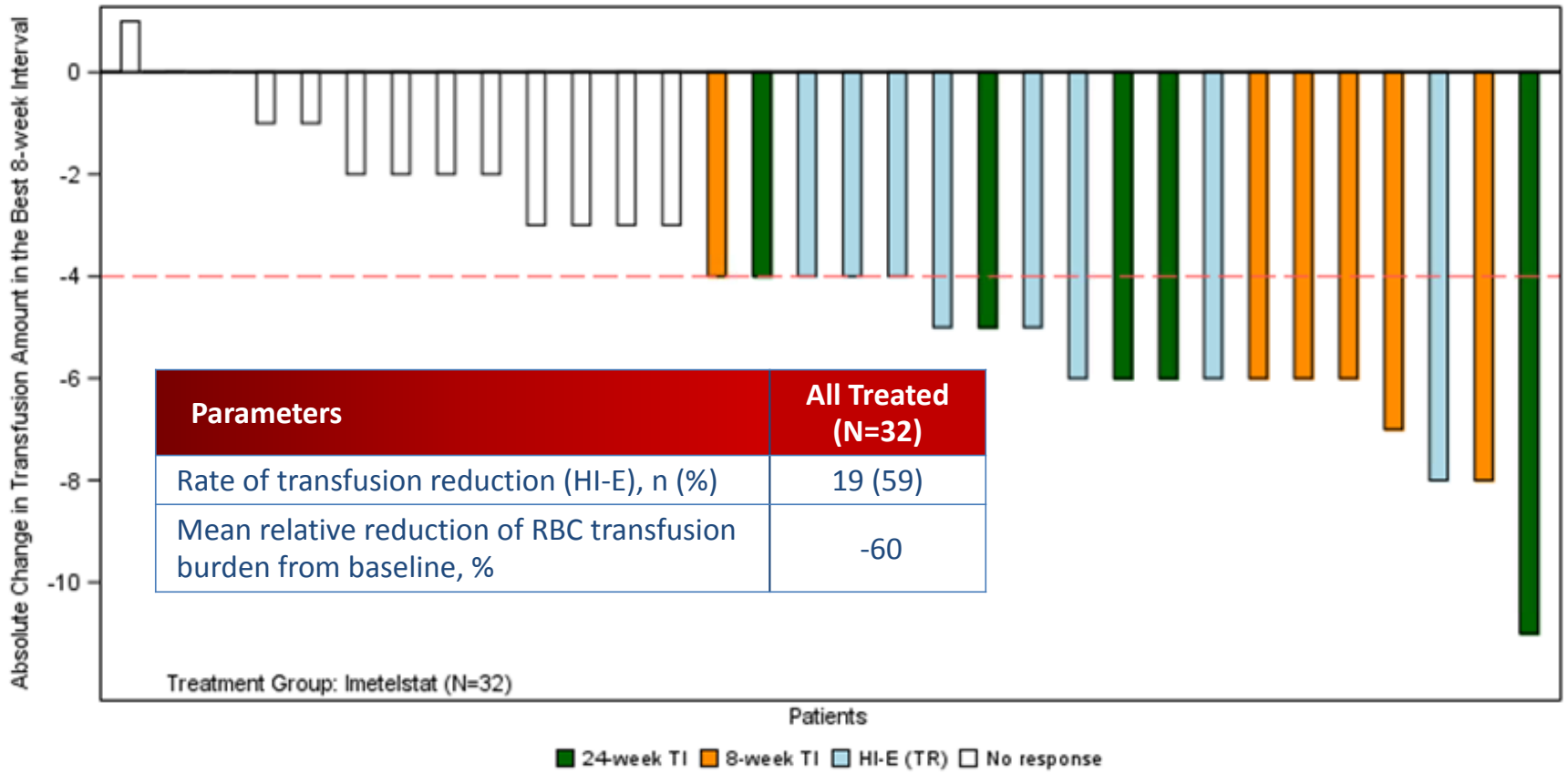
- Median follow-up for this analysis: 95 weeks
  - Clinical Cutoff: 10-May-2018
- Median number of treatment cycles: 6.5 (range: 1–28) cycles
- 7 patients had imetelstat dose escalation to 9.4 mg/kg
- 16 patients (50%) had dose reductions and 19 patients (59%) had cycle delays

IMerge: Longest Transfusion-Free Interval



Parameters	All Treated (N=32)
Rate of 8-week TI, n (%)	11 (34)
Rate of 24-week TI, n (%)	5 (16)
Median time to onset of TI (range), weeks	8.0 (0.1-33.1)
Median duration of TI (range), weeks	23.1 (8-105)

IMerge: Absolute Change in Transfusion Amount in the Best 8-Week Interval



Parameters	All Treated (N=32)
Rate of transfusion reduction (HI-E), n (%)	19 (59)
Mean relative reduction of RBC transfusion burden from baseline, %	-60

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IMerge: Key Efficacy Outcomes

Parameters	All Treated (N=32)	Lenalidomide and HMA naïve and Non-del(5q) (n=13)
Rate of 8-week TI, n (%)	11 (34)	7 (54)
Rate of 24-week TI, n (%)	5 (16)	4 (31)
Median time to onset of TI (range), weeks	8.0 (0.1-33.1)	8.3 (0.1-33.1)
Median duration of TI (range), weeks	23.1 (8-105)	42.9 (8-105)
Rate of transfusion reduction (HI-E), n (%)	19 (59)	9 (69)
Mean relative reduction of RBC transfusion burden from baseline, %	-60	-71
CR + marrow CR + PR (per IWG), n (%)	6 (19)	4 (31)

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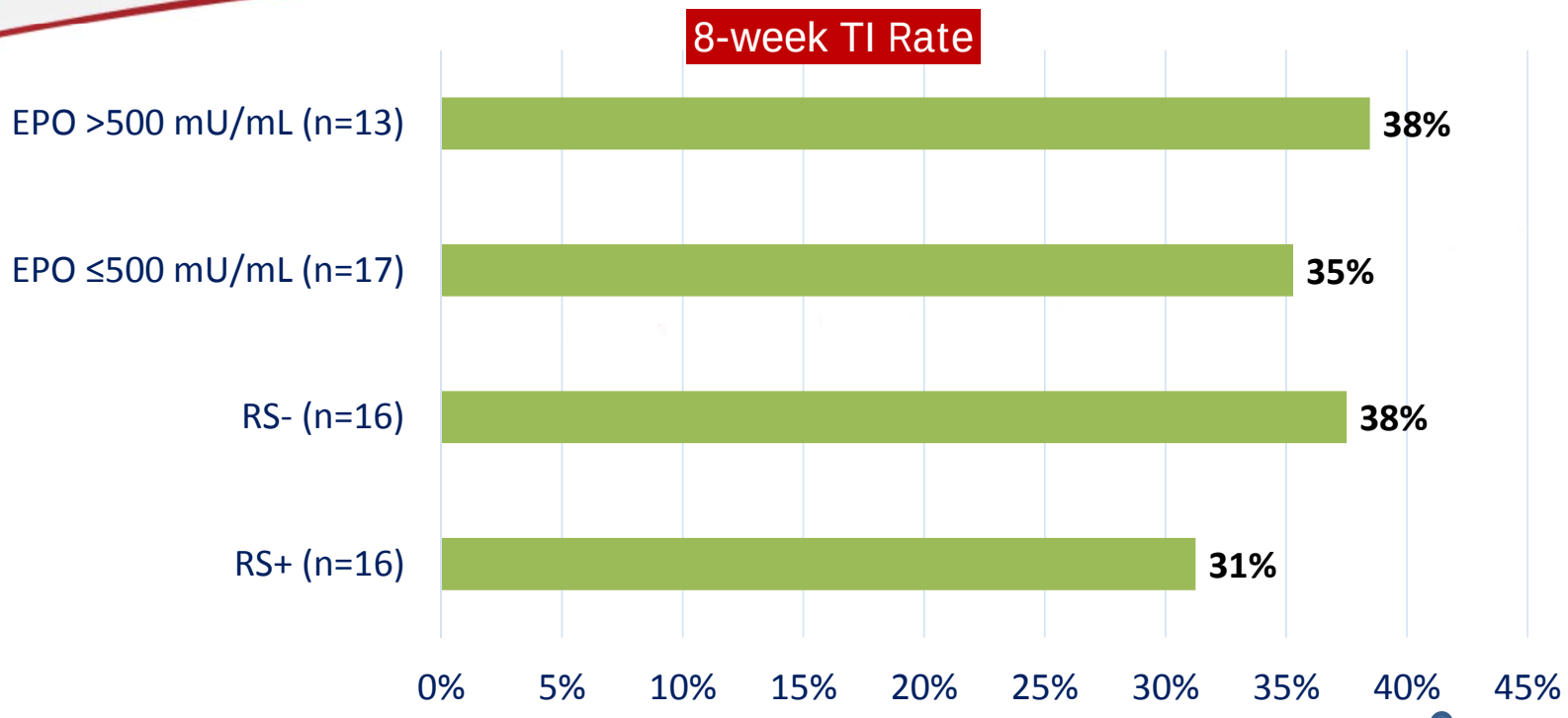
IMerge: Efficacy Results in EPO and RS Subgroups



Similar efficacy was observed across these subgroups

IMerge: Hemoglobin and Imetelstat Dosing Among Patients with Durable TI

Prior RBC Transfusion Burden

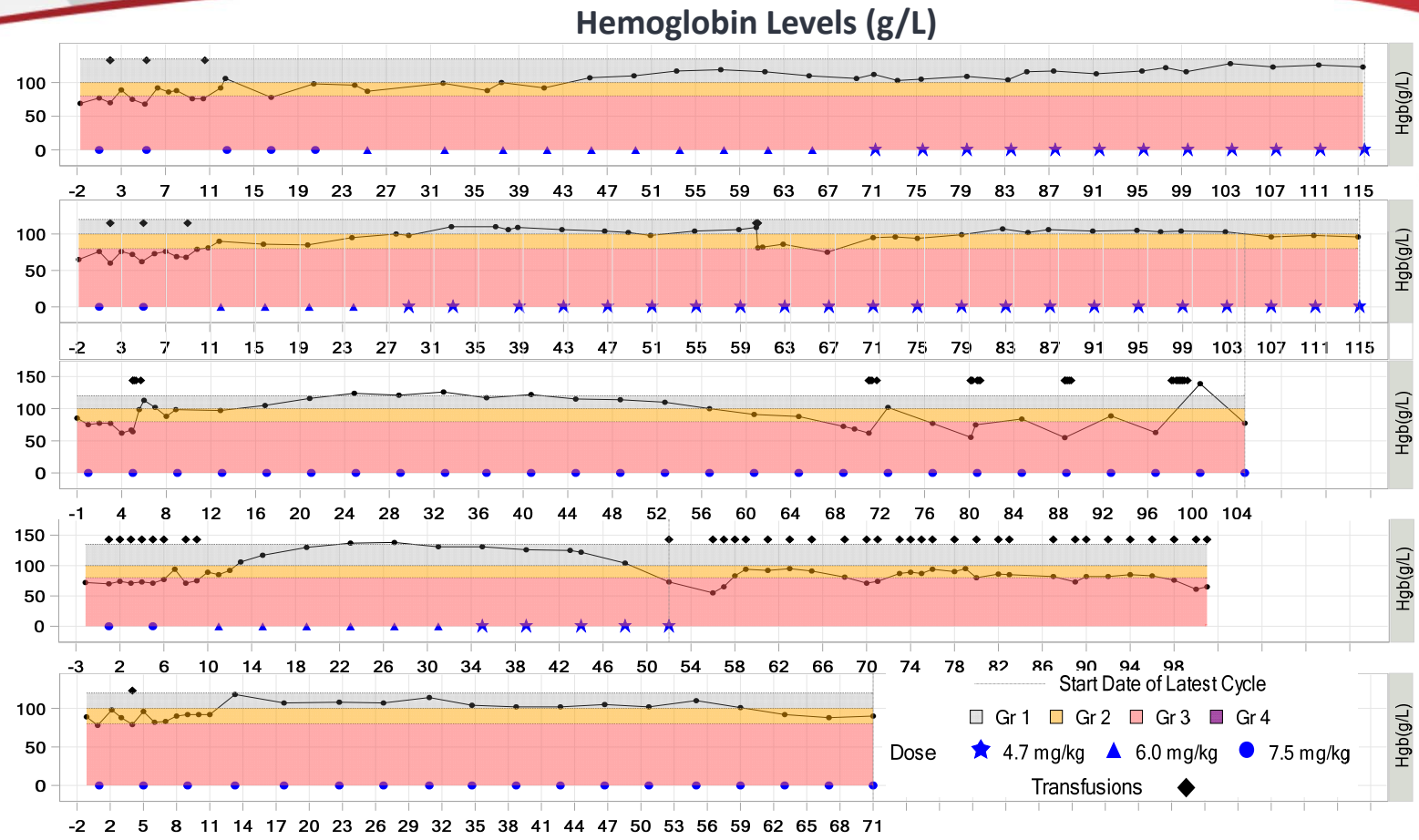
6 units/8 weeks

6 units/8 weeks

5 units/8 weeks

11 units/8 weeks

4 units/8 weeks



IMerge: Most Common Adverse Events (All Grades)

Safety findings for those who were lenalidomide/ HMA-naïve/ non-del(5q) were similar to the overall study population

≥10% of Patients in All Treated Patients	All Treated (N=32)	Lenalidomide and HMA naïve and Non-del(5q) (n=13)
Patients with ≥1 treatment-emergent AEs, n (%)	31 (97)	12 (92)
Neutropenia	23 (72)	7 (54)
Thrombocytopenia	18 (56)	8 (62)
Headache	8 (25)	2 (15)
ALT increased	6 (19)	3 (23)
AST increased	5 (16)	3 (23)
Leukopenia	5 (16)	2 (15)
Muscle spasms	5 (16)	2 (15)
Diarrhea	5 (16)	2 (15)
Anemia	4 (13)	2 (15)
Asthenia	4 (13)	4 (31)
Back pain	4 (13)	2 (15)
Constipation	4 (13)	2 (15)
Cough	4 (13)	1 (8)
Dyspnea	4 (13)	2 (15)
Influenza like illness	4 (13)	1 (8)
Nausea	4 (13)	2 (15)
Peripheral edema	4 (13)	2 (15)
Viral URI	4 (13)	4 (31)

IMerge: Occurrence and Reversibility of Gr 3/4 Cytopenias

	All Treated (N=32)	Lenalidomide and HMA naïve and Non-del(5q) (n=13)
Neutrophils, n (%)		
Grade 3	8 (25)	2 (15)
Recovered < 4 weeks	4 (50)	1 (50)
Grade 4	13 (41)	5 (38)
Recovered < 4 weeks	12 (92)	5 (100)
Platelets, n (%)		
Grade 3	10 (31)	5 (38)
Recovered < 4 weeks	9 (90)	5 (100)
Grade 4	8 (25)	3 (23)
Recovered < 4 weeks	6 (75)	3 (100)

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Conclusions (1)

- Overall, 8-week TI observed in 34% of all patients, with a 24-week TI rate of 16%
  - Median time to TI: 8.0 weeks
  - Median duration of TI: 23.1 weeks
- For those who were lenalidomide/HMA-naive and non-del(5q), the 8-week and 24-week TI rates were 54% and 31%, respectively
  - Median duration of TI: 42.9 weeks
- TR (HI-E) observed in 59% of all patients
  - Mean relative reduction of RBC transfusion burden from baseline = 60%

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Conclusions (2)

- AEs (mostly cytopenias) were predictable and reversible
- These results support further study of imetelstat (7.5 mg/kg /4 weeks) in IPSS Low/Int-1, TD, ESA-relapsed/refractory MDS
- In RBC TD patients with LR-MDS (median: 6 U/8 weeks), imetelstat treatment resulted in erythroid improvement in a majority of patients
- Based on improved efficacy in the cohort who were naïve to lenalidomide and HMA and non-del(5q), a new cohort of 25 additional patients have been fully enrolled

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