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Real-world Outcomes of Imetelstat: Interrogating Safety, Efficacy and Predictors of Response in Heavily Pretreated Lower-Risk MDS Patients

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INTRODUCTION

- Imetelstat is a first-in-class, direct and competitive inhibitor of telomerase enzymatic activity.
- Imetelstat was approved for lower-risk myelodysplastic syndromes (LR-MDS) based on ~40% ≥8-week RBC transfusion independence (TI) rate with a median duration of 51.6 weeks in patients with ESA failure LR-MDS on the Phase 3 IMerge randomized clinical trial.

AIM

We report the first real-world data on efficacy and safety of imetelstat.

METHODS

- We analyzed all patients (pts) who received imetelstat at Moffitt Cancer Center since FDA approval.
- We examined baseline characteristics, details of treatment, response, adverse events, and outcomes.
- Descriptive statistics were used for baseline characteristics and response.
- Kaplan-Meier estimates were used for overall survival.
- Univariable and multivariable linear logistic regression was used to analyze predictors of response.

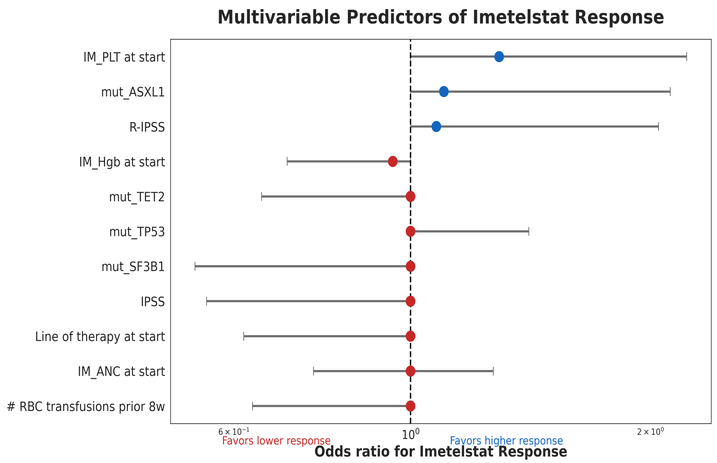
Table-1 Baseline characteristics	N (%)
Number of patients	40 (100)
Gender: Male	23 (57.5)
Median age at diagnosis (range), years	69.5 (51–79)
Ethnicity White	38 (95.0)
WHO 2022 classification	
MDS with low blasts	4 (10.0)
MDS-SF3B1	20 (50)
MDS/MPN-SF3B1	8 (20)
MDS-del(5q)	2 (5.0)
MDS-IB	1 (2.5)
Missing	5 (12.5)
IPSS-M risk	
Low	17 (42.5)
Moderate-low	13 (32.5)
Moderate-high	9 (22.5)
missing	1 (2.5)
Most common mutations	
SF3B1	(80%)
TET-2	(30%)
ASXL-1	(27.5%)

RESULTS

- Between July 2024 to October 2025, 40 LR-MDS pts were treated with imetelstat (36 TD at baseline). The median duration of follow up from start of treatment was 14.2 months (95% CI 12.6-15.8).
- The median age at diagnosis was 69.5 years, majority were Caucasian (38/40) and 58% (23/40) were male.
- By WHO 2022, 28 patients (70%) were MDS or MDS/MPN *SF3B1* and mean blast was 2%.
- The mean number of somatic mutations was 2.3 and most common mutations were *SF3B1* 80%, *TET-2* 30%, and *ASXL-1* 27.5%.
- By IPSS-R, 50% were very low/low, 42.5% intermediate, 5% high/very high and by IPSS-M, 75% were low/moderate low ad 22.5% were moderate high.
- The mean Hb before treatment was 7.4 g/dl (5.5-9.8 g/dl).The mean number of prior RBC transfusion units/16 weeks and 8 weeks was 8.5 (0-21) and 4.7 (0-10), respectively. The median time from diagnosis to start imetelstat treatment was 42.7 months (0.9-173.57).
- Imetelstat was used as later line of therapy (median as 3rd line; r 1-8), 35 pts (87.5%) had prior luspatercept, 28 pts (70%) had prior ESA, 15 pts (37.5%) had prior hypomethylating agent (HMA), 17 patients (42.5%) had prior lenalidomide (Len) therapy.
- **The best response in imetelstat-treated patients (RBC-TI > 8 weeks) was 37.5% (15/40)** with 7/15 responses ongoing. **The median duration of response was 185 days (67-492).** The median # of cycles received was significantly increased in responding pts (10 vs 5; p<0.0001). The median maximum hemoglobin in responding patients was 9.6 (r 8.7-14.8).
- Baseline EPO level, transfusion burden or *SF3B1* mutation were not predictive of response.
- Among 9 pts with *ASXL-1* mutation, 66.7% (6 pts) responded compared to 29% (9/31) WT, p= 0.04.
- Baseline platelet count of ≥ 192 was best univariable predictor of response, OR 7.0, AUC 0.68.
- There was trend for inferior response post HMA and Len use (26.7% vs 44%,p=0.27; 23% vs 28%, p=0.11). There was a trend for better response if imetelstat was used within first 3 lines of therapy (44% vs 26.7% p=0.27).
- **In exploratory predictive model for response, platelet count at baseline, *ASXL-1* mutation, and IPSS-R at diagnosis were the most important predictors of response.**
- Grade 3/4 neutropenia was observed in 14 pts (35%) after C1 and 9 pts (22.5%) after C2. Grade 3 / 4 thrombocytopenia was observed in 11 pts (27.5%) after C1 and 8 pts (20%) after C2. No febrile neutropenia episodes occurred. The median time between cycles was 31 days. One and two dose level reductions occurred in 37.5% (n=15) and 2.5% (n=1) pts, respectively. Plt transfusion was required in 5 pts (12.5%) and GCSF in 4 pts (10%).

Table-2 Response summary	
RBC-TI >8wk, % (n)	37.5 (15)
Ongoing treatment, n/N	7/15
Median max hemoglobin, g/dl (range)	9.6 (8.7-14.8)
mDOR, days (range)	185 (67-492)
Mean # of cycles in responding patients	10 vs 5 *P*<.0001
OS, mo (95% CI)	17.3 (15.7-18.7)

Table-3 Safety	
Grade 3/4 neutropenia, % (n)	
After C1, % (n)	35 (14)
After C2, % (n)	22.5 (9)
Febrile neutropenia, n	0
Median time between cycles, days	31
Dose reductions	
1, % (n)	37.5 (15)
2, % (n)	2.5 (1)
Platelet transfusions use, % (n)	12.5 (5)
GCSF use, % (n)	10 (4)



CONCLUSIONS

- Real world experience identifies safety and clinical efficacy of imetelstat in advanced, heavily transfusion dependent patients with MDS including patients with extensive prior therapies, molecularly higher risk disease and after luspatercept failure.
- We report novel predictors of response including baseline platelet count and *ASXL-1* mutation status.

CONTACT INFORMATION

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