Early Treatment Initiation in Myelodysplastic Syndromes (MDS) Produces Higher Rate of and Earlier Transfusion Independence

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Background

- MDS is a genetic and epigenetic bone marrow malignancy that causes cytopenias and propensity to Acute Myeloid Leukemia.
- MDS anemia often requires recurrent RBC transfusions[1-4]
  - Transfusion Dependence (TD) is associated with increased mortality and costs
- NCCN guidelines[5] recommend treatment with lenalidomide and HMAs in patients with:
  - Low to Intermediate risk MDS and symptomatic anemia
  - Higher risk MDS who are not candidates for hematopoietic cell transplant
- It is unclear when treatment is initiated in a real-world setting and whether timing of treatment initiation affects outcomes[6]

HMAs, hypomethylating agents; MDS, myelodysplastic syndromes; NCCN, National Comprehensive Cancer Network; RBC, red blood cell; TD, transfusion dependence.

1. Cogle et al. Curr Hematol Malig Rep. 2015;10:272-81.
2. Delea et al. Curr Med Res Opin. 2009;25:139-47.
3. Bux et al. Vox Sang. 2005;89:1-10.
4. Goldberg et al. J Clin Oncol. 2010;28:2847-52.
5. NCCN Guidelines – MDS. 2016;V1.2017.
6. Duong et al. Leuk Res. 2015;39:586-91.

Objective

- **To examine the importance of the timing of active treatment on the likelihood of achieving TI in lower risk MDS.**

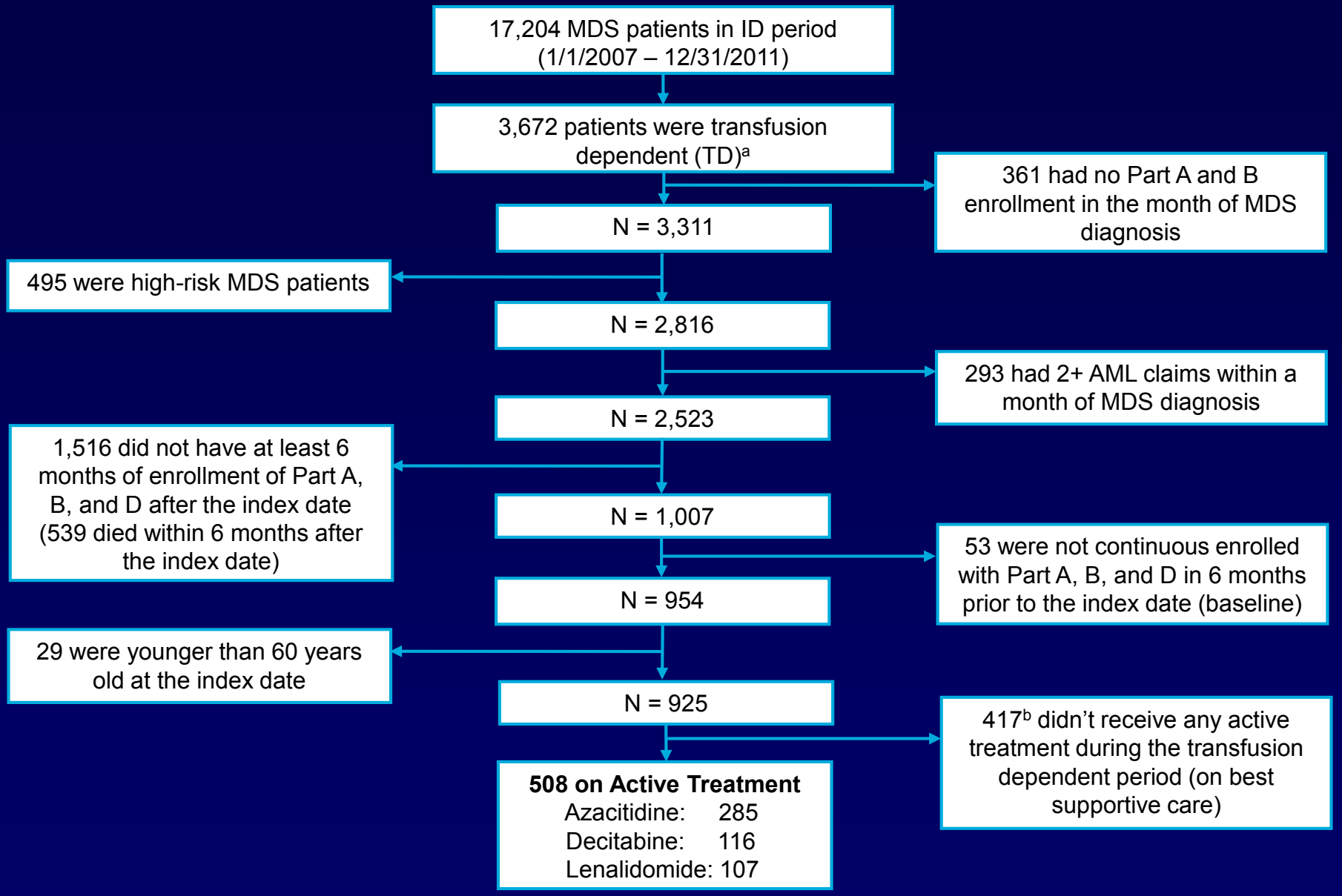
TI, transfusion independence.

Design, Data Source, and Population

- Retrospective cohort study using 2006–2012 SEER program-Medicare data
- Included patients who:
  - Had a diagnosis of MDS coded in SEER
    - ICD-O-3 codes 9980–9989
  - Were identified as TD between 2007 and 2011
  - Received active treatment (azacitidine, decitabine, or lenalidomide) while the patient was considered TD
- Excluded if:
  - First MDS diagnosis > 3 months after becoming TD
  - Not continuously enrolled in fee-for-service Medicare for 6 months before to 6 months after index date
  - Diagnosed with AML (ICD-9-CM: 250.0x) or high-risk MDS (ICD-9-CM: 238.73) within 30 days of the MDS diagnosis
  - Died within 6 months after becoming TD
  - ≤ 59-years-old on index date
- Cohorts
  - **Early initiators**: active treatment ≤ 3 months from start of TD
  - **Late initiators**: > 3 months from start of TD

AML, acute myeloid leukemia; ICD-O-3, International Classification of Diseases for Oncology, Third Edition; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; SEER, Surveillance, Epidemiology, and End Results.

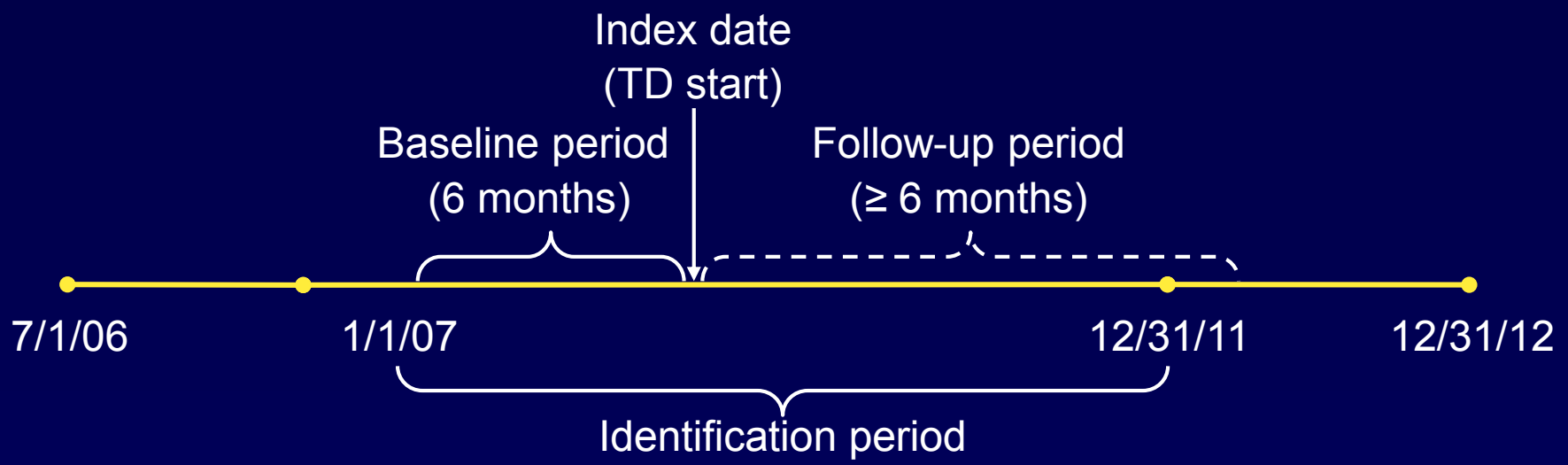
Attrition Flowchart



[a] TD defined as ≥ 1 RBC transfusion in each of 2 consecutive 8-week periods with the transfusions separated by less than 8 weeks

[b] Best supportive care included ESAs and transfusions

Timeline and Variable Definitions



- **TD: defined as ≥ 1 RBC transfusion in each of 2 consecutive 8-week periods with the transfusions separated by less than 8 weeks**
- **Index date: defined as date of first transfusion within that 16-week period**
- **TI: defined as ≥ 8 week RBC transfusion-free period**
- **Active treatment minimum exposure threshold was ≥ 3 fills for lenalidomide or ≥ 6 cycles of HMA**
- **Patients were observed until the following endpoints: the first transfusion after TI, TI, end of enrollment, or end of study**

Study Measures

Study measures

- **Primary outcomes: achievement of TI**
- **Primary explanatory variable: early (≤ 3 months) vs. late (> 3 months) initiation of active treatment**

Other measures

- **Patient demographics (age, sex)**
- **Disease characteristics [presence or absence of the del(5q) syndrome (ICD-O-3: 9986)]**
- **Time from MDS diagnosis to TD**
- **MDS disease category**
- **Treatment type (first active treatment during TD [lenalidomide, azacitidine, or decitabine], and use of ESAs)**
- **Minimum treatment exposure[a]**

[a]≥ 3 (for lenalidomide) or ≥ 6 (for azacitidine or decitabine) cycles of treatment (without discontinuation) during TD or reached TI before the minimum number of cycles.

ESAs, erythropoiesis-stimulating agents.

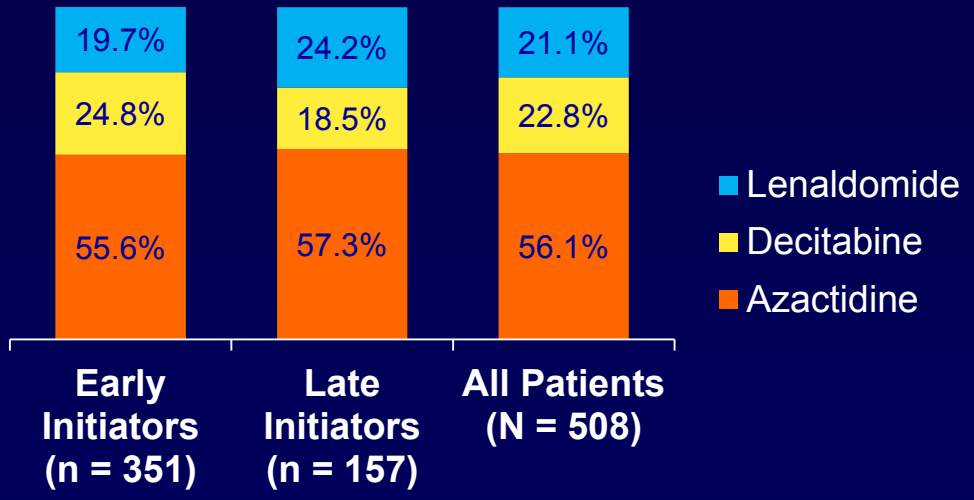
Demographics and Clinical Characteristics

	Early treatment initiators (≤ 3 months) (n = 351)	Late treatment initiators (> 3 months) (n = 157)	All patients (N = 508)	*P* value
Age at diagnosis (SEER), mean (SD)	76.2 (6.8)	76.3 (6.4)	76.2 (6.7)	0.788
Median (range)	77 (38–89)	76 (60–91)	77 (38–91)	
Female, n (%)	151 (43.0)	80 (51.0)	231 (45.5)	0.097
del(5q) syndrome, n (%)	21 (6.0)	11 (7.0)	32 (6.3)	0.661
MDS category, n (%)				< 0.001
Category 1 (refractory anemia or 5q deletion syndrome)	42 (12.0)	21 (13.4)	63 (12.4)	
Category 2 (refractory anemia with ringed sideroblasts)	15 (4.3)	19 (12.1)	34 (6.7)	
Category 3 (MDS, NOS)	168 (47.9)	84 (53.5)	252 (49.6)	
Category 4 (other MDS[a])	126 (35.9)	33 (21.0)	159 (31.3)	
Timing of MDS diagnosis relative to TD				
Patients with MDS diagnosis before TD, n (%)	324 (92.3)	112 (71.3)	436 (85.8)	< 0.001
Patients with MDS diagnosis ≤ 3 months after TD, n (%)[b]	27 (7.7)	45 (28.7)	72 (14.2)	

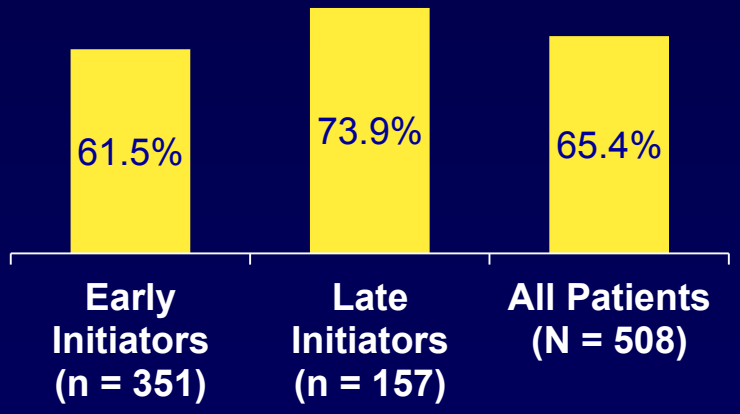
[a] Other MDS includes: refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, refractory cytopenia with multilineage dysplasia, or therapy-related MDS syndrome.
[b] Patients who received an MDS diagnosis more than 3 months after becoming TD were not included in the study.
NOS, none otherwise specified; SD, standard deviation.

Treatment During TD Among Patients on Active Treatment

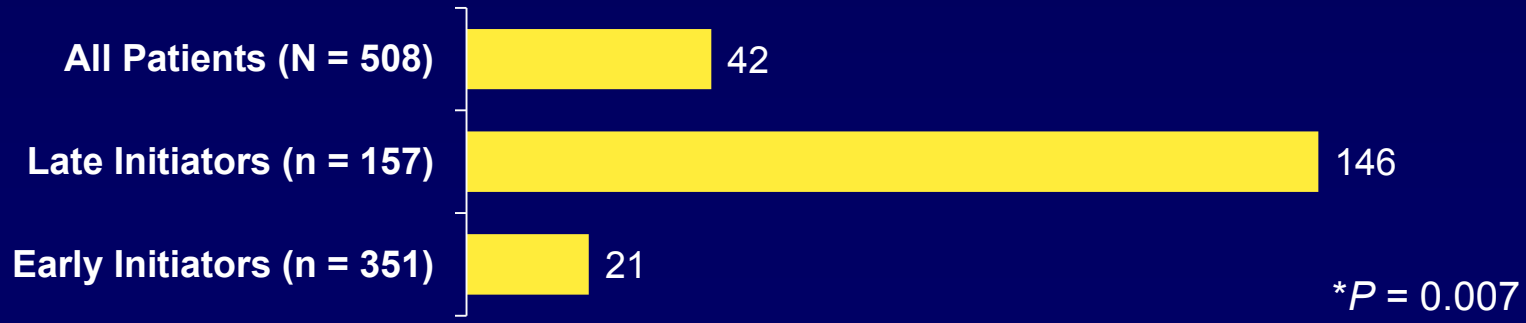
First active treatment during TD



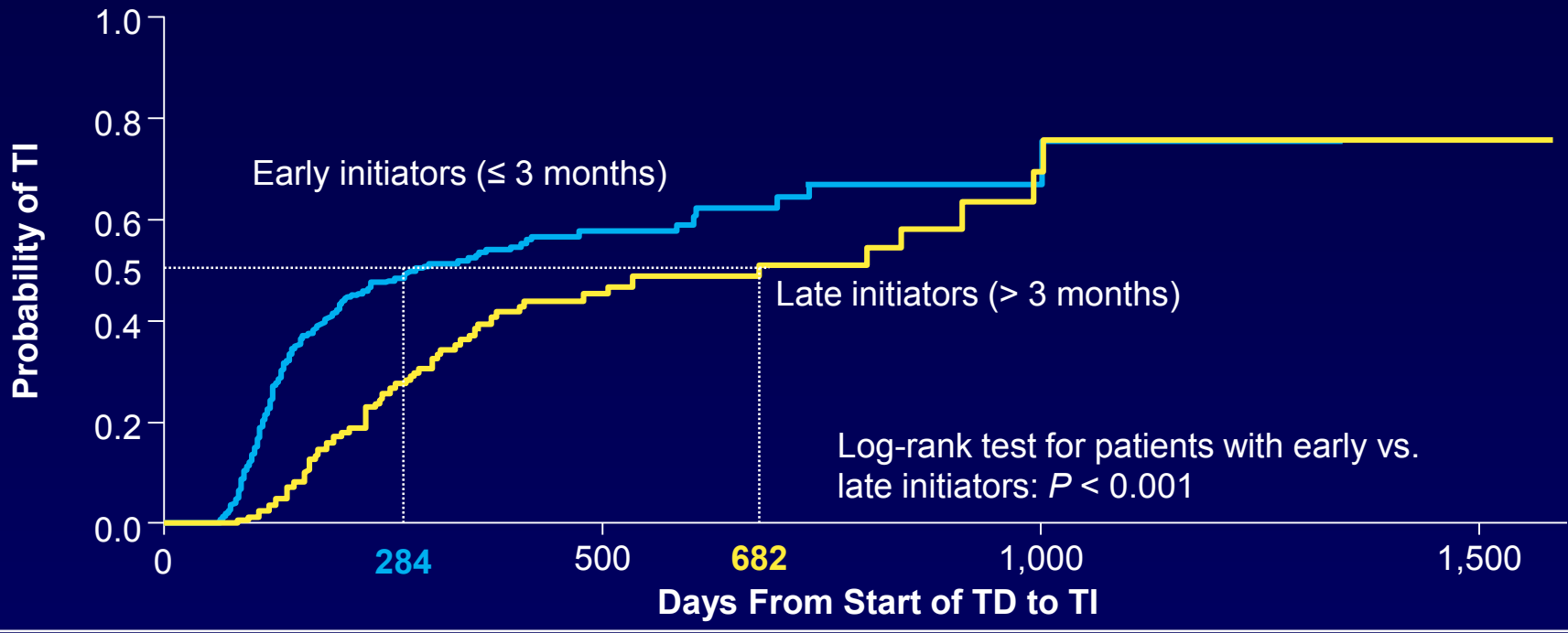
Any ESA use during TD



Median days from TD to active treatment*



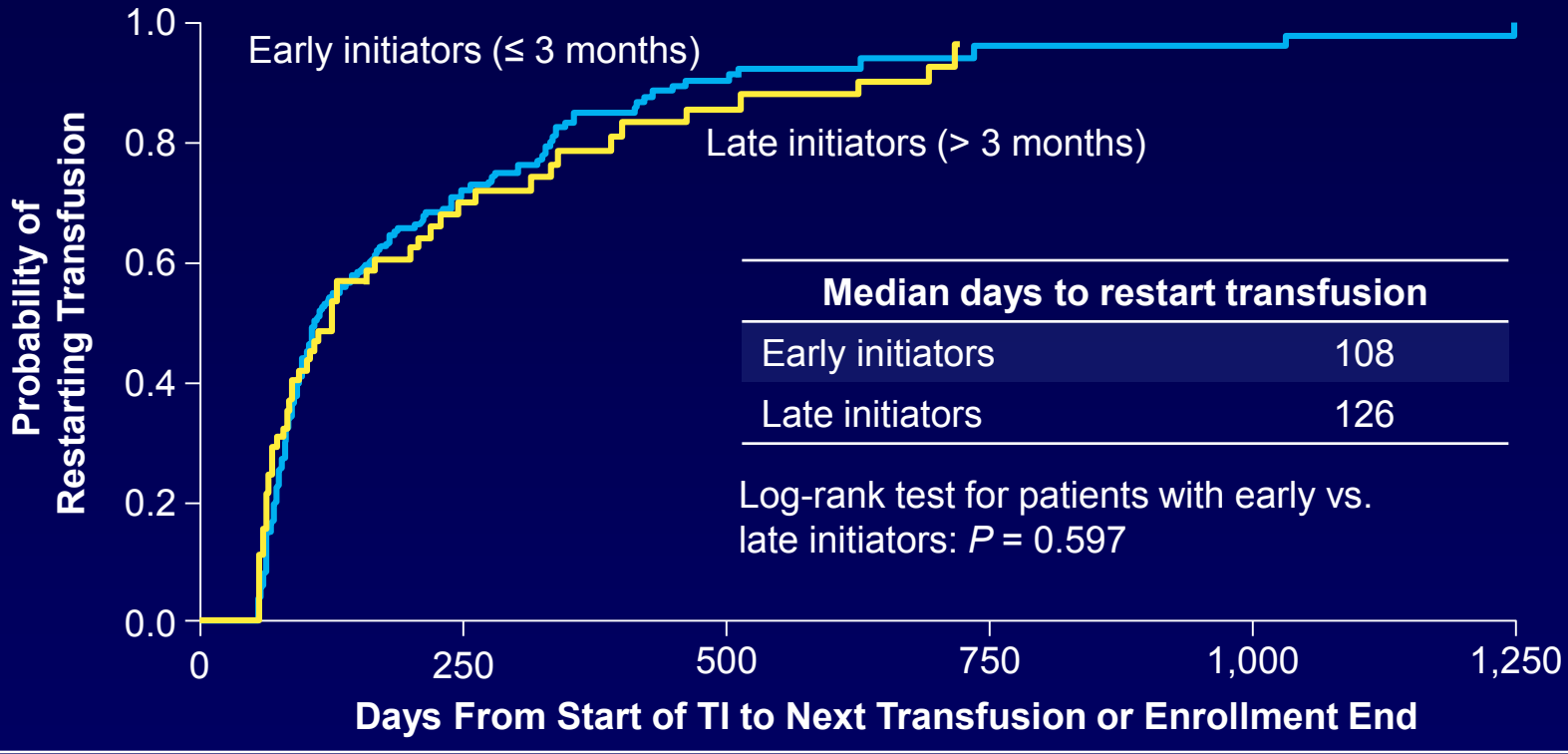
After Active Therapy, Time to TI Early vs. Late Initiators



	Early initiators	Late initiators	All patients
All patients taking active treatment, n	351	157	508
No. of patients who reached TI	189 (53%)	67 (42%)	256
Total TD patient years[a]	262.5	167.6	430.0
No. of TI PPY	0.720	0.400	0.595

[a] For patients with TI, person-years were the years from the index date to TI. For patients without TI, person-years were the years from the index date to the end of follow-up.
PPY, per patient year.

After Reaching TI, Time to Next Transfusion Between Early and Late Initiators



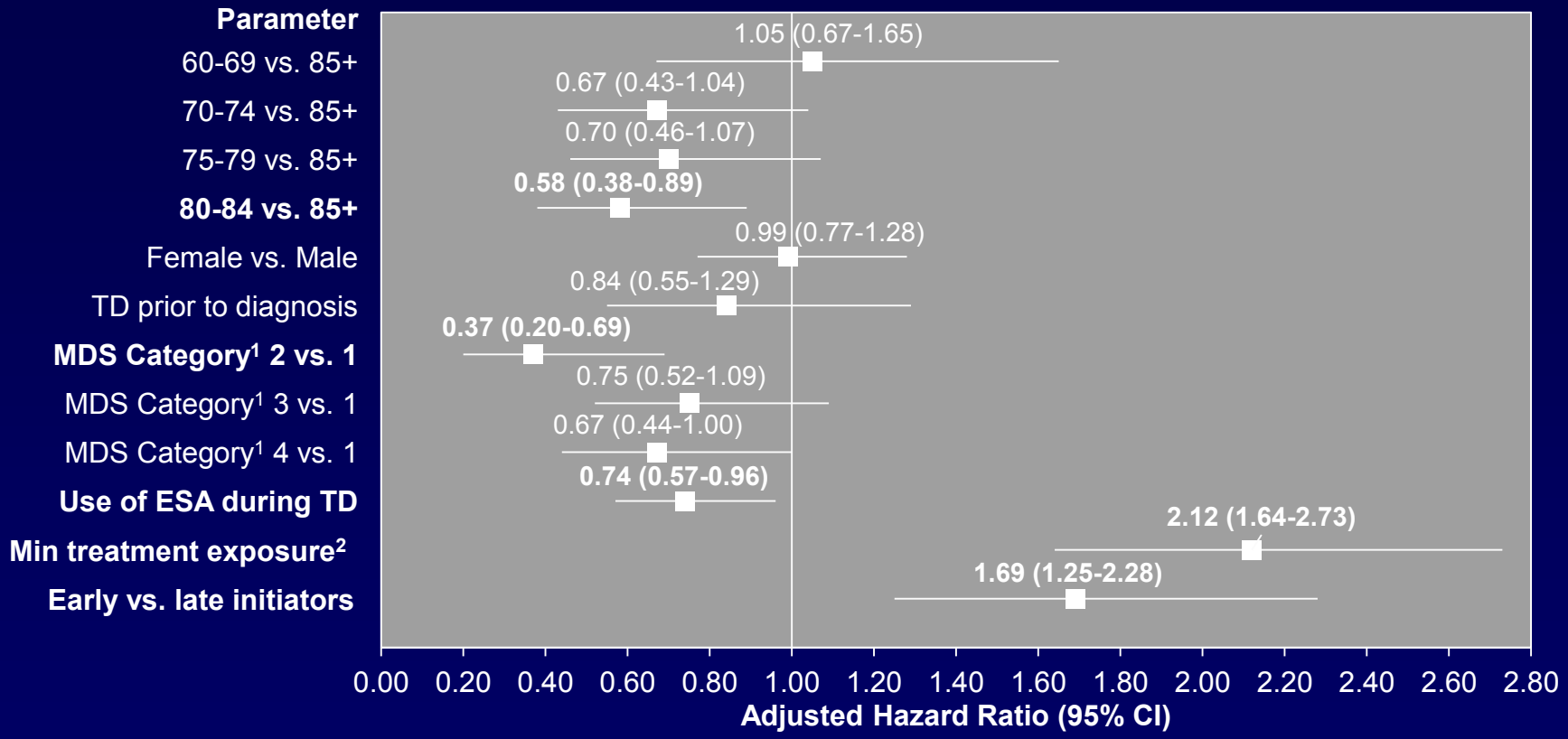
Median days to restart transfusion	
Early initiators	108
Late initiators	126

Log-rank test for patients with early vs. late initiators: $P = 0.597$

	Early initiators	Late initiators	All patients
Patients who reached TI, n	189	67	256
No. of patients who restarted transfusion after TI	156	54	210
Total TI patient years[a]	91.7	34.5	126.1
Rate of restarting transfusion, PPY	1.702	1.566	1.665

[a] For patients restarting transfusion, person-years were the years from the TI to the next transfusion. For patients without another transfusion, person-years were the years from the TI to the end of follow-up.

Patient and Disease Factors in Achieving Transfusion Independence After Active Therapy



[1] MDS categories: 1) refractory anemia or 5q deletion syndrome, 2) refractory anemia with ringed sideroblasts, 3) MDS, not otherwise specified, 4) other MDS which includes refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, refractory cytopenia with multilineage dysplasia, or therapy-related MDS syndrome.

[2] Patients with ≥3 (for lenalidomide) or ≥6 (for azacitidine or decitabine) cycles of treatment (without discontinuation) during TD or treated patients who reached transfusion independency before the minimum number of cycles.

•Cox Proportional Hazard models controlled for age, gender, ESA use, threshold treatment exposure, timing of MDS diagnosis and MDS risk based on the ICD-0-3 category variables. The adjusted hazard ratios (HR) with 95% confidence intervals (CI) were reported

Limitations

- **Lead Time Bias**: date of transfusion dependence was used as the starting point for measuring the likelihood of becoming transfusion independent.
  - Late initiators had less time to become TI following exposure to active treatment, potentially affecting our comparative estimates of TI rates
- **Generalizability**: Findings may not be generalizable to non-Medicare MDS patient populations
- **Claims Approach**: Medicare claims are collected for billing purposes; as such the current study likely under identifies the number of del(5q) and high risk MDS patients

Conclusions

- Transfusion dependent MDS patients who initiated active treatment within 3 months have a higher chance of achieving transfusion independence compared to late initiators
- Early initiation of active treatment leads to a shortened period of transfusion dependence
  - Shorter periods of TD may have benefits, including lower risk of infection, iron overload, organ damage, and mortality, although further research is needed[1-3]
  - Transfusion burden has a significant economic impact on MDS patients with high burden patients having total cost of care 53% higher than low burden patients[4]
  - Future analyses should explore the exact impact on cost and mortality associated with early TI.
- Studies of MDS clonal evolution may help to elucidate how early versus late treatment exposure impacts the subclonal architecture of MDS

1. Delea et al. Curr Med Res Opin. 2009;25:139-147.
2. Bux et al. Vox Sang. 2005;89:1-10.
3. Goldberg et al. J Clin Oncol. 2010;28:2847-2852.
4. Dezern et al. EHA 2016

Conclusions

- **Only 66% of TD MDS patients are treated with active therapy.**
  - only a minority of these patients received minimum treatment exposure[a]
- **Significantly higher likelihood of TI with early active therapy.**
  - higher likelihood of TI in patients with minimum treatment exposure
- **Shorter time to reach TI with early active therapy.**
- **Same duration of TI, whether early or late initiation of active therapy.**

[a]≥ 3 (for lenalidomide) or ≥ 6 (for azacitidine or decitabine) cycles of treatment (without discontinuation) during TD or reached TI before the minimum number of cycles.

Clinical Impact and Future Studies

- **Potential clinical benefits of early active therapy:**
  - **Earlier and shorter periods of TD may have several benefits, including lower risk of infections, iron overload, organ damage, and mortality, although further research is needed[1-3]**
  - **Transfusion burden has a significant economic impact on MDS patients with high burden patients having total cost of care 53% higher than low burden patients[4]**
  - **Future analyses should explore the exact impact on cost and mortality associated with early TI.**
- **Studies of MDS clonal evolution may help to elucidate how early versus late treatment exposure impacts the subclonal architecture of MDS**
- **Dose modification should be considered to help patients receive minimum treatment exposure and the associated benefits of greater likelihood of TI.**

1. Delea et al. Curr Med Res Opin. 2009;25:139-147.
2. Bux et al. Vox Sang. 2005;89:1-10.
3. Goldberg et al. J Clin Oncol. 2010;28:2847-2852.
4. Dezern et al. EHA 2016

Acknowledgements

Supplementary Information

Statistical analysis

- Means and SD for continuous variables, percentages for categorical variables
- TI compared between early vs. late initiators
  - Unadjusted rates
  - Kaplan–Meier survival estimates
  - Cox proportional hazards regression adjusted for: age, sex, timing of MDS diagnosis relative to start of TD, MDS category (disease severity), ESA use during TD, and minimum treatment exposure

Supplementary Information

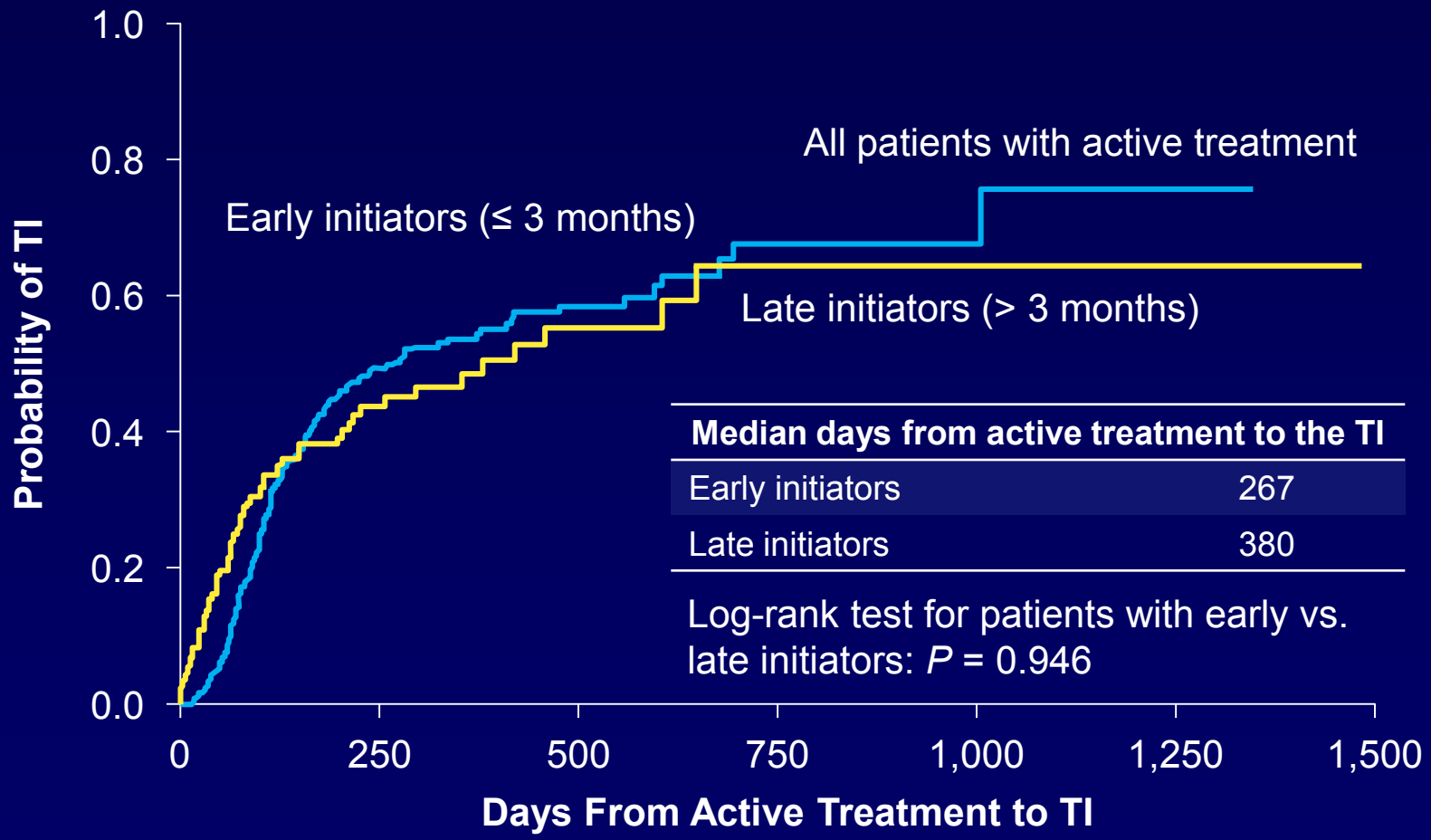
- **Unadjusted rate of achieving TI was higher in early vs. late initiators in both the subgroup that met the minimum treatment exposure as well as the subgroup that did not meet the minimum treatment exposure**

	Early Initiators (≤ 3 months) (n = 351)	Late Initiators (> 3 months) (n = 157)	All Patients (N = 508)
Patients who met the minimum treatment exposure[a]	132	58	190
No. of patients who reached TI	95	38	133
Total TD patient years	93.7	62.4	156.1
No. of TI PPY	1.014	0.609	0.852
Patients who did not meet the minimum treatment exposure[a]	219	99	318
No. of patients who reached TI	94	29	123
Total TD patient years[b]	168.7	105.2	273.9
No. of TI PPY	0.557	0.276	0.449

[a] Patients with ≥ 3 (for lenalidomide) or ≥ 6 (for azacitidine or decitabine) cycles of treatment (without discontinuation) during TD or treated patients who reached transfusion independency before the minimum number of cycles.
[b] For patients with TI, person-years were the years from the index date to TI. For patients without TI, person-years were the years from the index date to the end of follow-up.

Supplementary Information

Proportion of patients reaching TI from active treatment



Median days from active treatment to the TI	
Early initiators	267
Late initiators	380

Log-rank test for patients with early vs. late initiators: $P = 0.946$