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Abstract # 53

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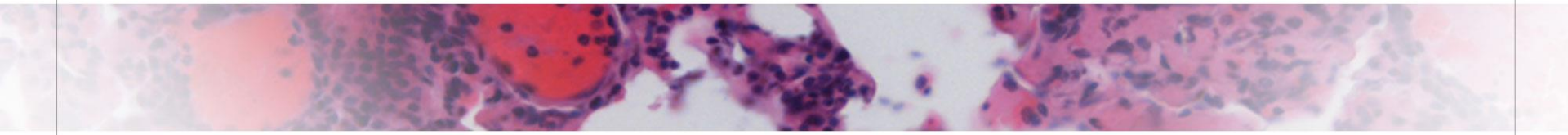

Favorable Overall Survival With Imetelstat Treatment Correlates With Other Clinical Benefits in Intermediate 2 or High Risk Myelofibrosis Relapsed/Refractory to Janus Kinase Inhibitor

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Disclosure

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- **Presenter:** John Mascarenhas, MD
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- **Disclosure:**
  - Consultancy: Celgene/BMS, Incyte, Roche, PharmaEssentia, Constellation, Kartos, Prelude, Geron, Abbvie
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Background

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- Myelofibrosis (MF) is a serious and life-threatening myeloproliferative neoplasm
- Patients who are relapsed after or refractory to (R/R) therapy with Janus kinase inhibitors (JAKi) have dismal overall survival (OS) of 13-16 months.[1,2]
- Imetelstat, a 13-mer oligonucleotide that specifically targets the RNA template of human telomerase, is a potent competitive inhibitor of telomerase enzymatic activity
- IMbark (MYF2001; NCT02426086) was a randomized, single-blinded, phase 2 study of imetelstat in R/R int-2/high-risk MF patients, that evaluated two doses of imetelstat: 9.4 mg/kg and 4.7 mg/kg IV every 3 weeks.
  - Dose-related clinical benefit, specifically in terms of symptom response and improvement in OS observed.[3]
  - The improvement in OS for patients treated with 9.4mg/kg imetelstat was further supported by analyses of IMbark patients with closely matched real world controls.[4]

[1]Kuykendall, et al. *Ann Hematol* 2018;97:435-441.
[2]Newberry, et al. *Blood* 2017;130:1125-1131.
[3]Mascarenhas, et al. *Blood* 2018;132:68.5.
[4]Kuykendall, et al. EHA 2019 #PS1456.

Imetelstat: First-in-Class Telomerase Inhibitor

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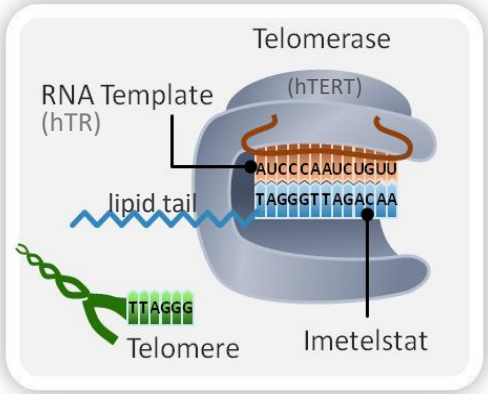
Imetelstat

- **Proprietary:** 13-mer thio-phosphoramidate oligonucleotide complementary to hTR, with covalently-bound lipid tail to increase cell permeability.
- **Potent, first in class competitive inhibitor of telomerase**: IC50 = 0.5-10 nM
- **Target:** selectively targets heme (MF) malignant stem and progenitor cell proliferation.[1, 2]

Imetelstat binds to RNA template preventing maintenance of telomeres



- Short telomere length (TL), high levels of telomerase activity (TA) and high expression of human telomerase reverse transcriptase (hTERT) correlated with higher risk, disease progression and shorter OS in patients with myeloid malignancies.[3-5]
- Nonclinical studies demonstrated that imetelstat reduces TA, hTERT expression level, and JAK2V617F^{+} hematopoietic progenitor cells in MF patient samples, indicative of mechanism based on-target activity.[1,2]
- **Cells with high levels of TA and hTERT and short TL, represent best target for treatment with telomerase inhibitor.**

[1]Wang, et al. *Blood Adv* 2018;2:2378-88.
[2]Mosoyan, et al. *Leukemia* 2017;31:2458-67.
[3]Briatore, et al. *Cancer Biol Ther* 2009;8:883-9.
[4]Kishtagari and Watts. *Ther Adv Hematol* 2017;8:317-26.
[5]Wang, et al. *Int J Lab Hematol* 2010;32:230-8.

Dose Related Clinical Benefits with Imetelstat Treatment

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Clinical Benefits	4.7 mg/kg (N = 48)	9.4 mg/kg (N = 59)
Median OS, months (95% CI)	19.9 (17.1, 33.9)	28.1 (22.8, 31.6)
Symptom Response at week 24 (TSS reduction ≥50%), n (%)	3 (6.3%)	19 (32.2%)
Spleen Response at week 24 (SVR ≥35% by IRC), n (%)	0	6 (10.2%)
Median PFS, months (95% CI)	14.8 (8.3, 17.1)	20.7 (12.0, 23.2)
Clinical improvement, per IWG-MRT, n (%)	8 (16.7%)	15 (25.4%)
Transfusion independence of 12 weeks, n/N (%)	2/14 (14.3%)	3/12 (25.0%)
Reduction in bone marrow fibrosis , n/N (%)	4/20 (20.0%)	16/37(43.2%)
≥ 25% Reduction in VAF of *JAK2, CALR* or *MPL* , n/N (%)	1/18 (5.6%)	8/19 (42.1%)

CALR = calreticulin gene, CI = confidence interval, JAK = Janus kinase, IWG-MRT = International Working Group – Myeloproliferative Neoplasms Research and Treatment, MPL = thrombopoietin receptor gene, OS = overall survival, PFS = progression free survival, SVR = spleen volume reduction, TSS = total symptom score, VAF = variant allele frequency

Objectives and Methods For Current Analysis

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Objectives:

- To evaluate the association between overall survival (OS) and spleen response, symptom response and fibrosis improvement.
- To explore the prognostic pretreatment baseline characteristic factors on OS.

Methods

- Spleen response: spleen volume reduction (SVR) ≥35% at Week 24.
- Symptom response: total symptom score (TSS) reduction ≥50% at Week 24.
- OS analysis was performed based on database lock in April 2020; median follow-up was 41.7 months (range 0.2, 49.2).
  - All 107 enrolled patients (n=59 in 9.4 mg/kg arm, n=48 in 4.7 mg/kg arm) were included in ITT analysis.
  - All correlation analyses were done irrespective of treatment dose.
- Bone marrow fibrosis was assessed by central pathology laboratory and graded by European Consensus method, including evaluation of reticulin and collagen changes.
  - Fibrosis improvement was defined as a decrease in fibrosis by ≥1 grade.

Potential OS Improvement with 9.4 mg/kg Imetelstat Treatment in Patients with MF R/R to JAKi

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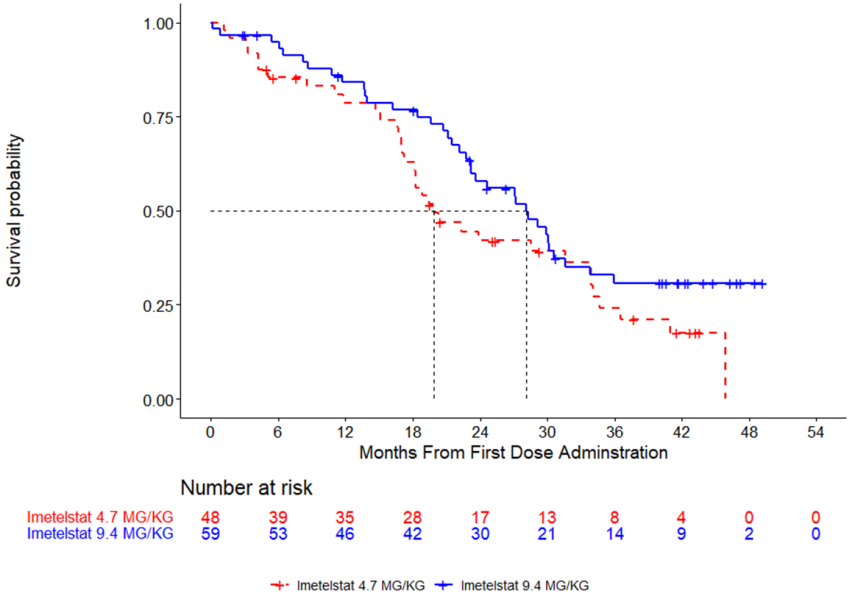

	4.7 mg/kg (N = 48)	9.4 mg/kg (N = 59)
Number of events, n (%)	35 (72.9%)	36 (61.0%)
Number censored, n (%)	13 (27.1%)	23 (39.0%)
Median Overall Survival (months) (95% CI)	19.9 (17.1, 33.9)	28.1 (22.8, 31.6)
12-months survival rate % (95% CI)	78.6 (63.9, 87.9)	84.0 (71.6, 91.4)
24-months survival rate % (95% CI)	42.0 (27.4, 56.0)	57.9 (43.6, 69.7)

OS analysis was performed based on database lock in April 2020; median follow-up was 41.7 months (range 0.2, 49.2)

Similar results were observed when sensitivity analyses accounted for confounding factors of subsequent therapies, including hematopoietic stem cell transplantation and dose escalation from 4.7 mg/kg to 9.4 mg/kg

Lower Risk of Death Significantly Correlates with Improved Bone Marrow Fibrosis in Patients Treated with Imetelstat

- **Dose related improvement in bone marrow fibrosis**
- **Patients with improved or stable bone marrow fibrosis had lower risk of death than those who had worsening bone marrow fibrosis**

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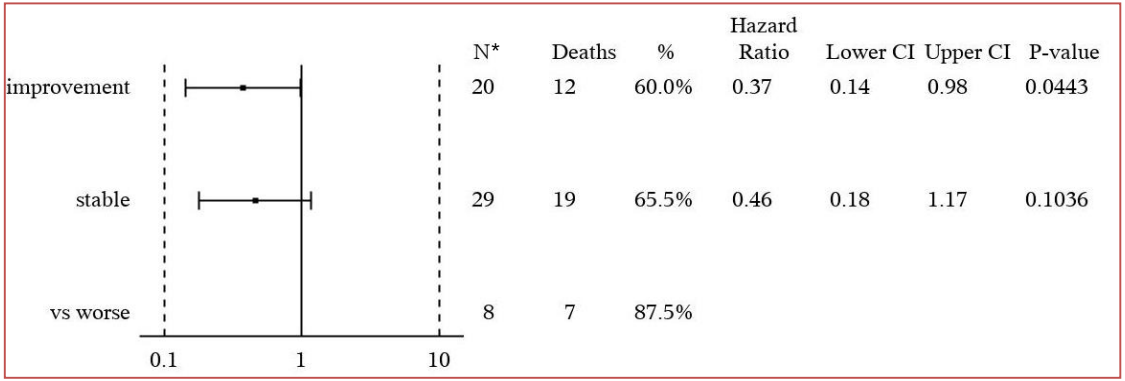
	4.7 mg/kg	9.4 mg/kg
Bone marrow fibrosis improvement, n/N (%)	4/20 (20.0%)	16/37(43.2%)



	N*	Deaths	%	Hazard Ratio	Lower CI	Upper CI	P-value
improvement	20	12	60.0%	0.37	0.14	0.98	0.0443
stable	29	19	65.5%	0.46	0.18	1.17	0.1036
vs worse	8	7	87.5%				

*N: 57 pts had baseline and at least one post-baseline bone marrow fibrosis assessment irrespective of dose.
Bone marrow fibrosis was assessed by central pathology laboratory and graded by European Consensus method, including evaluation of reticulin and collagen changes.
Fibrosis improvement was defined as a decrease in fibrosis by ≥1 grade.

Patients with Symptom Response Trend to Have Lower Risk of Death

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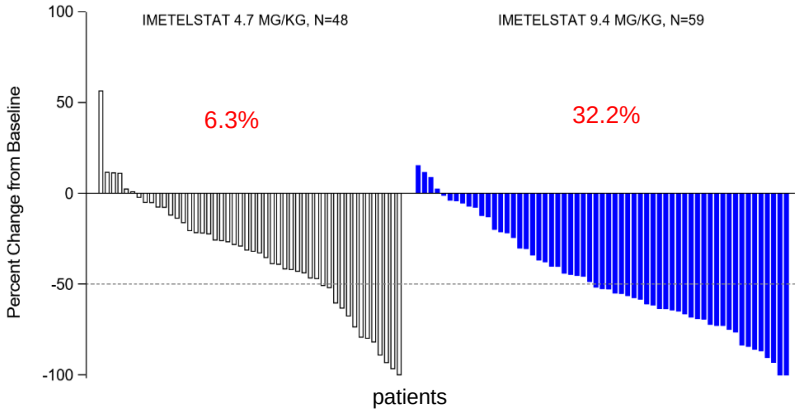
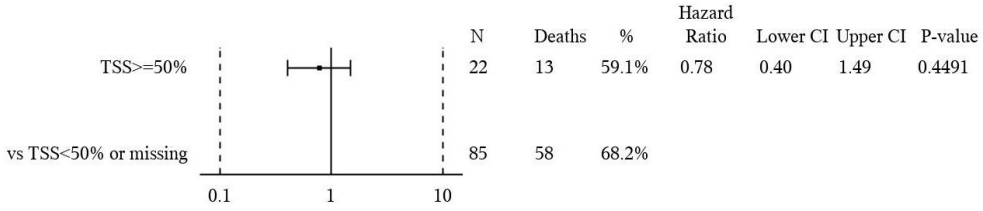
Dose-dependent symptom response: higher response rate seen in 9.4mg/kg arm than in 4.7 mg/kg arm



Symptom response: ≥ 50% total symptom score reduction at Week 24

Patients who achieved symptom response demonstrated a trend of lower risk of death compared to those who did not achieve symptom response



N: Number of patients in each (reference or non-reference) category irrespective of dose.

Deaths: Number of deaths in each category.

Hazard ratios (HR) and p-values are based on Cox regression models with Imtelelstat treatment cohort and response category as factors.

TSS: total symptom score

Patients with SVR Trend to Have Lower Risk of Death

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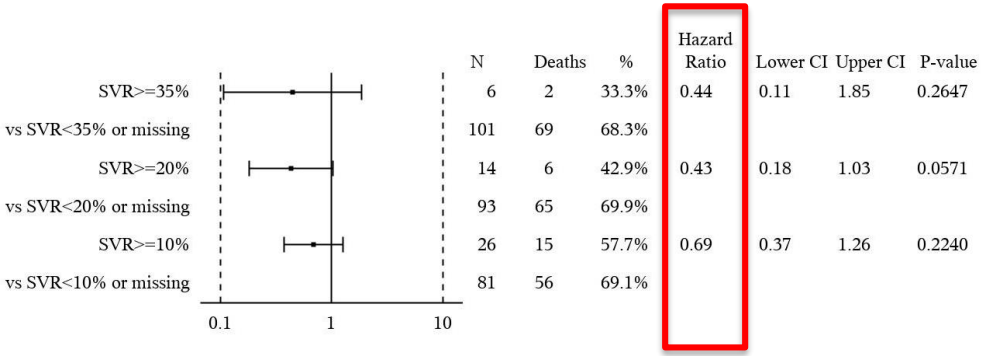
Dose-dependent spleen volume reduction (SVR) at week 24 or at any time

Spleen volume reduction	4.7 mg/kg (N = 48)	9.4 mg/kg (N = 59)
Max SVR at any time: >=10%		
Responders (%)	9 (18.8%)	32 (54.2%)
95% CI	(8.9%, 32.6%)	(40.8%, 67.3%)
Max SVR at any time: >=20%		
Responders (%)	5 (10.4%)	20 (33.9%)
95% CI	(3.5%, 22.7%)	(22.1%, 47.4%)
Max SVR at any time: >=35%		
Responders (%)	1 (2.1%)	7 (11.9%)
95% CI	(0.1%, 11.1%)	(4.9%, 22.9%)
SVR at week 24: >=10%		
Responders (%)	4 (8.3%)	22 (37.3%)
95% CI	(2.3%, 20%)	(25%, 50.9%)
SVR at week 24: >=20%		
Responders (%)	1 (2.1%)	13 (22%)
95% CI	(0.1%, 11.1%)	(12.3%, 34.7%)
SVR at week 24: >=35%		
Responders (%)	0	6 (10.2%)
95% CI	(0%, 7.4%)	(3.8%, 20.8%)

Patients who achieved at least >=10% SVR demonstrated a trend of lower risk of death compared to those who did not



N: Number of patients in each (reference or non-reference) category irrespective of dose.

Deaths: Number of deaths in each category.

Hazard ratios (HR) and p-values are based on Cox regression models with Imtelelstat treatment cohort and response category as factors.

SVR, spleen volume reduction.

Predictive Disease Characteristics for Survival After Imetelstat Treatment

Pretreatment DIPSS high risk, ECOG performance status, transfusion dependency, response to last JAKi, higher baseline neutrophils, lower baseline Hb and platelet values correlated with increased risk of death

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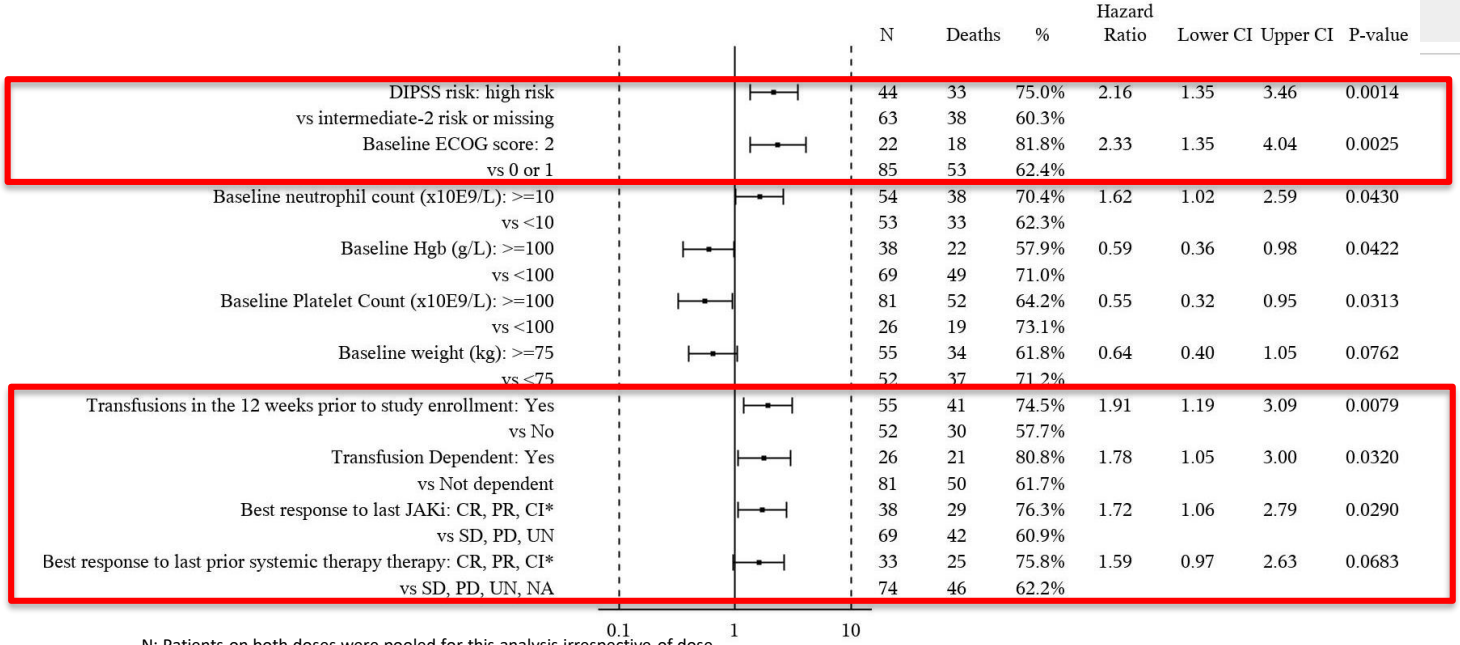

	N	Deaths	%	Hazard Ratio	Lower CI	Upper CI	P-value
DIPSS risk: high risk	44	33	75.0%	2.16	1.35	3.46	0.0014
vs intermediate-2 risk or missing	63	38	60.3%				
Baseline ECOG score: 2	22	18	81.8%	2.33	1.35	4.04	0.0025
vs 0 or 1	85	53	62.4%				
Baseline neutrophil count (x10E9/L): >=10	54	38	70.4%	1.62	1.02	2.59	0.0430
vs <10	53	33	62.3%				
Baseline Hgb (g/L): >=100	38	22	57.9%	0.59	0.36	0.98	0.0422
vs <100	69	49	71.0%				
Baseline Platelet Count (x10E9/L): >=100	81	52	64.2%	0.55	0.32	0.95	0.0313
vs <100	26	19	73.1%				
Baseline weight (kg): >=75	55	34	61.8%	0.64	0.40	1.05	0.0762
vs <75	52	37	71.2%				
Transfusions in the 12 weeks prior to study enrollment: Yes	55	41	74.5%	1.91	1.19	3.09	0.0079
vs No	52	30	57.7%				
Transfusion Dependent: Yes	26	21	80.8%	1.78	1.05	3.00	0.0320
vs Not dependent	81	50	61.7%				
Best response to last JAKi: CR, PR, CI*	38	29	76.3%	1.72	1.06	2.79	0.0290
vs SD, PD, UN	69	42	60.9%				
Best response to last prior systemic therapy therapy: CR, PR, CI*	33	25	75.8%	1.59	0.97	2.63	0.0683
vs SD, PD, UN, NA	74	46	62.2%				

N: Patients on both doses were pooled for this analysis irrespective of dose.
Deaths: Number of deaths in each category.
Hazard ratios (HR) and p-values are based on Cox regression models with Imtelelstat treatment cohort and demographic or baseline characteristic as factors.
CI: clinical improvement.

Conclusions

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- **Imetelstat showed dose-related improvement in OS in patients who are R/R to JAKi. The survival benefit observed with imetelstat was supported by the trend of correlation with other clinical benefits.**
  - **With a median follow-up of 41.7 months, the median OS was 28.1 months for the 9.4 mg/kg arm (95% CI: 22.8, 31.6) and 19.9 months for the 4.7 mg/kg arm (95% CI: 17.1, 33.9).**
  - **There was statistically significant correlation between bone marrow fibrosis improvement and lower risk of death, which together with the clinical data for improved survival suggests that imetelstat has disease modifying activity.**
  - **Patients who achieved symptom and spleen response at week 24 showed trend of longer OS compared to patients who did not achieve response**
  - **Pretreatment DIPSS high risk, ECOG performance status, transfusion dependency, response to last JAKi, higher baseline neutrophils, lower baseline Hb and platelet values correlated with increased risk of death.**
- **The Phase 3 study (IMpactMF, NCT04576156) of imetelstat in patients with refractory myelofibrosis with primary endpoint of OS is expected to be open for screening and enrollment in Q1-2021.**

Phase 3 Study Design

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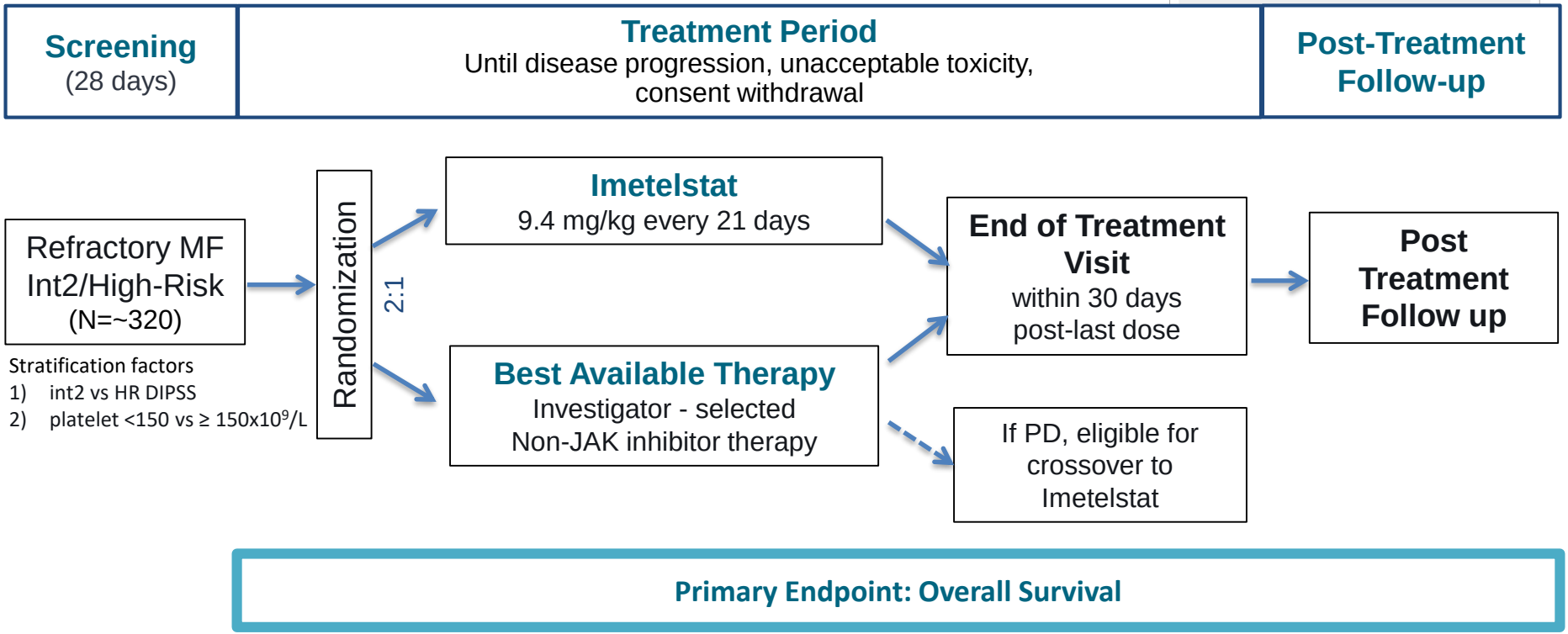

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