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Abstract #347

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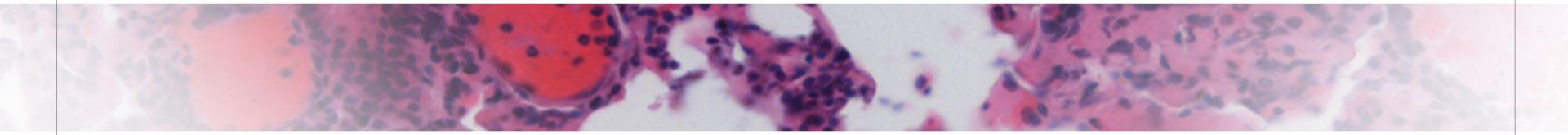

Telomerase Activity, Telomere Length and hTERT Expression Correlate With Clinical Outcomes in Higher-Risk Myelofibrosis (MF) Relapsed/Refractory (R/R) to Janus Kinase Inhibitor Treated With Imetelstat

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Disclosure

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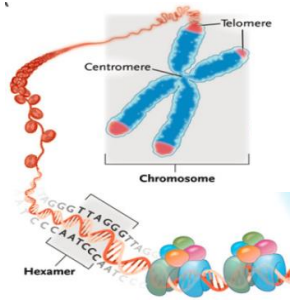
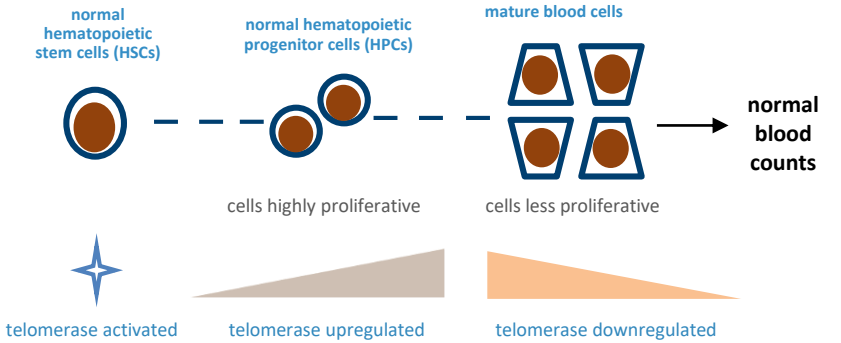
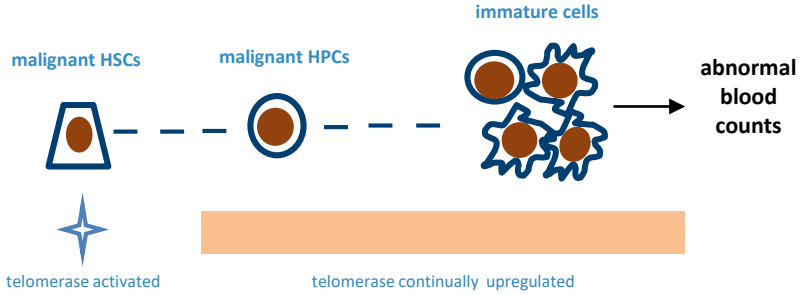
- **Disclosure:**
  - Consultancy: Celgene/BMS, Incyte, Roche, PharmaEssentia, Constellation, Kartos, Prelude, Geron, Abbvie
  - Research funding: CTI Biopharma, Incyte, Janssen, Merck, Novartis, Promedior, Roche, Merus, AROG, Kartos, Forbius

Telomerase As A Target in Hematologic Malignancies







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Telomeres

- Essential genetic elements
- TTAGGG repeats, cap chromosome ends
- Shorten without telomerase
- Accelerated loss under stress

Telomerase

- Synthesizes telomeric DNA required for cell immortality
- Not active in somatic cells; transiently upregulated in normal hematopoietic progenitor cells to support controlled proliferation
- Highly upregulated in malignant progenitor cells, enabling continued and uncontrolled proliferation

Nobel Prize in Medicine 2009

- Chromosomes are protected by telomeres and telomerase

Imetelstat: First-in-Class Telomerase Inhibitor

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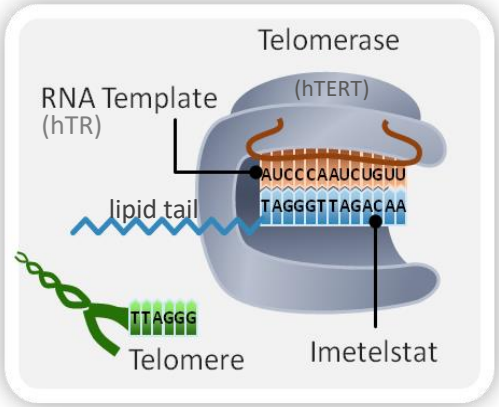
Imetelstat

- **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

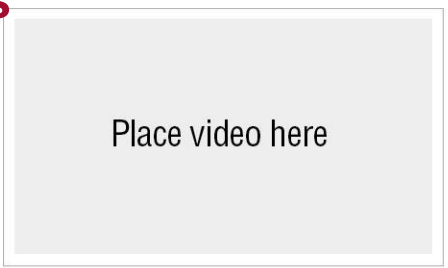


- Short telomere length (TL), high levels of telomerase activity (TA) and high expression of human telomerase reverse transcriptase (hTERT) correlated with higher risk, disease progression and shorter OS in patients with myeloid malignancies.[3-5]
- Nonclinical studies demonstrated that imetelstat reduces 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.

IMbark Phase 2 Trial: Dose-dependent Clinical Benefits Observed with Imetelstat Treatment

IMbark (MYF2001; NCT02426086) was a randomized, single-blind phase 2 study to evaluate the activity of 2 dose levels of imetelstat (9.4 mg/kg or 4.7 mg/kg, IV every 3 weeks) in intermediate-2/high-risk myelofibrosis (MF) relapsed/refractory (R/R) to prior Janus kinase inhibitor (JAKi) treatment.

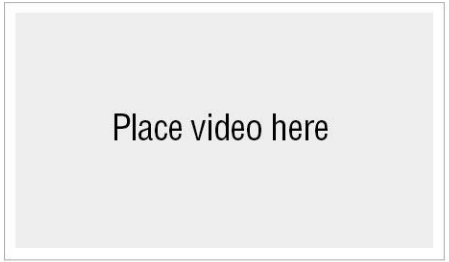


Clinical Benefits	4.7 mg/kg (N = 48)	9.4 mg/kg (N = 59)
Median OS, months (95% CI)	19.9 (17.1, 33.9)	28.1 (22.8, 31.6)
Symptom Response at week 24 (TSS reduction ≥50%), n (%)	3 (6.3%)	19 (32.2%)
Spleen Response at week 24 (SVR ≥35% by IRC), n (%)	0	6 (10.2%)
Median PFS, months (95% CI)	14.8 (8.3, 17.1)	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

Mascarenhas, et al. *Blood* 2018;132:68.5.
Mascarenhas, et al. EHA 2020 EP1107.

Objectives



- Evaluate on-target pharmacodynamic (PD) effect of imetelstat and relationship to dose and exposure levels in MF patients.
- Assess the correlation of the optimal PD effect with symptom or spleen response and OS.
  - Clinical cut off date April 21, 2020
- Explore the association between baseline telomere length, hTERT expression level and clinical benefits.
- Evaluate the change in allele burden of driver mutation, such as *JAK2, CALR, MPL*, by imetelstat treatment to assess disease-modifying activity.

Methods

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- Blood samples were collected to test for:
  - TA by quantitative telomeric repeat amplification protocol technology.
  - hTERT level by Taqman RT-PCR assay.
  - TL by high-throughput quantitative fluorescence in situ hybridization technology
  - Mutations and variant allele frequency (VAF) by next-generation sequencing.
- Optimal PD effect of imetelstat was defined as ≥50% reduction in TA or hTERT from baseline, as it correlated with antitumor activity in preclinical PK/PD/efficacy studies.
- Imetelstat plasma concentration was determined by a fully validated method, the high exposure was defined by C1-AUC0-24hr or Cmax value >Mean value.

Dose-dependent and Exposure-dependent PD Effects

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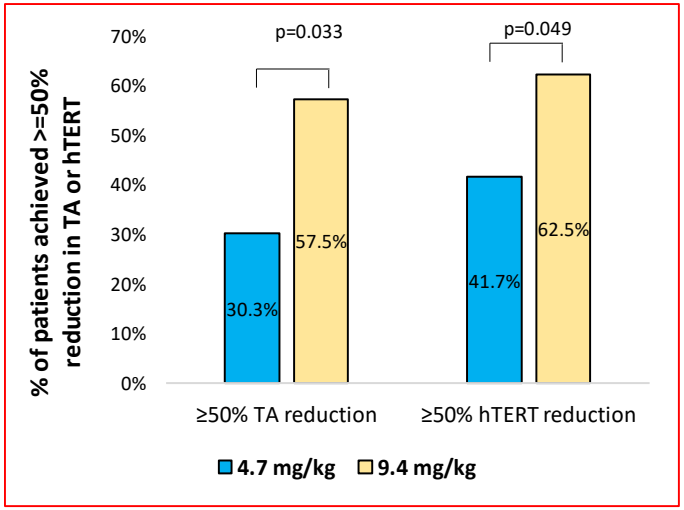
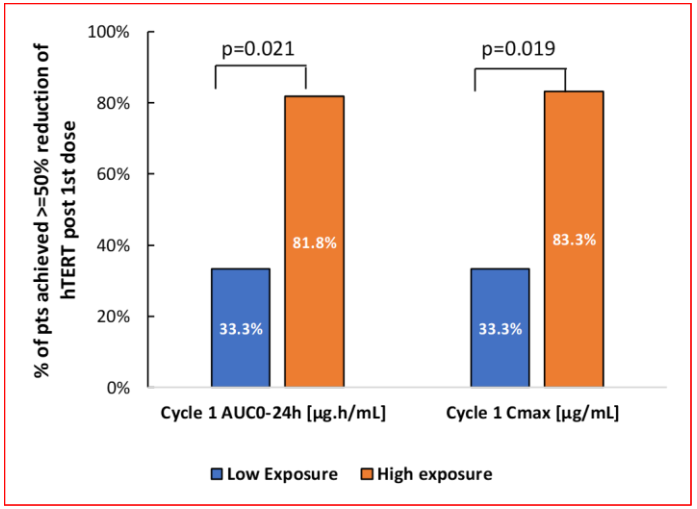
Significantly higher % of pts in 9.4mg/kg arm achieved optimal PD effect* compared to 4.7mg/kg arm



Significantly higher % pts with higher imetelstat exposure achieved ≥50% hTERT reduction**



*Optimal PD effect defined as >=50% reduction in telomerase activity (TA) or hTERT expression level.
**28 pts had serial (intense) PK samples collected during C1D1; Cmax and AUC0-24h were determined for exposure.

Optimal PD Effect Correlated with Clinical Responses and Longer OS

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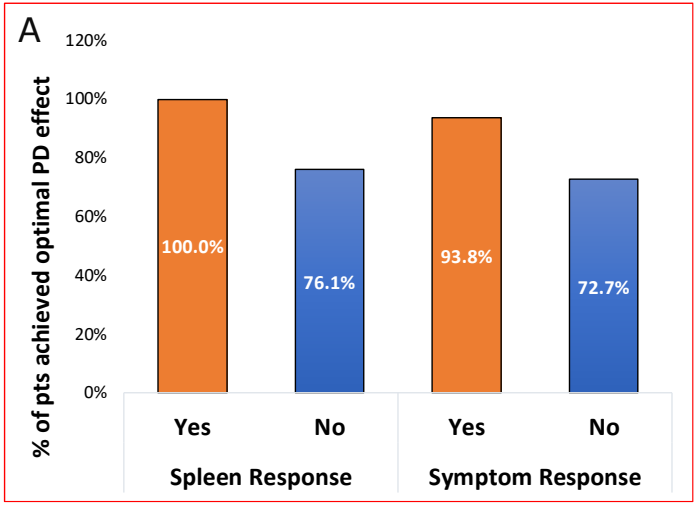
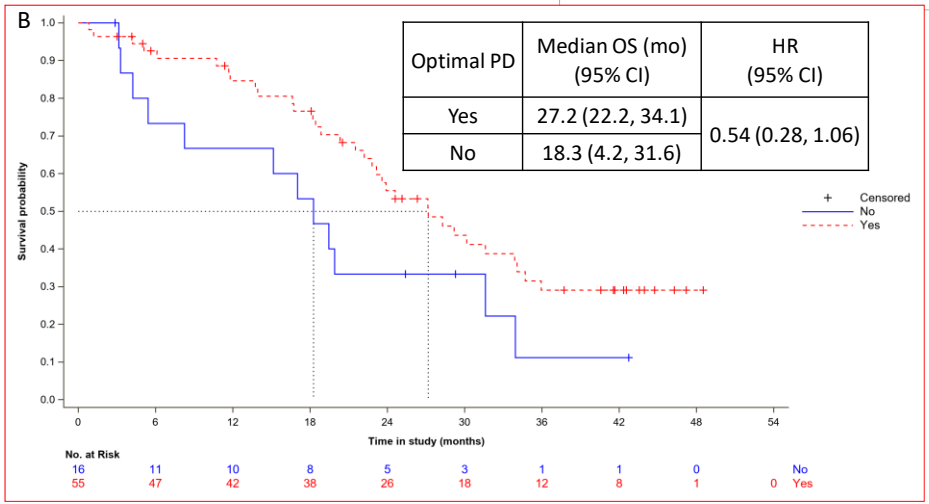
Higher % of patients who had spleen or symptom response achieved optimal PD effect*



Spleen response: ≥ 35% spleen volume reduction at Week 24
Symptom response: ≥ 50% total symptom score reduction at Week 24

Patients who achieved optimal PD effect had longer OS



Optimal PD	Median OS (mo) (95% CI)	HR (95% CI)
Yes	27.2 (22.2, 34.1)	0.54 (0.28, 1.06)
No	18.3 (4.2, 31.6)	

*Optimal PD effect (≥50% reduction in telomerase activity (TA) or hTERT expression level)

Imetelstat Has Potential Disease-modifying Activity by Targeting Malignant Clones

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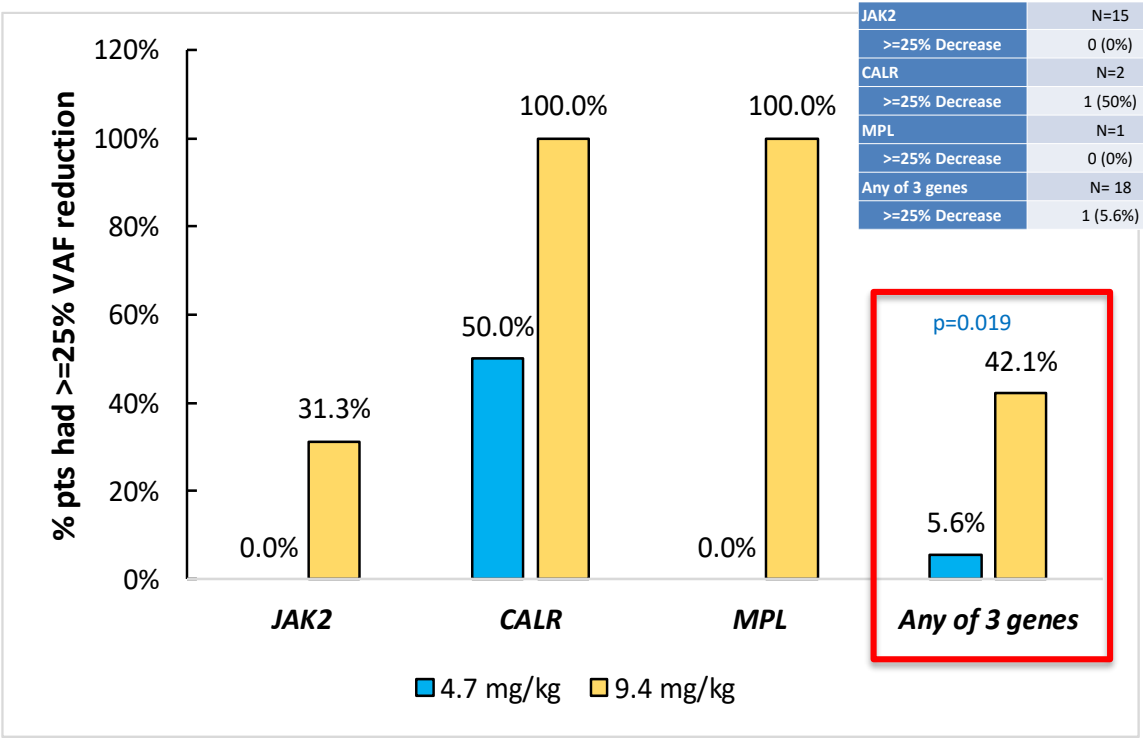
Imetelstat resulted in dose-dependent reduction in VAF of JAK2V617F, CALR and MPL mutations



	4.7 mg/kg	9.4 mg/kg
JAK2	N=15	N=16
>=25% Decrease	0 (0%)	5 (31.3%)
CALR	N=2	N=2
>=25% Decrease	1 (50%)	2 (100%)
MPL	N=1	N=1
>=25% Decrease	0 (0%)	1 (100%)
Any of 3 genes	N= 18	N=19
>=25% Decrease	1 (5.6%)	**8 (42.1%)**

Shorter Baseline Telomere Length Associated with Clinical Responses for 9.4 mg/kg Imetelstat

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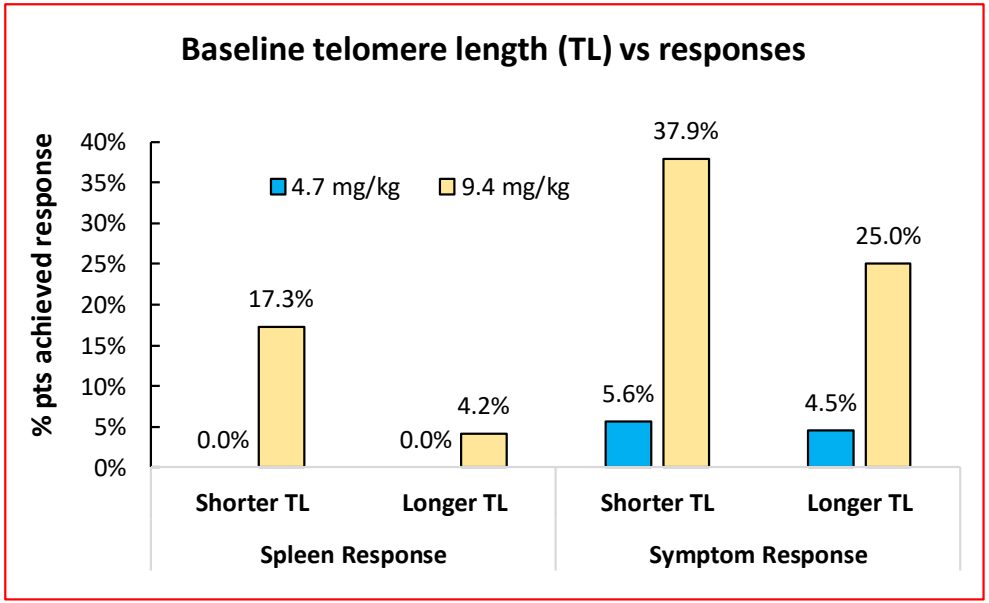
Patients with shorter baseline TL (≤median) had higher rates of spleen and symptom response in the imetelstat 9.4 mg/kg arm



Spleen response: ≥ 35% spleen volume reduction at Week 24

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

Correlation Between Shorter Telomere Length and Longer OS

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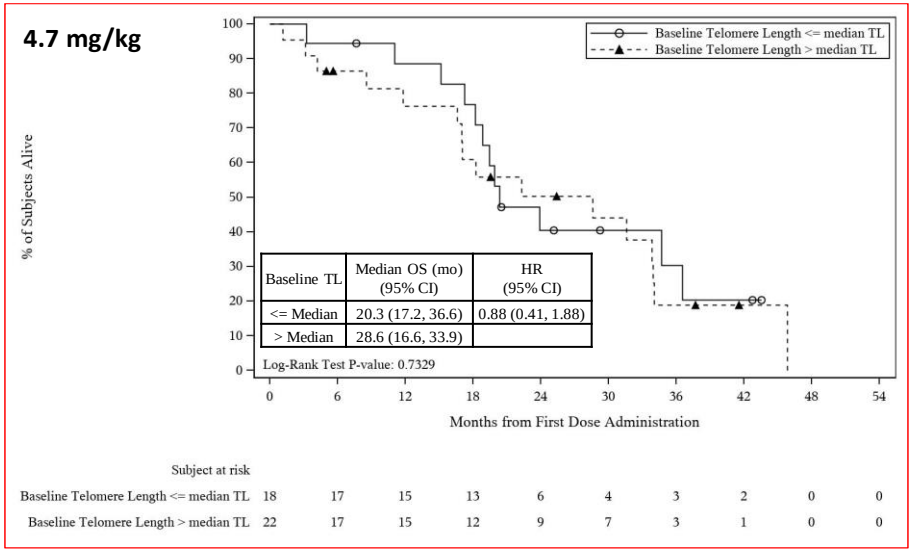
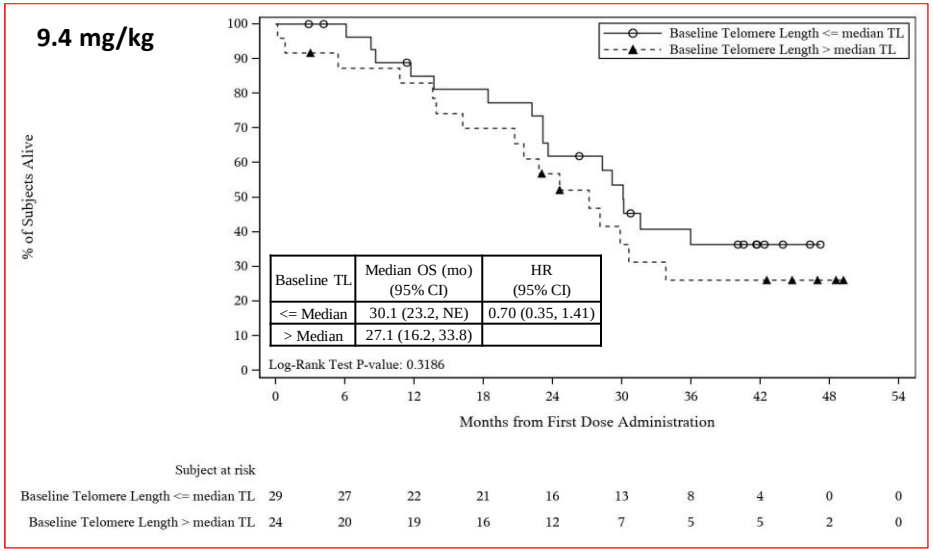
Compared to 4.7 mg/kg, patients with shorter baseline TL had a trend of improved OS when treated with 9.4 mg/kg of imetelstat

4.7 mg/kg



9.4 mg/kg



Higher Baseline hTERT Expression Level Associated with Clinical Responses to 9.4 mg/kg Imetelstat

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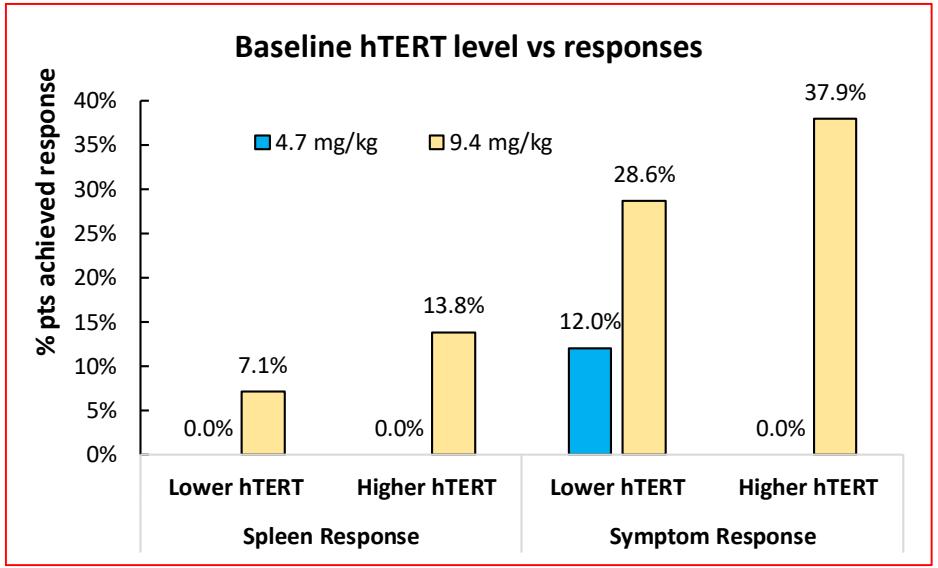
Patients with higher baseline hTERT level (>median) had higher rate of spleen and symptom response in imetelstat 9.4 mg/kg arm



Spleen response: ≥ 35% spleen volume reduction at Week 24

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

Conclusions

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- Imetelstat achieved dose- and exposure-dependent reduction of telomerase activity and hTERT expression level, demonstrating on-target mechanism of action.
- Achievment of the optimal PD effect (≥50% reduction of telomerase activity or hTERT level) in patients treated with imetelstat correlated with better clinical response rates and longer OS.
  - This validates the pre-clinical findings for correlation between PD and anti-tumor activity.
- Significant, dose-dependent, reduction in VAF of JAK2, CALR and MPL mutations were observed, indicating that imetelstat has disease-modifying activity by targeting the underlying MF malignant clones.
- Treatment with imetelstat at 9.4mg/kg improved clinical outcomes in patients with shorter telomeres or higher hTERT expression level at baseline.
  - The results are consistent with telomere biology in cancer cells and provide evidence for on-target mechanism of action of imetelstat through telomerase inhibition.
- This is the first clinical report to systematically evaluate the mechanism of action-based PD effect of imetelstat, and its relationship to exposure and clinical benefits.

Acknowledgements

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The authors thank all the patients for their participation in this study and acknowledge the collaboration and commitment of all investigators and their staff