Imetelstat, a Telomerase Inhibitor, Is Capable of Depleting Myelofibrosis Hematopoietic Stem and Progenitor Cells

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Background

Imetelstat (GRN163L, JNJ-63935937)

13-mer Oligonucleotide Complimentary to the Template Region of TERC (the RNA Component of Telomerase)

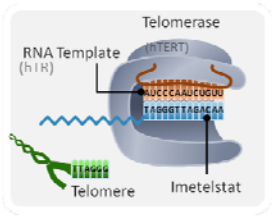


Image Source: Geron

What We Know about Imetelstat

- **Imetelstat inhibits telomerase activity and cell proliferation in various cancer cell lines and tumors in mouse xenograft models** (Ouellette et al, J Cell Mol Med, 2011)**; inhibits proliferation and induces apoptosis of cancer stem cells** (Joseph et al, Cancer Res, 2010; Clin Cancer Res, 2010; Bruediagm et al. Cell Stem Cell, 2014)**.**
- **Imetelstat has been tested in Phase I and I/II clinical trials in solid tumors, e.g. breast and lung** cancer (Kozloff et al. Journal of Clinical Oncology, 2010; Chiappori et al. Ann Oncol, 2015) **and hematological malignancies, e.g. chronic lymphoproliferative disease (**Röth et al. Small Molecules in Oncology. 2009)**, refractory and relapsed multiple myeloma (** Huff et al. Blood, 2012)**, myeloproliferative neoplasms** (Baerlocher et al; Tefferi et al. N Engl J Med. 2015).

Imetelstat In Myeloproliferative Neoplasms (MPN)

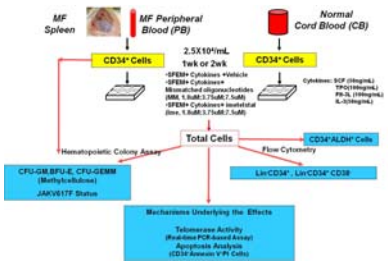
N Engl J Med. 2015 Sep 3;373(10):920-8.
Telomerase Inhibitor Imetelstat in Patients with Essential Thrombocythemia.
Baerlocher GM, Oppliger Leibundgut E, Ottmann OG, Spitzer G, Odenike O, McDevitt MA, Roth A, Daskalakis M, Burington B, Stuart M, Snyder DS.

N Engl J Med. 2015 Sep 3;373(10):908-19.
A Pilot Study of the Telomerase Inhibitor Imetelstat for Myelofibrosis.
Tefferi A, Lasho TL, Begna KH, Patnaik MM, Zblewski DL, Finke CM, Laborde RR, Wassie E, Schimek L, Hanson CA, Gangat N, Wang X, Pardanani A.

Question

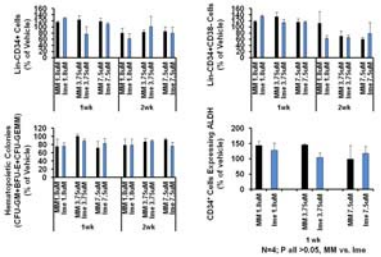
Can imetelstat selectively target myelofibrosis (MF) stem and progenitor cells?

Experimental Design I

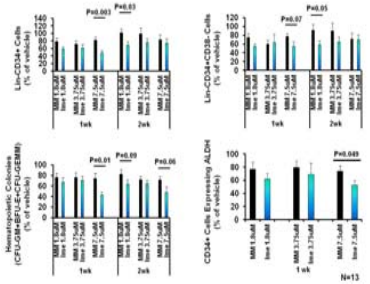


Results

Imetelstat Has Limited Effects on the Proliferation of Normal Hematopoietic Stem Cells (HSC)/Hematopoietic Progenitor Cells (HPC)



Imetelstat Inhibits the Proliferation of MF HSCs/HPCs

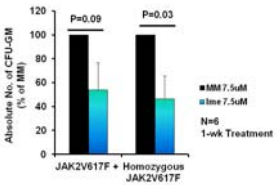


Treatment with Imetelstat Results in a Reduction in JAK2V617F+ HPCs from Some Patients with MF (1-wk Treatment)

Source of Hematopoietic colonies (CFU-GM) Assayed

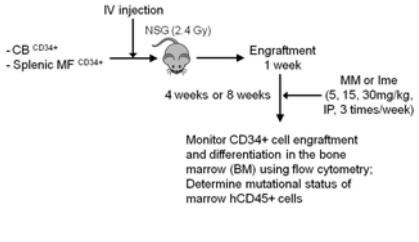
	CD34⁺ Cells Treated with Cytokines +vehicle		CD34⁺ Cells Treated with Cytokines + MM (7.5uM)		CD34⁺ Cells Treated with Cytokines + Ime (7.5uM)	
	JAK2V617F	% Homozygous JAK2V617F	JAK2V617F	% Homozygous JAK2V617F	JAK2V617F	% Homozygous JAK2V617F
SP18	38(8/18)*	31 (5/16)	56(10/27)	52(14/27)	9(2/23)	0(0/23)
SP19	100(27/27)	89(24/27)	100(22/22)	82(18/22)	100(30/30)	97 (29/30)
SP21	64 (9/14)	36 (5/14)	72 (13/18)	22 (4/18)	60 (12/20)	20 (4/20)
SP22	100 (20/20)	80(16/20)	100 (21/21)	90 (19/21)	100 (11/11)	73 (8/11)
PB177	63 (19/30)	37 (11/30)	80 (20/25)	56 (14/25)	82 (25/31)	39 (12/31)
PB195	96 (25/26)	81 (21/26)	86 (19/22)	68 (15/22)	70 (14/20)	60 (10/20)

Imetelstat Is Capable of Depleting Malignant HPCs from MF Patients

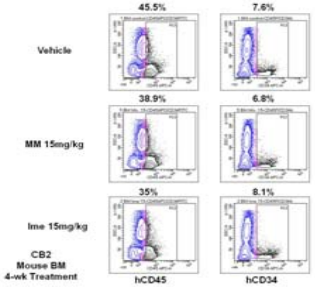


Experimental Design II

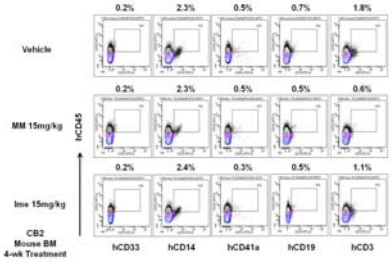
Treating NSG Mice Transplanted with Normal or MF Splenic CD34⁺ Cells Directly with Imetelstat



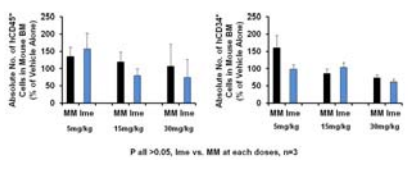
Imetelstat (15mg/kg) Treatment Mildly Affects Normal CD34+ Cell Engraftment in NSG Mice



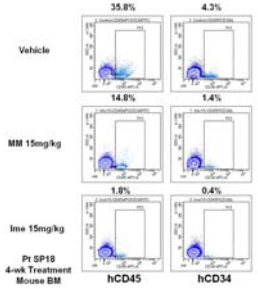
Imetelstat Treatment (15mg/kg) Mildly Affects Multi-lineage Differentiative Ability of Normal CD34⁺ Cells in NSG Mice



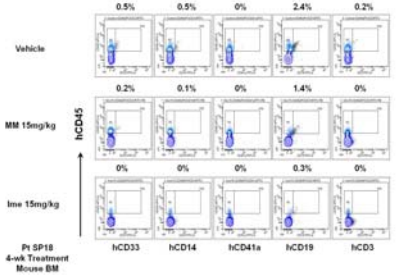
Effect of Imetelstat Treatment on Normal HSCs (4-wk Treatment)



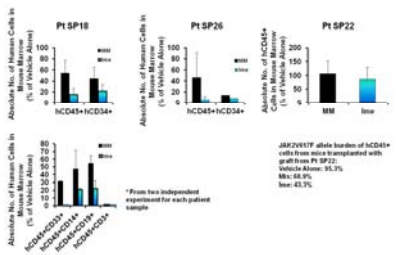
Imetelstat Treatment Reduces the Engraftment of MF CD34+ Cells in a Xenograft Mouse Model



Multi-lineage Cells Derived from MF Stem Cells Are Depleted by Imetelstat Treatment

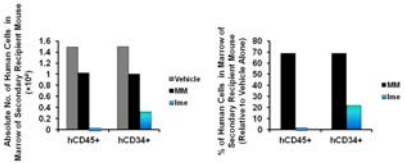


Imetelstat Is Capable of Selectively Eliminating MF Stem Cells

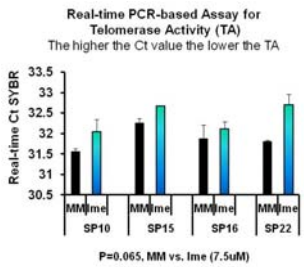


Imetelstat Treatment Affects Self-renewal Capacity of MF Stem Cells

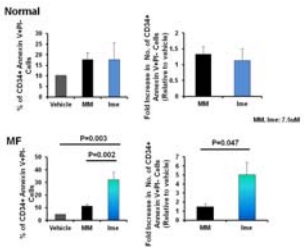
Secondary Transplantation with BMCs from Primary Recipient Mice Receiving Grafts from Pt SP18 Followed by Various Treatments



Imetelstat Treatment Inhibits Telomerase Activity of Splenic MF CD34⁺ Cells



Imetelstat Induces Apoptosis of MF but not Normal CD34⁺ Cells



Summary

- Imetelstat at the doses studied has minimal effects on normal hematopoiesis. By contrast, imetelstat is capable of inhibiting the proliferation of phenotypically and functionally defined MF HSCs and myeloid progenitor cells.
- Imetelstat in patients can preferentially deplete malignant MF hematopoietic progenitors.
- Imetelstat is capable of depleting MF long-term HSCs assayed using a patient-derived xenograft MF mouse model, although it has minimal effects on normal counterpart.
- These effects are associated with inhibition of telomerase activity, leading to the induction of apoptosis.

Conflict-of-Interest Disclosure

Wang, X. – Research funding, Janssen Research & Development, LLC