Effects of Imetelstat on the Stem Cells of Patients with Myelofibrosis

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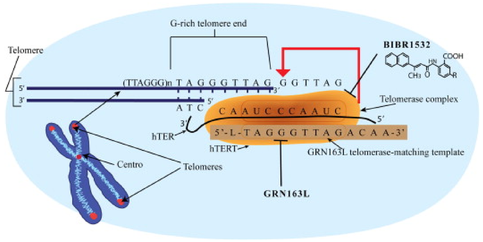
Background

Imetelstat (GRN163L) – Geron Corporation



Ruden&Puri, Cancer Treat Rev, 2013

- **A lipid modified 13-mer antisense oligonucleotide complimentary to the template region of TERC (telomerase RNA component)**
- **Binds to telomerase with high affinity and inhibits its activity .**
- **Showed the therapeutic potential in cancer cells in in vitro preclinical models and in vivo xenograft models (Dikmen ZG, et al. Cancer Res. 2005;65(17):7866-73; Hochreiter AE, et al. Clin Cancer Res. 2006;12(10):3184-92); inhibited proliferation and induced apoptosis of cancer stem cells (Joseph I, et al. Cancer Res. 2010;70(22):9494-504).**

Effects of Imetelstat on MPNs

• Myelofibrosis (MF) is one of myeloproliferative neoplasms (MPN) including polycythemia vera (PV)-, essential thrombocythemia (ET)-post MF and primary MF (PMF), which are thought to originate at the level of a pluripotent hematopoietic stem cell (HSC). Therapies that target MF stem cells (MF-SC), therefore, represent a promising therapeutic strategy for achieving efficacious and durable responses in MF patients.

•In vitro studies have demonstrated that Imetelstat selectively inhibits spontaneous megakaryocytic colony-forming unit (CFU-Meg) growth from the blood of patients with ET but not from healthy individuals (Brunold C, et al. Blood (ASH Annual Meeting Abstracts), Nov 2011; 118: 3843).

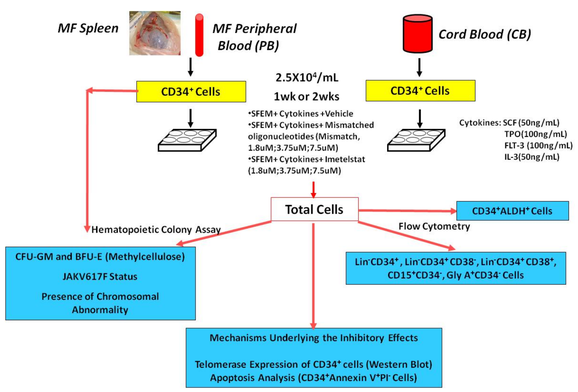
•Phase I studies indicate that Imetelstat inhibits telomerase activity in patients with ET and that Imetelstat rapidly induces and maintains hematologic responses in ET patients who have failed or are intolerant to conventional therapies. Substantial molecular responses have been observed in JAK2V617F-positive patients and inhibition of the neoplastic progenitor cell growth *ex-vivo* has been demonstrated (*Baerlocher G, et al.* Blood (ASH Annual Meeting Abstracts), Nov 2012; 120: 179)

•An investigator initiated clinical trial in MF showed that Imetelstat can achieve complete clinical remissions by IWG criteria. This includes the reversal of bone marrow fibrosis and induction of morphologic and molecular remissions in a subset of patients with MF. This suggests that Imetelstat has disease-modifying activity in MF (Tefferi A, et al. Blood (ASH Annual Meeting Abstracts), Nov 2013; 122:662)

Objectives

•How imetelstat achieves these beneficial effects on MF patients?
•Can Imetelstat selectively target MF stem and progenitor cells?

Experimental Design

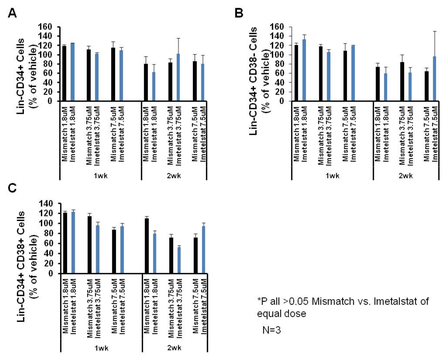


Conflict-of-Interest Disclosure

Wang, X. – Research funding, Geron Corporation

Results

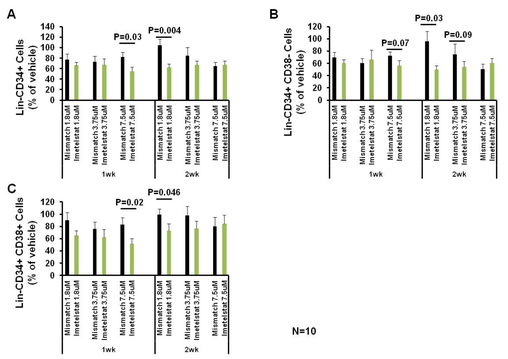
Imetelstat Has Limited Effects on the Proliferation of Phenotypically Defined CB HSCs/HPCs



*P all >0.05 Mismatch vs. Imetalstat of equal dose

N=3

Imetelstat Inhibits the Proliferation of Phenotypically Defined MF HSCs/HPCs

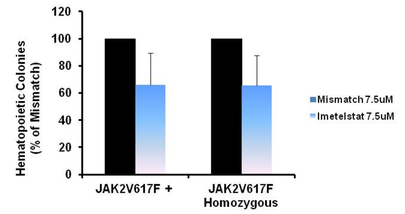


N=10

Treatment with Imetelstat Results in a Reduction in JAK2V617F+ Hematopoietic Progenitor Cells

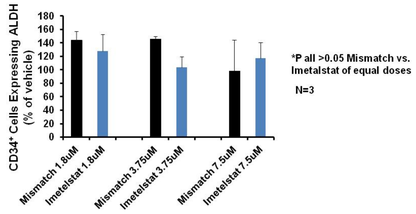
	Source of Hematopoietic colonies Assayed					
	CD34+ Cells Treated with Cytokines alone		CD34+ Cells Treated with Cytokines + Mismatch (7.5uM)		CD34+ Cells Treated with Cytokines + Imetelstat (7.5uM)	
	% JAK2V617F	% Homozygous JAK2V617F	% JAK2V617F	% Homozygous JAK2V617F	% JAK2V617F	% Homozygous JAK2V617F
SP11	41(7/17)*	29 (5/17)	57(16/28)	50(14/28)	9(2/23)	0(0/23)
SP12	100(27/27)	89(24/27)	100(22/22)	82(18/22)	100(30/30)	97 (29/30)
SP14	64(9/14)	36 (5/14)	72(13/18)	22(4/18)	60(12/20)	25 (5/20)
SP15	100 (20/20)	80(16/20)	100 (21/21)	90 (19/21)	100 (11/11)	73 (8/11)

The numbers in parentheses denote the actual number of JAK2V617F-positive or homozygous colonies/the total numbers of colonies analyzed.



N=4

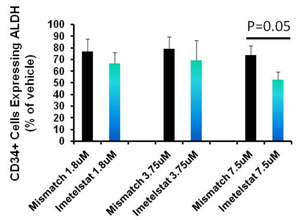
Imetelstat Does Not affect the Generation of CB CD34+ Aldehyde Dehydrogenase (ALDH) + Cells



*P all >0.05 Mismatch vs. Imetalstat of equal doses

N=3

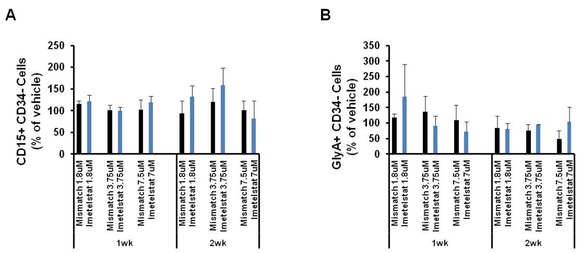
Imetelstat Inhibits the Generation of MF CD34+ ALDH+ Cells



1 Wk Culture

N=10

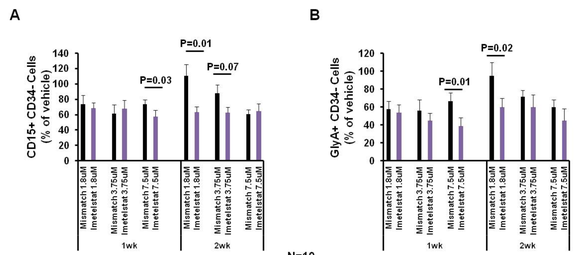
Imetelstat Does not Reduce the Generation of Myeloid and Erythroid Cells by CB CD34+ Cells



*P all >0.05 Mismatch vs. Imetalstat of equal doses

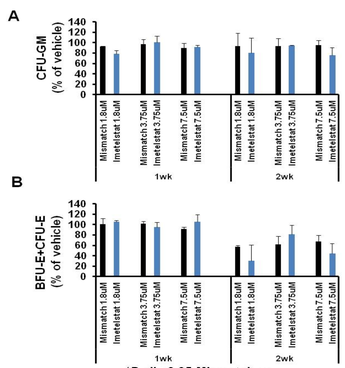
N=3

Imetelstat Reduces the Generation of Myeloid and Erythroid Cells by MF CD34+ Cells



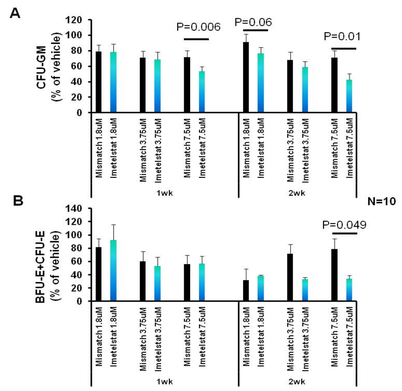
N=10

Imetelstat Does not Suppress Hematopoietic Colony Formation by CB CD34+ Cells



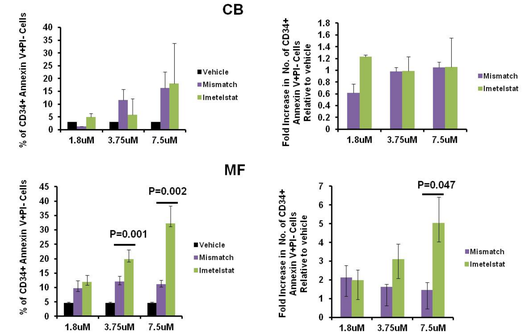
*P all >0.05 Mismatch vs. Imetalstat of equal doses

Imetelstat Inhibits Hematopoietic Colony Formation by MF CD34+ Cells



N=10

Imetelstat Induces Apoptosis of MF but not CB CD34+ Cells



Summary

•Imetelstat at the doses studied has minimal effects on normal CB hematopoiesis. By contrast, Imetelstat is capable of selectively inhibiting the proliferation of phenotypically and functionally defined MF hematopoietic stem cells and myeloid progenitor cells through promoting their apoptosis.

•Imetelstat in some patients can preferentially deplete malignant MF HPCs.

•Imetelstat represents a potentially promising drug for the treatment of MF which appears to affect primitive MF HSCs.