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)

What We Know about Imetelstat


• Imetelstat has been tested in Phase I and II clinical trials in solid tumors, e.g. breast and lung cancer (Kieckoff et al, Jornal of Clinical Oncology, 2016; Chiquet et al, Ann Oncol, 2015) and hematological malignancies, e.g. chronic lymphoproliferative disease (Roth et al, Small Molecules in Oncology 2009), refractory and relapsed multiple myeloma (Huff et al, Blood, 2012), myeloproliferative neoplasms (Baerlocher et al, Telfer et al, N Engl J Med, 2015).

Imetelstat In Myeloproliferative Neoplasms (MPN)

Telomerase Inhibitor Imetelstat in Patients with Essential Thrombocythemia.
Baerlocher GM, Oppliger Leibundgut E, Ottmann OG, Spitzer G, Gneffke O, McDevitt MA, Roth A, Daskalakis M, Burlington B, Stuart M, Snyder DL.

Experimental Design I

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

Experimental Design II

Imetelstat In Myeloproliferative Neoplasms (MPN)

Treatment with imetelstat results in a reduction in JAK2V617F+ HPCs from some patients with MF (1-wk Treatment)

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

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

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