Telomerase Inhibitor: Past, Present and Future

Hematology Fellow Conference

Janghee Woo, MD PhD
University of Washington

H. Joachim Deeg, MD
Fred Hutchinson Cancer Research Center
Telomere & End replication problem

The mysterious telomere
As early as the 1930s it was observed that broken chromosomes were unstable and prone to rearrangements and fusion. The chromosome ends, on the other hand, were protected from such events.

The ends of the chromosomes were named telomeres. They appeared to protect the chromosomes from damage. However, the mechanisms involved were unknown.

The end-replication problem
With growing understanding of how genes are copied another problem presented itself.

When a cell divides both strands of the DNA double helix in the chromosomes are copied, base by base, by DNA polymerase enzymes.

DNA polymerase is dependent on a preformed primer to initiate copying.

Copying of the lagging strand by DNA polymerase occurs in a stepwise fashion. The gaps are filled in to produce an intact DNA molecule.

Due to the lack of priming, DNA polymerase cannot fill the gap at the very end of the chromosome.

http://www.nobelprize.org
Telomere and Telomerase

- Telomeres are repeated DNA sequences, by Elizabeth Blackburn, 1978
- Telomeric DNA from Tetrahymena protected yeast cells from degradation and senescence during cell doubling, by Jack Szostak and Elizabeth Blackburn, 1982
- Telomerase, a riboprotein enzyme, discovered to extend telomere DNA, preventing senescence, by Carol Greider and Elizabeth Blackburn, 1985
- Telomerase uses a specific RNA template to specify the addition of telomeric repeats via a reverse transcriptase mechanism, by Carol Greider and Elizabeth Blackburn, 1989

Nobel Prize in Physiology or Medicine 2009
Elizabeth H. Blackburn, Carol W. Greider and Jack W. Szostak
"for the discovery of how chromosomes are protected by telomeres and the enzyme telomerase"
Telomerase and Predicted biological effects

Telomerase expression is essential for the proliferation of most cancer cells, but the enzyme is inactive in the majority of normal human tissues.
Imetelstat: First in Class Telomerase Inhibitor

- **Proprietary:** 13-mer thio-phosphoramidate oligonucleotide complementary to hTR, with covalently-bound lipid tail to increase cell permeability/tissue distribution

- **Long half-life** in bone marrow, spleen, liver (estimated human t½ = 41 hr with doses 7.5 – 11.7 mg/kg);

- **Potent competitive inhibitor of telomerase:** IC50 = 0.5-10 nM (cell-free)

- **Target:** malignant progenitor cell proliferation

Herbert et al., *Oncogene*, 2005
Imetelstat inhibits telomerase activity, hTERT, and telomere length in vitro

- Imetelstat inhibits telomerase activity in vitro, across multiple cell lines
- Imetelstat inhibits hTERT
- Imetelstat treatment induces reduction in telomere length

Shammas et al., *Leukemia*, 2008
Telomerase Puterbation Trials in Cancer

• Denmark’s Pharmexa prematurely halted in 2011, a phase 3 trial that was testing GV1001, a vaccine designed to prime the immune system to recognize telomerase, in 520 people with pancreatic cancer.

• Geron discontinued a phase 2 study of imetelstat in 166 patients with breast cancer in 2012

⇒ no survival benefit in interim analysis.

• A randomized phase 2 study of imetelstat as maintenance therapy for advanced non-small-cell lung cancer in 116 patients: no survival benefit (Chiappori et al., Ann Oncol. 2015)

Thrombocytopenia was noted as an adverse effect in earlier failed phase 2 trials of imetelstat in people with breast and lung cancer.
Dyskeratosis congenitata (DC)

- X-linked DC
  I. DKC1 gene, ribosomal RNA processing and telomerase function by stabilization of TERC RNA

- Autosomal dominant DC
  Heterozygous mutations in
  I. TERT gene, telomerase reverse transcriptase
  II. TERC gene, an essential RNA subunit of telomerase
  III. TINF2, a component of the shelterin telomere-associated protein complex

Disease manifestations may become progressively more severe and develop at an earlier age over generations, disease anticipation.
Telomere in MPN

- High telomerase activity in granulocytes from clonal polycythemia vera and essential thrombocythemia. (Ferraris et al., *Blood*, 2005)
Telomere in MPN

• High telomerase activity in granulocytes from clonal polycythemia vera and essential thrombocythemia. (Ferraris et al., *Blood*, 2005)

• Telomere length is reduced in JAK2V617F-positive and –negative myeloproliferative neoplasms. (Bernard et al., *Leukemia*, 2009)
Terc<sup>−/−</sup> LSC engraftment progressively decreased, demonstrating that Terc<sup>−/−</sup> LSCs are severely limited in their ability to expand.
Differential effects of Imetelstat on hematopoietic progenitor cells from MF and ET patients

- Imetelstat selectively inhibits the proliferation of MF hematopoietic progenitor cells by promoting apoptosis and depleting malignant MF HPCs.

- Imetelstat selectively affects malignant megakaryopoiesis in Myeloproliferative Neoplasms (MPN)

Wang et. al. and Iancu-Rubin et. al, 2014 ASH
A Pilot Study of the Telomerase Inhibitor Imetelstat for Myelofibrosis

Ayalew Tefferi, M.D., Terra L. Lasho, Ph.D., Kebede H. Begna, M.D.,
Mrinal M. Patnaik, M.D., Darci L. Zblewski, C.N.P., Christy M. Finke, B.Sc.,
Rebecca R. Laborde, Ph.D., Emnet Wassie, M.D., Lauren Schimek, B.S.,
Curtis A. Hanson, M.D., Naseema Gangat, M.D., Xiaolin Wang, Ph.D.,
and Animesh Pardanani, M.D., Ph.D.

Telomerase Inhibitor Imetelstat in Patients with Essential Thrombocytethemia

Gabriela M. Baerlocher, M.D., Elisabeth Oppliger Leibundgut, Pharm.D.,
Oliver G. Ottmann, M.D., Gary Spitzer, M.D., Olatoyosi Odenike, M.D.,
Michael A. McDevitt, M.D., Ph.D., Alexander Röth, M.D.,
Michael Daskalakis, M.D., Bart Burington, Ph.D., Monic Stuart, M.D.,
and David S. Snyder, M.D.
# A Pilot Open-Label Study of the Efficacy and Safety of Imetelstat in Myelofibrosis and Other Myeloid Malignancies of Study

## Patient Population
High risk or intermediate -2 (DIPSS Plus)
Primary or secondary (post-PV or post-ET) myelofibrosis

## Dosage Regimen
Single Agent Imetelstat (2 hr IV infusion):
- **Arm A (MF)** – 9.4mg/kg D1 of every 21-day cycle
- **Arm B (MF)** – 9.4mg/kg D1, 8, 15 of C1, then D1 of each subsequent 21-day cycle

## Endpoints
**Primary:**
- Overall response rate (CR, PR, CI) per IWG-MRT criteria

**Secondary:**
- Spleen response (by physical exam)
- Anemia response (per IWG-MRT criteria)
- Safety/tolerability
Primary Endpoint: Overall Response by revised IWG-MRT

<table>
<thead>
<tr>
<th>Response Type</th>
<th>N = 33 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response (CR+PR+CI)</td>
<td>12 (36.4%)</td>
</tr>
<tr>
<td>Complete Remission (CR)</td>
<td>4 (12.1%)</td>
</tr>
<tr>
<td>Partial Remission (PR)</td>
<td>3 (9.1%)</td>
</tr>
<tr>
<td>Clinical Improvement (CI) by Anemia</td>
<td>1 (3.0%)</td>
</tr>
<tr>
<td>Clinical Improvement (CI) by Spleen</td>
<td>4 (12.1%)</td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
<td>21 (63.6%)</td>
</tr>
<tr>
<td>Spleen Response (by palpation lasting ≥ 12 weeks)</td>
<td>8/23 (34.8%)</td>
</tr>
<tr>
<td>Transfusion dependent becoming transfusion independent</td>
<td>4/13 (30.8%)</td>
</tr>
</tbody>
</table>
Of 7 CR/PR patients...

• All 4 CR patients achieved reversal of BM fibrosis
Onset and Durability of Response for CR/PR/CI Patients

- Median onset of remission at 5 cycles (range 1-9)
- 6 CR/PR remain in remission with median duration of 11.1 months (range 6.9-16.2)
# Grade ≥3 Hematologic Toxicities

<table>
<thead>
<tr>
<th></th>
<th>Worst CTC Grade</th>
<th>Arm A (N=19)</th>
<th>Arm B (N=14)</th>
<th>Total (N=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>3</td>
<td>8 (42.1%)</td>
<td>1 (7.1%)</td>
<td>9 (27.3%)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>2 (10.5%)</td>
<td>5 (35.7%)</td>
<td>7 (21.2%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3</td>
<td>4 (21.1%)</td>
<td>2 (14.3%)</td>
<td>6 (18.2%)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>2 (10.5%)</td>
<td>4 (28.6%)</td>
<td>6 (18.2%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>3</td>
<td>7 (36.8%)</td>
<td>9 (64.3%)</td>
<td>16 (48.5%)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>3</td>
<td>3 (15.8%)</td>
<td>6 (42.9%)</td>
<td>9 (27.3%)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>2 (10.5%)</td>
<td>1 (7.1%)</td>
<td>3 (9.1%)</td>
</tr>
</tbody>
</table>
Liver Function Tests: Worsening in Grade from Baseline

<table>
<thead>
<tr>
<th></th>
<th>Any Worsening</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>13 (39.4%)</td>
<td>13 (39.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST</td>
<td>19 (57.6%)</td>
<td>18 (54.5%)</td>
<td>1 (3.0%)</td>
<td></td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>18 (54.5%)</td>
<td>11 (33.3%)</td>
<td>5 (15.2%)</td>
<td>2 (6.1%)</td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>16 (48.5%)</td>
<td>9 (27.3%)</td>
<td>6 (18.2%)</td>
<td>1 (3.0%)</td>
</tr>
</tbody>
</table>

- No hepatic adverse events
- None of the treatment discontinuations or holds was related to LFT abnormalities

Tefferi, ASH 2014, NEJM 2015
Outstanding questions

• Who will respond?:
  – splicing mutations (CR in 3 out of 8 patients with mutations vs 1 of 25 patients without mutations)
  – ASXL1 mutation (RR 32%, 7 of 22 patients without mutations vs 0 of 11 patients with an ASXL1 mutation (P = 0.07)

• Is telomere a real target? : no consistent pattern of drug effect on telomere length
No consistent pattern of drug effect on telomere length

Baseline and post-treatment evaluation of telomere length among 5 patients with complete or partial remissions.
Outstanding questions

• Who will respond?:
  – splicing mutations (CR in 3 out of 8 patients with mutations vs 1 of 25 patients without mutations)
  – *ASXL1* mutation (RR 32%, 7 of 22 patients without mutations vs vs 0 of 11 patients with an *ASXL1* mutation (P = 0.07)

• Is telomere a real target?: no consistent pattern of drug effect on telomere length

⇒ Predictive markers and Mechanism of action/resistance
Hutch Protocol #9435

A Randomized, Single-Blind, Multicenter Phase 2 Study to Evaluate the Activity of 2 Dose Levels of Imetelstat in Subjects with Intermediate-2 or High-Risk Myelofibrosis (MF) Relapsed/Refractory to Janus Kinase (JAK) Inhibitor

MF subjects (N ≈ 200) 1:1

- 9.4mg/kg IV q3wk (n=20)
- 4.7mg/kg IV q3wk (n=20)

Interim review (study enrollment continues)

- 9.4mg/kg IV q3wk
- 4.7mg/kg IV q3wk

- evaluate totality of the data and conduct exposure-response analyses with PK/PD, safety and efficacy modeling
- determine if enrollment in one or both treatment arms should continue, or select an alternative dose
**Inclusion Criteria**

**Worsening of splenomegaly-related abdominal pain**
- at any time after start of JAKi therapy

**AND EITHER**

**No reduction in spleen size / volume**
- after 12 weeks of JAKi therapy

**OR**

**Increase in Spleen size / volume**
- at any time after start of JAKi therapy

**Demonstrated by:**

**By MRI:** Spleen volume increase from nadir by 25%

**OR**

**By palpation:**
- New splenomegaly ≥5cm below LCM
- Baseline splenomegaly 5-10cm: ≥100% increase in palpable distance below LCM,
- Baseline splenomegaly >10cm: 50% increase in palpable distance below LCM
Primary endpoints

- **Spleen response rate**: the proportion of subjects who achieve ≥35% reduction in spleen volume from baseline as measured by MRI at Week 24

AND

- **Symptom response rate**: the proportion of subjects who have ≥50% reduction in total symptom score as measured by modified MFSAF v2.0 at Week 24
Secondary endpoints

- Proportion of subjects with CR or PR or CI per modified 2013 IWG-MRT criteria
- Spleen response, symptom response, anemia response
- Duration of responses: spleen, symptoms, anemia, CR or PR, CI
- Overall survival
Exploratory endpoints

- TA, TL and hTERT at baseline and the change from baseline
- Cytogenetic response and molecular response
- Leukemia free survival
Mr. P, 66 y/o male

- ET diagnosed in 1992, progressed Post-ET MF in 2005, CALR mutation (52bp deletion)
- Hydrea: diagnosis – 2008
- Jakafi: July 2013 –
- Pegylated Interferon: Aug 2015 –

- Portal hypertension, intractable ascites and variceal bleeding s/p TIPS in 2013, resolved.
- Non-transplantation candidate
- Refractory to Jakafi 20mg bid, increasing fatigue, splenomegaly symptoms, RBC transfusion dependent
- Spleen: 26.5 cm
- WBC 15.1, Hgb/Hct 5.2/16, Plt 138, CD34 in marrow 3.5 %, normal cytogenetics, peripheral blood blast 1.21%

- His DIPSS score is a 5 with a breakdown as follows:
  Age >65 = 1. Hemoglobin <10 = 2, Luekocytes >25K = 0, Circulating Blasts >1% = 1, Constitutional Symptoms = 1
Symptomatic improvement
• **PAST:** From bench to bedside: Telomerase inhibitor, imetelstat

• **PAST:** Proof of Concept phase I trials in patients with ET and MF
  – Molecular response
  – Reversal of marrow fibrosis

• **PRESENT:** Phase II trial in patients with MF, refractory to or non-tolerating JAK inhibitor, (non-transplant candidate)

• **FUTURE:** Biology of disease, Mechanism of action/resistance of imetelstat
Acknowledgements

• H. Joachim Deeg
• Bart Scott
• Elizabeth A. Stohr
• Sioban Keel
Q & A
## Grade ≥3 Non-hematologic Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>All (N=33)</th>
<th>Related (N=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>3 (9.1%)</td>
<td></td>
</tr>
<tr>
<td>APTT</td>
<td>2 (6.1%)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2 (6.1%)</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>2 (6.1%)</td>
<td></td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>2 (6.1%)</td>
<td></td>
</tr>
<tr>
<td>Ejection fraction decreased</td>
<td>1 (3.0%)</td>
<td></td>
</tr>
<tr>
<td>Intracranial hemorrhage #</td>
<td>1 (3.0%)</td>
<td>1 (3.0%) ¥</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>1 (3.0%)</td>
<td>1 (3.0%) ¥</td>
</tr>
<tr>
<td>Upper GI hemorrhage #</td>
<td>1 (3.0%)</td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>1 (3.0%)</td>
<td></td>
</tr>
<tr>
<td>Lipase increased</td>
<td>1 (3.0%)</td>
<td></td>
</tr>
<tr>
<td>Lung infection</td>
<td>1 (3.0%)</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>1 (3.0%)</td>
<td></td>
</tr>
<tr>
<td>Pyoderma gangrenosum # Σ</td>
<td>1 (3.0%)</td>
<td></td>
</tr>
<tr>
<td>Small intestinal obstruction</td>
<td>1 (3.0%)</td>
<td></td>
</tr>
</tbody>
</table>

@ Excluded myelosuppression and LFT abnormalities which are presented in separate tables; # Grade 5 event; ¥ 1 patient; Σ the pyoderma gangrenosum is associated with a post-op (splenectomy) complication.
Baseline telomere length comparisons in patients with or without complete/partial remissions following treatment with imetelstat
Alternative lengthening of telomeres (ALT)

O’Sullivan et al., Trends in Cell Biology, 2014