Preservation of telomere length is crucial to cell survival. Telomeres are hexa-nucleotide repeats that cap the ends of chromosomes and their sequence overlaps the template region of telomerase. Zhu Pirot, Amy Weise, Data from Patient 7-39 is presented in Figure 4. Telomerase activity was normalized to 100% in all patients with the highest activity. Most patients (22/25; 88%) received prior cytotoxic regimens (mean 4.0), 25 patients received at least 1 infusion of imetelstat. Immortalization is invariably accompanied by constitutive activation of telomerase. Tong Lin, Telomerase and cancer. Grade 3 and 4 thrombocytopenia was seen with the weekly intermittent dosing schedule. Preliminary pharmacodynamic (PD) evidence of target inhibition has been observed in selected patient tissues. The 9.4 mg/kg dose given on an intermittent dosing schedule (Days 1 and 8 of a 21-day cycle) is the recommended dose for single agent phase II studies of Imetelstat. Imetelstat is a thio-phosphoramidate oligonucleotide with a 5’palmitoyl thiol group that inhibits intracellular telomerase by binding to the RNA component of the enzyme in a sequence-specific manner, thereby preventing telomere extension and cell immortalization.

**Introduction**

**Purpose**

- Increase exposure of patients with solid tumors to levels of imetelstat that demonstrate telomerase inhibition and pharmacodynamics, with efficacy in preclinical models.
- Initial 1-day 1-hour weekly schedule of imetelstat is intended to achieve levels of biomarker changes consistent with an effect on tumor growth in patients.
- A 28-day schedule is also under evaluation.

**Methods**

- Design: Phase 1, repeated cohorts, 1:1 dose escalation, unrestricted trisomy 8 clone patients, and 0/1 dose escalation in normal volunteers
- Inclusion criteria: Patients with malignancies that are evaluable or that are refractory to standard regimens
- Exclusion criteria: Patients with malignancies that are refractory to standard regimens
- Cohorts 6 7 8 9 10 Dose (mg/kg) 4.8 6.0 7.5 9.4 11.7 Total # of Patients 6 4 3 6 6 25
- Baseline Characteristics
  - Gender: Male 12, Female 13
  - Karnofsky Status: 70%, anticipated life expectancy 1-3 years
  - Grade 1 75, Grade 2 100, Grade 3 27, Grade 4 100
  - Cohort 10 (11.7 mg/kg)
  - Platelet levels vs time with 4.8 mg/kg at 28, 56 days
  - Platelet count <100,000/mm; significant serum chemistry abnormality
- Baseline Characteristics
  - Grade 2 0 3 1 1 3 8
  - Grade 3 1 0 0 1 1 2
  - Grade 4 0 0 0 0 1 1
  - Baseline Pharmacokinetics
  - Weekly imetelstat AUC (/uni00B5g/mL*hr) 4.8 6.0 7.5 9.4 11.7
  - Telomerase Activity: Pharmacodynamics
  - Telomerase Activity was measured by a Hybridization-ELISA assay.

**Results**

**Safety**

- Adverse events that were considered to be related to study treatment were seen in 4 of 10 patients (40%).
  - Grade 2 0 3 1 1 3 8
  - Grade 3 1 0 0 1 1 2
  - Grade 4 0 0 0 0 1 1
- Platelet Levels: Grade 2 0 3 1 1 3 8
- Platelet count <100,000/mm; significant serum chemistry abnormality
- Preliminary pharmacokinetic assessment of the intermittent dosing schedule demonstrates achievement of imetelstat plasma levels that are consistent with efficacy in the preclinical models.
- Hematologic toxicity was dose-limiting with the weekly intermittent dosing schedule; other observed toxicities are either mild or infrequent.

**Patient Pharmacokinetics**

- Preliminary pharmacokinetic assessment of the intermittent dosing schedule demonstrates achievement of imetelstat plasma levels that are consistent with efficacy in the preclinical models.
- Baseline characteristics were enrolled on this schedule, and 25 had data reported by the cut-off date.
- Grade 2 0 3 1 1 3 8
- Grade 3 1 0 0 1 1 2
- Grade 4 0 0 0 0 1 1

**Discussion**

- The maximum tolerated dose (MTD) was exceeded at 4.8 mg/kg, and the highest dose administered was 11.7 mg/kg.

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**Figure 4.** The average mRNA telomerase activity of follicles per patient and post-treatment (TG/RA, ng/ml) in Patients 7-39.