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**Abstract 1 of 1** **Online Publication**

*Bone Marrow Failure*

## Oral Ezatiostat HCl (Telintra), a Glutathione Analog Prodrug GSTP1-1 Inhibitor, for Treatment of Patients with Myeloid Growth Factor-Resistant Idiopathic Chronic Neutropenia (ICN)

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**Abstract 4394**

**Introduction:** Idiopathic chronic neutropenia (ICN) is a group of diseases characterized by low circulating neutrophils, recurrent fevers, mucosal inflammation, and systemic infections. The risk of complications is inversely proportional to the absolute neutrophil count (ANC), with the most severe occurring with ANC of < $0.5 \times 10^9$/L. Most patients respond to daily s.c. administration of granulocyte colony stimulating factors (G-CSF); however, some patients do not respond. Patients undergoing G-CSF therapy also often have bone and muscle pain, thrombocytopenia and splenomegaly, complicating therapy. Ezatiostat, a glutathione S-transferase (GST) inhibitor that activates Jun kinase, promoting growth and maturation of hematopoietic progenitors, is an investigational agent in development for treatment of ICN. This report describes 4 patients with longstanding ICN who responded to ezatiostat, all of whom prior to treatment had frequent hospitalizations for sepsis, prolonged courses of antibiotics and poor response to myeloid growth factors.

**Methods:** Patients (pts) with severe ICN and inadequate ANC response to G-CSF were enrolled in this phase 2 trial. After initial starting dose of 2000 mg in divided doses twice daily (b.i.d.) dose-equilibration over 4 weeks, pts were treated with ezatiostat daily for 3 weeks followed by 1 week off. Treatment was given until lack of ANC response or unacceptable toxicity. Clinical benefit was determined by ANC response, infection-free periods, antibiotic use and hospitalizations for infections.

**Results:** Four female pts, age range 23–63, with median ANC of 200 (50–400) were enrolled. Patient 1 is 62 y.o. with longstanding history of infections and treatment with G-CSF. Before entering study, she had recurrent ear, labial, left thigh, pulmonary and sinus infections despite growth factor treatment, to which she had severe reactions. Baseline white blood cell (WBC)/ANC ratio was 2.2/0.7. WBC/ANC improved with ezatiostat for 4 mo to 3.62/1.71 and infections resolved. Patient 2, a 63 y.o. with ICN for 26 years, had a median baseline WBC/ANC on G-CSF treatment of 3.1/.180 and a history of multiple hospital admissions for sepsis, non-healing perineal and decubitus ulcers, and recurrent high fevers within 4 days of cessation of parenteral antibiotics, necessitating resumption. Post-ezatiostat treatment median ANC was 3.1 (range 1.6–3.75) with a persistent infection-free period of over 22 mo with no hospitalizations or antibiotic therapy required. Patient 3, a 23 y.o. with ICN since age 10, initially responded to G-CSF but stopped responding despite injections b.i.d., and ANC never rose above 1000. Her last hospitalization was for methicillin-resistant staphylococcus aureus skin infection, upper respiratory infection with cervical adenopathy, and oral ulcers. She had infections every 3 months and baseline WBC/ANC of 1.4/0.13. She had minimal response over 4 mo of observation, with highest values 2.65/0.92 and median ANC of 0.40, but had no further bacterial infection or use of G-CSF. Patient 4, a 39 y.o. with ICN of 10 years' duration, had severe bone pain with G-CSF and responses were brief (1–2days). Previously, she had hospital admissions and emergency room visits 4–5 times a year and was ill 2–3 times a week with recurrent urinary tract infections, pneumonias (4–5 times per year), oral ulcers, sinus and gastrointestinal infections, furuncles, and infection after dental work. Baseline

WBC/ANC was 1.23/0.20. Currently, her WBC/ANC is 1.50/0.26. While ANC did not increase, infection rate decreased and she had no ER visits or admissions for over 5 mo. She responded to a single 300 mcg dose of of G-CSF with an ANC of 1.0 for a week, suggesting re-sensitization to G-CSF. Most common ezatiostat-related adverse events were grade 1 nausea, abnormal urine/stool odor, and dysgeusia.

**Conclusions:** Ezatiostat, a novel GSTP1-1 inhibitor and jun kinase modulator as treatment of patients with ICN and grade 4 neutropenia not responsive to myeloid growth factors, results in a durable ANC response and clinically significant reductions in serious infections. Results suggest a potential role for ezatiostat as an oral therapy alternative or adjunct to G-CSF in the treatment of ICN in patients who are not responsive to G-CSF. Response to this targeted therapy may also give insight into the pathophysiology of ICN and further study is warranted.

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## Footnotes

* Asterisk with author names denotes non-ASH members.

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