Phase I/II Trial of Glasdegib in Patients With Primary or Secondary Myelofibrosis

Aaron Gerds1, Tetsuo Tauchi2, Ellen Ritchie3, Michael Deininger4, Catramia Jamesion5, Ruben Mesa6, Mark Heaney7, Norio Kamatsu8, Hironobu Minami9, Yun Su10, M Naved Shaik11, Xiaoxi Zhang12, Christine G. DiRienzo13, Mirjana Zeremski14, Adrian Woolfson15, Geoffrey Chan16, Moshe Talpaz17

1Cleveland Clinic, Cleveland, OH, USA; 2Temple University Health System, Philadelphia, PA; 3University of Texas Southwestern Medical Center, Dallas, TX; 4Institution of Medicine, Ministry of Health and Welfare of Japan, Tokyo, Japan; 5St. Joseph’s University Medical Center, Jersey City, NJ, USA; 6Department of Medicine, Massachusetts General Hospital, Boston, MA; 7Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA; 8Mayo Clinic, Scottsdale, AZ, USA; 9University Medical Center, New York, NY, USA, 10University of Medicine, Tokyo, Japan; 11Yale University Hospital, New Haven, CT, USA; 12Pharmacy, Inc, New York, NY, USA; 13Pharmacy, Inc, Los Angeles, CA, USA; 14Pfizer Oncology, Collegeville, PA, USA; 15Comprehensive Cancer Center, University of Michigan, Ann Arbor, MI

BACKGROUND

Glasdegib (OMD-207) is a potent, selective, oral Hedgehog (Hh) pathway inhibitor that is under investigation for the treatment of myelofibrosis (MF). Results from multiple preclinical models have demonstrated preliminary evidence of clinical activity, supporting further evaluation of the agent to be approved by the US Food and Drug Administration for the treatment of MF.

OBJECTIVES

The primary objectives were to: (1) assess the effect of glasdegib treatment on hematologic improvement (peripheral blood) in patients with primary or secondary MF previously treated with ≥1 JAKi; (2) assess Hematologic Improvement in Myeloproliferative Neoplasm–Cancer Institute Common Terminology Criteria for Adverse Events (HIM-CI-CTCAE); and (3) evaluate symptom response to glasdegib treatment.

METHODS

Treatment was designed with the following phases: an 8-week lead-in followed by 28 days on treatment (Cycle 1), followed by 14 days off treatment (Cycle Off). Patients were treated in a 2:1 randomization ratio in an open-label cohort. The starting dose of glasdegib could be increased to 150 mg daily in the event of a dose-limiting toxicity (DLT) or disease progression. DLTs were defined a priori. Quantitative assessment of spleen size was measured using magnetic resonance imaging (MRI) or computed tomography (CT) scans. The study was approved by the institutional review boards of the participating institutions.

RESULTS

Seventy-two percent of patients had undergone previous treatment with JAK inhibitors, and 38% had received ≥2 previous JAKi. Forty-two percent of patients included in the analysis had received ≥3 prior JAKi. Based on baseline symptom scores, 22% of patients were classified as severe symptoms. Baseline symptom scores were higher compared with the overall population.

Symptom response was higher using alternative responder definitions of ≥20% TSS reduction at Week 24. Specific symptom improvements observed included decreases in the following symptoms: fatigue, night sweats, itching, and bone pain.

An overall toxicity rate of 38% was observed using alternative responder definitions. The most common treatment-related AEs (≥20% incidence) included increased ALT/AST (76%), decreased appetite (28%), fatigue (23%), nausea (19%), vomiting (14%), and diarrhea (14%).

CONCLUSIONS

Glasdegib was safe and well tolerated in this patient population. Clinical benefit was observed for patients with MF and severe symptom burden. The overall toxicity rate was lower than expected. Despite the high baseline symptom scores, severe subset: significantly reduced symptoms in spleen-related symptoms compared with the overall population. The overall symptom response rate was 39%, with 14% of patients achieving complete response. Small patient numbers did not allow for a significant comparison of symptom response rates between Cycle 6 and Cycle 7.

REFERENCES

[10] International Working Group recommendations.10

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