Effect of Adding Ublituximab to Ibrutinib on PFS, ORR, and MRD Negativity in Previously Treated High-Risk Chronic Lymphocytic Leukemia: Final Results of the GENUINE Phase III Study

Jep P. Sharan, MD,1 Danielle M. Brander, MD,2 Anthony R. Mato, MD,3 Nilanjan Ghosh, MD,4 PhD;5 Stephen J. Schuster, MD,6 Suinin Kambhampati, MD,7 John M. Burke, MD,8 Frederick Lansigan, MD,9 Marshall T. Schreeder, MD,10 Scott D. Lurin, MD,11 Alexander Zebib, MD, PhD,12 Mikhail Shirkova, MD,13 Patrick M. Travis, MD14 Changyong Brandon, MD14 Kaytrin K. Kolbaba, MD,16 Peter Spornwein, MD14 Hari F. Malik, MD,16 Michael S. Weiss16 and Ian W. Filli, MD, PhD17

1Williamette Valley Cancer Institute/US Oncology Research, Eugene, OR; 2Duke University Medical Center, Durham, NC; 3Center for CLL, Memorial Sloan-Kettering Cancer Center, New York, NY; 4Leukemia Cancer Institute, Azusa Health, Charlotte, NC; 5University of Pennsylvania, Philadelphia, PA; 6University of Kansas Cancer Center, Kansas City, KS; 7Rocky Mountain Cancer Centers/US Oncology Research, Aurora, CO; 8Charlotte-Hickory Medical Center, Louisville, NC; 9Cleveland Cancer Institute, Humlsville, OH; 10University of Colorado Cancer Center, Denver, CO; 11Eisenhower Cancer Center and Research Center, Chandler, AZ; 12Highlands Oncology Group, Fayetteville, AR; 13Next Cancer Center, Memphis, TN; 14Compass Oncology/US Oncology Research, Vancouver, WA; 15SSS Therapeutics, Inc. New York, NY; 16Fortin Cancer Research Foundation, Nashville, TN.

Background

Chronic lymphocytic leukemia (CLL) is a heterogenous disease with genetic abnormalities including 17p deletion (del17p), 1q gain (del1q), and TP53 gene mutations (TP53mut) identified as markers of high-risk disease conferring poor prognosis. 

Ibrutinib (IB) is a Bruton’s tyrosine kinase (BTK) inhibitor approved for the treatment of CLL patients with high-risk genetic features. In preclinical studies, Ublituximab (UTX) demonstrated high activity against CLL cells in vitro and in animal tumor models. In phase 2 study in relapsed/refractory CLL patients with high-risk genetic features, patients treated with UTX+IB had significantly improved outcomes over ibrutinib monotherapy. 

Study design

This was a randomized, open-label, multicenter, phase III study. 200 patients with relapsed or refractory CLL 17p deletion or TP53 mutation (TP53mut) were randomized in a 1:1 ratio to receive UTX and IB (N=100) or IB (N=100). Randomization was stratified by prior ibrutinib use and baseline comorbidities.

Results

Patient Disposition

Data cut-off date was September 1, 2019 with a median follow-up time of 41.9 months. 132 (66%) of the 200 patients treated were included in the intent-to-treat (ITT) population. 53% of patients had del17p and 42% had TP53mut.

Study Objectives

Primary Endpoint

• Overall response rate (ORR) by independent review committee (IRC)

Secondary Endpoint

• Progression-free survival (PFS) by independent review committee

Key Eligibility Criteria

• Age ≤ 85 years
• CLL requiring treatment per IWCLL criteria1,2
• High-risk cytogenetics defined as del17p (del17p+), and/or TP53 mut
• EOG performance status ≤ 2
• History of transformation of CLL
• No prior BTK inhibitor therapy

Key Findings

ORR (

CR/CRi (%) CR (%) PR (%) Minor Response (%) PR-L (%) Complete Response Rate (%) Complete Response Rate (%)

5% CR/CRi 94.4% CR 64.3% PR 20.2% Minor Response 9.5% PR-L 9.5% CR/CRi 60.2% CR 39.4% PR 4.5% Minor Response 4.5% PR-L

Increased rates of undetectable MRD compared with ibrutinib monotherapy in patients with TP53mut or 17p deletion.

Efficacy

Efficacy was assessed at week 8, 16, 24, and every 12 weeks thereafter. At week 46, 6 patients had disease progression and 25 patients had discontinuations due to disease progression/death.

Adverse Events

Grade 3/4 adverse events included nausea (11%), vomiting (4%), diarrhea (4%), and constipation (4%). Adverse events of special interest included dermatitis (7%) and arthralgia (7%).

Safety

All-cause adverse events of any grade occurring in ≥ 20% of patients are listed in Table 2. The addition of ublituximab to ibrutinib did not significantly alter the known safety profile of ibrutinib; slightly higher rates of neutropenia and atrial fibrillation were observed with the combination of ublituximab + ibrutinib.

Conclusions

The addition of ublituximab to ibrutinib significantly improved ORR compared with ibrutinib monotherapy in patients with high-risk CLL. At a median follow-up of 41.9 months, PFS was significantly improved in patients treated with the combination with undetectable MRD. Improvement in PFS was driven by patients with del17p/TP53mut.

Figure 4. Best ORR

Figure 5. Undetectable MRD