iNNOVATE™ Substudy: Long-term Follow Up of Ibrutinib in Patients With Rituximab-Refractory Waldenström's Macroglobulinemia

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Background: Waldenström's macroglobulinemia (WM) is commonly treated with rituximab alone or combined with chemotherapy. Patients with rituximab-refractory disease have few effective treatment options. Ibrutinib, a first-in-class, once-daily inhibitor of Bruton's Tyrosine Kinase, is indicated in the US and EU for the treatment of WM. In a previous report of this open-label substudy of the phase 3 iNNOVATE™ study, treatment with single-agent ibrutinib in patients with rituximab-refractory WM resulted in a manageable toxicity profile and a major response rate of 71% (13% very good partial response [VGPR]; 58% PR) at 18.1 months of follow up. Long-term follow-up data are presented here.

Methods: Adults with centrally confirmed WM who failed to achieve at least minor response (MR) or relapsed <12 months after their last rituximab-containing therapy were eligible. Patients received oral, once-daily 420 mg ibrutinib until PD/unacceptable toxicity. Endpoints included ORR, PFS, OS, improvement in hemoglobin and IgM, time to next treatment (TTnT), and patient-reported outcomes.

Results: Thirty-one patients were enrolled and were heavily pretreated, with a median of 4 (range, 1–7) prior therapies (Table). At a median follow-up of 34 months (range, 9–38), the

investigator-assessed ORR (≥MR) was 90%; the major response rate (≥PR) was 77% (26% VGPR, 52% PR). Median duration of response was not reached (95% CI, 27 months, not estimable [NE]), nor was median PFS (95% CI, 28 months, NE) or OS (95% CI, 36 months, NE). At 36 months, the PFS rate was 56% (95% CI, 37–72) and the OS rate was 73% (95% CI, 35–91). Sustained hemoglobin improvement was observed in 71% of patients, including 17/21 (81%) patients with baseline hemoglobin ≤110 g/L. The median IgM level declined from 39.2 g/L (range, 8.7–107.0) at baseline (n=31) to 5.4 g/L (range, 0.3–58.5) at week 145 (n=15). Only 5 (16%) patients received subsequent treatment; thus, median TTnT was NE. The FACIT-Fatigue subscale score, FACT-AN score, and EQ-5D-5L visual analogue scale identified clinically meaningful improvements from baseline in patient-reported outcomes among 87%, 77%, and 65% of patients by 25 weeks, respectively. Median duration of ibrutinib treatment was 33 months (range, 0–37). TEAEs occurred in 97% of patients, and grade ≥3 TEAEs occurred in 74%. The most common (>20%, any grade) were diarrhea (42%), neutropenia (29%), back pain (26%), and bruising, hypertension, nausea, pyrexia, and thrombocytopenia (23% each). Common grade ≥3 TEAEs included neutropenia (16%) and hypertension (10%). Serious TEAEs occurred in 35% of patients; no events occurred in >1 patient. No atrial fibrillation or major hemorrhage events were reported. Dose reductions due to AEs occurred in 16% of patients; 55% continue to receive ibrutinib treatment and 45% have discontinued (32% due to PD; 7% each due to AEs or patient withdrawal).

Conclusions: Single-agent ibrutinib is highly active in patients with heavily-pretreated, rituximab-refractory WM. Responses to ibrutinib continue to deepen with prolonged therapy and remain durable with estimated median PFS of over 3 years. Consistent with prior studies, the safety profile of ibrutinib was manageable, and no new safety signals were identified.

Table. Baseline Characteristics

	N=31
Median age, years (range) Age ≥75 years, n (%)	67 (47–90) 7 (23)
ECOG, n (%) 0-1 2	 25 (81) 6 (19)
IPSSWM, n (%) Low Intermediate High	 7 (23) 11 (35) 13 (42)
Median number of prior therapies (range) ≤2 prior treatments, n (%) ≥3 prior treatments, n (%)	4 (1–7) 9 (29) 22 (71)
Median number of prior rituximab-containing therapies (range)	2 (1–6)
Prior autologous stem cell transplantation, n (%)	2 (6)
Median serum IgM, g/L (range)	39 (9–107)
Median hemoglobin, g/L (range)	103 (64–146)
Median platelets, 10^9/L (range)	218 (51–896)
Median absolute neutrophil count, 10^9/L (range)	3 (1–15)
Genetic subtype, n (%) $MYD88^{WT}/CXCR4^{WT}$ $MYD88^{L265P}/CXCR4^{WT}$ $MYD88^{L265P}/CXCR4^{WHIM}$ Unknown[a]	 1 (3) 17 (55) 7(23) 6 (19)
Reasons for initiating treatment,[b] n (%) Fatigue Constitutional symptoms Hemoglobin ≤10 g/dL Lymphadenopathy Hyperviscosity Peripheral neuropathy due to WM Serum IgM >50 g/L Symptomatic hepatomegaly/splenomegaly/organ tissue infiltration Platelet count <100 × 10^9/L	 22 (71) 13 (42) 13 (42) 7 (23) 5 (16) 4 (13) 4 (13) 3 (10) 2 (7)

[a]Mutation status was missing or unknown for 6 patients.
[b]Patients could have more than 1 reason for initiating treatment.