Title: Remibrutinib-induced decreases in B-cell biomarkers are associated with complete and sustained response in patients with chronic spontaneous urticaria

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Abstract

Background: Chronic spontaneous urticaria (CSU) is characterized by the spontaneous occurrence of itchy wheals and/or angioedema without a trigger lasting for >6 weeks. Remibrutinib, an oral, highly selective Bruton's tyrosine kinase inhibitor, showed superior efficacy vs placebo and a favorable safety profile in 52-week phase 3 studies (REMIX-1 and REMIX-2). We previously observed remibrutinib-induced decreases in B-cell biomarkers (soluble cluster of differentiation 23 [sCD23] and immunoglobulin G [IgG] autoantibodies) in patients with autoimmune CSU. Here, we asked whether a decrease in B-cell biomarkers at week 52 was associated with complete response (CR) in the REMIX studies or predicted relapse events in the EPOCH 1 extension study.

Methods: We profiled serum sCD23 and IgG autoantibodies in up to 564 patients with CSU from REMIX-1 and REMIX-2. For subgroup analysis, biomarker and clinical data from REMIX-1, REMIX-2, and the EPOCH 1 extension study (NCT05513001), in which patients either received placebo or continued remibrutinib for up to 24 weeks, were used.

Results: Following remibrutinib treatment for up to 52 weeks, the quartile of patients with the greatest reductions (Q1) in the biomarkers sCD23, anti-thyroglobulin, and autoantibodies against the high-affinity receptor for the Fc region of IgE (FcεRI) had higher CR rates and lower nonresponse rates compared with the quartile with the smallest reductions. At week 52, 60% (127/211) of patients with >20% reduction in at least 1 B-cell biomarker achieved CR vs 37% (16/43) of patients with no reduction in any biomarker. In EPOCH 1, patients in Q1 were less likely to relapse if they continued remibrutinib treatment. Overall, 82% (85/104) of patients with >20% reduction in at least 1 biomarker at week 52 had sustained response (SR) while continuing treatment compared with 48% (10/21) of patients without biomarker changes. Patients receiving

placebo had the lowest relapse rates and the longest time to relapse when the decrease in FcεRI autoantibodies was the highest (Q1). Overall, a weak association was observed between B-cell biomarkers and relapse rates in placebo-treated patients. Regression analysis confirmed a significant association between a decrease in B-cell biomarkers and CR (REMIX-1 and REMIX-2) and SR (EPOCH 1) with remibrutinib.

Conclusion: Results suggest that, in addition to the effect of remibrutinib on mast cells, its impact on autoreactive B cells contributes to clinical efficacy in CSU. The long-term effect of remibrutinib on autoantibody levels, together with the immediate blockade of FcεRI signaling, may further reduce mast cell stimulation, leading to a more profound and durable clinical response across CSU endotypes, including in patients who were previously difficult to treat.

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Conflicts of Interest:

Martin Metz is or recently was a speaker and/or advisor for AbbVie, Advanz, ALK-Abello, Allegria, Almirall, Amgen, Argenx, AstraZeneca, Astria, Attovia, Bambusa, Berlin-Chemie, Blueprint Medicines, Celldex, Celltrion, Deep Apple, Escient, FatiAbGen, Galderma, Granular, GlaxoSmithKline, Incyte, Jasper, Japan Tob, Lilly, Lycia, Novartis, Pfizer, Pharvaris, Regeneron, Sanofi, Santa Ana Bio, Septerna, Teva, Third Harmonic Bio, and Vifor.

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