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Nemtabrutinib in relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma: Phase 2 BELLWAVE-003 cohort J

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- In 2022, HHFT were below the national average score for Q52 cancer care reviews by the GP and Q53 emotional support in the community post EOT.
- In 2023, the results show an increased score in Q52 and Q53–55 meaning that HHFT are above the national average.

Conclusions: From the NPCES, it could be proposed that an EOT nurse led clinic with EOTS contributed to the improvement seen from 2022 to 2023. EOT nurse led clinics which include an EOTS continue to grow in practice. This could be potentially a cost-effective model which addresses the gap between primary care, secondary care, the patient and the charitable sector.

EP04.40 | Phase 2 BELLWAVE-003 study evaluating acquired genomic mutations in participants with CLL/SLL treated with nemtabrutinib

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Presented by **Mr Kyung-min Lee**¹ on behalf of the authors.

Introduction: In this exploratory analysis of the phase 2 BELLWAVE-003 study (NCT04728893), we present data on mutations in genes including BTK, PLCγ2 (acquired resistance mutations), and TP53, MAPK, NOTCH, MYD88, SF3B1, ATM, BCL2 (prognostic mutations), as well as efficacy outcomes in participants with relapsed/refractory (R/R) CLL/SLL treated with nemtabrutinib.

Methods: Eligible participants were R/R to covalent Bruton tyrosine kinase (cBTKi) and BCL2 inhibitors, or R/R after ≥1 prior line of therapy and BTKi-naïve or had 17p deletion or TP53 mutation. Participants received nemtabrutinib at the recommended phase 2 dose of 65 mg once daily until

unacceptable toxicity, disease progression (PD), or withdrawal. Sequencing was performed at various timepoints through end of treatment (EOT) utilising a comprehensive genomic profiling assay tailored for haematologic malignancies. Next-generation sequencing on DNA from >400 cancer-related genes was included. Data cutoff was July 1, 2025.

Results: Overall, 100 participants with CLL/SLL were biomarker evaluable (having both baseline and EOT or proxy samples [≥cycle 7]). Following treatment, 16 participants (16%) acquired mutations linked to poor prognosis, including TP53 (4 [4%]), MAPK (1 [1%]), NOTCH1 (5 [5%]), SF3B1 (5 [5%]), ATM (5 [5%]), and BCL2 (1 [1%]). Three participants (3%) acquired a rare PLCγ2 resistance mutation, and 2 (2%) acquired BTK non-C481 resistance mutations. Among biomarker evaluable participants, 71 (71%) were evaluable for best overall response (BOR) by central review. Partial response or partial response with lymphocytosis (per iwCLL 2018 criteria) was observed in 46 participants (65%), 18 had stable disease, 4 had PD, and 3 discontinued before response assessment. Overall, 62 of 71 participants (87%) evaluable for BOR had prognostic mutations at baseline and 23 (32%) had a BTK or PLCγ2 mutation. Two participants (3%) acquired a BTK or PLCγ2 resistance mutation.

Conclusion: Nemtabrutinib showed the potential to overcome or delay resistance within the B-cell receptor signaling pathway, unlike more selective BTKis. Clinical activity was observed in participants harbouring baseline or high-risk mutations (e.g., TP53, BTK non-C481), and progressive disease was not always linked to new resistance acquisition. Nemtabrutinib's broad, reversible inhibition of BTK and related kinases likely underlies its ability to achieve responses across genetically adverse subsets. Clinical data in participants with R/R CLL/SLL from the BELLWAVE-001 study show encouraging efficacy and manageable safety, supporting further evaluation in both first-line and BTKi-resistant disease. Future analyses with more mature data aim to assess clonal evolution at later timepoints and identify potential late-emerging or atypical resistance mutations.

EP04.41 | Nemtabrutinib in relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma: Phase 2 BELLWAVE-003 cohort J

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