ROSEWOOD Trial: A Landmark Trial in the Treatment of Relapsing/Remitting Follicular Lymphoma

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Bruton tyrosine kinase (BTK) plays a central role in the survival and proliferation of malignant B cells; the development of BTK inhibitors has been successfully used in various B-cell malignancies, including chronic lymphocytic leukaemia. However, their efficacy in relapsed/refractory (R/R) follicular lymphoma (FL) has historically been limited. The ROSEWOOD trial, a landmark study led by Pier Luigi Zinzani, demonstrated that zanubrutinib, a next-generation BTK inhibitor, combined with obinutuzumab offers significant clinical benefits over obinutuzumab monotherapy for patients with R/R FL.

Keywords

Bruton tyrosine kinase inhibitor, follicular lymphoma, ROSEWOOD, targeted therapy, zanubrutinib, relapsed/refractory

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Bruton tyrosine kinase (BTK) plays a functional and integral role in B-cell receptor (BCR) signalling and is expressed in normal and malignant B cells. Given BTK's central role in the survival and proliferation of malignant B cells, BTK inhibitors have been developed for use in various B-cell malignancies, with several US Food and Drug Administration approvals in chronic lymphocytic leukaemia (CLL), mantle cell lymphoma, marginal zone lymphoma and Waldenstrom macroglobulinaemia/lymphoplasmacytic lymphoma.[1] BTK inhibitors provide targeted, effective and less toxic treatment options for patients compared with traditional chemotherapy regimens. Next-generation BTK inhibitors, such as acalabrutinib and zanubrutinib, are more selective and have fewer side effects than ibrutinib. Despite the success of BTK inhibitors in these lymphomas, their efficacy in relapsed/refractory (R/R) follicular lymphoma (FL) has historically been limited.

Early clinical trials evaluating BTK inhibitors in R/R FL were disappointing. Response rates were modest, and the duration of response (DOR) was short. The phase II DAWN trial (An Open-label, Multicenter, Phase II Study of Ibrutinib as Treatment for Patients with Relapsed/Refractory Follicular Lymphoma; ClinicalTrials.gov identifier: NCT01779791) demonstrated that the BTK inhibitor ibrutinib, as monotherapy, displayed underwhelming efficacy results for treating R/R FL.[2] This was reiterated with the ACE-LY-003 trial (An Open-label, Phase 1B/II Study of Acalabrutinib Alone or in Combination Therapy in Subjects with B-cell Non-Hodgkin Lymphoma; ClinicalTrials.gov identifier: NCT02180711), which demonstrated limited efficacy of acalabrutinib monotherapy in R/R FL.[3] These results suggest that the biology of FL may render it less susceptible to BTK inhibition and/or that BCR resistance may increase after chemotherapy, prompting the exploration of combination strategies. In a phase IB study of obinutuzumab with zanubrutinib for CLL (A Phase 1B Study of Zanubrutinib plus Obinutuzumab in Patients with Chronic Lymphocytic Leukemia and Follicular Lymphoma; ClinicalTrials.gov identifier: NCT02180711), over 30 patients with FL were included, showing a high overall response rate (ORR) and prompting further investigation of this combination in R/R FL after at least two prior lines of therapy.[4]

Considering these challenges, the results of the ROSEWOOD 2 study represent a significant breakthrough. The ROSEWOOD trial (An International, Phase 2, Open-label, Randomized Study of BGB-3111 Combined with Obinutuzumab Compared with Obinutuzumab Monotherapy in Relapsed/Refractory Follicular Lymphoma; ClinicalTrials.gov identifier: NCT03332017), led by Pier Luigi Zinzani, evaluates the efficacy of zanubrutinib, a promising next-generation BTK inhibitor, combined with obinutuzumab (ZO) versus obinutuzumab monotherapy (O) in patients with R/R FL.[5] This study addresses a critical need for effective treatments in FL, particularly for patients who have not responded adequately to previous therapies or are unable to receive some of the novel immunotherapy available for this disease, such as bispecific antibodies.

The trial included 217 patients who had undergone at least two prior lines of systemic therapy, including an anti-CD20 (cluster of differentiation 20) antibody and an alkylating agent. Patients were randomized into two groups: 145 received the combination of zanubrutinib and obinutuzumab, while 72 received obinutuzumab alone. The primary endpoint was the ORR, which was assessed by

an independent central review. Secondary endpoints included complete response rate (CRR), DOR, progression-free survival (PFS), overall survival and safety.

The results showed a significant improvement in ORR for the combination therapy (69%) compared with obinutuzumab alone (46%), with a p-value of 0.001, meeting the study's primary endpoint. The CRR also favoured the combination therapy at 39 versus 19% for obinutuzumab alone, with an 18-month DOR at 69 versus 42%. Additionally, the median PFS was notably longer in the ZO arm (28.0 months) compared with the O arm (10.4 months), reflecting a hazard ratio of 0.50, indicating a 50% reduction in the risk of progression or death with the combination therapy.

The safety profile of the combination therapy was manageable, with the most common adverse events (AEs) being thrombocytopaenia and neutropaenia. Importantly, the incidence of treatment-emergent AEs leading to death was lower in the combination arm (8%) compared with the monotherapy arm (10%), and there were fewer infusion-related reactions (3 versus 10%). Non-haematological AEs, such as constipation, petechiae and herpes zoster infection, were slightly more common in the ZO arm, but the overall benefit–risk profile was favourable.

The trial also allowed patients receiving obinutuzumab alone to cross over to combination therapy if their disease progressed. Among the 29 patients who crossed over, the ORR was 24.1%, highlighting the potential of zanubrutinib to provide a therapeutic option even after the initial monotherapy failure.

The findings of the ROSEWOOD trial are relevant, given the challenging nature of treating R/R FL. With its superior efficacy in ORR, DOR and PFS, the combination of ZO presents a promising new option for patients. This is underscored by the deeper and more durable responses observed, as well as the extended time to the next anti-lymphoma treatment, which was not estimable for the ZO arm compared with 12.1 months for the O arm.

There were 50 patients with progression of disease within 24 months, who historically have had a poor prognosis and demonstrated a 60% response rate. There were 45 patients with a history of stem cell transplantation or chimeric antigen receptor (CAR) T cells. There were no patients with previous exposure to another BTK inhibitor, such as ibrutinib. It is important to remember that the results of testing ibrutinib in FL were underwhelming (ORR 20.9%) based on the DAWN study.[2]

FL is a very heterogeneous disease with varied clinical courses, presentations and treatment responses. With many other options available for R/R FL, the decision to choose zanubrutinib needs to be individualized for each patient in the clinic. That said, CAR T cell or bispecific antibodies are also not prime options for all candidates due to logistics and/or lack of a solid caregiver. The possible shortcomings of the ROSEWOOD study include its open-label study design, which poses a high risk of performance bias, and differences between treatment durations from the two arms. Despite this, the study combats this by conducting a blinded independent review evaluating treatment efficacy. We were pleasantly surprised to find the positive results of the ROSEWOOD study, particularly considering the previous negative studies of the DAWN study, making zanubrutinib a welcoming addition to the current therapeutic armamentarium against FL. Furthermore, current studies are underway to better define zanubrutinib's role in the R/R FL setting, including the MAHOGANY trial (An Open-label, Phase III Study of Zanubrutinib plus Anti-CD20 Antibodies vs Lenalidomide plus Rituximab in Patients with Relapsed or Refractory Follicular or Marginal Zone Lymphoma; ClinicalTrials.gov identifier: NCT05100862), which evaluates zanubrutinib plus anti-CD20 antibodies versus lenalidomide plus rituximab for those with R/R FL.[6]

In conclusion, the ROSEWOOD trial demonstrates that zanubrutinib combined with obinutuzumab offers significant clinical benefits over obinutuzumab monotherapy for patients with R/R FL. This combination therapy not only improves response rates and PFS, but also maintains a manageable safety profile and good tolerability, making it a valuable addition to the treatment landscape for this challenging disease. Further studies comparing this combination with other established second-line regimens for R/R FL could help solidify its place in clinical practice. New treatment options bring hope for improved outcomes and better well-being for patients with FL, particularly with oral therapy with relatively low toxicity. Advancements such as these underscore the importance of continued innovation and research into combination therapies in the quest to improve cancer care for patients with FL. ❑

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