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Degrading the BTK and blocking BCL2: a new path in marginal zone lymphomas

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In this issue of *Haematologica*, Arribas et al. provide a comprehensive preclinical evaluation of tacabrutideg (BGB-16673), a Bruton tyrosine kinase (BTK) degrader, in marginal zone lymphoma (MZL), and identify the second-generation BCL2 inhibitor sonrotoclax as a particularly promising combination partner.¹ Their study brings together two therapeutic concepts relevant to B-cell malignancies: targeted disruption of B-cell receptor (BCR) signaling and simultaneous inhibition of a complementary anti-apoptotic dependency. The feasibility and efficacy of combined BTK and BCL2 inhibition have already been demonstrated in chronic lymphocytic leukemia with fixed-duration ibrutinib plus venetoclax.² Arribas et al. now raise the question of whether this principle can be taken a step further in MZL by replacing BTK inhibition with BTK degradation.

This question is particularly relevant because important therapeutic needs in MZL remain unmet, not least because the disease is substantially underrepresented in clinical research.³ Although many patients experience prolonged survival, relapsed or refractory disease is generally managed with successive lines of therapy rather than curative treatment, and no universally accepted optimal strategy exists after failure of available therapies. The rarity and heterogeneity of MZL have also hindered dedicated drug development, with therapeutic advances frequently extrapolated from other indolent B-cell lymphomas.³ Consequently, there remains an important unmet need for effective, well-tolerated, and biologically rational strategies capable of inducing deeper and more durable remissions.

BTK inhibitors (BTKi) established BCR signaling as an actionable dependency in MZL. Ibrutinib provided clinical proof of principle, and the next-generation inhibitor zanubrutinib subsequently demonstrated durable activity with a

favorable benefit-risk profile.^{4,5} Nevertheless, relapse after BTKi therapy remains a clinical reality, reflecting both intrinsic and acquired mechanisms of resistance. Targeted BTK degradation represents a mechanistically distinct approach to suppressing this pathway. Tacabrutideg is a cereblon-dependent compound that promotes BTK ubiquitination and proteasomal degradation rather than merely occupying its catalytic site. Early clinical data suggest activity in relapsed or refractory indolent B-cell lymphomas, including MZL.⁶

Arribas et al. show that tacabrutideg efficiently depletes BTK and suppresses downstream PLCG2 and ERK phosphorylation across several MZL models.¹ Real-time monitoring further demonstrates sustained growth inhibition, supporting targeted protein degradation as a pharmacodynamically effective means of suppressing BCR signaling. Interestingly, however, BTK degradation and BTK inhibition produce largely overlapping biological effects. Transcriptomic changes induced by tacabrutideg substantially resemble those observed with zanubrutinib, including suppression of BCR- and NF- κ B-related programs.¹ Tacabrutideg additionally affects selected programs involving oxidative phosphorylation and ribosomal machinery, but whether these differences translate into a clinically meaningful advantage remains to be established. BTK degradation should therefore not simply be viewed as “stronger BTK inhibition”; its potential value may instead lie in sustained target depletion, elimination of kinase-independent BTK functions, or activity against selected resistance mechanisms.

Nevertheless, BTK degradation may not overcome every form of resistance to BTK inhibition. In this study, models with acquired resistance to BTK or PI3K inhibition show reduced sensitivity to tacabrutideg despite the absence of canonical BTK or PLCG2 resistance mutations.¹ Previous work in MZL has shown that resistance to targeted therapy may involve cytokine-mediated signaling and microenvironment-dependent pathway rewiring.⁷ This observation defines an important conceptual boundary: eliminating BTK cannot suppress a survival dependency that lymphoma cells have already learned to bypass. In this setting, combining mechanistically orthogonal strategies may be more effective than further intensifying blockade of a single signaling node.

This is where combined BCL2 inhibition becomes particularly compelling (Figure 1). Sonrotoclax was more than ten-fold more potent than venetoclax in several MZL cell lines and synergized with tacabrutideg across multiple models.¹ The combination enhanced apoptosis while modulating BCL2-family proteins, including BCL2, MCL1, and BCL-XL. Biologically, this strategy targets two distinct requirements of the malignant B cell: BTK degradation suppresses upstream BCR-dependent proliferative and survival signaling, whereas BCL2 inhibition lowers the mitochondrial apoptotic threshold. Such dual pressure may be more difficult for lymphoma cells to circumvent in vitro than more profound suppression of BCR signaling alone.

The translational relevance of this strategy is strengthened by experiments incorporating the tumor microenvironment. In three-dimensional co-culture with human bone marrow stromal cells, tacabrutideg retained activity, and its combination with sonrotoclax produced the most consistent growth inhibition, partially overcoming stromal protection.¹ Finally, tacabrutideg also reduced cell growth and ERK phosphorylation in primary MZL samples.

Although these observations extend the findings beyond conventional two-dimensional cell culture, the absence of in vivo validation and the limited number of primary samples remain important limitations. Moreover, the

biological heterogeneity of MZL means that splenic, nodal, and extranodal entities should not be assumed to share identical BTK or BCL2 dependencies.

The clinical rationale for dual-pathway targeting is compelling. Venetoclax has demonstrated single-agent activity in relapsed or refractory non-Hodgkin lymphoma, including MZL.⁸ More recently, ibrutinib plus venetoclax produced an overall response rate of 79% in MZL, with complete metabolic responses in 43% of evaluable patients and durable remissions in a subset achieving undetectable measurable residual disease.⁹ Sonrotoclax, designed as a more potent and selective BCL2 inhibitor, has also shown substantial activity in mantle cell lymphoma previously treated with a BTK inhibitor.¹⁰ Together with the success of BTK/BCL2 combinations in CLL,² these observations provide clinical precedent for simultaneously targeting BCR signaling and apoptotic dependency.

The study by Arribas et al. therefore addresses a genuine therapeutic gap rather than simply adding another preclinical combination. MZL requires dedicated clinical development rather than continued extrapolation from other B-cell malignancies.³ The next step should be prospective clinical evaluation of a fixed-duration tacabrutideg-sonrotoclax combination, with careful assessment of safety and the depth and durability of response, alongside translational studies aimed at identifying biomarkers of BTK and BCL2 dependency. Such trials may be challenging in a rare and heterogeneous lymphoma, but this is precisely why MZL-specific development strategies are needed. If clinically validated, dual targeting of BCR signaling and apoptotic dependency could provide a rational path toward deeper disease control and, ultimately, more effective treatment for patients with relapsed or refractory MZL, particularly after prior exposure to BTK inhibitors, an increasingly common clinical scenario.

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Figure 1. Dual targeting of signaling and apoptotic dependency in marginal zone lymphoma. Tacabrutideg promotes BTK degradation and suppresses downstream BCR signaling, whereas sonrotoclax inhibits BCL2 and lowers the mitochondrial apoptotic threshold. BCL2: B-cell lymphoma 2; BCR: B-cell receptor; BTK: Bruton tyrosine kinase; MZL: marginal zone lymphoma.

Dual targeting of signaling and apoptotic dependency in MZL

