BTKi + humanized anti-CD20 for advanced follicular lymphoma: ready for an ALTERNATIVE?

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In the present issue of *Haematologica*, Schmidt and colleagues report the results of the ALTERNATIVE trial, a single-arm phase II study designed to test the efficacy of a chemotherapy-free combination of ibrutinib and obinutuzumab for untreated advanced follicular lymphoma (FL).[1]

Based on the selected study design, the trial failed to meet its ambitious primary endpoint of achieving a 1-year progression-free survival of 95%, i.e., 10% more than the historical benchmark achieved with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy alone.[2] Thus, this combination is currently not likely to be adopted as the new standard of care in newly diagnosed FL patients; nevertheless, the study provides new insights in this field by exploring an unconventional targeted treatment approach and underscores once again the important role of minimal residual disease (MRD) assessment in predicting outcome in FL.

The ALTERNATIVE study showed a 3-year progression-free survival of 63%, which is lower than the results obtained with modern chemo-immunotherapy, for instance in the GALLIUM study (80% in the obinutuzumab arm) and in the FOLL12 study (86% in the standard arm), but with comparable overall survival.[3,4] Indeed, early progressing patients (the so-called "POD24" population) represented 29% of the overall series by Schmidt *et al*., compared to 20% in the LymphoCare study,[5] and they accounted for the majority of cases of progression in the first 3 years of observation. Thus, the currently available data on this combination of a Bruton tyrosine kinase Bruton tyrosine kinase inhibitor (BTKi) and an anti-CD20 seem not to support its use as first-line therapy for such high-risk patients.

As somewhat expected from BTKi-containing approaches, complete responses (CR) after induction were rare (5%), despite very good (90%) overall response rates, with a modest improvement over time, a striking difference compared to the 80% CR rates obtained with chemo-immunotherapy induction.[4] Of note, however, is that the response assessment in the ALTERNATIVE study followed the criteria published in 2007,[6] relying solely on (not centralized) computed tomography scans, rather than on fluorodeoxyglucose positron emission tomography as in current practice; this may have led to an underestimation of CR. Nonetheless, responses obtained were quite durable (the median duration of response was not reached), with 86% of responding patients having ongoing responses at 2 years, although maintenance was delivered with ibrutinib not in combination with anti-CD20 or with anti-CD20 alone. The safety profile of the study drugs was consistent with previously known data: the main adverse events during induction were linked to hematologic toxicity, while during ibrutinib maintenance and follow-up, the most frequent adverse events were infections such as pneumonia. Interestingly, four (4%) cases of hypertension and only two cases (2%) of atrial fibrillation were recorded, compared to 14% of cumulative cardiac events with ibrutinib + rituximab in a previous first-line study.[7]

The rationale for BTKi as treatment of lymphoproliferative diseases relies on blockade of the B-cell receptor signaling required for survival and proliferation of malignant B cells. Indeed, these agents have proven their efficacy and are routinely employed in several lymphoproliferative diseases, such as chronic lymphocytic leukemia, marginal zone lymphoma, lymphoplasmacytic lymphoma, and mantle cell lymphoma. However, approaches involving BTKi in FL have not yet entered clinical practice because of the disappointing results of the studies evaluating the activity of single-agent ibrutinib in relapsed/refractory cases.[8,9] The combination of BTKi with anti-CD20, and possibly their inclusion in "triplets" with other targeted agents (notably, lenalidomide[10]), may change this scenario. While previous studies have described the activity of ibrutinib + rituximab[7,11] the ALTERNATIVE study explores obinutuzumab + ibrutinib for the first time in the first-line setting.

In parallel to this line of research, similar studies are being

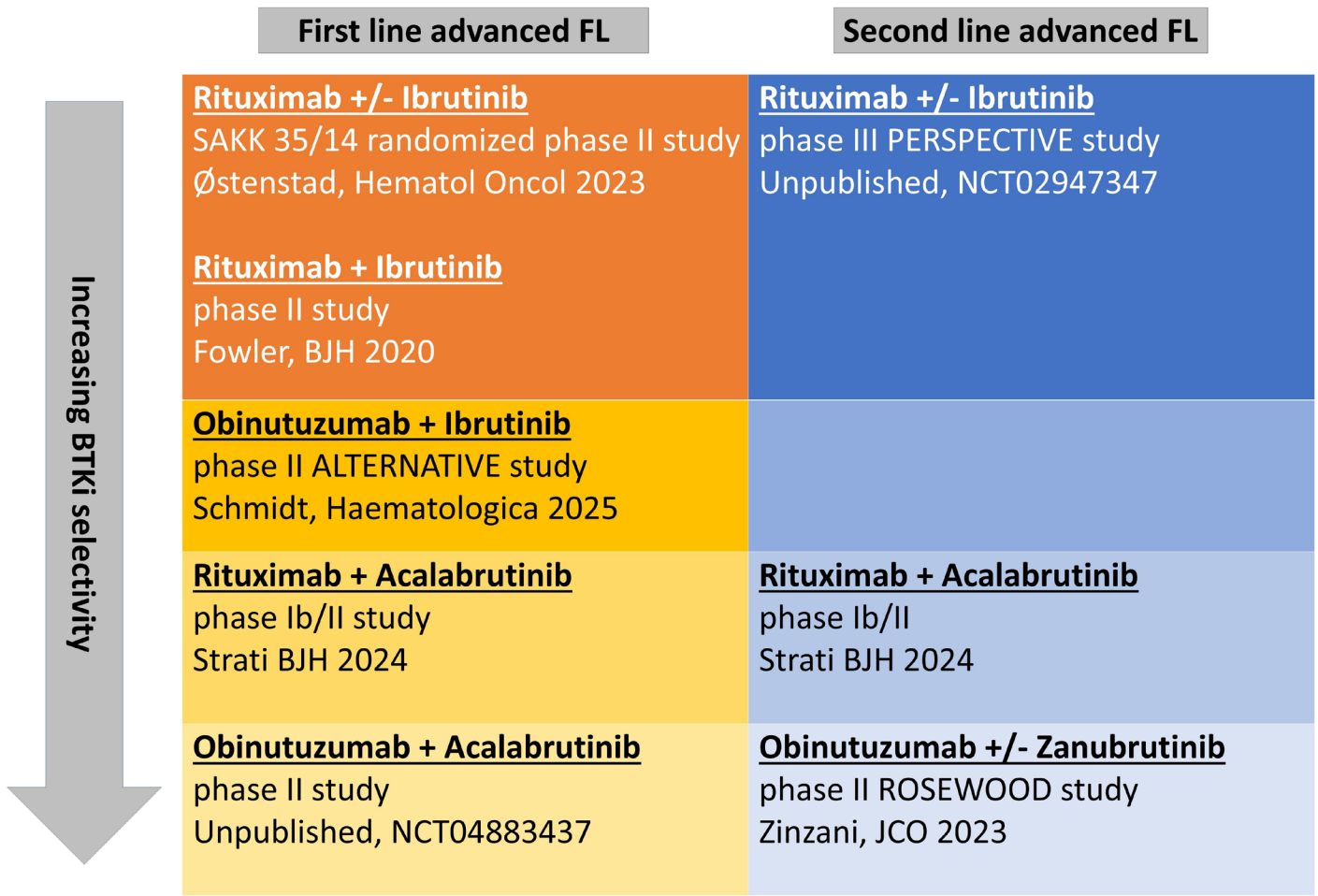

Figure 1. Summary of phase II/III combination studies with BTK inhibitors and anti-CD20 antibodies in patients with treatment-naïve and relapsed/refractory follicular lymphoma. FL: follicular lymphoma; BTKi: Bruton tyrosine kinase inhibitor.

conducted with acalabrutinib, a selective second-generation BTKi,[12] which has the theoretical advantage over ibrutinib of not affecting anti-CD20 antibody-dependent phagocytosis (Figure 1). The ROSEWOOD study, in contrast, tested the combination of zanubrutinib, an irreversible second-generation covalent BTKi with a manageable toxicity profile, and obinutuzumab in relapsed/refractory FL, showing good results that led to the European Commission granting approval of the regimen and to accelerated approval by the Food and Drug Administration.[13]

Interestingly, while MRD after chemo-immunotherapy has already been assessed in prospective phase III studies, the efficacy of the combination of BTKi and anti-CD20 in eradicating MRD has not yet been established. The first data reported in the ALTERNATIVE study showed a positivity rate after induction treatment of 29%, dropping to 22% at the end of ibrutinib maintenance, as compared to around 7-13% at the end of chemo-immunotherapy induction in the GALLIUM and FOLL12 studies.[4,14] Unfortunately, MRD was not evaluated in the ROSEWOOD study,[13] nor has it been reported in the ongoing acalabrutinib-rituximab study,[12] or after rituximab-ibrutinib-lenalidomide.[10] However, it is reasonable to consider that MRD results with these treatments might show slower kinetics than what was experienced with chemo-immunotherapy, with possible delayed negativizations, and that MRD negativity might increase if the BTKi + anti-CD20 combination maintenance is administered.

Targeted therapies, together with novel immunotherapies, have emerged as alternatives to conventional chemo-immunotherapy in newly diagnosed advanced FL. While these new therapies provide further options to patients, their superiority to chemo-immunotherapy in terms of efficacy, safety, and quality of life has yet to be determined. Furthermore, these therapies also carry specific adverse events that need to be addressed. Improved selection and characterization of patients may identify specific subgroups of advanced stage FL patients who are candidates to respond to the BTKi + anti-CD20 combination.

Disclosures

No conflicts of interest to disclose.

Contributions

ID and MF contributed equally to the conceptualization, writing, and editing of this manuscript.

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