

The use of Bruton-tyrosine kinase inhibitors in non-IgM lymphoplasmacytic lymphoma: a retrospective Italian study

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Non-IgM lymphoplasmacytic lymphoma (LPL) is a rare variant of LPL that differs from the more common Waldenström macroglobulinemia (WM), by the absence of an IgM paraprotein. Its biological features, prognosis, and optimal management remain poorly defined, with treatment strategies largely extrapolated from other indolent lymphomas despite shared histology with WM.

With the aim to better characterize clinical outcomes in this subgroup, we retrospectively analyzed 20 non-IgM LPL patients receiving cBTKi therapy across 8 Italian centers.

Patients' characteristics at time of cBTKi initiation are listed on table 1. Median age was 74.5 years. Four (20%) had extranodal involvement including central nervous system (n=2), kidney (n=1), and paranasal localizations (n=1). Anemia was the most common treatment criterion (11 cases, 55%).

Five patients received cBTKi (as first-line therapy, whereas the remaining 15 had a median of one prior line of therapy (range, 0–6). All previously treated patients had been exposed to chemoimmunotherapy, including five (25%) with ≥ 2 prior lines. Overall, zanubrutinib was used in 14 patients (70%, which included 5 frontline therapies) and ibrutinib in six (30%).

According to IWWM-11 consensus criteria, for 19 patients with secretory disease, overall response rate (ORR) was 84.2%, with very good partial response (VGPR) in 7 (36.8%), partial response (PR) in 7 (36.8%), minor response (MR) in 2 (10.6%), and stable disease (SD) in 3 (15.8%) patients. The only non-secretory LPL achieved a CR. Median time to best response was 7.8 months (95% CI: 5.5, 18.2).

None of baseline and disease characteristics impacted on response or quality of response to cBTKi (CR, VGPR or PR) at univariate analysis.

At a median follow-up of 28.8 months (range 6–54.4), 8 patients (40%) progressed. Six of them received a further line of therapy consisting in chemoimmuno- or bortezomib-based regimens. Overall, four patients died: two due to progression, one for invasive fungal infection (IFI) and 1 for a secondary malignancy.

24-month overall survival (OS), progression free survival (PFS) and event free survival (EFS) were 93.8% (95% CI 81.9%, 100.0%), 63.2% (95% CI 39.3%, 87.2%) and 48.8% (95% CI 23.7%, 73.9%), respectively (Figure 1).

Overall, 9 any-grade treatment-emergent adverse events (TEAE) were reported in 7/20 (35%) patients including two grade 3 (G3) non-febrile neutropenia; two infections (one G3 sepsis, one G5 IFI); one G3 non-infectious hepatitis and one G3 hemopericardium (in a patient on antiplatelet therapy). 3/20 (15%) patients discontinued due to toxicity (fatal IFI, acute hepatitis, and hemopericardium).

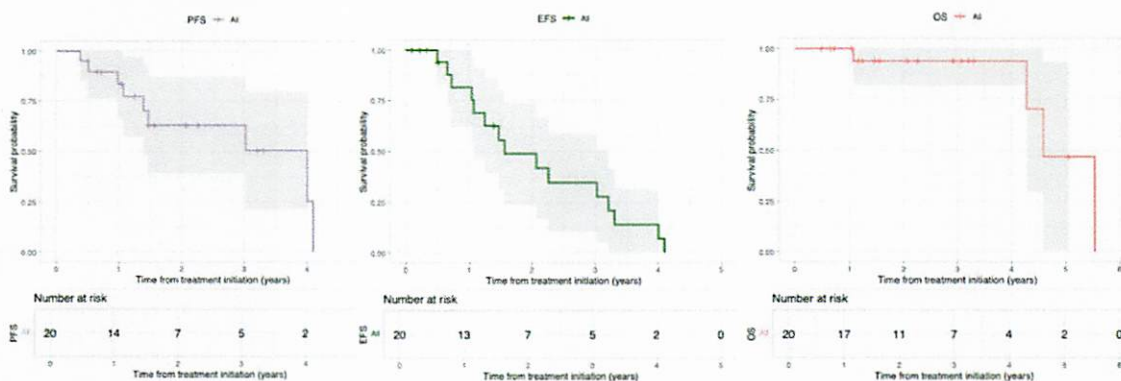
In this retrospective series, cBTKis achieved major responses ($\geq$ PR) in 75% of predominantly pretreated patients, with manageable safety profile and 2-year OS comparable to relapsed/refractory WM. Although PFS appears shorter than in WM, comparisons are limited by the lack of dedicated non-IgM LPL cohorts.

To the best of our knowledge this is the only series focused on cBTKis in non-IgM LPL. Acknowledging the limitations of its retrospective nature and small sample size, this study supports the use of cBTKis as a promising option and provides a rationale for prospective collaborative studies to investigate optimal treatment sequencing, drug combinations, and molecular predictors of response.

Table 1. Patients' characteristics

Characteristic	Pre-BTKi (n = 20)
Age (years), median (range)	74,5 (42-86)
Males (%)	13 (65)
Lymphadenopathies (%)	11 (55)
Splenomegaly, number of patients (%)	9 (45)
Extranodal involvement, number of patients (%)	4 (20)
Bone marrow involvement, number of patients (%)	20 (100)
Bone marrow infiltrate, median (range)	40 (10-90)
Hemoglobin (g/dL), median (range)	11.1 (8-14.9)
Absolute lymphocyte count ($\times 10^9/L$), median (range)	2090 (470-23000)
LDH elevation (%)	7 (35)
M-protein isotype	
IgA	5 (25)
IgG	14 (70)
Non-secretory	1 (5)
Light chain	
κ	3 (15)
λ	16 (80)
M protein concentration (g/dL), median (range)	2,5 (0,5 – 6,7)
MYD88 (L265P) mutation, number of patients (%)	13 (65)
CXCR4 somatic mutation, number of patients (%)	1/13 (7,7)
TP53 somatic mutation, number of patients (%)	2/10 (20)
Number of prior lines, median (range)	1 (0–6)

Figure 1. Two-years PFS, EFS and OS



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Abstract Title: The use of Bruton-tyrosine kinase inhibitors in non-IgM lymphoplasmacytic lymphoma: a retrospective Italian study

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