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Salvage treatment after BTKi failure: an unmet need in clinical practice in Waldenstrom macroglobulinemia

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Although Bruton tyrosine kinase inhibitors (BTKi) have become cornerstones in the treatment landscape of Waldenstrom Macroglobulinemia (WM), data on salvage after BTKi failure are scarce with very limited treatment options available, rending this scenario the most significant WM unmet clinical need. To describe outcomes after BTKi discontinuation, we conducted a retrospective study on patients receiving salvage therapy following BTKi (BTKi-S) in Italy.

This multicenter retrospective study involved WM patients who received subsequent lines following BTKi. We reviewed baseline clinical and disease characteristics, reasons for BTKi discontinuation, outcomes and subsequent therapies. Kaplan-Meier analysis was used to estimate post-BTKi outcomes from BTKi discontinuation to last follow-up. BTKi-S duration was calculated from BTKi salvage initiation to discontinuation.

From December 2015 to November 2023, 233 consecutive WM patients treated with BTKi across 22 Italian centers were included. Of these, 78 (33.5%) definitively discontinued BTKi (74 ibrutinib, 4 Zanubrutinib) and received subsequent salvage therapies, representing our study population (Table 1). All but 2 had been treated before BTKi with a median of 2 prior lines (range, 0-6). Median time on BTKi was 16.0 months (range, 1.2-98.4). Primary reasons for BTKi discontinuation included progression (69.2%), intolerance (29.5%), secondary malignancy (1.3%). Median age at BTKi-S was 75.5 years (range, 46.8-92.8). Of tested cases, 73% were $MYD88^{L265P}$; 23.8% $CXCR4^{mut}$. Median number of previous lines before BTK-S was 3 (range, 1-7). Anemia was the main reason for BTKi failure in 65.4%. In 2 patients disease progressed to diffuse large B cell lymphoma (2.6%), 1 (1.3%) developed Bing Neel syndrome. BTKi-S treatments included: chemoimmunotherapy (31 patients, 39.7%), proteasome inhibitors (16, 20.5%), venetoclax (9, 11.5%), non-covalent BTKi (7, 9.0%), alternative covalent BTKi in intolerants (11, 14.1%), and clinical trials (4, 5.1%). Overall response rate to BTKi-S was 50.0%, including 6 CR/VGPR. Additionally, 17.9% remained stable on post-BTKi salvage, 32.1% was refractory. Overall, 11 patients progressed while on BTKi-S and 4 underwent further lines of therapy. Median PFS and OS for the entire cohort were 8.1 and 21.0 months, respectively. When categorizing patients according to reason for BTKi discontinuation, PFS and OS for progressive versus intolerant were 6.2 versus 16.0 months ($p=.112$) and 17.3 months versus not reached ($p=.368$), respectively. When considering BTKi-progressive patients only, median PFS was 5.8 months with chemoimmunotherapy; 5.0 with proteasome inhibitors, 6.9 with venetoclax, 3.9 with non-covalent BTKi, and not reached with clinical trials. No differences in PFS and OS have been observed according to the first salvage regimen (Figure 1). Patients with 0-1 versus ≥2 lines before ibrutinib had a significantly better PFS, with each additional line of therapy affecting both PFS and OS.

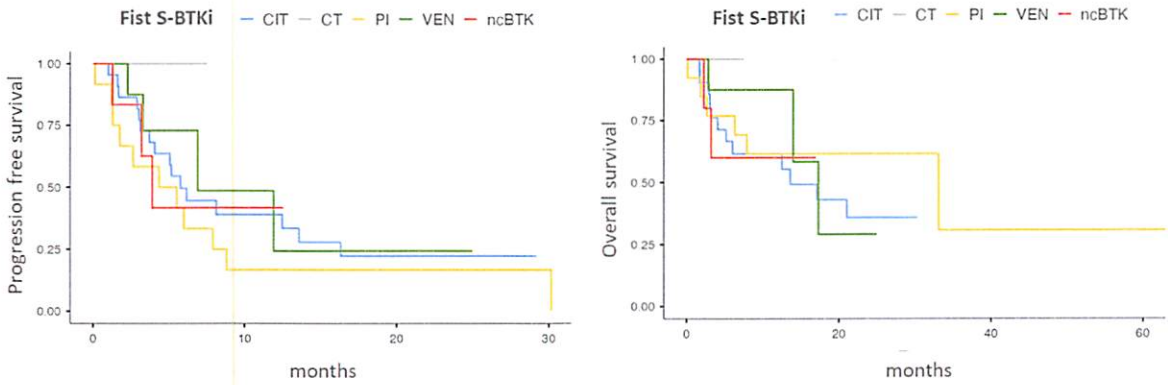
BTK-S outcomes in this real-life population are poor. A potential bias may stem from an adverse prognosis of this series presenting short BTKi exposure duration, and small sample

size. Data on the impact of the number of prior treatments on survival suggest that BTKi should be administered early in relapsed/refractory patients. The absence of approved salvage therapies post-BTKi remains a major challenge in WM treatment sequencing, warranting additional data from clinical practice.

Table 1. Patients' characteristics at BTK-S

	Progressive on BTKi N (%)	**Intolerant to BTKi N (%)**	**All patients N (%)**
	54 (69.2)	24 (30.8)	78 (100)
Sex			
male	32 (59.3)	18 (75)	50 (64.1)
female	22(40.7)	6 (25)	28 (35.9)
Age (median, range)	74.45 (46.8-92.8)	79.3 (59.5-90.1)	75.5 (46.8-92.8)
BTKi administered			
ibrutinib	50 (92.6)	24 (100)	74 (94.9)
zanubrutinib	4 (7.4)	0 (0)	4 (5.1)
Treatment status			
R/R	52 (96.3)	24 (100)	76 (97.4)
previously untreated	2 (3.7)	0 (0)	2 (2.6)
Median lines of therapies before BTKi (median, range)	2 (0-6)	1 (1-4)	2 (0-6)
MYD88L265P mutational status			
Mutated	31/43 (72.1)	15/20 (75)	46/63 (73.0)
Wild type	12/43 (27.9)	5/20 (25)	17/63 (27.0)
CXCR4 mutational status			
Mutated	4/16 (25)	1/5 (20)	5/21(23.8)
Wild type	12/16 (75)	4/5 (80)	16/21 (76.2)
IPSSWM			
very low-low	14 (25.9)	3 (12.5)	17 (21.8)
intermediate	29 (53.7)	8 (33.3)	37 (47.4)
high-very high	12 (22.2)	12 (50.0)	24 (30.8)
Months on BTKi therapy (median, range)	24.3 (0.1-98.4)	10.8 (0.8-27.2)	16.0 (0.1-98.4)
IgM value mg/dl (median, range)	2765 (110–8825)	2716 (61-6600)	2849 (61 – 8825)
Hb g/dl (median, range)	9.5 (7.3-15.2)	10.25 (8-12.6)	9.6 (7.3 – 15.2)
ECOG-PS			
0-1	42 (77.8)	16 (66.7)	58 (74.4)
2-3	12 (22.2)	8 (33.3)	20 (25.6)
CrCl			
≥50	39 (72.2)	18 (75)	57 (73.1)
<50	15 (27.8)	6 (25)	21 (26.9)
BTK-S			
Chemoimmunotherapy	22 (40.7)	9 (37.5)	31 (39.7)
Proteosome inhibitors-based	13 (24.1)	3 (12.5)	16 (20.5)
Venetoclax	9 (16.7)	0	9 (11.5)
Non-covalent BTKi	6 (11.1)	1 (4.2)	7 (9.0)
Alternative covalent BTKi	0	11 (45.8)	11 (14.1)
Clinical trials	4 (7.4)	0	4 (5.1)

Figure 1. Progression free survival and overall survival according to first treatment administered at BTKi-S in BTKi-progressive patients



CIT=chemoimmunotherapy; CT=clinical trial; PI=proteasome inhibitor; VEN=venetoclax; ncBTK=non-covalent BTK inhibitor