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LETTER

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

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Waldenstrom Macroglobulinemia (WM) therapeutic scenario has radically changed over the past 20 years with the development of effective therapies able to improve patients' outcomes.[1] The approval of covalent Bruton Tyrosine Kinase inhibitors (cBTKi), ibrutinib since 20 15[2] and zanubrutinib afterwards,[3] replaced the role of chemoimmunotherapy (CIT) at least in the relapsed/refractory setting. However, despite the remarkable efficacy of cBTKi, the continuous treatment paradigm is associated with resistance development, clonal evolution and relapses, with about 13% of progressions with both zanubrutinib and ibrutinib at the ASPEN trial final analysis.[4] Intolerance represents another main reason for discontinuation and this is more true with the first-in-class cBTKi (20% vs. 8.9% with zanubrutinib)[4] and in clinical practice, where unselected patients are treated. While toxicity-related withdrawal allows a window of opportunity for administering alternative cBTKi,[5] few therapeutic options have been evaluated for relapsed/refractory,[6,7] and none have received approval,

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TABLE 1 Patients' characteristics at BTK-S. (continued on next page)

	Progressive on BTKi, *N* (%) 54 (69.2)	**Intolerant to BTKi, *N* (%) 24 (30.8)**	**All patients, *N* (%) 78 (100)**
Sex			
Male	32 (59.3)	18 (75.0)	50 (64.1)
Female	22 (40.7)	6 (25.0)	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)
Months on cBTKi therapy (median, range)	24.3 (0.1–98.4)	10.8 (0.8–27.2)	16.0 (0.1–98.4)
Ibrutinib	25.4 (0.3–98.4)	10.8 (0.8–27.2)	16.8 (0.3–98.4)
Zanubrutinib	4.4 (0.1–12)	-	4.4 (0.1–12)
Median lines of therapies at BTK-S (median, range)	3 (1–7)	2 (2–5)	3 (1–7)
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 (75.0)	57 (73.1)
<50	15 (27.8)	6 (25.0)	21 (26.9)
Median CIRS score (range)	4 (0–10)	4 (0–12)	4 (0–12)
Patients with CIRS > 6	10 (18.5)	8 (33.3)	18 (23.1)
Patients with major comorbidity[a]	10 (18.5)	4 (16.7)	14 (17.9)
MYD88L265P mutational status			
Mutated	35/43 (81.4)	17/20 (85.0)	52/63 (83.0)
Wild type	8/43 (18.6)	3/20 (15.0)	11/63 (17.0)
CXCR4 mutational status			
Mutated	4/16 (25.0)	1/5 (20.0)	5/21(23.8)
Wild type	12/16 (75.0)	4/5 (80.0)	16/21 (76.2)
Revised IPSSWM[b]			
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)
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)
Reasons for cBTKi progression[c]			
Anemia	36 (66.7)	-	36 (46.2)
Symptomatic/bulky adenopathies	12 (22.2)	-	12 (15.4)
Thrombocytopenia	13 (24.1)	-	13 (16.7)
Hyperviscosity	6 (11.1)	-	6 (7.7)
B-symptoms	4 (7.4)	-	4 (5.1)
Splenomegaly	3 (5.6)	-	3 (3.8)
Autoimmune hemolytic anemia/immune thrombocytopenia	3 (5.6)	-	3 (3.8)
WM-related nephropathy	3 (5.6)	-	3 (3.8)
DLBCL-transformation	2 (3.7)	-	2 (2.6)
Neuropathy	1 (1.9)	-	1 (1.3)
Bing-Neel syndrome	1 (1.9)	-	1 (1.3)

TABLE 1 (Continued)

	Progressive on BTKi, *N* (%) 54 (69.2)	Intolerant to BTKi, *N* (%) 24 (30.8)	All patients, *N* (%) 78 (100)
Cryoglobulinemia	1 (1.9)		1 (1.3)
AL amyloidosis	1 (1.9)		1 (1.3)
Reasons for cBTKi intolerance			
Atrial fibrillation/arrhythmia	-	8 (33.3)	8 (10.3)
Major/recurrent bleeding	-	6 (25.0)	6 (7.7)
Major/recurrent infections	-	4 (16.7)	4 (5.1)
Arthralgia	-	3 (12.5)	3 (3.8)
Second malignancy	-	2 (8.3)	2 (2.6)
Recurrent stomatitis	-	1 (4.2)	1 (1.3)
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)	2 (8.3)	8 (10.3)
Alternative covalent BTKi	0	10 (41.7)	10 (7.8)
Clinical trials	4 (7.4)	0	4 (5.1)

[a]Major comorbidity: at least 1 grade 3-4 comorbidity in a single CIRS item.

[b]Kastritis E, Morel P, Duhamel A, et al. A revised international prognostic score system for Waldenström's macroglobulinemia. *Leukemia*. 2019;33:2654–2661.

[c]Reasons for cBTKi progression may overlap.

rendering this scenario the most significant unmet clinical need in WM. We conducted this retrospective analysis to assess salvage therapy outcomes following cBTKi (cBTKi-S) in 22 Italian centers. This study was institutional review board approved by each participating institution in accordance with the Declaration of Helsinki. All patients receiving at least one dose of cBTKi-S were considered. Baseline clinical and disease characteristics at cBTKi-S initiation were reviewed. *MYD88* and *CXCR4* mutation tests were locally performed by Sanger sequencing. Duration of first cBTKi was calculated from therapy initiation to discontinuation. Reasons for cBTKi discontinuation, type of cBTKi-S, responses and progression assessment, according to modified IWWM-11 criteria[8] and duration of response (DOR) were reviewed. DOR was calculated in responding patients from cBTKi-S initiation to progression. Progression-free survival (PFS) was defined as the time from cBTKi-S to progression or death due to any cause, OS as the time from cBTKi-S to death due to any cause. Kaplan-Meier analysis was used to estimate cBTKi-S survival outcomes and the log-rank test was applied to compare time to event outcomes between groups. From December 2015 to November 2023, 233 consecutive WM patients treated with cBTKi were included. Of these, 78 (33.5%) discontinued cBTKi (74 ibrutinib, 4 zanubrutinib) and received subsequent salvage therapies, representing our study population. Median age of the 78 patients was 75.5 years (range, 46.8–92.8). All but two received cBTKi for relapsed/refractory disease after a median of two prior lines (range, 1–6), including CIT in 92.3%. Primary reasons for cBTKi discontinuation were progression (69.2%), intolerance (29.5%) and secondary malignancy (1.3%). All the 24 intolerant patients had been treated with ibrutinib. Among them: 7 (29.2%) had permanently reduced dosage and 8 (33.3%) discontinued therapy for more than 7 days, then unsuccessfully rechallenged before shifting to a next generation inhibitor. Median time of cBTKi exposure was 16.0 months (range, 1.2–98.4), being 24.3 months in the group of progressive patients versus 10.8 months in intolerants. Patients' characteristics and reasons to receive cBTKi-S in progressive and intolerant population are reported in Table 1. cBTKi-S treatment included: CIT (31 patients, 39.7%), proteasome inhibitors in combination with rituximab (PI 16, 20.5%), venetoclax (9, 11.5%), non-covalent BTKi (ncBTKi 8, 10.3%), alternative cBTKi (10, 12.8%), and clinical trials (4, 5.1%). To avoid IgM rebound, the cBTKi was discontinued only after cBTK-S start in all cases except those enrolled in clinical trials as per protocol compliance. Table 1 reports treatment type stratified according to salvage reason. Median follow-up of cBTKi-S treatment was 10.5 months. Overall response (ORR) to cBTKi-S was achieved in 39 patients (50%), including six complete/very good partial remissions (7.7%). ORR according to different cBTKi-S were: 38.7%, 37.5%, 66.7%, 37.5%, 90.0% and 75.0% for CIT, PI, venetoclax, ncBTKi, alternative cBTKi and clinical trials, respectively. Disease remained stable in 14 patients (17.9%), while 25 (32.1%) progressed. Overall, 7/39 (17.9%) responders further progressed while on cBTKi-S and 2 underwent further lines of therapy. None of the baseline clinical and disease characteristics, including *MYD88* and *CXCR4* mutational status, influenced response to cBTKi-S. BTK mutational status at progression was not assessed. Median PFS, DOR and overall survival (OS) for the entire cohort were 8.1, 18.0 and 21.0 months, respectively. $MYD88^{L265P}$ mutated patients showed a significantly better PFS and OS compared to wild type patients ($p = 0.048$ and $p = 0.001$, respectively). A clinically meaningful difference with fewer PFS (HR 0.62, 95% CI 0.33–1.15) and OS events (HR 0.7, 95% CI 0.32–1.53) was observed in the intolerant population (median PFS: 16.0 months; OS: not reached) compared to the cBTKi progressive group (median PFS: 6.2 months; OS: 17.3 months). In fact, the 1-year PFS (65% versus 35%, respectively) resulted statistically significant ($p = 0.016$), while no difference was observed in terms of OS (78.3% versus 66.6%, respectively, $p = 0.26$).

When considering cBTKi-progressive patients only, PFS and OS were not affected by the regimen administered. PFS was 5.8, 5.0, 6.9, 3.9 months for CIT, PI, venetoclax and ncBTKi, respectively while it

was not reached for clinical trials. Patients pretreated with 1-2 versus ≥3 lines at cBTKi-S had a significantly better PFS, with each additional line of therapy affecting both PFS (HR 1.84, 95% CI 1.41–2.39, $p < 0.001$) and OS (HR 1.9, 95% CI 1.39–2.6, $p < 0.001$). Time on previous cBTKi instead, did not affect PFS or OS and did not differ between patients receiving cBTKi for ≥12 months versus <12 months.

Although cBTKi changed the WM treatment paradigm, representing the best salvage treatment after CIT failure, therapeutic challenges persist in case of progression or intolerance. There is a general consensus on the possibility to shift to a next generation cBTKi in case of toxicity-driven discontinuation.[9] In our series, despite the limitation of small sample number, we confirm cBTKi shift as a valid option in this setting, with only 2/10 patients (20%) showing disease progression and 18 months DOR in responders.

Differently from other lymphoproliferative disorders, in WM there is a lack of approved novel agents beyond ibrutinib and zanubrutinib. In this setting early phase clinical trials with new targeted agents showed promising results. Venetoclax allowed to achieve 75% ORR in cBTKi exposed patients with 30 months median PFS.[6] Similarly, in cBTKi-pretreated patients pirtobrutinib led to an ORR of 79%, 22.1 months being the median PFS observed in the whole population.[7] In our series, despite a high ORR achieved with venetoclax (67%), PFS was significantly shorter (6.9 months). In addition, we could not confirm the favorable outcomes with pirtobrutinib as only 37.5% showed a response.

Bortezomib and CIT may still be considered an option even more in those cases in which the accessibility to compassionate use programs is not readily available. Recently, in a small series of 16 patients relapsing after cBTKi, bortezomib showed an ORR of 88% with a median PFS and OS of 18 and 32 months, respectively.[10] In our retrospective series with the same sample size, only 37.5% of patients responded to bortezomib-based treatments with a PFS not reaching 6 months. Similar dismal results were also achieved with CIT (38.7% ORR and 5.8 months PFS). Interestingly, the number of lines received before cBTKi-S significantly impacted both PFS and OS, with the risk of progression or death increasing by approximately 84% to 90% for each additional line received.

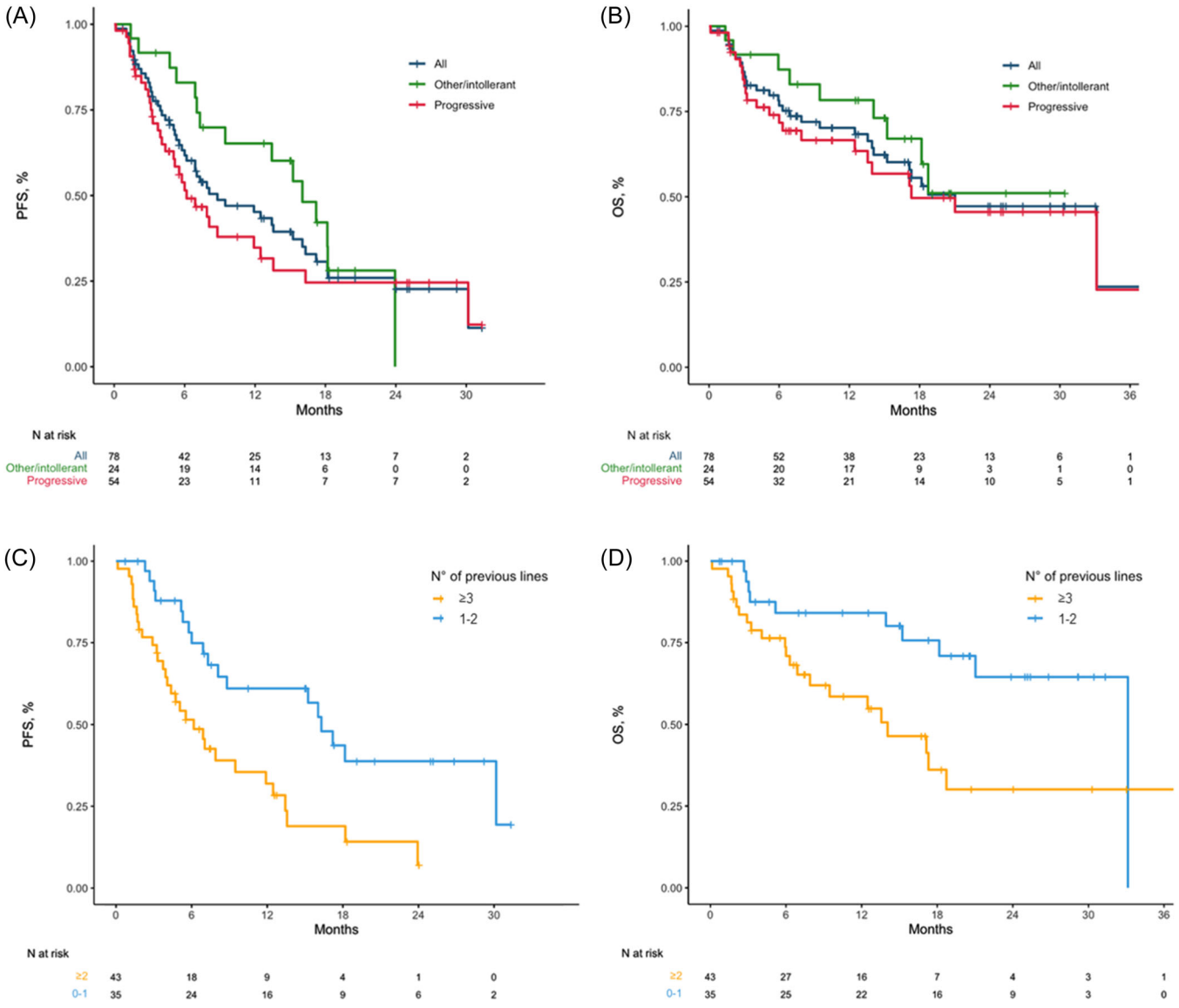

FIGURE 1 Progression-free survival (A) and overall survival (B) for all progressive and intolerant patients, and progression-free survival (C) and overall survival (D) according to number of previous lines at cBTK-S.

Our series mirrors an everyday clinical practice population. These suboptimal results may reflect the selection of a distinctive category of patients with a more aggressive disease considering that median cBTKi exposure was 16 months. In particular, our cohort was characterized by a higher rate of MYD88 wild type compared to literature. Of note, it is challenging to accurately determine the true biological risk characteristics of this population, considering that the evaluation of prognostic factors was conducted exclusively using Sanger sequencing and not in all patients, potentially underestimating the actual cohort of patients with high biological risk.

The lack of approved salvage treatment after cBTKi failure remains a critical need and raises issues regarding the immediate supply of effective drugs, thus translating in inadequate disease control and treatment initiation under deteriorated clinical conditions.

The evidence of better outcomes of cBTKi in second line, underlines the potential importance of initiating BTKi therapy earlier in the disease course, to maximize the benefit.

In conclusion, while acknowledging the limitations of this study primarily due to its retrospective nature, our findings provide a snapshot of the current therapeutic landscape in WM after cBTKi failure. Importantly, although none of the baseline disease characteristics influenced response to cBTK-S, the sample size is too small to make any powered evaluation. On this basis, there is an urgent need for approval in this setting. Prospective clinical trials with other targeted agents, immunotherapies, and cellular therapies are currently ongoing in cBTKi-exposed patients to address this therapeutic gap (Figure 1).

AUTHOR CONTRIBUTIONS

Anna Maria Frustaci and Alessandra Tedeschi conceived the work. Andrea Visentin, Michele Merli, Rita Rizzi, Isacco Ferrarini, Simone Ferrero, Vanessa Innao, Claudia Baratè, Pierluigi Zinzani, Benedetta Puccini, Francesco Autore, Monica Tani, Angela Ferrari, Gioacchino Catania, Maura Nicolosi, Raffaella Pasquale, Marina Motta, Roberta Murru, Silvia Gambara, Francesca Rezzonico, Marzia Varettoni, Emanuele Cencini, Enrico Lista, Nicolò Danesin, Bianca Maria Granelli, Marina Deodato, Francesco Piazza provided patients data. Anna Maria Frustaci and Arianna Zappaterra collected and assembled the data. Andrea Galitzia performed the statistical analysis. Anna Maria Frustaci, Alessandra Tedeschi, Andrea Galitzia, and Arianna Zappaterra analyzed the data and prepared the manuscript. All authors participated in the critical review and revision of this manuscript and provided approval of the manuscript for submission.

CONFLICT OF INTEREST STATEMENT

Anna Maria Frustaci received honoraria from Janssen, Beigene, Abbvie, AstraZeneca. Andrea Visentin participated scientific advisory boards organized by Johnson & Johnson, Abbvie, AstraZeneca, BeiGene, Takeda. Michele Merli participated scientific advisory boards organized by Eli Lilly. Alessandra Tedeschi received consulting fees and travel support for scientific events from Janssen, Beigene, Abbvie, Lilly, AstraZeneca. Andrea Visentin received advisory board participation fees from Janssen, Abbvie, Beigene, CSL Behring, Astrazeneca, Beigene, and Takeda. Isacco Ferrarini reports research fundings from Abbvie, BeiGene, and Eli-Lilly. Simone Ferrero is a consultant for Janssen, EUSA Pharma, Recordati, Abbvie, and Sandoz; is on the advisory board of Janssen, EUSA Pharma, Recordati, Incyte, Roche, Astra Zeneca, and Italfarmaco; received speaker's honoraria from Janssen, EUSA Pharma, Recordati, Lilly, Beigene, Gilead, Novartis, Sandoz, and Gentili; and received research funding from Gilead, Incyte and Morphosys. Roberta Murru received scientific advisory board participation fees and travel support from Abbvie, AstraZeneca, Beigene, Johnson & Johnson. Marzia Varettoni participated scientific advisory boards and received speaker honoraria from Abbvie, AstraZeneca, Beigene and received advisory board participation fees from Johnson & Johnson. Francesco Piazza participated to advisory board and received speaker honoraria from Kite Gilead, Roche, and BeiGene and participated to advisory board from Abbvie and Johnson & Johnson.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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