

**Safety and efficacy of zanubrutinib in Waldenstrom macroglobulinemia patients treated in common clinical practice: A retrospective-prospective study by Fondazione Italiana Linfomi (FIL)**

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The next-generation Bruton's tyrosine kinase inhibitor (BTKi) zanubrutinib (ZAN) was FDA approved in 2021 and reimbursed in Italy for patients with Waldenström macroglobulinemia (WM), both in the relapsed/refractory (RR) setting and for treatment-naïve (TN) patients ineligible for chemoimmunotherapy (CIT). Initially available through a Compassionate Use Program (CUP; October 2020–September 2022), it has been commercially available (Com-U) since October 2022. Real-world data are limited to small CUP cohorts, not reflecting the current population of less heavily pretreated patients. This study evaluated treatment management, safety and outcomes of patients receiving ZAN through CUP or Com-U in Italy.

FIL\_BRUCE (NCT06441214) is a retrospective-prospective multicenter study. Eligible patients were  $\geq 18$  years and received ZAN outside clinical trials through CUP or Com-U. ZAN was administered continuously at 320 mg once daily or 160 mg twice daily. Primary objective was treatment management, including definitive (Tox-DTD) and temporary discontinuation due to toxicity and permanent (PDR) and temporary dose reduction. Secondary included safety (AEs graded per CTCAE v5.0) and efficacy (ORR, PR, VGPR, CR, PFS, EFS [events: progression, death, Tox-DTD] and OS).

From October 2020 to December 2025, 211 patients were enrolled across 25 centers (28 CUP; 183 Com-U). Table 1 reports pts' characteristics. Median age was 78 years (range 69–85); 116 (55.0%) had RR disease with a median of one prior therapy (range 1–5), including six switched because of ibrutinib intolerance. TN pts were significantly older than R/R (median 81 years,  $p=.001$ ). Comorbidity was the main reason for choosing ZAN over CIT in TN.

At data cut-off, 189 pts had received  $\geq 1$  ZAN dose and were evaluable for management and safety. After a median follow-up of 24 months, 142 (75.1%) remain on treatment. Forty-seven discontinued because of: progression (PD, 24, 12.7%); AEs (14, 7.4%, median time to Tox-DTD 7.6 months); physician decision (4, 2.1%); non-PD/non-treatment related deaths (3, 1.6%); other causes (2, 1.1%). Infections accounted for half of Tox-DTD events (7/14). PDR occurred in 34 patients (18%) after a median of 8.1 months, mainly because of neutropenia. Age  $\geq 75$  years (OR 2.67,  $p.026$ ) and CUP treatment (OR 3.23,  $p.006$ ) independently increased the risk of Tox-DTD/PDR. Sixty-seven pts (35.4%) temporary discontinued ZAN for a median of 28 days.

Overall, 114 patients (60.3%) experienced  $\geq 1$  AE, 20 (10.6%) of grade  $\geq 3$ , mostly infections. Any grade atrial fibrillation/flutter occurred in 8 pts (4.2%); grade 5 hemorrhage in 1 (0.5%);

grade 3 hypertension in 2 (1.1%). Overall 20 patients died because of: PD (11), cerebrovascular disease (3), infection (1), acute renal failure (1), second cancer (1) or other causes (3).

Among 164 patients evaluable at 3 months, ORR was 81.7% (TN 87.7%, R/R 77.8%), major response rate 75.0%, including 25.6% VGPR/CR, while 8.5% achieved stable disease. Two-years PFS, EFS and OS were 82%, 78% and 92%, respectively. Bulky disease affected PFS ( $p.048$ ) whereas CUP pts had significantly worst PFS, EFS and OS than Com-U. Nine secondary malignancies, including one DLBCL transformation, were reported, and 21 patients (11%) received subsequent therapy.

In this real-world cohort, including CUP-treated patients, ZAN achieved efficacy comparable to the pivotal trial, with similar outcomes in TN and RR disease. Despite advanced age and substantial comorbidity burden, ZAN showed a favorable safety profile without new safety signals.

Table 1. Patients' characteristics

|                                              | <b>TN<br/>N=95</b>     | <b>R/R<br/>N=116</b>   | <b>p</b>     |
|----------------------------------------------|------------------------|------------------------|--------------|
| <b>Age at registration, median (IQR)</b>     | <b>81 (74-85)</b>      | <b>76 (69-82)</b>      | <b>0.001</b> |
| <b>Sex F, n (%)</b>                          | <b>42 (44)</b>         | <b>34 (29)</b>         | <b>0.031</b> |
| IPSSWM Intermediate/high risk, n (%)         | 60 (63)                | 78 (67)                |              |
| <b>Hb, mg/dL, median (IQR)</b>               | <b>11.0 (9.5-12.0)</b> | <b>12.0 (9.8-13.2)</b> | <b>0.033</b> |
| Plts, count 10 <sup>9</sup> /L, median (IQR) | 203 (143-261)          | 200 (134-261)          |              |
| sMC IgM g/gL, median (IQR)                   | 2.5 (1.7-3.1)          | 1.7 (0.6-3.3)          |              |
| Neutropenia, n (%)                           | 5 (5)                  | 12 (10)                |              |
| <b>MYD88, n (%)</b>                          | <b>60/66 (91)</b>      | <b>56/74 (76)</b>      | <b>0.024</b> |
| CXCR4, n (%)                                 | 6/22 (27)              | 9/33 (27)              |              |
| Bulky disease (≥ 5cm), n (%)                 | 4 (4)                  | 9 (8)                  |              |
| Extranodal sites, yes n (%)                  | 12 (13)                | 22 (19)                |              |
| Baseline neuropathy yes, n (%)               | 3 (3)                  | 11 (10)                |              |
| ECOG-PS>1, n (%)                             | 9 (10)                 | 16 (14)                |              |
| Any CIRS ≥3, n (%)                           | 25 (26)                | 34 (29)                |              |
| CIRS score, median (IQR)                     | 3 (2-4)                | 2 (1-4)                |              |
| CIRS score >6, n (%)                         | 19 (20)                | 27 (23)                |              |
| Cardiological comorbidity yes, n (%)         | 27 (28)                | 43 (37)                |              |
| Hypertention comorbidity yes, n (%)          | 33 (35)                | 40 (34)                |              |
| Number concomitant treat., median min-max)   | 3 (1-9)                | 3 (1-12)               |              |
| <b>Schedule</b>                              |                        |                        |              |
| 160x2 times day, n (%)                       | 82 (86)                | 102 (88)               |              |
| Once 320 a day, n (%)                        | 13 (14)                | 14 (12)                |              |

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