A phase II trial of Bendamustine, Rituximab and Acalabrutinib in previously untreated Waldenström's Macroglobulinemia (BRAWM)

Strategies to improve the outcomes from first line therapy for Waldenstorm's Macroglobulinemia are being explored. Historically, fixed duration chemo-immune therapy has been used, but most recently, continuous covalent BTK-inhibitor (BTK-I) monotherapy has become available. In a related disease, mantle cell lymphoma (MCL), the combination of chemo-immunotherapy with bendamustine and rituximab (BR) with continuous acalabrutinib until progression or toxicity was associated with improved progression-free survival without significant increased toxicities over BR alone.

The BRAWM clinical trial is prospective phase II trial of first-line fixed duration treatment with six 28-day cycles of BR (combination therapy) and 365 days of concurrent acalabrutinib (monotherapy).

We have completed accrual with a total of 63 participants from nine centres across Canada, however, this report includes data on 62 (June 5, 2024). The primary objective is to document the combined Complete and Very Good Partial Response (CR+VGPR) rates. Secondary objectives include best overall response (BoR), progression free and overall survival (PFS/OS), duration of response (DoR), and Minimal Residual Disease (MRD).

The median follow up is 350 days (IQR 503). The baseline characteristics including relationship to common mutational subgroups (*MYD88*, *CXCR4* and *TP53*) are shown in **Table 1**. The median age is 69. At baseline, the median hemoglobin was 104.5g/L, the median serum IgM was 37.05g/dL, and the median degree of bone marrow infiltration was 40% (n=57). The distribution of IPSSWM stage was 11.3% low risk, 38.7% intermediate risk, and 50% high risk. 56 participants had available samples for mutational analysis, *MYD88* mutation was observed in 89.3%, 28.6% *CXCR4* and 1.8% *TP53*. The initial symptoms of WM that lead to treatment initiation and their response to treatment is shown in **Table 2**.

At the time of this analysis, 47 participants reached the time of first response assessment (cycle 7), 2.1% of whom had a CR, 61.7% with a VGPR, (CR + VGPR = 63.8%), 34% with a Partial Response and one participant only had a minimal response. The median haemoglobin increased to 121g/L and the median IgM decreased to 2.18g/dL. Of participants with available samples for MRD analysis, 74% in the peripheral blood and 10% in bone marrow have become MRD undetectable at a sensitivity of 10^{-6}. So far, there have been no instances of progressive disease.

53/62 participants had treatment related adverse events (TRAEs). During combination therapy, there were 42 Grade 3/4 TRAEs. During the monotherapy, there were 15 Grade 3/4 TRAEs, the most common of which were pneumonia and neutropenia. There were 15 TRSAE's which included lung infection (n=2); 1 of each diarrhea, maculo-papular rash, allergic reaction, fever and flu-like symptoms and 4 of each febrile neutropenia and pneumonia. There have been no deaths recorded, treatment related or otherwise..

During combination therapy, 23 participants required dose interruptions, one permanent dose reduction and 3 discontinuations. During the monotherapy, there were a total of 11 dose interruptions, one dose reduction and two discontinuations. Two additional discontinuations were from unrelated adverse events.
Subgroup analysis of prognostic and molecular variables with CR and VGPR are ongoing.

We conclude that this combination 1-year fixed duration regimen is well tolerated in this older patient population and is associated with a higher CR/VGPR rate than expected with chemo-immunotherapy or BTK-I alone. The toxicity profile is manageable and consistent with expected AE for the agents individually and in combination.

Table 1: Baseline Characteristics

	All Participants n = 62	**Mutational Analysis n (%) = 56**		
		MYD88 **n = 50 (89)**	***CXCR4*** **n = 16 (28.6)**	***TP53*** **n = 1 (1.7)**
Sex				
Male (%) Female (%)	48 (77.4) 14 (22.6)	40 (80) 10 (20)	14 (87.5) 2 (12.5)	1 (100) 0 (0)
Age				
Median (range) - years > 65 yrs (%)	69 (39-85) 44 (71)	69.5 (44-85) 37 (74)	70.5 (45-81) 12 (75)	79 1 (100)
IPSSWM Score				
Low Risk (%) Intermediate Risk (%) High Risk (%)	7 (11.3) 24(38.7) 31 (50)	7 (14) 19 (38) 24 (48)	1 (6.3) 7 (43.8) 8 (50)	0 (0) 0 (0) 1 (100)
Serum IgM				
Median (range) - g/L > 40 g/L (%)	37.05 (0.2-99.1) 26 (41.9)	37.05 (0.2-76.8) 22 (44)	36.9 (1.17-76.8) 7 (43.8)	60.9 (60.9-60.9) 1 (100)
Hemoglobin				
Median (range) - g/L ≤ 115 g/L (%)	104.5 (69-157) 42 (67.7)	103.5 (69-157) 32 (64)	101 (69-144) 11 (68.8)	77 (77-77) 1 (100)
Platelet Count				
Median (range) - $x10^9$/L ≤ 100 $x10^9$/L (%)	226 (55-778) 7 (11.3)	235.5 (68-778) 4 (8)	176 (68-336) 3 (18.8)	251 (251-251) 0 (0)
Serum β2-microglobulin				
	n = 58	**n = 48**	**n = 16**	**n = 1**
Median (range) - g/dL < 3 g/dL (%)	3.5 (1.3-15.05) 15 (24.2)	3.62 (1.3-15.05) 12 (24)	3.6 (2.0-5.0) 4 (25)	3.8 (3.8-3.8) 0 (0)

Table 2: Symptoms of WM

Symptoms of WM				
Symptom	**Baseline n = 62**	**Cycle 7 n = 47**	**Cycle 12 n = 38**	**Month 18 n = 26**
Anemia with Fatigue	36	12	6	3
Neuropathy	18	11	7	5
Lymphadenopathy	7	0	0	0
Hyperviscosity	12	3	2	1
Cryoglobulinemia	1	0	0	0
Cold agglutinin	2	2	1	0
Renal dysfunction	3	0	0	0
Amyloidosis	1	1	1	0
Pleural effusions	2	0	0	0
Other	10	1	1	1
None	7	0	0	0