DANA-FARBER CANCER INSTITUTE

HARVARD MEDICAL SCHOOL

Relapsed and/or refractory Waldenström macroglobulinemia

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Disclosures

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Honoraria	N/A
Scientific Advisory Board	Abbvie, Pharmacyclics

Selected treatment options for previously treated WM

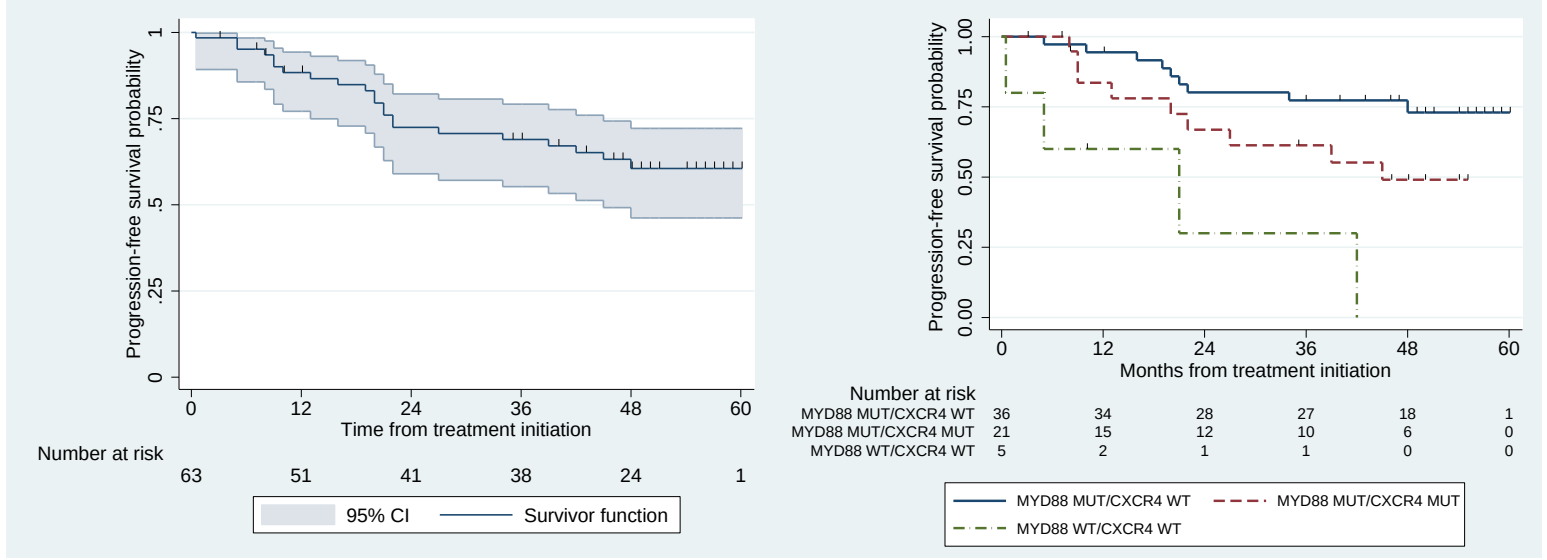
	CDR	Benda-R	Bortezomib-R	Fludarabine-R
ORR	83%	80-95%	80%	90%
≥VGPR	4%	20-25%	5%	30%
PFS	32 months	58 months	16 months	38 months
≥G3 Toxicity	Neutropenia Thrombocytop	Neutropenia Thrombocytop	Neutropenia Anemia Thrombocytop	Neutropenia Thrombocytop

Paludo et al. Br J Haematol 2017; Paludo et al. Ann Hematol 2018; Ghobrial et al. J Clin Oncol 2010; Tedeschi et al. Leuk Lymphoma 2015; Treon et al. Blood 2009

Ibrutinib in Previously Treated Waldenström's Macroglobulinemia

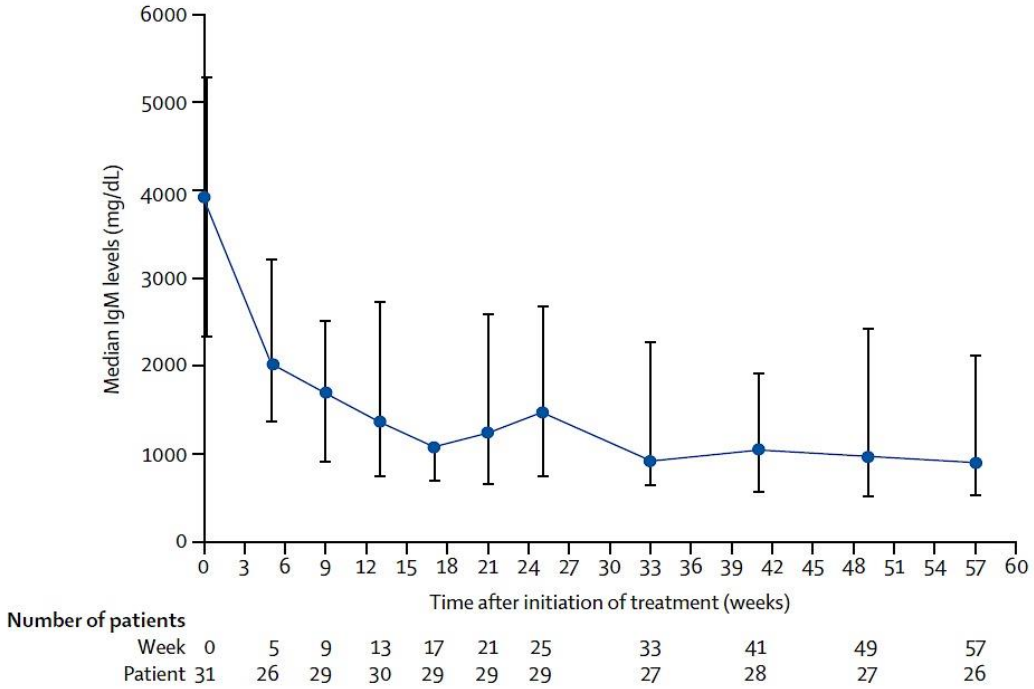
Table 1. Rate of Response to Ibrutinib in Patients with Waldenström's Macroglobulinemia, According to Mutation Status.*

Response Rate	Mutated *MYD88* and Wild-Type *CXCR4* (N=36)	Mutated *MYD88* and *CXCR4* WHIM (N=21)	Wild-Type *MYD88* and *CXCR4* (N=5)	P Value†
		percent		
Overall	100	85.7	60	0.005
Major	91.7	61.9	0	<0.001



Treon et al. N Engl J Med 2015
Treon et al. ICML 2019

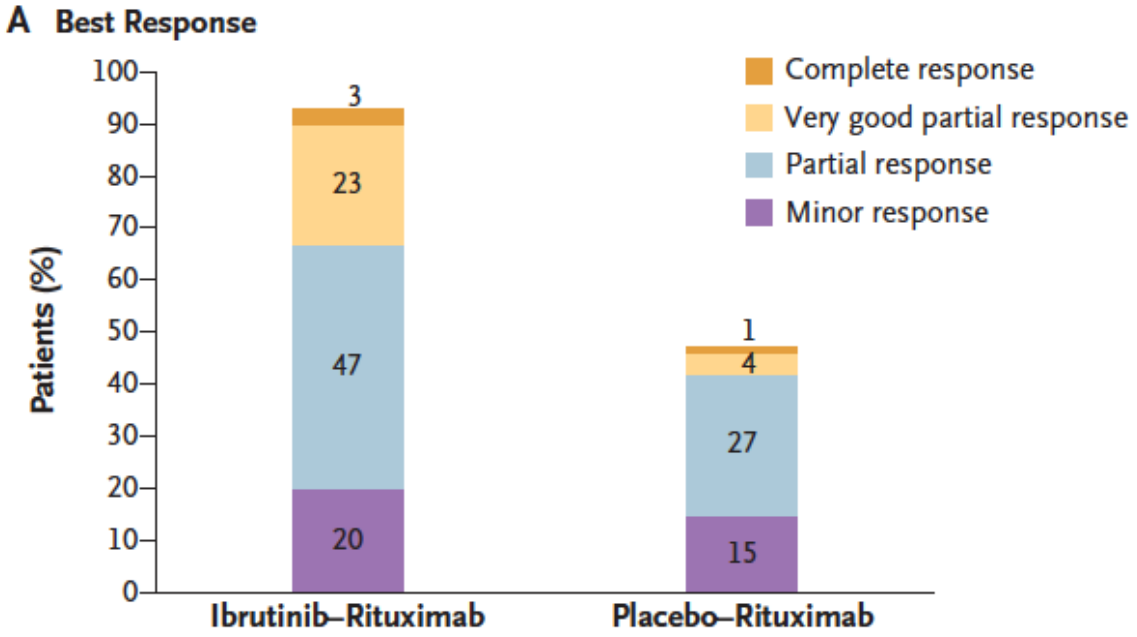
Ibrutinib for patients with rituximab-refractory Waldenström's macroglobulinaemia (iNNOVATE): an open-label substudy of an international, multicentre, phase 3 trial



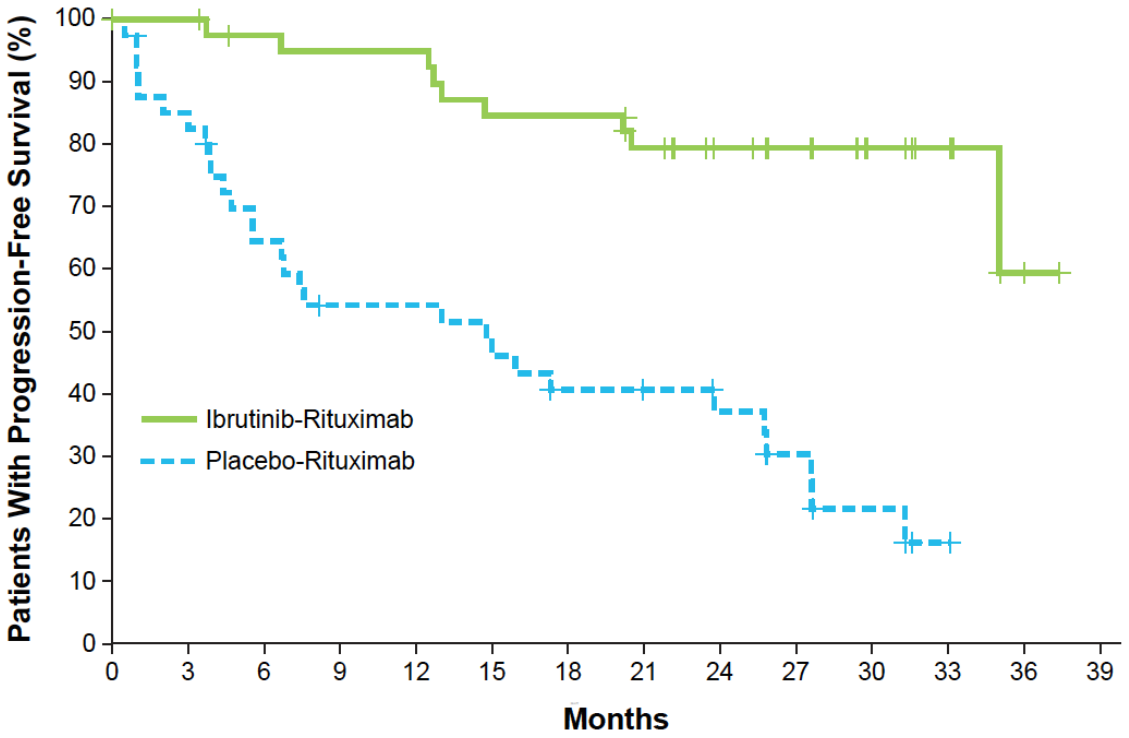
	All* (N=31)	MYD88 (Leu265Pro)/ CXCR4 (wild type; n=17)†	MYD88 (Leu265Pro)/ CXCR4 (WHIM; n=7)
Very good partial response	4 (13%)	3 (18%)	0
Partial response	18 (58%)	11 (65%)	5 (71%)
Minor response	6 (19%)	1 (6%)	2 (29%)
Overall response (%)	28 (90%)	15 (88%)	7 (100%)
Major response (%)	22 (71%)	14 (82%)	5 (71%)
18 month progression-free survival (%; 95% CI)	86% (66–94)	94% (63–99)	86% (33–98)
18 months overall survival (%; 95% CI)	97% (79–100)	100% (100–100)	100% (100–100)

Dimopoulos et al. Lancet Oncol 2017

Phase 3 Trial of Ibrutinib plus Rituximab in Waldenström's Macroglobulinemia



All patients



Relapsed/refractory patients

Dimopoulos et al. N Engl J Med 2018

Is ibrutinib-rituximab better than ibrutinib alone?

	Ibrutinib + rituximab	Ibrutinib relapsed	Ibrutinib INNOVATE arm C
N previously untreated	34	-	-
N previoulsy treated	41	63	31
ORR	92%	91%	90%
MRR	72%	73%	71%
VGPR	23%	27%	13%
PFS	30-mo: 82%	60-mo: 60%	18-mo: 86%

Treon et al. N Engl J Med 2015; Dimopoulos et al. Lancet Oncol 2017;
Dimopoulos et al. N Engl J Med 2018

Acalabrutinib in patients with Waldenström Macroglobulinemia

Characteristic	N (%)
Median age	69 (36-90)
Median IgM level	3615 (291-9740)
Treatment naïve	14 (13%)
Previously treated	92 (88%)
Prior therapies	2 (1-7)
Atrial fibrillation	3 (3%)
Bleeding	59 (57%)
ORR	94%
Major response	78%
VGPR	32%

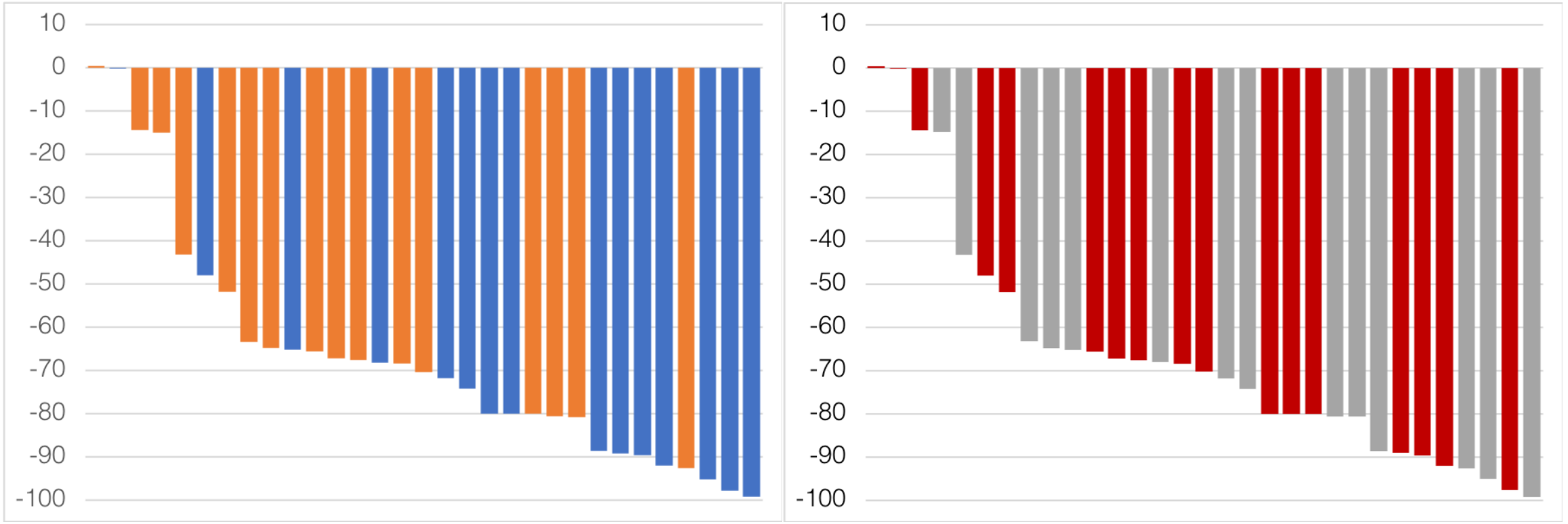
Owen et al. EHA 2018

Zanubrutinib In Patients With Waldenström Macroglobulinemia

Characteristic	N (%)
Median IgM level	3250 (530-8850)
Median hemoglobin	8.7 (6.3-9.8)
Prior therapies	NR (1-8)
Atrial fibrillation	4 (6%)
Bleeding	25 (37%)
ORR	92%
Major response	80%
VGPR	36%

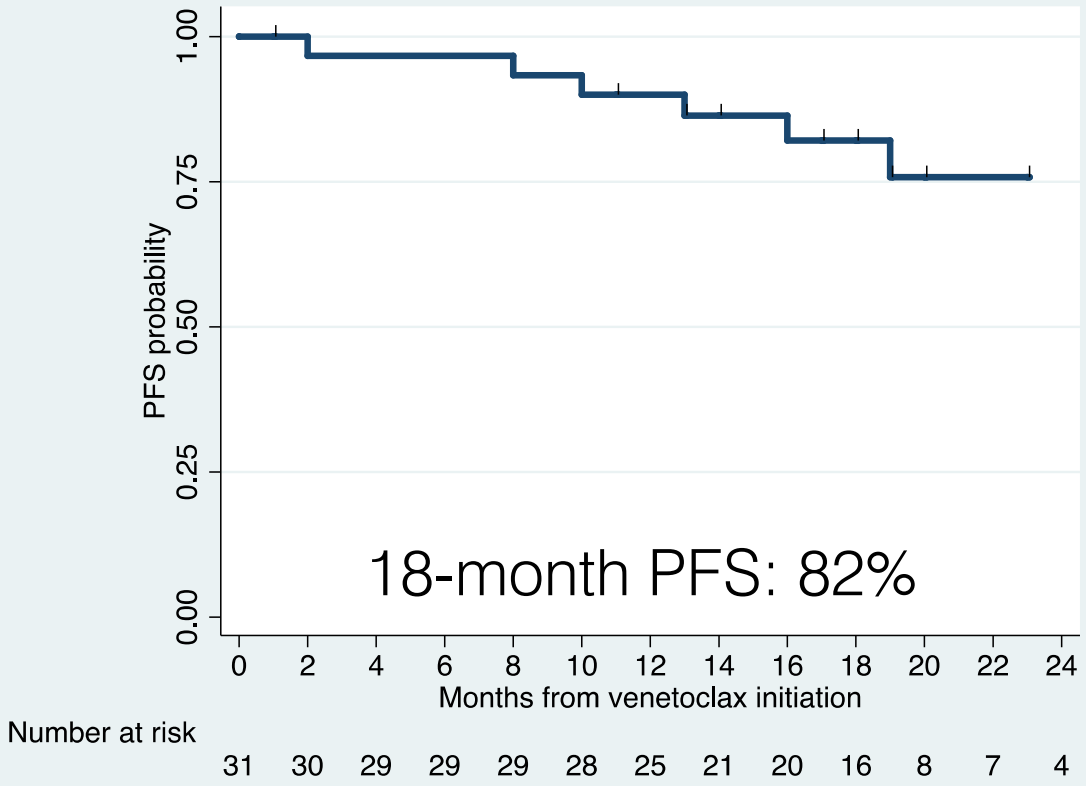
Trotman et al. EHA 2019

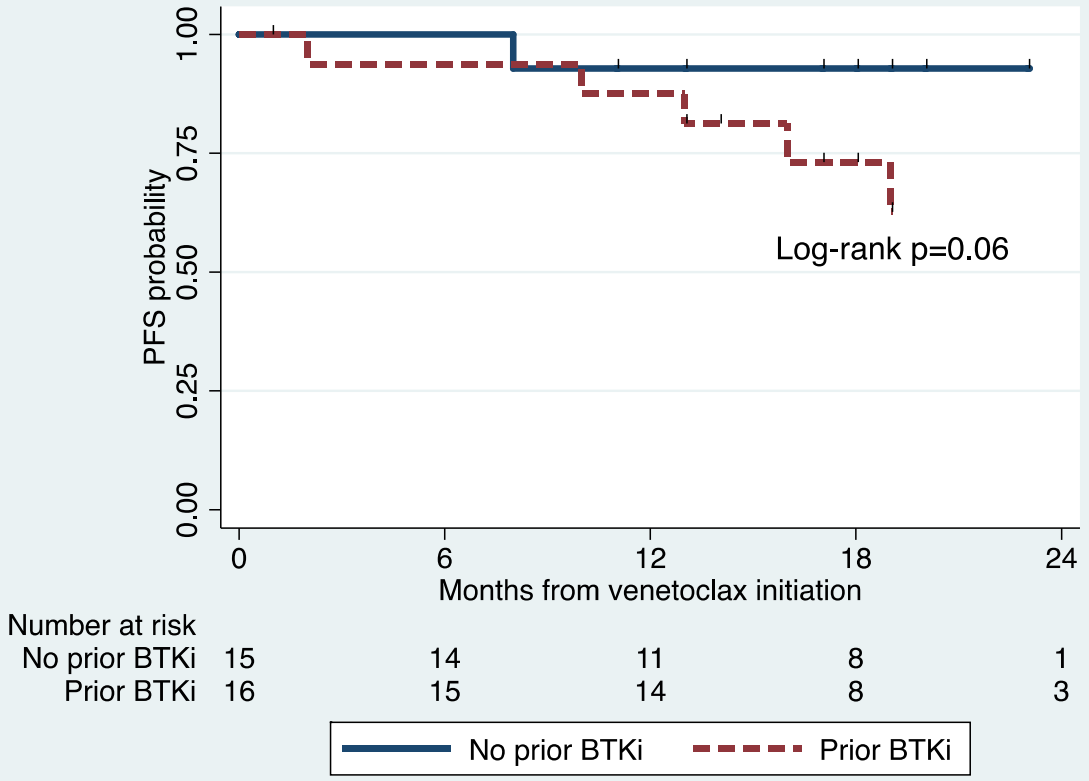
Multicenter prospective phase II study of venetoclax in patients with previously treated Waldenström macroglobulinemia



Castillo et al. IMW 2019

Multicenter prospective phase II study of venetoclax in patients with previously treated Waldenström macroglobulinemia





Castillo et al. IMW 2019

Selected clinical trials in previously treated WM

Phase III studies

- Zanubrutinib vs. ibrutinib (enrollment complete)

Phase I/II studies

- Ibrutinib + ulocuplumab
- Ibrutinib + daratumumab
- Ibrutinib + ixazomib
- Umbralisib
- Vecabrutinib

Conclusions

- Alkylators, proteasome inhibitors and BTK inhibitors with and without rituximab are standard relapsed/refractory treatment options.
- The choice of therapy is largely personalized.
- Clinical trial referral and participation are critical.