



BING-NEEL SYNDROME

Jorge J. Castillo, MD
Associate Professor of Medicine
Harvard Medical School
JorgeJ_Castillo@dfci.harvard.edu



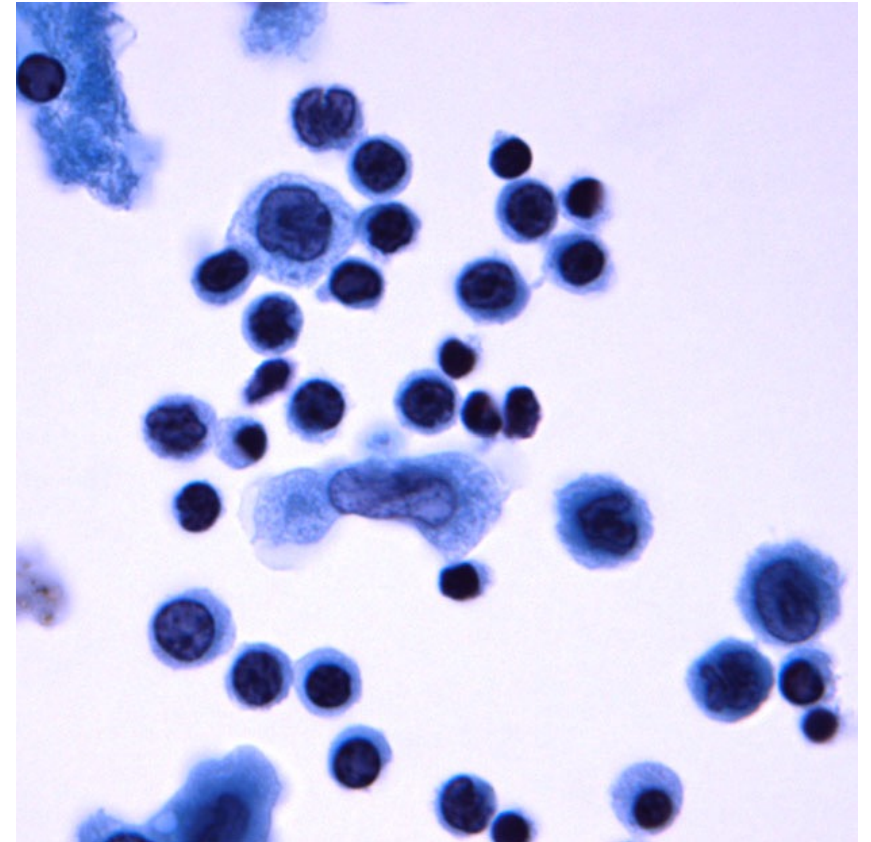
Dana-Farber
Cancer Institute

Disclosures

Company	Research support	Employee	Consultant	Stockholder	Speaker's Bureau	Scientific Advisory Board
AbbVie	X		X			X
AstraZeneca	X					
BeiGene	X		X			X
Casma Therapeutics			X			
Cellectar			X			
Janssen	X		X			
Pharmacyclics	X		X			X
Roche			X			
TG Therapeutics	X					

A case

- 73M with diagnosis of Waldenström macroglobulinemia (WM) in 2007 and treated with R-CVP in 2010 developed bilateral leg weakness while on therapy.
- Spinal MRI showed leptomeningeal enhancement of the cauda equina.
- CSF examination showed the presence of clonal lymphoplasmacytic cells, CD20+, CD5-, CD10-.
- A diagnosis of Bing-Neel syndrome (BNS) was made



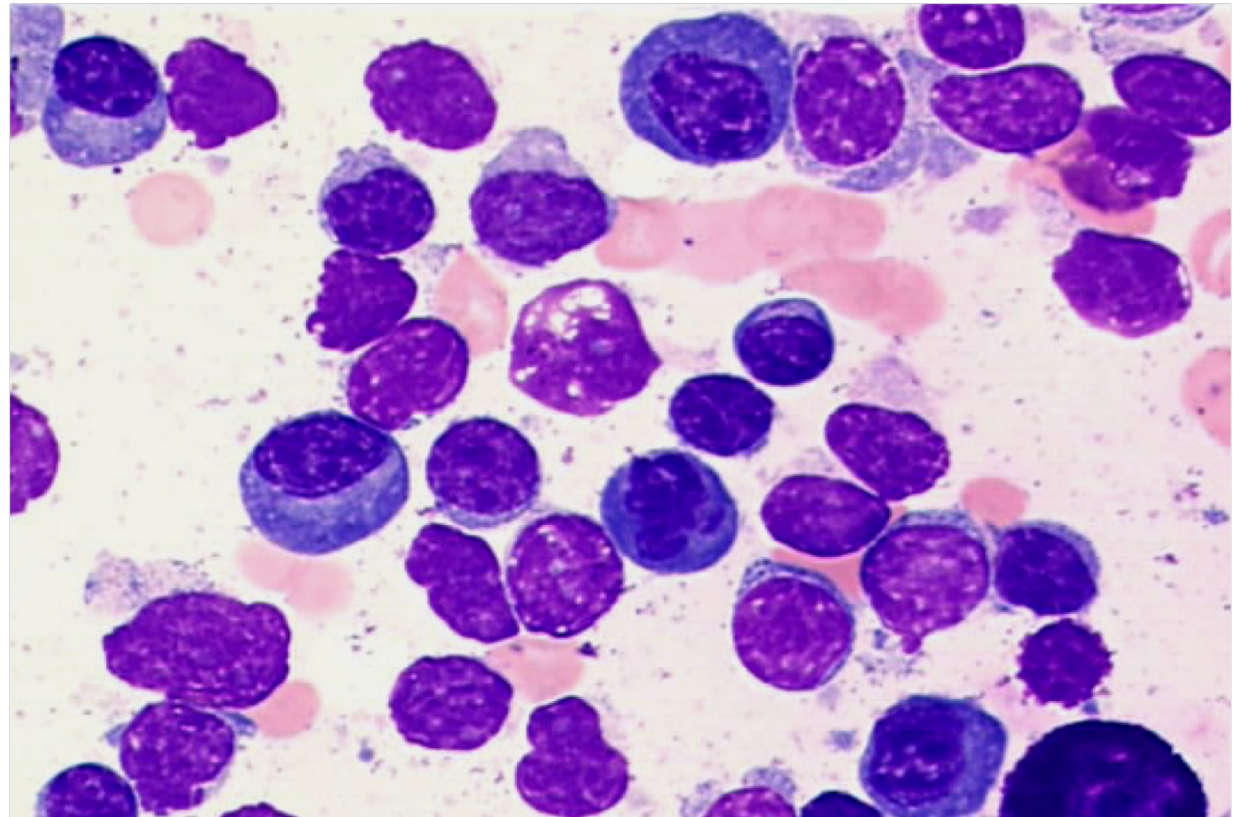


Objectives

- When to suspect BNS
- How to diagnose BNS
- How to treat BNS
- How to counsel BNS patients

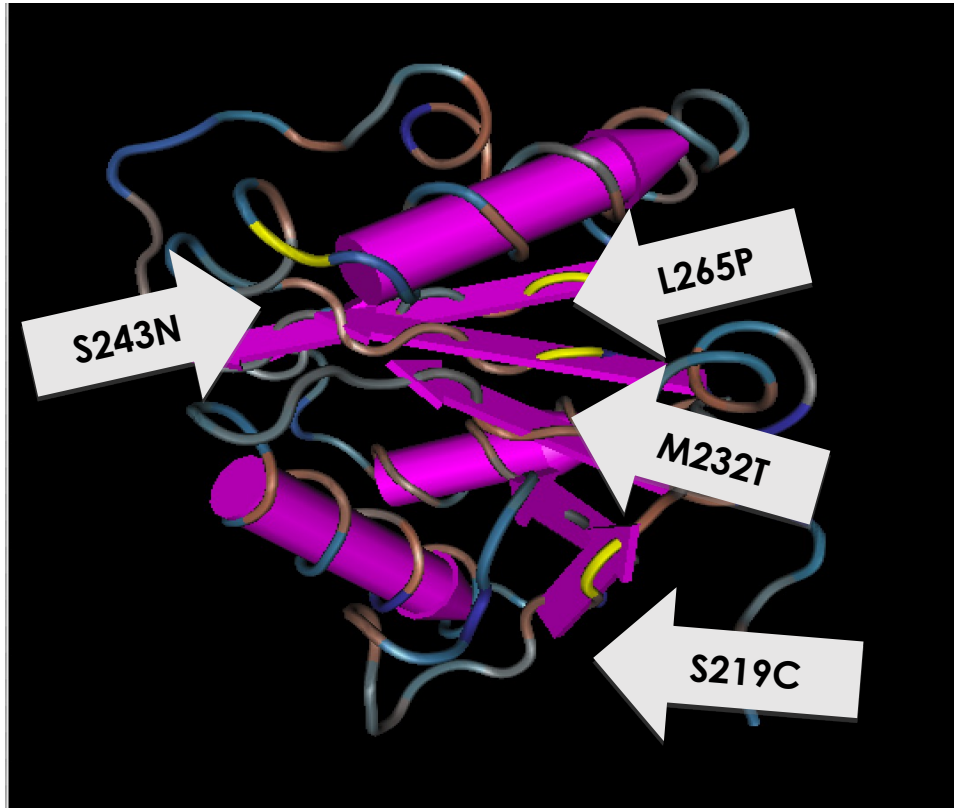
Diagnostic criteria

1. IgM monoclonal protein in serum protein electrophoresis and immunofixation
2. Lymphoplasmacytic lymphoma in the bone marrow
3. *MYD88 L265P* mutation by AS-PCR or NGS
















Alaggio et al. Leukemia 2022; ASH Image Bank 2022

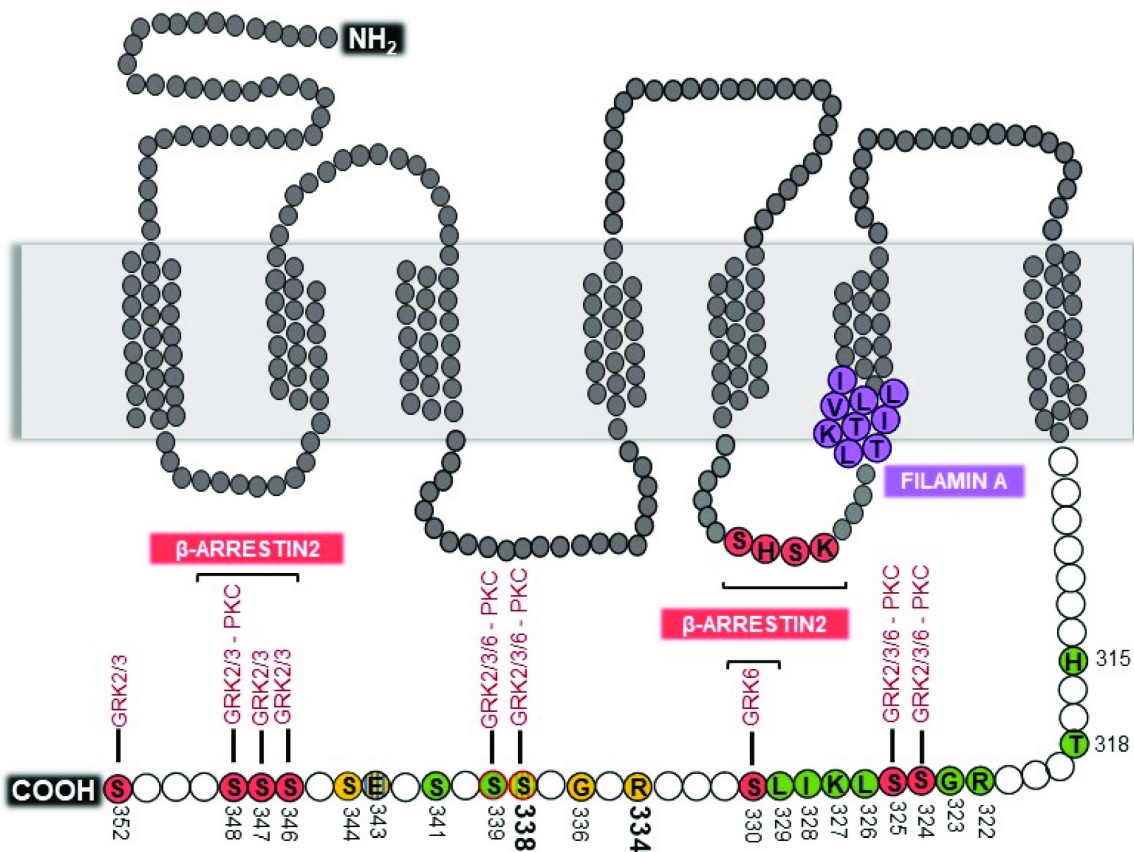
MYD88 mutations











Treon et al. N Engl J Med 2012
 Xu et al. Blood 2013

Study		Method	%
Xu		AS-PCR	93%
Poulain		PCR	80%
Varettoni		AS-PCR	100%
Landgren		Sanger	90%
Jimenez		AS-PCR	86%
Argentou		PCR-RFLP	92%
Willenbacher		Sanger	86%
Mori		AS-PCR	80%
Ansell		WES/AS-PCR	97%
Patkar		AS-PCR	85%
Cao		AS-PCR	92%
Giuliani		AS-PCR	95%
Riva		AS-PCR	89%

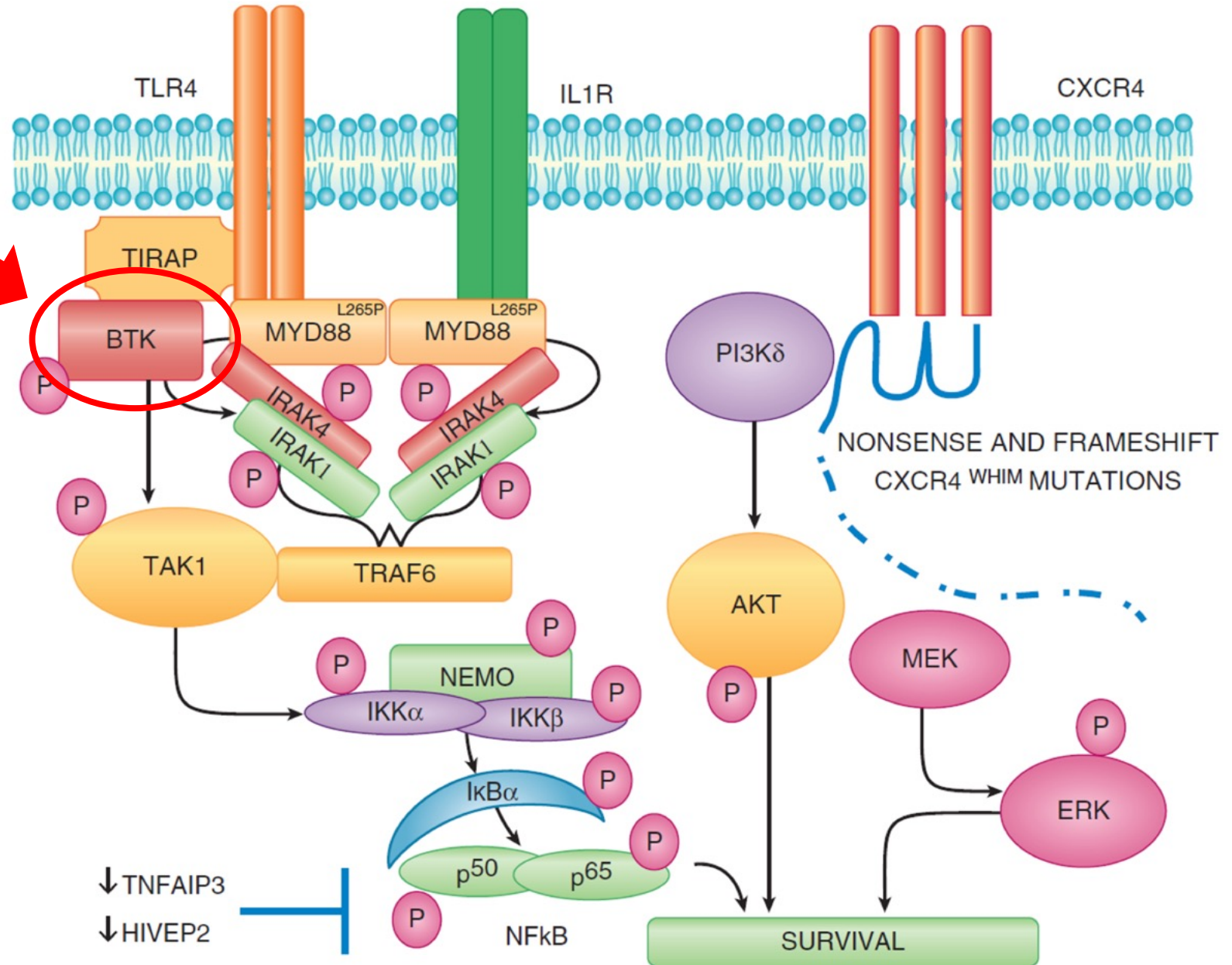
CXCR4 mutations



Milanesi et al. Int J Mol Sci 2020

Study	Method	%
Hunter 	WGS	27%
Roccaro 	AS-PCR	28%
Poulain 	NGS/Sanger	25%
Schmidt 	Sanger	36%
Xu 	AS-PCR/Sanger	40%
Ballester 	Sanger	25%
Cao 	Sanger	24%
Shin 	Target capture	19%

BTK is an important component of the activation pathway of MYD88 L265P



Manifestations of Waldenström Macroglobulinemia



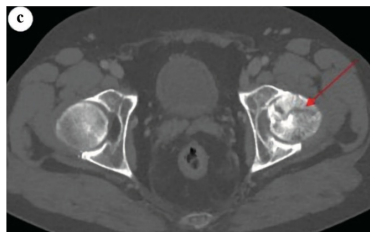
Renal involvement (2-3%)



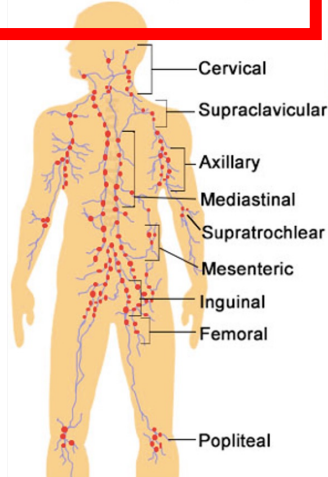
Bing Neel Syndrome (1%)



Pleural effusions (1-2%)



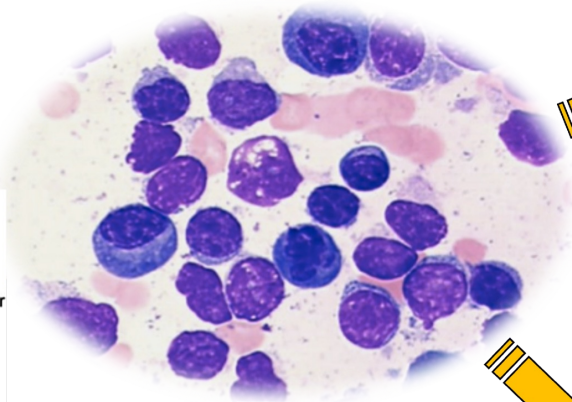
Lytic lesions (1-2%)



Extramedullary disease (20-50%)

Bone Marrow

↓HB>>> ↓PLT> ↓WBC



Hepcidin
↓Fe Anemia



Hyperviscosity Syndrome (15%)
Epistaxis, Headaches
Impaired vision



IgM Neuropathy (20%)
Cryoglobulinemia (10%)
Cold Agglutininemia (5%)
AL amyloidosis (5%)



Limitations

- No prospective studies
- Few retrospective case series
- Several case reports (anecdotes)



When to suspect BNS



Central nervous system involvement by Waldenström macroglobulinaemia (Bing-Neel syndrome): a multi-institutional retrospective study

Symptoms at BNS diagnosis

Limb motor deficits	12/34 (35%)
Altered mental status	12/34 (35%)
Cranial nerve symptoms	10/34 (29%)
Peripheral neuropathy	4/34 (12%)
Headaches	4/34 (12%)
Seizures	4/34 (12%)
Unsteady gait	4/34 (12%)
Limb pain	2/34 (6%)

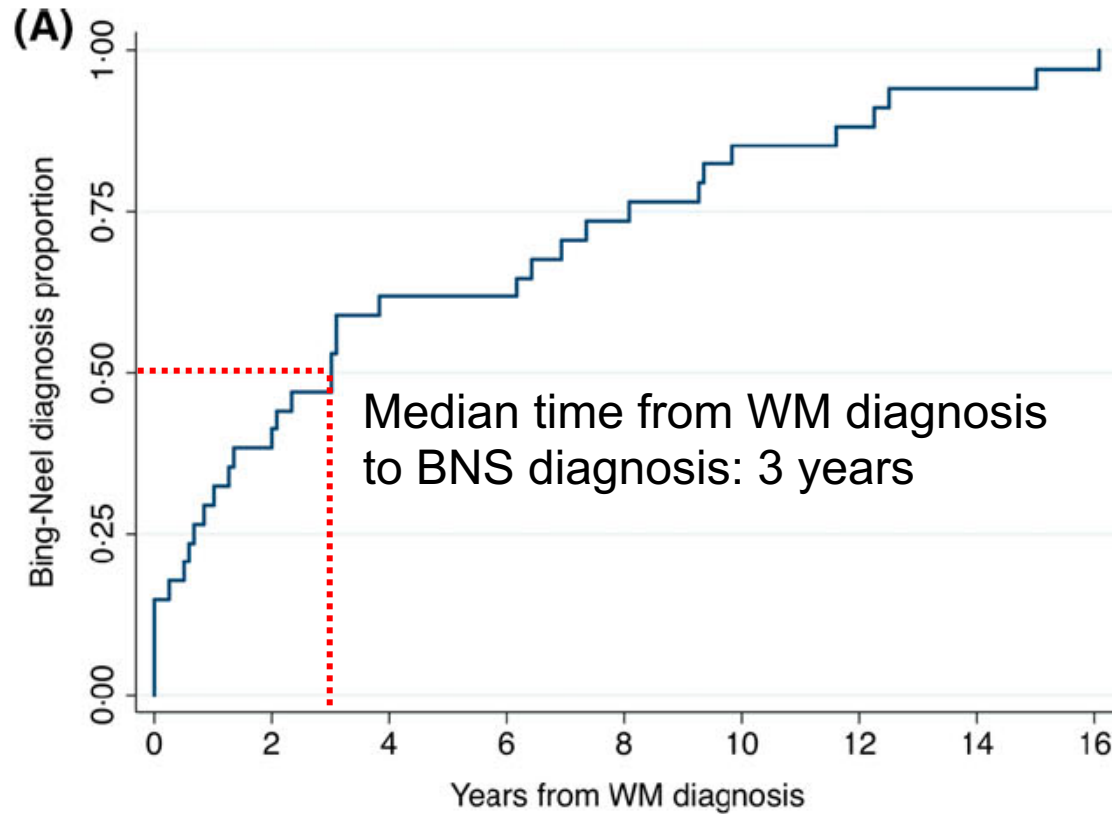
Castillo et al. Br J Haematol 2016

Bing-Neel syndrome, a rare complication of Waldenström macroglobulinemia: analysis of 44 cases and review of the literature. A study on behalf of the French Innovative Leukemia Organization (FILO).

Balance disorder/disturbed gait	48%
Cranial nerve involvement	36%
Cognitive impairment	27%
Paresthesia/dysesthesia	25%
Headache	18%
Limb pain	18%
Cauda equina syndrome	14%

Simon et al. Haematologica 2015

Central nervous system involvement by Waldenström macroglobulinaemia (Bing-Neel syndrome): a multi-institutional retrospective study



Settings for BNS diagnosis:

- At WM diagnosis
- In untreated patients
- While responding to therapy
- As a late relapse

Castillo et al. Br J Haematol 2016



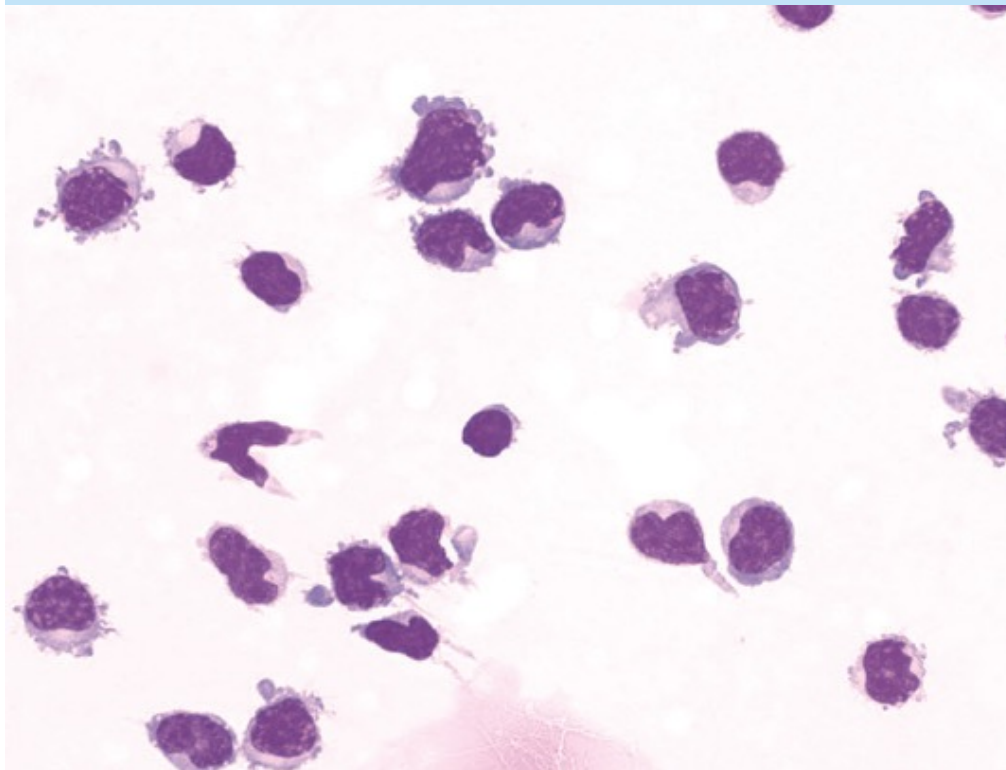
How to diagnose BNS



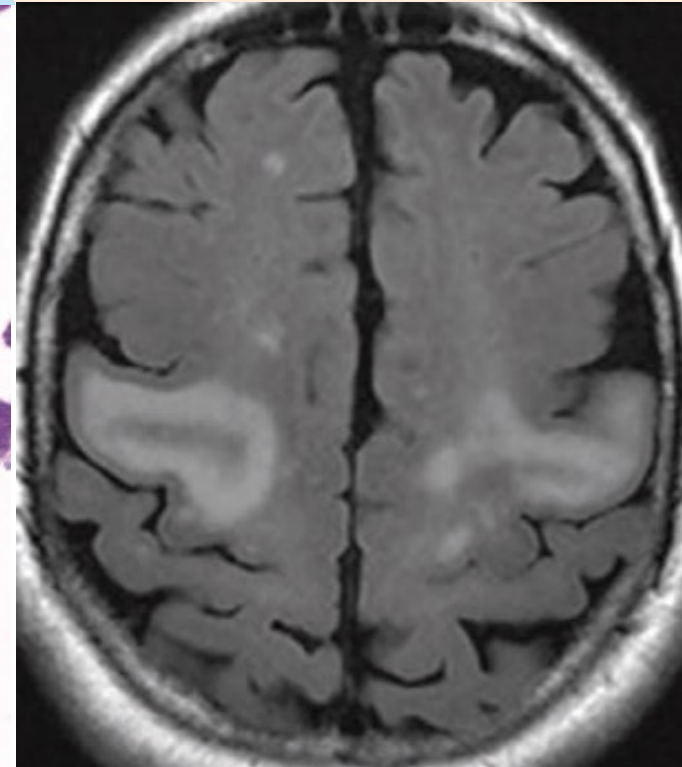
Guideline for the diagnosis, treatment and response criteria for Bing-Neel syndrome

DIAGNOSIS

CSF evaluation



Brain/spine MRI





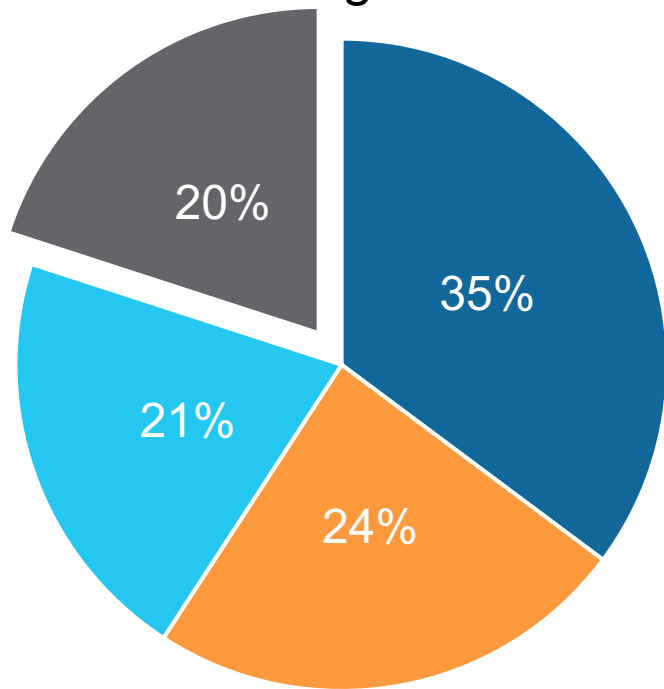
CSF analyses

- Cytology – beware of atypical lymphocytes
 - Flow cytometry
 - PCR for IgH gene rearrangement
 - PCR for MYD88 L265P
- } Should match systemic disease



Central nervous system involvement by Waldenström macroglobulinaemia (Bing-Neel syndrome): a multi-institutional retrospective study

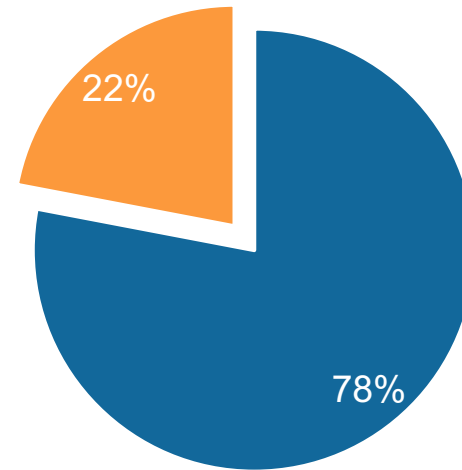
MRI findings in BNS



■ Brain ■ Spine ■ Brain and spine ■ Normal

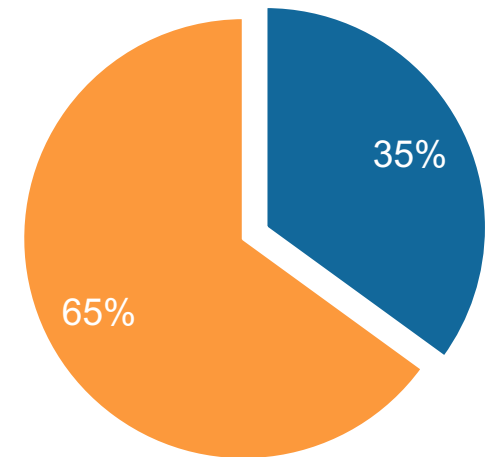
Bing-Neel syndrome, a rare complication of Waldenström macroglobulinemia: analysis of 44 cases and review of the literature. A study on behalf of the French Innovative Leukemia Organization (FILO).

MRI findings in BNS



■ Abnormal ■ Normal

CT findings in BNS



■ Abnormal ■ Normal



Definitive vs. probable BNS diagnosis

Definitive Diagnosis

- Presence of clonal B-cells in CSF or tissue biopsy with similar profile than systemic disease
- With or without leptomeningeal enhancement or masses in MRI

Probable Diagnosis

- Abnormal MRI findings
- Without evidence of clonal B-cells in CSF or tissue biopsy



How to treat BNS



Bing-Neel syndrome, a rare complication of Waldenström macroglobulinemia: analysis of 44 cases and review of the literature. A study on behalf of the French Innovative Leukemia Organization (FILO).

First-line treatments

Cytarabine or methotrexate-based high-dose regimens	52% (23/44)
Rituximab (alone or in combination)	45% (20/44)
Fludarabine-based regimens	14% (6/44)
Intrathecal chemotherapy (alone or in combination)	73% (32/44)
Autologous stem-cell transplantation	14% (6/44)
Radiotherapy	14% (6/44)

Response rates

Overall response rate	70% (31/44)
Complete response/Uncertain complete response	29% (13/44)
Partial response	41% (18/44)
Stable or progressive disease	30% (13/44)

Simon et al. Haematologica 2015



Central nervous system involvement by Waldenström macroglobulinaemia (Bing-Neel syndrome): a multi-institutional retrospective study

Therapies	N (%)	CR (%)	PR (%)	NR (%)
First line (<i>n</i> = 32)				
HDMTX-based	13 (41)	2 (15)	6 (46)	5 (38)
Intrathecal-based	6 (19)	1 (17)	2 (33)	3 (50)
HDMTX+HIDAC-based	5 (16)	4 (80)		1 (20)
Fludarabine-based	3 (9)	1 (33)	2 (67)	
Bendamustine-based	2 (6)		2 (100)	
Other regimens*	3 (9)	1 (33)		2 (67)

Castillo et al. Br J Haematol 2016



Chemotherapy

Effective treatment of Bing-Neel Syndrome with oral fludarabine: a case series of four consecutive patients

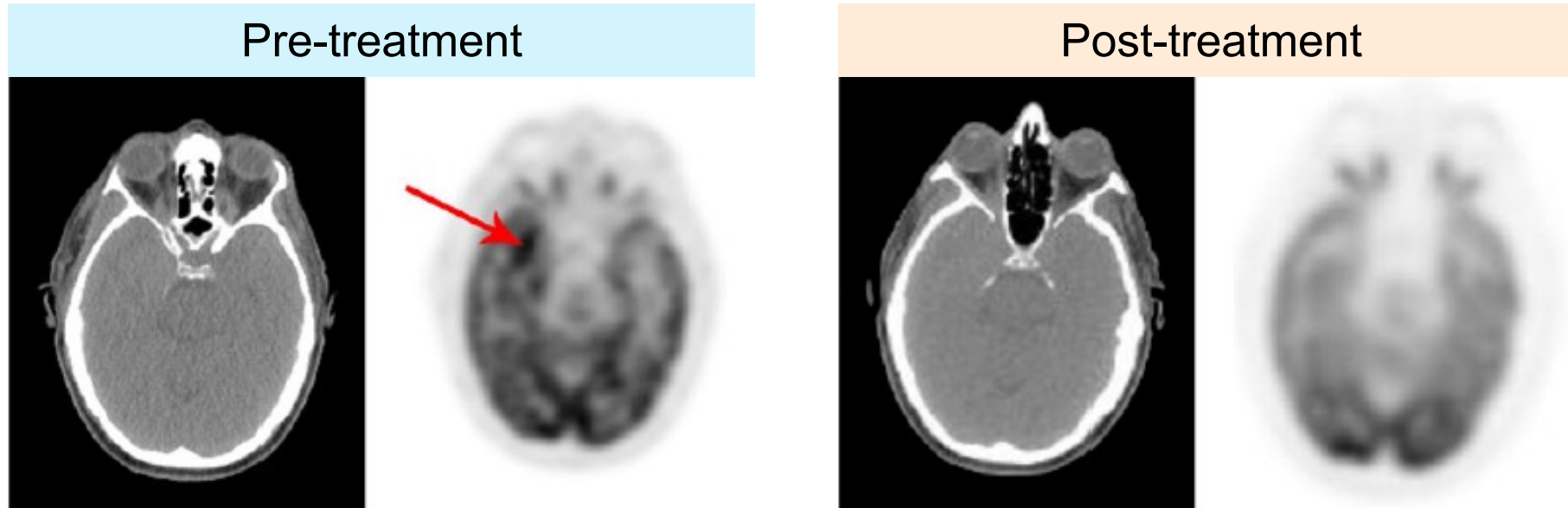
Vos et al. Br J Haematol 2016

Successful treatment with Rituximab and Bendamustine in a patient with newly diagnosed Waldenström's Macroglobulinemia complicated by Bing-Neel syndrome

Varettoni et al. Am J Hematol 2015



Ibrutinib penetrates the blood brain barrier and shows efficacy in the therapy of Bing Neel syndrome

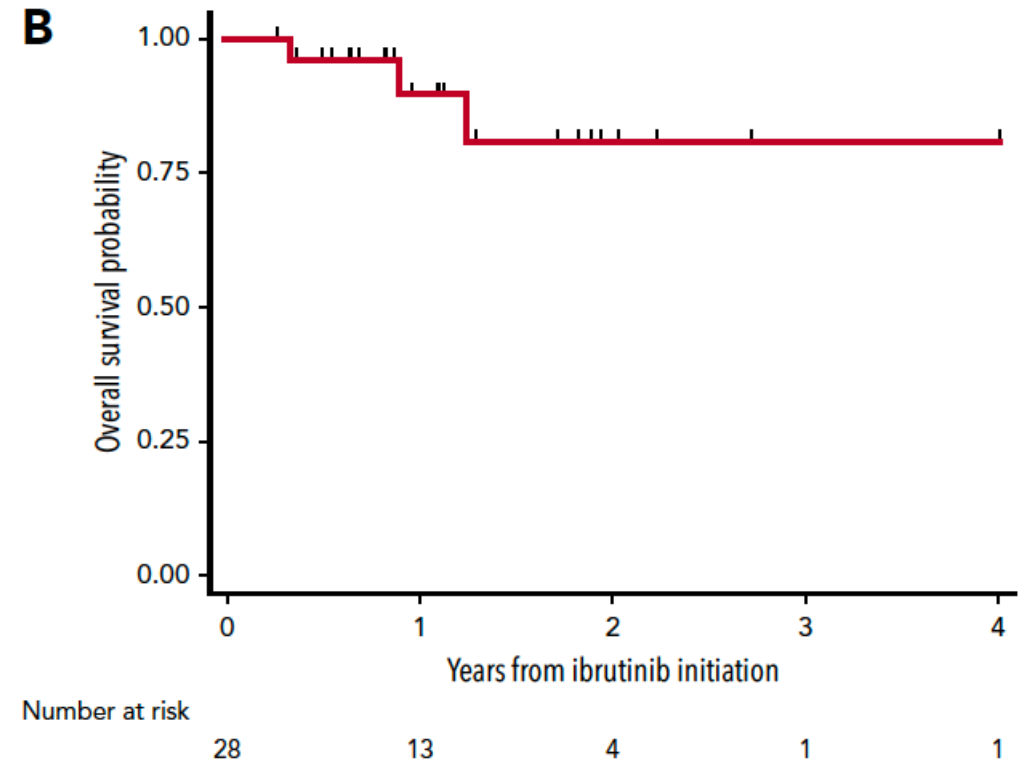


Study Day	Time post-dose (h)	Ibrutinib (nM)		
		CSF	Plasma	%CSF/Plasma
Day 1	0	BLQ	BLQ	NA
	2	34	1133	3.0
1 Month	3	16	463	3.5
4 Months	2-5	7	318	2.2

Mason et al. Br J Haematol 2017

Ibrutinib for the treatment of Bing-Neel syndrome: a multicenter study

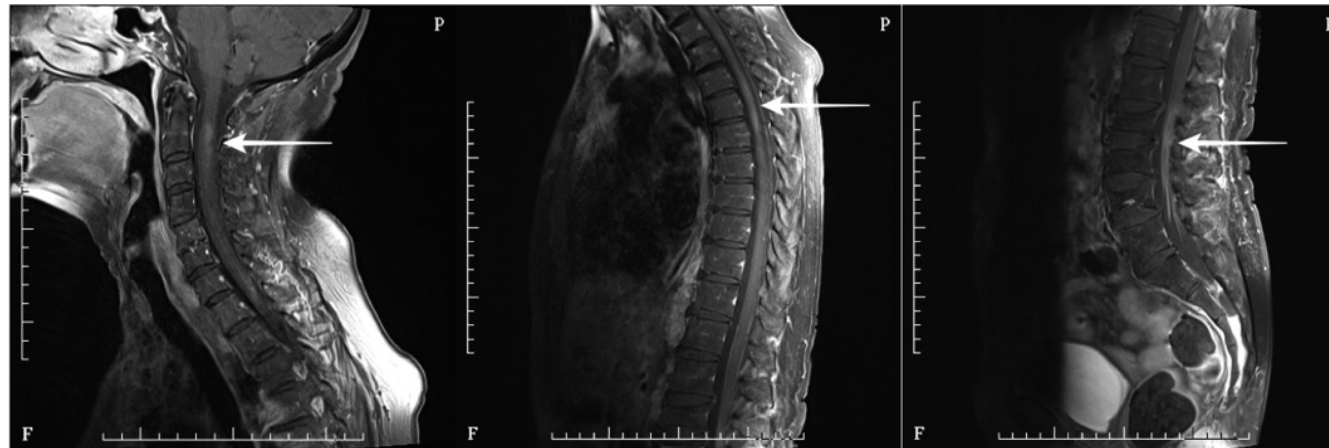
	n/N (%)			
	3 mo	6 mo	12 mo	Best response
Symptomatic				
Resolved	1/26 (4)	3/20 (15)	2/10 (20)	5/28 (18)
Improved	21/26 (81)	15/20 (75)	7/10 (70)	19/28 (68)
Unchanged	4/26 (15)	2/20 (10)	1/10 (10)	4/28 (14)
Radiologic				
Resolved	0/15 (0)	1/9 (11)	2/8 (25)	2/18 (11)
Improved	9/15 (60)	7/9 (78)	6/8 (75)	13/18 (72)
Unchanged	6/15 (40)	1/9 (11)	0/8 (0)	3/18 (17)
Cytologic				
Cleared	7/12 (58)	2/7 (29)	0/1 (0)	8/17 (47)
Persistent	5/12 (42)	5/7 (71)	1/1 (100)	9/17 (53)



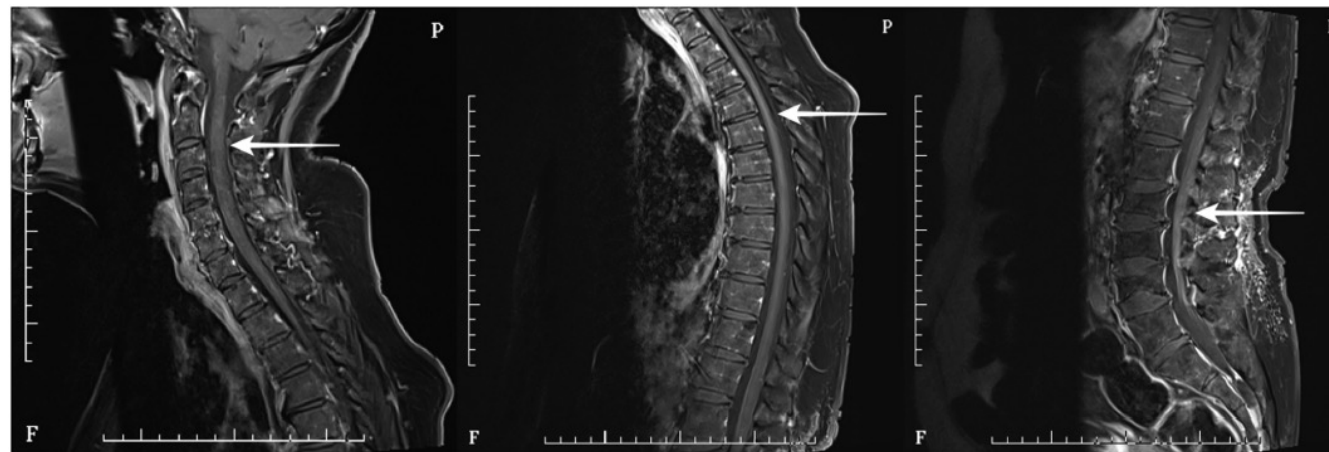
Castillo et al. Blood 2019



Efficacy of Zanubrutinib in the Treatment of Bing-Neel Syndrome

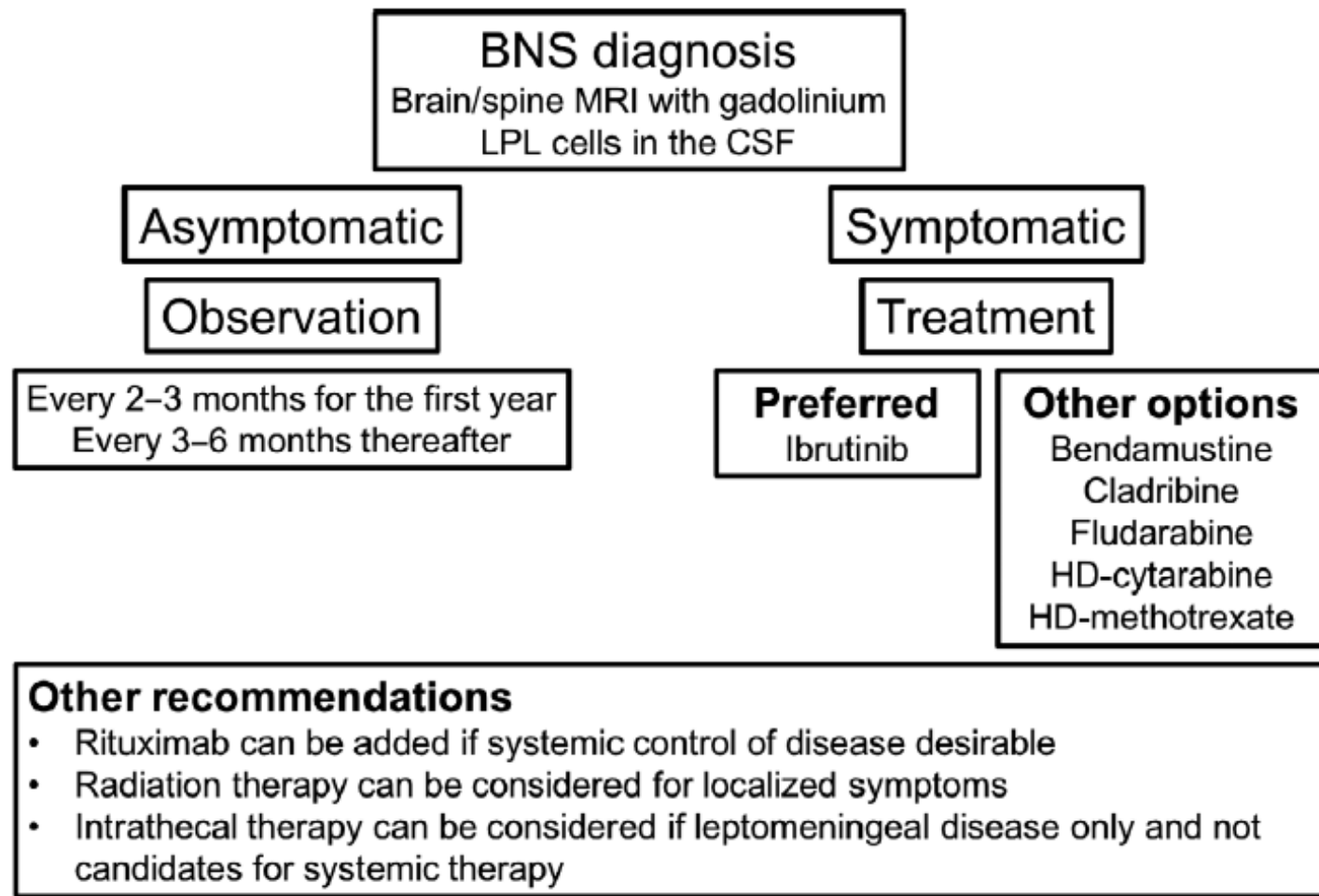


T1 sagittal post-contrast cervical spine T1 sagittal post-contrast thoracic spine T1 sagittal post-contrast lumbar spine



T1 sagittal post-contrast cervical spine T1 sagittal post-contrast thoracic spine T1 sagittal post-contrast lumbar spine

How we manage Bing–Neel syndrome



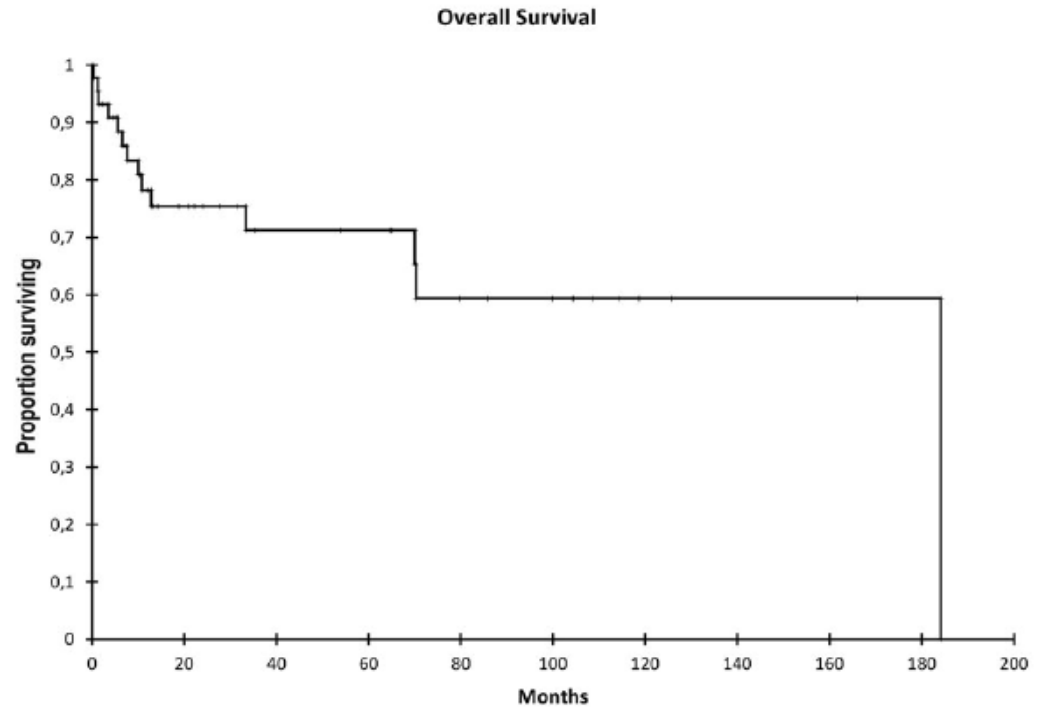
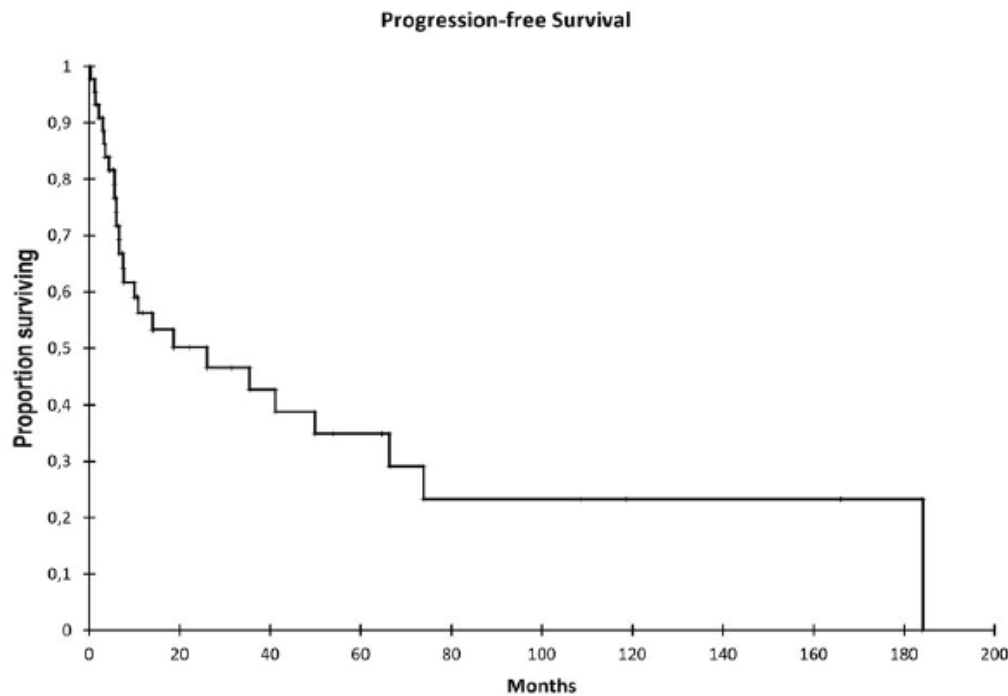
Castillo & Treon. Br J Haematol 2019



How to counsel patients with BNS

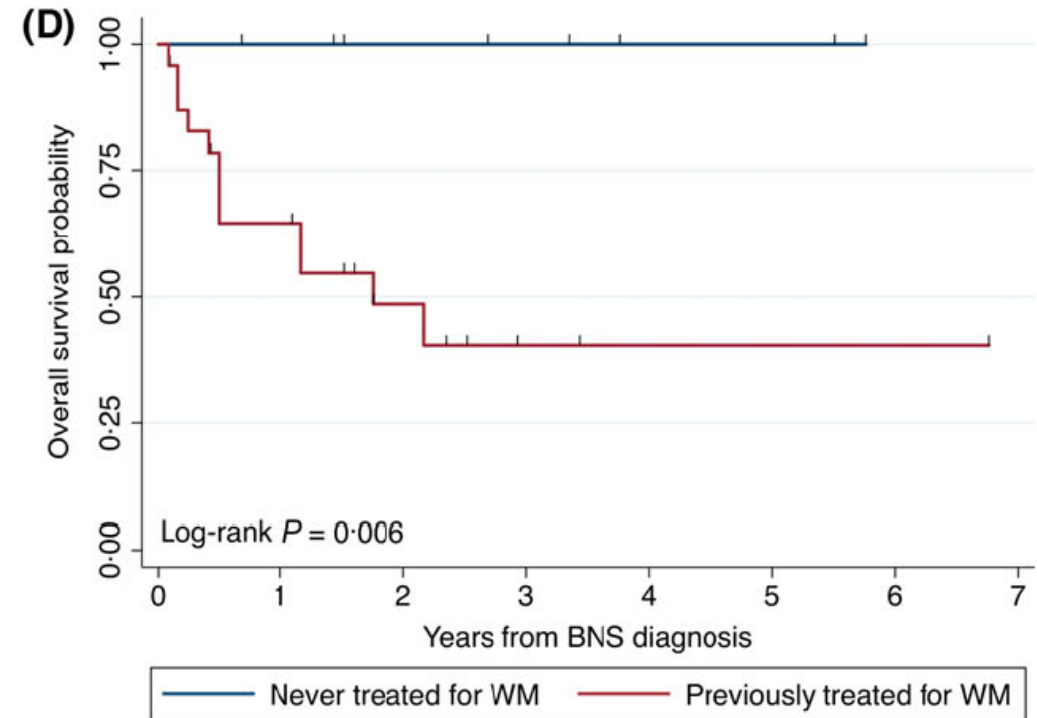
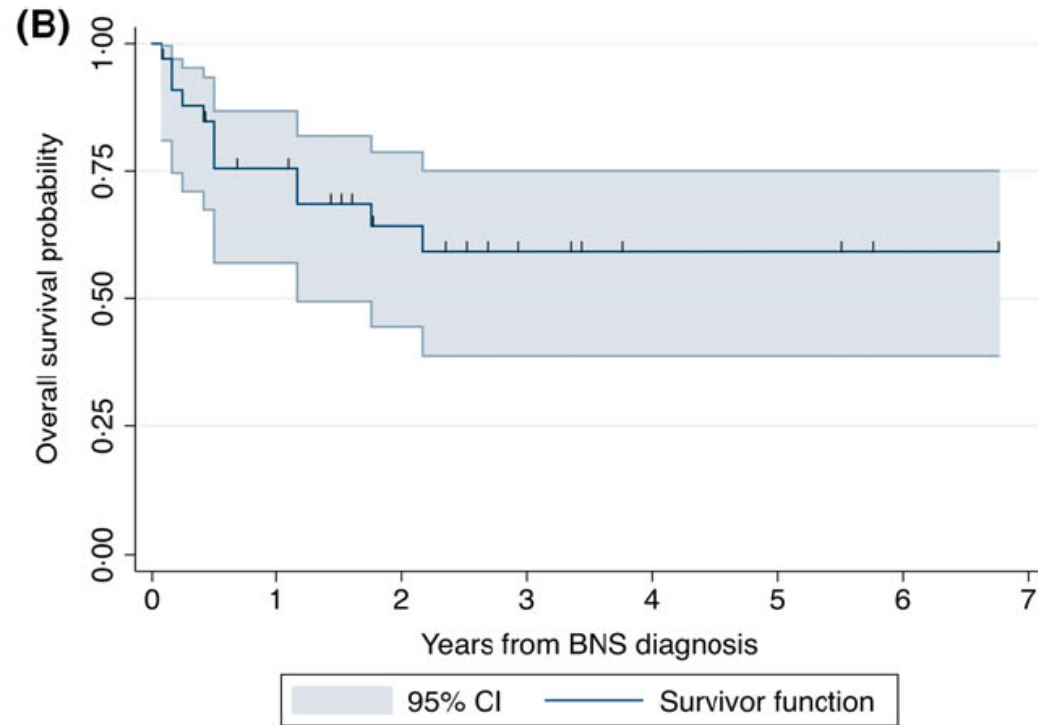


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Central nervous system involvement by Waldenström macroglobulinaemia (Bing-Neel syndrome): a multi-institutional retrospective study



Castillo et al. Br J Haematol 2016



Novel treatment strategies



New agents

Venetoclax penetrates in cerebrospinal fluid and may be effective in chronic lymphocytic leukemia with central nervous system involvement.

Reda et al. Haematologica 2019

Marizomib for central nervous system-multiple myeloma

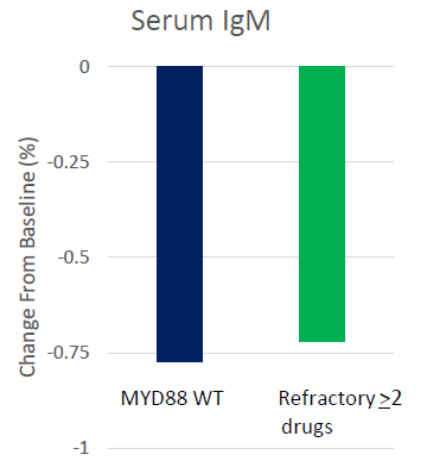
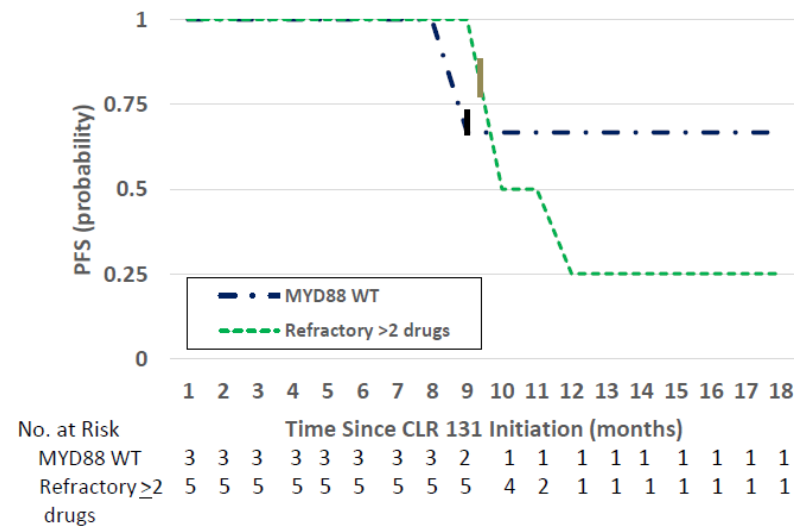
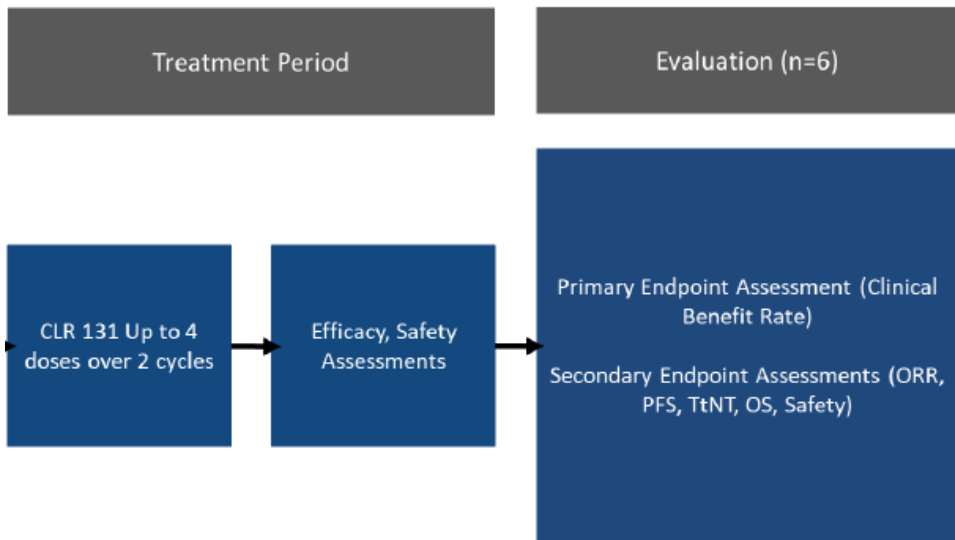
Badros et al. Br J Haematol 2017



Study of Iopofosine 131 (CLR-131) in Waldenström macroglobulinemia (CLOVER-WaM)

- Multicenter study
- 2+ lines of therapy (n=50)
- Only prospective study including BNS

[www.clinicaltrials.gov:
NCT02952508](http://www.clinicaltrials.gov/NCT02952508)



Ailawadhi et al. ASCO 2021



Conclusions

- BNS is a rare complication in patients with WM.
- It can occur at any time during the disease course.
- Diagnosis: CSF evaluation and neuroimaging (MRI)
- Treatment: BTK inhibitors (preferred), chemotherapy
- BCL2 inhibitors and iopofosine 131 are potential future treatment options



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