Waldenström macroglobulinemia

Current Treatment Options

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Topics to be covered -

- What is Waldenström macroglobulinemia?
- Who needs treatment?
- Standard treatment options –
  - Newly diagnosed patients
  - Relapsed patients

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What is Waldenström macroglobulinemia?

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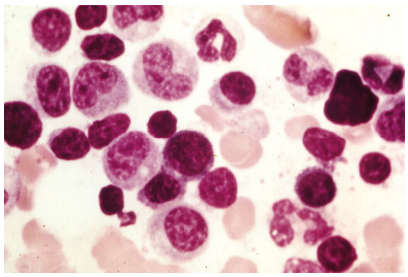
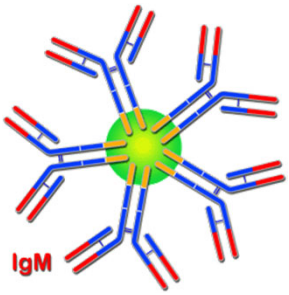
Waldenström macroglobulinemia
"A disease with two problems"



Lymphoplasmacytic infiltrate



Monoclonal IgM protein

Gertz et al. The Oncologist 2000;5:63-67

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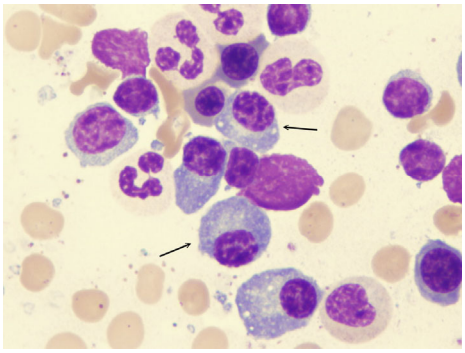
Waldenström macroglobulinemia Morphology and Immunophenotype



- Lymphoplasmacytic infiltrate (usually intertrabecular)
- Immunophenotype - surface IgM+, CD19+, CD20+, CD79a+ and PAX5+. CD5−, CD10−, CD23−.
- exclude CLL and mantle cell lymphoma
- MYD88 L265P is the most common genetic abnormality seen
- del(6)(q21) and CXCR4 mutations are also seen

Treon et al. N Engl J Med. 2012;367(9):826-33.
Hunter et al. Blood. 2014;123(11):1637-46.

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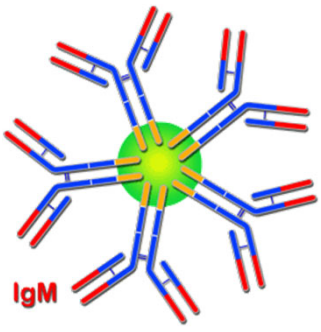
Waldenström macroglobulinemia Monoclonal IgM

- Symptoms related to the monoclonal IgM protein are attributable to -
  - its characteristics in the circulation,
  - its interaction with various body tissues when deposited,
  - and its autoantibody activity.



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Patient 1

- 66 year old man
- Went for an executive physical – in good health with no symptoms
- Found to be mildly anemic (Hgb 12.8g/dl). Other blood counts – normal
- Also noted to have increased total protein with an increased gammaglobulin level.
- Monoclonal IgM – 1.4 g/dl
- Bone marrow biopsy – 20% involvement by lymphoplasmacytic lymphoma
- CT scan – no lymph nodes

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Patient 2

- 67 year old man
- Severe fatigue, nausea, visual difficulties, increasing confusion and sleepiness, gums bleed easily.
- Anemic (Hgb 8.8g/dl). Platelets decreased to 96,000.
- Ulcers have developed on his ankles
- Monoclonal IgM – 6.6 g/dl. Viscosity – 5.8
- Bone marrow biopsy – 85% involvement by lymphoplasmacytic lymphoma
- CT scan – enlarged liver and spleen and multiple bulky lymph nodes in the abdomen

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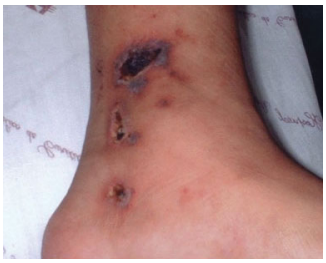
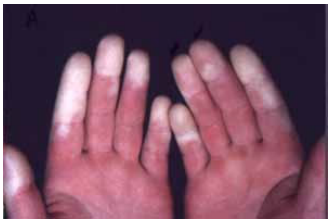
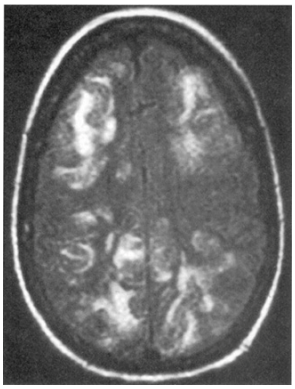
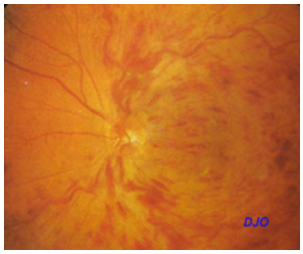
Hyperviscosity due to Waldenström macroglobulinemia









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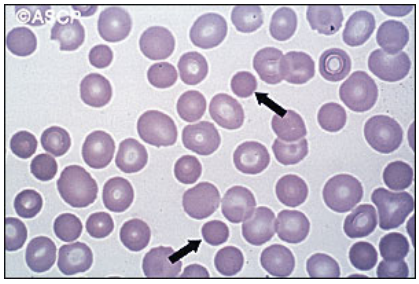
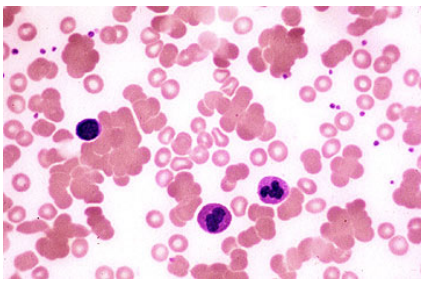
Autoimmune hemolysis and cold agglutinin disease secondary to Waldenström macroglobulinemia





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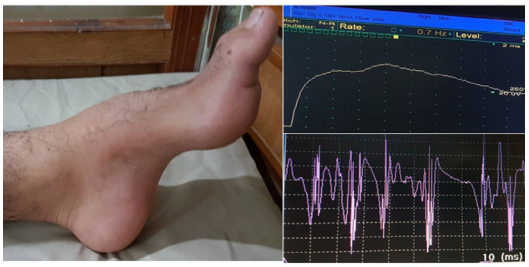
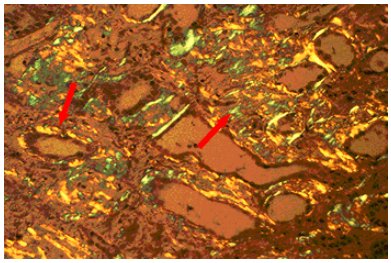
IgM deposition due to Waldenström macroglobulinemia





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Diagnostic Criteria for Waldenström macroglobulinemia

Waldenström macroglobulinemia
- IgM monoclonal gammopathy (regardless of the size of the M protein) with >10% bone marrow lymphoplasmacytic infiltration (usually intertrabecular) by small lymphocytes that exhibit plasmacytoid or plasma cell differentiation and a typical immunophenotype (surface IgM^+, $CD5^-$, $CD10^-$, $CD19^+$, $CD20^+$, $CD23^-$) that satisfactorily excludes other lymphoproliferative disorders, including chronic lymphocytic leukemia and mantle cell lymphoma

IgM MGUS
- Serum IgM monoclonal protein level <3 g/dL, bone marrow lymphoplasmacytic infiltration <10%, and no evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly

Smoldering Waldenström macroglobulinemia (also referred to as indolent or asymptomatic Waldenström macroglobulinemia)
- Serum IgM monoclonal protein level ≥3 g/dL and/or bone marrow lymphoplasmacytic infiltration ≥10% and no evidence of end-organ damage, such as anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly, that can be attributed to a lymphoplasmacytic proliferative disorder

Kyle et al. Leukemia. 2009 Jan;23(1):3-9.

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Waldenström macroglobulinemia – presenting symptoms

- 217 patients with serum monoclonal IgM protein ≥ 3 g/dl and > 20% bone marrow involvement -
  - Asymptomatic (27%)
  - Anemia (38%),
  - Hyperviscosity (31%),
  - B symptoms (23%),
  - Bleeding (23%)
  - Neurological symptoms (22%)

García-Sanz et al. Brit J Haematol. 115: 575-582, 2001

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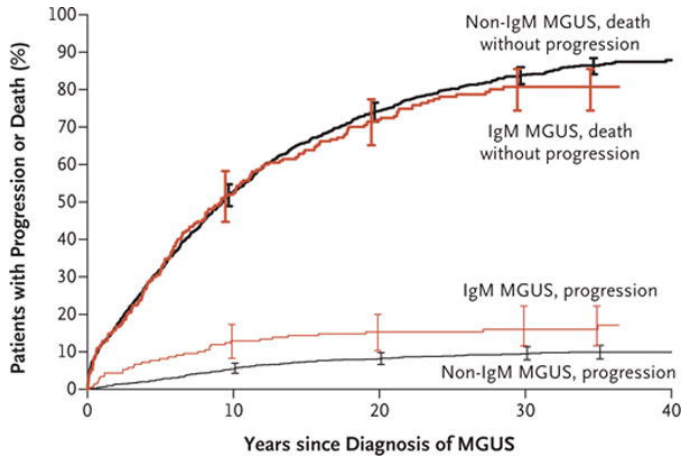
Risk of progression and death from IgM MGUS to WM or another B-cell malignancy



The risk of progression among patients with IgM MGUS is 2% per year in the first 10 years after diagnosis and 1% per year thereafter

Kyle R A et al. N Engl J Med. 2018;378(3):241-249.

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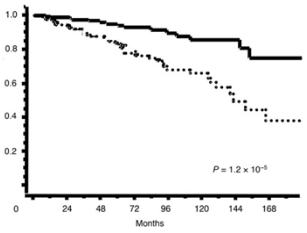
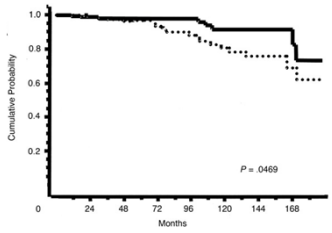
Time to developing WM and Survival in patients with Indolent WM or IgM MGUS

Time to evolution



Overall survival



(— **MGUS; ···IWM)**
MGUS (217 patients) and indolent Waldenström's macroglobulinemia (201 patients) groups

Baldini L et al. J Clin Oncol 2005;23:4662-4668

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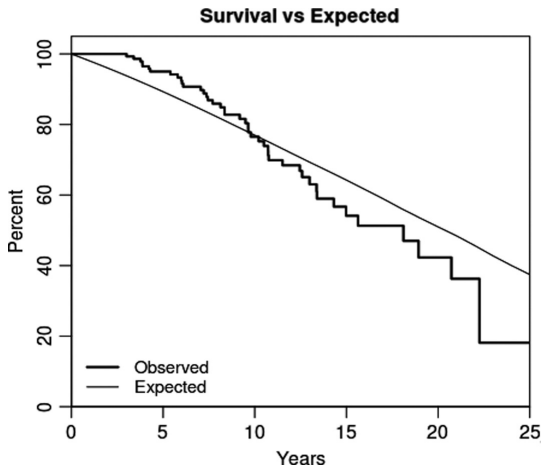
Disease outcome in smoldering Waldenström macroglobulinemia



Zanwar et al. Br J Haematol. 2021 Aug 2. doi: 10.1111/bjh.17691.

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Does everyone need treatment at diagnosis?

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What clinical findings suggest that treatment should be started?

- Fever, night sweats, or weight loss.
- Lymphadenopathy or splenomegaly.
- Hemoglobin ≤ 10 g/dL or a platelet count < 100 x 10(9)/L due to marrow infiltration.
- Complications such as hyperviscosity syndrome, symptomatic sensorimotor peripheral neuropathy, systemic amyloidosis, renal insufficiency, or symptomatic cryoglobulinemia.

Kyle et al. Semin Oncol. 2003 Apr;30(2):116-20

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Plasmapheresis for Waldenström patients with hyperviscosity

- Symptoms of hyperviscosity –
  - Visual deterioration
  - Neurological symptoms
  - Bleeding
- Rarely seen with IgM <4g/dL

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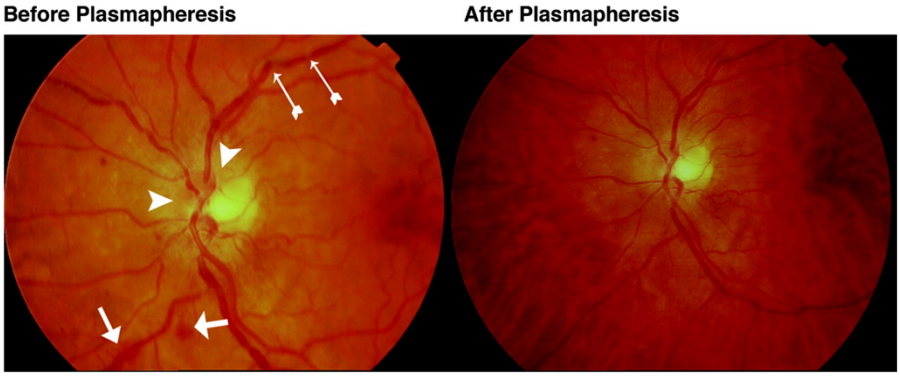
Efficacy of Plasmapheresis for Waldenström patients with hyperviscosity



Before plasmapheresis - optic disc edema (arrowheads), central retinal hemorrhages (bold arrows), and venous "sausaging" (thin arrows).

Menke et al. Invest Ophthalmol Vis Sci. 2008Mar;49(3):1157-60.

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Initial treatment for untreated symptomatic WM patients

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Common Treatments used as initial therapy for WM

- Alkylating agent based combinations –
  - R-Bendamustine
  - DRC
  - R-CHOP
- BTK inhibitors – Ibrutinib, acalabrutinib, zanubrutinib
- Proteosome inhibitor based combinations –
  - BDR
  - IDR
- Rituximab alone

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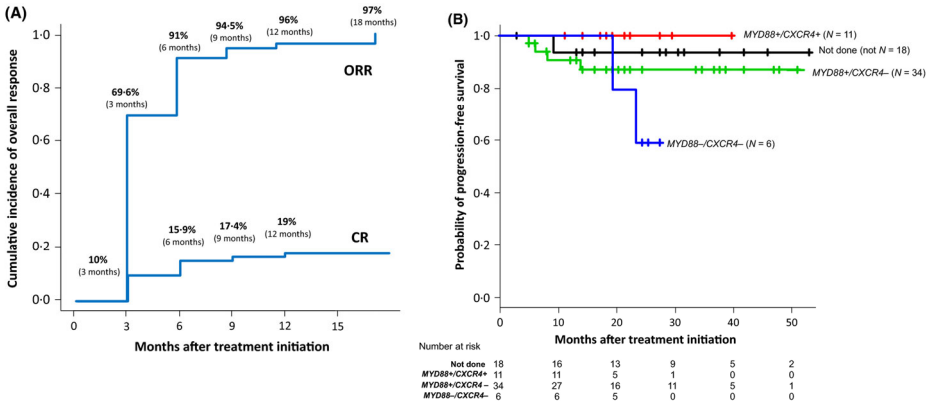
Bendamustine plus rituximab in newly-diagnosed Waldenström macroglobulinemia patients



Laribi K, et al. *Br J Haematol*. 2019;186(1):146-149.

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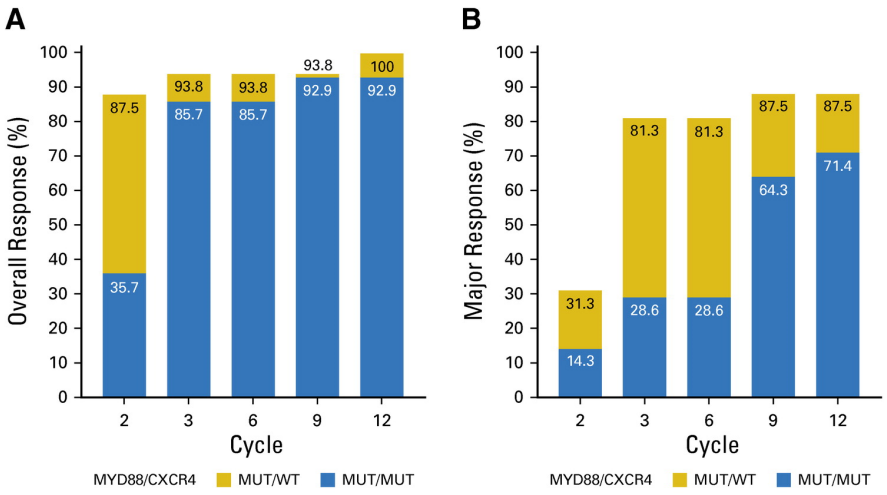
Ibrutinib in Symptomatic, Treatment-Naïve Patients With Waldenström Macroglobulinemia



Treon SP, et al. J Clin Oncol. 2018;36(27):2755-2761.

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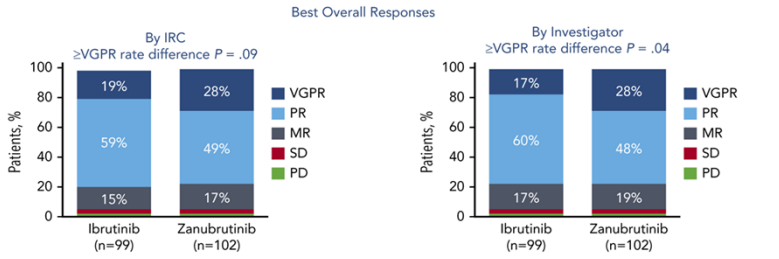
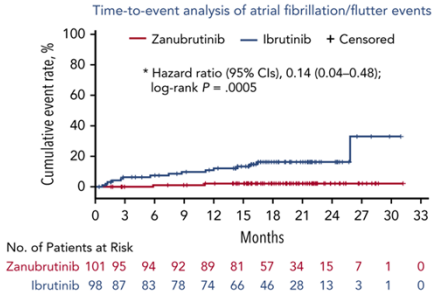
Zanubrutinib vs Ibrutinib in symptomatic Waldenström macroglobulinemia



AE Categories, n (%) (Pooled Terms)	All Grades	
	Ibrutinib (n=98)	Zanubrutinib (n=101)
Atrial fibrillation/flutter*	15 (15.3)	2 (2.0)
Diarrhea (PT)	31 (31.6)	21 (20.8)
Hemorrhage	58 (59.2)	49 (48.5)
Major hemorrhage	9 (9.2)	6 (5.9)
Hypertension	17 (17.3)	11 (10.9)
Neutropenia*	13 (13.3)	30 (29.7)
Infection	66 (67.3)	67 (66.3)

*Descriptive 2-sided $P < .05$

Data cutoff 31Aug2019



No. of Patients at Risk

Zanubrutinib	101	95	94	92	89	81	57	34	15	7	1	0
Ibrutinib	98	87	83	78	74	66	46	28	13	3	1	0

Tam et al. Blood. 2020 Oct 29;136(18):2038-2050.

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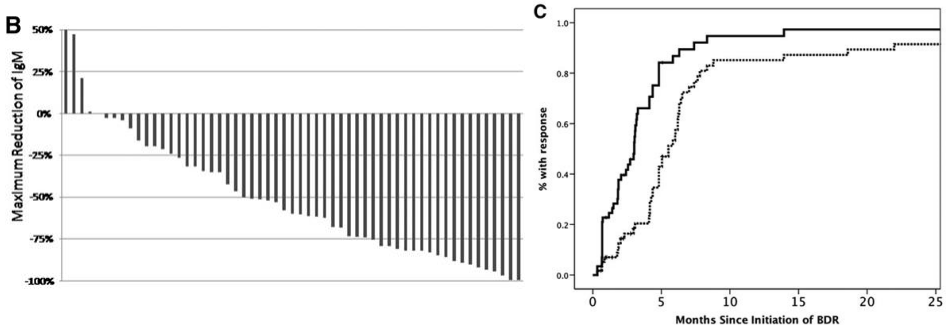
Primary therapy of WM with weekly bortezomib, low-dose dexamethasone, and rituximab (BDR)



Dimopoulos MA, et al. Blood. 2013;122(19):3276-3282.

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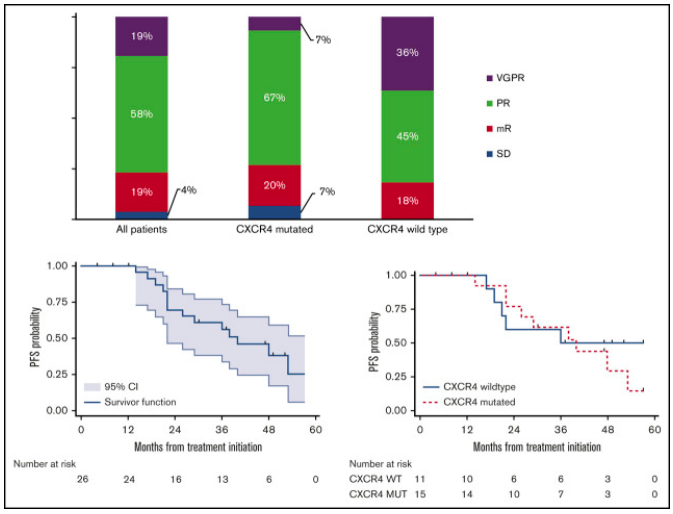
Ixazomib, dexamethasone, and rituximab in treatment-naive patients with Waldenström macroglobulinemia



Castillo JJ, et al. *Blood Adv*. 2020;4(16):3952-3959.

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Rituximab alone for Waldenström macroglobulinemia

69 symptomatic WM patients – rituximab x 4 doses
ORR 52% - 27% PR, 25% MR
Median duration of response – 27 months

Gertz et al, Leuk Lymphoma. 2004 Oct;45(10):2047-55.

Same study – evaluated IgM levels for "flare"
54% had an increase in IgM
27% still elevated at 4 months
No factors predicting an increase in IgM levels could be identified.

Ghobrial et al. Cancer. 2004 Dec 1;101(11):2593-8.

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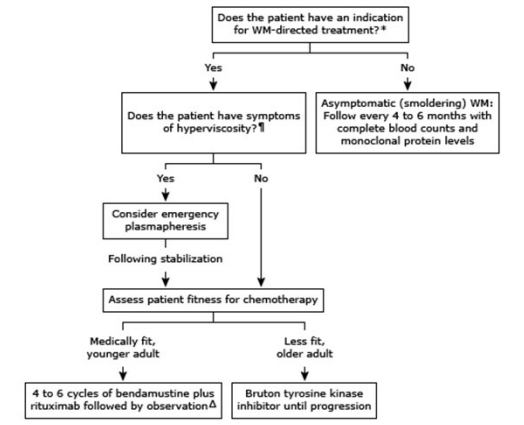
Initial treatment of Waldenström macroglobulinemia



WM: Waldenström macroglobulinemia; BTK: Bruton tyrosine kinase.
* Indications for treatment:
- Recurrent fever, night sweats, weight loss, fatigue
- Hyperviscosity
- Lymphadenopathy that is either symptomatic or bulky
- Symptomatic hepatomegaly and/or splenomegaly
- Symptomatic organomegaly and/or organ or tissue infiltration
- Peripheral neuropathy due to WM
- Symptomatic cryoglobulinemia
- Cold agglutinin hemolytic anemia
- Immune hemolytic anemia and/or thrombocytopenia
- Nephropathy related to WM
- Amyloidosis related to WM
- Hemoglobin of 10 g/dL or less
- Platelet count of 100 × 10^9/L or less

UptoDate 2021

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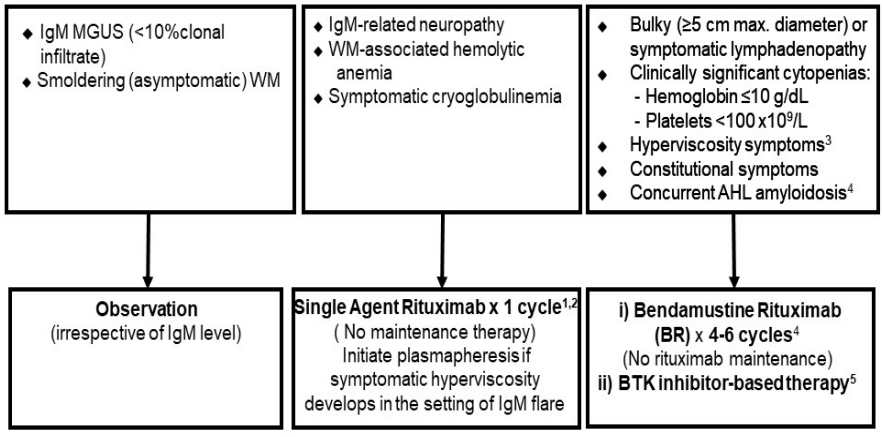
Mayo Clinic Consensus for Newly Diagnosed Waldenström Macroglobulinemia



mSMART.org Revised January 2021

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Subsequent treatment in relapsed WM patients

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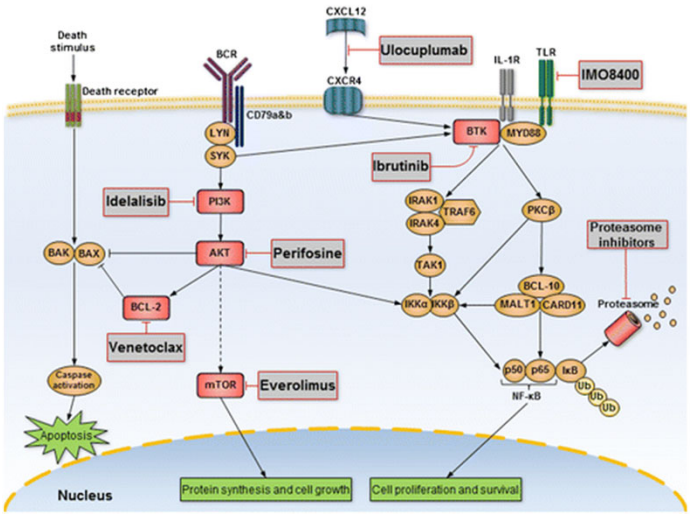
Therapeutic opportunities afforded by the biology of Waldenström macroglobulinemia



Kapoor et al. Curr Treat Options Oncol. 2016 Mar;17(3):16.

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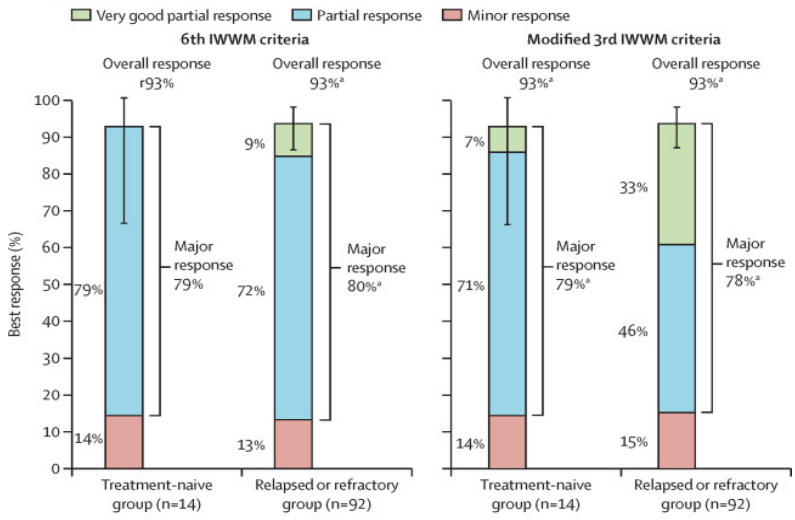
Acalabrutinib Monotherapy in Patients With Waldenström Macroglobulinemia



Owen RG, et al. Lancet Haematol. 2020;7(2):e112-e121.

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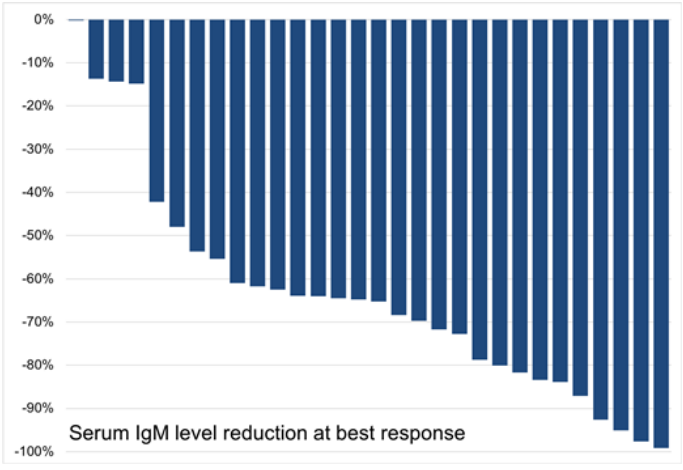
Phase II Study of Venetoclax in Patients with Previously Treated Waldenstrom Macroglobulinemia



Castillo J, et al. Blood (2018) 132 (Supplement 1): 2888.

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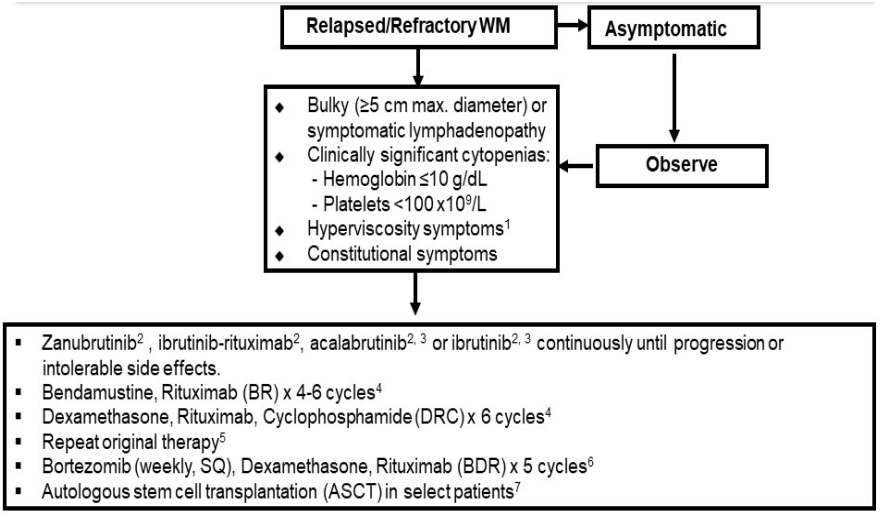
Mayo Clinic Waldenström Macroglobulinemia Consensus for Off-Study Salvage Therapy



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Transplantation in relapsed Waldenström macroglobulinemia.

Autologous transplant –

158 WM patients
Non-relapse mortality – 3.8%
5-year PFS – 40%
5-year OS – 68%

Kyriakou et al, J Clin Oncol. 2010 May 1;28(13):2227-32.

Allogeneic transplant –

86 WM patients (37 MAC and 49 RIC)
Non-relapse mortality – 33%(MAC), 23% (RIC)
5-year PFS – 56%
5-year OS – 62%

Kyriakou et al. J Clin Oncol. 2010 Nov 20;28(33):4926-34.

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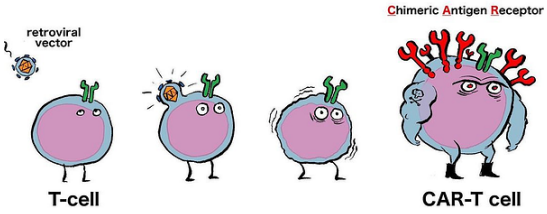
CAR T-cells - ZUMA-5: Efficacy endpoints in relapsed/refractory FL and MZL

Endpoint	FL (*n* = 80)	MZL (*n* = 16)
Overall response	95%	81%
Complete response	81%	75%
Partial response	14%	6%
Median DOR	20.8 months	10.6 months
Median PFS	23.5 months	11.8 months
12-month OS	93.4%	100%



Jacobson CA, et al. ASCO Virtual Scientific Program. 2020. Abstract 8008.

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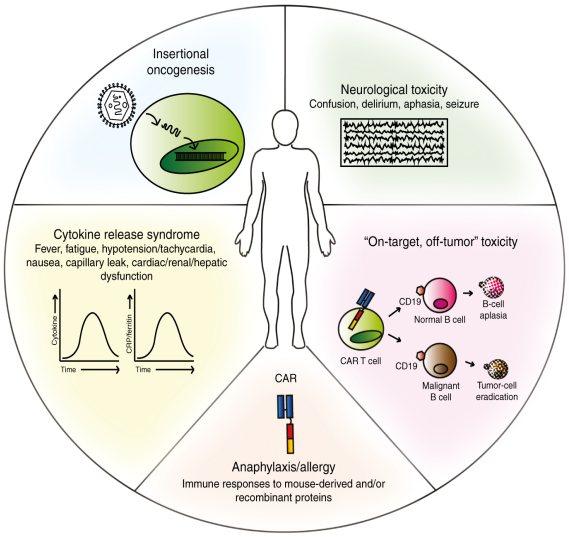
Toxicities of chimeric antigen receptor (CAR) T-cell therapy



Bonifant et al. Molecular Therapy — Oncolytics 3: 16011 (2016)

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Questions?

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