Light Chain (AL) Amyloidosis & Waldenström Macroglobulinemia

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Disclosures

Consulting Agreements	Amgen Inc, Bristol-Myers Squibb Company, Celgene Corporation, Janssen Biotech Inc, Kite Pharma Inc, Sanofi Genzyme, Takeda Oncology
Contracted Research	Amgen Inc, BioTheryX Inc, Spectrum Pharmaceuticals Inc

Case Presentation: Dr Khan

57-year-old woman

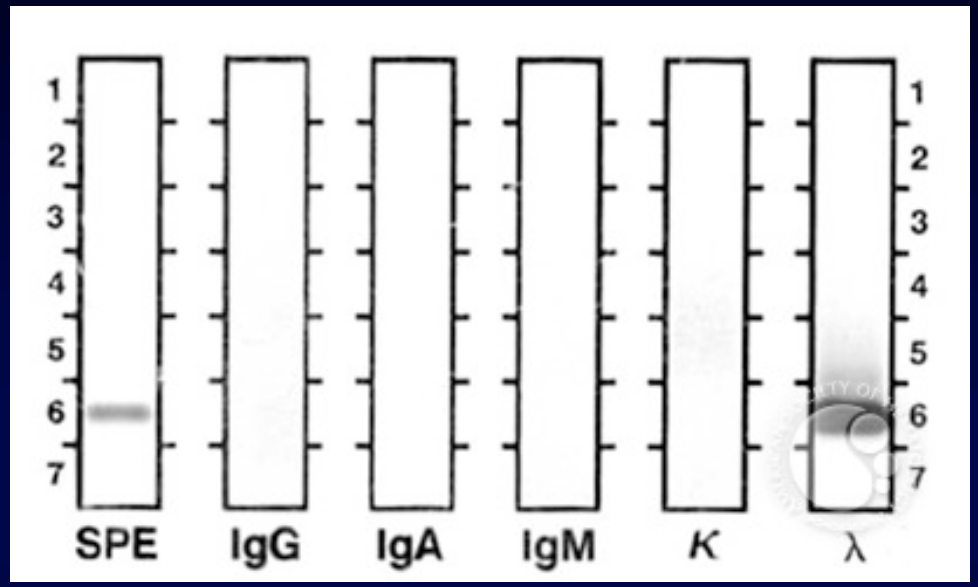
- Progressive chronic kidney disease, proteinuria, diabetes
- Diagnosis: Renal amyloidosis
  - Bone marrow biopsy: 16% plasma cells
  - Significant lower edema, BNP elevated, patient refuses cardiac evaluation

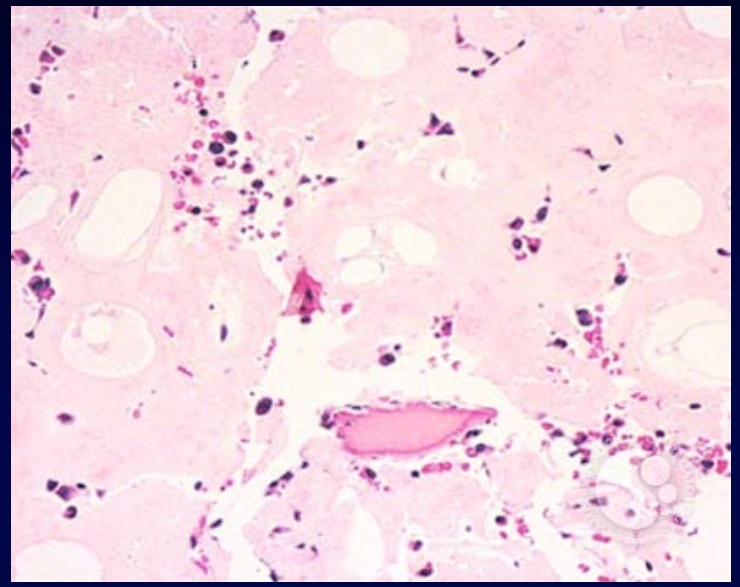
Case Presentation: Dr Lamar

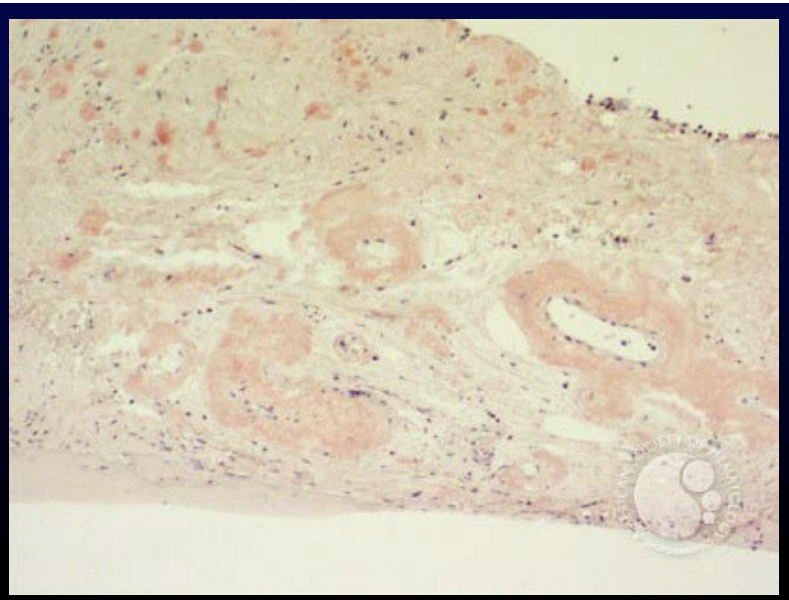
90-year-old man

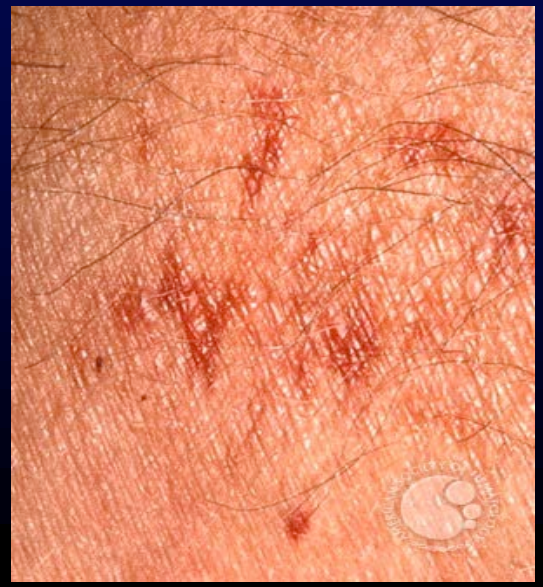
- Runs a few miles daily and does a “Marine workout” every morning
- Diagnosis: Waldenström macroglobulinemia
- Observation 4-5 years
  - Slowly progressive anemia and thrombocytopenia

Amyloidosis

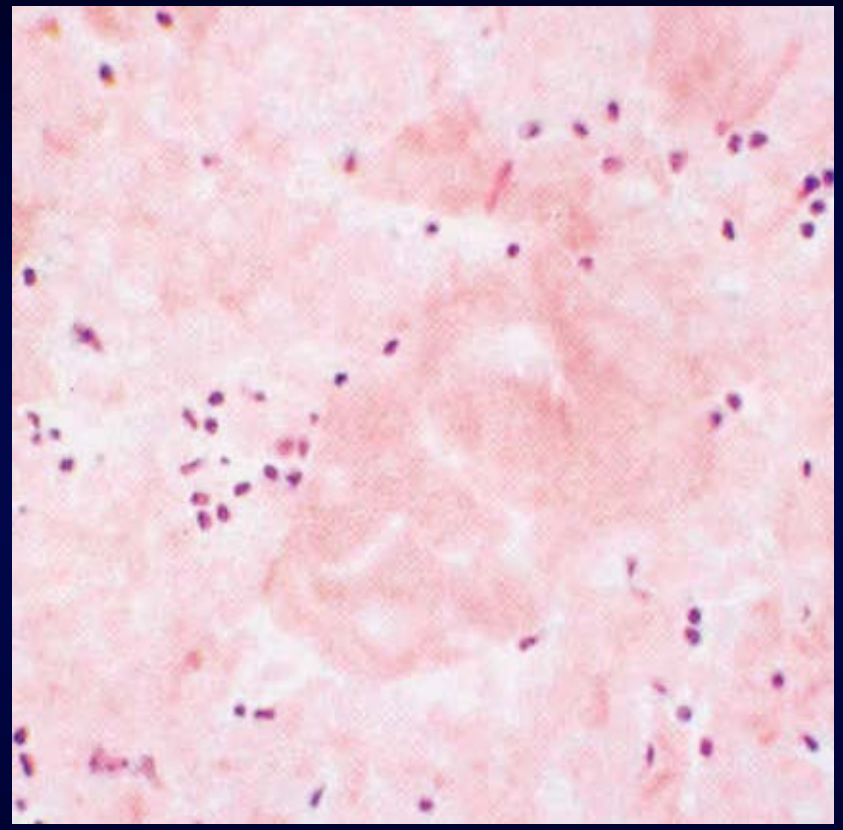








Forms of Amyloidosis

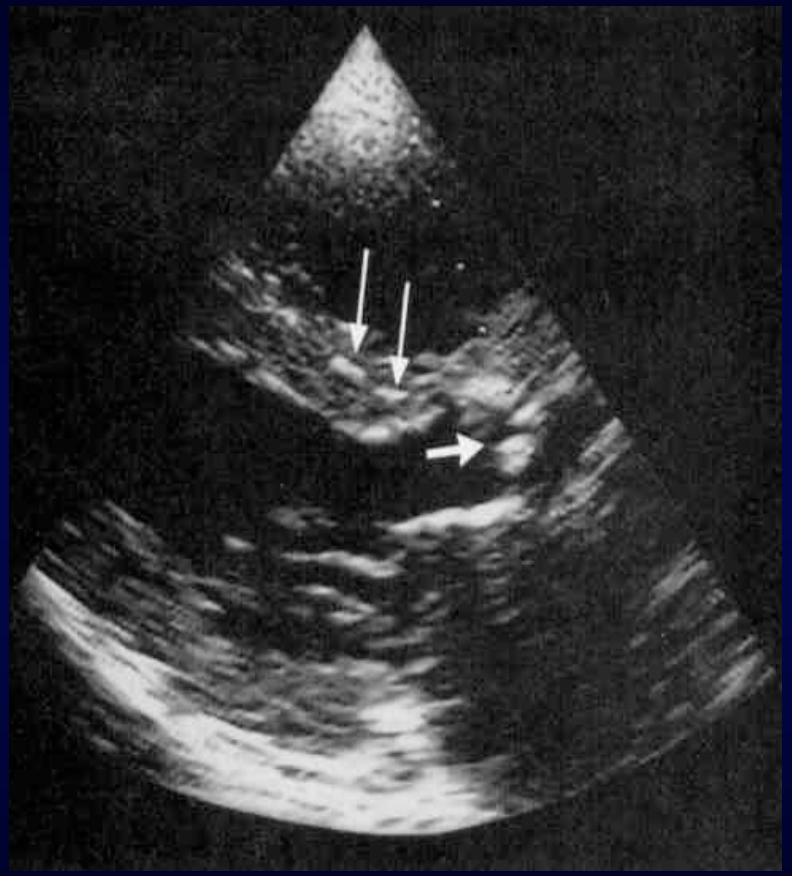


Lymph node with effacement of tissue by Congo Red-positive material
Gorson, KC et al. N Engl J Med 344:917, 2001.

- Found in ≥10% of myeloma patients
- Multiple other forms, including familial types
- Characterized by organ deposition of amyloid fibrils
  - In myeloma these are NH_2 residues of variable portion of light chain Ig
  - ~10 cases/million people

Forms of Amyloidosis

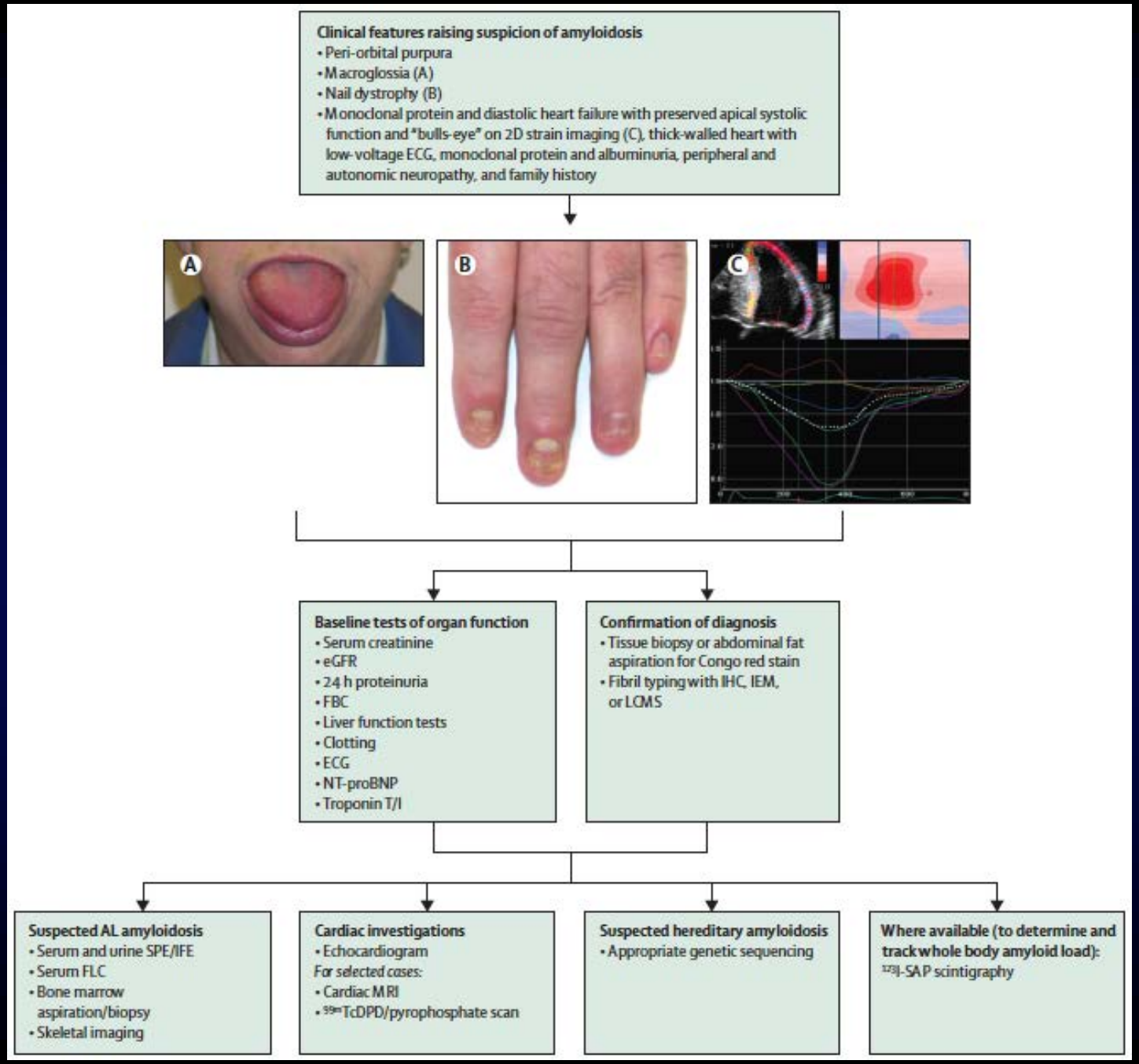
- Clinical features
  - Nephrotic syndrome
  - Cardiomyopathy
  - Hepatomegaly
  - Neuropathy
  - Macroglossia
  - Carpal tunnel syndrome
  - Periorbital purpura



ECHO findings of restrictive cardiomyopathy
DiSalvo,TG et al. N Engl J Med 342: 264, 2000.

Diagnostic Approach

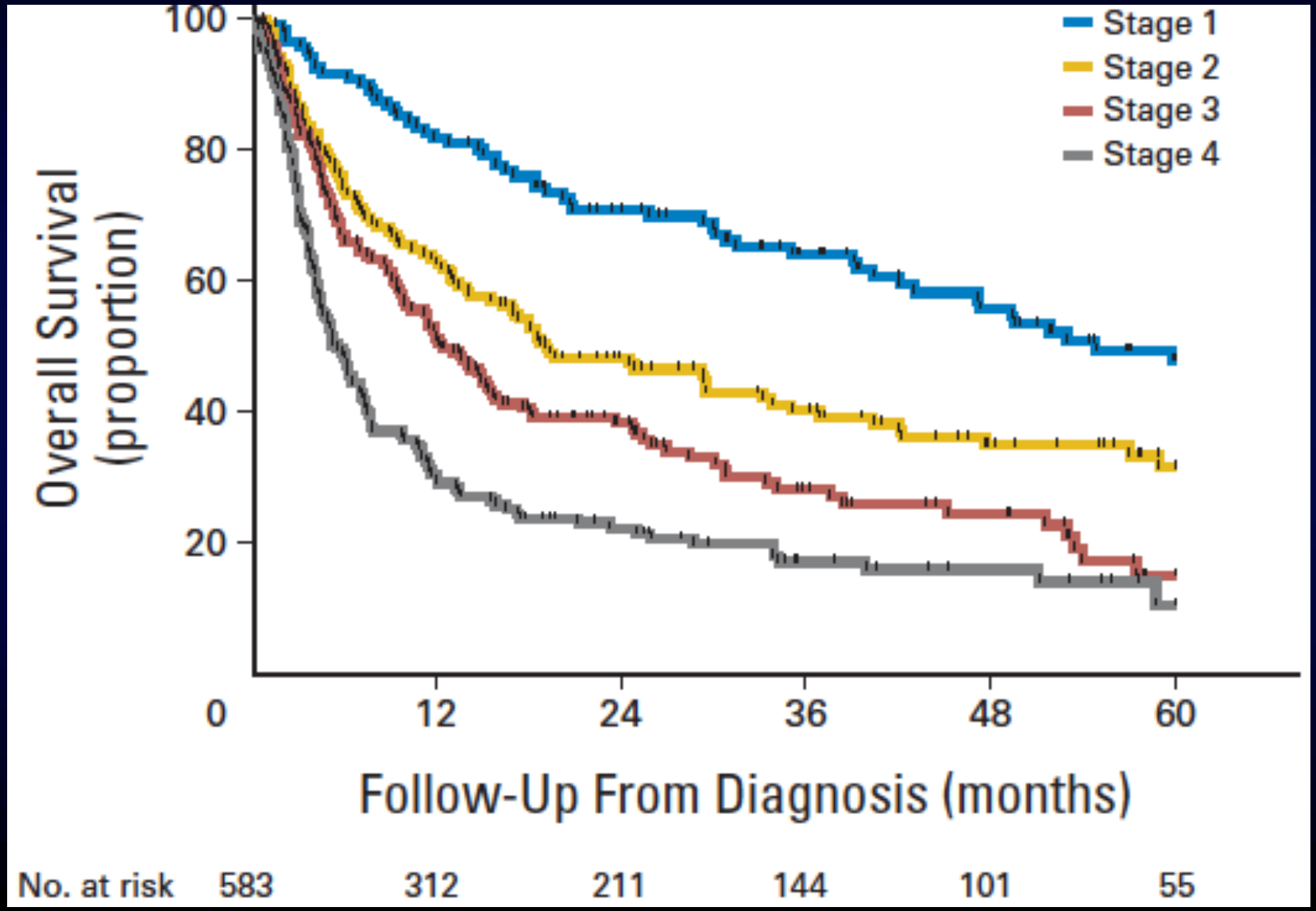
- Biopsy & typing of protein deposits are the key



Wechalekar, AD et al. Lancet 387:2641, 2016.

Staging

- FLC diff ≥ 18 mg/dL
- cTnT ≥ 0.025 ng/mL
- NT-ProBNP ≥ 1800 pg/mL



Kumar, S et al. J Clin Oncol. 30:989, 2012.

Organ Involvement Criteria

Kidney	24-h urine protein >0.5 g/d, predominantly albumin
Heart	Echo: mean wall thickness >12 mm, no other cardiac cause or an elevated NT-proBNP (>332 ng/L) in the absence of renal failure or atrial fibrillation
Liver	Total liver span >15 cm in the absence of heart failure or alkaline phosphatase >1.5 times institutional upper limit of normal
Nerve	Peripheral: clinical; symmetric lower extremity sensorimotor peripheral neuropathy Autonomic: gastric-emptying disorder, pseudo-obstruction, voiding dysfunction not related to direct organ infiltration
Gastrointestinal tract	Direct biopsy verification with symptoms
Lung	Direct biopsy verification with symptoms Interstitial radiographic pattern
Soft tissue	Tongue enlargement, clinical Arthropathy Claudication, presumed vascular amyloid Skin Myopathy by biopsy or pseudohypertrophy Lymph node (may be localized) Carpal tunnel syndrome

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Treatment Options

- For transplant-eligible patients

Preferred Regimen:
- **Bortezomib[3]/cyclophosphamide/dexamethasone**

Other Regimen:
- **Bortezomib[3] ± dexamethasone**
- **Bortezomib[3]/melphalan/dexamethasone**
- **Lenalidomide/cyclophosphamide/dexamethasone**
- **Lenalidomide/dexamethasone**
- **Oral melphalan/dexamethasone**

https://www.nccn.org; Version 1.2019

Treatment Options

- For transplant-ineligible patients

Preferred Regimen:
- **Bortezomib[3]/cyclophosphamide/dexamethasone**
- **Oral melphalan/dexamethasone**

Other Regimen:
- **Bortezomib[3] ± dexamethasone**
- **Bortezomib[3]/melphalan/dexamethasone**
- **Lenalidomide/cyclophosphamide/dexamethasone**
- **Lenalidomide/dexamethasone**

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Treatment Options

- For patients with relapsed/refractory disease

- **Consider initial therapy, especially if relapse-free for several years**
- **High-dose melphalan[4] with stem cell transplant**
- **Bortezomib[3] ± dexamethasone**
- **Bortezomib[3]/melphalan/dexamethasone**
- **Ixazomib ± dexamethasone**
- **Lenalidomide/cyclophosphamide/dexamethasone**
- **Lenalidomide/dexamethasone**
- **Oral melphalan/dexamethasone**
- **Pomalidomide/dexamethasone**

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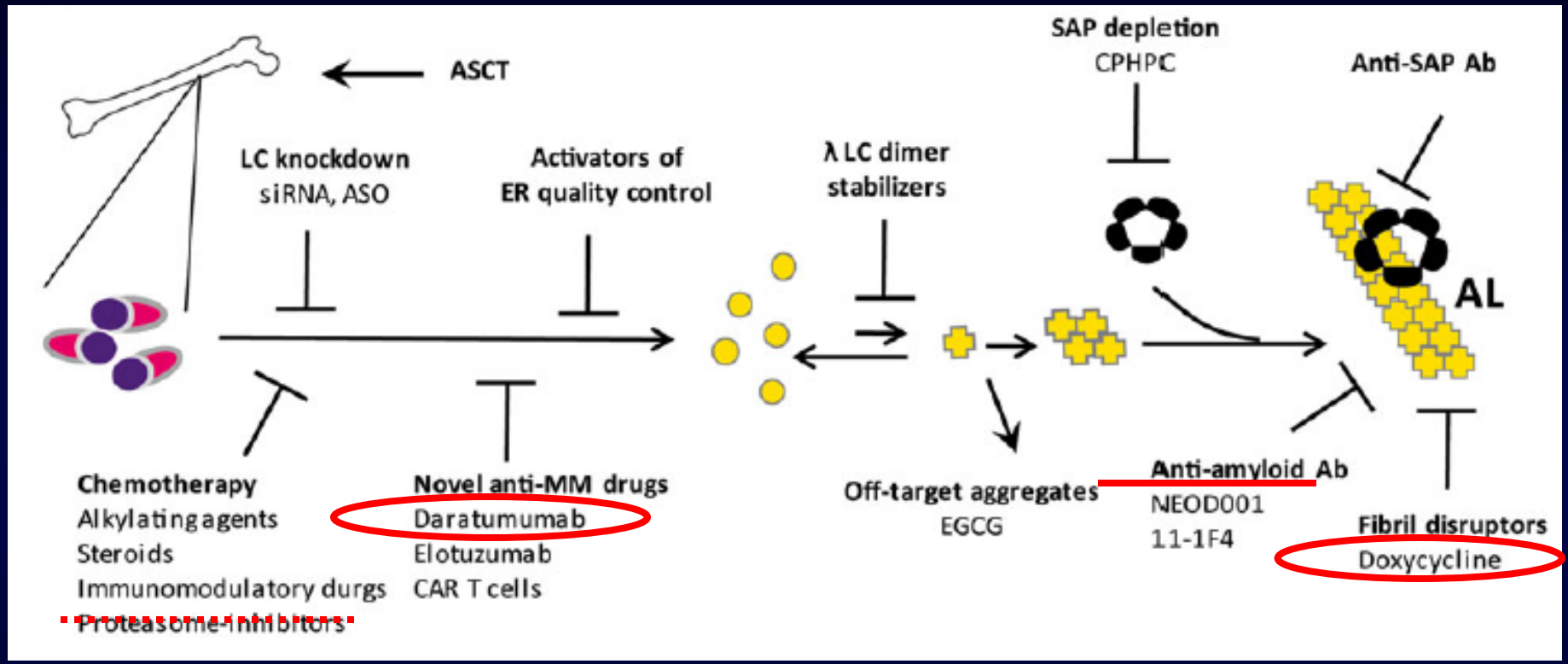
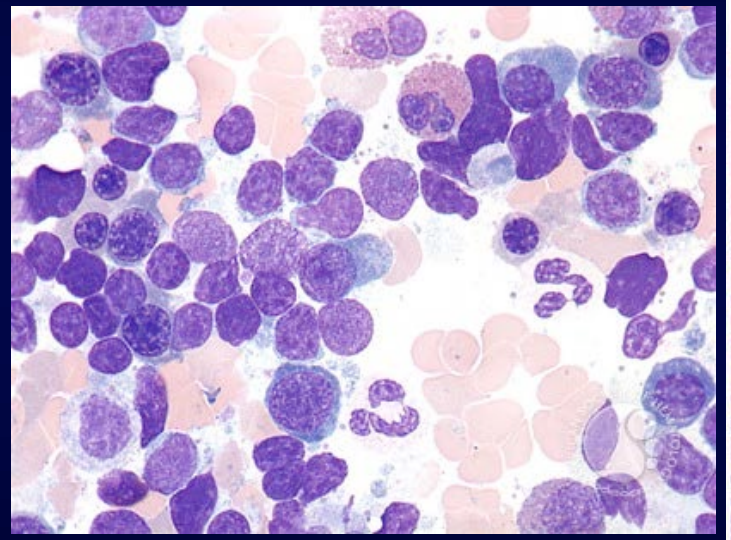
Therapeutic Overview

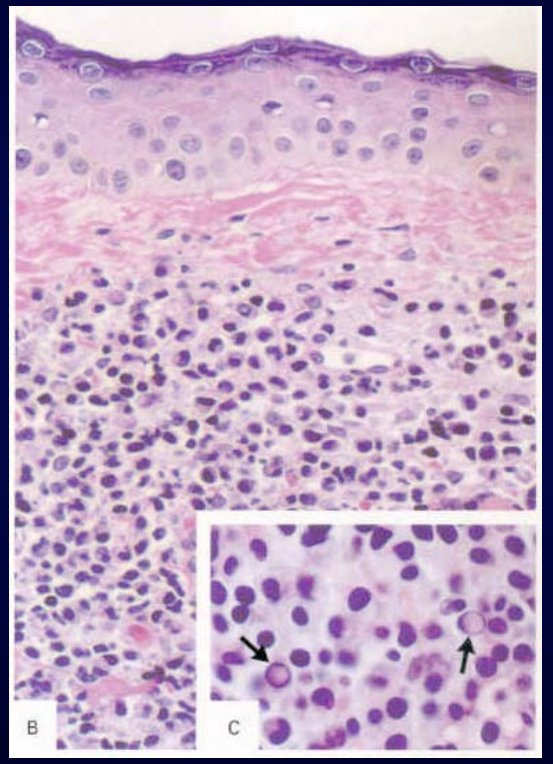


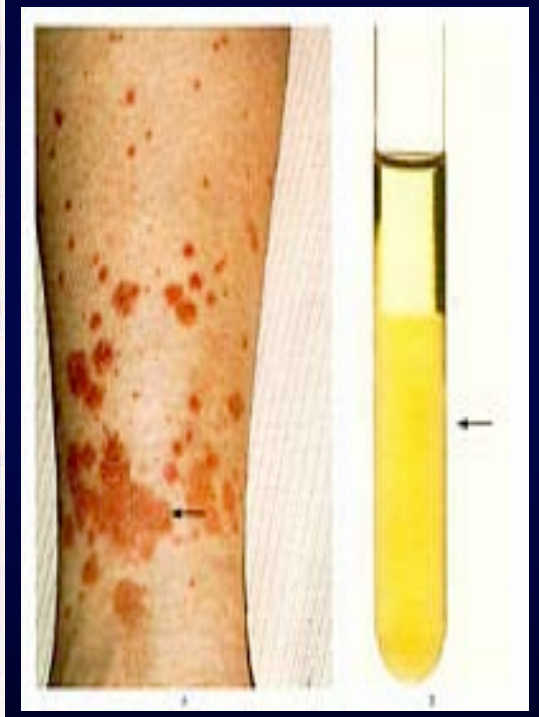
- Venetoclax attractive also due to higher rate of t(11;14)

Nuvolone, M & Merlini, G. Nephrol Dial Transplant. 32: 770, 2017.

Waldenström Macroglobulinemia







Diagnostic Criteria

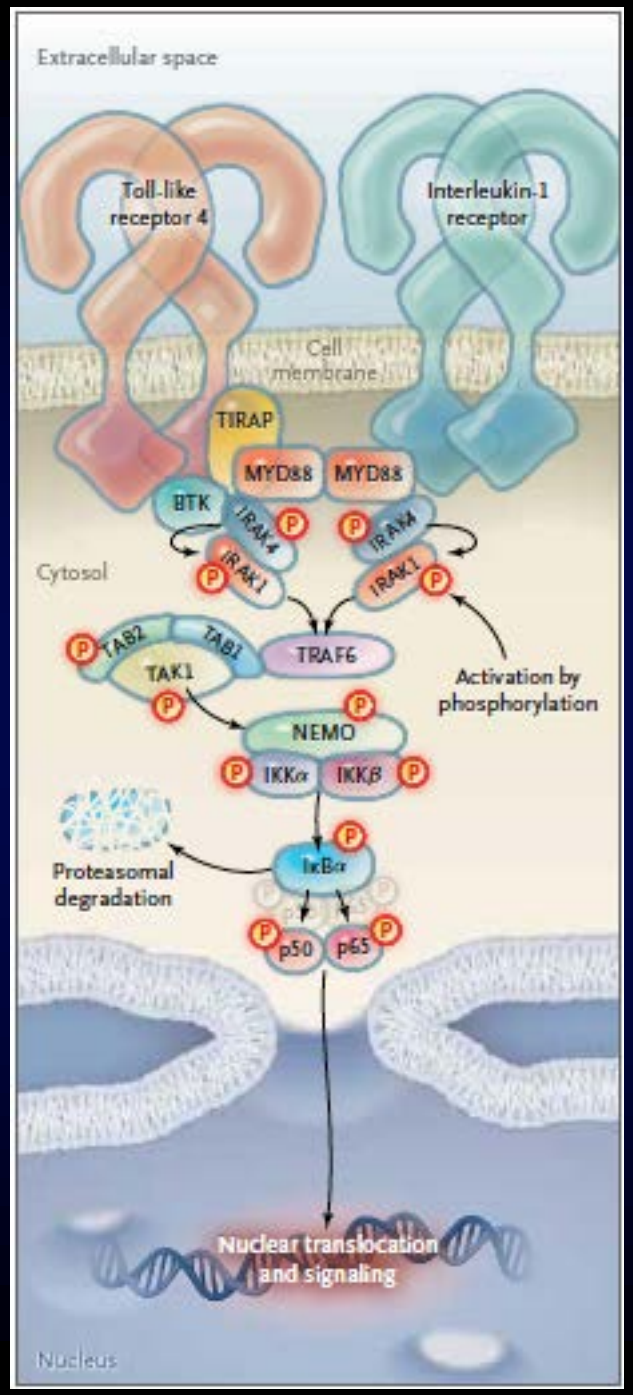
- Lymphoplasmacytic lymphoma with bone marrow involvement
  - Bone marrow infiltration with small lymphocytes, plasmacytoid cells, and plasma cells
  - Diffuse, interstitial, or nodular pattern of infiltration
  - Clonal cells are $CD19^+$, $CD20^+$, $sIgM^+$
    - CD5, CD10, CD23 can be expressed in 10-20% of cases, and don't exclude WM
- IgM monoclonal gammopathy of any concentration

Diagnostic Entities

- Asymptomatic Waldenström : Watch and wait
  - Absence of any of the symptoms below
- Symptomatic Waldenström : Candidates for therapy
  - Disease-related hemoglobin <10 g/dL
  - Platelets <100 x 10^9/L
  - Bulky adenopathy or organomegaly
  - Symptomatic hyperviscosity
  - Moderate/severe or advancing disease-related neuropathy
  - Symptomatic amyloidosis
  - Cryoglobulinemia or cold-agglutinin disease

Treon, SP. Blood 114:2375, 2009.

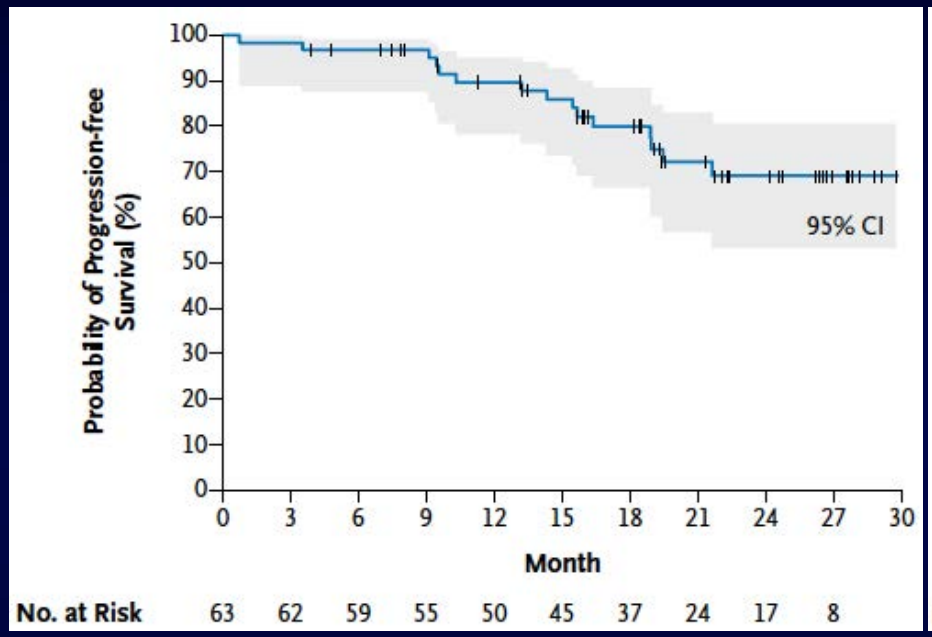
MYD88 L265P

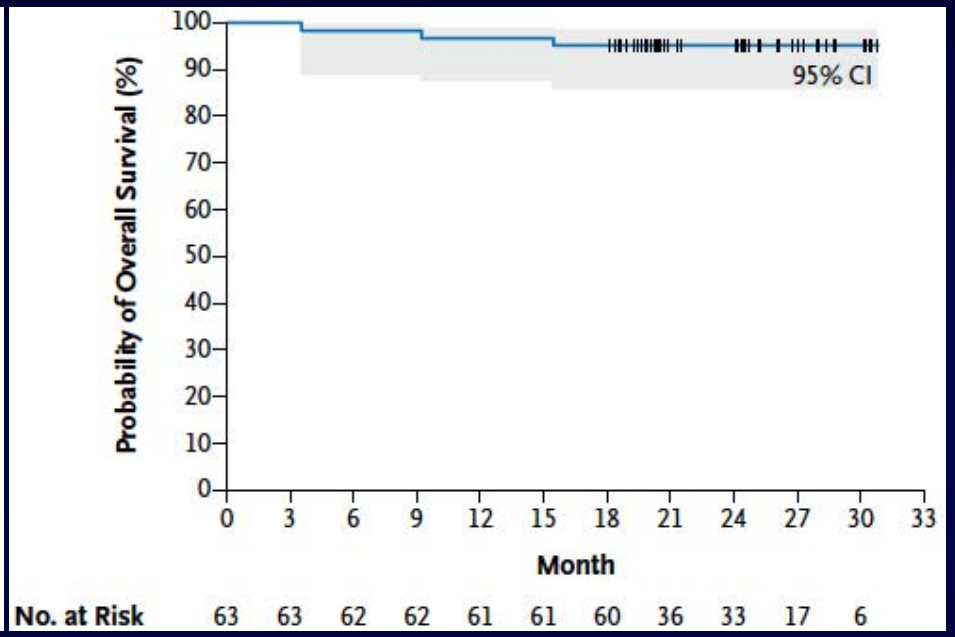


- Mutation found in 49/54 patients with WM
- Triggers BTK/IRAK-mediated activation of NF-κB signaling
- Provides molecular targets

Treon, SP et al. N Engl J Med. 367:826, 2012.

Ibrutinib : BTK Inhibitor





- Response rate of >90%
- Reduced if CXCR4 WHIM-like mutation

Treon, SP et al. N Engl J Med. 372:1430, 2015.

Treatment Approaches

- For newly diagnosed disease

Preferred Regimens

- **Bendamustine/rituximab**[1,2,7]
- **Bortezomib/dexamethasone/rituximab**[2,3,4,5,6,7]
- **Rituximab/cyclophosphamide/dexamethasone**[2,7]

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Treatment Approaches

- For newly diagnosed disease

Other Recommended Regimens

- Bendamustine[7]
- Bortezomib ± rituximab[2,3,4,5,6,7]
- Bortezomib/dexamethasone[4,5,6,7]
- Carfilzomib/rituximab/dexamethasone[2,4,7]
- Cladribine ± rituximab[2,4,8,9]
- Cyclophosphamide/doxorubicin/vincristine/prednisone/rituximab[2,5,7,10]
- Fludarabine ± rituximab[2,4,7,8,9]
- Fludarabine/cyclophosphamide/rituximab[1,2,4,7,8,9]
- Ibrutinib[11] ± rituximab
- Rituximab[2,7]
- Rituximab/cyclophosphamide/prednisone[2,7]

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Treatment Approaches

- For relapsed or refractory disease

Preferred Regimens
- Bendamustine/rituximab[1,2,7]
- Bortezomib/dexamethasone/rituximab[2,3,4,5,6,7]
- Ibrutinib[11] ± rituximab
- Rituximab/cyclophosphamide/dexamethasone[2,7]

Other Recommended Regimens
- Bendamustine[7]
- Bortezomib ± rituximab[2,3,4,5,6,7]
- Bortezomib/dexamethasone[4,5,6,7]
- Cladribine ± rituximab[2,4,7,8,9]
- Cyclophosphamide/doxorubicin/vincristine/prednisone/rituximab[2,5,7,10]
- Everolimus
- Fludarabine ± rituximab[2,4,7,8,9]
- Fludarabine/cyclophosphamide/rituximab[1,2,4,7,8,9]
- Rituximab[2,7]
- Rituximab/cyclophosphamide/prednisone[2,7]

Useful In Certain Circumstances
- Ofatumumab (for rituximab-intolerant individuals)[2,7,12]

Stem Cell Transplant
- In selected cases stem cell transplantation may be appropriate with either:
  - Autologous stem cell transplant
  - Allogeneic stem cell transplant (ablative or nonablative)[13]

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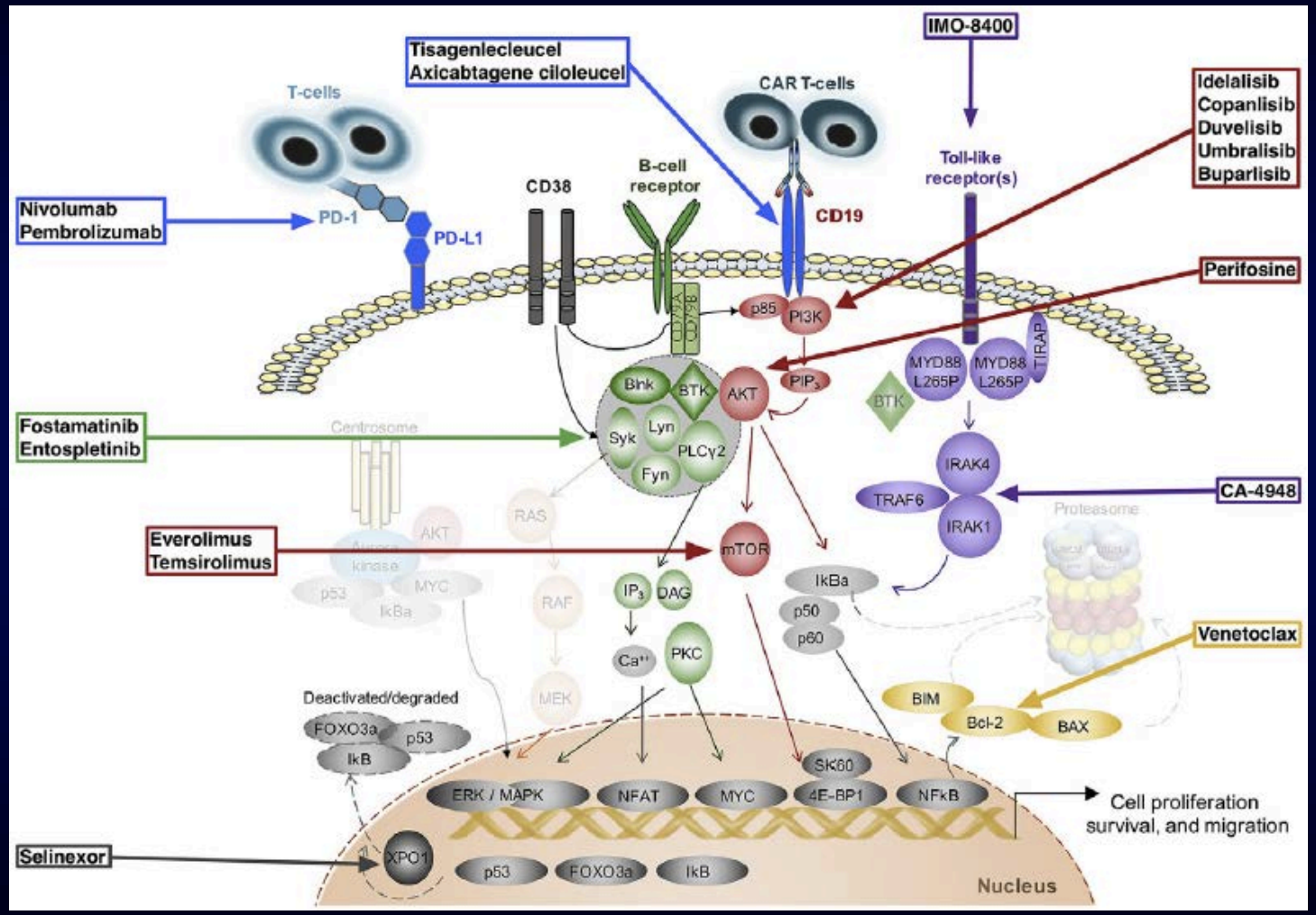
Molecular Targets



Spinner, MA et al. Hematol Oncol Clin North Am. 32: 875, 2018.