Multidisciplinary management of Waldenström's macroglobulinemia: Providing specialist care beyond hematology

Tuesday, May 18, 2021 | 17:00–18:30 (CEST)

Welcome and introductions

Chair: Dr. Alessandra Tedeschi

Disclaimers

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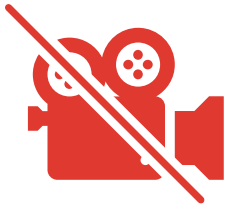
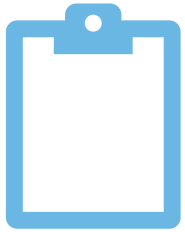
- Prescribing information (PI) may vary depending on local approval in each country. Therefore, before prescribing any product, always refer to local materials such as the PI and/or the summary of product characteristics (SPC).
- Zanubrutinib is not approved for the treatment of Waldenström’s macroglobulinemia outside Canada.

Housekeeping



Please note that personal recording of this meeting is not permitted

Exit full screen view at any time to submit a question for the panel to answer during the Q&A session



A post-meeting survey will be shared at the end of the webinar;
we would greatly appreciate your feedback

Introducing the speakers

Véronique Leblond
Pitié-Salpêtrière Hospital & Sorbonne University, France

Michael Lunn
National Hospital for Neurology and Neurosurgery, UK

Roger Owen
St James's Institute of Oncology, UK

Joe-Elie Salem
Pitié-Salpêtrière Hospital & Sorbonne University, France

Alessandra Tedeschi
Niguarda Cancer Center, Italy

Disclosures

- **Consulting services:** AbbVie, AstraZeneca, BeiGene, and Janssen-Cillag SpA

Agenda

17:00	**Welcome and introductions**	Alessandra Tedeschi
17:05	**Plenary presentation** Multidisciplinary management of WM: The hematologist's perspective	Roger Owen
17:20	**Focus on neuropathy** Diagnosis and management of peripheral neuropathies in WM and related IgM disorders	Michael Lunn
17:40	**Focus on cardiotoxicity** Cardiovascular toxicities associated with BTK inhibitors: A case study and review	Véronique Leblond and Joe-Elie Salem
18:10	**Discussion and audience Q&A**	**Moderator**: Alessandra Tedeschi **Panel**: All
18:25	**Summary**	Alessandra Tedeschi
18:30	**Meeting close**	

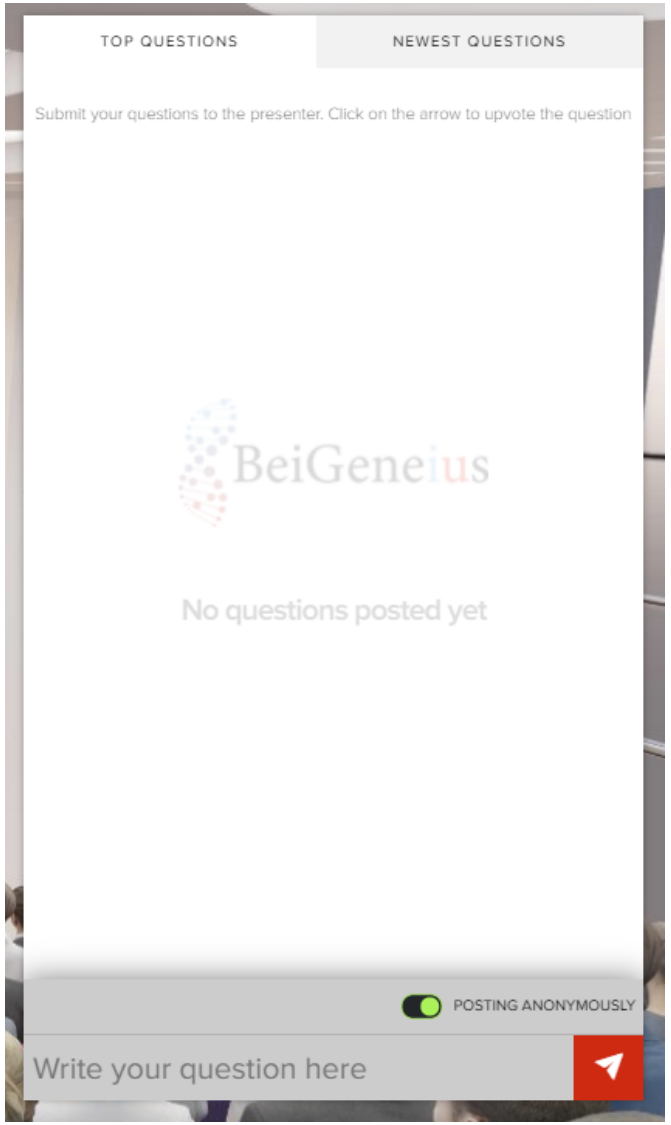
IgM, immunoglobulin M; WM, Waldenström's macroglobulinemia.

A guide to the meeting platform

Please exit full screen view to submit a question for the panel

Audience questions:

- Please enter your question in the submission box
- Because of the volume of questions expected today, some questions received might not be answered during the session

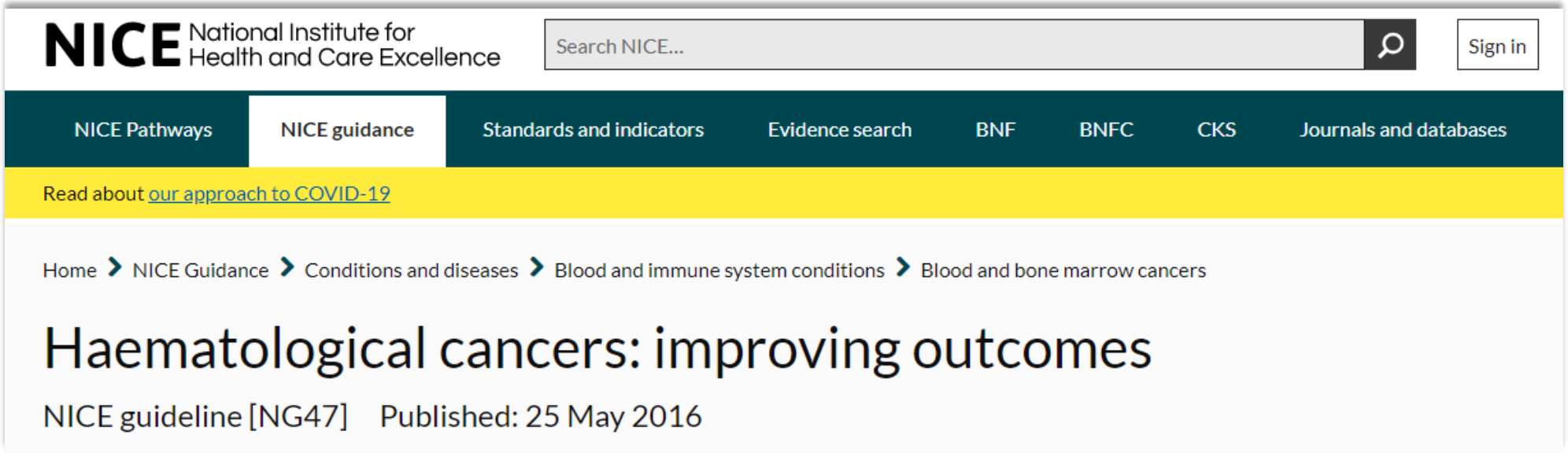


Multidisciplinary management of Waldenström's macroglobulinemia: The hematologist's perspective

Professor Roger Owen
St James's Institute of Oncology, UK

Disclosures

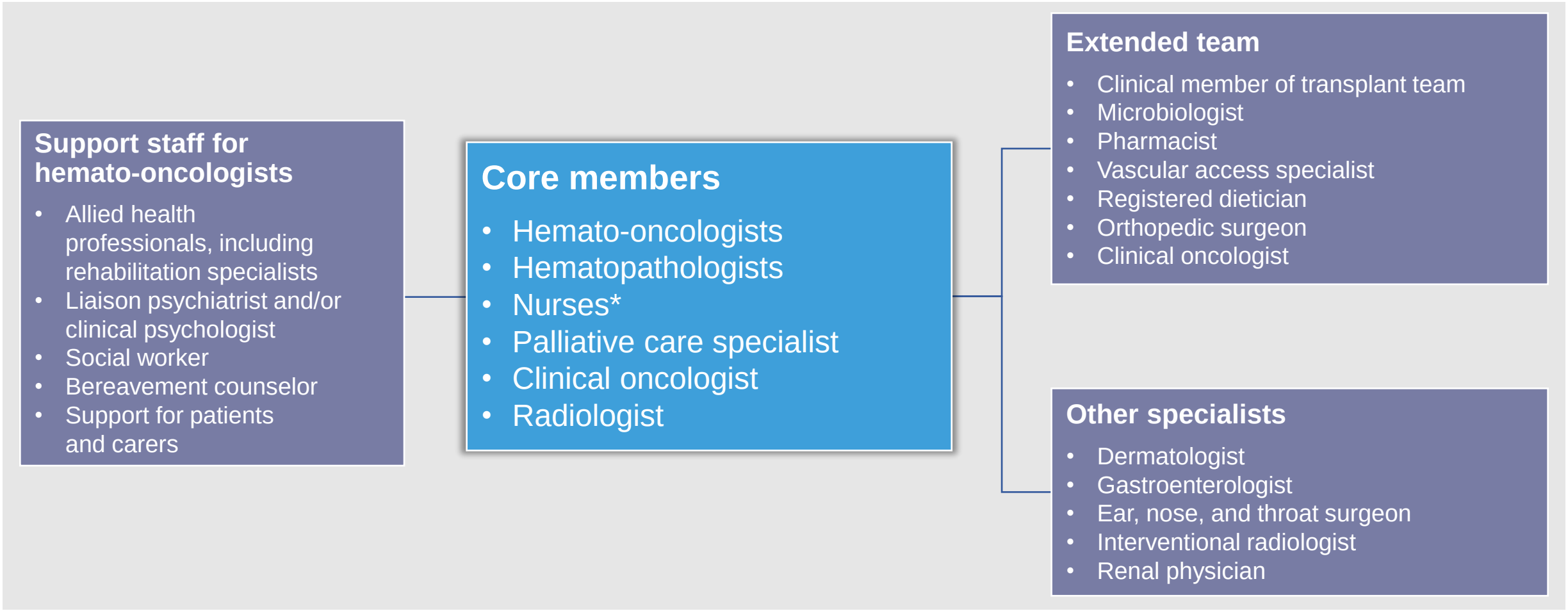
- **Honoraria:** AstraZeneca, BeiGene, Celgene, Janssen
- **Advisory board:** BeiGene, Janssen



- Guidance on multidisciplinary teams
- Hemato-oncology multidisciplinary team should serve a population of ≥500,000 people
- Weekly meetings
- Discuss management of all new diagnoses, relapses, and key decision points
- Diagnosis produced by specialist integrated laboratory
- Record management decisions and minimum data set

NICE. Haematological cancers: Improving outcomes. Available at: https://www.nice.org.uk/guidance/NG47/chapter/Recommendations#multidisciplinary-teams. Accessed May 2021.

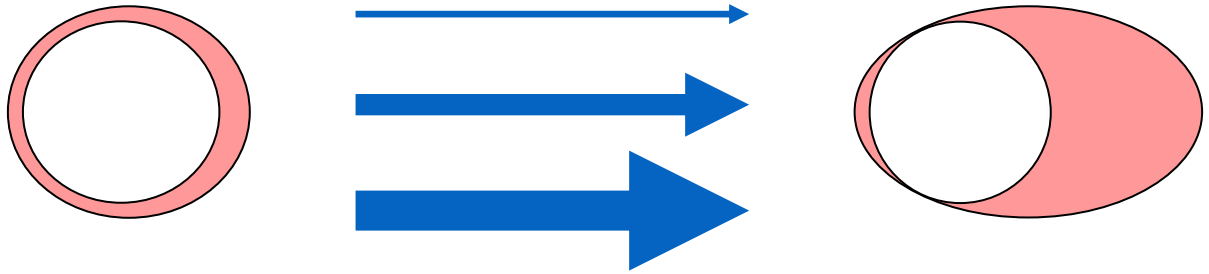
Hematologic cancers
The multi-disciplinary team



*At least one clinical nurse specialist, as well as ward sisters from hospitals that provide high-intensity chemotherapy.

NICE. Haematological cancers: improving outcomes. Available at: https://www.nice.org.uk/guidance/NG47/chapter/Recommendations#multidisciplinary-teams. Accessed: May 2021.

Plasma cell differentiation in WM



B-cell component

- Symptoms related to tumor bulk
- Anemia
- B symptoms
- Lymph nodes
- Spleen

Plasma cell component

- Symptoms attributable to M protein
- Hyperviscosity syndrome
- Neuropathy
- Hemolytic anemia
- Cryoglobulinemia
- Immunodeficiency

WM, Waldenström’s macroglobulinemia.

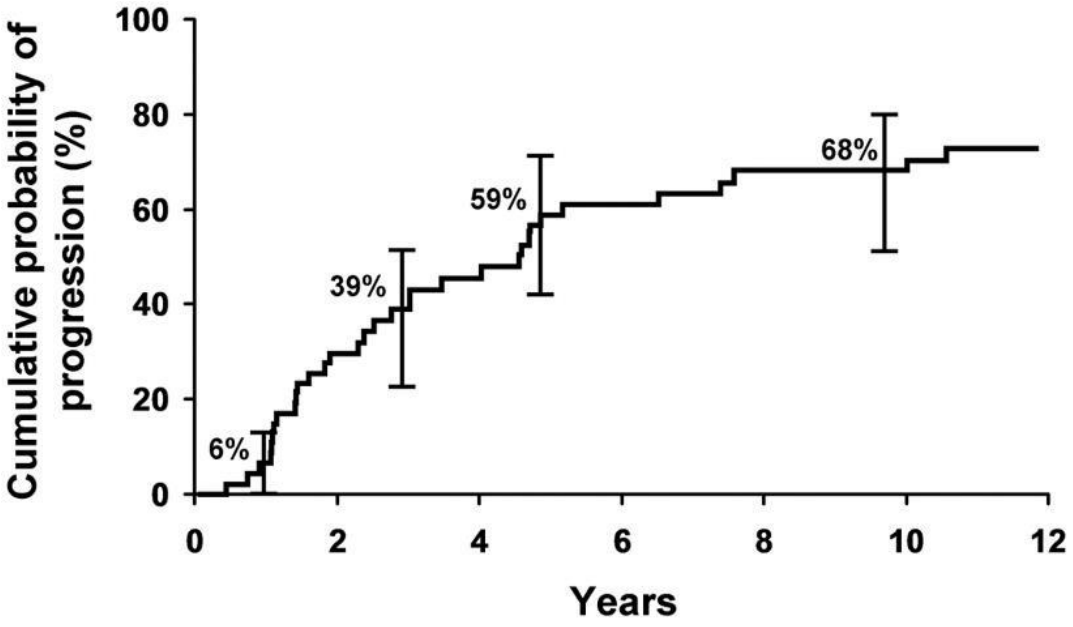
Areas to consider

Newly diagnosed	Beyond diagnosis
Symptomatic	Long-term complications
Asymptomatic	Treatment complications
IgM-related disorders	End-of-life care

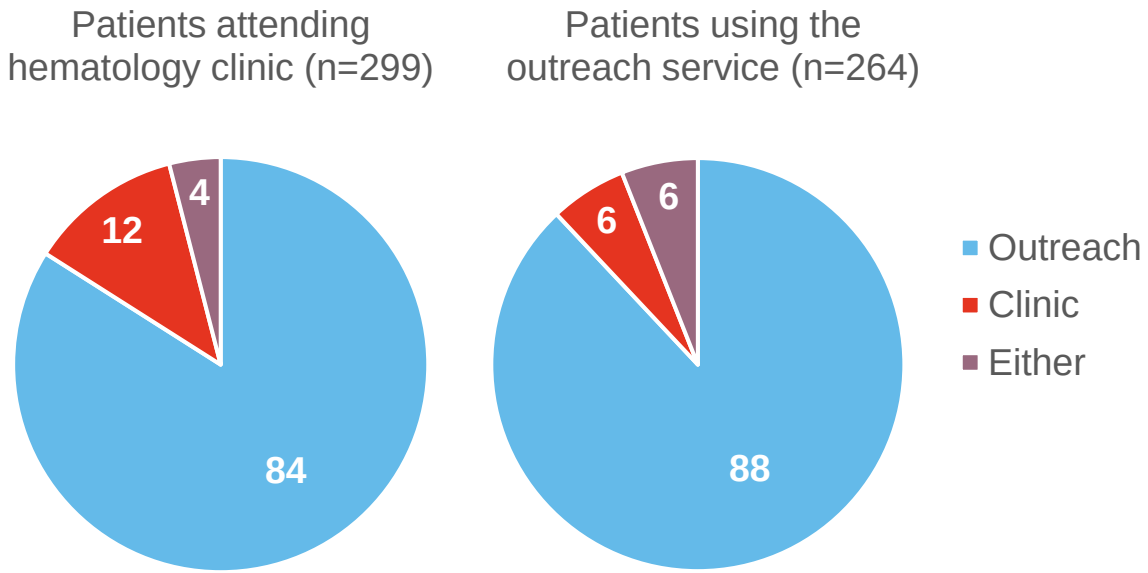
IgM, immunoglobulin M.

Disease monitoring
What works best for patients?

Cumulative probability of progression in smoldering WM[1]



Patient preferences for disease monitoring[2]

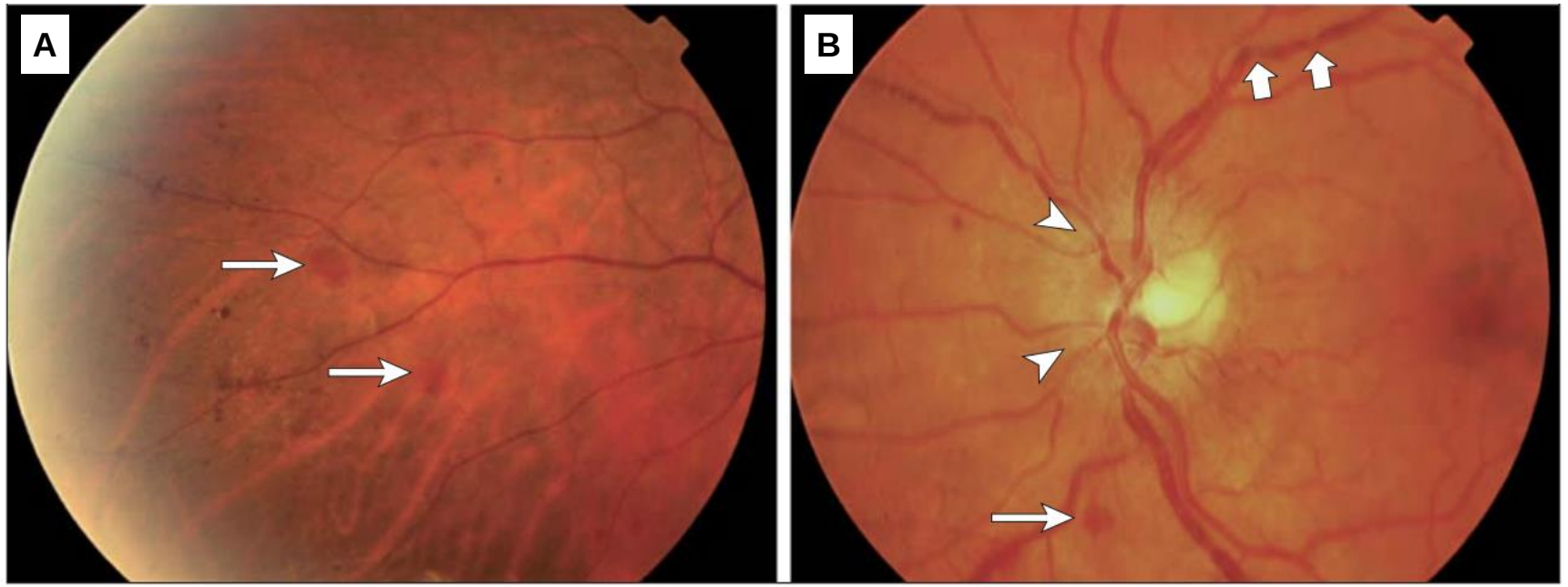


IWMF, International Waldenström's Macroglobulinemia Foundation; WM, Waldenström's macroglobulinemia.

1. Kyle RA *et al*. *Blood* 2012; 119 (19): 4462–4466. 2. Rawstron AC *et al. Br J Haematol* 2007; 139 (5): 845–848.

Hyperviscosity-related retinopathy in WM

Fundus images of eyes of patients with WM



A) Peripheral retinal hemorrhages (arrows).

B) Central retinal hemorrhage (thin arrow); optic disc edema (arrowheads); and venous sausaging (thick arrows).

Access to apheresis services?

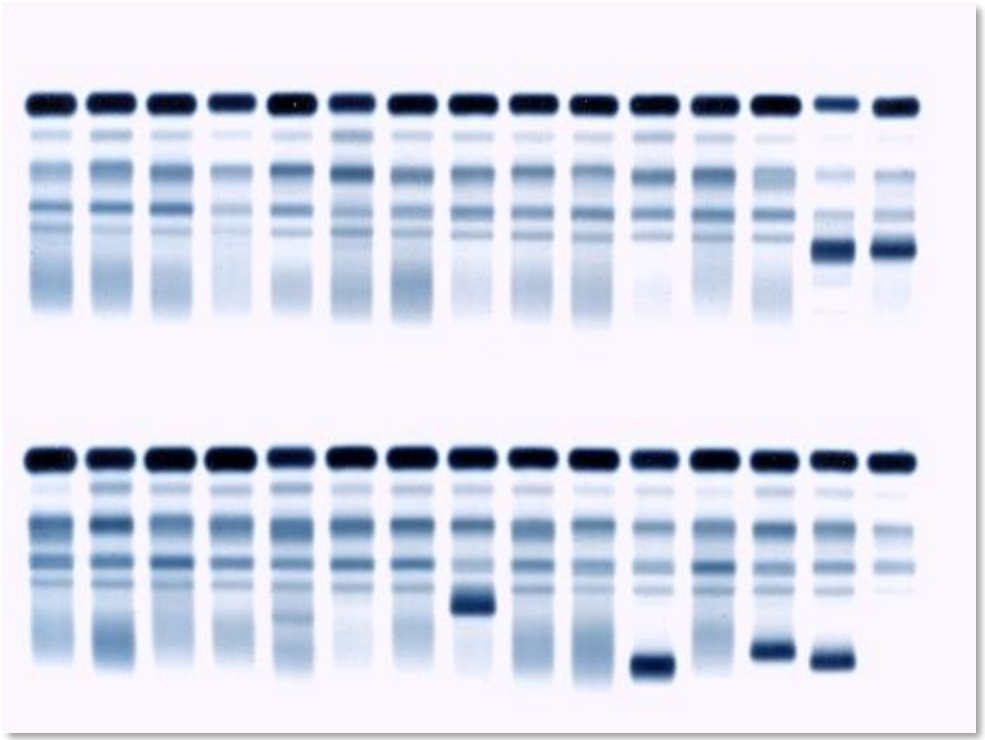
WM, Waldenström's macroglobulinemia.
Menke MN *et al. Arch Opthalmol*. 2006; 124 (11): 1601–1606.

IgM-related disorders: Dangerous small clones

- Peripheral neuropathy
- Cold agglutinin disease
- Cryoglobulinemia
- Amyloidosis
- Schnitzler syndrome
- Acquired von Willebrand disease
- Monoclonal gammopathy of renal significance

- **Diagnostic considerations**

SDS-PAGE analysis

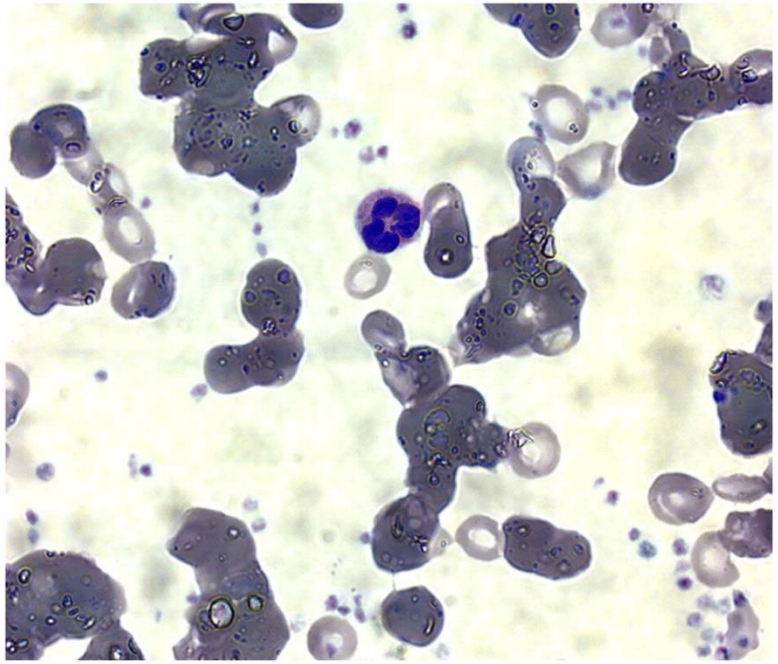


IgM, immunoglobulin M; SDS-PAGE, sodium dodecyl sulphate–polyacrylamide gel electrophoresis.

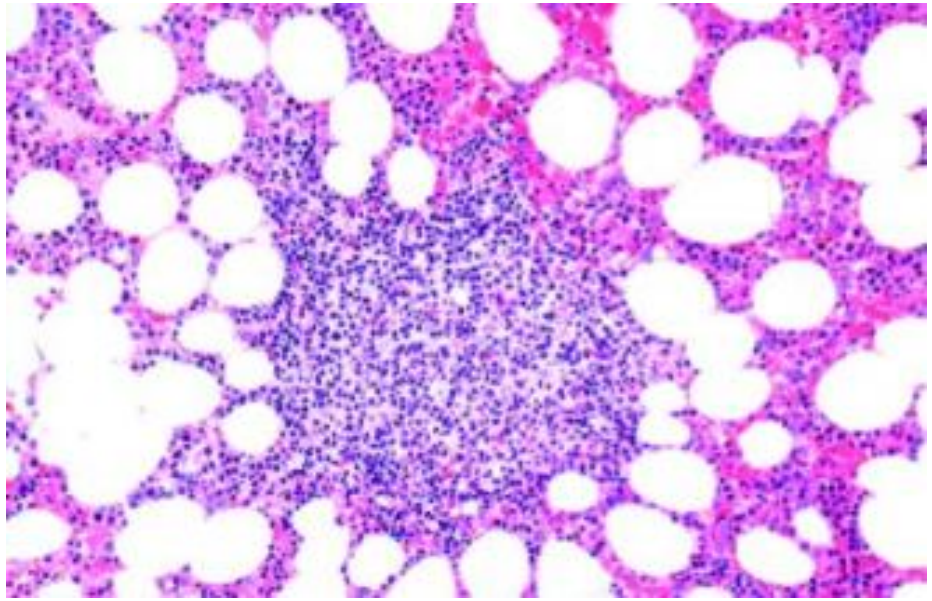
Cold agglutinin–associated lymphoproliferative disease

- Cold agglutinin–associated lymphoproliferative disease is a distinct entity from lymphoplasmacytic lymphoma

Peripheral blood smear from a patient with primary CAD[1]



Bone marrow trephine biopsy in CAD-associated lymphoproliferative disease[2]



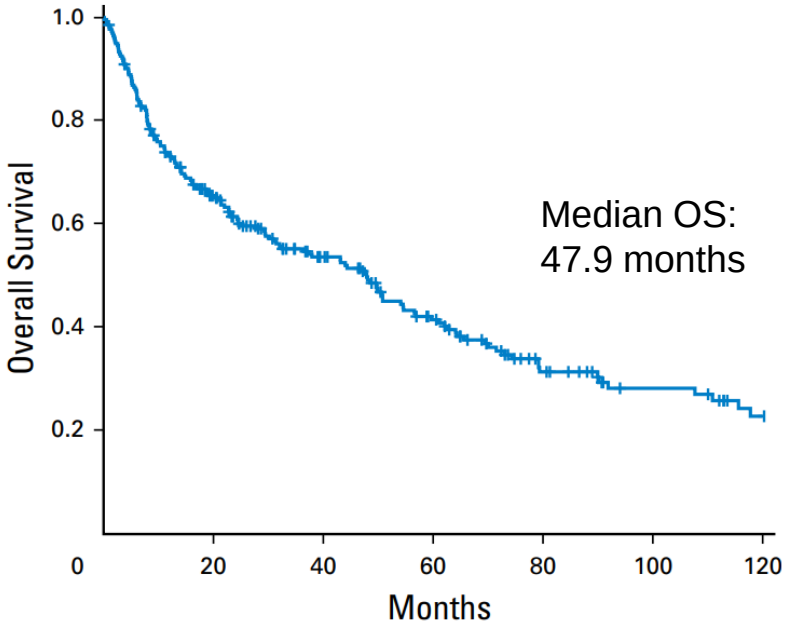
H&E-staining (200x)

CAD, cold agglutinin disease; H&E, hematoxylin and eosin.

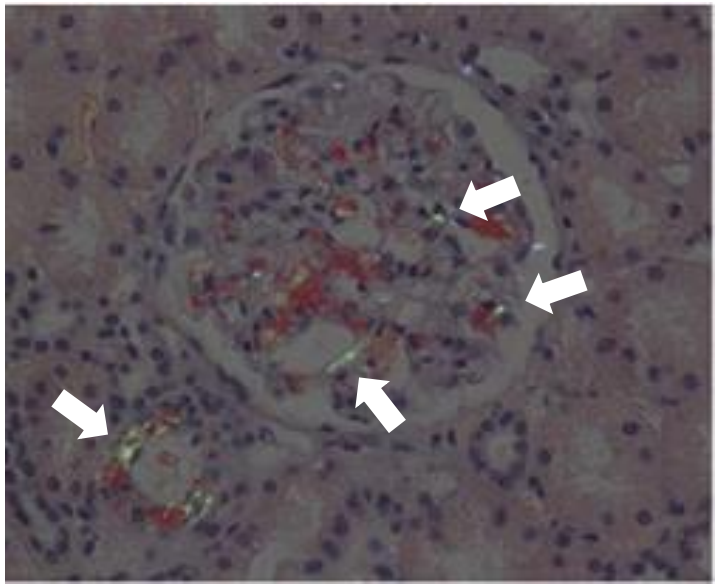
1. Berentsen S *et al. Blood Rev.* 2012; 26 (3): 107–115. 2. Randen U *et al. Haematologica* 2014; 99 (3): 497–504.

Monoclonal IgM–related light-chain amyloidosis

OS for patients with IgM-related light-chain amyloidosis in Europe (n=250)[1]



Amyloid in renal tissue: Congo red staining[2]



Amyloid deposits = white arrows

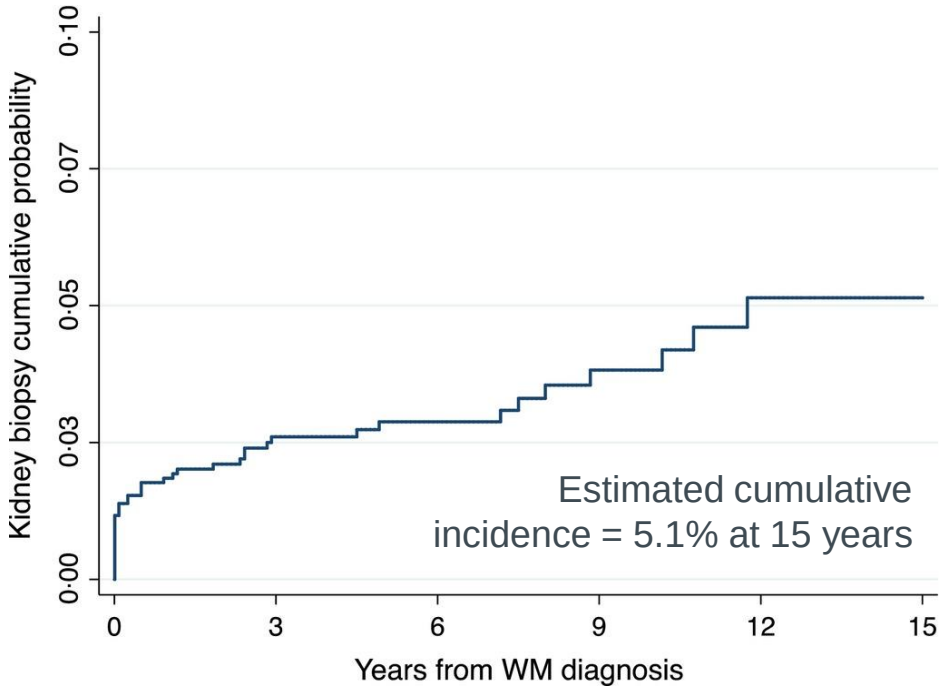
IgM, immunoglobulin M; OS, overall survival.

1. Sachchithanantham S *et al. J Clin Oncol*. 2016; 34 (17): 2037–2045. 2. Huang X *et al*. *Clin Kidney J* 2015; 8 (1): 120–126.

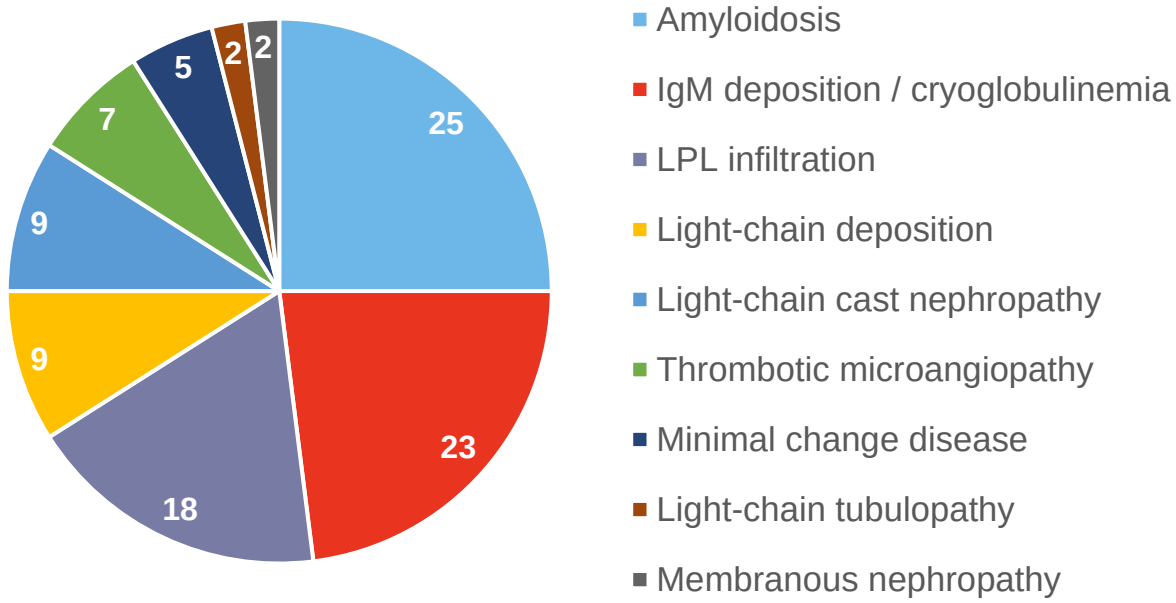
Renal pathologies related to WM

- Median OS in patients with WM and nephropathy was 11.5 years vs. 16 years in patients with WM without renal pathologies

Cumulative incidence of biopsy-confirmed nephropathy in a cohort of 1,391 patients with WM



Distribution of WM-associated renal complications as demonstrated by kidney biopsy (N=44)



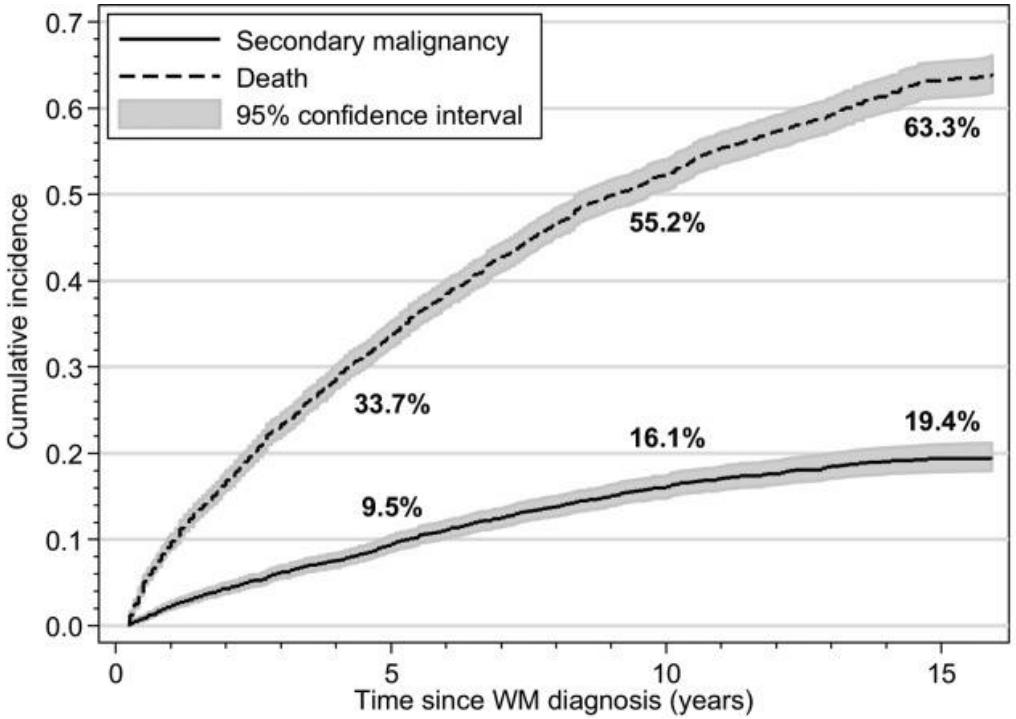
IgM, immunoglobulin M; LPL, lymphoplasmacytic lymphoma; OS, overall survival; WM, Waldenström's macroglobulinemia.

Vos JM *et al. Br. J. Haematol.* 2016; 175 (4): 623–630.

Beyond diagnosis: Secondary malignancies

- 4,676 patients from SEER database

Cumulative incidence of secondary malignancies and competing events among patients with WM



Types of secondary malignancies and cancer-specific MP–SIRs

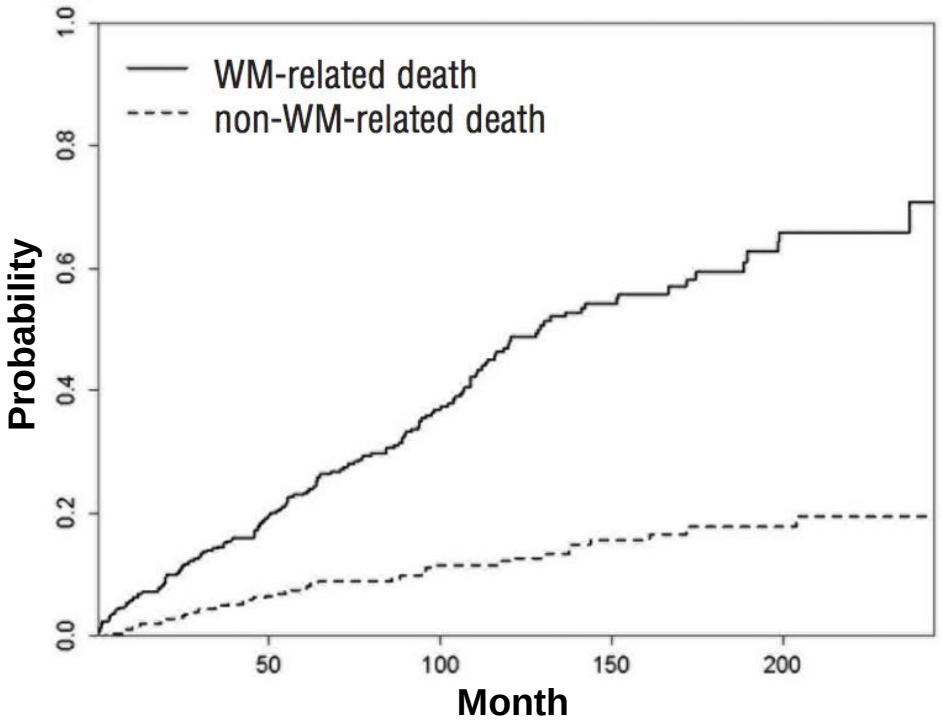
Type of cancer	Cases, n	MP–SIR	95% CI
All cancers	681	1.49	1.38–1.61
Solid tumors	484	1.20	1.10–1.32
Lung	101	1.48	1.21–1.80
Prostate	95	1.03	0.84–1.26
Urinary tract	62	1.41	1.08–1.81
Colorectal	48	0.92	0.68–1.23
Breast	43	1.04	0.75–1.40
Other gastrointestinal	43	1.01	0.73–1.36
Melanoma	35	1.94	1.35–2.69
Other gynecologic	21	1.32	0.82–2.02
Head and neck	13	0.95	0.50–1.62
Thyroid	10	2.67	1.28–4.92
All hematologic	174	4.24	3.63–4.92
All lymphomas	120	4.38	3.63–5.24

MP–SIR, multiple primary–standardized incidence ratio; SEER, Surveillance, Epidemiology, and End Results; WM, Waldenström's macroglobulinemia.
Castillo JJ *et al. Cancer* 2015; 121 (13): 2230–2236.

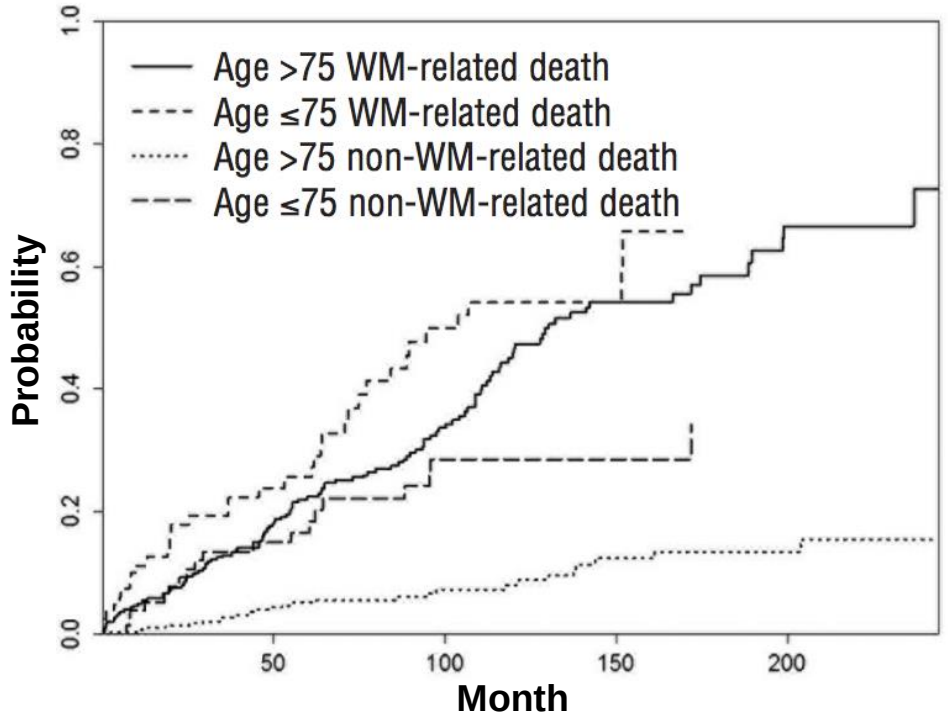
Beyond diagnosis: Non-WM mortality

- Unrelated mortality is significant, particularly in older patients

Survival curves (1-survival proportion) with WM-related and non-WM-related deaths as competing events

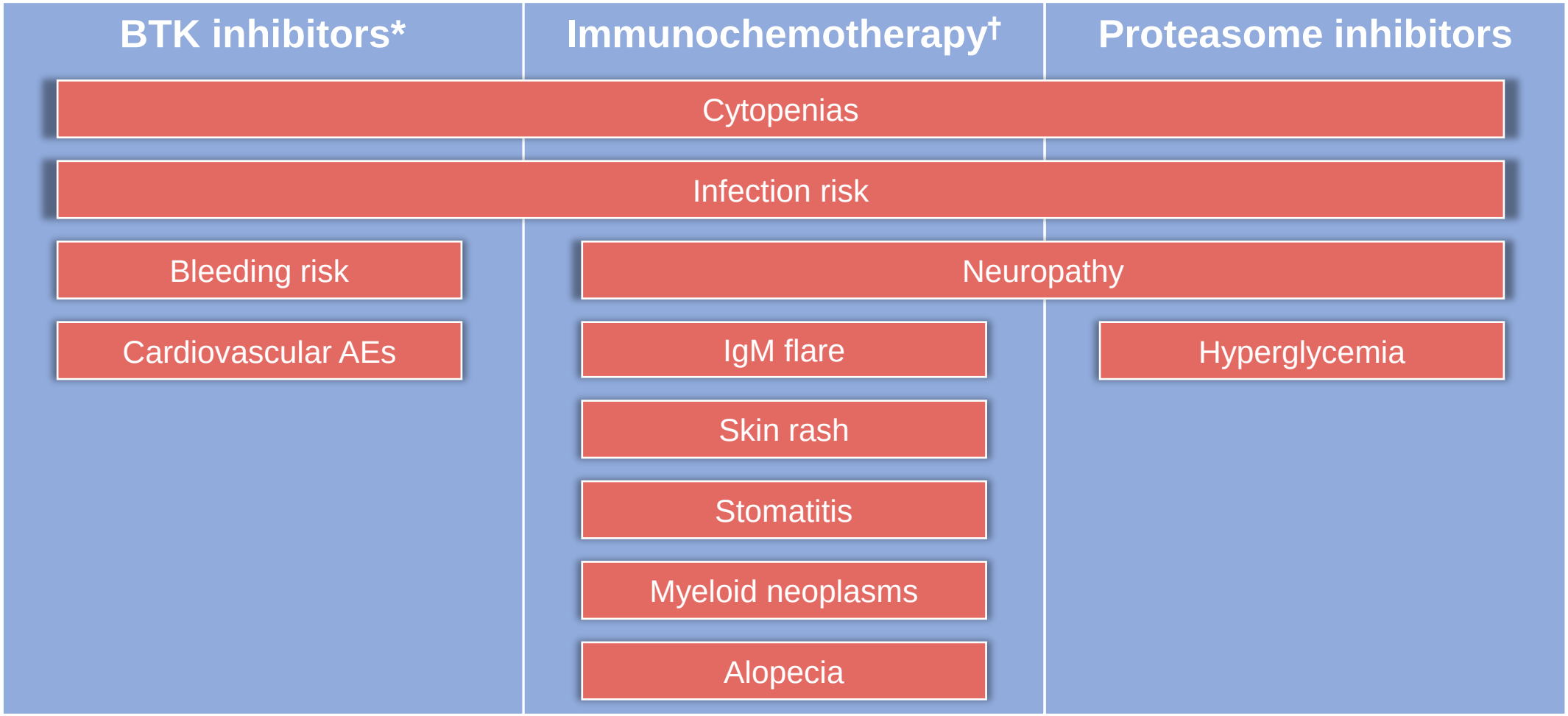


Survival curves with WM-related and non-WM-related deaths in patients >75 vs. ≤75 years



WM, Waldenström's macroglobulinemia.
Kastritis JJ *et al. Haematologica* 2015; 100: e447.

Beyond diagnosis: Treatment-related complications



*Side effects noted for each category in Castillo *et al*. 2020. †Includes risks associated with rituximab plus nucleoside analogs; cyclophosphamide, doxorubicin, vincristine, and prednisone; and bendamustine.
AE, adverse event; IgM, immunoglobulin M.
Castillo JJ *et al. Lancet Haematol* 2020; 7 (11): e827–e837.

Beyond diagnosis: Other considerations

- Patient information/advocacy
- Immune deficiency
- Managing continuous therapies – models of care
- Clinical networks – trials, specialist opinion/review
- End-of-life care

Summary

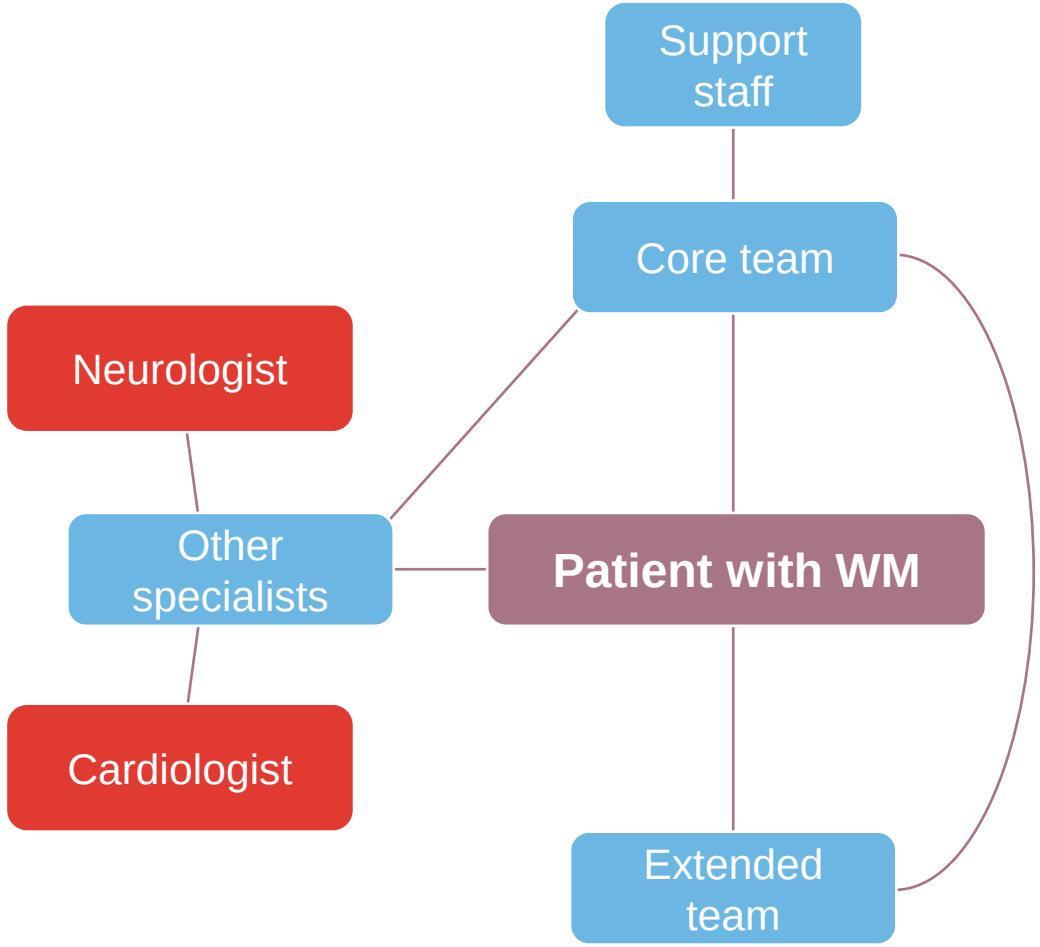
Multidisciplinary management for a multifaceted disease

Management of WM requires a core team with access to a broad range of specialists

- Key specialities in WM include neurology and cardiology

Factors to consider:

- Clinical features (IgM vs. non-IgM)
- Disease stage/status
  - Symptomatic vs. asymptomatic
  - Initial presentation or later stages of disease
- Comorbidities
- Therapies received



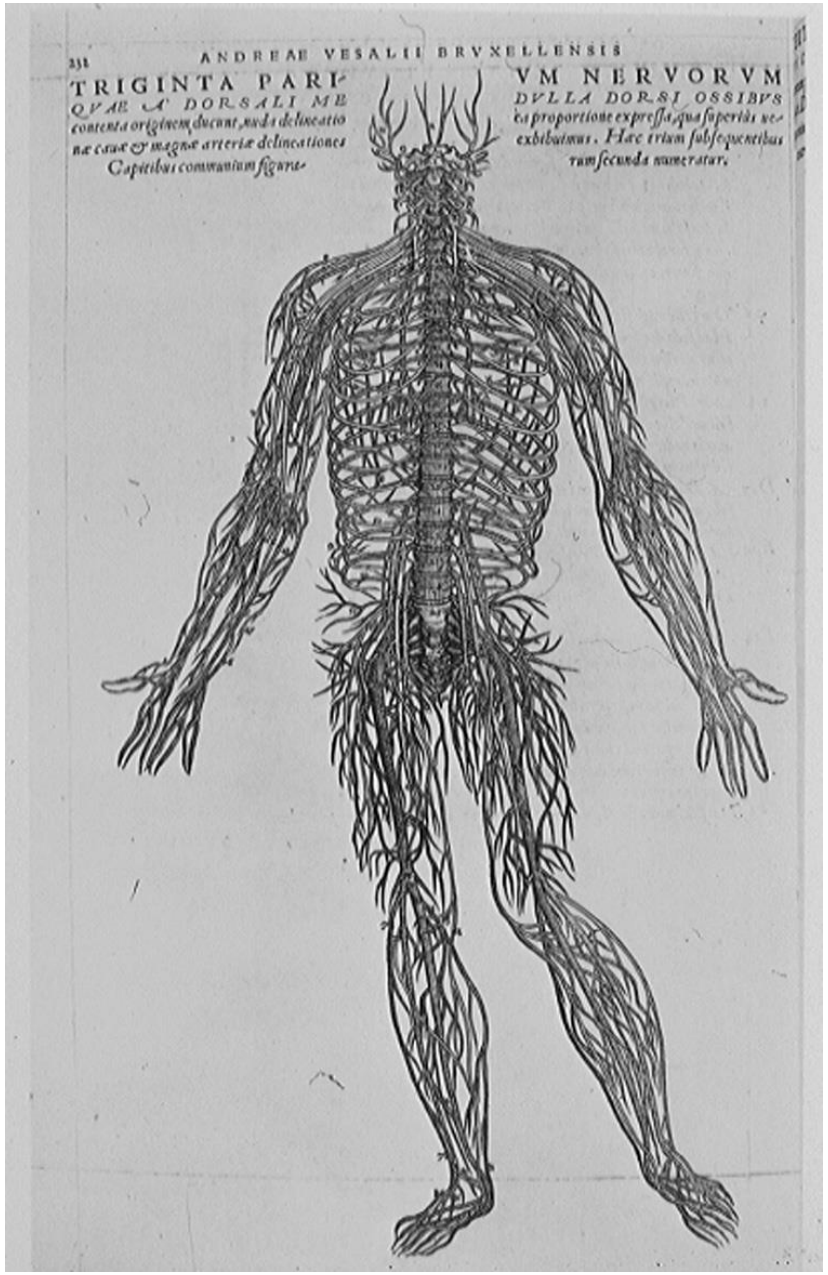
IgM, immunoglobulin M; WM, Waldenström's macroglobulinemia.

Diagnosis and management of peripheral neuropathies in Waldenström's macroglobulinemia and related IgM disorders

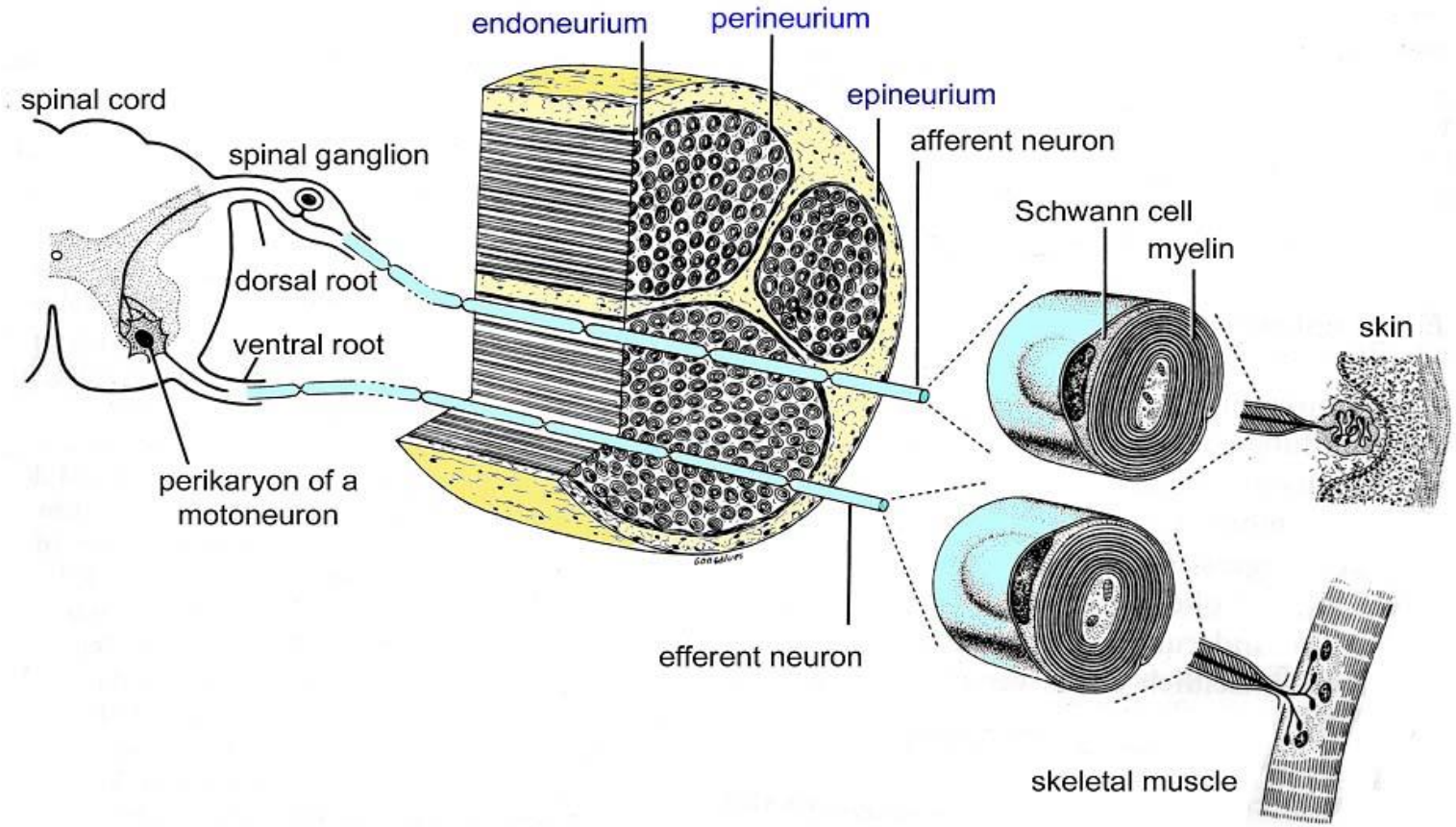
Professor Michael Lunn
National Hospital for Neurology and Neurosurgery, UK

Disclosures

- Consultant Neurologist and Joint Co-Ed Cochrane Neuromuscular
- Last 5 years:
  - Research funding
    - NHNN PI in PATH study
    - PI for trials with Novartis and UCB Pharma
    - PI on Investigator-led Optic, Perinoms and IMAGiNe studies
    - DSMB for Octapharma trial and Investigator led IoC trial
- **Honoraria**
  - Advisory role for CSL Behring, Grifols, Novartis, UCB Pharma, AstraZeneca
  - Ad hoc travel support grants from CSL Behring



Anatomy of a normal nerve



VESALIUS, Andreas (1514-1564), De humani corporis fabrica, Basel: Oporinus, 1543, lib. IV, pp.353-4, Wellcome Library, London. Speaker's personal files.

Inflammatory peripheral neuropathy

Idiopathic

Acute
- Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)
- Acute motor axonal neuropathy (AMAN)
- Acute motor-sensory axonal neuropathy (AMSAN)
- Fisher Syndrome and other regional variants
  - Pharyngeal-cervical-brachial
  - Paraparetic
  - Facial palsies
  - Pure oculomotor
- Functional variants of GBS
  - Pure dysautonomia
  - Pure sensory GBS
  - Ataxic GBS

Subacute
- Subacute inflammatory demyelinating polyradiculoneuropathy (SIDP)

Chronic
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
- Multifocal motor neuropathy with conduction block (MMNCB)
- Chronic relapsing axonal neuropathy
- Chronic ataxic sensory neuronopathy

Paraproteinaemic neuropathy
- Monoclonal gammopathy of undetermined significance (MGUS)
- Multiple myeloma
- Solitary plasmacytoma
- Lymphoma or chronic lymphocytic leukaemia
- Waldenström's macroglobulinaemia
- Cryoglobulinaemia
- Cold agglutinin disease
- Primary amyloidosis
- POEMS syndrome

Vasculitic Neuropathy

Primary vasculitis
- Polyarteritis nodosa and Churg-Strauss disease
- Wegener's vasculitis
- Isolated nerve vasculitis
- Temporal arteritis

Systemic autoimmune diseases with associated vasculitis
- Rheumatoid arthritis
- Systemic lupuserythematosus
- Sjörgren's syndrome
- Mixed connective tissue disease

Other
- Serum sickness
- Infectious, malignant, related to chemotherapy

Inflammatory neuropathy associated with infection
- HIV neuropathies, including CMV neuropathy
- Leprosy
- Lyme disease
- Chaga's disease

Paraneoplastic
- Sub-acute sensory neuropathy/neuronopathy - small cell lung carcinoma and anti-Hu Abs
- Other paraneoplastic tumour-antibody syndromes

Metabolic
- Diabetic lumbo-sacral plexopathy

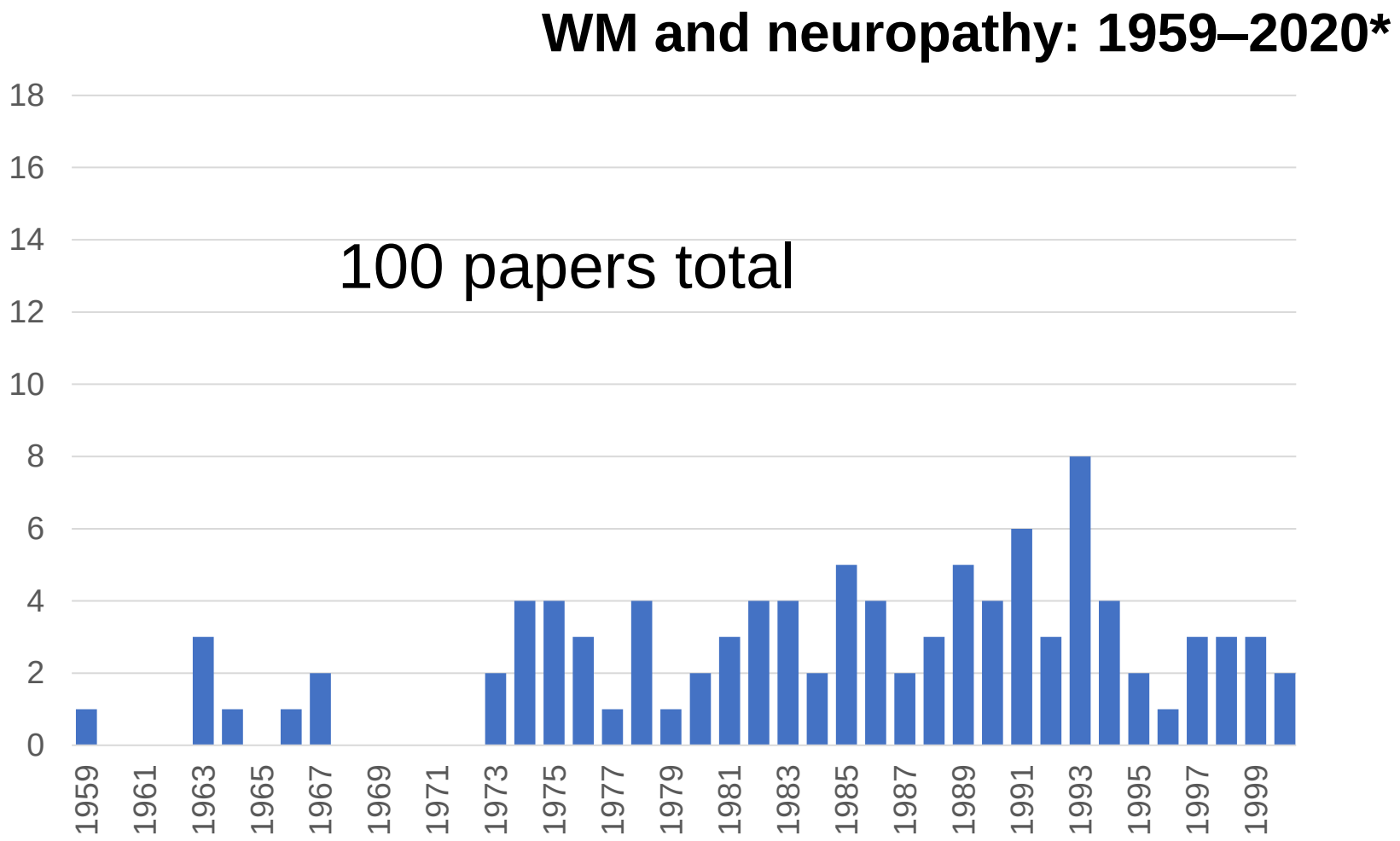
Lunn MP: Unpublished.

Neuropathies associated with paraproteins

- Monoclonal gammopathy of undetermined significance
  - IgM +/- anti-MAG paraproteinemia
  - IgG and IgA
  - Others?
- Waldenström's macroglobulinemia
- Lymphoma – neurolymphomatosis
- POEMS syndrome
  - Solitary myeloma (osseous/extraosseous – lytic/sclerotic)
- Amyloidosis
- Cryoglobulinemia
- Multiple myeloma

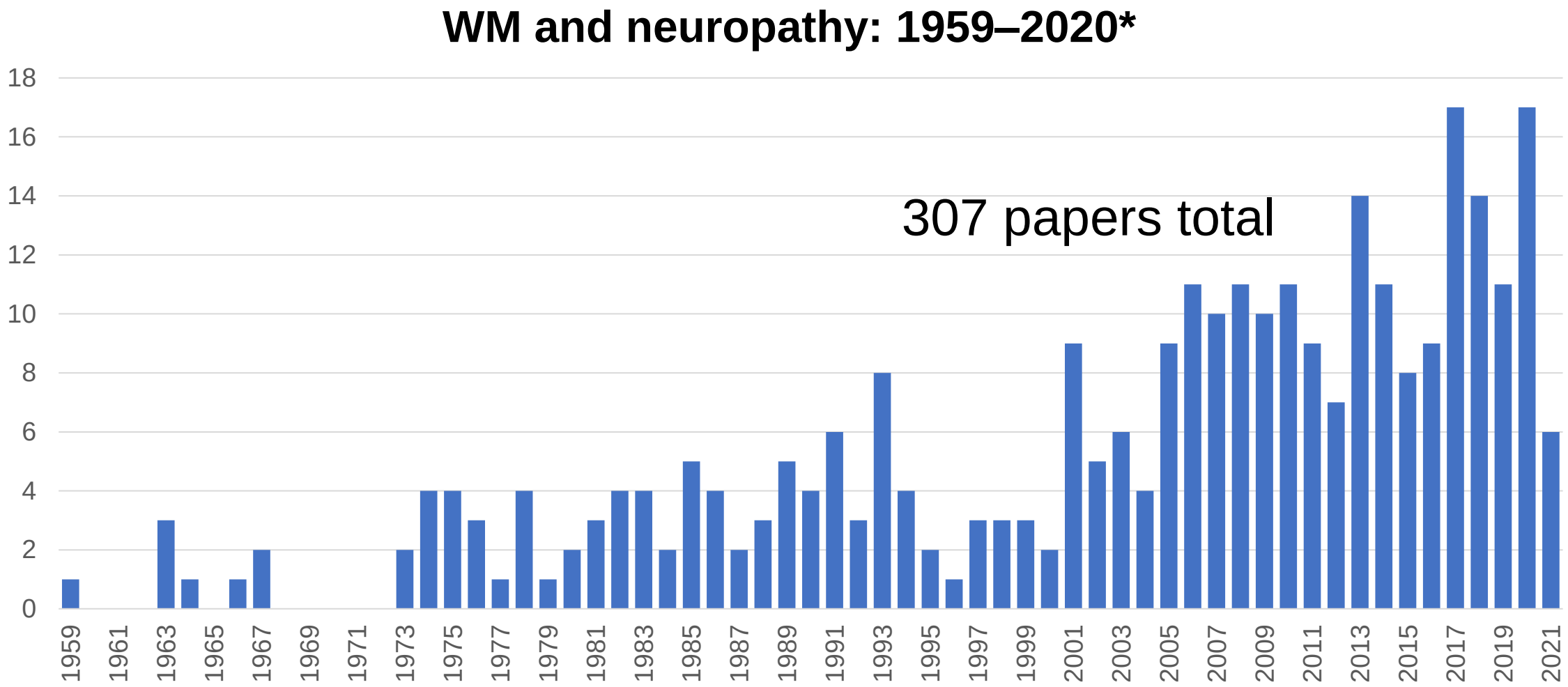
Ig, immunoglobulin; MAG, myelin-associated glycoprotein; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin lesions.

MGUS, MGNS, WM, or something else?



*Data from PubMed: Accessed May 2021. MGNS, monoclonal gammopathy of neurological significance; MGUS, monoclonal gammopathy of undetermined significance; WM, Waldenström's macroglobulinemia.

MGUS, MGNS, WM, or something else?



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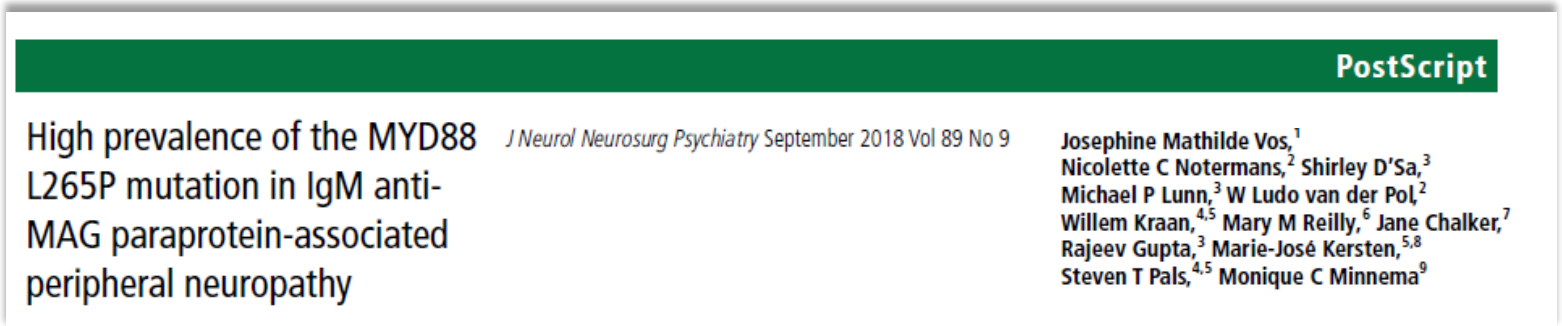
MGUS, MGNS, WM, or something else?

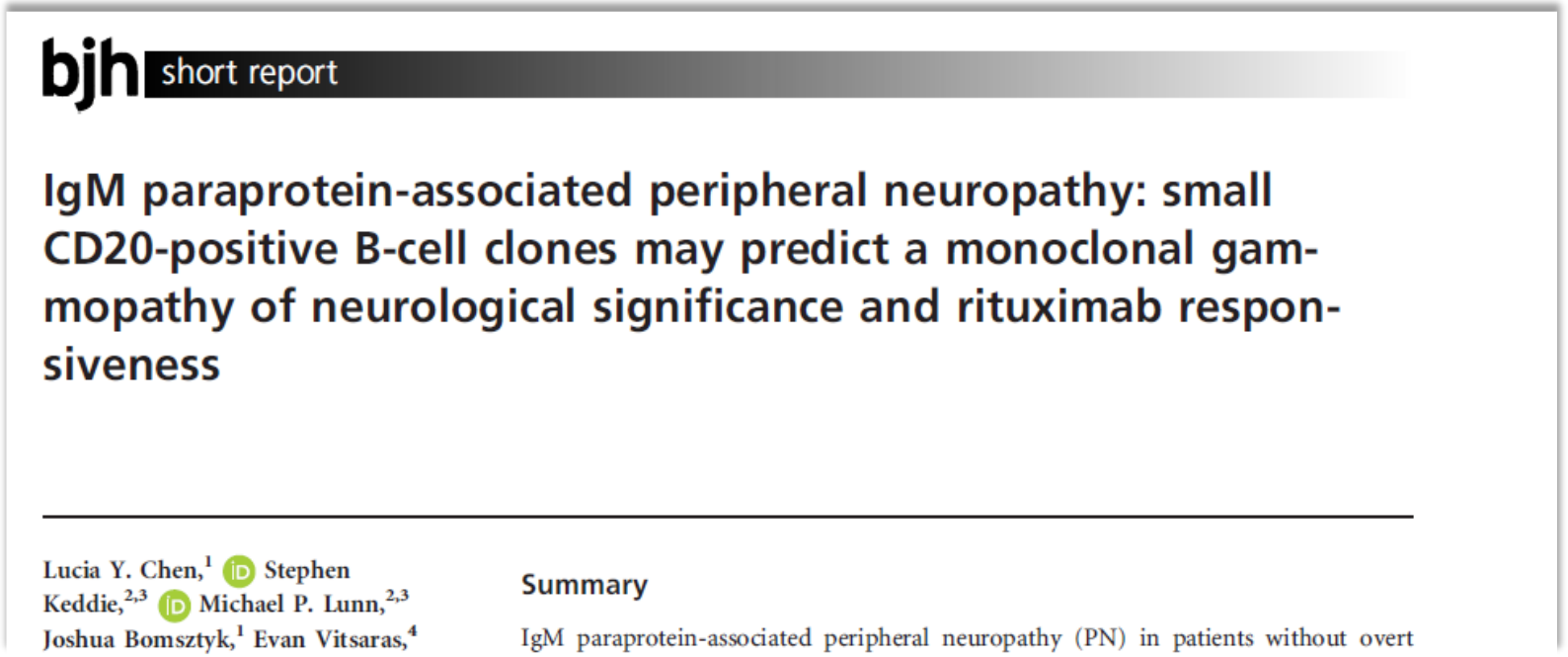


PostScript

High prevalence of the MYD88 L265P mutation in IgM anti-MAG paraprotein-associated peripheral neuropathy

J Neurol Neurosurg Psychiatry September 2018 Vol 89 No 9

Josephine Mathilde Vos,[1] Nicolette C Notermans,[2] Shirley D'Sa,[3] Michael P Lunn,[3] W Ludo van der Pol,[2] Willem Kraan,[4,5] Mary M Reilly,[6] Jane Chalker,[7] Rajeev Gupta,[3] Marie-José Kersten,[5,8] Steven T Pals,[4,5] Monique C Minnema[9]



bjh short report

IgM paraprotein-associated peripheral neuropathy: small CD20-positive B-cell clones may predict a monoclonal gammopathy of neurological significance and rituximab responsiveness

Lucia Y. Chen,[1] Stephen Keddie,[2,3] Michael P. Lunn,[2,3] Joshua Bomsztyk,[1] Evan Vitsaras,[4]

Summary

IgM paraprotein-associated peripheral neuropathy (PN) in patients without overt

IgM, immunoglobulin M; MGNS; monoclonal gammopathy of neurological significance; MGUS, monoclonal gammopathy of undetermined significance; WM, Waldenström's macroglobulinemia.

Vos JM *et al. J Neurol Neurosurg Psychiatry* 2018; 89 (9): 1007–1009. Chen LY *et al. Br J Haematol* 2020; 188 (4): 511–515.

History and examination: The basis of all diagnosis

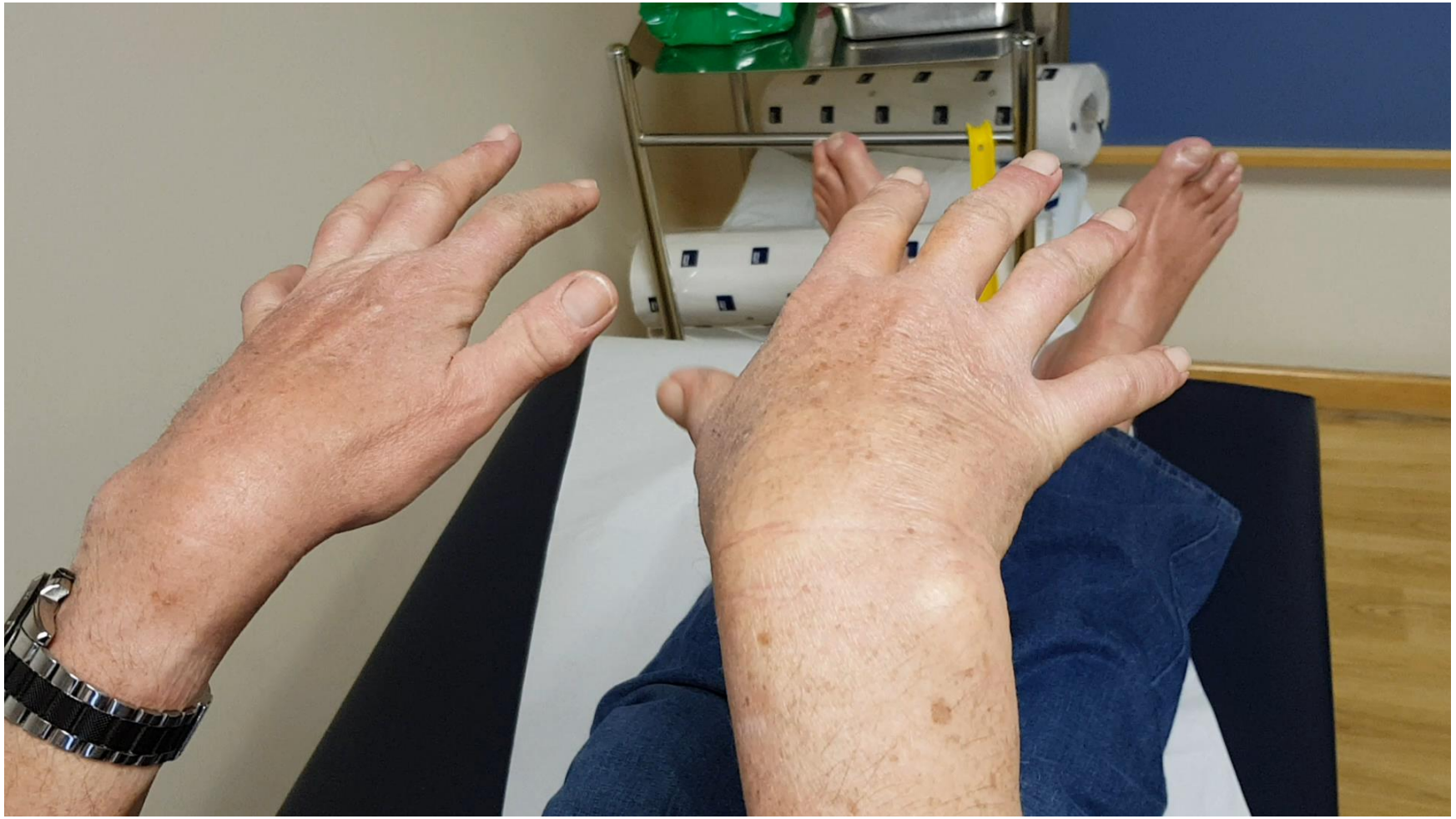
- *The history is the key*
  - All features of the disease
    - Onset, tempo, fluctuation, recurrence, recovery
    - Motor and sensory impairments
    - Disability
    - Autonomic, respiratory, cranial nerve involvement
    - Previous medical history, medication, diet, alcohol
    - Family history
    - Unusual, systemic, unexpected, irrelevant information
  - Don’t be afraid to come back to the history later

Anti-MAG paraproteinemic demyelinating peripheral neuropathy (DADS)

- Chronic progressive sensorimotor demyelinating neuropathy
  - Elderly, male, ataxia, and tremor
  - Little motor involvement
  - Sensory loss is key
    - VS often absent to costal margin
    - JPS almost normal
    - PP in short socks
- Serum IgMκ paraprotein
- Paraprotein has ‘anti-MAG’ activity
  - Sees HNK-1 epitope (also on P0, PMP22, SGPG, SGLPG)
  - Not clear which target is pathogenic in vivo ?MAG
- Characteristic neurophysiology and pathology

DADS, distal acquired demyelinating sensorimotor neuropathy; MAG, myelin-associated glycoprotein.

Anti-MAG tremor



MAG, myelin-associated glycoprotein.

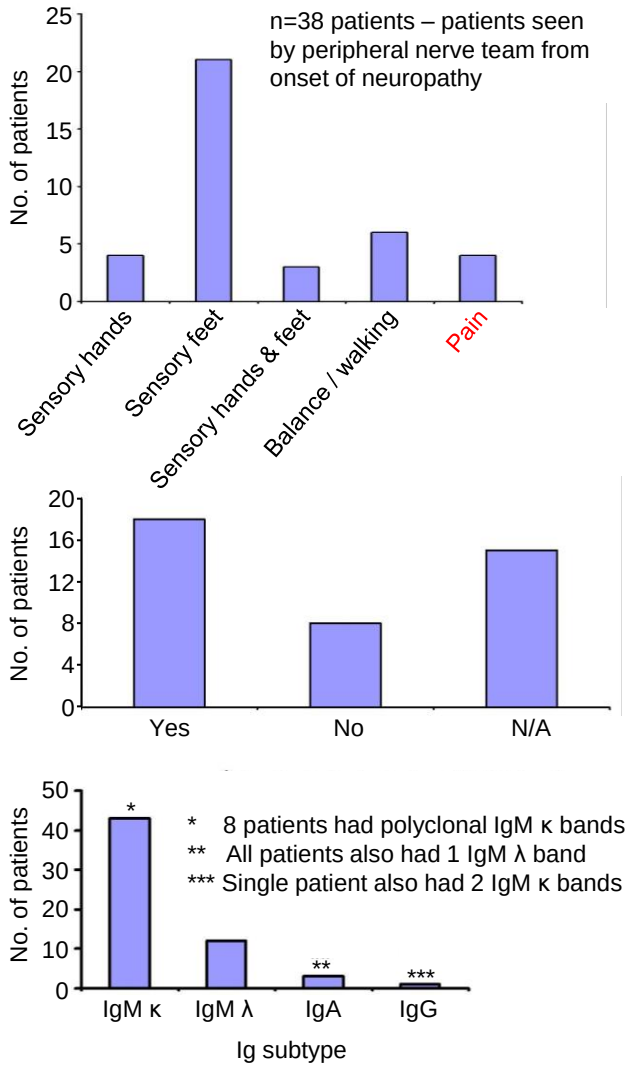
Anti-MAG paraproteinemic demyelinating peripheral neuropathy (DADS)

- Chronic progressive sensorimotor demyelinating neuropathy
  - Elderly, male, ataxia, and tremor
  - Little motor involvement
  - Sensory loss is key
    - VS often absent to costal margin
    - JPS almost normal
    - PP in short socks

- Serum IgMκ paraprotein
- Paraprotein has ‘anti-MAG’ activity
  - Sees HNK-1 epitope (also on P0, PMP22, SGPG, SGLPG)
  - Not clear which target is pathogenic *in vivo* ?MAG
- Characteristic neurophysiology and pathology

DADS, distal acquired demyelinating sensorimotor neuropathy; JPS, joint position sense; MAG, myelin-associated glycoprotein; PP, proprioception; VS, vibration sense.

The NHNN anti-MAG cohort



- >100 patients with anti-MAG antibodies
- NHNN diagnosis
- ‘Years’ of follow-up

- Inclusion
  - Typical clinical picture
  - >70,000 Bühlmann Units

  and/or
  - Typical neurophysiology
  - WSM on nerve biopsy

- 42 patients fulfilling inclusion criteria

Ig, immunoglobulin; MAG, myelin-associated glycoprotein; mISS, modified inflammatory neuropathy cause and treatment sensory sum score; MRC, Medical Research Council; NHNN, National Hospital for Neurology and Neurosurgery; WSM, wide spaced myelin. Bhattacharjee and Lunn 2012: Unpublished.

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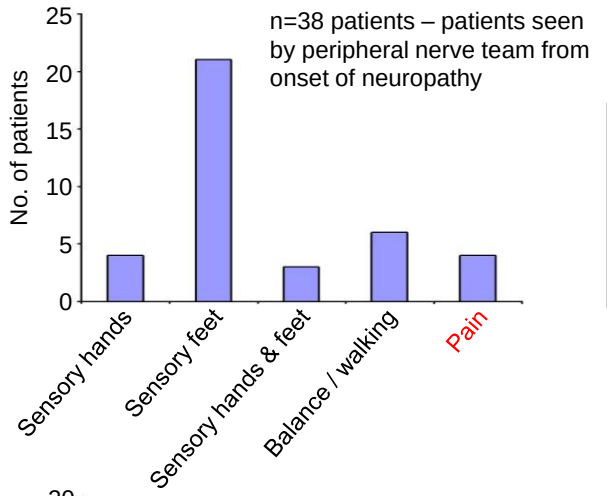

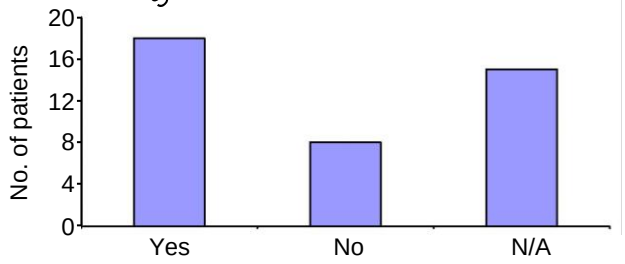

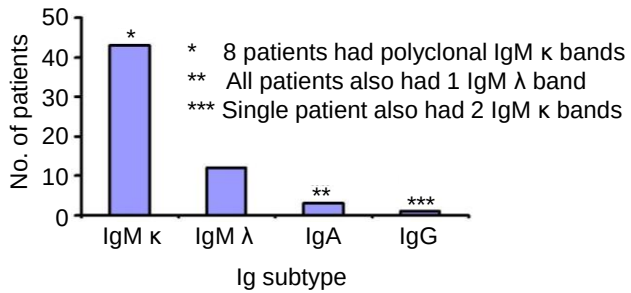

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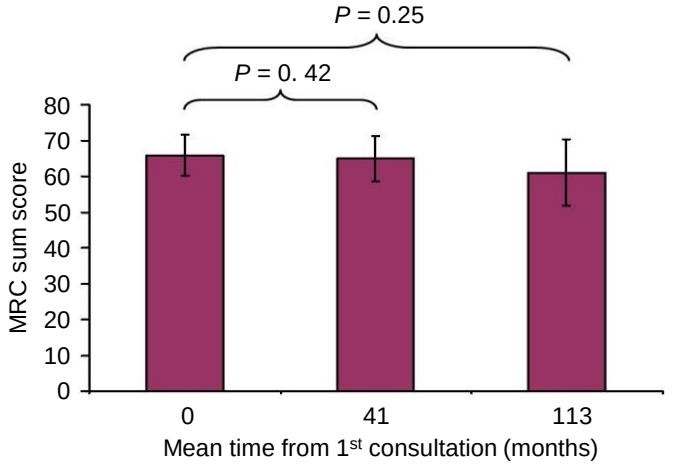

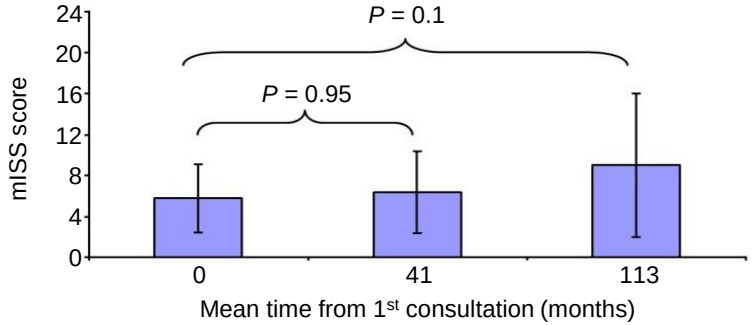

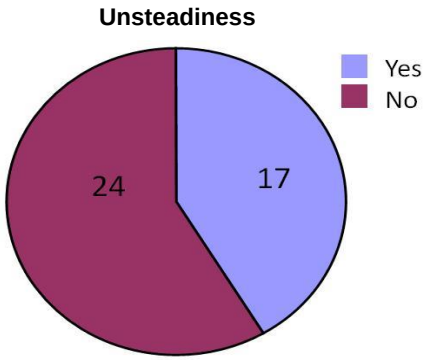

Ig, immunoglobulin; MAG, myelin-associated glycoprotein; mISS, modified inflammatory neuropathy cause and treatment sensory sum score; MRC, Medical Research Council; NHNN, National Hospital for Neurology and Neurosurgery; WSM, wide spaced myelin. Bhattacharjee and Lunn 2012: Unpublished.

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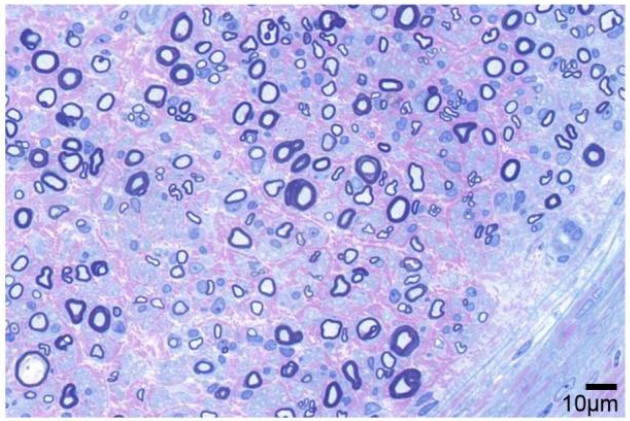
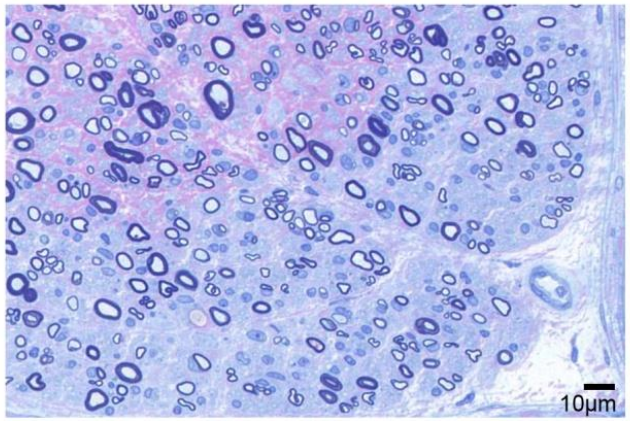
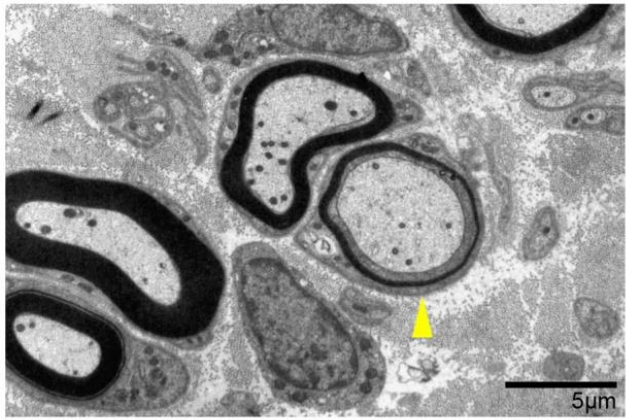
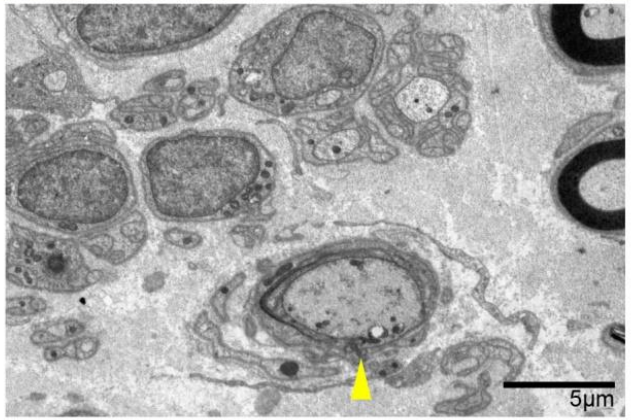
Semithin Resin Section (MBA-BF)

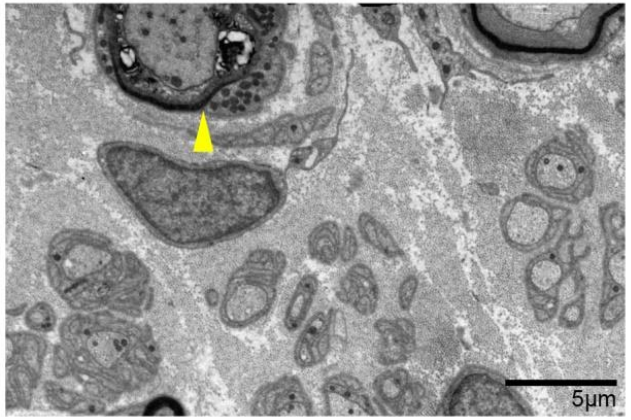


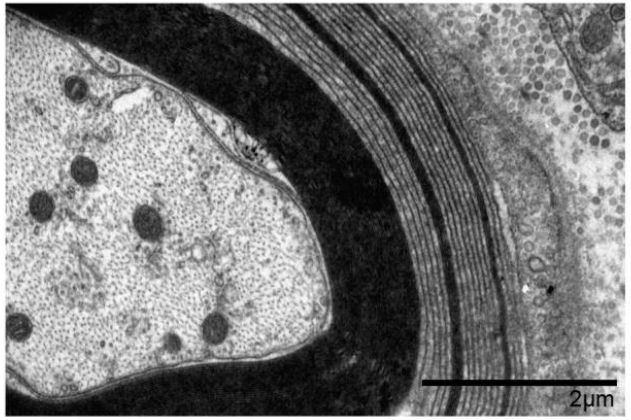


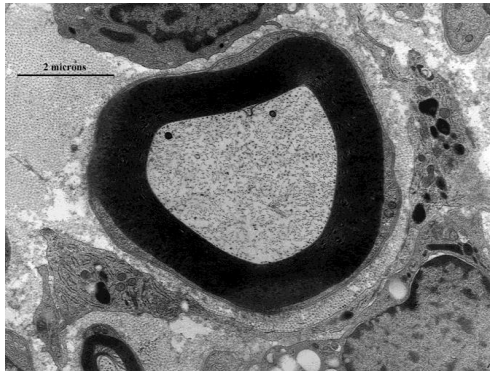
Electron Microscopy



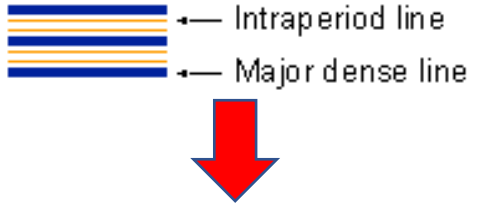


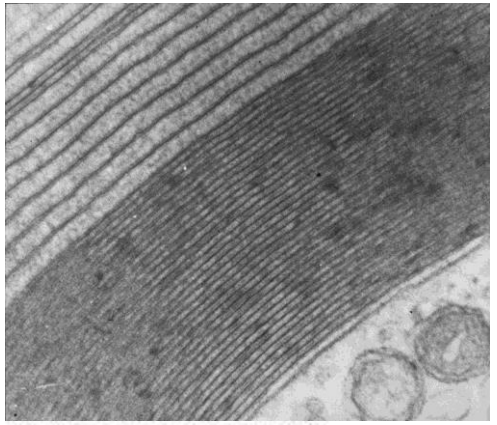




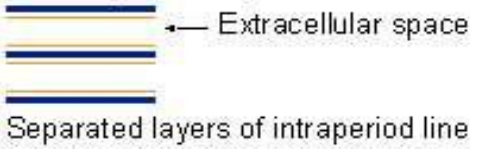


Normal myelin

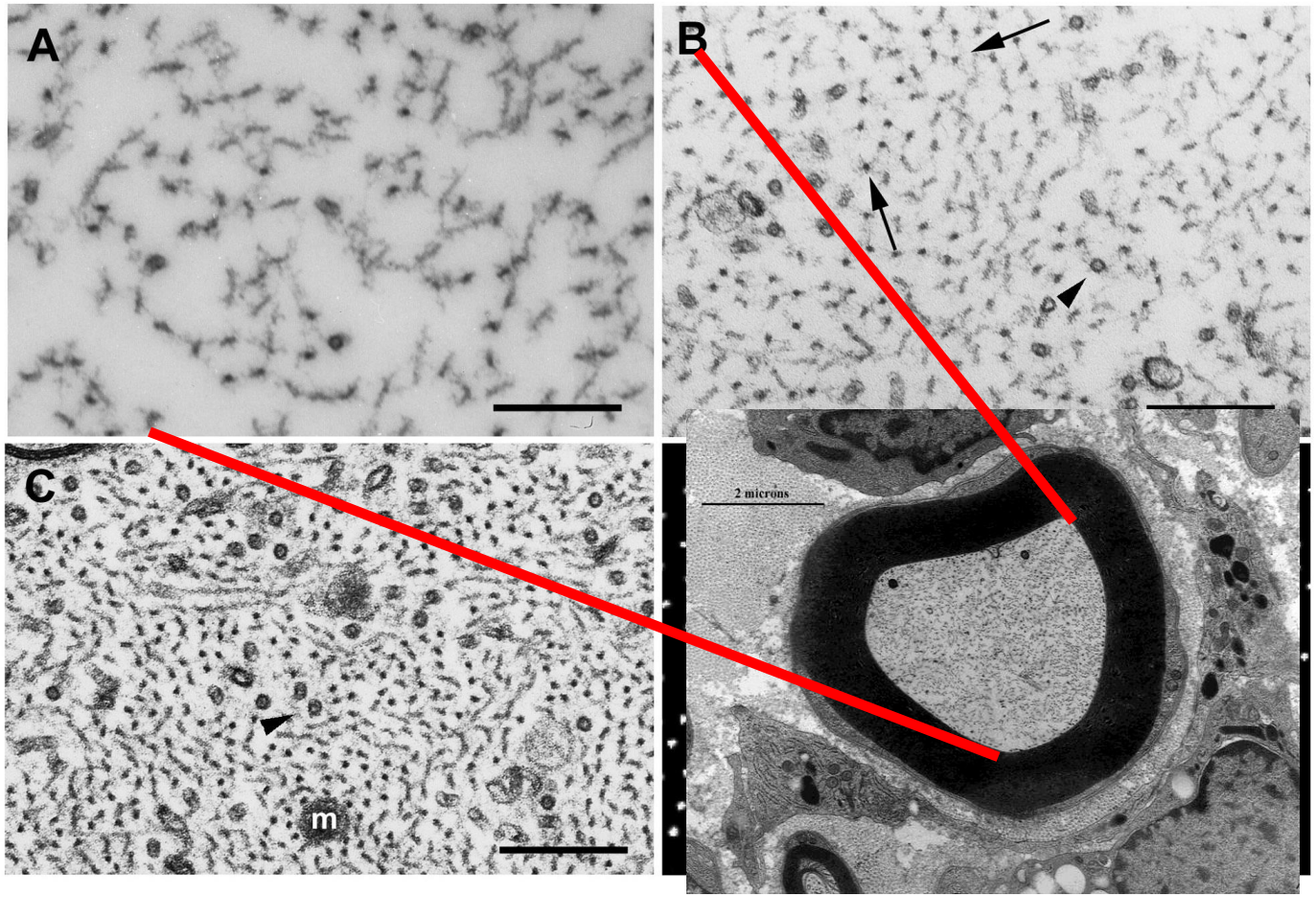


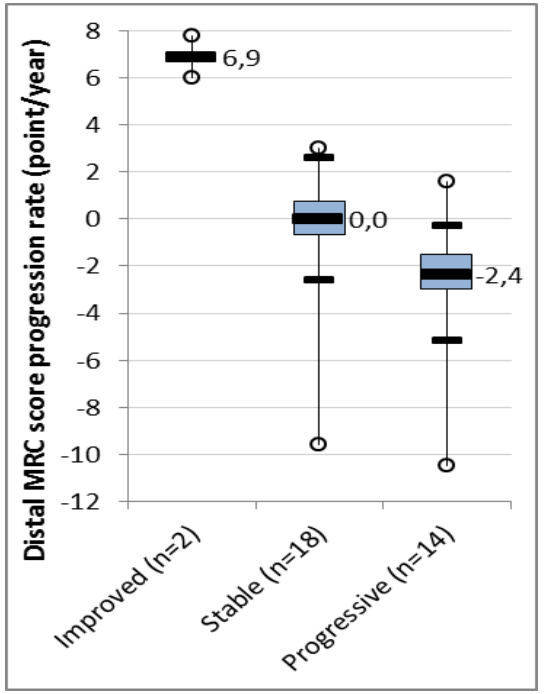


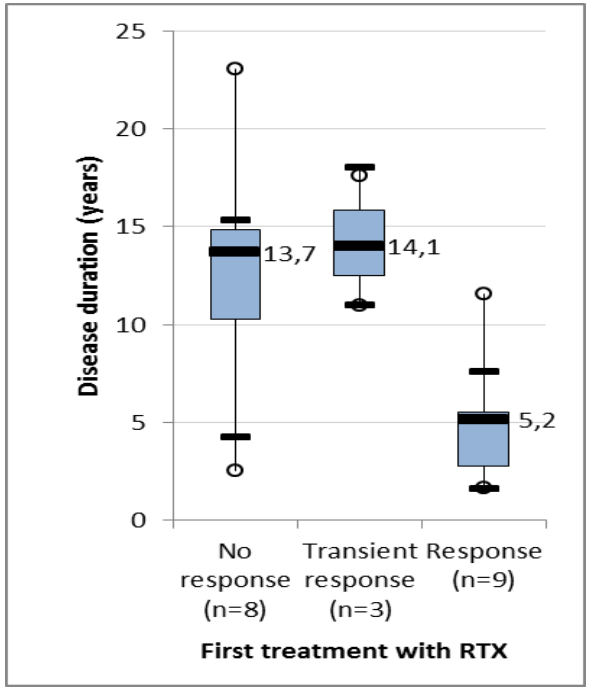
Wide spaced myelin

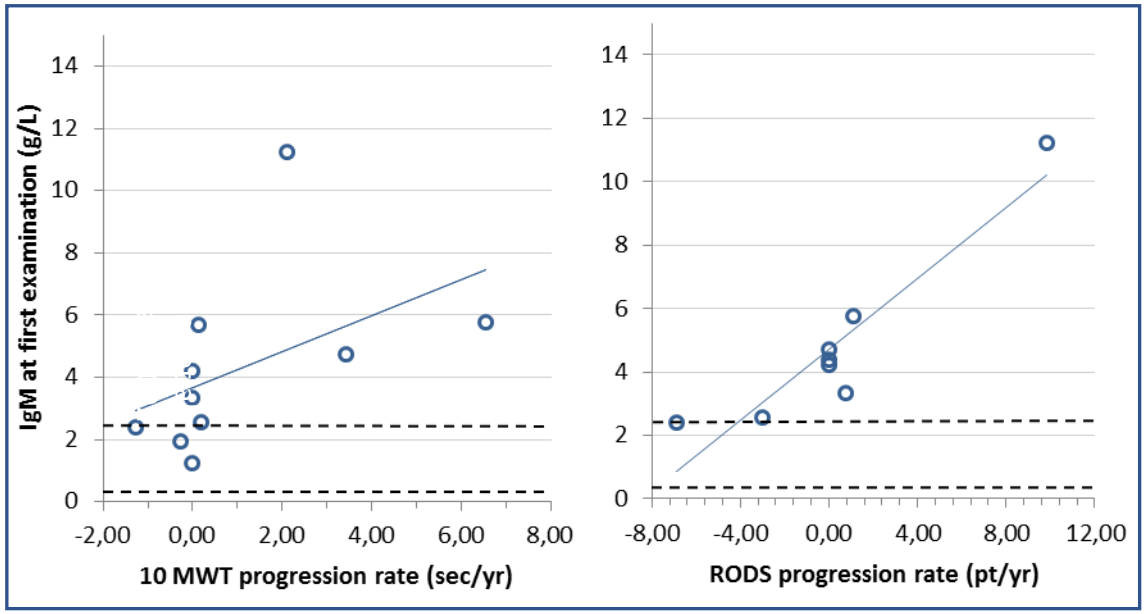


MBA-BF, methylene blue azure basic fuchsin. Lunn MP: Unpublished.









10 MWT, 10-meter walk test; IgM, immunoglobulin M; MRC, Medical Research Council; RODS, Rasch-built Overall Disability Scale; RTX, rituximab.
Pihan and Lunn 2014: Unpublished.

IgM paraproteinemic (anti-MAG) neuropathy treatment

- Is treatment required at all?
  - Elderly, male, mild ataxia, tremor, and unsteadiness – no falls
  - No weakness, distal PP loss, and VS to costal margin
  - IgMκ paraprotein and demyelinating neuropathy
  - Anti-MAG antibody positive >70,000 Bühlmann Units

Watch and wait…

You may do more good with a stick and some trainers…

IgM, immunoglobulin M; MAG, myelin-associated glycoprotein; PP, proprioception; VS, vibration sense.

IgM paraproteinemic (anti-MAG) neuropathy treatment

- Is treatment required at all?
  - Indications:
    - Hematologic
    - Progressive motor or sensory loss with instability
    - Progressive and disabling tremor
    - Younger age
    - Shorter disease duration

IgM, immunoglobulin M; MAG, myelin-associated glycoprotein.

IgM paraproteinemic (anti-MAG) neuropathy treatment

- “IVIg confers short-term benefit” – RCT
  - Multiple other immunosuppressants used
    - Melphalan, chlorambucil, cyclo +/- steroid, fludarabine

- Rituximab (anti-CD20) – promising in some studies
  - 8 non-randomized studies – 6 (79 pts) positive (1 (3 pts) negative)
  - 375 mg/m^2 usual dose – recent high-dose study added improvement
  - Several cases of worsening

IgM, immunoglobulin M; IVIg, intravenous immunoglobulin; MAG, myelin-associated glycoprotein; RCT, randomized controlled trial.
Comi G *et al*. *J Neurol* 2002; 249 (10): 1370–1377.

Immunotherapy for IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathies

Michael PT Lunn[1], Eduardo Nobile-Orazio[2]

[1]Department of Neurology and MRC Centre for Neuromuscular Diseases, National Hospital for Neurology and Neurosurgery, London, UK. [2]IRCCS Humanitas Clinical Institute, Neurology 2, Milan University, Milan, Italy

THE COCHRANE COLLABORATION®

Placebo-Controlled Trial of Rituximab in IgM Anti–Myelin-Associated Glycoprotein Antibody Demyelinating Neuropathy

Ann Neurol 2009;65:286–293

Marinos C. Dalakas, MD, Goran Rakocevic, MD, Mohammad Salajegheh, MD, James M. Dambrosia, PhD, Angelika F. Hahn, MD, Raghavan Raju, PhD, and Beverly McElroy, CNRN

Placebo-controlled trial of rituximab in IgM anti-myelin–associated glycoprotein neuropathy

Jean-Marc Léger, MD
Karine Viala, MD
For the RIMAG Study Group (France and Switzerland)

Neurology® 2013;80:2217-2225

IgM, immunoglobulin M.

Lunn MPT *et al. Cochrane Database Syst Rev*. 2016; 10 (10): CD002827. Dalakas MC *et al. Ann Neurol*. 2009; 65 (3): 286–293. Léger M-C *et al. Neurology* 2013; 80 (24): 2217–2225.

Figure 1: Numbers of patients improved on INCAT score at 8–12 months

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Dalakas 2009	4	13	0	13	12.8%	9.00 [0.53, 151.94]
Leger 2013	8	20	4	27	87.2%	2.70 [0.94, 7.73]
Total (95% CI)		**33**		**40**	**100.0%**	**3.51 [1.30, 9.45]**
Total events	12		4			

Heterogeneity: Chi² = 0.66, df = 1 (P = 0.41); I² = 0%
Test for overall effect: Z = 2.48 (P = 0.01)

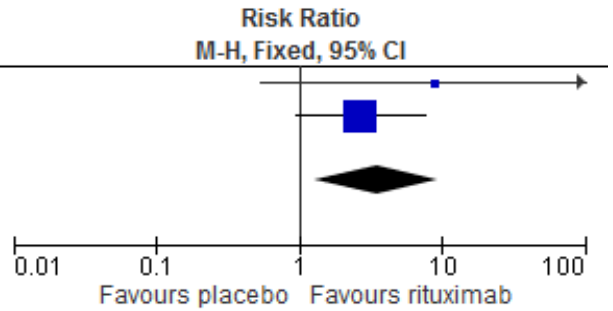


Figure 2: Improvement in INCAT score (whole and leg disability score) at 8–12 months

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Dalakas 2009	-0.38	0.67	13	0.09	0.7	13	58.7%	-0.47 [-1.00, 0.06]
Leger 2013	-0.2	1.28	20	0.22	0.75	27	41.3%	-0.42 [-1.05, 0.21]
Total (95% CI)			**33**			**40**	**100.0%**	**-0.45 [-0.85, -0.05]**

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.90); I² = 0%
Test for overall effect: Z = 2.18 (P = 0.03)

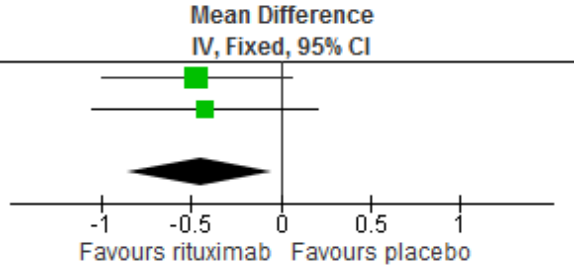


Figure 3: Numbers of patients improved or stabilized on PGIC 8–12 months

Study or Subgroup	Rituximab Events	Rituximab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Dalakas 2009	12	13	7	13	44.8%	1.71 [1.01, 2.90]
Leger 2013	15	19	10	25	55.2%	1.97 [1.16, 3.36]
Total (95% CI)		**32**		**38**	**100.0%**	**1.86 [1.27, 2.71]**
Total events	27		17			

Heterogeneity: Chi² = 0.14, df = 1 (P = 0.71); I² = 0%
Test for overall effect: Z = 3.20 (P = 0.001)

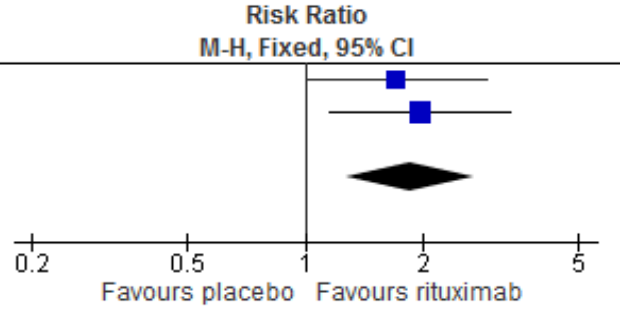
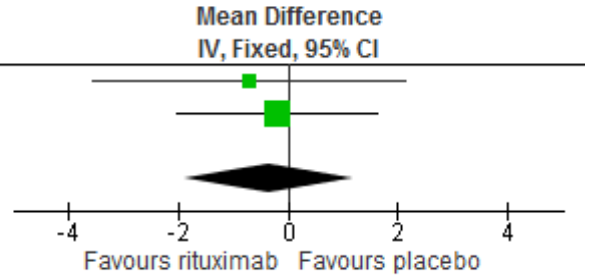


Figure 4: Improvement in 10-meter walk (s) at 8–12 months

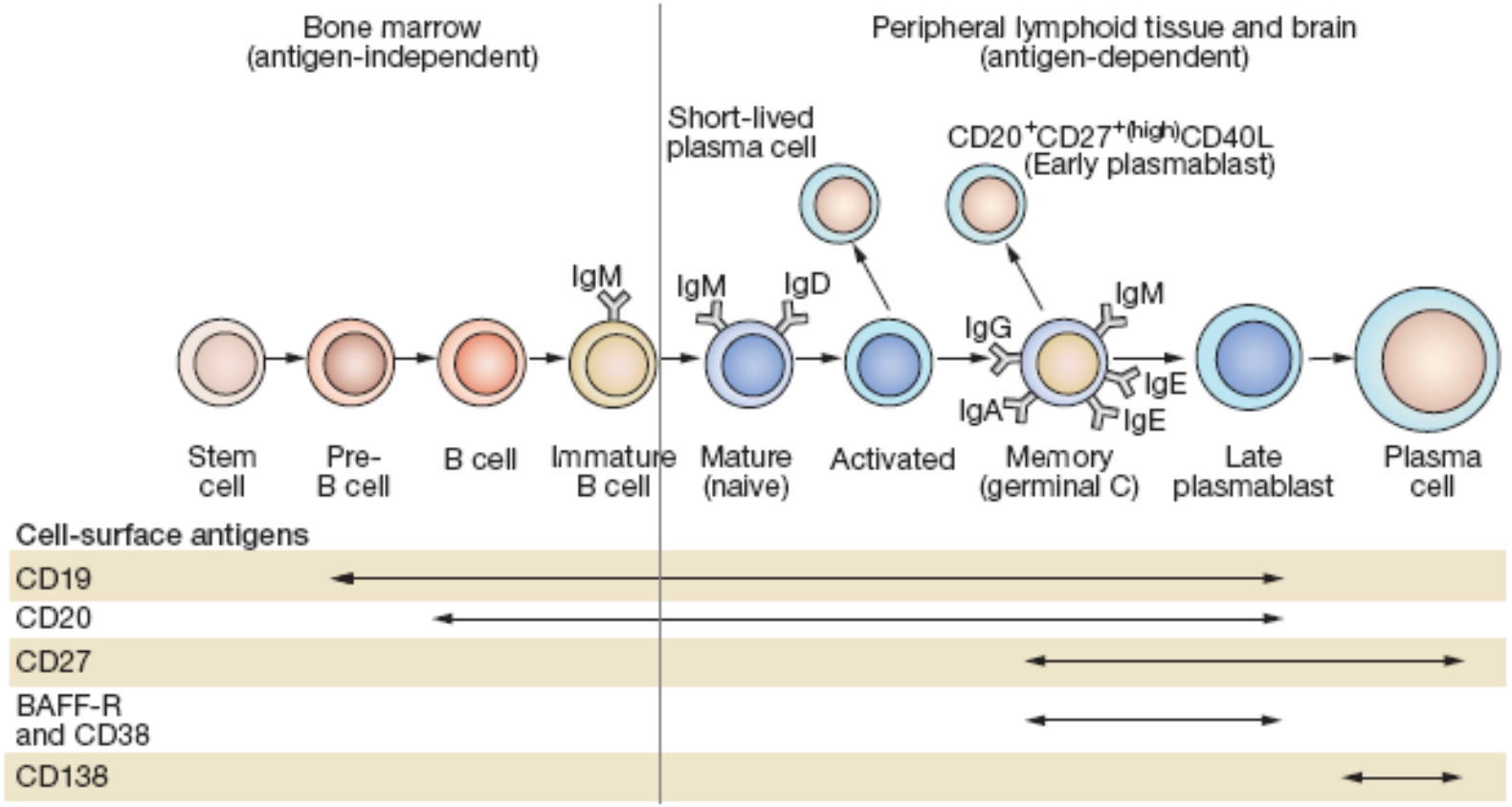
Study or Subgroup	Rituximab Mean	Rituximab SD	Rituximab Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Dalakas 2009	-0.9	3.2	13	-0.2	4.15	13	29.2%	-0.70 [-3.55, 2.15]
Leger 2013	-0.3	3.2	18	-0.1	2.7	24	70.8%	-0.20 [-2.03, 1.63]
Total (95% CI)			**31**			**37**	**100.0%**	**-0.35 [-1.89, 1.19]**

Heterogeneity: Chi² = 0.08, df = 1 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.44 (P = 0.66)



INCAT, Inflammatory Neuropathy Cause and Treatment; PGIC, Patients' Global Impression of Change.
Lunn MPT *et al. Cochrane Database Syst Rev*. 2016; 10 (10): CD002827

Rituximab: Efficiencies and deficiencies



Ig, immunoglobulin.
Dalakas MC. *Nat Clin Pract Neurol* 2008; 4 (10): 557–567.

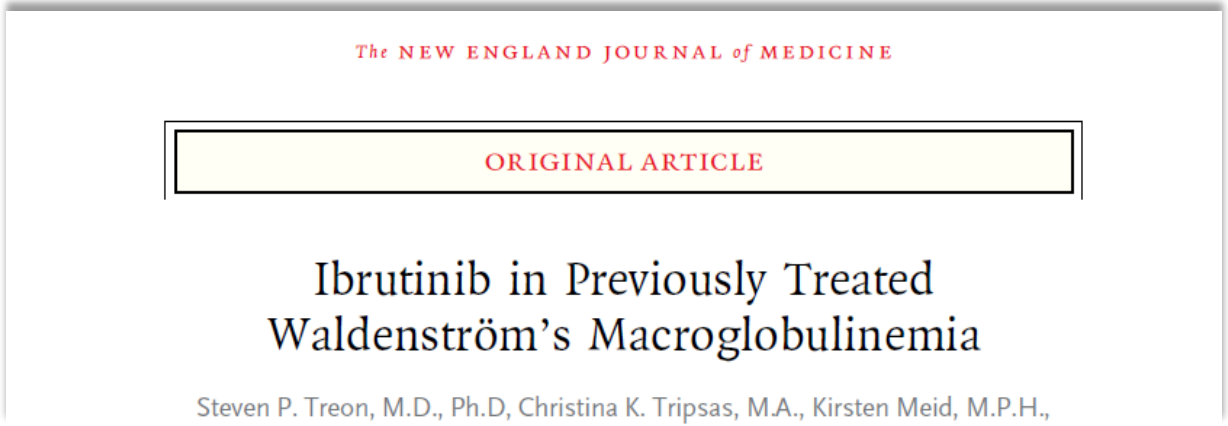
Other options?

- No studies
- Anti-MAG neuropathy seldom serious enough for some?

- Dexamethasone, rituximab, and cyclophosphamide
- Rituximab + bendamustine? Rituximab + fludarabine?
- Combination rituximab and BTK inhibitor?
- New-generation BTK inhibitors (no trials)
- Proteasome inhibitors
- Bortezomib – issues
- Carfilzomib

- Collaborative clinical trials needed with neurology, hematology, and pharma

MAG, myelin-associated glycoprotein; R, rituximab.



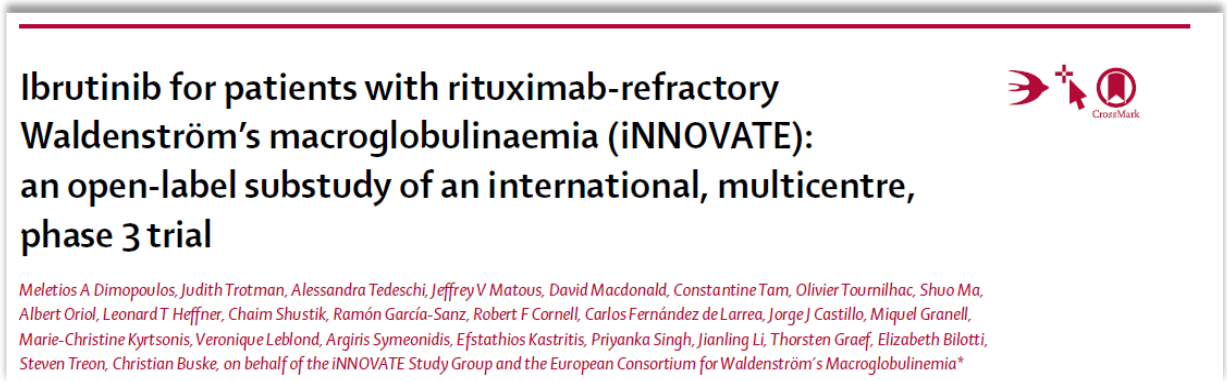
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ibrutinib in Previously Treated Waldenström's Macroglobulinemia

Steven P. Treon, M.D., Ph.D, Christina K. Tripsas, M.A., Kirsten Meid, M.P.H.,

- 9/63 patients with neuropathy treated for neuropathy
- ≥1 previous treatment
- 5 improved
- 4 stabilized
- No objective neuro measures



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

Meletios A Dimopoulos, Judith Trotman, Alessandra Tedeschi, Jeffrey V Matous, David Macdonald, Constantine Tam, Olivier Tournilhac, Shuo Ma, Albert Oriol, Leonard T Heffner, Chaim Shustik, Ramón García-Sanz, Robert F Cornell, Carlos Fernández de Larrea, Jorge J Castillo, Miquel Granell, Marie-Christine Kyrtsonis, Veronique Leblond, Argiris Symeonidis, Efstathios Kastritis, Priyanka Singh, Jianling Li, Thorsten Graef, Elizabeth Bilotti, Steven Treon, Christian Buske, on behalf of the iNNOVATE Study Group and the European Consortium for Waldenström's Macroglobulinemia*

- Rituximab–refractory
- 4/31 patients with neuropathy
- 2 improved – one total
- 2 stabilized
- No objective neuro measures

ARTICLE OPEN ACCESS CLASS OF EVIDENCE

The Bruton tyrosine kinase inhibitor ibrutinib improves anti-MAG antibody polyneuropathy

Francesca Castellani, MD,* Andrea Visentin, MD, PhD,* Marta Campagnolo, MD, Alessandro Salvalaggio, MD, Mario Cacciavillani, MD, PhD, Cinzia Candiotto, PhD, Roberta Bertorelle, MD, Livio Trentin, MD, and Chiara Briani, MD

Correspondence
Dr. Briani
chiara.briani@unipd.it

Neurol Neuroimmunol Neuroinflamm 2020;7:e720. doi:10.1212/NXI.0000000000000720

- 3 patients
- 2 rituximab–refractory
- All improved subjectively and objectively with measured changes

MAG, myelin-associated glycoprotein.

Treon SP *et al. N Engl J Med* 2015; 372 (15): 1430–1440. Dimopolous MA *et al. Lancet Oncol*. 2017; 18 (2): 241–250. Castellani F *et al. Neurol Neuroimmunol Neuroinflamm* 2020; 7 (4): e720.

IgM paraproteinemic (anti-MAG) neuropathy treatment

- Are you treating the right thing?
  - 62-year-old female
  - Long history of severe osteoarthritis and immobility
  - Smoker
  - Numb, painful red feet, and ‘venous ulcers’
  - Pronounced distal motor loss; PP=VS/JPS loss
  - Demyelinating neurophysiology
  - 4 × IgMκ paraproteins and ‘positive’ anti-MAG antibodies

IgM, immunoglobulin M; JPS, joint position sense; MAG, myelin-associated glycoprotein; PP, proprioception; VS, vibration sense.

IgM paraproteinemic (anti-MAG) neuropathy treatment

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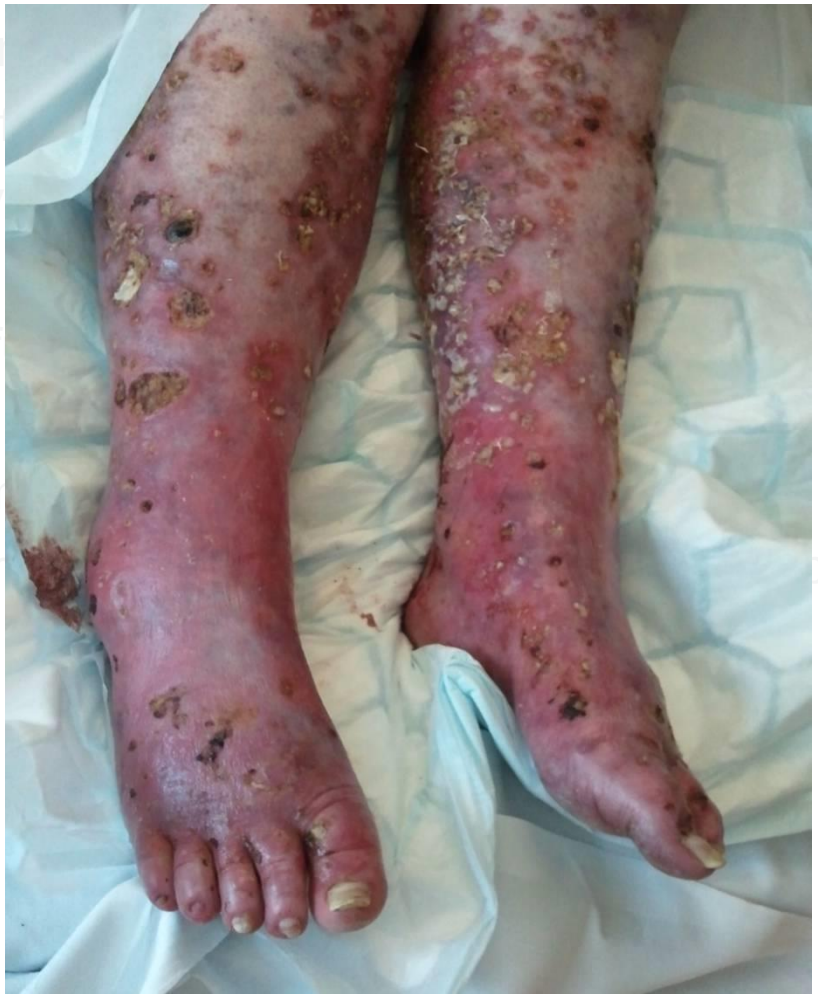

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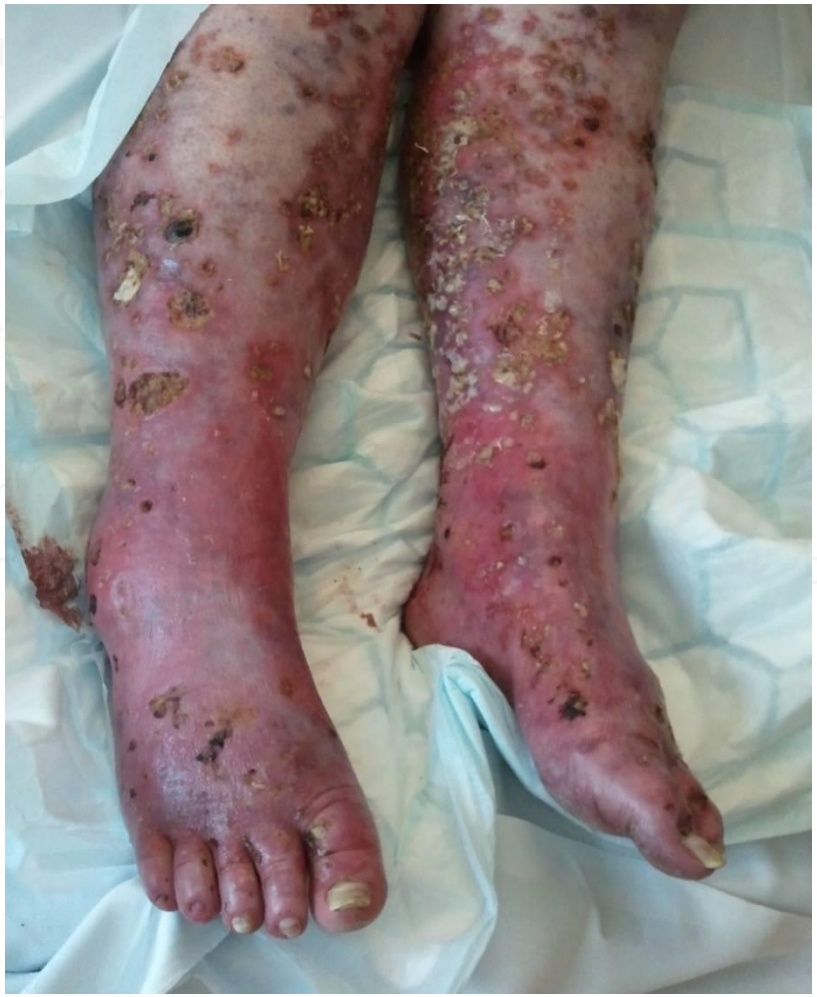

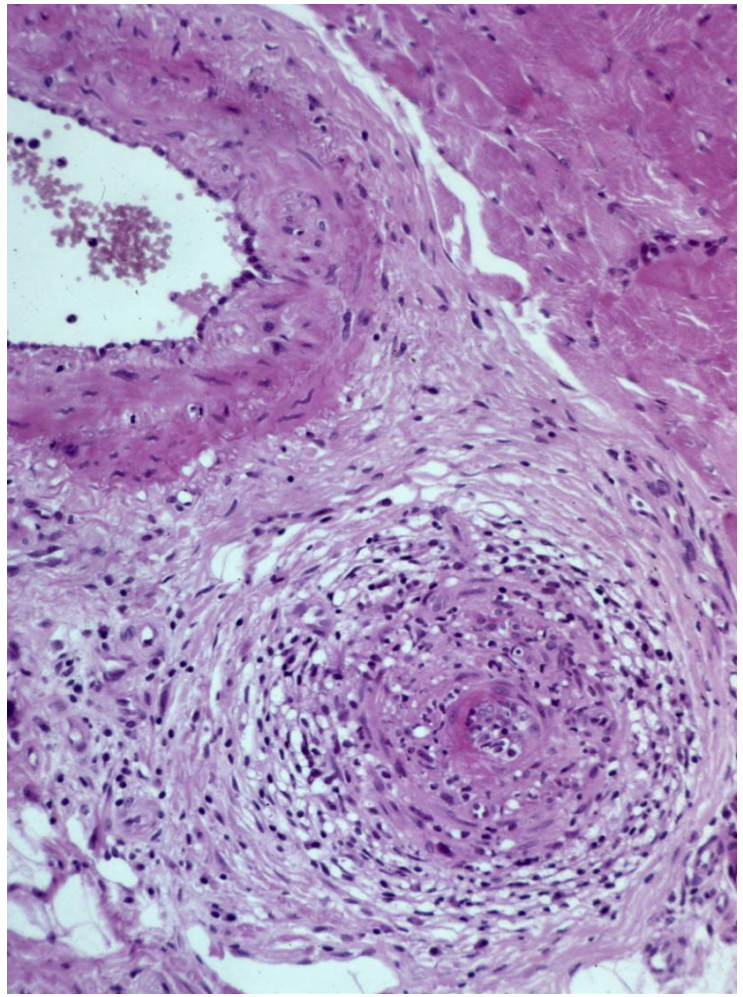

IgM, immunoglobulin M; MAG, myelin-associated glycoprotein.

IgM paraproteinemic (anti-MAG) neuropathy treatment

- Are you treating the right thing?
  - 62-year-old female
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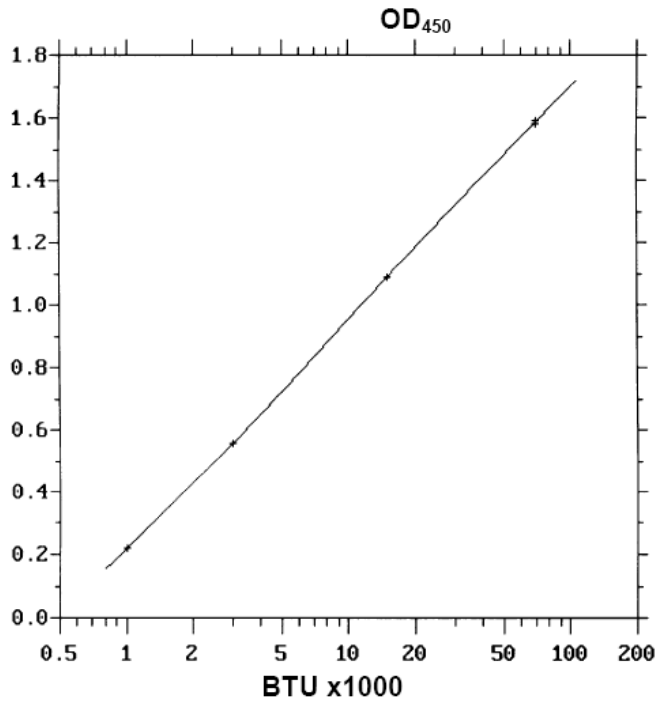
  - Smoker
  - Numb, painful red feet, and ‘venous ulcers’
  - Pronounced distal motor loss; PP=VS/JPS loss
  - Demyelinating neurophysiology
  - 4 × IgMκ paraproteins and ‘positive’ anti-MAG antibodies

- Vasculitis and acquired erythermalgia with vasculitic neuropathy
- CD138 <5% plasma cells but IgMκ restricted – ‘appearances are suggestive of myeloma than lymphoplasmacytic lymphoma… IgM very rare’*

*Quote from patient report.
IgM, immunoglobulin M; JPS, joint position sense; MAG, myelin-associated glycoprotein; PP, proprioception; VS, vibration sense.

The Bühlmann anti-MAG ELISA

- Used by almost every neuroimmunology laboratory
- Ubiquitous and easy to use
- Unclear what the antigen is and highly sensitive



Report	Titer
Negative	<1,000 Bühlmann Units
Weak positive	1,000–7,000 Bühlmann Units
Positive	7,000–70,000 Bühlmann Units
Strong positive	>70,000 Bühlmann Units

Caution in interpretation of results:
positive is not necessarily ‘positive’

BTU, Bühlmann Titer Units; ELISA, enzyme-linked immunosorbent assay; MAG, myelin-associated glycoprotein.

WM and direct invasion (1)

- 43-year-old male – 18.12.2013
- Sept 2013 – progressive numbness and tingling forefeet and fingers to knees/elbow
- Shooting pain and cramping in legs
- Loss of distal power and dexterity
- Occasional falls
- No autonomic or cranial nerve involvement
  - Mild tinnitus
- 3-stone weight loss

WM and direct invasion (2)

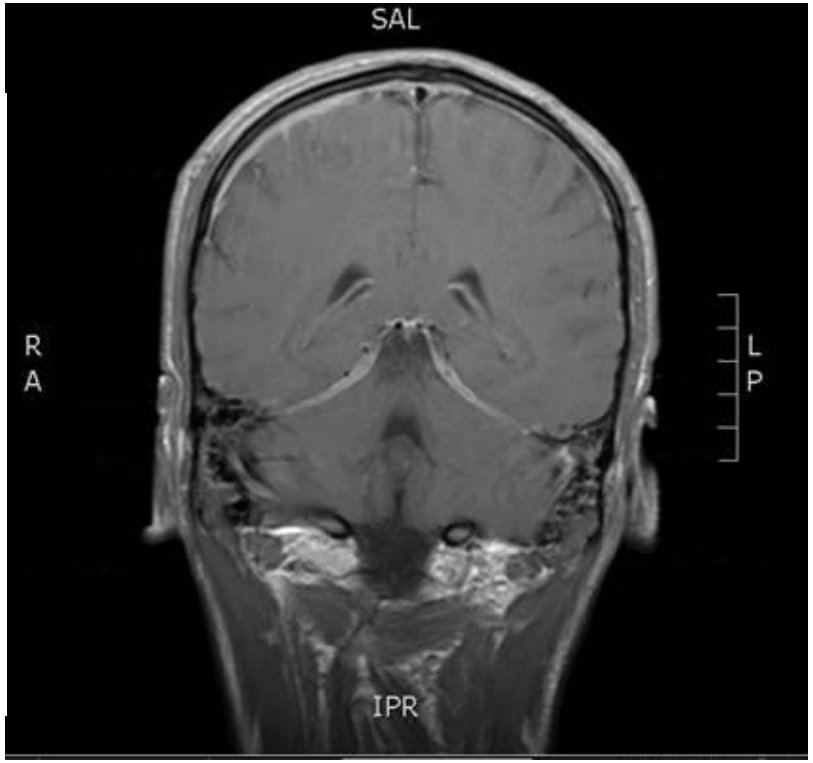
- Past medical history
  - Waldenstrom’s macroglobulinemia Dec 2011 – 30 g/L IgMκ paraprotein
- Treatment with six cycles of R-CVP with vincristine dose limitation
- Good response (30 g/L to 10 g/L)
- Mild vincristine neuropathy reducing

- Being hematologically monitored

IgM, immunoglobulin M; R-CVP, rituximab, cyclophosphamide, vincristine, and prednisone; WM, Waldenström’s macroglobulinemia.

A case of…

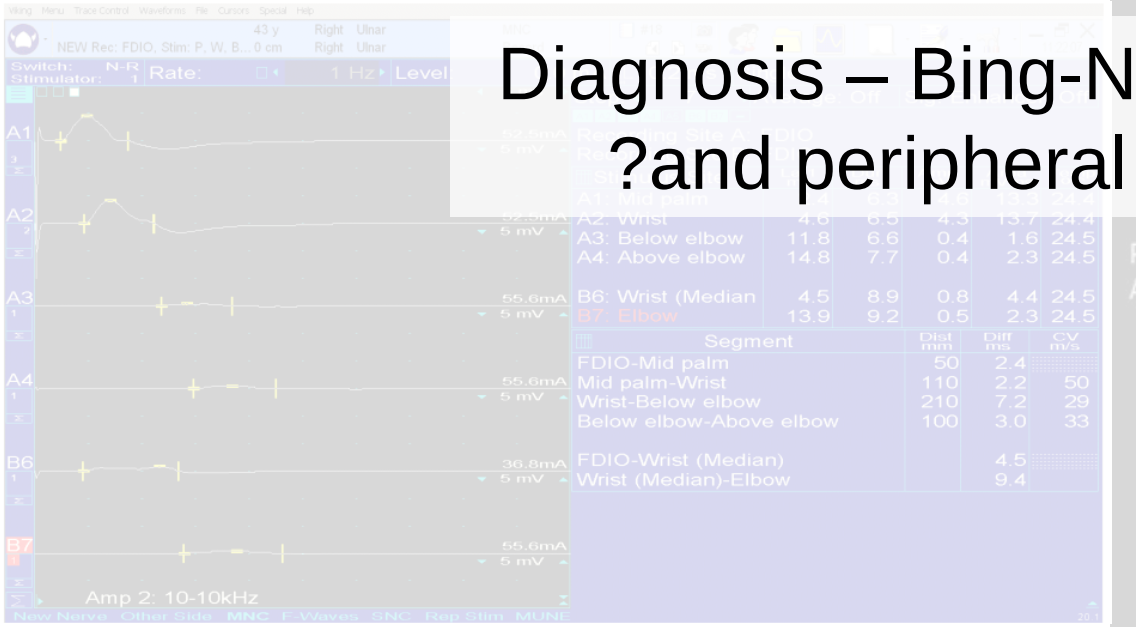
- CSF protein 3.45 g/L; CSF 12 WCC/cumm - lymphs – too few for flow
- IgMκ paraprotein 24 g/L
- Anti-MAG negative

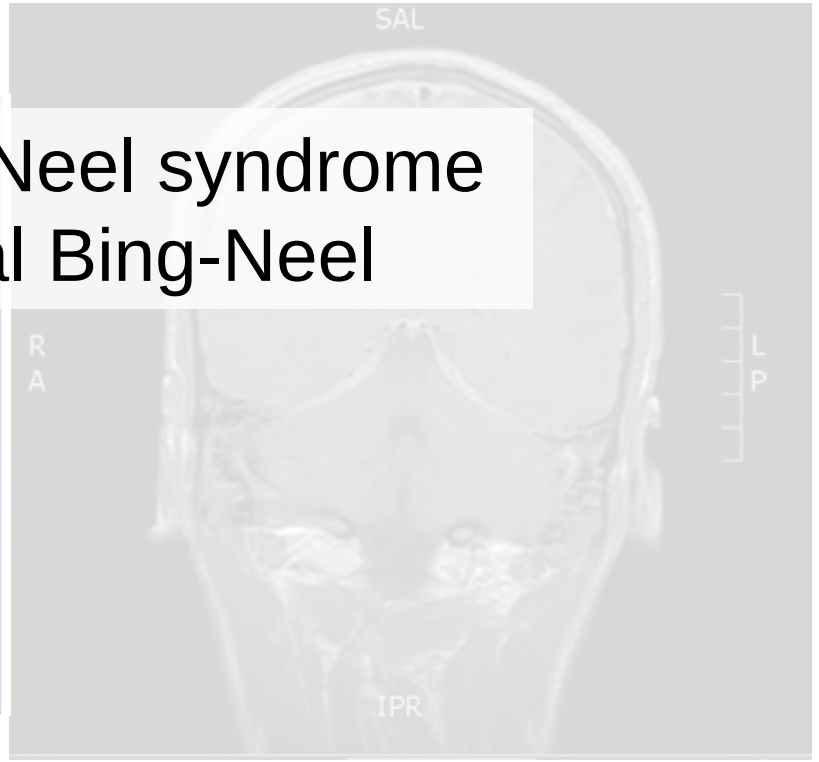


CSF, cerebrospinal fluid; MAG, myelin-associated glycoprotein.

Bing-Neel syndrome

- CSF protein 3.45 g/L; CSF 12 WCC/cumm - lymphs – too few for flow
- IgMκ paraprotein 24 g/L
- Anti-MAG negative

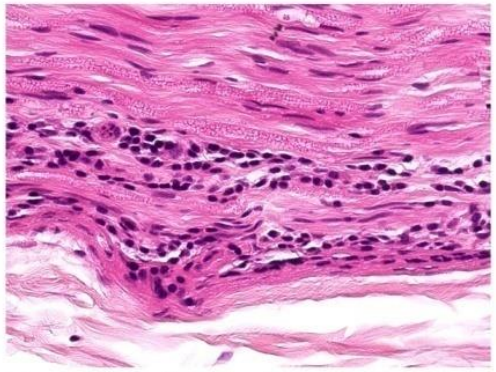


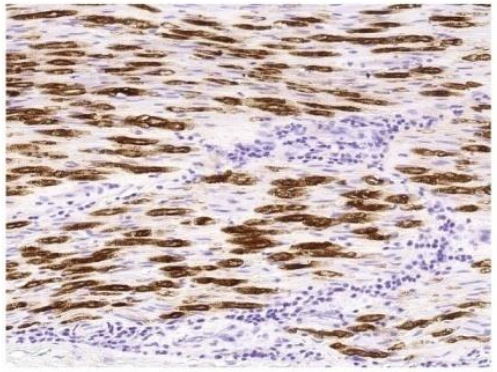


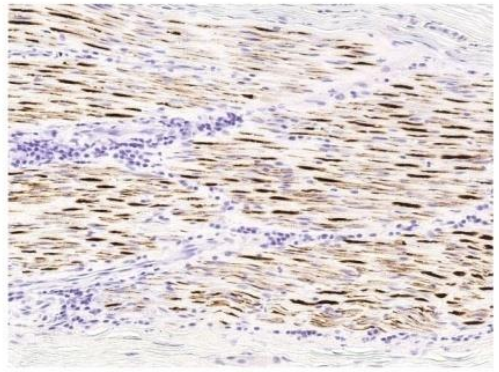
Diagnosis – Bing-Neel syndrome
?and peripheral Bing-Neel

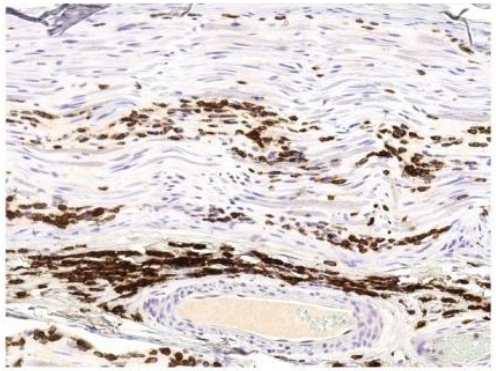
CSF, cerebrospinal fluid; MAG, myelin-associated glycoprotein.

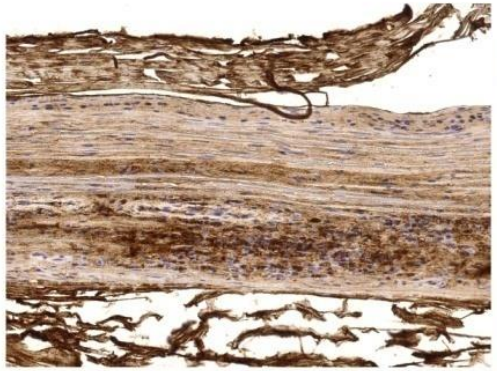
Neuropathology: Bing-Neel Syndrome of the periphery?

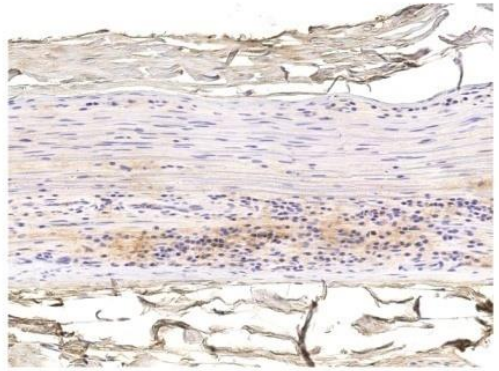

Haematoxylin&Eosin

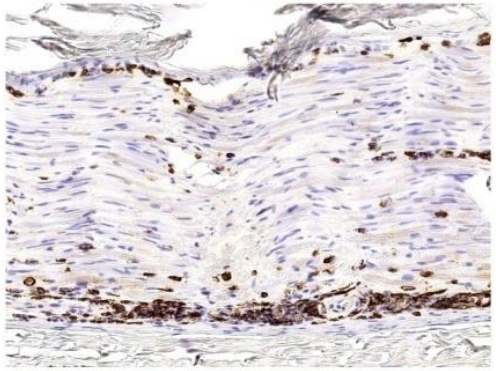

Myelin (SMI94)

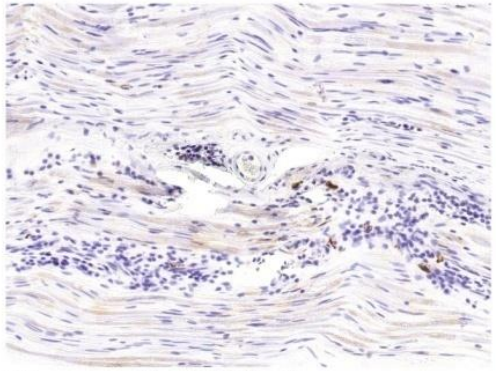

Axons (neurofilament cocktail)

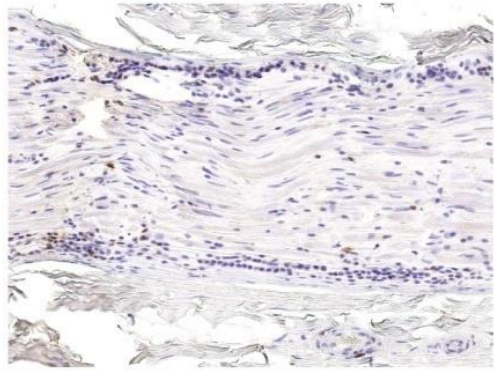

B lymphocytes,
including plasmacytoid (CD79a)


Kappa light chains


Lambda light chains


B lymphocytes (CD20)


Plasma cells (CD138)


T lymphocytes (CD3)

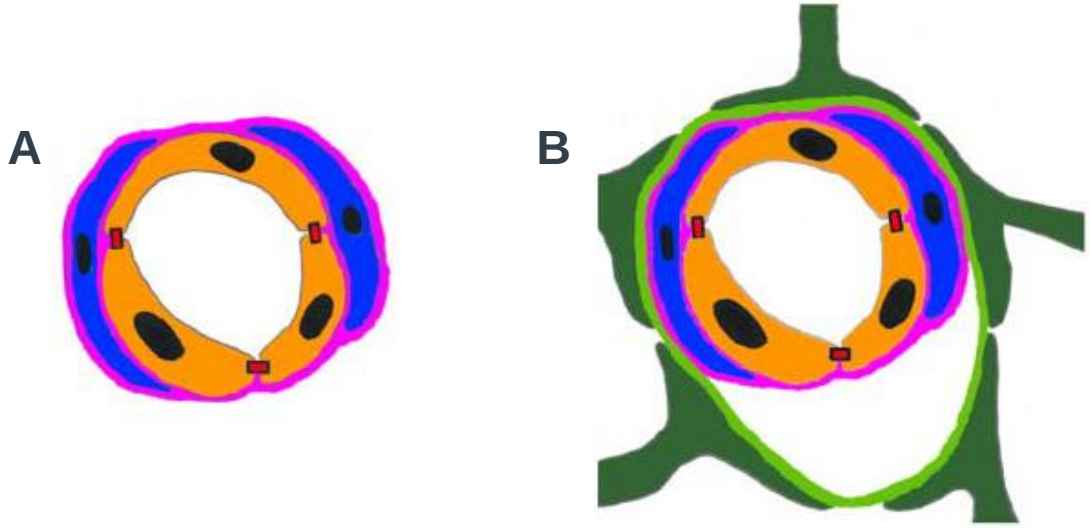
Scale bar: 100μm

Lunn: Unpublished.

The blood–nerve barrier[1,2]

- Intraneural homeostasis
- The perineurium is important but the BNB critical
- Non-fenestrated, pinocytic vesicle-poor, active exchange interface
- Macromolecular permeability of the BNB is probably equivalent to the BBB

Basic features of the A) BNB and B) BBB[2]



Endothelial cells (orange) of the BNB (A) and BBB (B) are connected by tight junctions (red rectangles) and embedded in a single basement membrane (pink) with surrounding pericytes (blue). In the BBB, the second basement membrane (light green) wraps the whole endothelial cell / first basement membrane / pericyte complex, and the astrocytic endfoot layer (dark green) surrounds the outer surface.

BBB, blood–brain barrier; BNB, blood–nerve barrier.

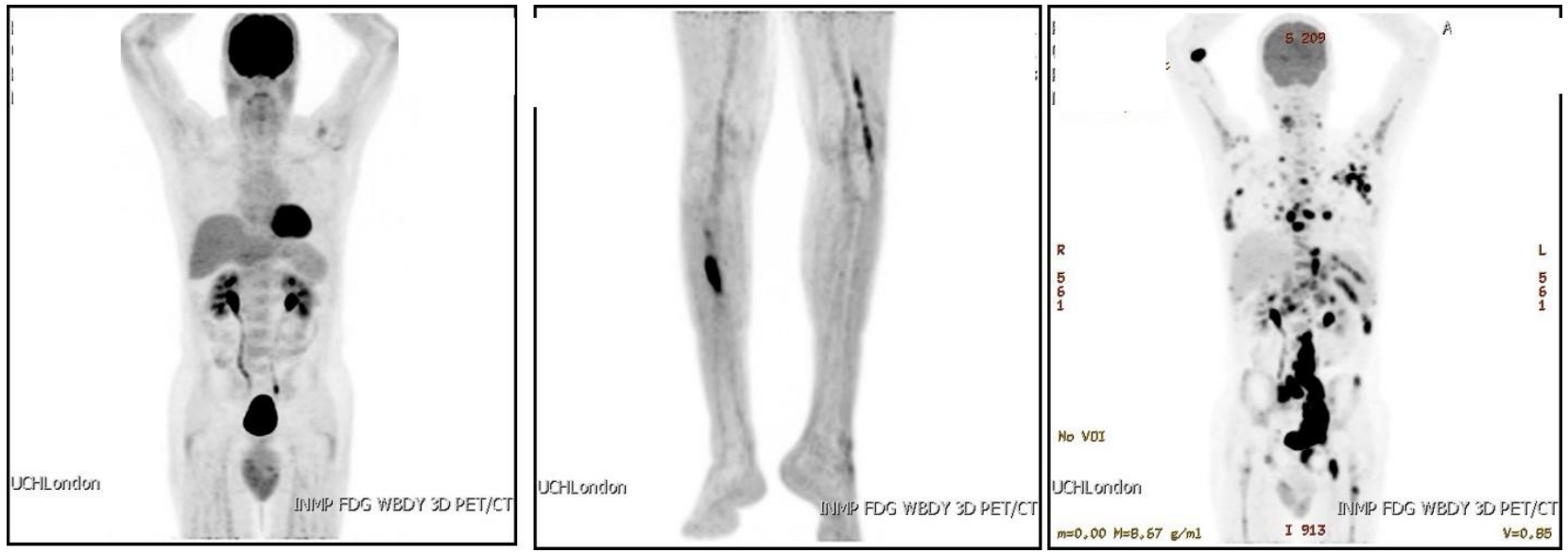
Poduslo JF *et al. Proc Natl Acad Sci USA* 1994; 91 (12): 5705–5709. Kanda T. *J Neurol Neurosurg Psychiatry* 2013 84 (2): 208–212.

The need to get behind the blood–nerve barrier

Primary sciatic nerve lymphoma: a case report and review of the literature

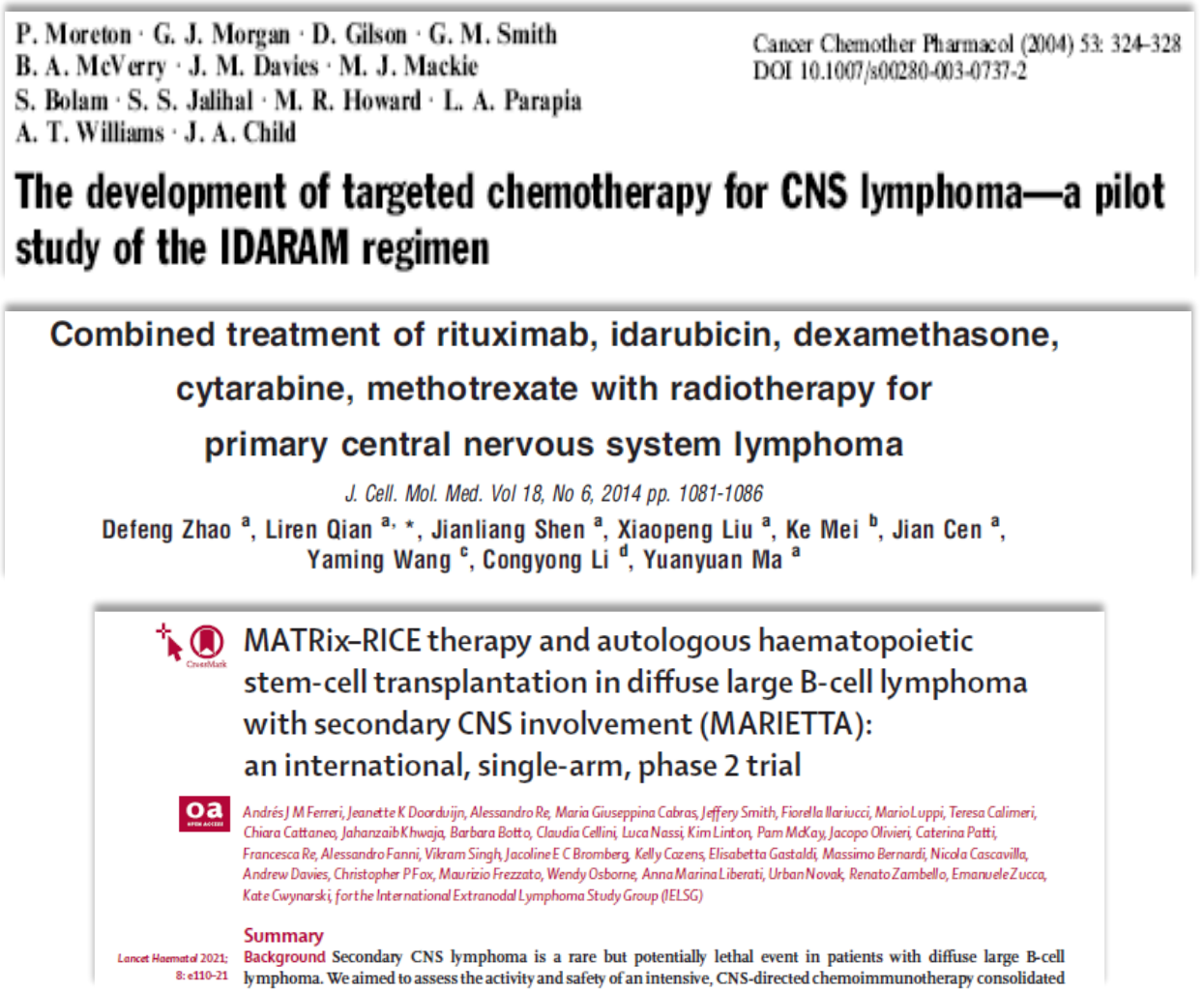
M J L Descamps, L Barrett, M Groves, L Yung, R Birch, N M F Murray, D C Linch, M P T Lunn, M M Reilly

J Neurol Neurosurg Psychiatry 2006;**77**:1087–1089. doi: 10.1136/jnnp.2006.087577



Descamps MJL *et al. J Neurol Neurosurg Psychiatry. 2006*; 77 (9): 1087–1089. Image from patient report.

Chemotherapy: Individualized ‘borrowed’ treatment



P. Moreton · G. J. Morgan · D. Gilson · G. M. Smith
B. A. McVerry · J. M. Davies · M. J. Mackie
S. Bolam · S. S. Jalihal · M. R. Howard · L. A. Parapia
A. T. Williams · J. A. Child

Cancer Chemother Pharmacol (2004) 53: 324–328
DOI 10.1007/s00280-003-0737-2

The development of targeted chemotherapy for CNS lymphoma—a pilot study of the IDARAM regimen

Combined treatment of rituximab, idarubicin, dexamethasone, cytarabine, methotrexate with radiotherapy for primary central nervous system lymphoma

J. Cell. Mol. Med. Vol 18, No 6, 2014 pp. 1081-1086

Defeng Zhao [a], Liren Qian [a, *], Jianliang Shen [a], Xiaopeng Liu [a], Ke Mei [b], Jian Cen [a], Yaming Wang [c], Congyong Li [d], Yuanyuan Ma [a]

MATRix–RICE therapy and autologous haematopoietic stem-cell transplantation in diffuse large B-cell lymphoma with secondary CNS involvement (MARIETTA): an international, single-arm, phase 2 trial

oa

Andrés J M Ferreri, Jeanette K Doorduijn, Alessandro Re, Maria Giuseppina Cabras, Jeffery Smith, Fiorella Ilariucci, Mario Luppi, Teresa Calimeri, Chiara Cattaneo, Jahanzaib Khwaja, Barbara Botto, Claudia Cellini, Luca Nassi, Kim Linton, Pam McKay, Jacopo Olivieri, Caterina Patti, Francesca Re, Alessandro Fanni, Vikram Singh, Jacoline E C Bromberg, Kelly Cazens, Elisabetta Gastaldi, Massimo Bernardi, Nicola Cascavilla, Andrew Davies, Christopher P Fox, Maurizio Frezzato, Wendy Osborne, Anna Marina Liberati, Urban Novak, Renato Zambello, Emanuele Zucca, Kate Cwynarski, for the International Extranodal Lymphoma Study Group (IELSG)

Lancet Haematol 2021; 8: e110–21

Summary

Background Secondary CNS lymphoma is a rare but potentially lethal event in patients with diffuse large B-cell lymphoma. We aimed to assess the activity and safety of an intensive, CNS-directed chemoimmunotherapy consolidated

CNS, central nervous system; IDARAM, idarubicin, dexamethasone, cytarabine, methotrexate.

Moreton P *et al. Cancer Chemother. Pharmacol*. 2004; 53 (4): 324–328. Zhao D *et al. J Cell Mol Med*. 2014; 18 (6): 1081–1086. Ferreri AJM *et al. Lancet Haematol*. 2021; 8 (2): e110–e121.

What do we need?

- Cohorts of patients
  - Collaborations
    - Neurology, Hematology, and Neurology and Hematology
    - Interinstitutional

- Accurate diagnosis
  - Clinical, electrophysiological, serum, and tissue
- Coherent and logical drug combinations
- Randomized trials of classic or novel design

IgM-related neuropathies: Summary

- Many and very different
  - Anti-MAG
  - Vasculitis
  - Direct invasion
  - Light-chain amyloidosis / light-chain deposition disease
- Differentiated by careful history-taking and examination
- Indolent and difficult to treat
- Treatment not always required
- New randomized controlled trials

IgM, immunoglobulin M; MAG, myelin-associated glycoprotein.

Cardiovascular toxicities associated with BTK inhibitors: A case study and review

Professor Véronique Leblond
Pitié-Salpêtrière Hospital &
Sorbonne University, France

Dr. Joe-Elie Salem
Pitié-Salpêtrière Hospital &
Sorbonne University, France

(Adjunct Associate Professor
VUMC, USA)

Disclosures

Professor Leblond

- **Speaker bureau:** Roche, Gilead, Janssen, AbbVie, BeiGene, GSK
- **Board:** Roche, Pharmacyclics, Janssen-Cilag, GSK, Gilead, AstraZeneca, AbbVie
- **Honoraria:** Roche, Pharmacyclics, Janssen-Cilag, GSK, Gilead, Lilly, Amgen, AstraZeneca, BeiGene

Dr. Salem

- **Speaker bureau:** BeiGene, AstraZeneca, BMS
- **Board:** BMS
- **Honoraria:** BMS

Initial case presentation: Mrs F

Patient

- 76-year-old female

Cardiovascular risk factors

- Active smoker, prediabetes
- Treatments: Aspirin 75 mg/day

Medical history

- WM diagnosed in 2016
  - *MYD88*^{MUT}/*CXCR4*^{WT}
- In remission for 3 years after 6 cycles of rituximab and bendamustine

In 2020

- Fatigue, shortness-of-breath
- Normal physical examination

Laboratory studies

Hemoglobin	8.9 g/dL
Platelets	120 × 10^9/L
WBC	3.7 × 10^9/L
PMN	62%
Serum creatinine	1.3 mg/dL
M spike	2.3 g/dL
IgM	3,700 mg/dL
24h urinary protein	Normal

IgM, immunoglobulin M; MUT, mutated; PMN, polymorphonuclear leukocyte; WBC, white blood cell; WM, Waldenström's macroglobulinemia; WT, wild-type.

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In 2020

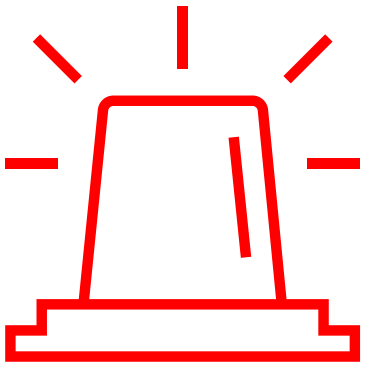
- Fatigue, shortness-of-breath
- Normal physical examination

Treatment by ibrutinib: 420 mg/day started in March 2020

• Platelets	120 × 10^9/L
• WBC	3.7 × 10^9/L
• PMN	62%
• Serum creatinine	1.3 mg/dL
• M spike	2.3 g/dL
• IgM	3,700 mg/dL
• 24h urinary protein	Normal

IgM, immunoglobulin M; MUT, mutated; PMN, polymorphonuclear leukocyte; WBC, white blood cell; WM, Waldenström's macroglobulinemia; WT, wild-type.

What are the **main cardiovascular toxicities** we should think about in the follow-up of patients on **ibrutinib**?



Cardiovascular toxicities associated with ibrutinib (1)

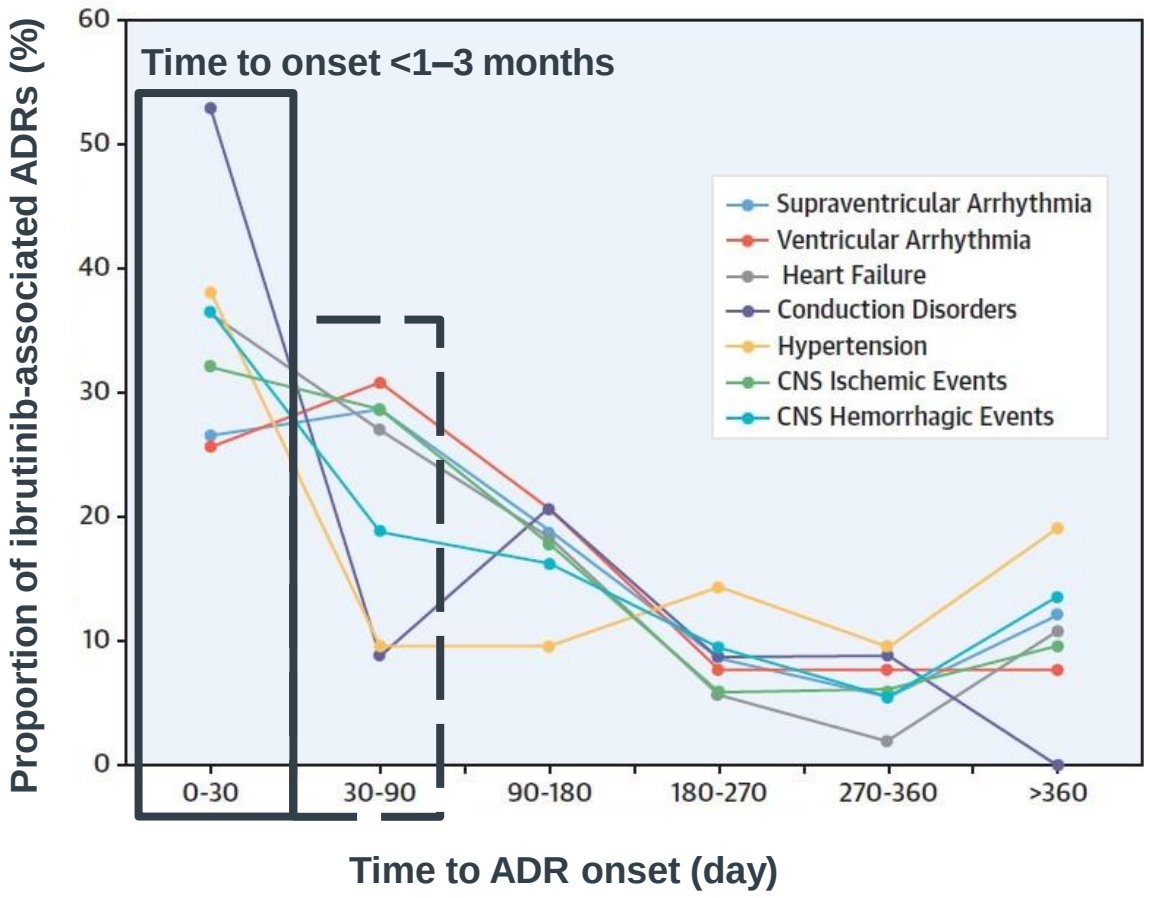
- Ibrutinib cardiovascular adverse drug reactions identified using the international pharmacovigilance database VigiBase
  - **16,343,451 safety case reports**

	Until January 2018	Ibrutinib, n (%)	IC_{025}
FDA FDA	**Cardiac supraventricular arrhythmias**	**959** (7.07%)	**3.97**
	CNS hemorrhagic events	**505** (3.72%)	**1.63**
New signal	**Heart failure**	**363** (2.67%)	**1.46**
FDA	**Cardiac ventricular arrhythmias**	**70** (0.52%)	**0.96**
New signal	**Cardiac conduction disorders**	**50** (0.37%)	**0.76**
New signal	**CNS ischemic events**	**254** (1.87%)	**0.73**
FDA	**Hypertension**	**295** (2.17%)	**0.40**
	Cardiac valve disorders	30 (0.22%)	−0.07
	Myocardial infarction	149 (1.10%)	−0.11
	Cardiac death or shock	131 (0.97%)	−0.13
	Venous thromboembolic events	108 (0.80%)	−0.34
	Vascular neoplasms	2 (0.01%)	−2.72
	Pulmonary hypertension	19 (0.14%)	−1.14
	Hyperglycemia, diabetes	112 (0.83%)	−1.07
	Torsade de pointes / QT prolongation	9 (0.07%)	−2.01
	Myocarditis	2 (0.01%)	−3.61
	Dyslipidemia	14 (0.10%)	−2.75

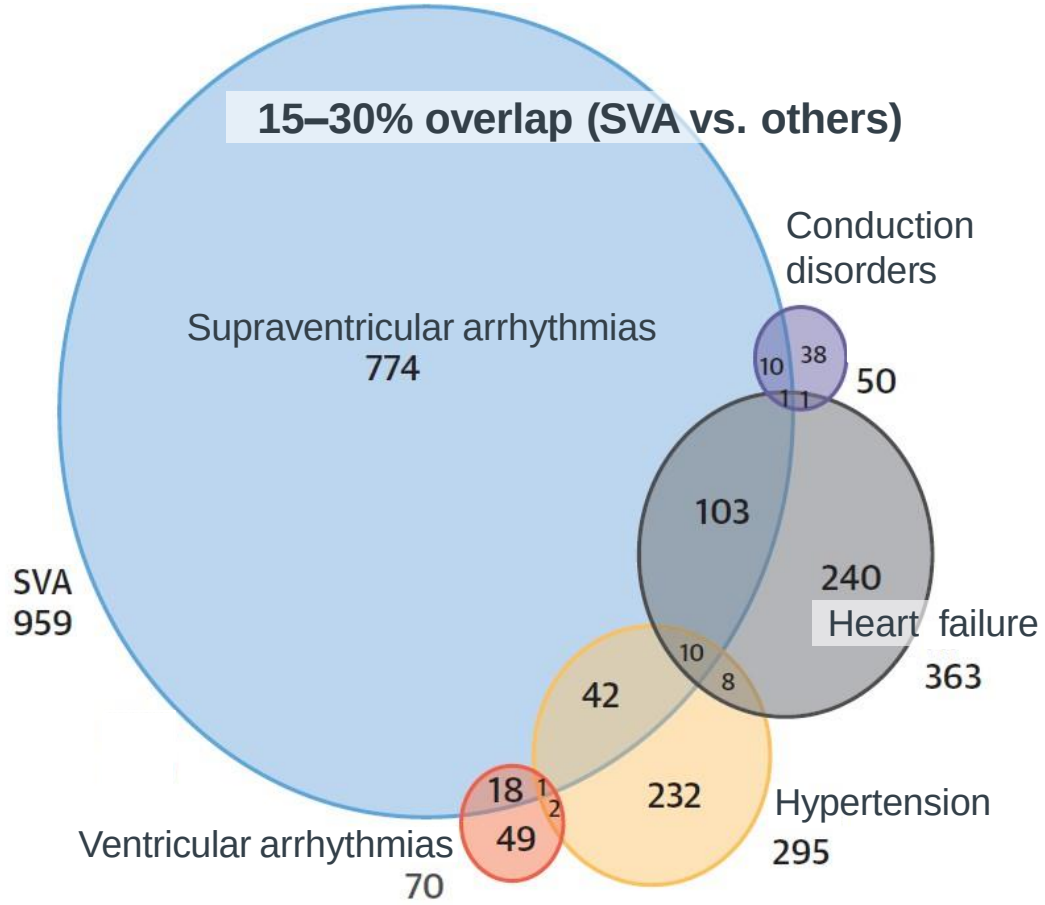
CNS, central nervous system.
Salem JE *et al*. *J Am Coll Cardiol* 2019; 74 (13): 1667–1678.

Cardiovascular toxicities associated with ibrutinib (2)

Time to adverse drug reaction onset associated with ibrutinib



Overlap of cardiovascular adverse drug reactions associated with ibrutinib in VigiBase*

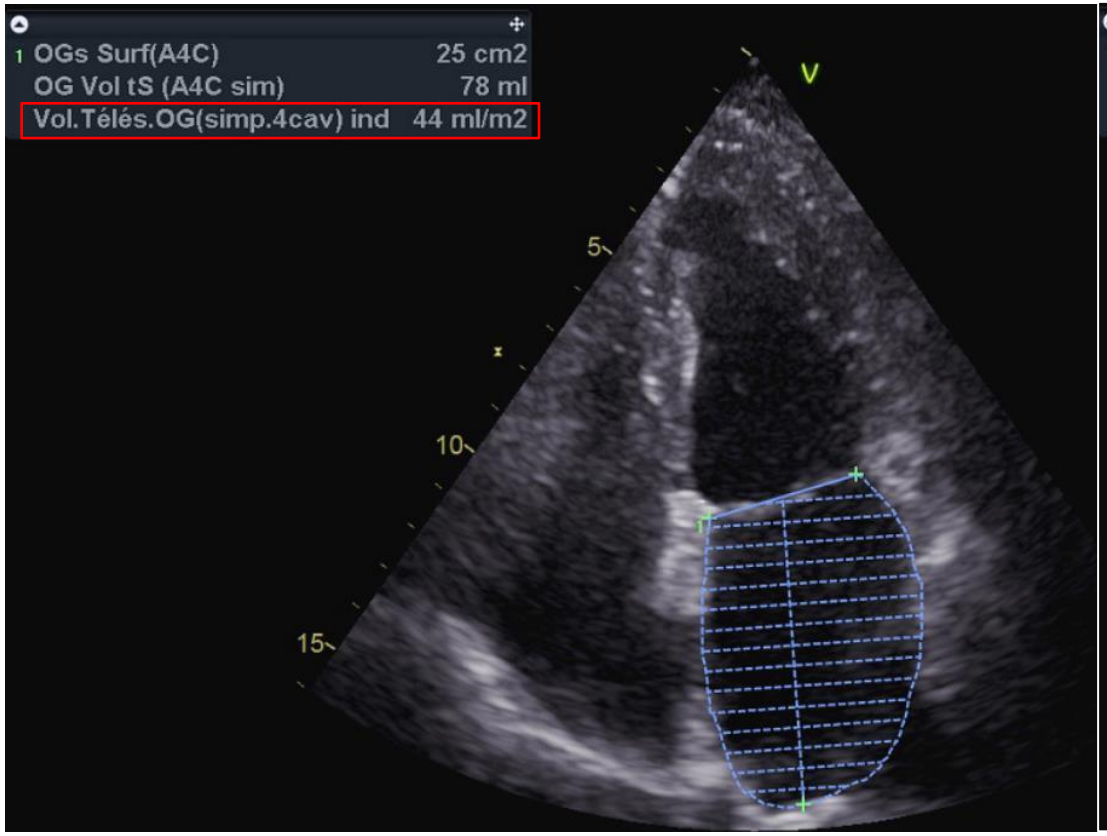


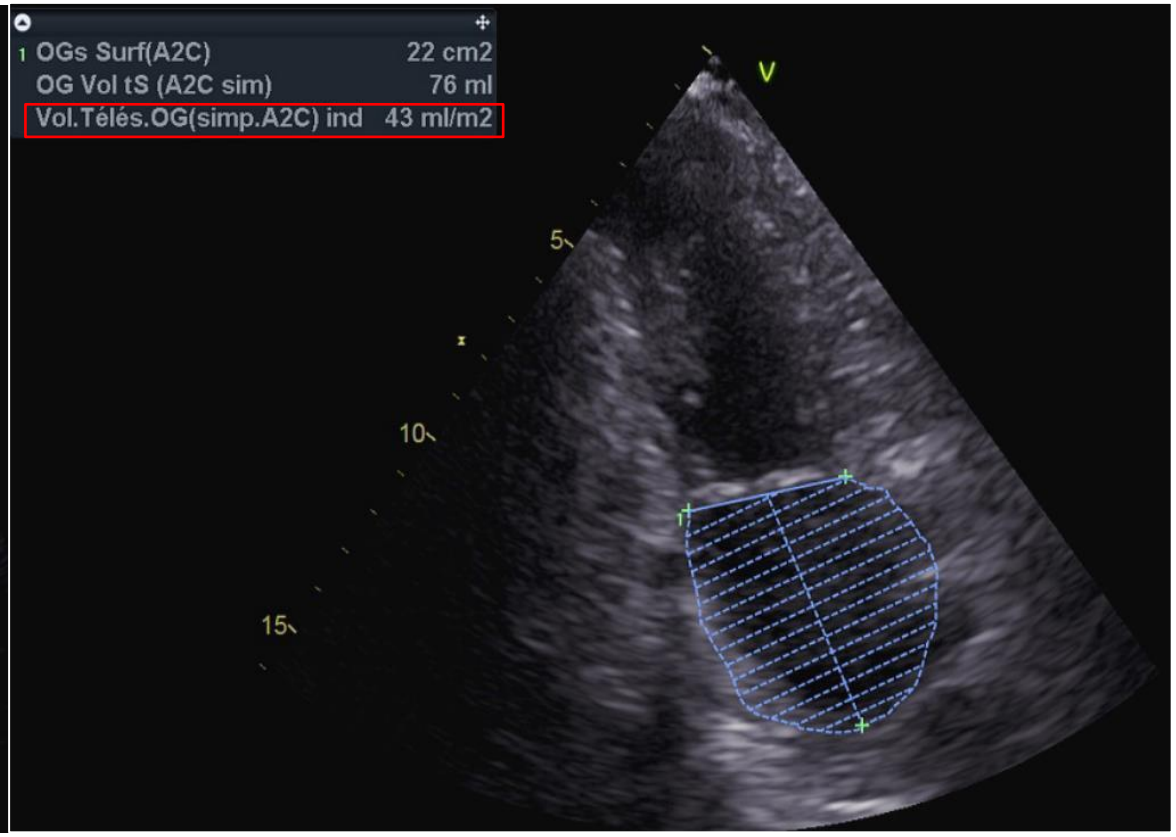
*Overlap between supraventricular arrhythmias, ventricular arrhythmias (VAs), conduction disorders (CDs), heart failure (HF) and hypertension; overlap between VA and CD (n=1) or VA and HF (n=7) are not displayed.
ADR, adverse drug reaction; CNS, central nervous system; SVA, supraventricular arrhythmia. Salem JE *et al*. *J Am Coll Cardiol* 2019; 74 (13): 1667–1678.

Mrs F: Baseline echocardiography

- Normal left ventricular ejection fraction, diameter, and volumes; no hypertrophy
- No valve abnormalities

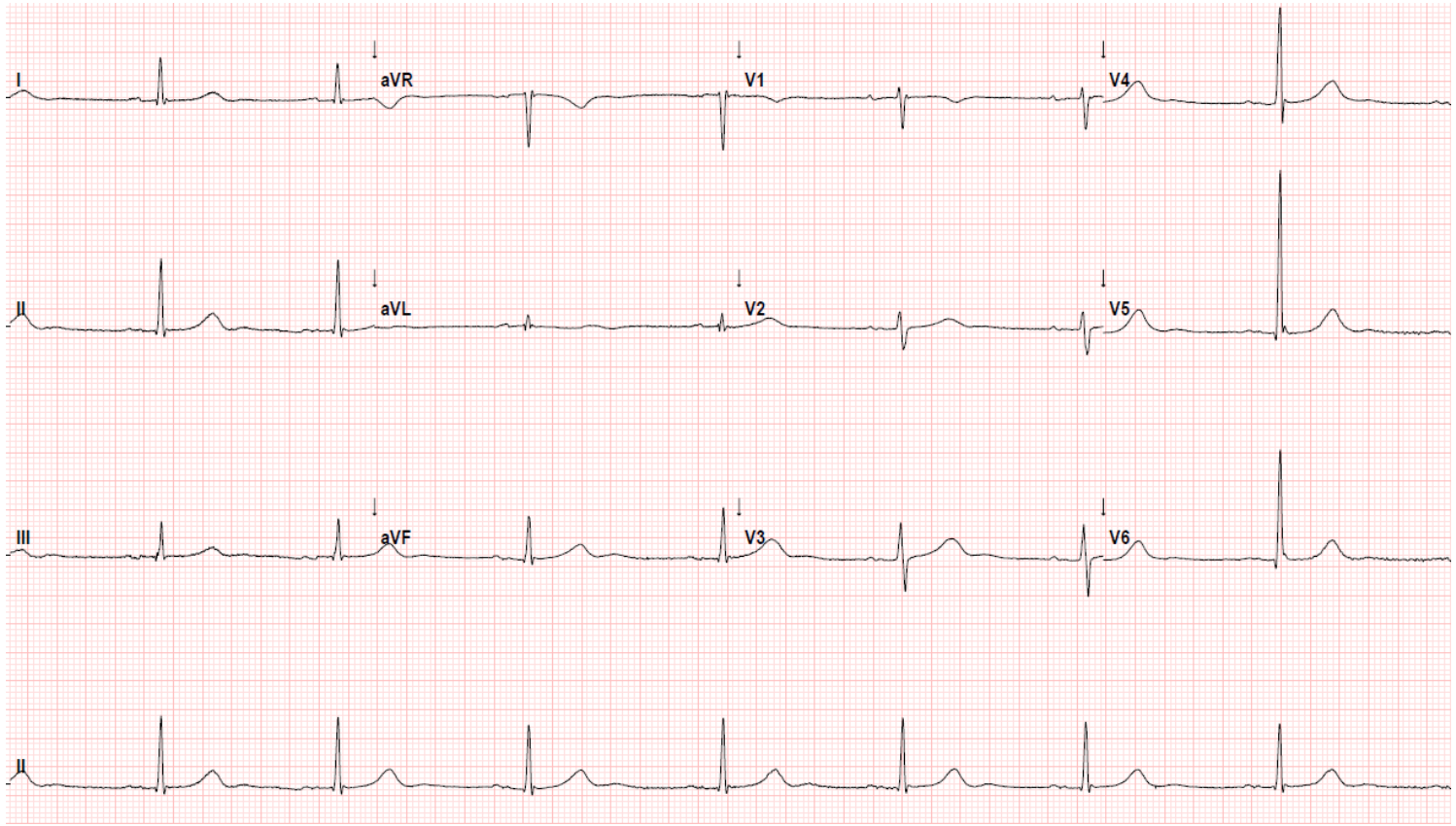
- Normal right ventricle and no pulmonary hypertension
- **Left atrial dilatation,**
  left atrial volume index (LAVI): 44 mL/m²

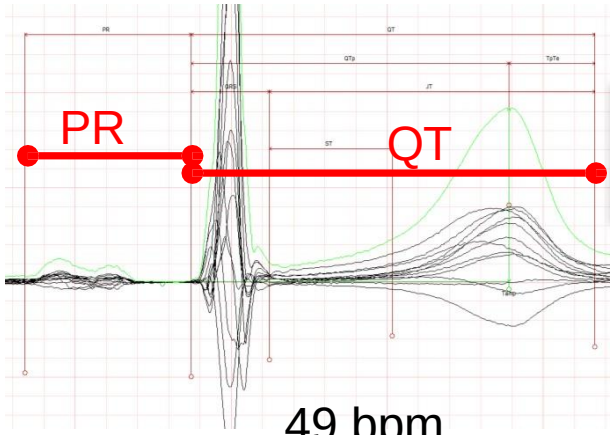




Mrs F: Pre-ibrutinib

Sinus rhythm, 1st degree atrioventricular block
Grade 2 long QT



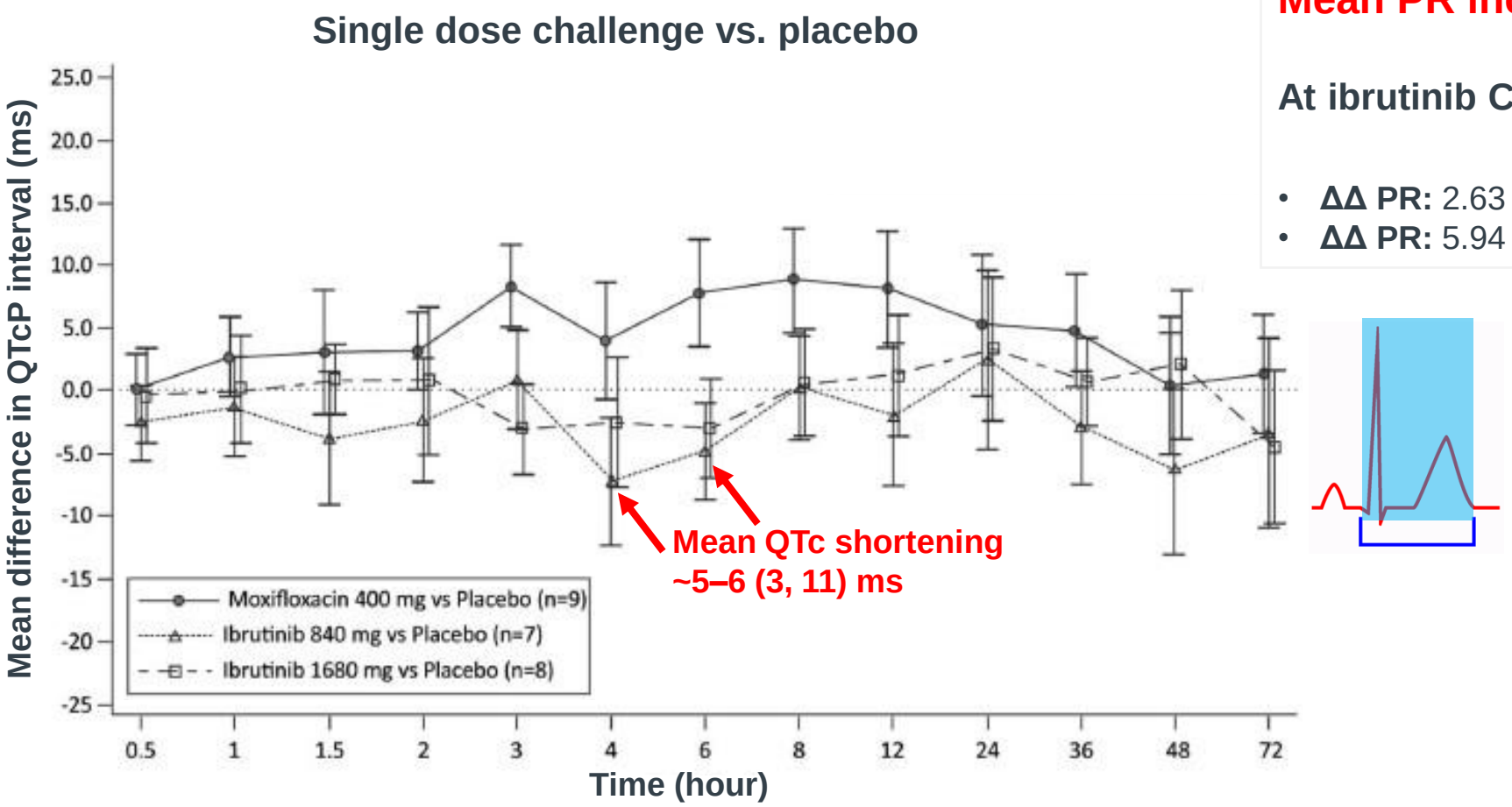


49 bpm

QT	517 ms
PR	213 ms
QRS	100 ms
JT	417 ms
ST	157 ms
Tamp	913 uV
QTp	407 ms
TpTe	110 ms
QTcB	465
QTcF	482

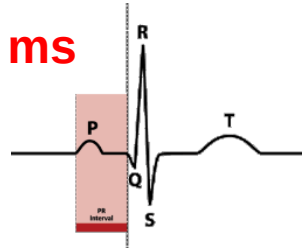
Blood pressure: 138/70 → Monitoring

Ibrutinib does not prolong the QT interval in healthy individuals



Mean PR increase ~3–6 (1, 11) ms

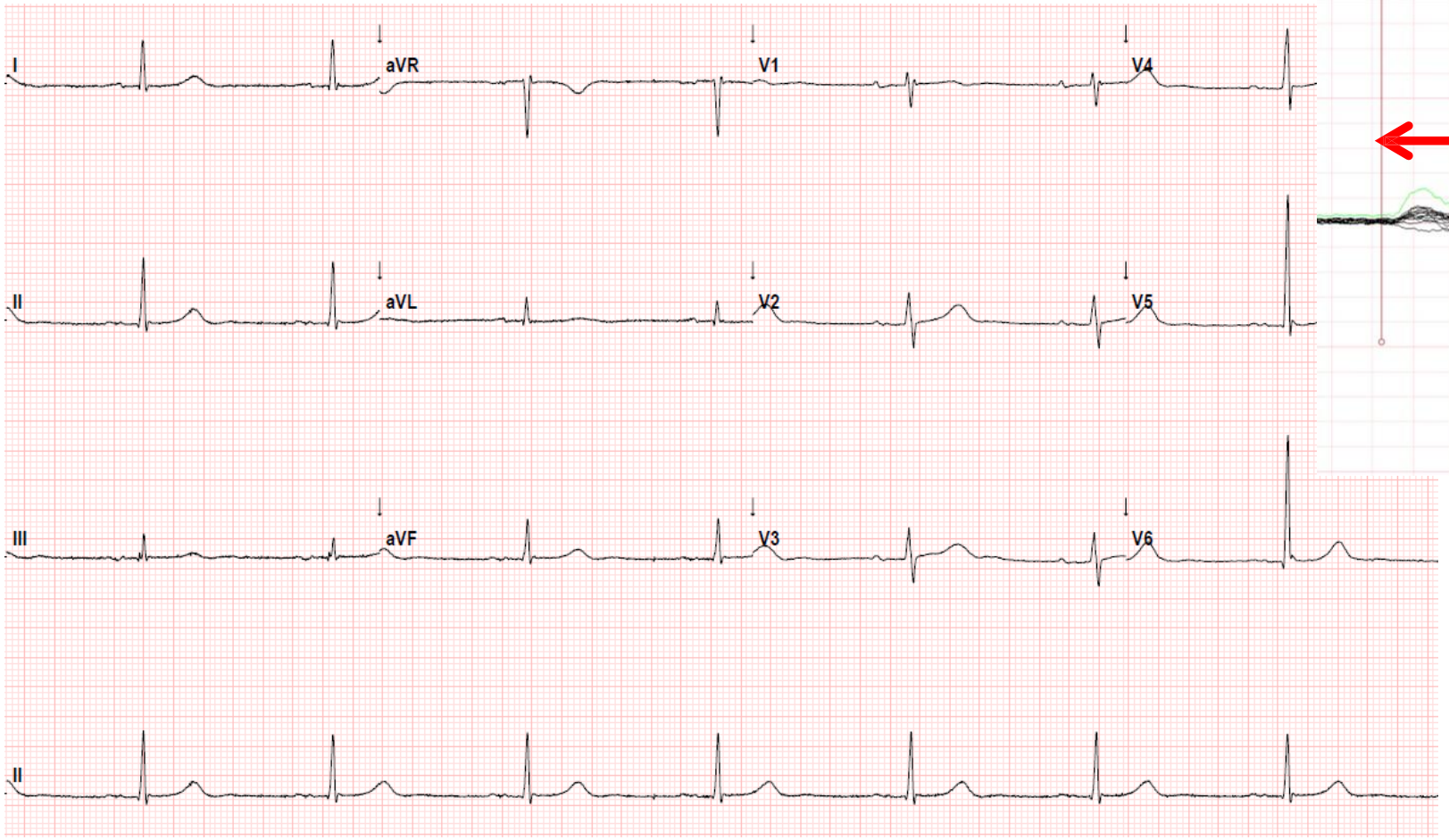
At ibrutinib C_{max}

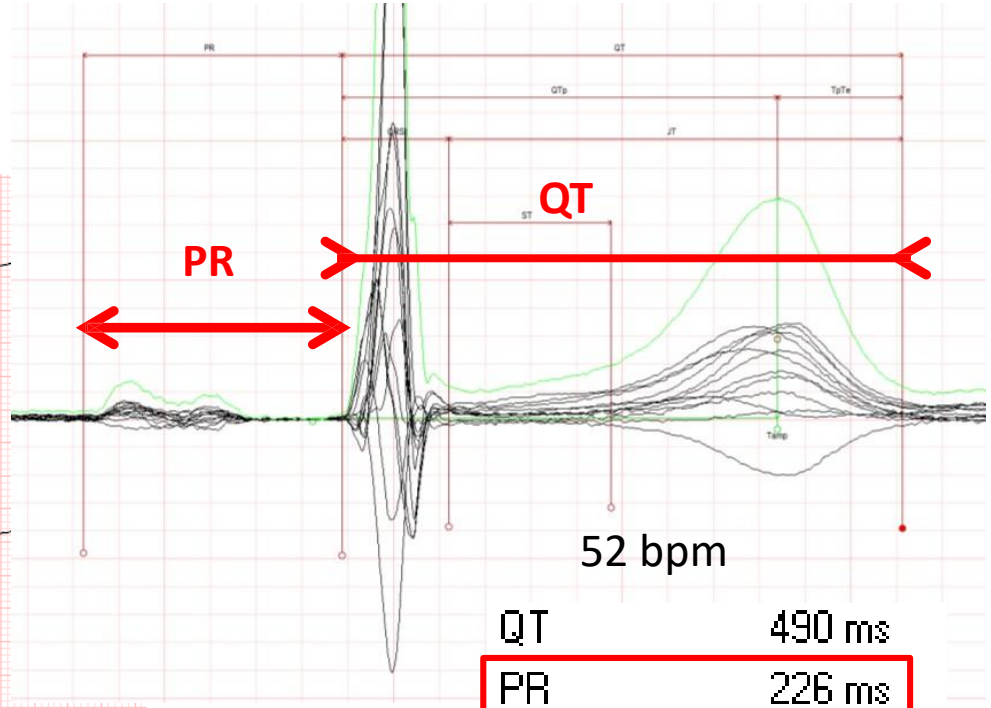


- **ΔΔ PR:** 2.63 ms IC90 (−0.01, 5.27); 840 mg
- **ΔΔ PR:** 5.94 ms IC90 (1.29, 10.58); 1,680 mg

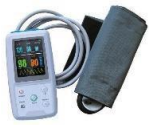
de Jong *et al. Cancer Chemother Pharmacol* 2017; 80 (6):1227–1237.

Mrs F: One month post-ibrutinib



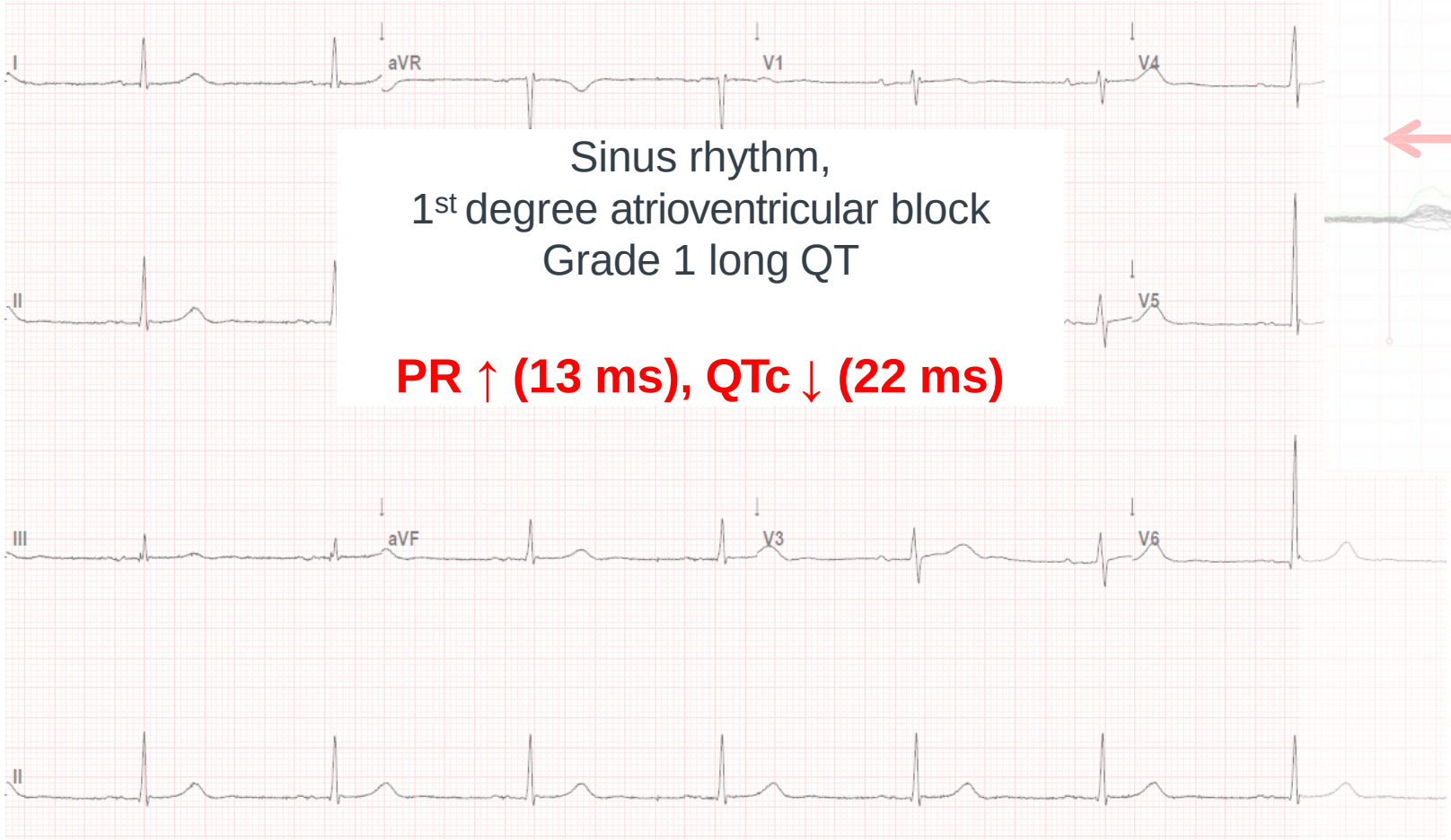


QT	490 ms
PR	226 ms
QRS	93 ms
JT	397 ms
ST	142 ms
Tamp	793 uV
QTp	381 ms
TpTe	109 ms
QTcB	445
QTcF	460



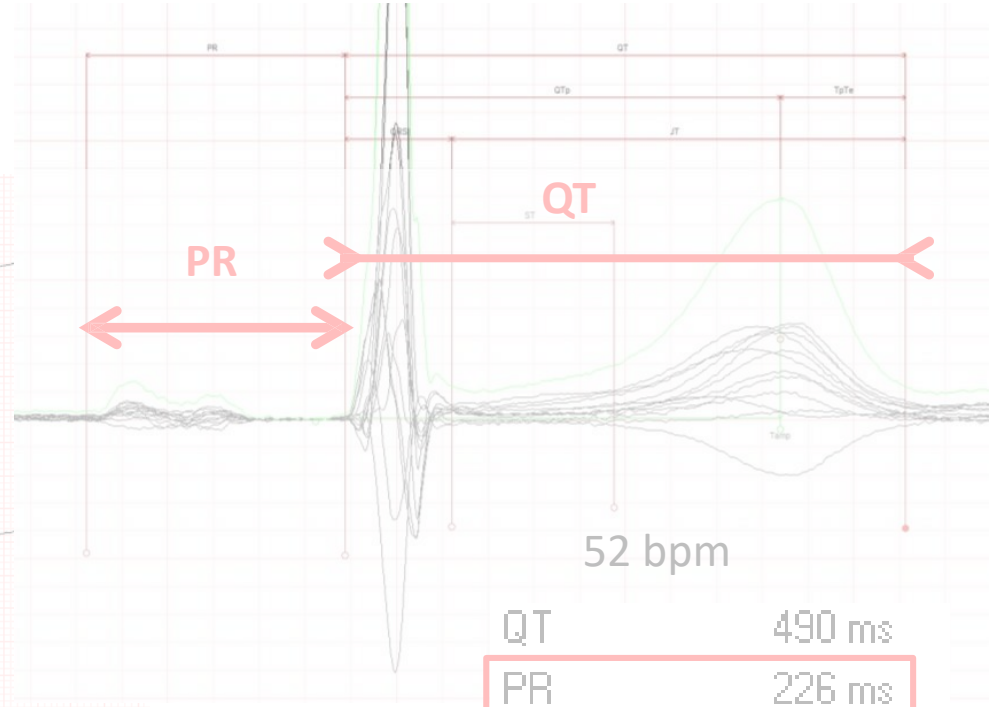
Blood pressure: 149/72 → Perindopril 5 mg/d, amlodipine 5 mg/d

Mrs F: One month post-ibrutinib



Sinus rhythm,
1st degree atrioventricular block
Grade 1 long QT

PR ↑ (13 ms), QTc ↓ (22 ms)



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QRS	93 ms
JT	397 ms
ST	142 ms
Tamp	793 uV
QTp	381 ms
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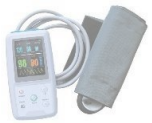
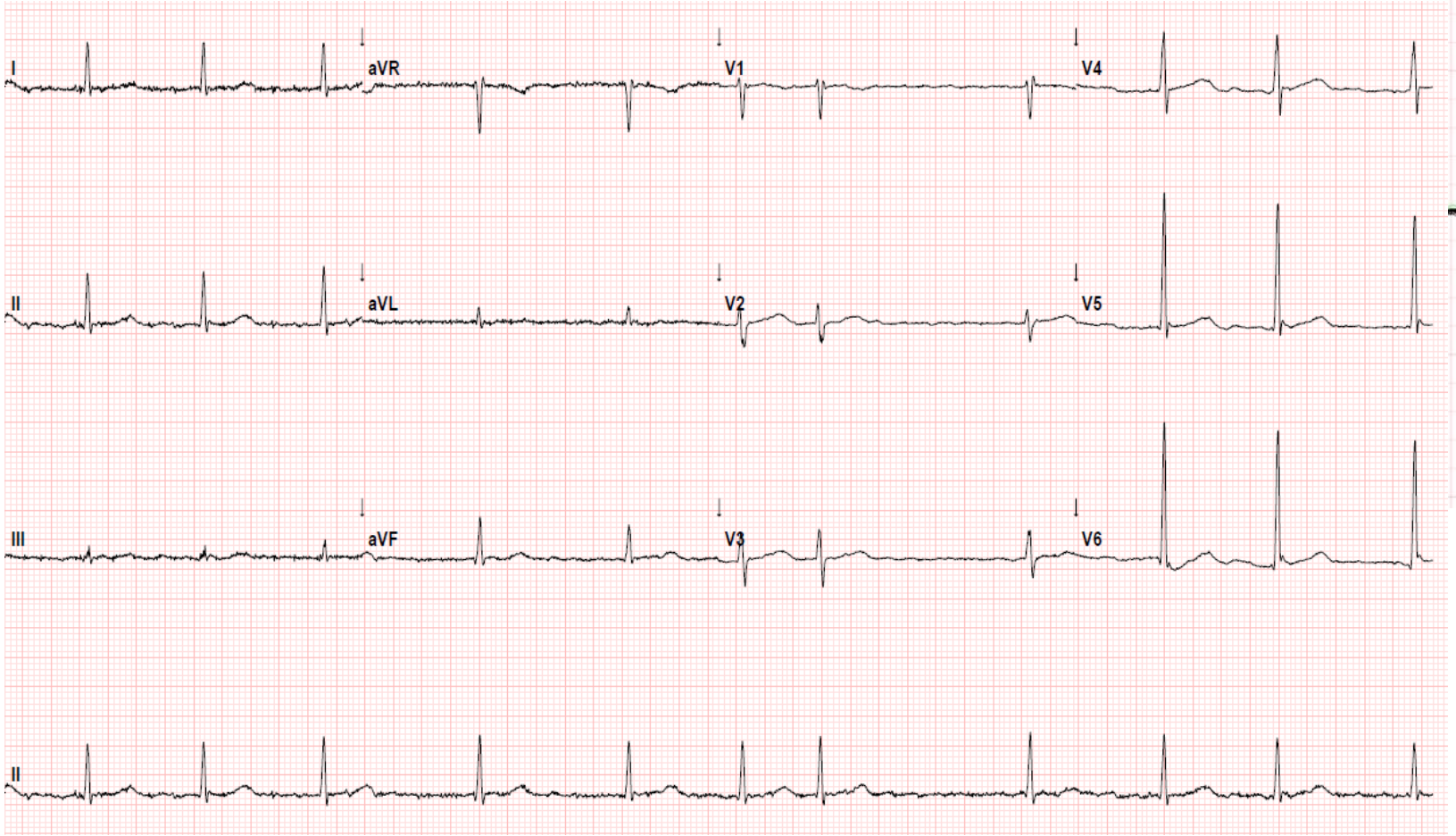
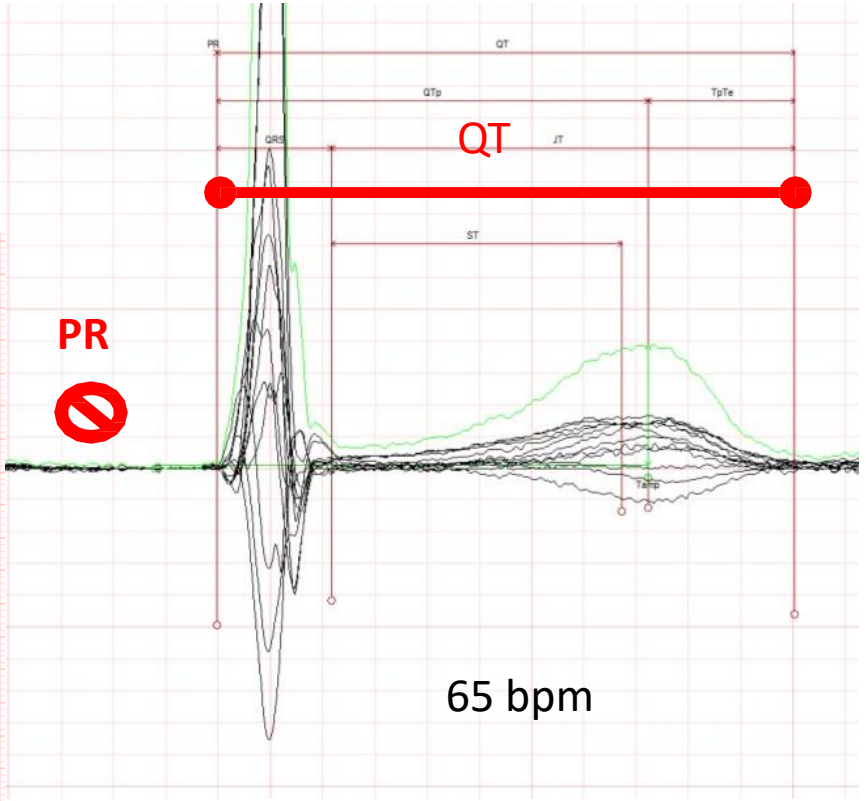
QTcB	445
QTcF	460



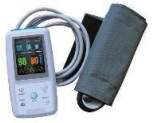
Blood pressure: 149/72 → Perindopril 5 mg/d, amlodipine 5 mg/d

Mrs F: Three months post-ibrutinib



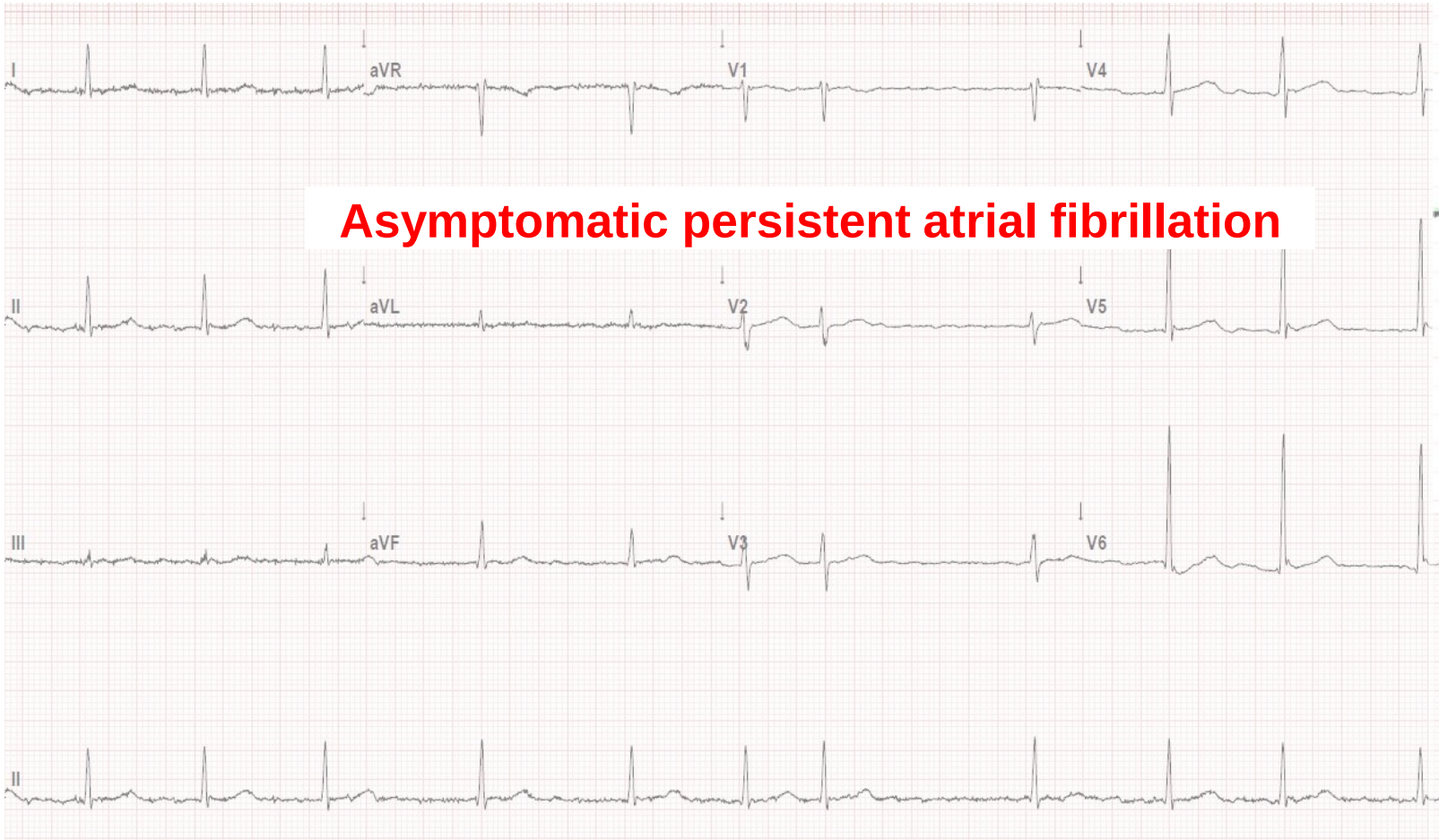


QT	442 ms
PR	[illegible]
QRS	88 ms
JT	354 ms
ST	222 ms
Tamp	373 uV
QTp	330 ms
TpTe	112 ms
QTcB	465
QTcF	457

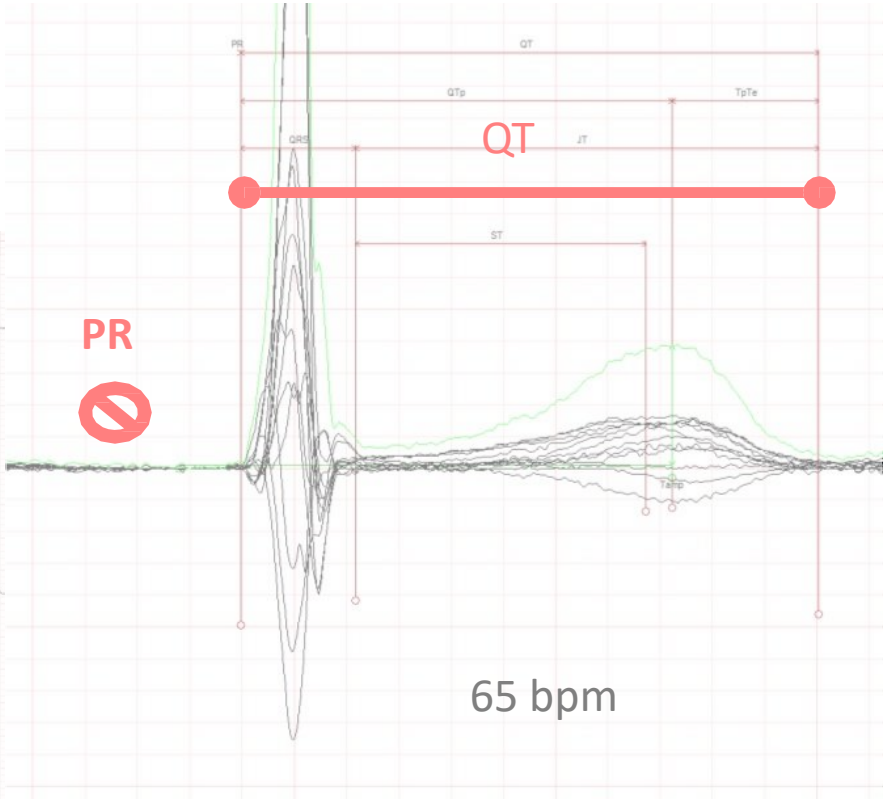


Blood pressure: 144/73 → Perindopril 10 mg/d, amlodipine 5 mg/d

Mrs F: Three months post-ibrutinib



Asymptomatic persistent atrial fibrillation



QT	442 ms
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ST	222 ms
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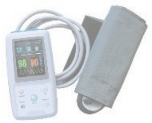
QTcB	465
QTcF	457



Blood pressure: 144/73 → Perindopril 10 mg/d, amlodipine 5 mg/d

Cardiac supraventricular arrhythmia

US FDA labels and randomized clinical trials meta-analyses:[1]

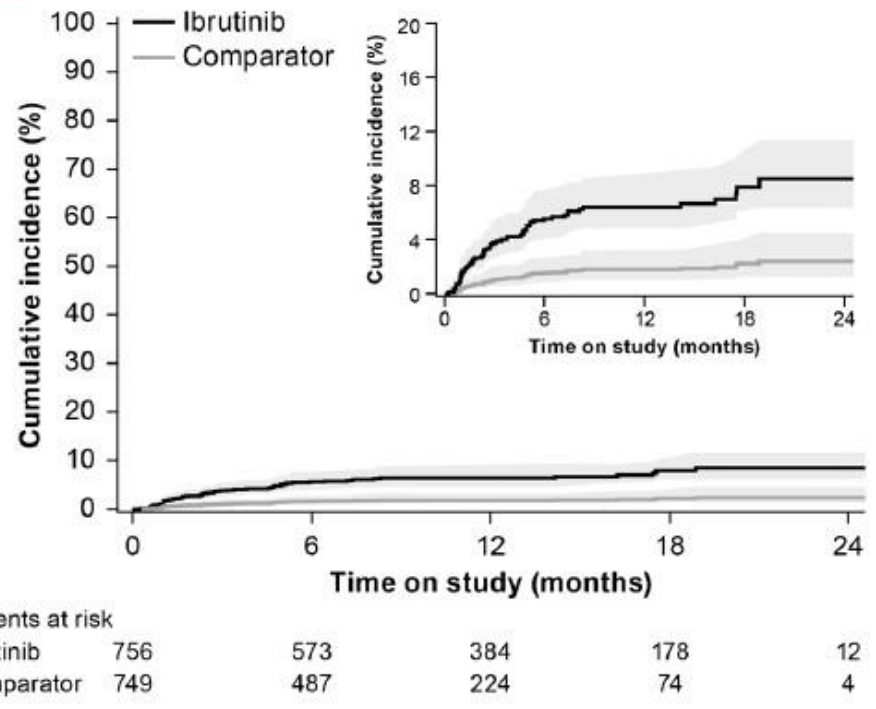
- **6.5%** after **16.6 months**
- **13.8%** at **36 months** (3.7% SAEs)

In real-life cohorts:[2]

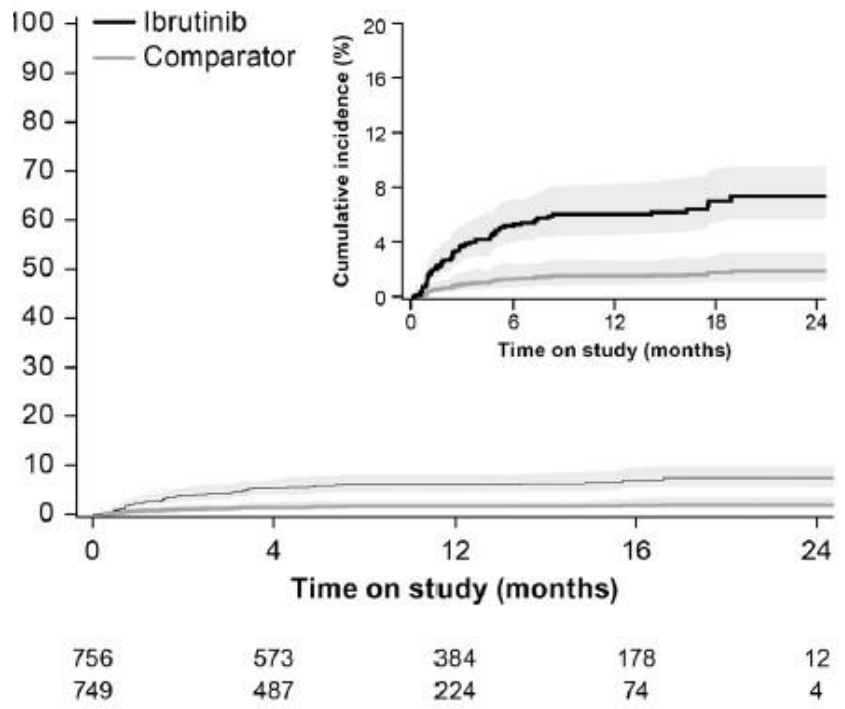
- **38% at 2 years**

Cumulative incidence (95% CI) of atrial fibrillation with ibrutinib vs. comparator[1]

Unadjusted analysis



Adjusted for competing events*



*Death and progressive disease.
CI, confidence interval; FDA, Food and Drug Administration; SAE, serious adverse event.
1. Brown JR *et al*. *Haematologica* 2017; 102 (10): 1796–1805. 2. Baptiste F *et al. Open Heart* 2019; 6 (1): e001049.

Cardiac supraventricular arrhythmia

US FDA labels and randomized clinical trials meta-analyses:[1]

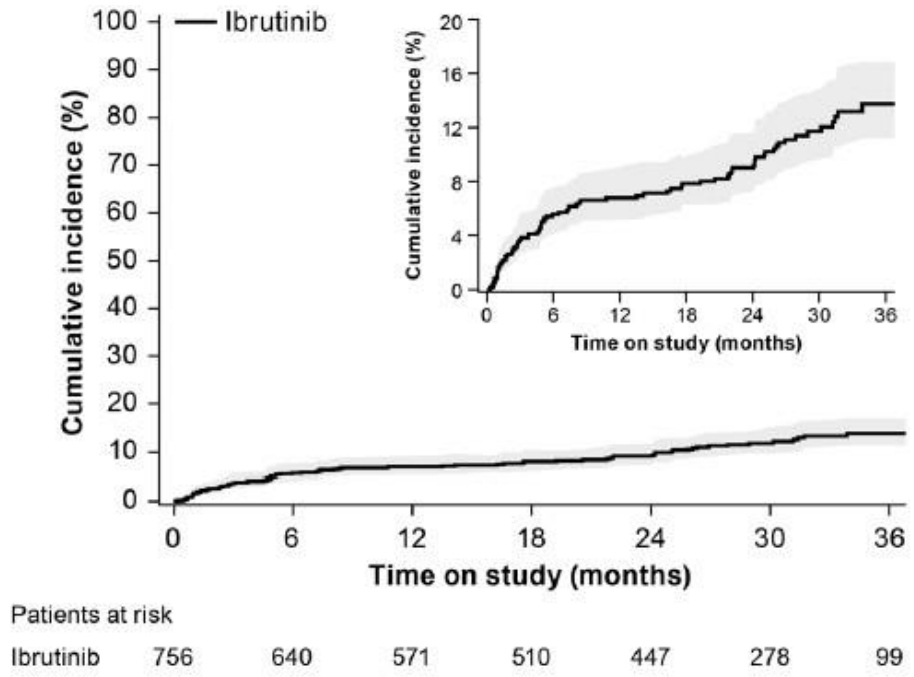
- **6.5%** after **17 months**
- **13.8%** at **36 months** (3.7% SAEs)

In real-life cohorts:[2]

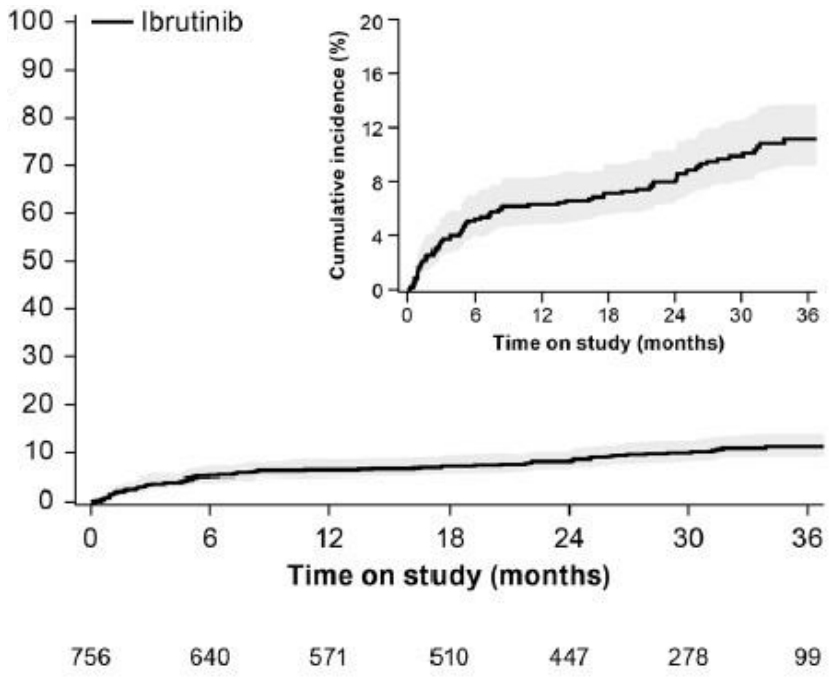
- **38% at 2 years**

Cumulative incidence (95% CI) of atrial fibrillation with ibrutinib: Extended analysis[1]

Unadjusted analysis



Adjusted for competing events*



*Death and progressive disease.
CI, confidence interval; FDA, Food and Drug Administration; SAE, serious adverse event.
1. Brown JR *et al*. *Haematologica* 2017; 102 (10): 1796–1805. 2. Baptiste F *et al. Open Heart* 2019; 6 (1): e001049.

Left atrial abnormality

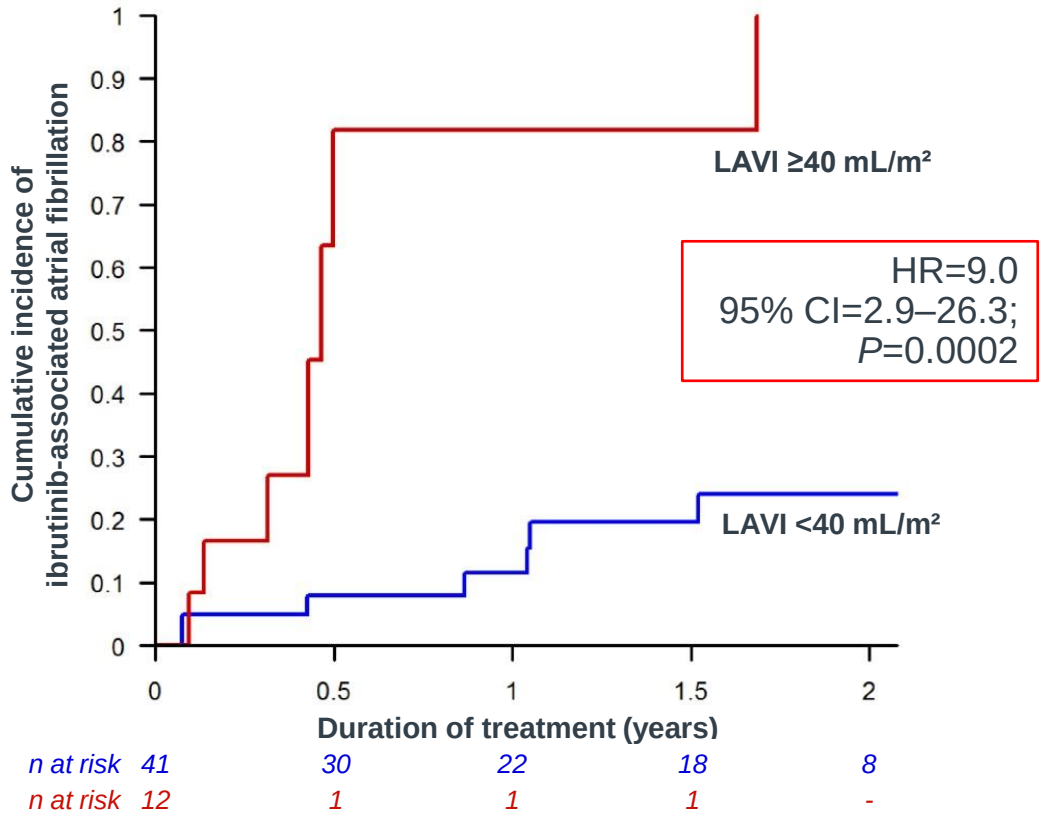
Cardiovascular characteristics associated with ibrutinib-associated atrial fibrillation[1]

Variable	OR (95% CI)	*P*-value
Left atrial appendage*	6.6 (1.5–29.2)	0.01
Baseline hypertension	1.6 (0.3–8.2)	0.59
Baseline coronary artery disease	1.7 (0.2–14.2)	0.61
Age	1.0 (0.94–1.1)	0.63

ECG as a predictor of ibrutinib-associated atrial fibrillation[1]

Characteristic	Value	95% CI
Sensitivity	79%	54–94
Specificity	71%	49–87
Positive likelihood ratio	2.7	1.4–5.3
Negative likelihood ratio	0.30	0.1–0.74
Positive predictive value	68%	45–86
Negative predictive value	81%	58–95

Left atrial volume index ≥40 mL/m² as a predictor of ibrutinib-associated atrial fibrillation[2]

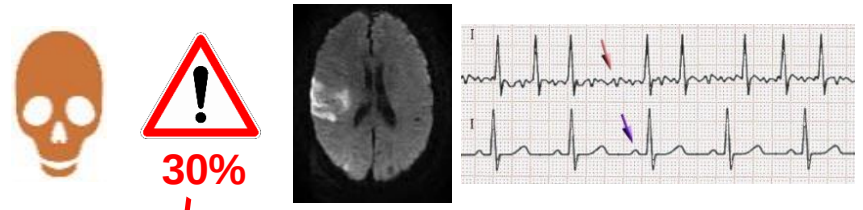


Mrs F: PR: 213 ms; LAVI: 44 mL/m²

*LAA defined as presence of one of the following: (1) Lead II-bifed P wave ("p mitrale") with 40 ms between peaks or >2.5 mm wide or >100ms in duration, (2) Lead V1-biphasic P wave with terminal portion >40 ms in duration or terminal portion >1 mm deep or (3) PR interval ≥200 ms (intra-atrial conduction delay).

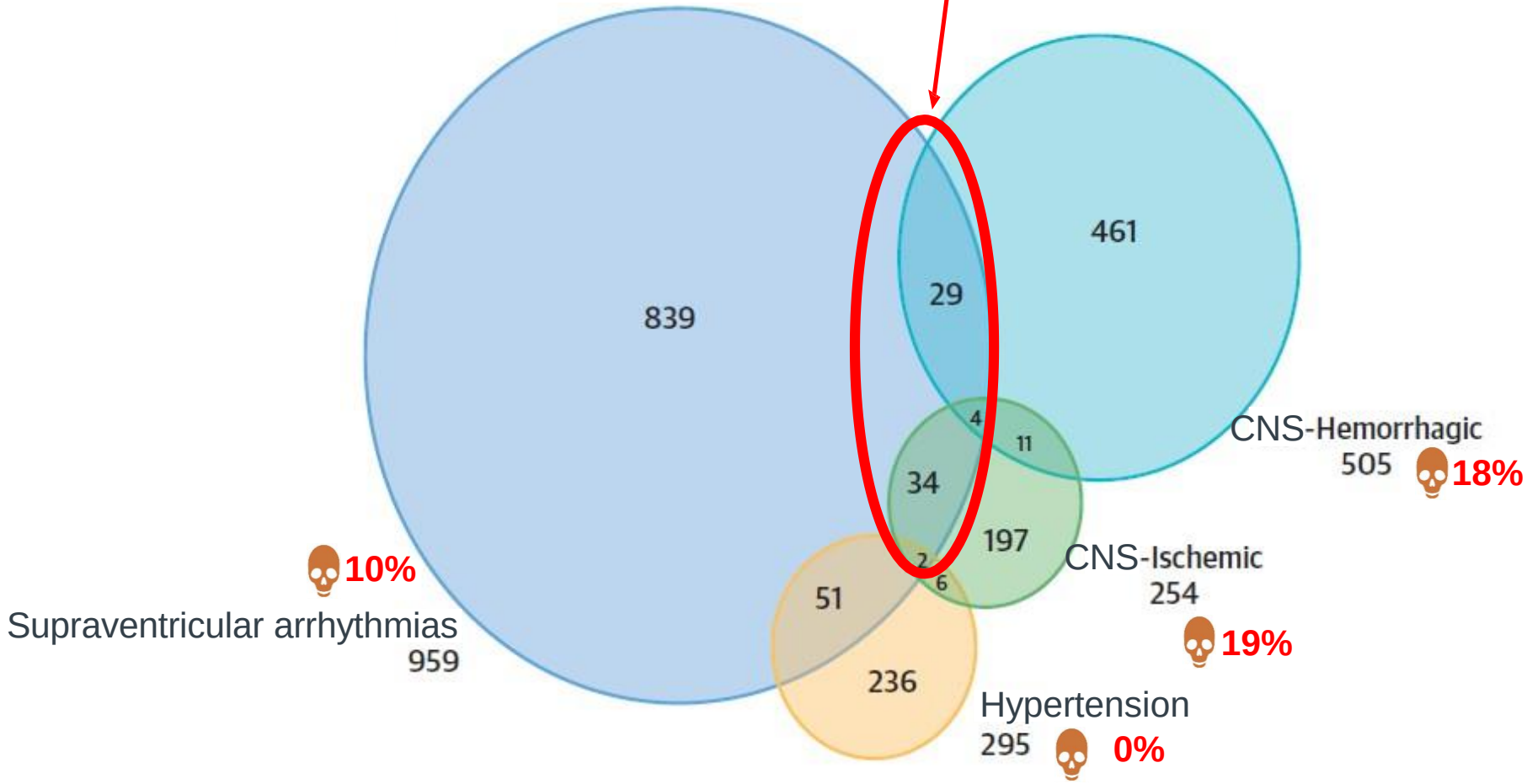
ECG, electrocardiogram; HR, hazard ratio; OR, odds ratio; LAVI, left atrial volume index. 1. Mato AR *et al. Cancer Biol Ther* 2018; 19 (1): 1–2. 2. Baptiste F *et al. Open Heart* 2019; 6 (1): e001049.

Overlap and fatalities: 10%–30% fatalities



Mrs F

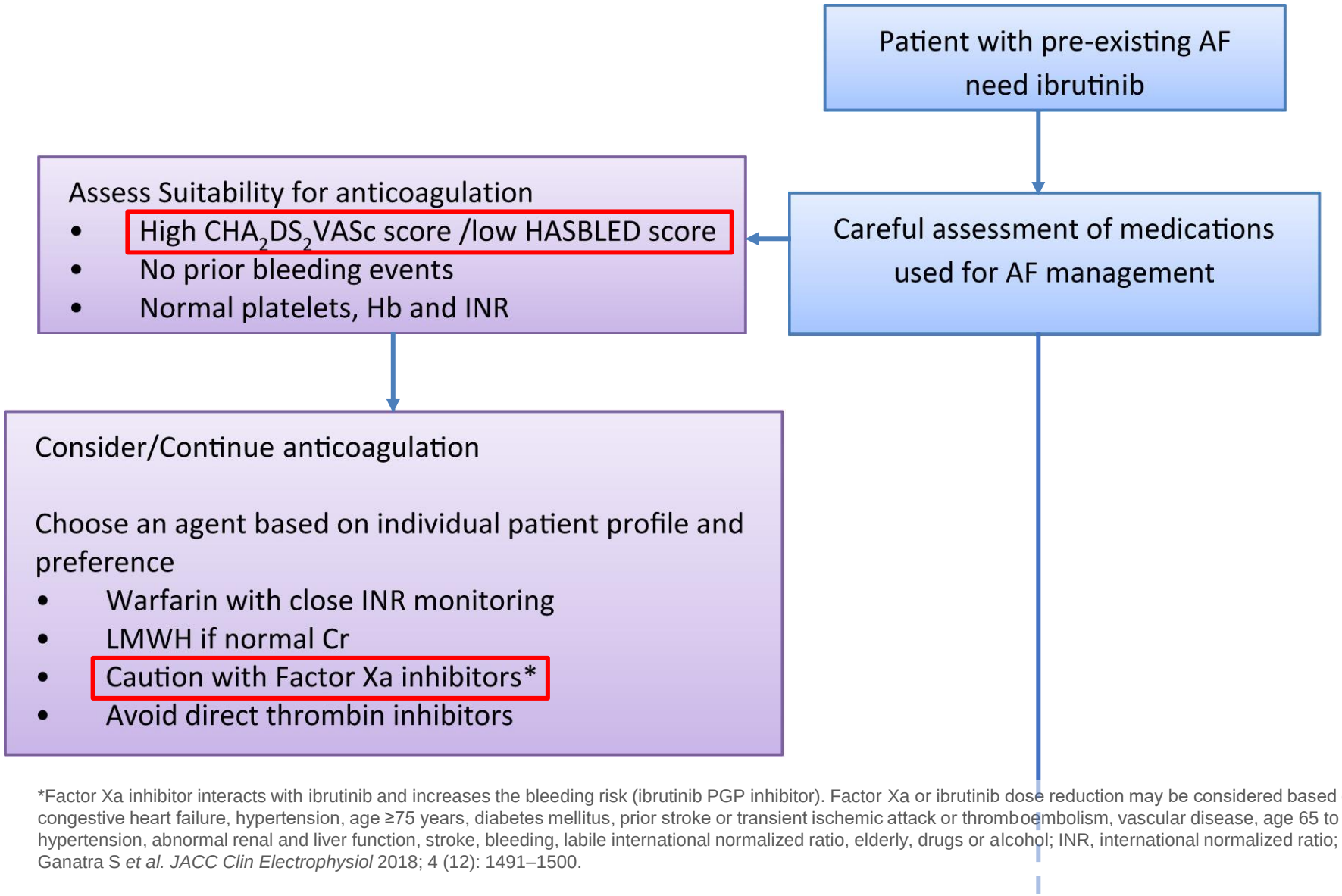
- **CHADS-VASC: 5**
- **HAS-BLED: 3**
- Hemoglobin: 13 g/dL
- Platelets: 132 x10^9 g/dL
- Leukocytes: 5 G/L
- INR: 1
- Creatinine clearance: 60 mL/min/m²
- On aspirin 75 mg/d



CHADS-VASC, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65–74 years, sex category; CNS, central nervous system; HAS-BLED, Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs or alcohol; INR, international normalized ratio.

Salem JE *et al*. *J Am Coll Cardiol* 2019; 74 (13): 1667–1678.

Anticoagulation strategy

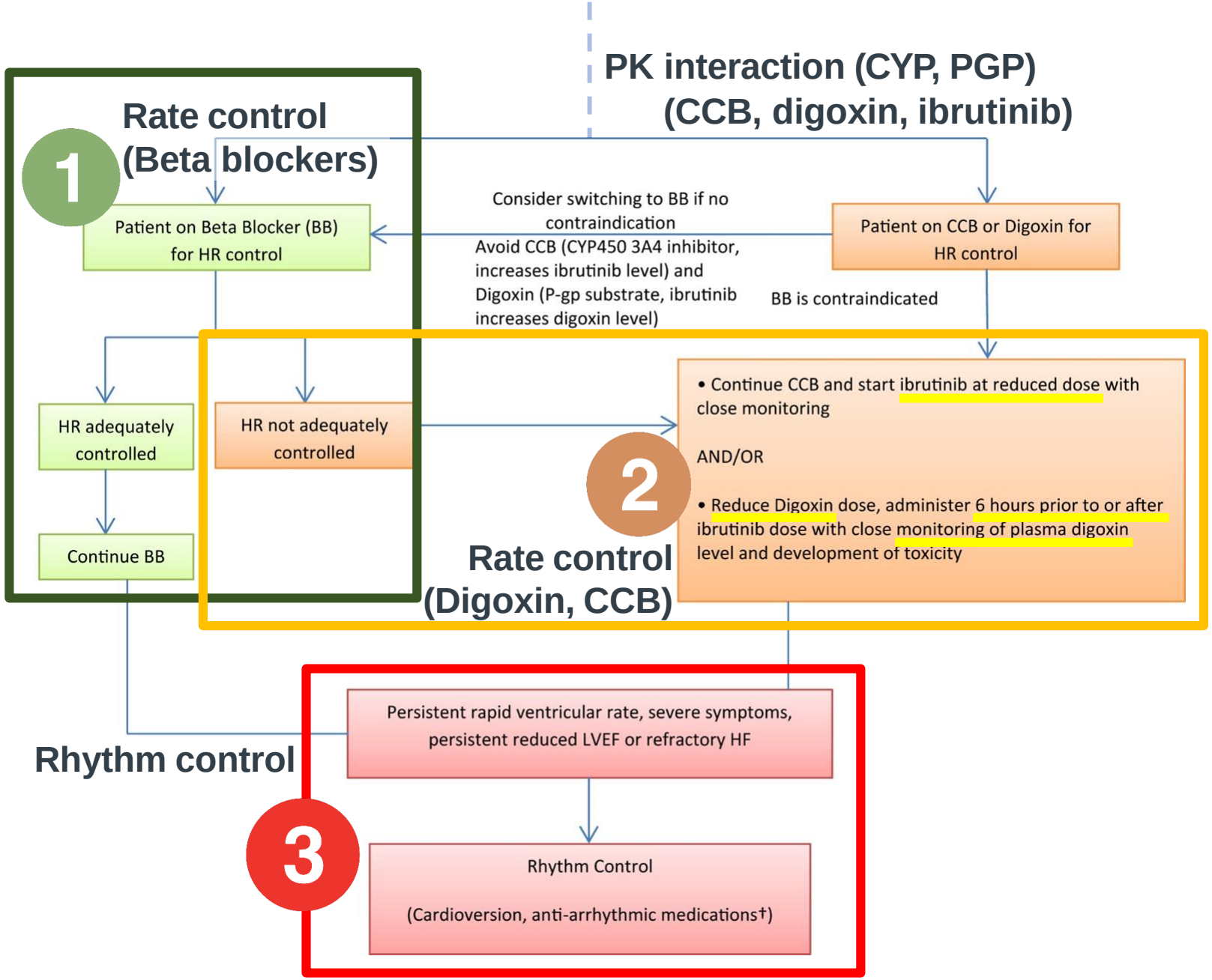


Mrs F

- **Apixaban** 5 mg*
  - Weight >60 kg (70 kg)
  - Age <80 years old (76)
  - Creatinine <133 µmol/L (93)
- **Stop aspirin**
- **Therapeutic drug monitoring**
  - Anti-Factor Xa levels (C_{max}, C_{min}) in expected range

*Factor Xa inhibitor interacts with ibrutinib and increases the bleeding risk (ibrutinib PGP inhibitor). Factor Xa or ibrutinib dose reduction may be considered based on individual case. AF; atrial fibrillation; CHA_2DS_2 VASc; congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65 to 74 years, sex category; Cr, creatinine; HASBLED, hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs or alcohol; INR, international normalized ratio; LMWH, low molecular weight heparin; PGP, P-glycoprotein.
Ganatra S *et al. JACC Clin Electrophysiol* 2018; 4 (12): 1491–1500.

Rate vs. rhythm control

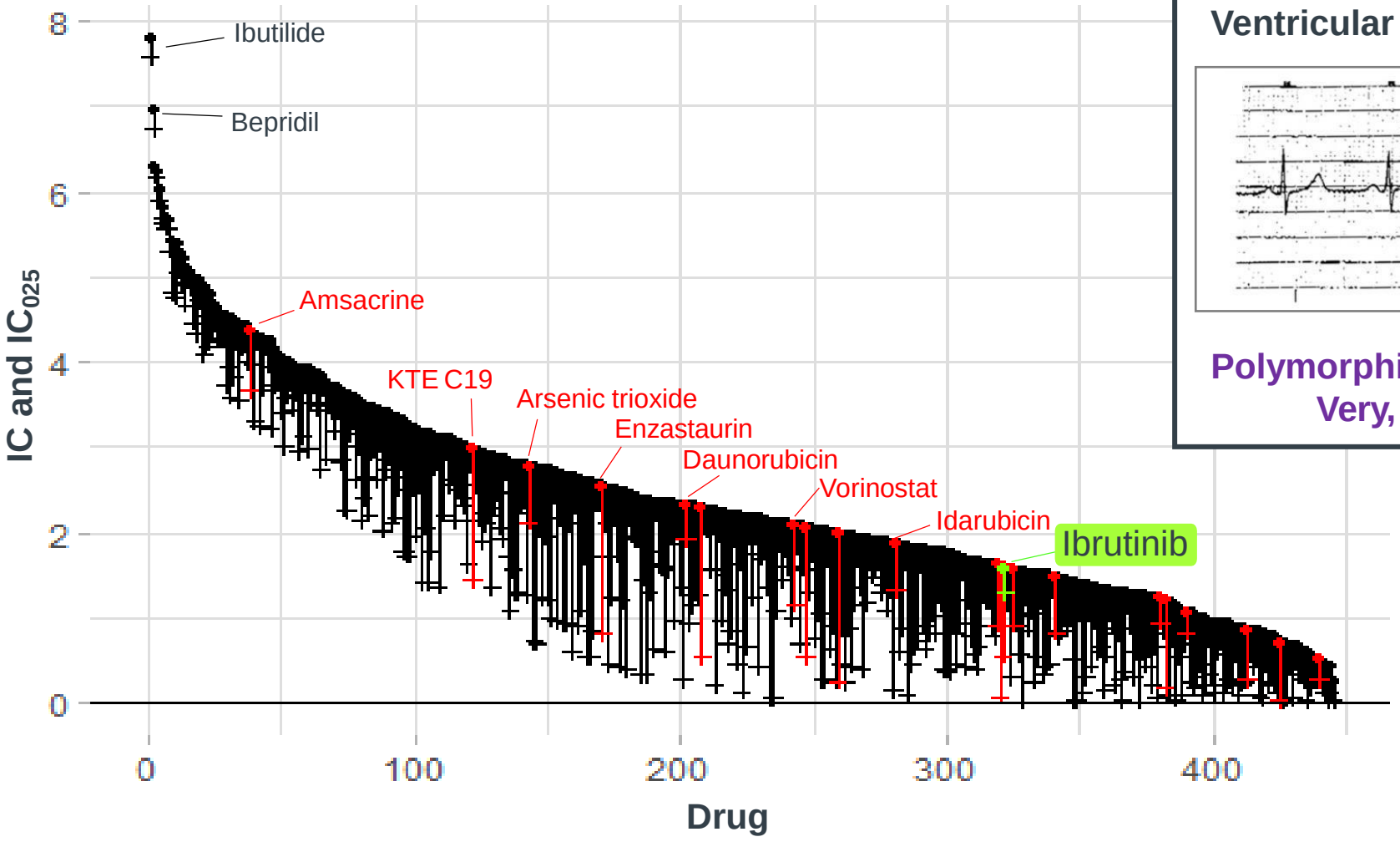


Mrs F

- Heart rate: 60–70 bpm spontaneously
- **Rate control**
- **No antiarrhythmic**

†Amiodarone interacts with ibrutinib and increases the risk of ibrutinib associated adverse events. Temporary withholding of ibrutinib or dose reduction might be considered.
BB, beta blocker; CCB, calcium-channel blocker; HF, heart failure; HR, heart rate; LVEF, left ventricular ejection fraction; P-gp, P-glycoprotein.
Ganatra S *et al. JACC Clin Electrophysiol* 2018; 4 (12): 1491–1500.

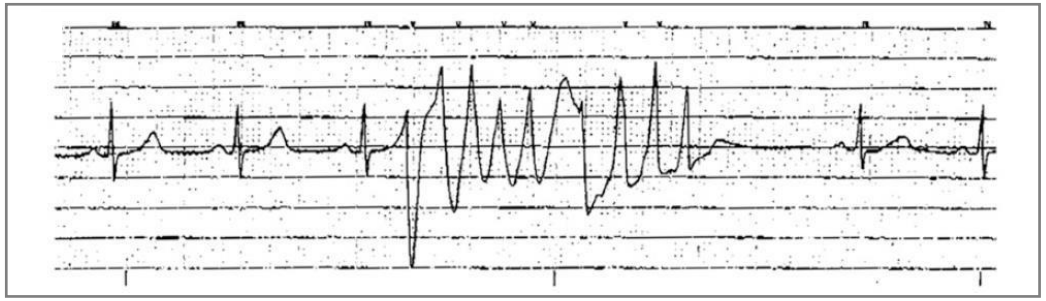
Ventricular arrythmias



2582 LETTERS TO *BLOOD*

Lampson BL *et al*. 2017

Ventricular tachycardia in a patient on ibrutinib



Polymorphic ventricular tachycardia, normal QTc => Very, very unusual!!! Mechanisms???

Anticancer drug-induced long QT, Torsade de Pointes and ventricular arrhythmias – a WHO reports analysis

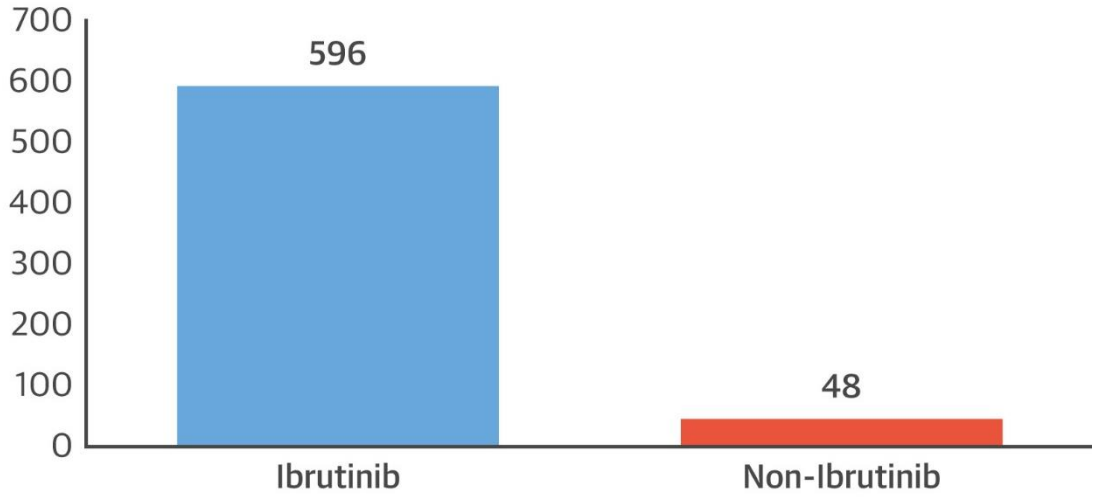
Salem JE et al. (Submitted)

Lampson BL *et al. Blood* 2017; 129 (18): 2581–2584.

Ventricular arrythmia after ibrutinib initiation for lymphoid malignancies

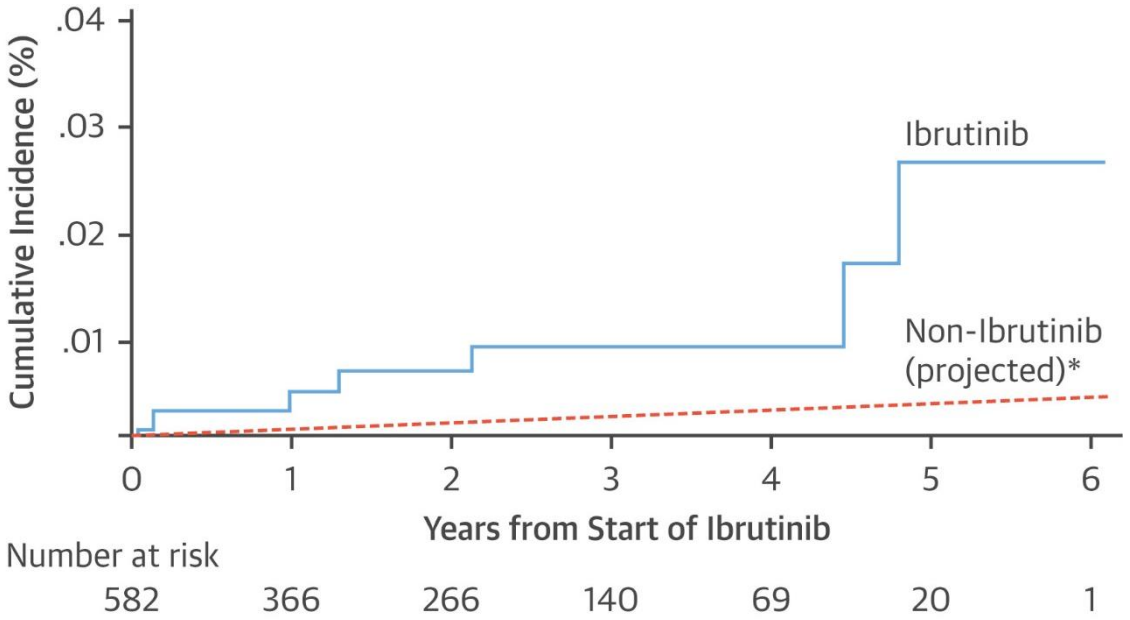
In published clinical trials, **VA occurred ~0.2% Grade ≥3**

VA incidence rate per 100,000 person-years



n=582

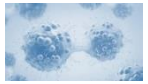
Cumulative incidence of VAs over time

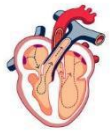


*Assumes a linear event rate over time.
FDA, Food and Drug Administration; VA, ventricular arrythmia.
Guha A *et al. J Am Coll Cardiol* 2018; 72 (6): 697–698.

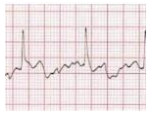
Acalabrutinib in relapsed chronic lymphocytic leukemia

Recombinant kinase inhibition assays: Acalabrutinib vs. ibrutinib (1)*





Kinase	IC_{50} (nM)	
	Acalabrutinib	Ibrutinib
BTK	5.1 ± 1.0 (N=4)	1.5 ± 0.2 (N=4)
BMX†	46 ± 12 (N=3)	0.8 ± 0.1 (N=3)
ITK†	>1,000 (N=4)	4.9 ± 1.2 (N=4)
TEC†	93 ± 35 (N=2)	7.0 ± 2.5 (N=2)
TXK†	368 ± 141 (N=3)	2.0 ± 0.3 (N=3)
EGFR†	>1,000 (N=3)	5.3 ± 1.3 (N=3)
ERBB2†	~1,000 (N=3)	6.4 ± 1.8 (N=3)
ERBB4†	16 ± 5 (N=3)	3.4 ± 1.3 (N=3)



Recombinant kinase inhibition assays: Acalabrutinib vs. ibrutinib (2)*

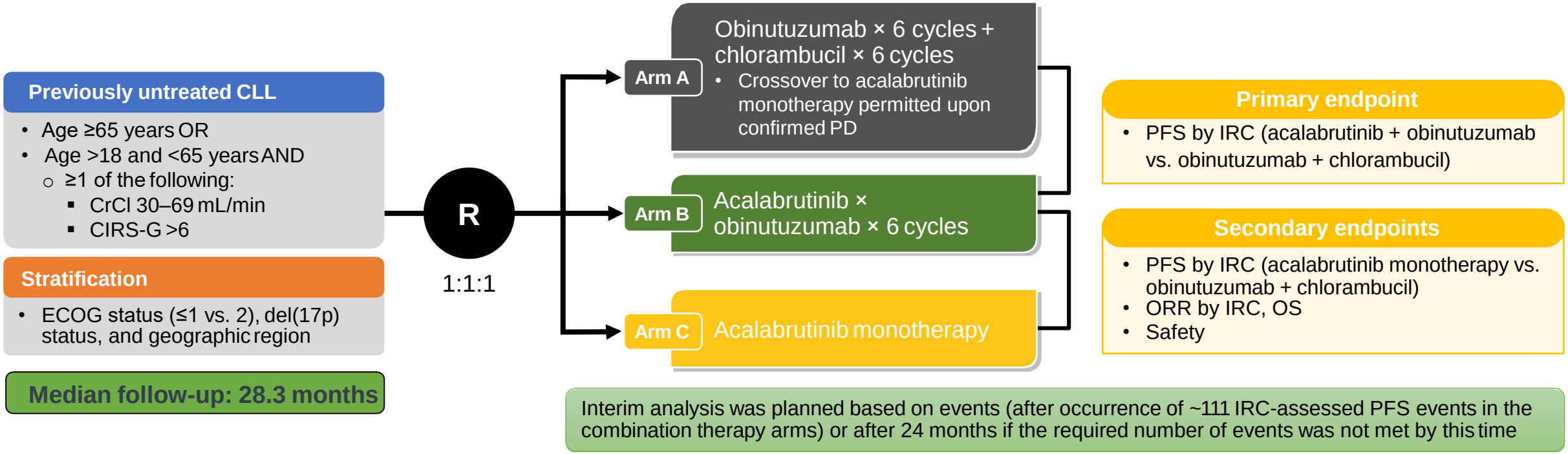
Kinase	IC_{50} (nM)	
	Acalabrutinib	Ibrutinib
JAK3†	>1,000 (N=3)	32 ± 15 (N=3)
BLK†	>1,000 (N=3)	0.1 ± 0.0 (N=3)
FGR	>1,000 (N=2)	3.3 ± 1.1 (N=2)
FYN	>1,000 (N=2)	29 ± 0 (N=2)
HCK	>1,000 (N=2)	29 ± 0 (N=2)
LCK	>1,000 (N=2)	6.3 ± 1.3 (N=2)
LYN	>1,000 (N=2)	20 ± 1 (N=2)
SRC	>1,000 (N=2)	19 ± 1 (N=2)
YES1	>1,000 (N=2)	4.1 ± 0.2 (N=2)

*Acalabrutinib and ibrutinib comparison of *in vitro* activity inhibitory profiles for recombinant enzymes of Tec, ErbB, Src family kinases, and other related kinases. For experiments with N=3 or N=4, plus/minus standard deviation is shown. For experiments with N=2, plus/minus the error/range over the two independent experiments is shown. IC_{50} denotes half maximal inhibitory concentration. †Kinases with a cysteine aligning with cysteine 481 in BTK.

Byrd JC *et al. N Engl J Med* 2016; 374 (4): 323–332.

ELEVATE-TN (ACE-CL-007): Study design

- Phase III study: Acalabrutinib with obinutuzumab or alone vs. obinutuzumab plus chlorambucil in treatment-naive chronic lymphocytic leukemia



Dosing: Arm A – Obinutuzumab and chlorambucil were administered for a maximum of six 28-day treatment cycles. Obinutuzumab 1,000 mg IV was administered on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), 8, and 15 of Cycle 1 followed by 1,000 mg on Day 1 of Cycles 2 up to 6. Chlorambucil 0.5 mg/kg was administered on Days 1 and 15 of Cycles 1 up to 6; Arm B – Acalabrutinib dosed at 100 mg BID until disease progression or unacceptable toxicity. Obinutuzumab was administered IV starting on Cycle 2 Day 1 for a maximum of six 28-day treatment cycles. Obinutuzumab 1,000 mg was administered on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), 8, and 15 of Cycle 2 followed by 1,000 mg on Day 1 of Cycles 3 up to 7; Arm C – Acalabrutinib dosed at 100 mg BID until disease progression or unacceptable toxicity.
BID, twice a day; CIRS-G, Cumulative Illness Rating Scale for Geriatric; CLL, chronic lymphocytic leukemia; CrCl, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; IRC, independent review committee; ORR, overall response rate; OS, overall survival; PD, progressive disease, PFS, progression-free survival; R, randomization.
Sharman JP *et al*. Abstract 31 presented at the 61st American Society of Hematology (ASH 2019); Orlando, FL, USA, December 7–10, 2019. This study is registered at ClinicalTrials.gov (NCT02475681).

ELEVATE-TN: Events of clinical interest for acalabrutinib

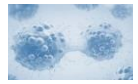
AEs, n (%)	Acalabrutinib + Obinutuzumab (n=178)		Acalabrutinib (n=179)		Obinutuzumab + chlorambucil (n=169)	
	Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3
Atrial fibrillation	6 (3.4)	1 (0.6)	7 (3.9)	0	1 (0.6)	0
Hypertension	13 (7.3)	5 (2.8)	8 (4.5)	4 (2.2)	6 (3.6)	5 (3.0)
Bleeding **Major bleeding***	76 (42.7) 5 (2.8)†	3 (1.7) 3 (1.7)	70 (39.1) 3 (1.7)‡	3 (1.7) 3 (1.7)	20 (11.8) 2 (1.2)§	0 0
Infections	123 (69.1)	37 (20.8)	117 (65.4)	25 (14.0)	74 (43.8)	14 (8.3)
Second primary malignancies, excluding non-melanoma skin cancer	10 (5.6)‖	6 (3.4)	5 (2.8)#	2 (1.1)	3 (1.8)¶	2 (1.2)

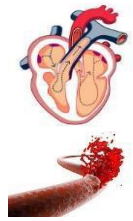
There were no reported events of ventricular tachyarrhythmias.
*Defined as any serious or Grade ≥3 hemorrhagic event, or any grade hemorrhagic event in the central nervous system. †Includes gastric ulcer hemorrhage, gastrointestinal hemorrhage, hematemesis, postprocedural hemorrhage, and subdural hemorrhage. ‡Includes hemarthrosis, postprocedural hematoma, and retinal hemorrhage. §Includes subdural hemorrhage and hemoptysis. ‖Includes non–small cell lung cancer (n=2), squamous cell carcinoma (n=2), basosquamous carcinoma, bladder transitional cell carcinoma, breast cancer, gastric cancer Stage IV, metastases to bone, prostate cancer, and renal cell carcinoma (all n=1). #Includes prostate cancer (n=2), glioblastoma, malignant melanoma *in situ*, transitional cell carcinoma (all n=1). ¶Includes prostate cancer, acute myelomonocytic leukemia, and lung adenocarcinoma (all n=1).
AE, adverse event.
Sharman *et al*. Abstract 31. Oral presentation at 61st American Society of Hematology (ASH 2019); Dec 7–10, 2019. This study is registered at ClinicalTrials.gov (NCT02475681).

Zanubrutinib: A potent and selective BTK inhibitor[1,2]

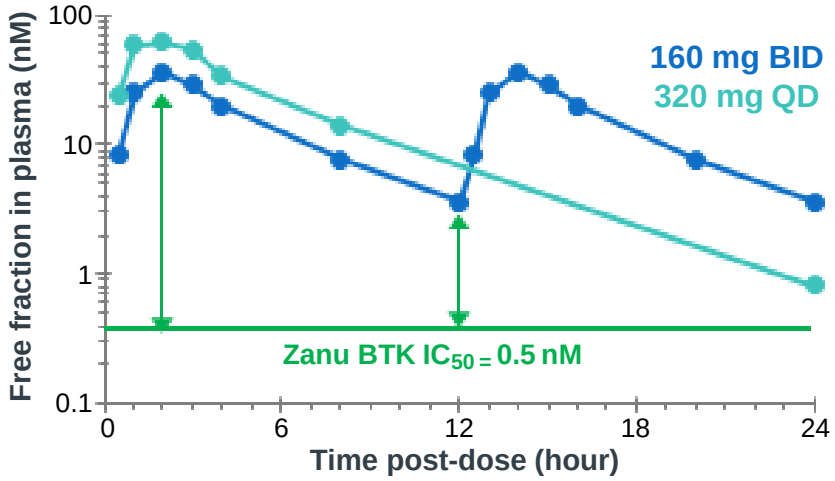
Kinase inhibition

Targets	Assays	Zanubrutinib IC_{50} (nM)	Ibrutinib IC_{50} (nM)	Ratio (Zanubrutinib:Ibrutinib)
BTK	BTK-pY223 Cellular Assay	1.8	3.5	0.5
	Rec-1 Proliferation	0.36	0.34	1.1
	BTK Occupation Cellular Assay	2.2	2.3	1.0
	BTK Biochemical Assay	0.22	0.2	1.1
EGFR	p-EGFR HTRF Cellular Assay	606	101	6
	A431 Proliferation	3210	323	9.9
ITK	ITK Occupancy Cellular Assay	606	189	17
	p-$PLC_{\gamma1}$ Cellular Assay	3433	77	45
	IL-2 Production Cellular Assay	2536	260	9.8
	ITK Biochemical Assay	30	0.9	33
JAK3	JAK3 Biochemical Assay	200	3.9	51
HER2	HER2 Biochemical Assay	661	9.4	70
TEC	TEC Biochemical Assay	1.9	0.8	2.4

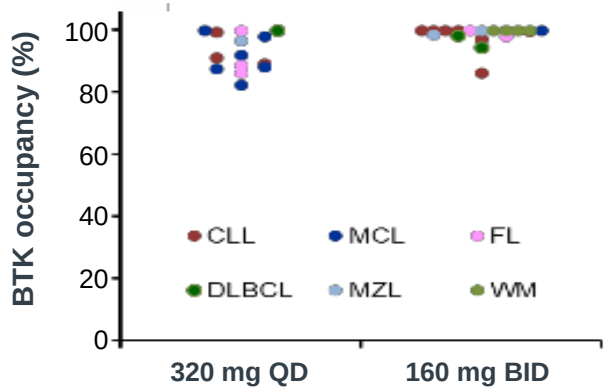




C_{max} and C_{trough} >BTK IC_{50} over 24 hours



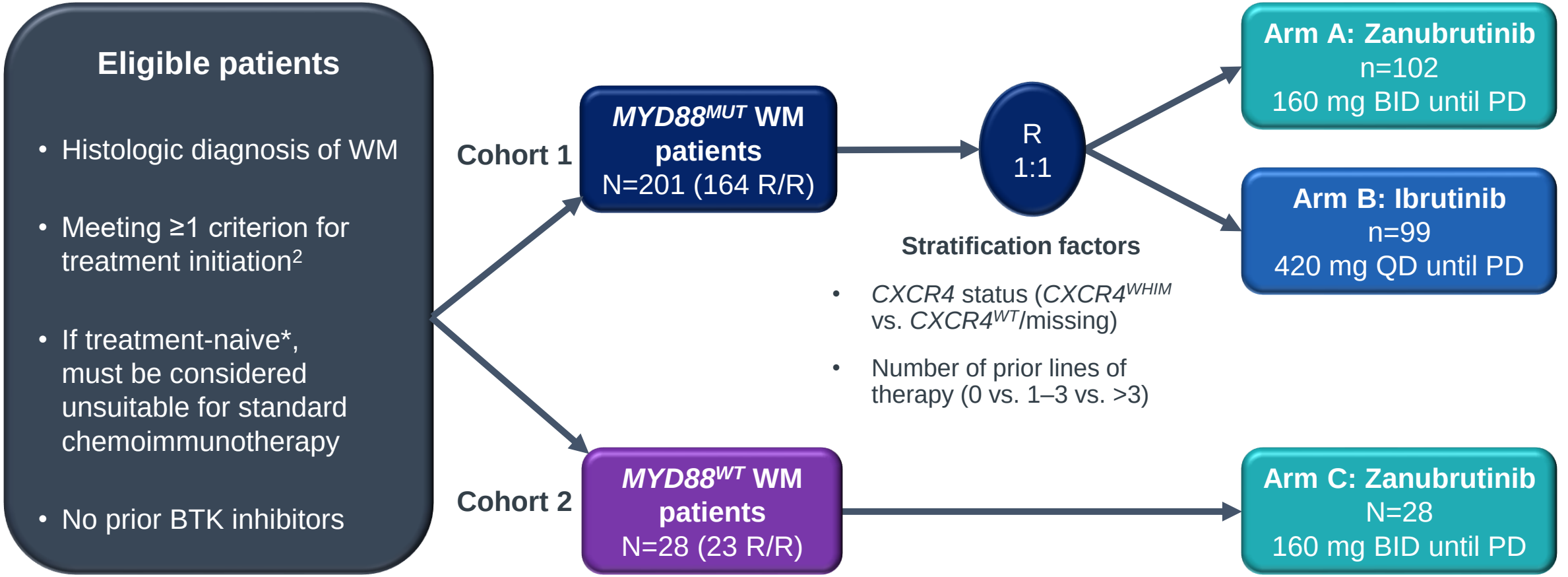
Complete, sustained BTK occupancy



BID, twice a day; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; IC_{50}, half maximal inhibitory concentration; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; QD, every day; WM, Waldenström macroglobulinemia; Zanu, zanubrutinib.

1. Guo Y *et al. J Med Chem* 2019; 62 (17): 7923–7940. 2. Tam CS *et al. Blood* 2019; 134 (11): 851–859.

ASPEN study design: Zanubrutinib vs. ibrutinib in *MYD88*^{MUT} WM[1]



Poster: EP1180

EUDRACT 2016-002980-33; NCT03053440

*Up to 20% of the overall population.

BID, twice a day; BTK, Bruton's tyrosine kinase; MUT, mutated; PD, progressive disease; QD, every day; R, randomization; R/R, relapsed/refractory; WHIM, warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis; WM, Waldenström's macroglobulinemia; WT, wild-type.

1. Tam CS *et al*. Abstract 8007 presented at the 2020 American Society of Clinical Oncology (ASCO) Annual Meeting (virtual); May 29– 31, 2020. 2. Dimopoulos MA *et al. Blood* 2014; 124 (9): 1404–1411.

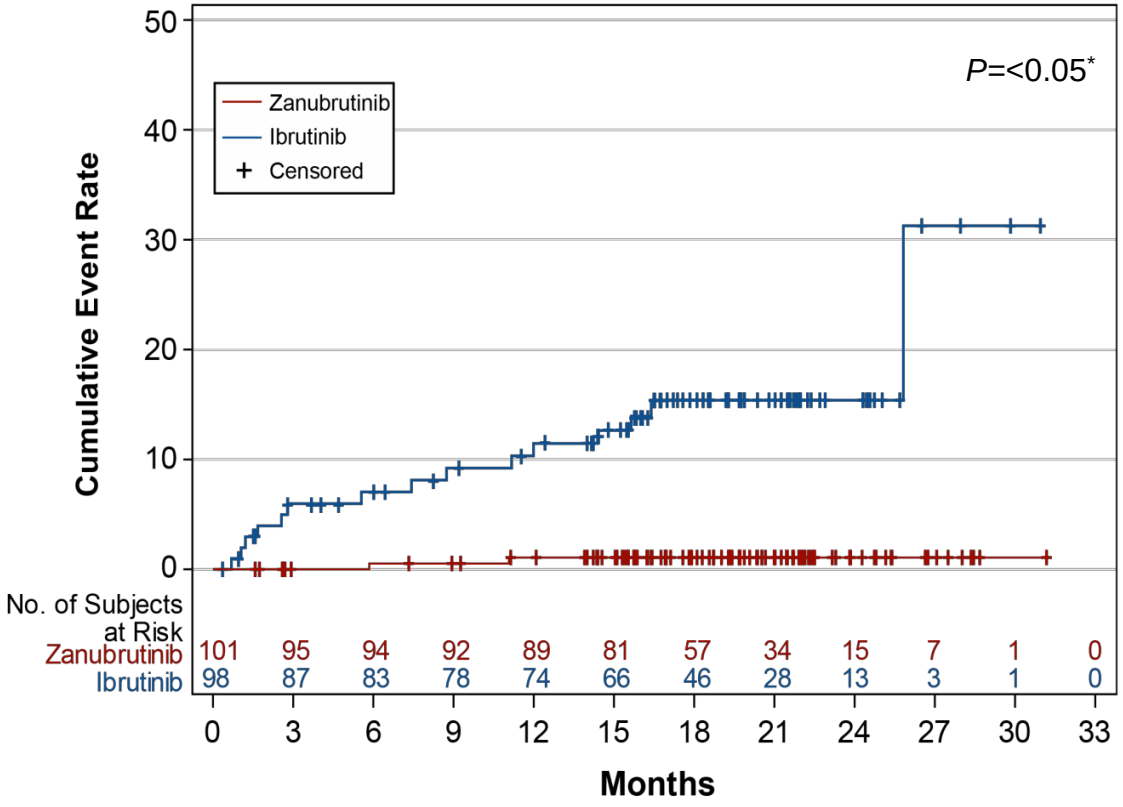
ASPEN study: Adverse event categories of interest
5-month follow-up

AE categories, n (%) *(pooled terms)*	All grades		Grade ≥3	
	Ibrutinib (n=98)	Zanubrutinib (n=101)	Ibrutinib (n=98)	Zanubrutinib (n=101)
Atrial fibrillation/flutter*	**18 (18.4%)**	3 (3.0%)	7 (7.1%)	0
Diarrhea (PT)	**32 (32.7%)**	22 (21.8%)	2 (2.0%)	3 (3.0%)
Hemorrhage	**59 (60.2%)**	51 (50.5%)	9 (9.2%)	6 (5.9%)
Major hemorrhage†	10 (10.2%)	6 (5.9%)	9 (9.2%)	6 (5.9%)
Hypertension	20 (20.4%)	13 (12.9%)	**15 (15.3%)**	8 (7.9%)
Neutropenia*,‡	15 (15.3%)	**32 (31.7%)**	8 (8.2%)	**23 (22.8%)**
Infection	70 (71.4%)	70 (69.3%)	23 (23.5%)	19 (18.8%)
Second malignancy	12 (12.2%)	13 (12.9%)	1 (1.0%)	3 (3.0%)

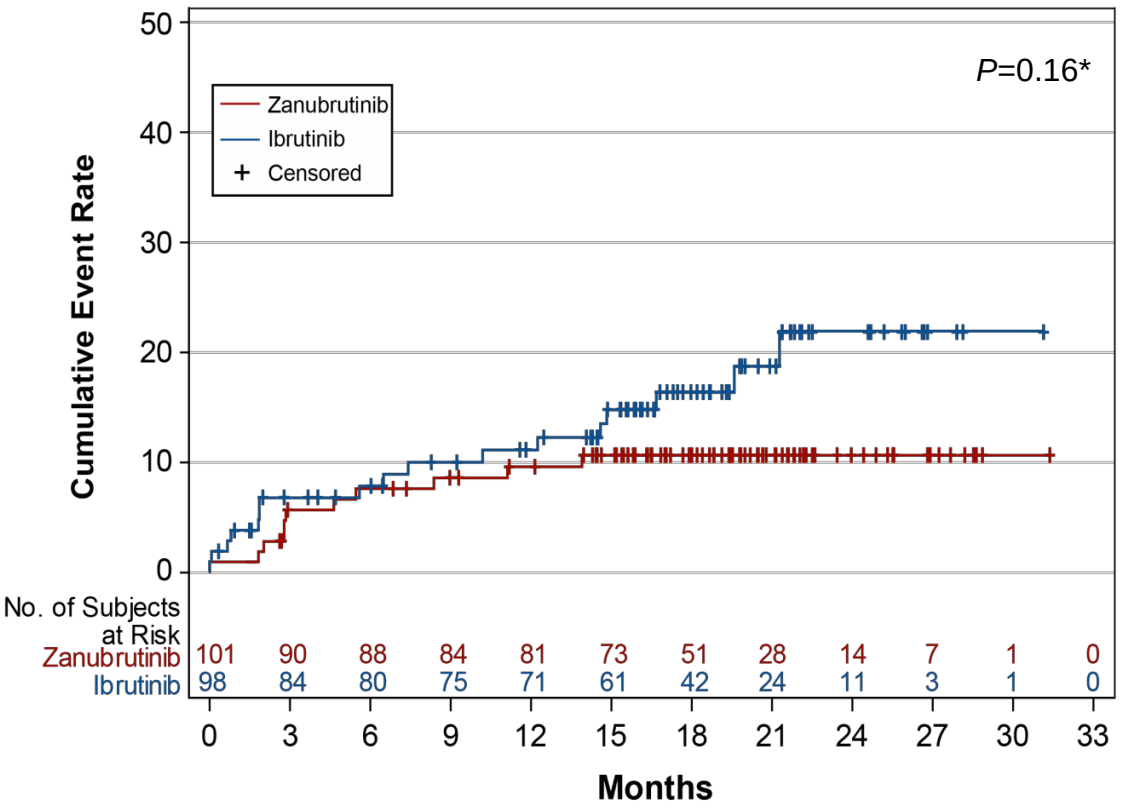
Data cut-off: January 31, 2020.
Higher AE rate in bold with ≥10% difference in any grade AEs or ≥5% difference in Grade ≥3 AEs.
*Descriptive two-sided *P*-value <0.05. †Defined as any Grade ≥3 hemorrhage or any grade central nervous system hemorrhage. ‡Including PTs of neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection, and neutropenic sepsis.
AE, adverse event; PT, preferred term.
Tam CS *et al*. Oral presentation at the 2020 American Society of Clinical Oncology (ASCO) Annual Meeting; May 29–31, 2020. This study is registered at ClinicalTrials.gov (NCT03053440).

Time to adverse event: Risk analysis over duration of treatment

Time to atrial fibrillation/flutter



Time to hypertension



*Descriptive purpose only.

Tam CS *et al*. Oral presentation at the 2020 American Society of Clinical Oncology (ASCO) Annual Meeting; May 29–31, 2020. This study is registered at ClinicalTrials.gov (NCT03053440).

Conclusions

- Cardiac supraventricular arrhythmias are the most frequent cardiovascular complications observed with BTK inhibitors
- In a prospective multicenter cohort study with systematic cardio-oncology follow-up the risk of ibrutinib-related atrial fibrillation was 38% at 2 years (15-fold the risk in the general population)[1]
  - Most cases occurred in asymptomatic patients within the first 6 months of ibrutinib initiation, justifying standardized and close monitoring during this period
- Management is based on reducing the risk of:
  - Thromboembolic and heart failure risks
  - BTK inhibitor arrest
- The risk of atrial fibrillation depends on the off-target kinome of the drugs and is lower in new-generation BTK inhibitors

- **Close cooperation between cardiologists and hematologists is needed to better manage patients with WM and other hematologic cancers treated with BTK inhibitors**

1. Baptiste F *et al. Open Heart* 2019; 6 (1): e001049.

Discussion and audience Q&A

Chair: Dr. Alessandra Tedeschi

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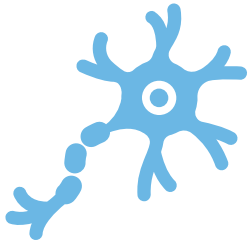
Summary

Chair: Dr. Alessandra Tedeschi

Summary

Optimal WM management requires co-ordination with an extended team comprising a diverse range of specialists



The varied neuropathic complications associated with WM demand careful history-taking and examination in diagnosis

Ibrutinib is associated with a significant risk of cardiovascular adverse events, particularly atrial fibrillation; new-generation BTK inhibitors may have greater specificity and reduced cardiovascular risks

WM, Waldenström's macroglobulinemia.

Save the date!

Management of hematologic malignancies during the COVID-19 pandemic

Join us in **July 2021** for a timely discussion on prioritizing and adapting treatment strategies

We would appreciate your feedback!

Please complete the post-meeting survey.

Thank you for your attention

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