Pick your Poison
or
Playing the Long Game

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IWMF 2024 Educational Forum May 3 - 5, 2024 Hyatt Regency Lake Washington

Pick your Poison
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Playing the Long Game

in managing your Waldenström Macroglobulinaemia

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concord haematology & CLINICAL RESEARCH UNIT

ALG AUSTRALASIAN LEUKAEMIA & LYMPHOMA GROUP

Trials funding to Institution:
Roche, BMS, Beigene, Takeda, Janssen, Pharmacyclics,
IWMF, Foundation for A Bloody Great Cause!
No personal financial COI

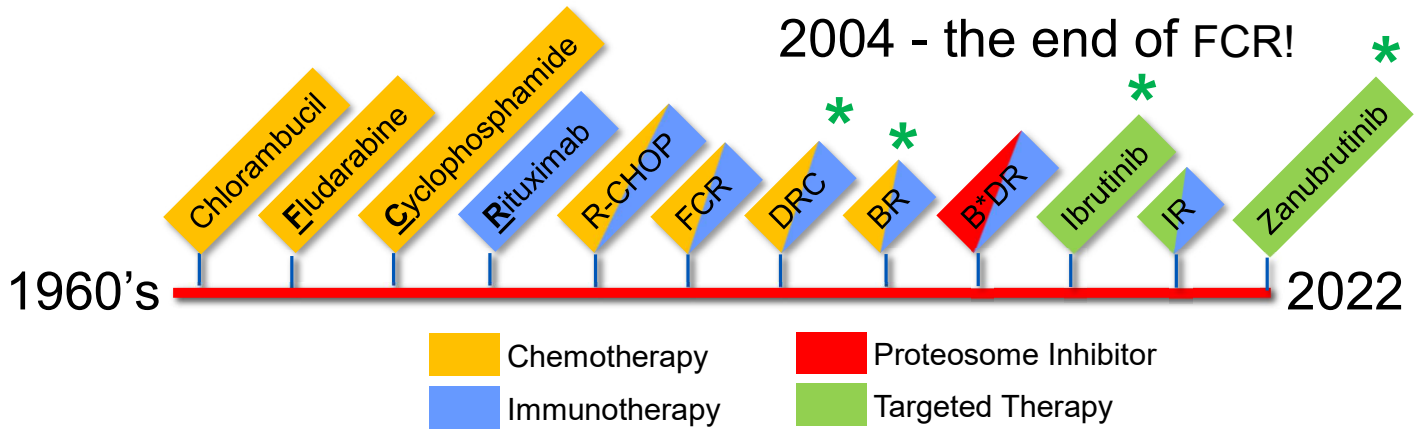
Thanks to Dr Jonas Paludo, Mayo Clinic, for his original slides

LEARNING OBJECTIVES

- Review current treatment options
- Emerging therapies in clinical trials
- Clinical trial participation

1 REVIEW OF CURRENT TREATMENT OPTIONS

TIMELINE OF NEW THERAPIES IN WM



R – Rituximab
D – dexamethasone
C – cyclophosphamide
B – bendamustine
B* – bortezomib
I – ibrutinib

Not an all-inclusive list of treatments …

WhiMSICAL patient population

- WhiMSICAL patient-derived data registry update in 2022
- n=650, median age at diagnosis 62 years, 61% male,
- Median lines of treatment 1 (IQR 1-2), Watch & Wait 18%
- Numerous first line treatments used, fewer since 2016

American Journal of Hematology AJH

CORRESPONDENCE | Free Access

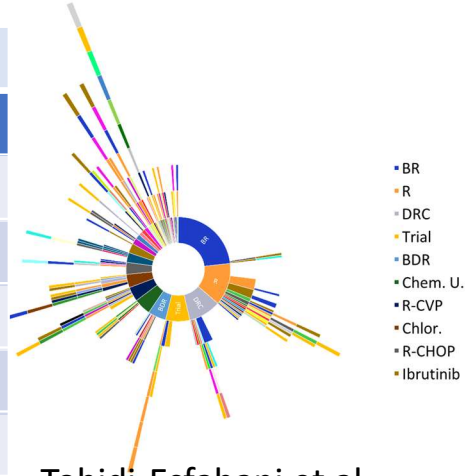
WhiMSICAL: A global Waldenström's Macroglobulinemia patient-derived data registry capturing treatment and quality of life outcomes

Ibrahim Tohidi-Esfahani, Andrew Warden, Elena Malunis, Peter L. DeNardis, Javier Haurat, Marita Black, Stephen Opat, Damien Kee, Shirley D'Sa, Marie José Kersten, Ruth L. Spearing, Maria Lia Palomba, Adam J. Olszewski, Carl Harrington, Clare L. Scott, Judith Trotman
... See fewer authors

First published: 23 March 2021 | https://doi.org/10.1002/ajh.26173 | Citations: 10

Before 2016 – First line (n=200)	
Regimen	**n (%)**
Rituximab monotherapy	38 (19)
R-CP/R-CVP/R-CHOP	28 (14)
Bendamustine Rituximab	23 (12)
Dexameth. Ritux. Cycloph.	21 (11)
Fludarabine-based	20 (10)
Bortezomib-based	17 (9)
BTK inhibitors	5 (3)

After 2016 – First line (n=233)	
Regimen	**n (%)**
Bendamustine Rituximab	102 (44)
BTK inhibitors	51 (22)
Rituximab monotherapy	26 (11)
Dexameth. Ritux. Cycloph.	18 (8)
Bortezomib-based	8 (3)
R-CP/R-CVP/R-CHOP	5 (2)
Fludarabine-based	2 (1)



Tohidi-Esfahani et al, Am J Hematology, 2021
IWWM-11 2022

The Tumor Board:

Helping you choose your poison

Quality, documented multidisciplinary peer-review of blood cancer care plan for a given patient.

*In Australia we call it the MDT – Multidisciplinary Team meeting

concord haematology

MDT Meeting Date: 20/04/2011
Consultant: Trotman

Haematology Multidisciplinary Team Meeting

Name: [redacted] MRN: 1103966
Date of Birth: 26/01 1945 Age: 66 Sex: Male

Medical History: Depression and chronic back pain

Social History: Divorced, socially isolated.

ECOG: LVEF (%): >50% Height (cm): 178 Weight (kg): 91

Show/Hide ECOG Performance Status Options

Presentation: Weight loss and vomiting due to gastric outlet obstruction. Fe deficiency anaemia. Gastroscopy 1.04.11 large pre pyloric ulcer: biopsy DLBCL H Pylori negative.

CT staging: gastric thickening with outlet obstruction, gastric and periportal nodes: Stage IIE or Stage IV?
PET-CT staging Gastric and omental involvement / plus upper abdominal lymph nodes. BMAT normal.

Diagnosis Category: NHL CLL Myeloma Hodgkin Leukaemia/MPD

Date of Diagnosis	Diagnosis	Stage/Class	Current Status
01/04/2011	Diffuse Large B Cell	IV	Newly Diagnosed

Show/Hide Ann Arbor Staging

Prognostic Indicators: IPI FLIPI Other

Age ≥ 60 yrs	Stage III/IV	> 1 extra nodal	Elevated LDH	ECOG ≥ 2	Score
☑	☑	☑	☐	☑	4
Risk Group	High	5 year survival	26%	CRR	44%

Treatment: Chemotherapy Select... Other
Cycles Start date
ASCT Select... Date

Hb: 91 WCC: 11.5 Neut: 7.2 Lymph: 2.9 Plt: 1145
Biochem: LDH 188 at diagnosis.

Show/Hide Figure Show/Hide Attach.

Proposed Management: R-CHOP14x6. To offer patient participation in either NHL21 or REMARC study. Haematologist preference for REMARC.
Underwent informed consent and enrolled on REMARC study. Currently tolerating R-CHOP well.

Timing of repeat gastroscopy? After C3?

MDT Conclusion: R-CHOP14x6 with PET-CT and gastroscopy after #3

Trial Option: ☑ Trial Name: NHL25 (REMARC)
NHL25 (REMARC) Protocol

Verified By: Estell

Attendees:
☐ Cunningham ☐ Curnow ☑ Estell ☐ Kwan ☑ Trotman ☑ Gordon
☑ Caroll/RadOnc ☑ Radiologist ☑ Pathologist ☐ Care Cordinat ☑ Clinical Trials ☐ Transplant
☐ Allied Health ☐ Other

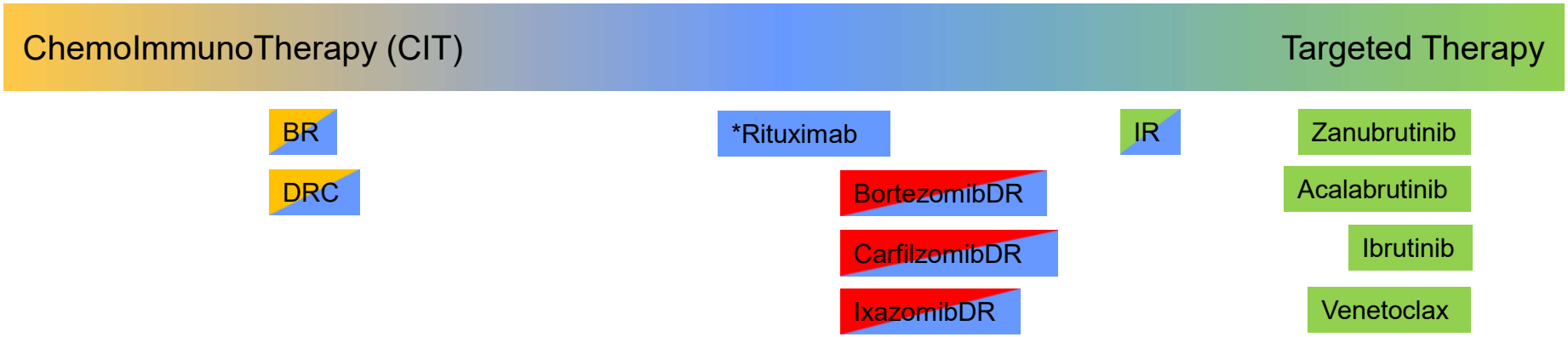
CLASSIFICATION

*Rituximab - antibody directed against the CD20 protein (antigen) expressed on the surface of all B-cells, including WM cells

Classification of treatment options

Duration of therapy

Drug class composition



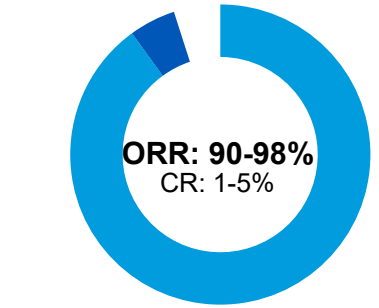
COMMONLY USED TREATMENTS

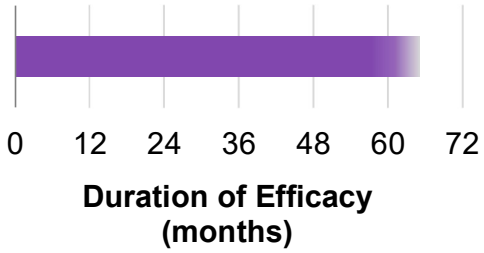
BR – Bendamustine + Rituximab

- Fixed Duration
- IV Infusion
- Chemo Immuno

- Preferred CIT regimen for young/fit when aiming for deep durable responses and/or rapid debulking of disease

- Schedule
  - IV infusion x2 days,
  - every 4 weeks, for 6 cycles
- Efficacy
  - 90-98% response
  - Duration of efficacy:
    - Median 58-69 months
  - Debate over dose & duration:
  - If someone not fit enough for full dose BR I give DRC …
- Common & serious side effects
  - Low blood counts, fatigue, increased risk of infections, infusion reactions (rituximab)
- Special considerations
  - With any chemo, risk of secondary MDS/AML (0 - 5%)





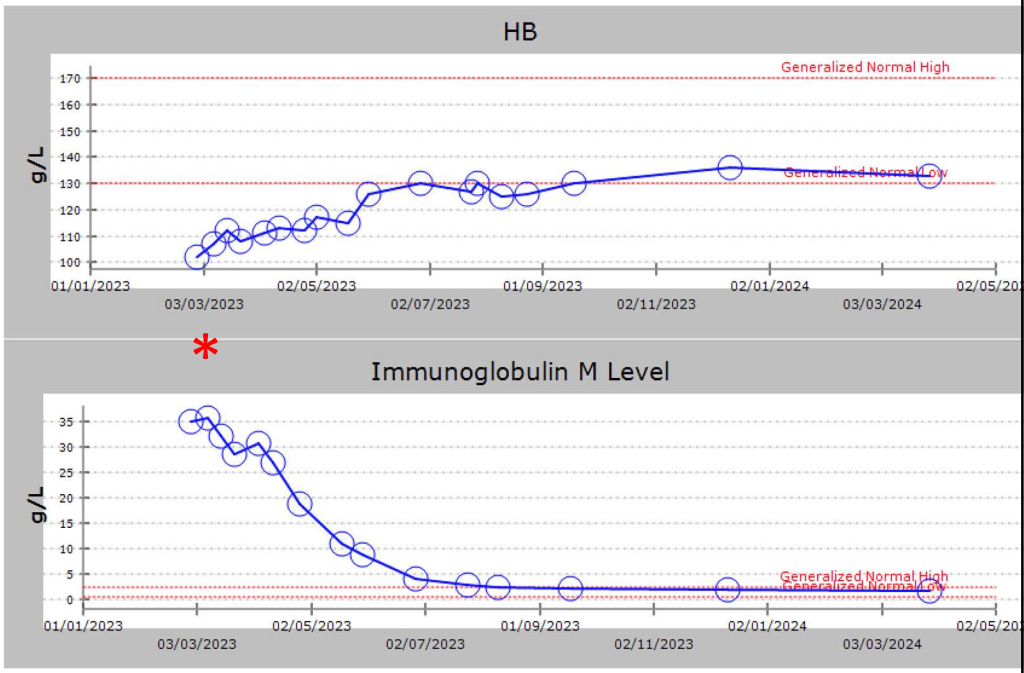
Zanwar S, Abeykoon JP. Treatment paradigm in Waldenström macroglobulinemia: frontline therapy and beyond. Ther Adv Hematol. 2022;13:20406207221093962. Published 2022 Apr 29.
Ravi G, Kapoor P. Current approach to Waldenström Macroglobulinemia. Cancer Treat Res Commun. 2022;31:100527.

1L treatment: fit 60-year-old man

- 60 y.o. manager working full time
- Fatigued, joint aches
- Hb 100g/L, IgM 36g/L*

- Treated with 6x BR from Mar 2023
- G-CSF injection for low neutrophils C6
- Well tolerated. No infections

- Hb rose from 100g/L to 132g/L
- IgM dropped from 36 to 2g/L



Hb 100g/L = 10g/dL
IgM 36g/L = 3600mg/dL

"In retrospect I was a lot more tired than I thought I was before treatment"

COMMONLY USED TREATMENTS

DRC – Dex + Rituximab + Cyclophosphamide

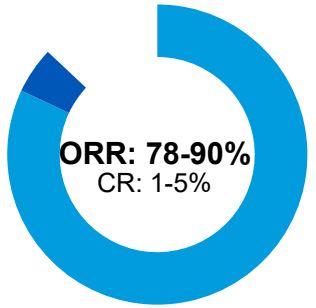
Fixed Duration

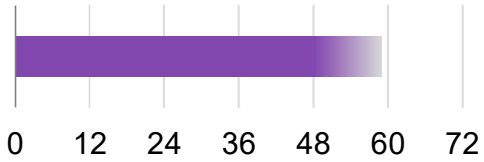
IV Infusion / oral

Chemo Immuno

- Preferred antibody/chemo combination when aiming for low toxicity.
- Less fit patients with (s)lower tumor burden.

- Schedule
  - IV infusion x1 day, tablets x5 days, every 3 weeks, for 6 cycles
- Efficacy
  - 80-90% response
  - Duration of efficacy:
    - Median 51-59 months
- Common & serious side effects
  - Low blood counts, fatigue, increased risk of infections, infusion reactions
  - Same but less profound as BR
- Special considerations
  - Small risk of secondary MDS/AML (0 -3%)





Duration of Efficacy (months)

Zanwar S, Abeykoon JP. Treatment paradigm in Waldenström macroglobulinemia: frontline therapy and beyond. Ther Adv Hematol. 2022;13:20406207221093962. Published 2022 Apr 29.
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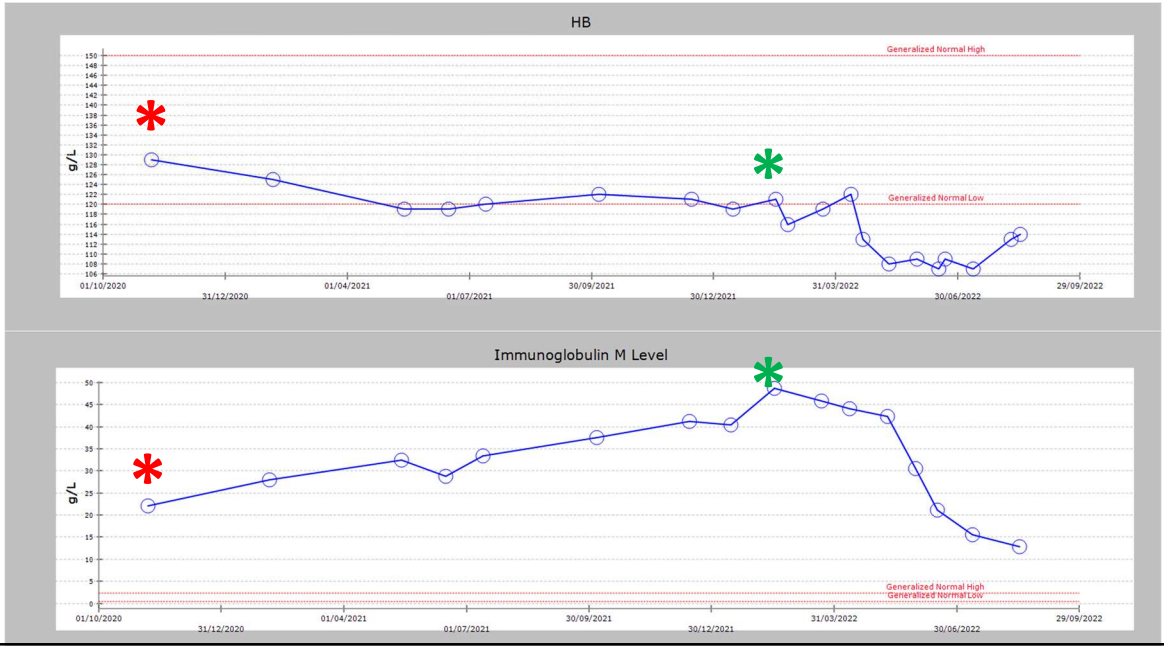
Consider the patient's life expectancy: fit 78 y.o. woman

- Aged 73 in 2016 when IgM 8g/L (800mg/dL).
  It really helps to know the tempo of the WM when choosing treatment.
- Referred in 2020:* IgM 27g/L. Hb 130g/L. (Ig M 2700mg/dL, Hb 13g/L)
- Very fit with no walking limitation despite heart valve disorder
- Early 2022 aged 78: fatigue walking up hills & Hb dropping to 115g/L, IgM 45g/L
- Treated with DRC x6*, a fixed duration therapy, in midst of Omicron COVID wave.
- Next line of treatment will be zanubrutinib – estimated aged 84?



(LESS) COMMONLY USED TREATMENT

R – Rituximab on its own

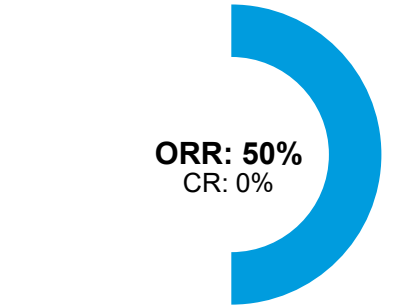
- Limited role in 2024 - inferior response rates & duration. Could be considered to treat hemolytic anemia, or a trial to stablise/treat peripheral neuropathy

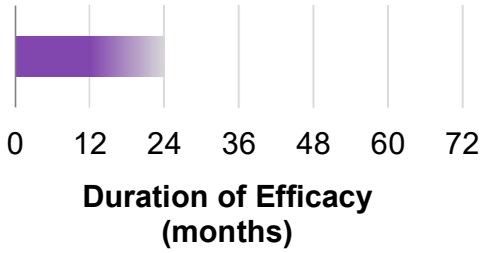
- Schedule
  - IV infusion weekly x1 month
- Efficacy
  - ORR: 50%
  - Duration of efficacy:
    - Median 14-24 months
- Common side effects
  - Infusion reactions, IgM flare in first 2 months in ~50%
- Special considerations
  - Very rare risk of PML

Fixed Duration

IV Infusion

Immunotherapy





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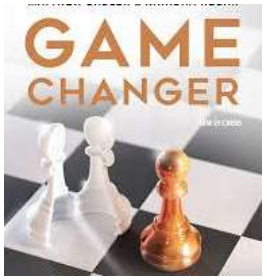
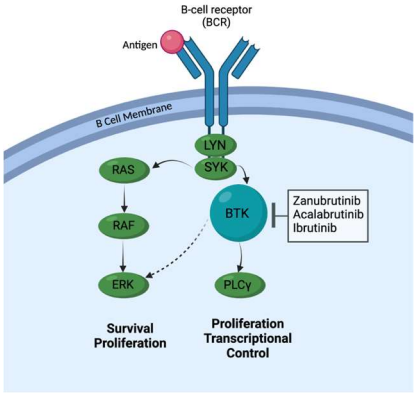
COMMONLY USED TREATMENTS

Ibrutinib





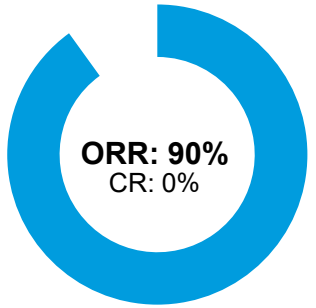
- First in-class BTK inhibitor
- Good tolerability & efficacy
- Good option for patients unfit for chemotherapy

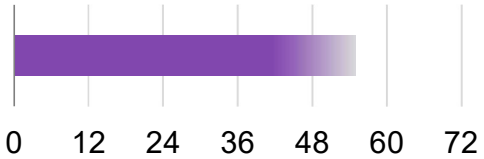
Continuous therapy

Oral

Targeted therapy

- Schedule
  - Oral, daily, no end date
- Efficacy
  - ORR: 90% (50-100%)
  - Duration of efficacy:
    - Median 39 (6-52+) months
    - PFS at 5yr: 54%
      (70% in MYD88^{mut} CXCR4^{WT})
- Common & serious side effects
  - Bruising
  - Low blood counts, hypertension, joint pain, atrial fibrillation
- Special considerations
  - Caution if risk of cardiac arrythmias
  - Withdrawal and IgM Flare





Duration of Efficacy (months)

Treon SP, Meid K, Gustine J, et al. Long-Term Follow-Up of Ibrutinib Monotherapy in Symptomatic, Previously Treated Patients With Waldenström Macroglobulinemia. J Clin Oncol. 2021;39(6):565-575.
Tam CS, Opat S, D'Sa S, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study. Blood. 2020;136(18):2038-2050.
Zanwar S, Abeykoon JP. Treatment paradigm in Waldenström macroglobulinemia: frontline therapy and beyond. Ther Adv Hematol. 2022;13:20406207221093962. Published 2022 Apr 29.

COMMONLY USED TREATMENTS

Ibrutinib

- First in-class BTK inhibitor
- Good tolerability & efficacy
- Good option for patients unfit for chemotherapy.

1st in class. Not best in class.

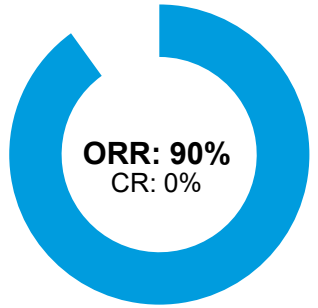
For patients currently on Ibrutinib – dose reductions for intolerance (more common in women {40% vs 20%}, esp. elderly) do not impair disease control.
If its working and well tolerated by you, don't change to a second generation BTK inhibitor.

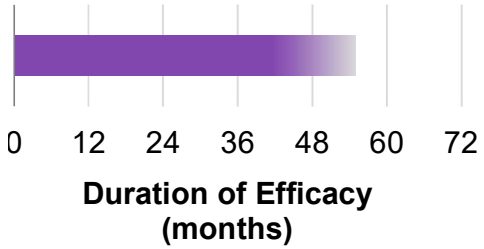
Sarosiek Br J Haem, 2022

Continuous therapy

Oral

Targeted therapy





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COMMONLY USED TREATMENTS

Zanubrutinib

- My preferred BTK inhibitor – efficacious & tolerable
- Better VGPR rates (>90% ↓IgM) than Ibrutinib (38 vs 25%) at 4 years follow-up of the 199 patient ASPEN Randomised Clinical Trial (RCT)

but most importantly

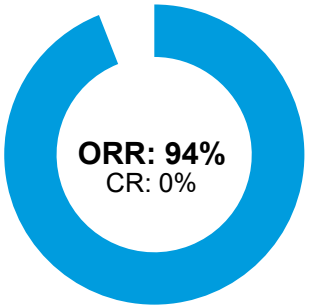
- Better QOL & lower rates of bruising, nausea, diarrhea, hypertension & cardiac effects than Ibrutinib. Discontinuation rate of 9 vs 21%.

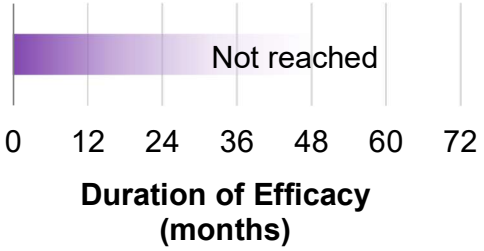
- Schedule
  - Oral daily, continuous
- Efficacy
  - ORR: 94% (80-100%)
  - Good response in the poor risk population MYD88^{WT,} & CXCR4^{mut}
  - ~4yr PFS 78%
- Common & serious side effects
  - Low blood counts, infection, bruising
- Special considerations
  - Increased risk of neutropenia

Continuos therapy

Oral

Targeted therapy



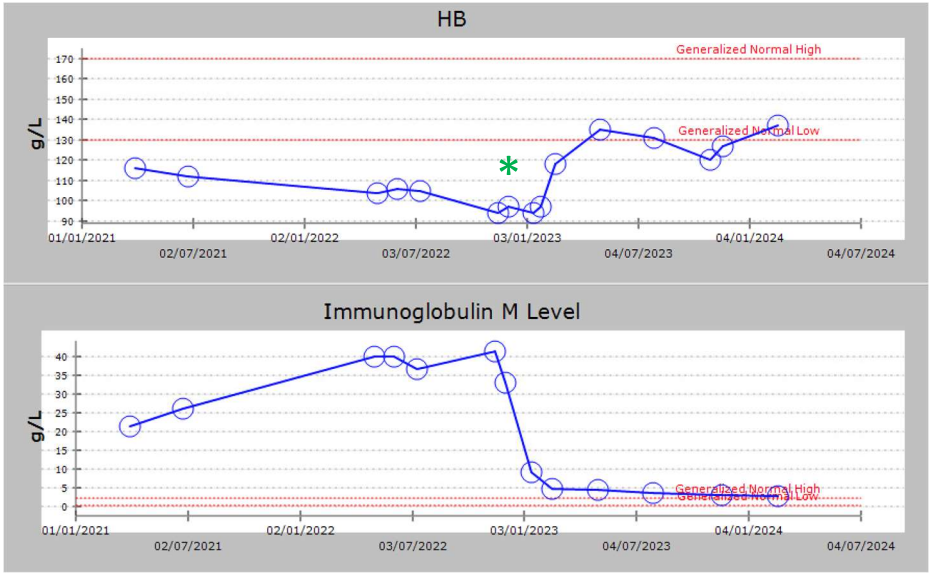


Tam CS, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study. Blood. 2020.
Trotman J, et al. Zanubrutinib for the treatment of patients with Waldenström macroglobulinemia: 3 years of follow-up. Blood. 2020
Dimopoulos M et al, Final analysis of the ASPEN study, J Clinical Oncology 2023

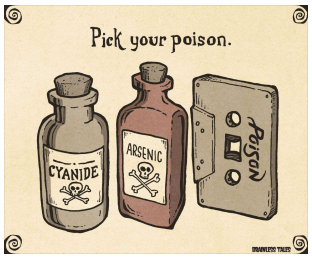
Case study: frail 84-year-old male

- Chronic sinusitis, heart issues
- WM diagnosed in 2009 (aged 69)
- W&W until 2020
- 1 cycle rituximab & bendamustine (aged 80)
  "No more chemo ever again"
  - IgM 44g to 20g/L
  - Hb 93g/L to 115g/L
- Referred in 2021
- Symptomatic progression (fatigue, SOB)
  Dec 2022 - commenced on Zanubrutinib*
- Rapid improvement in exercise tolerance
- Short pause 4 days for skin cancer removal

"Tell them I'm back at bowls"



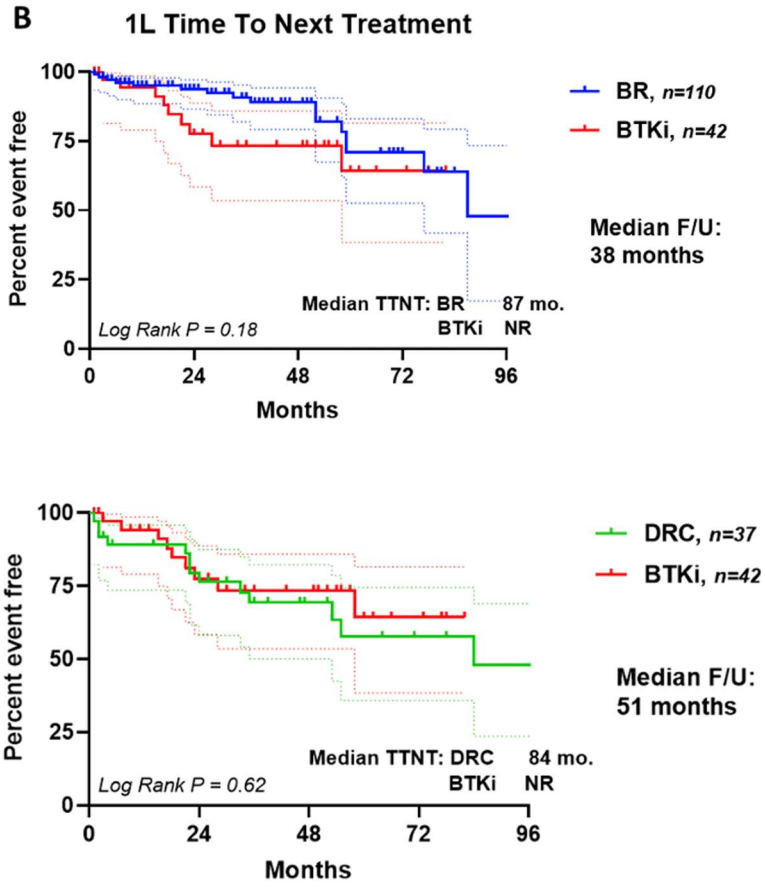
1st line therapy for WM in 2024



My preferred 1st line treatment for most patients is

- Rituximab-chemotherapy:
  - Bendamustine - Rituximab for younger/fitter
  - DRC for older with life expectancy >~7 years
- Zanubrutinib if life expectancy <~7 years
  Closest one can get to a "*set-and-forget*" medicine.
  We don't know how long BTK inhibition will last for.

WhiMSICAL Study of PROs



Tohidi-Esfahani, IWWM-11 Oct 2022

What matters to WM patients?

Cancer Medicine
Open Access

RESEARCH ARTICLE | Open Access

Patient preferences regarding treatment options for Waldenström's macroglobulinemia: A discrete choice experiment

Karima Amaador, Pythia T. Nieuwkerk, Monique C. Minnema, Marie José Kersten, Josephine M. I. Vos

First published: 26 July 2022 | https://doi.org/10.1002/cam4.5080 | Citations: 3

- Progression Free Survival (PFS) based on a 5g/L rise in IgM level is an impt. endpoint for drug registration trials:

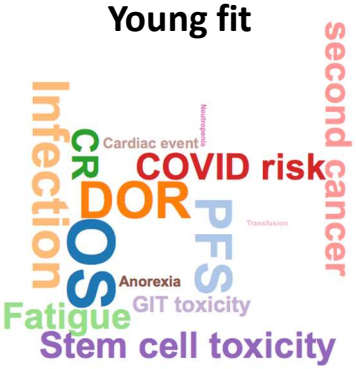
  #1 patient priority in a Dutch Discrete Choice Experiment

- **I argue that Time To Next Treatment and QOL are as/more relevant for patients.**
- We need a WM-specific Health Utility Index akin to the quality-adjusted life year (QALY) used to incorporate the impact of both quantity & quality of life for economic evaluation.
- How would we derive such a utility measure on which a group of clinicians, statisticians and patients (with different ages, comorbidities & cultural backgrounds) would substantially agree?

Frail Elderly

The majority in between

Young fit



The importance of 

a Case study

49 y.o male presents in 2004 (born 1955)

Referred from GP with elevated IgM 25g/L (2500mg/dL)

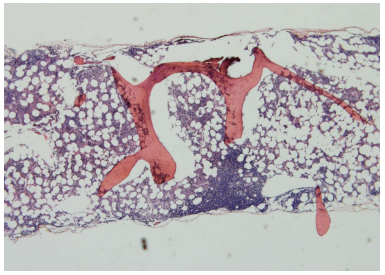
On review in my clinic

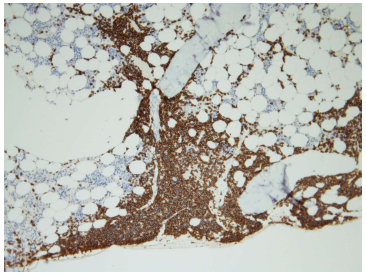
- mild leg cramps.
- occasional night sweat

Family history

- mother died of myeloma aged 72.
- sister lambda light chain MGUS.

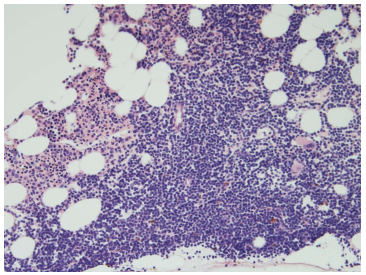
- BM biopsy – 40% lymphoplasmacytic cells / WM.
- Education re WM and "*watch & wait*".
- Plan to treat in the event of symptoms or
  - Hb approaching 100g/L, and/or
  - IgM approaching 50 g/L (5000mg/dL) (to accommodate any IgM flare with rituximab).
  - Timing of treatment arranged around patient's employment / social priorities.

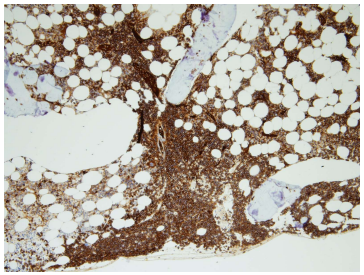




CD20 positive.

CD20 = B-cell protein targeted by rituximab





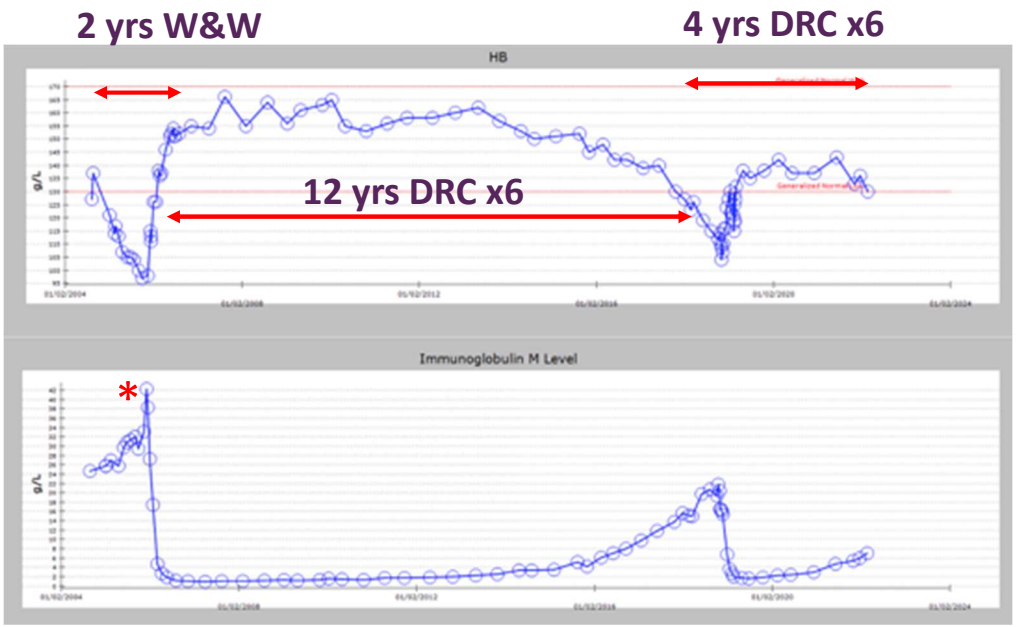
IgM positive

Treatments between 2005 - 2022

2005: Dexamethasone, Rituximab Cyclophosphamide (DRC) x6

- Proposed "*novel treatment without stem cell toxicity*"
- Well tolerated
- IgM flare* Jan 2006 42g/L,
- 10 years Very Good Partial Response:

  (VGPR >90% decrease in IgM)
- 2 years progressive rise in IgM



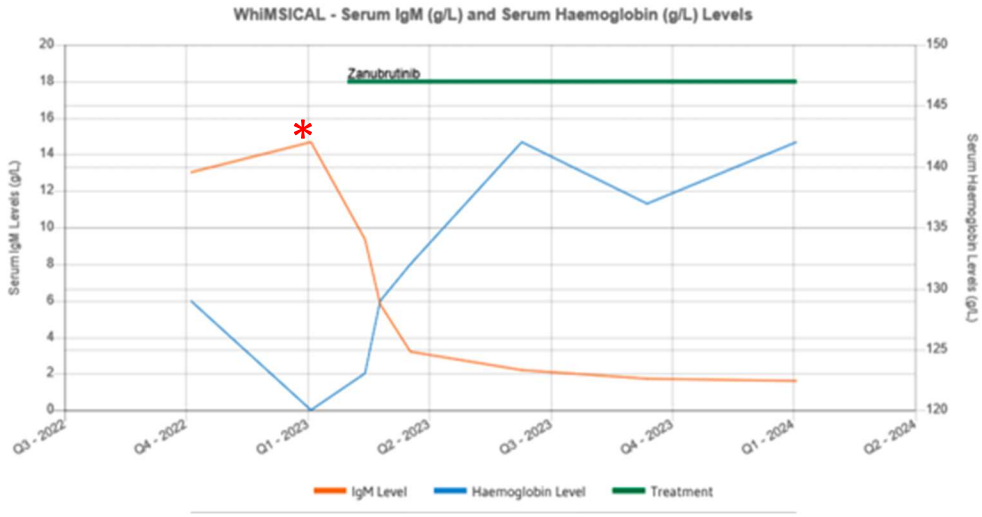
2018: DRC again for symptomatic progression

- Fatigue, leg cramps, night sweats
- DRC again - less well tolerated than in 1L.
- Recurrent sinusitis
- VGPR again for 4 years until July 2022

Dimopoulos JCO 2007, Kastritis Blood 2015

Jan 2023 – age 68

- Retired to South Coast of NSW, Australia
  Telehealth appointments & external blood tests
  - results entered into his WhiMSICAL profile
- Jan 2023* recurrent sweats, fatigue,
- ↑ IgM to 15g/L, Hb 120,
  Low albumin (an impt nutrition protein)
- Commenced Zanubrutinib 160mg bd
- Asymptomatic within 1 week
- Mild hand bruising
- IgM currently 1.6g/L, Hb 142 g/L, normal albumin



Summary: Playing the long game with WM

- Now 68 y.o with a 20-year history of WM
- Treated twice with Dexamethasone Cyclophosphamide Rituximab
- Now on Zanubrutinib: well tolerated, excellent QOL
- Est. 80% 4yr Progression Free Survival (PFS).
  I have some patients on Zanubrutinib >7 years.
- Patients die from secondary cancers & other (vascular) causes as often as from WM
- He wants to live to 85! Told him *"I love a stretch goal"*
- What novel therapy next?
  Pirtobrutinib, Sonrotoclax, BTK protein degrader …

2 POTENTIAL NEW THERAPIES

Promising novel treatments

- Novel combinations of established treatments being trialled
  - BTKi + proteasome inhibitor
  - Zanubrutinib + BCL2 inhibitor
- Covalent BTK inhibitor resistant/intolerant patients:
  - Other non-covalent BTKi: nemtabrutinib, pirtobrutinib
  - BCL2 inhibitors: sonrotoclax, lisaftoclax,
  - BTK protein degraders: BGB-16673, NX-2127, NX-5498

POTENTIAL NEW THERAPIES

Other BTK Inhibitors

- Covalent BTK inhibitors
  - Ibrutinib
  - Acalabrutinib
  - Zanubrutinib
  - Tirabrutinib
  - Orelabrutinib
- Non-covalent BTK inhibitors
  - Pirtobrutinib

Efficacy of Pirtobrutinib, a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor in Relapsed / Refractory Waldenström Macroglobulinemia: Results from the Phase 1/2 BRUIN Study (n = 72 pts)

- Schedule
  - Oral, continuous
- Efficacy
  - 68% major response rate
  - Prior BTKi: MRR of 64%
- Common Side effects
  - Low blood counts, diarrhea, bruising
  - 2% discontinuation rate.
- Good option if disease progressed on covalent BTK inhibitor
- Compassionate access issues globally

(nib = small molecule kinase inhibitor)

Palomba ML, et al. Efficacy of pirtobrutinib, a highly selective, non-covalent (reversible) btk inhibitor in relapsed / refractory Waldenström macroglobulinemia: results from the phase 1/2 BRUIN study. Blood. 2022;140(suppl 1):557-560.

POTENTIAL NEW THERAPIES

BCL-2 enzyme Inhibitors – also oral

Venetoclax

Not yet approved in any country.

In my limited experience:

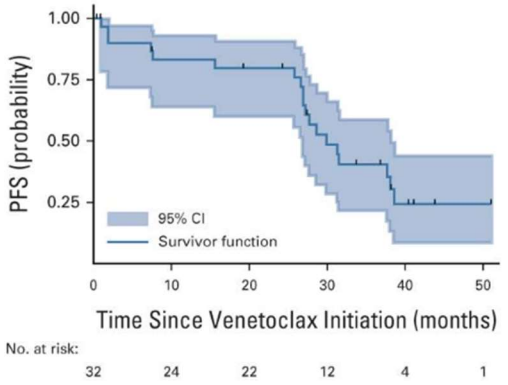
I like to add Rituximab in patients who have not had a major response to venetoclax: e.g. >50 reduction in IgM, improved albumin (nutrition protein) & transfusion independence/ reduction in need.

Sonrotoclax

Second generation bcl-2 inhibitor in clinical trials

Venetoclax in Previously Treated Waldenström Macroglobulinemia

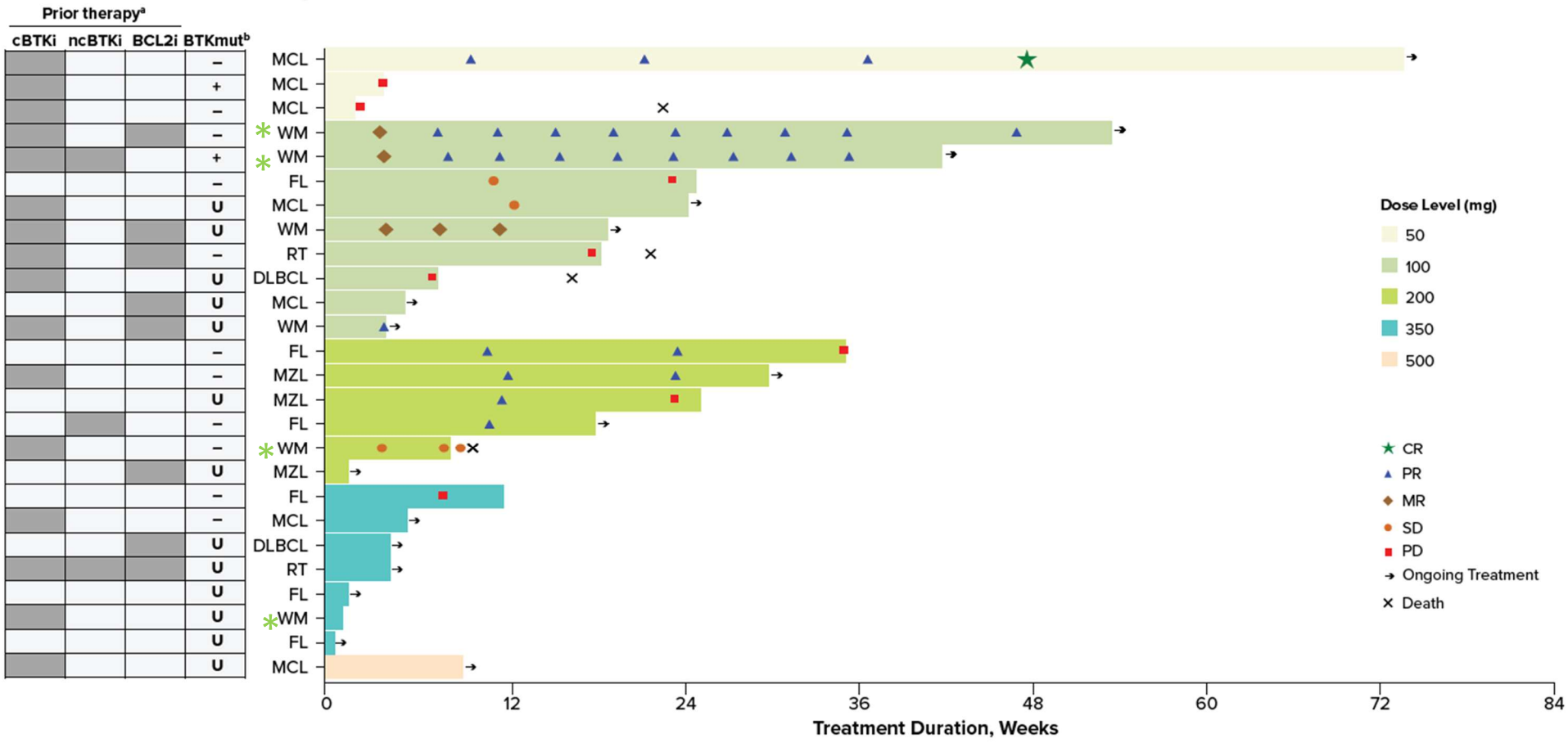
- Schedule
  - Oral, continuous daily treatment for 2 years
- Efficacy
  - ORR: 84%
  - Prior BTKi: ORR of 75%
- Common Side effects
  - Low blood counts, nausea, infections
- Good option with relapsed disease after a BTK inhibitor



Castillo JJ, Allan JN, Siddiqi T, et al. Venetoclax in Previously Treated Waldenström Macroglobulinemia. J Clin Oncol. 2022;40(1):63-71.

BTK protein degrader BGB-16673

very early data in a heavily pre-treated population but promising mechanism of action



Seymour ASH 2023

Other novel treatments studied in WM

- Multiply relapsed patients:
  - Bi-specific T-cell engagers: Epcoritamab, Mosunetuzuamb, glofitamab
  - Alternative antibody (immuno) therapy: loncastuximab, PSB202 (anti-CD20+CD37)
  - Cellular therapies: CAR-T cells, CAR-NK cells
  - Completely new ideas: Iopofosine 131, MALT1 inhib, Mavorixafor (oral CXCR4 inhibitor) for CXCR4 mutated

NOT POTENTIAL NEW THERAPIES

Class	Treatment	Reason
Anti-CD38 mab	Daratumumab	Low efficacy
Check point inhibitor	Atezolizumab / Tiselizumab	No efficacy/toxicity
BCL2 + BTK inhibitor	Venetoclax + ibrutinib	Increased toxicity (cardiac events)

Reminders of the importance of rigorous attention to safety (Priority #1) in clinical trials

Panayiotidis P, Tumyan G, Thieblemont C, et al. A phase-II study of atezolizumab in combination with obinutuzumab or rituximab for relapsed or refractory mantle cell or marginal zone lymphoma or Waldenström's macroglobulinemia. Leuk Lymphoma. 2022;63(5):1058-1069.
Castillo JJ, Libby EN, Ansell SM, et al. Multicenter phase 2 study of daratumumab monotherapy in patients with previously treated Waldenström macroglobulinemia. Blood Adv. 2020;4(20):5089-5092.
Castillo JJ SS, Branagan AR, et al. . Ibrutinib and Venetoclax in Previously Untreated Waldenström Macroglobulinemia. . Blood. 2022;140 (Supplement 1):564-5.

3 CLINICAL TRIAL PARTICIPATION

Drug Development Timeline

TIME IN YEARS

Pre-clinical Research & Development

2- 4 years

Phase 1

Phase 2

Phase 3

Clinical Research and Development

3 – 10 years

Total Cost ~$100 million

Safety

Efficacy: does it work?

Comparison with standard therapy

NEW DRUG APPLICATION – 1-2 years

Post Market Surveillance

Phase 4

Good clinical research / trials

- Asks the 'right' question (reflects (WM) community values / needs)
- Is ethically justifiable, and conducted ethically: Code of Good Clinical Practice (GCP)
- Asks a question that can be reliably answered with minimal bias

Hence a Clinical Trial is,

- **"A carefully designed study conducted under the code of GCP that seeks to determine, under controlled conditions, the safety and effectiveness of a new drug or treatment method"**

- This allows laboratory breakthroughs to be translated into the clinic.

Why participate in clinical trials?

- Direct benefit:
  - from studied therapy
  - even when treatment is standard
    "meticulous concierge care"
- Benefit to medicine / science
- Benefits future patients
  - speeds development of effective therapies
- Access to therapies not available through usual funding mechanisms

Another successful recruitment drive for the Collins University Medical Research Center.

Why not participate in a trial?

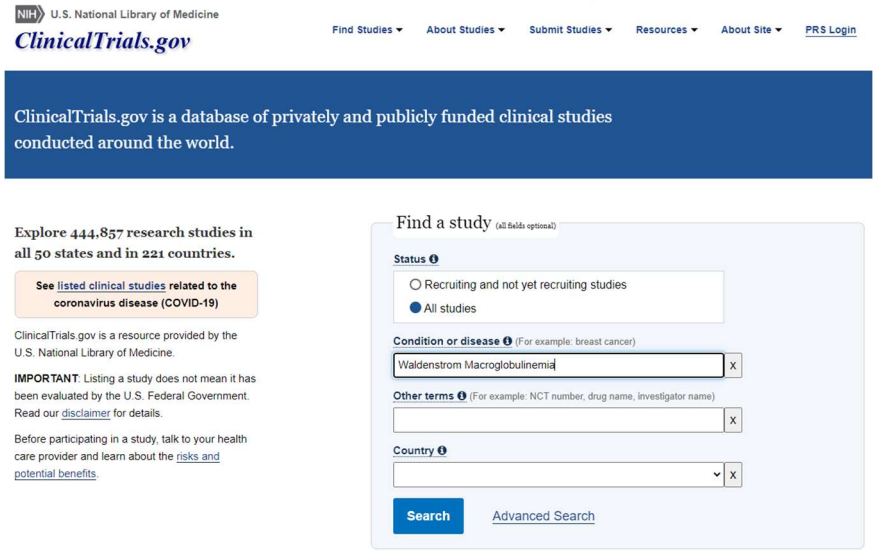
- Not quite the right question for you
- Direct risk (must be acknowledged, usually easily quantified)
- Easier to just have standard of care / best practice.
- Too much to think about – esp. when newly diagnosed
  Most WM patients have time to consider trials participation
- Onerous for patient & clinician (more tests, visits etc.)
- Who really benefits? Study sponsor, future patients or me?
  Will I get access to this drug afterwards?

Medical advances are based on clinical trials

We need to counter negative perceptions of ‘trials’

‘awareness’ ≠ understanding

Always consider a clinical trial if it fits well with your treatment goals, and that of the WM community



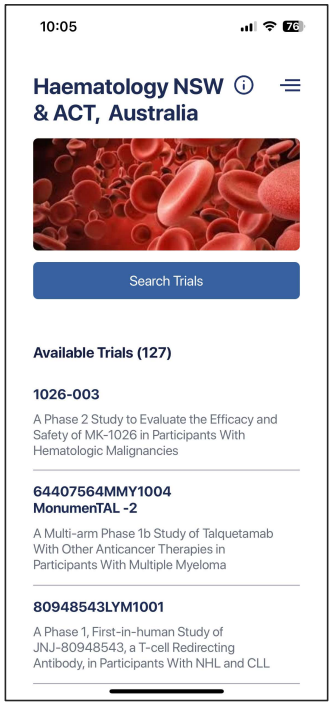
How to find a clinical trial:

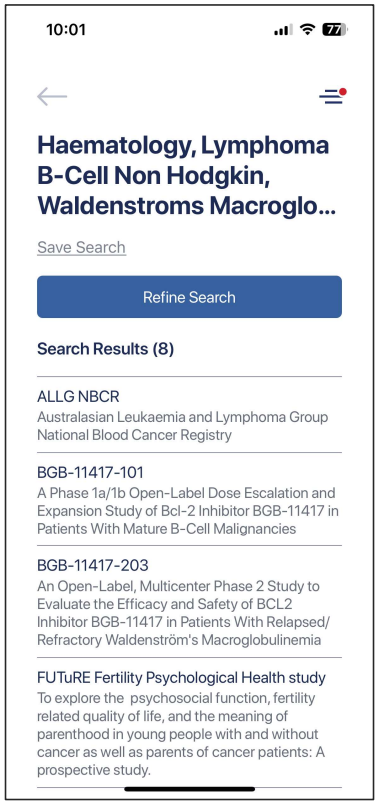
1. Ask your doctor
2. IWMF website
3. clinicaltrials.gov
4. In Australia the ClinTrial Refer App only lists the currently recruiting trials

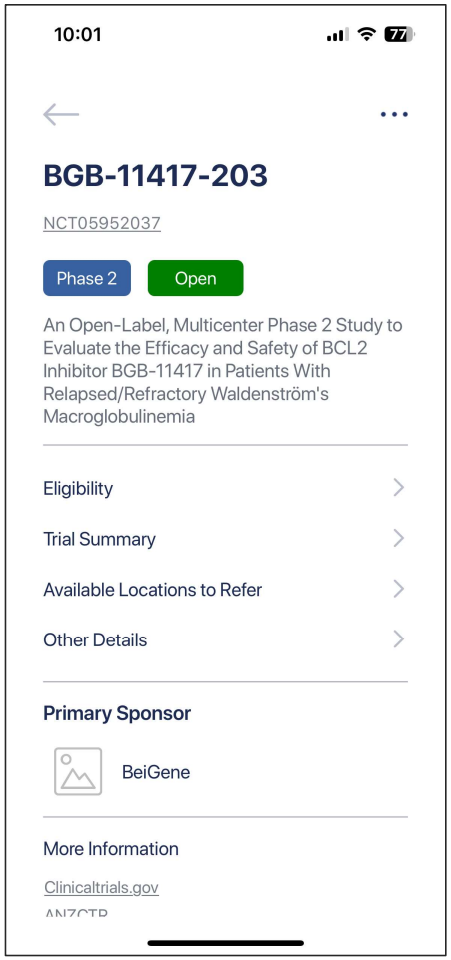
How to find a clinical trial

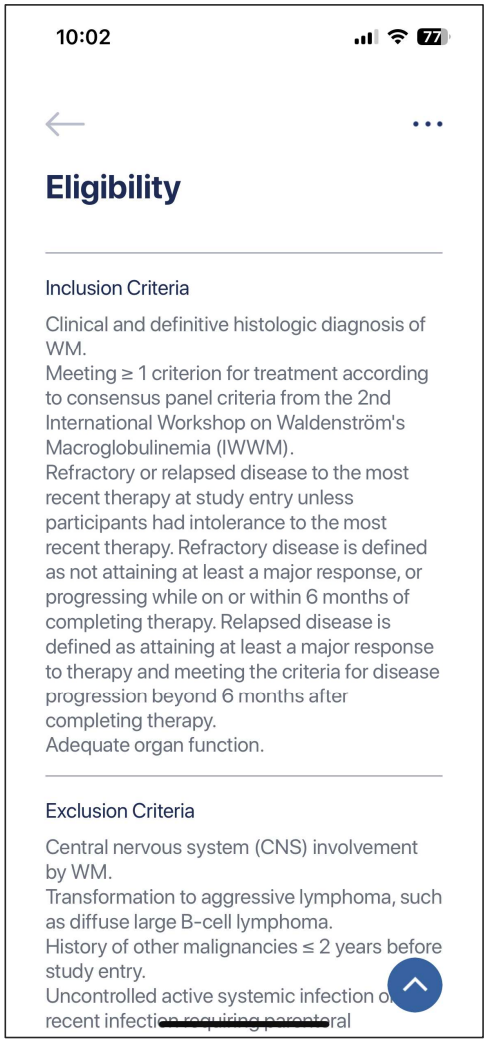
In Australia: ClinTrial Refer App

WM patients download this App









Conclusion

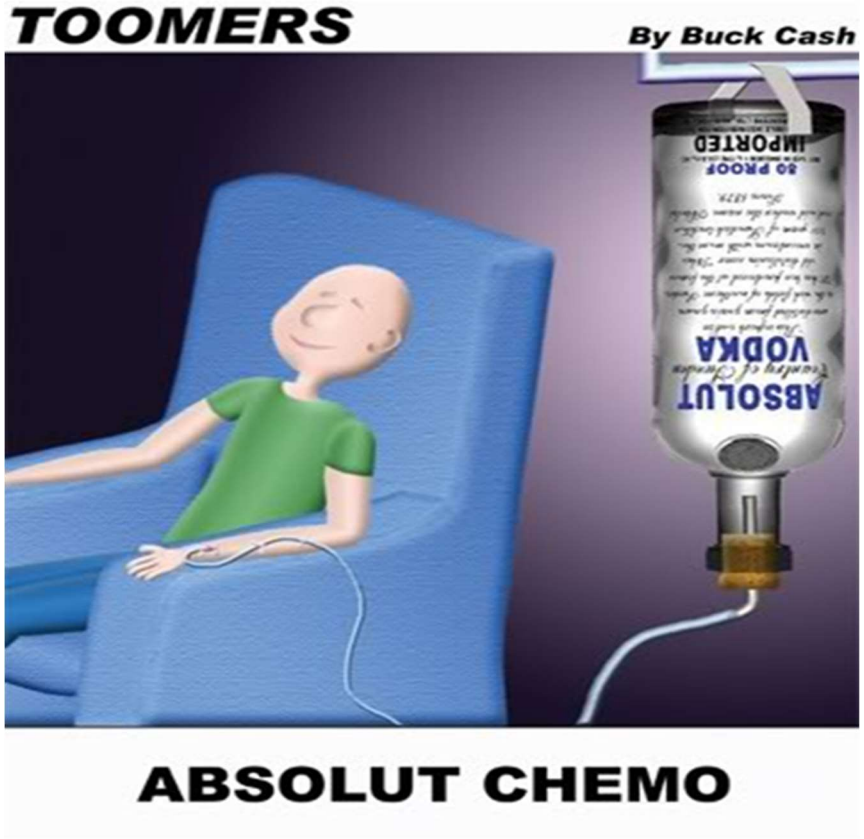
When you **"Pick your Poison"**
remember you are
"Playing the Long Game"
in managing your Waldenström Macroglobulinaemia

1. No single best treatment for all: a variety of appropriate treatments
   - Consider treatment characteristics - efficacy, duration, & side effects
   - Consider your characteristics – age, fitness (be honest), & priorities
2. Several potential new treatment options in the near future.
3. Always consider a clinical trial if available

concord haematology
& CLINICAL RESEARCH UNIT

DISCARD SLIDES

Lymphoma research is moving us away from just “blunderbuss” chemotherapy



Towards adding in:
smarter, targeted therapies

- Antibody therapy

  Rituximab,

- Lymphoma cell enzyme inhibitors

- Ibrutinib, Acalabrutinib, Zanubrutinib, etc (covalent and non-covalent BTK inhibitors)

- Venetoclax and other BCL2 inhibitors

- Cellular therapy

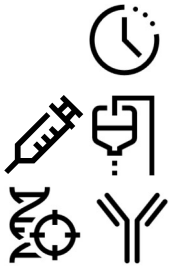
  T cell engaging antibodies &

  Modified (CAR) T-cells targeting cancer cells

Commonly Used treatments

B*DR – Bortezomib + Dex + Rituximab

(I rarely use it)



Fixed Duration

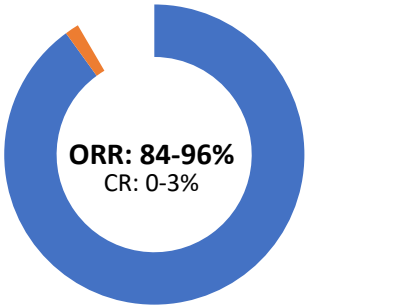
IV Infusion/SQ injection

PI / Immuno

- Alternative fixed-duration regimen without chemotherapy.
  - Bortezomib = proteosome inhibitor.
    Not a cytotoxic chemo nor targeted therapy

- Schedule (complex)
  - SQ injection weekly x4 months,
    IV infusion weekly x2 months.
    Duration of treatment: 5 months
- Efficacy
  - ORR: 84-96%
  - Duration of efficacy:
    - Median 42-59 months

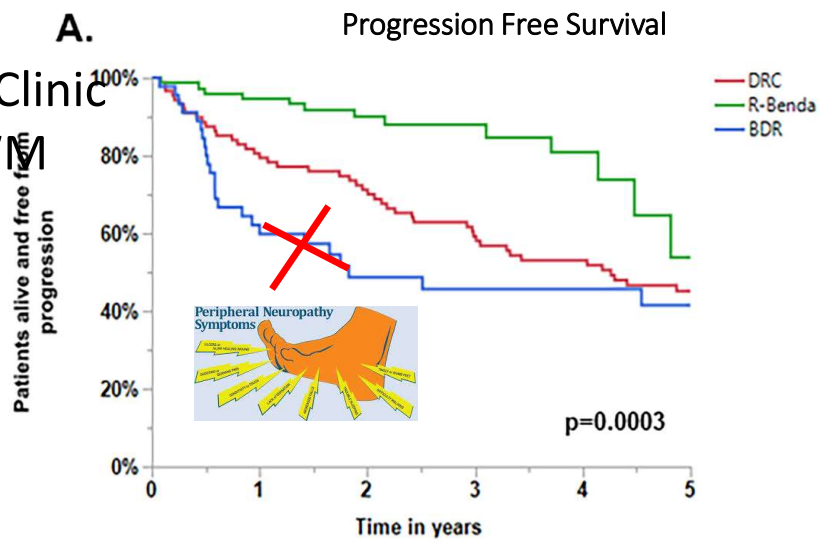
- Common & serious side effects
  - **Peripheral neuropathy**, low blood counts, infections
- Special considerations
  - Avoid in pts with peripheral neuropathy

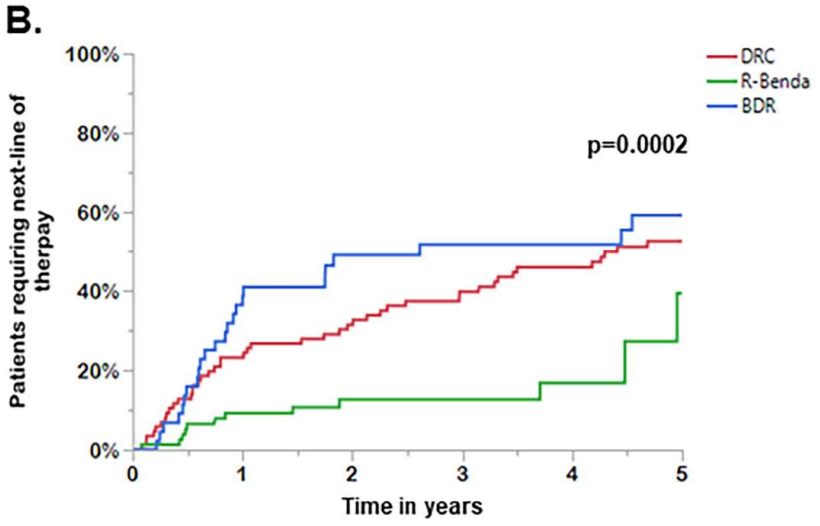


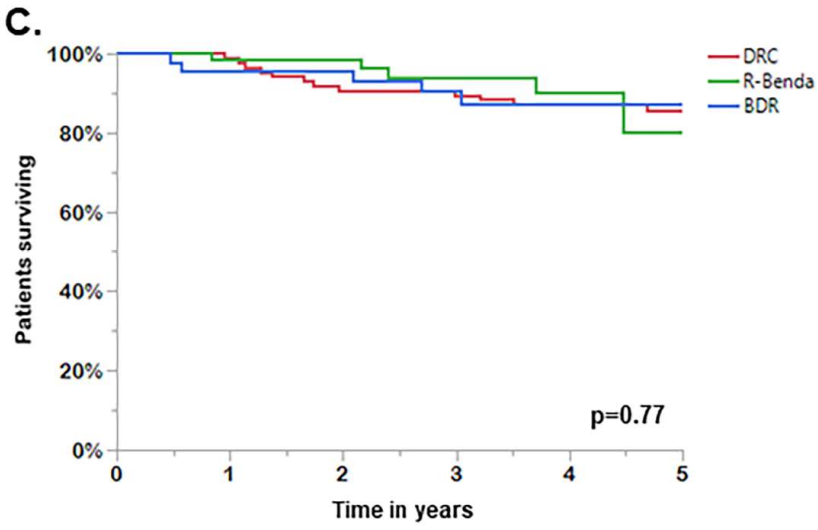
Zanwar S, Abeykoon JP. Treatment paradigm in Waldenström macroglobulinemia: frontline therapy and beyond. Ther Adv Hematol. 2022;13:20406207221093962. Published 2022 Apr 29.
Ravi G, Kapoor P. Current approach to Waldenström Macroglobulinemia. Cancer Treat Res Commun. 2022;31:100527.

Jithma Abeykoon, Mayo Clinic

- Retrospective 1L Rx WM
- N=220: BR, DRC, BDR







Side Note

Formula: proteosome inhibitor + steroid + rituximab

Treatment	Notable AEs
Bortezomib + Dex + Rituximab (BDR)	Peripheral neuropathy
Carfilzomib + Dex + Rituximab (CaRD)	Neutropenia, Cardiac complications
Ixazomib + Dex + Rituximab (IDR)	Infections, infusion reactions

Castillo JJ, Meid K, Flynn CA, et al. Ixazomib, dexamethasone, and rituximab in treatment-naive patients with Waldenström macroglobulinemia: long-term follow-up. Blood Adv. 2020 Aug 25;4(16):3952-3959.
Treon SP, Tripsas CK, Meid K, et al. Carfilzomib, rituximab, and dexamethasone (CaRD) treatment offers a neuropathy-sparing approach for treating Waldenström's macroglobulinemia. Blood. 2014;124(4):503-510.
Zanwar S, Abeykoon JP. Treatment paradigm in Waldenström macroglobulinemia: frontline therapy and beyond. Ther Adv Hematol. 2022;13:20406207221093962. Published 2022 Apr 29.

Side Note

iNNOVATE trial: Ibrutinib + rituximab vs. rituximab

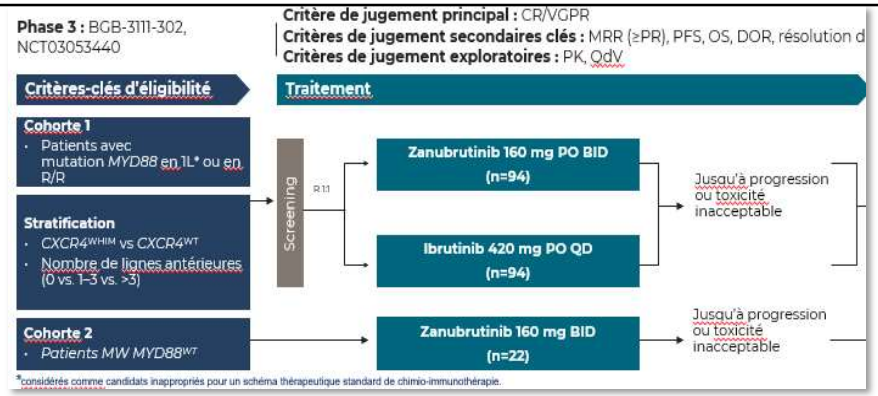
- Ibrutinib + rituximab combination was associated with increased efficacy compared to rituximab alone
  - ORR: 92% vs. 44%
  - PFS at 54-months: 68% vs 25%
- Ibrutinib + rituximab combination was associated with increased side effects compared to rituximab alone
  - Higher rates of diarrhea, joint pain, hypertension, atrial fibrillation, infections with the combination treatment.

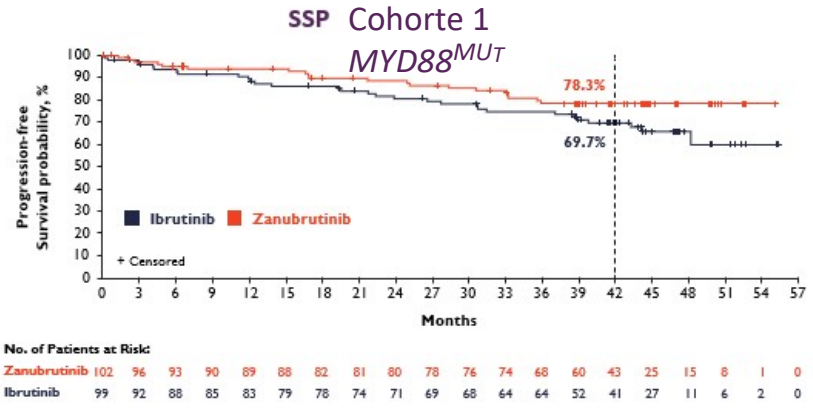
Dimopoulos MA, Tedeschi A, Trotman J, et al. Phase 3 Trial of Ibrutinib plus Rituximab in Waldenström's Macroglobulinemia. N Engl J Med. 2018;378(25):2399-2410..
Buske C, Tedeschi A, Trotman J, et al. Ibrutinib Plus Rituximab Versus Placebo Plus Rituximab for Waldenström's Macroglobulinemia: Final Analysis From the Randomized Phase III iNNOVATE Study. J Clin Oncol. 2022;40(1):52-62.

ASPEN* – FINAL ANALYSIS[1]

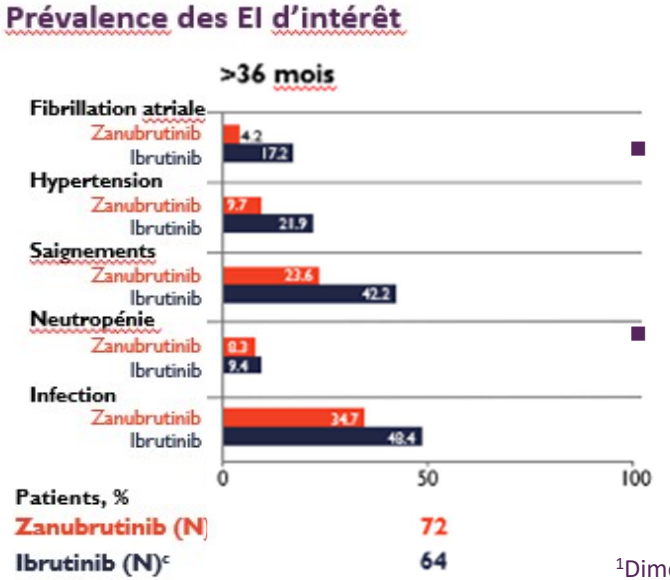
ZANUBRUTINIB *VS*. IBRUTINIB

- * 1 Endpoint (VGPR + CR) was not met
  - VGPR (36 % *vs*. 25 %), p = 0,07
- MRR 81 % *vs*. 80 %
- But in the Zanubrutinib arm
  - More patients presented with *CXCR4* mutations (32 *vs*. 20 %), with VGPR 21 *vs*. 10 %
  - VGPR occurred more rapidly (7 *vs*. 17 mois)
- After a median follow-up of 44 months





Cohort 2 *MYD88*^{WT} : ORR: 81 % ; PFS: 54 %



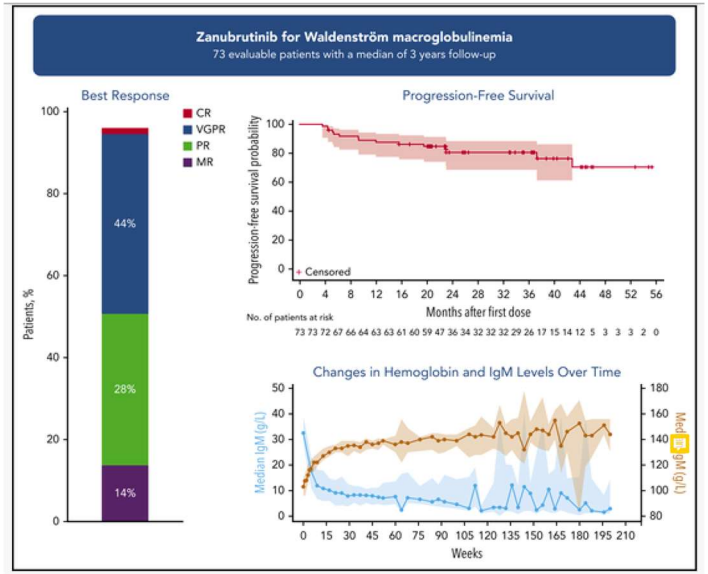
- Zanubrutinib was better tolerated, with treatment cessation due to AEs of 9 *vs*. 20%
- Better quality of life with zanubrutinib[2]

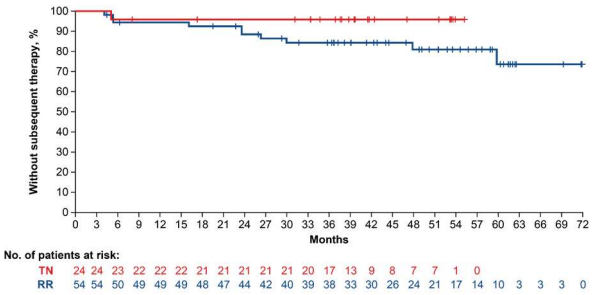
[1]Dimopoulos MA *et al. J Clin Oncol*. 2023
[2]Tedeschi A *et al. Hemasphere (EHA)* 2023

CR: complete response ; VGPR: very good partial response = ≥90% ↓ IgM ; MRR: major response rate = ≥PR = ≥50% ↓ IgM

ZANUBRUTINIB FOR THE TREATMENT OF WM

- N =77 (24 TN,53 R/R)
- 160 mg bd
- Med 43 months f/u
- ORR 96%, MRR 82%
- VGPR/CR 47%, ↑ over time
- Med PFS NR in RR and TN
- 4yr PFS 71% in TN, 65% in RR
- Very well tolerated
- 10% major bleeding,
  9% AF, 19% HTN
  3% Gd3 diarrhoea.
- No ventricular events



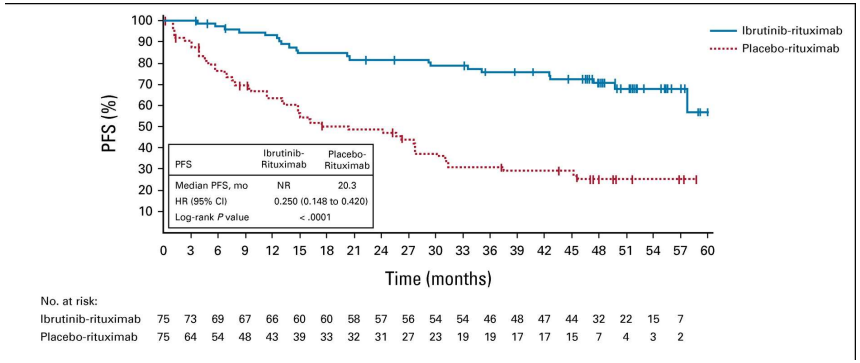


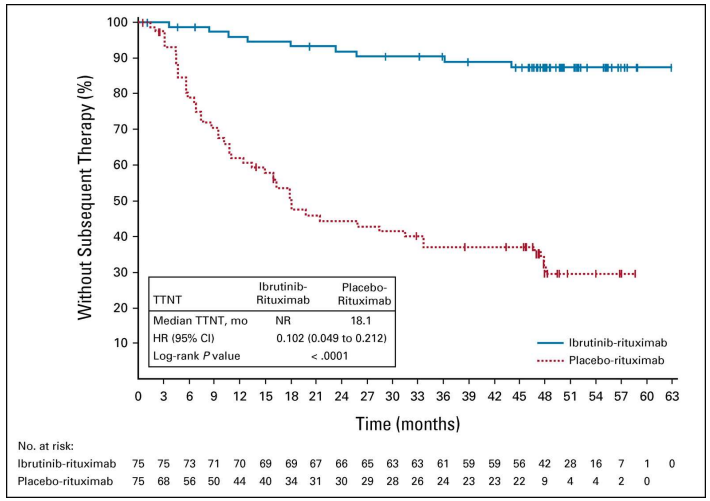
TTNT

Trotman et al, Blood 2020, IWWM 2022

Ibrutinib first-in-class BTKi: INNOVATE study: Ibrutinib-Rituximab vs. placebo-rituximab.

- N = 75 in each arm. RR and TN.
- Med f/u 50 months (range, 0.5-63)
- Med PFS NR with ibrutinib-rituximab versus 20 months (13 to 28) with placebo-rituximab (HR, 0.250; *P* < .0001).
- PFS benefit regardless of prior treatment status, *MYD88* & *CXCR4* mutation status.
- Higher major response rates (PR+) with (76% *v* 31% *P* < .0001).
- Median TTNT NR vs 18 months
- More sustained hemoglobin improvement (77% *v* 43% *P* < .0001).





Dimopoulos NEJM 2018, Buske J Clin Oncol 2022

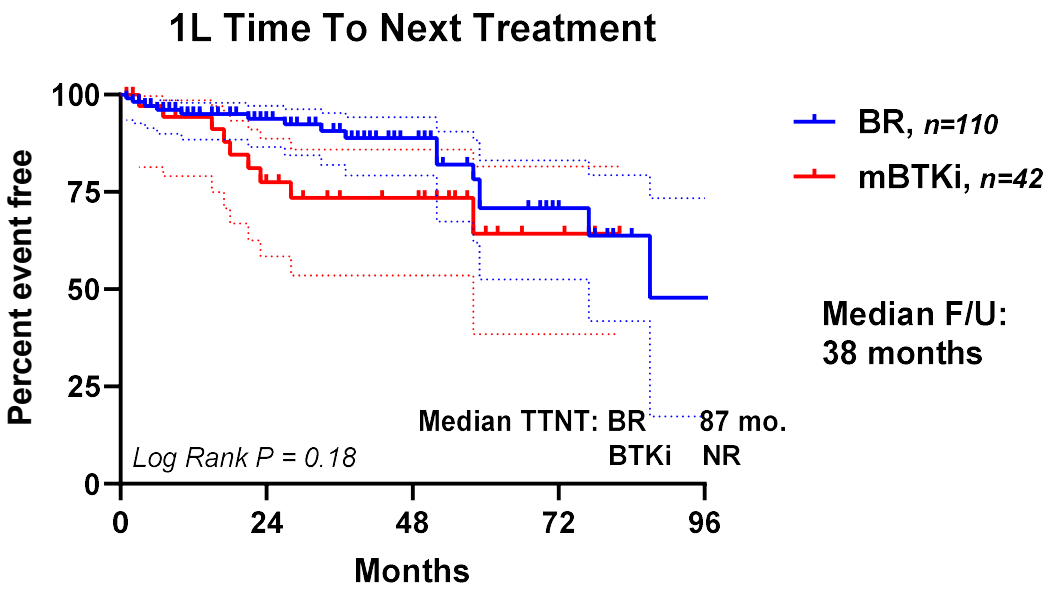
Pick your poison:

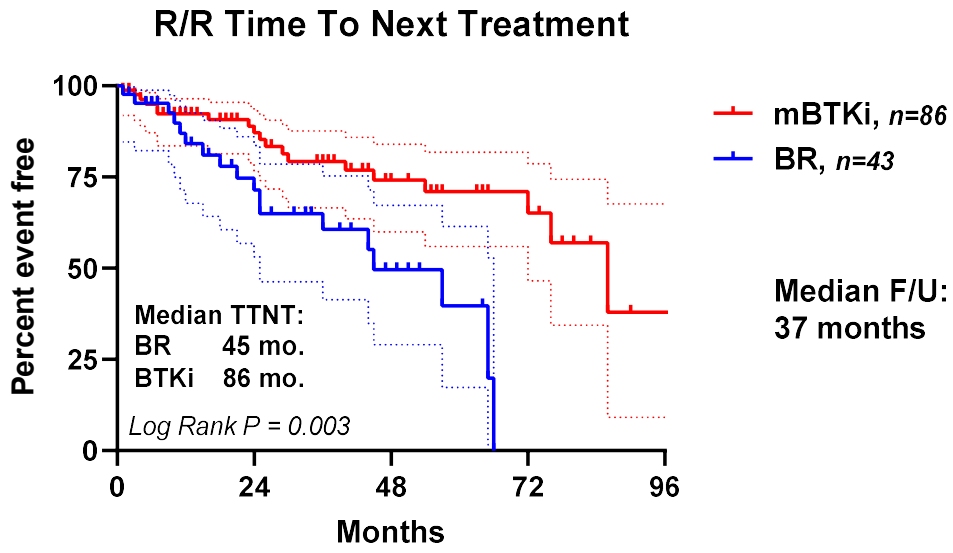
Comparison of best available treatments (First-Line)

Treatment	BR	DRC	Zanubrutinib
Duration	6 cycles (6 months)	6 cycles (4 months)	Ongoing
Response Rate	95%	95%	95-100%
Speed of response	Fast	Medium	Fast
Median PFS	5-6 years	~3 years	78% at 4yrs
Toxicities	Infections Low blood counts	Best tolerated chemo	Low white cells Infections Minor bleeding

How to sequence BR vs BTKi

- BR appears as effective in 1st line, but less effective in relapse setting





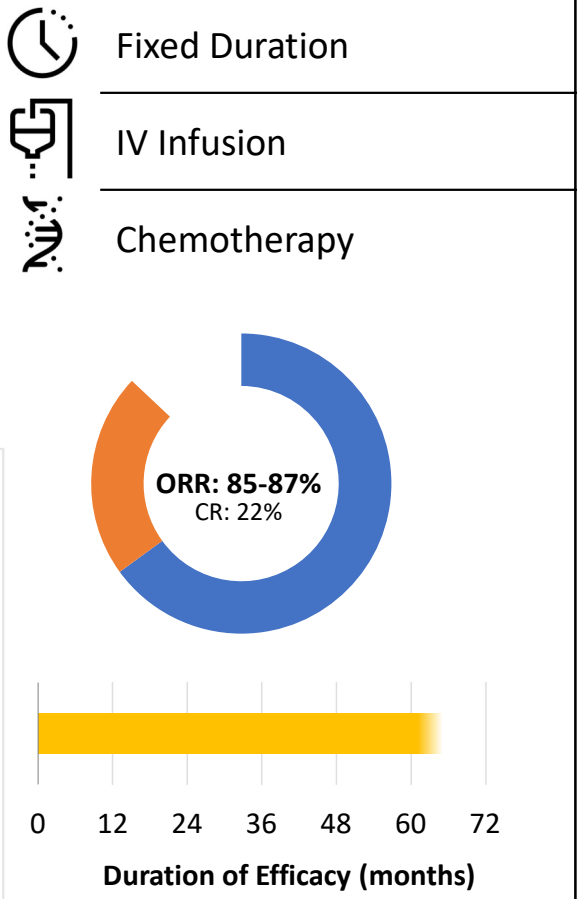
Tohidi Esfahani

Special circumstances

ASCT – Autologous Stem Cell Transplant

- High-dose chemotherapy. Potential option for young/fit patients that have relapsed after CIT and BTK inhibitor, or patients with amyloidosis. High efficacy / high toxicity.

- Schedule
  - One treatment (6-8 weeks), IV chemo
- Efficacy
  - ORR: 85-87%
  - Duration of efficacy:
    - Median 60-65months
    - PFS at 60m: 55%
- Common and serious side effects
  - Low blood counts, infection, fatigue,
  - Non-relapse mortality 4%
- Special considerations
  - For selected cases



Parrondo RD, Reljic T, Iqbal M, et al. Efficacy of Autologous and Allogeneic Hematopoietic Cell Transplantation in WM: A Systematic Review and Meta-analysis. Clin Lymphoma Myeloma Leuk. 2020;20(10):e694-e711.
Kyriakou C, Canals C, Sibon D, et al. High-dose therapy and ASCTin WM: the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol. 2010;28(13):2227-2232.

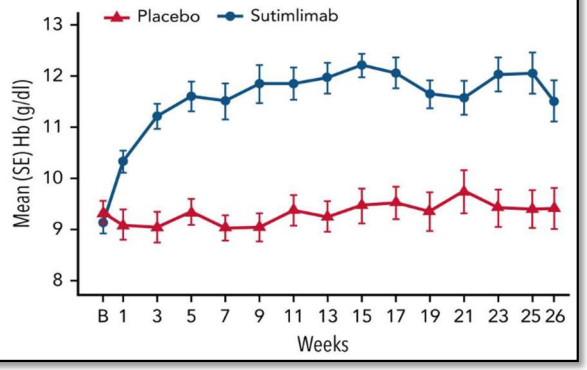
Potential new therapies – Cold Agglutinin Disease

Anti-C1 mab

Sutimlimab

Sutimlimab in patients with cold agglutinin disease: results of the randomized placebo-controlled phase 3 CADENZA trial

- Schedule
  - IV infusion, fixed-duration
- Efficacy
  - 72% of patients saw increase in Hb and no requirements for blood transfusions
- Reduced hemolysis, anemia, and fatigue in patients with CAD



Röth A, Berentsen S, Barcellini W, et al. Sutimlimab in patients with cold agglutinin disease: results of the randomized placebo-controlled phase 3 CADENZA trial. Blood. 2022;140(9):980-991.

Other Available treatments

- Acalabrutinib
- Ofatumumab
- R-CHOP
- R-CVP
- Everolimus

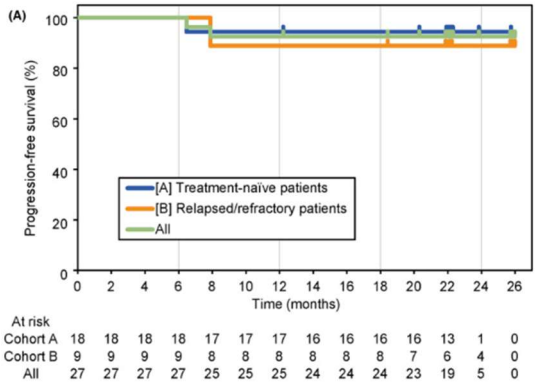
Potential new therapies

BTK Inhibitors

- Covalent BTK inhibitors
  - Ibrutinib
  - Zanubrutinib
  - Acalabrutinib
  - Tirabrutinib
  - Orelabrutinib
- Non-covalent BTK inhibitors
  - Pirtobrutinib

Two-year outcomes of tirabrutinib monotherapy in Waldenström's macroglobulinemia

- Schedule
  - Oral, continuous treatment
- Efficacy
  - ORR: 96%
- Common Side effects
  - Low blood counts, rash, pneumonia, mouth sores



Sekiguchi N, Rai S, Munakata W, et al. Two-year outcomes of tirabrutinib monotherapy in Waldenström's macroglobulinemia. Cancer Sci. 2022;113(6):2085-2096.

Potential new therapies

BTK Inhibitors

- Covalent BTK inhibitors
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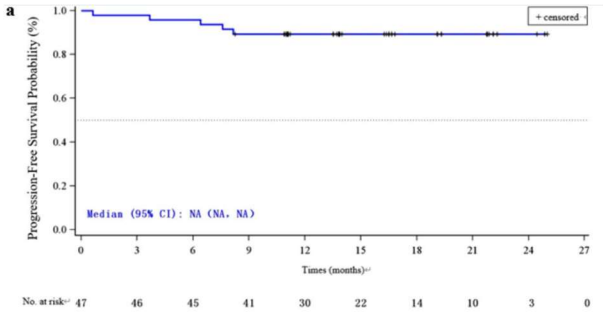
Evaluation of orelabrutinib monotherapy in patients with relapsed or refractory Waldenström's macroglobulinemia in a single-arm, multicenter, open-label, phase 2 study

- Schedule
  - Oral, continuous treatment
- Efficacy
  - ORR: 89%
- Common Side effects
  - Low blood counts, rash, Infections, mouth sores



Cao XX, Jin J, Fu CC, et al. Evaluation of orelabrutinib monotherapy in patients with relapsed or refractory Waldenström's macroglobulinemia in a single-arm, multicenter, open-label, phase 2 study. EClinicalMedicine. 2022;52:101682. Published 2022 Oct 4.

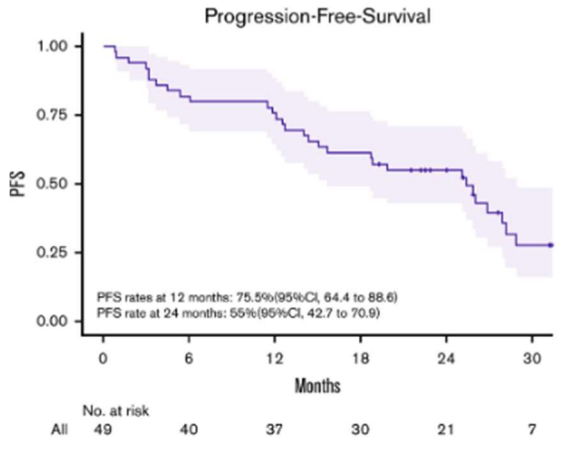
POTENTIAL NEW THERAPIES

PI3K Inhibitors

- Idelalisib + obinutuzumab

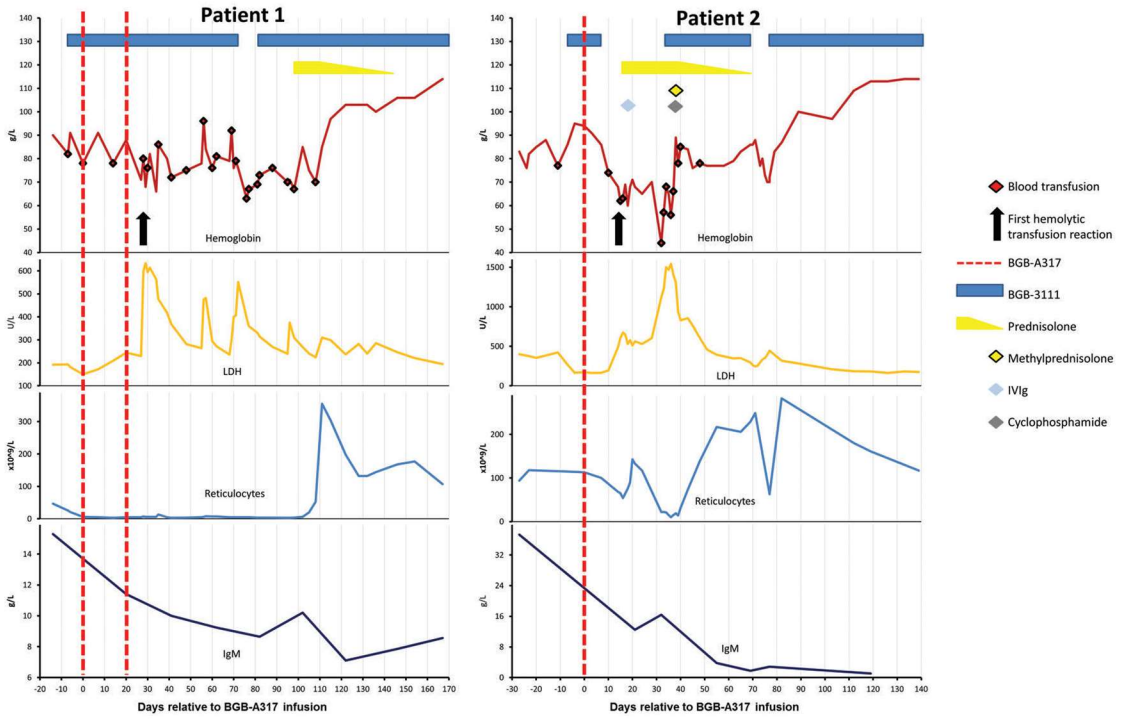
Obinutuzumab and idelalisib in symptomatic patients with relapsed/refractory Waldenström macroglobulinemia

- Schedule
  - Oral /IV infusion, fixed-duration
- Efficacy
  - ORR: 71%
  - PFS: median ≈25 m
- Common Side effects
  - Low blood counts, diarrhea, infections



Tomowiak C, Poulain S, Herbaux C, et al. Obinutuzumab and idelalisib in symptomatic patients with relapsed/refractory Waldenström macroglobulinemia. Blood Adv. 2021;5(9):2438-2446.

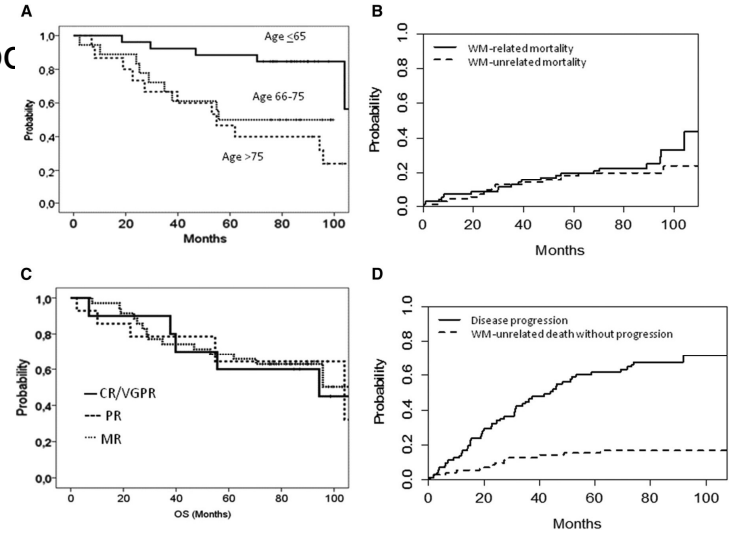
TIZELIZUMAB: OVERWHELMING RED CELL DESTRUCTION



DEX, RITUXIMAB, & CYCLOPHOSPHAMIDE AS PRIMARY TREATMENT OF WM: FINAL ANALYSIS OF A PHASE 2 STUDY.

KASTRITIS, E. BLOOD, 2015.

- 72 pts with newly diagnosed WM
- Dex 20mg, Rituximab, cyclo 100mg/m^2 bo d1 – 5, 6 q21d cycles
- ORR 83%, >PR of 75%. Well tolerated.
- Med 7yr follow-up
- 3yr PFS 45%, **median TTNT of 51 months.** Myelodysplasia 3%, DLBCL 10%,
- Med OS 95 months (8 years).
- At 100 months, mortality dt WM and unrelated to WM both ~20%.
- No improvement in survival based on the depth of response: patients achieving ≥ VGPR had the same outcome as patients who achieved a PR or minor response.



"It is imperative not to judge the efficdcy of therapy based on percentage reduction of IgM but on the endpoint for which therapy was initiated, such as anaemia".

TREATMENTS AVAILABLE IN AUSTRALIA FOR RELAPSE

- **CLINICAL TRIAL!!!**
- DRC (or BR if can get it) if not used before and prolonged response to 1L therapy (>3 years)
- Zanubrutinib (Preferred over Ibrutinib: lower toxicity profile in comparison study, and it's the only PBS-funded BTKi in Australia)
- If cannot do above and no available trials:
  - Review what compassionate access/funding schemes are available for: other BTK inhibitors, BCL2 inhibitors, Proteasome inhibitors, plus other novel treatments
  - Chemoimmunotherapy used for other Non-Hodgkin lymphomas/CLL

OTHER TREATMENTS AVAILABLE GLOBALLY FOR WM

- BTK inhibitors
  - Ibrutinib (with or without rituximab) – longest follow up data
  - Acalabrutinib – better toxicity profile than ibrutinib, like zanubrutinib
  - Non-covalent BTK inhibitors – reasonable responses post-ibrutinib
- Proteasome inhibitors (usually with dexamethasone and rituximab)
  - Bortezomib – RR 85-90%, PFS 3-5 years
  - Carfilzomib – RR ~90%, durability??
  - Ixazomib – RR 85%, PFS 2 yrs
- BCL2 inhibitors
  - Venetoclax – 75% response rate post BTK inhibitor, probably best in combination but too toxic with ibrutinib

PRACTICAL ADVICE – FATIGUE MANAGEMENT

- Treat medical/other causes
- Exercise proven (may need physiotherpy advice):
  - moderate intensity (jogging/swimming etc) for 30min 5 days/week or 75min 3 days/week
  - Muscle strengthening exercise 2+ days/week
- Correct sleep hygiene:
  - No electronic devices for 1hr pre-sleep
  - Avoid stimulants (coffee/smoking), late heavy meals
  - limit naps to <1hr