MAYO CLINIC

# CURRENT TREATMENT OPTIONS AND NEW THERAPIES ON THE HORIZON

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## LEARNING OBJECTIVE

- Review of current treatment options
- Potential new therapies
- Clinical trial participation



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# 1 REVIEW OF CURRENT TREATMENT OPTIONS



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## INTRODUCTION

- Treatment indications in WM has been covered elsewhere
- Available treatment options may be limited by country and insurance regulations
- Review of most commonly used and potential new treatments in WM. Not all treatment options are included.



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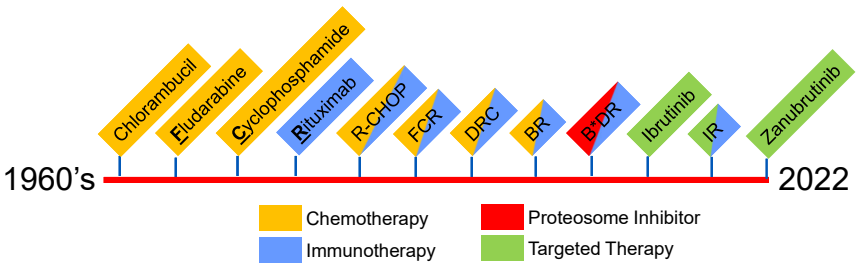
# TIMELINE OF TREATMENTS IN WM




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

Not an all-inclusive list of treatments



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# CLASSIFICATION

**Classification of treatment options**

**Duration of therapy**

Fixed Duration | Continuous Therapy

**Drug class composition**

ChemoImmunoTherapy (CIT) → Targeted Therapy

| | | | |
|---|---|---|---|
| BR | Rituximab | IR | Zanubrutinib |
| DRC | BortezomibDR | | Acalabrutinib |
| | CarfilzomibDR | | Ibrutinib |
| | IxazomibDR | | Venetoclax |



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# COMMONLY USED TREATMENTS

## BR – Bendamustine + Rituximab

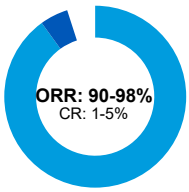
Fixed Duration

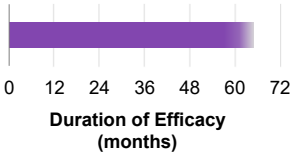
IV Infusion

Chemo Immuno

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

- Schedule
  - IV infusion x2 days, every 4 weeks, for 4-6 cycles
- Efficacy
  - ORR: 90-98%
  - Duration of efficacy:
    - Median 58-69 months
- Common and serious side effects
  - Low blood counts, fatigue, increased risk of infections, infusion reactions
- Special considerations
  - With any chemo, potential 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.



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# COMMONLY USED TREATMENTS

## DRC – Dex + Rituximab + Cyclophosphamide

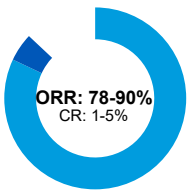
Fixed Duration

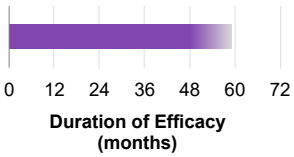
IV Infusion / oral

Chemo Immuno

- Preferred CIT regimen when aiming for low toxicity, less fit patients with lower tumor burden.

- Schedule
  - IV infusion x1 day, tables x5 days, every 3 weeks, for 6 cycles
- Efficacy
  - ORR: 78-90%
  - Duration of efficacy:
    - Median 51-59 months
- Common and serious side effects
  - Low blood counts, fatigue, increased risk of infections, infusion reactions
- Special considerations
  - With any chemo, potential risk of secondary MDS/AML (0% - 3%)

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Ravi G, Kapoor P. Current approach to Waldenström Macroglobulinemia. Cancer Treat Res Commun. 2022;31:100527.



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# COMMONLY USED TREATMENTS

## B*DR – Bortezomib + Dex + Rituximab

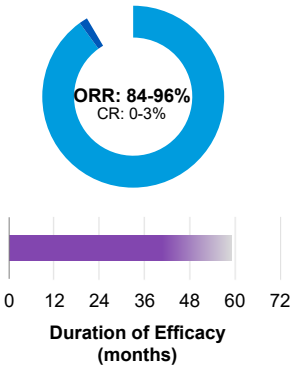
Fixed Duration

IV Infusion/SQ injection

PI / Immuno

- Good alternative as a fixed-duration regimen without chemotherapy.
  - Bortezomib = proteosome inhibitor. Not cytotoxic chemo, neither 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 and serious side effects
  - Peripheral neuropathy, low blood counts, infections
- Special considerations
  - Avoid in pts with peripheral neuropathy

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Ravi G, Kapoor P. Current approach to Waldenström Macroglobulinemia. Cancer Treat Res Commun. 2022;31:100527.



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# SIDE NOTE

## Formula: proteosome inhibitor + steroid + Anti-CD20 mab

| Treatment | Notable AEs |
|---|---|
| Bortezomib + Dex + Rituximab (BDR) | Peripheral neuropathy |
| Carfilzomib + Dex + Rituximab (CaRD) | Neutropenia, Cardiomyopathy |
| 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.



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# COMMONLY USED TREATMENTS

## R – Rituximab

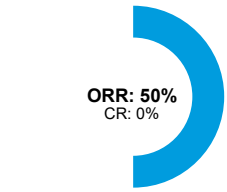
- Limited role given inferior outcomes. Could be considered in cases of hemolytic anemia, or peripheral neuropathy

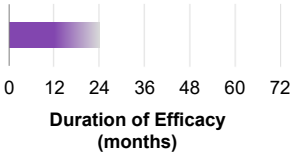
- Schedule
  - IV infusion weekly x1 month
- Efficacy
  - ORR: 50%
  - Duration of efficacy:
    - Median 14-24 months
- Common and serious side effects
  - Infusion reactions, IgM flare (IgM >4,000 mg/dL)
- Special considerations
  - Very rare risk of PML

Fixed Duration

IV Infusion

Immunotherapy

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Ravi G, Kapoor P. Current approach to Waldenström Macroglobulinemia. Cancer Treat Res Commun. 2022;31:100527.



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# COMMONLY USED TREATMENTS

## I – Ibrutinib

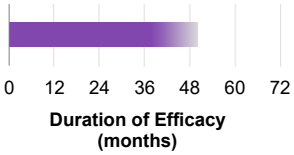
- First BTK inhibitor, with good tolerability and efficacy (MYD88 mutated cases). Good option for patients that are unfit or whish to avoid chemotherapy.

- Schedule
  - Oral treatment, daily, no end date
- Efficacy
  - ORR: 90% (50-100%)
  - Duration of efficacy:
    - Median 39 (6-52+) months
    - PFS at 18m: 88%
- Common and serious side effects
  - Low blood counts, hypertension, joint pain, atrial fibrillation
- Special considerations
  - Caution if history/risk of cardiac arrythmias
  - Withdrawal and IgM Flare

Continuos therapy

Oral

Targeted therapy


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.



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# 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.


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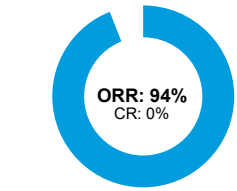
# COMMONLY USED TREATMENTS

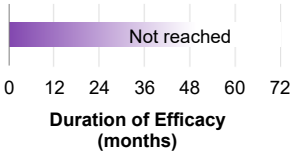
## Z – Zanubrutinib

- Preferred BTK inhibitor, with good tolerability and efficacy (better efficacy in MYD88 negative).

- Schedule
  - Oral treatment, daily, no end date
- Efficacy
  - ORR: 94% (80-100%)
  - Duration of efficacy:
    - PFS at 18m: 85%
- Common and serious side effects
  - Low blood counts, infection
- Special considerations
  - Increased risk of neutropenia

Continuos therapy
Oral
Targeted therapy

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Trotman J, Opat S, Gottlieb D, et al. Zanubrutinib for the treatment of patients with Waldenström macroglobulinemia: 3 years of follow-up. Blood. 2020;136(18):2027-2037.
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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# SIDE NOTE

## ASPEN trial: ibrutinib vs. zanubrutinib

| | Ibrutinib | Zanubrutinib |
|---|---|---|
| Efficacy | | |
| ORR, MYD88 mut | 93% | 94% |
| ORR, MYD88 wt | - | 81% |
| PFS at 18 months | 84% | 85% |
| Side effects (any grade) | | |
| Atrial fibrillation | 15% | 2% |
| Hypertension | 17% | 11% |
| Neutropenia | 13% | 30% |
| Major bleeding | 9% | 6% |
| Discontinuation rate due to side effects | 9% | 4% |

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 Oct 29;136(18):2038-2050..
Dimopoulos M, Sanz RG, Lee HP, et al. Zanubrutinib for the treatment of MYD88 wild-type Waldenström macroglobulinemia: a substudy of the phase 3 ASPEN trial. Blood Adv. 2020;4(23):6009-6018.


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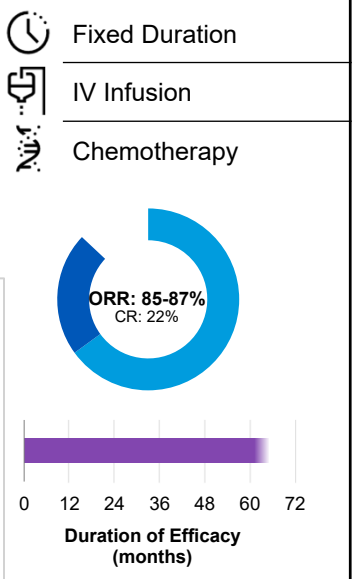
# SPECIAL CIRCUMSTANCES

## 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

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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.


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## OTHER AVAILABLE TREATMENTS

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



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# 2 POTENTIAL NEW THERAPIES



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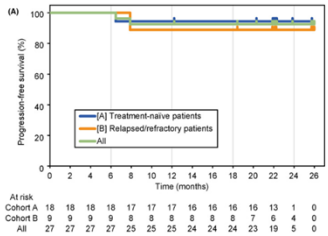
# POTENTIAL NEW THERAPIES

## 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.



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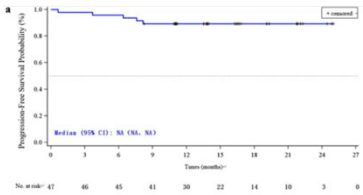
# POTENTIAL NEW THERAPIES

## BTK Inhibitors

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

### 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.



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# POTENTIAL NEW THERAPIES

## 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**

- Schedule
  - Oral, continuous treatment
- Efficacy
  - MRR: 68%
  - Prior BTKi: MRR of 64%
- Common Side effects
  - Low blood counts, diarrhea, bruising
- Good option in patients relapse disease on covalent BTK inhibitor

Paloma ML, Patel MR, Eyre TA, 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.



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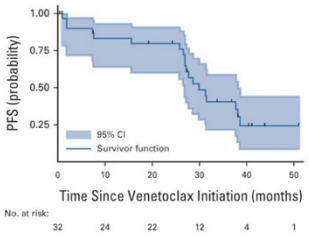
# POTENTIAL NEW THERAPIES

## BCL2 Inhibitors

- Venetoclax

**Venetoclax in Previously Treated Waldenström Macroglobulinemia**

- Schedule
  - Oral, continuous 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.



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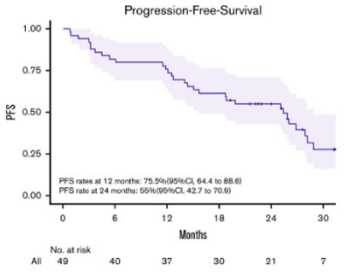
# POTENTIAL NEW THERAPIES

## 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.



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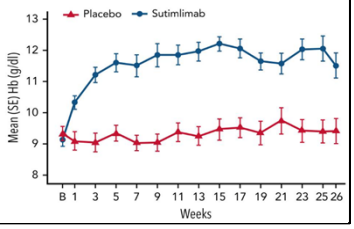
# POTENTIAL NEW THERAPIES – Cold Agglutinin Disease

## 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.



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## NOT POTENTIAL NEW THERAPIES

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

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.



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# 3 CLINICAL TRIAL PARTICIPATION



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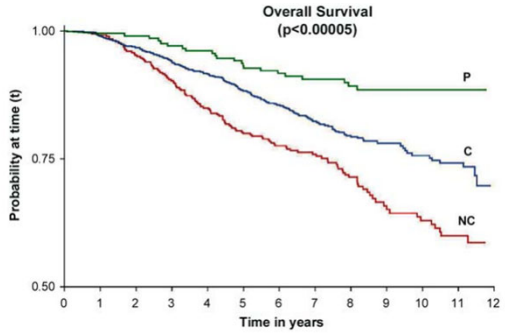
# CLINICAL TRIAL PARTICIPATION

## Advantages of clinical trials

"Women who participate to clinical trials experience, on average, a substantial reduction in mortality from all causes."




Hébert-Croteau N, Brisson J, Lemaire J, Latreille J. The benefit of participating to clinical research. Breast Cancer Res Treat. 2005;91(3):279-281.



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# CLINICAL TRIAL PARTICIPATION

## Advantages of clinical trials

https://clinicaltrials.gov/

1. Early access to better drugs/treatments
2. Free medication
3. Preserve stablished [illegible] use
4. Expand your treatment options

NIH U.S. National Library of Medicine ClinicalTrials.gov

- You should always consider a clinical trial if available and if it fits well with your treatment goals



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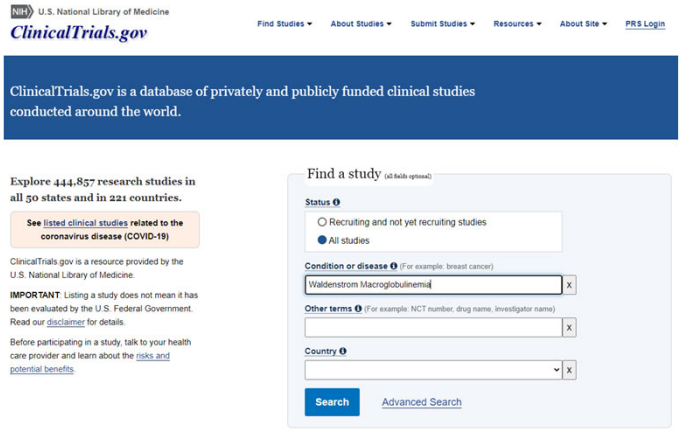
# CLINICAL TRIAL PARTICIPATION

## How to find clinical trials

1. Talk with your doctor
2. IWMF website
3. clinicaltrials.gov



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# TAKE HOME POINTS

## Waldenstrom macroglobulinemia

1. Broad variety of treatment options available
2. Consider treatment characteristics (efficacy, duration) and side effect profile
3. Several potential new treatment options to hopefully become available in the near future
4. ALWAYS consider a clinical trial if available.



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# THANK YOU !

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