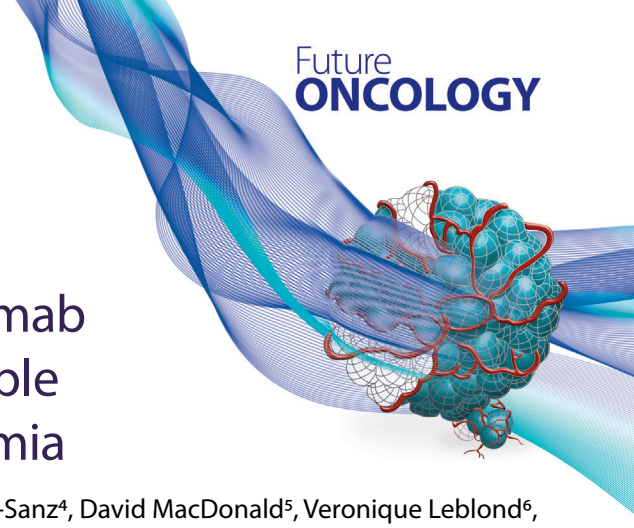
Plain Language Summary of Publication

Future ONCOLOGY



Plain language summary of the iNNOVATE study: ibrutinib plus rituximab is well-tolerated and effective in people with Waldenström's macroglobulinemia

Christian Buske[1], Alessandra Tedeschi[2], Judith Trotman[3], Ramón García-Sanz[4], David MacDonald[5], Veronique Leblond[6], Beatrice Mahe[7], Charles Herbaux[8], Jeffrey V Matous[9], Constantine S Tam[10], Leonard T Heffner[11], Marzia Varettoni[12], M Lia Palomba[13], Chaim Shustik[14], Efstathios Kastritis[15], Steven P Treon[16], Jerry Ping[17], Bernhard Hauns[17], Israel Arango-Hisijara[18] & Meletios A Dimopoulos[15]

[1]Institute of Experimental Cancer Research, Comprehensive Cancer Center Ulm, University Hospital of Ulm, Ulm, Germany; [2]ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy; [3]Concord Hospital, University of Sydney, Sydney, Australia; [4]Department of Hematology, University Hospital of Salamanca (HUS/IBSAL), CIBERONC and Cancer Research Institute of Salamanca-IBMCC (USAL-CSIC), Salamanca, Spain; [5]The Ottawa Hospital, University of Ottawa, Ottawa, Canada; [6]Département d'Hématologie Hôpital Pitié-Salpêtrière AP-HP, Sorbonne Université, Paris, France; [7]Centre Hospitalier Universitaire de Nantes, Hôtel Dieu Hematologie Clinique, Nantes, France; [8]Centre Hospitalier Régional Universitaire de Lille, Institute of Hematology-Transfusion, Lille, France; [9]Colorado Blood Cancer Institute, Denver, CO, USA; [10]The Alfred Hospital and the University of Melbourne, Melbourne, Australia; [11]Winship Cancer Institute of Emory University, Atlanta, GA, USA; [12]Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [13]Memorial Sloan Kettering Cancer Center, New York, New York, USA; [14]Royal Victoria Hospital at McGill University Health Centre, Montreal, Canada; [15]National and Kapodistrian University of Athens School of Medicine, Athens, Greece; [16]Dana-Farber Cancer Institute, Boston, MA, USA; [17]Pharmacyclics LLC, an AbbVie Company, South San Francisco, CA, USA; [18]Janssen Pharmaceuticals, Raritan, NJ, USA

First draft submitted: 13 October 2022; Accepted for publication: 20 January 2023; Published online: 23 February 2023

Summary

What is this summary about?
This article provides a short summary of 5-year results from the iNNOVATE trial. The original paper was published in the *Journal of Clinical Oncology* in October 2021.

How to say (double-click on the icon to play sound)...

Ibrutinib: eye-BREW-tin-ib
Rituximab: ri-TUX-i-mab
Waldenström's macroglobulinemia: wall-den-stroms mac-row-glob-u-lin-EE-mee-a

People with Waldenström's macroglobulinemia (WM) were randomly divided into two groups of 75 people each. One group received a combination treatment composed of two drugs, ibrutinib plus rituximab, and the other group took placebo ("sugar pill") plus rituximab. Ibrutinib (also known by the brand name Imbruvica®) is a drug that reduces cancer cells' ability to multiply and survive. Ibrutinib is an FDA-approved drug for the treatment of WM. Rituximab is a drug that helps the immune system find and kill cancer cells. Participants in the trial were treated and their health monitored for up to 5 years (63 months).

What were the results?
During the 5 years of monitoring, more people who took ibrutinib plus rituximab experienced an improvement in their disease and lived longer without their disease getting worse compared to those who took placebo plus rituximab. Side effects from ibrutinib and rituximab were manageable and generally decreased over time. Participants in both study groups reported improvements in quality of life, but those who took ibrutinib plus rituximab reported significantly greater improvement in their quality of life (as measured by FACT-An score) compared to those who took placebo plus rituximab.

What do the results mean?
These results show that ibrutinib plus rituximab is better than rituximab alone in people with WM and that ibrutinib plus rituximab is safe and effective in the long term.

This information confirms the role of ibrutinib plus rituximab as a standard of care for WM.

Future Medicine part of fsg

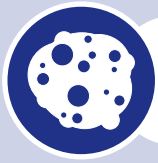
Where can I find the original article on which this summary is based?

You can read the original article published in the *Journal of Clinical Oncology* free of charge at:
https://ascopubs.org/doi/full/10.1200/JCO.21.00838

Who should read this article?

This summary may be helpful for people with newly diagnosed or previously treated WM and their family members or caregivers. Patient advocates and healthcare professionals searching for treatment options for patients may also find this information useful.

What is Waldenström's macroglobulinemia?



WM is a rare kind of non-Hodgkin lymphoma, a type of cancer that begins in B cells. B cells are an important part of the immune system and help the body fight infections.

The cancer cells make large amounts of a protein called immunoglobulin M (IgM). The excess IgM in the body can cause WM symptoms like weakness, loss of appetite, fevers, night sweats, numbness in legs and feet, and weight loss.

How do ibrutinib and rituximab work?

Ibrutinib works by inhibiting an enzyme called Bruton's tyrosine kinase, or BTK. BTK is important for cancer cell survival. Ibrutinib comes in capsule or tablet form and is taken by mouth once a day.

Rituximab sticks to a protein called CD20 on the surface of cancer cells. In this way, it helps the immune system find and kill cancer cells. Rituximab is given as an intravenous infusion.

Neither ibrutinib nor rituximab are considered chemotherapy.

What was the purpose of the study?

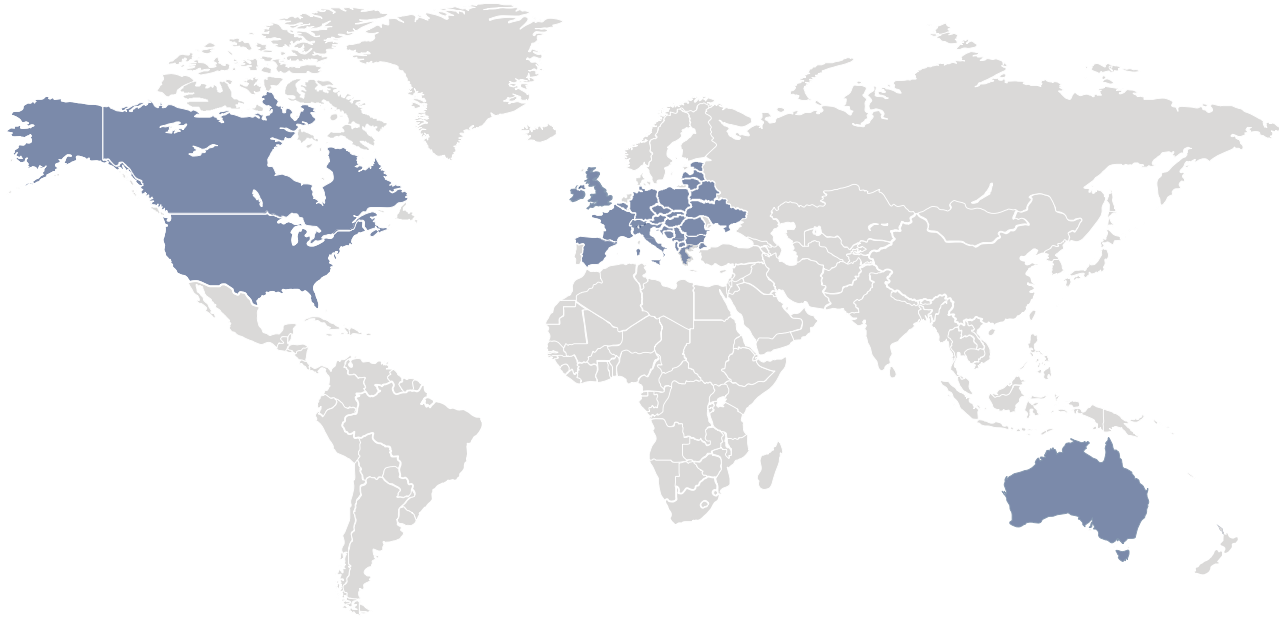
The main aim of the iNNOVATE study was to understand if ibrutinib plus rituximab treatment could help people with WM live longer without their disease getting worse compared to people taking placebo ("sugar pill") plus rituximab.

The researchers also looked at:

- How much disease improvement was experienced by participants in the two groups
- How long participants lived overall
- Any side effects that happened during treatment
- Improvement in patient's quality of life

Who took part in this study?

Participants were enrolled at **48 cancer centers** in the United States, Europe, Canada and Australia



A total of 150 adults with WM participated in iNNOVATE. People in the two groups were similar in age, ranging from 36 to 89 years in the ibrutinib plus rituximab group and 39 to 85 years in the placebo plus rituximab group. More than half of the participants in each group were men.

A little over half of the people in each group had been treated for WM before participating in this study.

To be eligible for the study, participants met these conditions:

- Confirmed diagnosis of WM and doctor was able to measure the disease through blood tests for a specific protein called IgM
- If previously treated for WM, the participant had worsening disease or no response to the most recent treatment
- Had symptoms of WM. These symptoms could include weight loss, fever, night sweats, fatigue, enlarged spleen or liver, or low red blood cell or platelet counts (cells that help blood clot), among others
- If previously treated with rituximab, participants had responded to treatment and had not taken rituximab within 12 months of enrolling in this study

What happened to the participants in this study?

iNNOVATE was a phase 3 **randomized**, **double-blind**, **placebo-controlled** study.

Randomized

- Participants were randomly split into two groups
- Dividing participants randomly between treatment groups means that any difference in outcomes is likely due to the treatment received rather than patient characteristics

Double-blind

- Neither the researchers nor the participants knew which treatment the participants received until the study was over
- This design decreases the chance of bias in the results

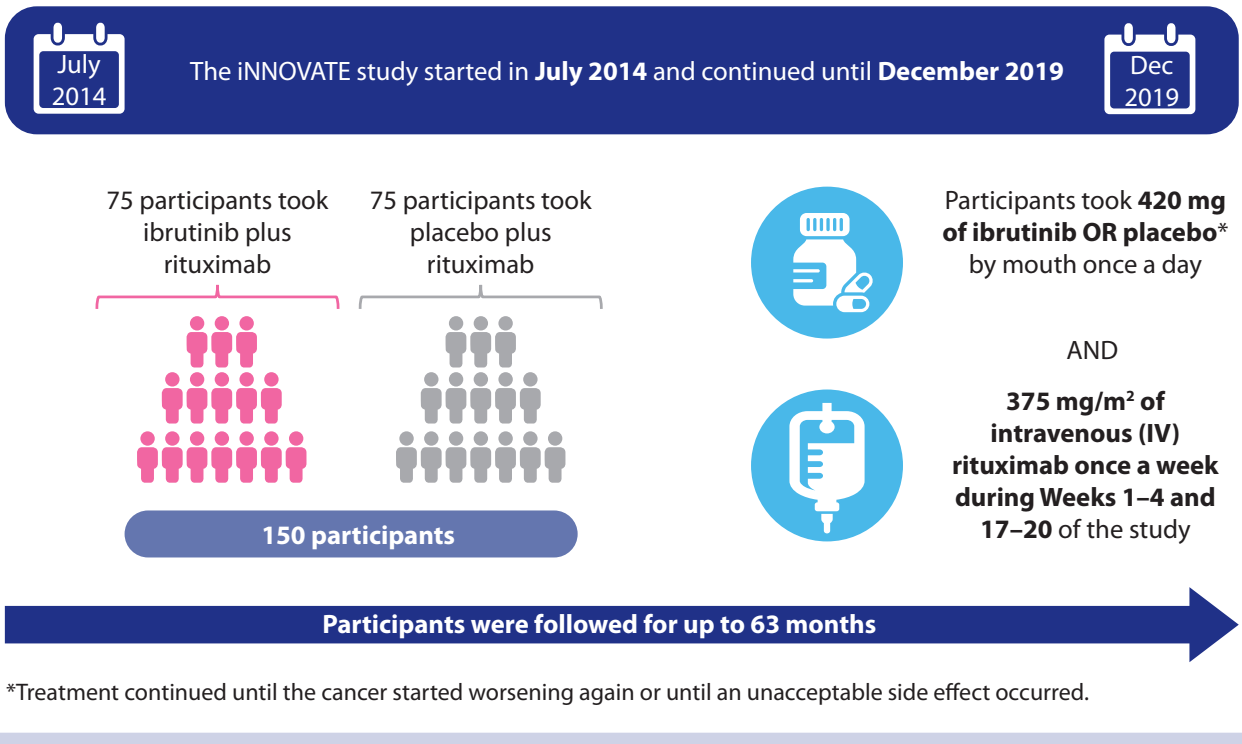
Placebo-controlled

- In this study, one group took ibrutinib plus rituximab while the other group took placebo plus rituximab
- A placebo is an inactive substance ("sugar pill") that looks like the treatment being tested
- Comparing results between the treatment group and placebo group helps researchers measure the effect of treatment

Participants were treated with ibrutinib for approximately 48 months (range: 1–59 months); those taking placebo plus rituximab were treated for approximately 16 months (range: 0.4–37 months).

Participants received follow-up care after finishing treatment; they saw a healthcare provider for regular medical check-ups for up to 63 months.

What were the results?



*Treatment continued until the cancer started worsening again or until an unacceptable side effect occurred.

- A blood sample was taken from each participant at the beginning of the trial and used to study two genes, *MYD88* and *CXCR4*
- Some participants were found to have changes in these genes, which, in the case of *CXCR4* alterations, are associated with more noticeable WM symptoms
- Researchers studied participants with these genetic changes to see how well ibrutinib plus rituximab worked compared to placebo plus rituximab
- Understanding how these genes affect symptoms and survival may help researchers develop better treatments for WM in the future

- In people with unchanged or "wild-type" *MYD88* genes, WM is typically more aggressive, with a higher risk of death
- People with wild-type *MYD88* genes may be less likely to respond to treatment with ibrutinib alone. People with mutated *MYD88* or wild-type *CXCR4* genes are more likely to respond to ibrutinib treatment

Participants who took ibrutinib plus rituximab had greater improvement in their disease than patients who took placebo plus rituximab

Improvements were seen both in participants who had been treated for WM before and in those who had never been treated before.

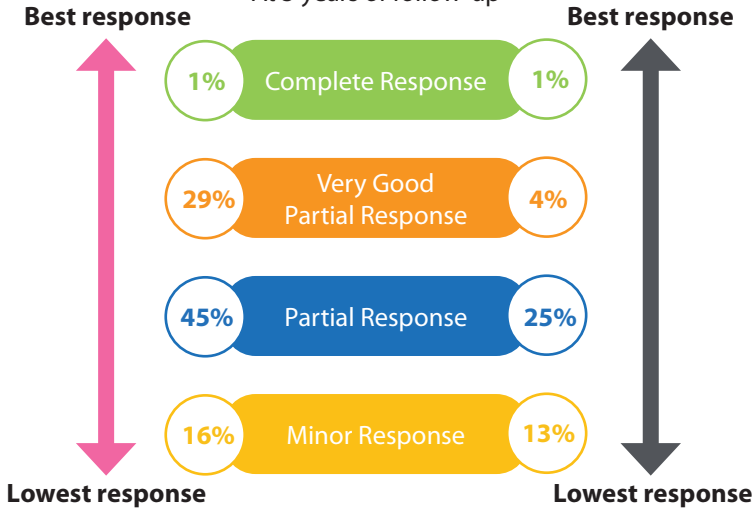
Participants who took ibrutinib plus rituximab had a 75% lower risk of their WM getting worse or of death compared to those who took placebo plus rituximab.

Participants with genetic changes that made their disease more aggressive also benefited from ibrutinib plus rituximab and had a higher rate of improvement compared to those who took placebo plus rituximab.

92% of participants who took ibrutinib plus rituximab responded to treatment

44% of participants who took placebo plus rituximab responded to treatment

At 5 years of follow-up



Treatment guidelines for WM divide response into the categories above. These categories take into account decreases in IgM protein levels and lymph node and spleen size.

Ibrutinib plus rituximab helped participants who had been treated for WM before live longer without their disease getting worse

More participants who took placebo plus rituximab received subsequent treatment for WM (47 of 75 participants; 63%) than participants who took ibrutinib plus rituximab (9 of 75 patients; 12%).

In people treated with ibrutinib plus rituximab, researchers estimated that 7 out of 10 participants (71%) who had been treated before would live for 4 years without their disease getting worse.

In contrast, researchers estimated that in people treated with placebo plus rituximab, approximately 3 out of 10 participants (32%) who had been treated before would live for 4 years without their disease getting worse.

At 4.5 years, the percentages of participants who were alive in each treatment group were similar (86% with ibrutinib plus rituximab versus 84% with placebo plus rituximab).

Participants in both study groups felt that their quality of life improved with treatment

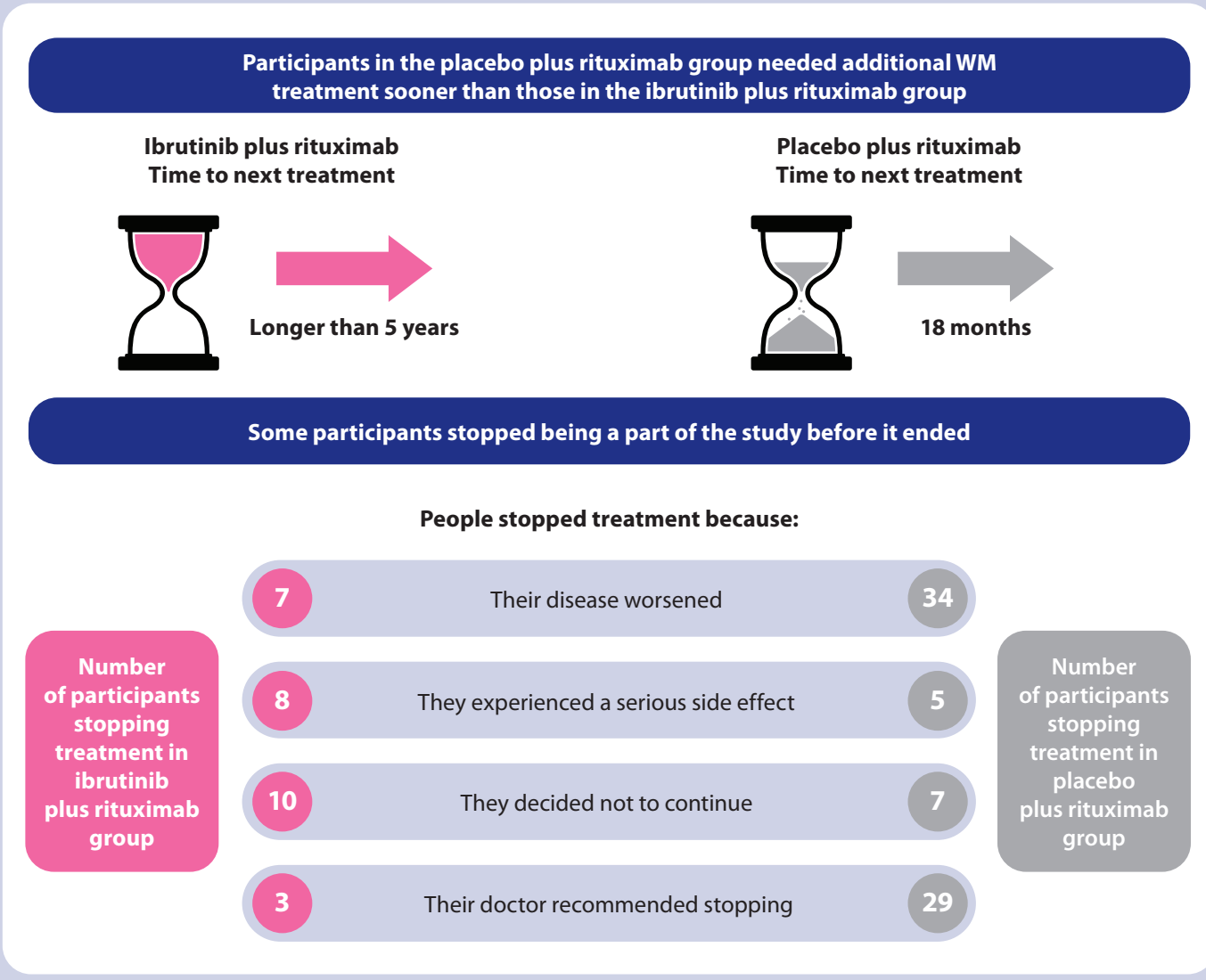
75% of participants who took ibrutinib plus rituximab felt their quality of life improved

59% of participants who took placebo plus rituximab felt their quality of life improved

Participants in the ibrutinib plus rituximab group benefited from treatment, surviving without their disease getting worse, regardless of any changes in their *MYD88* or *CXCR4* genes.

Nine people (12%) who took ibrutinib plus rituximab needed another WM treatment after the one taken in this study compared to 47 people (63%) who took placebo plus rituximab.

For participants who needed another treatment, the amount of time before the next treatment was approximately 18 months for those taking placebo plus rituximab. In participants taking ibrutinib plus rituximab, the amount of time before the next treatment was longer than measurable by this study.



Did participants experience side effects?

Side effects and safety were evaluated by study doctors. The impact of treatment on symptoms and quality of life was measured using patient-reported outcomes surveys, including the EuroQoL 5-Dimension 5-Level Questionnaire (EQ-5D-5L) and the Functional Assessment of Cancer Therapy-Anemia (FACT-An). The FACT-An score specifically measures changes in quality of life related to having low numbers of red blood cells, which can lower a person's oxygen level and lead to tiredness.

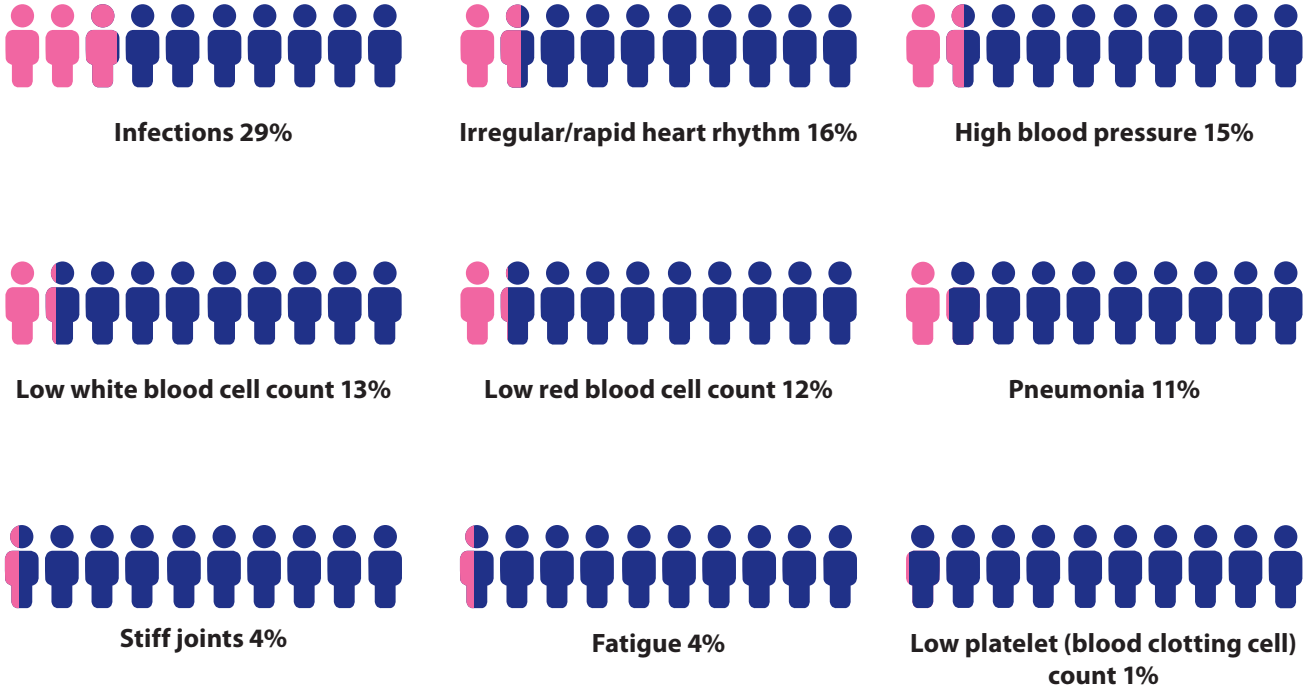
Side effects with ibrutinib plus rituximab were manageable and decreased over time.

Seventeen participants (23%) who took ibrutinib plus rituximab experienced a side effect that required them to take a lower dose of ibrutinib. The side effects got better in most patients (92%) after lowering the dose.

Eight participants had to stop taking ibrutinib due to a side effect.

No participants died because of a side effect considered to be related to ibrutinib or rituximab. One patient died due to a lung infection that was not considered related to ibrutinib or rituximab.

Some participants experienced serious side effects while taking ibrutinib plus rituximab that needed care by a doctor. These included:



What were the main conclusions reported by the researchers?

- Over 5 years of follow-up, more participants who took ibrutinib plus rituximab were likely to be alive without worsening disease compared with patients who took placebo plus rituximab.
- This benefit was also seen in participants who had been treated for WM before and those with specific genetic changes that make WM harder to treat. This is different than prior studies of ibrutinib alone, where outcomes were found to be related to certain genetic changes.
- Side effects of ibrutinib plus rituximab were manageable and participants tolerated the treatment well. The side effects seen in this study were consistent with those observed in previous studies.
- Participants in both study groups reported improvements in quality of life (as measured by both EQ-5D-5L and FACT-An anemia scores). Participants who took ibrutinib plus rituximab reported significantly greater improvement in their quality of life (as measured by FACT-An score) compared to those who took placebo plus rituximab.
- Although previous studies have shown that ibrutinib is effective on its own, even in participants whose disease did not respond to rituximab, results of this study suggest that combining ibrutinib and rituximab is beneficial. This may be particularly true for people with *CXCR4* or wild-type genes.
- Ibrutinib plus rituximab is an effective, chemotherapy-free, treatment for patients with WM.

What do the study results mean?

These results show that ibrutinib plus rituximab is better than rituximab alone in patients with WM, even if they had been treated before or had high-risk (aggressive) disease.

A 5-year follow-up showed that ibrutinib plus rituximab is safe and effective in the long term (5 years or longer).

This information confirms the role of ibrutinib plus rituximab as a standard of care for WM.

Who sponsored the study? Who prepared this summary?

This study was sponsored by Pharmacyclics LLC, an AbbVie Company.

The original authors of the presentation were involved in the preparation of this summary.

Where can I find more information on the study?

Original article:

"Ibrutinib Plus Rituximab Versus Placebo Plus Rituximab for Waldenström's Macroglobulinemia: Final Analysis From the Randomized Phase III iNNOVATE Study" published in the *Journal of Clinical Oncology*. You can read the original article at: https://ascopubs.org/doi/full/10.1200/JCO.21.00838

The full name of the iNNOVATE study is: Ibrutinib With Rituximab in Adults With Waldenström's Macroglobulinemia.

You can read more about the iNNOVATE study on the following website: https://clinicaltrials.gov/ct2/show/NCT02165397?term=NCT02165397&draw=2&rank=1

Acknowledgments

The authors thank the patients who participated in the study and their supportive families, as well as the investigators and clinical research staff from the study centers. Editorial support for development of this summary was provided by Cindi A. Hoover, PhD, and was funded by Pharmacyclics LLC, an AbbVie Company.

Financial & competing interests disclosure

Full author disclosure information can be found in the original article.