Clinical Trial Results – Layperson Summary

A study to look at whether longer rituximab treatment provides additional benefit in patients with non-Hodgkin lymphoma and whether this affects treatment safety (the MabCute study)

See the end of the summary for the full title of the study.

Thank you!

Thank you to the patients who took part in this clinical trial (called a 'study' in this document). The generous participation of these people is helping researchers answer important health questions about non-Hodgkin lymphoma (NHL) and how the study drug rituximab can be used to treat these patients.

We hope this summary helps you understand the results of this study and how they may be used to improve the care of patients with NHL.

About this summary

This is a summary of the results of a study written for:

- members of the public and
- patients who took part in the study.

The study started in December 2011 and the last patient completed the study in August 2018. This summary was written after the study had ended This summary is based on information known at the time of writing (February 2020).

No single study can tell us everything about the risks and benefits of a medicine. It takes lots of people in many studies to find out everything we need to know. The results from this study may be different from other studies with the same medicine. This means that you should not make decisions based on this one – **always speak to your doctor before making any decisions about your treatment**.

Contents of the summary

Key information about this study

- This study, named MabCute, was done in patients with non-Hodgkin lymphoma (NHL) who had already received **standard treatment**. Standard treatment involves an **initial treatment** period with a medicine called rituximab and chemotherapy (known as induction), followed by a period of rituximab on its own for 2 years (known as **'maintenance I'**). Currently on this standard treatment regimen, rituximab is given for approx. 2.5 years in total.
- MabCute was done to see if patients who have received the standard treatment regimen would benefit from an **additional 2 years** of rituximab treatment – called '**maintenance II**'.
- Patients who had received standard treatment (**initial treatment + maintenance I**) were split into two groups for the **'maintenance II'** phase:
  - One group was given rituximab for an **additional** 2 years (called **Rituximab group**)
  - The other group had **no additional** rituximab treatment (they were just observed, called **Observation group**).
- It was decided by chance which group each patient joined.
- 276 patients who had received standard treatment were included in the **'maintenance II'** phase of this study
- At the end of the study, only a small number of patients in either group showed signs of their cancer getting worse (known as 'disease progression').
  - Because this number of patients was so small, the study cannot make any firm conclusions about the effectiveness of **additional** rituximab treatment, beyond the **standard treatment**
- The number of patients experiencing side effects was similar in both groups. Nothing new was found with the overall safety of rituximab, and side effects were as expected based on previous clinical trials with rituximab.

1. General information about this study

Why was this study done?

Non-Hodgkin lymphoma (NHL) is a cancer of the lymphatic system. The lymphatic system is an important part of the immune system and helps the body to fight infections. It also helps fluids move through the body. NHL is a disease in which the body starts to produce too many abnormal (cancerous) infection-fighting cells (called lymphocytes). These abnormal lymphocytes may be present in any part of the lymphatic system (for example, the lymph nodes or the spleen), but can also spread to other parts of the body, such as the liver or brain.

Standard treatment for NHL involves an initial treatment with the combination of chemotherapy and a type of targeted therapy called rituximab. This combination is given over 6–8 rounds of treatment and is called '**induction treatment'**. This is followed by 2 years of treatment with rituximab alone, called '**maintenance I**' treatment. This standard treatment regimen lasts for a total of approx. 2.5 years, and was received by all patients in this study.

This study was done to see whether giving an **additional** 2 years of rituximab after **'maintenance I'** – called '**maintenance II**' – might give better outcomes (fewer patients showing signs of their cancer getting worse, known as "disease progression"), compared to the standard 2 years of **'maintenance I'** treatment.

What was the study medicine?

A medicine called 'rituximab' was the focus of this study.

Rituximab (Rituxan® or MabThera®) is a medicine approved to treat:

- A type of blood cancer called non-Hodgkin's lymphoma
- A type of blood cancer called chronic lymphocytic leukaemia
- Rheumatoid arthritis, which is an autoimmune disease of the joints
- Granulomatosis polyangiitis and microscopic polyangiitis, 2 types of autoimmune disease of the blood vessels in adults and in children
- Pemphigus vulgaris (a life-threatening autoimmune blistering disease on the skin and on the lining of the mouth and other mucous membranes)

In NHL, there is an increased number of abnormal (cancerous) B lymphocytes, a type of white blood cell that plays an important role the immune system by helping the body to fight infection. Rituximab is an effective treatment for NHL as it works by decreasing the number of cancerous B lymphocytes in the blood and other tissues.

What did researchers want to find out?

- Researchers did this study to understand, whether longer treatment with rituximab in '**maintenance II'** gives better results for the patients (see section 4 "What were the results of the study?").
- They also wanted to find out how safe the **additional** treatment with rituximab in '**maintenance II'** was – by checking how many patients had side effects during this study (see section 5 "What were the side effects?").

The main question that researchers wanted to answer was:

1. How long did patients stay free of signs and symptoms of their cancer getting worse (known as disease progression)?

Other questions that researchers wanted to answer included:

2. Did **additional** treatment with rituximab in **'maintenance II'** help patients live longer?
3. How safe was the **additional** treatment with rituximab in **'maintenance II'**, compared with no additional treatment?

What kind of study was this?

This study was a '**Phase 3**' study, which means that this study included a large number of patients with NHL.

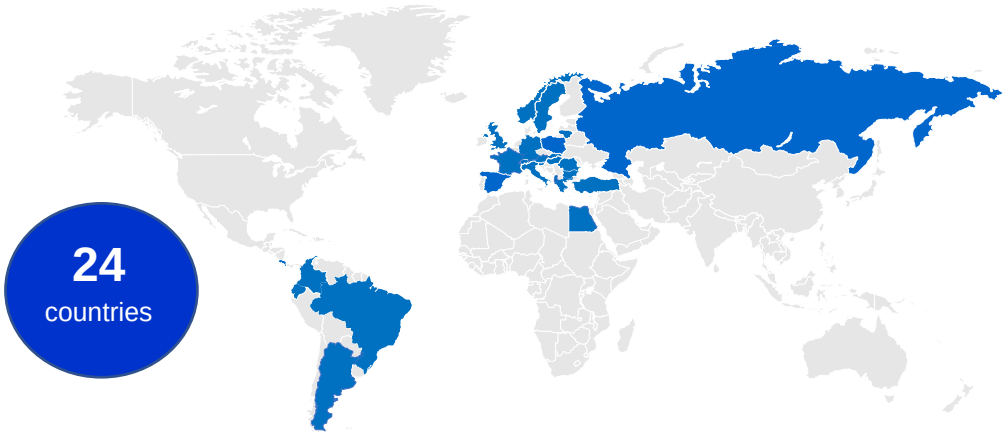
The study was '**randomised**'. This means that it was decided by chance which group patients would join which group – like tossing a coin.

The study was '**open label**'. This means that everyone, including the researchers and the patients, knew what treatment they were receiving.

When and where did the study take place?

The study started in December 2011 and the last patient completed the study in August 2018. This summary was written after the study had ended.

The study took place at 180 study centres – across 24 countries in three regions. The regions included Europe, South America and Africa (shown on the map below).



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- Argentina
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- France
- Germany
- Greece
- Hungary
- Italy
- Lithuania
- Norway
- Romania
- Russia
- Slovakia
- Slovenia
- Spain
- Sweden
- Switzerland
- Turkey
- United Kingdom

2. Who took part in this study?

In this study, 692 patients with NHL received standard treatment (a combination of chemotherapy and rituximab, followed by 2 years of rituximab treatment (**'maintenance I'**) for approx. 2.5 years in total.

Of these, 276 patients went on to receive either **additional** treatment with rituximab in **'maintenance II'** for up to 2 years (138 patients – **Rituximab group**), or no additional treatment (138 patients – **Observation group**).

In the **Rituximab group** receiving **additional** treatment with rituximab in **'maintenance II'**:

- 74/138 patients were male (53.6%).
- The average age of patients was 64 years.

In the **Observation group** receiving **no additional treatment**:

- 68/138 patients were male (49.3%).
- The average age of patients was 65 years.

Patients could take part in the study if they:

- Were at least 18 years of age.
- Had been diagnosed with NHL.
- Had previously received treatment for their NHL that either:
    - did not work, or,
    - worked for a while, but their NHL had come back.

Patients could not take part in the study if they:

- Had any other significant health problems.
- Were pregnant or breastfeeding.

3. What happened during the study?

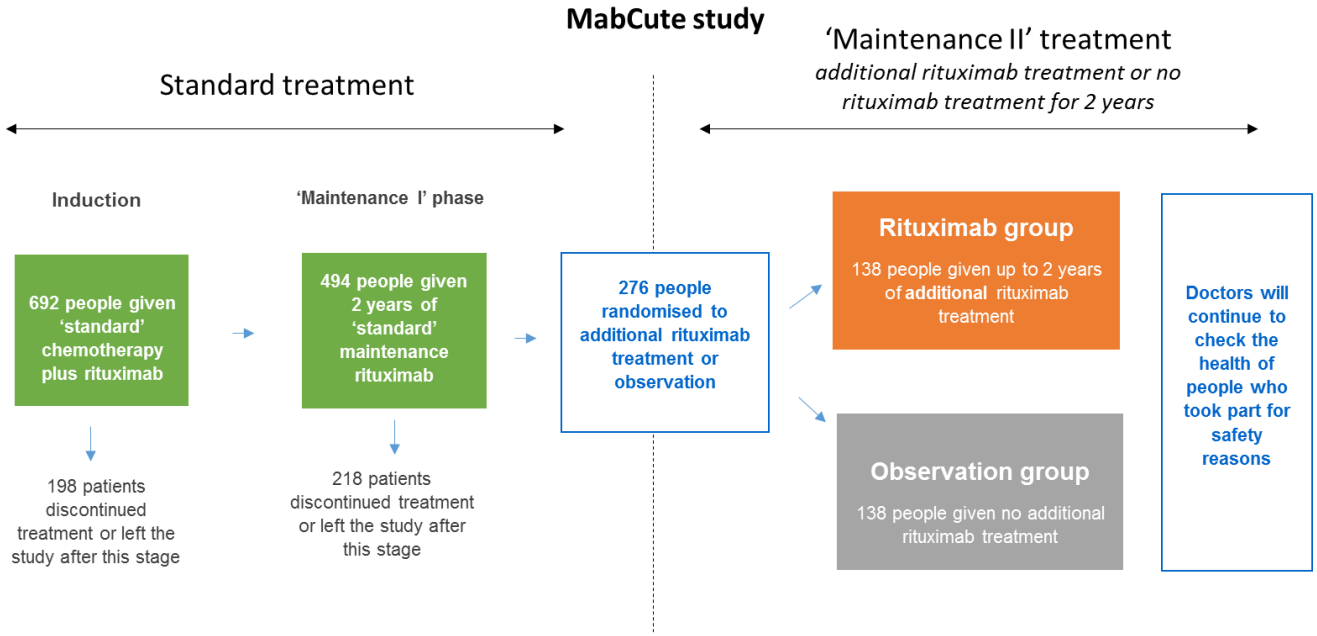
During the MabCute study, patients were randomised (selected by chance) by a computer to be in one of two groups in the **'maintenance II'** phase.

The groups were:

- **Rituximab group: additional** rituximab was given as an injection under the patients' skin every 8 weeks for up to 2 years.

- **Observation group:** no additional treatment was given

The diagram below shows the entire journey of patients who entered the MabCute study. Not all patients who received standard treatment (induction and 'maintenance I') entered the 'maintenance II' phase of the study:



4. What were the results of the study?

Question 1: How long did patients stay free of signs and symptoms of their cancer getting worse (known as disease progression)?

By the end of the study, most patients remained free from signs and symptoms of disease progression. In total, 46/276 patients showed signs of disease progression or died (19 from the **Rituximab group** who received **additional** rituximab treatment and 27 from the **Observation group** who received no additional treatment in 'maintenance II').

Rituximab group	Observation group
19/138 patients	**27/138 patients**
Disease progression (15 patients) Death (4 patients)	Disease progression (22 patients) Death (5 patients)

Because the number of patients with disease progression was so low, the study cannot make any firm conclusions about the benefits of **additional** treatment with rituximab in **'maintenance II'**.

Question 2: Did additional treatment with rituximab in "maintenance II" help patients live longer?

Another piece of information that researchers collected was how long the patients in the study lived for while on treatment.

By the end of the study, there was no indication that **Rituximab group** patients lived any longer than **Observation group** patients. However, because the number of patients with disease progression was so low, the study cannot make any firm conclusions.

- From the point that patients were randomised for the '**maintenance II'** phase, there were 18 deaths in total (due to disease progression – see above - or other reasons).
  - 10 in the Rituximab group
  - 8 in the Observation group

This section only shows the key results from the study. You can find information about all other results on the websites at the end of this summary (see section 8).

5. What were the side effects?

Side effects are unwanted medical problems (such as a headache) that happen during the study that may or may not be considered to be related to the treatment in the study by the physician

Not all of the patients in this study had all of the side effects.

Serious and common side effects are listed in the following sections.

Serious side effects

A side effect is considered 'serious' if it is life-threatening, needs hospital care, or causes lasting problems. All information on side effects was collected, whether they were due to the treatment, the patient's disease, or other causes.

Throughout the entire study (**induction, 'maintenance I' and 'maintenance II'**) 49% of patients had at least one serious side effect (which may or may not have been related to treatment with rituximab).

The study also looked at side effects just from the **'maintenance II'** part of the study. This was done for both groups even if the side effects were not related to the study treatment (meaning patients in the **Observation group** who did not receive any additional rituximab treatment were still checked for any side effects). Over the **'maintenance II'** period of the study, the number of patients with a serious side effect was similar between the **Rituximab group** (22.5% of patients) and the **Observation group** (23.2% of patients). The most commonly reported serious side effects during this period were pneumonia (5.8% and 2.9%) and blood poisoning (1.4% for both groups).

During the '**maintenance II'** part of the study, 10 out of 138 patients (7.2%) from the **Rituximab group** decided to stop taking their medicine because of side effects. Five patients in the **Rituximab group** and 6 patients from the **Observation group** experienced at least one side effect that resulted in death.

Most common side effects

Overall 111 out of 138 (80.4%) patients from the **Rituximab group** had at least one side effect, compared with 80/138 (58%) of patients from the **Observation group** during the **'maintenance II'** part of the trial.

The most common side effects were cough, pneumonia and bronchitis, chest infection, low white blood cell count and a stuffy nose.

Other side effects

You can find information about other side effects (not shown in the sections above) on the websites listed at the end of this summary – see section 8.

6. How has this study helped research?

The information presented here is from a single study of patients with NHL and these results helped researchers learn more about the role of rituximab in treating NHL.. There were no firm conclusions on the benefit of **additional** rituximab treatment (defined as **'maintenance II'** phase) beyond standard treatment **(induction and 'maintenance I')** in these patients. However, the additional treatment had no effect on the safety of rituximab, and there were no new safety concerns,

No single study can tell us everything about the risks and benefits of a medicine. It takes lots of people in many studies to find out everything we need to know. The results from this study may be different from other studies with the same medicine.

- This means that you should not make decisions based on this one summary – always speak to your doctor before making any decisions about your treatment.

7. Are there plans for other studies?

No more studies to look at the benefit of **additional** rituximab treatment beyond standard 'maintenance I' in patients with NHL are planned

8. Where can I find more information?

You can find more information about this study on the websites listed below:

- https://clinicaltrials.gov/ct2/show/study/NCT01461928
- https://www.clinicaltrialsregister.eu/ctr-search/trial/2010-023407-95/results
- https://forpatients.roche.com

Who can I contact if I have questions about this study?

If you have any further questions after reading this summary:

- Visit the ForPatients platform and fill out the contact form – https://forpatients.roche.com
- Contact a representative at your local Roche office.

If you took part in this study and have any questions about the results:

- Speak with the study doctor or staff at the study hospital or clinic.

If you have questions about your own treatment:

- Speak to the doctor in charge of your treatment.

Who organised and paid for this study?

This study was organised and paid for by F. Hoffmann-La Roche Ltd who have their headquarters in Basel, Switzerland.

Full title of the study and other identifying information

The full title of this study is:

Efficacy and safety of prolonged maintenance with subcutaneous rituximab in patients with relapsed or refractory indolent non-Hodgkin lymphoma: results of the Phase III MabCute study.

The study is known as 'MabCute'.

The protocol number for this study is: MO25455
The ClinicalTrials.gov identifier for this study is: NCT01461928.
The EudraCT number for this study is: 2010-023407-95