Summary of Clinical Trial Results

A study to test the safety and effectiveness of bevacizumab added to standard treatment versus standard treatment alone in children and young adults with a type of brain cancer called high-grade glioma (HERBY)

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

About this summary

This is a summary of the results of a clinical trial (called a 'study' in this document) – written for:

- members of the public and
- people who took part in the study and their families.

This summary is based on information known at the time of writing.

The study started in October 2011 and finished in January 2020. This summary was written after the study had ended.

No single study can tell us everything about the risks and benefits of a medicine. It takes many people in a large number of 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.**

Contents of the summary

Thank you to the people who took part in this study

The people who took part have helped researchers to answer important questions about children and young adults with high-grade glioma and the role of bevacizumab in treating these patients.

Key information about this study

- This study was done to look for new ways to treat children and young adults with high-grade gliomas (HGGs)
- In this study, children and young adults with HGGs were given either:
  - the medicine being studied called 'bevacizumab' plus the standard treatment with a medicine called 'temozolomide' and radiotherapy
  - OR standard treatment with temozolomide plus radiotherapy
- It was decided by chance which treatment each child or young adult was given
- This study included 121 children and young adults in 14 countries. Out of these, 116 children and young adults received treatment
- The main finding was that adding bevacizumab to temozolomide and radiotherapy did not give any additional benefit to children and young adults with HGGs
- Around 21% (12 out of 56 children and young adults) taking temozolomide plus radiotherapy had serious side effects, compared to around 32% (19 out of 60 children and young adults) taking bevacizumab plus temozolomide and radiotherapy.
- No further studies with bevacizumab are planned in this group of patients

1. General information about this study

Why was this study done?

Gliomas are the most common type of childhood cancer involving the brain or spinal cord and affect cells called glial cells. Glial cells are a special type of cell that help to protect neurons (important nerve cells that transmit information).

Gliomas can be categorised by how they look under a microscope. High-grade gliomas (or HGGs) look very unusual compared to normal brain cells and are relatively rare, with around 2 cases per million children reported each year.

Treatment for HGG is difficult – current treatment for children aged 3 and above includes surgery to remove as much of the tumour as possible, followed by a medicine called temozolomide and a course of radiotherapy. After radiotherapy, patients continue to take temozolomide. However, survival rates are poor and new treatments are urgently needed to help improve outcomes.

Bevacizumab is another medicine that is already approved to treat many other cancers and has shown promise for HGGs in other small studies. This study was done to see if adding bevacizumab to current treatment would benefit children and young adults with HGGs, and to see if it could be approved for doctors to use.

What were the study medicines?

This study looked at 2 medicines:
- **Temozolomide** – existing medicine
- **Bevacizumab** – the medicine that was studied.

'Temozolomide' (tem-oh-zol-oh-mide) is an existing medicine given to people with HGGs. It is the current standard of care and is used with radiotherapy after surgery.

'Bevacizumab' (bev-ah-siz-uh-mab) is the medicine that was studied here. It works by blocking signals that tell cancer cells to grow, and has been studied and approved in a number of other types of cancer.

Children and young adults in this study also received radiotherapy. This treatment uses a high dose of radiation to kill cancer cells and to reduce tumour size.

What did researchers want to find out?

- Researchers did this study to compare bevacizumab in combination with temozolomide and radiotherapy with temozolomide and radiotherapy – to see how well bevacizumab worked (see section 4 "What were the results of the study?").
- They also wanted to find out how safe the medicines were – by checking how many children and young adults had side effects and seeing how serious they were, when taking each of the medicines during this study (see section 5 "What were the side effects?").

The main question that researchers wanted to answer was:

1. Did adding bevacizumab to temozolomide and radiotherapy increase the amount of time before a child's or young adult's cancer got worse or came back?

Other questions that researchers wanted to answer included:

2. Did adding bevacizumab to temozolomide and radiotherapy help children and young adults to live longer?
3. How many children and young adults responded to treatment?
4. How safe was the combination of bevacizumab plus temozolomide and radiotherapy compared to temozolomide and radiotherapy?

What kind of study was this?

This study was a 'Phase 2' study. This means that bevacizumab had been tested in a small number of children and young adults with HGG before this study.

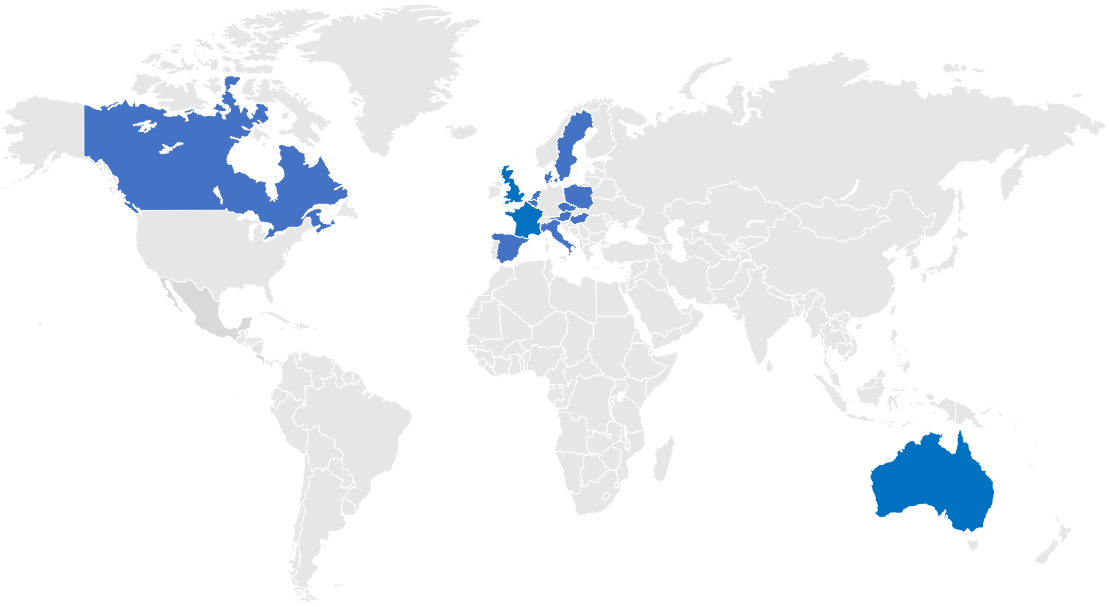
The study was 'randomised'. This means that it was decided by chance which of the medicines children and young adults in the study would receive – like tossing a coin. Randomly choosing which medicine children and young adults take makes it more likely that the types of children and young adults in both groups (for example, age, race) will be a similar mix. Apart from the exact medicines being tested in each group, all other aspects of care were the same between the groups.

The study was 'open-label'. This means that everyone knew which treatments children and young adults were receiving.

When and where did the study take place?

The study started in October 2011 and finished in January 2020. This summary was written after the study had ended.

The study took place at 51 study centres – across 14 countries. The following map shows the countries where this study took place.

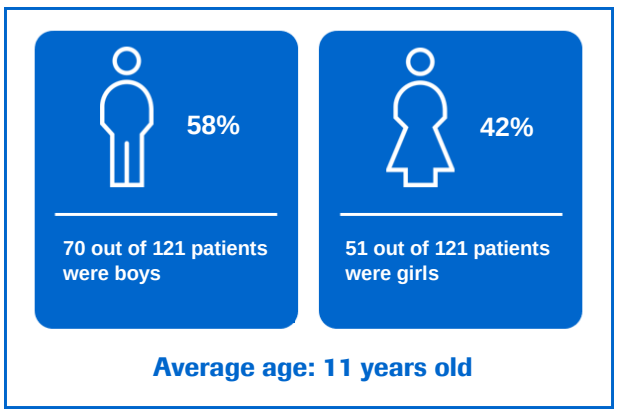


- Australia
- Austria
- Belgium
- Canada
- Czech Republic
- Denmark
- France
- Hungary
- Italy
- Poland
- Sweden
- Spain
- The Netherlands
- United Kingdom

2. Who took part in this study?

In this study, 121 children and young adults with HGG took part. Out of these, 116 received treatment.

Children and young adults who took part in the study were between 3 and 17 years of age. 70 of the 121 people (58%) were boys and 51 of the 121 people (42%) were girls.



Children and young adults could take part in the study if:

- They had been diagnosed with HGG that had not spread to other parts of the body and did not have any other significant medical conditions.
- They must have had surgery to remove tumour between 4–6 weeks before the study

The study also included a 'young patient group' that included infants and toddlers aged between 6 months and 3 years old. In this group, there were two infants aged 17 and 22 months and one toddler aged 32 months when they entered they study.

3. What happened during the study?

During the study, children and young adults were selected by chance to get one of the two treatments. The treatments were selected at random – by a computer.

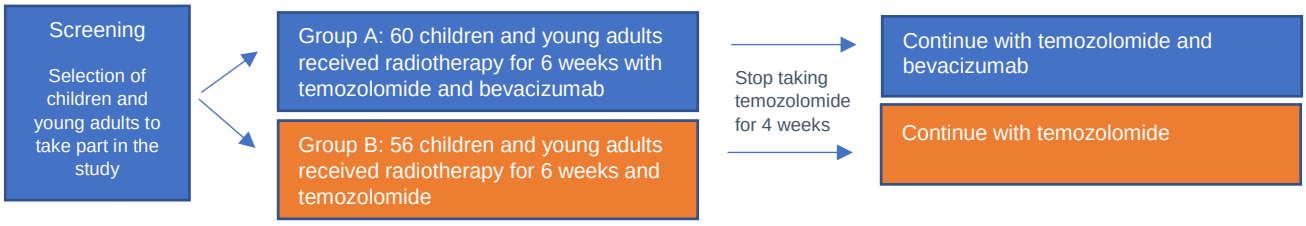
The treatment groups were:

- **Group A: Radiotherapy and temozolomide plus bevacizumab**
  - Radiotherapy given every day over 6 weeks and temozolomide given as a tablet to take by mouth every day for 5 days, and repeated every 28 days (for up to 49 days)
  - After finishing radiotherapy, children had a 4-week break off treatment, before restarting temozolomide for approximately 1 year (up to 48 weeks)
  - Bevacizumab given as an infusion into the vein every 2 weeks

62 children were selected for Group A, and 60 received treatment

- **Group B: Radiotherapy and temozolomide**
  - Radiotherapy given every day over 6 weeks and temozolomide given as a tablet to take by mouth every day for 5 days, and repeated every 28 days (for up to 49 days)
  - After finishing radiotherapy, children and young adults had a 4-week break off treatment, before restarting temozolomide for approximately 1 year (up to 48 weeks)

59 children and young adults were selected for Group B, and 56 received treatment



- ***Young patient group: Temozolomide plus bevacizumab***
  - *Temozolomide given as a tablet to take by mouth every day for 5 days, and repeated every 28 days*
  - *Bevacizumab given as an infusion into the vein every 2 weeks*

All 3 of the infants and toddlers received at least 2 doses of temozolomide, with 1 receiving a total of 13 temozolomide doses. All 3 of the infants and toddlers received at least 4 doses of bevacizumab, with 1 receiving a total of 24 bevacizumab doses.

Children and young adults in the study were planned to be treated for 58 weeks. When the study finished, the children and young adults who took part were asked to go back to

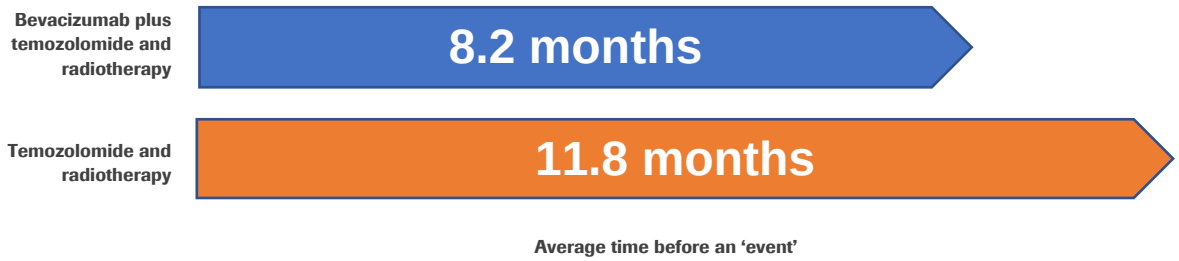
their study centre for more visits – to check their overall health. Look below to see more information about what happened in the study.

4. What were the results of the study?

Question 1: Did adding bevacizumab to temozolomide and radiotherapy increase the amount of time before a child or young adult's cancer got worse or came back?

Researchers looked at whether adding bevacizumab to temozolomide and radiotherapy could increase the amount of time before a child or young adult had what doctors refer to as an 'event'. An 'event' could be a child or young adult's cancer getting worse, coming back, or developing another cancer not related to HGG. It also included children and young adults who died, regardless of the cause.

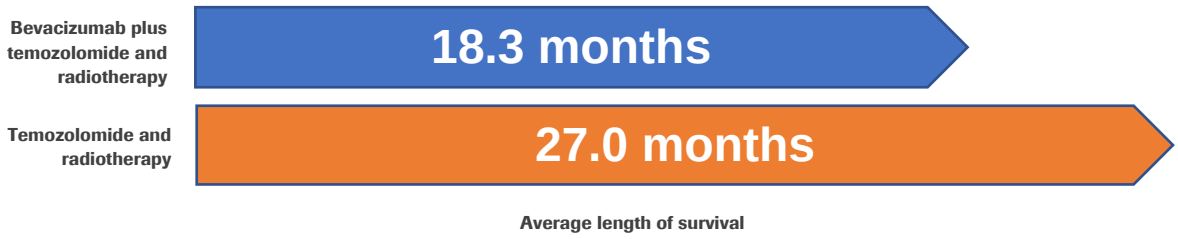
The results of the study found no improvement in the length of time before children and young adults had an 'event' between those treated with bevacizumab plus temozolomide and radiotherapy, compared to temozolomide and radiotherapy.



In the young patient group, the time until an 'event' was 50 days, 90 days and 545 days

Question 2: Did adding bevacizumab to temozolomide and radiotherapy help children and young adults to live longer?

Another piece of information that researchers collected was whether adding bevacizumab to temozolomide and radiotherapy helped children and young adults to live longer. The results of the study found no improvement in how long children and young adults lived for between those treated with bevacizumab plus temozolomide and radiotherapy, compared to temozolomide plus radiotherapy.



Question 3: How many children and young adults responded to treatment?

Another piece of information that researchers collected was how many children and young adults responded to treatment (meaning they had some improvement in their HGG). Overall, 41.7% of children and young adults treated with bevacizumab and temozolomide plus radiotherapy responded to treatment, compared with 40.0% of patients treated with temozolomide and radiotherapy.

This section only shows the key results from this 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 medical problems (such as feeling dizzy) that happened during the study.

- They are described in this summary because the study doctor believes the side effects were related to the treatments in the study.
- Not all of the people in this study had all of the side effects.
- Side effects may be mild to very serious and can be different from person to person.
- It is important to be aware that the side effects reported here are from this single study. Therefore, the side effects shown here may be different from those seen in other studies, or those that appear on the medicine label.
- Serious and common side effects that happened in this study 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.

During this study, 12 out of 56 children and young adults (21%) treated with temozolomide and radiotherapy had a serious side effect, compared to 19 out of 60 children (32%) treated with bevacizumab and temozolomide plus radiotherapy.

The most common serious side effects from the study are shown in the following table – these are the most common serious side effects related to treatment across both groups.

Serious side effects reported in this study	**Children and young adults taking temozolomide and radiotherapy** (56 people total)	**Children and young adults taking bevacizumab and temozolomide plus radiotherapy** (60 people total)
Vomiting	3.6% (2 out of 56)	6.7% (4 out of 60)
Fever	5.4% (3 out of 56)	6.7% (4 out of 60)
Fever with low white blood count	0% (0 out of 56)	6.7% (4 out of 60)

There were no serious side effects seen in the young patient group.

One child in the study died due to side effects that may have been related to one of the study medicines. This child died from B-cell leukaemia. Three other children or young adults died from secondary cancers (cancers that were not HGG) several months after end of treatment.

During the study, some people decided to stop taking their medicine because of side effects:

- In the **bevacizumab plus temozolomide and radiotherapy** group, 20% of children and young adults stopped taking bevacizumab and 5% of children and young adults stopped taking temozolomide.
- In the **temozolomide and radiotherapy** group, 5% of children and young adults stopped taking temozolomide and 2% of children and young adults stopped radiotherapy

Most common side effects

During this study, 57 out of 60 (95%) children and young adults treated with bevacizumab and temozolomide plus radiotherapy had at least one related side effect, compared with 51 out of 60 (91%) children and young adults treated with temozolomide and radiotherapy.

The most common side effects related to treatment are shown in the following table – these are the most common side effects across all treatment groups. Some children and young adults had more than one side effect – this means that they are included in more than one row in the table.

Most common side effects reported in this study	**Children and young adults taking temozolomide and radiotherapy** (56 people total)	**Children and young adults taking bevacizumab and temozolomide plus radiotherapy** (60 people total)
Vomiting	41.1% (23 out of 56)	40.0% (24 out of 60)
Nausea	39.3% (22 out of 56)	31.7% (19 out of 60)
Fatigue	39.3% (22 out of 56)	33.3% (20 out of 60)
Hair loss	48.2% (27 out of 56)	21.7% (13 out of 60)
Low platelet count	32.1% (18 out of 56)	31.7% (19 out of 60)
Low neutrophil count	26.8% (15 out of 56)	25.0% (15 out of 60)
Low white blood cell count	23.2% (13 out of 56)	26.7% (16 out of 60)
Low appetite	26.8% (15 out of 56)	23.3% (14 out of 60)

All three infants and toddlers in the young patient cohort experienced side effects. These were mostly mild, and included upper respiratory tract infection, vomiting, high blood pressure and low platelet, neutrophil and white blood cell count.

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 121 children and young adults with HGG (of which 116 received treatment). These results helped researchers learn more about HGG, and the role of bevacizumab for treating these children and young adults.

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?

At the time of writing this summary, no more studies looking at temozolomide and bevacizumab in HGG 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/results/NCT01390948
- https://www.clinicaltrialsregister.eu/ctr-search/trial/2010-022189-28/results
- https://forpatients.roche.com/en/trials/cancer/high-grade-glioma/a-study-of-bevacizumab--avastin--in-combination-with-te-29856.html

If you would like to find out more about the results of this study, the full title of the relevant scientific paper is: "Phase II, Open-Label, Randomized, Multicenter Trial (HERBY) of Bevacizumab in Pediatric Patients With Newly Diagnosed High-Grade Glioma". The authors of the scientific paper are: Jacques Grill, Maura Massimino, Eric Bouffet, Amedeo A Azizi, Geoffrey McCowage and others. The paper is published in the journal 'J Clin Oncol', volume number 36, on pages 951–958.

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: "A phase II open-label, randomized, multi-center comparative study of bevacizumab-based therapy in pediatric patients with newly diagnosed supratentorial, infratentorial, cerebellar, or peduncular high-grade glioma"

The study is known as 'HERBY'.

- The protocol number for this study is: BO25041.
- The ClinicalTrials.gov identifier for this study is: NCT01390948.
- The EudraCT number for this study is: 2010-022189-28