Clinical Trial Results – Layperson Summary

A study to look at how safe RO6874281 plus pembrolizumab was in people with skin cancer that has grown or spread in the body - and how well this experimental drug combination worked

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

This summary is based on information known at the time of writing (March 2023). More information may now be known.

The study started in June 2019 and was discontinued in July 2022 because the drug company, Roche, decided to prioritise the development of other, potentially more impactful medicines, and not because too many people had concerning side effects or because the experimental drug was not effective.

No single study can tell us everything about the risks and benefits of an experimental drug. 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 experimental drug.

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 in this study were affected by skin cancer (melanoma), which has grown or spread in the body and cannot be removed with surgery. They have helped researchers to answer important questions about how safe the experimental drug combination was and how well it may work to treat this disease.

Key information about this study

- This study was done to assess how safe an experimental drug called RO6874281 is, and how well it works when given with pembrolizumab in people with skin cancer (melanoma) that has grown or spread in the body and that could not be removed with surgery
- RO6874281 and pembrolizumab are drugs that help the immune system seek out and fight cancer cells (known as 'immunotherapies')
- This study included 83 people in 7 countries
- The main safety findings were:
  - 99% of people (82 out of 83 people) taking RO6874281 and pembrolizumab had non-serious side effects (unwanted medical problems) that were related to RO6874281
  - 30% of people (25 out of 83 people) had serious side effects - defined as a person being hospitalised for a short or prolonged time and which may, on rare occasions, be life threatening - that were related to RO6874281
- No person in this study stopped taking RO6874281 and pembrolizumab due to a side effect that was related to RO6874281
- Across treatment groups, between 1 in 20 people (5%) and 1 in 4 people (25%) responded to treatment (had cancer that reduced in size or disappeared) with RO6874281 and pembrolizumab
- This study did not include as many people as planned because the drug company (Roche) decided to discontinue the study. This was to prioritise the development of other, potentially more impactful medicines, and not because too many people had concerning side effects or because the experimental drug was not effective

1. General information about this study

Why was this study done?

Melanoma is a type of cancer that usually develops in the skin. It starts in cells called melanocytes, which produce the pigment melanin that gives your skin its colour. For the rest of this document, the term 'skin cancer' is used for melanoma. When diagnosed at early stages, skin cancer is usually treated with surgery. At later stages, skin cancer has grown (known as 'advanced') or spread to other organs in the body (called 'metastatic') and is harder to treat.

Current treatments for advanced and metastatic skin cancer that cannot be removed by surgery (known as 'unresectable' skin cancer) include immunotherapies, targeted therapies, chemotherapy, and radiotherapy. Cancer immunotherapies use the body's immune system to destroy cancerous cells. A new combination of immunotherapy treatments was looked at in this study to see how safe it is and if it may provide better health outcomes for people with advanced or metastatic skin cancer that cannot be removed with surgery.

What were the study medicines?

An experimental drug called **RO6874281** was the focus of this study.

- RO6874281 is an experimental drug because health authorities have not approved it for treating cancer
- RO6874281 is similar to a type of molecule the body naturally produces called a cytokine (you say this as 'sye-tow-kine') that stimulates the immune system. This type of drug is known as an 'immunotherapy'
- RO6874281 joins to a structure on cancerous tumours called FAP, which is short for fibroblast activation protein-alpha. FAP is part of the connective tissue that is needed for solid tumours to grow. RO6874281 delivers the immunotherapy to immune cells that filter into the solid tumours
- RO6874281 was designed to be given in combination with other medicines, such as pembrolizumab, to make them more effective by boosting the body's immune response to fight cancer cells

Pembrolizumab is an existing standard medicine which is approved by the Food and Drug Administration (FDA) in the United States and by the European Medicines Agency (EMA) for the treatment of several different types of cancer including early stage, advanced and metastatic skin cancer.

- You say this as 'pem-broh-LIZ-yoo-mab'
- Pembrolizumab is a type of immunotherapy medicine called a checkpoint inhibitor, or **CPI**. It blocks the interaction between a protein called PD-1, which is found on cells of the immune system, and PD-L1, which can be found on cancer cells. PD-L1 'hides' the cancer from the immune system. Blocking this interaction allows the body's immune system to see the cancer cells

RO6874281 was tested with pembrolizumab in this study

What did researchers want to find out?

Researchers did this study to see how safe RO6874281 and pembrolizumab were when taken together – by checking how many people had side effects and what these were when taking the experimental drug combination during this study (see Section 5 'What were the side effects?').

They also wanted to find out whether RO6874281, in combination with pembrolizumab worked in patients with skin cancer (see Section 4 'What were the results of the study?').

The main questions that researchers wanted to answer were:

- How safe was RO6874281 in combination with pembrolizumab for people with advanced or metastatic skin cancer?
- How well does RO6874281, given in combination with pembrolizumab, work in people with advanced or metastatic skin cancer?

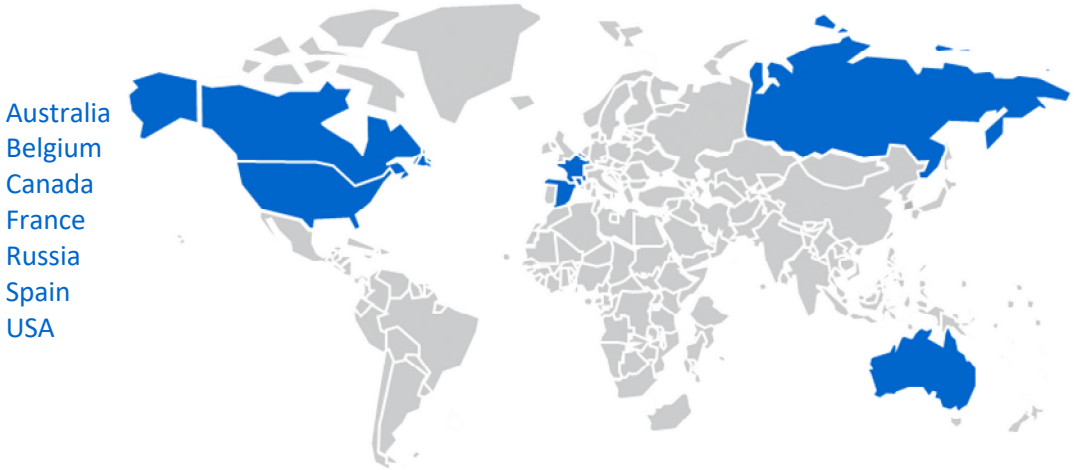
What kind of study was this?

This was a ‘phase I’ study, which means it was one of the first studies to look at RO6874281 and pembrolizumab treatment in people with skin cancer. 83 people with skin cancer took RO6874281 and pembrolizumab, and the researchers did medical tests on the people who took part to find out more about RO6874281 and pembrolizumab.

When and where did the study take place?

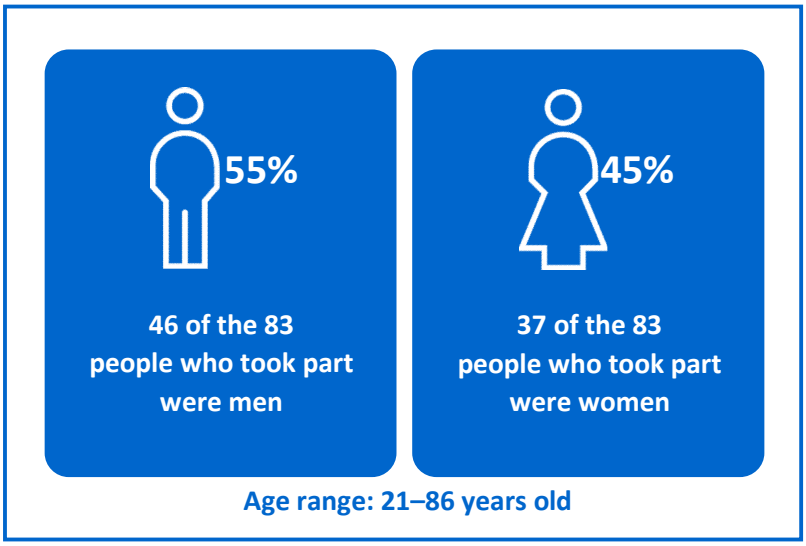
The study ran from June 2019 to July 2022.

The study took place at 23 study centres across 7 countries in Europe, Oceania, and North America. The following map shows the countries where this study took place.



2. Who took part in this study?

In this study, 83 people with advanced or metastatic skin cancer took part. People who took part in the study were between 21–86 years old. 46 of the 83 people (55%) were men and 37 of the 83 people (45%) were women.



To take part in the study, people had to meet certain medical criteria. This was to make sure that the study medicine was given to people as safely as possible and so that researchers could see how well the study medicine had worked in people with a similar medical condition. The main criteria that people had to meet are listed below.

People could take part in the study if they:

- Were over 18 years old
- Had been diagnosed with advanced or metastatic skin cancer that could not be removed with surgery
- Were untreated for skin cancer, or their cancer had worsened after treatment with either a CPI immunotherapy or a specific targeted therapy (called BRAF inhibitor)

People could not take part in the study if they:

- Had previously had certain side effects to cancer treatment and/or immunotherapies
- Had received certain medicines or treatments previously, including for skin cancer that had spread to the brain or spinal cord and did not cause symptoms
- Had certain other medical illnesses or conditions, including other types of cancer, autoimmune diseases, infections, or lung, liver, or heart problems
- Were pregnant or breastfeeding

3. What happened during the study?

The study was in 3 parts:

- In Part I (safety run-in), researchers looked at how safe RO6874281 was when given with pembrolizumab in a small number of people who either had or had not been treated with a CPI before. Researchers also looked at how well the treatment combination worked. 16 people joined Part I of the study

- In Part II, researchers looked at how safe RO6874281 was when given with pembrolizumab in a larger group of people who had not had CPI treatment before. Part II did not take place - the researchers decided that it was more important to begin Part III and give treatment to people who have had CPI treatment before. This was because people whose skin cancer worsens after CPI treatment do not have many other treatment options available to them. These people are in greater need of new treatments compared to those who have not had CPI treatment before

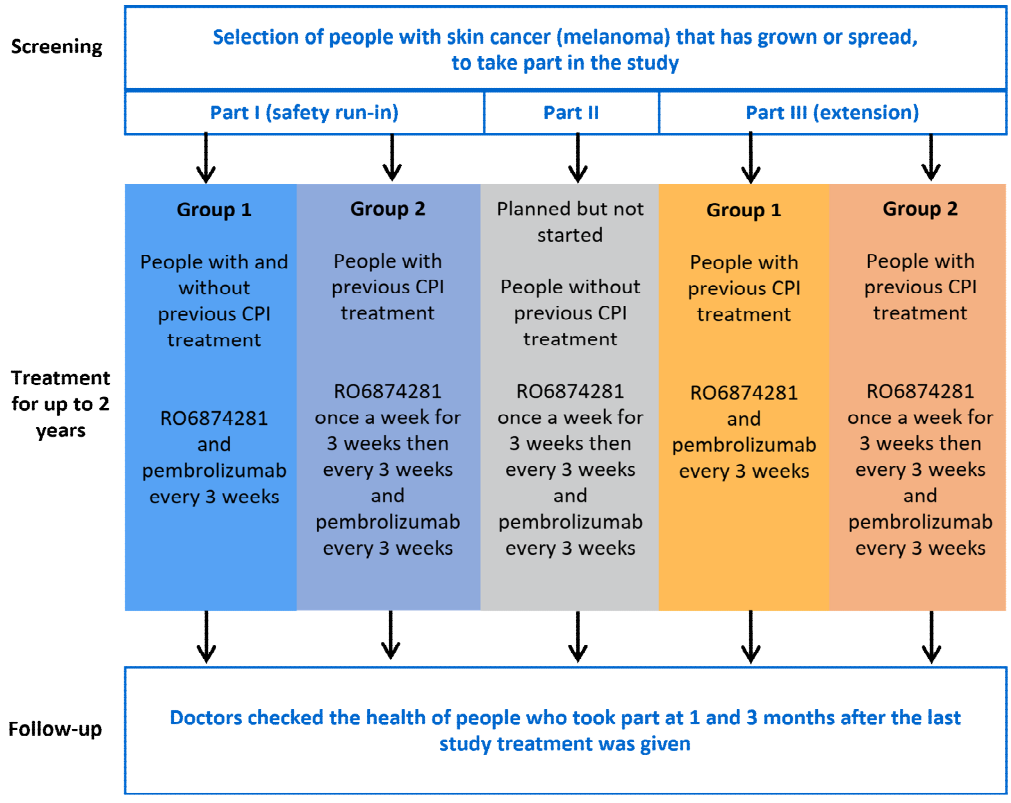
- In Part III (extension), researchers looked at how safe RO6874281 and pembrolizumab were and how well they worked in a larger group of people who had previously been given a CPI treatment. 67 people joined Part III of the study

During the study, groups of people were given RO6874281 with pembrolizumab in 2 different treatment schedules, as follows:

- RO6874281 plus pembrolizumab every 3 weeks given as an infusion (into a vein),
- RO6874281 given once a week for 3 weeks, followed by once every 3 weeks, given with pembrolizumab as an infusion every 3 weeks

People took part in the study for a maximum of 2 years or until their cancer started to get worse, or they stopped treatment due to side effects or for other reasons. After people finished receiving treatment, they were asked to go back to their study centre for a follow-up visit – to check their overall health.

The study flowchart below shows all planned stages and treatment groups of the study.



The study was discontinued and did not include as many people as planned because the drug company (Roche) decided to prioritise the development of other, potentially more impactful medicines, and not because too many people had concerning side effects or because the experimental drug was not effective.

4. What were the results of the study?

How safe was RO6874281 in combination with pembrolizumab for people with advanced or metastatic skin cancer?

RO6874281 in combination with pembrolizumab showed an acceptable safety profile. It is expected that people will experience unwanted medical problems (side effects) when taking medicines. In this study, all 83 people experienced side effects - all side effects had been seen in other people in previous studies of RO6874281 and pembrolizumab and were not unexpected. More information about the type, seriousness, and number of people with side effects is provided in Section 5.

How well does RO6874281 with pembrolizumab treatment work in people with advanced or metastatic skin cancer?

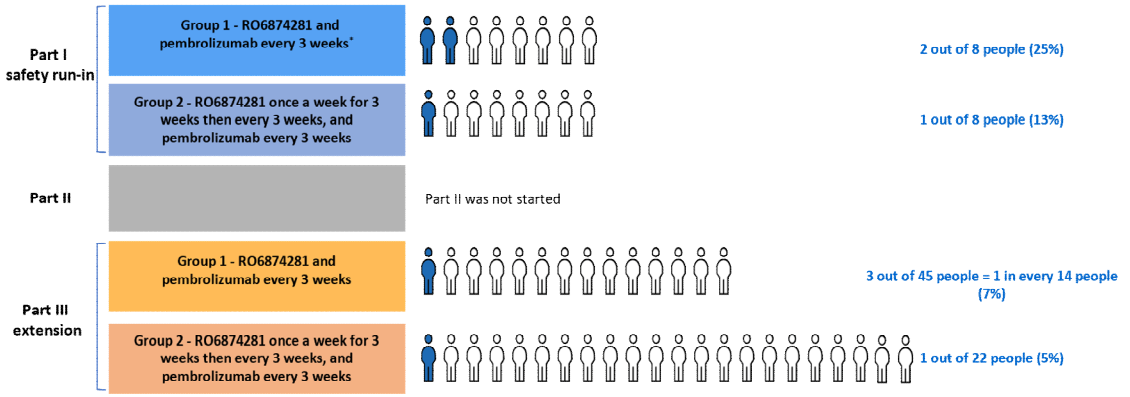
One piece of information that researchers collected was the number of people in each group who had cancer that:

- Reduced in size or disappeared (known as the 'objective response', or OR)
- Stayed the same, reduced in size or disappeared (known as 'disease control', or DC)

Objective response (OR)

- Between 5%–25% of the people in each group had cancer that reduced in size or disappeared following treatment
- One person in the study had cancer that disappeared (known as a 'complete response') – this person was in Part I, Group 1

Approximately how many people had cancer that had reduced or disappeared (OR)?



*People in this group could have had previous CPI treatment or not. Everyone in other groups had had previous CPI treatment.
CPI, checkpoint inhibitor (a type of immunotherapy).

Disease control (DC)

- Around half of all the people in this study had cancer that reduced in size or stayed the same for a certain period of time. This was seen across all groups in this study

5. What were the side effects?

Side effects of a medicine can be grouped in different ways:

- Side effects: these are side effects that are not serious (such as feeling sick)
- Serious side effects: these are side effects which are serious and can lead to a person being hospitalised for a short or prolonged time and, on rare occasions, may be life-threatening
- Common side effects: These are the non-serious side effects that occur most often
- Common serious side effects: These are serious side effects that occur most often

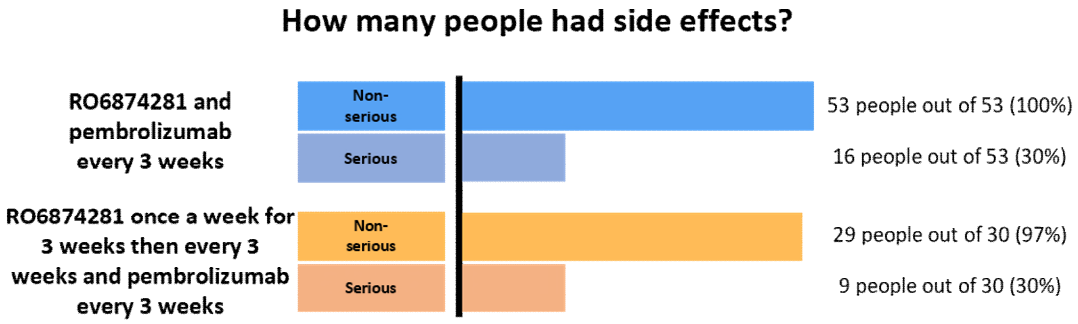
They are described in this summary because the study doctor believes the side effects were related to the experimental medicine.

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

An overview of side effects that were reported by any of the 83 people who were given RO6874281 in combination with pembrolizumab in this study are listed in the following sections.

Side effects and serious side effects

Almost everyone (82 out of 83 people - 99%) had at least 1 side effect that was due to taking RO6874281. Fewer people (35 out of 83 people - 30%) had serious side effects. The chart below shows the number of people who had a side effect or a serious side effect due to RO6874281 and pembrolizumab, and how they were given the treatment (known as the 'schedule').



Most common serious side effects

During this study, 30% of people had at least 1 serious side effect that was due to taking RO6874281.

The most common serious side effects that 2 or more people had are shown in the following table – these are the most common serious side effects across the 2 different treatment schedules.

Most common serious side effects reported in this study	**People taking RO6874281 with pembrolizumab every 3 weeks** (Group 1 in Part I and Part III - 53 people total)	**People taking RO6874281 once a week for 3 weeks then every 3 weeks, with pembrolizumab every 3 weeks** (Group 2 in Part I and Part III - 30 people total)
Fever	4% (2 out of 53)	3% (1 out of 30)
Immune system over-reaction (cytokine release syndrome)	6% (3 out of 53)	0% (0 out of 30)
Swelling (inflammation)	4% (2 out of 53)	0% (0 out of 30)
Reaction to the infusion (for example, fever or chills within 24 hours after the infusion)	8% (4 out of 53)	7% (2 out of 30)

No people died of side effects that were due to RO6874281 or pembrolizumab. However, 21 out of 83 people (25%) died during the study due to:

- Cancer (15 out of 83 people - 18%)
- Health problems that were not side effects of RO6874281 and pembrolizumab, or for unknown reasons (6 out of 83 people - 7%)

During the study, no people decided to stop taking the study medicine because of side effects.

Most common side effects

During this study, 99% of people (82 out of 83 people) had a side effect that was not serious and was thought to be due to taking RO6874281.

The most common side effects that were reported by at least 1 in every 3 people (30%) on average across all treatment groups are shown in the following table.

Most common side effects reported in this study	People taking RO6874281 with pembrolizumab every 3 weeks (Group 1 in Part I and Part III. 53 people total)	People taking RO6874281 once a week for 3 weeks then every 3 weeks, with pembrolizumab every 3 weeks (Group 2 in Part I and Part III. 30 people total)
Chills	40% (21 out of 53)	40% (12 out of 30)
Feeling sick (nausea)	38% (20 out of 53)	33% (10 out of 30)
Fever	49% (26 out of 53)	60% (18 out of 30)
Liver damage – shown by higher levels of something called 'ALT' in the blood	36% (19 out of 53)	20% (6 out of 30)
Liver, heart or kidney damage – shown by higher levels of something called 'AST' in the blood	38% (20 out of 53)	30% (9 out of 30)
Low energy level	28% (15 out of 53)	37% (11 out of 30)
Reaction to the infusion	47% (25 out of 53)	43% (13 out of 30)

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 83 people with advanced or metastatic skin cancer that could not be removed with surgery. These results helped researchers learn more about the safety of RO6874281, given in combination with pembrolizumab, for people with advanced skin cancer.

- RO6874281 plus pembrolizumab showed an acceptable safety profile that was similar to the known safety profiles of each individual drug
- RO6874281 plus pembrolizumab treatment did not provide any added benefit to people who had been given CPI before

No single study can tell us everything about the risks and benefits of a medicine or drug. 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 the combination of RO6874281 and pembrolizumab 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/NCT03875079
- https://forpatients.roche.com/en/trials/cancer/skin-cancer/a-phase-ib-study-to-evaluate-safety-and-therapeutic-act-73518.html

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/en/trials/cancer/skin-cancer/a-phase-ib-study-to-evaluate-safety-and-therapeutic-act-73518.html
- 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 IB Study to Evaluate Safety And Therapeutic Activity Of RO6874281, An Immunocytokine, Consisting Of Interleukin-2 Variant Targeting Fibroblast Activation Protein-A, In Combination With Pembrolizumab (Anti-Pd-1), In Participants With Previously Untreated Advanced And/Or Metastatic Melanoma'

- The protocol number for this study is: BP41054
- The ClinicalTrials.gov identifier for this study is: NCT03875079
- The EudraCT number for this study is: 2018-003872-11