Summary of Clinical Trial Results

A study to look at how safe different doses of RO6874281 were for people with solid tumours to take on its own and with existing cancer medicines – and how RO6874281 was processed through the body

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.

The study started in December 2015 and stopped early – in November 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 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**

Contents of the summary

Glossary

- Solid tumours includes breast cancer, cancers of the head and neck, oesophageal cancer and cervical cancer

Thank you to the people who took part in this study

The people who took part have helped researchers to answer important questions about solid tumours and the medicines studied – 'RO6874281' on its own and in combination with trastuzumab or cetuximab.

Key information about this study

- In this study, people with solid tumours that had grown (advanced) or spread to other parts of the body (metastatic) and could not be removed with surgery were given the experimental drug (called 'RO6874281') on its own or with an existing approved medicine (either 'trastuzumab' for people with breast cancer, or 'cetuximab' for people with head and neck cancer)
- This study was done to see:
    - how safe RO6874281 was on its own and the best dose to give without unmanageable side effects
    - how safe new combinations of immunotherapy treatments (RO6874281 with trastuzumab or cetuximab) were, and if these treatments may provide better health outcomes
- This study included 134 people in 9 countries
- The main findings were that RO6874281, on its own and combined with trastuzumab or cetuximab showed acceptable safety profiles
    - around 49% of people (66 out of 134 people) taking RO6874281 on its own or with trastuzumab or cetuximab had serious side effects
- Across treatment groups, between 1 in 2 people (50%) and 1 in 4 people (25%) had cancer that stayed the same, reduced in size or disappeared with RO6874281 on its own or with trastuzumab or cetuximab
- This study stopped early 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 ineffective

1. General information about this study

Why was this study done?

Breast cancer and cancers of the head and neck (which were focused on in parts of this study) are types of solid tumours which can sometimes be removed with surgery but are more difficult to treat if they have grown (advanced) or spread to other parts of the body (metastatic).

Current treatments for advanced and metastatic solid tumours include immunotherapies, targeted therapies, chemotherapy and radiotherapy. Cancer immunotherapies use the body's immune system to destroy cancerous cells.

An experimental immunotherapy drug called RO6874281 was given to people for the first time in this study. RO6874281 was tested on its own at different doses to find out how safe it was and how well it worked. RO6874281 was then given with existing medicines to see how safe new combinations of immunotherapy treatments were and if they may provide better health outcomes for people with metastatic or advanced solid tumours that cannot be removed with surgery.

What were the study medicines?

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

- RO6874281 is called an experimental drug because health authorities have not approved it for the treatment of advanced and/or metastatic solid tumours
- A part of RO6874281 is similar to a type of molecule that 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 recognises a structure on tumours called FAP, which is short for fibroblast activation protein-alpha. FAP is part of the connective tissue needed for solid tumours to grow. RO6874281 delivers the immunotherapy to immune cells that then enter the solid tumours

Trastuzumab is an existing medicine given to people with human epidermal growth factor receptor2 (HER2)-positive breast or stomach cancer. HER2 is a protein that is overproduced by some cancer cells and promotes the growth of this type of cancer.

- You say this as 'tras-too-zoo-mab'
- Trastuzumab sticks to HER2-positive cancer cells which:
    - blocks the activity of HER2 and stops them from growing
    - helps cells of the immune system 'see' and destroy them
- RO6874281 was tested with trastuzumab in this study

Cetuximab is an existing medicine given to people with epidermal growth factor receptor (EGFR)-positive intestine or head and neck cancer. EGFR is a protein that is produced by some cancer cells and promotes the growth and spread of this type of cancer.

- You say this as 'se-tux-i-mab'
- Cetuximab sticks to EGFR-positive cells which:
    - blocks the activity of EGFR and stops from growing
    - helps cells of the immune system 'see' and destroy them
- RO6874281 was tested with cetuximab in this study

What did researchers want to find out?

The main questions that researchers wanted to answer were:

1. How safe was RO6874281 on its own and in combination with trastuzumab or cetuximab, for people with solid tumours, and which dose should be used?
2. How did the body break down and process RO6874281 when given on its own or with an existing medicine?

Another question that researchers wanted to answer was:

3. How well did RO6874281 work as a treatment for cancer when given on its own or with an existing medicine?

What kind of study was this?

This study was a 'phase 1' study – the first study of RO6874281 in people. A small number of people with solid tumours took RO6874281 on its own or with an existing medicine, and the researchers did medical tests on the people who took part to find out more about RO6874281.

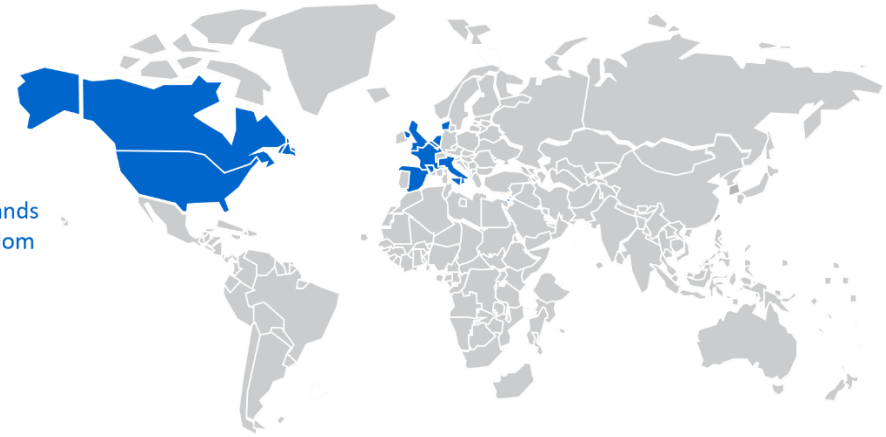
This was an 'open label' study. This means that both the people taking part in the study and the study doctors knew which of the study medicines people were taking.

When and where did the study take place?

The study started in December 2015 and stopped early. This summary presents the results of the study up until it was stopped in November 2022.

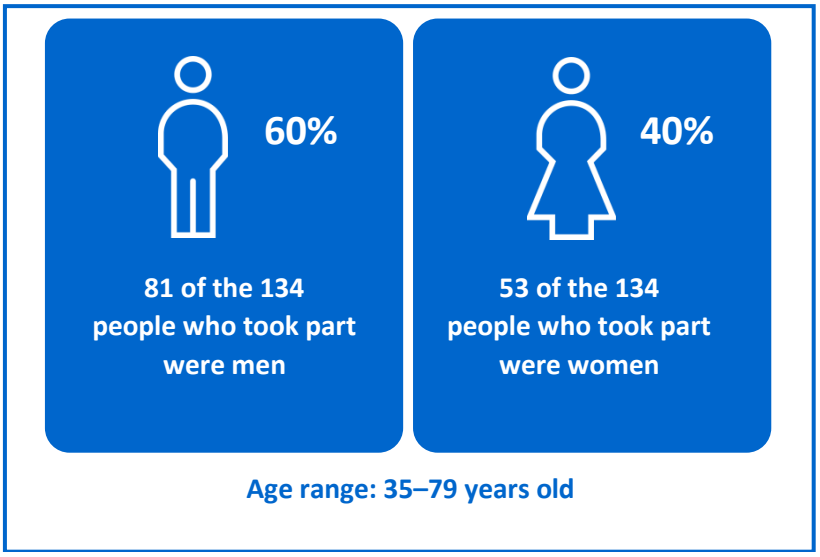
The study took place at 24 study centres – across 9 countries in Europe and North America. The following map shows the countries where this study took place.

- Belgium
- Canada
- Denmark
- France
- Italy
- Spain
- The Netherlands
- United Kingdom
- USA



2. Who took part in this study?

In this study, 134 people with various solid tumours took part. More information on the people who took part is given below.



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.

The study was in 3 parts. People could join one part of the study if they:

- Were at least 18 years of age
- Had been diagnosed with an advanced or metastatic solid tumour that could not be treated with existing medicines (Part A), OR
- Had been diagnosed with advanced or metastatic HER2-positive breast cancer, or HER2-positive breast cancer that had returned after previous treatment with trastuzumab or a similar medicine (Part B), OR
- Had been diagnosed with cancer of the head and neck (squamous cell carcinoma) that had returned after previous treatment, was not removable with surgery, or was metastatic (Part C)

People could not take part in the study if they:

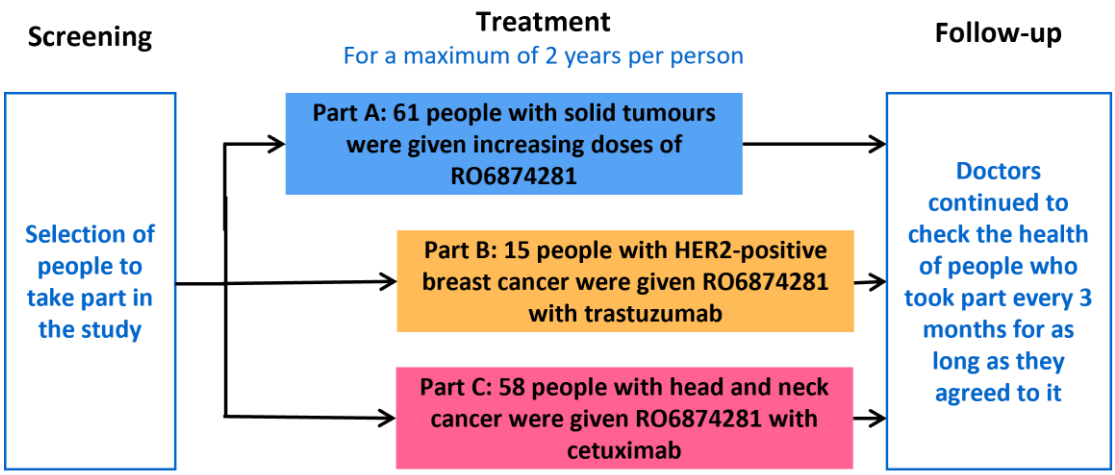
- Had cancer that had spread to the brain or spinal cord, a second cancer type, or certain other medical conditions such as infections, liver or heart disease
- Were pregnant or breastfeeding

3. What happened during the study?

Everyone who joined the study was treated with RO6874281 either on its own or in combination with trastuzumab or cetuximab for their type of cancer.

- In Part A, people with an advanced or metastatic solid tumour that could not be treated with existing medicines were given increasing doses of RO6874281 on its own – as a drip (infusion) into a vein once a week. By looking at the side effects that people experienced with different dose levels of RO6874281, researchers could decide on a recommended dose, collect more information on side effects at the recommended dose, and see how well RO6874281 works to treat solid tumours. Part A was completed before people were enrolled into Parts B and C
- In Part B, people with advanced or metastatic HER2-positive breast cancer, or HER2-positive breast cancer that had returned after previous treatment with trastuzumab or a similar medicine, were given different dose levels of RO6874281 and an approved dose level of trastuzumab – as a drip (infusion) into a vein either:
    - once a week, or
    - RO6874281 once a week for 4 weeks, then every 2 weeks, and trastuzumab every 2 weeks
- In Part C, people with cancer of the head and neck (squamous cell carcinoma) that had returned after previous treatment, was not removable with surgery, or was metastatic were given different dose levels of RO6874281 and an approved dose level of cetuximab – as a drip (infusion) into a vein either:
    - once a week, or
    - RO6874281 once a week for 4 weeks, then every 2 weeks, and cetuximab every 2 weeks, OR
    - RO6874281 once a week for 4 weeks then every 2 weeks, and cetuximab every week for 4 weeks then every 2 weeks

After people finished taking their medicine for this study, they were asked to go back to their study centre for more visits – to check their overall health. The study flowchart shows all stages planned for the study.



4. What were the results of the study?

Question 1: How safe was RO6874281 on its own and in combination with trastuzumab or cetuximab for people with solid tumours, and which dose was recommended to use?

RO6874281 on its own and combined with trastuzumab or cetuximab showed acceptable safety profiles. People are expected to experience unwanted medical problems (side effects) when taking medicines. In this study, 130 of 134 people experienced side effects.

More information about the type, seriousness and number of people with side effects is provided in Section 5.

In Part A, RO6874281 was given on its own:

- The maximum dose that could be given before people had unacceptable side effects was 20mg or 25mg if a smaller (20mg) dose was given the first time
- The unacceptable side effects (at doses of 20mg or higher) were low energy levels, tiredness (fatigue), liver problems and swelling/inflammation of the lungs (pneumonia)
- The recommended dose of RO6874281 that was given to additional people joining the study was 15mg for the first dose, then 20mg for the following doses

In Part B, RO6874281 was given with trastuzumab:

- The maximum dose of RO6874281 that could be given with trastuzumab before people had unacceptable side effects was not defined

In Part C, RO6874281 was given with cetuximab:

- The maximum dose of RO6874281 that could be given with cetuximab before people had unacceptable side effects was 10mg
- The unacceptable side effects (at doses of 10mg or higher) were swelling (inflammation), liver damage – shown by abnormal blood test results and low levels of the blood cell fragments that help the blood to clot – called 'platelets'

Question 2: How did the body break down and process RO6874281 when given on its own or with an existing medicine?

Another piece of information that researchers collected was how the body processed RO6874281 when given on its own or with trastuzumab or cetuximab.

The time it takes for half the dose of a drug to be removed from the body is called the 'half-life'.

- RO6874281 had a half-life which changed with dose and with time
    - at a dose of 10mg, the half-life of RO6874281 was about 1 day – it took about 1 day for half of the drug to leave the body
    - when multiple 10mg doses were given, the half-life of RO6874281 was shorter – it took less than 1 day for half of RO6874281 to leave the body
- RO6874281 was removed from the body in a similar amount of time when given on its own or with trastuzumab or cetuximab
- RO6874281 level in the blood did not increase after multiple doses were given

Question 3: How well did RO6874281 work as a treatment for cancer when given on its own or with an existing medicine?

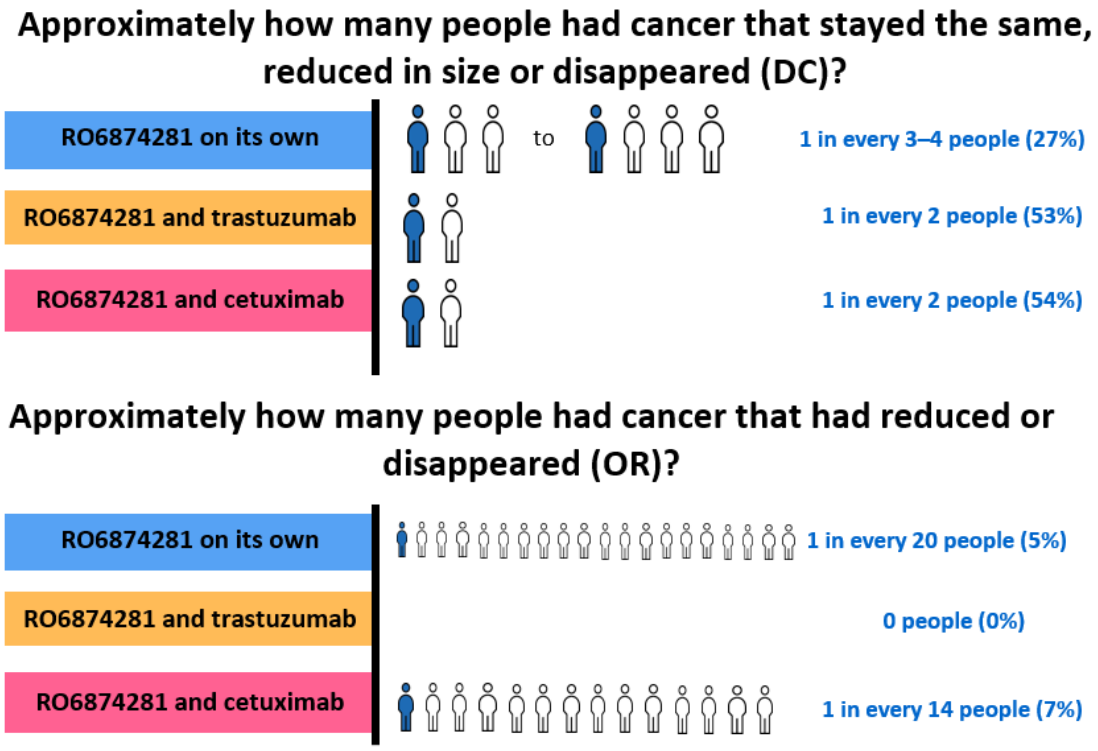
Other information that researchers collected was the number of people in each part of the study who had cancer that:

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

In Part A, overall, anti-cancer activity was seen with RO6874281 on its own that lasted for more than 6 months. Results were available from 59 out of 61 people with solid tumours. Cancer disappeared in 1 person, reduced in size in 2 people, and stayed approximately the same size in 13 people. Cancer did not respond to treatment in 39 people, and the response in 4 people could not be determined.

In Part B, RO6874281, in combination with trastuzumab did not show added benefit in people with breast cancer. Results were available from all 15 people. Of these, cancer stayed the same size in 8 people and did not respond to treatment in 7 people.

In Part C, few people had long-lasting anti-cancer responses when given RO6874281 with cetuximab. Results were available from 57 out of 58 people with head and neck cancer. Of these, cancer reduced in size in 4 people, stayed the same size in 27 people and did not respond to treatment in 22 people. The response in 4 people was not able to be determined.



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 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.

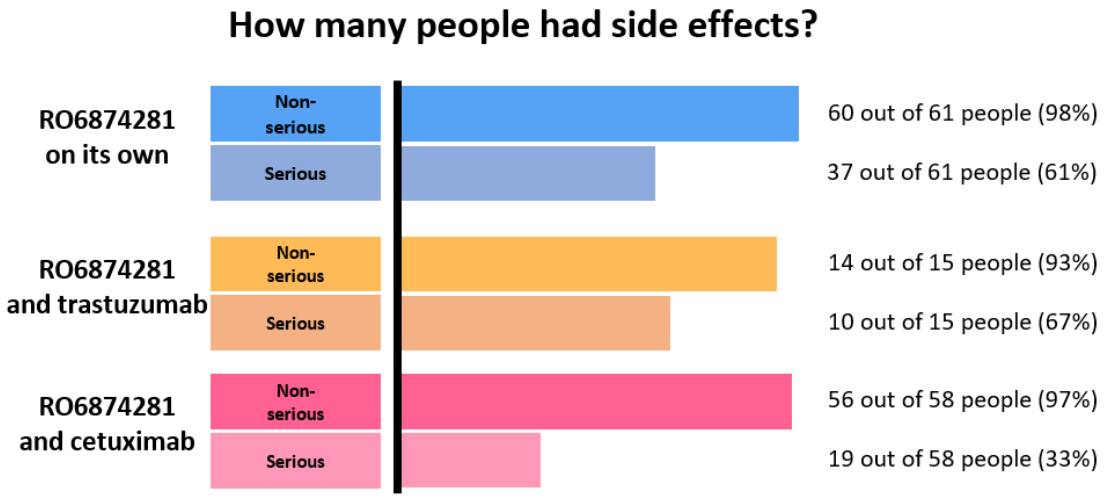
An overview of side effects that were reported by any of the 134 people in this study are listed in the following sections.

Side effects and serious side effects

Almost everyone (130 out of 134 people – 97%) had at least one side effect due to taking RO6874281. Fewer people (66 out of 134 people – 49%) had serious side effects.

Overall, people who were given higher doses of RO6874281 had more side effects.

The chart below shows the number of people who had a non-serious or serious side effect due to RO6874281 on its own or when taken with existing medicines (trastuzumab or cetuximab).



Most common serious side effects

The most common serious side effects that at least 2 people in any part of the study had are shown in the following table. Some people had more than one side effect – this means that they are included in more than one row in the table.

Serious side effects reported in this study	**People taking RO6874281 (Part A)** (61 people total)	**People taking RO6874281 and trastuzumab (Part B)** (15 people total)	**People taking RO6874281 and cetuximab (Part C)** (58 people total)
Reaction to the infusion*	28% (17 out of 61)	27% (4 out of 15)	19% (11 out of 58)
Low white blood cell count	3% (2 out of 61)	0% (0 out of 15)	9% (5 out of 58)
Fever Higher levels of something called 'bilirubin' in the blood	12% (7 out of 61) 2% (1 out of 61)	13% (2 out of 15) 13% (2 out of 15)	3% (2 out of 58) 0% (0 out of 58)
Low energy levels	5% (3 out of 61)	0% (0 out of 15)	0% (0 out of 58)
Tiredness (fatigue)	5% (3 out of 61)	0% (0 out of 15)	2% (1 out of 58)
Low levels of urine	3% (2 out of 61)	0% (0 out of 15)	0% (0 out of 58)
Kidney problems/failure	3% (2 out of 61)	7% (1 out of 15)	0% (0 out of 58)
Fluid leak from small blood vessels	5% (3 out of 61)	7% (1 out of 15)	0% (0 out of 58)
Low blood pressure	5% (3 out of 61)	7% (1 out of 15)	0% (0 out of 58)

*for example, fever or chills within 24 hours after the infusion.

No people died of side effects due to RO6874281, trastuzumab or cetuximab. However, 88 out of 134 people (66%) died during the study due to:

- Cancer (84 out of 134 people – 63%)
- Health problems that were not side effects of RO6874281, trastuzumab or cetuximab, or for unknown reasons (4 out of 134 people – 3%)

During the study, some people decided to stop taking their medicine because of side effects due to RO6874281, trastuzumab or cetuximab:

- In Part A, 6 out of 61 people (10%) stopped taking their medicine
- In Part B, 1 out of 15 people (7%) stopped taking their medicine
- In Part C, 4 out of 58 people (7%) stopped taking their medicine

Most common side effects

The most common side effects that were reported by at least 1 in every 3 people (30%) in any treatment group are shown in the following table. Some people 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	**People taking RO6874281 (Part A)** (61 people total)	**People taking RO6874281 and trastuzumab (Part B)** (15 people total)	**People taking RO6874281 and cetuximab (Part C)** (58 people total)
Fever	67% (41 out of 61)	80% (12 out of 15)	64% (37 out of 58)
Reaction to the infusion	67% (41 out of 61)	33% (5 out of 15)	41% (24 out of 58)
Chills	48% (29 out of 61)	20% (3 out of 15)	45% (26 out of 58)
Tiredness	43% (26 out of 61)	47% (7 out of 15)	43% (25 out of 58)
Feeling sick (nausea)	36% (22 out of 61)	67% (10 out of 15)	36% (21 out of 58)
Liver, heart or kidney damage – shown by higher levels of something called 'AST' in blood test results	26% (16 out of 61)	53% (8 out of 15)	27% (16 out of 58)
Liver damage – shown by higher levels of something called 'ALT' in blood test results	23% (14 out of 61)	40% (6 out of 15)	26% (15 out of 58)
Being sick (vomiting)	0% (0 out of 61)	47% (7 out of 15)	0% (0 out of 58)
Low energy levels	31% (19 out of 61)	40% (6 out of 15)	0% (0 out of 58)
Diarrhoea	26% (16 out of 61)	40% (6 out of 15)	0% (0 out of 58)
Decreased appetite	30% (18 out of 61)	27% (4 out of 15)	0% (0 out of 58)

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 134 people with different types of solid tumours. These results helped researchers learn more about solid tumours and RO6874281 given on its own, or with existing standard medicines.

- RO6874281 on its own showed an acceptable safety profile
- RO6874281 with trastuzumab or cetuximab showed an acceptable safety profile that was similar to the known safety profiles of each individual drug

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 the combination of RO6874281 and trastuzumab or cetuximab 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/NCT02627274
- https://forpatients.roche.com/en/trials/cancer/bc/a-study-evaluating-safety--pharmacokinetics--and-therapeutic-act.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/bc/a-study-evaluating-safety--pharmacokinetics--and-therapeutic-act.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: 'An Open-Label, Multicenter, Dose-Escalation, Phase Ia/Ib Study to Evaluate Safety, Pharmacokinetics, and Therapeutic Activity of RO6874281, an Immunocytokine Consisting of Interleukin-2 Variant (Il-2v) Targeting Fibroblast Activation Protein-α (FAP), as a Single Agent (Part A) or in Combination with Trastuzumab or Cetuximab (Part B or C)'.

- The protocol number for this study is: BP29842
- The ClinicalTrials.gov identifier for this study is: NCT02627274.
- The EudraCT number for this study is: 2015-002251-97.