NOVARTIS

Clinical Trial Results Summary

A clinical trial to learn about the safety of KAZ954 with and without other trial drugs in people with different types of advanced cancer

Thank you!

Thank you to the participants who took part in the clinical trial for **6 different types of advanced cancer**. Every participant helped the researchers learn more about the trial drug **KAZ954** with or without **PDR001**, also called **spartalizumab**, **NIR178**, also called **taminadenant**, and **NZV930**, although no participants received **NZV930** in this trial.

Novartis sponsored this trial and believes it is important to share what was learned from the results of this trial with the participants and the public. We hope this helps the participants understand their important role in medical research.

Trial information

Trial number: CKAZ954A12101

Novartis drugs studied: **KAZ954**, **PDR001**, also called spartalizumab, **NIR178**, also called taminadenant, and **NZV930**

Sponsor: Novartis

If you were a participant and have any questions about the results, please talk to the doctor or staff at the trial site.

This summary only shows the results of a single clinical trial.

What was the main purpose of this trial?

The purpose of this trial was to learn about the safety of the trial drug **KAZ954** given with and without other trial drugs in people with different types of advanced cancers. **Advanced** means cancer is unlikely to be cured with treatment, but can sometimes be controlled with treatment.

Immunotherapy is an available standard treatment for advanced cancer. **Immunotherapy** is a treatment that helps the immune system to kill cancer cells. However, available immunotherapies do not work well to treat certain types of advanced cancer.

KAZ954 is a trial immunotherapy. In this trial, researchers wanted to learn about the safety of **KAZ954**, given alone or with other immunotherapies.

The **advanced cancers** in this trial were **solid tumors**, which are cancers in organs and tissues, and not in body liquids such as blood. The 6 different types of advanced solid tumors in this trial were: bile duct cancer, colorectal cancer, esophageal cancer, gastroesophageal (GE) junction cancer, pancreatic cancer, and stomach cancer.

KAZ954 is a trial drug. It is an immunotherapy that attaches to and blocks a protein called ectonucleoside triphosphate diphosphohydrolase 2 (ENTPD2) on cancer cells. ENTPD2 can prevent the immune system from killing cancer cells. By blocking ENTPD2, **KAZ954** causes the immune system to become more active in tumors and killing cancer cells.

In this trial participants received **KAZ954** alone or with 1 of 2 **other trial drugs**.

The **other trial drugs were:**

PDR001, also called spartalizumab, is a trial drug. It is an immunotherapy that blocks a protein called programmed cell death protein 1 (PD-1). PD-1 prevents a cell in the immune system, called a T cell, from killing cancer cells. By blocking PD-1, **PDR001** helps T cells become more active to kill cancer cells.

NIR178, also called taminadenant, is a trial drug. It is a new type of immunotherapy that attaches to and blocks a protein called adesonine A2A receptor (A2AR) on T cells. Cancer cells have a protein that can attach to A2AR on T cells, which makes T cells less active to kill cancer cells. By blocking A2AR, **NIR178** makes T cells more active to kill cancer cells.

Trial drug
PDR001 also called spartalizumab
Pronounced as
spar-ta-liz-ue-mab

Trial drug
NIR178 also called taminadenant
Pronounced as
tam-in-uh-den-ant

NZV930 is trial drug that is an immunotherapy. This trial was designed to include **NZV930**, but because recruitment ended early, **NZV930** was not given to any participants.

This trial was the first time that **KAZ954** was given to people. Therefore, the researchers have to test increasing doses in different groups of participants to find the highest safe dose. The researchers also needed to carefully check all the medical problems that happened during the trial and identify any that could cause changes in dosing. This is what researchers call a dose escalation trial, which is the first step in testing a trial drug.

The trial's purpose was to answer these main questions:

- What were the highest doses of KAZ954 when given with or without other trial drugs that were safe for participants to receive?
- What medical problems, also called adverse events, happened during this trial?
  - ↳ An **adverse event** is any sign or symptom that participants have during a trial. Adverse events **may** or **may not** be caused by treatments in the trial.

How long was this trial?

The trial began in February 2020 and ended in September 2023. Each participant was in the trial for up to a year and a half.

This trial was designed to have 2 parts:

- **Part 1:** Small groups of participants were given **KAZ954** with or without other trial drugs. The first group of participants were given the lowest dose of **KAZ954** alone, then later groups were given higher doses of **KAZ954** with or without other trial drugs. The researchers reviewed the data to choose doses to use in Part 2.
- **Part 2:** Did not start but was planned to give the chosen doses of **KAZ954** with or without other trial drugs from Part 1 to more participants. However, the sponsor stopped recruitment early and no other participants joined the trial. Because of this, Part 2 did not start.

In June 2023, the sponsor decided to stop recruitment of participants due to business reasons after reviewing available data. The decision was not due to safety concerns. Participants who were already in the trial continued as planned.

Who was in this trial?

77 participants with different types of advanced cancer received treatment in this trial – 40 men and 37 women. Participants' ages ranged from 30 to 78 years. Their average age was 59 years.

The number of participants by race is shown below.

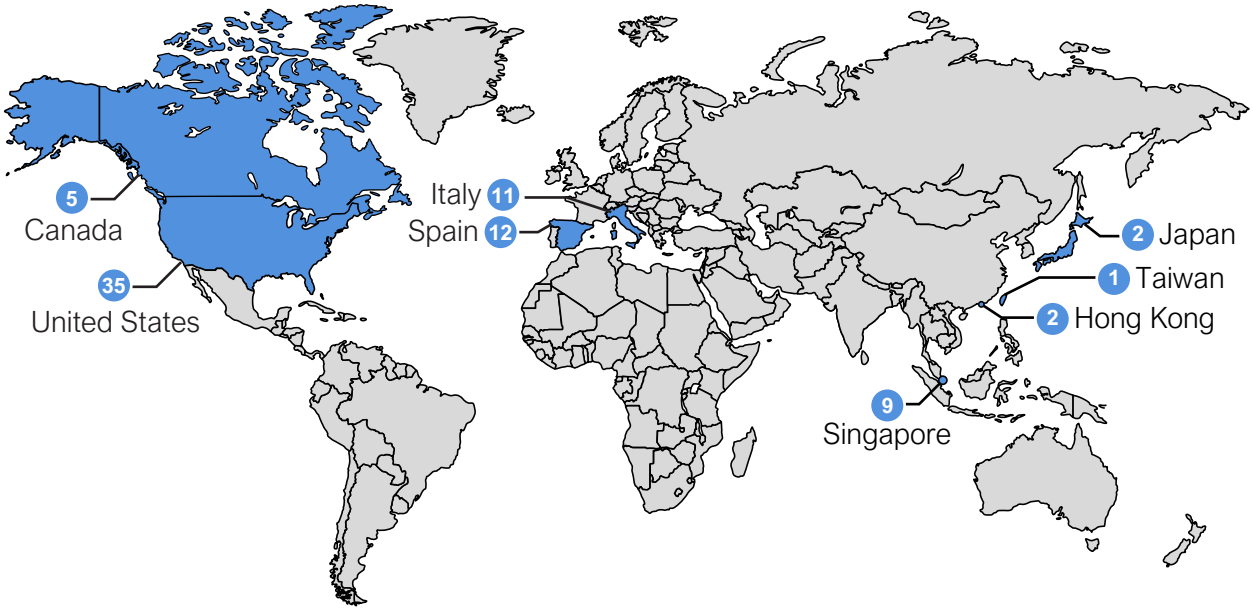
Race

17 Asian	1 Black or African American
58 White	1 Not reported

The participants could take part in this trial if they:

- Had one of these types of advanced solid tumors:
  - Bile duct cancer
  - Colorectal cancer
  - Esophageal cancer
  - GE junction cancer
  - Pancreatic cancer
  - Stomach cancer
- Did not have cancer spread to their brain or spinal cord that caused symptoms or needed certain treatments

77 participants from 8 countries received treatment. The map below shows the number of participants who took part in each country.



What treatments did the participants receive?

The treatments in this trial were given during 4-week cycles. A **cycle** is a treatment period that is repeated. The treatments in this trial were:

KAZ954, 30, 50, 100, 150, 300, 600, or 1,200 milligrams (mg), given through a needle in a vein as an intravenous (IV) infusion. Participants received it on days 1 and 15 of each cycle.

The first group of participants received the planned dose of 30 mg of **KAZ954**. After this dose was found to be safe, another group received a higher dose. This continued until the highest dose of **KAZ954** that was safe was found.

PDR001, 400 mg, given as an IV infusion on day 1 of each cycle.

NIR178, 160 or 240 mg, taken by mouth as capsules 2 times every day of each cycle.

NZV930, 100 mg, which would have been given as an IV infusion on days 1 and 15 of each cycle. Because recruitment ended early and Part 2 did not start, no participants received **NZV930**.

The participants, researchers, and trial staff knew what treatment each participant received.

The participants could continue trial treatment as long as they were benefiting from it, which means they could tolerate trial treatment, their cancer did not get worse, and the trial doctor allowed it.

What happened during this trial?

Before treatment — About 1 month

Trial staff checked to make sure the participants could be in this trial.

During treatment — Up to about 11 months

In each group, a small number of participants started treatment first with the lowest dose of **KAZ954**. If there were no safety concerns, the next group was opened to new participants to start treatment with a higher dose of **KAZ954**. The doses of the **KAZ954** went up until the researchers found the highest dose that was safe.

Trial doctors could lower the dose of any of the trial drugs, if needed.

77 participants received treatment in these groups:

	Treatment
Group A 43 participants	Participants received one of these doses of **KAZ954** alone: 30, 50, 100, 150, 300, 600, or 1,200 mg
Group B 18 participants	300 mg **KAZ954** + 400 mg **PDR001** 600 mg **KAZ954** + 400 mg **PDR001** 1,200 mg **KAZ954** + 400 mg **PDR001**
Group C 16 participants	300 mg **KAZ954** + 160 mg **NIR178** 600 mg **KAZ954** + 160 mg **NIR178** 600 mg **KAZ954** + 240 mg **NIR178**
Group D 0 participants	**KAZ954** + **NZV930** Because recruitment ended early and Part 2 did not start, no participants received **KAZ954** with **NZV930**

After treatment — About 5 months

Trail staff checked for participants' general health and for any medical problems for:

- 90 days after their last dose of **KAZ954** or **NIR178**
- 150 days after their last dose of **PDR001**

Trial staff checked the participants' general health throughout the trial.

What were the main results of this trial?

What were the highest doses of KAZ954 with and without other trial drugs that were safe for participants to receive?

Because recruitment ended early, researchers could not learn the highest doses of **KAZ954** with and without other trial drugs that were safe for participants to receive. The highest doses of the trial drugs that participants received were:

- 1,200 mg **KAZ954** alone and with 400 mg **PDR001**
- 600 mg **KAZ954** with 240 mg **NIR178**

To learn this, researchers kept track of how many participants in each Group had:

- **Dose limiting toxicities (DLTs)**. Before this trial started, the researchers decided which medical problems were DLTs based on their type, severity, and timing. Trial doctors kept track of DLTs that happened within 2 weeks after participants received their 2nd infusion of their assigned dose of **KAZ954**.
- **To pause a trial treatment**, which means they stopped treatment for a period of time before they received it again. This is called a **dose interruption**.
- **To lower the dose of a trial treatment**, which means they received a smaller amount or received it less often. This is called a **dose reduction**.

What are dose limiting toxicities (DLTs)?

DLTs are medical problems that:

- The trial doctors think could be related to the trial treatment
- Lead to a pause or lowering of the dose of treatment

The tables on the next pages show how many participants had DLTs out of the participants who completed 2 infusions of their assigned dose of **KAZ954**. They also show how many participants had to lower or pause their dose of trial treatment out of all participants.

How many participants had DLTs, had to lower the dose, or pause treatment?

Group A: KAZ954 alone

	30 mg KAZ954 3 participants	50 mg KAZ954 4 participants	100 mg KAZ954 4 participants	150 mg KAZ954 11 participants	300 mg KAZ954 5 participants	600 mg KAZ954 6 participants	1,200 mg KAZ954 10 participants
DLT	0 of 3 0%	0 of 4 0%	0 of 3 0%	0 of 10 0%	0 of 5 0%	1 of 6 17%	0 of 7 0%
Lower the dose	0 of 3 0%	0 of 4 0%	1 of 4 25%	0 of 11 0%	0 of 5 0%	0 of 6 0%	1 of 10 10%
Pause treatment	0 of 3 0%	0 of 4 0%	1 of 4 25%	1 of 11 9%	1 of 5 20%	1 of 6 17%	2 of 10 20%

The DLT reported by 1 participant in Group A was **a rare condition that causes blood clots and bleeding** (disseminated intravascular coagulation).

Group B: KAZ954 with PDR001

	300 mg KAZ954 + 400 mg PDR001 5 participants	600 mg KAZ954 + 400 mg PDR001 4 participants	1,200 mg KAZ954 + 400 mg PDR001 9 participants
DLT	1 of 4 25%	0 of 3 0%	0 of 7 0%
Lower the dose of KAZ954	0 of 5 0%	1 of 4 25%	0 of 9 0%
Pause treatment with KAZ954	1 of 5 20%	1 of 4 25%	2 of 9 22%
Lower the dose of PDR001	0 of 5 0%	1 of 4 25%	0 of 9 0%
Pause treatment with PDR001	0 of 5 0%	1 of 4 25%	0 of 9 0%

The DLT reported by 1 participant in Group B was **inflammation of the heart muscle** (myocarditis).

Group C: KAZ954 with NIR178

	300 mg KAZ954 + 160 mg NIR178 4 participants	600 mg KAZ954 + 160 mg NIR178 6 participants	600 mg KAZ954 + 240 mg NIR178 6 participants
DLT	0 of 2 0%	0 of 5 0%	0 of 5 0%
Lower the dose of KAZ954	0 of 4 0%	0 of 6 0%	0 of 6 0%
Pause treatment with KAZ954	1 of 4 25%	0 of 6 0%	0 of 6 0%
Lower the dose of NIR178	1 of 4 25%	1 of 6 17%	1 of 6 17%
Pause treatment with NIR178	1 of 4 25%	1 of 6 17%	2 of 6 33%

What medical problems, also called adverse events, happened during this trial?

Trial doctors keep track of all medical problems called **adverse events** that happen in trials, even if they think the adverse events are not related to the trial treatments.

Many trials are needed to know if a drug or treatment causes an adverse event.

This section is a summary of the adverse events that happened from the start of treatment up to:

- 90 days after their last dose of **KAZ954** or **NIR178**
- 150 days after their last dose of **PDR001**

An **adverse event** is:

- Any **sign or symptom** that the participants have during a trial
- Considered **serious** when it is life-threatening, causes lasting problems, the participant needs hospital care, or results in death

Adverse events **may** or **may not** be caused by treatments in the trial.

All 77 participants had at least 1 adverse event. 45 participants had adverse events that were considered serious. 5 participants left the trial due to an adverse event. 30 participants died.

The researchers concluded there were no safety concerns that would prevent future trials of **KAZ954** alone or with **PDR001** or **NIR178** in people with advanced cancer.

How many participants had adverse events?

Group A: KAZ954 alone

	30 mg KAZ954 3 participants	50 mg KAZ954 4 participants	100 mg KAZ954 4 participants	150 mg KAZ954 11 participants	300 mg KAZ954 5 participants	600 mg KAZ954 6 participants	1,200 mg KAZ954 10 participants
Had at least 1 serious adverse event	2 of 3	1 of 4	4 of 4	6 of 11	3 of 5	3 of 6	6 of 10
Had at least 1 other adverse event	3 of 3	4 of 4	4 of 4	11 of 11	5 of 5	6 of 6	10 of 10
Left the trial due to an adverse event	0 of 3	0 of 4	0 of 4	1 of 11	0 of 5	1 of 6	1 of 10
Died	1 of 3	2 of 4	1 of 4	1 of 11	1 of 5	2 of 6	7 of 10

Group B: KAZ954 with PDR001

	300 mg KAZ954 + 400 mg PDR001 5 participants	600 mg KAZ95 + 400 mg PDR001 4 participants	1,200 mg KAZ954 + 400 mg PDR001 9 participants
Had at least 1 serious adverse event	4 of 5	2 of 4	4 of 9
Had at least 1 other adverse event	5 of 5	4 of 4	9 of 9
Left the trial due to an adverse event	1 of 5	0 of 4	1 of 9
Died	2 of 5	1 of 4	5 of 9

Group C: KAZ954 with NIR178

	300 mg KAZ954 + 160 mg NIR178 4 participants	600 mg KAZ954 + 160 mg NIR178 6 participants	600 mg KAZ954 + 240 mg NIR178 6 participants
Have at least 1 serious adverse event	3 of 4	4 of 6	3 of 6
Have at least 1 other adverse event	4 of 4	6 of 6	6 of 6
Left the trial due to an adverse event	0 of 4	0 of 6	0 of 6
Died	2 of 4	2 of 6	3 of 6

What serious adverse events did the participants have?

30 of 77 participants died during this trial.

45 participants had serious adverse events. The most common serious adverse events that happened in **7 or more participants** were:

- **Cytokine release syndrome**, which is flu like symptoms, such as fever and chills, caused by the immune system making too many proteins called cytokines
- **Belly pain** (abdominal pain)

Additional serious adverse events happened in fewer participants.

What other adverse events did the participants have?

77 participants had other adverse events.

The other adverse events that happened in **15 or more participants** were:

- **Feeling sick to the stomach** (nausea)
- **Fever** (pyrexia)
- **Feeling weak or not having energy** (asthenia)
- **Chills**
- **Feeling weak and tired** (fatigue)
- **Belly pain** (abdominal pain)

Additional adverse events happened in fewer participants.

What was learned from this trial?

Researchers learned about the safety of **KAZ954** given with and without other trial drugs in people with different types of advanced cancers that were solid tumors. The sponsor stopped recruiting participants and did not start Part 2 due to business reasons and not due to safety concerns.

The researchers concluded that:

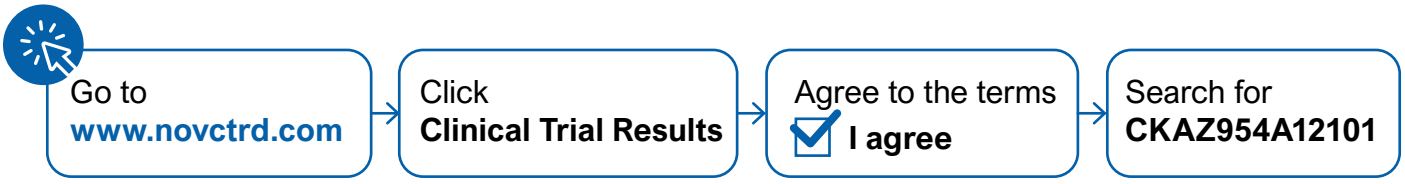
- They could not learn the highest doses of **KAZ954** with and without **PDR001** or **NIR178** that were safe for participants to receive because recruitment ended early
- There were no safety concerns that would prevent future trials of **KAZ954** alone and with other trial drugs in people with advanced cancer

When this summary was written, the sponsor had no plans for future trials of **KAZ954** with and without other trial drugs in people with advanced cancer.

Where can I learn more about this trial?

More information about the results and adverse events in this trial can be found in the scientific summary of the results available on the Novartis Clinical Trial Results website **www.novctrd.com**

Follow these steps to find the scientific summary:



For more information about this trial, go to this website:

- clinicaltrials.gov – search using the number **NCT04237649**

Other trials of **KAZ954** with and without other trial drugs may appear on the public website above. When there, search for **KAZ954**, **PDR001**, **spartalizumab**, **NIR178**, or **taminadenant**.

Full clinical trial title: Full clinical trial title: A phase I/Ib, open-label, multi-center, study of KAZ954 as a single agent and in combination with Spartalizumab, NZV930 and NIR178 in patients with advanced solid tumors

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