NOVARTIS

Clinical Trial Results Summary

A clinical trial to learn more about the safety of TNO155 given with PDR001 or LEE011 in people with advanced solid tumors and find the best dose of each combination for further study

Thank you!

Thank you to the participants who took part in the clinical trial for **advanced solid tumors**. Every participant helped the researchers learn more about the trial drug **TNO155**.

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: CTNO155B12101

Novartis drug studied: TNO155

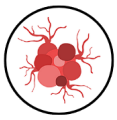
Sponsor: Novartis

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. Other clinical trials may have different results.

What was the main purpose of this trial?

The purpose of this trial was to learn about the safety of **TNO155** given with either **PDR001** or **LEE011** in people with **advanced solid tumors** and find the best dose of each combination for further study. The best dose was based on the safety and effects of the drug.



A **solid tumor** is a type of cancer that starts in an organ, muscle, or bone.

Advanced solid tumors are cancers that have spread to other parts of the body and can be hard to control with available treatments.

TNO155 is a trial drug created to block a protein called SHP2, which plays a role in cancer growth. By blocking SHP2, **TNO155** may shrink or slow down the growth of tumors.

PDR001, also known as **spartalizumab**, is a trial drug being tested for blocking a protein called PD-1. The protein prevents the immune system, the body's natural defense, from killing cancer cells. Blocking PD-1 prevents the growth of cancer cells.

LEE011, also known as **ribociclib**, blocks proteins called CDK4 and CDK6, which are involved in cell growth. Blocking these proteins may help control the growth of certain cancers.

LEE011 is approved for the treatment of a type of breast cancer in multiple countries.

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

Trial drug
LEE011 also called
ribociclib
Pronounced as
ry-boh-sy-klib

This trial was the first time that **TNO155** was given with either **PDR001** or **LEE011** to people. Therefore, the researchers had to test increasing doses of **TNO155** with either **PDR001** or **LEE011** in different groups of participants to find the best doses for further study.

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.

Researchers previously found that the highest safe dose of **LEE011** with another drug was lower in Japanese participants compared to those from other countries. So, this trial looked at the combination of **TNO155** and **LEE011** separately in people from Japan to find its best dose.

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

- What were the best doses of **TNO155** in combination with **PDR001** and with **LEE011** for participants?
- 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 July 2019. In March 2023, the sponsor decided to end this trial earlier than planned due to business reasons. This was not due to safety concerns with either of the drug combinations. The participants' last visit happened in January 2024.

Participants were in the trial for about 2 years.

This trial was designed to have 2 parts:

- **Part 1** looked at the safety of increasing doses of **TNO155** in combination with **PDR001** and **TNO155** in combination with **LEE011** to find the best dose for each combination to give to participants in Part 2.
- **Part 2** was designed to look at the effects of the best dose of **TNO155** in combination with either **PDR001** or **LEE011** at the same dose or a lower dose than in Part 1 in larger groups of participants. Because the trial was stopped earlier than planned by the sponsor, Part 2 did not start.

Due to the trial being ended early, there were not enough data from Japanese participants to draw any conclusion about the best dose for the combination of **TNO155** and **LEE011**.

When the trial ended, researchers created a report of the trial results. This summary is based on that report.

Who was in this trial?

122 participants with **advanced solid tumors** received treatment in this trial. There were 69 men and 53 women, with ages ranging from 19 to 81 years. The average age was 57 years.

The number of participants by race is shown below.

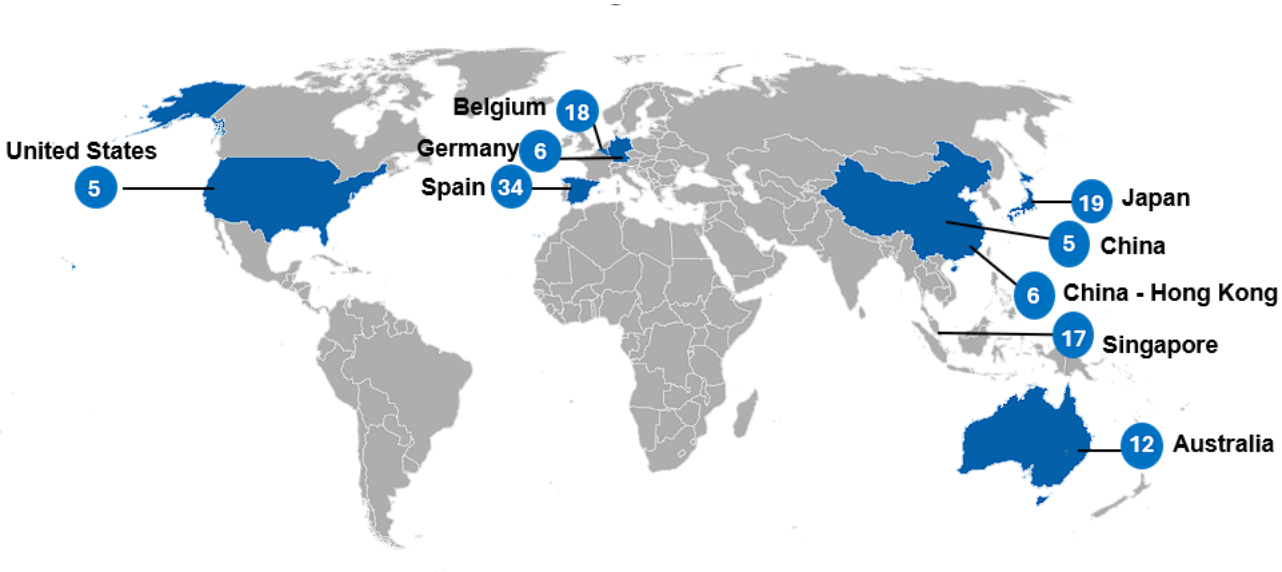
Race

49	Asian	72	White	1	Unknown

The participants could take part in this trial if:

- they were 18 years of age or older
- for treatment with **TNO155** with **PDR001**, they had a specific type of cancer of the lungs, head and neck, esophagus, or bowel that could not be controlled with other treatments
- for treatment with **TNO155** with **LEE011**, they had advanced solid tumors, except in the bowel, that could not be controlled with other treatments

122 participants from 9 countries received treatment in this trial. 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:

TNO155: Participants took different doses of **TNO155**, from 5 milligrams (mg) to 60 mg, as a capsule or tablet by mouth, once or twice a day. Different dosing plans were studied:

- A 3-week **cycle** comprising 2 weeks on and 1 week off
- A 4-week cycle comprising 3 weeks on and 1 week off

What is a cycle?

A **cycle** is a treatment period that is repeated.

The dosing plan shows the weeks with treatment (on) and the weeks without treatment (off) in a 3- or 4-week cycle.

PDR001: Participants received 300 mg of **PDR001** once every 3 weeks as an infusion into a vein.

LEE011: Participants took 150 mg or 200 mg of **LEE011**, as a capsule or tablet by mouth, once a day. Different dosing plans were studied:

- A continuous 3-week cycle
- A 3-week cycle comprising 2 weeks on and 1 week off
- A 4-week cycle comprising 3 weeks on and 1 week off

All participants were given **TNO155** in combination with either **PDR001** or **LEE011** in the trial. The participants, researchers, and trial staff knew what treatments each participant received.

The participants could continue their assigned treatment as long as they were benefiting from it.

What happened during this trial?

Before treatment

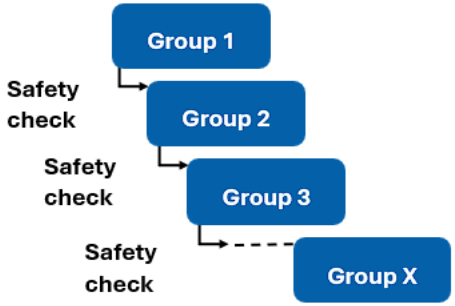
Up to 3 weeks

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

During treatment

Up to 1 year and 8 months

Participants were started on the lowest dose of **TNO155** in combination with either **PDR001** or **LEE011**. After this dose was found to be safe during the first treatment cycle, the next group was opened to new participants to start treatment with a higher dose of **TNO155**. This continued with each group receiving higher doses of **TNO155** until researchers found the highest dose that was identified as safe for participants.



TNO155 with PDR001

57 participants received this combination in a cycle of 3 weeks, with 2 weeks on and 1 week off **TNO155**. They took **PDR001** once every 3 weeks.

Groups	1	2	3	4	5	6	7	8	9
Total participants	5	19	6	5	5	6	7	3	1
TNO155	20 mg once daily	60 mg once daily	5 mg twice a day	10 mg twice a day	20 mg twice a day	30 mg twice a day	40 mg twice a day	50 mg twice a day	60 mg twice a day
PDR001	300 mg once every 3 weeks								

TNO155 with LEE011

46 participants from **across the world excluding Japan** and 19 participants from **Japan** received this combination. All participants took **TNO155** and **LEE011** in a:

- 3-week cycle either continuously or with 2 weeks on and 1 week off treatment which is presented as '2/1' in the table below, or
- 4-week cycle with 3 weeks on and 1 week off treatment which is presented as '3/1' in the table below

Total

Groups	1	2	3	4	5	6	7	8	9	10	11	12
Total participants	**5**	**8**	**5**	**4**	**8**	**1**	**5**	**4**	**9**	**1**	**6**	**9**
TNO155	**20 mg** once a day 2/1	**40 mg** once a day 2/1	**60 mg** once a day 2/1	**40 mg** once a day 3/1		**10 mg** twice a day 3/1	**20 mg** twice a day 3/1		**30 mg** twice a day 3/1	**40 mg** twice a day 3/1	**20 mg** once a day 2/1	**40 mg** once a day 2/1
LEE011	**200 mg** once everyday			**150 mg** once a day 3/1	**200 mg** once a day 3/1		**150 mg** once a day 3/1	**200 mg** once a day 3/1			**200 mg** once a day 2/1	

Researchers previously found that the highest safe dose of **LEE011** with another drug was lower in Japanese participants. As a result, participants from **across the world excluding Japan** and **Japan** had their data assessed separately in the following groups:

Across the world excluding Japan

Groups	1	2	3	4	5	6	7	8	9
Total participants	3	5	5	4	5	5	9	1	9
TNO155	20 mg once a day 2/1	40 mg once a day 2/1	60 mg once a day 2/1	40 mg once a day 3/1		20 mg twice a day 3/1	30 mg twice a day 3/1	40 mg twice a day 3/1	40 mg once a day 2/1
LEE011	200 mg once everyday			150 mg once a day 3/1	200 mg once a day 3/1	150 mg once a day 3/1	200 mg once a day 3/1		200 mg once a day 2/1

Japan

Groups	1	2	3	4	5	6
Total participants	2	3	3	1	4	6
TNO155	20 mg once a day 2/1	40 mg once a day 2/1	40 mg once a day 3/1	10 mg twice a day 3/1	20 mg twice a day 3/1	20 mg once a day 2/1
LEE011	200 mg once everyday		200 mg once a day 3/1			200 mg once a day 2/1

After treatment Up to 5 months

Trial staff checked participants' general health and for any medical problems for a maximum of 5 months after the last dose of **TNO155** in combination with **PDR001,** and for a maximum of 1 month after the participants' last dose of **TNO155** in combination with **LEE011**.

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

What were the main results of this trial?

What were the best doses of TNO155 in combination with PDR001 and with LEE011 for participants?

Researchers identified the best doses for participants:

- **TNO155** at **60 mg** once daily (for 2 weeks on and 1 week off) and **PDR001** at **300 mg** every 3 weeks
- **TNO155** at **40 mg** once daily and **LEE011** at **200 mg** once daily (both for 2 weeks on and 1 week off) **across the world excluding Japan**

There were not enough data from Japanese participants to draw any conclusion about the best dose for the combination of **TNO155** and **LEE011**.

To find these doses, researchers closely monitored the participants' health and recorded the number of participants who had**:**

- any **dose-limiting toxicities** (**DLTs**) during their first treatment cycle
- to receive a lower dose or pause the dose of a trial drug due to an adverse event during treatment

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

Some of the participants did not complete the first treatment cycle and were not considered in the DLT results. Therefore, the total number of participants with results for DLTs and those who received a lower dose or paused their trial drug could be different from the number who started the trial.

The DLT results for **TNO155** with **LEE011** were assessed separately for participants from **across the world excluding Japan** and from **Japan**, while the results for receiving a lowered dose or pausing a trial drug were assessed for all the participants who received this combination.

The tables below show how many participants had DLTs and how many had to receive a lowered dose or pause their trial drug during treatment.

TNO155 with PDR001

Groups	1	2	3	4	5	6	7	8	9
DLT	2 of 4 50%	1 of 15 7%	0 of 6	0 of 3	1 of 5 20%	0 of 4	1 of 4 25%	2 of 2 100%	0 of 0
Lowered the dose of **TNO155**	1 of 5 20%	3 of 19 16%	1 of 6 17%	0 of 5	2 of 5 40%	0 of 6	2 of 7 29%	1 of 3 33%	0 of 1
Paused TNO155	5 of 5 100%	9 of 19 47%	4 of 6 67%	4 of 5 80%	3 of 5 60%	6 of 6 100%	5 of 7 71%	1 of 3 33%	1 of 1 100%
Lowered the dose of **PDR001**	0 of 5	0 of 19	0 of 6	0 of 5	0 of 5	0 of 6	0 of 7	0 of 3	0 of 1
Paused PDR001	3 of 5 60%	5 of 19 26%	3 of 6 50%	1 of 5 20%	1 of 5 20%	3 of 6 50%	1 of 7 14%	0 of 3	0 of 1

Note: The number of participants included in the DLT results differed from those included in the results for lowered and paused doses of **TNO155** with **PDR001**, due to some participants not completing the first treatment cycle.

Out of 57 participants who received **TNO155** with **PDR001**, 43 were included in the DLT results. The DLTs observed for this combination were:

Reduced heart function (decreased ejection fraction), **brain inflammation caused by the immune system** (autoimmune encephalopathy), **fever with low count of white blood cells called neutrophils** (febrile neutropenia), **swelling**, **swelling in a specific part of the body due to fluid buildup** (localized edema), or **muscle breakdown** (rhabdomyolysis)

TNO155 with LEE011

	Across the world excluding Japan									Japan					
Groups	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**1**	**2**	**3**	**4**	**5**	**6**
DLTs	0 of 3	1 of 3 33%	2 of 5 40%	1 of 3 33%	0 of 2	0 of 4	3 of 7 43%	1 of 1 100%	1 of 7 14%	0 of 2	2 of 2 100%	2 of 3 67%	0 of 1	1 of 3 33%	0 of 4

Note: The number of participants included in the DLT results differed from the total number of participants in the **TNO155** with **LEE011** group, due to some participants not completing the first treatment cycle.

Out of 65 participants who received **TNO155** with **LEE011**, 35 were included in the DLT results for **across the world excluding Japan** group. The DLTs observed in this group were:

A decrease in the count of blood cells called platelets that help control bleeding (platelet count decreased), **lung inflammation** (pneumonitis), **a decrease in neutrophil count** (neutrophil count decreased), **an increase in the levels of a muscle enzyme called creatinine in the blood** (blood creatinine increased), **diarrhea**, **fluid buildup in the lungs** (pulmonary edema), **high levels of certain liver enzymes** (hypertransaminasemia), **high levels of uric acid in the blood** (blood uric acid increased), **low platelet count** (thrombocytopenia), **reduced heart function** (ejection fraction decreased), or **shortness of breath** (dyspnea)

Out of 65 participants who received **TNO155** with **LEE011**, 15 were included in the DLT results for the **Japan** group. The DLTs observed in this group were:

A decrease in platelet count (platelet count decreased) or **a decrease in neutrophil count** (neutrophil count decreased)

TNO155 with LEE011: Total

Groups	1	2	3	4	5	6	7	8	9	10	11	12
Lowered the dose of **TNO155**	0 of 5	0 of 8	0 of 5	0 of 4	0 of 8	0 of 1	0 of 5	0 of 4	1 of 9 11%	0 of 1	0 of 6	2 of 9 22%
Paused TNO155	3 of 5 60%	6 of 8 75%	3 of 5 60%	2 of 4 50%	5 of 8 63%	1 of 1 100%	1 of 5 20%	3 of 4 75%	7 of 9 78%	1 of 1 100%	4 of 6 67%	8 of 9 89%
Lowered the dose of **LEE011**	0 of 5	0 of 8	0 of 5	1 of 4 25%	2 of 8 25%	0 of 1	0 of 5	1 of 4 25%	2 of 9 22%	0 of 1	0 of 6	1 of 9 11%
Paused LEE011	3 of 5 60%	6 of 8 75%	3 of 5 60%	2 of 4 50%	5 of 8 63%	1 of 1 100%	1 of 5 20%	3 of 4 75%	5 of 9 56%	0 of 1	4 of 6 67%	8 of 9 89%

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

Trial doctors keep track of all medical problems, also called **adverse events**, that happen in trials. They track adverse events 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.

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.

This section is a summary of all the adverse events that happened from the start of treatment until:

- 5 months after participants took their last dose of **TNO155** with **PDR001**
- 1 month after participants took their last dose of **TNO155** with **LEE011**

In this section, adverse events will be presented for the total **TNO155** with **LEE011** group rather than separately for **across the world excluding Japan** and **Japan** groups.

- All participants (122 out of 122) had adverse events.
- 65 participants had adverse events that were considered serious.
- 11 participants left the trial due to an adverse event.
- 31 participants died due to any cause, including participants who died from the underlying cancer.
- Researchers concluded that there were no new safety concerns with the combination of **TNO155** with **PDR001** or **LEE011** in this trial, compared with when each drug was used individually in people with **advanced solid tumors** previously.

How many participants had adverse events?

TNO155 with PDR001

	TNO155 with PDR001 (57 participants)
Had at least 1 adverse event	57
Had at least 1 serious adverse event	37
Left the trial due to an adverse event	5
Died	26

TNO155 with LEE011

	TNO155 with LEE011 (65 participants)
Had at least 1 adverse event	65
Had at least 1 serious adverse event	28
Left the trial due to an adverse event	6
Died	5

What adverse events did the participants have?

TNO155 with PDR001

All participants had **adverse events**. The most common adverse events that happened in **30% or more** participants were:

- **High levels of a liver enzyme called aspartate aminotransferase (AST)** [aspartate aminotransferase increased]: 26 out of 57 participants
- **High levels of a liver enzyme called alanine aminotransferase (ALT)** [alanine aminotransferase increased]: 23 out of 57 participants
- **High levels of a muscle enzyme, known as creatine phosphokinase, in the blood** (blood creatine phosphokinase increased): 20 out of 57 participants
- **Low red blood cell count** (anemia): 19 out of 57 participants

TNO155 with LEE011

All participants had **adverse events**. The most common adverse events that happened in **30% or more** participants were:

- **High levels of a liver enzyme called aspartate aminotransferase (AST)** [aspartate aminotransferase increased]: 35 out of 65 participants
- **A decrease in platelet count** (platelet count decreased): 33 out of 65 participants
- **Low red blood cell count** (anemia): 28 out of 65 participants
- **High levels of a muscle enzyme, known as creatine phosphokinase, in the blood** (blood creatine phosphokinase increased): 28 out of 65 participants
- **High levels of a liver enzyme called alanine aminotransferase (ALT)** [alanine aminotransferase increased]: 27 out of 65 participants

What serious adverse events did the participants have?

TNO155 with PDR001

Out of 57 participants, 37 had **serious adverse events**. The most common serious adverse events that happened in **4% or more** participants were:

- **Lung infection** (pneumonia): 6 out of 57 participants
- **Fever** (pyrexia): 4 out of 57 participants
- **Serious complication of an infection** (sepsis): 3 out of 57 participants
- **Shortness of breath** (dyspnea): 3 out of 57 participants
- **Low red blood cell count** (anemia): 3 out of 57 participants

TNO155 with LEE011

Out of 65 participants, 28 had **serious adverse events**. The most common serious adverse event that happened in **4%** of participants was **fever** (pyrexia), experienced by 3 out of 65 participants.

What was learned from this trial?

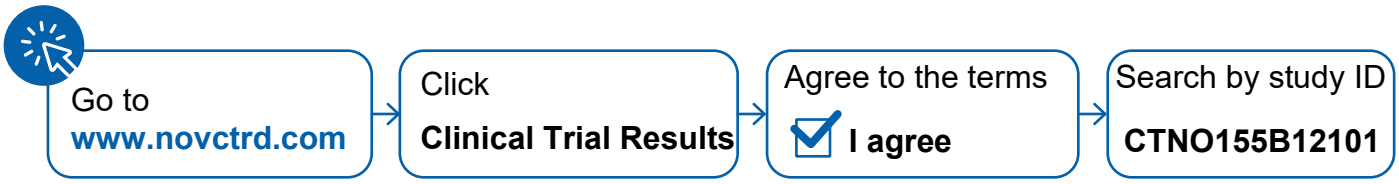
- Researchers learned about the best doses of **TNO155** given with **PDR001**. They also learned about the best doses of **TNO155** given with **LEE011** in people with advanced solid tumors from **across the world excluding Japan**.
- The trial ended early due to business reasons, so there were not enough data to draw any conclusion for the **Japan** group.
- The adverse events that participants had could be managed with other medicines and/or by changing or pausing their treatment.
- There were no additional safety concerns with the combinations compared to when the trial drugs were previously taken alone.

At the time of writing this summary, the sponsor had no plans for future trials of **TNO155** with **PDR001** and **TNO155** with **LEE011** in people with **advanced solid tumors**.

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 the following website:

- www.clinicaltrials.gov– search using the number **NCT04000529**

Other trials of **TNO155** plus **PDR001** and **TNO155** plus **LEE011** may appear on the public websites above. When there, search for **TNO155**, **PDR001** or **spartalizumab** and **LEE011** or **ribociclib**

Full clinical trial title: A Phase Ib, open-label, multi-center study to characterize the safety, tolerability, and preliminary efficacy of TNO155 in combination with spartalizumab or ribociclib in selected malignancies

Novartis is a global healthcare company based in Switzerland that provides solutions to address the evolving needs of patients worldwide.

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