

Clinical Trial Results Summary

A clinical trial to learn more about the safety of several drug combinations in people with advanced colorectal cancer

Thank you!

Thank you to the participants who took part in the clinical trial for **colorectal cancer**. Every participant helped the researchers learn more about the trial drugs **DRB436 (dabrafenib)**, **LTT462 (rineterkib)**, **TMT212 (trametinib)**, **LXH254 (naporafenib)**, **TNO155 (batoprotafib)**, **PDR001 (spartalizumab)**, and **VDT482 (tislelizumab)**.

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: CADPT01C12101

Novartis drugs studied: **DRB436 (dabrafenib)**, **LTT462 (rineterkib)**, **TMT212 (trametinib)**, **LXH254 (naporafenib)**, **TNO155 (batoprotafib)**, **PDR001 (spartalizumab)**, and **VDT482 (tislelizumab)**

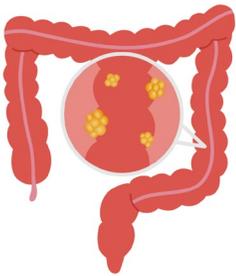
Sponsor: Novartis

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 more about the safety of different trial drug combinations and identify the recommended dose that can be given to people with **advanced colorectal cancer**.



Advanced colorectal cancer is a cancer that has spread from the colon or rectum to other parts of the body. This is also called **metastatic colorectal cancer (mCRC)**. This trial looked at a specific type of colorectal cancer with changes (mutations) in a gene called the **BRAF gene**. This gene normally helps control how cells grow. In some people with **colorectal cancer**, the **BRAF gene** has a mutation called **V600**, which causes cancer cells to grow and spread rapidly.

The trial looked at two main combinations: **DRB436** with **LTT462** and **DRB436** with **TMT212**.

- The first main combination of **DRB436 (dabrafenib)** with **LTT462 (rineterkib)** was first tested alone and then with one of the following drugs:
 - **TMT212 (trametinib)**
 - **LXH254 (naporafenib)**
 - **TNO155 (batoprotafib)**
 - **PDR001 (spartalizumab)**
 - **VDT482 (tislelizumab)**
- The second main combination of **DRB436 (dabrafenib)** with **TMT212 (trametinib)**, is already approved and safety already tested. Therefore, researchers directly tested this combination with a third drug, **TNO155**, without needing to re-test the combination of **DRB436** with **TMT212**.

DRB436 works by blocking the action of proteins that cause uncontrolled cell growth. **LTT462**, **TMT212**, **LXH254**, and **TNO155** aim to work by slowing down the growth of the cancer cells. **PDR001** and **VDT482** work by increasing the body's immune response against cancer cells.



Trial drugs

- **DRB436 (dabrafenib)**
Pronounced as duh-BRA-feh-nib
- **LTT462 (rineterkib)**
Pronounced as RIN-eh-ter-kib
- **TMT212 (trametinib)**
Pronounced as truh-MEH-tih-nib
- **LXH254 (naporafenib)**
Pronounced as NAH-po-ra-feh-nib
- **TNO155 (batoprotafib)**
Pronounced as BAT-oh-proh-ta-fib
- **PDR001 (spartalizumab)**
Pronounced as spar-tuh-LIZ-oo-mab
- **VDT482 (tislelizumab)**
Pronounced as TIS-le-LIZ-oo-mab



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

- What were the recommended dose combinations of the trial drugs 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 2020, and participants could continue trial treatment for as long as they were benefiting until the trial ended in September 2024. The sponsor decided to end the trial earlier than planned due to business reasons. This decision was not based on any safety concerns during the trial.

This trial was designed to have 2 parts:

- During **Part 1**, participants received a fixed dose of **DRB436**. The doses of **LTT462**, **TMT212**, **LXH254**, or **TNO155** were slowly increased to find the recommended dose combinations to use with **DRB436**. **PDR001** and **VDT482** were given at fixed doses with **DRB436**.
- It was planned that **Part 2** would further study the recommended dose combinations of drugs, which were determined in **Part 1**. However, this part did not happen as the trial ended early.

Who was in this trial?



122 participants with **colorectal cancer** received treatment in this trial – 66 men and 56 women. Participants' ages ranged from 31 to 86 years. Their average age was 58 years.

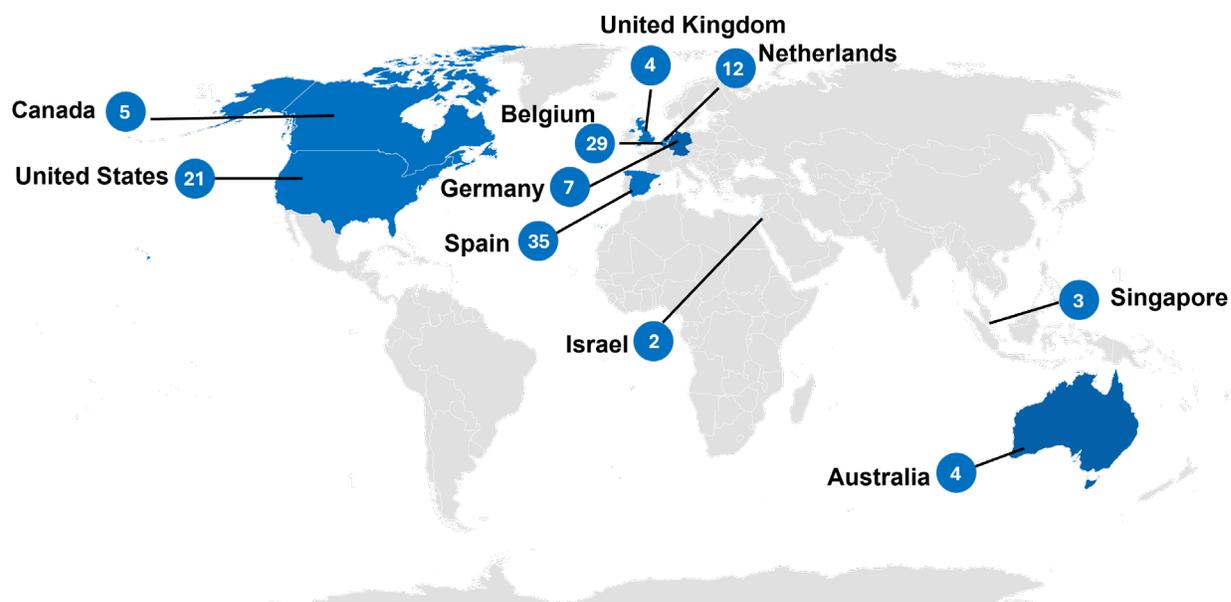
The number of participants by race is shown below.



The participants could take part in this trial if they:

- were at least 18 years of age
- were fully active and able to walk or carry out light work
- had advanced **colorectal cancer** with changes (mutations) called **V600** in the **BRAF gene**
- had worsening of their cancer that did not respond to standard treatment

122 participants from 10 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 in **cycles**.

What is a cycle?

A cycle is a treatment period that is repeated. In this trial, each **cycle** lasted for either 21 or 28 days depending on the drugs.

The drugs given in this trial were:



DRB436: taken twice daily as capsules by mouth.



LTT462: taken once daily as capsules by mouth.



TMT212: taken once daily as tablets by mouth.



LXH254: taken twice daily as tablets by mouth.



TNO155: taken once daily as capsules by mouth.



PDR001: taken once as an infusion into a vein on Day 1 of each cycle.



VDT482: taken once as an infusion into a vein on Day 1 of each cycle.

This trial was designed so that researchers could change the combinations of drugs being tested based on the results of the trial. This meant that the testing of some drug combinations could be stopped, and new trial drugs could be added during the trial.

The participants, trial doctors, and the trial staff knew which trial drugs each participant was receiving.

What happened during the trial?

Before treatment

Up to 1 month before receiving the first dose of treatment



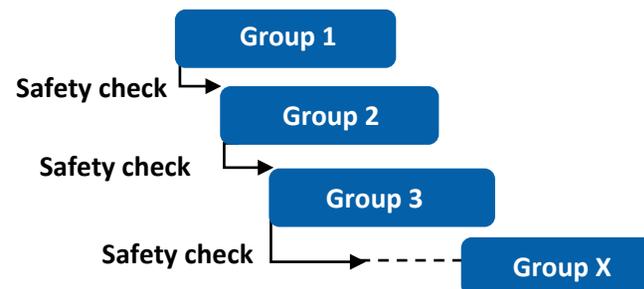
The trial staff checked to make sure the participants could be in this trial.

During treatment

For as long as participants were benefiting from the treatment

Researchers gave different doses of the trial drug combinations to a few participants. Researchers checked the safety of these combinations before giving the next combination to the next group of participants. This continued until the safety of each set of dose combinations had been checked.

The following drug combinations were given during this trial:



Combination A: DRB436 + LTT462

Groups	1	2	3	4	5
Total participants	9	11	9	7	2
DRB436	150 mg				
LTT462	100 mg	200 mg	250 mg	300 mg	400 mg

Combination B: DRB436 + LTT462 + TMT212

Groups	6	7	8	9
Total participants	6	4	4	6
DRB436	150 mg	150 mg	150 mg	150 mg
LTT462	100 mg	200 mg	100 mg	200 mg
TMT212	1 mg	1 mg	2 mg	2 mg

Combination C: DRB436 + LTT462 + LXH254

Group 10	
7 participants	
DRB436	75 mg
LTT462	100 mg
LXH254	200 mg

Combination D: DRB436 + LTT462 + PDR001

Group 11	
5 participants	
DRB436	150 mg
LTT462	100 mg
PDR001	400 mg

Combination E: DRB436 + LTT462 + TNO155

Groups	12	13	14	15	16
Total participants	4	4	4	4	4
DRB436	150 mg				
LTT462	100 mg	200 mg	100 mg	100 mg	200 mg
TNO155	20 mg (3w/1w)*	20 mg (3w/1w)*	40 mg (3w/1w)*	40 mg (2w/1w)#	40 mg (2w/1w)#

* 3w/ 1w - TNO155 taken for the first 3 weeks of the 28-day treatment cycle, followed by 1 week of no treatment.

2w/ 1w - TNO155 taken for the first 2 weeks of the 21-day treatment cycle, followed by 1 week of no treatment.

Combination F: DRB436 + TMT212 + TNO155

Groups	17	18	19	20	21
Total participants	3	6	4	4	4
DRB436	150 mg	150 mg	150 mg	150 mg	150 mg
TMT212	0.5 mg	1 mg	1 mg	1 mg	2 mg
TNO155	20 mg (3w/1w)*	20 mg (3w/1w)*	20 mg (2w/1w)#	40 mg (2w/1w)#	20 g (2w/1w)#

* 3w/ 1w - TNO155 taken for the first 3 weeks of the 28-day treatment cycle, followed by 1 week of no treatment.

2w/ 1w - TNO155 taken for the first 2 weeks of the 21-day treatment cycle, followed by 1 week of no treatment.

Combination G: DRB436 + LTT462 + VDT482

Groups	22	23	24
Total participants	2	5	4
DRB436	100 mg	150 mg	150 mg
LTT462	100 mg	100 mg	200 mg
VDT482	300 mg		

After treatment

Up to 5 months after the last dose of treatment



Depending on the trial drugs they received, participants were followed for up to 5 months after they received the last dose of trial treatment.

What were the main results of this trial?

What were the recommended dose combinations of the trial drugs for participants?



The trial ended earlier than planned. Due to this, the researchers did not identify the recommended dose combinations of the trial drugs for participants.

During the trial, 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 during treatment

What are dose-limiting toxicities (DLTs)?

DLTs are medical problems that the trial doctors think could be related to the trial treatment and are serious enough to either prevent increasing the dose or discontinue the trial drug.

Some of the participants did not complete the first treatment cycle for reasons other than drug-related medical problems 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 tables below show how many participants had **DLTs** during the first treatment cycle and how many had to receive a lowered dose or pause their trial drug for any reason throughout the trial.

Combination: A

Group	1	2	3	4	5
DLT (assessed for 27 participants who completed the first treatment cycle)	1 of 8 13%	0 of 7	1 of 5 20%	0 of 5	2 of 2 100%
Lowered the dose of DRB436	1 of 9 11%	2 of 11 18%	0 of 9	1 of 7 14%	1 of 2 50%
Paused DRB436	9 of 9 100%	11 of 11 100%	9 of 9 100%	7 of 7 100%	2 of 2 100%
Lowered the dose of LTT462	0 of 9	2 of 11 18%	2 of 9 22%	1 of 7 14%	1 of 2 50%
Paused LTT462	3 of 9 33%	7 of 11 64%	3 of 9 33%	5 of 7 71%	1 of 2 50%

The **DLTs** observed for this combination were: **weakness** (asthenia), **problems walking** (gait disturbance), **pain**, **fever** (pyrexia), and **inflamed pancreas** (pancreatitis).

Combination: B

Group	6	7	8	9
DLT (assessed for 19 participants who completed the first treatment cycle)	0 of 5	0 of 4	1 of 4 25%	1 of 6 17%
Lowered the dose of DRB436	1 of 6 17%	0 of 4	0 of 4	2 of 6 33%
Paused DRB436	6 of 6 100%	4 of 4 100%	4 of 4 100%	6 of 6 100%
Lowered the dose of LTT462	0 of 6	1 of 4 25%	0 of 4	1 of 6 17%
Paused LTT462	3 of 6 50%	3 of 4 75%	2 of 4 50%	2 of 6 33%
Lowered the dose of TMT212	1 of 6 17%	1 of 4 25%	0 of 4	2 of 6 33%
Paused TMT212	3 of 6 50%	3 of 4 75%	2 of 4 50%	2 of 6 33%

The **DLTs** observed for this combination were: **a condition where the left side of the heart does not function properly** (left ventricular dysfunction), and **fever** (pyrexia).

Combination: C

Group	10
DLT (assessed for 5 participants who completed the first treatment cycle)	0 of 5
Lowered the dose of DRB436	0 of 7
Paused DRB436	7 of 7 100%
Lowered the dose of LTT462	0 of 7
Paused LTT462	3 of 7 43%
Lowered the dose of LXH254	0 of 7
Paused LXH254	7 of 7 100%

No DLTs were observed for the participants who took this combination.

Combination: D

Group	11
DLT (assessed for 3 participants who completed the first treatment cycle)	0 of 3
Lowered the dose of DRB436	1 of 5 20%
Paused DRB436	5 of 5 100%
Lowered the dose of LTT462	1 of 5 20%
Paused LTT462	5 of 5 100%
Lowered the dose of PDR001	0 of 5
Paused PDR001	0 of 5

No DLTs were observed for the participants who received this combination.

Combination: E

Group	12	13	14	15	16
DLT (assessed for 17 participants who completed the first treatment cycle)	0 of 4	1 of 3 33%	1 of 4 25%	0 of 3	2 of 3 67%
Lowered the dose of DRB436	0 of 4	0 of 4	1 of 4 25%	0 of 4	1 of 4 25%
Paused DRB436	4 of 4 100%				
Lowered the dose of LTT462	1 of 4 25%	0 of 4	1 of 4 25%	0 of 4	1 of 4 25%
Paused LTT462	1 of 4 25%	0 of 4	4 of 4 100%	3 of 4 75%	3 of 4 75%
Lowered the dose of TNO155	1 of 4 25%	0 of 4	1 of 4 25%	0 of 4	1 of 4 25%
Paused TNO155	2 of 4 50%	0 of 4	3 of 4 75%	2 of 4 50%	3 of 4 75%

The DLTs observed for this combination were: **a condition where the heart pumps out less blood than normal** (ejection fraction decreased), **itchy rash** (rash pruritic), and **fever** (pyrexia).

Combination: F

Group	17	18	19	20	21
DLT (assessed for 18 participants who completed the first treatment cycle)	0 of 3	2 of 5 40%	0 of 3	0 of 3	1 of 4 25%
Lowered the dose of DRB436	0 of 3	1 of 6 17%	1 of 4 25%	0 of 4	1 of 4 25%
Paused DRB436	3 of 3 100%	6 of 6 100%	4 of 4 100%	4 of 4 100%	4 of 4 100%
Lowered the dose of TMT212	0 of 3	0 of 6	2 of 4 50%	0 of 4	1 of 4 25%
Paused TMT212	3 of 3 100%	3 of 6 50%	3 of 4 75%	3 of 4 75%	2 of 4 50%
Lowered the dose of TNO155	0 of 3	1 of 6 17%	0 of 4	0 of 4	1 of 4 25%
Paused TNO155	2 of 3 67%	4 of 6 67%	2 of 4 50%	2 of 4 50%	2 of 4 50%

The DLTs observed for this combination were: **a condition where the heart pumps out less blood than normal** (ejection fraction decreased), **allergic reaction** (hypersensitivity), and **low blood sodium level** (hyponatraemia).

Combination: G

Group	22	23	24
DLT (assessed for 9 participants who completed the first treatment cycle)	0 of 0	0 of 5	0 of 4
Lowered the dose of DRB436	1 of 2 50%	2 of 5 40%	1 of 4 25%
Paused DRB436	2 of 2 100%	5 of 5 100%	4 of 4 100%
Lowered the dose of LTT462	2 of 2 100%	1 of 5 20%	1 of 4 25%
Paused LTT462	2 of 2 100%	4 of 5 80%	3 of 4 75%
Lowered the dose of VDT482	0 of 2	0 of 5	0 of 4
Paused VDT482	0 of 2	1 of 5 20%	2 of 4 50%

No DLTs were observed for the participants who received this combination.

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.

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

- 1 month after participants took their last dose of **DRB436**, **TMT212**, **LTT462**, **LXH254**, or **TNO155**
- 4 months after participants took their last dose of **VDT482**
- 5 months after participants took 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 participants (122 of 122) had adverse events.
- 57 participants had adverse events that were considered serious.
- 10 participants left the trial due to an adverse event.
- 18 participants died due to any cause, including participants who died from the underlying cancer.
- The researchers concluded there were no new safety concerns for the combinations of **DRB436**, **LTT462**, **TMT212**, **LXH254**, **TNO155**, **PDR001**, or **VDT482** in this trial, compared with when each drug was used individually in people with **colorectal cancer**.

What serious adverse events did the participants have?

Combination: A

Out of 38 participants, 18 had **serious adverse events**. The most common serious adverse events that happened in participants were:

- **Stomach pain** (abdominal pain): 2 out of 38 participants
- **Fever** (pyrexia): 2 out of 38 participants
- **Back pain**: 2 out of 38 participants

Combination: B

Out of 20 participants, 9 had **serious adverse events**. The most common serious adverse events that happened in participants were:

- **Stomach pain** (abdominal pain): 2 out of 20 participants
- **Fever** (pyrexia): 3 out of 20 participants

Combination: C

Out of 7 participants, 3 had **serious adverse events**. A participant could have more than one serious adverse events. These were:

- **Stomach pain** (abdominal pain)
- **Back pain**
- **Swelling in the brain due to accumulation of excess fluid** (brain edema)
- **A state of confusion** (confusional state)
- **Diarrhea**
- **Decline in physical health** (general physical health deterioration).

Combination: D

Out of 5 participants, 3 had **serious adverse events**. A participant could have more than one serious adverse events. These were:

- **Low levels of hemoglobin** (anemia)
- **Increased blood levels of bilirubin, breakdown product of red blood cells** (blood bilirubin increased)
- **Decline in physical health** (general physical health deterioration)
- **Ulcer in the lining of small intestine** (duodenal ulcer)
- **Cough that brings up phlegm** (productive cough)
- **Collection of blood beneath the outer covering of the liver** (subcapsular hepatic hematoma)
- **Fainting** (syncope)

Combination: E

Out of 20 participants, 8 had **serious adverse events**. The most common serious adverse events that happened in participants were:

- **Diarrhea**: 2 out of 20 participants
- **Fever** (pyrexia): 3 out of 20 participants

Combination: F

Out of 21 participants, 10 had **serious adverse events**. A participant could have more than one serious adverse events. These were:

- **Infection of the deep layers of your skin** (cellulitis)
- **Stroke** (cerebrovascular accident)
- **Seizures** (epilepsy)
- **Fluid build-up inside the brain** (hydrocephalus)
- **Low blood sodium levels** (hyponatremia)
- **Blockage in the intestine** (intestinal obstruction)
- **Eye infection caused by herpes virus** (ophthalmic herpes simplex)
- **Symptoms due to damaged nerves in the arms, legs, hands and feet** (peripheral motor neuropathy)
- **Unexpected problem during or after a medical procedure** (procedural complication)
- **Blockage in the small intestines** (small intestinal obstruction)
- **Bacterial infection** (staphylococcal infection)

Combination: G

Out of 11 participants, 6 had **serious adverse events**. The most common serious adverse event that happened in participants was **fever** (pyrexia) which happened in 2 out of 11 participants.

What other (not including serious) adverse events did the participants have?

Combination: A

The most common other adverse events that happened in participants were:

- **Fever** (pyrexia)
- **Feeling sick** (nausea)
- **Diarrhea**
- **Stomach pain** (abdominal pain)
- **Reduced hunger** (decreased appetite)
- **Vomiting**

Combination: B

The most common other adverse events that happened in participants were:

- **Fever** (pyrexia)
- **Diarrhea**
- **Feeling sick** (nausea)

Combination: C

The most common other adverse event that happened in participants was **tiredness** (fatigue).

Combination: D

The most common other adverse events that happened in participants were:

- **Fever** (pyrexia)
- **Diarrhea**
- **Feeling sick** (nausea)
- **Tiredness** (fatigue)

Combination: E

The most common other adverse events that happened in participants were:

- **Feeling sick** (nausea)
- **Diarrhea**

Combination: F

The most common other adverse events that happened in participants were:

- **Diarrhea**
- **Fever** (pyrexia)
- **Swelling of the ankles and feet** (oedema peripheral)

Combination: G

The most common other adverse events that happened in participants were:

- **Low number of red blood cells** (anemia)
- **Fever** (pyrexia)
- **Diarrhea**

What was learned from this trial?

Researchers wanted to learn about the recommended doses of two main combinations of **DRB436** with **LTT462** and **DRB436** with **TMT212**, when a third drug (**TMT212**, **LXH254**, **TNO155**, **PDR001**, or **VDT482**) was added in people with **colorectal cancer**. However, the researchers decided to end the trial earlier than planned due to business reasons. This decision was not based on any safety concerns during the trial.



- The researchers could not identify the recommended dose combinations of the trial drugs for participants.
- The researchers concluded there were no new safety concerns for the drug combinations tested in this trial, compared with when each drug was used individually in people with **colorectal cancer**.

When this summary was written, the sponsor had no plans for future trials with these drug combinations in people with **colorectal 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 any of the following websites:

- www.clinicaltrials.gov – search using the number **NCT04294160**
- euclinicaltrials.eu – search using the number **2023-510379-77-00**

Other trials of **DRB436**, **LTT462**, **TMT212**, **LXH254**, **TNO155**, **PDR001**, and **VDT482** may appear on the public websites above. When there, search for **DRB436** (**dabrafenib**), **LTT462** (**rineterkib**), **TMT212** (**trametinib**), **LXH254** (**naporafenib**), **TNO155** (**batoprotafib**), **PDR001** (**spartalizumab**), and **VDT482** (**tislelizumab**)

Full clinical trial title: A phase Ib, multicenter, open-label dose escalation and expansion platform study of select drug combinations in adult patients with advanced or metastatic BRAF V600 colorectal cancer



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

1-888-669-6682 (US) | +41-61-324 1111 (EU)

www.novartis.com/clinicaltrials