AstraZeneca

Clinical Trial Results

Research Sponsor: AstraZeneca AB

Treatments Studied: Tremelimumab and durvalumab

Trial Purpose: This trial was done to learn how tremelimumab and durvalumab work and about their safety in people with a type of advanced liver cancer called hepatocellular carcinoma

Protocol Number: D419CC00002

Thank you

Thank you to the participants who took part in the clinical trial for the trial treatments tremelimumab and durvalumab.

All of the participants helped researchers learn more about tremelimumab and durvalumab to help people with a type of advanced liver cancer called "hepatocellular carcinoma".

AstraZeneca AB sponsored this trial and believes it is important to share the results of this trial with the participants and the public. An independent non-profit organization called CISCRP helped prepare this summary of the trial results. We hope it helps the participants understand and feel proud of their important role in medical research.

If you participated in this trial and have questions about the results, please speak with a trial doctor or staff at your trial site.

Overview of this trial

Why was the research needed? Page 5

Researchers are looking for a better way to treat hepatocellular carcinoma in adults. Hepatocellular carcinoma is also known as "HCC". Before a treatment can be approved for people to get, researchers do clinical trials to find out how it works and how safe it is.

What treatments did the participants get? Page 7

The participants in this trial got 1 of the following treatments:

- durvalumab alone
- durvalumab and a **higher** dose of tremelimumab
- durvalumab and a **lower** dose of tremelimumab
- standard treatment for HCC

What were the results of this trial? Page 11

The main questions the researchers wanted to answer in the trial were:

- **Did durvalumab and the higher dose of tremelimumab help the participants live longer than standard treatment?**

  Yes. Overall, the researchers found that the participants who got durvalumab and the higher dose of tremelimumab lived longer compared with the participants who got standard treatment.

- **Did durvalumab alone help the participants live at least as long as standard treatment?**

  Yes. Overall, the researchers found that the participants who got durvalumab alone lived at least as long as the participants who got standard treatment.

- **Did durvalumab alone help the participants live longer than standard treatment?**

  No. Overall, the researchers found that there were some differences between the durvalumab and standard treatment groups. But, the differences were too small for the researchers to decide if durvalumab alone helped participants live longer than standard treatment.

- **Did the participants feel that durvalumab and the higher dose of tremelimumab affected their symptoms and quality of life compared with standard treatment?**

  Yes. Overall, the participants who got durvalumab and the higher dose of tremelimumab had more of a meaningful improvement in some of their symptoms and their quality of life compared with those who got standard treatment.

- **Did the participants feel that durvalumab alone affected their symptoms and quality of life compared with standard treatment?**

  Yes. The participants who got durvalumab alone felt some improvement in their symptoms and quality of life compared with those who got standard treatment.

More details about the results of this trial are included later in this summary.

What medical problems did the doctors report as possibly related to the trial treatments? Page 14

There were 70.6% of participants who had medical problems that the trial doctors reported as possibly being related to the trial treatments. This was 919 out of 1,302 participants. The most common adverse reactions were diarrhea, rash, itchy skin, redness, swelling, or blistering of the hands or feet, and fatigue. More details about the medical problems from this trial are included later in this summary.

Where can I learn more about this trial? Page 20

You can find more information about this trial on the websites listed on the last page. When a full report of the trial results is available, it also can be found on those websites.

Who took part in this trial?

The researchers asked for the help of people with advanced HCC. The participants in this trial were 18 to 88 years old when they joined.

The participants:

- had cancer that could not be cured by surgery or radiation treatments
- had not previously gotten durvalumab, tremelimumab, or treatments that work in a similar way
- had not previously received chemotherapy for their cancer
- were able to do their daily activities when the trial began

This trial included 1,324 men and women in 16 countries:

Brazil	70 participants	Russia	85 participants
Canada	46 participants	South Korea	146 participants
France	107 participants	Spain	45 participants
Germany	73 participants	Taiwan	61 participants
Hong Kong	91 participants	Thailand	136 participants
India	45 participants	Ukraine	65 participants
Italy	79 participants	United States	91 participants
Japan	124 participants	Vietnam	60 participants

Why was the research needed?

Researchers are looking for a better way to treat advanced HCC in adults. Before a treatment can be approved for people to get, researchers do clinical trials to find out how it works and how safe it is.

In people with cancer, the body is not able to control the growth of some cells. The extra cells can form tumors. When cancer progresses to a late stage, tumors spread to other parts of the body or grow beyond the organ where they started. Sometimes the tumors are too difficult to remove by surgery because of where they are in the body, or because there are too many of them.

Normally, the immune system can help stop tumors from growing. But, in people with advanced HCC, the proteins on the tumor cells can interact with the immune cells. This may stop the immune cells from being able to attack the tumor cells.

The trial treatments, tremelimumab and durvalumab, were designed to boost the immune system's reaction to HCC tumors. This helps the immune cells attack the tumor cells, which could stop or slow the growth of the tumor, or shrink it.

What was the purpose of this trial?

This was a "Phase 3" trial. In this trial, the researchers wanted to find out how durvalumab alone, or durvalumab together with tremelimumab, worked in a large number of participants with advanced HCC. They also wanted to find out if the participants had any medical problems during the trial.

The main questions the researchers wanted to answer in this trial were:

- Did durvalumab and the **higher** dose of tremelimumab help the participants live longer than standard treatment?
- Did durvalumab alone help the participants live **at least as long as** standard treatment?
- Did durvalumab alone help the participants live **longer than** standard treatment?
- Did the participants feel that durvalumab and the **higher** dose of tremelimumab affected their symptoms and quality of life compared with standard treatment?
- Did the participants feel that durvalumab alone affected their symptoms and quality of life compared with standard treatment?
- What medical problems did the doctors report as related to the trial treatment?

The answers to these questions are important to know before other trials can be done to find out if tremelimumab and durvalumab help improve the health of people with advanced HCC.

What treatments did the participants get?

The participants in this trial got 1 of the following treatments:

- durvalumab alone
- durvalumab and a **higher** dose of tremelimumab
- durvalumab and a **lower** dose of tremelimumab
- standard treatment for HCC

"Standard treatment" means the treatment that the medical community thinks is an appropriate and widely used drug for the condition. For people with advanced HCC, the standard treatment is sorafenib tablets twice a day.

> In this summary, "trial treatment" means anything the participants got as a part of the trial. This includes tremelimumab, durvalumab, and the standard treatment. Tremelimumab and durvalumab are the treatments that the researchers wanted to learn more about.

This was an "open-label" trial. This means the participants, researchers, trial doctors, and other trial staff knew what each participant was getting.

A computer program was used to randomly choose the treatment each participant got. This helps make sure the groups are chosen fairly. Researchers do this so that comparing the results of each treatment is as accurate as possible.

The doses of treatment were measured in milligrams, also known as "mg". The chart below shows the treatment plan for the participants.

	Durvalumab alone	Durvalumab and a **higher** dose of tremelimumab	Durvalumab and a **lower** dose of tremelimumab	Standard treatment
	389 participants	393 participants	153 participants	389 participants
	Given through a needle into a vein, called an "IV infusion"	Given through a needle into a vein, called an "IV infusion"	Given through a needle into a vein, called an "IV infusion"	Taken as tablets by mouth
	• 1,500 mg of durvalumab alone every 4 weeks	• **300 mg** of tremelimumab 1 time • 1,500 mg of durvalumab every 4 weeks	• **75 mg** of tremelimumab every 4 weeks, 4 times • 1,500 mg of durvalumab every 4 weeks	• 400 mg of sorafenib twice a day
	• The participants were in the trial until their cancer got worse, the trial doctors thought they should stop trial treatment, or they left for another reason.			

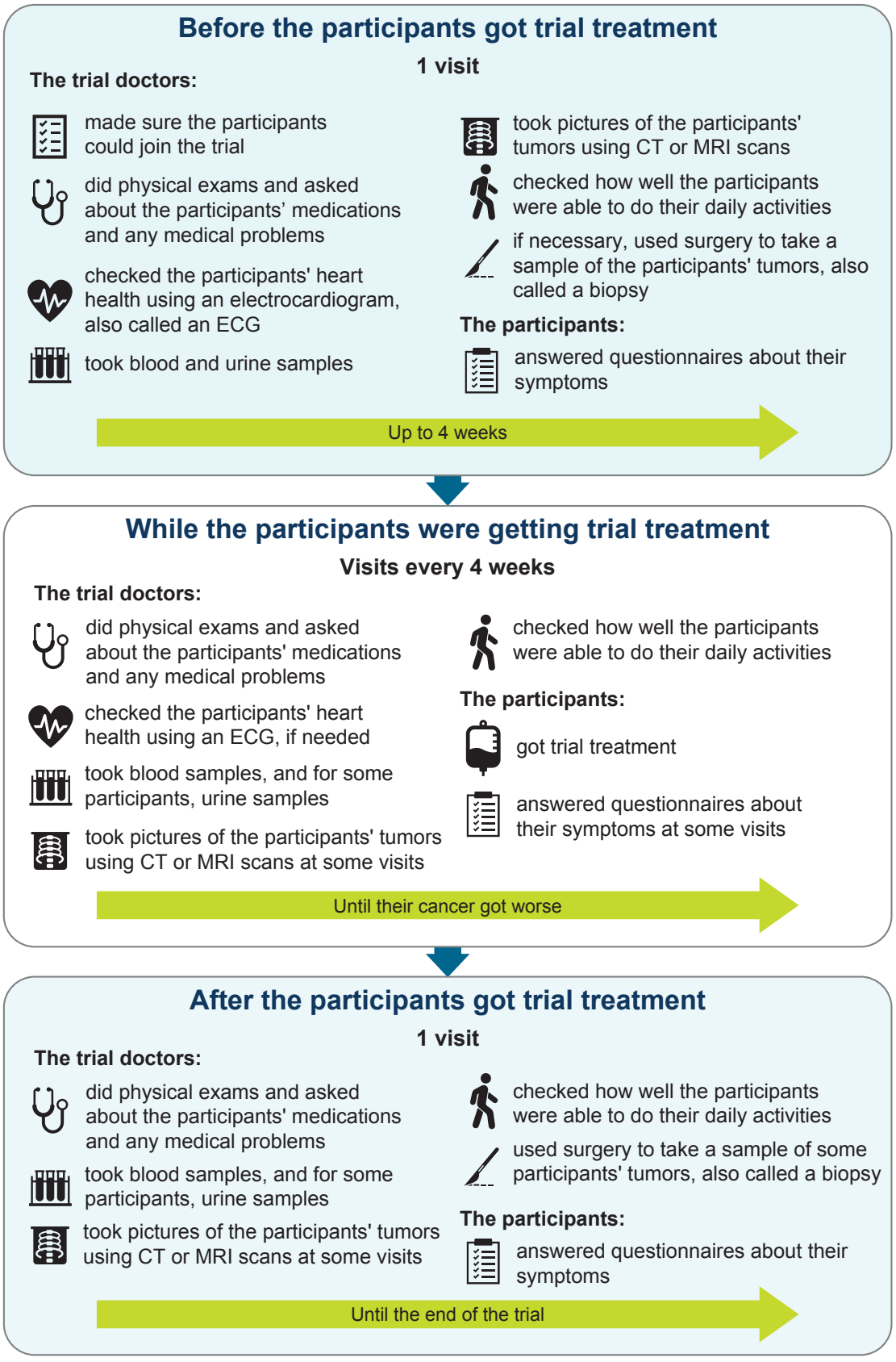
The researchers had planned to have more participants in the group who got durvalumab and the lower dose of tremelimumab, but the results of another trial showed that this treatment combination was not working. A decision was made to stop including more participants in this group. The results for how well the treatments worked in this group are not available in this summary, but may be found at one of the websites shown at the end of this summary.

What happened during this trial?

The participants were in the trial for up to 1.5 years. But, the entire trial took almost 4 years to finish.

The trial started in October 2017 and ended in August 2021.

The chart below shows what happened during the trial.



What were the results of this trial?

This is a summary of the main results from this trial overall. The individual results of each participant might be different and are not in this summary. A full list of the questions that researchers wanted to answer can be found on the websites listed at the end of this summary. When a full report of the trial results is available, it can also be found on these websites.

Researchers look at the results of many trials to decide which treatments work best and are safest. Other trials may provide new information or different results. Always talk to a doctor before making any treatment changes.

Did durvalumab and the higher dose of tremelimumab help the participants live longer than standard treatment?

Yes. Overall, the researchers found that the participants who got durvalumab and the **higher** dose of tremelimumab lived longer compared with the participants who got standard treatment.

To answer this question, the researchers counted how many months the participants lived with their cancer after starting trial treatment. They calculated the average number of months for each group.

The average number of months that the participants lived after starting trial treatment was:

- **16.4 months** for the participants who got **durvalumab and the higher dose of tremelimumab**
- **13.8 months** for the participants who got the **standard treatment**

Did durvalumab alone help the participants live at least as long as standard treatment?

Yes. Overall, the researchers found that the participants who got durvalumab alone lived at least as long as the participants who got standard treatment.

The average number of months that the participants lived after starting trial treatment was:

- **16.6 months** for the participants who got **durvalumab alone**
- **13.8 months** for the participants who got the **standard treatment**

Did durvalumab alone help the participants live longer than standard treatment?

No. Overall, the researchers found that there were some differences between the groups. But, the differences were too small for the researchers to decide if getting durvalumab alone helped participants live longer than getting standard treatment.

The average number of months that the participants lived after starting trial treatment was:

- **16.6 months** for the participants who got **durvalumab alone**
- **13.8 months** for the participants who got the **standard treatment**

The researchers then did statistical tests on these results that showed that getting durvalumab alone **did not help** participants live longer than getting standard treatment. The results for each participant in a group can be very different. So, even though the average number of months the participants lived was higher in the durvalumab group compared to the standard treatment group, the overall difference between the 2 groups was too small to be significant.

Did the participants feel that durvalumab and the higher dose of tremelimumab affected their symptoms and quality of life compared with standard treatment?

To answer this question, the trial doctors asked the participants to complete 2 different questionnaires. These were:

- The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30, also known as **EORTC QLQ-C30**
- The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Hepatocellular Carcinoma 18, also known as **EORTC QLQ-HCC18**

The researchers gave the participants a "score" based on their answers to each questionnaire about the severity of their symptoms or quality of life. The researchers measured how much the participants' scores changed during the trial. Then, they compared the scores of the participants who got durvalumab and the higher dose of tremelimumab to those who got standard treatment.

The **EORTC QLQ-C30** questionnaire showed that:

- The participants who got durvalumab and the higher dose of tremelimumab had a meaningful improvement in quality of life, ability to do daily tasks, appetite, fatigue levels, and nausea compared with those who got standard treatment.

The **EORTC QLQ-HCC18** questionnaire showed that:

- The participants who got durvalumab and the higher dose of tremelimumab had less shoulder pain, abdominal pain, and abdominal swelling than those who got standard treatment.

Did the participants feel that durvalumab alone affected their symptoms and quality of life compared with standard treatment?

To answer this question, the trial doctors looked at the results from the EORTC QLQ-C30 and EORTC QLQ-HCC18 questionnaires.

The **EORTC QLQ-C30** questionnaire showed that:

- The participants who got durvalumab alone felt some improvement in quality of life, ability to do daily tasks, appetite, and fatigue levels compared with those who got standard treatment.

The **EORTC QLQ-HCC18** questionnaire showed that:

- The participants who got durvalumab alone felt less abdominal pain than those who got standard treatment.

What medical problems did the doctors report as possibly related to the trial treatments?

This section is a summary of the medical problems that the participants had during this trial that the doctors reported as **possibly related** to the trial treatments. These medical problems are called "**adverse reactions**". An adverse reaction is considered "serious" when it is life-threatening, causes lasting problems, or requires hospital care. The results from several trials are needed to decide if a treatment causes an adverse reaction.

The websites listed at the end of this summary may have other information about adverse reactions or other medical problems that happened during this trial.

There were 22 participants who joined the trial but did not get any trial treatment. So, the results below are for 1,302 out of 1,324 participants.

Did any adverse reactions happen during this trial?

There were 70.6% of participants who had adverse reactions in this trial. This was 919 out of 1,302 participants.

	Durvalumab alone (out of 388 participants)	Durvalumab and the **higher** dose of tremelimumab (out of 388 participants)	Durvalumab and the **lower** dose of tremelimumab (out of 152 participants)	Standard treatment (out of 374 participants)
How many participants had serious adverse reactions?	8.2% (32)	17.5% (68)	18.4% (28)	9.4% (35)
How many participants had adverse reactions?	52.1% (202)	75.8% (294)	69.7% (106)	84.8% (317)
How many participants stopped getting trial treatment due to adverse reactions?	4.1% (16)	8.2% (32)	8.6% (13)	11.0% (41)

What serious adverse reactions happened during this trial?

The most common serious adverse reactions were diarrhea, lung inflammation, liver inflammation, and liver failure.

The table below shows the serious adverse reactions that happened in more than 1.0% of participants in any treatment group during the trial.

Most common serious adverse reactions

Serious adverse reaction	Durvalumab alone (out of 388 participants)	Durvalumab and the **higher** dose of tremelimumab (out of 388 participants)	Durvalumab and the **lower** dose of tremelimumab (out of 152 participants)	Standard treatment (out of 374 participants)
Diarrhea	0.3% (1)	1.8% (7)	2.6% (4)	1.6% (6)
Lung inflammation	0.5% (2)	0.8% (3)	2.0% (3)	0.0% (0)
Liver inflammation	0.3% (1)	0.8% (3)	2.0% (3)	0.0% (0)
Liver failure	0.3% (1)	0.3% (1)	1.3% (2)	0.5% (2)
Lung disease that causes scarring or inflammation	0.3% (1)	0.0% (0)	1.3% (2)	0.0% (0)
Bowel inflammation	0.3% (1)	1.5% (6)	0.7% (1)	0.0% (0)
Liver function not normal	1.3% (5)	0.3% (1)	0.7% (1)	0.3% (1)

There were 1.1% of participants who died because of serious adverse reactions. This was 14 out of 1,302 participants. These participants were:

- 2 out of 152 participants (1.3%) who got durvalumab and the **lower** dose of tremelimumab
- 9 out of 388 participants (2.3%) who got durvalumab and the **higher** dose of tremelimumab
- 3 out of 374 participants (0.8%) who got standard treatment

None of the participants who got durvalumab alone died because of serious adverse reactions.

What adverse reactions happened during this trial?

The most common adverse reactions were diarrhea, rash, itchy skin, redness, swelling, or blistering of the hands or feet, and fatigue.

The table below shows the adverse reactions that happened in 10.0% or more of participants in any treatment group during the trial. There were other adverse reactions, but these each happened in fewer participants.

Most common adverse reactions

Adverse reaction	Durvalumab alone (out of 388 participants)	Durvalumab and the **higher** dose of tremelimumab (out of 388 participants)	Durvalumab and the **lower** dose of tremelimumab (out of 152 participants)	Standard treatment (out of 374 participants)
Diarrhea	5.9% (23)	16.5% (64)	14.5% (22)	38.8% (145)
Rash	7.5% (29)	19.6% (76)	13.2% (20)	12.3% (46)
Redness, swelling, or blistering of the hands or feet	0.0% (0)	0.5% (2)	0.7% (1)	43.9% (164)
Itchy skin	7.2% (28)	17.0% (66)	12.5% (19)	5.6% (21)
Fatigue	6.4% (25)	7.7% (30)	11.2% (17)	14.7% (55)
Underactive thyroid	3.9% (15)	10.8% (42)	11.8% (18)	2.1% (8)
Decreased appetite	2.6% (10)	5.4% (21)	3.9% (6)	12.0% (45)
High blood pressure	0.5% (2)	0.8% (3)	1.3% (2)	15.0% (56)
Hair loss	0.8% (3)	0.3% (1)	0.7% (1)	12.6% (47)

What did researchers learn from this trial?

This trial helped researchers learn more about how tremelimumab and durvalumab affect people with advanced HCC.

Researchers look at the results of many trials to decide which treatments work best and are safest. This summary shows only the main results from this one trial. Other trials may provide new information or different results.

At the time this summary was made and approved by the sponsor, further clinical trials with tremelimumab and durvalumab were ongoing.

Where can I learn more about this trial?

You can find more information about this trial on the websites listed below. When a full report of the trial results is available, it can also be found here.

- www.clinicaltrials.gov. Once you are on the website, type **"NCT03298451"** into the **"Other terms"** search box and click **"Search"**.
- www.clinicaltrialsregister.eu. Once you are on the website, click **"Home and Search"**, then type **"2016-005126-11"** in the search box and click **"Search"**.
- www.AstraZenecaClinicalTrials.com. Once you are on the website, type **"D419CC00002"** into the search box and click **"Find a Study"**.

Full Trial Title: A Randomized, Open-label, Multi-center Phase III Study of Durvalumab and Tremelimumab as First-line Treatment in Patients with Advanced Hepatocellular Carcinoma (HIMALAYA)

AstraZeneca Protocol Number: D419CC00002

National Clinical Trials Number: NCT03298451

EudraCT Number: 2016-005126-11

AstraZeneca AB sponsored this trial and has its headquarters in Södertälje, Sweden.

The phone number for the AstraZeneca Information Center is +1-877-240-9479.

Thank you

Clinical trial participants belong to a large community of people who take part in clinical research around the world. They help researchers answer important health questions and find medical treatments for patients.

CISCRP

The Center for Information & Study on Clinical Research Participation (CISCRP) is a non-profit organization focused on educating and informing the public about clinical research participation. CISCRP is not involved in recruiting participants for clinical studies, nor is it involved in conducting clinical studies.

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Version 1.0 2022_08_09