AstraZeneca

Clinical Study Results

Research Sponsor: MedImmune, a wholly owned subsidiary of AstraZeneca

Drugs Studied: Durvalumab, tremelimumab, and bevacizumab

Study Purpose: A study to learn about the safety of durvalumab, tremelimumab, and bevacizumab in participants with advanced liver cancer

Protocol Number: D4190C00022

Thank you

Thank you for taking part in the clinical study for the study drugs durvalumab, tremelimumab, and bevacizumab. Durvalumab is also called MEDI4736.

MedImmune, a wholly owned subsidiary of AstraZeneca, sponsored this study and believes it is important to share the results of the study with the participants and the public. An independent non-profit organization called CISCRP helped prepare this summary of the study results for you.

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

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ABOUT THIS STUDY

Who took part in this study?

The researchers asked for the help of men and women with a type of advanced liver cancer called "hepatocellular carcinoma", also known as "HCC". The participants in this study were 26 to 89 years old when they joined.

The study included 433 participants in China, Hong Kong, Italy, Japan, Singapore, South Korea, Spain, Taiwan, and the United States.

Why was the research needed?

Researchers are looking for a better way to treat people with advanced liver cancer. Before a drug can be approved for people to get, researchers do clinical studies to find out how safe it is and how it works.

In people with cancer, the body is not able to control the growth of some cells. The extra cells can form tumors. "Advanced" cancer usually means that the cancer continues to grow even with treatment.

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

The study drugs, durvalumab and tremelimumab, were designed to boost the immune system's reaction. This helps the immune cells attack the tumor cells again and can stop the tumor from growing or shrink the tumor. Both durvalumab and tremelimumab are immunotherapy drugs, as they affect the immune system.

Tumors also make their own blood vessels, which help the tumors to grow. Another study drug, bevacizumab, helps to stop tumors from making their own blood vessels, which can also stop the tumor from growing or shrink the tumor. In this study, the researchers wanted to find out about the safety of durvalumab, tremelimumab, and bevacizumab in participants with advanced HCC.

What treatments did the participants get?

The participants in this study got 1 or 2 of the following:

- durvalumab
- tremelimumab
- bevacizumab

There were 4 groups in this study. The participants in each group received different treatments at different times and in different places. These groups are:

- Part 1
- Parts 2 and 3
- the China cohort
- Part 4

This summary presents the details and results of each group separately.

What was the purpose of this study?

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

- **What signs and symptoms did the participants have?**
  This includes a summary of the tests and measurements that were done throughout the study, as well as the adverse events that participants had during the study.
- **What medical problems did the participants have during the study?**
  This includes a summary of the medical problems the participants had during the study that the doctors thought might be related to the study drugs.

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

PART 1

Overview of Part 1

What treatments did the participants get during Part 1?

There were 40 participants in Part 1. All of them got durvalumab and tremelimumab for the first 4 treatments, then durvalumab on its own.

What were the results of Part 1?

The main questions the researchers wanted to answer in Part 1 were:

- **What signs and symptoms did the participants have during Part 1?**
  The most common symptom that the participants had during Part 1 was diarrhea. This may or may not have been caused by the study drugs.

- **What medical problems happened during Part 1?**
  In Part 1, 65.0% of participants had medical problems that the study doctors thought might be related to the study drugs. The most common medical problem was fatigue.

More details about the answers to these questions can be found later in this summary.

What treatments did the participants get during Part 1?

Participants could enter Part 1 of the study if they had not had an immunotherapy drug for their HCC before, and had not done well with sorafenib, another treatment commonly used in advanced HCC. There were 40 participants in Part 1. All of the participants got durvalumab and tremelimumab. The participants continued getting study treatment until they left the study or until the study doctors thought it was no longer helping them.

Part 1 was "open-label". Open-label means the participants, researchers, study doctors, and other study staff knew what treatment each participant was getting.

Durvalumab and tremelimumab were each given as an injection into a vein, also called an IV infusion. The doses were measured in milligrams per kilogram of body weight, also known as "mg/kg".

The chart below shows the treatments the researchers planned to study in Part 1.

	Part 1
	40 participants
	• 20 mg/kg of durvalumab • 1 mg/kg of tremelimumab
	• A combination of durvalumab and tremelimumab every 4 weeks for 4 doses • Then, 20 mg/kg of durvalumab once every 4 weeks

What happened during Part 1?

When this summary was made, Part 1 was still ongoing. The participants had been in the study for up to 51 months. Part 1 started in October 2015.

The chart below shows what happened during the study.

Before the participants got study treatment

1 visit

The study doctors:

- made sure the participants could join the study
- did a physical exam and asked about the participants' medications and any medical problems
- checked the participants' heart health using an electrocardiogram, also called an ECG
- took blood and urine samples
- took pictures of the participants' tumors using CT or MRI scans
- used surgery to take a sample of some participants' tumors, also called a biopsy

The participants:

- answered questionnaires about their symptoms

4 weeks

While the participants were getting study treatment

13 visits in the first 25 weeks, then every 4 weeks after that

The study doctors:

- did a physical exam and asked about the participants' medications and any medical problems
- took blood and urine samples
- took pictures of the participants' tumors using CT or MRI scans at some visits

The participants:

- got their study treatment
- answered questionnaires about their symptoms at some visits

Until the study treatments were no longer helping the participants

After the participants got study treatment

Visits once a month for 3 months, then once every 3 months for a year, then once every 6 months after that

At some visits, the study doctors:

- did a physical exam and asked about the participants' medications and any medical problems
- took blood and urine samples
- took pictures of the participants' tumors using CT or MRI scans

The participants:

- answered questionnaires about their symptoms

Until the end of the study

What were the results of Part 1?

This is a summary of the main results from Part 1 overall. The results each participant had might be different and are not in this summary.

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

The websites listed at the end of this summary may have a full report of the study results.

What signs and symptoms did the participants have during Part 1?

To answer this question, the study doctors did tests and measurements throughout Part 1. The doctors did physical exams and tested the participants' blood and urine samples to check their overall health. They also did ECGs to check the participants' heart health. Overall, the researchers found that there were no meaningful changes in the results of these tests and measurements.

The study doctors also kept track of the "adverse events" that the participants had. An adverse event is any sign or symptom that participants have during a study. Doctors keep track of all the adverse events that happen in studies, even if they do not think the adverse events might be related to the study drugs.

This section is a summary of all the adverse events in Part 1. An adverse event is considered "serious" when it is life-threatening, causes lasting problems, or the participant needs hospital care.

Adverse events may or may not be caused by the drugs in the study. A lot of research is needed to know whether a drug causes an adverse event. Later in this document, there will be a summary of the adverse events that the study doctors thought might be related to the study drugs in Part 1.

Summary of adverse events in Part 1

	Part 1 (out of 40 participants)
How many participants had adverse events?	95.0% (38)
How many participants had serious adverse events?	55.0% (22)
How many participants stopped getting study treatment due to adverse events?	12.5% (5)

The most common and serious adverse events that happened in 2 or more participants in Part 1 are listed below. These serious adverse events may or may not be caused by the drugs in the study. This list only includes the serious adverse events that the participants had after they started study treatment.

- reduced brain function caused by liver problems
- build-up of fluid in the abdomen
- inflammation of the large intestine

There were other serious adverse events, but these happened in only 1 participant.

The most common adverse events that happened in 10% or more of participants in Part 1 are listed below. This list only includes the adverse events that the participants had after they started study treatment.

- diarrhea
- fatigue
- itchiness
- increase in a liver protein called ALT
- increase in a liver protein called AST
- breathlessness
- low appetite
- stomach pain
- joint pain
- back pain
- increase in a digestion protein called lipase
- constipation
- build-up of fluid in the abdomen
- difficulty sleeping
- nausea
- vomiting
- fever
- cough
- rash
- decreased weight
- nose and throat infection
- pain in the limbs
- swelling in the arms and legs
- increase in a digestion protein called amylase
- dizziness

What medical problems happened during Part 1?

This section is a summary of the medical problems the participants had during Part 1 that the study doctors thought might be related to the study drugs. 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.

These adverse reactions may or may not be caused by the study drugs. A lot of research is needed to know whether a drug causes an adverse reaction. These adverse reactions have been, and will continue to be, reviewed together with all of the available data for durvalumab and tremelimumab.

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

Did any adverse reactions happen during Part 1?

	Part 1 (out of 40 participants)
How many participants had adverse reactions?	65.0% (26)
How many participants had serious adverse reactions?	17.5% (7)
How many participants stopped getting study treatment due to adverse reactions?	12.5% (5)

What serious adverse reactions happened during Part 1?

The only serious adverse reaction during Part 1 that happened in 2 or more participants was inflammation of the large intestine. This happened in 5% of participants, which was 2 out of 40 participants.

There were other serious adverse reactions, but each of these happened in only 1 participant. No participants died due to serious adverse reactions during Part 1.

What adverse reactions happened during Part 1?

The most common adverse reaction during Part 1 was fatigue.

The table below shows the adverse reactions that happened in 2 or more participants during Part 1. There were other adverse reactions, but each of these

happened in only 1 participant.

Most common adverse reactions in Part 1	
Adverse reaction	**Part 1 (out of 40 participants)**
Fatigue	25.0% (10)
Itchiness	22.5% (9)
Increase in a liver protein called ALT	17.5% (7)
Increase in a liver protein called AST	15.0% (6)
Low appetite	15.0% (6)
Diarrhea	15.0% (6)
Increase in a digestion protein called lipase	12.5% (5)
Rash	10.0% (4)
Vomiting	10.0% (4)
Increase in a digestion protein called amylase	7.5% (3)
Low levels in the blood of a protein called albumin	7.5% (3)
Fever	7.5% (3)
Inflammation of the large intestine	5.0% (2)
Stomach pain	5.0% (2)
Joint pain	5.0% (2)
Night sweats	5.0% (2)
Cough with phlegm	5.0% (2)
Decreased weight	5.0% (2)

PARTS 2 AND 3

Overview of Parts 2 and 3

What treatments did the participants get during Parts 2 and 3?

There were 332 participants in Parts 2 and 3. There were 6 participants who didn't get any treatment. The other 326 participants got 1 of the following:

- durvalumab
- tremelimumab
- a combination of durvalumab and tremelimumab, then durvalumab on its own

What were the results of Parts 2 and 3?

The main questions the researchers wanted to answer in Parts 2 and 3 were:

- **What signs and symptoms did the participants have during Parts 2 and 3?**
  The most common symptom that may or may not be caused by the study drugs that the participants had during Parts 2 and 3 was itchiness.

- **What medical problems happened during Parts 2 and 3?**
  There were 73.3% of participants in Parts 2 and 3 who had medical problems that the study doctors thought might be related to the study drugs during the study. The most common medical problem was itchiness.

More details about the answers to these questions can be found later in this summary.

What treatments did the participants get during Parts 2 and 3?

Participants could enter Parts 2 and 3 of the study if they had not done well with sorafenib, another treatment commonly used in advanced HCC. There were 332 participants in Parts 2 and 3. The participants got durvalumab on its own, tremelimumab on its own, or both durvalumab and tremelimumab. The participants continued getting study treatment until they left the study or until the study doctors thought it was no longer helping them.

Parts 2 and 3 were "open-label". Open-label means the participants, researchers, study doctors, and other study 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.

Durvalumab and tremelimumab were given as an injection into a vein, also called an IV infusion. The doses were measured in milligrams per kilogram of body weight, also known as "mg/kg".

The chart below shows the treatments the researchers planned to study in Parts 2 and 3.

	Group 1	Group 2	Group 3	Group 4
	104 participants	75 participants	69 participants	84 participants
	• 20 mg/kg of durvalumab	• 20 mg/kg of durvalumab • 4 mg/kg of tremelimumab	• 10 mg/kg of tremelimumab	• 20 mg/kg of durvalumab • 1 mg/kg of tremelimumab
	• Once every 4 weeks	• A combination of durvalumab and tremelimumab for 1 dose • Then, 20 mg/kg of durvalumab once every 4 weeks	• Once every 4 weeks for 7 doses, then once every 12 weeks	• A combination of durvalumab and tremelimumab once every 4 weeks for 4 doses • Then, durvalumab once every 4 weeks

What happened during Parts 2 and 3?

When this summary was made, Parts 2 and 3 were still ongoing. The participants had been in the study for up to 43 months. Parts 2 and 3 started in January 2017.

The chart below shows what happened during the study.

Before the participants got study treatment

1 visit

The study doctors:

- made sure the participants could join the study
- did a physical exam and asked about the participants' medications and any medical problems
- checked the participants' heart health using an electrocardiogram, also called an ECG
- took blood and urine samples
- took pictures of the participants' tumors using CT or MRI scans
- used surgery to take a sample of some participants' tumors, also called a biopsy

The participants:

- answered questionnaires about their symptoms

4 weeks

While the participants were getting study treatment

13 visits in the first 25 weeks, then every 4 weeks after that

The study doctors:

- did a physical exam and asked about the participants' medications and any medical problems
- took blood and urine samples
- took pictures of the participants' tumors using CT or MRI scans at some visits

The participants:

- got their study treatment
- answered questionnaires about their symptoms at some visits

Until the study treatments were no longer helping the participants

After the participants got study treatment

Visits once a month for 3 months, then once every 3 months for a year, then once every 6 months after that

At some visits, the study doctors:

- did a physical exam and asked about the participants' medications and any medical problems
- took blood and urine samples
- took pictures of the participants' tumors using CT or MRI scans

The participants:

- answered questionnaires about their symptoms

Until the end of the study

What were the results of Parts 2 and 3?

This is a summary of the main results from Parts 2 and 3 overall. The results each participant had might be different and are not in this summary. There were 332 participants who were planned to get study treatment, but only 326 got treatment. Of the participants who got the study treatments, 101 were in Group 1, 74 were in Group 2, 69 were in Group 3, and 82 were in Group 4.

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

The websites listed at the end of this summary may have a full report of the study results.

What signs and symptoms did the participants have during Parts 2 and 3?

To answer this question, the study doctors did tests and measurements throughout Parts 2 and 3. The doctors did physical exams and tested the participants' blood and urine samples to check their overall health. They also did ECGs to check the participants' heart health. Overall, the researchers found that there were no meaningful changes in the results of these tests and measurements.

The study doctors also kept track of the "adverse events" that the participants had. An adverse event is any sign or symptom that participants have during a study. Doctors keep track of all the adverse events that happen in studies, even if they do not think the adverse events might be related to the study drugs.

Later in this document, there will be a summary of the adverse events that the study doctors thought might be related to the study drugs in Parts 2 and 3. This section is a summary of all the adverse events in Parts 2 and 3, whether they might be related to the study drugs or not. An adverse event is considered "serious" when it is life-threatening, causes lasting problems, or the participant needs hospital care.

Adverse events may or may not be caused by the drugs in the study. A lot of research is needed to know whether a drug causes an adverse event.

Summary of adverse events in Parts 2 and 3

	Group 1 (out of 101 participants)	Group 2 (out of 74 participants)	Group 3 (out of 69 participants)	Group 4 (out of 82 participants)
How many participants had adverse events?	94.1% (95)	98.6% (73)	97.1% (67)	97.6% (80)
How many participants had serious adverse events?	44.6% (45)	43.2% (32)	52.2% (36)	45.1% (37)
How many participants stopped getting study treatment due to adverse events?	13.9% (14)	13.5% (10)	20.3% (14)	14.6% (12)

The most common and serious adverse events that happened in 2 or more participants in any of the treatment groups in Parts 2 and 3 are listed below. This list only includes the serious adverse events that the participants had after they started study treatment.

- abnormal liver function
- diarrhea
- lung infection
- fever
- bleeding from an enlarged vein in the tube between the mouth and stomach
- inflammation of the large intestine
- build-up of fluid in the abdomen
- stomach pain
- liver failure
- sudden damage to the kidneys
- inflammation of the lining of the abdominal cavity, caused by bacteria
- low number of red blood cells
- dehydration
- bleeding in the tube between the mouth and stomach, small intestine, or stomach
- raised level in the blood of bilirubin, a breakdown product of red blood cells
- inflammation of the pituitary gland, a gland that releases hormones into the blood stream
- breathlessness
- clot in a blood vessel in the lungs
- inflammation of the pancreas caused by the body's own defense system
- rash

There were other serious adverse events, but these happened in at most 1 participant in any of the treatment groups.

The most common adverse events that happened in 10% or more of participants in any of the treatment groups in Parts 2 and 3 are listed below. This list only includes the adverse events that the participants had after they started study treatment.

- itchiness
- increase in a liver protein called AST
- fatigue
- rash
- increase in a liver protein called ALT
- diarrhea
- decreased appetite
- stomach pain
- cough
- nausea
- swelling in the arms and legs
- fever
- constipation
- increase in a digestion protein called lipase
- increase in a digestion protein called amylase
- increased level in the blood of a breakdown product of red blood cells called bilirubin
- build-up of fluid in the abdomen
- low levels of thyroid hormones
- joint pain
- low number of red blood cells
- back pain
- increased level in the blood of a liver protein called alkaline phosphatase
- swelling of the abdomen
- breathlessness
- vomiting
- difficulty sleeping
- infection of the nose and throat
- rash with red bumps on a flat, red patch of skin
- headache

What medical problems happened during Parts 2 and 3?

This section is a summary of the medical problems the participants had during Parts 2 and 3 that the study doctors thought might be related to the study drugs. 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.

These adverse reactions may or may not be caused by the study drugs. A lot of research is needed to know whether a drug causes an adverse reaction. These adverse reactions have been, and will continue to be, reviewed together with all of the available data for durvalumab and tremelimumab.

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

Did any adverse reactions happen during Parts 2 and 3?

	Group 1 (out of 101 participants)	Group 2 (out of 74 participants)	Group 3 (out of 69 participants)	Group 4 (out of 82 participants)
How many participants had adverse reactions?	61.4% (62)	82.4% (61)	84.1% (58)	70.7% (58)
How many participants had serious adverse reactions?	10.9% (11)	18.9% (14)	24.6% (17)	15.9% (13)
How many participants stopped getting study treatment due to adverse reactions?	8.9% (9)	12.2% (9)	14.5% (10)	6.1% (5)

What serious adverse reactions happened during Parts 2 and 3?

The most common serious adverse reaction during Parts 2 and 3 was diarrhea.

The table below shows the serious adverse reactions that the study doctors thought might be related to durvalumab or tremelimumab. It shows the serious adverse reactions that happened in 2 or more participants in any group during Parts 2 and 3. There were other serious adverse reactions, but these each happened in only 1 participant in any treatment group.

Most common serious adverse reactions in Parts 2 and 3

Serious adverse reaction	Group 1 (out of 101 participants)	Group 2 (out of 74 participants)	Group 3 (out of 69 participants)	Group 4 (out of 82 participants)
Diarrhea	1.0% (1)	2.7% (2)	8.7% (6)	0.0% (0)
Abnormal liver function	4.0% (4)	0.0% (0)	0.0% (0)	2.4% (2)
Inflammation of the large intestine	0.0% (0)	4.1% (3)	0.0% (0)	1.2% (1)
Inflammation of the pituitary gland, a gland that releases hormones into the blood stream	0.0% (0)	0.0% (0)	2.9% (2)	0.0% (0)
Dehydration	0.0% (0)	2.7% (2)	0.0% (0)	0.0% (0)
Inflammation of the pancreas due to the body's own defence system	0.0% (0)	0.0% (0)	0.0% (0)	2.4% (2)

Of all the participants in Parts 2 and 3:

- 3% of participants in Group 1 died due to a serious adverse reaction. This was 3 out of 101 participants. The serious adverse reactions were inflammation in the lungs, liver failure, and abnormal liver function.
- 2.7% of participants in Group 2 died due to a serious adverse reaction. This was 2 out of 74 participants. One of the serious adverse reactions was lung infection. The other death was unexplained.
- No participants in Group 3 died due to serious adverse reactions.
- 1.2% of participants in Group 4 died due to a serious adverse reaction. This was 1 out of 82 participants. The serious adverse reaction was liver failure.

What adverse reactions happened during Parts 2 and 3?

The most common adverse reaction during Parts 2 and 3 was itchiness.

The table below shows the adverse reactions that happened in 5% or more of participants in any group during Parts 2 and 3. There were other adverse reactions, but these happened in fewer participants.

Most common adverse reactions in Parts 2 and 3				
Adverse reaction	**Group 1 (out of 101 participants)**	**Group 2 (out of 74 participants)**	**Group 3 (out of 69 participants)**	**Group 4 (out of 82 participants)**
Itchiness	11.9% (12)	32.4% (24)	27.5% (19)	15.9% (13)
Low levels of thyroid hormones	10.9% (11)	8.1% (6)	2.9% (2)	9.8% (8)
Diarrhea	8.9% (9)	10.8% (8)	20.3% (14)	12.2% (10)
Fatigue	8.9% (9)	10.8% (8)	17.4% (12)	11.0% (9)
Increase in a liver protein called AST	7.9% (8)	16.2% (12)	14.5% (10)	14.6% (12)
Increased level in the blood of a liver protein called alkaline phosphatase	6.9% (7)	6.8% (5)	1.4% (1)	1.2% (1)
Rash	6.9% (7)	35.1% (26)	21.7% (15)	13.4% (11)
Increase in a liver protein called ALT	5.0% (5)	14.9% (11)	10.1% (7)	9.8% (8)
Nausea	3.0% (3)	2.7% (2)	13.0% (9)	2.4% (2)
Increase in a digestion protein called amylase	2.0% (2)	14.9% (11)	4.3% (3)	7.3% (6)
Rash with red bumps on a flat, red patch of skin	2.0% (2)	2.7% (2)	10.1% (7)	6.1% (5)
Decreased appetite	1.0% (1)	4.1% (3)	7.2% (5)	11.0% (9)
Increase in a digestion protein called lipase	1.0% (1)	12.2% (9)	13.0% (9)	6.1% (5)
High levels of thyroid hormones	1.0% (1)	8.1% (6)	0.0% (0)	4.9% (4)
Stomach pain	0.0% (0)	2.7% (2)	7.2% (5)	4.9% (4)
Inflammation of the large intestine	0.0% (0)	5.4% (4)	1.4% (1)	1.2% (1)
Joint pain	2.0% (2)	0.0% (0)	5.8% (4)	2.4% (2)
Fever	0.0% (0)	6.8% (5)	5.8% (4)	2.4% (2)
Raised level in the blood of bilirubin, a breakdown product of red blood cells	3.0% (3)	5.4% (4)	2.9% (2)	4.9% (4)

CHINA COHORT

Overview of China cohort

Most of the participants in the study from China joined the study later than the participants from the rest of the world during Part 2. This group of participants is known as the "China cohort".

What treatments did the participants get during the China cohort?

There were 14 participants in the China cohort. One participant did not get any study treatment. The other 13 participants got 1 of the following:

- durvalumab
- tremelimumab
- a combination of durvalumab and tremelimumab, then durvalumab on its own

What were the results of the China cohort?

The main questions the researchers wanted to answer in the China cohort were:

- **What signs and symptoms did the participants have during the China cohort?**
  The most common symptom that may or may not be caused by the study drugs that the participants had during the China cohort was an increase in a liver protein called AST.
- **What medical problems happened during the China cohort?**
  There were 84.6% of participants in the China cohort who had medical problems that the study doctors thought might be related to the study drugs during the study. The most common medical problem was an increase in a liver protein called AST.

More details about the answers to these questions can be found later in this summary.

What treatments did the participants get during the China cohort?

Participants could enter the China cohort if they had not done well with sorafenib, another treatment commonly used in advanced HCC. There were 14 participants in the China cohort. All of these participants took part in the study in China. One participant did not get any study treatment. The other 13 participants got durvalumab on its own, tremelimumab on its own, or both durvalumab and tremelimumab.

The participants continued getting study treatment until they left the study or until the study doctors thought it was no longer helping them.

The China cohort was "open-label". This means the participants, researchers, study doctors, and other study 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.

Durvalumab and tremelimumab were each given as an injection into a vein, also called an IV infusion. The doses were measured in milligrams per kilogram of body weight, also known as "mg/kg".

The chart below shows the treatments the researchers planned to study in the China cohort.

	Group 1	Group 2	Group 3
	3 participants	5 participants	5 participants
	• 20 mg/kg of durvalumab	• 10 mg/kg of tremelimumab	• 15–20 mg/kg of durvalumab • 1 mg/kg of tremelimumab
	• Once every 4 weeks	• Once every 4 weeks for 7 doses • Then, once every 12 weeks	• A combination of durvalumab and tremelimumab once every 4 weeks for 4 doses • Then, durvalumab on its own once every 4 weeks

What happened during the China cohort?

The participants were in the study for up to 14 months. The China cohort started in October 2017 and ended in March 2019.

The chart below shows what happened during the study.

Before the participants got study treatment

1 visit

The study doctors:

- made sure the participants could join the study
- did a physical exam and asked about the participants' medications and any medical problems
- checked the participants' heart health using an electrocardiogram, also called an ECG
- took blood and urine samples
- took pictures of the participants' tumors using CT or MRI scans
- used surgery to take a sample of some participants' tumors, also called a biopsy

The participants:

- answered questionnaires about their symptoms

4 weeks

While the participants were getting study treatment

13 visits in the first 25 weeks, then every 4 weeks after that

The study doctors:

- did a physical exam and asked about the participants' medications and any medical problems
- took blood and urine samples
- took pictures of the participants' tumors using CT or MRI scans at some visits

The participants:

- got their study treatment
- answered questionnaires about their symptoms at some visits

Until the study treatments were no longer helping the participants

After the participants got study treatment

Visits once a month for 3 months, then once every 3 months for a year, then once every 6 months after that

At some visits, the study doctors:

- did a physical exam and asked about the participants' medications and any medical problems
- took blood and urine samples
- took pictures of the participants' tumors using CT or MRI scans

The participants:

- answered questionnaires about their symptoms

Until the end of the study

What were the results of the China cohort?

This is a summary of the main results from the China cohort overall. The results each participant had might be different and are not in this summary.

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

The websites listed at the end of this summary may have a full report of the study results.

What signs and symptoms did the participants have during the China cohort?

To answer this question, the study doctors did tests and measurements throughout the China cohort.

The doctors did physical exams and tested the participants' blood and urine samples to check their overall health. They also did ECGs to check the participants' heart health. Overall, the researchers found that there were no meaningful changes in the results of these tests and measurements.

The study doctors also kept track of the "adverse events" that the participants had.

An adverse event is any sign or symptom that participants have during a study. Doctors keep track of all the adverse events that happen in studies, even if they do not think the adverse events might be related to the study drugs.

Later in this document, there will be a summary of the adverse events that the study doctors thought might be related to the study drugs in the China cohort. This section is a summary of all the adverse events in the China cohort, whether they might be related to the study drugs or not. An adverse event is considered "serious" when it is life-threatening, causes lasting problems, or the participant needs hospital care.

Adverse events may or may not be caused by the drugs in the study. A lot of research is needed to know whether a drug causes an adverse event.

Although there were 3 groups in the China Cohort, the adverse events the participants had are presented together, as there were a small number of participants in each group.

Summary of adverse events in the China cohort

	China cohort (out of 13 participants)
How many participants had adverse events?	100% (13)
How many participants had serious adverse events?	61.5% (8)
How many participants stopped getting study treatment due to adverse events?	15.4% (2)

The most common and serious adverse events that happened in 2 or more participants in the China cohort are listed below. This list only includes the serious adverse events that the participants had after they started study treatment.

- abnormal liver function
- build-up of fluid in the abdomen

There were other serious adverse events, but these happened in only 1 participant.

The most common adverse events that happened in over 20% of the participants in the China cohort are listed below. This list only includes the adverse events that the participants had after they started study treatment.

- increase in a liver protein called AST
- increase in a liver protein called ALT
- fever
- low number of red blood cells
- low levels in the blood of a protein called albumin
- swelling of the abdomen
- increased level in the blood of a liver protein called alkaline phosphatase
- infection of the nose and throat
- low levels of thyroid hormones
- decreased appetite
- pain in the upper abdomen
- abnormal liver function
- swelling in the arms and legs

What medical problems happened during the China cohort?

This section is a summary of the medical problems the participants had during the China cohort that the study doctors thought might be related to the study drugs. 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.

These adverse reactions may or may not be caused by the study drugs. A lot of research is needed to know whether a drug causes an adverse reaction. These adverse reactions have been, and will continue to be, reviewed together with all of the available data for durvalumab and tremelimumab.

Although there were 3 groups in the China cohort, the adverse reactions the participants had are presented together, as there were a small number of participants in each group.

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

Did any adverse reactions happen during the China cohort?	
	China cohort (out of 13 participants)
How many participants had adverse reactions?	84.6% (11)
How many participants had serious adverse reactions?	30.8% (4)
How many participants stopped getting study treatment due to adverse reactions?	7.7% (1)

What serious adverse reactions happened during the China cohort?

The only serious adverse reaction during the China cohort that happened in 2 or more participants was abnormal liver function. This happened in 15.4% of participants, which was 2 out of 13 participants.

There were other serious adverse reactions, but each of these happened in only 1 participant. No participants died due to serious adverse reactions during the China cohort.

What adverse reactions happened during the China cohort?

The most common adverse reaction during the China cohort was an increase in the level of a liver protein called AST.

The table below shows the adverse reactions that happened in 2 or more participants during the China cohort. There were other adverse reactions, but each of these happened in only 1 participant.

Adverse reaction	China cohort (out of 13 participants)
Increase in a liver protein called AST	38.5% (5)
Increase in a liver protein called ALT	30.8% (4)
Fever	23.1% (3)
Cough	15.4% (2)

PART 4

Overview of Part 4

What treatments did the participants get during Part 4?

There were 47 participants in Part 4. All of them got durvalumab and bevacizumab.

What were the results of Part 4?

The main questions the researchers wanted to answer in Part 4 were:

- **What signs and symptoms did the participants have during Part 4?**
  The most common symptom that may or may not be caused by the study drugs that the participants had during Part 4 was decreased appetite.
- **What medical problems happened during Part 4?**
  There were 70.2% of participants in Part 4 who had medical problems that the study doctors thought might be related to the study drugs during the study. The most common medical problem was high levels of protein in the urine.

More details about the answers to these questions can be found later in this summary.

What treatments did the participants get during Part 4?

Participants could enter Part 4 of the study if they had not had any therapy that works throughout the whole body, also called a systemic therapy, for their HCC before. There were 47 participants in Part 4. All of the participants got durvalumab and bevacizumab. The participants continued getting study treatment until they left the study or until the study doctors thought it was no longer helping them.

Part 4 was "open-label". This means the participants, researchers, study doctors, and other study staff knew what each participant was getting.

Durvalumab and bevacizumab were each given as an injection into a vein, also called an IV infusion. The doses were measured in milligrams per kilogram of body weight, also known as "mg/kg".

The chart below shows the treatments the researchers planned to study in Part 4.

	Part 4
	47 participants
	• 15 mg/kg of durvalumab • 15 mg/kg of bevacizumab
	Once every 3 weeks

What happened during Part 4?

When this summary was made, Part 4 was still ongoing. The participants had been in the study for up to 17 months. Part 4 started in April 2019.

The chart below shows what happened during the study.

Before the participants got study treatment

1 visit

The study doctors:

- made sure the participants could join the study
- did a physical exam and asked about the participants' medications and any medical problems
- checked the participants' heart health using an electrocardiogram, also called an ECG
- took blood and urine samples
- took pictures of the participants' tumors using CT or MRI scans
- used surgery to take a sample of some participants' tumors, also called a biopsy

The participants:

- answered questionnaires about their symptoms

4 weeks

While the participants were getting study treatment

13 visits in the first 25 weeks, then every 3 weeks after that

The study doctors:

- did a physical exam and asked about the participants' medications and any medical problems
- took blood and urine samples
- took pictures of the participants' tumors using CT or MRI scans at some visits

The participants:

- got their study treatment
- answered questionnaires about their symptoms at some visits

Until the study treatments were no longer helping the participants

After the participants got study treatment

Visits once a month for 3 months, then once every 3 months for a year, then once every 6 months after that

At some visits, the study doctors:

- did a physical exam and asked about the participants' medications and any medical problems
- took blood and urine samples
- took pictures of the participants' tumors using CT or MRI scans

The participants:

- answered questionnaires about their symptoms

Until the end of the study

What were the results of Part 4?

This is a summary of the main results from Part 4 overall. The results each participant had might be different and are not in this summary.

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

The websites listed at the end of this summary may have a full report of the study results.

What signs and symptoms did the participants have during Part 4?

To answer this question, the study doctors did tests and measurements throughout Part 4. The doctors did physical exams and tested the participants' blood and urine samples to check their overall health. They also did ECGs to check the participants' heart health. Overall, the researchers found that there were no meaningful changes in the results of these tests and measurements.

The study doctors also kept track of the "adverse events" that the participants had. An adverse event is any sign or symptom that participants have during a study. Doctors keep track of all the adverse events that happen in studies, even if they do not think the adverse events might be related to the study drugs.

Later in this document, there will be a summary of the adverse events that the study doctors thought might be related to the study drugs. This section is a summary of all the adverse events, whether they might be related to the study drugs or not. An adverse event is considered "serious" when it is life-threatening, causes lasting problems, or the participant needs hospital care.

Adverse events may or may not be caused by the drugs in the study. A lot of research is needed to know whether a drug causes an adverse event.

Summary of adverse events in Part 4

	Part 4 (out of 47 participants)
How many participants had adverse events?	95.7% (45)
How many participants had serious adverse events?	36.2% (17)
How many participants stopped getting study treatment due to adverse events?	10.6% (5)

The most common and serious adverse events that happened in 2 or more participants in Part 4 are listed below. This list only includes the serious adverse events that the participants had after they started study treatment.

- brain damage caused by liver problems
- build-up of fluid in the abdomen
- joint pain
- fever

There were other serious adverse events, but these happened in only 1 participant.

The most common adverse events that happened in 10% or more of participants in Part 4 are listed below. This list only includes the adverse events that the participants had after they started study treatment.

- decreased appetite
- high levels of protein in the urine
- fatigue
- diarrhea
- stomach pain
- joint pain
- high blood pressure
- nosebleed
- build-up of fluid in the abdomen
- back pain
- increase in a liver protein called AST
- difficulty sleeping
- headache
- constipation
- indigestion
- nausea
- rash
- swelling of the arms and legs
- reduced levels of blood cells that help form clots

What medical problems happened during Part 4?

This section is a summary of the medical problems the participants had during Part 4 that the study doctors thought might be related to the study drugs. 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.

These adverse reactions may or may not be caused by the study drugs. A lot of research is needed to know whether a drug causes an adverse reaction. These adverse reactions have been, and will continue to be, reviewed together with all of the available data for durvalumab and bevacizumab.

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

Did any adverse reactions happen during Part 4?	
	Part 4 (out of 47 participants)
How many participants had adverse reactions?	70.2% (33)
How many participants had serious adverse reactions?	10.6% (5)
How many participants stopped getting study treatment due to adverse reactions?	6.4% (3)

What serious adverse reactions happened during Part 4?

There were no serious adverse reactions that happened in 2 or more participants during Part 4. There were some serious adverse reactions, but each of these happened in only 1 participant. No participants died due to serious adverse reactions during Part 4.

What adverse reactions happened during Part 4?

The most common adverse reaction during Part 4 was high levels of protein in the urine.

The table below shows the adverse reactions that happened in 5% or more of participants during Part 4. There were other adverse reactions, but they happened in fewer participants.

Adverse reaction	Part 4 (out of 47 participants)
High levels of protein in the urine	23.4% (11)
Fatigue	10.6% (5)
Diarrhea	10.6% (5)
Decreased appetite	8.5% (4)
High blood pressure	8.5% (4)
Changes in the sound of the voice	8.5% (4)
Low levels of thyroid hormones	6.4% (3)
Itchiness	6.4% (3)
Rash	6.4% (3)

MORE INFORMATION

How has this study helped patients and researchers?

This study helped researchers learn more about the safety of durvalumab, tremelimumab, and bevacizumab in participants with advanced HCC.

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

Further clinical studies with durvalumab, tremelimumab, and bevacizumab are ongoing.

Where can I learn more about this study?

You can find more information about this study on the websites listed below. If more information about the study results is available, it can also be found here.

- www.clinicaltrials.gov. Once you are on the website, type **"NCT02519348"** into the search box and click **"Search"**.
- www.AstraZenecaClinicalTrials.com. Once you are on the website, type **"D4190C00022"** into the search box, and click **"Find a Study"**.

Full Study Title: A Study of Durvalumab or Tremelimumab Monotherapy, or Durvalumab in Combination With Tremelimumab or Bevacizumab in Advanced Hepatocellular Carcinoma

AstraZeneca AB Protocol Number: D4190C00022

National Clinical Trials Number: NCT02519348

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

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

Thank you

Clinical study 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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