AstraZeneca

Clinical Study Results

Research Sponsor: AstraZeneca

Drug Studied: Durvalumab and tremelimumab

Study Purpose: This study was done to learn if durvalumab alone or together with tremelimumab is safe and effective at treating participants with advanced head and neck cancer

Protocol Number: D419LC00001

Thank you

Thank you for taking part in the clinical study for the study drugs durvalumab and tremelimumab.

All of the participants helped researchers learn more about how durvalumab and tremelimumab may be able to help people with advanced head and neck cancer. This type of cancer is known as head and neck squamous cell carcinoma, also called HNSCC.

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. We hope it helps the participants, their families, and caregivers understand and feel proud of their important role in medical research.

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

Overview of this study

Why was the research needed?

Researchers are looking for a better way to treat HNSCC that has come back after treatment or has spread to other parts of the body. The participants' cancer could also not be cured by surgery or radiation therapy. Before a drug can be approved for people to use as standard treatment, researchers do clinical studies to find out how safe it is and if it is effective.

What treatments did the participants get?

The participants in this study got either:

- Durvalumab with tremelimumab
- Durvalumab alone
- Standard treatment for HNSCC

What were the results of this study?

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

- **Did durvalumab help the participants with PD-L1 high cancer live longer than standard treatment?**

  The researchers wanted to learn more about how durvalumab affected participants with a specific type of HNSCC called PD-L1 high cancer. People with "PD-L1 high cancer" have a large amount of a protein called PD-L1 on the outside of their tumour cells.

  Overall, the researchers found that the participants with PD-L1 high cancer who got durvalumab alone did not live longer compared with the participants who got standard treatment.

- **Did the participants getting durvalumab with or without tremelimumab have less severe symptoms and improved health-related quality of life?**

  The researchers found that the participants who got durvalumab with tremelimumab reported having less nausea and mouth pain than the participants who got the standard treatment. They also found that the participants who got durvalumab with or without tremelimumab had fewer problems with their taste and sense of smell than the participants who got standard treatment. There were no other differences in symptoms between the groups.

What medical problems did the participants have during this study?

Medical problems that the study doctors thought might be related to the treatments the participants got during the study are called "adverse reactions".

- There were 60.3% of participants who got durvalumab with tremelimumab who had adverse reactions during the study. This was 246 out of 408 participants.
- There were 45.5% of participants who got durvalumab alone who had adverse reactions during the study. This was 92 out of 202 participants.
- There were 93.9% of participants who got standard treatment who had an adverse reaction during this study. This was 184 out of 196 participants.

The most common adverse reaction was a rash.

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

Where can I learn more about this study?

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

Who took part in the study?

The researchers asked for the help of people with advanced HNSCC whose cancer had:

- been treated and come back and/or
- spread to other parts of the body

The participants' cancer could not be cured by surgery or radiation therapy.

The participants had not previously had durvalumab, treatments that worked in a similar way to durvalumab, or chemotherapy for their cancer after it had come back or spread. The men and women in this study were 22 to 89 years old when they joined.

The study included a total of 823 participants in Austria, Belgium, Brazil, Canada, France, Germany, Greece, India, Italy, Japan, the Philippines, Poland, Romania, Russia, Slovakia, South Korea, Spain, Taiwan, Thailand, Ukraine, the United Kingdom, the United States, and Vietnam.

Why was the research needed?

Researchers are looking for a better way to treat advanced HNSCC. Before a drug can be approved for people to use as a standard treatment, researchers do clinical studies to find out how effective and safe it is. Researchers already did studies that showed durvalumab reduced the size of tumours and helped the participants with lung cancer who were in those studies live longer.

When this study started, the researchers wanted to find out if durvalumab and tremelimumab together worked in a large number of participants with HNSCC. They also wanted to find out if the participants had any adverse reactions during the study. After this study had started, another study showed that durvalumab and tremelimumab together were not any more effective for most participants with HNSCC than durvalumab by itself. Because of this new information, the researchers updated the goal of this study to measure how well durvalumab alone worked in participants with HNSCC. Even though the goal of the study changed, the researchers continued to collect information about how well tremelimumab works, how safe it is and about how the participants felt while they were getting it.

In people with cancer, the body is not able to control the growth of cells. The extra cells can form tumours. When cancer progresses to a late stage, tumours spread to other parts of the body or grow beyond the organ where they started. Sometimes the tumours 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 tumours from growing. But, in people with head and neck cancer, the proteins on the tumour cells can interact with certain proteins on the immune cells. This may stop the immune cells from being able to attack the tumour cells.

The study drugs, durvalumab and tremelimumab, were designed to boost the immune system's reaction. This helps the immune cells attack the tumour cells again and can stop the tumour from growing or shrink the tumour.

In this study, the researchers wanted to learn how durvalumab alone or with tremelimumab works in a large number of participants. The participants had advanced HNSCC that had come back after treatment or had spread and could not be removed by surgery. The researchers in this study wanted to compare durvalumab with and without tremelimumab to standard treatments. They also wanted to find out if the participants had any adverse reactions during the study.

What was the purpose of this study?

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

- Did durvalumab help the participants with PD-L1 high cancer live longer than standard treatment?
- Did the participants getting durvalumab with or without tremelimumab have less severe symptoms and improved health related quality of life?
- What medical problems did the participants have during the study?

The answers to these questions are important to know to find out if durvalumab with or without tremelimumab is safe and effective at treating people with advanced HNSCC.

What treatments did the participants get?

In this study, the participants got either:

- Durvalumab with tremelimumab
- Durvalumab alone
- Standard treatment for HNSCC

Each treatment was given through a needle into a vein. This is called an intravenous infusion, also known as an IV infusion.

The doses of durvalumab and tremelimumab were measured in milligrams, also known as mg.

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

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

The chart below shows the treatments the participants got.

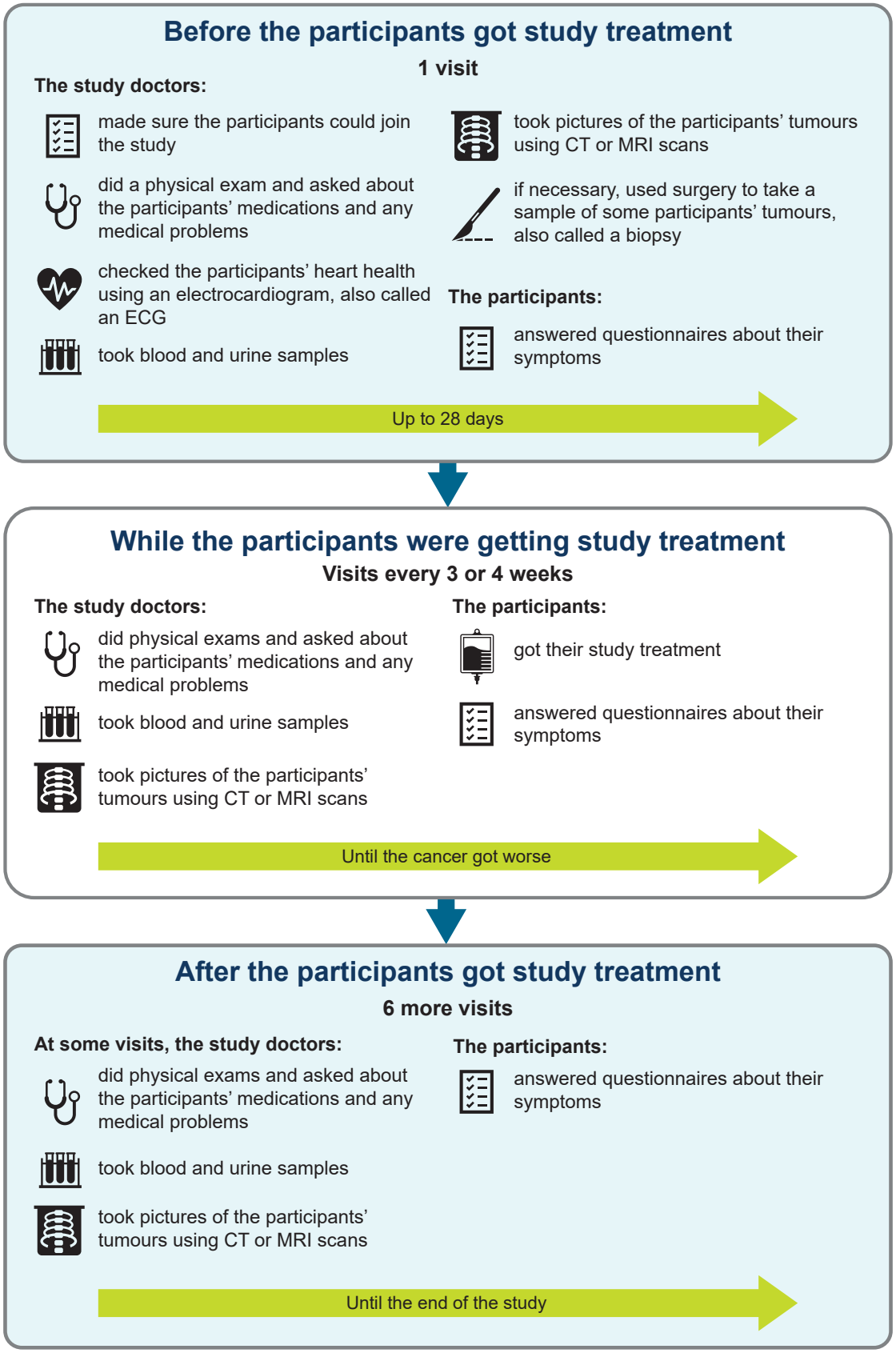
Group	Treatments and doses
Durvalumab with tremelimumab (413 participants)	• 1,500 mg of durvalumab and 75 mg of tremelimumab • Every 4 weeks, 4 doses total **then** • 1,500 mg of durvalumab • Every 4 weeks
Durvalumab alone (204 participants)	• 1,500 mg of durvalumab • Every 4 weeks
Standard treatment for HNSCC (206 participants)	• Chosen by the study doctor • Cisplatin, fluorouracil, and cetuximab **or** • Carboplatin, fluorouracil, and cetuximab • Standard doses • 6 or more treatment cycles where each cycle lasts for 3 weeks

What happened during the study?

The participants were in the study until their cancer got worse, the study doctors thought they should stop study treatment, or they left for another reason. The entire study took over 5 years.

The study started in October 2015 and ended in May 2021.

The chart below shows what happened during the study.



What were the results of the study?

This is a summary of the main results from this study overall. The results each participant had 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 study results is available, it can also be found on these websites.

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.

Did durvalumab alone help the participants with PD-L1 high cancer live longer than standard treatment?

The researchers wanted to know how durvalumab alone affected participants with a certain type of HNSCC called PD-L1 high cancer. People with this type of cancer have a large amount of the PD-L1 protein on their tumour cells. Durvalumab works by attaching to PD-L1 proteins on tumour cells. This lets the immune cells attack the tumour cells again and helps stop the tumour from growing.

For this question, the researchers looked only at the participants who had PD-L1 high cancer. Of these participants, there were 99 who got durvalumab and 94 who got the standard treatment.

There were 190 participants who got durvalumab and tremelimumab, but their results are not included in this section. This is because the main goal of the study changed after it had started. The new main goal was to focus on how effective durvalumab alone was in this group of participants, rather than how effective durvalumab and tremelimumab were together. There are some links on the last page of this summary where you can find more information about the results of these participants.

Overall, the researchers found that in the participants who had PD-L1 high cancer, the participants who got durvalumab alone and those who got the standard treatment lived for about the same amount of time after starting treatment.

The researchers used several methods to answer this question. First the researchers used a statistical test called a "hazard ratio". The hazard ratio shows how long the participants who got durvalumab survived compared with the participants who got standard treatment. A hazard ratio of 1.0 means that there is no difference between the groups in how long the participants survived.

In this study, the hazard ratio was 0.96. This means that the participants who got durvalumab survived for a similar amount of time as the participants who got standard treatment.

The researchers also counted how many months the participants lived with their cancer after getting study treatment. They calculated the median number of months for each group. A median is the middle number in a set of numbers. It is between the lowest and highest numbers. In this study, the median shows the point in time when 50% of participants were still alive in the study.

The median number of months that the participants with PD-L1 high cancer lived for after starting study treatment was:

- 10.9 months for the participants who got durvalumab alone
- 10.9 months for the participants who got the standard treatment

Did the participants getting durvalumab with or without tremelimumab have less severe symptoms and improved health-related quality of life?

To answer this question, the study 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 – Head and Neck 35, also known as EORTC QLQ-H&N35

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 study. They then compared the scores of the participants who got durvalumab with or without tremelimumab to those who got standard treatment.

The EORTC QLQ-C30 questionnaire showed that the participants who got durvalumab with tremelimumab had less nausea than those who got standard treatment. There were no differences in the other symptoms, ability to do daily tasks, or quality of life as measured by this questionnaire in the participants who got durvalumab alone, durvalumab with tremelimumab, or standard treatment.

The EORTC QLQ-H&N35 questionnaire showed that:

- The participants who got durvalumab with tremelimumab had less mouth pain than those who got standard treatment.
- The participants who got durvalumab with or without tremelimumab had fewer problems with their sense of smell and taste than those who got standard treatment.
- There were no differences in the other symptoms measured by this questionnaire in the participants who got durvalumab alone, durvalumab with tremelimumab or standard therapy.

What medical problems happened during this study?

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

These adverse reactions may or may not be caused by the study treatments. A lot of research is needed to know whether a treatment 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 "adverse events" that happened during this study. 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 treatment. Adverse events may or may not be caused by the treatments in the study.

There were 17 participants who did not get any doses of study treatment. The results below are for the 806 participants who got at least 1 dose of study treatment.

Did any adverse reactions happen during this study?

	Durvalumab with tremelimumab (out of 408 participants)	**Durvalumab alone** (out of 202 participants)	**Standard treatment** (out of 196 participants)
How many participants had adverse reactions?	60.3% (246)	45.5% (92)	93.9% (184)
How many participants had serious adverse reactions?	14.5% (59)	7.4% (15)	23.5% (46)
How many participants stopped getting study treatment due to adverse reactions?	6.9% (28)	2.5% (5)	23.5% (46)

What serious adverse reactions happened during this study?

The most common serious adverse reaction was diarrhoea. The table below shows the serious adverse reactions that happened in 1.0% or more of participants in any group during the study. There were other serious adverse reactions, but these happened in fewer participants.

Most common serious adverse reactions

Serious adverse reaction	Durvalumab with tremelimumab (out of 408 participants)	Durvalumab alone (out of 202 participants)	Standard treatment (out of 196 participants)
Diarrhoea	1.5% (6)	0.5% (1)	2.0% (4)
Lung inflammation	1.7% (7)	1.0% (2)	0.5% (1)
Inflammation of the large intestine	1.0% (4)	0.0% (0)	0.0% (0)
Rash	0.0% (0)	1.0% (2)	0.0% (0)
Fever and very low numbers of a type of white blood cell called neutrophils	0.0% (0)	0.0% (0)	3.6% (7)
Very low numbers of a type of white blood cell called neutrophils	0.2% (1)	0.2% (1)	2.6% (5)
Decreased numbers of blood cells that help form blood clots	0.0% (0)	0.0% (0)	2.0% (4)
Inflammation of the bowel wall	0.0% (0)	0.0% (0)	2.0% (4)
Allergic reaction	0.0% (0)	0.0% (0)	1.5% (3)
Life-threatening reaction to an infection	0.0% (0)	0.0% (0)	1.5% (3)
Fever and a loss of red bone marrow	0.0% (0)	0.0% (0)	1.0% (2)
Very low numbers of a type of white blood cell called leucocytes	0.0% (0)	0.0% (0)	1.0% (2)
Low levels of magnesium in the blood	0.0% (0)	0.0% (0)	1.0% (2)
Vomiting	0.5% (2)	0.0% (0)	1.0% (2)
Pain at the injection site	0.0% (0)	0.0% (0)	1.0% (2)

There were 1.4% of participants who died because of adverse reactions. This was 11 out of 806 participants.

- 2.0% of participants who got durvalumab with tremelimumab died because of a serious adverse reaction. This was 8 out of 408 participants.
- 0.5% of participants who got durvalumab alone died because of a serious adverse reaction. This was 1 out of 202 participants.
- 1.0% of participants who got standard treatment died because of a serious adverse reaction. This was 2 out of 196 participants.

What adverse reactions happened during this study?

There were 64.8% of participants who had adverse reactions during this study. This was 522 out of 806 participants. The most common adverse reaction was a rash.

The table below shows the adverse reactions that happened in 5.0% or more of the participants who got durvalumab alone or with tremelimumab or in 20.0% or more of participants who got standard treatment during the study. There were other adverse reactions, but these happened in fewer participants.

Most common adverse reactions			
Adverse reaction	**Durvalumab with tremelimumab** (out of 408 participants)	**Durvalumab alone** (out of 202 participants)	**Standard treatment** (out of 196 participants)
Rash	8.6% (35)	6.9% (14)	37.8% (74)
Fatigue	7.1% (29)	10.4% (21)	21.4% (42)
Diarrhoea	11.3% (46)	2.0% (4)	23.0% (45)
Nausea	4.4% (18)	3.0% (6)	34.7% (68)
An underactive thyroid	11.3% (46)	6.9% (14)	0.0% (0)
Itching	7.4% (30)	3.0% (6)	6.6% (13)
Feeling weak and lacking energy	5.9% (24)	4.5% (9)	15.8% (31)
Very low numbers of a type of white blood cell called neutrophils	0.5% (2)	0.5% (1)	30.1% (59)
Anaemia	2.5% (10)	2.0% (4)	27.0% (53)
Inflammation of the bowel wall	1.5% (6)	1.5% (1)	21.4% (42)
Decreased appetite	2.9% (12)	3.0% (6)	20.4% (40)

How has this study helped patients and researchers?

This study helped researchers learn more about whether durvalumab with or without tremelimumab worked in participants with advanced HNSCC.

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 and tremelimumab in other cancers are ongoing and planned.

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 **"NCT02551159"** into the search box and click **"Search"**.
- www.clinicaltrialsregister.eu. Once you are on the website, click **"Home and Search"**, then type **"2015-003589-10"** in the search box and click **"Search"**.
- www.AstraZenecaClinicalTrials.com. Once you are on the website, type **"D419LC00001"** into the search box, and click **"Find a Study"**.

Full Study Title: A Phase III Randomized, Open-label, Multi-centre, Global Study of Durvalumab Alone or in Combination with Tremelimumab versus Standard of Care in the Treatment of First-line Recurrent or Metastatic Squamous Cell Head and Neck Cancer Patients – (KESTREL)

AstraZeneca Protocol Number: D419LC00001

National Clinical Trials Number: NCT02551159

AstraZeneca sponsored this study and has its headquarters at Cambridge, UK.

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

Thank you

Clinical study participants and their families 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_2021_10_27