CLINICAL TRIAL RESULTS

This summary reports the results of only one study. Researchers must look at the results of many types of studies to understand if a study medicine works, how it works, and if it is safe to prescribe to patients. The results of this study might be different than the results of other studies that the researchers review.

Sponsor: Pfizer, Inc.

This trial was sponsored by Pfizer as part of an alliance with Merck KGaA, Darmstadt, Germany.

Medicine(s) Studied: Avelumab/PF-06834635/MSB0010718C

Protocol Number: B9991016

Dates of Trial: 28 November 2016 to 23 December 2019

Title of this Trial: Study to compare avelumab in combination with standard of care chemoradiotherapy (SoC CRT) versus SoC CRT for definitive treatment in patients with locally advanced squamous cell carcinoma of the head and neck (JAVELIN HEAD AND NECK 100)

[A randomized double-blind phase 3 study of avelumab in combination with standard of care chemoradiotherapy (cisplatin plus definitive radiation therapy) versus standard of care chemoradiotherapy in the front-line treatment of patients with locally advanced squamous cell carcinoma of the head and neck]

Date of this Report: 9 September 2020

– Thank You –

Pfizer, the Sponsor, would like to thank you for your participation in this clinical trial and provide you a summary of results representing everyone who participated. If you

090177e194de21a3\Approved\Approved On: 10-Sep-2020 10:17 (GMT)

have any questions about the study or results, please contact the doctor or staff at your study site.

WHY WAS THIS STUDY DONE?

Squamous cell carcinoma is a type of cancer that originates in the squamous cells, which are flat cells that line the outer layer of the skin and the mouth, nose, and throat. Squamous cell carcinoma is the most common type of cancer found in the head and neck.

Researchers are looking for treatments for squamous cell carcinoma of the head and neck. Avelumab is a medicine that may work by targeting a protein called "Programmed Death-Ligand 1" (PD-L1) found on the cancer cell. PD-L1 is involved in the body's immune system response to cancer.

When this study was started, avelumab was being tested for use in patients with locally advanced squamous cell carcinoma of the head and neck. Locally advanced refers to cancer that has spread to nearby body tissues. Although avelumab is approved in other types of cancer, it is not approved for use in head and neck cancer.

The standard treatment for squamous cell carcinoma of the head and neck includes a combination of radiation therapy and a chemotherapy medicine called cisplatin.

The main goal of this study was to determine if adding a new drug (avelumab) before, during, and after standard treatment would increase the amount of time it takes for cancer to worsen (progress). The study also evaluated the overall safety of avelumab in combination with standard radiation and chemotherapy treatment.

WHAT HAPPENED DURING THE STUDY?

This study included 2 groups of patients taking either:

- standard radiation and chemotherapy treatment plus avelumab
- standard radiation and chemotherapy treatment plus placebo

A placebo does not have any medicine in it, but it looks just like the study medicine and is given the same way.

090177e194de21a3\Approved\Approved On: 10-Sep-2020 10:17 (GMT)

The study included adult patients who:

- had squamous cell cancer of the head and neck (in the mouth or throat) that was locally advanced
- had cancer that was likely to spread or come back after treatment
- were appropriate to receive standard radiation and chemotherapy treatment with cisplatin
- had not yet received treatment for their cancer
- had adequate liver, kidney, and bone marrow function

The patients and researchers did not know who took avelumab and who took the placebo. This is known as a "double-blinded" study.

Potential patients were evaluated by the study doctor to make sure they met the criteria to participate in the study. This was known as the "screening period". Next, eligible patients were randomly assigned to 1 of 2 treatment groups:

- Group A (350 patients): Standard radiation and chemotherapy treatment plus avelumab
- Group B (347 patients): Standard radiation and chemotherapy treatment plus placebo

Patients were assigned to each group by chance. Putting people into groups by chance is called randomization. This helps make it more likely that the groups will be more even to compare before they start receiving the study treatments.

Avelumab and placebo were given by intravenous (IV) infusion (a needle into a vein). The study included 3 treatment phases:

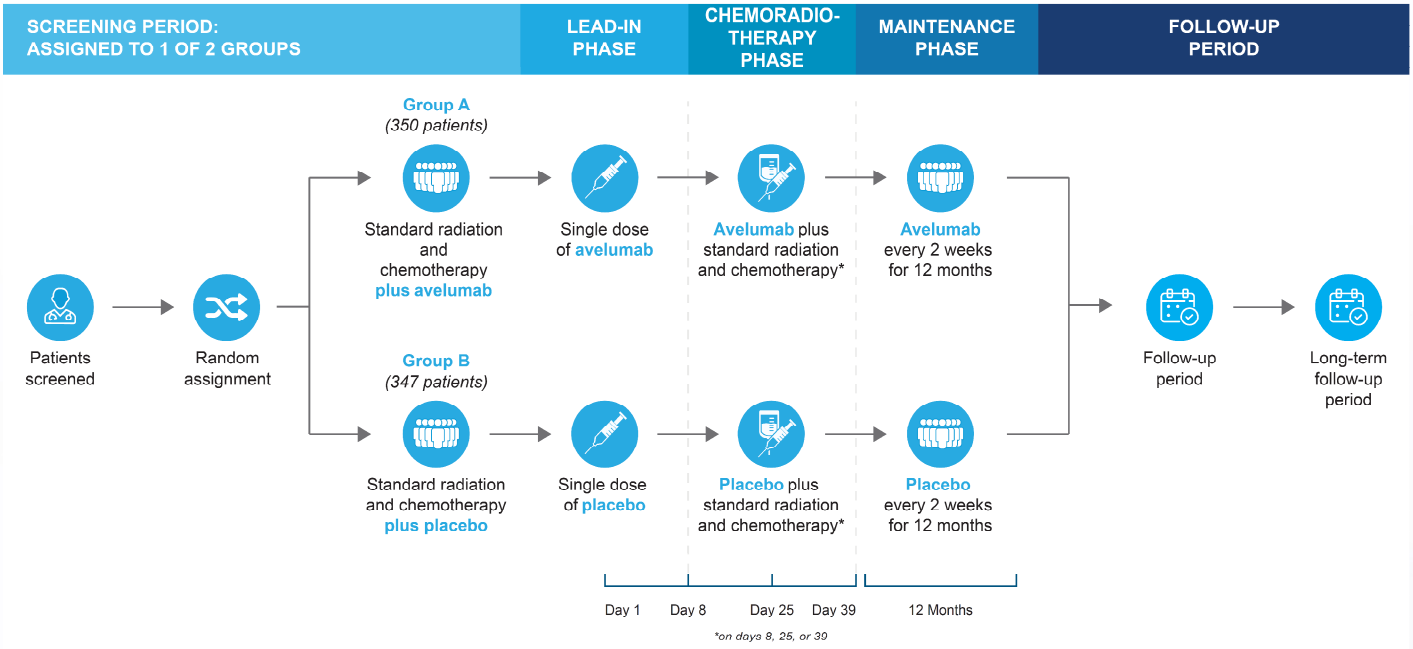
- 7-day Lead-In Phase: Patients received a single dose of avelumab or placebo on day 1
- Chemoradiotherapy Phase: Patients received avelumab or placebo on Days 8, 25, or 39 plus standard radiation and chemotherapy treatment
- Maintenance Phase: Patients received avelumab or placebo every 2 weeks for up to 12 months

090177e194de21a3\Approved\Approved On: 10-Sep-2020 10:17 (GMT)

Maintenance treatment means a treatment that is given to stop cancer from coming back after it has been treated in the initial phase.

After the last dose of maintenance treatment, there was a 90-day follow-up period that included regular safety assessments. There was a long-term follow-up period, which lasted until patients left the study or the study ended.

The figure below shows what happened during this study.



Patients were expected to be on treatment for about 15 months, but the entire study lasted about 3 years. The sponsor ran this study at 196 locations in 22 countries in Asia, Australia, Europe, and North America. The first patient was enrolled on 12 December 2016. 575 men (82%) and 122 women (18%) joined the study. Patients in the study were between the ages of 26 and 86.

Patients were expected to complete the lead-in, chemoradiotherapy, maintenance, and follow-up phases of the study. The tables below show how many patients completed treatment phases and how many patients did not complete treatment phases either by their choice or because a doctor decided it was best for a patient to stop being in the study.

090177e194de21a3\Approved\Approved On: 10-Sep-2020 10:17 (GMT)

Lead-In Phase
Group A: Out of 350 patients: • 345 (99%) completed treatment • 5 patients (1%) stopped taking study treatment early • The most common reasons for stopping study treatment were medical problems or patient choice
Group B: Out of 347 patients: • 343 (99%) completed treatment • 4 patients (1%) stopped taking study treatment early • The most common reasons for stopping study treatment were patient death, patient no longer met criteria to participate, or patient choice

Chemoradiotherapy Phase
Group A: Out of 345 patients who entered chemoradiotherapy phase: • 312 (90%) completed treatment with avelumab • 33 patients (10%) stopped taking avelumab early • 234 patients (68%) completed treatment with cisplatin and 322 patients (93%) completed radiation therapy • 111 patients (32%) stopped taking cisplatin early and 23 patients (7%) stopped radiation therapy early • The most common reasons for stopping study treatment were medical problems, patient death, patient choice, or a doctor decided it was best for a patient to stop treatment
Group B: Out of 340 patients who entered chemoradiotherapy phase: • 313 (92%) completed treatment with placebo • 27 patients (8%) stopped taking placebo early

090177e194de21a3\Approved\Approved On: 10-Sep-2020 10:17 (GMT)

- 236 patients (69%) completed treatment with cisplatin and 320 patients (94%) completed radiation therapy
- 104 patients (31%) stopped taking cisplatin early and 20 patients (6%) stopped radiation therapy early
- The most common reasons for stopping study treatment were medical problems, patient death, patient choice, or a doctor decided it was best for a patient to stop treatment

Maintenance Phase
Group A: Out of 291 patients who entered maintenance phase: • 149 patients (51%) stopped maintenance therapy early • 107 patients (37%) completed maintenance therapy • 35 patients (12%) were still under observation at the time of the data cutoff • The most common reasons for stopping maintenance therapy early were medical problems, worsening cancer, patient death, patient choice, or a doctor decided it was best for a patient to stop treatment
Group B: Out of 304 patients who entered maintenance phase: • 119 patients (39%) stopped maintenance therapy early • 137 patients (45%) completed maintenance therapy • 48 patients (16%) were still under observation at the time of the data cutoff • The most common reasons for stopping maintenance therapy early were medical problems, worsening cancer, patient death, patient choice, or a doctor decided it was best for a patient to stop treatment

090177e194de21a3\Approved\Approved On: 10-Sep-2020 10:17 (GMT)

Follow-Up Phases
Group A: Out of 231 patients who entered the 90-day follow-up phase: • 172 patients (74%) completed this phase • 24 patients (10%) left this phase early • 35 patients (15%) were still under observation at the time of the data cutoff • The most common reasons for stopping the follow-up phase early were patient death or patient choice Out of 209 patients who entered the long-term follow-up phase: • 43 patients (21%) left this phase early • 166 patients (79%) were still under observation at the time of the data cutoff • The most common reasons for stopping the long-term follow-up phase early were patient death or patient choice
Group B: Out of 236 patients who entered the 90-day follow-up phase: • 179 patients (76%) completed this phase • 18 patients (8%) left this phase early • 39 patients (17%) were still under observation at the time of the data cutoff • The most common reasons for stopping the follow-up phase early were patient death or patient choice Out of 201 patients who entered the long-term follow-up phase: • 29 patients (14%) left this phase early • 172 patients (86%) were still under observation at the time of the data cutoff • The most common reasons for stopping the long-term follow-up phase early were patient death or patient choice

In March 2020, the Sponsor began reviewing the information collected. The Sponsor then created a report of the results. This is a summary of that report.

090177e194de21a3\Approved\Approved On: 10-Sep-2020 10:17 (GMT)

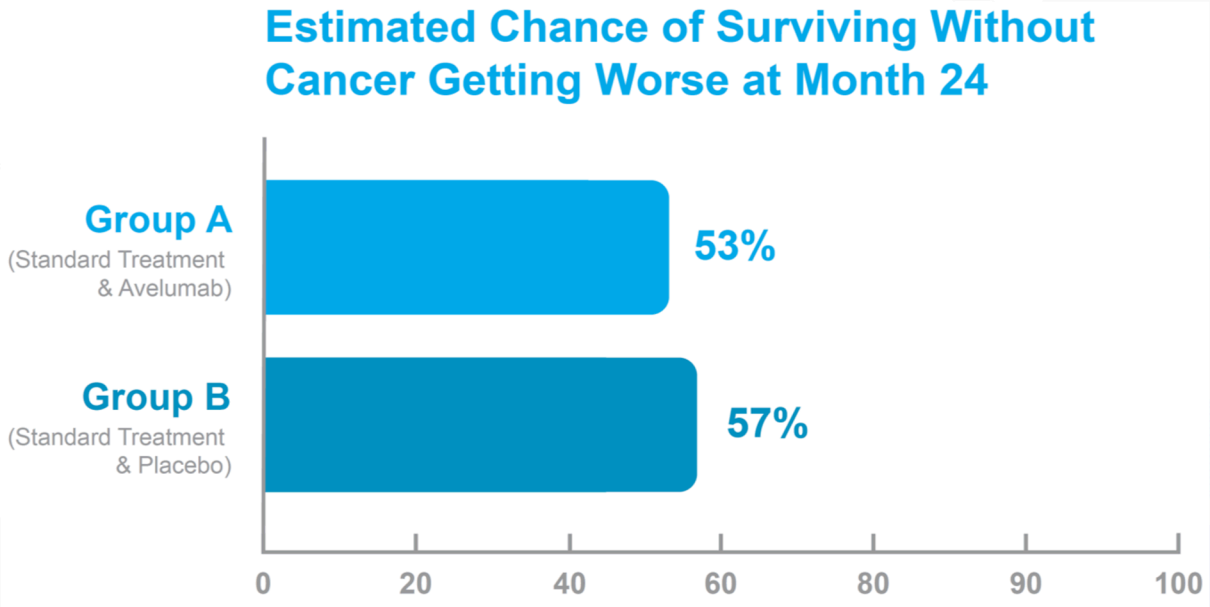
WHAT WERE THE RESULTS OF THE STUDY?

Did adding avelumab before, during, and after standard radiation and chemotherapy treatment increase the amount of time it takes for cancer to worsen (progress)?

To answer this question, the researchers compared the progression free survival (PFS), which is the time patients survived without their cancer getting worse. At the time the study results were analyzed:

- 118 out of 350 patients in Group A (34%) had their cancer worsen or had died
- 106 out of 347 patients in Group B (31%) had their cancer worsen or had died
- There was a 21% higher risk of cancer worsening in patients from Group A (avelumab and standard treatment), compared to patients from Group B (placebo and standard treatment)

The figure below shows the estimated chance of a patient surviving without cancer getting worse, at month 24 of the study:



The study data was reviewed by an independent Data Monitoring Committee (DMC). DMCs are used to ensure the safety of study participants and to determine if it is appropriate for a study to continue. There were no new or unexpected safety issues

090177e194de21a3\Approved\Approved On: 10-Sep-2020 10:17 (GMT)

identified with avelumab. However, the DMC concluded that there was little to no chance that the trial would demonstrate any benefit when adding avelumab to the standard radiation and chemotherapy treatment. The addition of avelumab did not increase the amount of time it takes for cancer to worsen, and consequently the study was stopped early to give patients an opportunity to seek other treatments.

These are just some of the main findings of the study, and more information may be available at the websites listed at the end of this summary.

WHAT MEDICAL PROBLEMS DID PATIENTS HAVE DURING THE STUDY?

The researchers recorded any medical problems the patients had during the study. Patients could have had medical problems for reasons not related to the study (for example, caused by an underlying disease or by chance). Medical problems could also have been caused by a study treatment or by another medicine the patient was taking. Sometimes the cause of a medical problem is unknown. By comparing medical problems across many treatment groups in many studies, doctors try to understand what the side effects of an experimental drug might be.

In this report, all medical problems that occurred during the treatment periods are discussed, regardless of whether or not the study doctors thought that the medical problems were related to taking the study treatment.

Of the 348 patients in Group A who received standard treatment and avelumab, 345 (99%) had at least 1 medical problem. A total of 87 patients in this group (25%) stopped taking study treatment because of medical problems.

Of the 344 patients in Group B who received standard treatment and placebo, 342 (99%) had at least 1 medical problem. A total of 88 patients in this group (26%) stopped taking study treatment because of medical problems.

The most common medical problems are listed below.

090177e194de21a3\Approved\Approved On: 10-Sep-2020 10:17 (GMT)

Most Common Medical Problems (Occurring in More Than 10% of Patients)		
Medical Problem	Group A Standard Treatment & Avelumab (348 Patients Treated)	Group B Standard Treatment & Placebo (344 Patients Treated)
Nausea	210 (60%)	201 (58%)
Low number of red blood cells (anemia)	205 (59%)	193 (56%)
Constipation	178 (51%)	154 (45%)
Weight loss	159 (46%)	171 (50%)
Dry mouth	151 (43%)	157 (46%)
Inflammation of mucous membranes	146 (42%)	130 (38%)
Trouble swallowing	146 (42%)	155 (45%)
Skin injury caused by radiation treatment	135 (39%)	136 (40%)
Low appetite	129 (37%)	124 (36%)
Feeling tired	116 (33%)	128 (37%)
Vomiting	114 (33%)	124 (36%)
Change in sense of taste	106 (31%)	119 (35%)
Low number of a type of white blood cells (neutrophils)	105 (30%)	100 (29%)
Inflammation of the mouth and lips	96 (28%)	97 (28%)
Fever	95 (27%)	46 (13%)

090177e194de21a3\Approved\Approved On: 10-Sep-2020 10:17 (GMT)

Most Common Medical Problems (Occurring in More Than 10% of Patients)		
Medical Problem	Group A Standard Treatment & Avelumab (348 Patients Treated)	Group B Standard Treatment & Placebo (344 Patients Treated)
Low magnesium level	92 (26%)	84 (24%)
Low potassium level	89 (26%)	73 (21%)
Increased level of creatinine in blood, which may indicate kidney disease	88 (25%)	73 (21%)
Low sodium level	84 (24%)	70 (20%)
Diarrhea	83 (24%)	67 (20%)
Throat pain	75 (22%)	91 (27%)
Cough	73 (21%)	64 (19%)
White blood cell count decreased	69 (20%)	64 (19%)
Feeling weak	65 (19%)	61 (18%)
Low number of white blood cells (leukopenia)	64 (18%)	46 (13%)
Painful swallowing	64 (18%)	48 (14%)
Neutrophil count decreased	64 (18%)	60 (17%)
Ringing in ears	59 (17%)	66 (19%)

090177e194de21a3\Approved\Approved On: 10-Sep-2020 10:17 (GMT)

Most Common Medical Problems (Occurring in More Than 10% of Patients)		
Medical Problem	Group A Standard Treatment & Avelumab (348 Patients Treated)	Group B Standard Treatment & Placebo (344 Patients Treated)
Increased level of enzyme in blood that may indicate liver damage (alanine aminotransferase)	57 (16%)	30 (9%)
Trouble sleeping	56 (16%)	44 (13%)
Increased level of enzyme in blood that may indicate liver damage (aspartate aminotransferase)	55 (16%)	24 (7%)
Inflammation and infection of lungs	54 (16%)	38 (11%)
Inflammation of skin	52 (15%)	42 (12%)
Underactive thyroid	51 (15%)	43 (13%)
Difficulty speaking	51 (15%)	47 (14%)
Headache	45 (13%)	40 (12%)
Rash	43 (12%)	35 (10%)
Low albumin level (a type of protein in blood)	42 (12%)	37 (11%)
Dizziness	41 (12%)	33 (10%)
Low number of platelets	46 (13%)	41 (12%)
Chills	40 (12%)	7 (2%)

090177e194de21a3\Approved\Approved On: 10-Sep-2020 10:17 (GMT)

Most Common Medical Problems (Occurring in More Than 10% of Patients)		
Medical Problem	Group A Standard Treatment & Avelumab (348 Patients Treated)	Group B Standard Treatment & Placebo (344 Patients Treated)
Mouth pain	40 (12%)	44 (13%)
Platelet count decreased	40 (12%)	33 (10%)
Dehydration	39 (11%)	42 (12%)
Cough that produces mucous	39 (11%)	32 (9%)
Itching	38 (11%)	24 (7%)
Lymphocyte count decreased	35 (10%)	36 (11%)
Trouble breathing	34 (10%)	37 (11%)
Increased potassium level	34 (10%)	32 (9%)
Low number of a type of white blood cells (lymphocytes)	33 (9%)	27 (8%)
Increased blood sugar	32 (9%)	33 (10%)

090177e194de21a3\Approved\Approved On: 10-Sep-2020 10:17 (GMT)

WERE THERE ANY SERIOUS MEDICAL PROBLEMS?

A medical problem is considered "serious" when it is life-threatening, needs hospital care, or causes lasting problems.

Of the 348 patients in Group A who received standard treatment and avelumab, 184 (53%) had serious medical problems. Of the 344 patients in Group B who received standard treatment and placebo, 175 (51%) had serious medical problems. The most common serious medical problems are listed below.

Most Common Serious Medical Problems (Occurring in More Than 2% of Patients)		
Medical Problem	Group A Standard Treatment & Avelumab (348 Patients Treated)	Group B Standard Treatment & Placebo (344 Patients Treated)
Inflammation and infection of lungs	25 (7%)	20 (6%)
Trouble swallowing	15 (4%)	13 (4%)
Sudden episode of kidney failure	12 (3%)	12 (4%)
Vomiting	11 (3%)	12 (4%)
Fever	11 (3%)	3 (1%)
Low number of a type of white blood cells (neutrophils) with fever	9 (3%)	5 (2%)
Dehydration	9 (3%)	15 (4%)
Low number of red blood cells (anemia)	8 (2%)	12 (4%)
Nausea	7 (2%)	9 (3%)

090177e194de21a3\Approved\Approved On: 10-Sep-2020 10:17 (GMT)

Most Common Serious Medical Problems (Occurring in More Than 2% of Patients)		
Medical Problem	Group A Standard Treatment & Avelumab (348 Patients Treated)	Group B Standard Treatment & Placebo (344 Patients Treated)
Inflammation of the mouth and lips	7 (2%)	4 (1%)
Increased level of creatinine in blood, which may indicate kidney disease	7 (2%)	5 (2%)
Serious condition caused by immune system reaction to infection (sepsis)	7 (2%)	5 (2%)
Trouble breathing	5 (1%)	7 (2%)
Low sodium level	4 (1%)	7 (2%)

73 patients in Group A (21%) died during the study. 58 patients in Group B (17%) died during the study. Most of these deaths were due to the cancer itself and not the treatment.

WHERE CAN I LEARN MORE ABOUT THIS STUDY?

If you have questions about the results of your study, please speak with the doctor or staff at your study site. For more details on this study protocol, please visit:

090177e194de21a3\Approved\Approved On: 10-Sep-2020 10:17 (GMT)

www.clinicaltrials.gov	Use the study identifier **NCT02952586**
www.clinicaltrialsregister.eu	Use the study identifier **2016-001456-21**

Please remember that researchers look at the results of many studies to find out which medicines can work and are safe for patients. No further studies with avelumab in patients with squamous cell carcinoma of the head and neck are planned.

Again, **thank you** for volunteering. We do research to try to find the best ways to help patients, and you helped us to do that!

090177e194de21a3\Approved\Approved On: 10-Sep-2020 10:17 (GMT)