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.

Medicine(s) Studied: Avelumab (Bavencio®), Axitinib (Inlyta®)

Protocol Number: B9991002

Dates of Trial: 15 October 2015 and is still ongoing

Title of this Trial: Testing the safety of avelumab and axitinib on patients with kidney cancer

[A Phase 1b, Open-Label, Dose-Finding Study to Evaluate Safety, Pharmacokinetics and Pharmacodynamics of Avelumab (MSB0010718C) in Combination With Axitinib (AG-013736) in Patients With Previously Untreated Advanced Renal Cell Cancer]

Date of this Report: 7 May 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 have any questions about the study or results, please contact the doctor or staff at your study site.

WHY WAS THIS STUDY DONE?

The kidneys are organs in the body that help get rid of waste while also controlling the amount of water in the body by producing urine. Renal cell carcinoma (RCC) is a type of kidney cancer that starts in the small tubes of the kidney. It is the most common kind of kidney cancer found in adults. Kidney cancer is called advanced when it has grown or spread outside of the kidney. Treatment for advanced RCC may include all or some of the following:

- surgery to remove a part of the kidney or the whole kidney
- radiation therapy, in which beams of intense energy are used to kill cancer cells
- treatment with chemical substances (chemotherapy)
- treatment that uses the body's own immune system to fight cancer. Substances made by the body or in a laboratory are used to boost, direct, or restore the body's own natural defense against cancer (immunotherapy/biotherapy/biologic therapy)

Avelumab is approved in certain countries for the treatment of some cancers and is a drug that stimulates the body's own defense system against cancer. Axitinib is approved in certain countries for the treatment of advanced RCC for certain patients after one prior treatment. At the time of this study, avelumab in combination with axitinib was not approved for treatment of patients with advanced RCC. Recently, avelumab in combination with axitinib has been approved in some countries as treatment for patients with advanced RCC.

The purpose of this study was to find the highest dose level tested of avelumab and axitinib taken together that is considered safe enough (less than 2 dose limiting toxicities [DLTs] in 6 patients) to test in advanced RCC patients in further studies. This is called the "maximum tolerated dose".

Researchers wanted to know:

- **What is the maximum tolerated dose level of avelumab in combination with axitinib?**

Dose Limiting Toxicities, DLTs, are certain medical problems caused by taking a medicine or medicines which require the patient to lower the dose they are taking or

to stop taking the medicine (permanently or temporarily). DLTs can be many things, and may include, for example, fever with a low count of white blood cells.

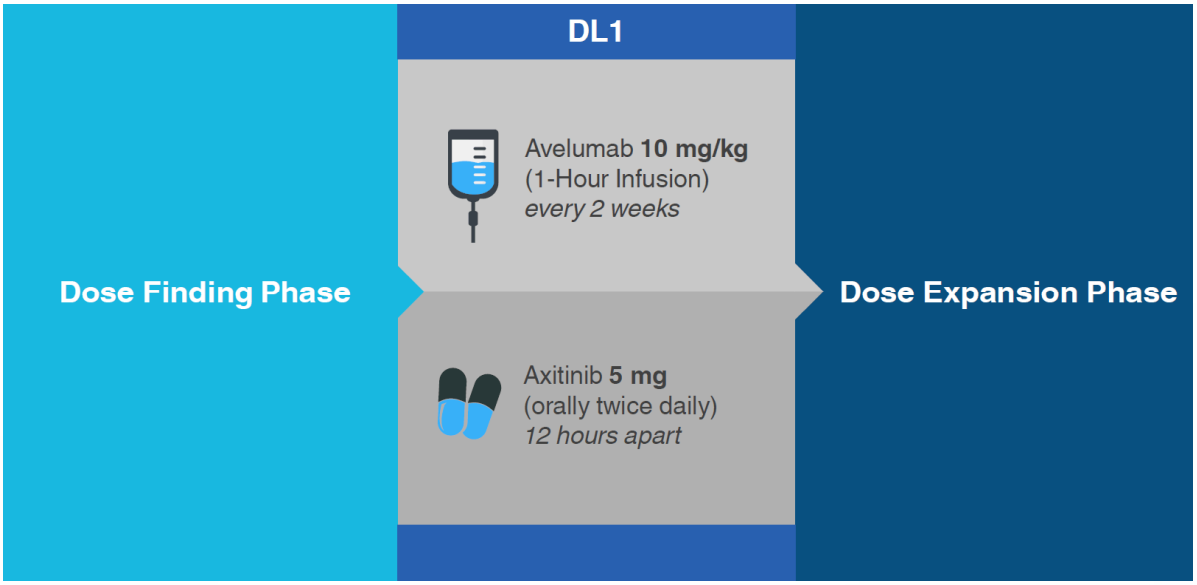
WHAT HAPPENED DURING THE STUDY?

The study evaluated a group of patients who did not receive any treatment for advanced RCC before joining this study, to find out what dose of avelumab was best to use in future clinical studies, when taken in combination with axitinib. Three different dose strength combinations of avelumab and axitinib were planned. The highest planned dose combination of avelumab and axitinib (DL1) was found to be an acceptable dose in this study, and therefore the other 2 combinations (DL-1A and DL-1B) were not explored. Avelumab was given into the vein through a small needle, and axitinib tablets were taken by mouth. The treatment groups for this "dose-finding phase" are shown below:

- DL1: avelumab 10 milligrams (mg) for each kilogram (kg) of the patient's body weight, every 2 weeks + axitinib 5 mg, 2 times a day
- DL-1A: avelumab 5 mg for each kg of body weight, every 2 weeks + axitinib 5 mg, 2 times a day (planned, but not investigated in this study)
- DL-1B: avelumab 10 mg for each kg of body weight, every 2 weeks + axitinib 3 mg, 2 times a day (planned, but not investigated in this study)

This was an "open-label" study, which means that the patients and the researchers knew which medicine the patients received.

The figure below shows what happened during this study.



There were 2 parts in the study. The first part was the "dose-finding phase". In this part of the study, the highest dose level, DL1, was tested to see if it is safe to use in further studies.

The second part was the "dose expansion phase". In this part of the study, the DL1 dose combination was given to patients to make sure that the right dose was chosen for future studies.

To understand what happens to axitinib in the body, 16 patients received axitinib tablets alone for 7 days (this was known as the "lead in period") prior to the combination (avelumab + axitinib).

The Sponsor ran this study at 14 locations in the United Kingdom, the United States, and Japan. It began 15 October 2015 and is ongoing. 42 men and 13 women participated. 38 patients were younger than 65 years, and 17 patients were 65 years or older. At the time of data collection, patients were in the study for almost 3 years; the study was ongoing.

Patients were to be treated in the dose-finding phase until DLT data from 6 patients on the highest dose of avelumab and axitinib were collected. This dose was then given in the "dose-expansion phase" of the study, to test the safety and effectiveness of the dose. Fifty-five patients received the study medications. At the time of data collection, 20 patients were still receiving the study medications: 31% (17 out of 55) of patients were still treated with both study medications, 2% (1 out of 55) of patients

were still treated with avelumab alone, and 4% (2 out of 55) of patients were still being treated with axitinib alone. Thirty-five patients discontinued study medication. The main reason why patients discontinued study medication was because their advanced RCC worsened.

When the data were collected in April 2018, the Sponsor began reviewing the information collected. The Sponsor then created a report of the results. This is a summary of that report.

WHAT WERE THE RESULTS OF THE STUDY?

What is the observed DLT of DL1?

There was 1 patient (out of 6) that had 1 medical problem that was considered a DLT. This medical problem was proteinuria, which is protein in the urine. So, since there was only a single DLT among the patients in the dose finding phase at DL1, DL1 was considered an acceptable dose. For this reason, the dose of avelumab in combination with axitinib recommended for the next study was determined to be avelumab 10 mg/kg through a needle in the vein every 2 weeks + axitinib 5 mg oral 2 times a day (DL1).

This does not mean that everyone in this study had these results. Other studies may produce different results, as well. 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 participants had during the study. Participants could have had medical problems for reasons not related to the study (for example, caused by an underlying disease or by chance). Or, medical problems could also have been caused by a study treatment, or by another medicine the participant 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.

All 55 patients in the study had at least 1 medical problem. A total of 24% (13 out of 55) of patients stopped treatment with avelumab or axitinib because of medical problems. The most common medical problems are listed below.

Most Common Medical Problems (Reported by More Than 10% of Patients)	
Medical Problem	**All Patients (55 Patients treated)**
Loose stools	37 (67%)
Feeling very tired	30 (55%)
Difficulty speaking	27 (49%)
High blood pressure	26 (47%)
Rash	20 (36%)
Constipation	18 (33%)
Hand-foot syndrome	18 (33%)
Alanine aminotransferase increased (high amount of this enzyme in the liver)	17 (31%)
High level of the enzyme that helps to break down sugars in the blood (amylase)	17 (31%)
Pain in a joint	17 (31%)
Aspartate aminotransferase increased (high amount of this enzyme in the liver)	17 (31%)
Cough	16 (29%)
Difficulty breathing	16 (29%)
Upset stomach	16 (29%)
Headache	15 (27%)
Underactive thyroid gland	15 (27%)

Loss of appetite	13 (24%)
Inflammation in the inner lining of some organs	13 (24%)
Vomiting	13 (24%)
High level of the enzyme that helps to break down fats (lipase)	12 (22%)
Medical problem related to receiving study drug through needle in the vein	11 (20%)
Weight loss	11 (20%)
Back pain	10 (18%)
Muscle pain	10 (18%)
Feeling cold	9 (16%)
Feeling dizzy	9 (16%)
Itching of the skin	9 (16%)
Blood creatinine increased (the kidneys are not working well)	8 (15%)
Dry mouth	8 (15%)
Bad taste in mouth	8 (15%)
Low level of sodium in the blood (sodium helps regulate the amount of water that is in and around cells)	8 (15%)
Difficulty sleeping	8 (15%)
Muscle spasms	8 (15%)
Common cold	8 (15%)
Protein in the urine	8 (15%)

Inflammation of the inner lining of the mouth	8 (15%)
Stomach pain	7 (13%)
Not enough red blood cells to carry oxygen to the organs	7 (13%)
Gamma-glutamyltransferase increased (high amount of this enzyme in the liver)	7 (13%)
Abnormally high level of uric acid in the blood	7 (13%)
Low level of phosphate in the blood	7 (13%)
Swelling of lower parts of the legs or hands	7 (13%)
Pain at the back of the mouth	7 (13%)
Nose and throat infection	7 (13%)
Urinary tract infection (infection in any part of the urinary system	7 (13%)
Blood alkaline phosphatase increased (high level of this enzyme in the liver)	6 (11%)
Dry skin	6 (11%)
Heartburn	6 (11%)
High level of the fat, triglycerides, in the blood	6 (11%)
Low blood pressure	6 (11%)
Pain in the limbs	6 (11%)
Open sore on the skin	6 (11%)

WERE THERE ANY SERIOUS MEDICAL PROBLEMS?

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

42% (23 out of 55) of patients had serious medical problems. 31% (5 out of 16) of patients in the DL1 group with lead-in and 46% (18 out of 39) of patients in the DL1 group had a serious medical problem. 24% (13 out of 55) of patients had serious medical problems related to study treatment as assessed by the investigator.
13 patients died during the study, of which 3 died because of a serious medical problem. Of the 3 patients that died due to a medical problem, the deaths of 2 patients were related to another underlying illness.

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:

www.clinicaltrials.gov	Use the study identifier **NCT02493751**
www.pfizer.com/research/research_clinical_trials/trial_results	Use the protocol number **B9991002**

Please remember that researchers look at the results of many studies to find out which medicines can work and are safe for patients. There is also an additional study for avelumab in combination with axitinib as treatment for patients with advanced renal cell cancer.

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!