Clinical Study 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 medication works, how it works, and if it is safe to prescribe to patients with a similar condition. 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 (MSB0010718C)
Protocol Number:	B9991023
Dates of Study:	21 December 2017 to 20 December 2022
Title of this Study:	A Study to Evaluate the Safety and Effectiveness of Avelumab in Combination With Chemotherapy for the Treatment of Advanced Cancer. [A Multicenter, Open-Label, Phase 1b/2 Study to Evaluate Safety and Efficacy of Avelumab (MSB0010718C) in Combination With Chemotherapy With or Without Other Anti-Cancer Immunotherapies as First-Line Treatment in Patients With Advanced Malignancies]
Date(s) of this Report:	5 September 2023

– Thank You –

If you participated in this study, Pfizer, the Sponsor, would like to thank you for your participation.

This summary will describe the study results. If you have any questions about the study or the results, please contact the doctor or staff at your study site.

Why was this study done?

What is advanced cancer?

Cancer occurs when cells in the body divide without control forming masses called “tumors”. Participants in this study had cancer that was “advanced” or “metastatic”. This means that the original cancer has spread from where it originally started and is more difficult to cure or control with treatment.

This study looked at participants with advanced or metastatic non-small cell lung cancer (NSCLC) or urothelial cancer (UC). NSCLC occurs when abnormal cells grow and multiply in lung tissues. UC starts in the urothelial cells. These cells line the bladder, kidneys and urethra (the tube that allows urine to pass out of the bladder and body).

What is Avelumab?

Cells in your immune system are designed to recognize and kill tumor cells. However, tumor cells can develop different processes by which they may avoid being killed.

A drug (known as an immunotherapy) that works by blocking one of these processes will be tested in this study. This immunotherapy is called avelumab.

Avelumab is an antibody which acts to free your immune cells from being trapped and stopped from working by a protein that may be produced by your tumor cells. This protein is called programmed death-ligand 1 (PD-L1).

Avelumab has been approved by the FDA to treat certain types of advanced cancer. Avelumab has not yet been approved for sale in the

countries where the study was done for the treatment of at least one of the types of cancer studied.

In this study, avelumab was given with “standard of care” chemotherapy (anti-cancer drugs). “Standard of care”, is a treatment that is accepted by medical experts as a proper treatment for a certain type of disease and that is widely used by medical professionals. Lung cancer patients were given pemetrexed plus carboplatin, and UC patients were given gemcitabine plus cisplatin as chemotherapy. These chemotherapy drugs have been found to be effective against lung and urothelial cancers. They work by killing tumor cells directly.

Researchers hope that the combination of chemotherapy and avelumab will slow or prevent the progress of cancer in participants.

What was the purpose of this study?

The purpose of this study was to look at the safety and anti-cancer activity of avelumab in combination with standard of care chemotherapy.

As part of the safety assessment, researchers enrolled a small group of participants in a “lead-in” phase. Researchers checked if participants in the lead-in phase had any major safety issue (dose-limiting toxicities, DLTs).

DLTs are medical problems that help researchers decide if it is safe to dose more participants and or give a higher dose of medication.

Researchers wanted to know:

- **How safe was treatment with avelumab in combination with chemotherapy in participants with advanced cancer?**
- **How effective was treatment with avelumab in combination with chemotherapy in participants with advanced cancer?**

What happened during the study?

How was the study done?

Researchers tested avelumab in combination with chemotherapy in 4 groups (cohorts) of study participants (Cohorts A1, A2, A3, and A4).

This was an “open-label” study. This means researchers and participants knew what study medication each patient was receiving.

Researchers tested 2 doses of avelumab (800 mg and 1200 mg) in combination with chemotherapy in participants with lung cancer (NSCLC) and UC, as shown below.

- Cohort A1 (lung cancer) = avelumab 800 mg + chemotherapy
- Cohort A2 (UC) = avelumab 800 mg + chemotherapy
- Cohort A3 (lung cancer) = avelumab 1200 mg + chemotherapy
- Cohort A4 (UC) = avelumab 1200 mg + chemotherapy

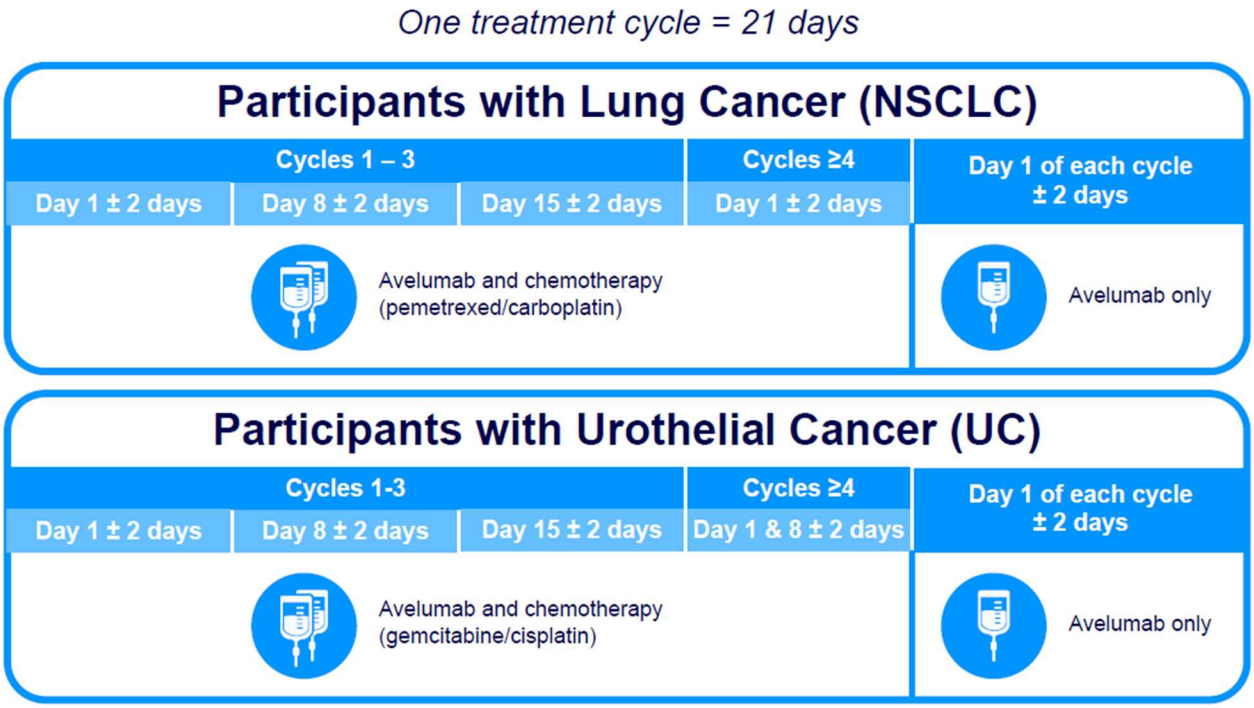
Participants were first enrolled in Cohorts A1 and A2 with 800 mg avelumab with chemotherapy. Once the safety of 800 mg of avelumab with chemotherapy had been confirmed, participants were enrolled in Cohorts A3 and A4 with 1200 mg avelumab + chemotherapy.

Treatment administration consisted of a 3-week period called a “cycle”. Day 1 of a cycle was the day of treatment with at least one study drug, and it was also possible to have Day 1 with chemotherapy only. For the first 3 cycles, participants visited the clinic on Day 1, Day 8, and Day 15 of each cycle. After the first 3 cycles, participants visited the clinic as follows (and as shown in Figure 1):

- On Day 1 of each 3-week cycle for participants with lung cancer
- On Day 1 and Day 8 of each 3-week cycle for participants with UC

When participants were no longer receiving chemotherapy, they continued to receive avelumab on Day 1 of each cycle.

Figure 1. Dosing for Each Cycle



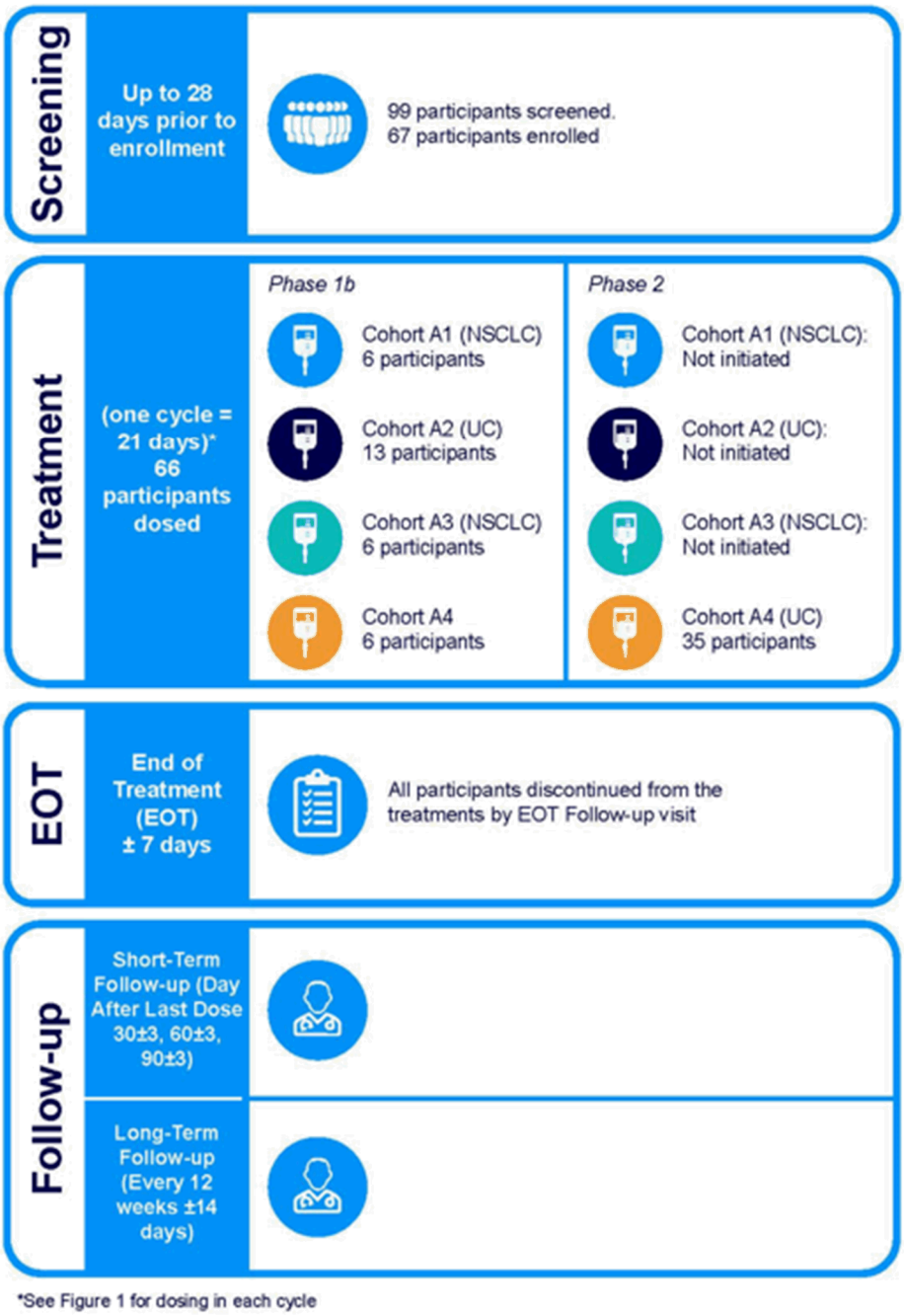
Overall, the study consisted of an initial consultation (Screening Visit), Treatment Period and Follow-up Period as shown in Figure 2.

All participants were “screened” to see if they qualified to be in the study. Participants who qualified for treatment after screening entered the Treatment Period. To ensure the safety of participants, dosing was done in 2 phases, as follows:

- Phase 1b “lead-in” phase: up to 12 participants were to be enrolled to assess the safety of avelumab in combination with chemotherapy and to monitor participants for DLTs during the first 2 cycles of treatment. The lead-in phase was completed for all 4 cohorts.
- Phase 2 “dose expansion” phase: up to 40 participants including those included in the lead-in phase were to be enrolled. This part of the study further assessed the safety and effectiveness (efficacy) of

avelumab in combination with chemotherapy. Phase 2 was only initiated for Cohort A4 (UC participants).

Figure 2. Study Design



*See Figure 1 for dosing in each cycle

Participants were to be treated until:

- their cancer got worse,
- they left the study by their own choice,
- they had unacceptable medical problems, or
- the study ended.

Where did this study take place?

The Sponsor ran this study at 24 hospitals in 8 countries.

When did this study take place?

It began 21 December 2017 and ended on 20 December 2022.

Who participated in this study?

The study included participants who were at least 18 years old, had lung or urothelial cancer, and had at least 1 tumor that could be measured by doctor.

- A total of 49 men participated
- A total of 17 women participated
- All participants were between the ages of 38 and 81 years

All the 12 participants in the lung cancer (NSCLC) cohorts stopped taking treatments of avelumab and chemotherapy. The most common reason for stopping avelumab and pemetrexed (a type of chemotherapy) was because their cancer got worse. The most common reason for stopping carboplatin (another type of chemotherapy) was because participants had completed the number of cycles (4 to 6 cycles) as recommended by the study researchers.

All the 54 participants in the UC cohorts also stopped taking treatments of avelumab and chemotherapy. The most common reason for stopping avelumab was because their cancer got worse. The most common reason for stopping chemotherapy was because participants had completed the number of cycles recommended per “standard of care” for their type of cancer.

How long did the study last?

The time participants were in the study, depended on their number of treatment cycles and follow-up time. The entire study took 5 years to complete.

When the study ended in December 2022, 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?

How safe was treatment with avelumab in combination with chemotherapy in participants with advanced cancer?

Researchers looked at the medical problems that participants had in the first 2 cycles of the lead-in phase for each cohort, to see if there were DLTs. This helped the researchers to decide if more participants and/or higher dose of medication could receive in Phase 2.

Medical problems throughout the whole of the study are discussed in full in the next section of this document.

Did participants who took avelumab in combination with chemotherapy have dose-limiting toxicities (DLTs)?

Of the 12 participants in lung cancer (NSCLC) Phase 1b cohorts, no participants had DLTs.

Of the 18 participants in the UC cohorts (12 participants in Cohort A2, and 6 participants in Cohort A4), 1 participant in each cohort had 1 DLT each.

One participant in Cohort A2 (avelumab 800 mg + chemotherapy) had a DLT of Grade 4 low level of blood platelets. Grade 4 means researchers considered this event to be severe. Blood platelets help your blood to clot. Researchers thought that the low level of blood platelets in these participants was due to avelumab and chemotherapy.

One participant in Cohort A4 (avelumab 1200 mg + chemotherapy) had a DLT of Grade 2 physical weakness/loss of strength. Grade 2 means researchers considered this event to be “moderate”. Researchers thought that the physical weakness in this participant was due to chemotherapy.

The recommended Phase 2 dose for avelumab in combination with chemotherapy (gemcitabine/cisplatin) was determined to be 1200 mg once every 3 weeks in participants with UC.

How effective was treatment with avelumab in combination with chemotherapy in participants with advanced cancer?

For the NSCLC cohorts, the percentage of participants whose disease decreased after treatment was 41.7% (5 participants out of 12).

For the UC cohorts, the percentage of participants whose disease decreased and/or disappeared after treatment was 42.6% (23 participants out of 54).

What effect did participants with advanced cancer have in treatment with avelumab in combination with chemotherapy?

Based on these results, the researchers have decided that treatment with avelumab in combination with chemotherapy did have an effect on NSCLC and UC but there was not enough data to tell if that effect was any different than other treatments.

This does not mean that everyone in this study had these results. This is a summary of just some of the main results of this study. Other studies may have different results.

What medical problems did participants 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 effects a study medication might have on a participant.

All 12 participants with lung cancer (NSCLC) and 53 out of 54 (98.1%) participants with UC in this study had at least 1 medical problem. The most common medical problems – those reported by more than 30% of participants in at least 1 cohort – are described below.

Below are instructions on how to read Table 1 and Table 2.

Instructions for Understanding Table 1.

- The **1st** column of Table 1 lists medical problems that were commonly reported during the study. All medical problems reported by more than 30% of participants are listed.
- The **2nd** column tells how many of the Cohort A1 participants taking the study medication reported each medical problem. Next to this number is the percentage of the 6 participants taking the study medication who reported the medical problem.
- The **3rd** column tells how many of the Cohort A3 participants taking the study medication reported each medical problem. Next to this number is the percentage of the 6 participants taking the study medication who reported the medical problem.
- Using these instructions, you can see that 4 out of the 6 (66.7%) participants in Cohort A1 taking the study medication reported platelet count decreased. A total of 4 out of the 6 (66.7%) participants in Cohort A3 taking the study medication reported nausea, low level of white blood cells, and thrombocytopenia.

Instructions for Understanding Table 2.

- The **1st** column of Table 2 lists medical problems that were commonly reported during the study. All medical problems reported by more than 30% of participants are listed.
- The **2nd** column tells how many of the Cohort A2 participants taking the study medication reported each medical problem. Next to this number is the percentage of the 13 participants taking the study medication who reported the medical problem.
- The **3rd** column tells how many of the Cohort A4 participants taking the study medication reported each medical problem. Next to this number is the percentage of the 41 participants taking the study medication who reported the medical problem.
- Using these instructions, you can see that 10 out of the 13 (76.9%) participants in Cohort A2 taking the study medication reported anemia (low red blood cell count). A total of 26 out of the 41 (63.4%) participants in Cohort A4 taking the study medication reported anemia (low red blood cell count).

Table 1. Commonly reported medical problems for more than 30% of study participants with lung cancer (NSCLC)

Medical Problem	Cohort A1 (Avelumab 800 mg + Pemetrexed/Carboplatin) NSCLC (6 Participants)	Cohort A3 (Avelumab 1200 mg + Pemetrexed/Carboplatin) NSCLC (6 Participants)
Platelet count decreased	4 out of 6 participants (66.7%)	1 out of 6 participants (16.7%)
Anemia (low red blood cell count)	3 out of 6 participants (50.0%)	1 out of 6 participants (16.7%)
Blood creatinine increased	3 out of 6 participants (50.0%)	0
Feeling tried	3 out of 6 participants (50.0%)	3 out of 6 participants (50.0%)
Low phosphate level in blood	3 out of 6 participants (50.0%)	0
Nausea	3 out of 6 participants (50.0%)	4 out of 6 participants (66.7%)
Low level of white blood cells (Neutropenia)	3 out of 6 participants (50.0%)	4 out of 6 participants (66.7%)
Abdominal pain	2 out of 6 participants (33.3%)	0
Increased liver enzyme (alanine	2 out of 6 participants (33.3%)	1 out of 6 participants (16.7%)

Table 1. Commonly reported medical problems for more than 30% of study participants with lung cancer (NSCLC)

Medical Problem	Cohort A1 (Avelumab 800 mg + Pemetrexed/Carboplatin) NSCLC (6 Participants)	Cohort A3 (Avelumab 1200 mg + Pemetrexed/Carboplatin) NSCLC (6 Participants)
aminotransferase [ALT]) in blood		
Increased pancreatic enzyme (amylase)	2 out of 6 participants (33.3%)	0
Joint pain (Arthralgia)	2 out of 6 participants (33.3%)	1 out of 6 participants (16.7%)
Increased liver enzyme (aspartate aminotransferase [AST]) in blood	2 out of 6 participants (33.3%)	0
Loss of strength or energy (Asthenia)	2 out of 6 participants (33.3%)	0
Decreased appetite	2 out of 6 participants (33.3%)	1 out of 6 participants (16.7%)
Diarrhea (loose stools)	2 out of 6 participants (33.3%)	3 out of 6 participants (50.0%)
Shortness of breath (Dyspnoea)	2 out of 6 participants (33.3%)	2 out of 6 participants (33.3%)

Table 1. Commonly reported medical problems for more than 30% of study participants with lung cancer (NSCLC)

Medical Problem	Cohort A1 (Avelumab 800 mg + Pemetrexed/Carboplatin) NSCLC (6 Participants)	Cohort A3 (Avelumab 1200 mg + Pemetrexed/Carboplatin) NSCLC (6 Participants)
Low potassium level in blood (Hypokalaemia)	2 out of 6 participants (33.3%)	0
Low magnesium level in blood (Hypomagnesaemia)	2 out of 6 participants (33.3%)	0
Insomnia	2 out of 6 participants (33.3%)	0
Lung inflammation (Pneumonitis)	2 out of 6 participants (33.3%)	2 out of 6 participants (33.3%)
Itching (Pruritis)	2 out of 6 participants (33.3%)	0
Fever (Pyrexia)	2 out of 6 participants (33.3%)	0
Nose, sinus, or throat infection (Upper respiratory tract infection)	2 out of 6 participants (33.3%)	0
Infection of the kidneys, bladder, or	2 out of 6 participants (33.3%)	1 out of 6 participants (16.7%)

Table 1. Commonly reported medical problems for more than 30% of study participants with lung cancer (NSCLC)

Medical Problem	Cohort A1 (Avelumab 800 mg + Pemetrexed/Carboplatin) NSCLC (6 Participants)	Cohort A3 (Avelumab 1200 mg + Pemetrexed/Carboplatin) NSCLC (6 Participants)
urethra (Urinary tract infection)		
Decreased white blood cell count	2 out of 6 participants (33.3%)	0
Thrombocytopenia	0	4 out of 6 participants (66.7%)
Weight decreased	0	2 out of 6 participants (33.3%)

Table 2. Commonly reported medical problems for more than 30% of study participants with urothelial cancer (UC)

Medical Problem	Cohort A2 (Avelumab 800 mg + Gemcitabine/Cisplatin) UC (N=13)	Cohort A4 (Avelumab 1200 mg + Gemcitabine/Cisplatin) UC (N=41)
Anemia (low red blood cell count)	10 out of 13 participants (76.9%)	26 out of 41 participants (63.4%)

Table 2. Commonly reported medical problems for more than 30% of study participants with urothelial cancer (UC)

Medical Problem	Cohort A2 (Avelumab 800 mg + Gemcitabine/Cisplatin) UC (N=13)	Cohort A4 (Avelumab 1200 mg + Gemcitabine/Cisplatin) UC (N=41)
Nausea	9 out of 13 participants (69.2%)	19 out of 41 participants (46.3%)
Feeling tired	8 out of 13 participants (61.5%)	15 out of 41 participants (36.6%)
Low level of white blood cells	8 out of 13 participants (61.5%)	23 out of 41 participants (56.1%)
Abdominal pain	5 out of 13 participants (38.5%)	3 out of 41 participants (7.3%)
Diarrhea (loose stools)	5 out of 13 participants (38.5%)	8 out of 41 participants (19.5%)
Vomiting	5 out of 13 participants (38.5%)	14 out of 41 participants (34.1%)
Constipation	4 out of 13 participants (30.8%)	18 out of 41 participants (43.9%)
Indigestion (Dyspepsia)	4 out of 13 participants (30.8%)	3 out of 41 participants (7.3%)
Platelet count decreased	4 out of 13 participants (30.8%)	9 out of 41 participants (22.0%)
Low blood platelets (Thrombocytopenia)	4 out of 13 participants (30.8%)	20 out of 41 participants (48.8%)

Table 2. Commonly reported medical problems for more than 30% of study participants with urothelial cancer (UC)		
Medical Problem	**Cohort A2 (Avelumab 800 mg + Gemcitabine/Cisplatin) UC (N=13)**	**Cohort A4 (Avelumab 1200 mg + Gemcitabine/Cisplatin) UC (N=41)**
Blood creatinine increased	2 out of 13 participants (15.4%)	13 out of 41 participants (31.7%)
Increased liver enzyme (ALT) in blood	1 out of 13 participants (7.7%)	13 out of 41 participants (31.7%)

Did study participants have any serious medical problems?

A medical problem is considered “serious” when it results in death, is life-threatening, needs hospital care, or causes lasting problems.

NSCLC Cohorts

Overall, 8 participants (66.7%) in NSCLC Cohorts (3 participants in Cohort A1 and 5 participants in Cohort A3) had at least 1 serious medical problem. Of the 8 participants, 4 participants (2 participants in Cohort A1 and 2 participants in Cohort A3) had serious medical problem related to study medication.

UC Cohorts

A total of 29 participants (53.7%) in UC Cohorts (9 participants in Cohort A2 and 20 participants in Cohort A4) had at least 1 serious medical problem. Of the 29 participants, 15 participants (3 participants in Cohort A2 and 12 participants in Cohort A4) had serious medical problem related to study medication.

Eight (8) participants (66.7%) in NSCLC Cohorts and 37 participants (68.5%) in UC Cohorts died during the study. The primary reason of death was progression of their cancer - 4 participants (33.3%) in NSCLC Cohorts and 33 participants (61.1%) in UC Cohorts.

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 your study protocol, please visit:

www.pfizer.com/research/research_clinical_trials/trial_results	Use the protocol number B9991023

The full scientific report of this study is available online at:

www.clinicaltrials.gov	Use the study identifier **NCT03317496**

Please remember that researchers look at the results of many studies to find out which medicines can work and are safe for patients.

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