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. 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), Utomilumab, PF 04518600, PD 0360324, and CMP-001

Protocol Number: B9991004

Dates of Study: 09 November 2015 to 23 March 2023

Title of this Study: A Study to Evaluate the Safety, Clinical Activity, Pharmacokinetics and Pharmacodynamics of Avelumab in Combination With Other Cancer Immunotherapies for the Treatment of Advanced Cancer.

[A Phase 1b/2 Open-Label Study to Evaluate Safety, Clinical Activity, Pharmacokinetics and Pharmacodynamics of Avelumab (MSB0010718C) in Combination With Other Cancer Immunotherapies in Patients With Advanced Malignancies]

Date(s) of this Report: 09 October 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 solid 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), small cell lung cancer (SCLC), melanoma, squamous cell carcinoma of the head and neck (SCCHN), triple negative breast cancer (TNBC), stomach (gastric) cancer, ovarian cancer 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 (tubes that connect the kidneys to the bladder). TNBC is a form of rare breast cancer that's challenging to treat as it does not respond to hormonal therapy medicines.

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 was tested in this study.

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 PD-L1.

Avelumab has been approved by the Food and Drug Administration (FDA) to treat certain types of advanced cancer. Avelumab was given as an intravenous (IV) (into the vein through a thin plastic tube called a catheter) cancer treatment. In this study, avelumab given in combination with other immunotherapies was considered to be an investigational medicine.

What are Utomilumab, PF-04518600, PD 0360324, and CMP-001?

Utomilumab, PF-04518600, PD 0360324, and CMP-001 are all medications made to help patients fight cancer in different ways. These drugs are approved or have been studied or have approval in other types of cancer.

Utomilumab, PD 0360324, and PF-04518600 was given as an IV cancer treatment. CMP-001 was given as an intratumoral (IT) injection (direct injection into the tumor) and also as a subcutaneous (SC) injection (under the skin). Researchers think that using combinations of these medications may help stop cancers from growing. Also, researchers hope that by giving avelumab with other immunotherapy drugs together may work better than giving only one drug by itself.

What was the purpose of this study?

The purpose of this study was to learn the effects of avelumab in combination with other immunotherapies to find the best treatment combination for various cancer types. Hence, researchers assessed the avelumab doublet combination (avelumab + one standard of care medication), if found safe, this was followed by checking the triplet combination (avelumab+ 2 standard of care medications).

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 single dose level of avelumab in combination with increasing dose levels of other immunotherapies in participants with locally advanced or metastatic solid tumors?**
- **How effective was treatment with single dose level of avelumab in combination with increasing dose levels of other immunotherapies in participants with locally advanced or metastatic solid tumors?**

What happened during the study?

How was the study done?

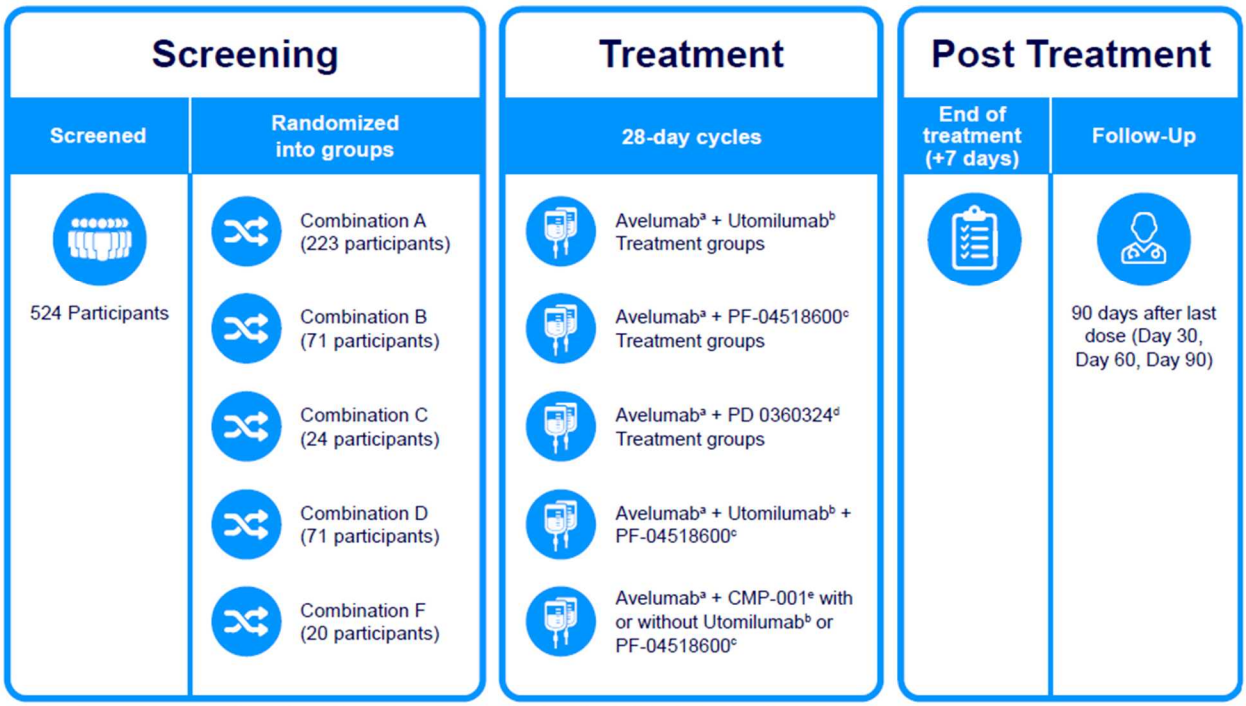
Researchers tested avelumab in combination with increasing dose levels of other immune modulators in adult participants with locally advanced or metastatic solid tumors (eg, NSCLC, melanoma, squamous cell carcinoma of the head and neck [SCCHN], TNBC, gastric cancer, ovarian cancer, bladder cancer, or SCLC).

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

Overall, the study consisted of an initial consultation (Screening Visit), Treatment Period and Follow-up Period as shown in Figure 1.

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.

Figure 1: Study design



[a]*Avelumab was administered as 1-hour intravenous infusion every 2 weeks on Day 1 and Day 15 of each cycle.*
[b]*Utomilumab treatment was administered in 4-week cycle (28-day cycle) and was administered as 1-hour intravenous infusion on Day 1 of each cycle*
[c]*PF-04518600 was administered as 1-hour intravenous infusion every 2 weeks on Day 1 and Day 15 of each cycle.*
[d]*PD 0360324 was administered as 30-minute intravenous infusion every 2 weeks on Day 1 and Day 15 of each cycle.*
[e]*CMP-001 was administered initially as 2 weekly Subcutaneous doses followed by Intratumoral dosing at weekly intervals for 5 additional doses. After the first 7 doses, CMP-001 was administered Intratumoral every 2 weeks (Q2W)*

To ensure the safety of participants, dosing was done in 2 phases, as follows:

- Phase 1b lead-in part to evaluate safety, and determine the maximum tolerated dose (MTD) or maximum administered dose (MAD) and recommended Phase 2 Dose (RP2D) (if applicable), of the combination, and

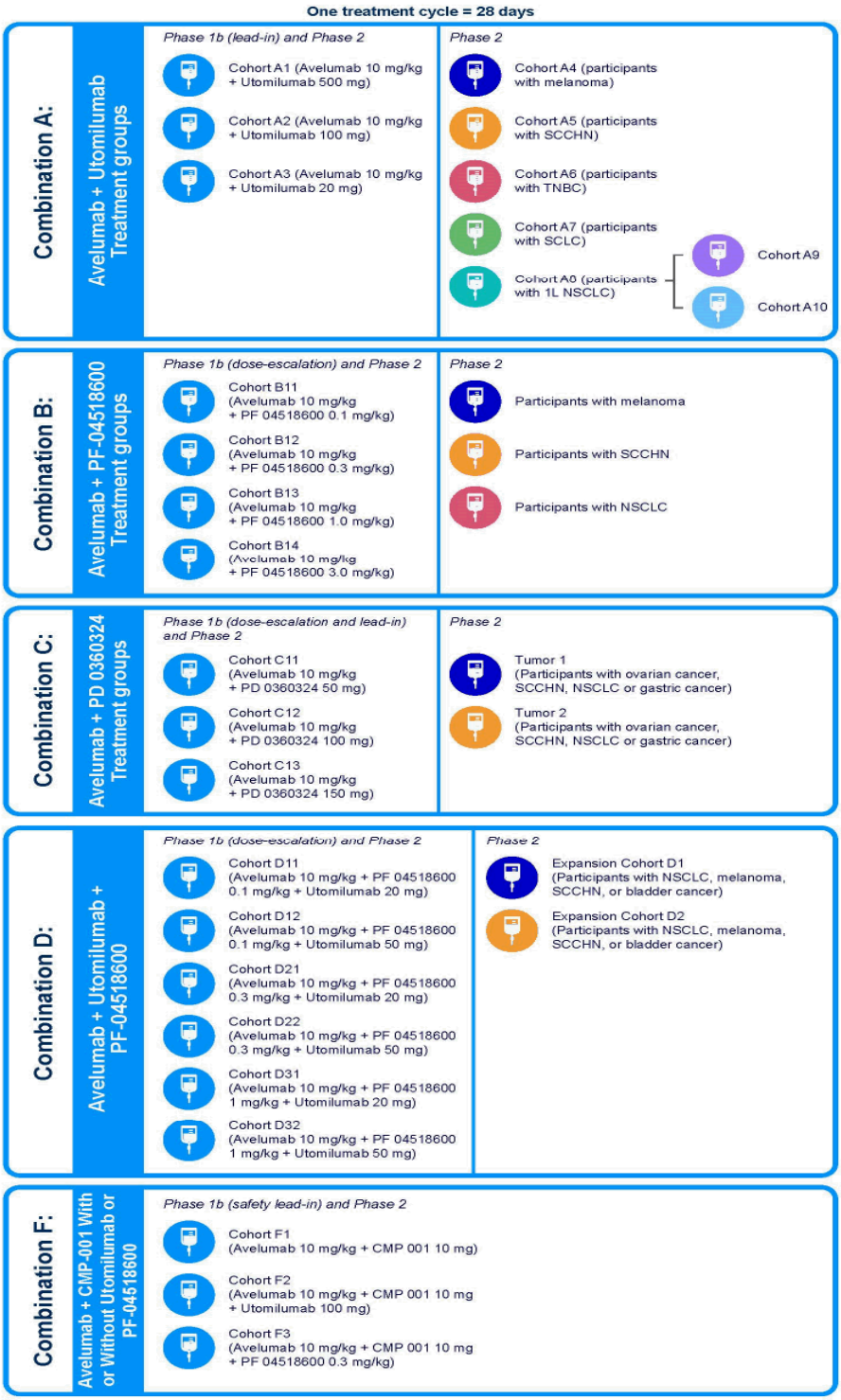
- Phase 2 part to evaluate efficacy and further evaluate safety of the selected dose from the Phase 1b part in pre-specified participant populations.

Researchers tested combinations of avelumab plus other immune modulator(s) as follows (Figure 2):

- Combination A: avelumab plus utomilumab (4-1BB agonist mAb);
- Combination B: avelumab plus PF-04518600 (OX40 agonist mAb);
- Combination C: avelumab plus PD 0360324 (M-CSF mAb);
- Combination D: avelumab plus utomilumab plus PF-04518600;
- Combination F: avelumab plus CMP-001 (TLR9 agonist) and utomilumab or PF-04518600:
    - Cohort F1: avelumab plus CMP-001;
    - Cohort F2: avelumab plus CMP-001 and utomilumab;
    - Cohort F3: avelumab plus CMP-001 and PF-04518600.

Treatment administration is broken up into cycles with each cycle consisting of 28 days. Participants were to be evaluated for DLTs after receiving study treatments in combination with avelumab twice weekly for 1 cycle (4 weeks) for Combination F or 2 cycles (8 weeks) for all other combinations. Participants visited the clinic on Day 1, Day 8, Day 15, and Day 28 of each cycle.

Figure 2: Study Design



Where did this study take place?

The Sponsor ran this study at 37 locations in Australia, Canada, France, Japan, Poland, Taiwan, United Kingdom, and United States.

When did this study take place?

It began 09 November 2015 and ended 23 March 2023.

Who participated in this study?

The study included participants who had at least 1 locally advanced or metastatic solid tumors (eg, NSCLC, melanoma, SCCHN, TNBC, gastric cancer, ovarian cancer, bladder cancer, or SCLC) that could be measured by doctor.

- A total of 260 men participated
- A total of 149 women participated
- All participants were between the ages of 24 to 90 years.

Participants were to be treated until

- their cancer got worse,
- they left the study by their own choice,
- they had unacceptable medical problems, or
- a doctor decided it was best for a participant to stop being in the study.

All the 409 participants in all combinations (A, B, C, D and F) stopped taking treatments of avelumab in combination with other immunotherapies. The most common reason for stopping avelumab in combination with other immunotherapies was because their cancer got worse.

How long did the study last?

Study participants were in the study for different lengths of time. The entire study took approximately 7 years to complete. The study was stopped in August 2022, as per the decision of Pfizer Management.

When the study ended in March 2023, 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 single dose level of avelumab in combination with increasing dose levels of other immune modulators in participants with locally advanced or metastatic solid tumors?

Researchers looked at the medical problems that participants had in the first 2 cycles of the Phase 1b lead-in phase for Combinations A, B, C and D and first cycle for Combination F only, to see if there were DLTs.

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 immunomodulators have dose-limiting toxicities (DLTs)?

No DLTs were reported in Combination A, B, and C. Of the 60 participants (Combination D) in the Phase 1b cohorts, DLTs were reported in 4 (6.7%) participants.

One participant in Cohort D11 had a DLT of Grade 3 type 1 high blood glucose levels. Grade 3 means researchers considered this event to be severe.

Two participants in Cohort D22 had DLTs. One participant had Grade 3 liver disorder, the other participant had Grade 3 infusion related reaction and Grade 3 electrocardiogram (ECG) QT prolonged. Grade 3 means researchers considered this event to be severe.

One participant in Cohort D31 had a DLT of Grade 4 low level of blood platelets. Grade 4 means researchers considered this event to be life-threatening. Researchers thought that the low level of blood platelets in these participants was due to avelumab and immunotherapy.

Out of the 18 participants, DLTs were reported in 2 (11.1%) participants in Combination F with SCCHN.

How effective was treatment with single dose level of avelumab in combination with increasing dose levels of other immunotherapies in participants with locally advanced or metastatic solid tumors?

For the Combination A, B and F, the percentage of participants whose disease decreased after treatment is presented in Figure 3, Figure 4, and Figure 5.

Figure 3:

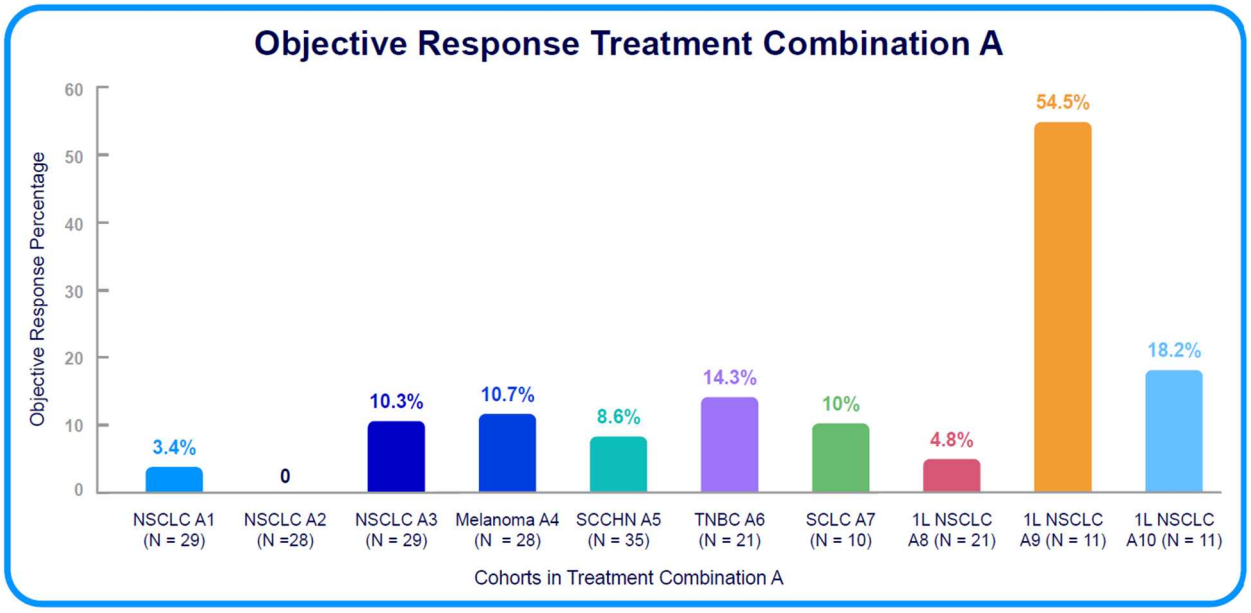


Figure 4:

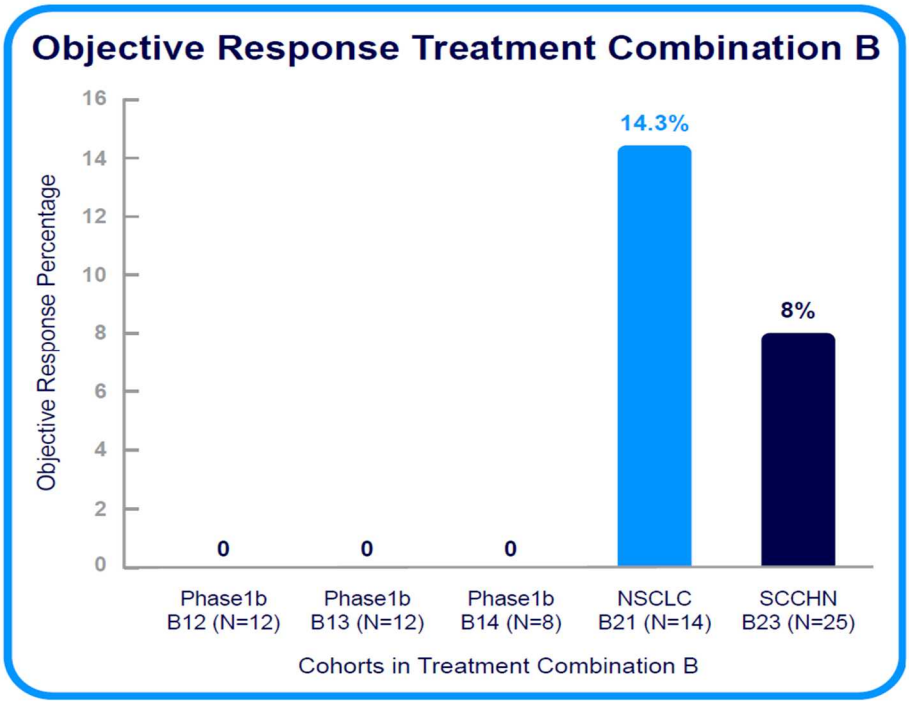
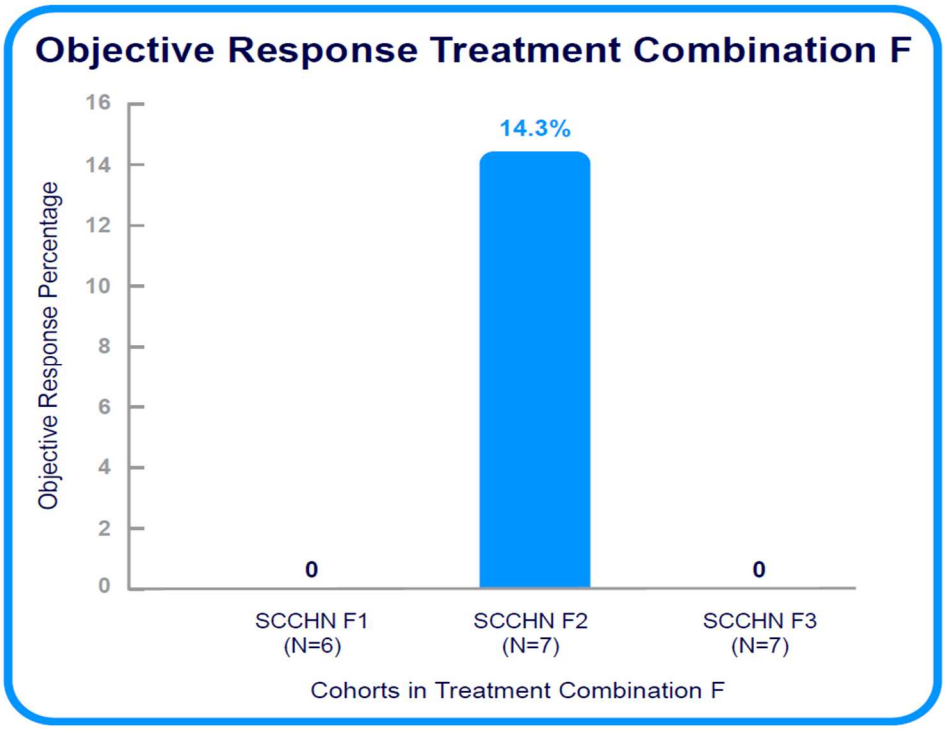


Figure 5:



What effect did participants with locally advanced or metastatic solid tumors have in with single dose level of avelumab in combination with increasing dose levels of other immunotherapies?

Based on these results, the researchers have decided that treatment with avelumab in combination with immunotherapies did have an effect on locally advanced or metastatic solid tumors 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.

406 out of 409 (99.2%) participants in this study had at least 1 medical problem. Most of the participants left the study because of medical problems. The most common medical problems – those reported by greater than or equal to 20% of participants – are described below.

Below are instructions on how to read Table 1.

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 greater than or equal to 20% of participants in any combinations are listed.
- The **2nd** column tells how many of the 222 participants in Combination A reported each medical problem. Next to this number is the percentage of the 222 participants in Combination A who reported the medical problem.

- The **3rd** column tells how many of the 71 participants in Combination B reported each medical problem. Next to this number is the percentage of the 71 participants in Combination B who reported the medical problem.
- The **4th** column tells how many of the 24 participants in Combination C reported each medical problem. Next to this number is the percentage of the 24 participants in Combination C who reported the medical problem.
- The **5th** column tells how many of the 71 participants in Combination D reported each medical problem. Next to this number is the percentage of the 71 participants in Combination D who reported the medical problem.
- The **6th** column tells how many of the 20 participants in Combination F reported each medical problem. Next to this number is the percentage of the 20 participants in Combination F who reported the medical problem.
- Using these instructions, you can see that 81 out of the 222 (36.5%) participants taking Combination A, 25 out of the 71 (35.2%) participants taking Combination B, 29 out of the 71 (40.8%) participants taking Combination D, and 15 out of the 20 (75.0%) participants taking Combination F reported fatigue. A total of 9 out of the 24 (37.5%) participants taking Combination C reported vomiting.

Table 1. Commonly reported medical problems for greater than or equal to 20% of study participants with locally advanced or metastatic solid tumors

Medical Problem	Combination A (222 Participants)	Combination B (71 Participants)	Combination C (24 Participants)	Combination D (71 Participants)	Combination F (20 Participants)
Low Red Blood Cell Count (Anaemia)	23 (10.4%)	8 (11.3%)	2 (8.3%)	10 (14.1%)	6 (30.0%)
Back pain	46 (20.7%)	7 (9.9%)	2 (8.3%)	8 (11.3%)	5 (25.0%)
Chills	35 (15.8%)	7 (9.9%)	3 (12.5%)	14 (19.7%)	9 (45.0%)
Constipation	44 (19.8%)	15 (21.1%)	4 (16.7%)	10 (14.1%)	7 (35.0%)
Cough	37 (16.7%)	8 (11.3%)	3 (12.5%)	18 (25.4%)	1 (5.0%)
Very High Levels of Small Immunomodulating Proteins (Cytokine	-	-	-	-	8 (40.0%)

Table 1. Commonly reported medical problems for greater than or equal to 20% of study participants with locally advanced or metastatic solid tumors

Medical Problem	Combination A (222 Participants)	Combination B (71 Participants)	Combination C (24 Participants)	Combination D (71 Participants)	Combination F (20 Participants)
Release Syndrome)					
Decreased Appetite	45 (20.3%)	16 (22.5%)	7 (29.2%)	12 (16.9%)	3 (15.0%)
Diarrhoea	47 (21.2%)	17 (23.9%)	5 (20.8%)	18 (25.4%)	8 (40.0%)
Dizziness	24 (10.8%)	7 (9.9%)	6 (25.0%)	9 (12.7%)	3 (15.0%)
Difficulty Swallowing (Dysphagia)	5 (2.3%)	3 (4.2%)	4 (16.7%)	4 (5.6%)	4 (20.0%)
Shortness of Breath (Dyspnoea)	58 (26.1%)	19 (26.8%)	8 (33.3%)	5 (7.0%)	1 (5.0%)

Table 1. Commonly reported medical problems for greater than or equal to 20% of study participants with locally advanced or metastatic solid tumors

Medical Problem	Combination A (222 Participants)	Combination B (71 Participants)	Combination C (24 Participants)	Combination D (71 Participants)	Combination F (20 Participants)
Feeling of Tiredness (Fatigue)	81 (36.5%)	25 (35.2%)	6 (25.0%)	29 (40.8%)	15 (75.0%)
Headache	32 (14.4%)	8 (11.3%)	6 (25.0%)	20 (28.2%)	6 (30.0%)
Low Blood Pressure (Hypotension)	9 (4.1%)	2 (2.8%)	-	4 (5.6%)	5 (25.0%)
Immune Reactions (Infusion Related Reaction)	40 (18.0%)	11 (15.5%)	4 (16.7%)	16 (22.5%)	1 (5.0%)
Injection site pain	1 (0.5%)	-	-	-	5 (25.0%)

Table 1. Commonly reported medical problems for greater than or equal to 20% of study participants with locally advanced or metastatic solid tumors

Medical Problem	Combination A (222 Participants)	Combination B (71 Participants)	Combination C (24 Participants)	Combination D (71 Participants)	Combination F (20 Participants)
Injection site reaction	-	-	-	-	6 (30.0%)
Sleep Disorder (Insomnia)	19 (8.6%)	11 (15.5%)	6 (25.0%)	5 (7.0%)	1 (5.0%)
Feeling sickness in the stomach (Nausea)	58 (26.1%)	18 (25.4%)	8 (33.3%)	15 (21.1%)	9 (45.0%)
Neck pain	16 (7.2%)	4 (5.6%)	2 (8.3%)	4 (5.6%)	4 (20.0%)
Pain	7 (3.2%)	2 (2.8%)	5 (20.8%)	4 (5.6%)	1 (5.0%)
(Pain in the Hands and Legs) Pain in extremity	24 (10.8%)	5 (7.0%)	1 (4.2%)	4 (5.6%)	4 (20.0%)

Table 1. Commonly reported medical problems for greater than or equal to 20% of study participants with locally advanced or metastatic solid tumors

Medical Problem	Combination A (222 Participants)	Combination B (71 Participants)	Combination C (24 Participants)	Combination D (71 Participants)	Combination F (20 Participants)
Accidental Infiltration of Food, Bacteria, and other substances into the Lungs (Pneumonia aspiration)	-	-	1 (4.2%)	3 (4.2%)	4 (20.0%)
Itchy Skin (Pruritus)	37 (16.7%)	9 (12.7%)	3 (12.5%)	17 (23.9%)	4 (20.0%)
Fever (Pyrexia)	29 (13.1%)	6 (8.5%)	3 (12.5%)	8 (11.3%)	6 (30.0%)
Vomiting	48 (21.6%)	14 (19.7%)	9 (37.5%)	13 (18.3%)	6 (30.0%)

Table 1. Commonly reported medical problems for greater than or equal to 20% of study participants with locally advanced or metastatic solid tumors

Medical Problem	Combination A (222 Participants)	Combination B (71 Participants)	Combination C (24 Participants)	Combination D (71 Participants)	Combination F (20 Participants)
Weight decreased	24 (10.8%)	9 (12.7%)	1 (4.2%)	6 (8.5%)	4 (20.0%)

Did study participants have any serious medical problems?

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

The most common serious medical problem reported in at least ≥2% participants in Combination A were worsening of disease (disease progression) (5.9%), shortness of breath (dyspnoea) (3.6%), lung infection (pneumonia) (3.2%), and immune reactions (infusion related reaction) (2.3%) which was only treatment-related. The serious medical problem of infusion related reaction was related to study medication.

The most common serious medical problem reported in at least ≥2% participants in Combination B were physical weakness (asthenia) (2.8%), worsening of disease (disease progression) (2.8%), and dyspnoea (2.8%).

The only most common serious medical problem reported in more than 1 participant in Combination C was worsening of cancer (malignant neoplasm progression) (8.3%).

The most common serious medical problem reported in at least ⩾2% participants in Combination D were disease progression (2.8%) and infusion related reaction (2.8%). The serious medical problem of infusion related reaction was related to study medication.

The most common serious medical problem reported in more than 1 participant in Combination F were very high levels of small immunomodulating proteins (cytokine release syndrome) (20.0%), accidental infiltration of food, bacteria, and other substances into the lungs (pneumonia aspiration) (15.0%), pneumonia (10.0%), and lymphocyte count decreased (10.0%). The serious medical problems of cytokine

release syndrome and lymphocyte count decreased were related to study medication.

A total of 146 out of 222 (65.8%) participants in combination A, 48 out of 71 (67.6%) participants in combination B, 13 out of 24 (54.2%) participants in Combination C, 48 out of 71 (67.6%) participants in Combination D, and 16 out of 20 (80.0%) participants in Combination F passed away during the study. The primary reason for death in all combinations was progression of their cancer. Only one death in Combination B was related to study medications.

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 B9991004

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

www.clinicaltrials.gov	Use the study identifier **NCT02554812**
www.clinicaltrialsregister.eu	Use the study identifier **2015-002552-27**

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!