Summary of Results for Laypersons

What was the Study Called?

A Randomized, Double-blind, Phase 2 Study of Erlotinib (Tarceva®) in Combination with OSI-906 or Placebo in Chemonaive Patients with Advanced Non-small Cell Lung Carcinoma (NSCLC) with Activating Mutations of the Epidermal Growth Factor Receptor (EGFR) Gene

Why was this Study Needed?

Non-small cell lung cancer (or NSCLC for short) is the most common type of lung cancer. Some NSCLC cells have a mutation, or change, in the gene for a protein (called EGFR) on the cell surface. The mutated EGFR helps the NSCLC cells grow faster. Erlotinib (also known as OSI-774 and Tarceva) is a medicine that blocks mutated EGFR. When EGFR is blocked, it can no longer help cancer cells grow. In advanced NSCLC, erlotinib may block certain mutated EGFR better than others. Therefore, there was a need to study new treatments for advanced NSCLC.

In this study, researchers looked at the effect of erlotinib taken together with linsitinib (erlotinib/linsitinib). Linsitinib (also known as OSI-906 and ASP7487) is an experimental medicine taken by mouth. It works by blocking 2 proteins (called IGF-1R and IR) that are often found at high levels in NSCLC. When these proteins are blocked, they can no longer help cancer cells grow or survive.

This study was conducted in patients who had advanced NSCLC with mutated EGFR. Patients took erlotinib/linsitinib or erlotinib together with placebo (erlotinib/placebo). (The section below describes what placebo is.) The main question this study helped answer was which study medicines (erlotinib/linsitinib or erlotinib/placebo) were better at improving progression-free survival. That is the length of time from the start of study medicine up until the time the cancer did not get worse in half of the patients in each treatment group. It was also important to find out what unwanted effects these patients had from the study medicines.

The study started in April 2011. The sponsor of this study (Astellas) did a review of the study results in February 2013. This was done to make sure the patients were benefiting from the study medicines. The review showed that progression-free survival was not better with linsitinib. Astellas then recommended that patients stop taking linsitinib. Patients who were in this study on 01 May 2013 could continue taking erlotinib. Some patients continued erlotinib treatment in a new study (OSI-906-209). The study ended in September 2014. When the study ended, Astellas reviewed all the study information and created a report of the results. This is a summary of that report.

What Kind of Study was This and Who Took Part in it?

This was a “blinded” study. This means that the patients and the researchers did not know who took which of the study medicines (erlotinib/linsitinib or erlotinib/placebo). A “placebo” is a dummy treatment such as a tablet or capsule that looks like a medicine, but does not have any medicine in it. Using a placebo helps make study results fair and

unbiased, because researchers and patients cannot tell who is taking a placebo, and who is taking the test medicine.

Clinical studies have a list of requirements for patients who can be in a study ("inclusion" criteria) and patients who cannot take part in a study ("exclusion" criteria). The requirements for this study are listed below.

Women and men aged 18 years or older could take part in the study if:

- Their doctor had confirmed that they had NSCLC that was in an advanced stage.
- Their NSCLC cells had a mutation, or change, in the gene for EGFR. The kind of mutation was known before study start.
- The size of their tumor could be accurately measured.
- They were active or they could perform light daily activities.

Patients could not take part in this study if:

- Within the past 3 years, they had another cancer besides NSCLC. It was acceptable if they were cured of a cancer that had stayed on the surface (skin). It was also acceptable if they were cured of a cancer that had not spread outside the organ where it started (breast, cervix and bladder). (The cervix is the lower end of the uterus [womb].) And it was also acceptable if they were cured of prostate cancer that had spread from where it started to nearby tissue or lymph nodes.
- They had diabetes and were taking insulin. Or they were taking a medication that enhanced the production of insulin.
- In the past, they had a poorly controlled disease of any part of the digestive tract. (The digestive tract is the tube that extends from your mouth to your anus.) This disease could affect how well the study medicine is absorbed into the body.
- In the last 6 months, they had serious heart disease that was poorly controlled.

During the study, the study doctor did a check-up of the patients at several study visits. At the first visit, patients were checked to see if they could be in the study. Patients who could be in the study were picked for 1 of 2 treatments by chance alone:

- Erlotinib/linsitinib: Patients took erlotinib tablets (150 mg) once a day and linsitinib tablets (150 mg) twice a day.
- Erlotinib/placebo: Patients took erlotinib tablets (150 mg) once a day and placebo tablets twice a day.

The patients could take study medicine until their cancer got worse, they had unwanted effects they could not tolerate, they asked to stop treatment or they died.

This study took place at 29 clinics in several countries. 88 patients were in the study. Out of these patients, 87 patients took at least 1 dose of study medicine.

	Number of Patients
Age Group	
Aged 65 years or younger	60
Aged older than 65 years	27
Sex	
Men	25
Women	62
Clinic Location	
European Union Countries	0
Outside European Union	87
Canada	19
Hong Kong	1
Singapore	9
South Korea	8
Thailand	10
US	40

What Were the Study Results?

This study in patients who had advanced NSCLC with mutated EGFR looked at the length of time from the start of study medicine up until the time the cancer did not get worse in half of the patients in each treatment group (progression-free survival).

The results showed that from the start of study medicine, the cancer did not get worse in half of the patients:

- For 254 days in the erlotinib/linsitinib group.
- For 376 days in the erlotinib/placebo group.

The difference was due to chance. Compared to erlotinib taken together with placebo, erlotinib taken together with linsitinib did not improve the progression-free survival.

What Adverse Reactions did Patients Have?

A lot of research is needed to know whether a medicine causes a medical problem. So when new medicines are being studied researchers keep track of all medical problems that patients have while they are in the study. These medical problems are called “adverse events” and are recorded whether or not they might be caused by the treatment taken. An “adverse reaction” is any medical problem or “adverse event” that is judged by the study doctor to be possibly caused by a medicine or treatment used in the study.

The table below shows the adverse reactions experienced by approximately 10% or more patients who took at least 1 dose of study medicine in this study. This means that those adverse reactions were experienced by at least 5 out of 44 patients in the erlotinib/placebo group and/or by at least 5 out of 43 patients in the erlotinib/linsitinib group.

Adverse Reaction	Erlotinib Taken Together With Placebo (out of 44 patients)	Erlotinib Taken Together With Linsitinib (out of 43 patients)
Any adverse reaction	44 (100%)	43 (100%)
Skin reaction to medication	43 (97.7%)	36 (83.7%)
Diarrhea	33 (75.0%)	29 (67.4%)
Dry skin	18 (40.9%)	20 (46.5%)
Fatigue or tiredness	16 (36.4%)	16 (37.2%)
Hair loss	14 (31.8%)	5 (11.6%)
Infection of the soft tissue around a fingernail	14 (31.8%)	8 (18.6%)
Itchy skin	12 (27.3%)	4 (9.3%)
Nausea or the urge to vomit	12 (27.3%)	19 (44.2%)
Decreased appetite	9 (20.5%)	18 (41.9%)
Painful swelling and sores inside the mouth	7 (15.9%)	11 (25.6%)
Taste changes	6 (13.6%)	7 (16.3%)
Deep skin cracks	5 (11.4%)	0
Dry eye	5 (11.4%)	7 (16.3%)
Vomiting	4 (9.1%)	13 (30.2%)
Dry mouth	3 (6.8%)	5 (11.6%)
Weight loss	2 (4.5%)	5 (11.6%)
Increased blood level of a liver enzyme (alanine aminotransferase)	1 (2.3%)	14 (32.6%)
Increased blood level of a liver enzyme (aspartate aminotransferase)	1 (2.3%)	12 (27.9%)
Increased blood sugar level	1 (2.3%)	8 (18.6%)
Increased blood level of creatinine (a substance normally eliminated by the kidneys into the urine)	0	5 (11.6%)
Increased blood level of a liver pigment (bilirubin) often a sign of liver problems	0	7 (16.3%)

An adverse reaction is considered “serious” when it is life-threatening, causes lasting problems or needs hospital care.

11 patients experienced serious adverse reactions. The table below shows the serious adverse reactions experienced by 2 or more patients.

Serious Adverse Reaction	Erlotinib Taken Together With Placebo (out of 44 patients)	Erlotinib Taken Together With Linsitinib (out of 43 patients)
Any serious adverse reaction	3 (6.8%)	8 (18.6%)
Dehydration (when your body does not have as much water and fluid as it should)	1 (2.3%)	1 (2.3%)
Decreased appetite	1 (2.3%)	2 (4.7%)
Increased blood level of a liver enzyme (alanine aminotransferase)	0	4 (9.3%)
Increased blood level of a liver enzyme (aspartate aminotransferase)	0	3 (7.0%)
Nausea or the urge to vomit	0	2 (4.7%)
Vomiting	0	2 (4.7%)

5 patients died during the study: 3 patients who took erlotinib together with placebo and 2 patients who took erlotinib together with linsitinib. None of these patients died because of the study medicines.

Where Can I Learn More About This Study?

This document is a short summary of the main results from this study and reflects the information available as of December 2014. You can find this summary and more information about this study online at http://www.astellasclinicalstudyresults.com.

Please remember that researchers look at the results of many studies to find out how well medicines work and which adverse reactions they might cause. This summary only shows the results of this 1 study.

Sponsor contact details:

Astellas Pharma Global Development
1 Astellas Way
Northbrook, IL 60062
USA