Summary of Results for Laypersons

What was the Study Called?

A Phase 1 Dose-escalation Study of OSI-906 and Erlotinib (Tarceva®) in Patients with Advanced Solid Tumors

Why was this Study Needed?

A solid tumor is an abnormal mass of tissue that usually does not contain cysts or liquid areas. Solid tumors may be benign (not cancer), or malignant (cancer). Different types of solid tumors are named for the type of cells that form them. Examples of solid tumors are sarcomas (cancers of the connective or supporting tissues, such as bone or muscle), carcinomas (cancers of the cells in the skin or in the tissues that line or cover organs in the body), and lymphomas (cancers of the organs that make and store cells that fight infection). The most commonly used treatments for solid tumors include some combination of surgery, radiation therapy and chemotherapy. However, some advanced solid tumors cannot be cured or controlled with these treatments. Therefore, there was a need to study new treatments for advanced solid tumors.

In this study, researchers looked at the effect of erlotinib taken together with linsitinib (erlotinib/linsitinib). Some solid tumors have a mutation, or change, in the gene for a protein (called EGFR) on the cell surface. The mutated EGFR helps the solid tumor 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 solid tumors, erlotinib may block certain mutated EGFR better than others. 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 solid tumors. When these proteins are blocked, they can no longer help cancer cells grow or survive.

This study was conducted in patients with any type of advanced cancer that forms solid tumors. Patients took erlotinib/linsitinib once or twice a day. The main question the study helped answer was what the highest dose of erlotinib/linsitinib was that patients could tolerate. The study also looked at finding the recommended dose for erlotinib/linsitinib given at different intervals. It was also important to find out what unwanted effects the patients had from the study medications.

The study started in October 2008 and ended in September 2011. When this study ended, the sponsor (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 an “open-label” study. This means that all patients knew that they took erlotinib/linsitinib once or twice a day.

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.

Men and women aged 18 years or older could take part in the study if:

- They had solid tumors that were in an advanced stage, OR
  They had stage 3B or 4 non-small cell lung cancer (NSCLC) (expansion group only). NSCLC is a disease where cancer cells form in the tissues of the lung. Stage 3B NSCLC is where the cancer is present on the opposite side of the chest or above the collar bone or involves organs such as the heart or trachea as well as lymph nodes in the center of the chest or near the windpipe. At stage 4, the cancer is found in both lungs, in the fluid that surrounds the lungs or heart, or has spread to other parts of the body such as the liver, brain or bones.
- They were active or they could perform light daily activities. Or they were ambulatory and capable of all self-care, but unable to carry out any work activities. And they were up and about more than 50% of waking hours. They were expected to live for at least 3 months.
- They had recovered from any previous therapies or surgery before the study started. Patients with prostate cancer that had gotten worse and had started hormone therapy that suppresses the function of the testicles, 3 months earlier, were allowed to continue to take it.
- Their fasting glucose (or sugar) level was ≤ 125 mg/dL at the start of the study.
- They were nonsmokers or former smokers who had stopped smoking at for least 3 months.
- Their liver and kidney worked sufficiently and their production of blood cells was sufficient.

Patients could not take part in this study if:

- They had diabetes (a disease in which the blood sugar level is too high).
- In the past, they had serious heart disease that was poorly controlled.
- They were currently taking other cancer treatments (other than hormone therapy).
- They had a history of prior EGFR or insulin-like growth receptor (IGFR) inhibitor therapy, stroke (stoppage of blood flow to the brain) or convulsions or seizures.
- Their cancer had spread to the brain.

During the study, the study doctor did a check-up of the patients at weekly 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 assigned to 1 of 4 treatments (tablets or capsules):

- Group 1: Patients received a starting dose of 50 mg linsitinib once a day on days 1 to 3, 8 to 10 and 15 to 17 every 21 days. Patients received a starting dose of 100 mg erlotinib once a day for 41 days.

- Group 2: Patients received a starting dose of linsitinib (based on the highest dose tolerated by group 1) once a day for 21 days. Patients received a starting dose of 100 mg erlotinib once a day for 41 days.
- Group 3: Patients received a starting dose of 100 mg linsitinib twice a day for 21 days. Patients received a starting dose of 100 mg erlotinib once a day for 41 days.
- Expansion group: Patients received a starting dose of 150 mg linsitinib twice a day for 42 days. Patients received a starting dose of 150 mg erlotinib once a day for 42 days.

The dose of erlotinib/linsitinib was "escalated" (increased) for the next group of patients. During the treatment, the study doctor checked the patients for unwanted effects. After 21 days, the patients returned to the clinic for a check-up. If no safety issues were seen, then the next group of patients could take an increased dose. The doses could be increased until the study doctor determined the patients could no longer tolerate the unwanted effects.

If the study doctor determined the patients could no longer tolerate the unwanted effects, then the patient was assigned to receive the last dose level of erlotinib/linsitinib (the dose before the unwanted effect occurred).

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 4 clinics, 3 clinics in the United States and 1 clinic in the United Kingdom. A total of 91 patients took at least 1 dose of study medicine.

	Number of Patients			
	Group 1 (out of 44 Enrolled Patients)	**Group 2 (out of 24 Enrolled Patients)**	**Group 3 (out of 12 Enrolled Patients)**	**Expansion Group (out of 15 Enrolled Patients)**
Age Group				
Younger than 65 years	27	15	9	10
65 years or older	17	9	3	5
Sex				
Men	23	12	6	6
Women	21	12	6	9
Clinic Location				
European Union Countries (*at the time of the study*)				
UK	15	9	4	6
Outside European Union				
US	29	15	8	9

What Were the Study Results?

The study was looking at finding the recommended dose of erlotinib/linsitinib given at different intervals. The main question the study helped answer was what the highest dose of

erlotinib/linsitinib that patients with advanced solid tumors could tolerate. The results showed that the highest dose of erlotinib/linsitinib that patients could tolerate were:

- Group 1: 450 mg linsitinib once a day and 150 mg erlotinib once a day
- Group 2: 400 mg linsitinib once a day and 100 mg erlotinib once a day
- Group 3: 150 mg linsitinib twice a day and 150 mg erlotinib once a day

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 5% or more of the patients who took at least 1 dose of study medicine in the study. This means that those adverse reactions were experienced by at least 2 out of 40 patients who were in group 1, 2 out of 24 patients who were in group 2, 1 out of 12 patients who were in group 3 and 1 out of 15 patients who were in the expansion group.

Adverse Reaction	**Group 1 (out of 40 Patients)**	**Group 2 (out of 24 Patients)**	**Group 3 (out of 12 Patients)**	**Expansion Group (out of 15 Patients)**
Any adverse reaction	19 (48%)	8 (33%)	3 (25%)	9 (60%)
Nausea or the urge to vomit	4 (10%)	3 (12%)	2 (17%)	1 (7%)
Vomiting	4 (10%)	1 (4%)	1 (8%)	1 (7%)
Fatigue or tiredness	4 (10%)	3 (12%)	1 (8%)	3 (20%)
Increased blood sugar level	3 (8%)	0	0	2 (13%)
Loss of appetite	2 (5%)	2 (8%)	0	1 (7%)
Abnormal electrical conduction within the heart	3 (8%)	3 (12%)	0	1 (7%)

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

10 patients in group 1 experienced serious adverse reactions. 3 patients in the expansion group experienced serious adverse reactions. The table below shows these serious adverse reactions.

Adverse Reaction	Group 1 (out of 40 Patients)	Group 2 (out of 24 Patients)	Group 3 (out of 12 Patients)	Expansion Group (out of 15 Patients)
Any adverse reaction	10 (25%)	0	0	3 (20%)
Increased blood level of a liver enzyme (alanine aminotransferase)	2 (5%)	0	0	0
Increased blood level of a liver enzyme (aspartate aminotransferase)	1 (2%)	0	0	0
Abnormal electrical conduction within the heart	1 (2%)	0	0	0
Abnormal blood level of a liver enzyme	1 (2%)	0	0	0
Diarrhea	1 (2%)	0	0	1 (7%)
Bleeding in or from the stomach	1 (2%)	0	0	0
Hole in the lining of the abdominal cavity	1 (2%)	0	0	0
Vomiting	1 (2%)	0	0	2 (13%)
Hole in the wall of part of the gastrointestinal tract	0	0	0	1 (7%)
Nausea or the urge to vomit	0	0	0	1 (7%)
Increased blood sugar level	2 (5%)	0	0	1 (7%)
Lack of enough red blood cells (anemia)	1 (2%)	0	0	0
Fatigue or tiredness	1 (2%)	0	0	0
General feeling of discomfort or being unwell or out of sorts	0	0	0	1 (7%)
Acute kidney failure	1 (2%)	0	0	0
Inflammation of the lungs that may cause difficulty breathing and can be life-threatening	1 (2%)	0	0	0
Skin drug rash	1 (2%)	0	0	0

9 patients died during part 1 of the study: 5 patients in group 1; 3 patients in group 3; and 1 patient in the expansion group. 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.

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