Summary of Results for Laypersons

What was the Study Called?

A Two-Stage Phase 1 Dose Escalation Pharmacokinetic Study of Tarceva® (erlotinib) in Patients with Stage IIIB/IV Non-small Cell Lung Cancer who Continue to Smoke After Failure of One or Two Prior Chemotherapy Regimens

Why was this Study Needed?

Non-small cell lung cancer is a disease in which cells in the tissues of the lung grow abnormally. Chemotherapy is a type of cancer treatment that uses medicines to destroy cancer cells. When non-small cell lung cancer is in an advanced stage, chemotherapy can no longer stop the growth of the cancer cells. Erlotinib is a prescription medicine that can prolong the lives of some patients with advanced non-small cell lung cancer. Erlotinib (also known as OSI-774 and Tarceva) works by blocking epidermal growth factor receptor (EGFR). EGFR is a molecule found on the surface of certain cancer cells, such as non-small cell lung cancer cells. When EGFR is blocked, it can no longer help cancer cells grow.

Cigarette smoke starts a chemical reaction that breaks down erlotinib. This lowers the blood level of erlotinib in smokers. Before this study started, the same dose of erlotinib was given to all patients with advanced non-small cell lung cancer. But researchers found that this dose was better at slowing down the cancer growth in patients who never smoked than in patients who smoked.

There was a need to study the right erlotinib dose for patients with advanced non-small cell lung cancer who smoke. This study was conducted in patients who had advanced non-small cell lung cancer and smoked cigarettes. Earlier chemotherapy had not stopped the growth of their cancer.

This study had 2 parts. Part 1 of this study helped determine the maximum tolerated dose (MTD) of erlotinib in smokers. The MTD is exceeded when a dose causes particular unwanted effects in at least 2 out of 6 treated patients. These unwanted effects are serious enough to prevent an increase in the dose. The MTD is the highest dose that causes these unwanted effects in fewer than 2 out of 6 treated patients.

Part 2 of this study helped answer how well erlotinib is absorbed into the body and how long it stays in the body. It was also important to find out what unwanted effects these patients had from the study medicine.

This study for erlotinib took place at 9 clinics in the UK and the US. The study started in January 2006 and ended in May 2014. All patients in the study (22 in Part 1 and 35 in Part 2) took at least 1 dose of study medicine. By September 2007, 21 patients in Part 1 and 19 patients in Part 2 completed the study. Seventeen patients (1 in Part 1 and 16 in Part 2) remained in the study until May 2014. 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. All patients knew that they took erlotinib.

Men and women could be in Part 1 or Part 2 of the study if:

- They had confirmed incurable advanced non-small cell lung cancer.
- They had been treated with 1 or 2 rounds of chemotherapy and their cancer had gotten worse.
- They had recovered from any unwanted effects from cancer before study start. They could still have hair loss, mild fatigue or tiredness or mild damage to the nerves outside of the spinal cord and brain.
- They smoked at least 10 cigarettes per day for the last year even though they received help to quit smoking.
- They were at least 18 years old.
- They were fully active or they were able to walk and do work of a light nature. They were expected to live for at least 12 weeks.

Patients with non-small cell lung cancer could not be in Part 1 or Part 2 of the study if:

- They were taking anticancer chemotherapy.
- During the 2 weeks before study start, they were taking products that activate or block enzymes that break down erlotinib. These products did not include tobacco.
- They had other cancers, unless they were disease-free and did not have cancer-specific treatment for at least the last 5 years.
- They had serious heart disease in the past unless the disease was under control.
- They had ongoing or uncontrolled infections or serious illnesses or medical conditions that could make it difficult for the patients to take part in the study.
- They had a psychiatric condition in the past that could decrease the patient's ability to understand or follow the requirements of the study or give permission for the study procedures.

At the first study visit, patients were checked to see if they could be in Part 1 of the study. On day 1, patients who could be in Part 1 started their erlotinib treatment. Doses of erlotinib were "escalated" for each group of patients. The first group of patients took 200 mg of erlotinib per day for 14 days. The study doctor called patients on day 7 to ask about any unwanted effects. On day 14, patients returned to the clinic for a check-up. If no safety issues were seen, then the next group of patients took an increased dose for 14 days with safety check-ups at days 7 and 14. This was repeated 2 times. The increased doses were 250, 300 and 350 mg per day.

After the MTD had been determined in Part 1, Part 2 of the study started. At the first study visit, patients were checked to see if they could participate in the study. Patients who had participated in Part 1 of the study could not be enrolled in Part 2.

On day 1, patients who could be in Part 2 were picked for 1 of the following treatments by chance alone:

- The Part 1 MTD (300 mg) of erlotinib for 14 days
- 150 mg of erlotinib for 14 days

The study doctor called patients on day 7 to ask about any unwanted effects. On day 14, patients returned to the clinic for a check-up. That same day, patients gave blood samples before and at several time points after they took erlotinib. If the study doctor thought that the treatment was helpful, patients could continue to take erlotinib after day 14. The patients could take treatment until their cancer got worse, they had unwanted effects they could not tolerate, they asked to stop treatment or they died.

A total of 22 patients in Part 1 of the study took at least 1 dose of study medicine:

- 3 patients took 200 mg of erlotinib
- 6 patients took 250 mg of erlotinib
- 8 patients took 300 mg of erlotinib
- 5 patients took 350 mg of erlotinib

A total of 35 patients in Part 2 of the study took at least 1 dose of study medicine:

- 17 patients took 150 mg of erlotinib
- 18 patients took the MTD (300 mg) of erlotinib

	Number of Patients	
	Part 1 of the Study (out of 22 Patients)	**Part 2 of the Study (out of 35 Patients)**
Age Group		
Aged 40 to 64 years	16	20
Aged 65 years or older	6	15
Sex		
Men	12	16
Women	10	19
Clinic Location		
European Union Countries	19	26
The UK	19	26
Outside European Union	3	9
The US	3	9

What Were the Study Results?

This study was conducted in patients who had advanced non-small cell lung cancer and smoked cigarettes. The study had 2 parts.

Part 1 of this study helped determine the MTD of erlotinib in smokers. Part 1 of the study used dose escalation, whereby the first group of patients took 200 mg of erlotinib per day for 14 days. When no safety issues were seen, the next group of patients took an increased dose for 14 days with safety check-ups at days 7 and 14. This was repeated 2 times. The increased doses were 250, 300 and 350 mg per day.

In Part 1 of the study, 350 mg of erlotinib per day caused particular unwanted effects in 2 out of 5 treated patients. These unwanted effects were serious enough to prevent an increase in the dose. This meant that 350 mg per day exceeded the MTD. The 300-mg daily dose caused these unwanted effects in 1 out of 6 treated patients. Thus, the MTD of erlotinib was determined to be 300 mg per day.

Part 2 of this study helped answer how well erlotinib is absorbed into the body and how long it stays in the body. Patients took 150 mg or the MTD (300 mg) of erlotinib per day for 14 days. The study showed that their blood levels of erlotinib increased with increasing dose.

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 most common adverse reactions experienced by patients who took at least 1 dose of study medicine in Part 1 of the study. None of the patients who took 200 mg of erlotinib per day had skin rash or diarrhea. In the other erlotinib groups, the number of patients who had skin rash was similar regardless of the dose of erlotinib (250, 300 or 350 mg per day). More patients who took 350 mg erlotinib per day than in the other erlotinib groups had diarrhea.

	Number of Patients Who Took Erlotinib in Part 1 of the Study				
Adverse Reaction	**200 mg per day (out of 3 Patients)**	**250 mg per day (out of 6 Patients)**	**300 mg per day (out of 8 Patients)**	**350 mg per day (out of 5 Patients)**	**Total (out of 22 Patients)**
Skin rash (various types)	0	4 (67%)	6 (75%)	3 (60%)	13 (59%)
Diarrhea	0	4 (67%)	4 (50%)	4 (80%)	12 (55%)

The table below shows the most common adverse reactions experienced by patients who took at least 1 dose of study medicine in Part 2 of the study. More patients who took 300 mg erlotinib per day compared to patients who took 150 mg of erlotinib per day had skin rash or diarrhea.

Adverse Reaction	Number of Patients Who Took Erlotinib in Part 2 of the Study		
	150 mg per day (out of 17 Patients)	300 mg per day (out of 18 Patients)	Total (out of 35 Patients)
Skin rash (various types)	5 (29%)	12 (67%)	17 (49%)
Diarrhea	3 (18%)	9 (50%)	12 (34%)

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

One patient experienced serious adverse reactions. This patient took 250 mg of erlotinib in Part 1 of the study. The serious adverse reactions were dehydration (when your body does not have as much water and fluid as it should), diarrhea, nausea or the urge to vomit and vomiting.

Four patients died in Part 1 of the study. Four patients died in Part 2 of the study. None of the patients died because of the study medicine.

Between September 2007 and May 2014, 17 patients remained in the study. During this period, 3 patients died and 1 patient experienced a serious adverse reaction (cloudiness of the eye [cataract]). None of the patients died because of the study medicine.

Where Can I Learn More About This Study?

Astellas may perform additional studies to better understand erlotinib.

This summary of the clinical study results is available 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. If you have questions about erlotinib, please discuss these with your doctor.

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