Summary of Results for Laypersons

What was the Study Called?

A Phase 1/2 Study Evaluating Intermittent and Continuous OSI-906 and Weekly Paclitaxel in Patients with Recurrent Epithelial Ovarian Cancer (and Other Solid Tumors)

Why was this Study Needed?

Ovaries are part of the female reproductive system. They produce eggs and female hormones. Ovarian cancer is cancer that starts in the ovaries. Ovarian cancer can be treated with chemotherapy with paclitaxel. Paclitaxel stops cancer cells from growing and dividing, and may kill them. But in some patients, ovarian cancer that has come back ("relapsed/recurrent ovarian cancer") may respond to paclitaxel treatment only for a short time. Therefore, there was a need to study new treatments for ovarian cancer that has come back.

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

This study consisted of 2 parts: part 1 and part 2.

Part 1 of the study was conducted in patients with any cancer type that forms solid tumors. (Solid tumors are abnormal tissue masses without sacs or liquid.) Patients took paclitaxel together with linsitinib. The main question part 1 of the study helped answer was what the highest dose of linsitinib was that patients could tolerate. The patients in part 2 of the study took this dose. It was also important to find out what unwanted effects the patients in part 1 had from the study medicines.

Part 2 of the study was conducted in patients with ovarian cancer that had come back; cancer of the fallopian tubes (tubes through which the eggs pass from the ovary to the uterus [womb]); or cancer of the peritoneum (the tissue that hold the organs in the abdomen). Patients took paclitaxel together with linsitinib (paclitaxel/linsitinib) or paclitaxel on its own. The main question part 2 of the study helped answer was which study medicines (paclitaxel/linsitinib or paclitaxel on its own) 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 of the 3 treatment groups. It was also important to find out what unwanted effects the patients in part 2 had from the study medicines.

The study started in August 2009 and ended in January 2014. 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 which study medicines they took (paclitaxel/linsitinib or paclitaxel on its own).

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.

Patients aged 18 years or older could take part in the study if:

- In part 1 of the study, they had a cancer that formed solid tumors and that could be treated with paclitaxel.
- In part 2 of the study, their doctor had confirmed that they had ovarian cancer that had come back; cancer of the fallopian tubes; or cancer of the peritoneum. And their doctor had confirmed that their cancer was getting worse. The size of their tumor could be accurately measured.
- They were active or they could perform light daily activities. They were expected to live for at 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 for which they took a medication, such as insulin.
- They had, or had in the past, another cancer unless their cancer signs and symptoms had decreased or disappeared in the past 3 years. 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 cervical cancer that had not spread outside the cervix (the lower end of the uterus [womb]) where it started.
- In the past, they had serious heart disease that was poorly controlled.

This study took place at 47 clinics in several countries. 58 patients were in part 1 of the study and took at least 1 dose of study medicine. 152 patients were in part 2 of the study. Out of these patients, 148 took at least 1 dose of study medicine.

	Number of Patients	
	Part 1 of the Study (out of 58 Patients)	**Part 2 of the Study (out of 148 Patients)**
Age Group		
Aged 65 years or younger	48	121
Aged older than 65 years	10	27
Sex		
Men	9	0
Women	49	148
Clinic Location		
European Union Countries (*at the time of the study*)	7	91
Czech Republic	0	9
Italy	0	31
Poland	0	15
Romania	0	3
UK	7	33
Outside European Union	51	57
Australia	0	10
Canada	8	25
Russia	0	3
Switzerland	15	8
US	28	11

During the study, the study doctor did a check-up of the patients at weekly study visits.

Part 1:

At the first visit, patients were checked to see if they could be in part 1 of the study. Patients who could be in part 1 of the study were assigned to 1 of 2 treatments:

- Part 1/Treatment 1: Patients took linsitinib tablets (300, 400, 450 or 600 mg) once a day 3 days a week. They received paclitaxel (80 mg/m^2) as an intravenous infusion once a week.
- Part 1/Treatment 2: Patients took linsitinib tablets (75 or 150 mg) twice a day each day. They received paclitaxel (80 mg/m^2) as an intravenous infusion once a week.

In both treatment groups, doses of linsitinib were "escalated" (increased) for each group of patients. The dose for the first group of patients was 300 mg in part 1/treatment 1 and 75 mg in part 1/treatment 2. During the treatment, the study doctor checked the patients for unwanted effects. After 4 weeks, 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.

The highest linsitinib doses that patients tolerated were

- Part 1/Treatment 1: 600 mg once a day 3 days a week.
- Part 1/Treatment 2: 150 mg twice a day each day.

These were the doses the patients took in part 2 of the study.

Part 2:

At the first study visit, patients were checked to see if they could participate in the study. Patients who could be in part 2 of the study were picked for 1 of 3 treatments by chance alone:

- Part 2/Treatment 1 (intermittent linsitinib/weekly paclitaxel): Patients took linsitinib tablets (600 mg) once a day 3 days a week. They received paclitaxel (80 mg/m^2) as an intravenous infusion once a week.
- Part 2/Treatment 2 (daily linsitinib/weekly paclitaxel): Patients took linsitinib tablets (150 mg) twice a day each day. They received paclitaxel (80 mg/m^2) as an intravenous infusion once a week.
- Part 2/Treatment 3 (weekly paclitaxel on its own): Patients received paclitaxel (80 mg/m^2) as an intravenous infusion once a week. They did not take linsitinib.

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.

What Were the Study Results?

Part 1:

Part 1 of the study looked at the highest dose of linsitinib that cancer patients could tolerate. When the patients took linsitinib 3 days a week plus weekly paclitaxel, the highest linsitinib dose they tolerated was 600 mg once a day. When the patients took linsitinib twice a day each day plus weekly paclitaxel, the highest linsitinib dose they tolerated was 150 mg twice a day. Patients in part 2 of the study took these doses.

Part 2:

Part 2 of the study looked at the length of time from the start of study medicine up until the time the cancer (namely ovarian cancer that had come back; cancer of the fallopian tubes; or cancer of the peritoneum) 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, these cancers did not get worse in half of the patients:

- For 84 days in the part 2/treatment 1 group (intermittent linsitinib/weekly paclitaxel)
- For 129 days in the part 2/treatment 2 group (daily linsitinib/weekly paclitaxel)
- For 169 days in the part 2/treatment 3 group (weekly paclitaxel)

These differences were due to chance. Compared to weekly paclitaxel on its own, intermittent or daily linsitinib taken together with weekly paclitaxel 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.

Part 1:

The table below shows the adverse reactions experienced by approximately 20% or more of the patients who took at least 1 dose of study medicine in part 1 of the study. This means that those adverse reactions were experienced by at least 6 out of 27 patients in the part 1/treatment 1 group and/or at least 7 out of 31 patients in the part 1/treatment 2 group.

Adverse Reaction	**Part 1/Treatment 1 (out of 27 patients)**	**Part 1/Treatment 2 (out of 31 patients)**
Any adverse reaction	26 (96.3%)	30 (96.8%)
Fatigue or tiredness	16 (59.3%)	19 (61.3%)
Nausea or the urge to vomit	14 (51.9%)	14 (45.2%)
Hair loss	12 (44.4%)	16 (51.6%)
Diarrhea	8 (29.6%)	13 (41.9%)
Lack of enough red blood cells (anemia)	8 (29.6%)	5 (16.1%)
Damage to the nerves outside of the spinal cord and brain	7 (25.9%)	8 (25.8%)
Dry skin	7 (25.9%)	3 (9.7%)
Inflammation (swelling and redness) or degeneration of the peripheral nerves (those nerves outside of brain and spinal cord) causing numbness, tingling, burning	7 (25.9%)	4 (12.9%)
Nail abnormality	6 (22.2%)	4 (12.9%)
Nose bleed	6 (22.2%)	2 (6.5%)
Skin reaction to medication	6 (22.2%)	6 (19.4%)
Taste changes	6 (22.2%)	8 (25.8%)
Vomiting	5 (18.5%)	7 (22.6%)
Loss of appetite	3 (11.1%)	8 (25.8%)

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

Seven patients experienced serious adverse reactions. The table below shows these serious adverse reactions.

Serious Adverse Reaction	Part 1/Treatment 1 (out of 27 patients)	Part 1/Treatment 2 (out of 31 patients)
Any serious adverse reaction	1 (3.7%)	6 (19.4%)
Blood clot in a deep vein, usually in the legs	1 (3.7%)	1 (3.2%)
Blockage in a lung artery	0	1 (3.2%)
Damage to the lung	0	1 (3.2%)
Decrease in ability to perform daily activities	0	1 (3.2%)
Decrease of a red blood cell protein (hemoglobin) that carries oxygen in the body	0	1 (3.2%)
Fast heartbeat usually originating in an area located above the ventricles (lower chambers of the hearts)	0	1 (3.2%)
Increased blood sugar level	0	1 (3.2%)
Severe illness in which the bloodstream is overwhelmed by bacteria	0	1 (3.2%)

Five patients died during part 1 of the study: 1 patient in the part 1/treatment 1 group (this patient took linsitinib 600 mg once a day for 3 days each week). The remaining 4 patients were in the part 1/treatment 2 group: 1 patient took linsitinib 75 mg twice a day each day and 3 patients took linsitinib 150 mg twice a day each day. All 5 patients received paclitaxel once a week. None of these patients died because of the study medicines.

Part 2:

The table below shows the adverse reactions experienced by approximately 20% or more of the patients who took at least 1 dose of study medicine in part 2 of the study. This means that those adverse reactions were experienced by at least 10 out of 50 patients in the part 2/treatment 1 group; by at least 10 out of 49 patients in the part 2/treatment 2 group; and/or by at least 10 out of 49 patients in the part 2/treatment 3 group.

Adverse Reaction	Part 2/Treatment 1 (out of 50 patients)	Part 2/Treatment 2 (out of 49 patients)	Part 2/Treatment 3 (out of 49 patients)
Any adverse reaction	50 (100%)	43 (87.8%)	47 (95.9%)
Nausea or the urge to vomit	28 (56.0%)	16 (32.7%)	21 (42.9%)
Fatigue or tiredness	21 (42.0%)	22 (44.9%)	25 (51.0%)
Diarrhea	17 (34.0%)	9 (18.4%)	10 (20.4%)
Abnormal electrical conduction within the heart	16 (32.0%)	2 (4.1%)	0
Vomiting	14 (28.0%)	5 (10.2%)	9 (18.4%)
Dangerously low levels of a type of white blood cell (neutrophils)	12 (24.0%)	3 (6.1%)	4 (8.2%)
Hair loss	10 (20.0%)	15 (30.6%)	19 (38.8%)
Weakness; lack of energy and strength	10 (20.0%)	4 (8.2%)	4 (8.2%)
Lack of enough red blood cells (anemia)	9 (18.0%)	10 (20.4%)	17 (34.7%)
Damage to the nerves outside of the spinal cord and brain	7 (14.0%)	7 (14.3%)	17 (34.7%)
Constipation	6 (12.0%)	10 (20.4%)	10 (20.4%)
Abnormality of the finger or toenails	5 (10.0%)	5 (10.2%)	11 (22.4%)

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

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

Serious Adverse Reaction	Part 2/Treatment 1 (out of 50 patients)	Part 2/Treatment 2 (out of 49 patients)	Part 2/Treatment 3 (out of 49 patients)
Any serious adverse reaction	7 (14.0%)	4 (8.2%)	2 (4.1%)
Vomiting	2 (4.0%)	1 (2.0%)	0

13 patients died during part 2 of the study: 1 patient in the part 2/treatment 1 group; 8 patients in the part 2/treatment 2 group; and 4 patients in the part 2/treatment 3 group. The death of 1 of the patients in the part 2/treatment 2 group could have been related to this patient’s study medicines. This patient experienced a serious adverse reaction of inflammation of the lungs that may cause difficulty breathing and can be life-threatening.

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 October 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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