ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 04/02/2012

Grantor: CDER IND/IDE Number: 074573 Serial Number: 0023

A Study of Vismodegib (GDC-0449, Hedgehog Pathway Inhibitor) As Maintenance Therapy in Patients With Ovarian Cancer in a Second or Third Complete Remission

This study has been completed.

Sponsor:	Genentech, Inc.
Collaborators:	
Information provided by (Responsible Party):	Genentech, Inc.
ClinicalTrials.gov Identifier:	NCT00739661

Purpose

The study was a Phase II, randomized, placebo-controlled, double-blind, multicenter clinical trial of vismodegib (GDC-0449) in patients with ovarian cancer in a second or third complete remission. Patients were randomized in a 1:1 ratio to either vismodegib or placebo. Randomization was stratified based on whether their cancer was in a second or third complete remission.

Condition	Intervention	Phase
Ovarian Cancer	Drug: Vismodegib 150 mg Drug: Placebo to vismodegib	Phase 2

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Investigator), Randomized
Official Title: A Phase II, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Vismodegib (GDC-0449) As Maintenance Therapy in Patients With Ovarian Cancer in a Second or Third Complete Remission

Further study details as provided by Genentech, Inc.:

Primary Outcome Measure:

- Progression-free Survival (PFS) [Time Frame: From randomization date through the data cut-off date of May 15, 2010, up to 100 weeks] [Designated as safety issue: No]

  PFS was defined as the time between randomization and disease progression, as confirmed by radiography, or death for any reason. Since patients were in remission at the start of the study, they had no evidence of the presence of tumors. Disease progression was defined as radiographic evidence of a tumor. Tumor assessments by computed tomography (CT) of the chest, abdomen, and pelvis were performed at screening and every 8 weeks during the study.

Secondary Outcome Measures:

- Progression-free Survival (PFS) in Patients With Versus Without Hedgehog Antigen Tumor Expression [Time Frame: From randomization date through the data cut-off date of May 15, 2010, up to 100 weeks] [Designated as safety issue: No]

  Hedgehog antigen expression was measured with immunohistochemical methods in tumor tissue taken from each patient prior to enrollment in the study. The percentage of cells with (> 0%) and without (0%) Hedgehog antigen expression was measured microscopically. PFS was defined as the time between randomization and disease progression, as confirmed by radiography, or death for any reason. Tumor assessments by computed tomography (CT) of the chest, abdomen, and pelvis were performed at screening and every 8 weeks during the study.
- Overall Survival [Time Frame: From randomization date through the data cut-off date of May 15, 2010, up to 100 weeks] [Designated as safety issue: No]

  Overall survival was defined as the time from randomization until death by any cause.

Enrollment: 104
Study Start Date: December 2008
Primary Completion Date: November 2010
Study Completion Date: November 2010

Arms	Assigned Interventions
Experimental: Vismodegib 150 mg Patients received vismodegib 150 mg orally once daily until radiographically confirmed disease progression, intolerable toxicity, or withdrawal from the study.	Drug: Vismodegib 150 mg Vismodegib 150 mg was provided in hard gelatin capsules. Other Names: GDC-0449
Placebo Comparator: Placebo to vismodegib Patients received placebo to vismodegib orally once daily until radiographically confirmed disease progression, intolerable toxicity, or withdrawal from the study.	Drug: Placebo to vismodegib Placebo to vismodegib consisted of the excipients for vismodegib without the active molecule in hard gelatin capsules matching the active drug product in color and size.

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Female
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- Histologic diagnosis of epithelial ovarian carcinoma, primary peritoneal carcinoma, or fallopian tube carcinoma
- Must be in second or third complete remission, have received chemotherapy (platinum-based and/or non-platinum-based) for recurrent disease, and have achieved a complete remission after their most recent chemotherapy regimen. Complete remission is defined as no symptoms suggestive of persistent cancer, computed tomography (CT) scan of the chest/abdomen/pelvis without evidence of ovarian cancer within 4 weeks of randomization, and normal CA-125 (measured within 2 weeks of randomization) following completion of prior chemotherapy. The study investigator should confirm the status of disease remission by CT scan before patient enrollment. If patient has lymphadenopathy by CT scan and the investigator thinks that it is unlikely due to ovarian cancer, this patient is considered eligible. If indicated, a confirmatory biopsy should be performed.
- Patients must have completed their most recent cytotoxic chemotherapy regimen (platinum-based or non-platinum based) no less than 3 weeks and no more than 14 weeks prior to randomization.
- Archival tissue must be available and requested.
- Negative pregnancy test on Day 1 (first day the patient receives vismodegib or placebo).
- For women of childbearing potential: Use of two effective methods of contraception, including one barrier method.

Exclusion Criteria:

- Pregnancy or lactation.
- Patients whose ovarian cancer is in first remission.
- Patients must not have experienced more than two prior recurrences of disease.
- Concurrent non-protocol-specified anti-tumor therapy, either approved or unapproved (eg, chemotherapy, hormonal therapy, other targeted therapy, radiation therapy, surgery, herbal therapy). Hormonal replacement therapies for treatment of postmenopausal symptoms do not exclude patients from this study.
- Current, recent (within 4 weeks of Day 1), or planned participation in an experimental drug study while enrolled in this study.
- History of other malignancies within 3 years of Day 1, except for tumors with a negligible risk for metastasis or death, such as adequately treated basal cell carcinoma (BCC) or squamous-cell carcinoma of the skin; ductal carcinoma in situ of the breast; or carcinoma in situ of the cervix.
- Uncontrolled medical illnesses such as infection requiring intravenous (IV) antibiotics.
- Life expectancy < 12 weeks.
- History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates use of an investigational drug or that might affect interpretation of the results of the study or render the patient at high risk from treatment complications.

Contacts and Locations

Investigators

Study Director:	Josina Reddy, M.D., Ph.D.	Genentech, Inc.

More Information

Responsible Party:	Genentech, Inc.
Study ID Numbers:	SHH4489g
Health Authority:	United States: Food and Drug Administration

Study Results

Participant Flow

Reporting Groups

	Description
Vismodegib 150 mg	Patients received vismodegib 150 mg orally once daily until radiographically confirmed disease progression, intolerable toxicity, or withdrawal from the study.
Placebo to Vismodegib	Patients received placebo to vismodegib orally once daily until radiographically confirmed disease progression, intolerable toxicity, or withdrawal from the study.

Overall Study

	Vismodegib 150 mg	Placebo to Vismodegib
Started	52	52
Completed	6	10
Not Completed	46	42
Adverse Event	2	0
Physician decision to withdraw patient	1	0
Patient decision to withdraw	9	4
Disease progression, radiographic	33	37
Reason for discontinuation not available	1	1

Baseline Characteristics

Reporting Groups

	Description
Vismodegib 150 mg	Patients received vismodegib 150 mg orally once daily until radiographically confirmed disease progression, intolerable toxicity, or withdrawal from the study.
Placebo to Vismodegib	Patients received placebo to vismodegib orally once daily until radiographically confirmed disease progression, intolerable toxicity, or withdrawal from the study.

Baseline Measures

	Vismodegib 150 mg	Placebo to Vismodegib	Total
Number of Participants	52	52	104
Age, Continuous [units: years] Mean (Standard Deviation)	57.3 (10.2)	58.6 (8.9)	57.9 (9.6)
Gender, Male/Female [units: participants]			
Female	52	52	104
Male	0	0	0

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Progression-free Survival (PFS)
Measure Description	PFS was defined as the time between randomization and disease progression, as confirmed by radiography, or death for any reason. Since patients were in remission at the start of the study, they had no evidence of the presence of tumors. Disease progression was defined as radiographic evidence of a tumor. Tumor assessments by computed tomography (CT) of the chest, abdomen, and pelvis were performed at screening and every 8 weeks during the study.
Time Frame	From randomization date through the data cut-off date of May 15, 2010, up to 100 weeks
Safety Issue?	No

Analysis Population Description

Intent-to-treat patient population: All randomized patients.

Reporting Groups

	Description
Vismodegib 150 mg	Patients received vismodegib 150 mg orally once daily until radiographically confirmed disease progression, intolerable toxicity, or withdrawal from the study.
Placebo to Vismodegib	Patients received placebo to vismodegib orally once daily until radiographically confirmed disease progression, intolerable toxicity, or withdrawal from the study.

Measured Values

	Vismodegib 150 mg	Placebo to Vismodegib
Number of Participants Analyzed	52	52
Progression-free Survival (PFS)	7.5 (5.59 to 11.24)	5.8 (4.14 to 7.49)

	Vismodegib 150 mg	Placebo to Vismodegib
[units: Months] Median (95% Confidence Interval)		

2. Secondary Outcome Measure:

Measure Title	Progression-free Survival (PFS) in Patients With Versus Without Hedgehog Antigen Tumor Expression
Measure Description	Hedgehog antigen expression was measured with immunohistochemical methods in tumor tissue taken from each patient prior to enrollment in the study. The percentage of cells with (> 0%) and without (0%) Hedgehog antigen expression was measured microscopically. PFS was defined as the time between randomization and disease progression, as confirmed by radiography, or death for any reason. Tumor assessments by computed tomography (CT) of the chest, abdomen, and pelvis were performed at screening and every 8 weeks during the study.
Time Frame	From randomization date through the data cut-off date of May 15, 2010, up to 100 weeks
Safety Issue?	No

Analysis Population Description

Intent-to-treat patient population: All randomized patients. Tissue for evaluation was only available for 29 patients in the vismodegib group and 28 patients in the placebo group.

Reporting Groups

	Description
Vismodegib 150 mg	Patients received vismodegib 150 mg orally once daily until radiographically confirmed disease progression, intolerable toxicity, or withdrawal from the study.
Placebo to Vismodegib	Patients received placebo to vismodegib orally once daily until radiographically confirmed disease progression, intolerable toxicity, or withdrawal from the study.

Measured Values

	Vismodegib 150 mg	Placebo to Vismodegib
Number of Participants Analyzed	29	28
Progression-free Survival (PFS) in Patients With Versus Without Hedgehog Antigen Tumor Expression [units: Months] Median (95% Confidence Interval)		
0% of cells with hedgehog punctate stain	7.00 (3.48 to 8.05)	5.32 (1.94 to NA) [1]
> 0% of cells with Hedgehog punctate stain	9.13 (1.81 to 11.24)	7.36 (3.12 to 10.97)

[1] The upper limit of the confidence interval could not be estimated due to the small sample size.

3. Secondary Outcome Measure:

Measure Title	Overall Survival
Measure Description	Overall survival was defined as the time from randomization until death by any cause.
Time Frame	From randomization date through the data cut-off date of May 15, 2010, up to 100 weeks
Safety Issue?	No

Analysis Population Description

Intent-to-treat patient population: All randomized patients.

Reporting Groups

	Description
Vismodegib 150 mg	Patients received vismodegib 150 mg orally once daily until radiographically confirmed disease progression, intolerable toxicity, or withdrawal from the study.
Placebo to Vismodegib	Patients received placebo to vismodegib orally once daily until radiographically confirmed disease progression, intolerable toxicity, or withdrawal from the study.

Measured Values

	Vismodegib 150 mg	Placebo to Vismodegib
Number of Participants Analyzed	52	52
Overall Survival [units: Months] Mean (Standard Deviation)	NA (NA) [1]	NA (NA) [2]

[1] The data were not mature for analysis. Only 2 deaths in the vismodegib group were reported as of the 15 May 2010 data cutoff.

[2] The data were not mature for analysis. Only 1 death in the placebo group was reported as of the 15 May 2010 data cutoff.

Reported Adverse Events

Time Frame	Adverse events and serious adverse events were recorded starting at randomization until 45 days after the last dose of treatment or after the initiation of new anti-tumor therapy, whichever was earlier, up to 100 weeks.

Additional Description	Adverse events were reported for the safety-evaluable population, which was defined as all patients who received at least one dose of study treatment.

Reporting Groups

	Description
Vismodegib 150 mg	Patients received vismodegib 150 mg orally once daily until radiographically confirmed disease progression, intolerable toxicity, or withdrawal from the study.
Placebo to Vismodegib	Patients received placebo to vismodegib orally once daily until radiographically confirmed disease progression, intolerable toxicity, or withdrawal from the study.

Serious Adverse Events

	Vismodegib 150 mg	Placebo to Vismodegib
	Affected/At Risk (%)	Affected/At Risk (%)
Total	6/52 (11.54%)	3/52 (5.77%)
Cardiac disorders		
Cardiac Failure Congestive [A] †	1/52 (1.92%)	0/52 (0%)
Gastrointestinal disorders		
Abdominal Pain [A] †	1/52 (1.92%)	0/52 (0%)
Small Intestinal Obstruction [A] †	0/52 (0%)	1/52 (1.92%)
General disorders		
Chest Pain [A] †	1/52 (1.92%)	0/52 (0%)
Infections and infestations		
Device Related Infection [A] †	0/52 (0%)	1/52 (1.92%)
Urinary Tract Infection [A] †	0/52 (0%)	1/52 (1.92%)
Investigations		
Hepatic Enzyme Increased [A] †	1/52 (1.92%)	0/52 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Lung Adenocarcinoma [A] †	1/52 (1.92%)	0/52 (0%)
Renal and urinary disorders		

	Vismodegib 150 mg	Placebo to Vismodegib
	Affected/At Risk (%)	Affected/At Risk (%)
Renal Colic [A] †	1/52 (1.92%)	0/52 (0%)
Respiratory, thoracic and mediastinal disorders		
Emphysema [A] †	1/52 (1.92%)	0/52 (0%)
Pneumothorax [A] †	1/52 (1.92%)	0/52 (0%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (Unspecified)

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Vismodegib 150 mg	Placebo to Vismodegib
	Affected/At Risk (%)	Affected/At Risk (%)
Total	51/52 (98.08%)	44/52 (84.62%)
Gastrointestinal disorders		
Abdominal Discomfort [A] †	2/52 (3.85%)	4/52 (7.69%)
Abdominal Distension [A] †	2/52 (3.85%)	4/52 (7.69%)
Abdominal Pain [A] †	10/52 (19.23%)	7/52 (13.46%)
Abdominal Pain Lower [A] †	3/52 (5.77%)	1/52 (1.92%)
Abdominal Pain Upper [A] †	9/52 (17.31%)	3/52 (5.77%)
Constipation [A] †	12/52 (23.08%)	5/52 (9.62%)
Diarrhoea [A] †	6/52 (11.54%)	8/52 (15.38%)
Dry Mouth [A] †	5/52 (9.62%)	1/52 (1.92%)
Dyspepsia [A] †	3/52 (5.77%)	2/52 (3.85%)
Flatulence [A] †	2/52 (3.85%)	4/52 (7.69%)
Nausea [A] †	17/52 (32.69%)	9/52 (17.31%)
Vomiting [A] †	8/52 (15.38%)	5/52 (9.62%)

	Vismodegib 150 mg	Placebo to Vismodegib
	Affected/At Risk (%)	Affected/At Risk (%)
General disorders		
Asthenia [A] †	5/52 (9.62%)	3/52 (5.77%)
Fatigue [A] †	14/52 (26.92%)	15/52 (28.85%)
Infections and infestations		
Influenza [A] †	4/52 (7.69%)	3/52 (5.77%)
Urinary Tract Infection [A] †	3/52 (5.77%)	0/52 (0%)
Investigations		
Weight Decreased [A] †	6/52 (11.54%)	1/52 (1.92%)
Metabolism and nutrition disorders		
Decreased Appetite [A] †	10/52 (19.23%)	1/52 (1.92%)
Hypomagnesaemia [A] †	3/52 (5.77%)	1/52 (1.92%)
Musculoskeletal and connective tissue disorders		
Arthralgia [A] †	8/52 (15.38%)	8/52 (15.38%)
Back Pain [A] †	6/52 (11.54%)	4/52 (7.69%)
Muscle Spasms [A] †	35/52 (67.31%)	1/52 (1.92%)
Musculoskeletal Pain [A] †	5/52 (9.62%)	3/52 (5.77%)
Myalgia [A] †	3/52 (5.77%)	2/52 (3.85%)
Pain In Extremity [A] †	4/52 (7.69%)	2/52 (3.85%)
Nervous system disorders		
Ageusia [A] †	4/52 (7.69%)	1/52 (1.92%)
Dizziness [A] †	4/52 (7.69%)	5/52 (9.62%)
Dysgeusia [A] †	35/52 (67.31%)	9/52 (17.31%)
Headache [A] †	5/52 (9.62%)	6/52 (11.54%)

	Vismodegib 150 mg	Placebo to Vismodegib
	Affected/At Risk (%)	Affected/At Risk (%)
Neuropathy Peripheral [A] †	2/52 (3.85%)	4/52 (7.69%)
Paraesthesia [A] †	3/52 (5.77%)	3/52 (5.77%)
Psychiatric disorders		
Anxiety [A] †	3/52 (5.77%)	2/52 (3.85%)
Depression [A] †	3/52 (5.77%)	0/52 (0%)
Insomnia [A] †	3/52 (5.77%)	3/52 (5.77%)
Respiratory, thoracic and mediastinal disorders		
Cough [A] †	5/52 (9.62%)	5/52 (9.62%)
Oropharyngeal Pain [A] †	2/52 (3.85%)	3/52 (5.77%)
Skin and subcutaneous tissue disorders		
Alopecia [A] †	28/52 (53.85%)	4/52 (7.69%)
Nail Disorder [A] †	0/52 (0%)	3/52 (5.77%)
Pruritus [A] †	4/52 (7.69%)	3/52 (5.77%)
Rash [A] †	6/52 (11.54%)	2/52 (3.85%)
Vascular disorders		
Hypertension [A] †	2/52 (3.85%)	3/52 (5.77%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (Unspecified)

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:
Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

The Study being conducted under this Agreement is part of the Overall Study. Investigator is free to publish in reputable journals or to present at professional conferences the results of the Study, but only after the first publication or presentation that involves the Overall Study. The Sponsor may request that Confidential Information be deleted and/or the publication be postponed in order to protect the Sponsor's intellectual property rights.

Results Point of Contact:

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