SYNOPSIS

Name of Sponsor/Company: Astellas Pharma US, Inc.		
Name of Finished Product: YM155		
Name of Active Ingredient: YM155 monobromide		
Title of Study: A Phase II, Multi-center, Open-label Study of YM155 in Subjects with Hormone Refractory Prostate Cancer (HRPC) Previously Treated with at Least One Prior Chemotherapy Regimen		
Responsible Medical Officer/Investigators: [redacted] MD, [redacted] MD, [redacted] MD, [redacted] MD, [redacted] MD, [redacted] MD, [redacted] MD, [redacted] MD, [redacted] MD, [redacted] MD, [redacted] MD, [redacted] MD, [redacted] MD		
Study Center(s): [redacted] England; [redacted] Netherlands; [redacted] Czech Republic; [redacted] Czech Republic; [redacted]		
Publication (reference): None		
Study Period: **Date of first enrollment:** 12/20/2005 **Date of last evaluation:** 3/30/2007 (main study) 8/7/2008 (survival)		**Phase of Development:** Phase II

Objectives: The primary objectives of this study were:

- To evaluate the efficacy of YM155 based on the percentage of subjects that obtain a Prostate Specific Antigen (PSA) response at anytime during the first 6 cycles. PSA response is defined as a ≥50% reduction in baseline PSA confirmed by a second PSA value at least 3 weeks apart without evidence of clinical or radiographic progression.

The secondary objectives of this study were:

- To evaluate the percentage of subjects who have a PSA response at any time during the study.
- To measure, in subjects with measurable disease, overall objective tumor response rate [RR] defined as complete response [CR] or partial response [PR] using Response Evaluation Criteria in Solid Tumors (RECIST) during the first 6 cycles of treatment.
- To measure the percentage of PSA decrease.
- To measure duration of PSA response.
- To measure the time to PSA progression.
- To measure, in subjects with measurable disease, overall objective tumor response rate [RR] defined as complete response [CR] or partial response [PR] using the RECIST.
- To measure change in Eastern Cooperative Oncology Group (ECOG) performance status.
- To evaluate overall survival (OS).
- To evaluate progression free survival (PFS).
- To measure one year survival.
- To measure median survival time.
- To evaluate safety based on clinical laboratory assessments, 12-lead ECGs, vital signs, physical examinations, and adverse events.

Methodology: This was an open label multicenter study in subjects with hormone refractory prostate cancer (HRPC) who progressed after at least one prior chemotherapy regimen. YM155 was administered by continuous IV infusion at a dose of 4.8 mg/m^2/day for 168 hours followed by a 14-day observation period. Retreatment criteria were assessed within three days of the start of the next cycle.

This study used a Simon 2-stage design with 13 evaluable subjects planned to be enrolled in stage 1. If 1 subject exhibited a PSA response within the first 6 cycles of treatment, an additional 14 evaluable subjects were planned to be enrolled. If 4 or more of the 27 evaluable subjects exhibited a PSA response within the first 6 cycles, then an additional 33 subjects (total enrolled = 60) were to be enrolled to further characterize the efficacy and toxicity of YM155. In order to have 27 evaluable subjects (complete stages 1 & 2), subjects who did not complete 2 cycles of YM155 along with PSA assessments were to be replaced (except for those subjects who withdrew due to clinical progression). Two subjects did not complete 2 cycles, but these subjects withdrew due to disease progression and were not replaced. Efficacy evaluations (PSA level and radiological imaging to assess tumor response) and safety evaluations (vital signs, physical exams, electrocardiograms (ECGs), adverse events and laboratory measurements) were collected.

Number of Patients (enrolled and analyzed):

Planned: Approximately 60 subjects

Enrolled: 35 subjects

Completed: Six subjects (17.1%) completed six cycles (infusion plus observation period). The reasons for discontinuation were: disease progression 20 (57.1%), adverse event 8 (22.9%), and withdrew consent unrelated to an AE [redacted] (2.9%).

Analyzed: All 35 subjects met the criteria for the full analysis set and were analyzed for efficacy. All subjects met the criteria for the safety set.

Diagnosis and Main Criteria for Inclusion: Subjects were to be male, at least 18 years of age, with histologically and/or cytologically- confirmed prostate cancer, serum testosterone levels <50 ng/dL, previously treated with at least 1 prior chemotherapy regimen (US subjects must have had at least 1 taxotere and prednisone regimen), a PSA level of 5 ng/mL or greater, receiving a stable dose of LHRH-agonist or LHRH-antagonist if medically castrated, and off anti-androgen therapy for at least 4 weeks prior to dosing for flutamide and other secondary hormonal therapy and 6 weeks for nilutamide and bicalutamide, with an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2, and life expectancy > 12 weeks. Subjects had to have evidence of disease progression on hormonal therapy and following at least one course of chemotherapy. Progression was defined as at least one new lesion on bone scan or x-ray compared to a previous evaluation OR appearance of a new soft tissue lesion or an increase of at least 20% in the sum of the largest diameters OR a rising PSA defined as increase in PSA on 2 consecutive measurements separated by at least 1 week. Subjects could not have had radiation therapy within 4 weeks prior to the start of YM155 treatment, could not have concurrent anticancer therapy within the last 4 weeks (6 weeks for nitrosoureas or mitomycin C, or other agents known to prolong marrow suppression), could not use alternative medications such as herbal supplements within 2 weeks prior to the start of study drug and could not have brain metastases. Subjects could not have had surgery within the past 21 days, could not have a urine protein of 2+ or greater and must have had adequate bone marrow, renal and hepatic function.

Test Product, Dose and Mode of Administration, Batch Numbers:

Test Product: YM155

Dose: Initial dose was 4.8 mg/m^2/day IV. In the event of YM155- related toxicities, the dose could be reduced to 3.6 mg/m^2/day IV. Additional dose reductions were to be discussed with the Medical Monitor.

Mode of Administration: Continuous IV infusion (central line or port)

Batch Numbers [redacted]

Duration of Treatment and Duration of Study: Subjects were to receive six cycles of YM155 infused over 168 hours (7 days) followed by a 14 day observation period. Subjects who had stable disease or a response at the end of 6 cycles were permitted to remain in the study for up to 10 cycles of treatment. Thirty-one subjects (88.6%) completed two cycles of YM155 infusion and eight subjects (22.9%) completed six cycles, but two of these dropped out during the observation period following infusion.

Reference Product, Dose and Mode of Administration, Batch Numbers: Not applicable. The study was conducted as a single-arm open-label study because the route of administration made blinding impractical.

Criteria for Evaluation:

Safety was assessed by evaluating clinical laboratory tests (e.g. hematology, chemistry, urinalysis, creatine phosphokinase [CPK], CPK-MB and troponin T), 12-lead ECGs, vital signs, physical examinations and adverse events.

Clinical response to YM155 was evaluated using PSA levels, and in subjects with measurable disease at baseline radiological imaging was used to assess tumor size using RECIST guidelines. Blood draws for PSA assessments were obtained between days 18 to 21 after every cycle and at the final assessment. Radiological imaging was performed after even numbered cycles. Subjects whose tumor response was a complete response (CR) or partial response (PR) had a confirmatory scan no less than 4 weeks after the criteria for response were met.

Statistical Methods:

Frequency distributions (number and percentage of subjects) were used to summarize categorical variables, and descriptive statistics (n, mean, median, standard deviation [SD]), minimum and maximum) were used to summarize continuous variables. Kaplan Meier estimates of the mean, standard error and quartiles were provided for time to PSA progression, duration of PSA response, progression-free survival and overall survival.

Summary

Demographics: Thirty-five subjects were enrolled. The majority of subjects were Caucasian (32/35, 91.4%). The mean age (± SD) was 67.1 (±7.37) years. The ECOG performance status at baseline was: Grade 0: 28.6% (10/35); Grade 1: 62.9% (22/35); and Grade 2: 8.6% (3/35). The majority of subjects were disease stage 4 (34/35, 97.1%), had a diagnosis of adenocarcinoma (34/35, 97.1%), and had prostate cancer with a mean disease duration (± SD) of 6.7 (±4.61) years. Metastases were mainly to the bone (34/35, 97.1%), lymph nodes (19/35, 54.3%), and lung (7/35, 20.2%). The majority (28/35, 80.0%) had previously received at least one surgery for their cancer, radiation (23/35, 65.7%), and all had previously received chemotherapy. The mean number of previous chemotherapies was 2.6 (1.75) and ranged from 1 to 7. The majority (32/35, 91.4%) had previously received other drug therapies for their primary cancer or metastases.

Drug Administration: Study drug was administered at 4.8 mg/m^2/day as an initial dose for all subjects. [redacted] had a dose reduction to 3.6 mg/m^2/day in cycles 2 and 3 due to [redacted] in cycles 1 (Grade 2) and 2 (Grade 1). The [redacted] following Cycle 3. [redacted] was inadvertently given a dose of 2.4 mg/m^2/day in cycle 4 but was treated with 4.8 mg/m^2/day in cycles 5 and 6.

Pharmacokinetic/Pharmacodynamic Results: Pharmacokinetic (PK) assessments were performed on 34 subjects during the first 6 cycles only. Plasma concentrations of unchanged YM155 were measured using a validated LCMS/MS method under GLP, with lower limit of quantification of 0.05 ng/mL.

The median plasma YM155 concentration on Days 4 and 6, and at 5 minutes prior to the end of infusion on Day 8 in Cycle 1 were 9.63, 9.17, and 9.50 ng/mL, respectively. The median CL_{total} was 44.01L/hr.

Efficacy Results: Two of 35 subjects (5.7%) had a PSA response (a decrease in PSA of at least 50% confirmed by a second PSA value at least 3 weeks later). These two subjects had PSA responses lasting 21 and 112 days respectively for a mean duration of 77 days (Kaplan-Meier estimate). Eight subjects (22.8%) had a decrease in PSA with the average percent decrease of 46.3% (range: 7.1% to 92.4%). [redacted] (6.25%) of the 16 subjects with measurable disease at baseline and post-baseline tumor assessments had a partial response (Investigator's Assessment and stable disease by Independent Reviewer) according to RECIST criteria and this response occurred following cycle 6 and was confirmed at Cycle 8. [redacted] of two who had a PSA response. The PSA response occurred in Cycle 5 and lasted through Cycle 9. [redacted] who had a PSA response did not have measurable disease at baseline so there were no tumor assessments for this subject.

Twenty of 35 subjects had objective disease progression while on study (excluding the follow up period for survival). The median progression-free survival time was 88 days (95% CI = 61-176 days).

Survival: All subjects who received YM155 were to be followed for survival for one year after the last subject completed or withdrew from the study. The subject or authorized representative was to be contacted every three months by site personnel in order to determine subject status (alive or dead). The last subject completed on March 30, 2007.

Maximum follow-up time for survival was over two years (800 days). Twenty-four deaths were observed among 35 subjects. Median survival time among all subjects was 313 days (95% CI = 212 to 687 days). The one-year survival probability was 0.41 (95% CI = 0.24 to 0.58).

Safety Results: All subjects experienced at least one adverse event (AE); 27 (77.1%) had a drug related AE;

18 subjects (51.4%) reported a total of 47 serious AE. Five patients (14.3%) had 6 SAEs considered related to YM155 and 8 subjects (22.9%) had ten AEs leading to permanent discontinuation of study drug (one of which was considered to be related).

The most common adverse events (AEs) (≥ 6% of all subjects) are presented in Table 1. The most common AEs were fatigue, nausea, anorexia, constipation, pyrexia, vomiting, arthralgia, back pain, bone pain, oedema peripheral, myalgia, cough, headache, urinary tract infection, dysgeusia, hyperhidrosis, hypokalaemia, hypomagnesaemia, and weight decreased. Grade 3, 4, or 5 AEs are shown in Table 2. Those occurring in more than 1 subject included fatigue: 3 (8.6%), back pain: 3 (8.6%), hyperglycaemia: 2 (5.7%), hypokalaemia: 2 (5.7%), and bone pain: 2 (5.7%). Related AEs that were Grade 3 or greater (Table 3) include coagulopathy: [redacted] (2.9%), neutropenia: ([redacted], 2.9%, Grade 4), thrombocytopenia: [redacted] (2.9%), fatigue: [redacted] (2.9%), upper respiratory tract infection: [redacted] (2.9%), platelet count decreased: [redacted] (2.9%), hypophosphataemia: [redacted] (2.9%) and hemorrhage intracranial: [redacted] (2.9%, Grade 5). Serious adverse events are given in Table 4. The most common serious adverse events were constipation: 2 (5.7%), pyrexia: 2 (5.7%), hyperglycaemia: 2(5.7%), hypokalaemia: 2 (5.7%), back pain: 2 (5.7%), and bone pain: 2 (5.7%). The ten events that led to discontinuation in 8 subjects were: disseminated intravascular coagulation, pain, performance status decreased, pneumonia, cachexia (2 subjects), back pain, hemorrhage intracranial, spinal cord compression, and mental status changes.

Six subjects died prior to the start of long-term survival follow-up. Three of these were due to their prostate cancer. Details of the 3 who died of other reasons are provided below.

- [redacted] who died of an [redacted] considered possibly related to study drug, was a [redacted] with Stage IV adenocarcinoma with metastases to bone and lymph nodes. Subject entered study with a [redacted]. Subject received one cycle of YM155 and during the second cycle experienced and adverse event of [redacted]. Subject was on [redacted] prior to entering the study (start day – 723) [redacted]. [redacted]. The last PSA value obtained was on Day 22 and was [redacted].
- [redacted] who died on Day 36 secondary to [redacted], was a [redacted] with Stage IV adenocarcinoma with metastases to lung, bone, adrenal, lymph nodes and skin. The [redacted] was considered unlikely related to YM155. Ten days prior to this event, the subject experienced adverse events of Grade 3 [redacted], Grade 2 [redacted], Grade 3 [redacted] and Grade 1 [redacted]. The subject had a significant medical history o [redacted].
- [redacted] died of [redacted] unrelated to study drug

[redacted] treated with 4.8 mg/m^2/day, had [redacted]. This subject was a [redacted] with Stage IV adenocarcinoma with metastases to bone and lymph nodes experienced [redacted], prior to starting YM155, and for multiple readings thereafter. An adverse event of [redacted] was reported starting Day (-) 29 through Day (-) 27 for which the subject was [redacted]. This subject had a [redacted] significant for [redacted]. This subject completed 10 cycles of YM155.

In addition, two subjects had cardiac rhythm adverse events reported. The [redacted] with Stage IV adenocarcinoma with metastases to lung, bone, lymph node had an adverse event reported on Day 3 of Cycle 1 of Grade 1 [redacted] considered possibly related to YM155 and Grade 1 [redacted] considered unlikely related to YM155. The subject had [redacted] significant for [redacted] The subject went onto complete 3 cycles of YM155 without further incidence. The second [redacted] with Stage IV adenocarcinoma with metastases to lung, bone, adrenal, lymph nodes and skin had an adverse event of [redacted] on Day 6 of cycle 1. This event was considered not related to study drug since the subject had [redacted] which was ongoing at the time of study entry. The event was [redacted]. The subject completed only one cycle of YM155.

The most common laboratory abnormalities that were reported in this study were mainly considered mild to moderate in severity and included the following: thrombocytopenia, platelet production decreased or platelet count decreased (5/35, 14.3%) with [redacted] of thrombocytopenia and [redacted] of platelet count decreased considered Grade 3 and the rest Grade 1 or 2; hypomagnesaemia (4/35, 11.4%) all events considered Grade 1; neutropenia (3/35, 8.6%) with 2 events considered Grade 1or 2 and one event Grade 4; anemia (3/35, 8.6%) with 2 events considered Grade 2 and one Grade 3; however, subjects in this study were allowed to received prophylactic erythropoietin and therefore this event may have been under reported, hypokalemia or decreased potassium (4/35, 11.4%) with 2 events considered Grade 3 and the rest grade 1 or 2; blood creatinine increase or renal failure (4/35, 11.4%) with renal failure ([redacted]) being reported as Grade 3 and the increase in creatinine as Grade 2 and Grade 1 (2 events).

CONCLUSIONS: YM155 given as monotherapy demonstrated some activity in hormone refractory prostate cancer (HRPC) with two subjects showing PSA response and one of these with measurable disease at baseline also showed objective tumor response per RECIST (judged a PR by the Investigator and SD by the Independent Reviewer). The mean duration of response for these 2 subjects was 77 days. The mean percent PSA decrease was 46.3% in the 8 subjects who experienced a decrease. Overall YM155 was well tolerated with the majority of adverse events being reported as Grade 1 or 2. Forty-seven SAEs were reported in 18 subjects during the study and 6 events reported in 5 subjects were considered related to YM155. Based upon the evidence of activity in this subject population with HRPC and with at least one prior taxane treatment regimen, and based upon the tolerability, future studies are warranted to evaluate YM155 in combination with standard of care in a combination setting in HRPC subjects.

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Synopsis Table 1: Most Common (≥ 6%) Treatment-Emergent Adverse Events

Preferred Term, MedDRA, v 6.1	YM155 Dose (mg/m^2/day) All Cycles		
	4.8 (n=35)	3.6 (n=1)	Overall (N=35)
	n (%)	n (%)	n (%)
Total Number of Subjects with ≥ 1 Adverse Event	35 (100.0)	1 (100.0)	35 (100.0)
Fatigue	22 (62.9)	0 (0.0)	22 (62.9)
Nausea	14 (40.0)	0 (0.0)	14 (40.0)
Anorexia	11 (31.4)	0 (0.0)	11 (31.4)
Constipation	11 (31.4))	0 (0.0)	11 (31.4)
Pyrexia	9 (25.7)	1 (100.0)	9 (25.7)
Vomiting	9 (25.7)	0 (0.0)	9 (25.7)
Arthralgia	7 (20.0)	0 (0.0)	7 (20.0)
Back Pain	7 (20.0)	0 (0.0)	7 (20.0)
Bone Pain	7 (20.0)	0 (0.0)	7 (20.0)
Oedema Peripheral	7 (20.0)	0 (0.0)	7 (20.0)
Myalgia	6 (17.1)	0 (0.0)	6 (17.1)
Cough	5 (14.3)	0 (0.0)	5 (14.3)
Headache	5 (14.3)	0 (0.0)	5 (14.3)
Urinary Tract Infection	5 (14.3)	0 (0.0)	5 (14.3)
Dysgeusia	4 (11.4)	0 (0.0)	4 (11.4)
Hyperhidrosis	4 (11.4)	0 (0.0)	4 (11.4)
Hypokalemia	4 (11.4)	0 (0.0)	4 (11.4)
Hypomagnesaemia	4 (11.4)	0 (0.0)	4 (11.4)
Weight Decreased	4 (11.4)	0 (0.0)	4 (11.4)
Anaemia	3 (8.6)	0 (0.0)	3 (8.6)
Neutropenia	3 (8.6)	0 (0.0)	3 (8.6)
Thrombocytopenia	3 (8.6)	0 (0.0)	3 (8.6)
Dyspepsia	3 (8.6)	0 (0.0)	3 (8.6)
Rigors	3 (8.6)	0 (0.0)	3 (8.6)
Blood Creatinine Increased	3 (8.6)	0 (0.0)	3 (8.6)
Hyperglycaemia	3 (8.6)	0 (0.0)	3 (8.6)
Groin Pain	3 (8.6)	0 (0.0)	3 (8.6)
Muscular Weakness	3 (8.6)	0 (0.0)	3 (8.6)

Synopsis Table 2: Grade 3, 4 and 5 Treatment-Emergent Adverse Events That Occurred in More Than 1 Subject

System Organ Class Preferred Term, MedDRA, v 6.1	YM155 Dose (mg/m^2/day) All Cycles								
	4.8 (n=35)			3.6 (n=1)			Overall (N=35)		
Grade	3	4	5	3	4	5	3	4	5
Maximum Grade Subject Experienced [1]									
Blood and lymphatic system disorders									
Anaemia	1						1		
Coagulopathy	1						1		
Disseminated Intravascular Coagulation	1						1		
Neutropenia		1						1	
Thrombocytopenia	1						1		
Cardiac Disorders									
Cardio-Respiratory Arrest			1						1
Gastrointestinal Disorders									
Haematemesis	1						1		
General disorders and administration site conditions									
Fatigue	2	1					2	1	
Pain	1						1		
Pain Exacerbated	1						1		
Performance Status Decreased	1						1		
Infections and infestations									
Candiduria	1						1		
Infection	1						1		
Infusion Site Infection	1						1		
Pneumonia			1						1
Staphylococcal Sepsis	1						1		
Upper Respiratory Tract Infect.	1						1		
Wound Infection	1						1		
Investigations									
Gamma-glytamyltransferase increased	1						1		
Platelet Count Decreased	1						1		
Metabolism and nutrition disorders									
Acidosis	1						1		
Cachexia			1						1
Dehydration	1						1		
Hyperglycaemia	2						2		
Hypocalcaemia	1						1		
Hypokalaemia	2						2		
Hypophosphataemia	1						1		
Musculoskeletal and Connective Tissue Disorders									
Back Pain	3						3		
Bone Pain	2						2		
Muscular Weakness	1						1		
Nervous system disorders									
Hemorrhage Intracranial			1						1
Spinal Cord Compression	1						1		

System Organ Class Preferred Term, MedDRA, v 6.1	YM155 Dose (mg/m^2/day) All Cycles								
	4.8 (n=35)			3.6 (n=1)			Overall (N=35)		
Grade	3	4	5	3	4	5	3	4	5
Psychiatric Disorders									
Agitation	1						1		
Depression	1						1		
Renal and Urinary Tract Disorders									
Renal Failure Acute	1						1		
Respiratory, Thoracic and Mediastinal Disorders									
Hypoxia	1						1		
Vascular Disorders									
Thrombosis	1						1		
Vena Cava Thrombosis	1						1		

Note: Cells without any counts indicate no events occurred in that category.

1. A subject is counted once for the most severe event experienced.

Synopsis Table 3: Related Treatment-Emergent Adverse Events by CTC Grade

System Organ Class Preferred Term, MedDRA, v 6.1	YM155 Dose (mg/m^2/day) All Cycles								
	4.8 (n=35)			3.6 (n=1)			Overall (N=35)		
Grade (1)	3	4	5	3	4	5	3	4	5
Maximum Grade Subject Experienced [1]									
Blood and lymphatic system disorders									
Coagulopathy	1						1		
Neutropenia		1						1	
Thrombocytopenia	1						1		
General disorders and administration site conditions									
Fatigue	1						1		
Infections and infestations									
Upper Respiratory Tract Infection	1						1		
Investigations									
Platelet Count Decreased	1						1		
Metabolism and nutrition disorders									
Hypophosphataemia	1						1		
Nervous system disorders									
Hemorrhage Intracranial			1						1

Note: Cells without any counts indicate no events occurred in that category.

Synopsis Table 4: Treatment-Emergent Serious Adverse Events

Preferred Term, MedDRA, v6.1	YM155 Dose (mg/m²/day) All Cycles		
	4.8 (n=35)	3.6 (n=1)	Overall (N=35)
Number of Subjects with ≥1 Serious Adverse Event	14 (40.0)	0	14 (40.0)
Neutropenia	1 (2.9)		1 (2.9)
Atrial fibrillation	1 (2.9)		1 (2.9)
Periorbital Haematoma	1 (2.9)		1 (2.9)
Constipation	1 (2.9)		1 (2.9)
Haematemesis	1 (2.9)		1 (2.9)
Catheter Site Related Reaction		1(100)	1 (2.9)
Infusion Site Reaction	1 (2.9)		1 (2.9)
Pain Exacerbated	1 (2.9)		1 (2.9)
Pyrexia	2 (5.7)		2 (5.7)
Infusion Site Infection	1 (2.9)		1 (2.9)
Upper respiratory tract infection	1 (2.9)		1 (2.9)
Urinary Tract Infection Enterococcal	1 (2.9)		1 (2.9)
Wound Infection	1 (2.9)		1 (2.9)
Device Failure	1 (2.9)		1 (2.9)
Head Injury	1 (2.9)		1 (2.9)
Blood Creatinine Increased	1 (2.9)		1 (2.9)
Cachexia	1 (2.9)		1 (2.9)
Hypokalaemia	2 (5.7)		2 (5.7)
Back Pain	1 (2.9)		1 (2.9)
Bone Lesion	1 (2.9)		1 (2.9)
Facial Palsy	1 (2.9)		1 (2.9)
Hemorrhage Intracranial	1 (2.9)		1 (2.9)
Headache	1 (2.9)		1 (2.9)
Loss of Consciousness	1 (2.9)		1 (2.9)
Spinal Cord Compression	1 (2.9)		1 (2.9)
Subarachnoid Haemorrhage	1 (2.9)		1 (2.9)
Renal Failure Acute	1 (2.9)		1 (2.9)
Pleural Effusion	1 (2.9)		1 (2.9)
Vena Cava Thrombosis	1 (2.9)		1 (2.9)

Note: Cells without any events were intentionally left blank.