Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: YM155		

SYNOPSIS

Title of Study: A Phase 2, Multicenter, Open-label Study of YM155 Plus Docetaxel in Subjects with Stage III (Unresectable) or Stage IV Melanoma (155-CL-034)

Investigators: [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): 10 sites in the US and 1 site in Canada

Publication (reference): None

Study Period: 2 years

Date of first enrollment (Study initiation date): 04 December 2009

Date of last evaluation (Study completion date): 26 April 2011 (primary analysis cutoff date)

Phase of Development: 2

Objectives: The primary objective of this study was to evaluate 6-month progression-free survival (PFS). Secondary objectives were to evaluate objective response rate (ORR), 1-year survival, overall survival (OS), duration of response (DOR), clinical benefit rate (CBR), time to response (TTR) and safety and tolerability. [redacted].

Methodology: This was a phase 2, multicenter, open-label study of YM155 plus docetaxel in patients with Stage III (unresectable) or Stage IV melanoma. The first part of the study was to determine the appropriate dose of docetaxel (100 mg/m^2 or 75 mg/m^2 given by intravenous infusion over 1 hour) to be administered in combination with YM155 (5 mg/m^2 per day, administered by continuous infusion over 168 hours, starting within 1 hour of completing the docetaxel infusion) in the second part. The recommended dose of docetaxel for part 2 was based on protocol defined dose limiting toxicities (DLTs) as well as the overall safety and tolerability during cycle 1 in patients treated in part 1. Each 21-day cycle consisted of a 7-day (168-hour) treatment period followed by a 14-day observation period, and each patient received the combination regimen until meeting discontinuation criteria. If a patient discontinued treatment with at least stable disease, the patient completed follow-up visits every 12 weeks for 2 years (starting after the end-of-treatment visit) or until they initiated another systemic antimelanoma treatment, exhibited progressive disease or died. Following the end-of-treatment visit, all patients (excepting those who withdrew consent or were lost to follow-up) were contacted by the study site every 12 weeks for survival status until they died or for no more than 2 years after the end-of-treatment. Clinical and safety data were reviewed on a monthly schedule or more frequently if needed.

Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: YM155		

Number of Patients (planned, enrolled and analyzed): The planned sample size was up to 9 patients in part 1 and 60 patients in part 2. A total of 64 patients were enrolled (3 in part 1, 61 in part 2) and all were included in the analyses of efficacy, safety and plasma concentrations of YM155.

Diagnosis and Main Criteria for Inclusion: Male and nonpregnant/nonlactating female patients aged ≥ 18 years who had histologically or cytologically confirmed Stage III (unresectable) or Stage IV melanoma and a life expectancy > 12 weeks at the baseline visit were eligible for this study. Patients were to have an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 at the baseline visit, no prior systemic treatment or cytotoxic chemotherapy for advanced melanoma (Stage III or Stage IV) and must have completed palliative radiation treatment if administered ≥ 4 weeks prior to the baseline visit. They were also to have at least 1 measurable target lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) (Version 1.1) and, if they had a previous history of nonmelanoma malignancy, they must have met the required criteria for a cancer survivor.

Test Product, Dose and Mode of Administration, Batch Numbers: YM155 was supplied as a solution for intravenous injection in 10-mL vials containing 75 mg (7.5 mL) of the cationic moiety of the drug substance at a concentration of 10 mg/mL, 100 mM/L lactic acid, 0.35% (weight/volume) sodium chloride, sodium hydroxide, hydrochloric acid and water for injection (pH 3.2 to 4.0). YM155 was administered by continuous intravenous infusion at a dose of 5 mg/m^2 per day for 168 hours (7 days) every 21 days. The manufacturing lots of YM155, numbered [redacted] and [redacted], were packaged as clinical trial materials and assigned packaging lot numbers [redacted] and [redacted] for investigational sites in the US and Canada and [redacted] for investigational sites in Europe with expiration dates of 30 April 2011, 31 March 2013 and 30 April 2011, respectively.

Duration of Treatment (or Duration of Study, if applicable): Patients could remain on treatment as long as they met retreatment criteria during the retreatment assessment period (days 18 to 21) of each cycle.

Reference Product, Dose and Mode of Administration, Batch Numbers: Not applicable.

Criteria for Evaluation: Efficacy and safety data, as well as pharmacokinetic (plasma concentration) data for YM155 and metabolites (YM-217562 and YM-278290) [redacted] were collected in this study. Efficacy was based on 6-month PFS, ORR (complete response [CR] or partial response [PR]), PFS, OS, 1-year survival, DOR, CBR (CR + PR + stable disease) and TTR for patients with CR or PR. Additional endpoints included: 6-month PFS per investigator's assessment; change from baseline in ECOG performance status; [redacted] Safety was assessed by evaluating adverse events (AEs), clinical laboratory evaluations, vital signs, 12-lead electrocardiograms (ECGs) and physical examination.

Statistical Methods: The primary efficacy endpoint was 6-month PFS, calculated with the corresponding 2-sided 95% confidence intervals (CIs) for the full analysis set (FAS) using Kaplan-Meier estimates. The study

Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: YM155		

was considered successful if the lower boundary of the 95% CI for 6-month PFS was greater than 20%. Subgroup analyses of 6-month PFS, based on age, race, sex, ECOG performance status, lactate dehydrogenase (LDH) levels, visceral disease, were also conducted, as was a sensitivity analysis of the primary variable and an analysis of the primary variable based on the per-protocol set (PPS). ORR (CR + PR) was calculated with a corresponding exact 2-sided 95% CI; PFS, OS, 1-year survival, 6-month PFS per investigator's assessment and DOR were calculated using Kaplan-Meier estimates with medians with corresponding 2-sided 95% CI; CBR was calculated along with a corresponding exact 2-sided 95% CI; TTR was summarized using descriptive statistics. Analysis of secondary variables was conducted on the FAS and PPS. Change from baseline in ECOG performance status was summarized for the FAS. Plasma YM155, YM-217562 and YM-278290 concentrations were listed and summarized by scheduled time window using descriptive statistics. Clinical safety data were summarized using descriptive statistics or frequency distributions, as appropriate. For continuous variables, descriptive statistics included: number of patients (n), mean, SD, median, minimum and maximum; categorical data were summarized by frequency and percentage.

Summary of Results/Conclusions:

Population: All 64 enrolled patients were white (100%), most were not Hispanic or Latino (98.4%) and approximately two-thirds were male (68.8%). Age ranged between 26 and 79 years (mean 61.0 years), with 57.8% of patients being below the age of 65. Weight ranged between 52.0 and 148.2 kg and body surface area (BSA) between 1.5 and 2.7 m^2. The majority of the 64 patients had LDH levels (89.1%) that were greater than the laboratory upper limit of normal, 6 patients (9.4%) had LDH values within the laboratory normal reference range, and 1 patient (1.6%) had no available LDH data. Evidence of visceral disease was documented in 47 (73.4%) patients at baseline. All patients had an ECOG status of 0 or 1 at baseline [Table 1].

At the time of primary analysis, 60 (93.8%) enrolled patients had discontinued treatment. Four (6.3%) patients did not discontinue treatment. The majority of discontinuations were due to objective disease progression (37 [57.8%]). Six patients (9.4%) discontinued due to AEs, 6 patients (9.4%) declined further treatment, 5 patients (7.8%) due to clinical deterioration, for 4 patients (6.3%) the investigator felt it was in the best interest of the patient to stop treatment and 2 patients (3.1%) discontinued treatment for other reasons (1 patient requested to come off treatment, 1 patient essentially had disease progression). Thirty-two (50%) of the enrolled patients discontinued the study for the following reasons: death 25 (39.1%), declined further participation 6 (9.4%) and 1 patient (1.6%) discontinued from the study because other treatment for melanoma had been received. The majority of patients (96.9%) did not complete follow-up for DOR or TTR and 39 (60.9%) did not complete follow-up for overall survival.

Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: YM155		

Table 1 Demographic and Baseline Characteristics

Characteristic	Total (n = 64)
Sex, n (%)	
Male	44 (68.8)
Female	20 (31.3)
Race, n (%)	
White	64 (100.0)
Ethnicity, n (%)	
Not Hispanic or Latino	63 (98.4)
Hispanic or Latino	1 (1.6)
Age (years)	
< 65, n (%)	37 (57.8)
≥ 65, n (%)	27 (42.2)
Mean (SD)	61.0 (10.79)
Median	59.0
Minimum, maximum	26, 79
Height (cm)	
Mean (SD)	173.42 (9.691)
Median	175.30
Minimum, maximum	149.9, 193.8
Weight (kg)	
Mean (SD)	91.29 (21.739)
Median	89.85
Minimum, maximum	52.0, 148.2
Body Surface Area (m^2)	
Mean (SD)	2.04 (0.262)
Median	2.00
Minimum, maximum	1.5, 2.7
ECOG Performance Status, n (%)	
Grade 0	41 (64.1)
Grade 1	23 (35.9)
LDH Status, n (%)	
Elevated	57 (89.1)
Normal	6 (9.4)
No data	1 (1.6)
Visceral Disease at Study Entry, n (%)	
Yes	47 (73.4)
No	17 (26.6)

All patients who initiated at least 1 dose of YM155 (Full Analysis Set).
ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase.
Source: Table 12.1.2.1

Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: YM155		

Efficacy Results: Based on independent radiology review, the 6-month PFS (95% CI) for the FAS and PPS was 34.8% (21.3%, 48.6%). In the sensitivity analysis, the lower boundary of the 95% CI was > 20% (33.6 [20.5%, 47.1%]) [Table 2]. Subgroup analysis parameters included: age, race, sex, baseline ECOG, LDH status, and visceral disease. Both age ≥ 65 years (43.1% for FAS and PPS) and no visceral disease (51.7% for FAS and PPS) appeared to show greater than 6‑month PFS compared to the other patient subsets [Table 2].

Table 2 6-month Progression-free Survival (Independent Radiology Review)

Subgroup	Total (n = 64)
All Patients, % (95% CI)†	34.8 (21.3, 48.6)
All Patients (Sensitivity Analysis), % (95% CI)‡	33.6 (20.5, 47.1)
Sex, % (95% CI)	
Male	29.0 (13.7, 46.2)
Female	44.5 (19.8, 66.7)
Race, % (95% CI)	
White	34.8 (21.3, 48.6)
Age, % (95% CI)	
< 65 years	29.1 (12.8, 47.7)
≥ 65 years	43.1 (21.5, 63.0)
Baseline ECOG Performance Status, % (95% CI)	
Grade 0	37.3 (19.2, 55.4)
Grade 1	29.8 (11.8, 50.5)
LDH Status, % (95% CI)	
Elevated	37.8 (23.1, 52.3)
Normal	0
Missing	0
Visceral Disease, % (95% CI)	
Yes	31.6 (17.2, 47.1)
No	51.7 (24.0, 73.7)

All patients who initiated at least 1 dose of YM155 (Full Analysis Set).

ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase.

† Calculated using Kaplan-Meier estimate at the 168th day after the first dose.

‡ Calculated using Kaplan-Meier estimate at the 168th day after the first dose based on sensitivity analysis data in which subjects who discontinued due to clinical deterioration were counted as progressed at the scheduled visit.

Source: Table 12.3.1.1, Table 12.3.1.3, Table 12.3.2.6

The ORR was 12.5% (95% CI: 5.9%, 24.6%), with 8 patients (12.5%) exhibiting PR and none CR. Using 37 days, the minimum time to perform the first follow-up imaging scan as the minimum duration of stable disease, 33 patients (51.6%) had stable disease; 17 (26.6%) had progressive disease and 6 (9.4%) had insufficient assessments for determination of best response. Overall, the clinical benefit rate from treatment with YM155 plus docetaxel was 64.1% (95% CI: 55.0%, 79.7%). When the definition of stable disease only

Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: YM155		

includes those patients who maintained stable disease or a response for 84 days, the breakdown is as follows: 8 patients (12.5%) had a PR, 17 patients (26.6%) had stable disease, and 15 (23.4%) had insufficient assessments for determination of best overall response, yielding a CBR of 39.1% (95% CI: 29.1%, 55.1%). The median duration of PFS was 127.0 days (95% CI: 81.0, 168 days) and probability of 1-year survival was 50.5% (95% CI: 33.2%, 65.5%). The median TTR was 83 days; OS and DOR could not be calculated. The estimate of 6-month PFS based on investigator assessment was 31.3% (95% CI: 19.5%, 43.9%). The lower bound of the 95% CI falling below 20%, would deem this an unsuccessful trial. All patients had an ECOG performance status of 0 or 1 at baseline; at the end of treatment visit, 5 patients (7.8%) had an ECOG status of 2 and 3 patients (4.7%) had an ECOG status of 3.

Pharmacokinetic Results: Median plasma concentration of YM155 on day 4 during the first, second and third infusions of YM155 (5 mg/m^2 per day) ranged between 6.510 ng/mL and 6.070 ng/mL and were similar to concentrations in samples collected before the end of YM155 infusion on day 8 of these cycles (between 6.740 and 6.890 ng/mL). Median concentrations of YM-217562 and YM-278290 were 0 at all time points with the maximum concentrations of YM‑217562 and YM‑278290 in any patient at any time point being 10.18 ng/mL and 0.37 ng/mL, respectively [Table 3].

Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: YM155		

Table 3 Plasma Concentrations of YM155 and Metabolites (YM-217562 and YM-278290)

	Time Point								
	Cycle 1			Cycle 2			Cycle 3		
		Day 8			Day 8			Day 8	
Analyte	Day 4	Before†	After‡	Day 4	Before†	After‡	Day 4	Before†	After‡
YM155 (ng/mL)									
n	59	52	54	59	55	54	35	36	36
Mean	10.177	12.279	6.707	6.789	12.379	8.977	20.247	7.653	22.137
SD	26.5478	28.9204	10.1688	2.2585	27.7237	16.5477	81.5885	8.5479	73.2332
Median	6.510	6.860	3.895	6.070	6.890	4.450	6.390	6.740	4.535
Minimum, maximum	3.01, 209.93	1.70, 208.06	0.46, 63.59	2.01, 14.99	1.45, 164.06	0.34, 98.41	3.13, 489.06	1.10, 54.75	1.70, 423.55
CV%	260.87	235.52	151.62	33.27	223.96	184.33	402.96	111.70	330.82
Geometric mean	6.793	7.314	4.317	6.431	7.297	4.895	7.108	5.885	5.901
YM-217562 (ng/mL)									
n	59	52	54	59	55	54	35	36	36
Mean	0.182	0.305	1.065	0.025	0.178	1.097	0.315	0.243	0.858
SD	0.7529	1.3229	2.2239	0.0592	0.7975	2.3421	1.7174	0.8425	1.9926
Median	0	0	0	0	0	0	0	0	0
Minimum, maximum	0, 4.49	0, 8.42	0, 8.94	0, 0.32	0, 4.88	0, 8.69	0, 10.18	0, 4.01	0, 7.16
CV%	414.75	434.02	208.82	239.23	448.06	213.42	545.44	346.23	232.15
Geometric mean	0.244	0.278	1.956	0.106	0.201	2.400	0.155	0.289	0.808
YM-278290 (ng/mL)									
n	59	52	54	59	55	54	35	36	36
Mean	0.004	0.009	0.005	0.010	0.011	0.012	0.006	0.016	0.023
SD	0.0240	0.0412	0.0220	0.0475	0.0486	0.0566	0.0372	0.0604	0.0665
Median	0	0	0	0	0	0	0	0	0
Minimum, maximum	0, 0.15	0, 0.28	0, 0.13	0, 0.31	0, 0.33	0, 0.37	0, 0.22	0, 0.30	0, 0.26
CV%	544.99	456.05	439.12	483.26	445.34	463.29	591.61	388.59	291.90
Geometric mean	0.128	0.091	0.085	0.171	0.123	0.115	0.220	0.147	0.135

All patients who received at least 1 dose of and had YM155 concentration for at least 1 time point (Pharmacokinetic Analysis Set).

† Sample taken before the end of YM155 infusion.

‡ Sample taken after the end of YM155 infusion.

Source: Table 12.4.1, Table 12.4.2, Table 12.4.3

Pharmacodynamic Results: [redacted]

Safety Results: All patients experienced treatment-emergent AEs (TEAEs); most commonly fatigue, which occurred in 85.9% of patients, nausea (64.1%), decreased appetite (62.5%) and neutropenia (62.5%).

Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: YM155		

Table 4 Summary of Treatment-emergent Adverse Events Occurring in at Least 10% of Patients

MedDRA (v12.1) **System Organ Class†** Preferred Term	**Number (%) of Patients (n = 64)**
All Systems, Any Adverse Event	**64 (100.0)**
General Disorders and Administration Site Conditions, Any Adverse Event	**61 (95.3)**
Fatigue	55 (85.9)
Mucosal inflammation	24 (37.5)
Pyrexia	21 (32.8)
Oedema peripheral	15 (23.4)
Pain	11 (17 2)
Asthenia	8 (12.5)
Oedema	8 (12.5)
Gastrointestinal Disorders, Any Adverse Event	**59 (92.2)**
Nausea	41 (64.1)
Diarrhoea	33 (51.6)
Constipation	19 (29.7)
Vomiting	18 (28.1)
Stomatitis	11 (17.2)
Abdominal pain	8 (12.5)
Metabolism and Nutrition Disorders, Any Adverse Event	**51 (79.7)**
Decreased appetite	40 (62.5)
Hypokalemia	14 (21.9)
Hyponatremia	11 (17.2)
Dehydration	10 (15.6)
Hypomagnesaemia	10 (15.6)
Hyperglycaemia	9 (14.1)
Hypophosphataemia	8 (12.5)
Skin and Subcutaneous Tissue Disorders, Any Adverse Event	**51 (79.7)**
Alopecia	37 (57.8)
Rash	24 (37.5)
Dry skin	8 (12.5)
Pruritus	8 (12.5)
Blood and Lymphatic System Disorders, Any Adverse Event	**47 (73.4)**
Neutropenia	40 (62.5)
Leukopenia	19 (29.7)
Anaemia	17 (26.6)
Febrile neutropenia	11 (17.2)
Nervous System Disorders, Any Adverse Event	**41 (64.1)**
Dysgeusia	20 (31.3)
Headache	15 (23.4)
Neuropathy peripheral	14 (21.9)
Dizziness	10 (15.6)
Table continued on next page	

Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: YM155		

Table 4 Continued

MedDRA (v12.1) **System Organ Class†** Preferred Term	**Number (%) of Patients (n = 64)**
Musculoskeletal and Connective Tissue Disorders, Any Adverse Event	**40 (62.5)**
Arthralgia	14 (21.9)
Back pain	13 (20.3)
Myalgia	12 (18.8)
Muscular weakness	9 (14.1)
Pain in extremity	9 (14.1)
Investigations, Any Adverse Event	**38 (59.4)**
Neutrophil count decreased	19 (29.7)
White blood cell count decreased	12 (18.8)
Weight decreased	8 (12.5)
Infections and Infestations, Any Adverse Event	**33 (51.6)**
Respiratory, Thoracic and Mediastinal Disorders, Any Adverse Event	**31 (48.4)**
Dyspnoea	18 (28.1)
Cough	9 (14.1)
Vascular Disorders, Any Adverse Event	**18 (28.1)**
Flushing	10 (15.6)
Psychiatric Disorders, Any Adverse Event	**16 (25.0)**
Insomnia	12 (18.8)
Anxiety	7 (10.9)
Renal and Urinary Disorders, Any Adverse Event	**16 (25.0)**
Eye Disorders, Any Adverse Event	**14 (21.9)**
Injury, Poisoning and Procedural Complications, Any Adverse Event	**7 (10.9)**

All patients who initiated at least 1 dose of study regimen (Safety Analysis Set).

† Within a system organ class, patients may have reported more than one type of adverse event. Adverse events are sorted by descending incidence by SOC, and within that descending order by preferred term.

Source: Table 12.6.1.2

All patients had at least 1 TEAE that was considered by the investigator to be related to YM155 and all had at least 1 TEAE that was considered by the investigator to be related to docetaxel. YM155-related TEAEs that occurred in > 50% of patients were fatigue (78.1%), neutropenia (59.4%), nausea (57.8%) and decreased appetite (53.1%). Docetaxel-related TEAEs that occurred in > 50% of patients were also fatigue (79.7%), neutropenia (62.5%), nausea (62.5%) and decreased appetite (59.4%), as well as alopecia (57.8%).

Three patients (4.7%) had Grade 5 TEAEs, including 2 patients with disease progression and 1 with respiratory failure; none of the Grade 5 TEAEs were considered to be related to treatment. A total of 39 patients (60.9%) had a total of 122 TEAEs that were of Grade 4 maximum severity; the most frequent treatment-related (YM155 or docetaxel) Grade 4 TEAEs were neutropenia, neutrophil count decreased, febrile neutropenia, leukopenia and WBC count decreased. A total of 17 patients (26.6%) had a total of 278 TEAEs that were of Grade 3 maximum severity; the most frequent treatment-related (YM155 or docetaxel) Grade 3 TEAEs were neutropenia,

Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: YM155		

leukopenia, fatigue, hyponatremia, neutrophil count decreased, mucosal inflammation, anemia, diarrhea, and for docetaxel-related only, anemia and white blood cell (WBC) count decreased.

A total of 25 patients (39.1%) died during the study, most due to disease progression (15 patients [23.4%]). None of the deaths were related to treatment. A total of 32 patients (50.0%) had a total of 99 treatment-emergent serious adverse events (SAEs). Treatment-related (YM155 or docetaxel) SAEs that occurred in ≥ 5% patients included: neutropenia, febrile neutropenia, anemia and diarrhea. Eight patients (12.5%) had a total of 16 TEAEs that resulted in permanent discontinuation of study drug.

Table 5 Summary of Serious Treatment-emergent Adverse Events, with Relationship to Treatment

	Number (%) of Patients with Adverse Events (n = 64)			
MedDRA (v12.1) Preferred Term†	**Total‡**	**YM155 Related**	**Docetaxel Related**	**Combination Related**
All Systems, Any Adverse Event	**32 (50.0)**	**22 (34.4)**	**22 (34.4)**	**21 (32.8)**
Neutropenia	9 (14.1)	8 (12.5)	9 (14.1)	8 (12.5)
Febrile neutropenia	8 (12.5)	8 (12.5)	8 (12.5)	8 (12.5)
Anaemia	5 (7.8)	4 (6.3)	4 (6.3)	4 (6.3)
Diarrhoea	5 (7.8)	4 (6.3)	5 (7.8)	4 (6.3)
Dehydration	4 (6.3)	3 (4.7)	3 (4.7)	3 (4.7)
Mucosal inflammation	3 (4.7)	3 (4.7)	3 (4.7)	3 (4.7)
Bacteremia	3 (4.7)	1 (1.6)	1 (1.6)	1 (1.6)
Pyrexia	3 (4.7)	1 (1.6)	1 (1.6)	0
Nausea	2 (3.1)	2 (3.1)	2 (3.1)	2 (3.1)
Vomiting	2 (3.1)	2 (3.1)	2 (3.1)	2 (3.1)
Catheter site cellulitis	2 (3.1)	1 (1.6)	1 (1.6)	1 (1.6)
Pneumonia	2 (3.1)	1 (1.6)	1 (1.6)	1 (1.6)
Renal failure	2 (3.1)	1 (1.6)	1 (1.6)	1 (1.6)
Deep vein thrombosis	2 (3.1)	1 (1.6)	0	0
Gastrointestinal haemorrhage	2 (3.1)	1 (1.6)	0	0
Disease progression	2 (3.1)	0	0	0
Hyponatremia	2 (3.1)	0	0	0

All patients who initiated at least 1 dose of study regimen (Safety Analysis Set).

† Only serious adverse events that occurred in more than 1 patient are listed.

‡ All adverse events, irrespective of relationship to treatment. Adverse events are sorted first by descending incidence in this category, then by incidence in the YM155 category.

Source: Table 12.6.1.11, Table 12.6.1.12.1, Table 12.6.1.12.2, Table 12.6.1.12.3, Table 12.6.1.12.4

Shifts of more than 1 grade from baseline to the maximum grade recorded during the study were observed for most laboratory parameters.

Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: YM155		

Table 6 Summary of Shifts in Laboratory Values of 2 or More Grades from Baseline to Maximum NCI-CTCAE (v. 4.02) Grade

	Number of Patients (n = 64)			
	Baseline	Maximum NCI-CTCAE Grade		
Laboratory Parameter	**Grade**	**2**	**3**	**4**
Hematology				
ANC	0	5	18	26
	1	NA	1	4
Hemoglobin	0	11	1	0
	2	NA	NA	2
Leukocytes	0	7	33	14
Lymphocytes	0	10	5	2
	1	NA	12	8
	2	NA	NA	3
Lymphocytes, absolute units	0	11	5	1
	1	NA	13	6
	2	NA	NA	2
PTT	0	6	0	0
PT INR	0	1	5	0
Chemistry				
Albumin	0	7	0	0
Alanine aminotransferase	0	1	1	0
Aspartate aminotransferase	0	1	0	0
Calcium	0	1	0	1
Gamma-glutamyltransferase	1	NA	3	0
Glucose	0	10	3	2
	1	NA	1	0
Magnesium	0	2	1	0
	1	NA	1	0
Phosphate/phosphorus	0	14	5	0
Potassium	0	2	6	0
	1	NA	2	0
Serum creatinine	0	2	1	0
Sodium	0	0	9	0
	1	NA	4	0
Total bilirubin	0	5	0	0
Urinalysis				
Urine protein	0	7	0	0

All patients who initiated at least 1 dose of study regimen (Safety Analysis Set).

ANC: absolute neutrophil count; NA: not applicable; NCI-CTCAE: National Cancer Institute-Common Terminology Criteria for Adverse Events; INR: international normalized ratio; PT: prothrombin time; PTT: partial thromboplastin time.

Source: Table 12.6.2.3.1, Table 12.6.2.3.2, Table 12.6.2.3.3

Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: YM155		

Grade 4 laboratory values were recorded at the end of final visit/early termination visit for absolute neutrophil count (ANC) (1 patient) and hemoglobin (1 patient). Grade 3 laboratory values were recorded at the end of final visit/early termination visit for lymphocytes (6 patients), lymphocytes absolute units (6 patients), gamma-glutamyltransferase (GGT) (3 patients), sodium (3 patients), ANC (1 patient), hemoglobin (1 patient), leukocytes (1 patient) and phosphate/phosphorus (1 patient).

Mean systolic and diastolic blood pressures decreased from baseline by 7.5 mm Hg and 3.5 mm Hg, respectively, and mean weight decreased from baseline by 2.43 kg. The maximum decrease in body surface area was 0.3 m^2. No patients had clinically significant abnormal ECG findings at any time during the study.

CONCLUSIONS: The combination of docetaxel and YM155, administered by continuous intravenous infusion at a dose of 5 mg/m^2 per day for 7 days, showed some modest clinical benefit in the treatment of Stage III (unresectable) or Stage IV melanoma. Steady-state plasma concentrations of YM155 were achieved by day 4 and were similar during cycles 1, 2 and 3. The tolerability and safety of YM155 given in combination with docetaxel were acceptable.

Date of Report: 19 April 2013