

Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: Not Applicable		
Name of Active Ingredient: ASP9853		

SYNOPSIS

Title of Study: A Phase 1, Multicenter, Open-label, Dose Escalation Study of ASP9853 in Combination with Either Docetaxel or Paclitaxel in Subjects with Advanced Non-hematologic Malignancies

Investigators/Coordinating Investigator: This was a multicenter study conducted in the United States. [REDACTED] served as a coordinating investigator for this study.

Study Center(s): This study was conducted across [REDACTED]

Publication Based on the Study: None.

Study Period: 1 year 10 months

Study Initiation Date (Date of First Enrollment): August 28, 2012

Study Completion Date (Date of Last Evaluation): June 11, 2014

Phase of Development: Phase 1

Objectives:

The primary objectives of the study were:

- To determine the safety and tolerability of ASP9853 in combination with docetaxel once every 3 weeks and with weekly paclitaxel in subjects with advanced non-hematologic malignancies.
- To determine the maximum tolerated dose (MTD) and the recommended phase 2 dose (RP2D) for ASP9853 in combination with docetaxel, and for ASP9853 in combination with paclitaxel.

The secondary objectives of the study were:

- To determine the pharmacokinetic profiles of ASP9853 and docetaxel, and paclitaxel administered in combination in subjects with advanced non-hematologic malignancies.
- To determine preliminary evidence of anti-tumor activity of ASP9853 in combination with docetaxel or paclitaxel in subjects with advanced non-hematologic malignancies.

Methodology:

This was an open-label, phase 1 dose escalation study of oral ASP9853 administered daily in combination with a taxane, either docetaxel or paclitaxel, in subjects with advanced non-hematologic malignancies. The study was planned to be conducted in 2 parts: Part 1 studied increasing dose levels of ASP9853 (25 mg, 37.5 mg and 50 mg) in combination with docetaxel administered intravenously once every 3 weeks on day 1, repeated every 21 days. Part 2 was planned to study increasing dose levels of ASP9853 once daily combined with weekly paclitaxel when administered intravenously on days 1, 8 and 15 repeated every 28 days, and was to begin when the MTD of

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ASP9853 was determined in part 1. The starting dose of ASP9853 in part 2 was to be one dose level below the MTD determined in part 1.

Both study parts were planned to determine the MTD and RP2D of ASP9853 in combination with each taxane. Following the determination of each ASP9853 MTD and RP2D, 3 to 6 additional subjects were to be have been enrolled into both RP2D level cohorts to further investigate the safety and tolerability of the ASP9853 RP2D with each taxane.

In this study, a dose-limiting toxicity (DLT) was defined as follows:

Hematologic Toxicity	Non-hematologic Toxicity
<ul style="list-style-type: none"> Grade 3 or 4 neutropenia with fever and/or documented infection where fever is defined as an oral temperature $\geq 38.5^{\circ}\text{C}$. Grade 4 neutropenia ($\text{ANC} < 500 \text{ cell}/\text{mm}^3$) lasting > 7 consecutive days. Grade 4 thrombocytopenia (platelets $< 25000 \text{ cells}/\text{mm}^3$ but $> 10000 \text{ cells}/\text{mm}^3$) lasting > 7 consecutive days; or Grade 3 or 4 thrombocytopenia with bleeding; or a platelet count $< 10000 \text{ cells}/\text{mm}^3$ at any time. 	<ul style="list-style-type: none"> Any Grade ≥ 3 non-hematological toxicity (excluding nausea, vomiting, diarrhea, anorexia, fatigue). Nausea, vomiting and diarrhea of \geq Grade 3 severity despite receiving optimal prophylaxis and/or treatment. Any study drug-related toxicity resulting in a treatment delay > 2 weeks. Any study drug-related toxicity resulting in discontinuation of treatment at the subject's assigned dose level.

ANC: absolute neutrophil count;

In Part 1, the starting dose of ASP9853 was started low and ASP9853 single agent 7-day lead-in phase was employed prior to Cycle 1 only in each subject. In addition the starting dose of docetaxel was low at $60 \text{ mg}/\text{m}^2$. This short lead-in phase was included to assess preliminary ASP9853 safety and pharmacokinetics, as well as the potential effects of docetaxel on ASP9853 pharmacokinetics. Dosing in Cohort 1 (ASP9853 25 mg once daily + docetaxel $60 \text{ mg}/\text{m}^2$) was initiated in a single subject based on accelerated escalation rules as specified in the protocol. Although it did not meet DLT criteria, a grade 3 event of neutropenia was noted in Cohort 1, thereby triggering a transition from single subject cohorts to a more conservative dose escalation schema of a traditional 3+3 dose design for ASP9853. No DLTs were observed in this single subject cohort and Cohort 2 was subsequently opened at a dose of 25 mg ASP9853 + docetaxel $75 \text{ mg}/\text{m}^2$. No DLT was observed in Cohort 1 (single subject cohort) at docetaxel $60 \text{ mg}/\text{m}^2$ + 25 mg of ASP9853.

In Cohort 2, 2 DLTs of neutropenic fever were observed in 2 of the 3 subjects receiving 25 mg ASP9853 + docetaxel $75 \text{ mg}/\text{m}^2$ and therefore an additional 3 subjects were not added at this dose level. Based upon review of the Cohort 2 data and in agreement with the Investigators, expanded safety testing of ASP9853 25 mg once daily + docetaxel $60 \text{ mg}/\text{m}^2$ in up to 6 additional subjects was undertaken, to be followed thereafter by escalation of ASP9853 in combination with $60 \text{ mg}/\text{m}^2$ of docetaxel.

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Cohort 3 tested 37.5 mg of ASP9853 in combination with docetaxel 60 mg/m². Cohort 3 used an alternating dose approach due to the strength of the smallest available ASP9853 tablet. In order to have achieved a dose that approximates a 50% increase from the 25 mg dose administered in the first 2 cohorts, dosing alternated between one and 2 tablets every other day (qod) to achieve an average daily dose of 37.5 mg. Dosing in Cohort 3 began with ASP9853 50 mg on day -6 (instead of on day -7) to ensure the collection of pharmacokinetic samples around ASP9853 50 mg doses on days -6, -2 and 1 of Cycle 1. Three subjects were dosed in this cohort and no DLTs were reported. Therefore, escalation of ASP9853 in combination with docetaxel 60 mg/m² commenced based on traditional 3+3 escalation rules as outlined in the protocol.

Cohort 4 tested ASP9853 at 50 mg + docetaxel 60 mg/m² in 3 subjects. One DLT occurred and the cohort was expanded to include 4 more subjects. Additional toxicities were noted in other subjects in the cohort including neutropenia. Although these may not have met the criteria for a DLT, they were nonetheless taken into consideration when evaluating the cohort.

In this study, docetaxel backbone was reduced below standard of care (75 mg/m²) to 60 mg/m² due to fever and neutropenia requiring growth factor support. Target exposure (AUC) of iNOS was not achieved with standard of care docetaxel due to dose-limiting toxicity. The docetaxel portion of the study was designed to gate the paclitaxel portion, although no objective evidence that ASP9853 caused the DLTs was observed. This relationship was based on Investigator's judgment. No significant anti-tumor activity has been observed during dose escalation in various tumor types (only 1/18 subjects previously responded to taxanes).

The study was terminated by the Sponsor at this time, and Part 2 was never implemented.

Number of Patients (Planned, Enrolled and Analyzed):

This study planned to enroll approximately 50 subjects based on enrollment of up to 6 subjects in each dose level cohort and 3 to 6 additional subjects in each RP2D cohort for further testing of safety and tolerability.

The full analysis set included 21 subjects. The safety and pharmacokinetic analysis sets each included 20 subjects. Six subjects were assigned to Cohort 1, 4 to Cohort 2 and 3 to Cohort 3. The full analysis set for Cohort 4 included 8 subjects; however, safety and pharmacokinetic analysis sets for Cohort 4 included only 7 subjects.

No subjects completed the study. The primary reason for discontinuation was progressive disease.

Diagnosis and Main Criteria for Inclusion:

In order to participate in the study, enrolled subjects had to be at least 18 years of age and must have had a life expectancy of at least 12 months. Additionally, patients must have had a histologically or cytologically confirmed incurable, locally advanced, or metastatic non-hematologic malignancy that has progressed or failed to respond to regimens or therapies known to provide clinical benefit and must have had an adequate bone marrow, renal, and hepatic function at baseline.

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

In this study, ASP9853 from Bulk Lot # -12030A, Lot # -CLR79074-001 was used as described in Methodology. Part 1 studied increasing dose levels of ASP9853 (25 mg, 37.5 mg and 50 mg) in combination with docetaxel administered intravenously once every 3 weeks on day 1, repeated every 21 days.

Duration of Treatment (or Duration of Study, if applicable): Duration of treatment is shown in [Table 1](#).

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

Docetaxel was administered as described in Methodology from a commercially available supply. In this study docetaxel backbone was reduced below standard of care (75 mg/m²) to 60 mg/m².

Criteria for Evaluation:

The following plasma pharmacokinetic parameters for ASP9853 and docetaxel were assessed:

For ASP9853:

- Area under the curve (AUC) for AUC₂₄, AUC_{last}, AUC_∞,
- Maximum plasma concentration (C_{max}), lowest concentration of a drug just before the next dose C_{trough}, time to reach C_{max} (t_{max}),
- Elimination half-life (t_{1/2}), clearance (CL/F), and volume of distribution (Vz/F).

For docetaxel:

- AUC₂₄, AUC_{last}, AUC_∞, C_{max}, t_{max}, t_{1/2}, CL, and volume of distribution at steady state (V_{dss}).

Safety of ASP9853 alone and in combination with docetaxel was assessed by evaluation of the following:

- Treatment-emergent adverse events (TEAEs) (National Cancer Institute [NCI] CTCAE toxicity grade, frequency, seriousness, relationship to study drug, leading to treatment discontinuation, leading to death, etc)
- Dose-limiting toxicity (DLT)s
- Clinical laboratory evaluations (chemistry, hematology, and urinalysis)
- Vital signs (oral temperature, respiration and pulse rate, blood pressure)
- Physical examination
- 12-lead electrocardiogram (ECG)

Objective response rate (ORR) and duration of response (DOR) were analyzed as efficacy measurements.

Statistical Methods:

Descriptive statistics including number of subjects, mean, standard deviation (SD), median, minimum, and maximum were used to summarize continuous variables. For pharmacokinetic summaries, geometric mean and

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coefficient of variation were also presented. Unless otherwise noted, for all statistical analyses, statistical significance was determined by a two-sided P value ≤ 0.05 .

Summary of Results/Conclusions:

Population:

Demographic characteristics were comparable among cohorts with the exception of weight and BMI which were slightly lower in Cohort 2 than in other cohorts. Approximately 30% of subjects in the study were women and 70% were men. Subjects were predominately White, non-Hispanic (90%), and 10% were African American. The mean of all subject ages was 59.4 years. All enrolled subjects had an ECOG performance status of 0 or 1; approximately 24% were Grade 0 and 76% Grade 1 at time of initial screening. Patient disposition and demographics is shown in [Table 2](#) and [Table 3](#).

Efficacy:

Data collected during the study suggest that ASP9853 did not demonstrate efficacy in slowing the progression of solid tumors in human subjects. No subjects showed an objective response (complete or partial response) by RECIST to treatment with ASP9853. Approximately 38% of subjects had a best overall response of stable disease.

Pharmacokinetics:

ASP9853 was rapidly absorbed with time to maximum concentration (t_{max}) within 1 to 2 hours. The $t_{1/2}$ for ASP9853 ranged between 3.5 and 6.8 hours, and generally >95% of ASP9853 was cleared from plasma within 24 hours after administration. Overall, ASP9853 plasma exposure as measured by AUC_{24} appeared lower when administered with docetaxel; however, the number of subjects in each cohort was too small to determine the statistical significance of this observation.

Safety Results:

Most study subjects (95%) experienced treatment-emergent adverse events (TEAEs), and 90% of subjects experienced TEAEs that were assessed as related to the study medications. A total of 9 subjects (2 subjects in the lead-in period and 7 subjects who received ASP9853 in combination with docetaxel) experienced serious TEAEs and 3 of these were considered to be drug-related. Three subjects experienced serious TEAEs that lead to discontinuation of the study medications.

Study subjects experienced a wide range of TEAEs as categorized by primary SOC and PTs. The most prevalent TEAEs occurred in the following primary SOCs: Blood and Lymphatic System Disorders (70% of subjects) and General Disorders and Administration Site Conditions and Gastrointestinal Disorders (60% of subjects each). Common TEAEs were neutropenia (50%), fatigue (45%), reduced white blood cell counts (35%), nausea (35%), decreased appetite (30%), and alopecia (30%). TEAEs noted in 10 percent or more of total subjects during the study are presented in [Table 4](#).

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The majority of the subjects (90%) experienced drug-related TEAEs during the study. These included Blood and Lymphatic System Disorders (45%), General System Disorders (45%), Gastrointestinal Disorders (35%), and Investigations (35%). The most frequently reported drug-related TEAEs were fatigue (45%), decreased white blood cell counts (25%), neutropenia (20%), diarrhea (20%), nausea (20%), and vomiting (20%).

Serious TEAEs were reported in 35% of study subjects. The most frequent serious TEAEs were in SOC Blood and Lymphatic System Disorders (25%) including leukocytosis (5%), leukopenia (10%), febrile neutropenia (15%), and neutropenia (10%). Serious TEAEs are provided in [Table 5](#).

The following subjects experienced AEs that were considered to be DLTs.

- Subject [REDACTED] (Cohort 2) experienced leukopenia with neutropenia requiring hospitalization.
- Subject [REDACTED] (Cohort 2) also experienced febrile neutropenia, which met the protocol-defined DLT criteria.
- Subject [REDACTED] (Cohort 1) experienced febrile neutropenia that met the protocol-defined DLT criteria

In addition, 2 subjects in Cohort 4 (Subjects [REDACTED]) experienced leukopenia with neutropenia. After review of the data, both cases were designated as DLTs by the medical monitor, treating physician and the dose-escalation committee, and were treated as DLTs, although neither met the formal protocol defined DLT criteria.

Although fever and neutropenia are not uncommon with docetaxel treatment, given the severity of neutropenia, potentiation by ASP9853 cannot be excluded.

A total of 3 subjects had TEAEs that lead to treatment discontinuation. One subject experienced severe musculoskeletal pain that did not resolve. Another subject experienced a balance disorder, and a third subject experienced febrile neutropenia concurrent with diarrhea that led to discontinuation.

Two subjects died during the study. Subject [REDACTED] died during the ASP9853 lead-in period of an unspecified reason (death NOS), prior to the first dose of docetaxel. Subject [REDACTED] in Cohort 2 died as a result of sepsis, aspiration of water, respiratory failure, and hypotension. Neither of these deaths were considered to be related to ASP9854 or docetaxel.

All study subjects exhibited neutropenia and all but 1 subject exhibited leukopenia after baseline. All study subjects had normal platelet counts and exhibited low lymphopenia at baseline of Grade 1 or greater and all experienced further reductions in lymphocyte counts over the duration of the study. The majority of subjects, 15 of a total of 20, exhibited decreases in hemoglobin values during the study.

CONCLUSIONS:

This was a phase 1, open label study of ASP9853 in combination with docetaxel in subjects with non-hematological malignancies. The study was intended to be conducted in two parts: Part 1 studied escalating

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doses of ASP9853 in combination with docetaxel, and Part 2 was to study escalating doses of ASP9853 in combination with paclitaxel. The MTD and RP2D of ASP9853 in combination with docetaxel and paclitaxel were to be established for use in future studies.

ASP9853 plasma concentrations peaked relatively quickly, between 1 to 2 hours after administration, and had a $t_{1/2}$ between 3 to 6 hours during the study.

ASP9853 did not appear to significantly slow tumor growth or prevent progression in study subjects. No subject experienced a complete or partial response during ASP9853 treatment and the majority of subjects discontinued the study due to disease progression. A total of 8 subjects (38.1%) had a best overall response of stable disease with a mean duration of 49.4 days.

Two deaths were reported in this study (one of these deaths occurred during the lead-in period). Neither death was considered related to ASP9853. ASP9853 appears to potentiate the adverse events of neutropenia and leukopenia associated with docetaxel and paclitaxel. Although neutropenic fever is known to occur with docetaxel, given the severity of neutropenia, potentiation by ASP9853 cannot be excluded.

In this study docetaxel backbone was reduced below standard of care (75 mg/m^2) to 60 mg/m^2 due to fever and neutropenia requiring growth factor support. Target exposure (AUC) of iNOS was not achieved with standard of care docetaxel due to dose limiting toxicity. The docetaxel portion of the study was designed to gate the paclitaxel portion, although no objective evidence that ASP9853 caused the DLTs was observed. This relationship was based on Investigator's judgment. No significant anti-tumor activity has been observed during dose escalation in various tumor types (only 1/18 subjects previously responded to taxanes).

As a result of these findings, the study was terminated by the Sponsor, and Part 2 of the study was never implemented. The MTD and RP2D were not established in this study. Further development of this compound is not planned due to the apparent lack of significant anti-tumor activity and the possible potentiation of combination toxicity of neutropenia seen in this study when ASP9853 was combined with docetaxel.

Date of Report: October 24, 2014

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Table 1 Study Drug Exposure (Safety Analysis Set)

Characteristic	ASP9853 Lead-in (n = 20)	ASP9853 Post Lead-in (n = 20)	Docetaxel (All Cycles) (n = 20)	ASP9853 Total (n = 20)
Duration (Days)†				
n	20	19		20
Mean	6.9	53.9	N/A	58.1
SD	0.37	43.99		44.39
Median	7.0	42.0		49.0
Min/Max	6/7	7/197		6/203
Duration (Range in days)				
≤ 28	20 (100%)	4 (20.0%)		3 (15.0%)
>28 to ≤ 56		10 (50.0%)	N/A	12 (60.0%)
>56 to ≤ 78		1 (5.0%)		1 (5.0%)
> 78		4 (20.0%)		4 (20.0%)
Duration (Cycles)				
n			19	
Mean	N/A	N/A	2.8	N/A
SD			1.96	
Median			2.0	
Min/Max			1/9	
Total Test Drug Used (mg)				
n	20	19	19	20
Mean	243.8	1994.1	169.5	2138.1
SD	83.06	1848.49	118.68	1884.30
Median	200.0	1575.0	120.0	1650.0
Min/Max	150/350	175/7388	60/540	150/7613
Dosing				
Increases	0	0	0	0
Decreases	0	1 (5.0%)	3 (15.0%)	1 (5.0%)
Interruptions	0	8 (40.0%)	0	8 (40.0%)

N/A: not available

†Duration is the total time (days) in which the subject was receiving ASP9853 and/or docetaxel.

Source: End-of-Text Table 12.2.1

Table 2 Subject Disposition

	Cohort 1† (n = 6)	Cohort 2† (n = 4)	Cohort3† (n = 3)	Cohort 4† (n = 7)	Total‡ (n = 20)
Study Discontinuation	6 (100%)	4 (100%)	3 (100%)	8 (100%)	21 (100%)
Primary Reason for Discontinuation					
Adverse Event	0	0	0	0	0
Withdrawal By Subject	0	0	1 (33.3%)	0	1 (4.8%)
Allows Follow-Up After Withdrawal	0	0	0	0	0
Does Not Allow Follow-Up After Withdrawal	0	0	1 (33.3%)	0	1 (4.8%)
Subject Lost To Follow Up	0	0	0	0	0
Protocol Violation	0	0	0	0	0
Study Terminated By Sponsor	0	0	0	0	0
Progressive Disease	6 (100%)	2 (50.0%)	2 (66.7%)	7 (87.5%)	17 (81.0%)
Death	0	0	0	0	0
Randomized/Registered But Never Received/ Dispensed Study Drug	0	0	0	1 (12.5%)	1 (4.8%)
Other	0	2 (50.0%)	0	0	2 (9.5%)

†Single agent 7-day lead-in (6 days in Cohort 3) with ASP9853 only followed by; Cohort 1: 25 mg ASP9853 + 60 mg/m² docetaxel, Cohort 2: 25 mg ASP9853 + 75 mg/m² docetaxel, Cohort 3: 37.5 mg ASP9853 (50mg/25mg) + 60 mg/m² docetaxel, Cohort 4: 50 mg ASP9853 + 60 mg/m² docetaxel.

‡Total refers to 'Total ASP9853 Combination with docetaxel.'

Source: End-of-Text Table 12.1.1.2

Table 3 Summary of Demographic Characteristics (Full Analysis Set)

Parameter	Category/Statistic	Cohort 1† (n = 6)	Cohort 2† (n = 4)	Cohort 3† (n = 3)	Cohort 4† (n = 8)	Total‡ (n = 21)
Sex	Male	6 (100%)	3 (75.0%)	2 (66.7%)	4 (50.0%)	15 (71.4%)
	Female	0	1 (25.0%)	1 (33.3%)	4 (50.0%)	6 (28.6%)
Race	White	5 (83.3%)	4 (100%)	2 (66.7%)	8 (100%)	19 (90.5%)
	Black Or African American	1 (16.7%)	0	1 (33.3%)	0	2 (9.5%)
	Asian	0	0	0	0	0
	American Indian Or Alaska Native	0	0	0	0	0
	Native Hawaiian Or Other Pacific Islander	0	0	0	0	0
	Other	0	0	0	0	0
Ethnicity	Not Hispanic Or Latino	6 (100%)	4 (100%)	3 (100%)	8 (100%)	21 (100%)
	Hispanic Or Latino	0	0	0	0	0
Age (Years)	Mean	53.2	59.0	64.0	62.6	59.4
	SD	9.62	15.77	6.24	11.12	11.25
	Median	51.0	64.5	66.0	60.5	60.0
	Min/Max	43/68	36/71	57/69	52/87	36/87
Weight (kg)	Mean	78.2	72.8	74.1	78.1	76.6
	SD	13.77	6.12	12.68	26.81	18.06
	Median	73.8	71.4	78.3	70.0	70.6
	Min/Max	62/96	67/81	60/84	57/140	57/140
Height (cm)	Mean	171.7	178.7	173.7	168.4	171.7
	Std	5.10	1.45	6.23	10.95	8.27
	Median	171.1	178.0	172.7	169.4	172.7
	Min/Max	166/180	178/180	168/180	155/184	155/184
BMI (kg/m ²)§	Mean	26.7	22.9	24.8	27.2	26.0
	SD	5.63	2.59	5.53	7.07	5.77
	Median	25.7	22.3	27.7	25.4	25.2
	Min/Max	21/34	21/26	18/28	22/44	18/44
ECOG Status¶	Grade 0	1 (16.7%)	1 (25.0%)	1 (33.3%)	2 (25.0%)	5 (23.8%)
	Grade 1	5 (83.3%)	3 (75.0%)	2 (66.7%)	6 (75.0%)	16 (76.2%)
	Grade 2	0	0	0	0	0
	Grade 3	0	0	0	0	0
	Grade 4	0	0	0	0	0
	Grade 5	0	0	0	0	0

Footnotes appear on next page

†Single agent 7-day lead-in (6 days in Cohort 3) with ASP9853 only followed by; Cohort 1: 25 mg ASP9853 + 60 mg/m² docetaxel, Cohort 2: 25 mg ASP9853 + 75 mg/m² docetaxel, Cohort 3: 37.5 mg ASP9853 (50/25) + 60 mg/m² docetaxel, Cohort 4: 50 mg ASP9853 + 60 mg/m² docetaxel.

‡Total refers to 'Total ASP9853 combination with docetaxel.'

§Body mass Index (BMI) = Weight (kg)/Height (m²).

¶At Screening.

Source: End-of-Text Table 12.1.2.1

Table 4 Treatment-emergent Adverse Events in ≥10% of Subjects Overall (Safety Analysis Set)

Primary System Organ Class† Preferred Term	ASP9853 Lead-in (n = 20)	Cohort 1‡ (n = 6)	Cohort 2‡ (n = 4)	Cohort 3‡ (n = 3)	Cohort 4‡ (n = 7)	Total§ (n = 20)
Overall	15 (75.0%)	6 (100%)	3 (75.0%)	3 (100%)	7 (100%)	19 (95.0%)
Blood and lymphatic system disorders	1 (5.0%)	6 (100%)	3 (75.0%)	2 (66.7%)	3 (42.9%)	14 (70.0%)
Anemia	0	3 (50.0%)	1 (25.0%)	0	1 (14.3%)	5 (25.0%)
Leukocytosis	0	2 (33.3%)	1 (25.0%)	0	0	3 (15.0%)
Leukopenia	1 (5.0%)	3 (50.0%)	0	0	2 (28.6%)	5 (25.0%)
Febrile neutropenia	0	1 (16.7%)	2 (50.0%)	0	0	3 (15.0%)
Neutropenia	0	3 (50.0%)	2 (50.0%)	2 (66.7%)	3 (42.9%)	10 (50.0%)
Gastrointestinal disorders	7 (35.0%)	3 (50.0%)	3 (75.0%)	1 (33.3%)	5 (71.4%)	12 (60.0%)
Diarrhea	0	2 (33.3%)	2 (50.0%)	1 (33.3%)	0	5 (25.0%)
Dyspepsia	1 (5.0%)	0	0	0	2 (28.6%)	2 (10.0%)
Abdominal pain upper	1 (5.0%)	1 (16.7%)	0	0	1 (14.3%)	2 (10.0%)
Constipation	2 (10.0%)	1 (16.7%)	0	1 (33.3%)	2 (28.6%)	4 (20.0%)
Nausea	1 (5.0%)	1 (16.7%)	2 (50.0%)	1 (33.3%)	3 (42.9%)	7 (35.0%)
Vomiting	1 (5.0%)	0	3 (75.0%)	0	2 (28.6%)	5 (25.0%)
General disorders and administration site conditions	5 (25.0%)	4 (66.7%)	3 (75.0%)	2 (66.7%)	3 (42.9%)	12 (60.0%)
Asthenia	2 (10.0%)	0	2 (50.0%)	0	0	2 (10.0%)
Fatigue	0	2 (33.3%)	3 (75.0%)	2 (66.7%)	2 (28.6%)	9 (45.0%)
Pyrexia	1 (5.0%)	0	1 (25.0%)	0	1 (14.3%)	2 (10.0%)
Mucosal inflammation	1 (5.0%)	1 (16.7%)	0	0	1 (14.3%)	2 (10.0%)
Edema peripheral	0	1 (16.7%)	1 (25.0%)	1 (33.3%)	1 (14.3%)	4 (20.0%)
Investigations	1 (5.0%)	3 (50.0%)	1 (25.0%)	2 (66.7%)	4 (57.1%)	10 (50.0%)
Neutrophil count decreased	0	1 (16.7%)	0	1 (33.3%)	1 (14.3%)	3 (15.0%)
White blood cell count decreased	0	3 (50.0%)	0	2 (66.7%)	2 (28.6%)	7 (35.0%)
Metabolism and nutrition disorders	1 (5.0%)	3 (50.0%)	2 (50.0%)	2 (66.7%)	3 (42.9%)	10 (50.0%)
Decreased appetite	0	1 (16.7%)	1 (25.0%)	1 (33.3%)	3 (42.9%)	6 (30.0%)
Hyperglycemia	0	1 (16.7%)	0	1 (33.3%)	0	2 (10.0%)
Hypophosphatemia	0	2 (33.3%)	0	0	0	2 (10.0%)
Hypoalbuminemia	0	1 (16.7%)	1 (25.0%)	0	1 (14.3%)	3 (15.0%)
Dehydration	1 (5.0%)	1 (16.7%)	1 (25.0%)	0	0	2 (10.0%)

Table continued on next page

Primary System Organ Class† Preferred Term	ASP9853 Lead-in (n = 20)	Cohort 1‡ (n = 6)	Cohort 2‡ (n = 4)	Cohort 3‡ (n = 3)	Cohort 4‡ (n = 7)	Total§ (n = 20)
Musculoskeletal and connective tissue disorders	2 (10.0%)	2 (33.3%)	0	2 (66.7%)	4 (57.1%)	8 (40.0%)
Arthralgia	1 (5.0%)	0	0	1 (33.3%)	2 (28.6%)	3 (15.0%)
Back pain	0	0	0	1 (33.3%)	1 (14.3%)	2 (10.0%)
Neck pain	0	1 (16.7%)	0	0	1 (14.3%)	2 (10.0%)
Nervous system disorders	4 (20.0%)	3 (50.0%)	0	1 (33.3%)	2 (28.6%)	6 (30.0%)
Headache	1 (5.0%)	1 (16.7%)	0	1 (33.3%)	1 (14.3%)	3 (15.0%)
Dizziness	1 (5.0%)	1 (16.7%)	0	1 (33.3%)	2 (28.6%)	4 (20.0%)
Psychiatric disorders	1 (5.0%)	0	1 (25.0%)	2 (66.7%)	1 (14.3%)	4 (20.0%)
Insomnia	0	0	0	2 (66.7%)	1 (14.3%)	3 (15.0%)
Respiratory, thoracic and mediastinal disorders	2 (10.0%)	1 (16.7%)	1 (25.0%)	2 (66.7%)	4 (57.1%)	8 (40.0%)
Cough	0	0	0	1 (33.3%)	2 (28.6%)	3 (15.0%)
Oropharyngeal pain	0	0	0	1 (33.3%)	1 (14.3%)	2 (10.0%)
Skin and subcutaneous tissue disorders	0	3 (50.0%)	2 (50.0%)	2 (66.7%)	2 (28.6%)	9 (45.0%)
Alopecia	0	3 (50.0%)	0	1 (33.3%)	2 (28.6%)	6 (30.0%)
Pruritus	0	1 (16.7%)	1 (25.0%)	1 (33.3%)	0	3 (15.0%)
Vascular disorders	0	2 (33.3%)	1 (25.0%)	1 (33.3%)	1 (14.3%)	5 (25.0%)
Hot flush	0	2 (33.3%)	0	1 (33.3%)	0	3 (15.0%)
Hypotension	0	0	1 (25.0%)	0	1 (14.3%)	2 (10.0%)

†Within a system organ class, a subject may have reported more than one type of adverse event.

‡Single agent 7-day lead-in (6 days in Cohort 3) with 25 mg ASP9853 only followed by; Cohort 1: 25 mg ASP9853 + 60 mg/m² docetaxel, Cohort 2: 25 mg ASP9853 + 75 mg/m² docetaxel, Cohort 3: (37.5) mg ASP9853 (50/25) + 60 mg/m² docetaxel, Cohort 4: 50 mg ASP9853 + 60 mg/m² docetaxel. Subject [REDACTED] only received lead-in therapy and discontinued treatment prior to first dose of docetaxel.

§Total refers to 'Total ASP9853 combination with docetaxel.'

Source: End-of-Text Table 12.6.1.2

Table 5 Summary of Serious Treatment-emergent Adverse Events

Primary System Organ Class Preferred Term†	ASP9853 Lead-in (n = 20)	Cohort 1‡ (n = 6)	Cohort 2‡ (n = 4)	Cohort 3‡ (n = 3)	Cohort 4‡ (n = 7)	Total§ (n = 20)
Overall	2 (10.0%)	2 (33.3%)	3 (75.0%)	0	2 (28.6%)	7 (35.0%)
Blood and lymphatic system disorders	0	1 (16.7%)	2 (50.0%)	0	2 (28.6%)	5 (25.0%)
Leukocytosis	0	1 (16.7%)	0	0	0	1 (5.0%)
Leukopenia	0	0	0	0	2 (28.6%)	2 (10.0%)
Febrile neutropenia	0	1 (16.7%)	2 (50.0%)	0	0	3 (15.0%)
Neutropenia	0	0	0	0	2 (28.6%)	2 (10.0%)
Cardiac disorders	1 (5.0%)	0	0	0	0	0
Atrial fibrillation	1 (5.0%)	0	0	0	0	0
Gastrointestinal disorders	0	1 (16.7%)	1 (25.0%)	0	0	2 (10.0%)
Diarrhea	0	0	1 (25.0%)	0	0	1 (5.0%)
Abdominal pain upper	0	1 (16.7%)	0	0	0	1 (5.0%)
General disorders and administration site conditions	1 (5.0%)	0	1 (25.0%)	0	0	1 (5.0%)
Fatigue	0	0	1 (25.0%)	0	0	1 (5.0%)
Death	1 (5.0%)	0	0	0	0	0
Infections and infestations	0	0	1 (25.0%)	0	0	1 (5.0%)
Sepsis	0	0	1 (25.0%)	0	0	1 (5.0%)
Musculoskeletal and connective tissue disorders	0	1 (16.7%)	0	0	0	1 (5.0%)
Neck pain	0	1 (16.7%)	0	0	0	1 (5.0%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	1 (16.7%)	0	0	0	1 (5.0%)
Metastases to central nervous system	0	1 (16.7%)	0	0	0	1 (5.0%)
Respiratory, thoracic and mediastinal disorders	0	0	1 (25.0%)	0	0	1 (5.0%)
Pneumothorax	0	0	1 (25.0%)	0	0	1 (5.0%)
Respiratory failure	0	0	1 (25.0%)	0	0	1 (5.0%)
Aspiration	0	0	1 (25.0%)	0	0	1 (5.0%)
Vascular disorders	0	0	1 (25.0%)	0	0	1 (5.0%)
Hypotension	0	0	1 (25.0%)	0	0	1 (5.0%)

SAE: serious adverse event

†Number of subjects (n) and percentage of subjects (%) are shown. Includes SAEs upgraded by the Sponsor based on review of the Sponsor's list of always serious terms, if any upgrade was done.

Footnotes continued on next page

‡Single agent 7-day lead-in (6 days in Cohort 3) with 25 mg ASP9853 only followed by; Cohort 1: 25 mg ASP9853 + 60 mg/m² docetaxel, Cohort 2: 25 mg ASP9853 + 75 mg/m² docetaxel, Cohort 3: (37.5) mg ASP9853 (50/25) + 60 mg/m² docetaxel, Cohort 4: 50 mg ASP9853 + 60 mg/m² docetaxel. Subject [REDACTED] only received lead-in therapy and discontinued treatment prior to first dose of docetaxel.

§Total refers to 'Total ASP9853 combination with docetaxel.'

Subject [REDACTED] was assigned post-lead in to Cohort 2; however, this subject never received docetaxel and therefore all treatment-emergent adverse events occurred during ASP9853 monotherapy.

Source: End-of-Text Table 12.6.1.6