SYNOPSIS

Title of the study: A Multicenter, Open-Label, Single Arm Study of Weekly Alvocidib in Patients with Previously Treated B-Cell Chronic Lymphocytic Leukemia (CLL) or Prolymphocytic Leukemia (PLL) Arising from CLL – EFC6663

Investigator(s): [redacted]

Study center(s): There were 34 active study centers in Australia, Belgium, France, Germany, Italy, the Netherlands, Puerto Rico, the United Kingdom, and the United States of America.

Publications (reference): None

Study period:

Date first patient enrolled: 21 Mar 2007

Date last patient completed: 6 Dec 2011

Phase of development: 2

Objectives:

Primary: The primary objective of this study was to determine the overall objective response rate for alvocidib administered as a 30-minute infusion followed by a 4-hour continuous infusion in previously treated patients with CLL or PLL arising from CLL.

Secondary: Secondary objectives of this study were:

- To assess the overall safety profile of the treatment;
- To assess the objective duration of response (DR), progression-free-survival (PFS) and overall survival (OS) following this treatment;
- To assess the clinical benefit by assessing reduction in incidence and severity of B-symptoms and time to relief of B-symptoms, reduction in frequency and amount of blood and platelet transfusions, and reduction in incidence opportunistic infections and in cytomegalovirus (CMV) reactivation; to assess the pharmacokinetics of this schedule of administration;
- To assess the pharmacokinetics of the schedule of administration.

In April 2010, the Sponsor requested a pre-NDA (New Drug Application) meeting with the US Food and Drug Administration (FDA) to review data from an interim analysis of study EFC6663, as well as supporting efficacy and safety data from other studies in CLL, in support of a potential NDA filing for accelerated approval of alvocidib in patients with bulky lymphadenopathy (≥ 5 cm). In their response to the meeting request in July 2010, the FDA recommended that the Sponsor not submit the NDA. The recommendation was based on FDA's review of the EFC6663 study design (open-label, single arm, non-comparative study), their overall benefit risk assessment based on the provided interim efficacy and safety data, and the fact that the Sponsor had failed to demonstrate that the targeted CLL subpopulations lacked available therapy (ie represented unmet medical need). The recommendation also implied a request for additional studies. As a result, the Sponsor decided to terminate internal development of alvocidib and to modify the study design by reducing the post-treatment follow-up from 12 months to 6 months and to no longer follow patients until death.

Methodology: This was an open-label, multicenter, multinational, single-arm study of weekly doses of alvocidib in patients with previously treated CLL or PLL arising from CLL. After a 4-week screening period and registration, patients were to receive alvocidib every week for 4 consecutive weeks followed by a 2-week rest period (1 cycle of study treatment is 6 weeks in length), up to a maximum of 6 cycles of treatment. Patients were followed until 6 months after the final treatment. Per the original protocol, the post-treatment follow-up period was to have been 12 months, and survival was to have been followed until death. As outlined above, following the Sponsor's decision to terminate the internal development of alvocidib and the issue of Amendment 6, patients were followed until 6 months after the final treatment.

Number of patients: 165 planned, 165 enrolled

Treated: 159

Evaluated: 159

Efficacy: 159

Safety: 159

Diagnosis and criteria for inclusion:
Patients with histologically confirmed and measurable CLL or PLL arising from CLL with the following characteristics:

- Documented lymphocytosis of >5 x 10^9/L since the initial diagnosis of CLL;
- B-cells that co-expressed CD5 (CD5 molecule) with CD19 (CD19 molecule) or CD20 (MS4A1, membrane-spanning 4-domains, subfamily A, member 1) and CD23 (FCER2, Fc fragment of IgE, low affinity II, receptor for) surface antigens and had low expression of surface immunoglobin chains; if surface expression of immunoglobin chains on B-cells was high or the cells were CD23-negative, they must have lacked the 11:14 translocation;
- Must have had symptomatic Rai Stage III or IV or Binet Stage B or C. Patients were also eligible if they presented with Rai stage I, II or Binet Stage A, accompanied by rapid doubling time of peripheral lymphocyte count or symptomatic splenomegaly/hepatomegaly or symptomatic or progressive lymphadenopathy or B-symptoms;
- Progressive or symptomatic disease as defined by any of a number of specific criteria including presence of B-symptoms, symptomatic splenomegaly, hepatomegaly or progressive lymphadenopathy, or recent rapid lymphocyte count increase or anticipated doubling time of less than 6 months;
- Prior receipt by the patient of alkylating agent(s) and refractory to fludarabine, either as a single agent or in combination with other agents.

Study treatment: Investigational medicinal product (IMP): alvocidib (HMR1275)

Formulation: Alvocidib was supplied as 50 mg (free base) / 5 mL solution in flint glass vials. Each vial contained 54.5 mg of alvocidib HCl, equivalent to 50 mg of free base and 15 mg of acetic acid.

Route(s) of administration: 30-minute intravenous (IV) infusion followed by a continuous 4-hour infusion

Dose regimen:
Dose: 60 mg/m^2 or 80 mg/m^2 (based on body mass index) every week for 4 weeks (1 cycle)

For Cycle 1, Dose 1, all patients received 60 mg/m^2 alvocidib (30 mg/m^2 as a 30-minute intravenous (IV) infusion followed by 30 mg/m^2 as a 4-hour infusion). Patients who experienced (TLS) tumor lysis syndrome requiring hemodialysis following the first dose continued to receive 60 mg/m^2 for all remaining doses in the study. All other patients underwent a 1-time dose escalation to 80 mg/m^2 (30 mg/m^2 over 30 minutes followed by 50 mg/m^2 over 4 hours) for Dose 2 of Cycle 1 and for all remaining doses in the study.

Batch number(s): [redacted]

Duration of treatment: Until disease progression or no evidence of treatment response; occurrence of unacceptable toxicity, intercurrent medical problem, or adverse event (AE); or a maximum of 6 cycles (4 weeks/cycle followed by a 2-week rest period)

Duration of observation: Six months after the last treatment with alvocidib

Criteria for evaluation: This is a synopsized report. Efficacy and safety results are presented.

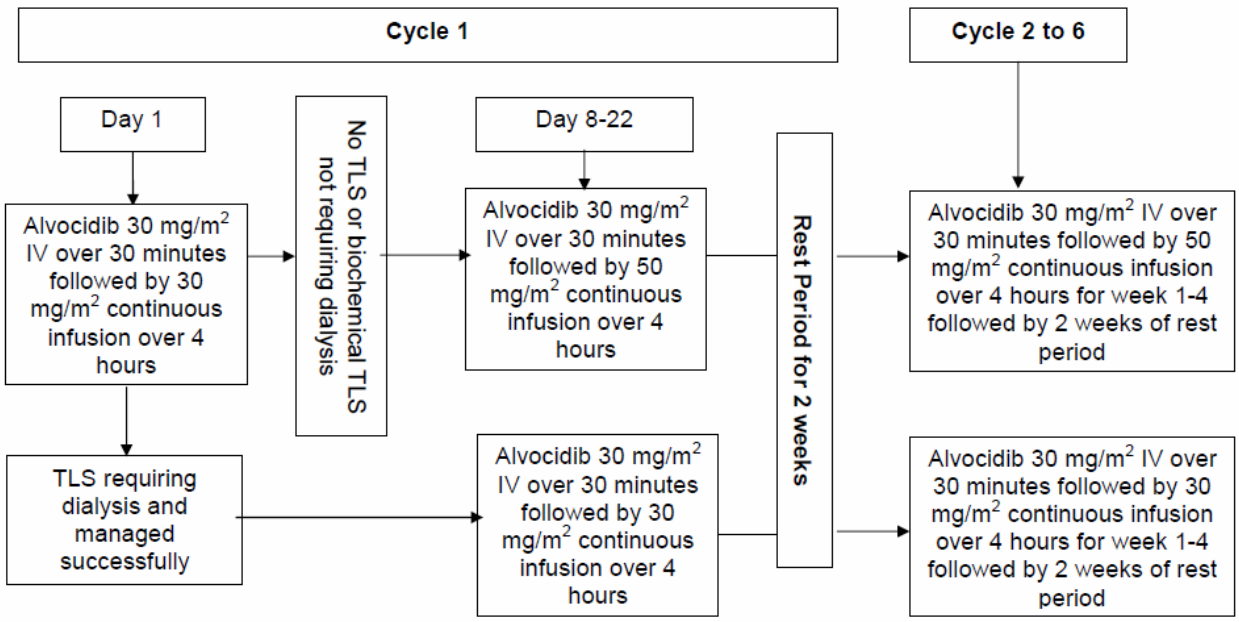
The following efficacy variables were evaluated: best overall objective response rate, PFS, DR, and OS. All patients were evaluated by Investigators for best overall objective response rate using both NCI-96 (National Cancer Institute) criteria and hybrid criteria, which consisted of the NCI-96 criteria as well as evaluations of nodal disease based on computed tomography (CT) scans.

The following safety criteria were evaluated: The safety profile was determined by the incidence of clinically significant AE's, including serious adverse events (SAE's) and laboratory abnormalities. Vital signs, physical examinations, Eastern Cooperative Oncology Group (ECOG) performance status, electrocardiograms (ECG's), and laboratory tests were performed prior to drug administration and at specified regular intervals throughout the study. AE's were graded according to NCI Common Terminology for Adverse Events (CTCAE) version 3.0 and coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 14.1.

Statistical methods: The Intent-to-treat (ITT) population consisted of all patients who signed the consent form and were registered on the study. In the primary analysis, the overall objective response rate (complete response [CR] + partial response [PR] + nodular partial response [nPR]) using the hybrid criteria and associated exact 95% confidence intervals (CI) were estimated. Similar calculations were done using the NCI-96 criteria. For the secondary efficacy time-to-event variables, progression-free survival, objective DR, and overall survival, Kaplan-Meier estimates with corresponding 95% CI's were calculated for the as-treated (AT) population.

AE's were analyzed using descriptive statistics. The primary analysis of AE's was based on treatment-emergent adverse events (TEAE's). The safety profile was determined by the incidence of clinically significant AE's, including SAE's and laboratory abnormalities.

Summary: A summary of the study design is provided below. After the treatment period, patients were followed for 6 months.



The patient will continue to receive the treatment for up to a maximum of 6 cycles provided evidence of response as defined by a ≥ 25% decrease in blood lymphocyte count and/or lymphadenopathy from baseline as assessed by physical examination after completion of at least 2 cycles.

Date of report: 17-Apr-2012 same as on the cover page

Patient disposition: A total of 165 patients was enrolled in the study, of whom 159 were treated with alvocidib. Of these, 126 did not complete the study treatment period. The most common reason for discontinuing alvocidib was disease progression (29.7%), followed by AE's (24.8%). At last study contact, 65.5% of patients had died. No patients were lost to follow-up. Table 1 summarizes patient disposition, including reasons for treatment discontinuation, as well as status at last study contact.

Table 1 - Patient disposition in the ITT population

	HMR1275 (N=165)
Registered and treated	159 (96.4%)
Did not complete the study treatment period	126 (76.4%)
Reason for treatment discontinuation	
Disease progression	49 (29.7%)
Adverse event	41 (24.8%)
Subject lost to follow-up	0
Subject request	4 (2.4%)
Other reasons	32 (19.4%)
Status at last study contact	
Alive	57 (34.5%)
Dead	108 (65.5%)
Lost to follow-up	0

Note: Percentages are calculated using the number of patients registered as denominator
N= number of patients
HMR1275 = alvocidib

Demography of patients: The ITT population was 77.6% male; race was 89.7% White, 6.1% Black, 0.6 % Asian, and 3.6% other; mean age was 60.8 years (standard deviation [SD] = 9.5 years).

Disease staging: Table 2 summarizes the staging, ECOG performance status, p53 (TP53, tumor protein 53) gene deletion status, ataxia-telangiectasia mutated (ATM) gene deletion status, and bulky lymphadenopathy status for the 165 patients in the ITT population at initial diagnosis and at the baseline visit of the study. Of patients whose disease was staged by Rai criteria, 79.8% were either Stage 1 or Stage 2 at initial diagnosis; 19.3% had Rai Stage 1 or Stage 2 disease at the beginning of the study. Of patients whose disease was staged by Binet criteria, 52.3% were Stage A at initial diagnosis; 2.8% had Stage A disease at the beginning of the study. A total of 40.9% of patients had ECOG status 0, 46.5% had ECOG status 1, and 12.6% had ECOG status 2 at the beginning of the study.

A total of 34.8% of patients tested had a p53 gene deletion and 34.5% had an ATM gene deletion.

A total of 69.7% of patients had bulky lymphadenopathy (at least 1 lymph node >5 cm in the longest diameter) at baseline.

Table 2 - Disease staging for the ITT population

	HMR1275 (N=165)
Staging at initial diagnosis using Rai [n(%)]	
Number	84
Stage I, II	67 (79.8%)
Stage III, IV	17 (20.2%)
Staging at initial diagnosis using Binet [n(%)]	
Number	88
Stage A	46 (52.3%)
Stage B, C	42 (47.7%)
Staging at current state using Rai [n(%)]	
Number	150
Stage I, II	29 (19.3%)
Stage III, IV	121 (80.7%)
Staging at current state using Binet [n(%)]	
Number	109
Stage A	3 (2.8%)
Stage B, C	106 (97.2%)
Baseline ECOG performance status	
Number	159
0	65 (40.9%)
1	74 (46.5%)
2	20 (12.6%)
P53 deletion (17p13.1)	
Number	141
Negative	88 (62.4%)
Other	4 (2.8%)
Positive	49 (34.8%)
ATM deletion (11q22.3)	
Number	145
Negative	88 (60.7%)
Other	7 (4.8%)
Positive	50 (34.5%)

	HMR1275 (N=165)
Bulky adenopathy	
Number	165
No	50 (30.3%)
Yes	115 (69.7%)

Note: Number corresponds to the count of patients with non missing data used for calculation of the percentages
ATM = ataxia telangiectasia mutated; ECOG= Eastern Cooperative Oncology Group; HMR1275 = alvocidib; p53 = TP53, tumor protein 53;
N = number of patients
n = percentage of patients with a particular classification
Bulky adenopathy (lymphadenopathy) is defined as at least 1 lymph node >5 cm in the longest diameter.

Summary of prior treatment regimens: Table 3 summarizes the type and number of prior anti-cancer therapies for the ITT population. Patients had experienced a mean of 4.6 (median = 4.00) treatment regimens prior to the study: 98.8% of patients were previously treated with an alkylating agent; all patients were previously treated with fludarabine; 95.8% of patients were fludarabine-refractory. A total of 37.6% of patients were previously treated with alemtuzumab; 30.3% of patients were alemtuzumab-refractory; 29.1% of patients were refractory to both fludarabine and alemtuzumab. Refractory disease was defined as stable disease after at least 2 cycles of therapy or progressive disease in a patient who has been on therapy for ≤ 6 months.

Table 3 - Summary of prior treatment regimens for the ITT population

	HMR1275 (N=165)
Patients receiving a regimen containing alkylating agent	163 (98.8%)
Patients receiving a regimen containing fludarabine	165 (100%)
Patients receiving a regimen containing both alkylating agent and fludarabine	163 (98.8%)
Patients receiving a regimen containing alemtuzumab	62 (37.6%)
Patients receiving a regimen containing rituximab	143 (86.7%)
Patients who are refractory to fludarabine (SD or progressed on therapy/within 6 months of completion)	158 (95.8%)
Patients who are refractory to alemtuzumab (SD or progressed on therapy/within 6 months of completion)	50 (30.3%)
Patients who are double refractory to both fludarabine and alemtuzumab	48 (29.1%)
Prior regimen	
Number	165
Mean (SD)	4.60 (2.43)
Median	4.00
Min : Max	1.0 : 12.0

SD = stable disease; mean (SD) = mean (standard deviation); HMR1275 = alvocidib;
N = number of patients

Analysis of Investigator-reported best overall response rate for the ITT population: Investigators classified 24.8% of patients as responding to treatment, according to the hybrid criteria, and 30.3% as responding to treatment, according to NCI-96 criteria. Responders include those who had CR's, PR's, and nPR's. Table 4 summarizes the Analysis of Investigator-reported best overall response rate in the ITT population.

Table 4 - Analysis of Investigator-reported best overall response rate in the ITT population

	HMR1275 (N=165)	
	Hybrid criteria	**NCI 96 criteria**
Objective response rate (%)	41 (24.8%)	50 (30.3%)
95% Exact C.I.	(18.5, 32.2)	(23.4, 37.9)

CI = confidence interval; HMR1275 = alvocidib; NCI = National Cancer Institute
N = number of patients

Summary of Investigator-reported best overall response: Investigators reported 1.8% of patients as having a CR and 21.8% as having a PR, using the hybrid criteria. 32.1% had stable disease, using the hybrid criteria. Table 5 summarizes best overall objective response for the ITT population.

Table 5 - Summary of Investigator-reported best overall response in the ITT population

	HMR1275 (N=165)	
Category	**Hybrid criteria**	**NCI 96 criteria**
Complete response	3 (1.8%)	6 (3.6%)
Partial response	36 (21.8%)	42 (25.5%)
nPR	2 (1.2%)	2 (1.2%)
Stable disease	53 (32.1%)	66 (40.0%)
Disease progression	21 (12.7%)	26 (15.8%)
Not assessed	50 (30.3%)	23 (13.9%)

nPR - Nodular partial response
HMR1275 = alvocidib; NCI = National Cancer Institute
N = number of patients

Analysis of Investigator-reported best overall response rate: Patients in the ITT population with an ATM (ataxia telangiectasia mutated) deletion had a response rate (CR, PR, or nPR), using the hybrid criteria, of 26%, whereas patients with a p53 deletion had a response rate, using these criteria, of 14.3%. Patients with bulky lymphadenopathy (>5 cm) had a response rate, using the hybrid criteria, of 25.2%. Patients who were refractory to both fludarabine and alemtuzumab had a response rate, using the hybrid criteria, of 10.4%. Table 6 summarizes the Investigator-reported best overall objective response rate, by subgroup, for the ITT population.

Table 6 - Analysis of Investigator-reported best overall response rate in the ITT population

	HMR1275 (N=165)	
	Hybrid criteria	**NCI 96 criteria**
P53 deletion (17p13.1)		
Positive	7/49 (14.3%)	13/49 (26.5%)
Negative	28/88 (31.8%)	29/88 (33.0%)
Other	1/4 (25.0%)	1/4 (25.0%)
Unknown	5/24 (20.8%)	7/24 (29.2%)
ATM deletion (11q22.3)		
Positive	13/50 (26.0%)	14/50 (28.0%)
Negative	22/88 (25.0%)	28/88 (31.8%)
Other	2/7 (28.6%)	2/7 (28.6%)
Unknown	4/20 (20.0%)	6/20 (30.0%)
Bulky adenopathy>5cm		
Yes	29/115 (25.2%)	33/115 (28.7%)
No	12/50 (24.0%)	17/50 (34.0%)
Double refractory		
Yes	5/48 (10.4%)	7/48 (14.6%)
No	36/117 (30.8%)	43/117 (36.8%)

ATM = ataxia telangiectasia mutated; HMR1275 = alvocidib; NCI = National Cancer Institute; p53 = TP53, tumor protein 53
N = number of patients
Bulky adenopathy (lymphadenopathy) is defined as at least 1 lymph node >5 cm in the longest diameter.

Summary of progression-free survival: Median PFS in the alvocidib-treated population was 7.6 months. 43% survived at least 9 months with no disease; 32% survived at least a year with no progression. Table 7 summarizes the PFS of the alvocidib-treated population.

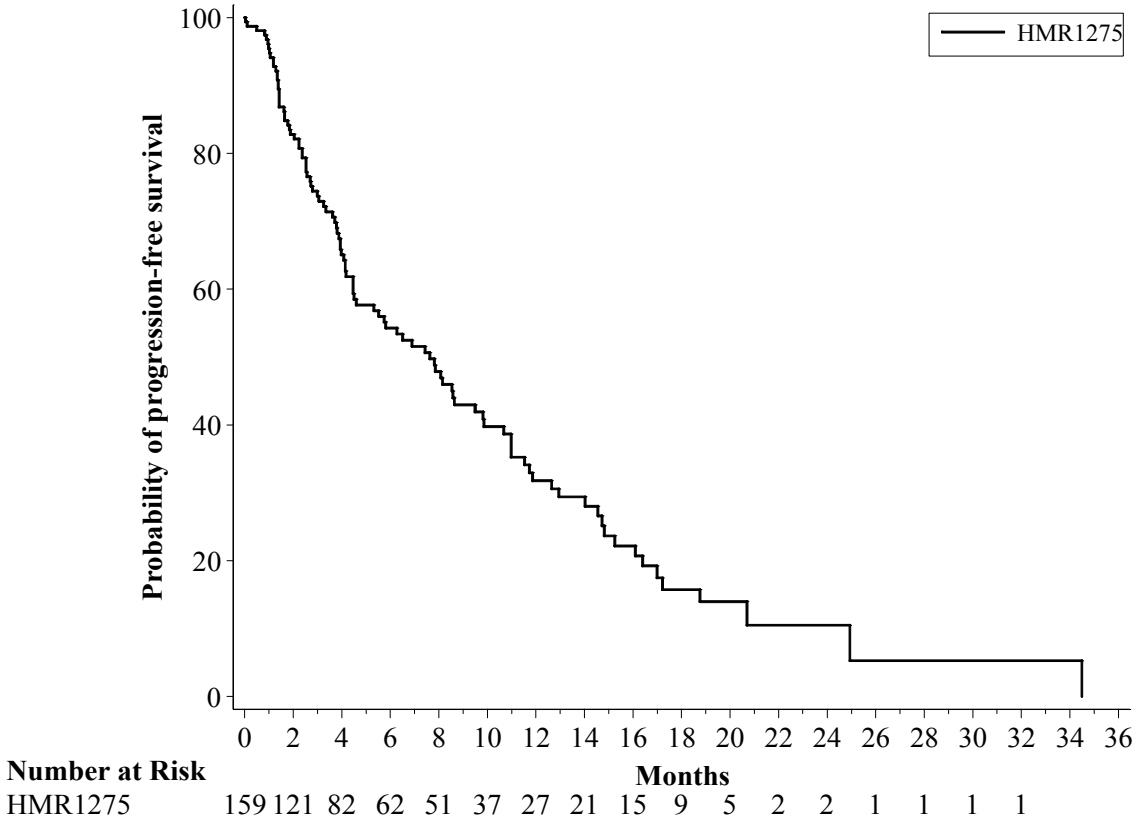
Table 7 - Summary of progression-free survival in the AT population

	HMR1275 (N=159)
Number assessed	159
Number of events (%)	100 (62.9%)
Median PFS (95% CI) (months)	7.6 (4.5 - 9.8)
Probability (95% CI) of progression-free survival	
3 months	0.74 (0.66,0.80)
6 months	0.54 (0.45,0.62)
9 months	0.43 (0.34,0.52)
12 months	0.32 (0.23,0.41)

PFS - Progression Free Survival
CI = confidence interval; HMR1275 = alvocidib; NCI = National Cancer Institute
N = number of patients

Figure 1. Median time without disease progression or death in alvocidib (HMR1725)-treated patients was 7.6 months.

Figure 1 - Kaplan-Meier plot for progression-free survival in the AT population



HMR1275 = alvocidib

Summary of duration of response: Median DR in alvocidib-treated patients was 10.4 months. Table 8 summarizes the DR for the AT population. This analysis was based on response as determined by the NCI-96 criteria and represents those patients where response was noted at 2 consecutive visits in the case report form and database. Table 4 gives data for the 50 patients with best confirmed response and duration of response assessed and documented by Investigators.

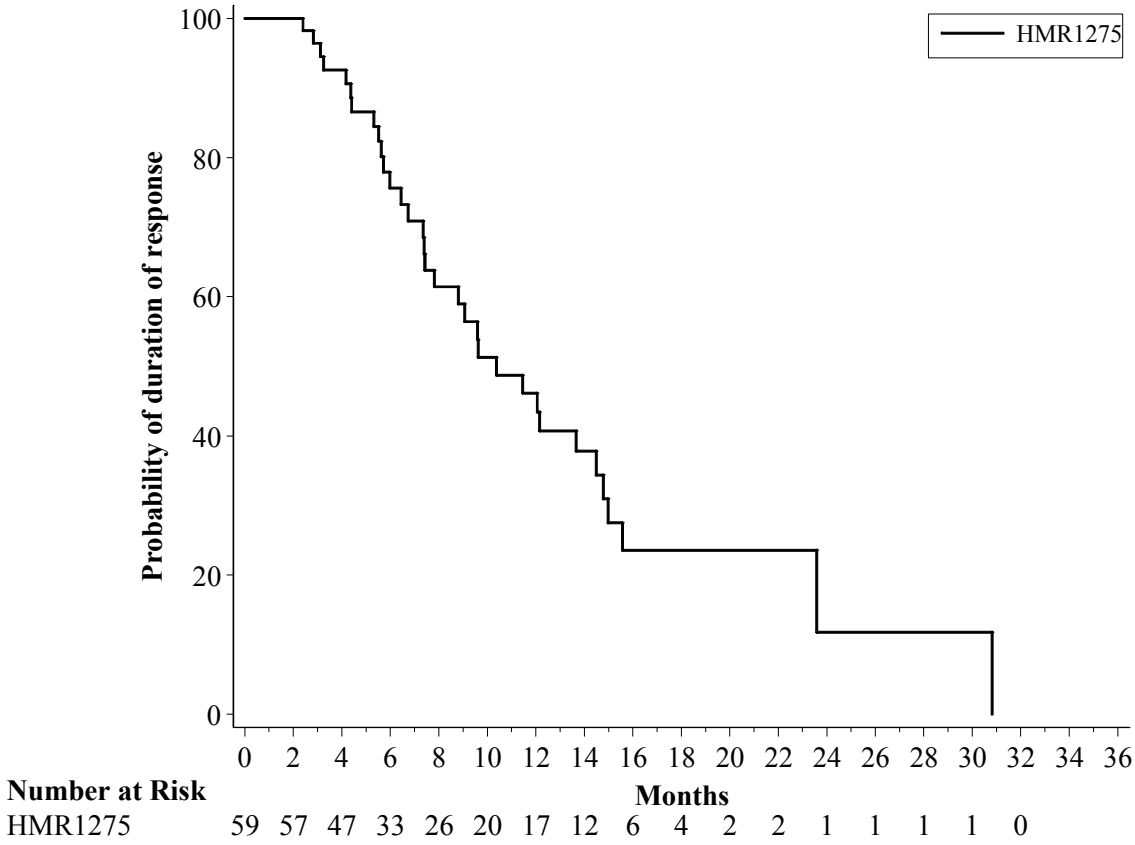
Table 8 - Duration of response in the AT population

	HMR1275 (N=159)
Number assessed	59
Number of events (%)	33 (20.8%)
Median DR (95% CI) (months)	10.4 (7.4 - 14.5)
Probability (95% CI) of duration of response	
3 months	0.96 (0.86,0.99)
6 months	0.76 (0.61,0.85)
9 months	0.59 (0.43,0.72)
12 months	0.46 (0.31,0.60)

DR - Duration of response
CI = confidence interval; HMR1275 = alvocidib
N = number of patients

Figure 2. At twelve months, 46% (95% CI = 31 - 60%) of the alvocidib-treated group was responding to treatment. Median duration of response for this group was 10.4 months (95% CI = 7.4 -14.5 months).

Figure 2 - Kaplan-Meier Plot for duration of response in the AT population



HMR1275 = alvocidib

Summary of DR (Investigators' assessments): The median Investigator-assessed DR in the alvocidib-treated population was 13.7 months. Patients with CR, PR, or nPR were considered to be responders. Table 9 summarizes the Investigators' assessments of DR for the AT population determined using the NCI-96 criteria. Four patients did not have adequate follow-up for DR to be calculated. The number assessed is less in this table than in Table 8 because this table represents those patients for whom duration of response was assessed by Investigators, as opposed to by the Sponsor.

Table 9 - Investigators' assessments of duration of response in the AT population

	HMR1275 (N=159)
Number assessed	46
Number of events (%)	23 (14.5%)
Median DR (95% CI) (months)	13.7 (9.1 - 15.6)
Probability (95% CI) of duration of response	

	HMR1275 (N=159)
3 months	0.98 (0.85,1.00)
6 months	0.89 (0.74,0.96)
9 months	0.71 (0.53,0.83)
12 months	0.58 (0.40,0.73)

DR - Duration of response
CI = confidence interval; HMR1275 = alvocidib
N = number of patients

Summary of Overall Survival: Median OS of the alvocidib-treated population was 14.6 months. Table 10 summarizes OS in the AT population.

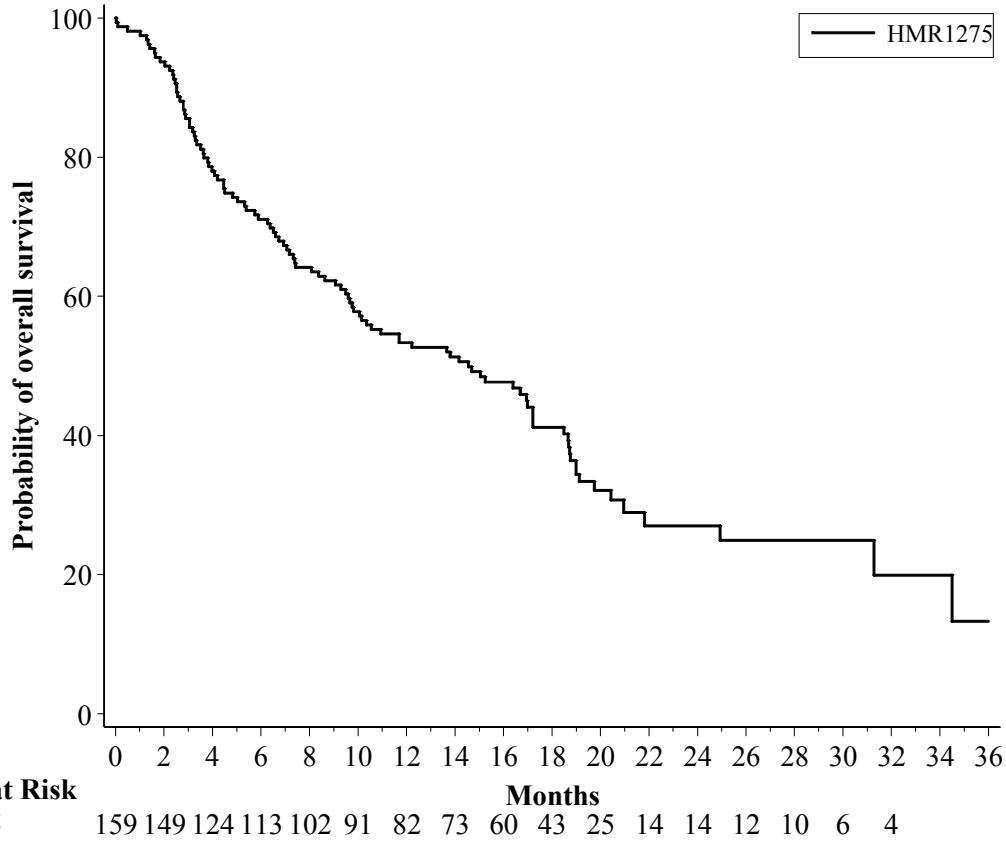
Table 10 - Summary of overall survival in the AT population

	HMR1275 (N=159)
Number assessed	159
Number of events (%)	104 (65.4%)
Median OS (95% CI) (months)	14.6 (9.8 - 17.2)
Probability (95% CI) of overall survival	
3 months	0.86 (0.79,0.90)
6 months	0.71 (0.63,0.77)
9 months	0.62 (0.54,0.69)
12 months	0.53 (0.45,0.61)

CI = confidence interval; HMR1275 = alvocidib
N = number of patients

Figure 3. At 12 months, 53% (95% CI [confidence interval] = 45 – 61%) of the treated population was alive. Median survival was 14.6 (95% CI = 9.8 - 17.2) months.

Figure 3 - Kaplan-Meier plot for overall survival in the AT population



Summary of causes of death: At last study contact, 108/165 patients in the ITT population had died: 66.7% of these died of disease progression; 15.7% died of AE's; and 17.6% of these died of other causes. Within 30 days of the end of alvocidib treatment, 7 patients died of disease progression, and 5 died of AE's. Table 11 summarizes causes of death for the ITT population. The 17 patients who are listed in this table as dieing of adverse events include patients who were never treated or died of AE's that were not treatment-emergent.

Table 11 - Summary of causes of death for the ITT population

	HMR1275 (N=165)
Deaths	
Number	108
Disease progression	72 (66.7%)
Adverse event	17 (15.7%)
Other	19 (17.6%)
Deaths within 30 days from end of study treatment	
Number	13
Disease progression	7 (53.8%)
Adverse event	5 (38.5%)
Other	1 (7.7%)

HMR1275 = alvocidib
N = number of patients

Exposure to alvocidib: Patients in the alvocidib-treated group received a mean cumulative dose of 850.0 mg/m^2 of alvocidib across a mean of 3.1 cycles. Patient exposure to alvocidib in the alvocidib-treated group is presented in Table 12.

Table 12 - Exposure to alvocidib in the AT population

	HMR1275 (N=159)
Dose group	
Non-escalated group(60 mg/m^2)	22 (13.8%)
Escalated group(80 mg/m^2)	137 (86.2%)
Number of cycles	
Number	159
Mean (SD)	3.1 (1.9)
Median	2.0
Min : Max	1 : 6
Cumulative dose (mg/m^2)	
Number	157
Mean (SD)	850.0 (579.6)
Median	622.0
Min : Max	59 : 2020

	HMR1275 (N=159)
Actual dose intensity (mg/m^2/wk)	
Number	157
Mean (SD)	55.077 (10.702)
Median	54.908
Min : Max	30.19 : 80.00
Planned dose intensity (mg/m^2/wk)	
Number	159
Mean (SD)	50.133 (4.179)
Median	51.667
Min : Max	40.00 : 52.78
Relative dose intensity	
Number	157
Mean (SD)	1.105 (0.230)
Median	1.060
Min : Max	0.57 : 1.84

HMR1275 = alvocidib; SD = standard deviation
N = number of patients

Overview of the safety profile -- treatment-emergent adverse events: TEAE's occurred in all patients in the treated group. A total of 86.8% had a TEAE of Grade ≥3; 25.2% of patients had a TEAE leading to permanent discontinuation of treatment with alvocidib. SAE's were reported in 73.6% of patients. An overview of TEAE's is presented in Table 13.

Table 13- Overview of adverse event profile: treatment emergent adverse events in the AT population

n (%)	HMR1275 (N=159)
Patients with any TEAE	159 (100%)
Patients with any grade ≥3 TEAE	138 (86.8%)
Patients with any treatment emergent SAE	117 (73.6%)
Patients with any TEAE leading to death	24 (15.1%)
Patients with any TEAE leading to permanent treatment discontinuation	40 (25.2%)

TEAE: Treatment emergent adverse event, SAE: Serious adverse event
n (%) = number and percentage of patients with at least one TEAE
HMR1275 = alvocidib
N = number of patients

Patients with TEAE's of at least 5% rate of incidence: Table 14 displays TEAE's appearing in at least 5% of AT patients sorted by SOC (system organ class) internationally-agreed order and alphabetically by MedDRA term hierarchy. The most common grade ≥3 TEAE's involved the blood SOC (46.5%), followed

by metabolism (32.1%), infections (30.2%), general disorders (27.0%), gastrointestinal (24.5%) and respiratory (17.0%). Among the metabolic disorders, TLS was reported as a grade ≥3 event in 20.8% of patients (see also the comprehensive analysis of TLS below, which is not restricted to TLS reported as a TEAE).

TLS is undercounted in TEAE's as shown in Table 14. TLS forms, but not AE forms were filled out for 2 patients. Thus Table 14 should have had a count of 39 patients, instead of 37 patients, for events of TLS.

TEAE grade data are missing for one event, an event of euthanasia. One patient chose to be euthanized on Day 3 of the study. She lived in Belgium, where euthanasia is legal and socially-accepted. She had considered euthanasia before the study, reversed her decision, and then reversed it again, after a difficult night. In the MedDRA classification, euthanasia is an adverse event. The Investigator responsible for 1 patient did not respond to requests that he grade this event.

Table 14 - Numbers and percentages of patients with TEAE's of at least 5% rate of incidence in the AT population

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HMR1275 (N=159) Missing [1]	 All grades	 Grade ≥3
Any class	1 (0.6%)	159 (100%)	138 (86.8%)
INFECTIONS AND INFESTATIONS	0	90 (56.6%)	48 (30.2%)
HLGT: Infections - pathogen unspecified	0	71 (44.7%)	31 (19.5%)
HLT: Infections nec	0	16 (10.1%)	9 (5.7%)
Device related infection	0	9 (5.7%)	5 (3.1%)
HLT: Lower respiratory tract and lung infections	0	20 (12.6%)	13 (8.2%)
Pneumonia	0	12 (7.5%)	10 (6.3%)
HLT: Upper respiratory tract infections	0	38 (23.9%)	2 (1.3%)
Nasopharyngitis	0	11 (6.9%)	0
Sinusitis	0	10 (6.3%)	2 (1.3%)
Upper respiratory tract infection	0	17 (10.7%)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	81 (50.9%)	74 (46.5%)
HLGT: Anaemias nonhaemolytic and marrow depression	0	20 (12.6%)	12 (7.5%)
HLT: Anaemias nec	0	20 (12.6%)	12 (7.5%)
Anaemia	0	20 (12.6%)	12 (7.5%)
HLGT: Platelet disorders	0	30 (18.9%)	30 (18.9%)
HLT: Thrombocytopenias	0	30 (18.9%)	30 (18.9%)
Thrombocytopenia	0	30 (18.9%)	30 (18.9%)
HLGT: White blood cell disorders	0	58 (36.5%)	55 (34.6%)
HLT: Neutropenias	0	57 (35.8%)	54 (34.0%)
Febrile neutropenia	0	27 (17.0%)	24 (15.1%)
Neutropenia	0	34 (21.4%)	34 (21.4%)

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HMR1275 (N=159) Missing [1]	All grades	Grade ≥3
METABOLISM AND NUTRITION DISORDERS	0	96 (60.4%)	51 (32.1%)
HLGT: Appetite and general nutritional disorders	0	27 (17.0%)	0
HLT: Appetite disorders	0	26 (16.4%)	0
Decreased appetite	0	26 (16.4%)	0
HLGT: Bone, calcium, magnesium and phosphorus metabolism disorders	0	20 (12.6%)	5 (3.1%)
HLT: Calcium metabolism disorders	0	16 (10.1%)	3 (1.9%)
Hypercalcaemia	0	8 (5.0%)	2 (1.3%)
HLGT: Electrolyte and fluid balance conditions	0	73 (45.9%)	44 (27.7%)
HLT: Electrolyte imbalance nec	0	39 (24.5%)	35 (22.0%)
Tumour lysis syndrome	0	37 (23.3%)	33 (20.8%)
HLT: Potassium imbalance	0	47 (29.6%)	14 (8.8%)
Hyperkalaemia	0	43 (27.0%)	11 (6.9%)
HLGT: Glucose metabolism disorders (incl diabetes mellitus)	0	13 (8.2%)	9 (5.7%)
HLT: Hyperglycaemic conditions nec	0	11 (6.9%)	8 (5.0%)
Hyperglycaemia	0	11 (6.9%)	8 (5.0%)
PSYCHIATRIC DISORDERS	0	32 (20.1%)	3 (1.9%)
HLGT: Sleep disorders and disturbances	0	17 (10.7%)	1 (0.6%)
HLT: Disturbances in initiating and maintaining sleep	0	16 (10.1%)	1 (0.6%)
Insomnia	0	16 (10.1%)	1 (0.6%)
NERVOUS SYSTEM DISORDERS	0	74 (46.5%)	7 (4.4%)
HLGT: Headaches	0	34 (21.4%)	2 (1.3%)
HLT: Headaches nec	0	34 (21.4%)	2 (1.3%)
Headache	0	30 (18.9%)	2 (1.3%)
HLGT: Neurological disorders nec	0	46 (28.9%)	3 (1.9%)
HLT: Neurological signs and symptoms nec	0	23 (14.5%)	1 (0.6%)
Dizziness	0	22 (13.8%)	1 (0.6%)
HLT: Sensory abnormalities nec	0	20 (12.6%)	0
Dysgeusia	0	14 (8.8%)	0
VASCULAR DISORDERS	0	31 (19.5%)	6 (3.8%)
HLGT: Vascular disorders nec	0	13 (8.2%)	1 (0.6%)
HLT: Peripheral vascular disorders nec	0	12 (7.5%)	1 (0.6%)
Hot flush	0	8 (5.0%)	1 (0.6%)

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HMR1275 (N=159) Missing [1]	All grades	Grade ≥3
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	97 (61.0%)	27 (17.0%)
HLGT: Respiratory disorders nec	0	90 (56.6%)	20 (12.6%)
HLT: Breathing abnormalities	0	44 (27.7%)	10 (6.3%)
Dyspnoea	0	37 (23.3%)	9 (5.7%)
HLT: Coughing and associated symptoms	0	51 (32.1%)	3 (1.9%)
Cough	0	41 (25.8%)	3 (1.9%)
Productive cough	0	9 (5.7%)	0
HLT: Upper respiratory tract signs and symptoms	0	19 (11.9%)	0
Oropharyngeal pain	0	12 (7.5%)	0
HLGT: Upper respiratory tract disorders (excl infections)	0	25 (15.7%)	1 (0.6%)
HLT: Nasal disorders nec	0	13 (8.2%)	1 (0.6%)
Epistaxis	0	13 (8.2%)	1 (0.6%)
GASTROINTESTINAL DISORDERS	0	141 (88.7%)	39 (24.5%)
HLGT: Gastrointestinal motility and defaecation conditions	0	133 (83.6%)	29 (18.2%)
HLT: Diarrhoea (excl infective)	0	130 (81.8%)	29 (18.2%)
Diarrhoea	0	130 (81.8%)	29 (18.2%)
HLT: Gastrointestinal atonic and hypomotility disorders nec	0	35 (22.0%)	0
Constipation	0	34 (21.4%)	0
HLGT: Gastrointestinal signs and symptoms	0	113 (71.1%)	10 (6.3%)
HLT: Dyspeptic signs and symptoms	0	8 (5.0%)	0
Dyspepsia	0	8 (5.0%)	0
HLT: Flatulence, bloating and distension	0	11 (6.9%)	1 (0.6%)
Abdominal distension	0	11 (6.9%)	1 (0.6%)
HLT: Gastrointestinal and abdominal pains (excl oral and throat)	0	39 (24.5%)	6 (3.8%)
Abdominal pain	0	29 (18.2%)	6 (3.8%)
HLT: Nausea and vomiting symptoms	0	100 (62.9%)	4 (2.5%)
Nausea	0	92 (57.9%)	1 (0.6%)
Vomiting	0	65 (40.9%)	3 (1.9%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	83 (52.2%)	8 (5.0%)
HLGT: Epidermal and dermal conditions	0	39 (24.5%)	2 (1.3%)
HLT: Erythemas	0	8 (5.0%)	0
Erythema	0	8 (5.0%)	0
HLT: Rashes, eruptions and exanthems nec	0	20 (12.6%)	2 (1.3%)
Rash	0	19 (11.9%)	2 (1.3%)

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HMR1275 (N=159) Missing [1]	All grades	Grade ≥3
HLGT: Skin appendage conditions	0	57 (35.8%)	7 (4.4%)
HLT: Apocrine and eccrine gland disorders	0	51 (32.1%)	7 (4.4%)
Hyperhidrosis	0	9 (5.7%)	0
Night sweats	0	48 (30.2%)	7 (4.4%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	73 (45.9%)	13 (8.2%)
HLGT: Joint disorders	0	18 (11.3%)	3 (1.9%)
HLT: Joint related signs and symptoms	0	18 (11.3%)	3 (1.9%)
Arthralgia	0	16 (10.1%)	3 (1.9%)
HLGT: Muscle disorders	0	28 (17.6%)	3 (1.9%)
HLT: Muscle pains	0	11 (6.9%)	0
Myalgia	0	11 (6.9%)	0
HLT: Muscle related signs and symptoms nec	0	14 (8.8%)	3 (1.9%)
Muscle spasms	0	12 (7.5%)	2 (1.3%)
HLGT: Musculoskeletal and connective tissue disorders nec	0	45 (28.3%)	8 (5.0%)
HLT: Musculoskeletal and connective tissue pain and discomfort	0	44 (27.7%)	5 (3.1%)
Back pain	0	24 (15.1%)	3 (1.9%)
Musculoskeletal pain	0	8 (5.0%)	0
Pain in extremity	0	12 (7.5%)	2 (1.3%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.6%)	136 (85.5%)	43 (27.0%)
HLGT: Body temperature conditions	0	60 (37.7%)	8 (5.0%)
HLT: Febrile disorders	0	60 (37.7%)	8 (5.0%)
Pyrexia	0	60 (37.7%)	8 (5.0%)
HLGT: General system disorders nec	0	121 (76.1%)	37 (23.3%)
HLT: Asthenic conditions	0	102 (64.2%)	29 (18.2%)
Asthenia	0	13 (8.2%)	3 (1.9%)
Fatigue	0	96 (60.4%)	27 (17.0%)
HLT: Feelings and sensations nec	0	13 (8.2%)	0
Chills	0	10 (6.3%)	0
HLT: General signs and symptoms nec	0	15 (9.4%)	10 (6.3%)
Disease progression	0	8 (5.0%)	8 (5.0%)
HLT: Oedema nec	0	41 (25.8%)	1 (0.6%)
Oedema peripheral	0	38 (23.9%)	1 (0.6%)

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HMR1275 (N=159) Missing [1]	 All grades	 Grade ≥3
INVESTIGATIONS	0	48 (30.2%)	14 (8.8%)
HLGT: Physical examination topics	0	24 (15.1%)	2 (1.3%)
HLT: Physical examination procedures	0	24 (15.1%)	2 (1.3%)
Weight decreased	0	22 (13.8%)	2 (1.3%)

TEAE: Treatment emergent adverse event, SOC: System organ class, HLGT: High level group term, HLT: High level term, PT: Preferred term
MEDDRA 14.1
n (%) = number and percentage of patients with at least one TEAE
N= number of patients
Note: Table sorted by SOC internationally-agreed order and HLGTs, HLTs, and PTs by alphabetical order by alphabetic order
SOCs with at least one TEAE with at least 5% incidence in at least one group are presented
[1] One patient underwent euthanasia, which the Investigator did not grade in severity, despite the Sponsor's request that he do so.
HMR1275 = alvocidib

Treatment emergent SAE's by primary SOC, HLGT, HLT and PT: Table 15 displays treatment-emergent SAE's appearing in at least 5% of AT patients, sorted by SOC (system organ class) internationally-agreed order and then sorted alphabetically by MedDRA term hierarchy. The most common grade ≥3 treatment-emergent SAE's involved the infections SOC (25.8%), followed by blood (18.9%), and metabolism (17.0%). Among the metabolic disorders, TLS was reported as a grade ≥3 treatment-emergent SAE in 11.9% of patients (see also the comprehensive analysis of TLS below, which is not restricted to TLS events reported as TEAE's).

Table 15 - Treatment-emergent SAE's by primary SOC, HLGT, HLT and PT in the AT population

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HMR1275 (N=159) Missing [1]	 All grades	 Grade ≥3
Any class	1 (0.6%)	117 (73.6%)	107 (67.3%)
INFECTIONS AND INFESTATIONS	0	46 (28.9%)	41 (25.8%)
HLGT: Infections - pathogen unspecified	0	29 (18.2%)	26 (16.4%)
HLT: Lower respiratory tract and lung infections	0	11 (6.9%)	10 (6.3%)
Pneumonia	0	9 (5.7%)	8 (5.0%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	34 (21.4%)	30 (18.9%)
HLGT: White blood cell disorders	0	28 (17.6%)	26 (16.4%)
HLT: Neutropenias	0	28 (17.6%)	26 (16.4%)
Febrile neutropenia	0	25 (15.7%)	23 (14.5%)

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HMR1275 (N=159) Missing [1]	 All grades	 Grade ≥3
METABOLISM AND NUTRITION DISORDERS	0	30 (18.9%)	27 (17.0%)
HLGT: Electrolyte and fluid balance conditions	0	27 (17.0%)	25 (15.7%)
HLT: Electrolyte imbalance nec	0	22 (13.8%)	21 (13.2%)
Tumour lysis syndrome	0	20 (12.6%)	19 (11.9%)
GASTROINTESTINAL DISORDERS	0	17 (10.7%)	13 (8.2%)
HLGT: Gastrointestinal motility and defaecation conditions	0	9 (5.7%)	7 (4.4%)
HLT: Diarrhoea (excl infective)	0	9 (5.7%)	7 (4.4%)
Diarrhoea	0	9 (5.7%)	7 (4.4%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.6%)	28 (17.6%)	14 (8.8%)
HLGT: Body temperature conditions	0	14 (8.8%)	4 (2.5%)
HLT: Febrile disorders	0	14 (8.8%)	4 (2.5%)
Pyrexia	0	14 (8.8%)	4 (2.5%)
HLGT: General system disorders nec	0	13 (8.2%)	11 (6.9%)
HLT: General signs and symptoms nec	0	10 (6.3%)	10 (6.3%)
Disease progression	0	8 (5.0%)	8 (5.0%)

TEAE: Treatment emergent adverse event, SOC: System organ class, HLGT: High level group term, HLT: High level term, PT: Preferred term
MEDDRA 14.1
n (%) = number and percentage of patients with at least one treatment emergent SAE
N= number of patients
Note: Table sorted by SOC internationally-agreed order and HLGTs, HLTs, PTs by alphabetic order
SOCs with at least one TEAE with at least 5% incidence in at least one group are presented
[1] One patient had an adverse event of euthanasia, which the Investigator did not grade, despite the Sponsor's request that he do so.
HMR1275 = alvocidib

Patients with TEAE's leading to treatment discontinuation: Details for patients with TEAE's leading to treatment discontinuation classified by SOC in internationally-agreed order and MedDRA preferred terms (PT's) alphabetically are provided in Table 16. A total of 25.2% of patients had a TEAE leading to treatment discontinuation.

Table 16 - Patients with TEAE's leading to treatment discontinuation

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred term n(%)	HMR1275 (N=159) Missing [1]	 All grades	 Grade ≥3
Any class	1 (0.6%)	40 (25.2%)	30 (18.9%)
INFECTIONS AND INFESTATIONS	0	9 (5.7%)	9 (5.7%)
HLGT: Bacterial infectious disorders	0	3 (1.9%)	3 (1.9%)
HLT: Escherichia infections	0	1 (0.6%)	1 (0.6%)
Escherichia sepsis	0	1 (0.6%)	1 (0.6%)
HLT: Pseudomonal infections	0	1 (0.6%)	1 (0.6%)
Pseudomonal sepsis	0	1 (0.6%)	1 (0.6%)
HLT: Staphylococcal infections	0	1 (0.6%)	1 (0.6%)
Staphylococcal sepsis	0	1 (0.6%)	1 (0.6%)
HLGT: Fungal infectious disorders	0	4 (2.5%)	4 (2.5%)
HLT: Aspergillus infections	0	1 (0.6%)	1 (0.6%)
Bronchopulmonary aspergillosis	0	1 (0.6%)	1 (0.6%)
HLT: Fungal infections nec	0	3 (1.9%)	3 (1.9%)
Fungal infection	0	1 (0.6%)	1 (0.6%)
Lower respiratory tract infection fungal	0	1 (0.6%)	1 (0.6%)
Pneumonia fungal	0	1 (0.6%)	1 (0.6%)
HLGT: Infections - pathogen unspecified	0	2 (1.3%)	2 (1.3%)
HLT: Infections nec	0	1 (0.6%)	1 (0.6%)
Neutropenic infection	0	1 (0.6%)	1 (0.6%)
HLT: Sepsis, bacteraemia, viraemia and fungaemia nec	0	1 (0.6%)	1 (0.6%)
Sepsis	0	1 (0.6%)	1 (0.6%)
HLGT: Viral infectious disorders	0	1 (0.6%)	1 (0.6%)
HLT: Epstein-barr viral infections	0	1 (0.6%)	1 (0.6%)
Epstein-barr virus infection	0	1 (0.6%)	1 (0.6%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	2 (1.3%)	2 (1.3%)
HLGT: Miscellaneous and site unspecified neoplasms malignant and unspecified	0	1 (0.6%)	1 (0.6%)
HLT: Neoplasms malignant site unspecified nec	0	1 (0.6%)	1 (0.6%)
Squamous cell carcinoma	0	1 (0.6%)	1 (0.6%)
HLGT: Respiratory and mediastinal neoplasms malignant and unspecified	0	1 (0.6%)	1 (0.6%)
HLT: Non-small cell neoplasms malignant of the respiratory tract cell type specified	0	1 (0.6%)	1 (0.6%)
Lung adenocarcinoma	0	1 (0.6%)	1 (0.6%)

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred term n(%)	HMR1275 (N=159) Missing [1]	 All grades	 Grade ≥3
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	10 (6.3%)	9 (5.7%)
HLGT: Haemolyses and related conditions	0	1 (0.6%)	1 (0.6%)
HLT: Anaemias haemolytic nec	0	1 (0.6%)	1 (0.6%)
Haemolytic anaemia	0	1 (0.6%)	1 (0.6%)
HLGT: Platelet disorders	0	3 (1.9%)	3 (1.9%)
HLT: Thrombocytopenias	0	3 (1.9%)	3 (1.9%)
Idiopathic thrombocytopenic purpura	0	1 (0.6%)	1 (0.6%)
Thrombocytopenia	0	2 (1.3%)	2 (1.3%)
HLGT: White blood cell disorders	0	6 (3.8%)	5 (3.1%)
HLT: Neutropenias	0	6 (3.8%)	5 (3.1%)
Febrile neutropenia	0	5 (3.1%)	4 (2.5%)
Neutropenia	0	1 (0.6%)	1 (0.6%)
METABOLISM AND NUTRITION DISORDERS	0	3 (1.9%)	2 (1.3%)
HLGT: Electrolyte and fluid balance conditions	0	3 (1.9%)	2 (1.3%)
HLT: Electrolyte imbalance nec	0	2 (1.3%)	2 (1.3%)
Tumour lysis syndrome	0	2 (1.3%)	2 (1.3%)
HLT: Potassium imbalance	0	1 (0.6%)	0
Hyperkalaemia	0	1 (0.6%)	0
NERVOUS SYSTEM DISORDERS	0	2 (1.3%)	1 (0.6%)
HLGT: Central nervous system vascular disorders	0	1 (0.6%)	1 (0.6%)
HLT: Central nervous system haemorrhages and cerebrovascular accidents	0	1 (0.6%)	1 (0.6%)
Thrombotic stroke	0	1 (0.6%)	1 (0.6%)
HLGT: Encephalopathies	0	1 (0.6%)	0
HLT: Encephalopathies nec	0	1 (0.6%)	0
Leukoencephalopathy	0	1 (0.6%)	0
EAR AND LABYRINTH DISORDERS	0	1 (0.6%)	1 (0.6%)
HLGT: Hearing disorders	0	1 (0.6%)	1 (0.6%)
HLT: Hearing losses	0	1 (0.6%)	1 (0.6%)
Deafness	0	1 (0.6%)	1 (0.6%)
CARDIAC DISORDERS	0	1 (0.6%)	1 (0.6%)
HLGT: Cardiac arrhythmias	0	1 (0.6%)	1 (0.6%)
HLT: Ventricular arrhythmias and cardiac arrest	0	1 (0.6%)	1 (0.6%)
Ventricular arrhythmia	0	1 (0.6%)	1 (0.6%)

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred term n(%)	HMR1275 (N=159) Missing [1]	 All grades	 Grade ≥3
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	3 (1.9%)	2 (1.3%)
HLGT: Lower respiratory tract disorders (excl obstruction and infection)	0	1 (0.6%)	1 (0.6%)
HLT: Pulmonary oedemas	0	1 (0.6%)	1 (0.6%)
Acute respiratory distress syndrome	0	1 (0.6%)	1 (0.6%)
HLGT: Pleural disorders	0	1 (0.6%)	0
HLT: Pneumothorax and pleural effusions nec	0	1 (0.6%)	0
Haemothorax	0	1 (0.6%)	0
HLGT: Respiratory disorders nec	0	1 (0.6%)	1 (0.6%)
HLT: Lower respiratory tract signs and symptoms	0	1 (0.6%)	1 (0.6%)
Hiccups	0	1 (0.6%)	1 (0.6%)
GASTROINTESTINAL DISORDERS	0	5 (3.1%)	2 (1.3%)
HLGT: Gastrointestinal inflammatory conditions	0	1 (0.6%)	1 (0.6%)
HLT: Colitis (excl infective)	0	1 (0.6%)	1 (0.6%)
Colitis	0	1 (0.6%)	1 (0.6%)
HLGT: Gastrointestinal motility and defaecation conditions	0	3 (1.9%)	0
HLT: Diarrhoea (excl infective)	0	3 (1.9%)	0
Diarrhoea	0	3 (1.9%)	0
HLGT: Gastrointestinal vascular conditions	0	1 (0.6%)	1 (0.6%)
HLT: Haemorrhoids and gastrointestinal varices (excl oesophageal)	0	1 (0.6%)	1 (0.6%)
Haemorrhoidal haemorrhage	0	1 (0.6%)	1 (0.6%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	1 (0.6%)	1 (0.6%)
HLGT: Skin appendage conditions	0	1 (0.6%)	1 (0.6%)
HLT: Apocrine and eccrine gland disorders	0	1 (0.6%)	1 (0.6%)
Night sweats	0	1 (0.6%)	1 (0.6%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	1 (0.6%)	0
HLGT: Musculoskeletal and connective tissue disorders nec	0	1 (0.6%)	0
HLT: Musculoskeletal and connective tissue pain and discomfort	0	1 (0.6%)	0
Flank pain	0	1 (0.6%)	0

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred term n(%)	HMR1275 (N=159) Missing [1]	 All grades	 Grade ≥3
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.6%)	5 (3.1%)	3 (1.9%)
HLGT: Body temperature conditions	0	1 (0.6%)	0
HLT: Febrile disorders	0	1 (0.6%)	0
Pyrexia	0	1 (0.6%)	0
HLGT: Fatal outcomes	1 (0.6%)	1 (0.6%)	0
HLT: Death and sudden death	1 (0.6%)	1 (0.6%)	0
Euthanasia	1 (0.6%)	1 (0.6%)	0
HLGT: General system disorders nec	0	3 (1.9%)	3 (1.9%)
HLT: General signs and symptoms nec	0	3 (1.9%)	3 (1.9%)
Disease progression	0	2 (1.3%)	2 (1.3%)
General physical health deterioration	0	1 (0.6%)	1 (0.6%)
INVESTIGATIONS	0	1 (0.6%)	1 (0.6%)
HLGT: Haematology investigations (incl blood groups)	0	1 (0.6%)	1 (0.6%)
HLT: White blood cell analyses	0	1 (0.6%)	1 (0.6%)
White blood cell count increased	0	1 (0.6%)	1 (0.6%)

TEAE: Treatment emergent adverse event, SOC: System organ class, HLGT: High level group term, HLT: High level term, PT: Preferred term
MEDDRA 14.1
n (%) = number and percentage of patients with at least one TEAE leading to treatment discontinuation
N= number of patients
Note: Table sorted by SOC internationally-agreed order and HLGTs, HLTs, PTs by alphabetic order
[1] One patient had an adverse event of euthanasia, which the Investigator did not grade, despite the Sponsor's request that he do so.

Patients with fatal TEAE's: Table 17 displays SOC categorization and MedDRA PT's for treated patients with fatal TEAE's. SOC's appear in internationally-agreed order and MedDRA hierarchy appears alphabetically. A total of 15.1% of treated patients had fatal TEAE's. Fatal grade ≥3 general disorders and administration site conditions accounted for 5.7% of patients with fatal TEAE's (4.4% were due to disease progression); 1.9% of treated patients had fatal grade ≥3 respiratory, thoracic, and mediastinal disorders; 1.3% had fatal grade ≥3 neoplasms; 0.6% had one of fatal blood, metabolism, and nervous system disorders. One patient had an AE of euthanasia, which the Investigator did not grade, despite the Sponsor's request.

Table 17- Patients with fatal TEAE's in the AT population

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HMR1275 (N=159) Missing [1]	 All grades	 Grade ≥3
Any class	1 (0.6%)	24 (15.1%)	23 (14.5%)
INFECTIONS AND INFESTATIONS	0	6 (3.8%)	6 (3.8%)
HLGT: Bacterial infectious disorders	0	1 (0.6%)	1 (0.6%)
HLT: Pseudomonal infections	0	1 (0.6%)	1 (0.6%)
Pseudomonal sepsis	0	1 (0.6%)	1 (0.6%)
HLGT: Fungal infectious disorders	0	2 (1.3%)	2 (1.3%)
HLT: Fungal infections nec	0	2 (1.3%)	2 (1.3%)
Fungal infection	0	1 (0.6%)	1 (0.6%)
Pneumonia fungal	0	1 (0.6%)	1 (0.6%)
HLGT: Infections - pathogen unspecified	0	3 (1.9%)	3 (1.9%)
HLT: Abdominal and gastrointestinal infections	0	1 (0.6%)	1 (0.6%)
Infectious peritonitis	0	1 (0.6%)	1 (0.6%)
HLT: Sepsis, bacteraemia, viraemia and fungaemia nec	0	2 (1.3%)	2 (1.3%)
Sepsis	0	2 (1.3%)	2 (1.3%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	2 (1.3%)	2 (1.3%)
HLGT: Metastases	0	1 (0.6%)	1 (0.6%)
HLT: Metastases to specified sites	0	1 (0.6%)	1 (0.6%)
Metastases to meninges	0	1 (0.6%)	1 (0.6%)
HLGT: Respiratory and mediastinal neoplasms malignant and unspecified	0	1 (0.6%)	1 (0.6%)
HLT: Non-small cell neoplasms malignant of the respiratory tract cell type specified	0	1 (0.6%)	1 (0.6%)
Lung adenocarcinoma	0	1 (0.6%)	1 (0.6%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	1 (0.6%)	1 (0.6%)
HLGT: White blood cell disorders	0	1 (0.6%)	1 (0.6%)
HLT: Neutropenias	0	1 (0.6%)	1 (0.6%)
Febrile neutropenia	0	1 (0.6%)	1 (0.6%)
METABOLISM AND NUTRITION DISORDERS	0	1 (0.6%)	1 (0.6%)
HLGT: Electrolyte and fluid balance conditions	0	1 (0.6%)	1 (0.6%)
HLT: Electrolyte imbalance nec	0	1 (0.6%)	1 (0.6%)
Tumour lysis syndrome	0	1 (0.6%)	1 (0.6%)

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HMR1275 (N=159) Missing [1]	All grades	Grade ≥3
NERVOUS SYSTEM DISORDERS	0	1 (0.6%)	1 (0.6%)
HLGT: Central nervous system vascular disorders	0	1 (0.6%)	1 (0.6%)
HLT: Central nervous system haemorrhages and cerebrovascular accidents	0	1 (0.6%)	1 (0.6%)
Thrombotic stroke	0	1 (0.6%)	1 (0.6%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	3 (1.9%)	3 (1.9%)
HLGT: Lower respiratory tract disorders (excl obstruction and infection)	0	1 (0.6%)	1 (0.6%)
HLT: Pulmonary oedemas	0	1 (0.6%)	1 (0.6%)
Acute respiratory distress syndrome	0	1 (0.6%)	1 (0.6%)
HLGT: Respiratory disorders nec	0	2 (1.3%)	2 (1.3%)
HLT: Respiratory failures (excl neonatal)	0	2 (1.3%)	2 (1.3%)
Respiratory failure	0	2 (1.3%)	2 (1.3%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.6%)	10 (6.3%)	9 (5.7%)
HLGT: Body temperature conditions	0	1 (0.6%)	1 (0.6%)
HLT: Febrile disorders	0	1 (0.6%)	1 (0.6%)
Pyrexia	0	1 (0.6%)	1 (0.6%)
HLGT: Fatal outcomes	1 (0.6%)	1 (0.6%)	0
HLT: Death and sudden death	1 (0.6%)	1 (0.6%)	0
Euthanasia	1 (0.6%)	1 (0.6%)	0
HLGT: General system disorders nec	0	9 (5.7%)	9 (5.7%)
HLT: General signs and symptoms nec	0	9 (5.7%)	9 (5.7%)
Disease progression	0	7 (4.4%)	7 (4.4%)
General physical health deterioration	0	2 (1.3%)	2 (1.3%)

TEAE: Treatment emergent adverse event, SOC: System organ class, HLGT: High level group term, HLT: High level term, PT: Preferred term
MEDDRA 14.1
n (%) = number and percentage of patients with at least one fatal TEAE
N= number of patients
Note: Table sorted by SOC internationally-agreed order and HLGTs, HLTs, PTs by alphabetic order
[1] One patient had an adverse event of euthanasia, which the Investigator did not grade, despite the Sponsor's request that he do so.
HMR1275 = alvocidib

Tumor Lysis Syndrome: Table 18 which includes all occurrences of TLS, regardless of whether they were reported as TEAE's, summarizes the onset and management of TLS in alvocidib-treated patients. Among the 159 patients treated with alvocidib, 27% (43) experienced TLS, which was life-threatening in 5 and fatal in 1. TLS was managed with dialysis in 8.2% of patients and

managed with different medical treatment in 20.8% of patients. In 40 of the 43 patients who experienced TLS, the onset occurred during the first cycle of treatment. The total number of patients who actually experienced TLS in the AT population is 39. Upon verification, 2 patients, who are included in the count in this table, were found not to have experienced TLS.
Two patients had events of TLS, but because the grade was not ≥3, the AE terms were changed to hyperkalemia for 1 patient and to hyperkalemia and hyperphosphatemia for 1 patient.
In Table 18, these patients are included in the category of medically managed TLS.
In addition, 1 patient received Fasturtec (rasburicase) for the management of TLS on Days 1 and 15 of Cycle 1, which was reported as "other," rather than as "medically-managed."
Thus the total number of patients with medically managed TLS should be 30, rather than 33.

Table 18 - Tumor lysis syndrome in the AT population

	HMR1275 (N=159)
Number of patients who experienced TLS	43 (27.0%)
Life-threatening	5 (3.1%)
Fatal	1 (0.6%)
Approach to manage TLS	
Dialysis	13 (8.2%)
Medically managed	33 (20.8%)
Other, specify[1]	1 (0.6%)
Onset of TLS	
Cycle 1	40 (25.2%)
Cycle 2	9 (5.7%)
Cycle 3	1 (0.6%)

Note: The same patient may be counted more than once for the onset of TLS and the approach to manage TLS.
Reporting data were originated from the TLS data panel.
[1] One patient received Fasturtec for the management of TLS on Days 1 and 15 of Cycle 1.

Tumor lysis syndrome and disease response in the AT population: Table 19 displays response rate by presence or absence of TLS. Among alvocidib-treated patients, 27.9% of those who experienced TLS during the study had response (CR, PR, or nPR) according to the hybrid criteria and 37.2% according to the NCI-96 criteria. 25.0% of those who did not have TLS experienced response according to the hybrid criteria and 29.3% according to the NCI-96 criteria.
Because they did not have TLS, 4 patients should not have been included in patients with TLS, the total number of patients with TLS during the trial should have been 39, not 43.
Thus the investigator-reported response rate for patients with TLS during the trial should have been 12/39 (30.8%) for the hybrid criteria and 15/39 (38.0%) of patients with TLS responded to treatment, according to the NCI-96 criteria.
According to the hybrid criteria, 29/120 (24.4%) patients without TLS responded to treatment; according to the NCI-96 criteria, 35/120 (29.2%) patients without TLS responded to treatment.

Table 19 - Investigator-reported best overall response rate by presence or absence of tumor lysis syndrome

	HMR1275 (N=159)	
	Hybrid criteria	**NCI 96 criteria**
TLS during the trial		
Yes	12/43 (27.9%)	16/43 (37.2%)
No	29/116 (25.0%)	34/116 (29.3%)

HMR1275 = alvocidib; NCI = National Cancer Institute; TLS = tumor lysis syndrome
N = number of patients

Conclusions: [redacted]