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Final Results of EFC6663: A Multicenter, International, Phase 2 Study of Alvocidib for Patients with Fludarabine-Refractory Chronic Lymphocytic Leukemia

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Conflicts of Interest: JRB served as a consultant for Sanofi after conclusion of this trial.
RAL received research support to the University of Chicago from Sanofi.
SS received honoraria and research support from Sanofi.
JD is an employee of Sanofi.
JCB and MRG have an unprosecuted use patent for the schedule of alvocidib utilized in this trial.

Authorship: All authors reviewed and approved the manuscript.
Contribution: Designed research: JCB, MRG
Collected, analyzed, and interpreted data: MCL, JD, SS, NH, AB, JCB, MRG
Referred patients and provided patient care: MCL, LA, JRB, JB, FCC, PG, RAL, TJK, VL, DWM, AJ, SS, AB, MH
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Abstract

Purpose—Chronic lymphocytic leukemia (CLL) patients refractory to fludarabine based therapies have poor outcomes with currently available therapies. Early phase studies of alvocidib showed activity in relapsed CLL including patients with high risk genomic features and those refractory to fludarabine. A multi-center, international, phase II study of alvocidib in fludarabine refractory CLL was undertaken to validate these early results.

Patients and Methods—Patients with fludarabine refractory CLL or prolymphocytic leukemia arising from CLL were treated with single agent alvocidib. The primary outcome measure was overall response rate, with secondary outcomes including survival, toxicity, and response duration.

Results—One hundred and sixty five patients were enrolled at 34 centers, and 159 patients were treated. The median age was 61 years, the median number of prior therapies was 4, and 96% of patients were fludarabine refractory. The investigator-assessed overall response rate was 25%; the majority of responses were partial. Response rates were lower among patients with del(17p) (14%), but equivalent in patients with del(11q) or bulky lymphadenopathy. Median progression free and overall survival were 7.6 and 14.6 months respectively. Tumor lysis occurred in 39 patients (25%), and 13 received hemodialysis. Diarrhea, fatigue, and hematologic toxicities were common.

Conclusion—Alvocidib has clinical activity in patients with advanced, fludarabine refractory CLL. Clinical responses were observed in patients with high risk clinical and genomic features. With careful monitoring, alvocidib has a manageable safety profile. Future studies should focus on discovery of biomarkers of clinical response and tumor lysis, and enhanced supportive care measures.

Introduction

Chronic lymphocytic leukemia (CLL) is the most common leukemia in the United States and Europe and is quite heterogeneous in clinical behavior[1,2]. Despite this variable clinical course, approximately two-thirds of affected patients will become symptomatic and require therapy. Treatment is not curative, and clinical outcomes among patients with relapsed CLL are poor, with disease related complications arising from bone marrow failure, lymphadenopathy, and immunosuppression. Patients with either no response or response shorter than 6 months to purine-nucleoside analogue based chemotherapy ("fludarabine refractory CLL") have a dismal prognosis, with an anticipated survival of 10 months [3,4]. Treatment options for such patients are currently limited [5]. Alemtuzumab, no longer indicated for the treatment of CLL in the United States with label withdrawal by the manufacturer, induces response in approximately 35% of patients, but median progression free survival (PFS) is only 5 – 8 months [6,7]. Among patients refractory to both alemtuzumab and fludarabine, ofatumumab showed an overall response rate (ORR) of 58%, though PFS was only 5.7 months[8]. Novel therapeutic approaches are needed for this high risk patient population.

Alvocidib (HMR1275; flavopiridol) is a semisynthetic flavonoid that inhibits cyclin-dependent kinases (CDKs) by competing with ATP for the kinase enzymatic site [9,10]. Alvocidib induces apoptosis in primary CLL cells *in vitro* at pharmacologically achievable concentrations with a mechanism of action that is independent of *TP53*[11-13]. Early clinical studies of alvocidib utilizing a 24 to 72 hour continuous intravenous infusion (CIVI) failed to show clinical activity among a variety of malignancies including CLL [14-17]. Subsequent preclinical studies showed high protein binding of alvocidib in human serum, and led to the development of a pharmacologically derived dosing schedule of a 30 minute intravenous bolus (IVB) followed by a 4 hour CIVI. Using this schedule, significant clinical activity was observed in a phase 1 study of patients with relapsed CLL, with an ORR of 40% including patients with bulky lymphadenopathy or high risk genetic features such as del(17p)[18,19]. Dose limiting toxicity was hyperacute tumor lysis syndrome (TLS). A subsequent single institution, phase 2 study utilizing this dosing strategy showed an ORR of 53% and median PFSl among responding patients of 12 months [20]. Given the response rates observed among high risk patients, the EFC6663 study was initiated to assess the efficacy and safety of alvocidib in a multicenter, international phase 2 clinical study.

Patients and Methods

Study Design and Subjects

Patients had confirmed CLL as established by NCI 96 criteria or prolymphocytic leukemia (PLL) arising from CLL [21]. Patients must have received at least one prior therapy including an alkylating agent(s) and be fludarabine refractory, either as asingle agent or in combination. Refractory to fludarabine was defined as a lack of response or relapse ≤ 6 months following completion of fludarabine-containing therapy[3]. Patients requiring treatment according to NCI 96 criteria were eligible for this phase II clinical trial. Additional eligibility criteria included: age ≥ 18 years, ECOG performance status 0 – 2, adequate hepatic function (AST and ALT < 2.5 × ULN), adequate renal function including normal potassium level and creatinine≤ 2 mg/dL, and WBC ≤ 150×10^9 / L. Institutional Review Boards at the participating institutions approved the protocol and all study participants provided written informed consent. This study was registered with ClinicalTrials.gov, numberNCT00464633.

Treatment Plan

Alvocidib was administered through a central venous catheter at a dose of 30 mg/m^2 by 30 minute IVB followed by 30 mg/m^2over 4 hoursby CIVI on day 1 of cycle 1. Patients who did not develop TLS underwent dose escalation to 30 mg/$m^2$by 30 minute IVB followed by 50 mg/m^2 CIVI onday 8of cycle 1 and for all subsequent treatments. Patients received alvocidib every week for 4 consecutive weeks, followed by a 2-week rest period (42 days per cycle) for up to a total of 6 cycles. Patients must have achieved at least a 25% reduction in lymphocytosis or nodal volume after completion of 2 cycles of therapy in order to continue. In the absence of meeting these criteria, treatment was discontinued. Supportive therapy consisted of acyclovir and trimethoprim / sulfamethoxazole for the duration of treatment. Ciprofloxacin was administered during periods of neutropenia; granulocyte

colony stimulating factors were discouraged. Dexamethasone 20 mg orally was administered on days 1, 2, 8, and 9 of cycle 1 and day 1 of all subsequent cycles.

Prophylaxis and Management of TLS

Because severe TLS was observed in prior alvocidib studies in CLL [18,20], patients were closely observed for TLS and, when present, urgently managed. The first 2 doses of alvocidib were administered in an inpatient setting with frequent laboratory assessments and 24 hour observation post-dose. All patients received allopurinol 300 mg daily, and rasburicase 0.15 mg/kg was administered 2 hours before the first two doses of alvocidib. In the event of hyperkalemia, hemodialysis was immediately available. If TLS did not occur, patients were transitioned to outpatient therapy on day 15 of cycle 1 (dose 3). Patients who required hemodialysis for severe TLS were allowed to continue therapy, but continued at a dose of 30mg/m^2 IVB followed by 30mg/m^2 CIVI.

Assessment of Patient Outcomes

Clinical and biologic assessments performed at baseline included assessments of ECOG performance status;bone marrow aspirate and biopsy, cross sectional imaging of the chest, abdomen, and pelvis; and interphase cytogenetics (FISH). Clinical response was assessed after each treatment cycle using the NCI 96 Criteria as well as “hybrid” criteria, which incorporated bi-dimensional lymph node assessments by cross-sectional imaging into the NCI 96 criteria [21]. Patients were followed for at least 6 months after the completion of therapy. PFS was calculated from the date of first treatment administration until the time of disease progression or death, whichever came first, censoring patients alive and relapse free at last follow-up. The safety profile was determined by the incidence of clinically significant adverse events (AEs) and serious adverse events (SAEs), graded according to the NCI CTCAE, version 3.0, and coded using the Medical Dictionary for Regulatory Activities(MedDRA) version 14.1.

Statistical Analysis

The primary endpoint was the overall objective response rate (ORR; CR + PR + nPR) as assessed by hybrid response criteria. Secondary endpoints included an evaluation of toxicity; determination of response duration (DR), PFS, and overall survival (OS). Based on an expected ORR of 20% among patients with fludarabine refractory CLL, the preplanned study size was 165 patients to yield a 2-sided 95% exact confidence interval of 14 – 27%. A preplanned interim futility analysis was performed after 66 evaluable patients received 2 cycles of therapy, and an independent data monitoring committee reviewed the safety data after treatment of 20 and 50 patients.

The intent-to-treat (ITT) population consisted of all patients who signed the consentform and were registered on the study. In the primary analysis, the ORRusing the hybrid criteriaand associated exact 95% confidence intervals (CI) were estimated. Similar calculations were performed using the NCI 96 criteria. For the secondary efficacy time-to-event variables PFS, objectiveDR, and OS, Kaplan-Meier estimates with corresponding 95% CI's were calculated for the AT(as-treated) population. Logistic regression analyses were performed modeling both the probability of observing a response (CR, PR, nPR) and the

probability of developing TLS; these analyses were not pre-planned. Both univariate and multivariate analyses were performed.

Results

Patient Characteristics and Disposition

A total of 165 patients (ITT population) were enrolled and followed between March 2007 and December 2011 at 34 sites in 9 countries. The ITT patient characteristics are shown in Table 1. The median age was 61 years (range 29 - 82). The study population was 78% male, and 90% Caucasian. Mean creatinine clearance was 98.2 mL/min (range 41.1 - 275.2). One hundred twenty-one of 150 assessed patients (81%) were Rai Stage III or IV. Bulky lymphadenopathy (≥1 lymph node > 5 cm by cross sectional imaging) was present in 115 (70%). High risk cytogenetic feature del(17p) was present in 35% of patients, and del(11q) was present in 31%. The median number of prior therapies was 4 (range 1 – 12). All patients had received prior fludarabine, and 96% were fludarabine refractory. Additionally, 99% had received a prior alkylating agent, 87% had prior rituximab, 38% had prior alemtuzumab, and 29% were refractory to both fludarabine and alemtuzumab.

One hundred fifty-ninepatients were treated with alvocidib, comprising the as-treated (AT) population. Thirty-five patients (22% of the ITT population) completed the planned 6 cycles of therapy. Seventy-nine patients (50%) received three or more cycles of therapy. The median number of treatment cycles administered was 2 and the mean number was 3.1 (S.D. = 1.9). Forty-nine patients discontinued therapy due to disease progression (30%), and 41 (25%) stopped due to an adverse event. Twenty-two patients (14%) did not dose escalate due to TLS. At the time of last study contact 57 patients (35%) were alive; no patients were lost to follow-up. Median follow-up for all treated patients was 19.8 months (95% CI: 19.1, 20.6).

Response to Therapy

All 165 patients in the ITT population were included in the response assessment (Table 2). Response was evaluated by the investigator and was reported as best response achieved after study registration. Using the hybrid response criteria, 41 patients (ORR 25%; 95% CI: 19 – 32) responded to therapy. By NCI 96 criteria, 50 patients responded (ORR 30%; 95% CI: 23 – 38). The best response by hybrid criteria included 3 CRs (2%), 2 nPRs (1%), and 36 PRs (22%). Fifty-three patients (32%) had SD, and 21 patients (13%) progressed on therapy. Fifty patients (30%) were not assessed for response by hybrid criteria. NCI 96 criteria responses were similar: 6 CRs (4%), 2 nPRs (1%), 42 PRs (26%), 66 (40%) patients with SD, 26 (16%) patients with PD, and 23 patients were not assessed (14%).

Clinical and biologic factors associated with inferior response to cytotoxic-based therapies were overall not associated with response to alvocidib, though the study was not powered to detect potential differences (Tables 2 and 3). Among the 49 patients with del(17p) ORRs were statistically inferior by hybrid criteria on univariate, but not multivariate analysis (hybrid: 14% vs. 32%, univariateodds ratio of response (OR) = 0.36, $p < 0.05$; NCI 96: 27% vs. 33%, OR = 0.73, $p = 0.6$). As observed in prior studies of alvocidib in CLL, the presence

of del(11q) or bulky lymphadenopathy were not associated with differences in ORR using either response criteria ($p > 0.5$ for all comparisonsl)[20]. Patients refractory to both fludarabine and alemtuzumab ("double refractory") were statistically less likely to respond to therapy (hybrid: 10% vs. 31%, OR = 0.26, $p< 0.01$). Patients experiencing TLS were not more likely to respond to therapy (hybrid: 28% vs. 25%, OR = 1.2, $p > 0.5$. Multivariate logistic regression showed that Rai stage at study entry (I/II vs. III/IV) and number of prior regimens were associated with response using either hybrid (Table 3) or NCI 96 criteria (data not shown).

Survival, Duration of Response, and Clinical Benefit

Secondary endpoints of this study included prospective assessments of PFS, OS, and DR. Median PFS for all patients in the AT population was 7.6 months (95% C.I. 4.5 – 9.8), with 100 patients (63%) having progressed during the period of study follow-up (Figure 1A). Among the 50 patients achieving a CR, nPR, or PR by NCI 96 criteria, 46 had adequate follow-up to assess DR. The median investigator-assessed DR in these patients was 13.7 months (95% C.I. 9.1 – 15.6), with 58% of patients maintaining a response to alvocidib for 12 months. Median OS for all patients in the AT population was 14.6 months (95% C.I. 9.8 – 17.2). There was no improvement in disease related fatigue, weight loss, or need for red blood cell or platelet transfusions with alvocidib therapy when compared to baseline.

Toxicity

Treatment-emergent adverse events (TEAE) occurred in all patients inthe ATpopulation. A total of 138 (87%) had a TEAE of Grade ≥3, and SAEs were reported in 117 (74%) patients. Anoverview of TEAE's is presented in Table 4. The side effect profile was similar to that observed in prior phase I and II studies of alvocidib [18,20]. Gastrointestinal AEs were most common, with a majority of patients having diarrhea (82%), nausea (58%), or vomiting (41%). Infections occurred in 90 patients (57%), with 48 (30%) having severe (grade ≥ 3) infections. Constitutional symptoms including fatigue (60%), fever (38%), night sweats (30%), anorexia (16%), and weight loss (14%) were also common, though typically not severe.

A total of 13 patients died within 30 days of the last study treatment. Seven of the deaths were attributed to disease progression. One death was from euthanasia, occurring at a site where state-sanctioned euthanasia was permitted. Four deaths were due to an infectious cause. One death was due to hyperacute TLS causing ventricular arrhythmia with a potassium level of 8.4 mmol/L measured 4.5 hours after initiation of alvocidib on day 1 of cycle 1.

Among the 159 alvocidib-treated patients, 39 (25%) developed TLS by Cairo-Bishop criteria ncluding 5 life-threatening events and 1 fatal event. TLS was managed with dialysis in 13 patients (8% of the entire AT population had hemodialysis), and the remaining patients were medically managed. In 37 of the 39 patients experiencing TLS, the onset occurred during the first cycle of therapy. Two patients had TLS onset during cycle 2. Six patients (4%) had TLS occur in more than 1 treatment cycle. Multivariate logistic regression showed

that only baseline creatinine was significantly associated with risk of TLS (Supplemental Tables 1 and 2).

Discussion

The management of patients with fludarabine refractory CLL remains difficult due to several factors. Earlier studies of alvocidib showed promising response rates in heavily pretreated CLL patients and response rates that were independent of high risk cytogenetic features [19,20]. The EFC6663 study was undertaken both to validate the observed response rates and to demonstrate that alvocidib could be safely administered in a multi-center, international clinical trial. This study is one of the largest undertaken in patients with fludarabine refractory CLL, and met the preplanned objective of showing an ORR of > 20% among this heavily pretreated patient population. The ORR of 30% is similar to that achieved with alemtuzumab [6,7], and median PFS of 7.6 months equaled the 5 to 8 months observed with either alemtuzumab and ofatumumab [8].

Both the overall response rate and toxicity reflected that observed in earlier alvocidib studies. The investigator assessed overall response rate of 30% (95% C.I. 23 – 38%) using the NCI 96 criteria is similar to the ORR of 41% observed in the pre-amendment cohort reported by Lin *et al*[20] and 40% reported in a phase I study from the same institution by Phelps et al[19]. In the EFC6663 study, patients not achieving a 25% response after 2 cycles of therapy discontinued treatment, potentially decreasing the ORR and PFS when compared to prior alvocidib studies. Toxicities were also comparable, with TLS and neutropenic infections being the most common serious complications. Importantly, the single-site phase II study showed both improved response rates and tolerability with administration of alvocidib weekly for 3 weeks followed by a single week of rest: the ORR for the 4- and 6 – week treatment cycles were 63% and 41%, respectively. The 4 week treatment regimen improved treatment tolerance, patient compliance, and clinical response. Because the ORR and toxicity of the EFC6663 study mirrors the results of the pre-amendment phase II cohort, we conclude that future studies of alvocidib in CLL should utilize a 4 week treatment schedule.

In an effort to reduce the risk of TLS, study enrollment required a WBC of $< 150 \times 10^9$ / L. Nonetheless, TLS occurred in 25% of treated patients. Though the protocol mandated frequent laboratory monitoring and required hemodialysis immediately available when needed, one episode of TLS resulted in a fatal outcome from severe hyperkalemia. Thirty-eight other episodes of TLS were successfully managed, with hemodialysis employed in 13 cases without additional sequelae. Approximately 1/3 of these patients subsequently responded to therapy. Because patients with fludarabine refractory CLL frequently cannot be cytoreduced prior to initiation of therapy, TLS may remain a risk of alvocidib therapy. Multivariate analysis showed that disease bulk and renal function were most predictive of TLS, suggesting that patient clinical features, rather than intrinsic sensitivity to alvocidib, best predict TLS. We conclude that alvocidib can be administered with careful monitoring during the first doses and subsequently transitioned to ambulatory outpatient administration.

Perhaps the most significant interval development in the clinical management of CLL since the initiation of the EFC6663 study is the clinical development of inhibitors of B cell receptor and related signaling pathways. Agents such as ibrutinib [23-25] and idelalisib[26] have shown considerable clinical activity in relapsed CLL with favorable toxicity profiles in early phase clinical studies. The clinical responses, response duration, and toxicity profile with these novel agents exceed the outcomes with alvocidib reported herein. Nonetheless, these novel targeted therapies are ultimately not curative, and agents with novel mechanisms of action such as alvocidib will be needed for those patients who progress after B cell receptor signaling inhibitors. One potential benefit of alvocidib therapy is that responding patients have a period of disease quiescence of duration adequate for allogeneic transplantation.

The EFC6663 study validated the clinical activity of alvocidib observed in earlier clinical studies. Alvocidib yielded clinical responses of 9 to 16 months in patients with extensively pretreated, fludarabine refractory CLL. Plans for further clinical development of alvocidib are underway and include high-risk CLL as well as several other hematologic malignancies both as a single agent and as part of combination regimens[27,28]. The demonstrated clinical activity of alvocidib in refractory CLL and in genetically high-risk disease suggests a potential role for alvocidib as part of the treatment of these patients. Evaluation of the activity of alvocidib in combination with additional agents is planned as part of the further clinical development of alvocidib. Future studies should focus on identification of biomarkers of clinical response[29] and risk for TLS[30]. Enhanced supportive care strategies may yield further improvement in patient adherence and response rates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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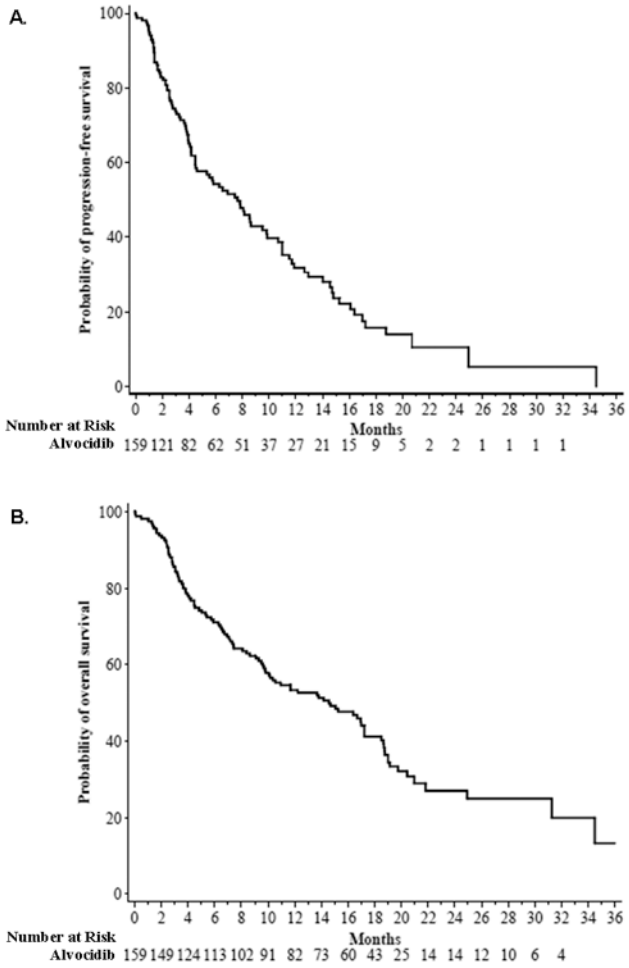

Figure 1.

Progression free survival (A) and overall survival (B) among patients in the AT population treated with alvocidib.

Table 1
Patient Characteristics in the ITT population

Characteristic (n)	ITT Population (n = 165)	
	Number	%
Age, years (standard deviation)	60.8 (9.5)	
Male Gender	128	78
Race		
Caucasian	148	90
Black	10	6
Asian	1	1
Other	6	4
Creatinine Clearance (mL/min, 159)	98.2 (34.7)	
≥ 30 - < 50	6	4
≥ 50 - ≤ 80	50	31
> 80	103	65
ECOG Performance Status (159)		
0	65	41
1	74	47
2	20	13
Rai Stage (150)		
I, II	29	19
III, IV	121	81
Binet Stage (109)		
A	3	3
B, C	106	97
Bulky Lymphadenopathy[a]	115	70
Cytogenetic Abnormalities[b]		
del(17p) (141)	49	35%
del(11q) (145)	43	31%
Number of prior therapies (range)	4 (1 – 12)	
Prior Therapies		
Alkylating agent	163	99
Fludarabine	165	100
Rituximab	143	87
Alemtuzumab	62	38
Fludarabine refractory	158	96

[a] Defined as at least 1 lymph node > 5 cm in longest diameter by cross sectional imaging at study registration.

[b] Classified according to Döhner, *et al*[31].

Table 2
Investigator-Reported Best Overall Responseto Alvocidib in the ITT Population

	Hybrid Criteria[a]		NCI-96 Criteria[b]	
	Number	Percent	Number	Percent
Overall Response Rate	41	25	50	30
Complete Response	3	2	6	4
Nodular Partial Response (nPR)	2	1	2	1
Partial Response	36	22	42	26
Stable Disease	53	32	66	40
Disease Progression	21	13	26	16
Not assessed	50[a]	30	23[b]	14
del(17p) (n = 49)	7	14	13	27
del(11q) (n = 43)[c]	11	26	12	28
Bulky lymphadenopathy (n = 115)	29	25	33	29
"Double refractory"[d] (n = 48)	5	10	7	15
TLS (n = 39)	12	31	15	38

[a] Of the 50 patients not assessed for best response, 6 were never treated with alvocidib and 28 receivedonly one treatment cycle. The remaining 16 patients received between 2 and 6 cycles of treatment, but the investigator failed to report a best response by hybrid criteria. No missing data imputation was performed.

[b] Of the 23 patients who were not assessed for best response, 6 were never treated with alvocidib and 14 had only one treatment cycle. The remaining 3 patients received 2 or 3 cycles of treatment, but the investigator failed to report a best response by NCI 96 criteria. No missing data imputation was performed.

[c] Classified according to Döhner, *et al*[31].

[d] Refractory to both fludarabine and alemtuzumab

Table 3
Multivariate Logistic Regression Analysis of Hybrid Overall Response Rate

	Univariate Model		Multivariate Model[a]	
Factor	**Odds Ratio (95% CI)**	**P-value**	**Odds Ratio (95% CI)**	**P-value**
Age	1.004 (0.967, 1.041)	0.8353		
Male gender	0.863 (0.376, 1.980)	0.7279		
Rai Stage at entry:Stage III, IV	0.265 (0.113, 0.623)	0.0023	0.277 (0.108, 0.710)	0.0075
Presence of del(17p)	0.362 (0.145, 0.902)	0.0292	0.554 (0.203, 1.512)	0.2490
Presence of del(11q)	1.017 (0.445, 2.325)	0.9682		
Presence of bulky lymphadenopathy	1.068 (0.493, 2.314)	0.8679		
Baseline WBC	0.589 (0.216, 1.609)	0.3019		
Baseline LDH	0.863 (0.711, 1.047)	0.1379	0.895 (0.724, 1.106)	0.3038
Baseline β2-microglobulin	0.478 (0.034, 6.672)	0.5831		
Number of prior anti-cancer regimens	0.843 (0.712, 0.995)	0.0433	0.806 (0.655, 0.993)	0.0427
Refractory to fludarabine	0.819 (0.153, 4.393)	0.8161		

[a] A multivariate logistic regression analysis was run with all covariates for which $p < 0.20$ in aunivariate model. Using backward selection for covariates, low risk Rai stage and fewer prior regimens with final ORs of 0.252 (0.100, 0.636 p-value: 0.0035) and 0.813 (0.663, 0.998 p-value: 0.0483) respectively, were associated with a response.

Table 4
Common Toxicities by Severity in the AT Population

Toxicity	Grade	
	All grades	Grade ≥ 3
Gastrointestinal	141 (89%)	39 (25%)
Diarrhea	130 (82%)	29 (18%)
Nausea	92 (58%)	1 (1%)
Vomiting	65 (41%)	3 (2%)
Fatigue	96 (60%)	27 (17%)
Infections	90 (57%)	48 (30%)
Febrile Neutropenia	27 (17%)	24 (15%)
Pneumonia	12 (8%)	10 (6%)
Catheter infection	9 (6%)	5 (3%)
Hematologic[a]	78 (49%)	72 (45%)
Neutropenia	57 (36%)	54 (34%)
Thrombocytopenia	30 (19%)	30 (19%)
Anemia	20 (13%)	12 (8%)
Fever	60 (38%)	8 (5%)
Cough	51 (32%)	3 (2%)
Night Sweats	48 (30%)	7 (4%)
Musculoskeletal Pain	44 (28%)	5 (3%)
Edema	41 (26%)	1 (1%)
Tumor Lysis Syndrome	39 (23%)	33 (21%)
Headache	34 (21%)	2 (1%)
Decreased Appetite	26 (16%)	0
Dizziness	22 (14%)	1 (1%)
Weight loss	22 (14%)	2 (1%)
Rash	19 (12%)	2 (1%)
Sleep disturbance	17 (11%)	1 (1%)

[a] Does not include baseline toxicity; only included if hematologic toxicity worsened by ≥ 1 grade level.