Published in final edited form as:
Leuk Res. 2013 October ; 37(10): 1195–1199. doi:10.1016/j.leukres.2013.06.006.

Cyclophosphamide, Alvocidib (Flavopiridol), and Rituximab, a Novel Feasible Chemoimmunotherapy Regimen for Patients with High-Risk Chronic Lymphocytic Leukemia

Deborah M. Stephens[1,2], **Amy S. Ruppert**[2], **Kami Maddocks**[1,2], **Leslie Andritsos**[1,2], **Robert Baiocchi**[1,2], **Jeffrey Jones**[1,2], **Amy J. Johnson**[1,2,5], **Lisa L. Smith**[1,2], **Yuan Zhao**[3], **Yonghua Ling**[2], **Junan Li**[4], **Mitch A. Phelps**[2], **Michael R. Grever**[1,2], **John C. Byrd**[1,2,5], and **Joseph M. Flynn**[1,2]

[1]Division of Hematology, Department of Internal Medicine, The Ohio State University

[2]Comprehensive Cancer Center, The Ohio State University

[3]Division of Pharmaceutics, College of Pharmacy, The Ohio State University

[4]College of Public Health, The Ohio State University

[5]Division of Medicinal Chemistry, College of Pharmacy, the Ohio State University

Abstract

Alvocidib has demonstrated efficacy in high-risk chronic lymphocytic leukemia (CLL) patients. In this phase I study, we combined cyclophosphamide, alvocidib and rituximab (CAR) in a schema designed to mitigate tumor lysis syndrome (TLS) seen previously with alvocidib. Nine nucleoside analog-naïve, high-risk patients received escalating doses of CAR therapy. Dose limiting toxicity was not experienced. No instances of TLS were observed. Patient responses included three complete remissions and four partial remissions. CAR was tolerable and active in high-risk CLL patients without TLS toxicity. With continued monitoring of toxicities, a phase Ib/II study of this combination as frontline therapy is warranted.

Keywords

chronic lymphocytic leukemia; flavopiridol; high-risk cytogenetics; cyclin-dependent kinase inhibitor; chemoimmunotherapy; alvocidib; del(17p); del(11q)

Introduction

Despite significant changes and progress in the treatment of chronic lymphocytic leukemia (CLL) patients, specific genomic [del(17p13.1), del(11q22.3), un-mutated immunoglobulin heavy chain variable region (IgV_H)] and clinical [age ≥70 years and β2microglobulin (B2M) level ≥ 4] risk factors continue to be associated with poor clinical outcomes [1, 2]. Chemoimmunotherapy has become the standard of care in frontline CLL therapy secondary to improvements in progression-free survival (PFS) and overall survival (OS) [3]. However, standard regimens are not curative and efforts are ongoing to optimize therapy for CLL patients.

Corresponding Author: Deborah M. Stephens, DO Division of Hematology The Ohio State University Medical Center 365M Starling Loving Hall 320 W. 10th Ave Columbus, Ohio 43210 deborah.stephens@osumc.edu Phone (614) 355-4467 Fax (614) 293-7484.

In contrast to standard chemoimmunotherapies, alvocidib (flavopiridol), a cyclindependent kinase (CDK) inhibitor, has been shown to be effective in high-risk groups of CLL patients and does not promote the same cellular immune suppression typically seen with chemotherapy agents, such as fludarabine. Combined analysis of two early clinical phase I/II trials of alvocidib [4-6] included 112 heavily pre-treated patients [36% with del(17p13.1) and 33% with del(11q22.3)] demonstrated an impressive overall response rate (ORR) of 46% and a median progression-free survival (PFS) of approximately 10 months. There were no significant differences in ORR or PFS among cytogenetic groups [7] or in patients older versus younger than age 70 [8], suggesting efficacy of alvocidib in these high-risk populations.

However, during the phase I trials, the dose limiting toxicity (DLT) of alvocidib was hyperacute tumor lysis syndrome (TLS), occurring in 48% of patients, with 19% requiring dialysis [9]. To limit TLS, eligibility was modified in the phase II trial [6], by restricting enrollment to patients with white blood cell (WBC) count $<200\times10^9$/L, implementing aggressive TLS prophylaxis, and reducing cycle length and number of treatments per cycle. With these modifications, more patients completed therapy, and the severity of TLS decreased. The overall rate of TLS on the phase II trial was 44% with 6% requiring dialysis. TLS occurred most frequently in patients with Rai Stage III/IV, female gender, adenopathy ≥10cm, elevated WBC count, increased B2M, decreased albumin, and higher plasma levels of alvocidib–glucuronide (a glucuronidated metabolite of alvocidib) [9]. Concerns related to the onset of acute TLS portends to a potential limitation to its use. Therefore, we combined cyclophosphamide, alvocidib, and rituximab (CAR) with the aims of developing an effective regimen for high-risk CLL patients, while limiting toxicities and demonstrating potential feasibility of administration as an out-patient.

Materials and Methods

Patients

Patients were enrolled on the National Cancer Institute (NCI)-sponsored and The Ohio State University institutional review board-approved study following written informed consent. Enrollment criteria included: age over 17 years, symptomatic CLL or SLL by NCI criteria [1] with poor-risk genetic or clinical risk factors [presence of del(17p13.1), del(11q22.3), unmutated IgV_H (≥98% homology), age over 70 years and/or elevated B2M(≥4)], no prior therapy with purine analogs, Eastern Cooperative Oncology Group (ECOG) [10] performance status less than 3, no active infection, and adequate renal and hepatic function. Patients with cytopenias were not excluded from participation.

Study Design, Treatment Plan, and Dose Escalation Schema

The study was designed as a traditional 3×3 phase I model, where 3-6 patients were enrolled at each dose level. The maximum tolerated dose (MTD) was defined as the dose level below which 2 or more of a cohort of 6 patients experienced dose-limiting toxicity (DLT), as defined in the following section. At the MTD, the study initially planned for an expansion cohort of 12 patients for a total of 18 patients treated for further evaluation of safety for phase II trials. Table 1 provides a detailed dose schedule description for each cohort.

Dose Limiting Toxicity

DLT was defined as the occurrence of any of the following events during the first two cycles of therapy when judged to be clinically significant (as further defined below) and possibly, probably, or definitely related to the study treatment. Adverse events that were clearly the result of disease progression, concomitant medical illness, or accidental injury were not considered DLT. Toxicity grading was performed using the CTEP Active Version of the

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) [11]. DLT for this study was defined as follows: (1) any grade 3 or 4 non-hematologic toxicity (with the exceptions of: reversible electrolyte or glucose abnormalities, liver function test abnormalities that returned to ≤ grade 2 in < 5 days, and TLS not requiring dialysis); (2) grade 3 or 4 hematologic toxicity that did not resolve to 20% of baseline by day 35 of therapy (unless disease-related); and (3) grade 3 infection or febrile neutropenia.

Supportive Care

All patients received allopurinol (300mg daily) for the duration of the trial. For the first 2 doses of alvocidib, patients received inpatient pretreatment hydration, urine alkalization, and prophylactic phosphate binder therapy, rasburicase (4.5mg) 2 hours prior to dose. Other supportive care measures were as detailed in previous reports [4, 6].

Response Assessment

International Workshop on Chronic Lymphocytic Leukemia Guidelines [1] were used for assessment of response. For patients not demonstrating disease progression, response status was evaluated after Cycles 2, 4, and 6 (if applicable) and 2 months following therapy completion.

Pharmacokinetics

Plasma pharmacokinetics (PK) of alvocidib and alvocidib-glucuronide were assessed in each patient on Day 8 of both Cycle 1 and 2. Plasma samples were collected pre-dose and at 0.5, 4.5 and 24 hours after the start of alvocidib infusion. PK samples were analyzed using methods as described previously [12, 13]. Non-compartmental PK parameters were determined for alvocidib and alvocidib-glucuronide in Phoenix WinNonlin v.6.3. Population PK parameter estimates for both agents were determined by incorporating plasma concentration data versus time, body weight, and sex from this study into a previous dataset and population PK/pharmacodynamic model for alvocidib-induced TLS [14].

Statistics

The primary endpoint of the study was to define the MTD of CAR, using the traditional 3×3 phase I design as described above in the Study Design section. Secondary endpoints included describing response rates, PFS, and OS following administration of CAR. Common hematologic and non-hematologic toxicities are summarized with frequencies by dose level and for all patients. Baseline characteristics are described using frequencies and medians with ranges for categoric and continuous variables, respectively. PFS was measured from the date of first treatment to the date of progression or death from any cause, censoring patients alive at last follow-up. OS was measured from the date of first treatment to the date of death or date of last follow-up. Best response, PFS, and OS are provided for each patient. Observed PK parameters were evaluated and summarized in graphic and table format. No inferential statistical tests of hypotheses were planned due to the small sample size.

Results

Patient Characteristics

A group of 9 patients were treated on Cohorts 1 (n=3), 2 (n=3), and 3 (n=3). Median age was 55 years (range 42-77) and 7 patients were male. Patients had the following high-risk features: del(17p13.1) (n=3), del (11q22.3) (n=4), un-mutated IgV_H (n=6), age >70 years (n=2), and B2M>4 (n=1). Only 3 of the patients had previous treatment, all with alemtuzumab, and 1 of these patients had also received 4 weekly doses of rituximab as treatment for autoimmune hemolytic anemia. All patients completed 6 planned cycles of

therapy with exception of one patient in Cohort 2, who stopped therapy secondary to lack of response. Baseline patient characteristics are summarized in Table 2.

Toxicity

The CAR regimen was well tolerated by the patients on this trial and DLT was not observed. The most common toxicities were hematologic, including: anemia (n=8), neutropenia (n=7), leukopenia (n=6), and thrombocytopenia (n=6). The most common non-hematologic toxicities included: fatigue (n=5), electrolyte disturbances (n=5), and gastrointestinal (GI) toxicity [diarrhea (n=7), abdominal discomfort (n=5), nausea/vomiting (n=4), and liver dysfunction (n=4)]. The majority of grade 3 and 4 toxicities were hematologic: anemia (grade 3: n=1), leukopenia (grade 3: n=2, grade 4: n=2), neutropenia (grade 4: n=6), and thrombocytopenia (grade 3: n=2). No patients experienced grade 4 non-hematologic toxicity and only one grade 3 non-hematologic, treatment-related adverse event was reported (electrolyte disturbance). One patient experienced grade 3 diarrhea that resolved within 24 hours during Cycle 1, but had received two doses of kayexylate, a potassium binder that induces diarrhea. Therefore, this was not considered a treatment-related adverse event and was not considered a DLT. There were three episodes of grade 2 cytokine release syndrome (CRS; 2 patients in Cohort 2 and 1 patient in Cohort 3). All toxicities resolved by the end of therapy. Notably, no patients experienced TLS or infection. The most common adverse events are summarized in Supplemental Table 1.

Response

All nine patients were evaluable for response, as summarized in Table 3. All patients demonstrated cytoreduction following initial dose of cyclophosphamide and rituximab as represented by a decrease from the initial median ALC on Cycle 1, Day 1 of 62.2 (range=3.0-215.3) to a median ALC of 2.25 (range=0.71-26.1) on Cycle 1, Day 8 of therapy as depicted in Supplemental Figure 1. Three patients achieved complete response (CR), 4 achieved partial response, 1 had stable disease, and 1 had progressive disease (PD). The patient with PD had previously been treated with alemtuzumab and had three high-risk factors, including an age of 77 years and presence of del(17p13.1) and un-mutated IgV_H cytogenetics. This patient remains alive at 19.1 months following first treatment. In fact, all 9 patients are still alive with a median follow-up of 15.6 months (range: 4.6-22.7 months).

Pharmacokinetics

Plasma concentration was calculated on Day 8 of Cycles 1 and 2 (See Supplemental Figure 2). Observed maximum concentrations and areas under the plasma concentration-time curves, along with population PK parameter estimates are summarized in Supplemental Table 2. Overall, PK data was similar in this study to previous reports by our group [5, 6].

Conclusions

This phase I feasibility study showed that the CAR regimen was well tolerated and active when used as frontline therapy for CLL patients considered to have high-risk genomic and clinical characteristics. Despite high-risk genomic and clinical characteristics, 7 of the 9 patients achieved a response and 1 patient achieved SD. These results are impressive and promising in this patient population typically resistant to standard chemotherapy. Notably, 2 of the 3 patients on this trial with del(17p13.1), and hence dysfunctional p53, achieved a CR, which supports in vitro [15] and in vivo data [6, 7] that alvocidib can induce cell apoptosis in a manner independently of the p53 pathway. In comparison, among the patients with del(17p13.1) karyotype in the landmark CLL8 trial, no patients who received FC (n=29) and only one patient who received FCR (n=22) achieved a CR [3] . With CAR therapy in the current study, all patients (n=4) with del(11q22.3) achieved response (CR=1, PR=3), which

supports data suggesting that this subgroup benefits from cyclophosphamide and chemoimmunotherapy [16, 17]. Although the one patient with progressive disease had 3 high-risk factors [age>70, del(17p13.1), and un-mutated IgV_H status], he remains alive at 19.1 months following treatment with this regimen. This individual's CLL has since been proven to be highly refractory as his CLL has progressed through three subsequent standard regimens.

In contrast to early phase I/II studies with alvocidib, patients in this trial did not experience severe TLS. The novel dosing schedule of this trial, which did not introduce alvocidib until Cycle 1, Day 8, allowed for cytoreduction of CLL burden by cyclophosphamide and rituximab, presumably lowering the risk for TLS. However, this may also be due to the fact that patients treated in the early clinical trials were relapsed/refractory versus treatment-naïve and had a higher Rai Stage, indicating more volume of disease versus the generally lower Rai Stage in this trial (Rai Stage I/II: n=7), leading to better tolerance of the regimen. Other previously reported factors associated with TLS after treatment with alvocidib [9], including female gender, adenopathy ≥10cm, elevated WBC count $>200\times10^9$/L, and increased B2M, were also not heavily represented in this clinical trial. Lastly, the first 2 doses of alvocidib were given as an inpatient with aggressive supportive care, which likely helped to provide for early recognition and treatment of TLS.

This study closed enrollment early, without allowing for enrollment of 3 additional patients at the highest dose level as intended with a traditional 3×3 phase I design. The trial was disadvantaged by rate of accrual, potentially related to the requirement for hospitalization while receiving the first 2 doses of alvocidib, which caused many insurance companies to deny participation in the trial. However, this regimen was designed to allow transition to outpatient administration of therapy following the first 2 doses of alvocidib minimizing inpatient time requirement.

Although toxicity assessment was limited by small patient numbers, combined therapy with CAR was well tolerated. The severe side effects of grade 3/4 TLS and CRS were not observed with the novel timing of alvocidib (with delayed introduction until Cycle 1, Day 8) allowing for cytoreduction by rituximab and cyclophosphamide. This trial's importance lies in this novel concept of delayed introduction of the CDK inhibitor in combination therapy with the goal of limiting toxicity. This patient group of high cytogenetic and clinical risk CLL patients have very limited effective treatment options and development of regimens, such as CAR therapy, that appear to have clinical activity should be further investigated to provide options for this tough-to-treat patient population. Secondary to potential safety and efficacy suggested by this trial, other phase I/II trials are currently underway at our institution using this concept in chemoimmunotherapy regimens with alvocidib and other novel CDK inhibitors.

The major barrier alvocidib has faced in clinical development and pharmaceutical support has been toxicity, such as TLS. With the innovative concept demonstrated in this trial, significant interest has emerged in the form of pharmaceutical support for this drug. The right to develop and commercialize alvocidib has recently been purchased by Tolero Pharmaceuticals, Inc. The company has publicly announced its intentions to proceed with phase II investigation of alvocidib in CLL patients in the near future.

In summary, the CAR combination reported in this trial could offer advantages over standard frontline therapies for CLL patients in this high-risk group. Given other potential benefits of the CDK inhibitors such as decreased infectious complications and potentially decreased risk of myelodysplasia, further study of this regimen is warranted in the setting of a phase Ib/II clinical trial with continued monitoring for toxicities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations

B2M	beta 2 microglobulin
CAR	cyclophophamide, alvocidib, rituximab
CDK	cyclin-dependent kinase
CLL	chronic lymphocytic leukemia
CR	complete response
CRS	cytokine release syndrome
DLT	dose limiting toxicity
ECOG	Eastern Cooperative Oncology Group
FC(R)	fludarabine, cyclophosphamide, (rituximab)
IgV_H	immunoglobulin heavy chain variable region
MTD	maximum tolerated dose
NCI	National Cancer Institute
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic
ORR	overall response rate
OS	overall survival
TLS	tumor lysis syndrome
WBC	white blood cell

References

1. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Dohner H, Hillmen P, Keating MJ, Montserrat E, Rai KR, Kipps TJ, International Workshop on Chronic Lymphocytic Leukemia. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008; 111(12):5446–56. [PubMed: 18216293]
2. Bazargan A, Tam CS, Keating MJ. Predicting survival in chronic lymphocytic leukemia. Expert Rev Anticancer Ther. 2012; 12(3):393–403. [PubMed: 22369330]
3. Hallek M, Fischer K, Fingerle-Rowson G, Fink AM, Busch R, Mayer J, Hensel M, Hopfinger G, Hess G, von Grunhagen U, Bergmann M, Catalano J, Zinzani PL, Caligaris-Cappio F, Seymour JF, Berrebi A, Jager U, Cazin B, Trneny M, Westermann A, Wendtner CM, Eichhorst BF, Staib P, Buhler A, Winkler D, Zenz T, Bottcher S, Ritgen M, Mendila M, Kneba M, Dohner H, Stilgenbauer S, International Group of Investigators, German Chronic Lymphocytic Leukaemia Study Group. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, openlabel, phase 3 trial. Lancet. 2010; 376(9747):1164–74. [PubMed: 20888994]
4. Byrd JC, Lin TS, Dalton JT, Wu D, Phelps MA, Fischer B, Moran M, Blum KA, Rovin B, Brooker-McEldowney M, Broering S, Schaaf LJ, Johnson AJ, Lucas DM, Heerema NA, Lozanski G, Young DC, Suarez JR, Colevas AD, Grever MR. Flavopiridol administered using a pharmacologically

derived schedule is associated with marked clinical efficacy in refractory, genetically high-risk chronic lymphocytic leukemia. Blood. 2007; 109(2):399–404. [PubMed: 17003373]

5. Phelps MA, Lin TS, Johnson AJ, Hurh E, Rozewski DM, Farley KL, Wu D, Blum KA, Fischer B, Mitchell SM, Moran ME, Brooker-McEldowney M, Heerema NA, Jarjoura D, Schaaf LJ, Byrd JC, Grever MR, Dalton JT. Clinical response and pharmacokinetics from a phase 1 study of an active dosing schedule of flavopiridol in relapsed chronic lymphocytic leukemia. Blood. 2009; 113(12): 2637–45. [PubMed: 18981292]
6. Lin TS, Ruppert AS, Johnson AJ, Fischer B, Heerema NA, Andritsos LA, Blum KA, Flynn JM, Jones JA, Hu W, Moran ME, Mitchell SM, Smith LL, Wagner AJ, Raymond CA, Schaaf LJ, Phelps MA, Villalona-Calero MA, Grever MR, Byrd JC. Phase II study of flavopiridol in relapsed chronic lymphocytic leukemia demonstrating high response rates in genetically high-risk disease. J Clin Oncol. 2009; 27(35):6012–8. [PubMed: 19826119]
7. Woyach JA, Lozanski G, Ruppert AS, Lozanski A, Blum KA, Jones JA, Flynn JM, Johnson AJ, Grever MR, Heerema NA, Byrd JC. Outcome of patients with relapsed or refractory chronic lymphocytic leukemia treated with flavopiridol: impact of genetic features. Leukemia. 2012; 26(6): 1442–4. [PubMed: 22289993]
8. Stephens DM, Ruppert AS, Blum K, Jones J, Flynn JM, Johnson AJ, Ji J, Phelps MA, Grever MR, Byrd JC. Flavopiridol treatment of patients aged 70 or older with refractory or relapsed chronic lymphocytic leukemia is a feasible and active therapeutic approach. Haematologica. 2012; 97(3): 423–7. [PubMed: 22271900]
9. Blum KA, Ruppert AS, Woyach JA, Jones JA, Andritsos L, Flynn JM, Rovin B, Villalona-Calero M, Ji J, Phelps M, Johnson AJ, Grever MR, Byrd JC. Risk factors for tumor lysis syndrome in patients with chronic lymphocytic leukemia treated with the cyclindependent kinase inhibitor, flavopiridol. Leukemia. 2011; 25(9):1444–51. [PubMed: 21606960]
10. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5(6):649–55. [PubMed: 7165009]
11. National Cancer Institute. Common Terminology Criteria for Adverse Events. v4.0. NCI, NIH, DHHS; May 29. 2009 NIH publication # 09-7473
12. Phelps MA, Rozewski DM, Johnston JS, Farley KL, Albanese KA, Byrd JC, Lin TS, Grever MR, Dalton JT. Development and validation of a sensitive liquid chromatography/mass spectrometry method for quantitation of flavopiridol in plasma enables accurate estimation of pharmacokinetic parameters with a clinically active dosing schedule. J Chromatogr B Analyt Technol Biomed Life Sci. 2008; 868(1-2):110–5.
13. Blum W, Phelps MA, Klisovic RB, Rozewski DM, Ni W, Albanese KA, Rovin B, Kefauver C, Devine SM, Lucas DM, Johnson A, Schaaf LJ, Byrd JC, Marcucci G, Grever MR. Phase I clinical and pharmacokinetic study of a novel schedule of flavopiridol in relapsed or refractory acute leukemias. Haematologica. 2010; 95(7):1098–105. [PubMed: 20460644]
14. Ji J, Mould DR, Blum KA, Ruppert AS, Poi M, Zhao Y, Johnson AJ, Byrd JC, Grever MR, Phelps MA. A Pharmacokinetic/Pharmacodynamic Model of Tumor Lysis Syndrome in Chronic Lymphocytic Leukemia Patients Treated with Flavopiridol. Clin Cancer Res. 2013
15. Parker BW, Kaur G, Nieves-Neira W, Taimi M, Kohlhagen G, Shimizu T, Losiewicz MD, Pommier Y, Sausville EA, Senderowicz AM. Early induction of apoptosis in hematopoietic cell lines after exposure to flavopiridol. Blood. 1998; 91(2):458–65. [PubMed: 9427698]
16. Tsimberidou AM, Tam C, Abruzzo LV, O'Brien S, Wierda WG, Lerner S, Kantarjian HM, Keating MJ. Chemoimmunotherapy may overcome the adverse prognostic significance of 11q deletion in previously untreated patients with chronic lymphocytic leukemia. Cancer. 2009; 115(2):373–80. [PubMed: 19117034]
17. Kay NE, Geyer SM, Call TG, Shanafelt TD, Zent CS, Jelinek DF, Tschumper R, Bone ND, Dewald GW, Lin TS, Heerema NA, Smith L, Grever MR, Byrd JC. Combination chemoimmunotherapy with pentostatin, cyclophosphamide, and rituximab shows significant clinical activity with low accompanying toxicity in previously untreated B chronic lymphocytic leukemia. Blood. 2007; 109(2):405–11. [PubMed: 17008537]

Table 1

Dose Escalation Schema for Cyclophosphamide, Alvocibib, and Rituximab Regimen

Cohort	Rituximab	Cyclophosphamide	Alvocidib
1 (n=3)	100mg IV C1D1; 375mg/m^2 IV C1D2 & C2-6D1	300mg/m^2 IV C1-6D1-3	30mg/m^2 IV (30min), 30 mg/m^2 IV (4hrs) C1D8; C2-6D1&8
2 (n=3)			30mg/m^2 IV (30min), 50 mg/m^2 IV (4hrs) C1D8, C2-6D1&8
3 (n=3)		375mg/m^2 IV C1-6D1-3	

IV=intravenous, C=cycle, D=day

Table 2

Pretreatment Patient Characteristics

Characteristic	Patients (n=9)
Median Age in Years (range)	55 (43-77)
Male	7
Caucasian	8
ECOG Performance Status [10]	
0	7
1	2
Number of Prior Treatments	
0	6
1	2
2	1
Rai Stage at Treatment	
Intermediate Risk (I-II)	7
High Risk (III-IV)	2
Del(17p)	3
Del(11q)	4
Complex Cytogenetics	3
Unmutated IgV_H status (n=7)	6
β2microglobulin >4	1
Bulky Adenopathy >5cm	0
Median Leukocyte Count × 10^9/L (range)	66.9 (3.4-217.0)
Median Hemoglobin, g/dL (range)	11.8 (9.5-14.2)
Median Platelet Count × 10^9/L	138 (75-250)

Table 3

Response by Risk Factor and Dose Level

Dose Level	UPN	High Risk Factors					Response	PFS (mos)	OS (mos)
		Del(17p)	Del(11q)	Un-mut IgVH	Age >70	B2 M≥4			
1	1	Y	N	Y	Y	N	CR	22.7	22.7
	2	N	Y	U	N	N	PR	7.4†	22.1
	3	N	N	Y	N	N	SD	5.1†	10.1
2	4	Y	N	U	N	N	CR	6.2	6.2
	5	N	Y	Y	N	N	PR	16.8†	17.6
	6	Y	N	Y	Y	Y	PD	3.4†	19.1
3	7	N	Y	Y	N	N	CR	15.6	15.6
	8	N	N	Y	N	N	PR	10.3	10.3
	9	N	Y	N	N	N	PR	4.6	4.6

† Progressive Disease

Un-mut=un-mutated, B2M=beta-2-microglobulin, Y=yes, N=no, U=unknown, CR=complete response, PR=partial response, SD=stable disease, PD=progressive disease, UPN=unidentified patient number, PFS=progression-free survival, OS=overall survival