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Dinaciclib is a Novel Cyclin Dependent Kinase Inhibitor with Significant Clinical Activity in Relapsed and Refractory Chronic Lymphocytic Leukemia

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Abstract

Dinaciclib (SCH727965) is a selective CDKi chosen for clinical development based upon a favorable therapeutic index in cancer xenograft models. We performed a phase I dose escalation study of dinaciclib in relapsed and refractory CLL patients with intact organ function and WBC < 200×10^9/L. Five separate dose levels (5 mg/m^2, 7 mg/m^2, 10 mg/m^2, 14 mg/m^2, and 17 mg/m^2) were explored dosing on a weekly schedule × 3 with one week off (4 week cycles) using a standard 3+3 design with expansion cohorts to optimize safety. Fifty two patients were enrolled with relapsed and refractory CLL. Escalation through cohorts occurred with two DLTs at the 17 mg/m^2 dose (TLS and pneumonia). The phase II expansion occurred at 14 mg/m^2 with sixteen patients receiving this dose with one DLT (TLS). Additional stepped up dosing to the MTD was examined in 19 patients at this dose. Adverse events included cytopenias, transient laboratory abnormalities, and tumor lysis syndrome. Responses occurred in 28 (54%) of patients independent of del(17)(p13.1) with a median progression free survival of 481 days. Dinaciclib is clinically

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Contribution JF, RB and JCB designed the study, monitored toxicity, assessed response, and drafted the first version of the paper. JJ, LA, KM, and MG enrolled patients, reviewed drafts of the manuscript and approved the final version; AJJ, JH, EM, HZ, YZ, and KS contributed to the performance of study, laboratory and pharmacodynamic studies, reviewed drafts of the manuscript and approved the final version.

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active in relapsed CLL including those patients with high risk del(17)(p13.1) disease and warrants future study.

Keywords

Dinaciclib; CDK inhibitor; tumor lysis syndrome; chronic lymphocytic leukemia

Introduction

CLL represents the most prevalent type of adult leukemia and is currently incurable with available therapies. The introduction of fludarabine (F)(1, 2), fludarabine/cyclophosphamide (FC)(3, 4), and either of these combined with rituximab (FR(5, 6) or FCR(7)) has improved outcome for younger patients with CLL. Treatment options available for patients, in the setting of relapsed disease following receipt of chemoimmunotherapy, are fewer, where most patients have high risk genomic findings including IgV_H un-mutated disease, del(17)(p13.1), and del(11)(q22.3) associated with poor treatment response (reviewed in(8)). Identifying therapies with novel mechanisms of action, that lack immune suppression, is important for this patient group.

One class of drugs that has promise for the treatment of relapsed CLL are the cyclin dependent kinase (CDK) inhibitors. Flavopiridol is the first member of this class to be extensively tested based upon pre-clinical work by several groups(9) (10, 11) which, while having a narrow therapeutic window, was shown to be clinically active in genomic high risk patients with a dose limiting side effect of hyper-acute tumor lysis syndrome (TLS).(12, 13) Other toxicities associated with flavopiridol including diarrhea, fatigue, anorexia, and cytokine release syndrome required significant supportive care to effectively deliver therapy. A multicenter phase II trial confirmed activity of flavopiridol including in patients with del(17)(p13.1) but also toxicity associated with its narrow therapeutic index(14). These results provide support for development of CDK inhibitors that have an improved therapeutic index given their unique ability to target del(17p13.1) and refractory disease.

Dinaciclib (SCH 727965)(15) is a selective inhibitor of CDK 1, 2, 5 and 9 (IC_{50} of < 5nM) that was selected pre-clinically by an in vivo screen that identified it as having a favorable therapeutic index of maximally tolerated dose to effective dose in an ovarian carcinoma xenograft mouse model(16). Specifically, the therapeutic index of dinaciclib was 10 versus 2 for BMS-387032 (now known as SNS-032) and < 1 for flavopiridol(16). Dinaciclib has completed phase I testing in solid tumors, where the dose limiting side effect of neutropenia and cytokine release syndrome was observed with a relatively favorable therapeutic index(16) (i.e. no diarrhea and less fatigue as compared to flavopiridol(17)). Pre-clinical studies by our group demonstrated this agent had improved therapeutic efficacy against CLL cells as compared to flavopiridol and was not cytotoxic to T-cells(18). This prompted initiation of the phase I dose escalation study described herein in CLL where we demonstrate significant clinical activity and tolerability of dinaciclib.

Patients

Patients were enrolled on this single institution company-sponsored clinical study (NCT00871663) following approval by The Ohio State University Institutional Review Board. All patients provided written informed consent. Patients had institutionally confirmed diagnosis of chronic lymphocytic leukemia (CLL) according to NCI-WG criteria(19) or small lymphocytic lymphoma (SLL)(20). All patients had received at least one prior therapy having either relapsed or not responded to this. Additional enrollment requirements included: age ≥ 18 years, Eastern Cooperative Oncology Group (ECOG) performance status of less than 3, creatinine ≤2.0 mg/d), transaminases ≤ 2.5 times the upper limit of normal (ULN), and bilirubin <1.5 times ULN. Patients could not have received chemotherapy within 4 weeks of enrollment, though palliative corticosteroids were allowed 7 days prior to treatment initiation. Patients could not have a serious or uncontrolled infection. Pregnant women and patients with HIV infection were excluded.

Treatment plan

This phase I trial was a nonrandomized, dose-escalation study to determine the maximum tolerated dose (MTD) for single-agent dinaciclib administered using the 2 hour infusion once weekly for 3 of every 4 weeks (1 cycle of therapy) which continued until progression, toxicity, patient choice, or transition to allogeneic stem cell transplant. Dose escalation proceeded according to a 3 + 3 design within each disease cohort, enrolling 3 to 6 patients at each of the dose levels as defined in Table 1. The beginning dose of 5 mg/m^2 was chosen based upon pharmacokinetic modeling approximating the attainment of end-of-infusion dinaciclib levels at concentrations that produced 50% cytotoxicity in vitro in our pre-clinical work(18). A 10 patient expansion cohort was included at the maximally tolerated dose to further assess toxicity and feasibility of extended dosing of dinaciclib. Following this, one of two stepped up dosing strategies were explored in order to further diminish the frequency of TLS. Beginning week 1, treatment at 10 mg/m^2 followed by 14 mg/m^2 thereafter or 7 mg/m^2 week 1, 10 mg/m^2 week 2, and 14 mg/m^2 thereafter was employed.

As TLS has been previously reported with flavopiridol when used to treat CLL, the first dinaciclib infusion was delivered as an inpatient supported by vigorous IV hydration (for at least 10 hours pre- and post-treatment) and with careful monitoring for and aggressive management of hyperkalemia according to an established protocol previously described.(21) All patients received rasburicase 3 mg IV 2 hours prior to the first dose of dinaciclib. Patients were subsequently transitioned to outpatient treatment on day 8 of therapy. Cytokine release prophylaxis using dexamethasone 20 mg IV prior to dinaciclib during the first cycle of treatment, with subsequent tapering and/or discontinuing during subsequent courses at the discretion of the treating physician. Prophylactic antimicrobials (bactrim, ciprofloxacin, and valtrex) were administered to all patients. Neulasta was administered on day 16 of therapy to all patients.

Assessment of toxicity and response

NCI Common Toxicity Criteria for Adverse Events (version 3.0) were used to define and grade toxicity associated with therapy. Patients were assessed initially for clinical response

after each cycle with laboratory studies, and physical exam. Response assessment was evaluated using the 1996 NCI-WG criteria initially(19) but CT scans were added early into the study to assess response in agreement with the 2008 IWCLL response criteria(22). All those included in the recommended phase II dosing cohorts were assessed by IWCLL 2008 criteria.

Dose-limiting toxicity

Patients were evaluated for dose limiting toxicity (DLT) during the first cycle of treatment for each dose level during dose escalation. Dose limiting toxicity was defined as any Grade 3 or Grade 4 hematologic toxicity lasting > 1 week or any Grade 3 or Grade 4 nonhematologic toxicity. Because severe cytopenias are a characteristic of CLL, hematologic toxicity was not used to assess for DLT if the baseline value was Grade 3 or Grade 4 at time of study enrollment. However, severe cytopenias were considered a DLT if they persisted to Day 42 and beyond, and bone marrow assessment showed response to treatment (> 50 % reduction in marrow CLL cells compared to pretreatment marrow). Untreated nausea, vomiting, fatigue, anorexia, anemia, alopecia or local reactions were not included in the determination of DLT, unless the project physician and the investigator concluded that such inclusion was necessary. If a patient started with a Grade 1 or Grade 2 AST and/or ALT at screening, then a doubling of the baseline value to > Grade 3 was considered a DLT. Any other abnormal nonhematologic laboratory values > Grade 3 were considered DLTs, only if medical intervention or hospitalization were required or the value persisted for > 1 week. Also, because of the known sensitivity of CLL to the CDK inhibitor flavopiridol, TLS was not considered a DLT in the dose escalation cohorts, unless dialysis was required.

Pharmacokinetics and Pharmacodynamics

Whole blood samples were collected for pharmacokinetic (PK) analysis on day 1 and 15 of cycle 1 of therapy. Blood samples were collected in sodium heparin tubes, and plasma was immediately separated and stored at −70°C for later analysis. Dinaciclib quantification in plasma samples was achieved using a validated liquid chromatography-tandem mass spectrometry assay as previously described(23). PK parameters were estimated using validated WinNonlin Professional Version 5.3 software (Pharsight Corporation, Mountain View, CA). Protein expression of mcl-1, XIAP, and bcl-2 was assessed by protein expression by Western Blot at baseline, 2 hours, 4 hours, and 24 hours post-treatment with the first dose of dinaciclib using methods previously published.(24)

Statistical considerations

No formal hypothesis testing was planned. Descriptive statistics were provided for the primary end points of safety and tolerability. The evaluable population included all patients completing one cycle of therapy or discontinuing therapy during the first cycle secondary to toxicity. Progression free survival (PFS) was defined as the time from the initial day of therapy to disease progression or death due to any cause, whichever occurs first, and the non-parametric Kaplan-Meier method was used to estimate the median PFS. Patients proceeding to allogeneic transplant or changing therapy to ibrutinib after effective

cytoreduction or improvement in blood counts were censored at this time for PFS. Response duration was calculated from the date of first CR/PR based on NCI-WG criteria to earliest time of either disease progression or death, and median response duration among responding patients was estimated using the Kaplan-Meier method.

Results

Patient Characteristics

The demographics of CLL patients enrolled in this phase I trial between January, 2009 and October, 2012 are summarized in Table 2. The median age was 62 (range 43–79), with 65% being advanced Rai stage, 69% having bulky (> 5 cm) nodes, and 45% having high risk del(17p13.1) at the time of enrollment. The median number of prior therapies for this patient group was 4 (range 1–15) with 92% having received fludarabine.

Toxicity Assessment

Dose escalation of dinaciclib in this study proceeded according to Table 1 with a single dose limiting toxicity noted in cohort 2 (sepsis) that required cohort expansion and two additional DLT's in four patients treated at 17 mg/m^2 dose (tumor lysis syndrome requiring dialysis and pneumonia) suggesting the maximally tolerated dose was exceeded. Three additional patients were treated at the 14 mg/m^2 dose without DLT. An expansion cohort of 10 additional patients was enrolled at this dose, in which one patient had tumor lysis syndrome requiring dialysis and 3 other patients had tumor lysis that required very aggressive medical management. In an attempt to mitigate tumor lysis with the first dose of dinaciclib, a stepped up dosing strategy was employed in a cohort of six patients using a 10 mg/m^2 dose of dinaciclib during week 1 and escalating to 14 mg/m^2 week 2 and thereafter. In this cohort, 2 patients had tumor lysis that required aggressive medical management. We explored using a 7 mg/m^2 dose of dinaciclib during week 1, escalating to 10 mg/m^2 week 2 and 14 mg/m^2 week thereafter in 13 additional patients. One patient in this cohort required dialysis. This cohort was deemed the recommended method for dosing in future studies.

There were 3 deaths within 30 days of last dose of dinaciclib with two being due to disease progression. One patient in the 7mg/m^2 dose level completed 1 cycle of treatment with dinaciclib. On day 27 of cycle 1, the patient was hospitalized with sepsis, renal failure, and respiratory failure resulting in death on this day. Five other patients discontinued therapy due to toxicity. The adverse events leading to treatment discontinuation included urosepsis (1), tumor lysis syndrome (1), fatigue and headache (1), sepsis (1), and pneumonia (1). In addition, grade 3 and 4 neutropenia, transient transaminitis and hyperglycemia was noted.

Other toxicities reported with dinaciclib are summarized in Table 3 and were generally moderate and not cumulative over time. Notably, CTC grade 3 or 4 diarrhea and cytokine release syndrome were infrequent toxicities observed with dinaciclib using steroid prophylaxis. Transient grade 3 and 4 liver function abnormalities were noted after therapy which were reversible and did not require therapy discontinuation. Similarly, hyperglycemia was noted transiently and attributed to use of corticosteroids for prevention of cytokine

release syndrome. Additionally, cumulative fatigue and anorexia were not observed over time.

Efficacy

Within this dose escalation trial, IWCLL 2008 responses were observed at all dose levels as summarized in Table 4. Response to therapy generally was delayed in the lower dose cohorts whereas patients receiving dinaciclib at doses of 10 mg/m^2 and above had more rapid tumor cytoreduction. The overall response to therapy for all 52 patients enrolled on this trial was 54% (28 of 52), with all of these being partial responses by IWCLL 2008 criteria(22). Isolating response criteria to patients treated with the recommended phase II dose (14 mg/m^2) at the final dose, 22 of 35 (63%) attained response. Response to dinaciclib was equally effective in the 25 patients with del(17)(p13.1) who had a response rate of 56% as compared to the 57% response in 21 patients without this aberration who had available interphase cytogenetic studies. The response rate was 71% among patients with non-bulky (< 5 cm nodes) versus 52% among those individuals with bulky disease. Response was 38% for those with prior flavopiridol exposure whereas it was 61% for those not previously treated with this agent. The median time to response was 85 (27–244) days. For patients with del(17)(p13.1), the median time was 61 days whereas for those without this aberration it was 90 days. Patients receiving the recommended stepped up final dose of 14 mg/m^2 received a median of 148 days of therapy (range 15–309 days). Patients enrolled on this study had an estimated progression free survival of 481 days. Progression free survival was similar among those patients with and without del(17p13.1). Patients came off therapy for adverse events (10%), progression of disease (27%), subject wished to discontinue (56%) due to improvement in normal blood counts that enabled receipt of ibrutinib on trial or availability of access to this therapy, withdrawal of consent (6%), and protocol noncompliance (2%). Patients who went off therapy due to desire to pursue ibrutinib were censored for PFS. At this time, all patients who received treatment on this study have progressed or been censored for receiving alternative therapy in the absence of progression.

Pharmacokinetics

The pharmacokinetic features of dinaciclib in this clinical trial among CLL patients was similar to those observed previously in two separate studies of subjects with solid tumors(23). Following the end of 2-hr IV infusion (Table 5), plasma dinaciclib concentrations rapidly declined from peak concentration bi-exponentially with an estimated terminal phase half-life of 2.31 to 2.95 hours (geometric mean). The transition between the two phases occurred at roughly 1 hour after the end of infusion (3 hours after the initiation of 2-hr IV infusion). Although not designed for a definitive assessment of dose proportionality, these data suggest that there were dose-related increases in exposure to dinaciclib over the dose range evaluated in this trial. The increases in exposure (Cmax and AUC) were greater than dose-proportional at 17 mg/m^2, which may be due to the high variability (CV: 63–140%) in exposure and small sample size at this dose level. Dinaciclib did not accumulate in plasma following weekly 2-hour IV infusion. Plasma concentration-time profiles on Day 15 were similar to those on Day 1 including terminal half life. Pharmacokinetic features did not correlate with response to therapy.

Pharmacodynamic Studies

Tumor metabolic change in response to dinaciclib treatment was evaluated using FDG PET/CT imaging collected pretreatment (Baseline) and on Cycle 1 Day 22. FDG-PET was chosen as an exploratory imaging pharmacodynamic marker to assess if decreased FDG uptake in the tumor occurred as a result of dinaciclib treatment. A reduction in tumor metabolic changes as measured by 30% or more decrease in SUV from baseline to post-treatment was considered as a responder for tumor metabolism given the absence of previous serial measurement of PET scan assessments in CLL. Out of the 29 treated CLL subjects who had PET/CT scans, 4 were not evaluable, 15 were responders and 10 were non-responders. There was no association between PET response and NCI 96 CLL response (p=. 99). Similarly, assessment of bcl-2, XIAP, and MCL-1 protein levels at baseline, 2 hours, and 4 hours of treatment was assessed. MCL-1 protein showed significantly reduced expression at 2 and 4 hours of treatment as compared to pretreatment ($P<0.0001$) whereas no significant change in XIAP or BCL2 protein level was noted. No correlation with response to baseline or serial change in these protein pharmacodynamic markers was noted.

Discussion

Herein, we describe a single institution CLL disease specific phase I study of the cyclin dependent kinase inhibitor dinaciclib. The starting dose of dinaciclib was lower than that identified in the solid tumor cohort of this trial given the known potential occurrence of tumor lysis syndrome with another cyclin dependent kinase inhibitor, flavopiridol(25). The maximally tolerated dose of dinaciclib identified was 14 mg/m^2, with dose limiting toxicity being tumor lysis syndrome requiring dialysis in one patient and pneumonia in a second. Further refinement using a stepped up dosing schedule beginning at 7 mg/m^2 week 1, 10 mg/m^2 week 2, and 14 mg/m^2 week three and thereafter was identified in a third expansion cohort to be best tolerated and should be utilized for subsequent phase II studies. Toxicity observed with dinaciclib was predominately hematopoietic and metabolic as a consequence of tumor lysis syndrome. Infections, fatigue, and diarrhea were not commonly noted with dinaciclib treatment despite the highly refractory group of patients treated on this trial. Despite a very high genomic risk group that included 45% del(17)(p13.1) CLL patients, response rate was high (54%) and occurred at all dose levels and were durable with median progression free survival approximating 1 year. This high del(17)(p13.1) frequency in this study is likely reflective of our group being a referral center for such patients. Responses occurred independent of del(17)(p13.1), del(11)(q22.3) or bulky lymph node status. While down-modulation of mcl-1 protein occurred in all patients treated with dinaciclib and provides a potential pharmacodynamic marker for CDK9 inhibition, this did not correlate with response to therapy. This suggests mcl-1 modulation in tumor CLL cells may not significantly contribute to mechanism of action of dinaciclib. Similarly, early decrease (day 21) in PET SUV uptake did not correlate with response to dinaciclib using a 30% change criteria. These data should not be interpreted for usefulness of PET scan for identifying Richter's transformation or other diagnoses other than CLL which has been well documented by other studies.(26, 27) Although several doses of dinaciclib were tested as part of this trial, responses across all dose levels and the large number of patients (n=52) provide significant support for the clinical activity of this agent in refractory CLL. Indeed,

35 patients were treated at the phase 2 dose of 14 mg/m^2 with 63% responding. The patient number treated at this dose provides a 95% confidence interval of 47–79% suggesting that the significant efficacy observed is a true finding and not one of small patient numbers. However, it is notable that no complete responses were obtained despite the observation of tumor lysis syndrome. Reasons for this could include stromal protection in select niches such as the bone marrow or mechanisms of resistance present in a subset of tumor cells. Further study of this in the future should be considered.

A notable finding of this study is clinical validation of the favorable tolerability of dinaciclib as a therapeutically active agent as predicted by the pre-clinical work justifying selection of this molecule. Notably, dinaciclib was selected for clinical development based upon having a favorable tumor to healthy tissue therapeutic index as assessed in human cancer xenograft models(16). In contrast to flavopiridol, dinaciclib could be administered for an extended period of time with durable remissions in a majority of refractory patients. Cumulative toxicity such as fatigue and diarrhea was not frequently noted with dinaciclib as has been observed with flavopiridol. While this study does not directly compare dinaciclib with flavopiridol, our group's extensive experience with each of these agents in similar patient population leaves the impression that dinaciclib has at least similar activity to flavopiridol though is better tolerated, thereby justifying further development.

While dinaciclib was acceptably tolerated in CLL patients, acute tumor lysis in some cases requiring dialysis still occurred as previously described with another cyclin dependent kinase inhibitor flavopiridol. In our study, stepped up dosing administration of dinaciclib lowered the frequency of this complication. However, an even better strategy to pursue in the future might include cytoreduction with alternative therapy prior to introduction of dinaciclib therapy. This was previously performed successfully with flavopiridol where pre-treatment with rituximab and cyclophosphamide greatly reduced the risk of tumor lysis syndrome(28). Our group is currently pursuing such a strategy with pre-treatment with ofatumumab as part of an ongoing phase I/II study (NCT01515176). Outside of cytoreductive strategies, efforts to identify pre-treatment molecular features predictive of tumor lysis will further enhance the ability to identify patients at high risk and thus facilitate safe administration of dinaciclib.

During the phase I development of dinaciclib for CLL several highly active therapeutic agents such as obinutuzumab(29), ibrutinib(30, 31), ABT199(32), and idelalisib(33, 34) have come forward through clinical trials and offer to change significantly the landscape of CLL therapy. Indeed, the 56% of patients who withdrew from therapy is reflective of availability of ibrutinib when blood counts improved or trial access became available. This raises the very relevant question of the value of an intravenous therapeutic agent that, although well tolerated, still requires significant supportive care with the first 1–2 doses due to risk of acute tumor lysis syndrome. While the oral targeted therapies ibrutinib, ABT199, and idelalisib all are highly active in CLL, they are likely going to be expensive and does not produce complete remissions in the majority of patients. Additionally, the durability of response among del(17p)(13.1) patients to ibrutinib and idelalisib appears to be significantly shorter(30,34) than genomic low risk patients. In other tumor types, resistance to ABT199 occurs in part through up-regulation of the anti-apoptotic protein MCL-1. Given that

dinaciclib is highly active in del(17p)(13.1) CLL, works through alternative mechanisms than the new molecularly targeted agents and with respect to ABT-199 targets the resistance mediating protein MCL-1, this agent represents an ideal therapeutic agent to incorporate in combination regimens. Such combination regimens including novel targeted agents and dinaciclib would target achievement of high complete response rates and also prevention of resistance.

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Table 1

Dose Escalation Schedule of Dinaciclib

Cohort	No Pts Treated	Median Rx (Days)	Maximum Rx Duration (Days)	Pts with DLT	Pts with TLS (Dialysis)	No Pts with Dose Reduction
5 mg/m^2	4	36	346	0		0
7 mg/m^2	6	180	470	1		0
10 mg/m^2	3	232	345	0		1
14 mg/m^2	16	145	342	1	4 (1)	5
17 mg/m^2	4	148	309	2	1 (1)	1
10→14 mg/m^2	6	163	218	-	2	1
7→10→14 mg/m^2	13	148	308	-	1 (1)	1

Key: No-number; Pt-patients; Rx-Treatment; DLT-dose limiting toxicity; TLS-tumor lysis syndrome.

Table 2

Patient demographics

	Total (N = 52)
Age, median (range)	62 (43–79)
N (%) ≥ 65 years	24 (46)
Female, n (%)	15 (29)
Rai stage at study entry [n (%)]	
I/II	18 (35)
III/IV	34 (65)
ECOG performance status [n (%)] 19/28/5	
0	19 (37)
1	28 (54)
2	5 (9)
Organomegaly	
N (%) with lymphadenopathy > 5 cm	36 (69)
Interphase cytogenetic abnormalities	
N (%) with del(13q14.3)	29 (59)
N (%) with del(11q22.3)	25 (51)
N (%) with del (17p13.1)	22 (45)
N (%) with Trisomy 12	7 (14)
Treatment history	
Prior therapies, median (range)	4 (1–15)
N (%) prior fludarabine	48 (92)
N (%) prior rituximab	50 (96)
N (%) prior chlorambucil or cyclophosphamide	45 (87)
N (%) prior flavopiridol	16 (31)

Table 3

Treatment Related Events

Toxicity	No (%) Grade 1	No (%) Grade 2	No (%) Grade 3	No (%) Grade 4	Total (%)
Hematopoiesis					
Anemia	8 (15)	17 (33)	14 (27)	1 (2)	40 (77)
Neutropenia	3 (6)	2 (4)	22 (21)	28 (54)	44 (85)
Thrombocytopenia	10 (19)	6 (12)	11 (21)	10 (19)	37 (71)
Gastrointestinal					
Constipation	4 (8)	1 (2)	1 (2)	0 (0)	6 (12)
Diarrhea	14 (27)	7 (13)	2 (4)	0 (0)	23 (44)
Nausea	10 (19)	3 (6)	0 (0)	0 (0)	13 (25)
General/Lab					
Fatigue	7 (13)	8 (15)	2 (4)	0 (0)	17(33)
Cytokine release	1 (2)	6 (12)	1 (2)	0 (0)	8 (15)
Increased bilirubin	5 (10)	0 (0)	0 (0)	0 (0)	5 (10)
Increased ALT	6 (12)	9 (17)	5 (10)	0 (0)	20 (38)
Increased AST	11 (21)	8 (15)	13 (25)	2 (4)	34 (65)
Increased Alkaline Phosphatase	8 (15)	1 (2)	0 (0)	0 (0)	9 (17)
Increased creatinine	11 (21)	3 (6)	0 (0)	0 (0)	14 (27)
Hyperglycemia	8 (15)	16 (31)	11 (21)	0 (0)	35 (67)
Hyperkalemia	7 (13)	3 (6)	3 (6)	3 (6)	16 (21)
Hypokalemia	17 (33)	1 (2)	9 (17)	0 (0)	27 (52)
Hyperphosphatemia	6 (12)	1 (2)	0 (0)	0 (0)	7 (13)
Hypophosphatemia	6 (12)	5 (10)	6 (12)	1 (2)	18 (35)
Hypocalcemia	17 (33)	1 (2)	9 (17)	0 (0)	27 (52)
Hyponatremia	18 (35)	0 (0)	1 (2)	0 (0)	19 (37)
Hypoalbuminemia	12 (23)	3 (6)	0 (0)	0 (0)	15 (29)
Tumor lysis syndrome	0 (0)	0 (0)	7 (13)	1 (2)	8 (15)
Infection (all)					

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Toxicity	No (%) Grade 1	No (%) Grade 2	No (%) Grade 3	No (%) Grade 4	Total (%)
Sepsis	0 (0)	0 (0)	1 (2)	0 (0)	1 (2)
Pneumonia	0 (0)	0 (0)	2 (4)		2 (4)
Herpes infection	2 (4)	1 (2)	0 (0)	0 (0)	3 (6)
Pharyngitis/sinusitis/respiratory infection	2 (4)	2 (4)	0 (0)	0 (0)	4 (8)
Urosepsis	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)

Table 4

Response to Dinaciclib by Dose Level

Dose Level	No Pts	No (%) of Responders
5 mg/m^2	4	1 (25)
7 mg/m^2	5	1 (20)
10 mg/m^2	3	2 (67)
14 mg/m^2	16	11 (69)
17 mg/m^2	4	1 (25)
10→14 mg/m^2	6	4 (67)
7→10→14 mg/m^2	13	7 (53)
14 mg/mg/m^2 dosing during treatment	35	22 (63)
Total	52	28 (54)

Table 5

Pharmacokinetics of Dinaclib on Days 1 and 15 of Therapy

Day 1 Pharmacokinetics	**No Pts**	**Cmax (ng/mL)**		**AUC(I) (ng·hr/mL)**		**T1/2 (hr)**		**CL (L/hr/m_2)**		**Vd (L/m_2)**	
Dose		**Mean**	**CV%**	**Mean**	**CV%**	**Mean**	**CV%**	**Mean**	**CV%**	**Mean**	**CV%**
5 mg/m^2	4	95.4	41	191	53	2.45	31	26.2	53	92.8	37
7 mg/m^2	18	208	29	403	38	2.65	32	17.3	38	66.2	35
10 mg/m^2	9	277	23	501	26	2.85	33	19.9	26	81.8	42
14 mg/m^2	16	404	28	775	33	2.85	14	18.1	33	74.4	32
17 mg/m^2	4	624	63	1290	88	2.93	6.6	13.2	88	55.9	79
Day 15 Pharmacokinetics											
5 mg/m^2	3	150	52	310	49	2.50	38	16.1	50	60.3	100
7 mg/m^2	8	157	27	294	26	2.31	25	23.8	26	79.5	27
10 mg/m^2	7	299	29	592	36	2.82	41	16.8	36	68.4	58
14 mg/m^2	27	428	24	827	25	2.92	27	17	26	71.4	38
17 mg/m^2	3	634	110	1260	140	2.95	15	13.8	140	58.9	110