A Phase II study of intermittent duvelisib dosing in patients with chronic lymphocytic leukemia/ small lymphocytic lymphoma (CLL/SLL)

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Introduction

Targeting phosphatidylinositol 3-kinase (PI3K) has emerged as an efficacious approach for treatment of chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL).[1] However, toxicities of the PI3K inhibitors are an important concern limiting their use.[2] Duvelisib is a potent oral inhibitor of both the PI3K-δ and PI3K-γ isoforms with proven efficacy in CLL/SLL.[3] The proposed mechanism of action is illustrated in Figure 1. Here we report the results of a phase 2 study evaluating efficacy and safety of duvelisib with intermittent dosing in patients with relapsed/refractory CLL/SLL.

Methods

- Open-label, single arm, phase 2 study
- Enrolled patients with CLL/SLL treated with at least 1 prior line of therapy with active disease as defined by the iWCLL 2008 criteria
- Duvelisib induction was given at 25 mg PO BID for 28-day cycles for a total of 12 weeks, followed by maintenance at a dose of 75 mg PO BID 2 days on and 5 days off for repeated 28-day cycles until death, intolerance or disease progression
- Primary endpoint: progression free survival (PFS) at 12 months
- Secondary endpoints: safety and clinical benefit
- The trial was originally planned to enroll 27 patients but was stopped early due to difficulties with enrollment following changing FDA guidance for the use of PI3K inhibitors.

Table 1. Dosing Schema

Dose Phase	Duvelisib (28-day cycle)	Number of Cycles
Induction	25 mg PO BID	3
Maintenance	75 mg PO BID 2 days on and 5 days off	Until death, intolerance or progression

Dose Limiting Toxicities

- Grade ≥ 4 hematologic toxicities persisting for > 7 days
- All Grade ≥ 3 non-hematologic toxicities except:
  - Asymptomatic Grade 3 laboratory abnormalities that are reversible to ≤ Grade 2 within 72 hours
  - Grade 3 tumor lysis syndrome (TLS)
  - Grade ≥ 3 increase in amylase/lipase if present for <10 days, is asymptomatic with no evidence of pancreatitis;
  - Grade ≥ 3 hyperglycemia or Grade 3 hypertension if present for < 7 days, unless requires hospitalization
- Hepatic toxicities: ALT/AST > 8 X ULN, or ALT/AST > 5 X and ≤ 8 X ULN, that fails to return to Grade 0-1 within 2 weeks despite medical intervention, or bilirubin > 5 ULN
- Febrile Neutropenia defined as a fever ≥100.4 concurrent with an absolute neutrophil count <500
- Grade 2 pneumonitis

Figure 1. Proposed Mechanism of Action

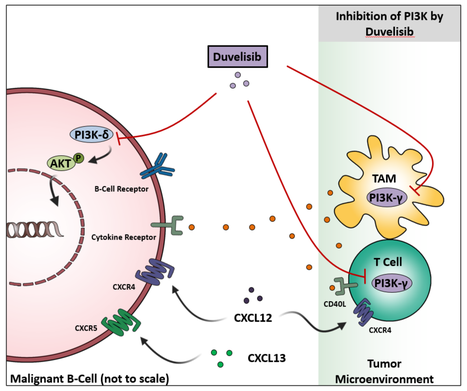


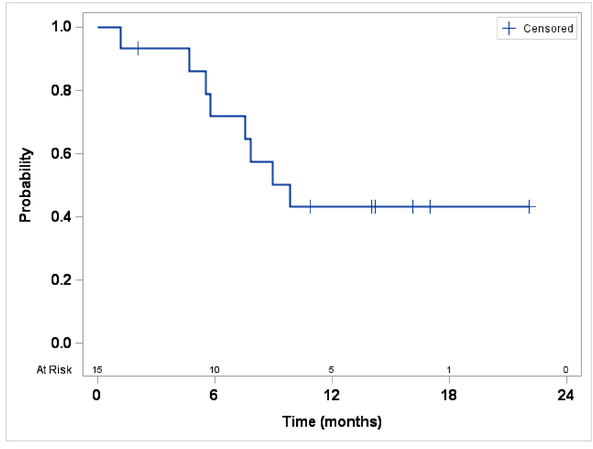
Table 2. Patient Characteristics (n=15)

Characteristics	All patients N = 15	(%)
Age		
Median (range)	74	(59 – 82)
Prior Lines of Therapy		
Median (range)	3	(1 – 6)
Race		
Black	1	(7)
Asian	1	(7)
Caucasian	13	(86)
Sex		
Female	8	(57)
Male	7	(43)
ECOG performance status		
0	4	(86)
1	11	(14)
Genetic Alterations		
FISH abnormalities	11	(79)
TP53 gene loss	4	(29)
Del(13q)	3	(21)
Del(11q)	2	(14)
IGHV unmutated	8	(57)
Response	Efficacy Evaluable = 11	
Overall Response Rate	9	(82)
Partial Response	9	(82)
Stable Disease	2	(18)

Table 3. Adverse events of all grades (>10% frequency) and grade 3-4 (2+ patients) (n=15)

Adverse Event	n (%)
All Grades (>10%)	
Fatigue	5 (33%)
Leukocytosis	4 (27%)
Vomiting	4 (27%)
ALT increased	4 (27%)
AST increased	4 (27%)
Diarrhea	4 (27%)
Alkaline phosphatase increased	4 (27%)
Lymphocyte count increased	3 (20%)
Nausea	3 (20%)
Abdominal pain	3 (20%)
Platelet count decreased	3 (20%)
Chills	2 (13%)
Blood bilirubin increased	2 (13%)
Neutrophil count decreased	2 (13%)
Colitis	2 (13%)
Mucositis oral	2 (13%)
Hypertension	2 (13%)
Arthralgia	2 (13%)
Rash maculopapular	2 (13%)
Grade 3-4 (2+ patients)	
Leukocytosis	3 (20%)
ALT increased	2 (13%)
AST increased	2 (13%)
Colitis	2 (13%)
Mucositis Oral	2 (13%)

Figure 2. PFS among all patients (n=15). Median PFS: 9.9 months (95% CI: 5.5-NA).



Results

- Characteristics of the 15 patients enrolled are summarized in Table 2
  - Median age was 74 (59-82) years, 8/15 (53%) were female
  - Patients were primarily Caucasian (13/15; 87%)
  - 27% (4/15) had ECOG 0 and 73% (11/15) ECOG 1
- Heavily pre-treated with median of 3 prior lines of therapy (range 1-6)
  - 14 patients had FISH results available, 79% (11/14) were abnormal
  - 29% with *TP53* gene loss, 21% del(13q), and 14% del(11q)
  - Fifty-seven percent (8/14) had unmutated IGHV
- Of the 15 patients treated, 4 were not evaluable for efficacy due to coming off study early for toxicity (2), development of MDS unrelated to study drug (1) or death due to COVID-19 infection (1).
- Among 11 efficacy-evaluable patients, 82% achieved PR and 18% SD
- 12-month PFS was 43% (95%CI: 18%-66%) and median PFS was 9.9 months (95% CI: 5.5-NA) (Figure 2).
- Among 9 responders, median DOR was 5.3 months (95%CI: 1.9-NA) and 12-month DOR was 22% (95%CI:3%-51%).
- Five patients (33%) discontinued therapy due to adverse events, which occurred during the induction phase in 4/5 of the patients.
- Five patients (33%) discontinued due to progressive disease – all during the maintenance phase of treatment.
- Additionally, 2 patients discontinued due to MD decision; one patient developed MDS which was unrelated to duvelisib; one patient died during treatment due to complications from COVID-19.
- Treatment was generally well tolerated with the most common AEs summarized in Table 3.
- The adverse events leading to treatment discontinuation occurred primarily during induction.

Conclusions

- Patients who received duvelisib on an intermittent schedule achieved some clinical benefit, however, the desired 12-month PFS goal of 50% was not reached.
- Adverse events in general were manageable and mainly related to gastrointestinal and liver toxicity
- After an initial 12 weeks of continuous duvelisib treatment, the incorporation of intermittent dosing appears to be a viable option for patients with previously treated CLL/SLL

References

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3. Flinn IW, Hillmen P, Montillo M, et al. The phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL. Blood. 2018;132(23):2446. Epub 2018 Oct 4.