Updated Results from a Phase I/II Study of Duvelisib and Venetoclax in Patients with Relapsed or Refractory (R/R) Chronic Lymphocytic Leukemia (CLL) or Richter's Syndrome (RS)

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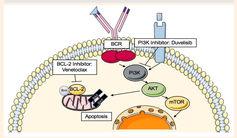
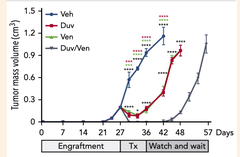
BACKGROUND

- **Venetoclax (VEN) plus rituximab is an effective regimen for R/R CLL/SLL, but includes 2 years of treatment and an infusional component** (Seymour et al., *N Engl J Med*., 2018)
- **Duvelisib (DUV) is an oral inhibitor of PI3K-δ/γ approved for R/R CLL/SLL after 2 prior therapies**
- **Preclinical data demonstrated PI3K inhibition enhances BCL2-dependency** (Davids et al., *Blood*, 2012; Patel et al., *Leukemia*, 2017)
- **DUV+VEN are synergistic in Richter's syndrome PDX models[1]**
- **We previously established the RP2D of VEN 400mg QD in combination with DUV 25mg BID, with promising initial safety and efficacy data** (Crombie et al., ASH 2020)

Mechanism of action of DUV + VEN



DUV + VEN achieves significant tumor reduction in RS-PDX models



[1]Iannello et al., *Blood*, 2021

Hypothesis

The combination of DUV + VEN will achieve deep remissions in patients with CLL/SLL and RS with high rates of undetectable MRD (uMRD) that will allow for an all-oral, time-limited therapy

METHODS

Phase I Study Endpoints

- Primary: DLTs, MTD, and RP2D for DUV + VEN
- Secondary: PKs of DUV + VEN

Phase II Study Endpoints

Primary:

- Best rate of CR of DUV + VEN at the MTD, as defined by iwCLL 2008 criteria and Lugano 2014 criteria for CLL/SLL and RS, respectively

Secondary:

- Clinical efficacy: Best ORR, DOR, PFS, OS
- Rates of undetectable peripheral blood (PB) and bone marrow (BM) MRD

Key Eligibility Criteria

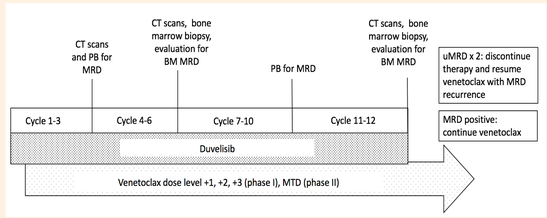
Inclusion

- Confirmed diagnosis of CLL/SLL requiring treatment per iwCLL 2008 criteria OR biopsy-confirmed RS
- Disease that has progressed or relapsed after at least 1 previous CLL/SLL therapy; no prior therapy required for RS cohort
- Age ≥ 18 years
- Hematologic criteria (unless marrow involvement): ANC ≥ 500 cells/mm^3, Platelets ≥ 25,000 cells/mm^3
- Adequate renal and hepatic function
- ECOG PS ≤ 2

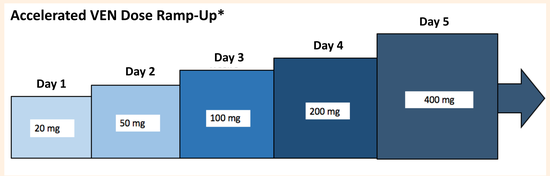
Exclusion

- CLL/SLL cohort only: previous treatment with VEN or DUV
- RS cohort only: VEN within 1 year of enrollment
- Currently active gastrointestinal disease, including colitis, inflammatory bowel disease, and diarrhea requiring therapy
- Confirmed CNS involvement
- Use of warfarin and other anticoagulants allowed

STUDY DESIGN



Accelerated VEN Dose Ramp-Up*



- **7-day lead-in of DUV 25mg BID; VEN started on day 8**
- **In Phase II: VEN started at 10mg (outpatient) or 20mg (inpatient) with weekly ramp-up to 400mg daily**
- ***Patients with RS could undergo accelerated daily VEN ramp-up to 400mg daily over 5 days**
- **Treatment continued for a maximum of 12 cycles of combination DUV + VEN with continuation determined by MRD status**
- **Assessments: toxicity by CTCAE v4.03, response by 2008 iwCLL criteria (for CLL/SLL) & Lugano 2014 criteria (for RS)**
- **MRD: 8-color flow cytometry (sensitivity 10^{-4}) in PB and BM; undetectable MRD considered < 0.01% CLL cell percentage**

RESULTS

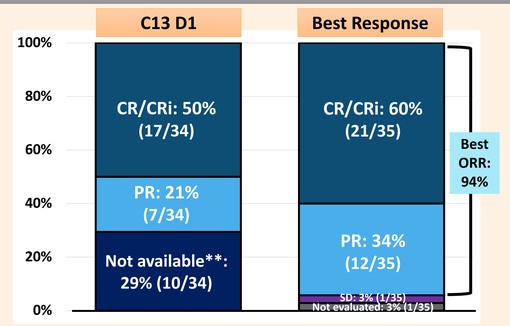
Baseline Patient Characteristics (n = 43 total)

Characteristic	CLL Cohort (n=35)	RS Cohort (n=8)
Median age (range, years)	69 (50-79)	64 (55-72)
Male	24 (68.6%)	6 (75.0%)
Rai Stage 3 or 4	15 (42.9%)	N/A
IGHV Status Unmutated	27 (77.1%)	3 (37.5%)
ZAP-70 Positive	21 (60.0%)	3 (37.5%)
FISH Cytogenetics		
17p deletion	10 (28.6%)	1 (12.5%)
11q deletion	4 (11.4%)	0
Trisomy 12	8 (22.9%)	2 (25.0%)
Complex karyotype (≥3 cytogenetic abnormalities)	11 (31.4%)	3 (27.5%)
TP53 Mutation	15 (42.9%)	2 (25.0%)
NOTCH1 Mutation	8 (22.9%)	2 (25.0%)
Median # of prior therapies (range)	2 (1-6)	2 (1-4)
Prior BTK inhibitor (all ibrutinib)	15 (42.9%)	3 (37.5%)

RESULTS

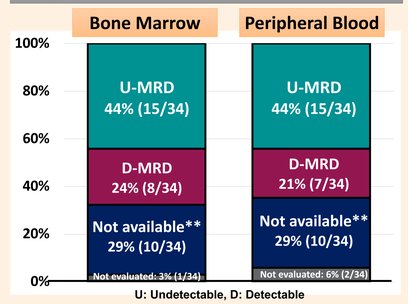
Efficacy

CLL/SLL Patients: Response by iwCLL Criteria

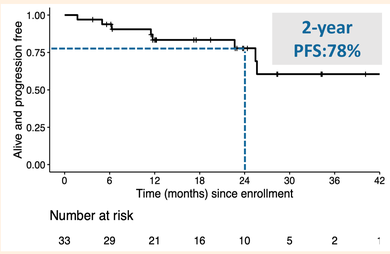


- **Median follow-up: 22.8 months (range 1.3 - 43.3)**
- **35% of patients** (12/34) **achieved a CR/CRi with BM uMRD after 12 cycles of DUV + VEN; n=11 electively discontinued therapy**
- **Best overall response rate (ORR): 94%** (33/35)
- **C13D1 ORR in patients with *TP53*-aberrant disease** (n=16)**: 50%** [CR: 44% (n=7), PR: 6% (n=1)]
- **C13D1 ORR in patients with prior BTKi** (n=15)**: 47%** [CR: 33% (n=5), PR: 13% (n=2)]
- ****Not available* - 10 patients discontinued treatment prior to C13 due to:** electively proceeding to allogeneic SCT (n=2), treatment-related toxicity (n=4), progressive disease (n=2), initiating treatment for pancreatic NET (n=1), death due to COVID-19 (n=1)

CLL/SLL Patients: C13D1 MRD Status



CLL/SLL Patients: Progression-Free Survival

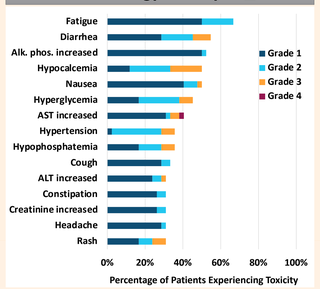


RS Patients: Clinical Outcomes

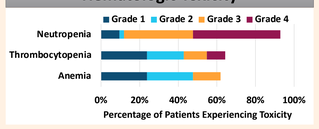
- **Best clinical responses: n=2 CR, n=2 SD, n=4 PD**
- **1 patient who achieved a CR successfully underwent consolidative allogeneic SCT**
- **5 patients now deceased with progressive disease**
- **2 patients who had electively discontinued therapy at C13 in CR BM-uMRD were found to have PB MRD-only disease recurrence at C25 restaging**
- **Both patients restarted venetoclax monotherapy and 1 has re-achieved PB-uMRD**

Safety Analysis

Non-Hematology Toxicity in ≥30%



Hematologic Toxicity



Notable AEs:

- **Febrile neutropenia: 7% Gr3/4 (26% of patients received growth factor support)**
- **Severe infections: 9% Gr3, n=1 Gr5 COVID-19 pneumonia**
- **3 cases of laboratory TLS**
- **1 patient with clinical TLS with AKI after the 20mg VEN dose during ramp-up; renal function fully resolved and patient resumed VEN monotherapy**
- **1 Gr4 gastric perforation while on high-dose steroids to manage diarrhea; subsequently discontinued study therapy**
- **1 Gr5 hepatic failure in the setting of biopsy-proven RS liver involvement**

CONCLUSIONS

- **DUV + VEN is active for patients with R/R CLL/SLL, including those with *TP53*-aberrant disease and those who have relapsed after BTKi**
- **Relatively high rates of CR, uMRD seen with this MRD-guided, time-limited, all-oral regimen**
- **DUV + VEN safety profile is manageable, and the most common AEs are cytopenias and Gr1/2 fatigue & diarrhea**
- **Further exploration of this regimen is warranted in R/R CLL and RS**

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