A Phase I Study of Duvelisib and Venetoclax in Patients with Relapsed or Refractory CLL/SLL

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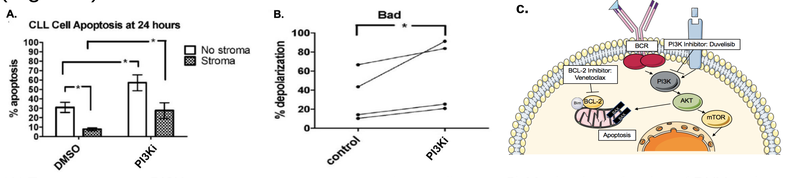
Background

Rationale

- Duvelisib (DUV), an oral inhibitor of PI3K-δ/γ, and venetoclax (VEN), an oral inhibitor of BCL-2, are approved for relapsed/refractory (R/R) CLL
- Duration of response to monotherapy is limited, especially for patients who have failed BTK inhibitors or have TP53 dysfunction
- PI3K inhibitors kill *ex vivo* CLL cells even in the presence of stroma and enhance cell dependence on the anti-apoptotic protein, BCL-2, for survival (Fig. A/B).



(A) Treatment with a PI3K inhibitor demonstrates an ability to kill *ex vivo* CLL cells from peripheral blood even in the presence of stroma. (B) PI3K inhibition restores higher levels of apoptotic priming in stroma-exposed CLL cells (Davids et al., *Blood*, 2012).

C) Mechanism of action of DUV and VEN.

- DUV plus VEN are synergistic in Richter's syndrome PDX model (Iannello et al., ASH Abstract #2862, 2019)
- We hypothesized that DUV plus VEN would lead to deep remissions with high rates of uMRD that allow for an all oral, time-limited therapy

Aims/Methods

Key Eligibility Criteria

Inclusion Criteria:

- Confirmed diagnosis of CLL or SLL requiring therapy, as per IW-CLL 2008 criteria
- Disease that has progressed during or relapsed after at least one previous CLL/SLL therapy
- Hematologic criteria (unless marrow involvement):
  - Absolute neutrophil count ≥500 cells/mm^3
  - Platelet count ≥25,000 cells/mm^3

Exclusion Criteria:

- Previous treatment with VEN or DUV
- Currently active gastrointestinal disease, including colitis, inflammatory bowel disease and diarrhea requiring therapy
- Confirmed CNS involvement
- Use of warfarin, other anticoagulants allowed

Endpoints

Primary Endpoint:

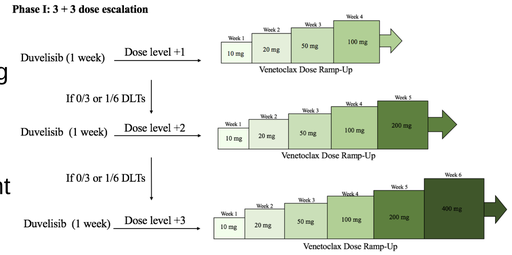
- MTD and RP2D for VEN when given in combination with DUV in R/R CLL/SLL

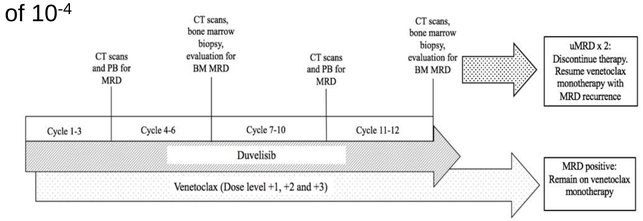
Secondary Endpoints:

- Pharmacokinetics (PK) of DUV and VEN
- Preliminary efficacy: ORR, CR rate, DOR, PFS, OS
- Rate of MRD negativity (uMRD) in the peripheral blood and bone marrow

Study Design

- 3+3 Design
- DUV 25 mg BID
- VEN added on day +8 starting at 10 mg
- VEN started at 20 mg in last three pts
- VEN ramp-up weekly inpatient to one of three dose levels (100 mg, 200 mg, 400 mg)
- MRD measured by at least 8-color flow cytometry with a sensitivity of 10^{-4}





Results

Patient Characteristics

Baseline Characteristics, n=12	
Median age (range)	69 (50-78)
Male/Female	75/25% (9/3)
Del(17p)	25% (3/12)
Del(13q)	67% (8/12)
Del(11q)	8% (1/12)
Trisomy 12	25% (3/12)
TP53 mutant	42% (5/12)
NOTCH1 mutant	58% (7/12)
Complex karyotype	50% (6/12)
IGHV-unmutated	100% (12/12)

Baseline Characteristics, n=12	
Median # of prior therapies (range)	3 (1-6)
Prior BTK inhibitor	83% (10/12)
Median WBC (range)	26 (4-97)
Median ANC (range)	3 (1.2-7.8)
Median HGB (range)	12 (7.6-15.4)
Median PLTs (range)	135 (21-221)
Median B2M (range)	3 (2.2-13.1)

Safety Analysis

- No DLTs observed
- SAEs (all grade 3): Asymptomatic elevation in amylase and/or lipase (n=2), febrile neutropenia (n=1), pneumonia (n=1)
- No laboratory or clinical TLS per Cairo-Bishop criteria, but VEN hold for one day in two patients (starting at 20 mg VEN) for rise in LDH (244 to 615 and 204 to 417) after initial VEN dose, which improved with IVFs
- DUV drug holds and/or dose reductions:
  - Seven patients: Diarrhea (n=5), asymptomatic elevation in amylase and/or lipase (n=3), allergic reaction (n=1), rash (n=1), pneumonia (n=1), gastritis (n=1). Seven patients were treated with steroids to manage presumed immune-mediated toxicity and were able to resume DUV therapy
- MTD and RP2D of VEN is 400 mg QD when given with 25 mg BID DUV

Hematologic Toxicity	Grade 1-2 (%)	Grade 3 (%)	Grade 4 (%)	Total %
Anemia	8 (67)	4 (33)	0	100
Neutropenia	2 (17)	5 (42)	5 (42)	100
Thrombocytopenia	8 (67)	0	1 (8)	75

- 9 patients required growth factor support

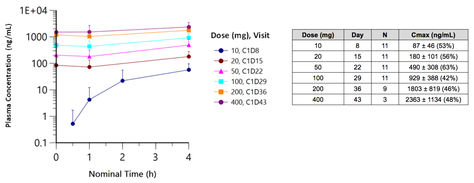
Non-Hematologic Toxicity	Grade 1-2 (%)	Grade 3 (%)	Total %
Hyperglycemia	10 (83)	2 (17)	100
Hypocalcemia	6 (50)	6 (50)	100
Fatigue	11 (92)	0 (0)	92
Hypophosphatemia	5 (42)	3 (25)	67
Elevated Alk Phos	7 (58)	0 (0)	58
Elevated AST	7 (58)	0 (0)	58

- No grade 4 non-hematologic toxicities observed

Non-Hematologic Toxicity	Grade 1-2 (%)	Grade 3 (%)	Total %
Hypoalbuminemia	6 (50)	0 (0)	50
Hypomagnesemia	6 (50)	0 (0)	50
Rash	5 (42)	1 (8)	50
Diarrhea	4 (33)	1 (8)	42
Hyponatremia	4 (33)	1 (8)	42

Pharmacokinetics

VEN plasma levels in patients dosed with DUV 25 mg BID

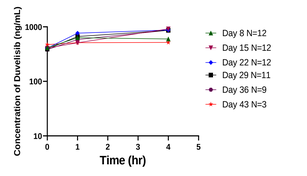


Dose (mg)	Day	N	Cmax (ng/mL)
10	8	11	87 ± 46 (53%)
20	15	11	180 ± 101 (56%)
50	22	11	490 ± 308 (63%)
100	29	11	929 ± 388 (42%)
200	36	9	1803 ± 819 (46%)
400	43	3	2363 ± 1134 (48%)

Concentration data on days 15 to 43 (doses of 20 to 400 mg) were based on samples taken at 0 (pre-dose), 1 and 4 h

- VEN plasma levels increased with dose as expected
- PK of VEN up to 400 mg QD co-administered with 25 mg BID DUV were similar to the PK of VEN given alone (*Salem et al., J. Clin. Pharmacol., 2017)*

DUV plasma levels in patients dosed with VEN



- DUV PK is similar on Days 8, 15, 22, 29, 36 and 43 when co-administered with doses of 10, 20, 50,100, 200, and 400 mg VEN daily
- 25 mg BID DUV PK consistent with PK observed in the phase I trial of DUV in patients with advanced hematological malignancies (Flinn et al. *Blood*. 2018)

Efficacy

	Patient	Age	Prior BTK inhibitor	# Prior Therapies	*IGHV* Mutational Status	FISH	Cytogenetics	Best Response	MRD Blood	MRD Marrow
Dose Level +1 (100 mg VEN)	1	50	Yes	6	Unmutated	Del17p Del13q	Complex	PR	Detectable	Detectable
	2	66	Yes	2	Unmutated	Del17p Del13q	Complex	Stable	Undetectable	Undetectable
	3	76	Yes	3	Unmutated	Del13q Trisomy 12	Complex	PR	Detectable	Detectable
Dose Level +2 (200 mg VEN)	4	61	No	3	Unmutated	Del13q	Not Complex	PR	Detectable	Detectable
	5	70	Yes	3	Unmutated	Del13q Trisomy 12	Not Complex	CR	Undetectable	Undetectable
	6	72	Yes	1	Unmutated	Trisomy 12	Not Complex	CR	Undetectable	Undetectable
Dose Level +3 (400 mg VEN)	7	66	Yes	3	Unmutated	Del17p Del13q	Complex	CR	Detectable	Detectable
	8	53	Yes	1	Unmutated	None	Not Complex	PR	Detectable	Detectable
	9	74	Yes	3	Unmutated	Del6q	Not Complex	CRi	Undetectable	Undetectable
	10	78	Yes	2	Unmutated	Del17p Del13q	Complex	PR (CR by CT)	Detectable	N/A
	11	69	Yes	3	Unmutated	Del13q Del6q	Complex	PR (CR by CT)	Detectable	N/A
	12	75	No	1	Unmutated	Del11q	Not Complex	PR	Detectable	N/A

Best Response to Date:

- ORR: 92% (11/12)
- CR/CRi: 33% (4/12)
- uMRD Blood: 33% (4/12)
- uMRD Marrow: 33% (4/12)
- To date, 3/12 pts completed 4 cycles, 7/12 completed 7 cycles and 2/12 completed 12 cycles

- Median # of cycles (range): 7 (6-13)
- Patient with SD with minimal nodal disease achieved uMRD in blood and bone marrow and elected to proceed to alloSCT
- Two patients have completed 12 cycles of combination therapy, one discontinued all therapy (CR, uMRD) and one is continuing VEN monotherapy (PR, detectable MRD)

Conclusions

- DUV plus VEN is promising in pts with R/R CLL/SLL, with no DLTs observed
- RP2D of VEN is 400 mg QD in combination with DUV 25 mg BID
- No significant drug drug interaction was observed
- Although neutropenia was common, febrile neutropenia and other infections were rare
- Early efficacy data for this 1-year, time-limited, all oral regimen are encouraging, with CRs and uMRD already observed despite short follow-up
- A phase II portion of the trial is now accruing for R/R CLL/SLL and includes a separate cohort for Richter's syndrome

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