Long term Results of a Phase I/Ib Study of Ibrutinib in Combination with Umbralisib in Patients with Relapsed/Refractory CLL or MCL

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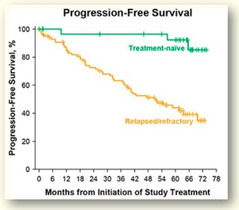
Leukemia & Lymphoma Society | Blood Cancer Research Partnership (LLS/BCRP)

EHA Abstract: EP689

Background

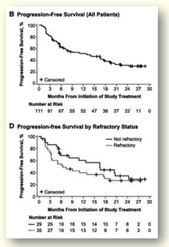
Ibrutinib is highly active in R/R CLL and MCL

CLL



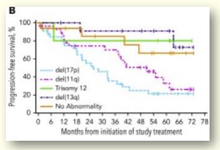
O'Brien et al., *Blood*, 2018

MCL

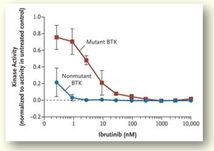


Wang et al., *Blood*, 2015

High risk subgroups have less durable response, and resistance mutations have been observed with ibrutinib monotherapy



O'Brien et al., *Blood*, 2018

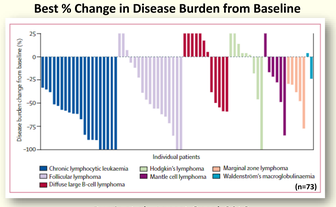


Woyach et al., *N Engl J Med*, 2014

Umbralisib is a potent, well-tolerated next-generation PI3Kδ inhibitor

Efficacy

Best % Change in Disease Burden from Baseline



Burris et al., *Lancet Oncol*, 2018

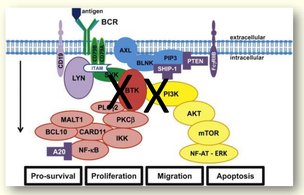
Safety

An integrated safety analysis (N = 347) demonstrated immune-mediated AEs were infrequent after a median duration of 6.5 months of exposure, and were generally mild to moderate in severity:

- transaminitis(9%; Gr 3/4 2%)
- colitis (<1.5%; Gr 3/4 <1%)
- pneumonitis (<1.5%; Gr 3/4 <0.5%)

Davids et al, EHA 2018

Targeting two BCR pathway kinases may help overcome resistance



Niemann et al., *Seminars in Cancer Biology*, 2013

Umbralisib + Ibrutinib is a well-tolerated and active combination

- We previously published the initial results of this investigator-initiated, multicenter study of ibrutinib in combination with umbralisib in R/R CLL and MCL (NCT02268851) (Davids et al., *Lancet Haem*, 2019)
- The combination was well-tolerated and active, but follow-up at that time was relatively short, at just over 2 years
- Here, we assess the long term safety and efficacy of ibrutinib given in combination with umbralisib in patients (pts) with R/R CLL and MCL

Methods

Study Endpoints

Primary

- Maximum tolerated dose (MTD) of umbralisib when used in combination with ibrutinib in patients with relapsed or refractory CLL or MCL
- Safety and dose limiting toxicities (DLTs) of umbralisib in combination with ibrutinib in patients with relapsed or refractory CLL or MCL

Secondary

- Clinical efficacy: ORR, CR, PR, PR-L, PFS, and remission duration
- Association of CLL prognostic factors (e.g. FISH, *IGHV*, etc.) with response

Key Eligibility Criteria

Inclusion

- CLL/SLL or MCL progressed after at least 1 prior standard therapy, an indication for therapy, and at least 1 measurable site of disease
- ECOG PS ≤2
- Adequate hematologic and organ function
- In Ph I portion, patients with prior BTK or PI3Ki therapy were eligible

Exclusion

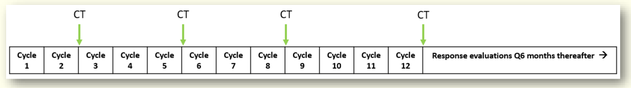
- AutoHCT within 3 mo. or alloHCT within 12 mo. of study entry
- Post-allo patients must not have active GVHD and be off immune suppression
- Active hepatitis, HIV infection, or central nervous system involvement
- Patients who require warfarin for anticoagulation

Study Design

- Patients received continuous simultaneous daily oral dosing of ibrutinib (420 mg CLL, 560 mg MCL) and umbralisib starting in an initial cohort at 400 mg daily and escalating in a standard 3 + 3 design to 600 and 800 mg cohorts

Dose Level	Umbralisib Dose	Ibrutinib Dose CLL	Ibrutinib Dose MCL
1	400 mg daily	420 mg daily	560 mg daily
2	600 mg daily	420 mg daily	560 mg daily
3	800 mg daily	420 mg daily	560 mg daily
If > 2 DLTs in Cohort 1, 3- 6 pts enroll in Cohort -1 as follows:			
-1	200 mg	420 mg	560 mg
If > 2 DLTs in Cohort –1, study will be terminated			

- Patients continue both drugs until progression or unacceptable toxicity
- Response evaluations: after cycles 2, 5, 8, 12, and Q6 months thereafter
- Imaging with CT scans for CLL patients and PET/CT for MCL patients



Statistical Design

- Phase I with a standard 3 + 3 design with up to 4 dose levels of umbralisib
- Separate phase 1 dose-escalation cohorts for CLL and MCL, with umbralisib dose escalated independently
- 91% probability of dose escalation if the true rate of DLT is 10% and 17% probability of escalation if the true DLT rate is 50%
- Phase Ib expansion cohorts of 12 pts each in CLL and MCL
- Estimation of toxicity rates in 12 pt cohorts: 90% CI will be within +/- 25%
- Toxicity analyses: CTCAE v4
- Efficacy analyses: CLL: 2008 iwCLL criteria, MCL: 2014 Lugano criteria with PET

Results

Patient Characteristics (N = 42)

	Mantle cell lymphoma (n=21)	Chronic lymphocytic leukaemia (n=21)	Total (n=42)
Median age, years (range)	68 (50-83)	67 (48-85)	68 (48-85)
Sex			
Men	16 (76%)	12 (57%)	28 (67%)
Women	5 (24%)	9 (43%)	14 (33%)
ECOG performance status			
0	11 (52%)	7 (33%)	18 (43%)
1	9 (43%)	14 (67%)	23 (55%)
2	1 (5%)	0	1 (2%)
Median number of previous therapies (IQR)	2 (2-3)	1 (1-2)	2 (1-3)
1	3 (14%)	11 (52%)	14 (33%)
2	7 (33%)	5 (24%)	12 (29%)
3 or more	9 (43%)	4 (19%)	13 (31%)
Previous autologous stem cell transplantation	6 (29%)	0	4/42 (10%)
Previous ibrutinib treatment	2 (10%)	2 (10%)	4/42 (10%)
Previous PI3Ki treatment	0	4 (19%)	4/42 (10%)
Median white blood cell count, K/uL (IQR)	5·2 (4·1–8·3)	28·4 (13·2–73·6)	9·6 (4·7–29·9)
Median haemoglobin concentration, g/dL (IQR)	13 (10·7–13·5)	11·1 (10·2–12·3)	11·7 (10·2–13·3)
Median platelet count, K/uL (IQR)	140 (88–205)	175 (97–220)	155 (88–220)
Median β-2 microglobulin concentration, mg/L (IQR)	3·1 (2·5–4·3)	4·3 (3·5–5·2)	4·0 (2·8–4·8)
Median Ki-67% (IQR)	40% (20–50)	NA	NA
Del(17p)	1/19 (5%)	4/20 (20%)	5/39 (13%)
Del(11q)	NA	7/19 (37%)	
Unmutated *IGHV*	NA	13/19 (68%)	
TP53 mutation	NA	4/21 (19%)	
NOTCH1 mutation	NA	2/21 (10%)	

(Adapted from Davids et al., *Lancet Haem*, 2019)

Safety Analysis

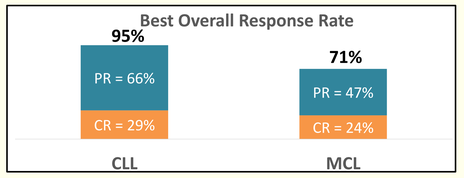
- As of this updated data cut on 8 Feb 2020:
  Median follow-up among survivors is now 43.5 months (range 8.4-61)
- As previously reported, the recommended phase 2 dose of umbralisib was 800 mg daily when given with standard dose ibrutinib
- All-grade adverse events occurring in >25% of patients, and Grade 3-4 AEs in all patients are presented in the table below:

Adverse Events	All grades (N = 42)	Grade 3/4 (N = 42)
Diarrhea, N (%)	22 (52%)	4 (10%)
Infection, N (%)	21 (50%)	7 (17%)
Nausea, N (%)	18 (43%)	1 (2%)
Neutropenia, N (%)	17 (40%)	5 (12%)
Thrombocytopenia, N (%)	16 (38%)	2 (5%)
Fatigue, N (%)	16 (38%)	2 (5%)
Transaminitis, N (%)	16 (38%)	1 (2%)
Anemia, N (%)	13 (31%)	2 (5%)
Hyperglycemia, N (%)	12 (29%)	1 (2%)

- No cumulative or recurrent late onset toxicities observed, including no new episodes of atrial fibrillation (rate still 10%) and no Gr 3/4 bleeding events
- Only 1 additional patient developed hypertension (updated rate 14%)
- The rate of transaminitis rose from 24% to 38%, but all of these were Gr1 events, with the exception of the previously reported single Gr3 event
- No other new immune-mediated toxicities arose, with a cumulative rate of Gr3 diarrhea of 10% and no colitis or Gr4 diarrhea
- Two additional SAEs occurred: a patient with a Gr2 gastrlc ulcer admitted and medically managed, and a patient with prior FCR, in radiographic CR on this study and diagnosed with Gr4 MDS about 3 years into this study
- 12 patients remain on both drugs, 2 remain on umbralisib only
- 10 patients discontinued due to PD, 7 due to AEs, 5 due to pt/physician decision, 4 due to death (2 PD, 1 AE, 1 in CR put on hospice due to progressive dementia), and 2 due to intercurrent illness

Efficacy Analysis

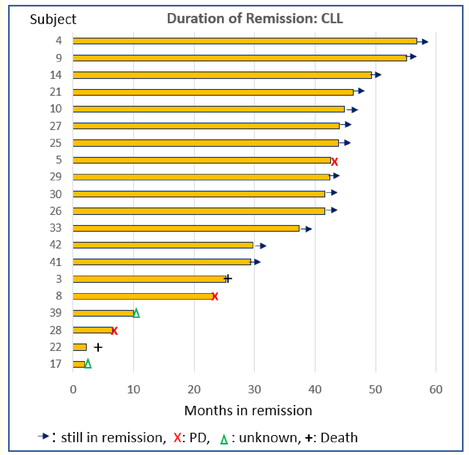
- Best ORR in CLL and MCL rose to 95% and 71%, respectively
- The best CR rate for CLL remained 29%, and rose in MCL to 24%

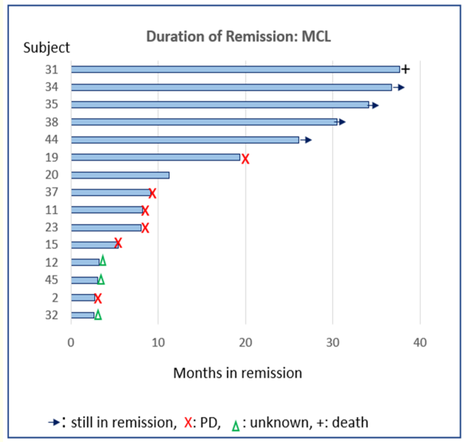


- Radiographic CR rate in CLL was 43% (2 of these pts did not have a confirmatory marrow, 1 had low-level residual marrow disease)

Efficacy (cont.)

- Duration of remission by histology is depicted in the figures below





- Median DOR in CLL has still not been reached, and for MCL it is 19.4 months
- In CLL, median PFS and OS have not been reached
- 4 yr PFS and OS in CLL are estimated to be 78% and 90%, respectively, and did not differ based on IGHV mutation status
- In MCL, the updated median PFS and OS are 10.8 and 30.7 mo., respectively

Conclusions

- With long term follow-up, ibrutinib plus umbralisib continues to demonstrate good tolerability, with the convenience of an all oral regimen
- In R/R MCL, efficacy is similar as would be expected for ibrutinib alone
- In R/R CLL, the 4-year PFS and OS of 78% and 90%, respectively, are promising in light of historical results with ibrutinib alone
- This approach warrants further study, particularly in BTKi-naïve CLL patients, including those with either intolerance to or progression on a venetoclax-based regimen

Acknowledgements:

- This investigator-sponsored trial was supported by TG Therapeutics (New York, USA) and a Leukemia & Lymphoma Society (LLS) BCRP/TAP grant
- COI: Drs. Davids and Brown: SAB/consulting fees from Pharmacyclics, Inc. and Janssen, Dr. Davids: SAB and additional institutional research funding from TG Therapeutics; Sportelli and Miskin: Employees of TG Therapeutics. All other authors have no relevant disclosures.
- Dr. Davids is supported by a Scholar in Clinical Research Award through LLS, and is a graduate of the ASH CRTI and ASCO/AACR Vail Workshop
- The authors thank the patients and their families for participating

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