NEWEVIDENCE

Preliminary results of a phase II, open-label study of venetoclax monotherapy in patients with CLL relapsed after or refractory to ibrutinib or idelalisib therapy

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Background

- Prognosis is quite poor for patients with CLL who relapse after or become refractory to treatment with BCR signalling antagonists, such as ibrutinib or idelalisib
    - Median overall survival after ibrutinib discontinuation ranges from 3 to 18 months following Richter's transformation[1,2] or CLL[2]
- Venetoclax is a potent, orally bioavailable agent with a mechanism of action independent of the BCR pathway, and with substantial activity in patients with heavily pre-treated CLL[3]
- This was a phase II, open-label, two-arm study that evaluated venetoclax monotherapy in patients with CLL relapsed after or refractory to ibrutinib or idelalisib (NCT02141282)
- The objectives were to evaluate the investigator-assessed ORR and to assess safety

1. Jain P, et al. Blood 2015;125:2062–7.
2. Maddocks KJ, et al. JAMA Oncol 2015;1:80–7.
3. Roberts AW, et al. N Engl J Med 2016;374:311–22.

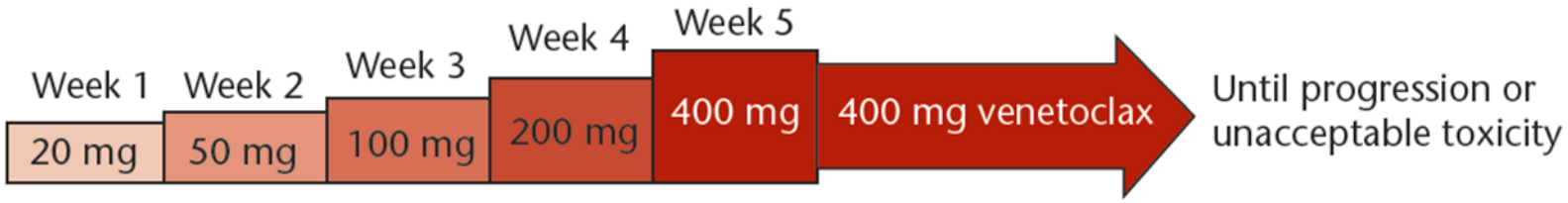
BCR = B-cell receptor; CLL = chronic lymphocytic leukemia; ORR = overall response rate

Study Design

- Inclusion criteria:
  - Progressive disease during treatment with or after discontinuation of ibrutinib or idelalisib
  - ECOG performance score ≤2
- Exclusion criteria:
  - PET scan and biopsy-confirmed Richter's transformation
  - Active and uncontrolled autoimmune cytopenias
  - Unresolved toxicities from prior therapy
  - Allogeneic stem cell transplant within one year of study entry
- Assessments:
  - Disease assessment was performed using modified iwCLL criteria at Weeks 8 and 24, and then every 12 weeks thereafter for up to one year
  - AEs were monitored throughout the study

AE = adverse event; ECOG = Eastern Cooperative Oncology Group; iwCLL = International Workshop on Chronic Lymphocytic Leukemia; PET = positron emission tomography

Venetoclax Dosing Schedule



- All patients had tumour burden assessment by imaging for nodal size and absolute lymphocyte count at enrolment, and received prophylaxis for TLS with uric acid reducers and hydration
- Patients with high tumour burden were hospitalized prior to dosing to facilitate TLS prophylaxis
- Laboratory values were monitored for evidence of tumour lysis for at least 24 hours after the first dose at each dose level

TLS = tumour lysis syndrome

Baseline Characteristics

		Ibrutinib (n = 41)	Idelalisib (n = 13)
Median age, years (range)		67 (48–80)	69 (56–75)
Male, n (%)		31 (76)	9 (69)
Prior therapies	Median (range) 1–4, n (%) ≥5, n (%)	5 (1–12)* 19 (46) 22 (54)	3 (1 – 9)† 6 (46) 7 (54)
Prior ibrutinib, n (%) **Median time on ibrutinib, months (range)**		41 (100) 16 (1–56)	3 (23) 5 (2–10)
Prior idelalisib, n (%) **Median time on idelalisib, months (range)**		3 (7) 10 (2–31)	13 (100) 10 (1–27)
Intolerant to prior ibrutinib/idelalisib, n (%)		11 (27)	6 (38)

As of August 25, 2015
* Two patients received only frontline ibrutinib.
† Two patients received only frontline idelalisib.

Disease Burden and Biologic Characteristics

Disease burden at study entry, n (%)		Ibrutinib (n = 41)	Idelalisib (n = 13)
ALC	≥25 x 10^9/L ≥100 x 10^9/L	16 (39) 7 (17)	5 (39) 4 (31)
Bulky disease	One or more nodes >5 cm One or more nodes >10 cm	14 (34) 8 (20)	7 (54) 5 (39)
Prognostic factors*, n/N (%)			
Unmutated IGHV		24/28 (86)	6/8 (75)
Del(17)(p13.1)		19/39 (46)	0/13 (0)
Del(11)(q22.3)		12/41 (29)	3/13 (23)
TP53 mutation		14/39 (36)	0/12 (0)†
CD38 positive		20/40 (50)	7/12 (58)
ZAP-70 positive		11/22 (50)	3/9 (33)

As of August 25, 2015
* Site-reported data.
† n = 1 was indeterminate.

ALC = absolute lymphocyte count; CD = cluster of differentiation; del(11)(q22.3) = deletion of 11q22.3; del(17)(p13.1) = deletion of 17p13.1; IGHV = immunoglobulin heavy chain variant; TP53 = tumour protein 53; ZAP = zeta-chain-associated protein kinase

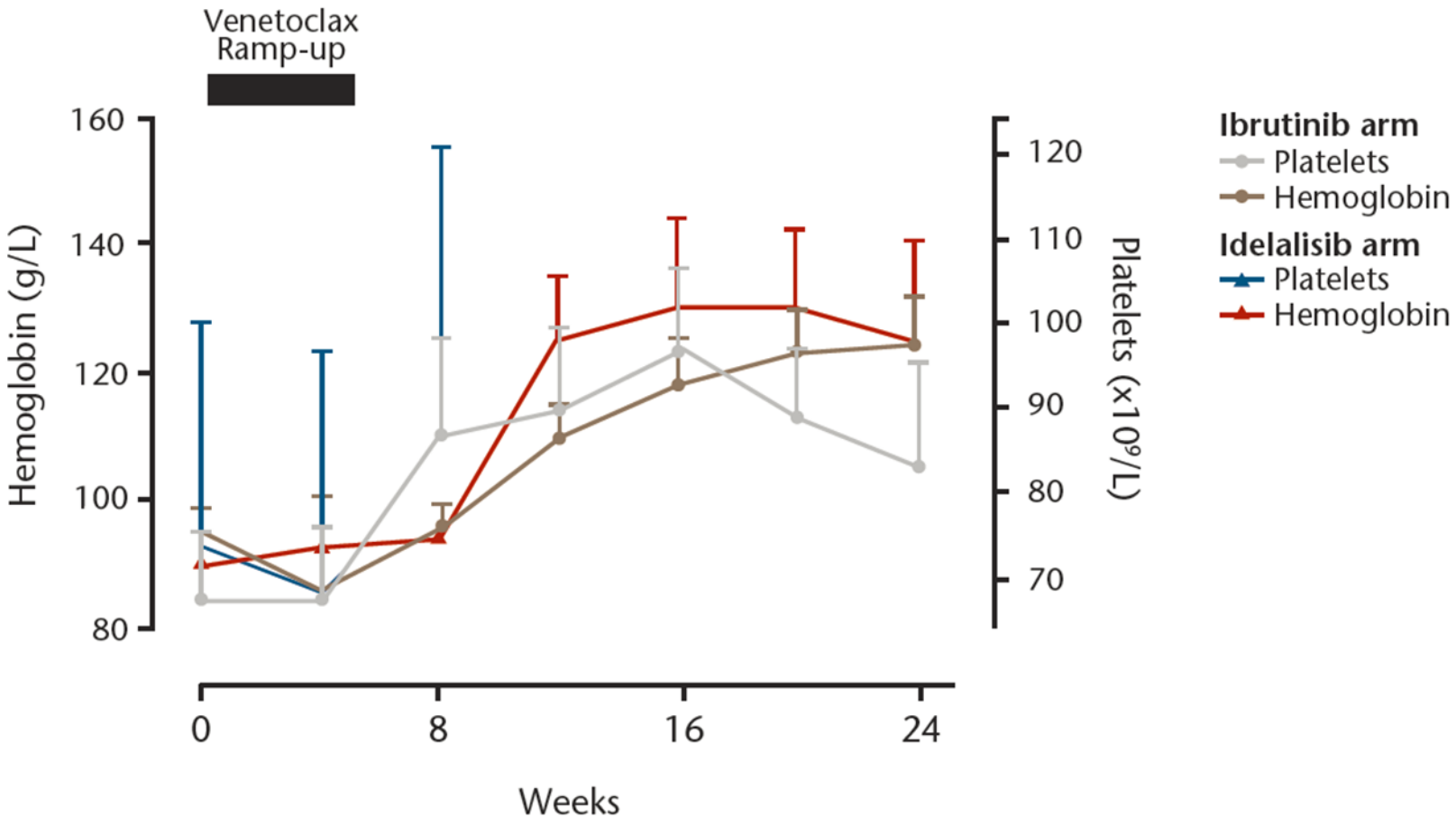
Current Status

	Ibrutinib (n = 41)	Idelalisib (n = 13)
Median time on venetoclax, weeks (range)	19 (0.5–39)	10 (0.1–29)
Active, n (%)	33 (80)	11 (85)
Discontinued venetoclax, n (%)	8 (20)	2 (15)
PD, n	4*	1
AE, n	2†	0
Withdrew consent, n	1	0
Death, unknown cause, n	1	0
Non-response, n	0	1‡

* One Richter's Transformation at Week 30 and one CLL progression at Week 32, both after achieving a PR at Week 24.
† AEs of multi-organ failure and respiratory failure, not related to progression.
‡ After stable disease at Week 24.

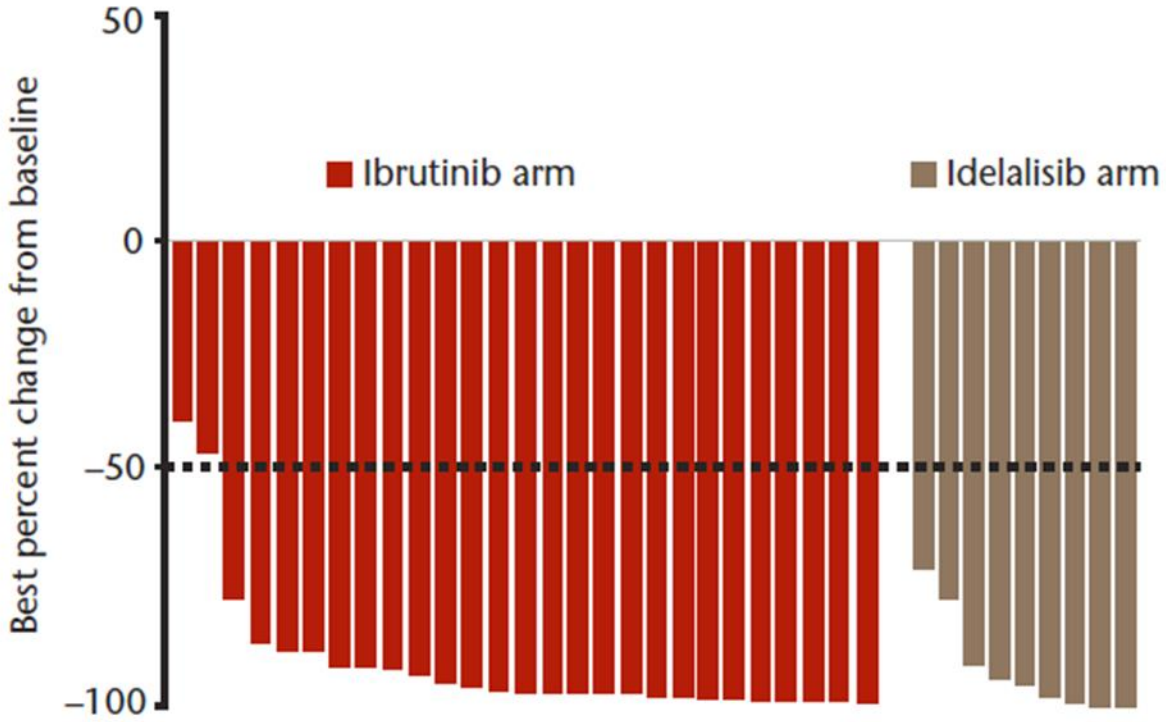
AE = adverse event; CLL = chronic lymphocytic leukemia; PD = disease progression; PR = partial response

Resolution of B Symptoms



- The majority of patients had resolution of B symptoms at Week 8

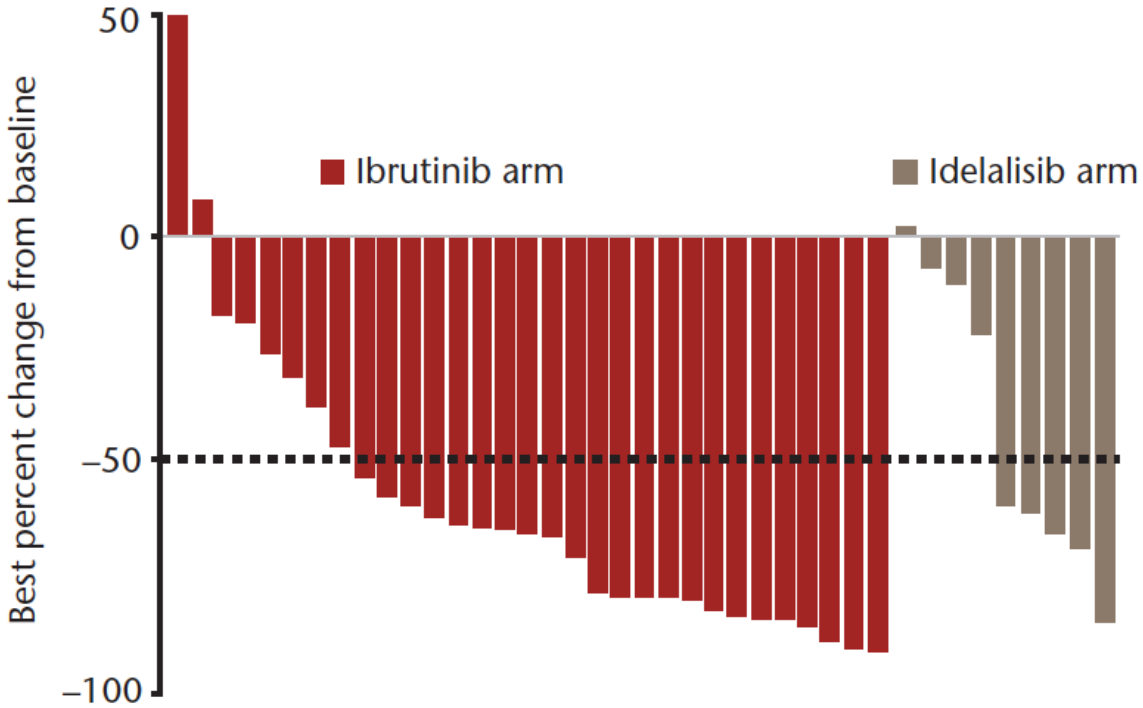
Best Percent Change from Baseline in ALC



	Ibrutinib arm (n = 41)	Idelalisib arm (n = 13)
Baseline lymphocytosis, n (%)	27 (66)	9 (69)
Achieved ALC normalization, n/N (%)	22/27 (81)	7/9 (78)
Median time to ALC normalization, days (range)	16 (3–107)	29 (4–49)

ALC = absolute lymphocyte count

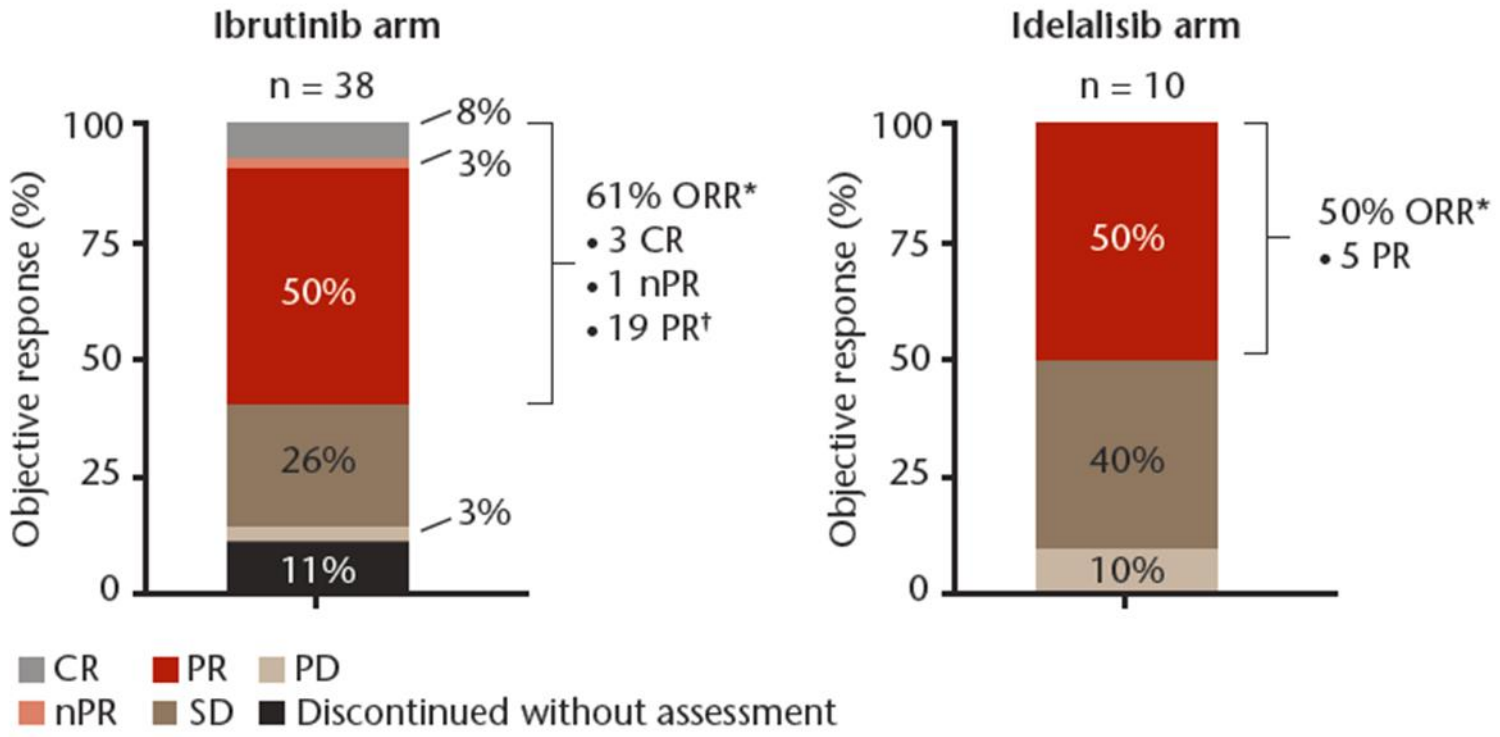
Best Percent Change from Baseline in Nodal Mass



	Ibrutinib arm (n = 41)	Idelalisib arm (n = 13)
Assessed, post baseline CT or MRI scans, n (%)	31 (76)	9 (69)
Achieved ≥50% reduction in nodal masses, n/N (%)	23/31 (74)	5/9 (56)
Median time to ≥50% reduction in nodal masses, days (range)	50 (44–162)	50 (49–52)

CT = computed tomography; MRI = magnetic resonance imaging

Best Objective Responses to Date (Up to Week 36)



CLL = chronic lymphocytic leukemia; CR = complete response; nPR = nodal partial response; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease

** Patients who have not reached assessment were not included in best objective response rate calculation.*
† Two patients subsequently progressed after achieving a PR at Week 24: one Richter's Transformation at Week 30 and one CLL progression at Week 32.

Adverse Events

All grade AEs in ≥20% of patients, n (%)	Total (N = 54)	Grade 3/4 AEs in ≥10% of patients, n (%)	Total N = 54
Any AE	51 (94)	**Any grade 3/4 AE**	34 (63)
Neutropenia	27 (50)	**Neutropenia***	21 (39)
Nausea	18 (33)	**Anemia**	10 (19)
Diarrhea	17 (32)	**Thrombocytopenia**	13 (24)
Anemia	15 (28)	**White blood cell count decreased**	7 (13)
Fatigue	12 (22)		

- Two patients (4%) had laboratory TLS without clinical sequelae
- Seventeen patients (31%) had neutropenia of any grade prior to study drug administration

As of August 25, 2015.
* 7/21 (33%) had grade 3/4 neutropenia prior to study drug administration.

AE = adverse event; TLS = tumour lysis syndrome

Serious Adverse Events

Serious adverse events in ≥2 patients, n (%)	Total (N = 54)
Any SAE	22 (41)
Febrile neutropenia	4 (7)
Pneumonia	4 (7)
Blood potassium increased	2 (4)
Multi-organ failure	2 (4)
Septic shock	2 (4)

- There were four deaths on study (one each from respiratory failure, multi-organ failure, PD, and death from unknown cause)

As of August 25, 2015.

PD = disease progression; SAE = serious adverse event

Summary and Conclusion

- Venetoclax was the first agent to demonstrate activity in a phase II trial in patients with R/R CLL who were previously treated with BCR signalling antagonists
- Venetoclax monotherapy demonstrated an ORR of 61% in the ibrutinib arm and 50% in the idelalisib arm
  - Early responses were observed at eight weeks, three weeks after reaching the target 400-mg daily dose; responses were confirmed at 24 weeks
  - Responses were similar in patients who had discontinued BCR inhibitors for refractory disease versus intolerance
  - Continued treatment and extended follow-up will be required to fully determine response rates and durability of response
- Venetoclax exhibited a tolerable safety profile
  - Incidence of laboratory TLS was low and was managed effectively
  - Neutropenia was managed effectively per standard of care

BCR = B-cell receptor; CLL = chronic lymphocytic leukemia; ORR = overall response rate; R/R = relapsed/refractory; TLS = tumour lysis syndrome