Safety and Efficacy of the BCL Inhibitors Venetoclax and Navitoclax in Combination with Chemotherapy in Patients with Relapsed/Refractory Acute Lymphoblastic Leukemia and Lymphoblastic Lymphoma

AMLxxx

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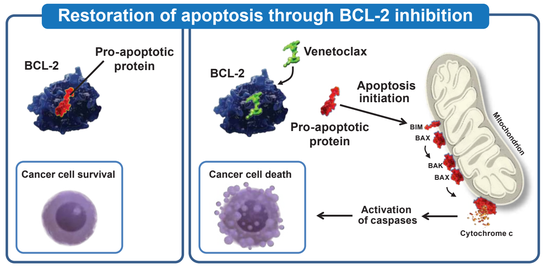
INTRODUCTION

- Despite intensive chemotherapy and novel therapeutic approaches, patients with R/R acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LL) have a poor prognosis[1-4]
- Venetoclax is a highly selective BCL-2 inhibitor (**Figure 1**),[5] and navitoclax is a BCL-2, BCL-X_L, and BCL-W inhibitor[5]
- Preclinical studies have demonstrated venetoclax and navitoclax each have anti-tumor activity as monotherapies in ALL cell lines and xenograft models.[6-8] The combination of BCL-2 and BCL-X_L inhibitors has been shown to result in synergistic antitumor activity in ALL xenografts[9]
- Addition of venetoclax to low-dose navitoclax might mitigate the DLTs previously observed with standard doses of navitoclax monotherapy[10]

Figure 1. Venetoclax Mechanism of Action



BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins.

Venetoclax binds selectively to BCL-2, freeing pro-apoptotic proteins that initiate programmed cell death (apoptosis).

OBJECTIVE

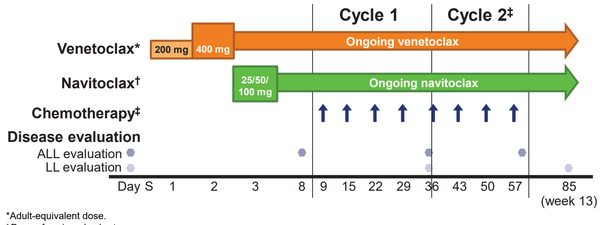
- To investigate efficacy and safety of venetoclax in combination with navitoclax and chemotherapy in patients with R/R ALL and LL

METHODS

STUDY DESIGN

- Phase 1, open-label, multicenter, dose-escalation trial enrolling patients (≥4 yrs) with R/R ALL or LL (NCT03181126; **Figure 2**)
- Venetoclax was administered orally on a daily basis, starting with a 200 mg weight-adjusted equivalent on day 1, and 400 mg equivalent thereafter
- Navitoclax was administered orally on day 3 onwards, with up to 3 dose levels for patients ≥45 kg (25, 50, 100 mg) and up to 2 dose levels for patients <45 kg (25, 50 mg)
- From day 9 onwards, patients could also receive chemotherapy comprising:
  - Peg-asparaginase: 1,250 IU/m^2 intravenous (IV) (maximum: 3,750 IU) on days 9 and 22
  - Vincristine: 1.5 mg/m^2 IV (maximum: 2 mg) on days 9, 15, 22, and 29
  - Dexamethasone: 20 mg/m^2/day orally or IV equivalent on days 9–13 and 22–26

Figure 2. Study Design



*Adult-equivalent dose.
†Dose of assigned cohort.
‡Chemotherapy may be delayed, not administered, or repeated for a second cycle.
S, screening.

METHODS (CONTINUED)

Table 1. Enrollment Criteria

Key Inclusion Criteria	Key Exclusion Criteria
▪ Measurable disease (ALL), radiographic evidence of disease (LL) ▪ Age ≥4 years ▪ Weight ≥20 kg ▪ Adequate organ function ▪ Adequate performance status: – Patients ≤16 years: Lansky ≥50 – Patients >16 years: Karnofsky ≥50 or ECOG <3 ▪ Ability to swallow pills	▪ Overt CNS disease ▪ <100 days post-transplant, or >100 days post-transplant with active GVHD, or post-transplant immunosuppressant therapy <7 days prior to first dose ▪ Received any of the following prior to first dose: – A biologic agent, CAR T infusion, or inotuzumab within 30 days – Any anti-cancer therapy including blinatumomab, chemotherapy, RT, targeted small molecule agents, or investigational agents within 14 days, or 5 half-lives, whichever is shorter – Steroid therapy within 5 days – Ongoing hydroxyurea (permitted up to the first dose)

CAR, chimeric antigen receptor; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; GVHD, graft-versus-host disease; RT, radiation therapy.

RESULTS

PATIENT CHARACTERISTICS

Table 1. Patient Baseline Characteristics and Demographics

	Patient								
	A	B	C	D	E	F	G	H	I
ALL Immuno-phenotype	Pre-B-ALL	Pre-B-ALL	Pre-B-ALL	Pre-B-ALL	Pre-B-ALL	T-ALL: ETP	T-ALL: ETP	T-ALL: medullary	T-ALL: medullary
Age, yrs	45	19	25	22	31	29	36	25	43
Sex	M	F	M	F	M	M	M	M	M
No. prior ALL therapies	6	4	3	2	1	8	3	1	3
Prior stem cell transplant	Y	N	Y	N	N	N	N	N	N

ALL, acute lymphoblastic leukemia; ETP, early T cell precursor; F, female; M, male.

- Nine adult patients (5 with B-cell ALL and 4 with T-cell ALL) have been enrolled as of the data cutoff of June 1, 2018 (**Table 1**)
- All patients treated have received 400 mg QD venetoclax and 25 mg QD navitoclax (Dose Level 1). Chemotherapy was started on day 9 for 7 patients; patient A began chemotherapy on day 169 and patient H began on day 10

SAFETY

Table 2. Adverse Events by Grade

Adverse Event*, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Total Events	Related to Ven and/or Nav
Muscle spasms	4 (44)	–	–	–	4 (44)	1/4 (25)
Nausea	2 (22)	–	1 (11)	–	3 (33)	2/3 (67)
Vomiting	2 (22)	–	1 (11)	–	3 (33)	1/3 (33)
Pain	–	1 (11)	2 (22)	–	3 (33)	0/3 (0)
Myalgia	3 (33)	–	–	–	3 (33)	1/3 (33)
Back pain	–	1 (11)	2 (22)	–	3 (33)	0/3 (0)

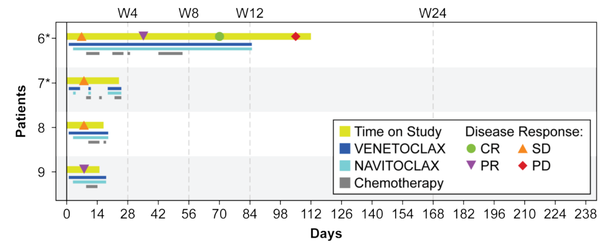
Ven, venetoclax; Nav, navitoclax.
*Occurring in more than 3 patients.

- Most AEs were grade 1 or 2, and the most common grade 3/4 AEs were pain and back pain (n=2 each; **Table 2**)
- There was one dose limiting toxicity (DLT) of delayed count recovery
- The most common AEs leading to treatment interruption were nausea and vomiting
- One serious AE of febrile neutropenia was possibly related to venetoclax plus navitoclax
  - Other serious AEs included nausea (n=2), vomiting (n=2), febrile neutropenia (n=2), upper abdominal pain (n=1), pseudomonal sepsis (n=1), somnolence (n=1), septic shock (n=1), acute pancreatitis (n=1), and pulmonary embolism (n=1)
- Two patients experienced grade 4 leukopenia
- Two deaths have been reported to date: 1 due to disease progression and 1 due to an AE not related to study drug (event was associated with not wearing a LifeVest personal defibrillator)

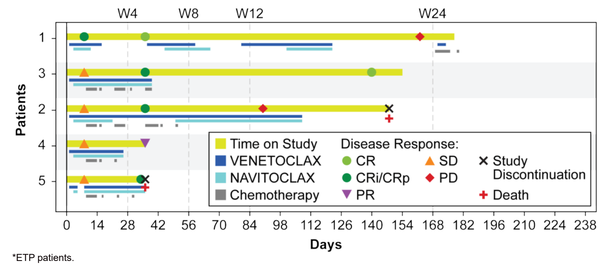
RESULTS (CONTINUED)

Figure 3. Efficacy in Patients with T-ALL (A) and pre-B ALL (B)

A. Efficacy Summary: T-ALL (n=4)



B. Efficacy Summary: Pre-B ALL (n=5)



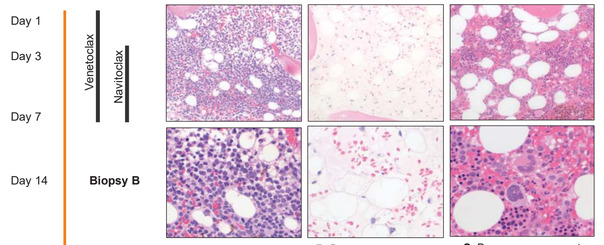
*ETP patients.

- At the data cutoff, participants had been on study for 0.6 months – 5.9 months
- Overall, 4 B-ALL (**Figure 3A**) and 1 T-ALL (**Figure 3B**) achieved a complete response (CR), including CR with incomplete marrow recovery (CRi) and CR with incomplete platelet recovery (CRp). 1 patient achieved a partial response (PR)
- Two patients with CR had no detectable MRD
- Three patients have not reached the day 36 assessment; of these, 1 had PR and 2 had stable disease (SD)

PATIENT CASE STUDY

- 45-year-old male with Ph(-) pre-B ALL
- He had hypodiploidy with complex karyotype and was refractory to induction according to the CALGB 10403 protocol
- Immunohistochemistry (IHC) revealed positive staining for CD19 and CD22
- This patient's history with prior lines of therapy included:
  - Induction per CALGB 10403 → Refractory Disease
  - Blinatumomab → Refractory Disease
  - Inotuzumab → Refractory Disease
  - CD19 CAR T Trial → MRD-negative Remission
  - Matched related donor transplant → Sudden pancytopenia at Day +180
- The patient was pancytopenic at the beginning of treatment, with a white blood cell count of 0.1×10^3 cells/μL, hemoglobin of 7.7 g/dL, and platelets of 20×10^3 cells/μL
- A baseline bone marrow biopsy displayed 100% cellularity composed of 97% B-lymphoblasts by flow cytometry and increased reticulin fibrosis, consistent with relapsed B-ALL (**Figure 4A**)
- The patient started venetoclax and navitoclax on days 1 and 3, respectively, and held on day 7 after a bone marrow biopsy revealed markedly hypocellular marrow with no morphologic evidence of B-ALL and 4.3% lymphoblasts by flow cytometry
- A bone marrow biopsy on day 14 (**Figure 4B**). By day 20, the patient was noted to have neutrophil recovery with an absolute neutrophil count of 1,330 cells/μL
- On day 30, the patient's platelet count had recovered to 130×10^3 cells/μL. A repeat biopsy showed normal trilineage hematopoiesis without reticulin fibrosis and without morphologic or cytometric evidence of B-ALL to a level of 10^{-3} (**Figure 4C**)
- The patient was restarted on venetoclax plus navitoclax following the assessment on day 30

Figure 4. Experience of One Patient on Venetoclax Plus Navitoclax



A. Bone marrow core prior to treatment. Top, 200x; Bottom, 400x.

B. Bone marrow core at Day +14. Top, 200x; Bottom, 400x.

C. Bone marrow core at Day +30. Top, 200x; Bottom, 400x.

CONCLUSIONS

- The combination of venetoclax and navitoclax with chemotherapy is well tolerated, without any unexpected adverse events
- Based on preliminary data from 9 patients, the combination of venetoclax and navitoclax with chemotherapy is efficacious in patients with R/R ALL, who have had multiple lines of therapy, including prior SCT
- Of the 9 total patients enrolled, 5 have achieved CR (CR, CRi, or CRp), including 2 patients with no detectable MRD; 3 patients have not reached the day 36 assessment
  - Response is ongoing in 3 of 7 responders
- Long-term follow-up assessing durability of response and safety in these patients is ongoing; the study remains open for enrollment

REFERENCES

1. Ko RH, et al. *J Clin Oncol.* 2010;28:648-54.
2. Driessen EM, et al. *Leukemia.* 2016;30:1184.
3. Kantarjian HM, et al. *N Engl J Med.* 2016;375:740.
4. Burkhadt B, et al. *J Clin Oncol.* 2009;27:3363.
5. VENCLEXTA [package insert]. AbbVie Inc., North Chicago, IL. Genentech USA Inc., South San Francisco, CA, 2016.
6. Tse C, et al. *Cancer Res.* 2008;68:3421.
7. Jones L, et al. *Leukemia.* 2016;30:2133.
8. Suryani S, et al. *Clin Cancer Res.* 2014;20:4520.
9. Khaw S, et al. *Blood.* 2016;128:1382.
10. Wilson WH, et al. *Lancet Oncol.* 2010;11:1149.

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