Target dependency and Trial Design Drive Variable outcomes with Bh3 Mimetics in Hematologic Malignancies

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Disclosure: Authors: are employees of Ascentage Pharma Group, Inc.

BACKGROUND

Bh3 mimetics validate apoptosis as a therapeutic target, but variable benefit across hematologic malignancies suggests that survival benefits is driven by apoptotic dependency rather than target expression alone.

METHODS

We reviewed pivotal venetoclax studies, including VIALE-A, AGILE, BELINI, CANOVA, VERONA, and CAVALLI, focusing on disease biology, BCL-2 dependence, combinations, and trial design.

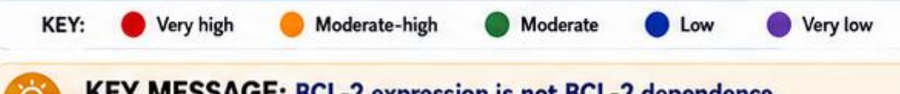
RESULTS

Venetoclax benefited biologically aligned settings, including AML with MM3 and IDH1-mutated AML, but showed limited benefit in high-risk MDS, t(11q) selected myeloma, and DLBCL, identifying apoptotic dependency as the key determinant of efficacy.

DISEASE MAP OF BCL-2 DEPENDENCE

Highest BCL-2 dependence → Lower BCL-2 dependence

CLL	AML	MDS	DLBCL	MM
Very High	Variable	Moderate	Low	Low (except t(11;14))
Strong and consistent BCL-2 dependence	Heterogeneous and dynamic BCL-2 dependence	Partial BCL-2 dependence	Multiple survival pathways; limited BCL-2 dependence	Dependency restricted to subset (e.g., t(11;14))



KEY: Very high · Moderate-high · Moderate · Low · Very low

KEY MESSAGE: BCL-2 expression is not BCL-2 dependence.
Clinical benefit occurs when the malignant cell state is BCL-2 dependent or is shifted toward it.

PIVOTAL VENETOCLAX STUDIES: LESSONS BY DISEASE

A. CLINICAL BENEFIT DEMONSTRATED

VIALE-A (AML)
Venetoclax + HMA vs HMA
OS: 14.7 vs 9.9 months
HR 0.66; p<0.001

AGILE (IDH1-mut AML)
Ivosidenib + Venetoclax + Aza vs Placebo + Aza
OS: 24.0 vs 7.9 months
HR 0.39; p<0.001

B. LIMITED/NO BENEFIT DEMONSTRATED

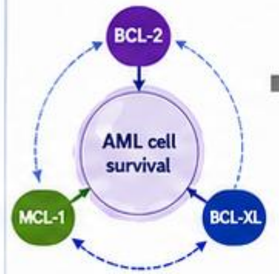
VERONA (MDS)
Venetoclax + Aza vs Aza
⊖ No OS benefit

BELINI (MM)
Venetoclax + Vd vs Vd
PFS benefit; No OS benefit; Increased early mortality

CAVALLI (DLBCL)
Venetoclax + R-CHOP vs R-CHOP
⊖ No PFS or OS benefit

AML: DYNAMIC BCL-2 DEPENDENCE AND WHY VENETOCLAX COMBINATIONS WORK

1 Baseline AML
BCL-2 dependence variable and dynamic

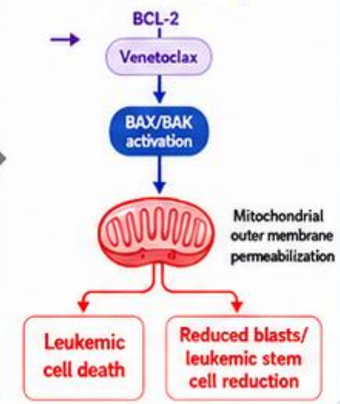


2 Partner drug rewires survival wiring

- Hypomethylating agents (HMA)
  - Increase priming
  - Suppress alternate pathways
- MDM2 inhibitors
  - Reduce P53-M interaction
  - Therapeutic
  - Increase priming
  - Reduce MCL-1 buffering
- Other targeted agents
  - Inhibit survival signaling (e.g. BCL-XL,FLT 3, IDH1/2, etc.)
  - Increase apoptotic vulnerability

Increased apoptotic priming; Reduced compensatory survival pathways

3 Enhanced venetoclax activity



In these combinations, the partner drug does not simply add cytotoxicity—it increases apoptotic priming or reduces compensatory survival pathways, making venetoclax more effective.

TRIAL DESIGN PRINCIPLES FOR BCL-2 INHIBITOR THERAPY IN AML AND MDS

1. **Enrich for biology likely to be BCL-2 dependent**
   - Use biomarkers (e.g., gene expression signatures)
   - Select molecular subtypes (e.g., IDH1/2, TP53 wt or mut)
2. **Use combinations that increase apoptotic priming**
   - HMA, IDH1/2 inhibitors, menin inhibitors, FLT3 inhibitors, others
   - Suppress compensatory pathways (MCL-1, BCL-XL)
3. **Avoid schedules that promote excess toxicity**
   - Optimize ramp-up, dose, and duration
   - Balance efficacy with hematologic recovery
4. **Build in biomarker-informed adaptation**
   - Monitor response and MRD
   - Adapt therapy based on biology and tolerability

The best trial design matches biology, drug mechanism, patient selection, partner, and schedule to deliver survival benefit.

CONCLUSION

The variable clinical performance of BH3 mimetics reflects a mismatch between drug mechanism/ disease biology, and trial design—not a lack of pharmacologic efficacy.

Apoptosis (something) vulnerability, not a surrogate biomarker (e.g., 2-globulin is most effective when malignant cells are BCL-2 dependent or when partner therapies shift the cell state toward that dependency.

Future development should move beyond target expression alone and focus on functional apoptotic dependency, biomarker-informed selection, rational combinations, trial designs, schedules, and biologically aligned indications,

When we match the right drug to the right biology in the right way, BH3 mimetics can translate into durable survival benefit.

MAIN TAKE-HOME MESSAGE: Venetoclax should not be applied broadly across hematologic malignancies. Success requires biological matching—targeting apoptotic dependency in the right disease, with the right partner(s) and trial architecture.

Right drug. Right dependency. Right partner. Right design.