REGULATORY CONSIDERATIONS FOR USE OF MRD IN AML AND CLL

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- No Disclosures

Outline

- U.S. Regulatory Framework
  - Therapeutic Approval
  - Surrogate Acceptance
- MRD in AML and CLL

U.S. Regulatory Considerations

- Requirements for New Drug Approval
  - Substantial evidence of efficacy with acceptable safety in adequate and well-controlled studies
  - FDA examines the evidence in the context of the disease state, available therapy, study design, endpoints selected, and strength of the evidence
  - Ability to generate product labelling that
    - Defines an appropriate patient population
    - Provides adequate information to enable safe and effective use

Federal Food, Drug, and Cosmetic Act, Section 505

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U.S. Regulatory Considerations

- Regular Approval
  - Approval is based on demonstration of clinical benefit or an effect on an established surrogate

- Accelerated Approval
  - Treatment of serious or life-threatening illness
  - Provides a meaningful benefit over available therapies
  - Approval is based on an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than mortality or morbidity
  - May require post-approval trials to verify anticipated clinical benefit

21 CFR 314.510

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Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Nicole Gormley at 240-402-0210 or (CBER) Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010

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U.S. Regulatory Considerations
Surrogate Endpoint Acceptance or Qualification

- FDA's Biomarker Qualification Program
  - Purpose of formal qualification is that "within the stated context of use, a biomarker can be relied upon to have a specific interpretation and application in drug development and regulatory review"
  - Also known as DDT Qualification

- Discussions with the Review Division

FDA Draft Guidance. Hematologic Malignancies: Regulatory Considerations for use of MRD in Development of Drug and Biological Products for Treatment

U.S. Regulatory Considerations
Surrogate Endpoint Acceptance or Qualification

- FDA's Biomarker Qualification Program
  - DDT or Biomarker is qualified for a specific context of use
  - Qualified DDT is made publicly available
  - Qualified DDT can be used in a submission without need for reconsideration or review by the FDA
  - Higher evidentiary standard if biomarker is to be used as a surrogate endpoint

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U.S. Regulatory Considerations
Surrogate Endpoint Acceptance or Qualification

- Discussions with the Review Division
  - Pharmaceutical company or group meets with review division
  - Scientific data from previous clinical trials or meta-analysis
  - Surrogate reasonably likely to predict clinical benefit or a validated surrogate
    - Examples: Pathologic complete response in neoadjuvant breast cancer, or complete response at 30 months in follicular lymphoma

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U.S. Regulatory Considerations
Surrogate Endpoint Acceptance or Qualification

- Strength of evidence to support Surrogacy depends on:
  - The biologic plausibility of the relationship between the surrogate endpoint and the clinical outcome
  - Demonstration of the prognostic value of the surrogate endpoint for the clinical outcome
  - Evidence from clinical trials that treatment effects on the surrogate endpoint correspond with effects on the clinical outcome

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U.S. Regulatory Considerations
Surrogate Endpoint Acceptance or Qualification

- Meta-analysis for validation of MRD as a surrogate endpoint
- Technology Considerations
- Caveats regarding use of surrogate endpoint
  - Use of surrogate may not be appropriate for subpopulations or future trial populations if there are significant differences between the population in the meta-analysis and the trial population.
  - Use of surrogate may not be appropriate for therapeutic modalities that have substantially different MOA (e.g., cytotoxic vs. immunotherapies).

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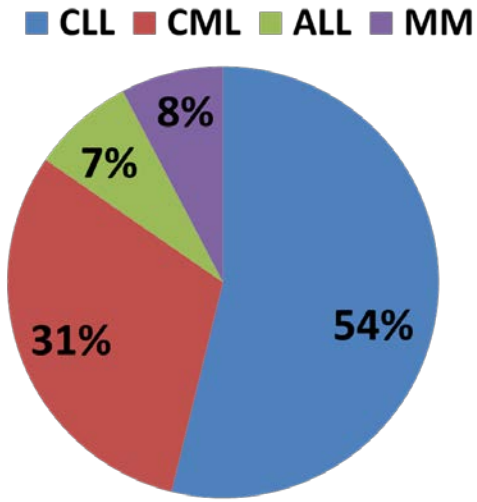
Outline

- U.S. Regulatory Framework
  - Therapeutic Approval
  - Surrogate Acceptance
- MRD in AML and CLL

MRD data in FDA Applications

- Review of Internal Databases between 2014 and 2016
  - 34 original or supplemental applications submitted to the DHP.
  - 13 (38%) included MRD data
    - CML, CLL, ALL, and MM



Gormley N et al., 2017, JCO, 35:2541.

MRD data in FDA Applications

- Review of Internal Databases between 2014 and 2016
  - Outcome of FDA MRD review

Category	n (%); Total n=13
Not proposed for inclusion in USPI	**3 (23%)**
MRD deemed adequate	**6 (46%)**
MRD deemed inadequate	**4 (31%)**

Gormley N et al., 2017, JCO, 35:2541.

MRD data in FDA Applications

- Reasons for Exclusion
  - Missing Data
  - Inconsistent testing across sample sources
    - Blood vs. Marrow
  - High amounts of test failure rates
    - Inability to detect a clonal rearrangement
  - Lack of test validation in the disease setting
  - Incomplete test characteristics data (i.e., LOD)
  - Incomplete planned statistical analysis

Gormley N et al., 2017, JCO, 35:2541.

MRD in CLL

- Guidance Recommendations for CLL
  - MRD in patients with CLL is associated with prolonged PFS and OS.
  - CLL is a multicompartmental disease; multiple reservoirs for residual disease.
  - MRD should be measured by a standardized method with a quantitative lower limit of detection less than 10^{-4} (0.01%).
  - MRD should be consistently measured in the BM or peripheral blood, with consideration of the therapy administered.
    - PB may be an appropriate screening assessment with confirmation in BM, if PB suggests MRD negativity
  - MRD should be assessed in patients in CR with justification for inclusion of other response categories.
  - MRD should be assessed at the end of treatment response assessment.

- MRD results have been included in Prescribing Information
  - Venetoclax, Obinutuzumab

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MRD in CLL

- Venetoclax example: Murano Trial

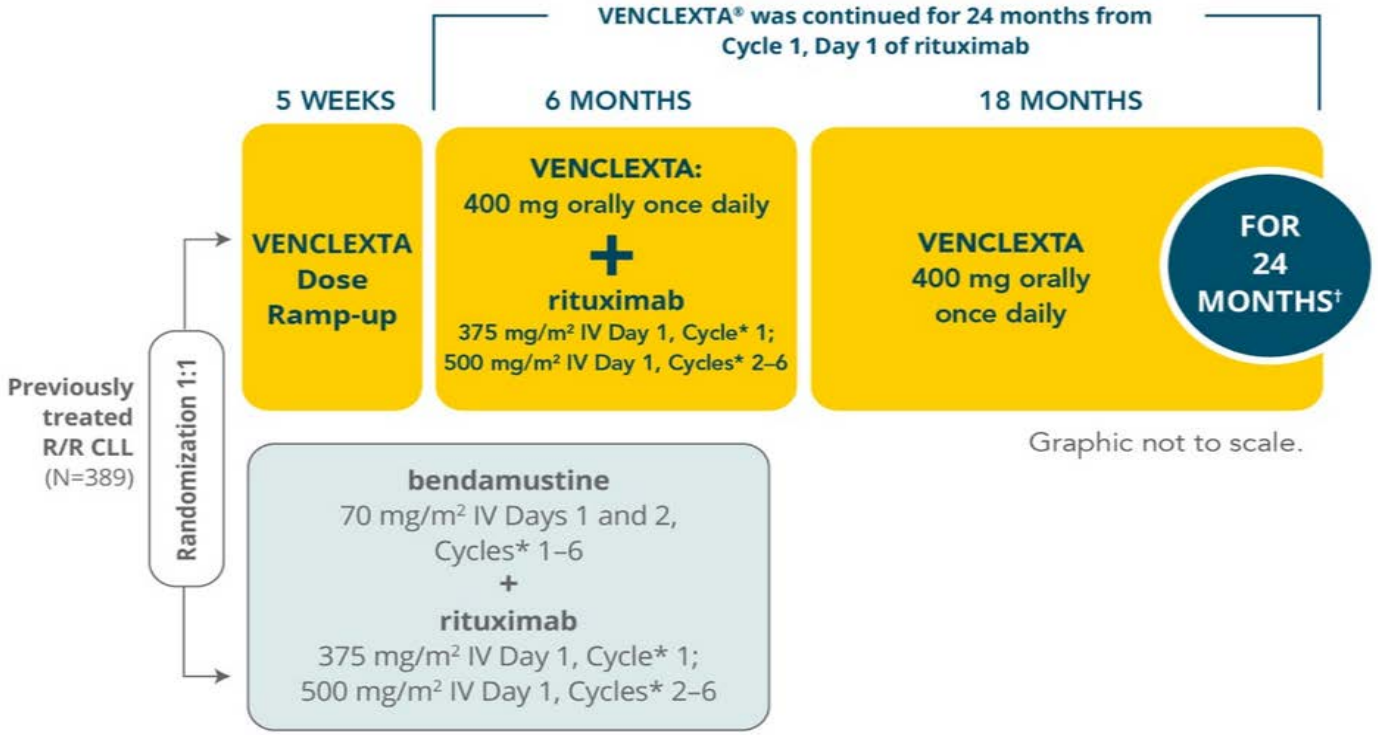
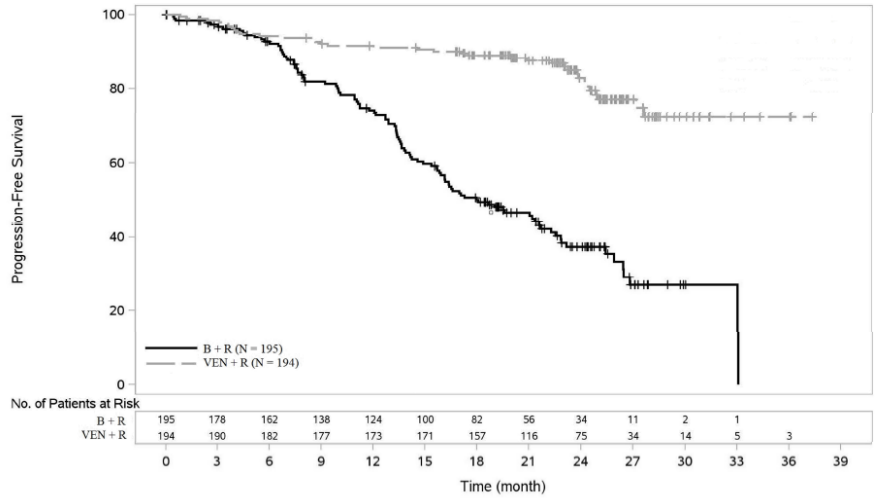


Figure 1. Kaplan-Meier Curve of IRC-Assessed Progression-free Survival in MURANO



Endpoint	VENCLEXTA + Rituximab (N = 194)	Bendamustine + Rituximab (N = 195)
Progression-free survival[a]		
Number of events, n (%)	35 (18)	106 (54)
Disease progression, n	26	91
Death events, n	9	15
Median, months (95% CI)	Not Reached	18.1 (15.8, 22.3)
HR (95% CI)[b]	0.19 (0.13, 0.28)	
p-value[b]	<0.0001	
Response Rate[c]**, n (%)**		
ORR	179 (92)	141 (72)
95% CI	(88, 96)	(65, 78)
CR+CRi	16 (8)	7 (4)
nPR	3 (2)	1 (1)
PR	160 (82)	133 (68)

https://www.venclextahcp.com

Venetoclax U.S. Prescribing Information

MRD in CLL

Minimal residual disease (MRD) was evaluated using allele-specific oligonucleotide polymerase chain reaction (ASO-PCR). The definition of negative status was less than one CLL cell per 10^4 leukocytes. At 3 months after the last dose of rituximab, the MRD negativity rate in peripheral blood in patients who achieved PR or better was 53% (103/194) in the VEN+R arm and 12% (23/195) in the B+R arm. The MRD-negative CR/CRi rate at this timepoint was 3% (6/194) in the VEN+R arm and 2% (3/195) in the B+R arm.

MRD in AML

- Guidance Recommendations for AML
  - The molecular heterogeneity of AML poses substantial challenges to the use of MRD as a biomarker.
  - Bone marrow is the preferred substrate for measurement of MRD.
  - CR with recovery of blood counts is the preferred time for measurement of MRD.

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MRD in AML

- Guidance Recommendations for AML

  - For the marker (e.g., cell surface or genetic mutation) selected to assess MRD, the sponsor should provide data showing that the marker reflects the leukemia and not underlying clonal hematopoiesis (false positive result). The sponsor should also describe the false-negative rate that might result from relapse from a marker-negative clone. If multiple markers and/or multiple platforms are used, the sponsor should provide an analysis of the risk of false-positive and false-negative results for each marker individually and for the panel as a whole.

  - For studies of targeted therapies where the MRD marker is the target of the therapy, the sponsor can use nonclinical data to identify the mutations in the marker that are known to be sensitive to the therapy and those that are known to be resistant to the therapy. If using only the target of therapy as the MRD marker, the sponsor should provide justification for not using other MRD markers to avoid false-negative results.

- MRD results have not been included in Prescribing Information to date.

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Conclusions

- We encourage assessment of MRD in clinical trials
- If planning to incorporate MRD in clinical trial, recommend meeting with the Agency
- Specific regulatory considerations exist in the evaluation of potential surrogate endpoints.
- Various pathways exist for FDA acceptance of a surrogate marker.
- FDA is committed to working with the community on the development of MRD in heme malignancies.


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