REGULATORY CONSIDERATIONS FOR MRD AND ctDNA Development

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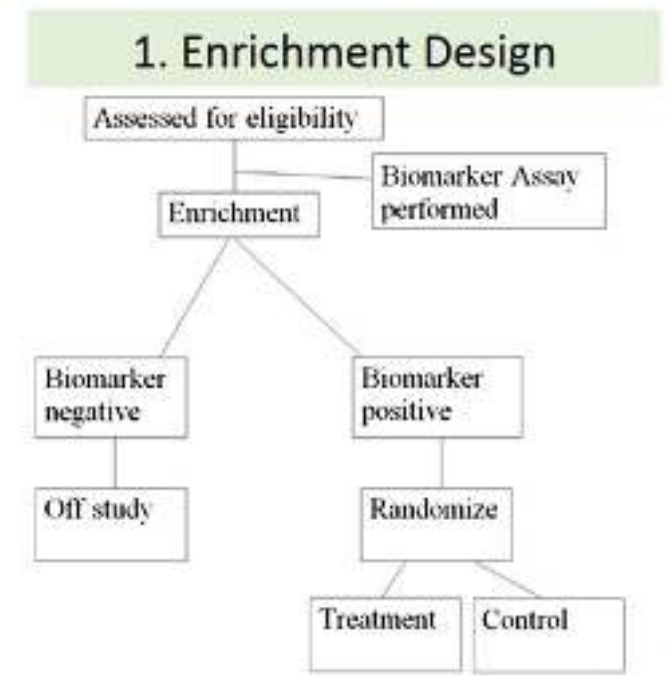
Disclosure Information

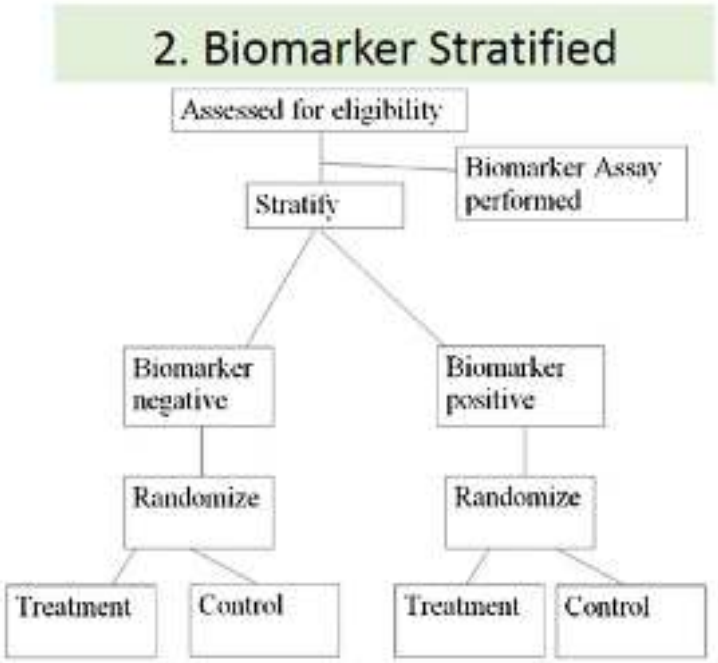
- I have no financial relationships to disclose.
- I will not discuss off label use and/or investigational use in my presentation.

Potential uses of MRD and ctDNA

- Prognostic Biomarker
- Clinical Uses
  - Screening/Early Detection
  - Monitor for relapse
  - Guide therapeutic decisions
- Regulatory Uses
  - Patient Stratification
  - Patient Selection/Enrichment
  - Risk-based treatment assignment
  - Intermediate Endpoint or Surrogate Endpoint

Patient Stratification or Enrichment





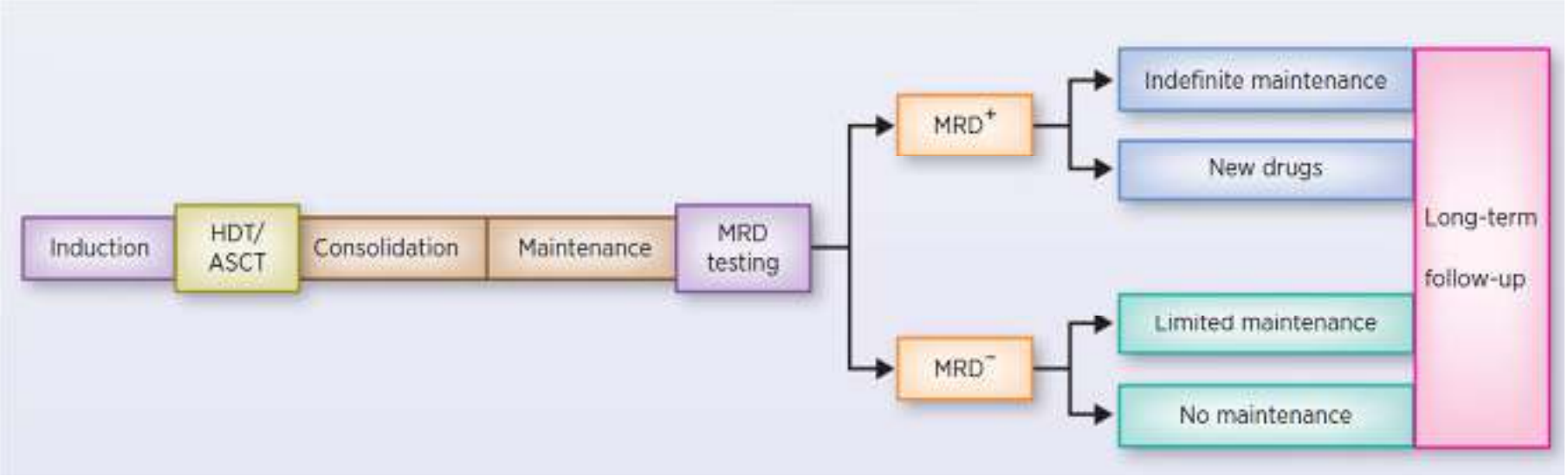
- Should be used when there is very convincing data that treatment benefits are limited to the biomarker positive subpopulation

- Can be used when treatment is more likely to be effective in the biomarker positive subpopulation, but an effect cannot be ruled out in the biomarker negative subpopulation

Dobbin Journal for Immunotherapy of Cancer 2016

Risk-Based Treatment Assignment

- MRD/ctDNA as Escalation or De-escalation



Anderson CCR 2017

Endpoint: 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
  - Takes into account the severity, rarity, or prevalence of the condition and the availability of lack of alternative treatments
  - Approval is based on an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict clinical benefit
  - May require post-approval trials to verify anticipated clinical benefit

21 CFR 314.510
FDA Guidance for Industry: Expedited Programs for Serious Conditions- Drugs and Biologics

Development of Endpoints for Regulatory Use: Validation as a Surrogate

- Prentice Criteria
  - The surrogate must be a correlate of the true clinical endpoint
  - The treatment effect on the surrogate should capture the full effect of treatment on the clinical endpoint
- Meta-analytical methods
  - Patient-level data
  - Allow for assessment of Individual Level and Trial Level Surrogacy
    - Individual Surrogacy- Correlation between candidate surrogate and true clinical endpoint on an individual level
    - Trial Level Surrogacy- Correlation between effect of treatment on the candidate surrogate and the effect of treatment on the true clinical endpoint
  - Surrogate Threshold Effect
    - Minimum treatment effect on the surrogate necessary to predict an effect on the true clinical endpoint

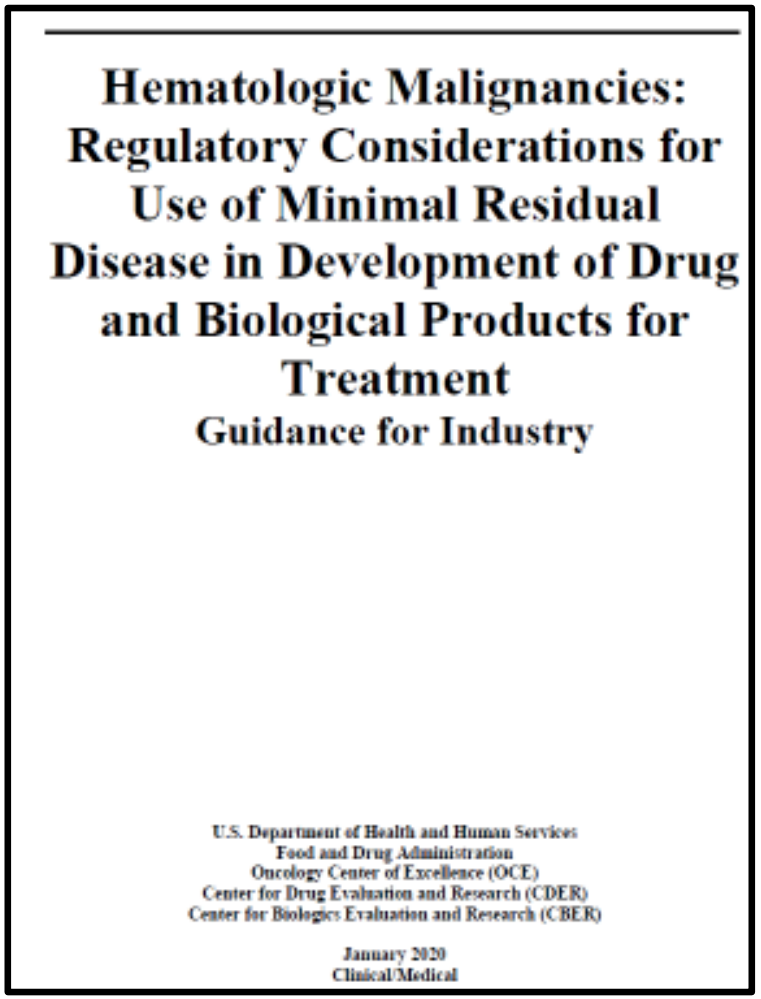
Buyse Nat Rev Oncol 2010
Sargent JCO 2015

Evidentiary Criteria

- Meta-analysis Considerations
  - Inclusion of more trials increases the statistical rigor of the analysis and may allow for more interrogation of the data to address uncertainties.
  - Inclusion of trials with a range of treatment effects (positive and negative trials) increases the accuracy and precision of trial level surrogacy assessment.
  - When designing a meta-analysis, consideration of MRD timing of assessment, missing data is important.
  - The trial populations and treatments included in the meta-analysis inform future applicability of the surrogate biomarker.

Buyse Biomet J 2016
Sargent Clinical Trials 2013

MRD Guidance



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

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

January 2020
Clinical/Medical

Scope

- Development of MRD as a Biomarker for Regulatory Use
  - Regulatory Uses and Biomarker Definitions (BEST Criteria)
  - Pathways for Surrogate Endpoint Acceptance or Qualification
  - Meta-analytical Approaches
  - MRD as an Endpoint in Clinical Trials
  - MRD for Patient Selection or Enrichment
- Technology
- Disease Specific Considerations
  - ALL, AML, APL, CLL, CML, MM
- Regulatory Submissions which Utilize MRD

Development of MRD for Regulatory Use: Validation of MRD as a Surrogate

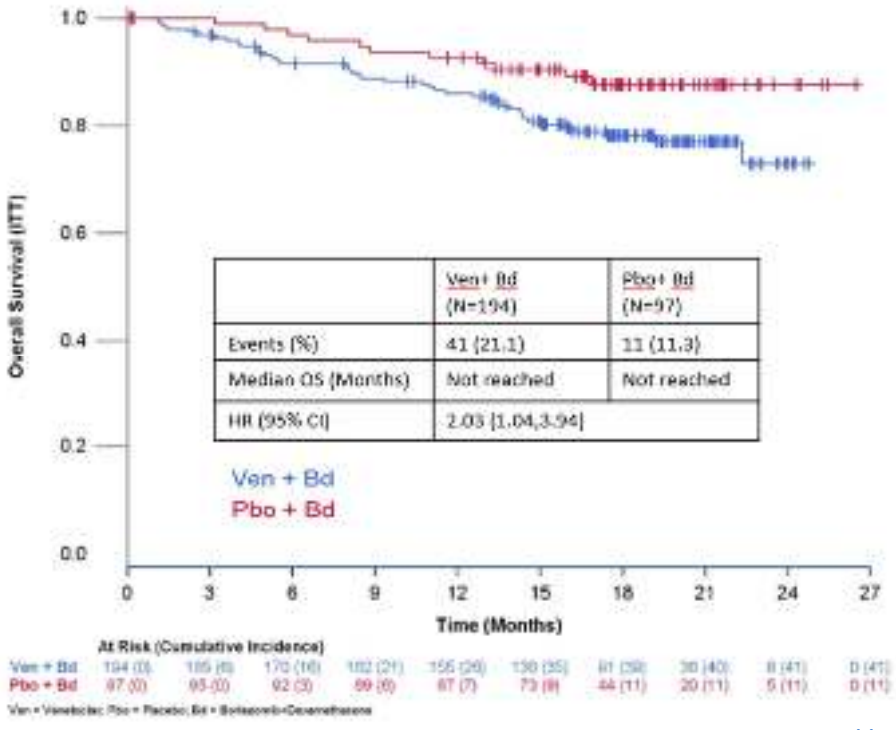
- Caveats regarding use of surrogate endpoint
  - Use of surrogate may not be appropriate for subpopulations or future trial populations if there are significant differences between the population in the meta-analysis and the trial population.
  - Use of surrogate may not be appropriate for therapeutic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

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

A Cautionary Tale: BELLINI Trial

- Phase 3, double-blind, randomized, placebo-controlled trial of bortezomib and dexamethasone with or without venetoclax in patients with relapsed/refractory, multiple myeloma who had received 1-3 prior lines of therapy

	Venetoclax Arm	Placebo Arm
ORR	82.0% (75.8, 87.1)	68.0% (57.8, 77.1)
MRD negativity rate (10^{-5})	13.4% (8.9, 19.0)	1.0% (0.0, 5.6)
Median PFS (mos) (95% CI)	22.4 (15.3, NR)	11.5 (9.6, 15.0)
Hazard Ratio (95% CI)	0.63 (0.44, 0.90)	



	Ven+ Bd (N=194)	Pbo+ Bd (N=97)
Events (%)	41 (21.1)	11 (11.3)
Median OS (Months)	Not reached	Not reached
HR (95% CI)	2.03 (1.04,3.94)	

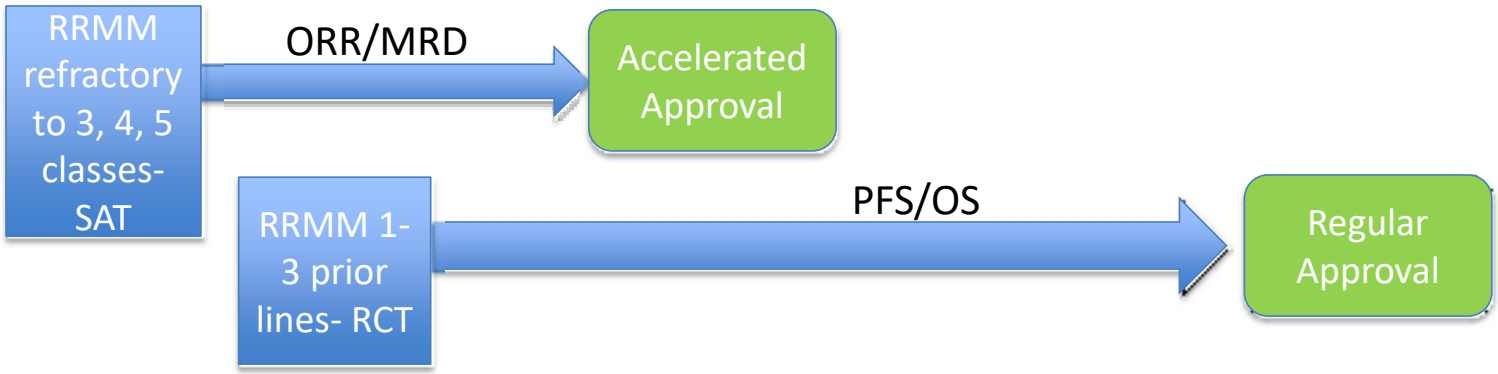
https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-risks-associated-investigational-use-venclexta-multiple-myeloma

A Cautionary Tale: BELLINI Trial

- Implications
  - Divergent results between ORR, PFS, MRD and OS concerning
  - Need evaluation of endpoints that can be assessed at early timepoints *and* Late endpoints that provide definitive evidence of clinical benefit
  - Trials should be followed for OS, even when it is not the primary endpoint

Drug Development Approach

- Multiple Trial Model



- Single Trial Model

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MRD and ctDNA Today and Future Considerations

- MRD results used to support accelerated approval in ALL
  - Blinatumomab approval in MRD-positive B-cell Precursor ALL
    - Accelerated approval based on MRD response rate and hematological relapse-free survival
- MRD results have been included in Prescribing Information in CLL
  - Venetoclax, Obinutuzumab
- MRD results have been included in the Prescribing Information in MM
  - Daratumumab, Abecma
  - Currently recommended as a secondary endpoint
- Ongoing efforts in various diseases to formally evaluate MRD and ctDNA

Conclusions

- ctDNA and MRD are prognostic biomarkers, but not validated surrogate endpoints
- Existing uncertainty and remaining questions regarding these endpoints for regulatory purposes
- MRD assessments in clinical trials should be discussed with the Agency
- FDA is committed to working with the community on the development of MRD and ctDNA.

Thanks…

- Marc Theoret
- Julia Beaver


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