Use of External Control Data in Hematology and Oncology Drug Applications – Regulatory review experience

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Outline

- **Studies using an external control data**

  - regulation/guidance

- **Considerations of using an external control**

  - design, data, analysis, and regulatory

- **Examples from hematology and oncology**

  - Mar 2018 ODAC: **Blinatumomab** (**BLINCYTO)** for B-precursor ALL with CR1/CR2 and MRD+
  - Feb 2019 ODAC: **Selinexor** (**XPOVIO)** for relapsed refractory multiple myeloma
  - Aug 2020 ODAC: **Remestemcel-L** for steroid-refractory acute graft-versus-host disease

Externally Controlled Trials

- Studies involving data from a predefined clinical investigation, wherein treatment in a study arm is assigned according to a protocol, and treatment in a control arm is observed using predefined "external" patient-level data from either
  a) a trial arm of a different interventional study, or
  b) defined population from a non-interventional study or a database (RWD)
- Studies that use external control data to supplement the control arm in a randomized trial

- Not considered as external control:
  - population-level estimates as a comparator,
  - patients serving as their own controls in analyses
  - design and analysis of a natural history study as a stand-alone activity
  - validation of linking real-world data to a regulatory endpoint.

Randomized Trials vs. Externally Controlled Trials

- In general, **randomized trials**, considered as **gold standard** for comparing treatment, are preferred for providing evidence of treatment efficacy
- However, disease or population characteristics may require a non-randomized study design
- In the case that a randomized control arm is not feasible, an external control arm may be an option for estimating comparative treatment effect

Regulatory Guidance and Resources

- **21CFR 314.126[1]**

"…historical control designs are usually **reserved for special circumstances**. Examples include studies of diseases with **high and predictable mortality** (for example, certain malignancies) and studies in which the effect of **the drug is self-evident** (general anesthetics, drug metabolism)"

- **FDA Guidance on demonstrating substantial evidence[2] and ICH E10 (May 2001)[3]**

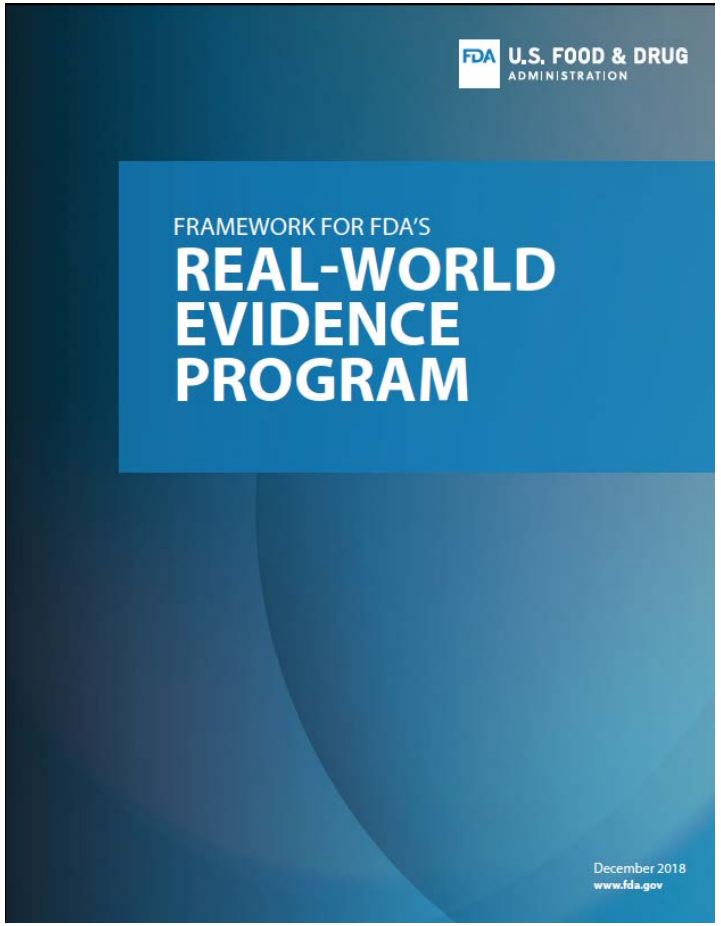
"The inability to control bias **restricts use of the external control design** to situations in which the effect of **treatment is dramatic** and the usual **course of the disease highly predictable**"

"An externally controlled trial should generally be considered **only when** prior belief in the superiority of the test therapy to all available alternatives is so strong that alternative designs appear unacceptable and the disease or condition to be treated has a well-documented, highly predictable course."

Regulatory Guidance and Resources

- December 2018: FDA provided the **Framework for the Real-World Evidence Program**[4], which includes some information on how **real world data** and **evidence** will be incorporated into regulatory decision making:
  - to help support new indications for drugs that are already approved, **or**
  - to help support or satisfy post approval study requirements

- However, the use of these data sources (RWD) and the evidence derived from them (RWE) should **meet the established rigor and standards** required for regulatory decisions.



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Design Consideration

- **Avoid differences in the populations that result in groups that cannot be compared**
  - Baseline characteristics
  - Attributes of treatment
  - Comparable endpoints
  - Validity assessment (e.g. prognostic/diagnostic, Temporal and/or geographic, COAs, etc.)
- **Minimize the need for analytic tools to deal with bias or confounding**
- **Determination of appropriate external control**
- **Identification of external data source**
- **Minimizing bias**
- **Other design considerations**

Data Considerations

- **Data from real world (Non-interventional data)**
  - Data derived from electronic health records (EHRs)
  - Medical claims and billing data
  - Data from product and disease registries
  - Patient-generated data
  - Data gathered from other sources that can inform on health status (eg, mobile devices)

- **Data from clinical trials**
  - historical
  - concurrent

- **High-quality and complete patient-level data is key for comparative efficacy**

Analysis Considerations

- **Analytic methods to control for bias and confounding**
  - Estimand of interest
  - Causal inference framework vs. other frameworks
  - Analytic methods for missing data
- **No common analytical methods fit all cases of external control**
  - Sensitivity analysis

Regulatory Considerations

- **Communication with FDA**
- **Documentation, Maintaining study integrity**
- **Reporting study results, Privacy issues, etc.**

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Blinatumomab (BLINCYTO) supplemental approval (March 2018 ODAC)

- **Indication**: treatment of minimal residual disease (MRD)-positive B-cell precursor acute lymphoblastic leukemia (ALL)

- **Study MT103-203 (BLAST)**
  - Single-arm trial
  - Primary efficacy endpoint: complete MRD response (<0.01%) within the first cycle
  - Evaluable populations: 86 patients in CR with MRD >= 0.1%
  - Results (**accelerated approval**):

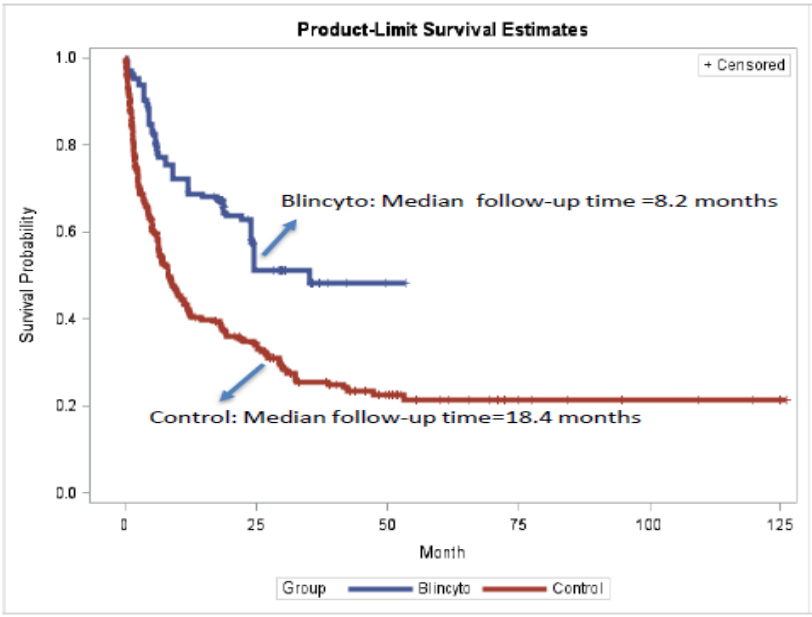
    Response in 69 patients (79%; 95% CI: 70%, 88%).

    Estimated median RFS was 22.3 months.

- **Supporting analysis** (exploratory; not included in the label): Compare the single arm trial (Study MT103-203: reduce from n=113 to n=73) vs historical control arm (Study 20120148;n=182)
  - Efficacy Endpoints: **RFS and OS**
  - Propensity score analysis
    - Selected baseline factors are balanced by using a weight function **stabilized inverse probability of treatment weight**

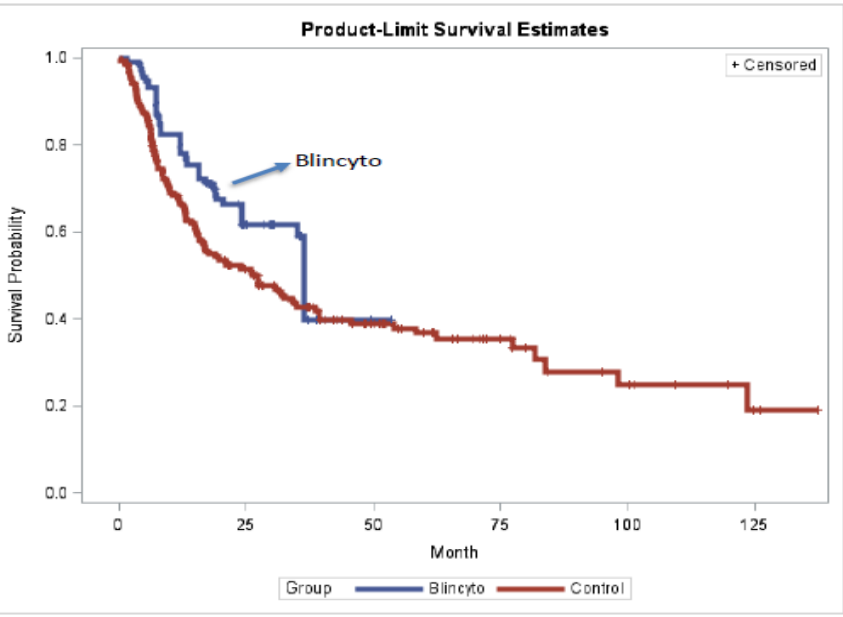
Limitations in Blinatumomab supportive Results

RFS



HR (95% CI)=0.50 (0.32-0.78)

OS



HR (95% CI) =0.76 (0.47-1.24)

In summary, while RFS appears to be in favor of Blincyto treated arm, there are limitations of the propensity score analysis:

- 35% of Blinatumomab patient data excluded to match with external control group
- Confounding due to subsequent treatment, e.g. differential rates of HSCT and data are not contemporaneous
- Differential follow-up time between two arms

Selinexor (XPOVIO) Approval (February 2019 ODAC)

- **Indication**: in combination with dexamethasone for relapsed or refractory multiple myeloma (RRMM)

- **Study KCP-330-012, Part 2 (STORM)** :

- Single-arm trial of the combination of Selinexor and dexamethasone
- Endpoint: IRC-assessed ORR
- Evaluable patient population: 83 patients, pre-specified subgroup of 122 total patients
- Results (**accelerated approval**):
    - Overall Response in STORM: 21 patients (25%; 95% CI: 16%, 36%)
    - Duration of response of 3.8 months (95% CI: 2.3, not estimable)

- **Supporting analysis** (exploratory; not included in the label)**:** Study KS-50039: "Real-World Overall Survival in Patients with Penta-Exposed, Triple-Class Refractory Multiple Myeloma" to demonstrate isolation of treatment effect of selinexor vs. dexamethasone in STORM
    - primary endpoint: **OS**
    - **RWD**: Flatiron (FHAD) population, 64 patients selected out of about 38679 total

KS-50039: Flatiron (FHAD) Population

ICD code for MM, ≥2 visits on or after 01 January 2011: **(N = 38679)**

↓

Medication orders for bortezomib, carfilzomib, and daratumumab: (N = 364)

↓

Pathology consistent with MM on or after 01 January 2011: (N = 258)

↓

Oral episodes for lenalidomide and pomalidomide: (N = 174)

↓

Treatment initiation no more than 30 days before the start of structured activity: (N = 144)

↓

Confirmed treatment with bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab; treatment not received in clinical trial setting: (N = 126)

↓

MM documented as triple-class refractory: (N = 69)

↓

Baseline ECOG performance status ≤2: **(N = 64)**

Abbreviations: FHAD = Flatiron Health Analytic Database; ECOG = Eastern Cooperative Oncology Group

KS-50039: Real-World Data Study Conclusion

FHAD:	STORM:
• Excluded patients who received therapy on a clinical trial • Included patients who did not receive subsequent anti-myeloma therapy • High % of ECOG status missing • No requirements for minimum platelet count, hemoglobin or organ function	• Excluded patients with life expectancy < 4 months • Excluded patients with severe disease presentation (i.e., amyloidosis, plasma cell leukemia) • Minimum thresholds for platelet count, hemoglobin and organ function

- Selection criteria were not aligned resulting in critical differences between the FHAD population and the population evaluated in STORM
- Comparison of survival between FHAD and STORM is not appropriate

In summary, KS-50039 was not pre-specified or discussed with the Agency and has design issues that lead to bias and confounding.

Remestemcel-L
(August 2020 ODAC)

- **Proposed indication**: treatment of steroid-refractory acute graft-versus-host disease (SR-aGVHD) in pediatric patients
- **Study MSB-GVHD001**:
  - One single-arm trial as the basis of efficacy
  - Primary endpoint: Day-28 ORR and Durability
    - success if Day-28 ORR is > 45%
  - Analysis population: 55 full analysis set (54 treated)
  - Results (FDA analysis):
    - Day-28 ORR: 38 (69% ; 95% CI: 55%, 81%)
    - median DoR (range, days): 54 (7, 159+)
- **Supporting analysis:**
  - 3 external trials **Study 275 (**single-arm) and **Study 265**, **Study 280** (RCT) to demonstrate the efficacy of remestemcel-L in pediatric patients with steroid refractory aGvHD in Study MSB-GVHD001

Remestemcel-L: Pivotal Trial VS External Control Trials

	Protocol 001	Protocol 280	Protocol 275	Protocol 265
Phase	Phase 3	Phase 3	Expanded access	Phase 3
Ages	Pediatric	Adult and pediatric	Pediatric	Adult
Population	SR-aGVHD grade B-D aGVHD (no skin only grade B)	SR-aGVHD grade B-D aGVHD (skin only grade B allowed)	SR-aGVHD grade B-D aGVHD (skin only grade B allowed)	Newly-diagnosed grade B-D aGVHD (skin only grade B allowed)
Design	Single arm, multi-center	Randomized, double-blind, placebo- controlled, multicenter	Single arm	Randomized, double-blind, placebo-controlled, multicenter
Primary Endpoint	Day-28 ORR	CR $\geq$ 28 days duration	Day-28 ORR	CR $\geq$ 28 days duration
Control Arm	-	SOC + Placebo	-	Steroids + Placebo
Treatment Arm	Remestemcel-L 2×10^6 cells/kg x 2 infusions/week x Weeks 1-4, then 1 infusion/week x Weeks 5-8 (continuation)	SOC + remestemcel-L 2×10^6 cells/kg x 2 infusions/ week x Weeks 1-4, then 1 infusion/week x Weeks 5-8	SOC + remestemcel-L 2×10^6 cells/kg x 2 infusions/ week x Weeks 1-4, then 1 infusion/week x Weeks 5-8	Steroids + remestemcel-L 2×10^6 cells/kg x 2 infusions/ week x Weeks 1-2, then 1 infusion/week x Weeks 3-4

Abbreviations: CR, complete response; EAP, expanded access protocol; ORR, overall response rate; SOC, standard care salvage therapy.

- **Difference in patient populations**
  - Study 265 included adult, newly-diagnosed aGVHD
- **Studies 280 and 275 allowed new salvage therapy for aGVHD**

Remestemcel-L: Comparisons of Pediatric Day-28 ORR

	Protocol 001	Protocol 280 (Pediatric subgroup)		Protocol 275
Arm	Rem-L	SOC + Rem-L	SOC + Placebo	SOC + Rem-L
Number of treated patients	54	14	13	241
Day-28 ORR[b] (95% CI)	69.1% (55.2, 80.9)	64.3% (35.1,87.2)	38.5% (13.9, 68.4)	65.1% (58.8, 71.1)

- **Small numbers of patients**
- **Study 280 subgroup analysis not persuasive (large CI)**

Remestemcel-L: Comparisons of Overall Day-28 ORR

	Protocol 001	Protocol 265		Protocol 280	
	Rem- L	Steroids + Rem-L	Steroids + Placebo	SOC + Rem-L	SOC + Placebo
Number of patients	54	97	95	173	87
CR lasting ≥ 28 days	-	45%	46%	35%	30%
Day-28 ORR[b] (95% CI)	70.4% (56.3, 82.0)	60% (49.3, 69.6)	61% (50.5, 70.9)	54% (46.0, 61.3)	47% (36.3, 58.1)
Day-28 CR	29.6%	41%	49%	25%	23%
Day-28 PR	40.7%	19%	12%	29%	24%

- **No treatment effect in RCTs**
- **ORR in the remestemcel-L treatment arms ranged from 54-70% with wide confidence intervals**

ODAC Voting results: 9:1 for approval.

Summary

- Randomized controlled trial is the gold standard; single arm trials supported with external controls only reserved for special circumstances, e.g.
  - Disease with high and predicable mortality
  - The effect of the drug is self-evident
  - Rare disease

- If an external control arm is used to support a submission, adequate data based on pre-determined patient selection criteria and pre-specified statistical analysis plan are required.

References

1. CFR Part 314, subpart D, Sesd 314.126, Adequate and well-controlled studies : https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=314.126
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3. ICH E10: Choice of control group and related issues in clinical trials: https://database.ich.org/sites/default/files/E10_Guideline.pdf
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