Real-World Evidence (RWE) Studies Supported Hematologic Oncology United States Food and Drug Administration (US FDA) Approval: What Do They Look Like?

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Introduction/Background: Although randomized controlled trials are considered the gold standard of evidence for safety and efficacy of a drug, they are subject to several limitations such as difficulty in recruiting patients with rare diseases or randomization of patients to studies with treatments that lack an established standard of care owing to efficacy or toxicity concerns. RWE can help overcome these challenges. RWE collects patient data from historical trials or retrospective observational studies and compares or contextualizes these data to experimental treatments by using proper statistical adjustments.

The 21st Century Cures Act inspired the framework for the US FDA to use RWE to assess product effectiveness of approved drugs to support regulatory decision-making. Consequently, RWE is increasingly used in New Drug Applications (NDAs) and Biologics License Applications (BLAs) for hematologic malignancies, and findings suggest that submissions using RWE may receive faster approval. However, data are lacking on adoption of RWE for regulatory submissions and its use in regulatory decision-making. Here, we outline RWE utilization and limitations of regulatory submissions for hematologic malignancy therapeutics, which received accelerated or full approval in the US.

Methods: Between 2017 and 2021, all NDA and BLA approvals from the Division of Hematological Malignancies were reviewed for hematology/oncology drugs or indications. The FDA Oncology Drug Advisory Committee (ODAC) briefing and/or multidisciplinary review documents were evaluated to identify the drug approvals using RWE. This assessment was performed by 4 independent reviewers who evaluated FDA comments regarding RWE. RWE sources, study methodology, drug indications, pivotal trial information, statistical analyses, and results were summarized.

Results: A total of 74 hematologic malignancy approvals were identified, of which 7 (9.4%) provided RWE that supported regulatory approval. Detailed analyses of the FDA ODAC briefing and/or multidisciplinary review documents for these 7 drug compounds including comparison of trial and RWE data source, patient population, clinical endpoints and outcomes, comparison strategy, and FDA comments are shown in the **Table**.

The FDA identified several key considerations for RWE use for drug applications based on single-arm studies. These included pivotal trials that demonstrated a high response or large treatment effect, an improved drug toxicity profile, or a novel drug mechanism of action.

The most common RWE sources included retrospective observational studies from medical records, data from other clinical trials, commercial electronic health record databases, and literature reviews. The most common hematologic indications for RWE submissions were relapsed/refractory (R/R) large B-cell lymphoma and R/R multiple myeloma.

The most common endpoints for RWE included presence of measurable residual disease, complete response rate, and duration of response. In contrast, the most common endpoints in pivotal trials included survival endpoints (eg, progression-free survival). The most common statistical methods used to adjust for baseline imbalances included propensity-score matching and inverse-probability of treatment weighting.

The FDA identified several areas that may compromise the reliability of RWE: lack of early engagement and discussion of the study design with the FDA, absence of a prespecified statistical analysis plan or protocol, lack of transparency in data collection methods, dissimilar inclusion/exclusion criteria, dissimilar study endpoints, and an inconsistent method or frequency of outcome assessments. Comparator arms often missed baseline covariates, had selection bias, and used different outcome assessment criteria.

Conclusion: Good data quality, comparable patient populations, consistent endpoints, prespecified protocols, and the establishment of statistical analysis plans before the start of a study may be the most important factors in the FDA's approval of RWE regulatory submissions. Although the use of RWE to define a direct comparator was limited by flaws in study design and statistical analyses, RWE can be used to establish historical outcomes for patients with currently available treatment.

Table: Summary of the FDA Approved Products With Hematologic Malignancy Indications That Included RWE in Their Submissions

Drug name, year Indication	Trial	RWE
Axicabtagene ciloleucel[a,] 2017 DLBCL	**Pivotal trial or RWE data source** ZUMA-1: Phase 1/2, open label, single-arm, multicohort, multicenter study **Patient population** R/R LBCL after anti-CD20 antibody, anthracycline and either refractory after ASCT or no response to last therapy **Endpoints** OS (median) = 15.4 mo DOR (median) = 9.2 mo PFS (median) = 6.9 mo ORR = 72% CR = 51%	**Pivotal trial or RWE data source** Scholar-1: Pooled data from • Phase 3 study: LYSARC-CORAL • Phase 3 study: Canadian Cancer Trials Group-LY.12 • Observational cohort MD Anderson Cancer Center • Observational cohort Mayo Clinic/University of Iowa Specialized Program of Research Excellence **Patient population** DLBCL refractory to any prior therapy or relapsed ≤12 months from ASCT **Endpoints** OS (median) = 6.3 mo ORR = 26% CR = 7% **Comparison strategy** RWE provided historical reference for endpoints **FDA comments** RWE provided context for interpreting ZUMA-1 results and confirm the prespecified control response rate (20%)
Blinatumomab, 2018 B-ALL	Two single-arm trials	Synthetic control using retrospective cohort
Selinexor, 2019 Multiple myeloma	Single-arm trial	Health analytic database
Polatuzumab vedotin, 2019 DLBCL	Randomized trial	Literature review using prospective and retrospective studies
Tazemetostat, 2020 Follicular lymphoma	Single-arm trial	Retrospective cohort, patient medical records, molecular data, institutional databases
Tafasitamab, 2020 DLBCL	Single-arm trial	Synthetic control using respective cohort

Idecabtagene vicleucel, 2021 Multiple myeloma	Single-arm trial	Synthetic control using retrospective cohort from registries, clinical trial sites, and external research databases

ASCT, autologous stem cell transplant; B-ALL, B-cell acute lymphoblastic leukemia; CR, complete response/remission; DLBCL, diffuse large B cell lymphoma; DOR, duration of response; FDA, United States Food and Drug Administration; LBCL, large B-cell lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory; RWE, real-world evidence.
[a]An example of the detailed analyses that will be presented for each of the 7 drug compounds listed in the table.