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Health Policy Analysis

Use of Real-World Evidence to Support FDA Approval of Oncology Drugs

Bruce A. Feinberg, DO,* Ajeet Gajra, MBBS, MD, Marjorie E. Zettler, PhD, MPH, Todd D. Phillips, PharmD, Eli G. Phillips Jr, PharmD, JD, Jonathan K. Kish, PhD, MPH

ABSTRACT

Objectives: Real-world evidence (RWE) has gained increased attention in recent years as a complement to traditional clinical trials. The use of RWE to establish the efficacy of oncology drugs for Food and Drug Administration (FDA) approval has not been described. In this paper, we review 5 recent examples where RWE was submitted in support of the FDA approvals of original or supplementary indications for oncology drugs.

Methods: To identify cases where RWE was used, we reviewed drug approval packages available at Drugs@FDA for oncology drugs approved between 2017 and 2019. Five cases were selected to present a broad overview of different types of RWE, different circumstances under which RWE has been used for regulatory approvals, and how FDA evaluated the data in each case. The type of RWE submitted, the indication, limitations identified by FDA reviewers, and the outcome of the submission are discussed.

Results: RWE, particularly historical controls for rare or orphan indications, has been used to support both original and supplementary oncology drug approvals. Types of RWE included data from electronic health records, claims, post-marketing safety reports, retrospective medical record reviews, and expanded access studies. Small sample sizes, data quality, and methodological issues were among concerns cited by FDA reviewers.

Conclusion: By bridging the gap between the constraints of the trial setting and the realities of clinical practice, RWE can add value to a regulatory submission. These early examples provide insight into how regulators evaluated RWE submitted as evidence of efficacy for oncology drugs.

Keywords: Food and Drug Administration, oncology drug approval, real-world data, real-world evidence.

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Introduction

In December 2016, the 21st Century Cures Act ("Cures Act") was signed into United States (US) law.[1] The Cures Act, designed to improve the efficiency and speed of new medical product development and regulatory approval, mandated that the Food and Drug Administration (FDA) establish a program to evaluate the potential use of real-world evidence (RWE) to support the approval of new indications for drugs, and to satisfy post-approval study requirements. The Framework for the FDA's Real-World Evidence Program ("Framework") was published in December 2018.[2] In this document, the FDA defines real-world data (RWD) as data related to patient health status or the delivery of healthcare that is routinely collected from a variety of sources, such as electronic health records (EHRs), claims and billing reports, and registries, in addition to other sources such as mobile devices. RWE, derived from analysis of RWD, provides clinical insights with respect to the usage, benefits, or risks of a medical product.[2]

Historically, the FDA has primarily used RWE to inform regulatory decisions related to drug safety in the post-marketing setting. Through the Sentinel System, the FDA actively monitors post-market safety signals from multiple data sources covering over 100 million patient lives.[3] Label changes resulting from safety signals identified through post-marketing surveillance occur routinely. The use of RWE for regulatory decisions related to drug efficacy has occurred much less frequently.

Although draft guidance will not be issued until 2021,[1] with the passing of the Cures Act and the development of the Framework, it is expected that the number of regulatory approvals incorporating RWE will increase. A review of recent drug approvals that included RWE in their submission could provide insight into regulators' thinking as they evaluated the data. In this paper, we describe examples from 2017 to 2019 where RWE was included in New

* Address correspondence to: Bruce A. Feinberg DO, Vice President & Chief Medical Officer, Cardinal Health Specialty Solutions, 7000 Cardinal Place, Dublin, OH 43017, USA. Email: bruce.feinberg@cardinalhealth.com

Drug Application (NDA) or Biologics License Application (BLA) submissions.

Methods

To identify cases where RWE was used, we reviewed drug approval packages available within the Drugs@FDA database for oncology drugs approved between 2017 and 2019. Forty original marketing application approvals for oncology drugs were identified in this time period, with drug approval packages available for all 40 (Fig. 1). Five of the 40 made reference to RWE submitted in support of the approval. During the same time period, 71 supplemental indication approvals were identified (for 38 oncology drugs); however, drug approval packages were only available for 13. Three of the 13 made reference to RWE submitted in support of the approval. All 8 of the approvals with submitted RWE involved indications with an unmet need for effective therapies. For 5 of the 8 approvals with submitted RWE, the data represented historical controls; in 2 cases the RWE was derived from expanded access studies, and in 1 case the RWE was collected from off-label use of an approved therapy in a new patient population. The submitted RWE was rejected by FDA in 3 of the 8 approvals.

Five cases were selected to present a broad overview of different types of RWE submitted, different purposes the RWE served, and different outcomes for the FDA's evaluation. Three cases were selected from original marketing application approvals (1 where RWE was rejected, 1 where a historical control was accepted, and 1 where expanded access data were accepted), and 2 from supplemental indication approvals (1 where a historical control was accepted, and 1 where RWE from off-label use of an approved drug was accepted). For each of the 5 cases profiled, the indication, clinical trial conducted, RWE submitted, and relevant comments from FDA reviewers were collected. Briefing documents and product prescribing information (PI) were reviewed for additional details.

Results

Table 1 presents an overview of the 8 approvals with submitted RWE. Table 2 presents a comparison of the clinical trials and RWE submitted for each of the 5 cases profiled in this paper.

Case Study #1: Avelumab

Drug and disease

Avelumab is an anti-PD-L1 monoclonal antibody developed for the treatment of metastatic Merkel cell carcinoma (MCC), a rare, aggressive skin cancer with a poor prognosis. The FDA granted avelumab orphan drug designation for this indication.

Clinical trial

The pivotal trial supporting the approval of avelumab was the JAVELIN Merkel 200 trial, a single-arm, open label, phase 2 study which enrolled 88 patients with MCC.[4] The primary endpoint of the trial was objective response rate (ORR); duration of response (DOR) was a key secondary endpoint. The ORR in the trial was 33% (95% confidence interval [CI]: 23-44), whereas median DOR was not reached.

RWE component

The RWE included in the BLA submission consisted of a historical control with data from 14 patients with metastatic MCC who were treated with chemotherapy, obtained from the iKnowMed database (an oncology-specific EHR system).[4] In the historical control, the ORR was 28.6% (95% CI: 8.4-58.1) and median DOR was 1.7 months (95% CI: 0.5-3.0).

FDA review

Reviewers acknowledged "the limitations of the small sample size and selection bias inherent in the use of historical control data" and concluded that the data were "exploratory and reviewed only in order to further characterize the risk:benefit profile of avelumab in metastatic MCC in the context of the natural history of MCC and treatment outcomes with cytotoxic chemotherapy."[4]

Approval and label

The FDA granted avelumab accelerated approval on March 23, 2017. The approval came with a post-marketing requirement (PMR) to conduct a confirmatory clinical trial with avelumab in patients with MCC. The PI for avelumab describes the results of the JAVELIN Merkel 200 trial but does not reference the historical control.[5]

Case Study #2: Lutetium Lu177 Dotatate

Drug and disease

Lutetium Lu177 dotatate is a radiolabeled somatostatin analog developed for the treatment of somatostatin receptor-positive (SSTR-positive) gastroenteropancreatic neuroendocrine tumors (GEP-NETs), a heterogeneous group of rare malignancies with limited treatment options.[6] The FDA granted lutetium Lu 177 dotatate orphan drug designation for this indication.

Clinical trial

The randomized, open label, active-controlled Neuroendocrine Tumors Therapy (NETTER-1) trial evaluated the efficacy and safety of lutetium Lu 177 dotatate plus octreotide versus octreotide alone in 229 patients with progressive, well-differentiated, locally advanced/inoperable or metastatic SSTR-positive midgut carcinoid tumors.[6] The primary endpoint of the trial was; key secondary endpoints included ORR and DOR. Median progression-free survival was not reached for patients in the lutetium Lu 177 dotatate arm compared to 8.5 months (95% CI: 5.8-9.1) in the octreotide arm. The ORR was significantly greater among lutetium Lu 177 dotatate-treated patients compared to those treated with octreotide alone (13% [95% CI: 7, 19] versus 4% [95% CI 0.1, 7]); median DOR was not reached in the lutetium Lu 177 dotatate arm. Safety data were prospectively collected at prespecified timepoints for the 111 patients receiving lutetium Lu 177 dotatate.

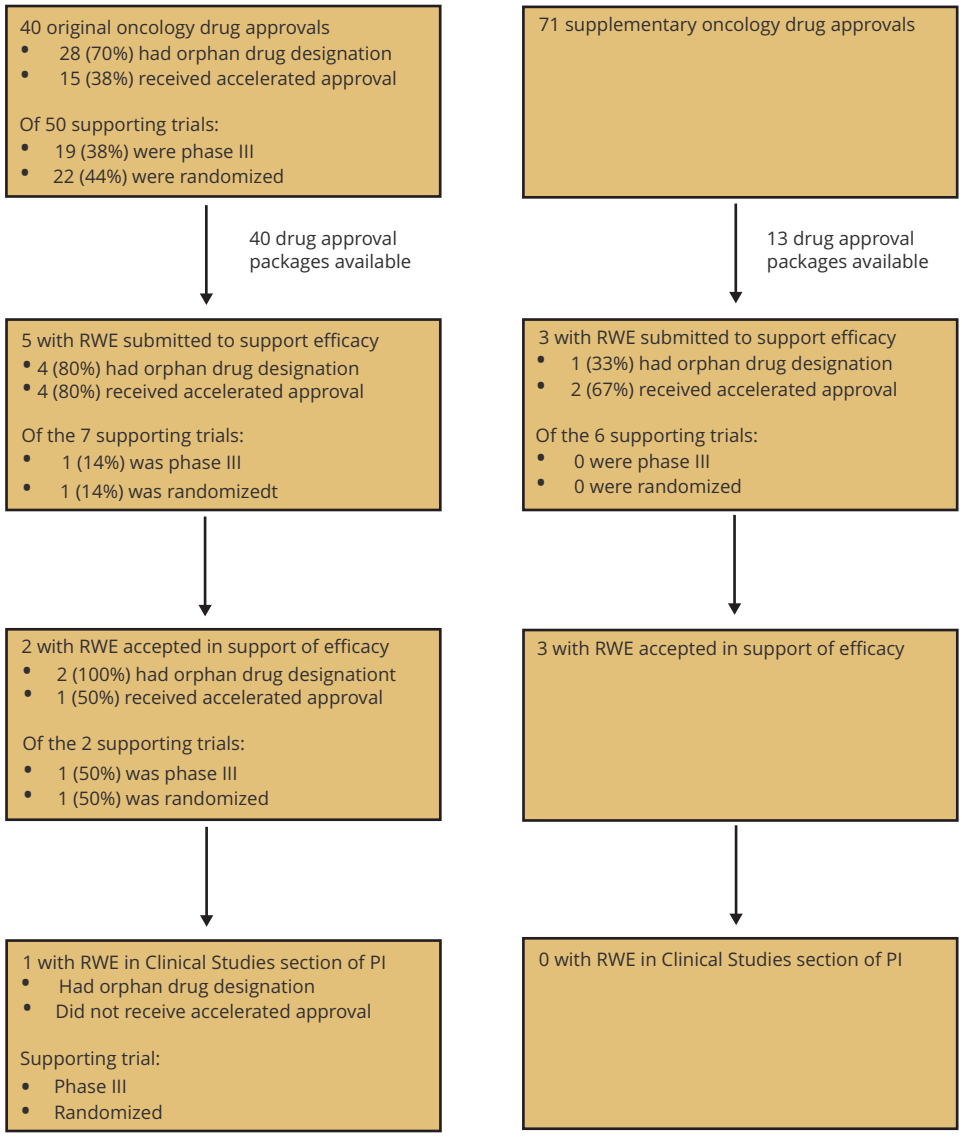
RWE component

The ERASMUS Medical Center trial (ERASMUS), an investigator-sponsored, open label, single-arm, expanded access study of 1214 patients with SSTR-positive neuroendocrine tumors, retrospectively evaluated investigator-assessed ORR and DOR and provided additional safety data to support lutetium Lu 177 dotatate in this indication.[6] Investigator-assessed ORR was 16% (95% CI: 13, 20) in the 360 patients with GEP-NETs; median DOR in the 58 responding patients was 35 months (95% CI: 17, 38). Retrospective medical record review was conducted on a subset of 811 patients from ERASMUS; however only serious adverse reactions were documented.[6]

FDA review

In comparing ERASMUS data to NETTER-1 data, FDA reviewers noted differences in the tumor types evaluated, eligibility criteria in the studies, dosing schedules, timing of tumor response, and safety assessments, and in grading criteria used for safety assessments.[6] The ERASMUS study lacked a formal clinical protocol,

Figure 1. Selection of real-world evidence cases from oncology drug approvals, 2017 to 2019.



RWE indicates real-world evidence.

a prespecified statistical analysis plan, and an independent blinded assessment of efficacy outcomes.[6]

Approval and label

The FDA approved lutetium Lu 177 dotatate on January 26, 2018 for the indication of SSTR-positive GEP-NETs (a broader, more heterogenous indication than that supported by NETTER-1 alone). Both safety and efficacy data from the ERASMUS study appear in the PI for lutetium Lu 177 dotatate.[7]

Case Study #3: Blinatumomab

Drug and disease

Blinatumomab was initially approved in 2014 for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL), a condition for which the FDA granted blinatumomab orphan drug designation.[8] ALL is a rare, rapidly progressing cancer, and patients in remission who have detectable minimal residual disease (MRD) are more likely to relapse.

Clinical trial

The efficacy of blinatumomab for the treatment of MRD-positive B-cell precursor ALL was evaluated in the open label, single-arm BLAST study.[9] The study enrolled 116 patients in first or second hematologic complete remission (CR1 or CR2) who had received at least 3 chemotherapy blocks of standard ALL therapy and had MRD positivity at a level of $\geq$ 0.1%, although the FDA determined that only 87 were in true CR and had adequate MRD assay standards.[10] The primary efficacy endpoint was achievement of undetectable MRD within 1 cycle of blinatumomab treatment; hematological relapse-free survival (RFS) was a key secondary endpoint. Among the 80 patients with an assay sensitivity of at least 0.005%, undetectable MRD was achieved by 65 of 80 patients (95% CI: 71.0%, 89.1%).[11] The median RFS among the 80 patients

Table 1. Case characteristics of regulatory approvals for which real-world evidence was submitted.

Drug	FDA approval date	Type of RWE	Regulatory action supported	Limitations of RWE identified by FDA reviewers	FDA decision
Avelumab	March 23, 2017	EHR data as historical control for efficacy	Original marketing application approval for MCC	Exploratory nature of analyses Small sample size Selection bias	Accepted
Pembrolizumab	May 23, 2017	Expanded access study data (submitted as part of a major amendment to the sBLA) to support clinical efficacy	Supplementary indication approval for microsatellite instability-high or mismatch repair deficient cancers (Original marketing application approval was for unresectable or metastatic melanoma)	No specific comments on RWE	Accepted
Lutetium Lu 177 dotatate	January 26, 2018	Expanded access study data (events captured through retrospective medical record review) to support clinical efficacy and safety	Original marketing application approval for SSTR-positive GEP-NETs	Differences in patient populations Differences in drug dose Differences in timing and criteria used for efficacy and safety assessments Exploratory nature of analyses	Accepted
Blinatumomab	March 29, 2018	Retrospective data from clinical sites as historical control for efficacy	Supplementary indication approval for MRD-positive ALL (Original marketing application approval was for Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL)	Small sample size Differences in lengths of follow-up Confounding	Accepted
Palbociclib	April 4, 2019	EHR data, claims data, and post-marketing safety reports to support clinical efficacy and safety in new patient population	Supplemental indication approval for male breast cancer (Original marketing application approval was for post-menopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced or metastatic breast cancer)	Small sample size Differences in patient populations	Accepted
Erdafitinib	April 12, 2019	EHR data and next-generation sequencing data as historical control for clinical efficacy	Original marketing application approval for locally advanced or metastatic urothelial carcinoma and susceptible FGFR3 or FGFR2 genetic alterations	Small sample size Selection bias Misclassifications Missing data	Rejected
Selinexor	July 3, 2019	EHR data as historical control for efficacy	Original marketing application approval for RRMM	Small sample size Immortal time bias Selection bias Misclassifications Confounding Missing data	Rejected
Entrectinib	August 15, 2019	EHR data as historical control for efficacy	Original marketing application approval for metastatic non-small cell lung cancer with *ROS1*-positive tumors	Small sample size Selection bias Missing data Analysis considered post-hoc as protocol was not submitted in advance	Rejected

ALL indicates acute lymphoblastic leukemia; EHR, electronic health record; FDA, Food and Drug Administration; FGFR, fibroblast growth factor receptor; GEP-NET, gastroenteropancreatic neuroendocrine tumors; MCC, Merkel cell carcinoma; MRD, minimal residual disease; RRMM, relapsed or refractory multiple myeloma; sBLA, supplementary biologic license application; SSTR, somatostatin receptor.

Table 2. Clinical trials and real-world evidence submitted in support of regulatory approval.

	Clinical trial	RWE
Avelumab		
Population	Metastatic Merkel cell carcinoma	Metastatic Merkel cell carcinoma
Intervention	Avelumab	Chemotherapy
Comparison	None	None
Outcome	ORR, DOR	ORR, DOR
Study design	Prospective, single-arm, open label, phase 2	Retrospective EHR data collection
Lutetium Lu 177 dotatate		
Population	Progressive, well-differentiated, locally advanced/inoperable or metastatic SSTR-positive midgut carcinoid tumors	SSTR-positive GEP-NETs
Intervention	Lutetium Lu 177 dotatate plus octreotide	Lutetium Lu 177 dotatate
Comparison	Octreotide	None
Outcome	PFS, ORR, DOR	ORR, DOR
Study design	Prospective, randomized, open label, active-controlled phase III	Investigator-sponsored, open label, single-arm, expanded access; events captured through retrospective medical record review
Blinatumomab		
Population	MRD-positive B-cell precursor ALL in CR1 or CR2	MRD-positive B-cell precursor ALL in CR1 or CR2
Intervention	Blinatumomab	Chemotherapy
Comparison	None	None
Outcome	Undetectable MRD, RFS	RFS
Study design	Prospective, open label, single-arm phase 2	Retrospective medical record data collection
Palbociclib		
Population	N/A*	Men with HR-positive, HER2-negative advanced or metastatic breast cancer
Intervention	N/A	Palbociclib plus aromatase inhibitors or fulvestrant
Comparison	N/A	Other endocrine therapy-based regimen
Outcome	N/A	Real-world tumor response
Study design	N/A	Retrospective EHR, claims data and post-marketing safety report collection
Selinexor		
Population	Relapsed refractory multiple myeloma	Relapsed refractory multiple myeloma
Intervention	Selinexor plus dexamethasone	Treatment at physician's discretion
Comparison	None	None
Outcome	ORR, DOR, OS	OS
Study design	Prospective, open label, single-arm phase 2b	Retrospective EHR data collection

CR indicates complete response; EHR, electronic health record; DOR, duration of response; GEP-NET, gastroenteropancreatic neuroendocrine tumor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MRD, minimal residual disease; N/A, not applicable; ORR, objective response rate; OS, overall survival; SSTR, somatostatin receptor.
*No clinical trials were conducted to demonstrate the efficacy of palbociclib in male patients with breast cancer; however, the FDA's review relied in part on the data from the prospective, randomized, double-blind, active-controlled phase III trial in female patients with breast cancer.

using the higher sensitivity assay was 24.2 months (95% CI: 17.9, NE).[11]

RWE component

The RWE utilized consisted of a historical comparison group of patients in CR1 or CR2 with MRD-positive ALL diagnosed between 2000 and 2014 in 8 European countries and was submitted with the supplemental BLA (sBLA).[9] To align the inclusion criteria between the BLAST study and that of the historical control, 73 patients from the BLAST study and 182 patients from the control were selected for a propensity analysis to compare RFS. The analysis found that RFS was significantly longer in the blinatumomab-treated patients compared to the control (35.18 months [95% CI: 24.16 to not evaluable] for the blinatumomab group versus 8.30 months [95% CI: 6.23, 11.90] for the control group).

FDA review

The FDA noted several limitations, including small sample size, different lengths of follow-up, and potentially different treatment patterns between the trial patients and the historical controls. They concluded: "In the presence of the confounding and time-dependent effect of HSCT [hematopoietic stem cell transplantation] and the issues of propensity score analyses, the actual benefit of blinatumomab is difficult to estimate."[10]

Approval and label

The accelerated approval of blinatumomab for the sBLA was granted on March 29, 2018. A PMR for a confirmatory randomized clinical trial (RCT) of blinatumomab in patients with ALL in remission with detectable MRD was mandated. The results of the BLAST study appear in the PI for blinatumomab; no reference is made to the historical control.[11]

Case Study #4: Palbociclib

Drug and disease

Initially approved in 2015, palbociclib is a cyclin-dependent-kinase 4/6 inhibitor, indicated for the treatment of post-menopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced or

metastatic breast cancer. Although an estimated 2670 cases of male breast cancer will be diagnosed in 2019,[12] few treatment options are indicated in men, and male patients with breast cancer were ineligible to participate in the clinical trials supporting palbociclib's approval.

Clinical trial

No clinical trials were conducted to demonstrate the efficacy of palbociclib in male patients with breast cancer.

RWE component

A supplemental NDA (sNDA) was submitted proposing to broaden the palbociclib indication to include male patients and included a retrospective outcomes analysis using EHR data from the Flatiron Health Analytic Database.[13] A total of 59 male patients were identified; 25 were treated with palbociclib and 34 were treated with other agents. The primary efficacy outcome was real-world tumor response, evaluation of which required on-study radiographic tumor assessments to have occurred. Only 12 patients in the palbociclib group and 29 in the non-palbociclib group had these assessments. Additionally, 13 patients in the non-palbociclib group whose endocrine therapy only included a tamoxifen agent were excluded, leaving only 16 in this group with adequate data for analysis.

Other RWE data submitted included a retrospective, descriptive analysis of IQVIA Pharmacy Claims and Medical Claims databases related to prescription order duration in male breast cancer patients.[13] A total of 37 patients received palbociclib + aromatase inhibitor/fulvestrant in the first line setting, versus 214 who received aromatase inhibitor/fulvestrant alone, and analysis appeared to show a longer prescription order duration with palbociclib therapy versus endocrine therapy alone.

Safety information submitted with the sNDA included EHR data from the Flatiron Health Database on 25 male patients who received palbociclib, 362 post-marketing safety reports from the Pfizer Global Safety Database, and 2 phase 1 studies.[13]

FDA review

With respect to the EHR data, the FDA expressed concerns about the limited sample size and poorly matched cohorts.[13] Similarly, it was noted that the claims data should be interpreted with caution because the groups were not balanced by age or stage of disease.[13]

In assessing the safety data, the reviewer commented that it was difficult to derive any conclusions based on the Pfizer database and phase 1 study data, but "in general the AE profile for male patients appears to be consistent with the known AE profile of palbociclib."[13]

Approval and label

The FDA approved the sNDA on April 4, 2019. No efficacy data from male patients appear in the palbociclib PI; however, the following statement appears in the adverse reactions, post-marketing experience section: "Based on limited data from post-marketing reports and electronic health records, the safety profile for men treated with IBRANCE is consistent with the safety profile in women treated with IBRANCE."[14]

Case Study #5: Selinexor

Drug and disease

Selinexor, a first-in-class, oral, small molecule inhibitor of the nuclear export protein, exportin 1, and was developed in combination with dexamethasone for the treatment of patients with relapsed refractory multiple myeloma.[15] The FDA granted selinexor orphan drug designation for this indication.

Clinical trial

The efficacy and safety of selinexor was evaluated in the open label, single-arm Selinexor Treatment of Refractory Myeloma (STORM) trial. The primary endpoint of the trial was ORR; DOR and overall survival were key secondary endpoints. After an Oncologic Drugs Advisory Committee meeting and major amendment of the NDA, a subpopulation of 83 patients from the STORM trial who had received at least 4 prior therapies and whose disease was refractory to at least 2 proteasome inhibitors, at least 2 immunomodulatory agents, and an anti-CD38 monoclonal antibody was selected.[15] In this population, the ORR was 25.3% (95% CI: 16.4-36), and the median DOR was 3.8 months (range, 0.7–8.1 months).

RWE component

A retrospective observational study using EHR data from the Flatiron Health Analytic Database was also submitted.[15] The intent of the retrospective analysis was to compare OS in a population similar to that studied in the STORM trial to the OS results from STORM.

FDA review

In the initial NDA submission, the FDA expressed concerns about major methodological issues with the EHR data and found that the results were inadequate to support regulatory decision making.[15] After conducting their own analysis of the data, which resulted in "very limited sample size and unstable estimates," it was concluded that the evidence generated could not provide context or comparison for the OS observed in the STORM patients.[15]

Approval and label

After the Oncologic Drugs Advisory Committee meeting and discussion with the FDA, efficacy data from the ongoing phase III, randomized BOSTON trial was submitted. The FDA subsequently granted selinexor accelerated approval on July 3, 2019. A PMR to submit the final study report for the BOSTON trial accompanied the approval. Because the EHR data were not considered in the approval decision, they were not included in the PI.[16]

Discussion

In our case study analysis of oncology drug submissions to the FDA, we found that 4 of the 5 drugs reviewed had orphan drug designation, and the fifth was for a rare subset within a larger patient population (palbociclib for male patients with breast cancer). Three of the 5 drugs (avelumab, blinatumomab, and selinexor) received accelerated approval for the indications for which RWE was submitted; all 3 had PMRs for confirmatory clinical trial data, with avelumab and blinatumomab both requiring new clinical trials. The types of RWE used in the regulatory submissions included EHR data, claims data, post-marketing safety reports, retrospective medical record reviews, and expanded access study data. Both the lutetium Lu 177 dotatate and blinatumomab submissions used RWE data from outside the US. A comparison of the clinical trials and RWE submitted with the NDA/BLA for each of the 5 cases shows that when the clinical trial had no control or comparator arm, the RWE collected for the historical control attempted to match the patient population to that of the clinical trial, and the intervention was standard of care treatment. In the case where the clinical trial was conducted with

a comparator arm, the RWE served to broaden the patient population, and the intervention was the investigational agent. In all cases, attempts were made to replicate at least 1 clinical trial endpoint with RWE.

Overall, we found that RWE was rejected in 3 of the 8 cases where it was submitted. In all 3 cases, the RWE submitted was intended to serve as a historical control, and methodological issues/poor data quality were the reasons for rejection in each case. All 3 of the drugs were approved, despite rejection of the RWE. Even when accepted, there were no instances where historical control RWE appeared in the PI. Of the 3 cases we identified where the RWE submitted was not a historical control, the RWE appeared in the clinical studies section of the PI for only one: lutetium Lu 177 dotatate (expanded access study data). Expanded access data were also submitted as RWE for the microsatellite instability-high or mismatch repair-deficient cancer supplemental indication for pembrolizumab; however, there were only 6 patients, and the data comprised part of an amendment to the sBLA to support efficacy.[17] In the case of palbociclib, the approval of the male breast cancer indication appeared to rely heavily on the strength of the efficacy data in the original patient population (female breast cancer patients). Only RWE supporting the safety of palbociclib in men with breast cancer appears in the PI.

Do these observations tell a bigger story? Amid the increasing costs and known limitations of traditional RCTs, are our findings a harbinger for RWE to have a greater role in establishing the efficacy of new drugs? Can we contextualize these observations from a historical perspective on the use of RWE by the FDA?

During the preceding decade, there was significant precedent for the FDA's embrace of RWE in its approvals of drugs for rare and orphan indications. Many cancers are rare diseases: from 2008 to 2017, 42.5% of orphan drug marketing approvals were for oncology indications.[18] Furthermore, the increasing use of precision medicine principles to define cancers by their genome rather than organ of origin is resulting in common cancers becoming a collection of rare subtypes. The smaller number of patients available is a barrier to conducting traditional RCTs, and the serious or life-threatening nature of the condition and unmet medical need often makes the therapy eligible for expedited programs, such as accelerated approval. In this setting, the FDA regularly demonstrates flexibility and accepts single-arm studies to support approval: 34% of oncology indication approvals granted by the FDA between 2013 and 2018 were based on single-arm trials.[19] As a result, clinical safety and efficacy data supporting approval are limited. Additionally, less than 5% of adult cancer patients participate in clinical trials, with enrollment disproportionately favoring patients who are younger, healthier, and less diverse, resulting in data that are not necessarily representative of the patient population as a whole. [20]

Because some safety signals cannot be identified until a large number of patients have been treated or until a long follow-up period has elapsed, the FDA has been reliant on real-world post-marketing safety surveillance to provide that information. For example, an increased risk of veno-occlusive disease observed within the first year after approval of gemtuzumab ozogamicin for the treatment of relapsed acute myelogenous leukemia prompted the FDA to require a black box warning to be added to the product label; this drug was eventually withdrawn from the market over safety concerns.[21,22] The FDA has also requested real-world effectiveness data (rather than new RCT data) for oncology drugs through PMRs and post-marketing commitments (PMCs). The initial approval of osimertinib for EGFR T790M+ non-small cell lung cancer was accompanied by the PMC to "provide data on overall response rate with osimertinib from one or more 'real world' cohorts."[23] A clear difference between these examples and our case studies is the incorporation of RWE in support of efficacy in a submission for a new indication rather than a component of post-marketing safety surveillance or fulfillment of PMRs/PMCs.

Although the Cures Act formally set in place an agenda to evaluate the potential use of RWE efficacy to support the approval of new drug indications, such use of RWE was not unprecedented. The use of historical controls in particular is well established.[24] An oft-cited example is the original marketing application approval of blinatumomab for ALL in 2014.[8] The single-arm trial was supported by a historical control group of data derived from chart review of 694 patients from US and European study sites.[8] Blinatumomab also provides an example of the use of RWE to support supplementary indication approval: in 2016, blinatumomab was approved for the ALL indication in the pediatric population, supported in part by data from 41 children under the age of 18 in a single-arm, open label, expanded access protocol.[25] These examples provide a basis for expanding the use of RWE to support FDA approvals.

In accordance with the Cures Act directive, the FDA issued the Framework, outlining 3 key factors they will consider in evaluating RWE in regulatory submissions: whether the RWDs are fit for use (whether the clinical study methodology is acceptable and the data are reliable and relevant); whether the study design used to generate the RWE can provide adequate scientific evidence to answer the regulatory question; and whether the conduct of the study meets FDA regulatory requirements.[2] With the Framework as the foundation of FDA's structural proposals for RWE, in May 2019 the Agency added a draft guidance plan proposing a uniform document format to simplify tracking[26] and has communicated future plans to issue multiple guidance documents related to specific aspects of generating quality RWD and RWE to support regulatory decision making.[2]

Although the FDA considers each submission with RWE on a case-by-case basis, as the Agency continues to build its knowledge base and refine its understanding of the potential for—and limitations of—RWE, it is anticipated that the requirements for RWE to support regulatory decision making will become more stringent. To this end, the Agency is undertaking a series of demonstration projects to gain insight into best practices for studies generating RWD and to help inform guidance development. These include projects to assess study designs using RWD to support efficacy, to assess data collection and data quality of RWD from multiple sources for use in regulatory decisions, and to harmonize data standards across RWD networks.[2] One project to provide insight into the feasibility of answering clinical efficacy questions with RWD is RCT DUPLICATE, which will attempt to replicate the results of 30 completed phase III and 4 RCTs using RWD from claims databases, with standardized, high-quality methodology.[27]

Integrating RWE into the drug development and approval process has the potential to reduce the time, cost, and patient burden associated with clinical trials while providing clinically relevant information to all stakeholders. In light of recent negative press,[28] it is critical to highlight that the RWE process is not intended to replace prospective clinical trials, has scientific validity, and is subject to stringent regulatory oversight.

Conclusion

Despite the inherent limitations of RWD research, we anticipate that the proportion of regulatory submissions containing RWE to support product efficacy will increase, and that we will see a broader scope of RWE utilized, with more frequent incorporation of RWE into the PIs of approved products. We believe this presentation of case studies exploring the use of RWE supporting drug efficacy in FDA submissions post-Cures Act will provide

healthcare stakeholders with a greater understanding of the process and critical issues in this unfolding story.

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Author Affiliations: Cardinal Health Specialty Solutions, Cardinal Health, Dublin, OH, USA

Author Contributions: *Concept and design:* Feinberg, Gajra, Zettler, Kish
Acquisition of data: Feinberg, Gajra, Zettler, T Phillips
Analysis and interpretation of data: Feinberg, Gajra, Zettler, T Phillips, E Phillips, Kish
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