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Revolutionizing Oncology: Advancements in Disease Identification, Drug Development, and Regulatory Approaches

Arvind Uttiramerur

Programmer Analyst at Thermofisher Scientific, USA

ABSTRACT

There is a lot of excitement around creating clinical trials that incorporate adaptive features to deliver new medications to patients faster. These trials aim to enhance efficiency, increase the likelihood of showing the drug's efficacy, provide more valuable insights and comprehensively gather clinical evidence. Progress in enhancing our capacity to develop learning systems and enhance data gathering, in order to connect clinical objectives and quantifiable results, is now shaping clinical research on the way patients are cared for, ought to be cared for and desire to be cared for using these innovative treatments in actual practice. Consequently, there is a chance to gain insights from ongoing initiatives aimed at gathering, analyzing, and implementing real world evidence in pharmaceutical development.

Keywords: Oncology, Randomized controlled trials, Breakthrough Therapy Designation

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REAL WORLD EVIDENCE

Real world evidence (RWE) pertains to information obtained from sources beyond the conventional clinical trial environment. This includes data from electronic health records (EHRs) that cover patients receiving both on label and off label treatments, pragmatic clinical trials, patient registries, individuals treated via expanded access programs, administrative claims, surveys, as well as data generated through mobile health technologies like smartphones, wearables, the internet, and social media. Real world evidence (RWE) is believed to offer a more accurate portrayal of the overall population and the medical treatment they receive. This is because clinical trials typically include only patients with specific characteristics, leading to limited enrollment and restricted eligibility criteria. As a result, high quality RWE can offer diverse and sometimes broader insights into the safety and efficacy of treatments compared to certain traditional clinical trials that have strict eligibility criteria.

Randomized controlled trials (RCTs) are considered the best method to reduce biases, but Real-World Evidence (RWE) can also be valuable in specific situations. For instance, when evaluating a drug with a strong effect size that outweighs potential confounding variables and when there is high confidence in the initial efficacy data, such as for a treatment classified as a breakthrough Therapy. Although there are some worries about the reliability of data due to issues like incomplete information and inconsistent data gathering methods, using Electronic Health Records (EHRs) enables the collection of data from a larger pool of patients in a diverse patient population faster than conventional phase 4 trials meant for post market compliance. Therefore, when it comes to groundbreaking treatments, determining the practicality and adequacy of verifying clinical benefits in real world scenarios is a crucial matter that requires thoughtful evaluation. The Breakthrough Therapy Designation (BTD) was established in 2012 to speed up the development of medications for illnesses that lack treatment options. Decisions regarding Breakthrough Therapy designation are based on data showing significant improvements compared to existing treatments. This designation aims to streamline the review process for new drugs and reduce the exposure of patients to less effective treatments throughout their development and post market phases. Medications targeting life threatening conditions with medical needs can receive expedited approval by demonstrating a strong impact on surrogate markers, like tumor response, which are likely

indicators of clinical benefit. Drugs that are approved based on an endpoint typically need assessment to confirm their actual clinical benefits especially when there is uncertainty, about the connection between the surrogate endpoint and the clinical benefit or between the observed clinical benefit and the outcome. When a significant improvement in survival is expected, such as with drugs receiving Breakthrough Therapy Designation (BTD) there may be a lack of balance for conducting a randomized trial with an effective treatment to confirm clinical benefits after accelerated approval. This situation underscores the importance of exploring methods like Real World Evidence (RWE) to validate the benefits of highly potent anticancer treatments, like those designated with BTD.

When considering trial methods, it's important to look beyond the models. Adaptive clinical studies that mirror world practices offer a chance to gain deeper insights into new treatments. Pragmatic clinical trials (PCTs) make use of healthcare facilities to evaluate interventions in clinical environments aiming to maximize their practicality and relevance, across a wider patient population. While PCTs are typically described by the FDA as studies there are also instances of nonrandomized trials. Take, for instance the Targeted Agent and Profiling Utilization Registry (TAPUR) Study initiated by ASCO in March 2016. This trial, not based on randomization, aims to gather information on the safety and efficacy of approved treatments, in disease scenarios. Despite preparation including validation studies assessing sensitivity, specificity negative predictive values to ensure reliable data collection, for safety and efficacy evaluation it can still be difficult to pinpoint confounding variables that influence study outcomes and applicability.

CHALLENGES AND CONSIDERATIONS

The progress in technology and the increased use of EHRs have made it easier to gather information outside of trials. This data has the potential to enhance care complement existing clinical trial approaches. Accelerate drug development. While collecting real world data (RWD) faces obstacles such as varying data quality, diverse collection methods and privacy issues significant advancements have been achieved in this field recently. However, there are still challenges that need to be addressed to fully integrate real world evidence (RWE) into healthcare practices.

1. Data sources
2. Potential variables needed
3. Data standards

The challenges that hinder the integration of Real-World Evidence Electronic Health Records (RWE EHRs), from sources like academic institutions, hospitals, community oncology centers and registries involve gathering data such as lab results, claims, and billing codes. This data may include inputs from patient reported outcomes (PROs) patient advocate groups and other relevant organizations. The essential information needed comprises diagnosis details using International Classification of Disease (ICD) codes; dates of subsequent diagnoses; disease staging information; dates and locations of metastases; histological details; radiology and pathology reports; treatment timelines including start/stop dates for subsequent treatments along with CPT codes; laboratory test results with dates, names, values in units and normal ranges; demographic data like smoking status; biomarker statuses; gene sequencing details; performance statuses; medication administration records including dates, drugs used, dosages, routines followed and units administered. Adverse events reporting involves collecting information on Grade 3+ or serious adverse events. Outcomes data includes details such as the date of death or other endpoints. Depending on inquiries additional unique variables may need consideration. While regulatory trials have adopted Clinical Data Interchange Standards Consortium (CDISC) standards for data exchange requirements, in research settings there is an effort to establish universal data standards within the Electronic Health Record (EHR) infrastructure. In the way electronic data capture (EDC) systems have become more uniform reducing the need for validation processes. In hospital environments there might still be variations in electronic records management software. A shift towards using commercial systems, like EPIC is noticeable. Comparison, between merging data and using third party aggregators; Although there isn't a method for combining real world data (RWD) sources various external entities have started implementing this process in the field of oncology. Examples include Flatiron and USO within oncology and Humedica beyond oncology. For instance, the Flatiron dataset includes electronic health record (EHR) information, over time integrating structured and unstructured EHR data streams.

Factors to consider when merging data include the diversity of data sources variations, in health record (EHR) platforms, customized adaptations at different sites, such as unique workflows and specialized logic as well as the mix of structured and unstructured data. The data itself is often intricate and ambiguous, especially when dealing with financial information. Issues like interoperability gaps and the complexities of merging, mapping and standardizing data require programming and informatics efforts to ensure that datasets are ready for research purposes. It's also crucial to link or trace the individual across EHR systems and disparate real-world data (RWD) platforms to comprehensively track a patients care journey, across multiple sources. Challenges related to unstructured and missing data There is a variation among EHR systems/providers particularly in the types of data collected through structured versus unstructured components of an EHR. For example, some systems capture disease stage information while others do not. It is estimated that around half of the variables needed for oncology focused Real World Evidence (RWE) are found in documents necessitating either technology enabled solutions or manual chart review (with Natural Language Processing also being considered).

Structured data comprises data points such as fields whereas unstructured data may include free text entries from physician notes or scanned pathology reports. Derived variables like "lines of therapy" and "real world progression" can enhance RWE datasets by combining unstructured data elements based on predefined business rules. Given that each variable originates from sources it is essential to describe the reliability and validity of these variables. Furthermore, addressing missing data. An issue in clinical trial reports. Is crucial regardless of whether the data collection method's structured or unstructured. Challenges and considerations arise when extracting variables, from data including issues with data quality, missing variables and the methods used to extract content. The audit trails vary depending on the Electronic Health Record (EHR) system being utilized. Hospitals employ extraction systems showcasing a diversity in Information Technology (IT) capabilities. The data was recorded by clinicians.

Collaborating with an oncology EHR data aggregator could simplify the process by utilizing existing procedures to map data from providers and present it in formats. This approach would minimize variability. Streamline the extraction process. Nonetheless challenges like limited access to a range of populations hinder the ability to generalize results broadly. Ideally EHR fields could be tailored for data collection based on provider preferences. Considerations and challenges arise when defining endpoints, in settings. Each type of endpoint whether it be endpoints like survival (OS) surrogate endpoints like progression free survival (PFS) or other clinically significant endpoints such as response rate (RR) present unique hurdles in terms of data collection, reliability, and accuracy in electronic health records (EHR).

It is crucial to engage in discussions and reach agreements with the bodies. Is it feasible to measure tumor reduction by analyzing radiology reports? Should tumor shrinkage be assessed with the level of precision as the established RECIST criteria? Is there value in combining a clinician’s evaluation of a patient with a radiologist’s interpretation of scans to create measures reflecting tumor load? Can metrics like time until the treatment or time until treatment failure as determined by the treating physician serve as indicators of treatment efficacy Documenting treatment decisions may pose challenges (e.g. determining endpoints for adjusting treatments or selecting therapies). What additional collaboration might be needed with EHR providers to update records, for purposes beyond billing? How can we verify if endpoints evaluated using real world data are dependable, valid, and clinically relevant? Issues related to HIPAA and obtaining consent may arise as information is necessary, for data linkages, adverse event reporting and other purposes. This could lead to the availability of physician data for auditing purposes.

Currently information from health records (EHRs) lacks patient consent, which might necessitate procedures and policy adjustments. Obtaining consent for registries could be feasible. These studies are closely monitored and may not fully represent real world evidence (RWE). While obtaining consent may pose challenges, upcoming trials utilizing EHRs might require consent along with a clear explanation of the data collection purpose.

DATA QUALITY AND UTILITY

There are still challenges when it comes to merging organizing and examining data from various sources such as electronic health records (EHRs) insurance claims, biosensors, genomics datasets and patient reports. However, there is an interest in utilizing real world evidence (RWE) for evaluating drugs and other clinical interventions.

Initiatives like Sentinel and PCORnet gather data from sources like claims and EHRs to accumulate extensive health information for research purposes particularly in comparative efficacy studies.

The importance of EHRs is underscored by the launch of the ™ system by the American Society of Clinical Oncology (ASCO) aimed at enhancing patient outcomes and quality of life through EHR data analysis. Nonetheless the suitability of data for regulatory use remains uncertain at this point. If appropriate standards and methodologies for collecting, verifying, and analyzing real world data are established RWE could potentially support activities impacting drug development and delivery.

Data completeness, variable reliability, and variable validity are crucial quality elements that need consideration, and these elements should indeed vary by data source, such as electronic health records (EHRs) The extractability of relevant fields is also important and should be evaluated differently for various databases, including community versus academic sources, to ensure the data's usability and relevance. Sources of variables and data provenance are essential to understand where the data comes from and how it was collected, which can significantly impact the quality and trustworthiness of the data. Community and academic databases may have different structures and capabilities, making it important to assess how easily you can get the information you need from each. Community databases might be more practical and focused on direct patient care, while academic databases could offer more detailed research data. The ability to pull out specific information, like patient demographics or treatment outcomes, varies between databases. This means you should check if the database you're using can give you the details necessary for your research or patient care. It's also essential to understand that the technology and methods used to collect and store data can affect how you extract it. Some systems might be more advanced, offering easier access to a wide range of data, while others might be more limited.

- Data Completeness: Report how much information is available for each variable, indicating if any data points are missing and to what extent, as this affects the reliability of the analysis. Setting a threshold for acceptability, such as 90% completeness, can help in evaluating the quality.
- Variable Reliability: Describe how consistently a variable measure is supposed to measure across different data entries or sources. A high reliability score means the data is consistent; consider thresholds based on standard reliability tests.
- Variable Validity: Explain whether the data accurately represents the real-world conditions it is supposed to reflect. Validity scores should be based on established benchmarks for each type of data, indicating how closely the data matches real-world conditions.
- Sources of Variables and Data Provenance: Clearly document where each piece of data comes from and the process of its collection. This includes detailing the original source of the data and any transformations it has undergone, which is crucial for assessing its credibility and relevance.

When choosing people for a study using real-world data (RWD), it's important to clearly describe who is being included, like their age, health condition, and where they live. This helps us understand who the study is about. You should also explain how you pick these people, such as what health records or databases you use. This makes it easier for others to know how the study was done. It's good to share why some people might not be chosen for the study. For example, if the study is about a certain medicine, people who haven't taken it would not be included. Lastly, it's helpful to talk about any extra checks you do, like looking at the data in different ways, to make sure your findings are strong and reliable. To make sure the information we get from real-world data (RWD) is strong and can be trusted, we need to do extra checks like sensitivity analyses. This means looking at the data in different ways to see if we still get the same answers, which helps us be more sure about our findings.

Sensitivity analyses are important because they help us understand how changes in the way we pick our study group or how we define our measurements might affect what we learn from the study. This is a key step in making sure our results are reliable and can be used to make decisions. When using real-world evidence (RWE), it's important to look at how well a treatment works in real-life settings, not just in carefully controlled trials. This includes seeing if the treatment improves patients' health, quality of life, or survival rates. To pick the best endpoints and outcome measures, think about what is meaningful for patients and doctors. This could be how long a patient lives without their disease getting worse, how much their health improves, or how their symptoms change with treatment.

Safety reporting based on real-world data (RWD) collected from electronic health records (EHR) must include all known safety events, which means any health problems that happen during the study need to be recorded, even if they seem unrelated to the drug being tested. Regulatory advice for marketed drugs suggests that additional reporting in EHR should go beyond what doctors note in their daily activities, ensuring that any side effects or unexpected health issues are fully captured according to Good Clinical Practice guidelines. This extra reporting is needed to make sure that the safety of the drug is well understood in a wide range of people and in real-life conditions, not just under the controlled conditions of early trials.

In certain situations, like when a drug is being used by more people after it's been sold, or if it's being tested for new uses, there's a need to closely watch and report on how safe the drug is to help protect patients. For post-market commitments, data requirements focus on long-term safety and efficacy in the general population, requiring ongoing collection of real-world data (RWD) to monitor any adverse events or outcomes not seen in clinical trials. When considering label expansion, the data must demonstrate the drug's efficacy and safety in new patient groups or conditions not originally approved, often involving additional real-world studies or analyses to support these new claims. Improving dose selection involves collecting detailed RWD on how different doses affect patients in real-life settings, including information on dose modifications, interruptions, and the impact of food on drug absorption. Defining safety in broader populations requires a comprehensive analysis of RWD to identify any potential risks or adverse effects across diverse patient groups, including those with comorbidities or those receiving concomitant medications.

To keep up with changing data characteristics and needs for RWD, it's important to regularly update and validate the data collection methods, ensuring they capture relevant and accurate information over time. This might involve adjusting electronic health record (EHR) systems to collect new types of data as medical practices evolve. Adapting to new technologies and data sources, such as wearable devices or patient-reported outcomes, can help capture a broader range of health information, providing a more comprehensive view of patient health and treatment outcomes. Collaborating with data aggregators and leveraging advanced data processing technologies can address the challenges of data variability and interoperability, making it easier to merge and analyze data from different sources to support ongoing research and regulatory needs.

EHR systems need to ensure data is collected and formatted according to Clinical Data Interchange Standards Consortium (CDISC) guidelines, which help in standardizing data for regulatory submission. It's important to address interoperability issues, meaning EHR systems should be capable of sharing data in a format that can be easily used by other systems, including those used by the FDA. Privacy and consent protocols must be strictly followed, ensuring that any patient data transferred to the FDA complies with HIPAA regulations and has appropriate patient consent for use in research. Data quality and completeness need to be prioritized, with efforts to minimize missing information and ensure accuracy in the data recorded, as this is critical for FDA submissions.

While there are electronic health record systems, like EPIC, that gather health data each module differs based on disease specialization and often remains proprietary hindering interoperability. Therefore, it is crucial to assess if any of the gathered data can be evaluated to meet requirements. data fields can vary with the study design because different studies aim to answer different questions and thus require different information. For example, a study focusing on the efficacy of a treatment will need data fields related to patient outcomes, while a safety study might focus more on side effects and adverse events. These data fields can indeed be grouped based on the type of information they provide, such as demographics, diagnosis details, treatment information, and outcomes. Grouping similar types of data fields helps in organizing the data for analysis and can make it easier to manage and understand the data collected in the study.

- Demographics: Information like age, gender, and ethnicity helps understand who the study is about and can show if the treatment works differently in different groups of people
- Diagnosis Details: This includes the type of disease, its stage, and how long the patient has had it. It helps to know exactly what condition is being studied.
- Treatment Information: What treatments patients receive, including drugs and dosages, and how long the treatment lasts. This shows what is being tested in the study.
- Efficacy Outcomes: These are results that show if the treatment is working. It could be improvement in symptoms or complete recovery from the disease.

- Subsequent Treatments: Information on any other treatments given after the study treatment. This helps to understand the long-term care of the condition.
- Co-morbidities: Other health conditions the patient has, which can affect how they respond to the treatment being studied.
- Toxicities and Side-effects: Any negative effects of the treatment. This is important for understanding the safety of the treatment.

Before starting a big study, it's possible to check if the study's ideas can work by doing a smaller, simpler study that doesn't change how patients are treated. This helps see if the study can be done and if the information needed can be collected. By looking at things like what kind of patients are in the study and what happens to them because of the treatment, researchers can understand if their study will give helpful answers without needing to change the patient's care. This smaller study can help figure out the best way to collect and look at the data, making sure the bigger study will be useful and can answer important questions about the treatment. Before starting a full-scale study, it's possible to test the study's design and data collection methods by conducting a smaller, simple study that doesn't involve changing patient treatment, to see if the main study can be done effectively.

This approach allows researchers to identify any potential issues with data collection or study design, such as what information is needed and how to get it, in a more controlled and less costly environment. By doing this, researchers can make sure that the larger study will be able to provide useful and accurate information, helping to avoid wasting time and resources on a study that might not work as planned. Taking the above challenges into consideration, the work group reviewed scenarios where RWD has been collected and identified opportunities to apply this evidence towards answering specific clinical questions in routine clinical care. The following case studies, while broad in scope, are intended to illustrate possible uses for RWE collection. Safety (Ceritinib) - Ceritinib (Zykadia) was approved by the FDA in 2014 for treating patients with anaplastic lymphoma kinase-positive (ALK+) metastatic non-small cell lung cancer (NSCLC) who have either progressed on or are intolerant to crizotinib.

Reports from patients indicated that the gastrointestinal (GI) tolerability of ceritinib might be enhanced when taken with food, although this approach could potentially elevate the systemic exposure of the drug. Subsequent safety data prompted a post-market commitment to assess a lower dose of ceritinib when consumed with a meal, aiming to enhance GI tolerability. Additionally, as the FDA reviewed ceritinib, it observed indications of pancreatitis (such as pancreatic enzyme elevations alongside gastrointestinal symptoms) in multiple instances, with only one investigator-reported case of pancreatitis occurring in a supportive clinical trial. Post-approval exploration of Real-World Data (RWD) for ceritinib could have offered further insights into the drug's safety profile and its potential connection to pancreatitis.

Moreover, the collection of real-world data on the usage of ceritinib, which includes information on dose interruptions, dose adjustments (with or without food), concurrent medications, gastrointestinal side effects, diarrhea, treatment duration, and other adverse reactions, can significantly aid in the thorough assessment of the optimal dosage of the medication in a post-market environment. Treatment Sequencing (Ramucirumab) – Docetaxel has been considered a standard treatment approach for second-line metastatic NSCLC, irrespective of histology. The use of ramucirumab (Cyramza) in conjunction with docetaxel was granted approval in December 2014 for patients who have experienced disease progression following platinum-based combination therapy and have undergone EGFR or ALK targeted therapy as required. In the subsequent month of October 2015, the FDA green-lighted two novel immunotherapies, namely nivolumab and pembrolizumab, for use in the second-line or subsequent NSCLC therapy settings, showcasing remarkable clinical efficacy.

These innovative agents offer flexibility in terms of treatment sequencing for these patients, with the possibility of being administered in various stages of therapy. They are even occasionally employed before the initiation of chemotherapy, demonstrating the evolving landscape of treatment strategies in metastatic NSCLC.

While there is no established reasoning indicating that the safety outcomes of combining ramucirumab and docetaxel would be negatively impacted by prior administration of an immune checkpoint inhibitor, the approval of this combination was grounded on preexisting clinical trials that were conducted before the introduction of immune checkpoint inhibitors into the pharmaceutical market. Conducting formal clinical trials can provide valuable insights into the potential effects of different treatment sequences on the safety and efficacy profiles of these therapies. However, the execution of such trials may present challenges due to the

considerable time and costs involved. Moreover, the dynamic nature of the pharmaceutical landscape, where new treatments are frequently approved, can further complicate the design and execution of these trials. Given these complexities, comprehensively studying all possible permutations of treatment sequences becomes increasingly arduous, particularly in an environment where treatment options evolve annually.

Real-world evidence (RWE) has emerged as a potential pragmatic solution to address these challenges. By gathering real-world data (RWD) on factors such as patient characteristics, safety outcomes, and mortality rates among individuals with advanced non-small cell lung cancer (NSCLC) who are undergoing treatment with ramucirumab in combination with docetaxel and a PD-1 inhibitor, irrespective of the treatment setting, utilizing a relatively modest patient cohort of around 100 individuals that align with the study's inclusion criteria, it may be possible to facilitate the determination of optimal treatment sequencing strategies.

On September 12, 2013, the FDA approved orphan drug status for denosumab (XGEVA) to treat hypercalcemia of malignancy (HCM) after reviewing data from a study conducted utilizing electronic health records (EHR) collected from various oncology clinics. This landmark decision marked the first instance where the FDA granted orphan drug designation predominantly based on real-world evidence (RWE), signifying a pivotal shift in regulatory approval processes. The decision to consider RWE was influenced by the limited scope of published medical literature on HCM, which reported varying prevalence rates ranging from less than 1% to 30% based on tumor types, with most studies being confined to individual institutions or specific tumor categories. The RWE presented in the orphan drug application (ODA) was derived from an examination of the Oncology Services Comprehensive Electronic Records (OSCER) database, originally established by Amgen for observational research and now operated by Flatiron Health.

This database collects outpatient data for a substantial cross-section of over 569,000 cancer patients who received treatment at 52 community and hospital-associated oncology practices (comprising 565 clinics) starting from the year 2004. The widespread integration of electronic health records (EHR) within community oncology practices has significantly enhanced the utility of this database as a valuable resource for conducting observational studies in the field of oncology

EHR, which stands for Electronic Health Records, was utilized to analyze routine laboratory results such as serum calcium and albumin values in order to estimate the prevalence of Hypercalcemia of Malignancy (HCM) across different tumor types and grades. This process confirmed existing findings in the scientific literature and tracked trends over a recent five-year period from 2009 to 2013, which also involved monitoring the use of bone resorptive therapies like intravenous bisphosphonates (specifically pamidronate and zoledronic acid) and denosumab. Moreover, the EHR analyses delved into detailing renal impairment among individuals diagnosed with HCM, while also examining the survival rates of a specific subgroup of patients by linking to external data sources to determine their vital status.

Expansion of Indication (Vemurafenib) – The approval of vemurafenib (Zelboraf) tablets by the FDA on August 17, 2011, was specifically granted for the purpose of treating patients who are suffering from unresectable or metastatic melanoma and who possess the BRAFV600E mutation, as identified through a test that has received approval from the FDA. The primary efficacy endpoints that were focused on during the clinical trial included the assessment of overall survival (OS) and progression-free survival (PFS) as evaluated by the investigators involved in the study. Although not as frequently encountered in non-small cell lung cancer (NSCLC), BRAF mutations do occur in approximately 1 to 3% of patients, typically those with a history of smoking and predominantly of adenocarcinoma subtype.

A phase ll basket study that was not limited by histology revealed the efficacy of vemurafenib in NSCLC cases. It is worth noting that the exploration of whether there exists additional valuable data related to BRAF-positive NSCLC patients within Electronic Health Records (EHRs) could potentially contribute towards the argument for broadening the scope of approved indications, thereby avoiding the necessity of conducting a traditional clinical trial for confirmation purposes. Supplementing patients' data from the Basket trial with approximately 40-50 additional patient records containing information regarding real-world response rates, duration of therapy, previous treatments, and safety profiles could be considered adequate for characterizing patient responses in BRAF V600E Mutation-Positive NSCLC.

This comprehensive approach may offer valuable insights into the efficacy and safety of treatments in a real-world setting, providing a more holistic understanding of patient outcomes beyond the controlled environment of clinical trials.

In August 2011, the FDA provided accelerated approval for crizotinib (Xalkori) for treating patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is ALK-positive. This approval was given with the condition that two phase lll randomized clinical studies be completed, one involving treatment-naïve patients (N=343) and the other involving previously treated patients (N=347) with ALK+ NSCLC. The full approval was officially granted in November 2013, primarily based on the progression-free survival (PFS) outcomes from the trial conducted on treatment-naïve patients. A supplemental New Drug Application (sNDA) label update for the second phase lll study on previously treated patients was sanctioned in September 2015. Subsequently, in 2016, crizotinib was designated as a Breakthrough Therapy Designation (BTD) for the ROS1-positive development initiative. The supplemental new drug application (sNDA) application aimed at patients with ROS1-positive disease went through a Priority Review process and ultimately obtained approval in March 2016.

In hindsight, and within the context of the groundbreaking efficacy of crizotinib in the specific patient cohort, could a Real-World Evidence (RWE) study have been deemed appropriate as a validating investigation for ALK+ NSCLC? After the approval of crizotinib, a retrospective analysis was carried out in the United States and Canada, focusing on a real-world cohort of 212 ALK+ NSCLC patients who had commenced crizotinib either as their initial or subsequent line of therapy. This study yielded additional insights into the utilization of crizotinib, and the outcomes observed among the patients, consequently lending support to the findings of the phase lll clinical trials. Notably, the response rates documented in the real-world cohort analysis (66% overall; 69% in first-line treatment and 60% in second-line or beyond) closely mirrored the response rates recorded among treatment-naïve patients (74%) and those who had received prior treatments (65%) in the clinical trials. One-year survival rates among first-line patients (85%) extracted from the real-world chart review corresponded well with the one-year survival rate noted in the clinical trial involving treatment-naïve patients (84%). These real-world data serve to reinforce the favorable outcomes associated with crizotinib treatment in ALK+ NSCLC patients, aligning closely with the data previously documented in clinical trials.

After reviewing the initial phase outcomes, it is worth considering whether real-world data (RWD) could serve as a complementary or potential alternative to conventional criteria for post-market obligations within upcoming developmental initiatives. Enhanced comprehension regarding the ability of real-world studies to validate the outcomes of clinical trials would significantly bolster the credibility of this proposition. In essence, validations derived from real-world observations that corroborate clinical trial results have the potential to open-up avenues for innovative trial frameworks that integrate real-world evidence at an earlier stage in the developmental process. This could lead to a paradigm shift in the way development programs are structured and executed, emphasizing the importance of real-world evidence in shaping future clinical research endeavors.

Building on the examples, the work group proceeded to explore potential opportunities for designing prospective pilot studies aimed at evaluating the feasibility of utilizing Real-World Evidence (RWE) to bolster regulatory decision-making processes. The primary objective of this undertaking would involve the testing and validation of data collection methodologies, as well as the identification of innovative endpoints that are indicative of clinical benefit and demonstrate connections between clinical practice and trial environments. The potential strategies for formulating a pilot study are outlined in the following sections. Among a variety of tumor types, individuals with melanoma and Non-Small Cell Lung Cancer (NSCLC) have exhibited the most favorable responses to immunotherapies, potentially owing to the high number of somatic mutations present in these cases. Indeed, initial investigations have indicated a correlation between tumor mutational burden and treatment efficacy. For instance, patients displaying elevated levels of microsatellite instability (MSI-high), a marker of flawed mismatch repair mechanisms, have shown notably positive responses to PD-1 inhibitors and other agents targeting immune checkpoints. While this relationship has been extensively studied in colorectal cancer (CRC), there is a growing body of clinical evidence in other types of gastrointestinal malignancies, as well as gynecological cancers, among others.

A recent publication highlighted that in CRC patients, the objective response rate to the PD-1 inhibitor pembrolizumab was 40% in cases with MSI-high (compared to 0% in those with proficient mismatch repair). Moreover, out of the 7 non-CRC patients examined, 5 also exhibited positive responses to the treatment. Ongoing studies are investigating the association between MSI-high status and the efficacy of immune checkpoint blockade, while there is a possibility of identifying additional biomarkers of mutational burden to enhance the selection of responders, such as quantifying mutational load or detecting mutations in other DNA repair proteins.

To this day, research has not demonstrated the safety and efficacy of immune checkpoint inhibitors for broad use in tumors with high mutation rates. Consequently, the clinical justification for recommending PD-1 inhibitors to individuals displaying signs of mutational burden, like microsatellite instability, is present but inadequate. Given this rationale, an investigation into the use of currently approved PD-1 inhibitors in patients with highly mutated tumors could be conducted in a real-world scenario.

The viability of this preliminary study would initially necessitate a retrospective examination of current databases (e.g., the Flatiron Health dataset along with targeted chart abstraction and linked claims data) to tackle lingering queries, such as testing protocols (e.g., timing, disease stage, test variations, etc.) and treatment protocols (inclusive of adverse reactions and observed results) in cancers with indications of mutational burden. Once all essential elements are identified, the development of a prospective trial would rely on scoping (e.g., cancer category, study magnitude, etc.), refining the biomarker and test utilization, and ultimately establishing mechanisms for gauging efficacy.

With a myriad of advantages associated with the collection of Real-World Data (RWD), which include but are not limited to enhancing post-market data collection efforts, reducing costs and development timelines, introducing innovative outcomes, and limiting the exposure of patients to therapies with lower efficacy levels, the present working group puts forth a recommendation to leverage RWD for the purpose of addressing specific clinical inquiries and, when suitable, updating product labels in various key areas.

These areas encompass, firstly, broadening the safety profiles of a therapeutic, secondly, pinpointing patient populations that exhibit a superior benefit-risk balance for an already sanctioned treatment to guide clinical decision-making, thirdly, initiating studies to explore potential correlations between practical real-world metrics (such as time to treatment switching) and more conventional clinical trial endpoints (like time to disease progression), fourthly, establishing a foundation of evidence for a supplementary dossier to extend the approved uses of a therapeutic, fifthly, corroborating the efficacy findings witnessed in a clinical trial environment, particularly in domains with unmet medical requirements, when a new medication demonstrates significant clinical advantages.

Real-world investigations capable of substantiating the initial level of effectiveness in a larger pool of patients might be deemed adequate to serve as post-market validation of clinical efficacy. These recommendations are designed to assist drug developers in contemplating the collection of RWD throughout the drug development process; nonetheless, thorough deliberation and consultations with regulatory bodies will be imperative to address any potential outcomes, such as diminished efficacy, identified within RWD studies.

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