Review

Real-World Data and Evidence in Lung Cancer: A Review of Recent Developments

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Real-World Data and Evidence in Lung Cancer: A Review of Recent Developments

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Simple Summary: The use of real-world data (RWD) to generate real-world evidence (RWE) is increasing in oncology. RWD studies provide valuable information to regulators, sponsors, and clinicians. RWD studies rely on collecting and analyzing observational data, offering insights into the practical application of cancer treatment in real-world settings. However, the quality of RWD can compromise the reliability of the RWE. Hybrid methodological analyses that combine the strengths of RCTs and RWD studies, known as R2WE, are being conducted to address these challenges. RWD sources include patient registries and electronic health records (EHRs). High-quality data are essential for generating credible RWE. To obtain RWD, it is necessary to obtain data from relevant sources, clean and harmonize the data, and ensure compliance with the laws and regulatory requirements.

Abstract: Conventional cancer clinical trials can be time-consuming and expensive, often yielding results with limited applicability to real-world scenarios and presenting challenges for patient participation. Real-world data (RWD) studies offer a promising solution to address evidence gaps and provide essential information about the effects of cancer treatments in real-world settings. The distinction between real-world data (RWD) and data derived from randomized clinical trials lies in the method of data collection, as RWD by definition is obtained at the point of care. Experimental designs resembling those used in traditional clinical trials can be utilized to generate RWD thus offering multiple benefits including increased efficiency and a more equitable balance between internal and external validity. Real-world data can be utilized in the field of pharmacovigilance to facilitate the understanding of disease progression and to formulate external control groups. By utilizing prospectively collected real-world data (RWD), it is feasible to conduct pragmatic clinical trials (PCTs) that can provide evidence to support randomized study designs and extend clinical research to the patient's point of care. To ensure the quality of real-world studies, it is crucial to implement auditable data abstraction methods and develop new incentives to capture clinically relevant data electronically at the point of care. The treatment landscape is constantly evolving, with the integration of front-line immune checkpoint inhibitors (ICIs), either alone or in combination with chemotherapy, affecting subsequent treatment lines. Real-world effectiveness and safety in underrepresented populations, such as the elderly, patients with poor performance status (PS), hepatitis, or human immunodeficiency virus-infected patients, are still largely unexplored. Similarly, the cost-effectiveness and sustainability of these innovative agents are important considerations in the real world.

Keywords: oncology; real-world data; real-world evidence; epidemiology; safety; efficacy; artificial intelligence; machine learning; data quality; lung cancer

1. Introduction

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The utilization of real-world data (RWD) to generate real-world evidence (RWE) in conjunction with interventional clinical trial-based research is rapidly increasing. This burgeoning field, particularly in the context of oncology, has seen a significant number of publications and increased use of RWD in medical regulation in recent years. It is essential to improve the quality of RWE for the benefit of patients, scientific community, and healthcare authorities.

Oncology research presents a multitude of particularities, including specific variables, biomarkers, therapies, and outcomes, which are not adequately addressed by the existing reporting guidelines. Furthermore, contemporary technologies such as artificial intelligence (AI), machine learning (ML), and deep learning (DL) have been integrated into various stages of data analysis in real-world evidence (RWE) studies. Although guidelines for interventional studies involving AI are now available [1,2], similar guidance specifically tailored for RWE research remains absent.

Real-world data (RWD) studies have several advantages such as increased sample sizes, quicker achievement of research objectives, and reduced costs compared to conventional clinical trials [3], [4,5]. Nevertheless, when conducting RWD studies, several challenges must be addressed, such as accessibility and protection of data, compliance with relevant laws and regulations, and the necessity for meticulous study design and analysis.

2. Role of RWD in Oncology

Real-world data (RWD) studies are increasingly being utilized as alternative sources of evidence in clinical cancer research. These studies provide valuable information to inform the decisions of regulators, sponsors, and clinicians. RWD studies primarily rely on collecting and analyzing observational data, which offers insights into the practical application of cancer treatment in real-world settings.

RWD's poor quality sometimes compromises the reliability of real-world evidence (RWE). In such cases, randomized controlled trials (RCTs) are necessary to answer specific research questions definitively. Hybrid methodological analyses that combine the strengths of RCTs and RWD studies, known as R2WE, are currently being conducted to address these challenges. The European Organization for Research and Treatment of Cancer (EORTC) is developing a strategy to build solid, high-quality RWE by prioritizing realistic clinical trials. This approach aimed to provide evidence to support new therapeutic approaches in clinical practice [6].

Research using real-world data (RWD) has several advantages including access to larger datasets, greater generalizability, and shorter study duration. However, obtaining data and ensuring compliance with laws and regulatory requirements can be challenging. Despite these obstacles, RWD studies have the potential to address evidence gaps and provide crucial information about the effects of cancer treatment in real-world settings [6,7].

RWD sources include patient registries and electronic health records (EHRs). Patient registries are structured systems that gather specific information about patients with a particular condition or treatment, whereas EHRs are digital versions of patients' medical records. Other sources of RWD include patient questionnaires, mobile devices, smartphones, and social media [8,9].

High-quality data are the foundation for credible real-world evidence (RWE). To generate RWE, it is essential to obtain data from relevant real-world data (RWD) sources, clean and harmonize the data, and link them to fill in gaps. Additionally, the data must include endpoints relevant to the research question. Quality criteria must be applied throughout the process of generating RWE, from data sources to processing, to ensure that appropriate use cases are defined.

The importance of patient follow-up during daily clinical practice in the field of oncology is becoming increasingly recognized as a valuable means of data collection. Such follow-up studies offer valuable insights into the safety and efficacy of interventions in specific patient populations, including those with chronic viral diseases, brain metastases, or poor performance status. By incorporating data analysis and evaluating their impact on healthcare budgets, real-world population follow-up studies have the potential to inform more appropriate treatment choices and may even be considered part of the regulatory approval process in the future [10].

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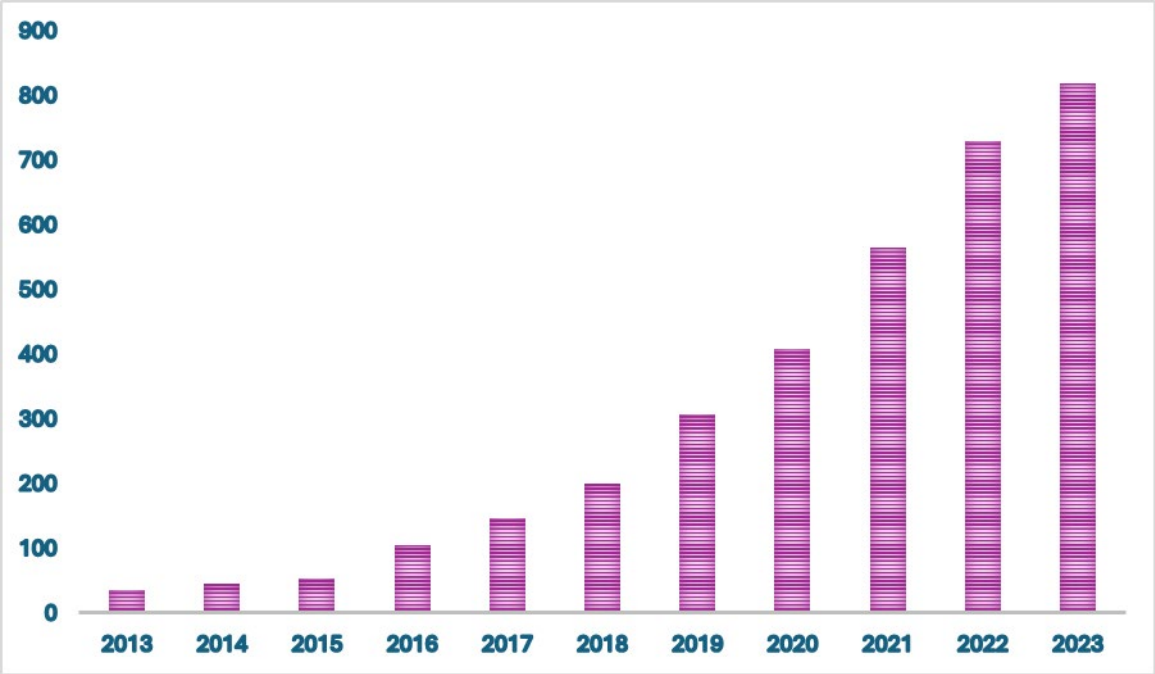

Figure 1. Number of citations/year of real-world evidence in oncology between January 2013 and January 2024**.**

3. Potential Use of RWE

Regulatory-grade real-world evidence (RWE) has the potential to provide critical information for informed decision making by clinicians, patients, and regulatory authorities. Traditional Phase IV and other post-marketing studies can be burdensome and face numerous obstacles in patient enrollment, such as evolving practice patterns. Well-designed RWE studies can generate innovative hypotheses for future research in basic sciences, drug development, health outcomes, and clinical trials. Longitudinal real-world evidence (RWE) could potentially aid the identification of rare side effects across extensive populations. By employing thorough RWE studies, it may be possible to uncover adverse event trends in real time rather than relying solely on voluntary reporting. Through a comprehensive assessment of both structured and unstructured real-world data (RWD) for individual patients, real-world evidence (RWE) can rigorously document safety and effectiveness at the necessary level of quality and detail to support label expansion.

When a new oncological therapeutic is in the process of development, it is subject to various decision points that determine whether it will continue to be developed. The use of real-world evidence (RWE) can aid in optimizing these decisions during predevelopment and in guiding clinical development strategies by clarifying unmet needs in the real world. The incorporation of real-world evidence (RWE) into clinical development can also play a role in the planning and execution of clinical trials. By offering insights into specific populations, RWE can aid in reducing the excessively restrictive exclusion criteria. Furthermore, knowledge of the prevalence patterns of potential trial candidates such as rare cancers that progress despite chemotherapy can facilitate patient recruitment for clinical trials. The use of synthetic control arms based on RWE is also being investigated, particularly for cancers with well-established standards of care, poor prognoses, and low incidences (e.g., small cell lung cancer). In contrast to historical controls, synthetic controls may possess greater recency, which can help to account for changes in supportive care over time.

Treatment decisions are often determined by the risk-benefit ratio for each individual patient. Although it is impossible to completely eliminate clinical uncertainty, the utilization of real-world evidence (RWE) can aid in refining this assessment and facilitating personalized medicine tailored to both the patient and tumor. The extent and significance of potential RWE use cases necessitate stringent quality assessments, particularly when utilized for regulatory decision making.

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The complexities of lung cancer treatment, coupled with the diverse range of therapeutic options currently available, require delicate and informed clinical decision-making on the part of healthcare providers and those responsible for resource allocation (e.g., payers and regulators) [11]. This highlights the need for rapid and ongoing insights into these decisions. Such insights are typically provided by data from randomized controlled trials (RCTs) and real-world evidence (RWE). RWE can offer information that would not be readily obtainable through RCTs, generating data that reflects routine clinical practice in larger, real-life treatment populations. In the field of lung cancer drug development, there are many examples of the usefulness of RWE in providing complementary data to reinforce and support clinical trial data. For instance, recent real-world studies have evaluated the safety and/or effectiveness of lung cancer treatments, often in patient cohorts ineligible for clinical trials [12–15], investigated the real-world burden of lung cancers and related treatment patterns and survivorship [13,14,16–18] and assessed treatment-related costs/healthcare resource utilization (HCRU)[13,14,17,19].Therefore, data from both observational real-world studies and traditional RCTs are important in informing the best clinical practice, and regulatory bodies recognize that these two methodologies are complementary in both the pre- and post-authorization stages of drug development [14].

4. RWE in Cancer Drug Development

The current regulatory framework of the FDA affords sufficient flexibility to integrate novel forms of clinical evidence into decision-making processes [20]. To this end, efforts should concentrate on devising suitable study designs and strategies for acquiring high-quality data from EHRs in the context of real-world data utilization.

1) Real-world Evidence for Digital Pharmacovigilance

Regulatory agencies primarily rely on passive surveillance to ensure post-market pharmacovigilance. This approach entails the analysis of voluntary reports of adverse events submitted by healthcare professionals and patients as well as mandatory reporting from pharmaceutical companies [21]. However, passive reporting has several limitations, including the influence of extraneous factors, such as media attention and the length of time a product has been on the market. To address these challenges, the FDA established the Sentinel Initiative, which seeks to develop an active surveillance system that proactively investigates real-world data (RWD) to detect new safety signals [22,23]. The advent of advanced information technology presents an opportunity to create an integrated approach that leverages RWD from electronic health records (EHRs) and patient-generated sources, such as mobile applications and internet search logs, to modernize pharmacovigilance [24,25]. Adopting a digital pharmacovigilance system that merges real-world data (RWD) from healthcare providers through electronic health records (EHRs) and online platforms that are used by patients to researchers and experts in the pharmaceutical industry and regulatory authorities can develop a proactive monitoring system, permitting the application of protective measures to recognize certain safety concerns. In a digital drug safety monitoring system, the efficiency of safety indicators can be analyzed using techniques such as data mining, like proportional reporting ratios and empirical Bayesian geometric mean scores, which have already been utilized by regulatory authorities like the FDA [26,27]. Furthermore, a digital system that integrates various streams of real-world data can use deep learning methods with the help of artificial intelligence and natural language processing to amplify safety signal detection methods. [28–30].

2) Utilizing RWE to investigate disease progression and establish external control

The natural history of a disease refers to the progression of the disease from its onset to the presymptomatic phase, through various clinically symptomatic stages, and finally to the resolution of the disease or the patient's death, without any intervention [31]. One way to elucidate this continuum is to examine the effect of two types of variables that affect the likelihood of developing an asymptomatic disease from a healthy state and progression to the symptomatic stage of the disease

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[32]. Real-world data (RWD) present a valuable opportunity to investigate the covariates that affect the natural history of diseases in populations where a significant portion is regularly monitored and treated. For instance, retrospective analysis of electronic health record (EHR) data can be employed to identify covariates that contribute to the onset of cancer in healthy individuals. This analysis can help elucidate the patient and environmental factors that influence disease occurrence. Similarly, examining EHR data retrospectively can aid in identifying covariates associated with cancer progression from the asymptomatic to the symptomatic stage. Such investigations can provide crucial insights into the design of future prospective clinical trials to assess the impact of cancer screening and early intervention on patient outcomes.

In clinical studies, such as single-arm trials, utilizing external control data can potentially aid in the establishment of comparative benchmarks for regulatory decision-making, particularly for serious conditions with high unmet medical needs, such as advanced malignancies [33]. If preliminary clinical evidence from a single-arm trial indicates a significant treatment effect, evaluating outcomes in comparable patient groups using real-world data (RWD) can offer a reliable assessment of the safety and efficacy of available therapies for comparison.

Advancements in genomic sequencing and computational proteomics have led to the identification of a growing number of rare tumor variants resulting from somatic mutations, proteomic signatures, and alterations in cell signaling pathways with oncogenic potential [34], [35,36]. Retrospective analysis of real-world data (RWD) can provide an adequate approach to the evaluation of biomarkers and their prognostic significance regarding disease outcomes in rare subgroups during clinical development. Clinical results from RWD registries may be connected to genomic and proteomic profiles predicting outcomes and establishing guidelines. This will require enhancing big data analytics capabilities to effectively analyze complex and rare patterns identified by multi-omics pipelines, aiming to improve patient care and outcomes.

3) Observational Real-World studies

There is a growing convergence between the outcomes of randomized controlled trials (RCTs) and well-designed observational studies, which presents an opportunity to develop robust methodologies that support electronic health record (EHR)-based observational research [20,37,38]. Data collection from real-world settings through observational studies have the ability to contribute valuable information, that can be utilized in randomized controlled trials or regulatory decision-making. Furthermore, observational studies offer an opportunity to evaluate the effectiveness and safety of treatments in patient populations that are often occluded from conventional cancer clinical trials. New regulatory incentives for drug developers to submit real-world data (RWD) to patients excluded from conventional clinical trials can improve the generalizability of FDA label information, enabling prescribers to make informed treatment decisions [39].

4) Practical clinical studies

Electronic health records (EHRs) serve as primary instruments for conducting practical clinical trials (PCTs). EHRs are widely accessible tools in the healthcare sector that can aid in establishing a clinical trial program based within the point of care and linked to patients digitally through innovative technologies like sensors and mobile apps. Through facilitating the deliberate gathering of pertinent clinical data that accurately represents the diverse range of cancer patients, EHRs play a role in bringing real-world evidence to pharmaceutical research, while emphasizing advancements in quality, patient safety, and value in cancer treatment delivery [40].

In the realm of cancer drug development, pragmatic clinical trials (PCTs) present numerous advantages compared to traditional clinical trials, which are typically limited to specialized facilities with the required resources and capacity to maintain research initiatives. The limited involvement rates in cancer trials, particularly among minority groups, the elderly, individuals with low income, and those living in rural areas (less than 5%), underscore the obstacles presented by the division of clinical research across geographically dispersed locations [20,41–43]. The primary reason for the low participation in cancer trials is the obstacles to accessing convenient experimental treatments, rather

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than patient preferences [44,45]. PCTs have the ability to adhere to the existing standards of methodological, ethical, legal, and regulatory oversight in clinical research while enhancing access to experimental treatments in a secure and effective manner.

5) Evaluating risks to the internal validity of real-world studies

The internal validity of studies conducted in real-world settings, particularly those utilizing nonrandomized designs, necessitates the effective management of bias stemming from provider-patient interactions, methodologies employed in data collection and processing, and the diverse practice patterns present within regional healthcare systems.

5. RWD on ICIs Outcomes and Safety

In recent years, the introduction of immune checkpoint inhibitors (ICIs) has significantly improved the treatment of lung cancer. Anti-PD1 (pembrolizumab and nivolumab) and anti-PD-L1 (atezolizumab and durvalumab) agents, are capable of omitting the immune evasion mechanisms used by tumors and restore the immune system's antitumor response. At the beginning, Immune Checkpoint Inhibitors (ICIs) were used as primary or secondary therapies for patients with advanced-stage disease, both for those selected based on PD-L1 expression (such as pembrolizumab) and for the overall patient population. Afterward, durvalumab was integrated as a consolidation therapy in a treatment algorithm for PD-L1 positive locally advanced non-small cell lung cancer (NSCLC). Currently, ICIs are employed as adjuvant and neoadjuvant treatments.

Randomized controlled trials (RCTs) are widely regarded as the most robust form of evidence and, therefore, serve as the gold standard for evaluating the efficacy of an intervention. Nonetheless, the translation of this evidence into real-life clinical practice can be problematic, as a substantial number of patients encountered in everyday practice are often underrepresented in RCTs. In light of the incorporation of immune checkpoint inhibitors (ICIs) as the standard of care for lung cancer, oncologists are confronted with the dearth of data pertaining to patient subsets that are typically excluded from pivotal clinical trials. In particular, it is of utmost importance to gather information concerning the safety and efficacy of ICIs in individuals with chronic viral diseases, as well as in those presenting with brain metastases or an Eastern Cooperative Oncology Group (ECOG) performance status (PS) 2 or worse.

The majority of data available on the application of immunotherapy in lung cancer pertain to its efficacy, as measured by objective response rate (ORR), overall survival (OS), and progression-free survival (PFS), as well as its safety profile, with respect to the most frequently utilized immune checkpoint inhibitors (ICIs) in clinical practice.

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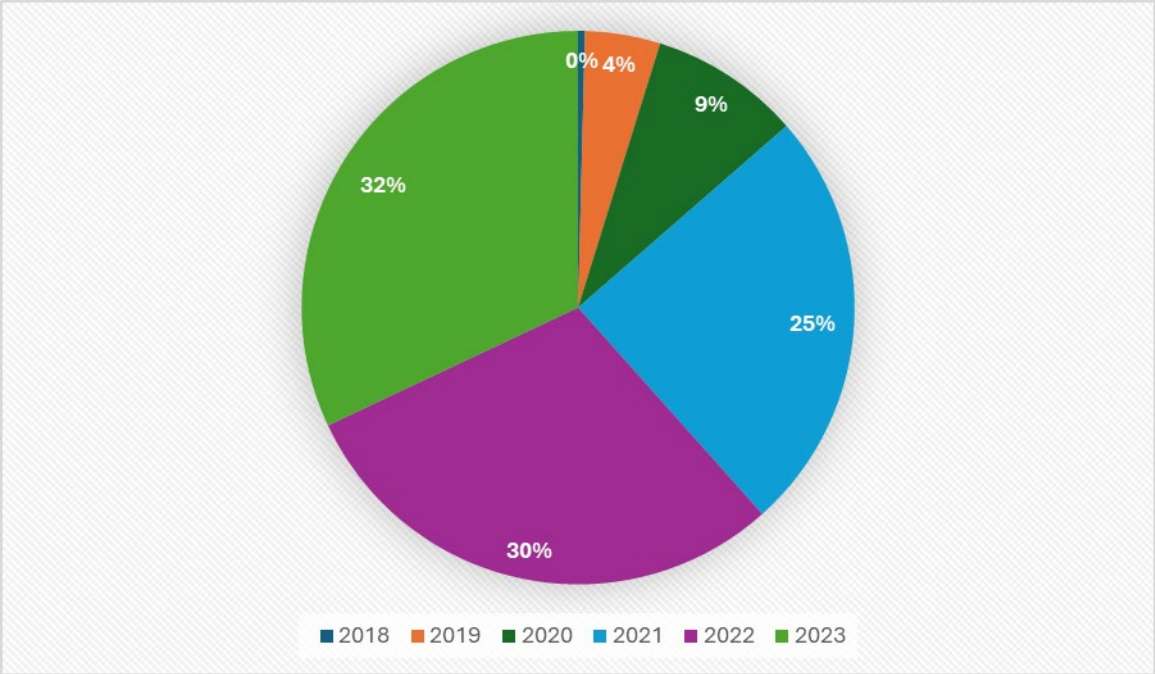

Figure 2. Amount of real-world data on ICIs between 2018 and 2024**.**

6. Real-World Evidence on Special Populations

1) Elderly

The typical age of individuals at the time of lung cancer diagnosis is 70 years old [46]. It is worth noting that the elderly population is often underrepresented in randomized controlled trials (RCTs). All the studies examined indicated that the efficacy of ICI monotherapy did not differ statistically between older and younger patients, and that tolerability was not influenced by age [34,47–50]. Muchnik et al. reported that the incidence of immune-related colitis was higher in patients aged > 80 years [34].

2) ECOG performance status 2

The primary pivotal trials for immune checkpoint inhibitors (ICIs) in lung cancer strictly excluded patients with poor performance status (PS), confining the inclusion criteria to PS 0 or 1 according to the ECOG classification, whereas only a limited number of clinical trials enrolled patients with PS 2 [51,52]. Nevertheless, both the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) granted approval for the four available ICIs without regard to the PS of patients. As a result, the use of ICIs in clinical practice for patients with PS 2 has been permissible, leading to the accumulation of real-world data.

The absence of solid data from randomized controlled trials (RCTs) warrants caution regarding the use of immune checkpoint inhibitors (ICIs) in patients with poor performance status (PS), as the demonstrated safety profile may not suffice to justify the high costs in the absence of a survival benefit [53]. The PePS2 trial is a Phase II clinical study that aims to assess the safety and tolerability of pembrolizumab in the treatment of NSCLC patients with an ECOG Performance Status of 2 [54]. The trial has co-primary endpoints that include measuring durable clinical benefit (DCB), objective response rate (ORR), and the incidence of dose interruptions or discontinuations due to immune-related adverse events (irAEs). A pre-liminary analysis of data from a subgroup of 60 patients revealed a DCB rate of 33%, an ORR of 30%, and an irAE incidence of 8%. Although these initial results are encouraging, when analyzing the results of survival rates, it is crucial to proceed with caution, as the median PFS was 5.4 months and OS was 11.7 months, and only 15% of patients (9 out of 60) received first-line pembrolizumab, resulting in no responses and a PFS of 1.9 months. In a

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retrospective study conducted by Facchinetti et al., the outcomes of patients with PS 2 who received first-line pembrolizumab treatment were evaluated. The results indicated that patients with PS 2 related to comorbidity had a median overall survival (OS) of 11.8 months, while those with PS 2 driven by lung cancer had a median OS of 2.8 months. The hazard ratio (HR) for OS was 0.5 (p = 0.001) in favor of the former group [55].

3) Central nervous system metastases

The central nervous system (CNS) is a common site of metastases in patients with non-small cell lung cancer (NSCLC), with an estimated incidence of brain metastases (BM) of approximately 40%. Patients with BM often experience symptoms, necessitating treatment with corticosteroids, and have a poor prognosis. As a result, this particular patient population is underrepresented in clinical trials, where individuals with BM are typically included only when the CNS disease is inactive and does not require active treatment. In pivotal trials of immunotherapy in lung cancer, the proportion of patients with inactive and asymptomatic BM ranges from 6% to 17.5%, and no preplanned analysis of CNS metastasis subgroups has been conducted [56–60].

Currently, available empirical data are limited. However, a study conducted by Pasello has provided valuable insights by examining 255 individuals with BM who were participants in a multicenter, prospective research project and were administered ICIs [61]. The study population comprised approximately 40% individuals with active brain metastasis (BM) and 14% symptomatic patients. Despite a lower rate of disease control and a higher incidence of progressive brain disease compared to patients without central nervous system (CNS) metastasis, the presence of BM was not found to be an independent predictor of overall survival (OS) in multivariate analysis, taking into account steroid treatment and performance status (PS) [61]. Moreover, the administration of cranial radiotherapy, whether in the form of whole-brain or stereotactic radiotherapy, did not demonstrate a significant impact on survival. Including patients with CNS metastasis, the Italian Expanded Access Program (EAP) using nivolumab demonstrated no disparities in overall survival (OS) between the squamous and non-squamous populations when compared with the general population OS [62–64]. Correspondingly, the French EAP with nivolumab, which included 130 patients with brain metastasis (BM), yielded similar outcomes [65]. Generally, the body of real-world data derived from NSCLC patients with CNS metastasis who have been treated with immunotherapy offers more compelling evidence of both safety and efficacy than randomized controlled trials (RCTs) in this particular patient population.

4) Patients with pre-existing autoimmune disorders

Immune checkpoint inhibitors (ICIs) act on molecular pathways involved in physiological immune self-tolerance. These treatments are associated with immune-related adverse events (irAEs), which are essentially new autoimmune disorders triggered by therapy. Owing to this risk, patients with pre-existing autoimmune diseases (AIDs) were excluded from clinical trials for ICIs, except those with vitiligo, type I diabetes mellitus, or residual hypothyroidism that only requires hormone replacement. This exclusion was based on fear of unacceptable immune reactions and severe toxicities. Individuals with these disorders are susceptible to malignant tumors, particularly lung cancer [66]. Almost one-fifth of all lung cancer patients have an underlying autoimmune disease (AID)[67],[68]. Several retrospective studies have investigated the potential risks and benefits of immunotherapy in a specific subset of patients. In a noteworthy study, Leonardi et al. examined 56 patients with advanced non-small cell lung cancer (NSCLC) and autoimmune disease (AID), who were treated with either anti-PD-1 or anti-PD-L1 therapy [69]. Researchers have reported that the incidence of immune-related adverse events (irAEs) was similar to that observed in clinical trials. Additionally, they noted that AID exacerbations occurred in only a minority of patients, particularly those who were already experiencing symptoms of their AID at the time of initiating immunotherapy. A comprehensive retrospective study was conducted on a substantial cohort of patients (n = 751) diagnosed with advanced solid malignancies who were treated with anti-PD-1 agents. This study aimed to assess the safety and efficacy of these treatments in relation to the

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presence of pre-existing autoimmune diseases (AIDs) [68]. Two-thirds of the patients were diagnosed with non-small cell lung cancer (NSCLC). This study revealed that the incidence of immune-related adverse events (irAEs) of any grade was higher in patients with pre-existing AIDs, regardless of whether the AIDs were symptomatic. However, no significant differences were observed in the incidence of grade 3–4 irAEs, overall response rate (ORR), progression-free survival (PFS), or overall survival (OS) between the two groups. It was also discovered that nearly half of the patients with pre-existing AIDs experienced a flare-up of their autoimmune disorder, with a wide range of incidence depending on the AID subtype. Specifically, the incidence ranges from 10% for rheumatologic disorders to 100% for gastrointestinal and hepatic diseases [68]. These real-world findings suggest that pre-existing AIDs should not necessarily be considered absolute contraindications for immunotherapy.

5) Patients with chronic viral diseases

The majority of clinical trials involving immune checkpoint inhibitors (ICIs) for non-small cell lung cancer (NSCLC) have typically occluded patients with chronic viral infections, including HIV, HBV, and HCV. Concerns regarding potential viral reactivation and the need for antiviral therapy raise questions about treatment efficiency and safety. However, retrospective case series have shown that ICI treatment is safe for NSCLC patients who are HIV-positive, with no evidence of viral rebound, with similar safety profiles among 30 advanced NSCLC patients [51,70]. There is limited information available on the use of ICI in NSCLC patients with HBV or HCV. A retrospective study of 10 patients with NSCLC and HBV or HCV that received immunotherapy had similar toxicity and efficacy rates as those without viral infections [71], without any impact on viral load or replication.

6. Conclusion and Feature Directions

The use of real-world data (RWD) in oncology is increasing to generate real-world evidence (RWE). RWD studies offer valuable information to regulators, sponsors, and clinicians. These studies relied on observational data and provided insights into real-world cancer treatment. Hybrid methodological analyses such as R2WE are being conducted to address the challenges of RWD quality. The European Organization for the Research and Treatment of Cancer (EORTC) is developing a strategy to create high-quality RWE by prioritizing realistic clinical trials.

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Conflicts of Interest: The authors declare no conflicts of interest.

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