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WHITE PAPER

The value of real-world evidence in supporting targeted therapies for patients with rare oncogenic drivers in mNSCLC

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ABSTRACT

With the ongoing discovery of various oncogenic driver mutations in metastatic non-small cell lung cancer (mNSCLC), a precision medicine approach has emerged, characterized by targeted therapies for select patient populations. Randomized controlled trials (RCT) remain the gold standard for evaluating efficacy and safety of such therapies; however, RCTs evaluating treatments for rare oncogenic drivers still face limitations, given small populations, potentially long-time horizon for outcome events to occur, and underrepresentation of certain subgroups. For these targeted therapies, the complementary nature between real-world evidence (RWE) and RCT may expand the totality of evidence available, to better inform treatment decision-making. In particular, treatments for rare oncogenic drivers can benefit from RWE that provides additional, generalizable clinical insights for subgroups underrepresented or ineligible for RCT, or confirms outcomes observed in RCT. As a discipline, RWE has seen significant advances in methodology and healthcare stakeholder acceptability, with potential for even greater innovation, and presents a valuable opportunity to support decision-making around access and use of targeted therapies for rare oncogenic drivers in mNSCLC.

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Metastatic non-small cell lung cancer; rare oncogenic drivers; real-world evidence; targeted therapy; precision medicine; treatment decision-making

1. Introduction

Over the last two decades, metastatic non-small cell lung cancer (mNSCLC) has materially shifted from being viewed as a single broad disease to a more segmented one, largely due to discovery of a variety of oncogenic driver mutations, with varying prevalence (Figure 1) [1,2]. As a result, a precision medicine approach to treating patients with biomarker-specific mNSCLC emerged in the early 2000s, targeting molecular oncogenic pathways driven by these mutations. In particular, development of therapies directed against specific oncogenes, such as *EGFR* tyrosine kinase inhibitors (TKIs) like gefitinib – initially approved by the US Food and Drug Administration (FDA) for mNSCLC in 2003 [3] – paved the way for discovery and development of additional first-generation targeted therapies for other, less common oncogenic drivers, such as crizotinib for *ALK/ROS1* [4] and dabrafenib-trametinib for *BRAF* [5]. To date, there are now several FDA-approved biomarker-directed therapies, including those targeting nine rare (i.e., ≤5% frequency) oncogenic drivers in NSCLC (*ALK, BRAF V600E, HER2, MET, NTRK, RET, ROS1, EGFR exon 20 insertions, NRG1 fusion*) [1,2,6].

Targeted therapies have proven successful in greatly improving outcomes for eligible patient populations, demonstrating longer duration of therapy, extended survival, and fewer toxicities, relative to historical standard of care chemotherapies [7]. Development of additional targeted therapies continues to further advance these clinical benefits, including recent regulatory approval of new treatments for various mNSCLC subtypes, such as tepotinib, a *MET* inhibitor, and amivantamab, an *EGFR-MET* bispecific antibody. In parallel, ongoing research may lead to the discovery of new targetable oncogenic drivers. Further, as more drugs become available in the first- and second-line settings, targeted agents for common oncogenic drivers in later lines may also end up with small or skewed base patient populations, similar to rare oncogenic drivers, due to attrition between lines of therapy. With greater understanding of their actionable potential, these novel drivers can further personalize mNSCLC treatment, for potentially smaller patient populations [8].

While randomized controlled trials (RCTs) are the benchmark for evidence generation, small patient populations, given low prevalence of some oncogenic drivers, may result in data challenges and subsequent gaps in evidence. For mNSCLC in particular, researchers are recognizing an opportunity for real-world evidence (RWE) to address these challenges, as observed in recent gray literature and congress presentations. For example, Flatiron Health has published multiple case studies of RWE generation in patients with rare oncogenic driver mutations in mNSCLC, to demonstrate unmet medical need, identify indicators of acquired resistance to targeted therapies, inform trial eligibility criteria for greater diversity, or characterize natural history of disease [9,10]. A session by Ontada at the International Society for Pharmacoeconomics and Outcomes Research conference in 2024 similarly highlighted a case study illustrating how RWE

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Article highlights

Introduction
- With ongoing research into oncogenic drivers, metastatic non-small cell lung cancer (mNSCLC) treatment has become increasingly personalized, with targeted therapies available for select patient populations.
- For rare oncogenic drivers in mNSCLC with smaller patient populations, there is opportunity for real-world evidence (RWE) to complement randomized controlled trial (RCT), addressing data challenges and providing critical evidence to inform treatment decision-making.

Limitations of RCT data generation for targeted therapies in mNSCLC
- While RCTs remain the gold standard, there are potential limitations related to patient enrollment, patient representation, and trial duration when evaluating targeted therapies for rare oncogenic drivers in mNSCLC.
- As an example, a hypothetical head-to-head RCT of lorlatinib and alectinib in *ALK*+ mNSCLC would be impactful but impractical, due to time requirements for enrollment, trial duration, and result readout.

Rationale for RWE in mNSCLC, in the context of data challenges
- In recent years, RWE methodology has evolved significantly, alongside increasing stakeholder acceptability, with potential to further strengthen and expand on totality of evidence available for treatments targeting rare oncogenic drivers in mNSCLC.

Future enablers to support RWE in patients with rare oncogenic drivers in mNSCLC
- Future RWE generation may be supported by an innovative RWE capability in mNSCLC, comprising triangulation of multimodal data sets, commitment to data management and governance, and an aligned view on most pressing use cases.

could assess clinical outcomes associated with a product in the rare (therefore small) *ROS1*-positive population [11].

Furthermore, articles focused on utility of RWE in lung cancer are also beginning to emerge and advance RWE acceptance across healthcare stakeholders. Nazha et al., Gristina & Eze, and Kokkotou et al. outline benefits of RWE, as rationale for considering it alongside RCT data, in relatively broad disease settings of EGFR NSCLC (Nazha et al.) and lung cancer (Gristina & Eze, Kokkotou et al.), with brief examples in rare subtypes [12–14]. Additionally, in a review by Harada et al., opportunities to support adoption of treatments for rare molecular lung cancer subtypes are described, with RWE generation identified as one such next step [15].

Despite these examples, peer-reviewed literature supportive of RWE acceptability remains limited, especially in the context of rare biomarker-driven mNSCLC populations. Therefore, this article aims to serve as one of the first white papers to articulate the complementary role and value of RWE in expanding the totality of evidence available for therapies targeting rare oncogenic drivers in mNSCLC. To do so, we (i) outline potential limitations of RCT data generation in this setting, including demonstration of infeasibility of a hypothetical head-to-head RCT scenario, and (ii) provide rationale for the complementary value of RWE, with preliminary ideas around future enablers. Through this article, we hope to drive further acceptance of RWE, to inform on and assist in treatment decision-making around access and use of targeted therapies for patients with rare oncogenic drivers in mNSCLC.

2. Limitations of RCT data generation for targeted therapies in mNSCLC

RCTs are the gold standard for evaluating treatment efficacy and safety, with pivotal trials informing decision-making for regulatory approval, payer access and reimbursement, clinician treatment selection, and clinical guidelines inclusion. However, RCTs are not without limitations related to patient enrollment, patient representation, and trial duration, especially in the context of treatments for rare, biomarker-driven mNSCLC molecular subtypes. As rare oncogenic drivers each typically make up less than 5% of NSCLC [2], RCT enrollment requires intensive, time-consuming efforts for eligible patient identification. Even among clinical trial participants identified and enrolled, certain subgroups (e.g., patients with brain metastases, specific comorbidities, or Eastern Cooperative Oncology Group Performance Status greater than 2; patients who identify as belonging to a racial/ethnic minority [16–19]) may be underrepresented, potentially limiting the generalizability of trial results. Lastly, relative to historical chemotherapy trials, duration of targeted therapy trials may be longer, as improved efficacy prolongs accrual of a sufficient number of outcome events. This longer duration can result in a lag between RCT results and the rapidly evolving treatment landscape.

One such example of a rare oncogenic driver in mNSCLC faced with these RCT limitations is *ALK* rearrangement. Lorlatinib, an *ALK* TKI approved for *ALK*-positive (*ALK*+) mNSCLC, was investigated as 1 L treatment in its pivotal Phase 3 CROWN trial, designed pre-2017 [20]. Similar to second generation *ALK* TKIs such as alectinib in ALEX [21] and brigatinib in ALTA-1 L [22], lorlatinib was compared against a control group receiving crizotinib, the accepted standard of care *ALK* TKI at the time of trial design. In the years since CROWN initiated, positive data for alectinib supported a shift in utilization of crizotinib, and many patients with *ALK*+ mNSCLC now receive alectinib as 1 L treatment. While a head-to-head trial comparing lorlatinib to alectinib would undoubtedly be impactful and provide contemporary, up-to-date evidence, it is likely unfeasible due to RCT constraints.

A hypothetical head-to-head RCT calculation between lorlatinib and alectinib (Figure 2) demonstrates that conducting such an RCT would be impractical due to time requirements pertaining to enrollment, trial duration, and result readout. In addition to the small overall population of *ALK*+ mNSCLC to identify and recruit from, physicians may be less willing to randomize patients and patients may be less willing to participate in a rigorous RCT for two already-approved products. As observed in other *ALK* TKI RCTs such as CROWN – where lorlatinib median progression-free survival (PFS) and overall survival (OS) have not yet been reached at 5-year follow-up [23] – such a hypothetical trial would entail a lengthy duration for enough outcome events to occur (e.g., more than 7 years for PFS, more than 12 years for OS). Realistically, patients cannot afford to wait this long for additional RCT data on existing treatments. While the trial duration is calculated based on a target sample size of 300 – similar to CROWN, ALEX, and ALTA-1 L – it could hypothetically be shorter if the number of participants was even greater. However, achieving such high enrollment would present as another infeasible hurdle, especially given the unwillingness mentioned previously, of physicians to randomize and/or patients to participate. Furthermore, with newer therapies also simultaneously in development,

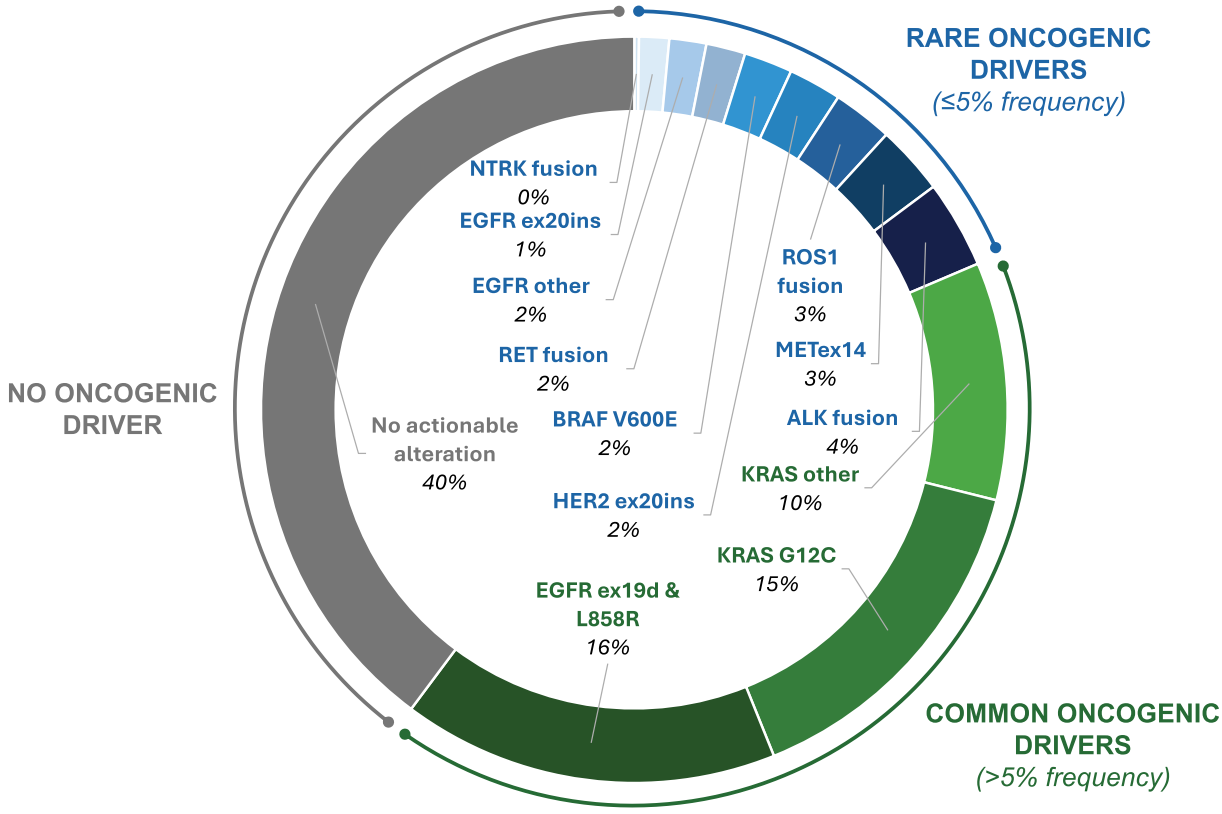

Figure 1. Oncogenic driver mutation frequency in Western NSCLC populations (2022).

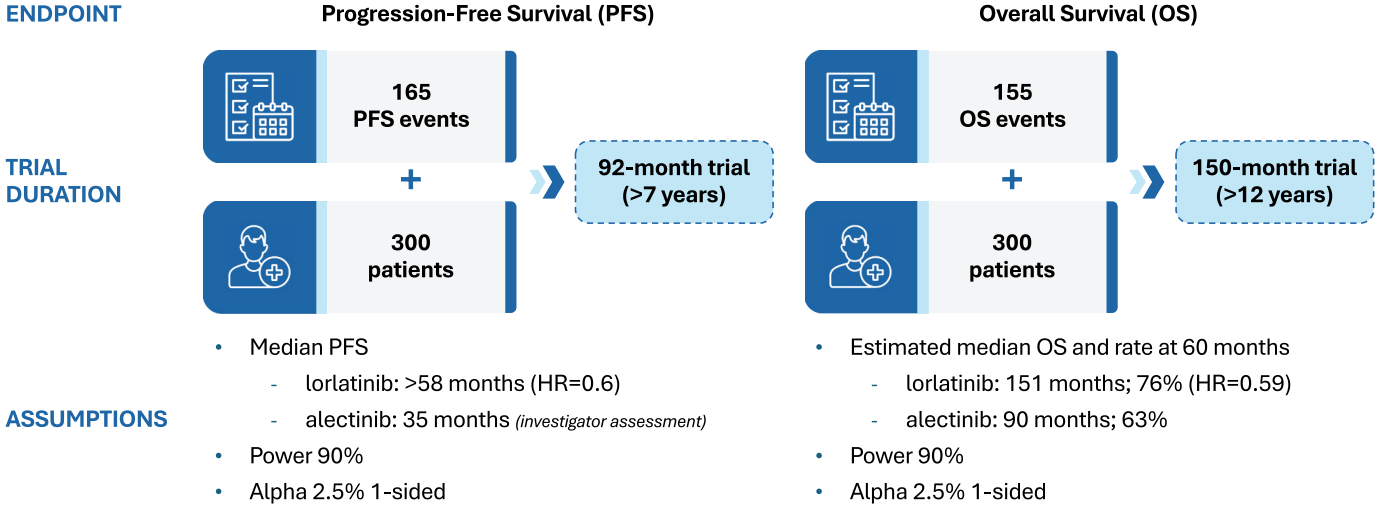

Figure 2. Hypothetical RCT calculation for lorlatinib vs alectinib in 1 L *ALK*+ mNSCLC.
HR: Hazard Ratio; OS: Overall Survival; PFS: Progression-Free Survival.

the future treatment paradigm will likely be far different by the time RCT results become available.

3. Rationale for RWE in mNSCLC, in the context of data challenges

RWE – resulting from analysis of real-world data (RWD) (data relating to patient health status and/or delivery of healthcare collected routinely [24]) – is not a new concept in clinical research. However, in recent years, RWD sourcing approaches and RWE methods have evolved significantly, alongside increasing stakeholder acceptability. In essence, it is now possible to employ an array of evidence generation methods in real-world settings, extending beyond traditionally limited single-site studies or chart reviews. Global regulatory bodies and professional societies have also recognized and endorsed the potential role that RWE may play, as being complementary to RCT. For example, the FDA has issued a series of guidances for industry – with one as recent as September 2024 [25] – on RWD assessment and standards, and RWE design considerations and inclusion in

regulatory submission [26–32]. The European Medicines Agency released guidance in April 2024 on use of RWE, covering study design, processes for requesting studies, and types of research questions that can be addressed [33]; and, the European Society of Clinical Oncology developed Guidance for Reporting Oncology real-World Evidence (ESMO-GROW) to provide detailed recommendations on oncology RWE research, for harmonized interpretation [34]. Similarly, Canada's Drug Agency provided guidance for RWE reporting in May 2023, in partnership with Health Canada and other Canadian authorities [35].

There is precedence of such government agencies and organizations accepting RWE as part of decision-making, particularly in oncology. Notably, the FDA approval of blinatumomab, for patients with precursor B-cell acute lymphoblastic leukemia in complete remission with detectable minimal residual disease, was supported in part by RWE, via an external control arm based on a retrospective cohort study [36]. The European Union authorities authorized alectinib coverage for *ALK*+ mNSCLC in 20 countries following evidence from an external comparator study [37]. The National Comprehensive Cancer Network has also found utility in RWE on targeted therapies, citing evidence in NSCLC guidelines in instances such as clinical characterization of patients with *BRAF* mutations [38] and outcomes in EURAF, the retrospective, real-world European BRAF cohort [39].

For treatments targeting rare oncogenic drivers in mNSCLC, RWE has the potential to further strengthen and expand on the totality of evidence available. Use cases may include providing generalizable clinical data on outcomes in subgroups that were underrepresented in or ineligible for RCT (e.g., patients with moderate or poor performance status) or further evidence to confirm RCT results. For example, brain metastases frequently occur in several biomarker-driven mNSCLC populations (both rare, like *ALK* and *ROS1*, and common, like *EGFR* and *KRAS*), however, patients with symptomatic brain metastases are often excluded from RCTs [40]; to observe their specific survival outcomes with a targeted therapy, real-world cohorts may be identified and analyzed. Additionally, in rare and common biomarker populations alike, RWE on dose modification can support deeper understanding of targeted therapies, especially in the absence of prospective trials for dose optimization [41–43]. Finally, in rare mNSCLC populations such as *BRAF V600E* where data are inherently limited, RWD collected from routine care settings may be analyzed to better understand contemporary, real-world treatment patterns, adverse event (AE) management, and effectiveness of treatment options, offering more pragmatic insights [44].

While RWE can complement RCT data and address some challenges that persist, particularly in rare oncogenic drivers in mNSCLC, potential drawbacks around RWD sourcing and RWE methods – irrespective of therapy area or disease – should still be acknowledged. Given the wide variety of potential RWD sources, the quality and completeness of data, leveraged for real-world research, may be questionable and/or vary significantly (e.g., prospective collection vs. clinician-populated electronic medical record vs. medical claims recorded for non-research purposes). The volume of patients and data attributes collected are also likely limited, with a single data set typically not fit-for-purpose in answering a wide variety of research questions. In terms of RWE methods, study designs selected may be potentially less rigorous relative to RCT, though RWE methodology has greatly improved in recent years. Additionally, the observational nature of many RWE studies can lead to confounding, necessitating appropriate statistical methods such as propensity score-matching or inverse probability of treatment weighting, which are not required in RCTs due to randomization.

4. Future enablers to support RWE in patients with rare oncogenic drivers in mNSCLC

To enable future evidence generation and RWE applications in rare patient segments, an innovative RWE capability in mNSCLC may be pursued, supported by three components comprising: (1) triangulation of multimodal data sets; (2) commitment to consistent, ongoing data management and governance; and (3) an aligned view on most pressing RWE use cases/evidence requirements for specific populations (Figure 3).

As brief elaboration on each of the three components:

(1) A portfolio of multimodal data sets to deliver answers to key research questions, by comprehensively capturing both breadth and depth of data attributes, and a patient sample capable of powering research (recognizing that a single data set will likely be unable to adequately meet these data attribute and patient sample requirements for rare populations).
(2) A technology platform capable of harmonization and integration of anonymized patient-level data from disparate data sets, with initial protocols and consents allowing for such data transfers, that onboards and hosts the standardized data with clear rules governing access and permissible use.
(3) A set of targeted RWE use cases tailored to the rare mNSCLC population of interest to support actionable stakeholder decision-making (e.g., genetic testing practices/strategies, AE management).

This capability can drive innovation in RWE for mNSCLC based on inherent features such as multidisciplinary collaboration, multimodal data sourcing, and resulting fit-for-purpose research potential. Such a capability will require concerted collaboration across stakeholders (e.g., health technologists, clinicians, and patients all serving as data providers), especially as the three components would need to be developed concurrently, to extract maximum value. Once assembled, the capability can enable ongoing access to a bespoke data set made easily available for more rapid generation of RWE.

5. Conclusions

As new treatment options continue to be discovered for rarer oncogenic drivers, mNSCLC, which was previously viewed in a more generalized manner, can now be considered a segmented disease. In response, new targeted therapies will continue to be developed, with potential to provide transformative care to patients with these actionable biomarkers. When investigating the therapies via gold standard RCT, we recognize

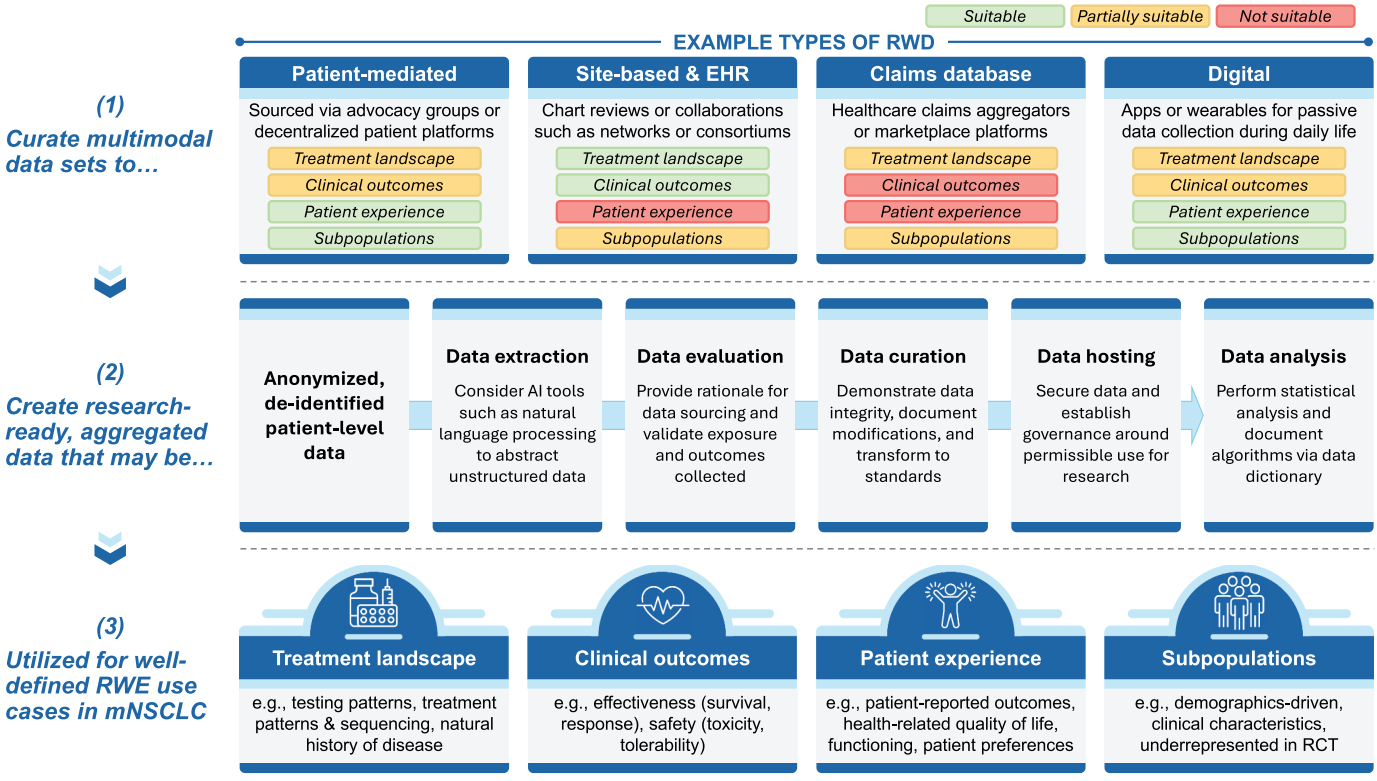

Figure 3. Illustrative schematic of an innovative RWE capability in mNSCLC.

AI: Artificial Intelligence; EHR: Electronic Health Record; mNSCLC: Metastatic Non-Small Cell Lung Cancer; RCT: Randomized Controlled Trial; RWD: Real-World Data; RWE: Real-World Evidence.

several possible challenges, including small populations, potentially long-time horizons for outcome events to occur, and underrepresentation of certain subgroups. The growing discipline of RWE can play an important role in addressing the challenges by strengthening and expanding the totality of evidence available. Given the absence of any single data source that meets research needs of targeted therapies for rare mNSCLC populations, there is an opportunity for greater innovation in RWE. Such innovation would be timely, considering widespread acceptance of RWE remains suboptimal. However, efforts from stakeholders, including articles, such as this one, to guidance documents sponsored by globally influential stakeholders (i.e., US FDA), can shift the field closer toward greater acceptance and understanding of value messages behind RWE data generation. Looking ahead beyond just acceptance, approaches such as an innovative RWE capability may then be explored, with healthcare stakeholders working in tandem toward fit-for-purpose and timely RWE with the most impact and utility for treatment decision-making.

Declaration of interest

M.N. is on an advisory board for AstraZeneca, Daiichi Sankyo, Takeda, Novartis, EMD Serono, Janssen, Pfizer, Eli Lilly and Company, Bayer, Regeneron, BMS, and Genentech; consultant for Caris Life Sciences (virtual tumor board); speaker for Blueprint Medicines, Janssen, Mirati and Takeda; and reports travel support from AnHeart Therapeutics, and stock/stock options from MBrace Therapeutics. U.B.R. reports receiving grant support directly paid to their institution and not related to the project from the following: AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Jazz Pharma, Genentech, Eli Lilly, Janssen, Takeda, Daiichi Sankyo, Blueprint Medicines, Janssen, Amgen; they also received consulting fees and travel support from Eli Lilly not related to the project. A. B. is employed by Oracle Health and Life Sciences. G.L. reports participation on a data safety monitoring or advisory board for AstraZeneca, Pfizer, EMD Serono, Merck, AbbVie, Jazz, Takeda, Nuvation Bio, Roche, BMS, Novartis, Amgen, Bayer, GSK, Regeneron, Gilead, and Lilly; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events for AstraZeneca, Pfizer, EMD Serono, and Takeda; and grants or contracts from NCI (US), CIHR (Canda), CCSRI (Canada), AstraZeneca, Takeda, Boehringer Ingelheim, Amgen, EMD Serono, Lung Cancer Canada, Breathe Biomedical, Adela, OxCan, Pfizer, and Bayer. E.N. reports payments from AstraZeneca (speaker, consultant), BMS (speaker), Regeneron (speaker, consultant), and EMD Serono (speaker). D.A. receives stock and is employed by Pfizer. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Author contributions

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