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REVIEW

Advancing real-world research in thoracic malignancies: learnings from the international I-O Optimise initiative

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ABSTRACT

In recent years, the thoracic malignancies treatment landscape has become more complex with the emergence of novel targeted and immunotherapy-based treatments. Although beneficial to patients and physicians, this fast-paced therapeutic evolution has increased the complexity of clinical decision-making and amplified the importance of real-world evidence to support data from randomized controlled trials. The international I-O Optimise initiative was established in 2016 to provide real-world insights into the thoracic malignancies treatment landscape, and has since collaborated with 14 data sources across Europe and Canada, allowing access to data from ~ 500,000 patients with non-small-cell lung cancer, small-cell lung cancer, and malignant pleural mesothelioma. This article reviews pertinent I-O Optimise research, with discussion of the methodological/data-related learnings and expectations for future insights.

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1. Introduction

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer death worldwide, accounting for ~ 12% of all new cancers and ~ 19% of all cancer-related deaths in 2022 [1]. In Europe, there were almost 4.5 million new cases of lung cancer in 2022 and almost 2 million deaths; in North America, there were over 2.5 million new cases and around 700,000 deaths [2,3]. Non-small-cell lung cancer (NSCLC), mostly comprising adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma, is the most common subtype of lung cancer globally, accounting for around 90% of cases [4]; small-cell lung cancer (SCLC) and malignant pleural mesothelioma (MPM) represent less prevalent thoracic malignancies [4–6]. Five-year survival rates for lung cancer have typically been below 20% in most countries, with prognosis especially poor for patients with advanced lung cancers [1,7,8].

Over the past two decades, the treatment landscape for thoracic malignancies has become more complex with the emergence of various novel targeted and immunotherapy-based treatment options. At present, European and North American guideline-based recommendations for the treatment of NSCLC, SCLC, and MPM include a variety of targeted small molecule/tyrosine kinase inhibitors, anti-programmed death 1 (PD-1)/PD-1 ligand 1 (PD-L1) immune checkpoint inhibitors, and/or vascular endothelial growth factor (VEGF)/VEGF receptor inhibitors, alongside surgery-, radiotherapy-, and chemotherapy-based options [5,6,9–18]. Moreover, the specific recommended use of these agents, either alone or more commonly in a variety of combinations, is driven by multiple factors, including patient- and healthcare system-related characteristics, disease stage, treatment history, histology/histopathology, organ function, and/or tumoral biomarkers [5,6,9–18].

These therapeutic advances have moved us closer to an era of personalized medicine, and the fast-paced evolution of the thoracic malignancies treatment landscape has increased the complexity of clinical decision-making for patients and treating physicians. Through official treatment guidance in the form of international and local guidelines, the clinical decision-making process is typically guided by data from randomized

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Article highlights

The I-O Optimise initiative
- I-O Optimise is an international collaborative initiative designed to leverage existing real-world data sources (RWDS) to provide timely insights into the thoracic malignancies landscape.
- To date, 14 RWDS have engaged with the I-O Optimise initiative, providing access to ~ 500,000 patients with non-small-cell lung cancer, small-cell lung cancer, or malignant pleural mesothelioma.
- The program is also contributing toward methodological advances in real-world research via development of algorithms designed to assign treatment intent and line of therapy when this information is missing from real-world datasets or is incomplete.

Lessons learned
- The I-O Optimise experience provides insights into potential areas of improvement for other real-world research programs.
- The diverse RWDS portfolio will facilitate the generation of both broad and deep data, enabling the adoption of common protocols for comparisons across data sources and/or countries, and allowing the program to adapt to changes outside of the target therapy area.

Future perspective
- Through continued collaborations with multiple data sources, I-O Optimise will facilitate future evaluations of the impact of emerging immunotherapy-based or targeted therapies for patients with thoracic malignancies, as well as novel therapies based on newer treatment modalities.

controlled trials (also termed explanatory trials) and via real-world evidence (RWE) from observational studies and/or pragmatic or practical clinical trials [19,20]. RWE can provide information that is difficult to capture in explanatory clinical trials (e.g., burden of disease, treatment patterns, and effectiveness in populations usually excluded from explanatory clinical trials) [20–25]. Furthermore, in support of the increasing importance of RWE, there is widespread recognition that high-quality real-world data can also complement data from clinical trials in health technology assessments (HTAs) and the regulatory decision-making process, as well as supporting post-marketing surveillance efforts [20,26,27].

The I-O Optimise initiative was conceived in 2016 to capture data on emerging new treatment options for thoracic malignancies by providing a comprehensive multicountry research platform focused on generating high quality real-world data from representative patient populations. In this article, we review RWE generated as part of I-O Optimise, with discussion of the methodological and data-related learnings from the program and expectations for future insights.

2. The I-O Optimise initiative

I-O Optimise is an international collaborative initiative designed to leverage existing real-world data sources (RWDS) to provide up-to-date information on treatment patterns and outcomes among patients with thoracic malignancies. Detailed methodology for the conception and initial build of the initiative has been described previously [28]. In brief, I-O Optimise functions as a collaboration between the respective RWDS owners, Bristol Myers Squibb, and IQVIA (the initiative facilitator). Expert input on the research focus, data review and interpretation, and publication activities is provided through regular meetings with the I-O Optimise External Scientific Committee – comprising a multinational team of clinicians, oncologists, epidemiologists, and RWDS owners – and through additional interactions with relevant stakeholders (e.g., other RWDS owners, experts on the clinical management of thoracic malignancies, and patient advocates).

The research objectives for I-O Optimise are based on five overarching topics: (1) epidemiology and clinical outcomes, (2) treatment patterns, (3) safety, (4) healthcare resource utilization, and (5) patient-reported outcomes [28]. Throughout the lifetime of the initiative, specific research objectives have been determined in collaboration with the External Scientific Committee and other stakeholders and are primarily based on relevant therapeutic and non-therapeutic advances in the thoracic malignancies landscape.

As part of I-O Optimise, individual studies are designed and conducted to address specific research topics and objectives, and associated data are provided by the RWDS involved in the study. Studies may be conducted using data from a single RWDS or, alternatively, across multiple data sources to enable comparisons across data source types and/or geographies. All data analyzed as part of I-O Optimise are aligned with specific study protocols that are approved by relevant ethics authorities in compliance with country-specific regulatory processes and meet European Union (EU) General Data Protection Regulation (GDPR) requirements or the national equivalent outside of the EU.

2.1. Research portfolio

To date, 14 RWDS have engaged with the I-O Optimise initiative, providing access to data from ~ 500,000 patients residing in nine European countries (Denmark, England, France, Germany, Italy, Norway, Portugal, Spain, and Sweden) and Canada (Figure 1). Data capture spans the period from 2005 to the present day, with consistent access to large patient populations with different thoracic malignancies (e.g., > 50,000 patients per year with NSCLC). There are a variety of data source types, including national and regional clinical or administrative registries, electronic medical record (EMR) databases, clinical cohort study datasets, and multisource/multi-country databases (Figure 1). The coverage provided by the collaborating data sources is extensive, with target populations ranging from those attending a single hospital to all patients in a particular country, as captured in national cancer registries. In addition, Oncology Dynamics (an IQVIA proprietary data asset) has recently been utilized to further contextualize I-O Optimise populations and tumor biomarker testing. This database comprises a cross-sectional survey collecting treatment profiles from a representative panel of physicians across Europe and the rest of the world.

Since the initiation of I-O Optimise, the number of patients providing analyzed data within research studies has increased over time, from ~ 2400 in 2019, up to ~ 100,000 patients in 2023, and an estimated 130,000 in 2024. The cumulative number of patients analyzed and providing RWE as part of I-O Optimise studies now exceeds 400,000, and data have been generated for several specialized patient populations, including > 9000 patients treated with immune checkpoint inhibitors, > 2000 patients expressing PD-L1, and > 150 patients with *ROS1*-positive NSCLC.

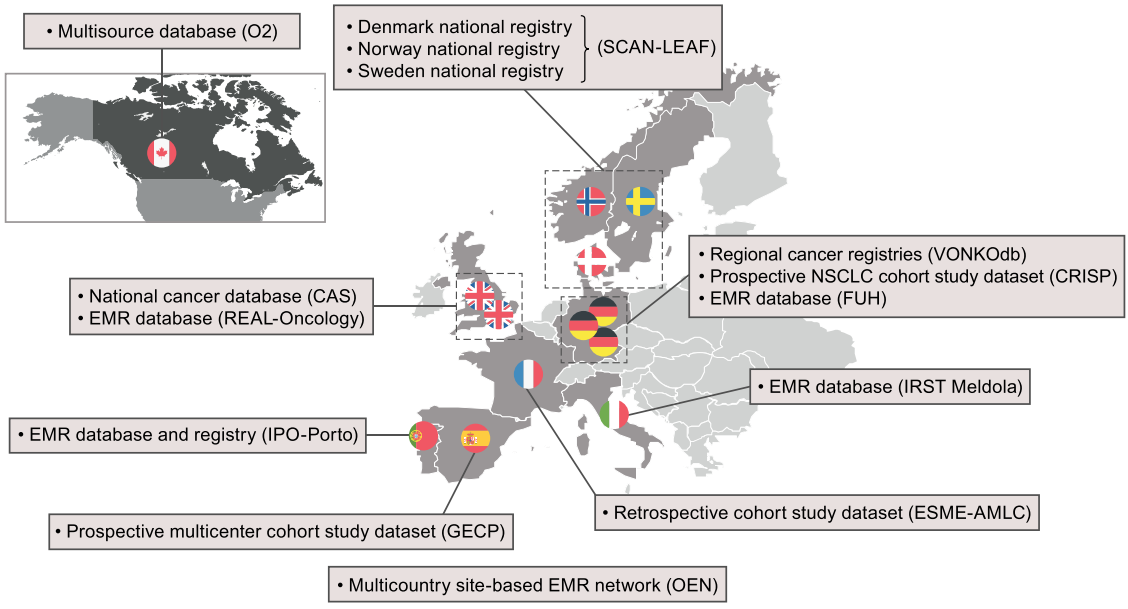

Figure 1. I-O Optimise collaborations.

CAS: Cancer Analysis System; CRISP: Clinical Research platform Into molecular testing, treatment and outcome of non-Small cell lung carcinoma Patients; EMR: electronic medical record; ESME-AMLC: Epidemiological-Strategy and Medical Economics Advanced and Metastatic Lung Cancer; FUH: Frankfurt University Hospital; GECP: Grupo Español de Cáncer de Pulmón (Spanish Lung Cancer Group); IPO-Porto: Instituto Português de Oncologia do Porto Francisco Gentil, EPE; IRST, Istituto scientifico Romagnolo per lo Studio dei Tumori "Dino Amadori;" O2: Oncology Outcomes; OEN, Oncology Evidence Network; REAL-Oncology: Real-world Evidence Alliance at Leeds-Oncology; SCAN-LEAF: Long-term Epidemiological Follow-up of Non-small Cell Lung Cancer in Scandinavia; VONKOdb: Versorgungsforschung in der ONKOlogie (Oncological Health Care Research) database.

2.2. Research themes and data output

Throughout the lifetime of the I-O Optimise initiative, several research themes have emerged that are closely aligned with the overarching research topics and associated objectives (Table 1). In the following sections, these research themes are discussed, alongside some of the generated data and expectations for future research (for descriptions of RWDS named in the following sections, see Figure 1).

2.2.1. Theme 1: Understanding the epidemiology of thoracic malignancies

Data from collaborating RWDS have provided insights into the characteristics and management of patients with specific thoracic malignancies. Indeed, most RWDS have included comprehensive information on various patient/disease characteristics including age, sex, Tumor-Node-Metastasis (TNM) stage, and histology/histopathology for relevant populations of patients with NSCLC, SCLC, or MPM [29–42]. Moreover, although not uniformly available, several RWDS have also provided data on other important baseline factors such as patient performance status or score, sites of metastases, comorbidities, and smoking status [30,32–35,38–41]. Across some RWDS, it has also been possible to assess patterns of biomarker testing, including oncogenic drivers such as epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) mutations, as well as tumor PD-L1 expression [29,38–41]. These data have provided insights into similarities and variations across different data source types. For example, among four RWDS capturing relatively comprehensive data on performance status for patients with NSCLC, two in Germany (CRISP and FUH) and one in Spain (GECP) included mostly patients with good performance status [39–41], while the English data source (REAL-Oncology) included a sizable proportion of patients (> 50%) with poor performance status, which would disqualify them from participating in most clinical trials [33,34].

Several collaborating RWDS have also provided important data on patterns of diagnosis. For example, RWDS in Denmark (SCAN-LEAF), England (REAL-Oncology), Portugal (IPO-Porto), and Sweden (SCAN-LEAF) indicated that more than half of all patients with NSCLC were diagnosed at an advanced stage of the disease (stage IIIB or IV) [29,33,35,36], highlighting the considerable size of this patient population. Analysis of NSCLC diagnoses over the period immediately prior to immunotherapy approvals using data from SCAN-LEAF and REAL-Oncology also provided temporal diagnostic information. In these data sources, while the proportions of patients diagnosed with advanced NSCLC within each calendar year declined over time, they remained > 50% for all of the evaluated years [33,35].

Extensive data on treatment patterns have been obtained across different types of RWDS, including overall treatment rates and treatments administered, with many sources allowing further analysis of treatment patterns by age, disease stage, histology, performance status, time period or year of diagnosis, and/or line of therapy [29–34,36,37,39,40]. Furthermore, due to collaborations with various data source types – including those with a narrower scope such as medical oncology practices following referred patients who are candidates for systemic anticancer therapy (SACT) and those with a broader reach into all diagnosed patients, regardless of the site of care – the initiative has provided unique insights into real-world treatment patterns. For example, analyses at a Portuguese single-site oncology hospital (IPO-Porto) showed a relatively high treatment rate of 76% among referred patients with advanced NSCLC [29]. In contrast, analyses from the broader REAL-

Table 1. I-O Optimise research themes.

Theme	Related outputs	Future goals
Understanding the epidemiology of thoracic malignancies	• Epidemiological data from multiple data sources providing insights into patient characteristics and patterns of diagnosis and treatment, mostly in the period before approvals of immunotherapies for the respective thoracic malignancies	• Expansion to additional territories to capture broader population data • Evaluation of changes in epidemiology and diagnosis and treatment patterns with advances in disease care and management
Assessing the burden of advanced NSCLC in the pre-immunotherapy era	• Provision of both broad and deep data on survival outcomes across multiple populations with advanced NSCLC in the period before immunotherapy approvals	• Expansion to additional territories to capture a broader population of treated patients with advanced NSCLC • Continued assessment of efficacy outcomes among patients with advanced NSCLC receiving newly approved immunotherapies and targeted therapies, as well as therapies based on newer alternative treatment modalities • Using pooled data from multiple RWDS to allow assessment of relatively rare patient populations (e.g., *ROS1*-positive NSCLC) • Evaluation of geographic similarities and differences in the uptake of new treatments and related patient outcomes
Evaluating the impact of immunotherapy after approval for advanced NSCLC	• Preliminary data on uptake of approved immunotherapies in large, representative populations in Canada, France, and Germany, and insights into the potential impact of these new therapies on patient outcomes	
Understanding unmet needs in other thoracic malignancies	• Data on survival outcomes for populations of patients with rare thoracic malignancies (SCLC and MPM) in the period before immunotherapy approvals	• Assessment of the uptake of newly approved immunotherapies and targeted therapies, as well as therapies based on newer alternative treatment modalities • Continued assessment of these patient populations as they receive treatment • Evaluation of geographic similarities and differences in the uptake of new treatments and related patient outcomes
Assessing the burden of non-metastatic NSCLC in the pre-immunotherapy era	• Provision of both broad and deep data on survival outcomes across populations with non-metastatic NSCLC in the period before immunotherapy approvals	• Expansion to additional territories to capture a broader population of treated patients with non-metastatic NSCLC • Continued assessment of the burden of non-metastatic NSCLC in the pre-immunotherapy era • Assessment of the uptake of newly approved immunotherapies and targeted therapies, as well as therapies based on newer alternative treatment modalities • Continued assessment of these patient populations as they receive treatment • Evaluation of geographic similarities and differences in the uptake of new treatments and related patient outcomes
Investigating potential advances in methodology for real-world research	• Development of algorithms to identify radiotherapy treatment intent in real-world populations with NSCLC when relevant data are missing or incomplete	• Incorporation of learnings into the creation of a more expansive algorithm that describes a patient's treatment pathway, from early-stage treatments with curative intent (surgery, [neo]adjuvant SACT, radiotherapy) to treatments in the advanced setting

MPM: malignant pleural mesothelioma; NSCLC: non-small-cell lung cancer; RWDS: real-world data source; SACT: systemic anticancer therapy; SCLC: small-cell lung cancer.

Oncology data source showed a much lower treatment rate of ~30% [34], which was similar to that reported for other large-scale population-based data sources from Canada and the United States [43–45]. Further insight from REAL-Oncology showed that treatment rates varied considerably depending on both age and performance status, ranging from only 3% in patients aged ≥ 75 years with an Eastern Cooperative Oncology Group (ECOG) performance status > 2, up to 69% in patients aged < 65 years with an ECOG performance status of 0–1 [34,46]. Thus, the striking difference in treatment rates may be largely explained by the broader patient population at REAL-Oncology, as well as the availability of detailed information on performance status [34,46]. Continued engagement with collaborating RWDS will permit further evaluation of temporal shifts in patterns of patient characteristics and treatment across numerous countries and regions.

2.2.2. Theme 2: Assessing the burden of advanced NSCLC in the pre-immunotherapy era

The burden of advanced NSCLC in the period before immunotherapy approvals (or prior to widespread use of these agents) has been assessed using data extracted from several collaborating RWDS. For example, broad data from > 60,000 patients in Danish and Swedish national registries (SCAN-LEAF) showed that 1-year overall survival (OS) tended to improve among patients with stage IV non-squamous (NSQ) NSCLC between 2005 and 2015 (the decade immediately before the first immunotherapy approval) [35,36]. However, similar temporal improvements were not seen for 1-year OS in patients with stage IV squamous (SQ) NSCLC or for longer-term survival outcomes (2-, 3-, or 5-year OS) in patients with either stage IV NSQ or SQ disease [35,36]. Analyses from REAL-Oncology showed temporal improvements in OS (2007 to 2017) among ~650 patients with advanced NSCLC receiving SACT [34]. However, detailed patient and treatment information revealed that patients who did not receive SACT (almost two-thirds of all diagnosed patients) had a very poor prognosis (median OS of < 2 months) and that older age and worse performance status were significantly associated with lower odds of receiving SACT [34]. Similarly, analyses from IPO-Porto including ~1000 patients with advanced NSCLC showed that older age and a diagnosis of stage IV disease were significantly associated with both a lower likelihood of receiving SACT and an increased risk of death [29].

2.2.3. Theme 3: Evaluating the uptake and impact of immunotherapy after approval for advanced NSCLC

Based on the collection of data on advanced NSCLC treatment patterns over extended periods, several RWDS provided evidence of substantial real-world uptake of immunotherapies following approvals/reimbursement. In a population-based analysis of 2244 patients receiving first-line (1L) treatment for advanced NSCLC conducted in collaboration with a Canadian multisource database (O2), proportions of patients receiving 1L and second-line (2L) immunotherapy increased from < 0.5% and 8%, respectively, before reimbursement, to 17% and 47%, respectively, after reimbursement [37]. Similarly, in a study of 332 patients with locally advanced/metastatic NSQ or SQ NSCLC without known *EGFR*/*ALK* aberrations who received 1L therapy at FUH, proportions receiving an immunotherapy-based treatment increased from 6% and 3%, respectively, before reimbursement, to 57% and 53%, respectively, after reimbursement [40]. The evolution of immunotherapy uptake was also assessed in > 10,000 patients with advanced NSCLC without known *EGFR*/*ALK* aberrations across the ESME-AMLC and CRISP cohort study datasets [39]. In this analysis, the proportions receiving immunotherapy in both RWDS consistently increased in the periods following the first country-specific approvals/reimbursement, with more than 50% of all evaluated patients receiving an immunotherapy-based regimen over the course of their treatment [39].

Some of these analyses also suggested a possible association between the observed uptake of immunotherapies and patient survival. In the O2 population-based analysis, median OS increased alongside the adoption of immunotherapies for advanced NSCLC (from 10.2 months pre-reimbursement to 12.1 months post-reimbursement) [37]. In the FUH analysis, median OS increased between the pre- and post-reimbursement periods among patients with NSQ NSCLC, with a noteworthy increase in patients receiving a 2L therapy (from 5.4 to 9.6 months) [40]. Nevertheless, neither analysis was designed to directly assess relationships between immunotherapy uptake and OS; therefore, it was not possible to assign causality. Moreover, small patient numbers for specific treatment and/or histology subgroups and relatively short follow-up times further limited the scope of analyses into any direct or indirect relationships [37,39,40].

In contrast, due to the large size of the ESME and CRISP cohort study datasets, and because nivolumab has been an established 2L treatment for advanced NSCLC for several years, associations between treatment and clinical outcomes could be more directly assessed [38]. Indeed, in an analysis of ~ 2800 patients with advanced NSCLC treated with 2L+ nivolumab, real-world survival outcomes were consistent between the two databases and aligned with outcomes reported in explanatory clinical trials [38]. Moreover, it was also possible to conduct regression modeling analyses to identify factors significantly associated with treatment duration and OS, such as performance status and time from start of previous line of therapy [38].

Through continued engagement with existing data sources (as well as new collaborations), further assessment of the impact of increased immunotherapy use on patient outcomes should be possible, particularly as the number of patients receiving 1L immunotherapy-based treatments for advanced NSCLC grows and relevant post-treatment follow-up periods lengthen. Furthermore, it may be possible to expand the scope of research in these populations to assess the impact of newer immunotherapy-based or targeted treatments for advanced NSCLC, as and when they may be approved in the respective territories.

2.2.4. Theme 4: Understanding unmet needs in other thoracic malignancies

While the incidence of lung cancer varies considerably across Europe [47], the proportion of patients with SCLC is consistently lower than those with NSCLC. Indeed, SCLC is reported to account for only 13–15% of all lung cancers [47,48], with a prevalence of just 1–5 per 10,000 people in Europe [5]. MPM is a rare malignancy, with incidence rates of only 1.7 and 0.4 per 100,000 people in Europe (for males and females, respectively) [6]. One consequence of this relative low prevalence/incidence is that it is often challenging to identify sufficiently sizable real-world patient populations for analysis.

Two RWDS collaborating with I-O Optimise provided data on sufficiently large populations of patients with SCLC, allowing analysis of treatment patterns and survival outcomes. Analyses of 227 and 425 patients with SCLC at IPO-Porto and REAL-Oncology, respectively, showed that around one-third of each population did not receive active treatment with SACT, and OS outcomes for these patients were very poor (median OS ranged from 0.7 to 2.8 months) [30,49]. Furthermore, among patients with the most advanced form of SCLC – extensive-disease SCLC – who received SACT (mostly platinum-based chemotherapy regimens), outcomes remained poor in both analyses, with median OS ranging from 5.4 to 7.2 months. These findings emphasized the high disease burden for patients with SCLC and the relatively poor outcomes associated with platinum chemotherapy alone in patients with advanced disease. These data may also represent a useful benchmark for comparison with existing real-world data from studies of chemo-immunotherapy regimens approved for extensive-disease SCLC (recently summarized by Damiano and colleagues [50]), as well as future analyses of newer treatments for advanced SCLC [5,17].

It was possible to obtain data on ~ 9500 patients diagnosed with MPM in England between 2013 and 2017 from a nationwide cancer registry (CAS), allowing a thorough analysis of treatment patterns and OS outcomes over this timeframe, prior to approval/guideline recommendation of immunotherapy-based treatments [32]. In this analysis, 60% of the patients received best supportive care or palliative radiotherapy alone (i.e., no surgery or SACT), which was associated with poor survival (median OS of 4.6 months). One-third of the patients with MPM (33%) received SACT with/without radiotherapy and 7% underwent surgery, with a median OS of 14 and 17 months, respectively. The analyses also showed a significantly worse prognosis was associated with older age (≥ 65 vs 18–64 years), a worse ECOG performance status (≥ 2 vs 0–1), or non-epithelioid histology (sarcomatoid, biphasic, and "not otherwise specified" vs epithelioid) [32]. Additional data on MPM have been provided by a historical cohort study conducted as part of SCAN-LEAF and including adults newly diagnosed with MPM between 2011 and 2018 in Denmark

[51]. Of the patients in this study with known disease stage, 54% of those with advanced MPM ($n = 390$) and 46% of those with non-advanced MPM ($n = 325$) had no recorded treatment within 6 months of diagnosis. Median OS was 10.0 months in patients with advanced MPM and 18.0 months in those with non-advanced MPM. The study also showed that age ≥ 75 years at diagnosis (vs < 65 years), sarcomatoid or unspecified histology (vs epithelioid), and stage IV disease (vs all other stages) were associated with an increased risk of mortality [51]. European and North American guidelines now recommend immunotherapy options for MPM, such as nivolumab plus ipilimumab for 1L+ disease and nivolumab with or without ipilimumab after progression in patients naïve to immune checkpoint inhibitors [6,18]; European guidelines also recommend pembrolizumab as a post-progression treatment option. Continued work with CAS will allow evaluation of the impact of these new immunotherapy options on outcomes for patients with MPM, for which the original published data will serve as useful points of reference.

2.2.5. Theme 5: Assessing the burden of non-metastatic NSCLC in the pre-immunotherapy era

The treatment landscape for non-metastatic NSCLC has changed substantially over recent years [9,10], necessitating a new I-O Optimise theme on the burden of non-metastatic disease before the emergence of immunotherapy options. Although this theme is relatively new, data from 5147 patients diagnosed with stage I – IIIC NSCLC in Sweden between 2014 and 2019 (SCAN-LEAF) have highlighted the influence of treatment choice on survival outcomes, with median OS from treatment start date longest for patients receiving surgery alone, surgery with adjuvant SACT ± radiotherapy, or surgery with neoadjuvant SACT ± radiotherapy versus all other treatment categories, regardless of disease stage [42]. Overall, the study dataset (comprising data from 17,433 patients diagnosed between 2008 and 2019) provided valuable initial insights into the characteristics of patients with non-metastatic NSCLC and how they were managed in real-world settings prior to the availability of immunotherapy options [42]. In addition, an analysis of 1838 patients diagnosed with stage IIIA or IIIB NSCLC between 2010 and 2019 (based on 7th or 8th American Joint Committee on Cancer/International Union Against Cancer classification), performed in collaboration with GECP, showed a similar influence of treatment on survival, with median OS ranging from 4 months among patients with stage IIIB NSQ NSCLC receiving radiotherapy alone, up to 69 months among patients with stage IIIA NSQ NSCLC receiving neoadjuvant SACT then surgery [41]. Finally, initial results from another pre-immunotherapy analysis were presented at the 2023 World Conference on Lung Cancer and provided insights into epidemiology, treatment patterns, and survival outcomes for patients with non-metastatic NSCLC from data sources in Canada (O2), England (CAS), Germany (VONKOdb), and Sweden (SCAN-LEAF) [52]. Taken together, these pre-immunotherapy analyses will serve to establish real-world baselines, allowing future evaluation of the impact of emerging immunotherapy-based and targeted treatment options for patients with non-metastatic NSCLC. Indeed, with the current recommended use of consolidation durvalumab therapy for patients with unresectable stage III NSCLC not progressing on chemoradiotherapy, and recent approvals of neoadjuvant and adjuvant immunotherapy or targeted therapy options for patients with resectable NSCLC [10,15,16,53–60], continued engagement with multiple I-O Optimise data sources will provide important data on the subsequent impact of these newer immunotherapy-based and targeted treatment options on patient outcomes.

2.2.6. Theme 6: Investigating potential advances in methodology for real-world research

Although the primary focus of I-O Optimise has been on patterns of treatment and clinical outcomes, data collected as part of the program have also facilitated methodological analyses. Indeed, analyses are currently underway to evaluate the utility of algorithms in assessing real-world treatment patterns, including those designed to assign treatment category and/or intent (where relevant treatment information is lacking) or assign line of therapy to SACT recorded along the patient treatment pathway. For example, algorithms to determine radiotherapy treatment intent in real-world data from patients with non-metastatic NSCLC have been developed using data from IPO-Porto and REAL-Oncology (one based on radiotherapy duration, one on radiotherapy duration and type, and one on radiotherapy dose) [61]. All three algorithms showed good overall algorithmic accuracy (91–100%) for patients receiving radiotherapy plus SACT, and those based on radiotherapy duration and type or on dose alone also showed good accuracy (> 99%) for patients receiving radiotherapy alone [61]. Continued engagement with RWDS of different types and scope will facilitate validation studies for such algorithms to maximize their generalizability outside of I-O Optimise.

3. Lessons learned

As well as generating an abundance of useful RWE, experience from I-O Optimise has provided essential learnings relevant to real-world research in the thoracic malignancies arena and beyond. One of the key learnings has been the importance of a diverse portfolio of RWDS, not just in terms of geography, but also in relation to the data source type. Individual data sources usually provide data that are either broad (e.g., disease epidemiology and overarching data on treatment patterns and outcomes from large, representative patient populations, as captured in regional or national registries) or deep (e.g., detailed data on disease characteristics, treatment patterns, and clinical outcomes, as captured from a defined patient population referred to a specialist oncology hospital or practice). Moreover, broad datasets often capture data on patients who are not treated and/or who live in areas not served by specialist oncology hospitals, while deep datasets can be probed for data on molecular subtypes, planned and administered treatment (including treatment intent, reasons for discontinuation, and/or line of therapy) and potentially data on disease progression and/or tumor responses. However, a diverse portfolio of RWDS can allow the generation of both broad and deep data in relation to specific research topics/objectives. In I-O Optimise, the inclusion of

national and regional registries has provided broad, representative data, while the inclusion of EMR databases, clinical cohort study datasets, and multisource/multi-country databases has provided a mixture of broad and deep data, with the opportunity to interrogate clinically rich, deeper datasets (Figure 2). The diverse portfolio of I-O Optimise has also allowed inclusion of increased numbers of patients with relatively less common malignancies, such as SCLC and MPM, as well as those with NSCLC carrying rare oncogenic driver mutations/alterations or biomarkers. Indeed, the ability to actively explore new data source partnerships to further diversify the portfolio has allowed for agility when faced with changing research priorities and new questions to answer. As an example, Oncology Dynamics was recently leveraged to provide data on testing patterns and positivity rates of a rare oncologic driver mutation, *ROS1*, among patients with NSCLC across several European countries [62].

Another key learning has been the importance of standardizing methodology across research studies to facilitate comparative analyses. Within I-O Optimise, several studies have been conducted across multiple RWDS and, for those studies, a common methodological approach has been developed, with consistency in factors such as patient eligibility and inclusion/follow-up periods (whereby preexisting patient inclusion/exclusion criteria and study periods are aligned as much as possible) and full alignment on other factors such as treatment classifications/categories, clinical outcome measures, and statistical methodology. In addition, to address the challenge of inconsistent recording of treatment intent or the treatments administered to patients, I-O Optimise research has been, and continues to be, used to develop algorithms that assign treatment intent, treatment category, and/or line of therapy (as described in Theme 6), with the goal of full standardization across different RWDS. Through alignment with and consideration of similar published methodological approaches [63–65], these algorithms may serve to increase the validity of any comparisons made between RWDS and, by association, the overall research findings.

The need for research programs to be adaptable to changes outside of the therapeutic landscape represents another key learning from I-O Optimise. For example, since the initiation of I-O Optimise, patient privacy has become increasingly relevant to real-world research, particularly with the need for compliance with EU GDPR requirements and relevant national/regional equivalents outside of the EU. The first effects on I-O Optimise came early in the initiative with the realization that the original proposed methodology, based around a single pooled database collating data from multiple RWDS transformed under a common data model, would be extremely challenging in light of the emerging privacy regulations. This ultimately led to the adoption of a more pragmatic, stepwise approach to building the I-O Optimise portfolio – from single-site EMR RWDS to larger regional/national registries and clinical cohort study datasets and the more recent multisource/multi-country databases. Furthermore, these privacy regulations have resulted in many RWDS being reluctant to share patient-level data. While this does not impact most of the real-world research conducted as part of I-O Optimise, where data are analyzed directly by the RWDS and/or provided externally in aggregate form, it poses a challenge for research requiring off-site analysis of data from more than one RWDS. To address this challenge, approaches have been developed that facilitate the de-identification of patient-level data from multiple RWDS, transfer of these data into a secure environment managed by the initiative facilitator, and harmonization of the data to a single protected dataset before analysis, all of which is conducted in strict accordance with relevant ethical approvals and data privacy regulations (Figure 3). As well as allowing access to useful patient-level data, this approach helps in accessing larger numbers of patients with the less common thoracic malignancies or rare oncogenic driver mutations/alterations via data pooling across RWDS. Importantly, the utility of this methodology is not limited to thoracic malignancies, with application across numerous other therapy areas.

Finally, it is important to note that the I-O Optimise experience has provided insights into other potential areas of improvement for real-world research. These include (1) a need for more large-scale EMR – based RWDS that are epidemiologically representative of their catchment area; (2) the systematic inclusion of data on drug safety, healthcare resource utilization, and patient-reported outcomes across RWDS; and (3) a need for consistently shorter lag times in collecting/curating real-world data to facilitate the timely dissemination of relevant RWE to practicing physicians.

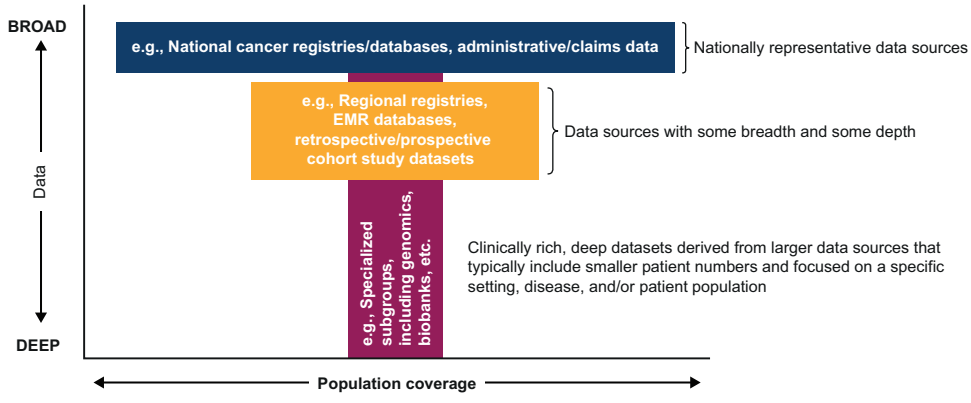

Figure 2. Diversification of the I-O Optimise portfolio through collaborations with multiple data source types.
EMR: electronic medical record.

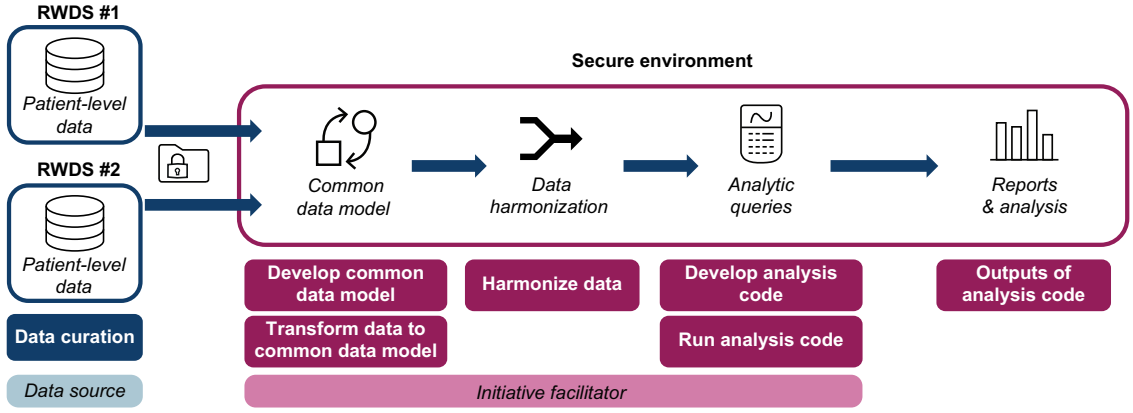

Figure 3. Overview of novel pooling methodology for real-world patient-level data.
RWDS: real-world data source.

4. Complementary real-world oncology research programs

Although there were available data from individual real-world studies of patients with lung cancers, a primary reason for the conception of I-O Optimise in 2016 was that there were no comprehensive multicountry real-world research platforms for thoracic malignancies in Europe at that time. Since then, other large-scale European-based research activities have emerged that have provided, or have the potential to provide, real-world data on the thoracic malignancies landscape. For example, PACIFIC-R (NCT03798535), a large, focused observational study, has generated data on the real-world use of durvalumab after chemoradiotherapy in predominantly European patients with unresectable stage III NSCLC treated within a multi-country early access program [66]. Another example is the European learning health system in precision oncology (DigiONE) that is designed to identify optimal cancer treatments via interrogation of patient EMRs [67], which, although not specific to any cancer type, has potential to generate future data on patients with thoracic malignancies. Similarly, broader European non-cancer-specific initiatives such as GetReal and the Data Analysis and Real World Interrogation Network (DARWIN EU) have been designed to capture real-world data on the use of medicines with the objective of informing and contributing to the regulatory drug development process [68,69]; again, this could include medicines for use in patients with thoracic malignancies. Finally, the KINDLE retrospective, non-interventional study has recently provided an abundance of real-world data on patients with stage III NSCLC in Asia, the Middle East, North Africa, and Latin America [70,71]; these important data could be assessed alongside data on patients with stage III disease from I-O Optimise and similar US-based programs to provide a global picture for this patient population.

While these emergent research activities have provided or have potential to provide important insights, I-O Optimise remains the only large-scale real-world research platform specifically dedicated to thoracic malignancies, with a focus on describing changes in the treatment landscapes and associated patient outcomes. Nevertheless, while I-O Optimise has and will continue to provide a focused initiative for patients with thoracic malignancies in Europe, there is potential for expanded collaborations, as demonstrated by the recently established HARMONY Alliance BigData Platform, which currently incorporates 140 organizations (comprising data providers such as pharmaceutical companies, biobanks, hospitals, and interventional/non-interventional studies) from 38 countries across the world with a single mission of accelerating the development of more effective treatments for people with blood cancers [72,73]. A similar initiative for lung cancers, incorporating I-O Optimise, would undoubtedly provide additional insights that would benefit patients with thoracic malignancies in Europe and worldwide.

5. Future perspective

Through regular engagement with existing RWDS and collaboration with new data sources, the I-O Optimise initiative is expected to facilitate continued generation of data on patients with thoracic malignancies. Moreover, with continued approval of various immunotherapy-based or targeted therapies, as well as therapies based on newer treatment modalities, prolonged engagement with multiple I-O Optimise data sources will enable ongoing and future analysis of their real-world adoption and effectiveness.

As well as furthering our academic understanding of the evolving therapy area and potentially aiding in the identification of unmet patient needs, the data generated within I-O Optimise can also be utilized in regulatory decision-making processes. Indeed, epidemiologic data and information on treatment patterns for patients with MPM captured in the CAS database were used in regulatory submissions to the UK National Institute for Health and Care Excellence, which led to a marketing authorization for nivolumab plus ipilimumab in the 1L treatment of unresectable MPM [74]. With the increased widespread recognition that high-quality RWE can play a complementary role alongside data from explanatory clinical trials in regulatory submissions and HTAs [20,26,75], as well as evidence that RWE is increasingly being used for such activities [76–78], it is likely that future data outputs from I-O Optimise will increasingly contribute to relevant regulatory activities.

Finally, while the primary focus for I-O Optimise will continue to be the generation of quality RWE on the emerging new treatment options for thoracic malignancies, additional aspirational future directions for the initiative could include research into relationships between socioeconomic status and access to cancer therapy, assessment of the potential for linking claims data to other primary data sources to address the challenges of information gaps in this data source type, and potentially using RWE to evaluate the environmental sustainability of modern treatment and care approaches for patients with thoracic malignancies.

6. Conclusion

Due to the fast-paced emergence of newer therapies and treatment strategies for patients with thoracic malignancies, there is a continued need for high quality real-world data on the available therapeutic options to help inform both the clinical and regulatory decision-making processes, including HTAs. Over the past 9 years, the I-O Optimise initiative has facilitated engagements with multiple RWDS that have informed our understanding of the patient characteristics, disease burden, treatment/management approaches, and clinical outcomes associated with thoracic malignancies. Moreover, by adopting a unique approach of forging collaborations with existing RWDS, rather than conducting prospective standalone studies, there have been time and cost savings for the research conducted. Importantly, sustained collaboration with these RWDS, as well as new collaborations, will allow future timely evaluations of the impact of emerging immunotherapy-based or targeted therapies for patients with thoracic malignancies, as well as novel therapies based on newer treatment modalities.

Author contributions

Conceptualization: MJ Daumont, JR Penrod, and JC O'Donnell; Methodology: SP Johnsen, P Baas, JB Sørensen, C Chouaid, F Griesinger, MJ Daumont, C Rault, G Emanuel, JR Penrod, H Jacobs, M Muwaffak, MJ Schoemaker, REJ Munro, D Baskaran, I Durand-Zaleski, and JC O'Donnell; Writing – original draft preparation: SP Johnsen, P Baas, JB Sørensen, C Chouaid, F Griesinger, MJ Daumont, C Rault, G Emanuel, JR Penrod, H Jacobs, M Muwaffak, MJ Schoemaker, REJ Munro, D Baskaran, I Durand-Zaleski, and JC O'Donnell; Writing – review and editing: SP Johnsen, P Baas, JB Sørensen, C Chouaid, F Griesinger, MJ Daumont, C Rault, G Emanuel, JR Penrod, H Jacobs, M Muwaffak, MJ Schoemaker, REJ Munro, D Baskaran, I Durand-Zaleski, and JC O'Donnell; Funding acquisition: MJ Daumont, G Emanuel, JR Penrod, H Jacobs, and JC O'Donnell.

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SP Johnsen reports receipt of consulting fees and support for attending meetings and/or travel from Bristol Myers Squibb. P Baas reports institutional receipt of consulting fees from MSD; and institutional receipt of consulting fees, honoraria, support for attending meetings and/or travel, and research funding from Bristol Myers Squibb. JB Sørensen reports receipt of consulting fees and support for attending meetings and/or travel from Bristol Myers Squibb. C Chouaid reports receipt of consulting fees, honoraria, and support for attending meetings and/or travel from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Chugai, Eli Lilly, GSK, Janssen, MSD, Novartis, Pfizer, Roche, Sanofi Aventis, Takeda, and Viatris. F Griesinger reports receipt of institutional research funding from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, GSK, MSD, Novartis, Pfizer, Roche, Sanofi Aventis, Siemens, and Takeda; and consulting fees, support for attending meetings and/or travel, and support for participation on DSM or advisory boards from Amgen, AstraZeneca, BeiGene, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi-Sankyo, Eli Lilly, GSK, MSD, Novartis, Pfizer, Roche, Sanofi Aventis, Siemens, and Takeda. MJ Daumont, JR Penrod, and JC O'Donnell report ownership of stock in Bristol Myers Squibb, and were employees of Bristol Myers Squibb at the time of the described I-O Optimise initiative conception and facilitation. C Rault and H Jacobs are independent consultants paid by Bristol Myers Squibb. G Emanuel was an employee of Bristol Myers Squibb at the time of the described I-O Optimise initiative facilitation. M Muwaffak, MJ Schoemaker, and D Baskaran are employees of IQVIA. REJ Munro reports ownership of stock in IQVIA and is an employee of IQVIA. I Durand-Zaleski reports receipt of consulting fees from Bristol Myers Squibb. 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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Ethical conduct of research

Ethical conduct for the overarching I-O Optimise initiative is summarized in Section 2. The cited I-O Optimise studies were all conducted in accordance with the International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices, with relevant country-specific guidelines and recommendations for ensuring good epidemiological practice, and/or with the ethical principles set forth in the Declaration of Helsinki. Each study followed the laws and regulatory requirements of the respective country in which the study was conducted, with ethical approval of the protocol provided by the lead institution(s) or relevant regional- or country-specific ethics committees (note, for some data sources, the need for ethics approval was waived due to the non-interventional and retrospective design of the study). For retrospective studies, existing pseudo-anonymized data were presented in aggregate form and, as such, informed patient consent was not required. For studies involving prospective patient enrollment, informed consent was obtained from all participants.

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Data sharing statement

Data from the cited I-O Optimise studies are not publicly available, and no data sharing is planned. Patient-level data cannot to be shared due to relevant regulatory and confidentiality reasons. Aggregate results from the cited studies are presented in this article.

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