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EDITORIAL

Merging clinical research and standard healthcare – Nordic Precision Cancer Medicine Symposium 2025

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Introduction

The second Acta Oncologica Nordic Precision Cancer Medicine Symposium (NPCM2025), held from September 15 to 17, 2025, in Oslo, Norway, focused on the intersection of clinical research and standard healthcare in precision oncology and was hosted by Oslo University Hospital and the Norwegian Centre for Clinical Cancer Research, MATRIX. This biannual event, part of the Acta Oncologica conference series, brought together 180 participants from altogether 15 countries to learn more about and discuss innovative approaches and practices in precision cancer diagnostics and treatment.

In the changing landscape of oncology, the integration of precision medicine into clinical practice represents a significant shift toward a more tailored approach to cancer care, driven by advanced molecular profiling, innovative clinical trials, and an expanding array of targeted therapies and treatment options. Comprehensive genomic profiling (CGP) provides a detailed analysis of a patient's tumor DNA (and RNA) to uncover a wide array of genetic alterations. This information helps in selecting targeted therapies that are specifically designed to address the identified disruptions, thereby improving treatment efficacy and reducing unnecessary side effects. On the other hand, cellular phenotype, mirrored by comprehensive proteomics and functional analyses, assesses cancer cell responses to different drugs in controlled *in vitro* settings. The latter involves evaluating the effectiveness of specific therapies against cancer cells derived from the patient's tumor. By examining the functional responses of these cells to various treatments, clinicians can identify the most effective therapeutic options tailored to the individual's unique tumor biology. Together, CGP, proteomics and functional precision oncology create a synergistic framework for precision cancer medicine (PCM). While CGP and proteomics identify the genetic landscape of the tumor and host response, functional assays validate and refine treatment options based on the actual patient's tumor cell responses. This multimodal approach enhances the likelihood of successful outcomes, allowing patients to receive more personalized and effective cancer treatments.

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The implementation of PCM in standard healthcare is progressing but several hurdles remain. Key challenges include unequal access to advanced diagnostics, uncertainties regarding the real-world effectiveness of targeted treatments, and issues related to reimbursement and co-payment for patients. In addition, there is a need for enhanced education and training for healthcare providers to effectively interpret genomic data and integrate it into clinical practice. Overcoming these barriers requires coordinated efforts among healthcare providers, policymakers, and stakeholders to ensure that PCM can be effectively incorporated into routine clinical practice, ultimately enhancing patient outcomes and equity in cancer care.

The second Nordic Precision Cancer Medicine Symposium brought together experts from different areas important for PCM implementation into standard healthcare, and topics addressed during the conference included precision diagnostics, functional precision oncology, precision immune-oncology, clinical trials as well as PCM implementation. In addition, current Nordic cancer strategies and PCM was discussed. This special edition focusing on PCM, includes publications from altogether 13 speakers and poster presenters from the NPCM2025 conference.

Keynote insights: Pioneering advances in precision oncology and therapeutics

At NPCM2025, three keynote speakers showcased the latest advancements in the field of PCM.

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Edwin Cuppen from the Hartwig Medical Foundation provided an insightful overview of the diagnostic applications of whole genome sequencing (WGS) in oncology across the Netherlands. Currently, around 1,100 patients from 30 hospitals are screened annually. In June 2025, the Dutch healthcare authorities approved reimbursement for all patients who were in sufficient condition to undergo treatment. Although routine WGS-based cancer diagnostics can be beneficial for patient care, there are still significant challenges to widespread implementation. Key obstacles include the requirement for high-quality, non-formalin fixed paraffin embedded (FFPE) tissue samples and high sequencing costs. To enhance cancer care, a WGS database is being built at Hartwig to support research efforts, with new findings continually integrated into the database, thus refining cancer care practices over time. Finally, Cuppen discussed the potential for reusing data from this comprehensive database, which not only encompasses sequencing data but also includes clinical metadata. International data sharing is feasible, and fostering global collaborations will be crucial for optimizing the use of this and similar resources.

Andreas Bjerrum from Copenhagen University Hospital in Denmark emphasized the significance of secondary use of health data for advancing precision oncology. He pointed out that patients with the same diagnosis can respond differently to identical treatments, making it crucial to analyze real-world data (RWD) from diverse patient populations to identify potential patterns. By leveraging these insights, healthcare providers can better understand which patients are likely to benefit from specific therapies and which may not respond, ultimately enhancing patient care. To facilitate this process, data can be structured and harmonized using frameworks such as OMOP-CDM (Observational Medical Outcomes Partnership – Common Data Model), which enables federated analyses. The standardization and harmonization of RWD allows us to learn from every patient, providing a robust platform for advancing PCM. Bjerrum's presentation on leveraging data from the Capital Region of Denmark exemplified how real-world applications of precision medicine can enhance patient outcomes through informed treatment choices. In this Acta Oncologica special edition, Bjerrum et al. commented on a qualitative study and highlighted the shared responsibility between the public and private sectors in supporting evidence generation for post-approval assessment of precision medicine [1].

Patricia LoRusso from the Yale Cancer Center presented an overview of antibody drug conjugates (ADCs) in cancer treatment, discussing both current challenges and new, innovative strategies. ADCs have transformed drug delivery, with 450 different ADCs entering clinical development by September 2025, 13 of which have received U.S. Food and Drug Administration (FDA) approval. Key barriers for enhancing ADC efficacy and reducing toxicity include limited payload diversity, linker stability, and the translation of results from preclinical models to humans. LoRusso highlighted the modular nature of ADCs and various optimization opportunities. The next-generation ADCs focus on overcoming the abovementioned barriers. Notable advancements include bispecific ADCs targeting two different antigens, potentially overcoming resistance and enhancing specificity. While many bispecific ADCs are in clinical development, most utilize the same payloads. However, dual-payload ADCs are now entering clinical development. In addition, combining ADCs with standard therapies shows substantial promise.

Conference sessions: Shaping the future of precision cancer care

The conference consisted of four sessions, each exploring key areas of PCM: precision diagnostics, functional precision oncology and precision immune oncology, clinical trials and the implementation of PCM in standard healthcare. Each session featured three internationally renowned speakers who presented cutting-edge research in their respective fields. In addition, selected short talks from abstract submissions enriched the program.

Session one explored advances in precision diagnostics with insights from three invited speakers: Alona Sosinsky from Genomics England, Janne Lehtiö from Karolinska Institutet in Stockholm and Kushtrim Kryeziu from Oslo University Hospital. Sosinsky described ways to optimize genomic testing, presenting tools for variant interpretation and stressing the importance of translating new technologies into clinical practice. Lehtiö highlighted the critical role of proteomics within precision medicine, demonstrating its application in identifying cancer subtypes and refining patient stratification via proteogenomics. He advocated for a multimodal diagnostic approach, including MS-based proteomics, in clinical trials and to support routine clinical decision making, while noting the current lack of large cohort studies combining proteogenomics and clinical outcomes. Kryeziu discussed functional precision oncology, sharing insights from the EVIDENT trial that uses multimodal diagnostics for treating metastatic colorectal cancer (CRC). This includes *ex vivo* drug-sensitivity testing on patient-derived tumor organoids (PDOs) in addition to molecular profiling, both DNA, RNA and selected proteins, of tumor tissue as well as PDOs. To catch tumor heterogeneity, several PDOs are generated per tumor. Moreover, the large living CRC biobank enables discovery of drug and combination sensitivities in rare patient subgroups. In this NPCM2025 special edition, Welén et al. present SPRINTR (Swedish Prostate Cancer Initiative for Novel Treatment Regimens), a national research structure for better diagnosis and studies of prostate cancer [2].

Session two focused on functional precision oncology and precision immune oncology. Diana Azzam from Florida International University described how technological advancements and the growth in approved drugs are facilitating the integration of genomics with functional drug testing as clinical decision support tools, thereby enhancing patient care [3]. Her data showed improved clinical outcomes for several paediatric cancer patients guided by functional

precision medicine. Thorsten Zenz from the Univeristy Hospital Zurich described how drug perturbation of primary cancer cells can elucidate pathway connectivity within tumors and capture the effects and functions of mutations. He introduced the innovative INTERCEPT project, targeting children and adults with aggressive blood cancers. The project aims to overcome treatment resistance through intercepting of clonal expansion. By analyzing tumor material together with healthy blood cells, researchers can create a detailed map of therapy response at the single-cell level. This approach enhances the understanding of how tumor and healthy immune cells interact and respond to various treatments. Heidi Haikala from the University of Helsinki delivered a talk on precision immune oncology with a focus on lung cancer. She discussed the development of complex patient-derived organoids and tumor-on-chip models, which incorporate various cell types. These innovative systems replicate the complexity of cancer seen in patients, enabling researchers to uncover new mechanisms of drug resistance and response. Furthermore, they facilitate the testing of therapeutic interventions in a context relevant to patient care.

Session three highlighted the necessity for innovative clinical trials in the field of PCM. Anna Martling from the Karolinska Institutet in Stockholm presented findings from the Nordic ALASCCA trial [4]. This biomarker-driven, double-blinded and randomized controlled trial (RCT) included patients with primary rectal or colon cancer who had somatic alterations in PI3K pathway genes. Participants received either 160 mg of aspirin or a placebo daily as adjuvant therapy after surgery for 3 years. The ALASCCA trial is the first RCT to demonstrate that aspirin significantly reduces the recurrence rate in PI3K-altered primary CRC. This finding has the potential to change clinical practice for approximately one-third of patients with early CRC by repurposing a safe, inexpensive and globally accessible drug. Short talk speaker Sheraz Yaqub presented findings from the ASAC trial, which examined the role of aspirin as a secondary prevention for CRC liver metastases. The data revealed that adjuvant treatment with 160 mg aspirin over 3 years does not reduce the recurrence rate in this patient group. Thus, the protective effect of aspirin observed in CRC is not transferable to metastatic disease. In this special edition, Yaqub and colleagues report outcomes after resection of distal cholangiocarcinoma in a European patient cohort [5]. Ruth Plummer from Newcastle University provided insights into the academic drug discovery of rucaparib from a clinician's perspective. Developed in collaboration with Cancer Research UK (CRUK) and Agouron-Pfizer, rucaparib is a poly (ADP-ribose) polymerase) (PARP) inhibitor that impedes cancer cells' DNA repair mechanisms and is primarily used for patients with BReast CAncer gene (BRCA) mutations. Clinical trials, initiated in Newcastle in 2003, led to FDA and European Medicines Agency approvals in 2016 and 2018, respectively. Plummer highlighted that the success of the CRUK Newcastle Drug Discovery Unit is largely due to industry partnerships that facilitate the rapid transition of early drug projects to be progressed from the laboratory to the clinic. Kimmo Porkka from the University of Helsinki and Helsinki University Hospital emphasized the importance of cancer drug repurposing in precision cancer care. He found that relying solely on genomics for repurposing can be challenging, as many mutations are not actionable. In addition, it is difficult to predict treatment responses for patients with an actionable mutation. Porkka advocated for integrating functional and omics platforms to assess drug effects on patients' cells in real-time. He emphasized the necessity of large-scale studies and close collaboration with the pharmaceutical industry, highlighting the advantages of European and global personalized medicine trials, such as the PRIME-ROSE network of DRUP-like clinical trials [6], for data generation and evidence building. In addition, he discussed the need to capture drug responses beyond clinical trials and described federated clinical data networks such as FinOMOP, VALO and DARWIN, which are designed for the generation and analysis of RWD. In this special edition, van der Pol et al. [7] and Augudo et al. [8] described data merging procedures in PRIME-ROSE. Furthermore, Slørdahl et al. described clinical outcomes following genomically guided trametinib monotherapy across cancer types in the IMPRESS-Norway trial [9]. Abel et al. introduced the new Swedish DRUP-like clinical trial, FOCU.SE [10], and Tryggvadottir et al. presented data on targeted therapy for lung cancer in Iceland [11]. Sommervoll et al. presented patient-reported quality of life data from a sub-study of the DART trial for patients with locally advanced non-small-cell lung cancer [12].

Session four centred on the implementation of PCM within standard healthcare systems. Christine Leopold from the Utrecht University presented the WHO Regional Office for Europe's framework for use of managed entry agreements (MEA), providing practical checklists and advice. Moreover, she highlighted the clinician-initiated Drug Access Protocol (DAP) [13] platform in the Netherlands, which links evidence generation and reimbursement for precision cancer treatments. Leopold stressed the necessity of a collaborative platform that integrates clinicians, health technology assessment (HTA) bodies, payers and industry for effective implementation, and in this special edition, Leopold et al. described the stakeholders' experiences with DAP [14]. David Thomson from the National Institute for Health and Care Excellence (NICE) in the UK shared insights from his experience with outcome-based MEA, advocating for the use of straightforward, hard endpoints, such as overall survival, to streamline these frameworks. As global spending on cancer medications continues to rise, payers are likely to implement policies and develop mechanisms to manage this increasing expenditure. Per-Olof Thuresson from Roche introduced the concept of data transportability for RWD, emphasizing the use of foreign data to inform decision-making. He highlighted the industry's need for seamless data updates and predictability in the European data-sharing initiatives. In this Acta Oncologica special edition, short talk speaker Oskar Frisell from the Swedish Institute for Health Economics and coworkers presented a conceptual health economic modelling framework to assess the cost-effectiveness of molecular target driven treatment regimens in oncology [15].

Cancer strategies in the Nordics

Cancer care and research in the Nordic countries are characterized by a collaborative and comprehensive approach to tackling cancer. Denmark, Norway and Sweden have recently launched updated national cancer strategies, while Finland released its first national cancer plan in November 2025.

Mef Nilbert from Lund University emphasized that key elements important for precision medicine have been incorporated into the updated Swedish cancer strategy, including the need for a national diagnostic network to ensure efficient services and equity of care. Additional initiatives include a pilot program for nationally coordinated implementation of advanced and innovative analyses, molecular tumor boards (MTBs) and formation of a precision medicine trial network. Recently, Sweden launched the national clinical trial FOCU.SE [10], a DRUP-like clinical trial that has received financial backing from the Swedish government. Ole Alexander Opdalshei from the Norwegian Cancer Society presented key elements of Norway's new cancer strategy, which will guide initiatives over the next decade. Inspired by Europe's Beating Cancer Plan, this ambitious strategy emphasizes cancer prevention, early detection, and access for all patients to comprehensive cancer centers and world-class cancer research. A notable goal of the strategy is to ensure that all cancer patients are offered genomic profiling when relevant to their treatment decisions. In addition, the national strategy for personalized medicine aims to make personalized medicine an integral part of the health service. Kimmo Porkka highlighted that Finland's first national cancer strategy will be launched in late 2025, covering the coming decade. An accompanying action plan is scheduled for publication in 2026. Key focus areas include prevention and early detection, equitable and effective cancer care and adaptability within an evolving healthcare landscape. This includes plans for a Finnish Health Data Space. Denmark, in conjunction with its fifth cancer strategy launched in 2025, also introduced a new strategy for personalized medicine. Ulrik Lassen from Copenhagen University Hospital focused on the implementation of a fast-track approval system for clinical trials, which will reduce the assessment time for Phase I and Phase I/II trials to just 2 weeks starting in August 2025. Taken together, the Nordic countries are prioritizing cohesion, MTBs, the integration of genetic testing in earlier lines of treatment, the use of RWD and expedited approvals for clinical trials as they advance their cancer care and research initiatives.

Conclusion

The second Nordic Precision Cancer Medicine Symposium brought together internationally renowned speakers and facilitated enhanced international collaboration. The presentations sparked engaging discussions, creating a vibrant and interactive atmosphere.

Looking ahead, there is a pressing need for more multimodal diagnostic approaches, clinical trials and collaborative international initiatives, including treatment of patients across borders. Additionally, a significant focus area will be the secondary use of data, where standardization, harmonization and federated analyses will be vital. Furthermore, international collaboration is essential for addressing and harmonizing legal frameworks to support these efforts.

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Conflicts of interest

The authors have no competing interests to declare.

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REVIEW ARTICLE

A conceptual health economic modelling framework to assess the cost-effectiveness of molecular target–driven treatment regimens in oncology

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ABSTRACT

Background and purpose: Molecularly targeted cancer therapies challenge conventional health economic evaluation frameworks that are structured around tumour-specific indications, comparators, and trial designs. Existing models often rely on pooled estimates from heterogeneous early-phase evidence or single-indication analyses, creating uncertainty for reimbursement decision-makers. We propose a conceptual modelling framework that aligns cost-effectiveness analyses with the biological rationale of precision oncology, evaluating therapies according to shared molecular alterations across tumour types.

Patient/material and methods: We examined the methodological limitations of conventional partitioned survival models (PSMs) commonly applied in oncology and evaluated their suitability for tumour-agnostic indications. Based on the collected literature, we developed a dynamic, modular PSM framework that integrates multiple tumour sites expressing a common biomarker. The framework supports pooled and tumour-specific analysis of cost-effectiveness and enables progressive disaggregation of subgroups as additional evidence becomes available.

Results: The proposed modelling approach facilitates transparent synthesis of heterogeneous evidence across tumour types using epidemiologically informed weighting, while preserving the ability to estimate tumour-specific cost-effectiveness where data permit. It addresses key challenges in tumour-agnostic evaluation, including variation in standard of care, treatment effects, and resource use across cancer sites. The modular design promotes internal consistency, reduces duplication of analytical effort, and enables iterative re-assessment of both overall and subgroup-specific cost-effectiveness.

Interpretation: A dynamic, weighted multi-site modelling framework represents a coherent and adaptable extension of current health-technology assessment-practice for tumour-agnostic therapies. By structuring evidence around molecular targets, the framework can improve transparency and robustness of cost-effectiveness estimates, thereby supporting more equitable and efficient reimbursement decisions in the context of precision oncology.

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Introduction

Precision cancer medicine and precision diagnostics have rapidly transformed the landscape of cancer care [1]. The sequencing of tumour genomes and the ability to identify actionable molecular alterations have allowed clinicians to prescribe molecularly targeted therapies that require specific genomic alterations to be effective. This shift challenges the traditional logic of treatment and drug discovery in oncology where treatments were developed, tested in trials, and reimbursed based on the tumour location. In recent years, therapies have been developed and granted marketing approval for any cancer carrying a given genomic variant [2–6]. These therapies have become symbolic of a new paradigm, where patients expressing a particular molecular biomarker or epitope independent of tumour location represent the main patient population, and tumour location instead serves to define patient subgroups.

This new type of 'pan-cancer' or 'tumour-agnostic' approach to the indication for a targeted therapy implies a shift in the definition of an indication from being for a specific form of cancer to the indication being a genomic alteration, which may appear in various tumour types expressing a resulting variant of relevance. For these types of indications, health economic evaluation models need to switch from a framework based on one tumour, one treatment, one comparator and one value assessment to a new framework of one genomic alteration, one treatment, numerous tumour types and numerous comparators.

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A review of methods for economic evaluation of tumour-agnostic therapies identified that key challenges stem from non-randomised, single-arm basket trials with small and heterogeneous patient populations with limited long-term outcome data. This lack of robust evidence on effectiveness and relative effectiveness of therapies leads to uncertainty in both clinical and cost-effectiveness estimates. An incomplete understanding of the prognostic effects of biomarkers also makes it difficult to construct and define appropriate biomarkers. Suggested solutions to the challenges with clinical evidence include greater use of real-world data to define counterfactuals, increased statistical power, and making reasonable assumptions on longer term effects such as long-term health outcomes [7]. Adaptive, life-cycle health-technology assessment (HTA) frameworks such as managed entry agreements and ongoing re-evaluation of tumour-agnostic therapies are also called for in order to keep up with evidence generation and ensure sound health system resource allocation [7].

Model-based economic evaluations are commonly used to inform reimbursement decisions when survival benefits extend beyond observed trial follow-up. Molecular targets may be present across multiple tumour types with varying prevalence and tumour-specific standards of care, leading to heterogeneity in comparators, relative effectiveness, and adverse event profiles. The impact of targeted therapies on survival and health-related quality of life (HRQoL) further depends on the accuracy of diagnostic strategies used to identify biomarker-positive populations.

These sources of heterogeneity challenge the suitability of conventional tumour-specific cost-effectiveness models, which may inadequately capture variation across indications [9]. As a result, decision-makers face substantial uncertainty when determining whether and under what conditions targeted therapies should be reimbursed.

Previous studies on evaluation of tumour-agnostic therapies

The literature on tumour-agnostic cost-effectiveness evaluations identified in an exploratory review in MEDLINE collectively points towards the value of a modular, weighted modelling framework rather than a single static approach. Early economic evaluations of, for example, larotrectinib and entrectinib adopt pragmatic pooled-effect models under substantial evidentiary constraints with tumour-specific comparators and weighting by tumour prevalence to enable assessment of therapy cost-effectiveness under limited evidence from single-arm trials [10–14].

Methodological work comparing alternative counterfactual constructions highlights that no single comparator strategy is sufficient and that triangulation or weighting across approaches may be necessary to characterise uncertainty when relative effectiveness cannot be directly observed due to heterogeneity in standard of care across tumour sites [9, 15]. More recent analyses challenge the assumption of homogeneous effects by modelling tumour-specific outcomes, using external controls to generate predicted tumour-level health outcomes and exploratory cost-effectiveness estimates, alongside aggregate value summaries [16, 17]. Together, the evidence from these studies supports an implicit progression, from pooled estimation towards selective tumour-level breakout only when evidence supports robust tumour-specific inference, while retaining weighted aggregation to reflect overall value across the eligible population [7, 18, 19]. A dynamic framework that combines early pooled evidence, modular tumour-specific components, and epidemiologically weighted costs, health effects and cost per quality-adjusted life years (QALY) offer a coherent and defensible alternative for evaluating tumour-agnostic therapies that can accommodate reanalysis as new evidence emerges.

This article presents a conceptual health economic modelling framework intended to support consistent, transparent, and biologically relevant assessments of cost-effectiveness for molecularly targeted oncology therapies. The framework aims to handle challenges with data availability and currently used research design of modern precision oncology, in which the same mutation can drive disease in diverse clinical contexts. The framework will translate into a decision analytic model to evaluate the cost-effectiveness of the PRIME-ROSE consortium Drug Repurposing Protocol (DRUP)-like clinical trials that use a combined umbrella-basket design where efficacy of drugs targeted to specific molecular alterations or biomarkers are investigated in parallel in different tumour types [20, 21].

Partitioned survival models and cost-effectiveness analysis

Cost-effectiveness analysis (CEA) in late-stage oncology commonly employs partitioned survival models (PSMs), which remain the dominant modelling framework for evaluating new cancer therapies [22–24]. PSMs are particularly well suited to oncology because they rely directly on time-to-event outcomes routinely reported in clinical trials, most notably overall survival (OS) and progression-free survival (PFS).

In a typical PSM-based CEA, the target population, intervention, and comparator are defined based on phase III randomised controlled trial evidence. Published OS and PFS Kaplan–Meier curves are reconstructed, and parametric survival functions are fitted and extrapolated beyond trial follow-up to a sufficiently long, often lifetime, time horizon [22, 24]. Candidate distributions are assessed using statistical goodness-of-fit, visual inspection, and clinical plausibility, including external validation against registry data or expert opinion [22, 25]. Long-term survival projections may be adjusted for background mortality to ensure consistency with general population life expectancy.

PSMs usually comprise three mutually exclusive health states: progression-free disease, progressed disease, and death. State occupancy at each time point (t) is derived directly from the survival functions, with the proportion of progression-free defined by PFS(t), the proportion of dead by 1 – OS(t), and the

proportion of progressed disease by OS(t) – PFS(t). Time spent in each state corresponds to the area under the respective survival curves. Because transitions between states are not explicitly modelled, PSMs can be implemented without individual patient-level data and align closely with reported trial endpoints [22, 24].

Health state-specific costs and utilities are assigned to estimate total discounted costs and QALYs. Costs typically include drug acquisition and administration, adverse event management, and end-of-life care, with the cost categories depending on the analytic perspective [8, 26, 27]. The key outcome metric is the incremental cost-effectiveness ratio (ICER) which describes the cost to gain one more QALY compared to, for example, SoC, which is compared against a context-specific willingness-to-pay threshold [28]. Parameter- and structural uncertainty are assessed using deterministic and probabilistic sensitivity analyses [8, 22, 24].

PSMs offer several advantages, including conceptual simplicity, transparency, and close alignment with regulatory trial evidence [22, 24]. However, they also have well-recognised limitations. The absence of explicit state transitions restricts their ability to capture complex disease pathways, treatment sequencing, or post-progression heterogeneity. In addition, independent extrapolation of OS and PFS makes results sensitive to parametric assumptions and may bias long-term survival and QALY estimates, particularly in heterogeneous or tumour-agnostic populations [15, 16, 22].

Suggested new approach

Added features

Building on existing evidence [9, 10], we propose an extension of the conventional framework that integrates weighted evidence across multiple tumour sites within a single, adaptive model structure (Figure 1). Clinical and economic data from tumour-specific indications are combined to estimate an aggregated ICER that reflects the average value of the therapy across the biomarker-defined population.

Weighting can theoretically be applied at different stages of the analysis, including individual cost components or health outcomes within tumour-specific submodels. However, because ratios cannot be meaningfully averaged, the level at which weighting is applied has important implications for the resulting aggregated ICER. Applying weights at highly granular levels is unlikely to support decision-making and may reduce transparency, particularly when cost structures and comparators differ across tumour types [22].

To ensure internal consistency and interpretability, we recommend applying weights to total or incremental costs and QALYs, from which a single aggregated ICER is derived. Weights should reflect the relative contribution of each tumour type to the overall biomarker-positive population, consistent with principles used for pooling clinical effectiveness evidence.

To address the limitations of static, single-indication models, we further propose that the framework allows for gradual

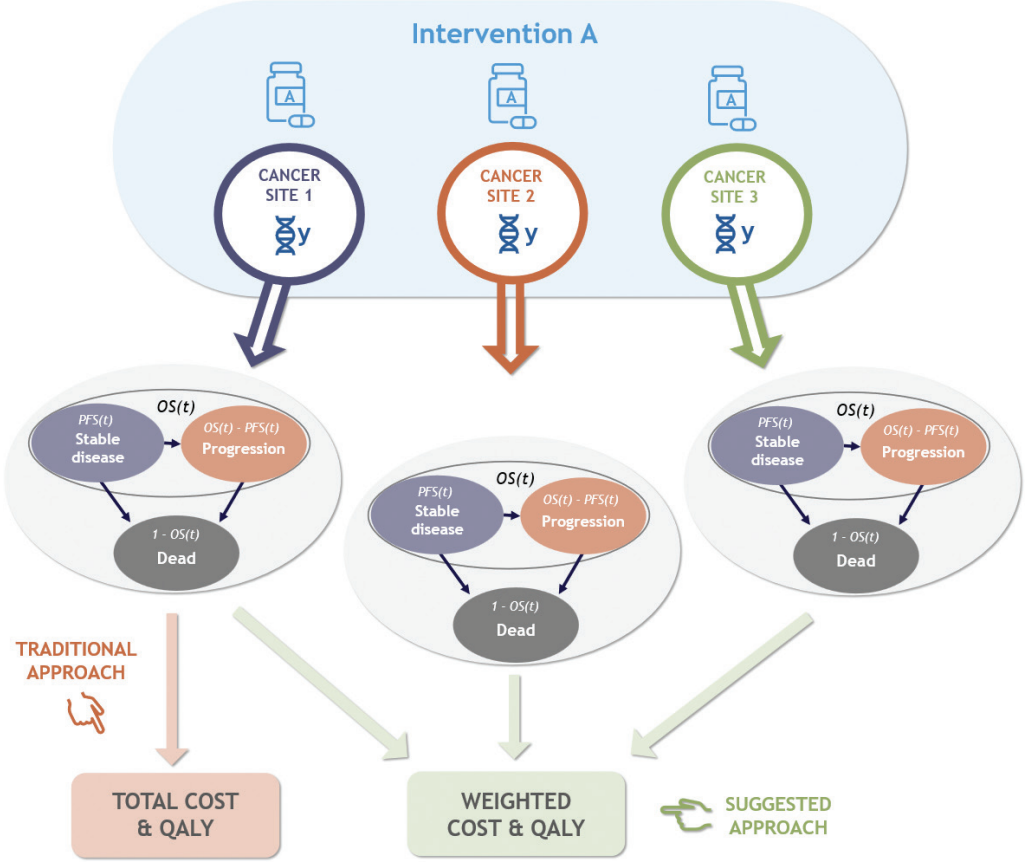

Figure 1. Model schematic: a comparison between a traditional PSM framework and the proposed weighted framework.

disaggregation of tumour subgroups as evidence accumulates and uncertainty around subgroup-specific effects diminishes. This would entail a modular PSM design in which each tumour site or biomarker-defined subgroup can be evaluated both individually and as part of the aggregated model. As the evidence base for a given subgroup matures, that subgroup can be 'broken out' from the aggregate population to run its own dedicated submodel while remaining embedded within the overarching framework [7, 18]. Each submodel would incorporate the most relevant subgroup-specific inputs, such as OS and PFS data, health-state utilities, and cost parameters while maintaining consistency in structural assumptions, modelling conventions, and methodological choices across the full system (Figure 1). The approach with a fully aggregated analysis may lead to both over- and underestimation of the true value of molecularly targeted therapies when heterogeneity in clinical benefit or cost structures between tumour types is substantial.

A weighted, modular approach would preserve the interpretability of the aggregated analysis while providing greater granularity for subpopulations where sufficient data exist. This approach should give decision-makers a clearer understanding of both the average, overall, as well as the individual cost-effectiveness profiles across tumour sites. If a particular subgroup indicates that treatment with a specific therapy would not be cost-effective, this may be counterbalanced by other subgroups where the therapy demonstrates a more favourable cost-effectiveness profile. Importantly, this structure allows for transparent assessments of trade-offs between indications while maintaining a single evaluative framework, thereby supporting informed decisions on implementation or reimbursement of tumour-agnostic treatments.

Implementing this dynamic approach requires flexibility in technical design and modularity in programming. The proposed model should be constructed as a modular system, that can be reused and extended as new data emerge. This avoids the need to rebuild separate models for each re-analysis or indication expansion. Moreover, it should enhance internal validity over time: as modules are reused and updated prior iterations remain validated and consistent.

Applications of PSM and new framework

Two central challenges arise in operationalising this framework. The first concerns timing of re-analysis, that is, determining when the accumulation of new evidence warrants updating the model and re-estimating cost-effectiveness. Frequent re-analyses may impose substantial analytical burden on decision-makers and consume unnecessary resources, whereas infrequent updates of cost-effectiveness estimate risk delaying access or sub-optimal use of health care resources. Evidence-based thresholds or pre-specified triggers for re-analysis, such as the availability of new subgroup-specific survival data or real-world evidence exceeding a defined sample size, could help manage this balance [7].

The second challenge relates to the collection and integration of real-world effectiveness data. For molecularly targeted therapies with tumour-agnostic indications, real-world evidence is likely essential to refine and validate subgroup-specific estimates of clinical effectiveness, especially when clinical trial data are limited or heterogeneous. However, such data collection can be complex as there may be differences in baseline prognosis, response rates, reporting of molecular profiling results and standard of care across tumour types. Furthermore, complexities arise by the variability in diagnostic testing and treatment sequencing in clinical practice. Additionally, variations in post-progression treatment paradigms and resource use complicate the estimation of relative effectiveness and incremental cost.

Aggregating all tumour sites into a single estimate of OS and PFS as well as costs, both for the intervention and the comparator(s), implicitly assumes homogeneity in treatment effect, disease trajectory, and healthcare resource use across cancers, which rarely holds true in practice. For example, the same genomic alteration may have a different prognosis or treatment response depending on the localisation of the tumour it is expressed in and the relevant standard of care. Ignoring such heterogeneity risks biasing the estimated ICER either upward or downward, depending on the relative distribution of favourable and unfavourable subgroups.

Despite these practical challenges, the proposed dynamic PSM framework offers several conceptual and methodological advantages. It promotes continuity between assessments, avoiding duplication of work while enabling evidence-based evolution of the model over time. It facilitates transparency by explicitly demonstrating how incremental data alter the cost-effectiveness of individual subgroups and overall assessments of molecularly targeted treatments [29]. It also potentially allows policymakers to visualise both overall and indication-specific value for money, strengthening the relevance of subsequent decisions. For therapies with wide-ranging or tumour-agnostic indications, this approach may support more equitable access by ensuring that clinically effective treatments remain available to patients, even if certain subgroups are less cost-effective in isolation. Conversely, this dynamic framework would also allow policy makers to identify subgroups for which treatment is cost-effective, even if the aggregated analysis suggests that using the evaluated therapy would not be cost-effective.

Sensitivity analyses such as deterministic one-way analyses (DSA) and probabilistic sensitivity analysis (PSA), where the latter is a method to assess the overall uncertainty of the model outcomes and inform subsequent decisions, can be conducted using standard approaches [8]. The key distinction relative to tumour-specific models lies not in the number of parameters per se, but in how parameters are structured and varied, particularly with respect to shared versus tumour-specific sources of uncertainty. Parameters representing common assumptions should be varied jointly across tumour sites, whereas tumour-specific parameters may be explored independently. This allows uncertainty to be examined both at the aggregate level and within individual tumour subgroups, supporting transparent interpretation of the drivers of decision uncertainty. One dimension of uncertainty not captured through PSAs or DSAs relates to structural assumptions

embedded in the model design. For example, inadequate representation of the care pathway, or omission of relevant adverse events, health effects, or costs may influence model outcomes and can be, for example, examined through alternative structural specifications or scenario analyses.

In summary, a dynamic partitioned survival modelling framework that can evolve as evidence is generated could represent a logical extension of current HTA practice for molecularly targeted therapies in oncology. It would maintain the strengths of the traditional PSM structure while addressing the growing complexity of cancer treatment and the need for ongoing reassessment of value as real-world evidence emerges. As genomic-driven and tumour-agnostic therapies continue to expand, adopting such a flexible modelling paradigm will likely be essential for generating meaningful cost-effectiveness estimates to support implementation and reimbursement decisions for these therapies.

Discussion

Shifting the perspective of health economic modelling and cost-effectiveness evaluation of molecularly targeted therapies in oncology, from a tumour-oriented to a mutation-oriented analysis, has the potential to reduce the uncertainty around whether these therapies provide good value for money.

The PRIMEROSE consortium was established to address evidence gaps in the clinical and economic evaluation of repurposing cancer drugs beyond their original tumour indications. One aim for the consortium is to develop and test methodological frameworks for assessing the value of molecularly guided therapies across tumour types [20]. The framework proposed in this paper will inform the development of a PRIMEROSE model and serve as a proof of concept for a modular and dynamic approach that supports re-evaluation as the evidence base evolves.

Alternative modelling approaches could also be applied within a similar tumour-agnostic paradigm. Discrete event simulation may ultimately be better suited to capture complex disease trajectories as it does not explicitly model each pathway [30], but such models currently require extensive data that may not yet be widely available. As tumour-agnostic therapies and comprehensive genomic profiling become more common, future data availability may warrant re-evaluation of the reliance on PSMs in this setting.

More conventional approaches, including Markov cohort models or microsimulation [31], may also be adapted to incorporate weighted subgroup evidence on cost-effectiveness using the same underlying rationale proposed here and represent important areas for future methodological research.

Current practice typically relies on separate economic models for each tumour site, resulting in methodological heterogeneity and potential duplication of effort. Integrating evidence across tumour sites into a unified modelling framework can improve internal consistency and enhance the transparency and reproducibility of economic evaluations for tumour-agnostic therapies.

A weighted PSM extends the conventional single-indication oncology model to the tumour-agnostic context by enabling joint estimation of overall and site-specific cost-effectiveness across cancers sharing a common biomarker. Its modular and nested structure can support efficient incorporation of new evidence and may facilitate re-analysis as data accumulate, allowing clinically meaningful subgroups to be evaluated with relatively limited additional modelling effort.

A key challenge for HTA bodies is to define transparent criteria for when accumulated evidence warrants re-analysis or subgroup delineation. Prospectively specified thresholds would balance methodological rigour with the need for timely reassessment, reduce ad hoc re-evaluations, and provide clearer expectations for manufacturers generating post-authorisation evidence.

The principal advantage of a harmonised modelling approach is its ability to capture heterogeneity in treatment effects, costs, comparators, and disease trajectories across tumour sites within a single analytical framework. This enables decision-makers to assess where tumour-agnostic therapies deliver the greatest incremental value and supports equitable, evidence-based resource allocation. A shared model structure also promotes methodological standardisation, reproducibility, and validation across re-analyses.

Recent work on multi-use disease models supports the use of dynamic economic modelling frameworks that are designed to evolve as evidence accumulates, rather than relying on static, single-use models developed for individual decisions [29]. These principles are relevant for tumour-agnostic oncology, where early evidence will need to be pooled across tumour sites and can then, if relevant, progressively be disaggregated as data matures. This approach enables reassessment of value while maintaining transparency, consistency, and methodological rigour across the technology life cycle. The dynamic nature of the PSM methodology and the modular approach suggested allows for a copy-paste expansion of the core model framework, where a new PSM module is easily incorporated as a stand-alone component and easily connected to the weighting convention.

Assuming an HTA perspective, the practical implementation of such a framework would benefit from clearly defined requirements for re-assessment. This could, for example, build on the Joint Clinical Assessment (JCA) process within the EU by requiring manufacturers and/or health care providers to collect, report and re-analyse evidence on relative treatment effects in tumour subgroups as a collaborative effort. Subsequently, updates on recommendations and re-assessments of these therapies could be performed in a unison and well-informed manner. Alternatively, such re-analyses could be leveraged through joint European initiatives such as the European Health Data Space (EHDS), facilitating data sharing and collaborative evidence generation. Introducing these obligations as conditional elements of marketing authorisation could potentially strengthen the link between HTA-body approval, data collection, and economic re-evaluation over time.

Adopting a weighted, multi-site model may involve important social and ethical trade-offs. Pooling evidence across

tumour sites inherently needs to balance considerations on efficiency and equity. On one hand, weighted analyses can allow subgroups with favourable cost-effectiveness profiles to offset those with less favourable ones, thereby broadening access to clinically effective treatments. On the other hand, this may lead to less efficient resource allocation, as scarce healthcare resources are diverted towards subgroups that may not independently meet cost-effectiveness thresholds. This could lead to a reduction in overall health output in the health care system. The desire to maximise aggregate health benefits and ensuring equitable access could be a fundamental policy challenge for tumour-agnostic evaluations. By providing disaggregated and overall cost-effectiveness results, our proposed modelling framework enables a transparent visualisation and consideration of the potential trade-offs and equity considerations for molecularly targeted therapies in cancer care.

Decision- and policymakers are likely to prioritise patient subgroups with the most favourable cost-effectiveness profiles and, depending on perspective, this may be an appropriate approach to resource allocation. Similarly, pharmaceutical manufacturers have strong incentives to seek marketing authorisation in populations where commercial returns are expected to be greatest. While the proposed framework does not resolve these strategic considerations, it provides a methodological basis for evaluating tumour-agnostic therapies in a manner that is more consistent with their underlying clinical rationale. Specifically, it conceptualises tumour type as a subgroup within a biomarker-defined population, rather than treating the molecular target as a subgroup within a single tumour indication.

Conclusion

A weighted multi-tumour-site modelling framework based on a modular structure offers a credible and transparent approach to the economic evaluation of tumour-agnostic therapies. By enabling structured evidence synthesis across tumour sites, it supports CEAs that reflect the evolving realities of precision oncology and facilitates both efficient and equitable decision-making. Importantly, its successful implementation will depend on clear regulatory expectations, robust data infrastructure, and sustained dialogue on the ethical limits of pooled economic evaluation. Ultimately this will lead to the alignment of tumour-agnostic innovation in oncology with a fair, adaptive, and forward-looking framework for assessing cost-effectiveness and value of these technologies.

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Conflicts of interest

OF, KSC, and PL are employees of the Swedish Institute for Health Economics, which provides consulting services for governmental bodies, academic institutions, and commercial life science enterprises. GLF, KT, EHH, EA and PH report no conflict of interest.

Data availability statement

No data was processed in this work.

Ethics declarations & trial registry information

Not relevant.

Author contributions

OF and KSC conceived the study idea. OF drafted the manuscript. PH, PL, and EA contributed to the development of the study concept and critically revised the manuscript. GLF and KT provided additional comments and revisions. EHH and all remaining authors reviewed and approved the final manuscript.

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ORIGINAL ARTICLE

Procedures of data merging in precision cancer medicine: the PRIME-ROSE project

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ABSTRACT

Background and purpose: As more interventional clinical trials in Precision Cancer Medicine (PCM) are introduced, molecular descriptions of tumours have led to multiple subtypes, even within common tumour types. Therefore, the main limitation of these trials is the small number of eligible patients to assess the clinical benefit. The PRIME-ROSE project addresses this limitation by pooling data from multiple European Drug Rediscovery Protocol (DRUP)-like clinical trials, such that slowly accruing cohorts are accelerated. To achieve this task, a well-documented commonly approved procedure for data merging needs to be established.

Patient/material and methods: Data sharing is achievable when there is an organisation that includes people from different disciplines who can navigate institutional and country-specific information and governance requirements. Furthermore, alignment of all the study procedures are needed before data are shared. Next, the process of merging data requires harmonisation and standardisation. Implementation of the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) facilitates future data aggregation.

Results: By aggregating data from European DRUP-like clinical trials, cohorts are completed that were unable to do so in stand-alone studies. Since initiation, the PRIME-ROSE project monitors over 300 cohorts across more than 20 treatments encompassing over 1,000 patients. At least 20 cohorts have progressed after interim analysis.

Interpretation: Data sharing across European trials is feasible and enhances the advancements of PCM studies. The methodologies developed in the PRIME-ROSE project provide a foundation for future data integration efforts in PCM clinical trials, underscoring the viability of conducting robust trials in a global context.

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Introduction

Numerous Precision Cancer Medicine (PCM) trials have been conducted globally for several years, including the TAPUR trial in the United States, the BELIEVE trial in Japan, and the Drug Rediscovery Protocol (DRUP) in the Netherlands [1–3]. In Europe, several national DRUP-Like Clinical Trials (DLCTs) have been launched [4, 5], and these countries are now collaborating within the PRIME-ROSE project (Precision Cancer Medicine Repurposing System Using Pragmatic Clinical Trials), funded by the European Commission [5, 6]. The DLCT network is now pooling patient data to accelerate the assessment of drug efficacy in cohorts defined by specific treatment, tumour type and biomarker combinations.

The PRIME-ROSE project and other initiatives in Europe advance PCM trials by creating a platform to share and analyse data [7]. By pooling patient information from the individual trials, the likelihood of completing cohorts increases significantly. The project continues the work of PCM4EU (Personalised Cancer Medicine for all EU Citizens), which initiated the implementation

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of DLCTs across Europe as part of Europe's Beating Cancer Plan. Furthermore, as new treatments are developed, it is crucial to have a platform that allows rapid assessment of efficacy across different tumour types and biomarkers, using standardised methods and guidelines to support future data sharing.

In this report, we focus on the procedures for data merging in PCM and share the knowledge gained in the area of data pooling. Results show that data integration can be done effectively, and the first cohorts are currently under analysis.

Patients/material and methods

The aim of this report is to document the data merging process between the DLCTs. Specifically, we will address patient safety considerations, data alignment, and standardisation. In addition, we will discuss the process of data sharing and the rules established for merging cohorts. All trials have signed a Data Sharing Agreement (DSA), and share data in one central server, which facilitates the merging process.

Organisation

Currently, there are 11 active or soon-to-start DLCTs across Europe (see Figure 1). The network is steadily expanding by sharing documents and expertise. To further support the development of new trials, a buddy system has been implemented in the PCM4EU project [5], providing mentoring and guidance to emerging studies. The governance structure, detailed in the Data Management Plan (DMP), ensures that each trial retains ownership of its data, while the data processor serves as a central data hub. Inclusion numbers from each trial are shared monthly to track the inclusion rate in the merged cohorts. The complete dataset for each patient in a cohort, defined within the Data Sharing Protocol (DSP), is shared with the central processor upon completion after approval by each national Principal Investigator (PI). Moreover, each DLCT also has the option to withhold data for specific cohorts. A publication committee, which includes the PI from each data sharing trial, grants approval to proceed with the analysis and publication of shared cohorts. The DLCT governance structure is designed to respect and integrate each participating trial's existing national governance frameworks.

Monthly meetings

Key representatives from each trial meet monthly to review patient recruitment status and assess completed cohorts across DLCTs. Before each meeting, updated inclusion rate specific data from each trial's electronic Case Report Forms (eCRFs) is

Figure 1. An overview of all ongoing, ended and soon-to-start DRUP-like clinical trials in Europe. DRUP in the Netherlands., ProTarget in Denmark. FINPROVE in Finland. IMPRESS-Norway in Norway. FOCUSE and MEGALiT in Sweden., MOSTplus and megaMOST in France. DETERMINE in the United Kingdom. PROGRESS in Ireland.POP in Portugal. ESTOPRET in Estonia. PANTUMOUR-LT in Lithuania.

sent to the data processor, who then standardises, harmonises, and merges the data. This monthly data is limited to support ascertainment of recruitment status within cohorts. These meetings provide an overview of cohort recruitment, enables cross-trial decisions to either advance or close cohorts based on efficacy data from each trial. Furthermore, the monthly meetings facilitate discussions to align tumour types and biomarker definitions for specific cohorts, and assign responsibility for final analysis and reporting of closed cohorts.

Publication plan

An updated overview of merged cohorts is available to all members of the DLCT community through a secured website. Additionally, the conclusion from each meeting is shared monthly in the internal newsletter along with decisions regarding the continuation of cohorts, closing of cohorts, and potential opening of expansion or new cohorts.

A final report evaluating the treatment effect, based on the statistical analysis plan (SAP), will be published after a cohort is closed to accepting new patients, either through completion or early closure. This will be done in agreement with each trial that provided data, as outlined in the DMP, and in coordination with the (pharmaceutical) company providing the drug.

Alignment of each DLCT

The prerequisite for merging data between DLCTs, and clinical trials in general, is the alignment of key components of each protocol to ensure that the analysis is carried out with homogenous data, thus minimising potential biases. This section discusses alignment of endpoints, schedule of activities, inclusion- and exclusion criteria, and adverse events (AEs).

Endpoints

Although the complete list of primary and secondary endpoints varies between the DLCTs (Table 1), the trials share five primary and secondary endpoints:

1. Treatment-related grade greater than or equal to 3 and Serious Adverse Events (SAEs)
2. Progression-Free Survival (PFS)
3. Overall Survival (OS)
4. Disease Control Rate (DCR) assessed as complete response (CR), partial response (PR), or stable disease (SD) at 16 weeks of treatment initiation according to established response criteria.
5. Duration of time on drug.

Regarding endpoint 4, while all DLCTs measure DCR, the MOST trial observes disease control at 9 and 18 weeks, and the DETERMINE trial at 24 weeks post treatment initiation. For DETERMINE, disease control information is also measured at 16 weeks (for arms where the treatment is given on a 4-weekly cycle) or at 18 weeks (for arms where the treatment is given on a 3-weekly cycle). Therefore, treatment information is shared from these timepoints to allow for better harmonisation of endpoints. Additionally, Time on Treatment/Drug, and the percentage of patients treated according to their molecular profile are endpoints common to 80% of the DLCTs (see Table 1 for an overview of the most shared endpoints).

All trials participating in the PRIME-ROSE project will collect Health-Related Quality of Life (HRQoL) data using standardised instruments (e.g. EORTC QLQ-C30, EQ-5D, Risk Attitude Questionnaire and WISP QoL surveys). The assessment is collected by most trials in the screening phase, every 3 months during and at the end of treatment. This provides sufficient data for analysis (Table 2).

Inclusion and exclusion criteria

To assess merged cohorts, it is essential to ensure that each DLCT has a comparable pool of patients eligible for inclusion. Most trials have general and drug-specific inclusion and exclusion criteria. A complete overview of the general inclusion and exclusion criteria in all trials has been conducted and shared within the consortium. Differences in the general criteria must be considered when merging cohorts. The most significant differences are as follows:

Table 1. An overview of the most shared endpoints between the trials.

Endpoints	DRUP	ProTarget	IMPRESS	POP	FOCUSE	FINPROVE	PANTUMOUR-LT	ESTOPRET	DETERMINE	MOST
Treatment-related grade ≥ 3 and SAEs	X	X	X	X	X	X	X	X	X	X
Progression-Free Survival	X	X	X	X	X	X	X	X	X	X
Overall Survival	X	X	X	X	X	X	X	X	X	X
DCR (objective complete response, partial response or stable disease) at 16 weeks of treatment initiation according to established response criteria	X	X	X	X	X	X	X	X	X*	X**
Duration of time on drug	X	X	X	X	X	X	X	X	X	X
Percentage of patients that are included and treated based on their molecular tumour profile	X	X	X	X	X	X	X			
Description of mutational concordance between first (pre-treatment) biopsy and subsequent biopsies in the study	X	X	X	X	X			X		

(*) The DETERMINE trial observes DCR at 24 weeks. (**) The MOST trial observes DCR at 9 and 18 weeks.

Table 2. The DLCTs share similar study procedures.

Study Procedures	1–28 days	W8	W16	Every 3 months	EOT
AE/SAE assessment	+++	+++	++	+++	++
Tumour assessment	+++	+++	++	+++	+
Laboratory assessments	+++	+	+	++	
Physical examination	+++			+	+
Concomitant medication	+++			+	++
HRQoL	+			+	+
Informed consent	+++				
Medical history	+++				
ECG	+++				
Pregnancy test	+++				

Key: W = week, EOT = End of Trial, (+++) = shared by all trials, (++) = shared by 10 out of 11 trials, (+) = shared by eight or nine out of 11 trials. First column: screening phase. Second column: Treatment phase. Third column: End of Treatment phase.

- The MOST trial includes only patients with ECOG performance status of 0–1, and the DETERMINE trial includes only patients with ECOG status 0–1 (those with a performance status of 2 are considered on an individual basis). This is in contrast to an ECOG performance status of 0–2 inclusion criteria in other trials. This may result in a higher proportion of healthier patients, which may affect the results.
- Some trials require a mandatory fresh frozen biopsy prior to starting treatment. This could influence patient populations, as some patients might be excluded based on this criterion.
- Variation in health-related requirements between trials. Although considered low risk, as all trials require that patients are likely to benefit from treatment. An evaluation of medical history and concomitant therapy should still be performed.

If a cohort is completed and analysed, the difference in criteria needs to be considered. This depends on the patient population of each cohort.

Adverse events

When combining data from different trials, a common AE dictionary is essential. AEs are defined in all protocols as any undesirable experience that a patient experiences during the study, regardless of whether it is related to the study treatment or not. The safety reporting and handling of AEs and SAEs are consistent across all trials.

In addition, Suspected Unexpected Serious Adverse Reactions (SUSARs) are managed identically. Grading AEs severity is performed using either the National Cancer Institutes (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 or version 5.0, with only the DRUP trial using version 4.03. A complete overview of all differences in AEs is shared between the consortium.

Schedule of activities

The DLCTs are aligned with the original DRUP protocol [3], and the schedule of activities is similar across trials, facilitating data merging. Table 2 shows the common core set of activities for all trials, which is sufficient to cover the variables for merging and evaluating endpoints, except for HRQoL.

Merging data

Harmonising and standardisation of the data

Each DLCT uses its local eCRF system to capture and store patient data, ensuring the completeness and accuracy of patient information. The selected variables, as described in the DSP, must be harmonised and standardised. The DSP contains a list of variables that are shared at the end of a patient's participation in their respective trial, monthly basis, and upon cohort completion. Note, some of these transfers may be combined.

To securely manage data in such a way that it is safe and complies with privacy regulations, the Services for Sensitive Data (TSD) platform is used. This ensures that data collection, storage, analysis, and sharing comply with GDPR Articles 6 and 9. Researchers who have been assigned the privileges can access the data from each trial through the TSD. The TSD project administrator for PRIME-ROSE provides a periodic import link to the data stewards of each DLCT, allowing them to upload data into the TSD. In this step, the data stewards of the individual DLCTs collects full records of patient level data before anonymisation to ensure data quality. The data processor preprocesses the data and harmonises the individual outcome variable to ensure consistency across all DLCTs.

Harmonisation is required to ensure that the variable lists from each DLCT are consistent. We define *harmonisation* as the process of ensuring that data formats across DLCTs are uniform (e.g. converting different clinical outcome data formats to a standard format). The data from each trial is collected in a structured manner through the eCRF system, and the standard variables are uniformly measured and recorded, for example, tumour assessment through RECIST. *Standardisation* involves aligning data according to a central or established standardisation method (e.g. AE grades are measured by the CTCAE).

Data collected in the eCRF systems are structured data. However, harmonisation of tumour type and biomarker definition remains one of the main challenges. To address this, we have developed a standardised list of biomarkers and tumour types, with definitions agreed upon by all DLCTs. More specifically, the biomarker definition will be harmonised according to a predefined list of actionable targets and assessed by a molecular biologist from each trial during cohort evaluation.

Standardisation to a Common Data Model

The combined data will be standardised using a Common Data Model (CDM) to facilitate future data analysis and data sharing outside the trial network. In this project, we will standardise using the Observational Medical Outcomes Partnership (OMOP) CDM [8]. The OMOP CDM is an open-source CDM by the Observational Health Data Sciences and Informatics (OHDSI)

community. Each outcome variable is first harmonised to an OMOP standard. Once all outcome variables have been harmonised and standardised, merging data from DLCTs, data quality checks and statistical analyses can be done efficiently through existing tools developed for OMOP. Moreover, standardising to the OMOP CDM enables federated data merging with similar trials.

Merging data for monitoring inclusion

Once the variables from different trials are aligned and standardised, cohorts with the same tumour type, biomarker target, and treatment can be merged. This allows for pooling of results across the PRIME-ROSE project. The cohort merging is approved manually during the monthly meetings to ensure accurate merging. Inclusion numbers for each cohort are updated monthly and presented at the evaluation meetings.

Decision making process

When merging the data from different DLCTs, there are three critical decision triggering time-points:

1. The first decision involves choosing the cohorts to merge from the individual trials. Due to the high complexity of particularly genomic biomarkers and cancer type definitions, this is not limited to the biomarker/tumour type/treatment-definition of a cohort. For example, cohorts may be tumour-agnostic, histology-specific or tumour types that are naturally grouped together. Therefore, the decision to merge cohorts is on a cohort-by-cohort basis and is documented and decided during the monthly meetings.
2. Cohorts that are monitored in the monthly meetings may undergo interim assessments to examine whether there is sufficient data to make a definitive conclusion or whether recruitment should continue. The decision to continue cohort recruitment depends on the number of Clinical Benefit (CB) (defined as CR, PR or SD at week 16) in a cohort. To avoid selecting cohorts to merge based on responses, number of patients with CB are omitted from the monthly meetings.
3. Lastly, a third decision is made when patient recruitment is stopped due to a cohort having accrued enough patients. Here analysis includes all patients level data to evaluate the shared endpoints of the trials of which a cohort is completed (Table 1).

During the monthly meetings, cohorts are evaluated by the PIs from the trials that treated the patients. Decisions on expanding or closing cohorts are recorded and shared to all the participating trials through the distribution of minutes and the monthly meetings.

Guidelines for merging cohorts

Even with cohorts that are aligned and standardised, there will still exist aggregated cohorts with limited sample sizes that may benefit from additional merging. The decision to merge these small cohorts is made by the Data-Sharing and Aggregation Working group. Merging these small cohorts together depends on whether a treatment is, for example, evaluated as tumour agnostic, such that all cohorts with a specific treatment and different tumour types may be merged. Another example is to merge mutated and amplified onco-genes if research shows that a treatment may benefit in both cases. The merging of these cohorts will be published along with the biological rationale for doing so.

Results

Data sharing and merging in the PRIME-ROSE project have been actively ongoing since Q2 2024. As of Summer 2025, we have monitored more than 300 merged cohorts across more than 20 treatments, including more than 1,000 patients enrolled in all active trials. Twenty cohorts have progressed after interim analysis and none of the merged cohorts have been closed due to lack of clinical benefit. This means that for each cohort in which the inclusion rate increases, none of the cohorts fail to experience clinical benefit. Currently, four cohorts have completed recruitment and are under analysis. These results show that data sharing in PCM within the PRIME-ROSE project can be successfully achieved and provides a foundation for future collaborative data sharing. Moreover, the use of OMOP CDM will be determinant to demonstrate that these processes can be achieved in a harmonised and standardised manner.

Discussion and conclusion

Sharing data among the DLCTs allows for more rapid assessment of efficacy, particularly for rare combinations of tumour type and biomarkers. The PRIME-ROSE consortium creates benefits for various stakeholders, patients, clinicians and healthcare payers by enabling decisions to be made in cohorts, which would not be possible if each cohort is considered in isolation. The data sharing structure also makes sure that the data quality is validated, as the data steward from each participating trial collects and verifies complete patient records before anonymisation and exporting it to the TSD. Additionally, the data steward in the TSD revalidates all collected records afterwards. Furthermore, using the OMOP CDM, the future of PCM is both federated and united under one umbrella. Maintaining transparency and thorough documentation in data merging is vital for the validity of the results.

Nevertheless, merging data across PCM trials is challenging. Protocols must be sufficiently aligned, as differences in inclusion and exclusion criteria, endpoints and schedule of activities can create heterogeneity that compromises comparability. Therefore, if protocol diverge to substantially, meaningful analyses may not be possible. Another practical limitation is that eCRF data from participating trials currently require manual merging by the data steward of PRIME-ROSE. A process that the OMOP CDM will streamline in the future.

Based on experiences from the PRIME-ROSE consortium, data sharing in PCM is mostly a practical endeavour with respect to communication. Aligning study design, endpoints and study procedures reduces complexity, while the monthly meetings provide a helpful forum for cohort merging and monitoring the inclusion rate of the many cohorts that exists in PRIME-ROSE. The PRIME-ROSE data sharing platform serves as a pioneering example of data sharing in practice, with the potential expansions to other PCM trials.

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Data availability statement

Documents detailing the data merging process discussed in this report may be shared. However, patient information will not be shared.

Ethics declarations and trial registry information

All patients have signed informed consent and are informed about the data sharing in the PRIME-ROSE network. Each trial is approved by their ethics committee and registered in CTIS. DRUP study: 2023-509152-33-0. ProTarget: 2023-510527-29-00. IMPRESS: 2020-004414-35. FINPROVE: 2024-517478-68-01. megaMOST: 2019-001494-88. DETERMINE: NCT05722886.

Authors' contributions

HP: Investigation, methodology, conceptualisation, investigation, writing – original draft, visualisation, data curation, formal analysis, data curation.
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Stakeholders' experiences with a clinician-led access programme linking evidence generation and reimbursement for precision cancer treatments: the drug access protocol in the Netherlands

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ABSTRACT

Background and purpose: In the current landscape of tumour-agnostic oncology drugs receiving European Medicines Agency (EMA) authorisation, Health Technology Assessment (HTA) bodies face challenges in assessing these innovative drugs. Due to these products' non-randomised, single-arm nature, uncertainty exists regarding their real-world benefit. In the Netherlands, the Drug Access Protocol (DAP), a programme developed by oncologists, insurers and the healthcare public institute, aims to provide an innovative solution to address this uncertainty. This study aims to investigate the key characteristics, enablers and challenges of the programme by exploring stakeholders' perceptions.

Patient/material and methods: A qualitative, semi-structured interview study was conducted. A supporting interview guide was drafted using available literature and a flowchart figure to illustrate the process. Interviews were conducted with market authorisation holders (MAHs) who participated in the programme, the insurer, the DAP study management and the DAP's governance committee. Recorded interviews were transcribed, pseudonymised and subsequently coded using NVivo software. Inductive thematic analysis was used to identify common themes, enablers and challenges for participating in the programme.

Results: In total, eight organisations were interviewed. Although MAHs indicated several enablers (e.g. providing patient access, collecting real-world data), several challenges (e.g. the lack of transparency) lead to questions regarding the feasibility of the programme. Health insurers acknowledge these outcomes and expect products that obtain regular reimbursement to serve as an example.

Interpretation: As the Drug Access Protocol may be a promising solution to mitigate uncertainties for healthcare decision-makers, implementation challenges can hamper its feasibility. Addressing these challenges could realise the potential of such programmes.

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Introduction

In recent years, increased spending on oncology medicines is a rising problem of global concern as well as in the Netherlands [1].

This is mostly due to the increasing number of approvals of new oncology medicines combined with rising prices for new medicines [2–4]. At the same time, for many new innovations, there is uncertainty about their clinical effectiveness, especially when evidence comes from non-randomised, single-arm trial designs [5]. This uncertainty challenges current health technology assessment (HTA) processes including the assessment of a product's cost- and clinical effectiveness as well as reimbursement negotiations, often leading to delays in reimbursement [6, 7].

To overcome these HTA and pricing challenges, there has been a shift towards outcome-based managed entry agreements (OB-MEAs), which aim to provide earlier access to medicines while collecting real-world evidence (RWE) on the clinical effectiveness [8–10].

In the Netherlands, an innovative early access scheme (a coverage with evidence collection programme) linking evidence generation and reimbursement for anti-cancer drugs, the so-called Drug Access Protocol (DAP), was introduced in February 2021 by the Dutch Health Insurer umbrella organisation (Zorgverzekeraars Nederland, ZN, from hereon after referred to as payer) together with the Dutch Association for Medical Oncology (NVMO) and the Netherlands Cancer Institute (NKI). The DAP is a prospective, open-label, non-randomised protocol that collects real-world efficacy and safety data. The original purpose of the DAP was to create a platform that provides an overview of all Compassionate Use Programs and Named Patient Programs in oncology in the Netherlands to provide equal

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participation opportunity for patients and facilitating data collection when needed. However, the platform quickly developed a parallel reimbursement programme, managed by the payer, to provide faster, controlled and coordinated access to cancer therapies (including potentially off-label indications) awaiting reimbursement in the Netherlands. Simultaneously, the programme mitigates the risk of adopting therapies with uncertain effectiveness by collecting prospective real-world data (RWD) on the efficacy and safety of these drugs [11–15]. A drug for a certain indication can only be part of the DAP if it meets the clinical relevance boundaries, specifically for non-randomised controlled trials for solid tumours: the PASKWIL-NRS (Table 1) [16–23].

To date, no research has been conducted taking a health system's perspective on the DAP process, including stakeholders' experiences. Hence, the aim of this study is to describe the key characteristics, benefits and challenges of the DAP, as a unique example of a bottom-up collaborative initiative, with a novel OB-MEA, and to explore stakeholders' experiences with the programme.

Patients/material and methods

This qualitative study consisted of in-depth semi-structured 60-min interviews that took place via Microsoft Teams between the period of 28th November 2024 and 24th of February 2025. For the interviews all relevant stakeholders including representatives from the Dutch payer, the DAP study management, as well as the DAP's governance committee, and all involved marketing authorisation holders who have participated in the DAP programme were invited to participate. Participants recruitment was coordinated via the co-authorship team.

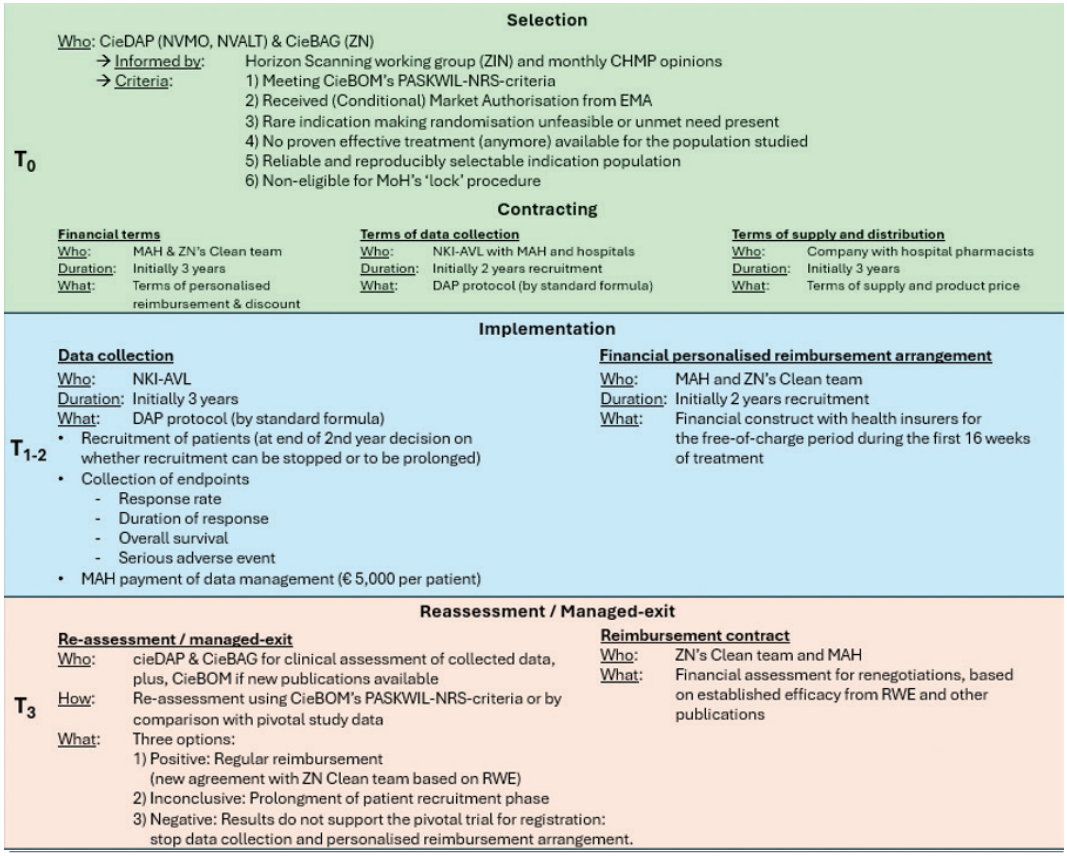
The interview guide consisted of a flowchart of the DAP process (see Figure 1) as well as of open-ended questions. Questions were divided into four topics: the DAP process, financial agreement, data collection and overall thoughts (see Annex A). The interview guide and the DAP process flowchart were shared with participants prior to the interview. During the interviews, participants were invited to use the flowchart as a starting point to share their experiences on the DAP process. In one case, a participant shared additional written

Table 1. Products incorporated in the DAP programme, as of 27th January, 2025.

Drug	Indication	EMA authorisation status	DAP admission	Reimbursed*
Cemiplimab	Locally advanced or metastatic cutaneous squamous cell carcinoma (laCSCC; mCSCC)	CA on June 2019, Standard MA as of July 2022	February 2021	Regular, as of January 2024
Larotrectinib	Adults and paediatric patients with locally advanced or metastatic solid tumours expressing NTRK gene fusion and who have no satisfactory reaction to standard treatment(s) or where no standard treatment exists, or is indicated	CA as of September 2019	October 2021, No contract ZN, through VT trajectory	Regular, as of September 2023
Entrectinib	Adults and paediatric patients (aged 12 years and older) with locally advanced or metastatic solid tumours expressing NTRK gene fusion and who have no satisfactory reaction to standard treatment(s) or where no standard treatment exists, or is indicated	CA as of July 2020	October 2021, No contract ZN	Regular, as of September 2023
Capmatinib	Locally advanced or metastatic NSCLC for which standard anti-cancer treatment is no longer available or indicated. Only MET exon 14 skipping mutations, second-line treatment after immunotherapy and/or platinum-based chemotherapy	Standard MA as of June 2022	NPP June 2020, No contract ZN	No, inclusion stopped in 2022 due to the end of MAH collaboration
Selpercatinib	Advanced RET-fusion positive non-small cell lung cancer	CA as of February 2021	May 2022	Regular reimbursment upon completion of the DAP period and based on available randomised data in the first-line setting, July 2024
Selpercatinib	Advanced RET-mutant medullary thyroid cancer	CA as of February 2021	May 2022	Regular reimbursment upon completion of the DAP period and based on available randomised data in the first-line setting, July 2024
Selpercatinib	Advanced RET fusion-positive solid tumours, when treatment options not targeting RET provide limited clinical benefit or have been exhausted	CA as of April 2024	March 2025	Recuiting
Tepotinib	Advanced NSCLC harbouring MET exon 14 skipping mutations, who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy	Standard MA as of February 2022	July 2022	Regular, as of July 2025
Amivantamab	Locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutation, requiring systemic therapy after platinum-based chemotherapy	CA as of December 2021	November 2022	No, currently in the follow-up phase (expected results by end of 2025)

CA: Conditional Authorisation; MA: (Standard) Market Authorisation; MAH: Marketing authorisation holder; VT: Voorwaardelijke Toegang (OB-MEA programme by Dutch HTA body together with Dutch Ministry of Health); NPP: Named Patient Programme.

* = Reimbursement status specific for the indication initiated in DAP.



Term	Definition
CieBAG	Commissie Beoordeling Add-on Geneesmiddelen: A collaboration between health insurers on the area of expensive medicine, which aims to improve clarity, transparency and decrease workload. Advises regarding the reimbursement of intramural medicines and add-on applications for such products
CieBOM	NVMO-commissie ter Beoordeling van Oncologische Middelen: assesses the value and use of new oncological medicines and advices CieBAG
cieDAP	DAP's commission. Provides initial assessment of new medicine that are offered for inclusion in the DAP program
DAP	Dutch Drug Access Protocol. Aims to gather real-world effectivity and safety data. Initiated by NVMO, NVALT, Antoni van Leeuwenhoek hospital (DRUP study management team), the Healthcare Institute (ZINL) and the Dutch Health Insurers Association (Zorgverzekeraar Nederland).
MAH	Market Authorisation Holder, the company or other legal entity that has the authorisation to market a medicine in one, several or all European Union Member States.
NKI-AVL	Netherlands Cancer Institute – Antoni van Leeuwenhoek hospital, a Dutch cancer research center that constitutes an organization together with the Antoni van Leeuwenhoek hospital, a cancer treatment and research center.
NVALT	Dutch Society of Pulmonology and Tuberculosis
NVMO	The Dutch Association for Medical Oncology. Commits itself to promoting both the quality of medical oncology and the improving the availability and accessibility of oncology care.
NRS	Non-Randomized Study
PASKWIL	"*Palliatief, Adjuvant, Specifieke bijwerkingen, Kwaliteit van Leven, Impact van de behandeling en Level of evidence*"-criteria. CieBOM uses this critera to assess the added value of a product for patients. In 2021, new criteria specific for NRS products were developed.
RWE	Real-World Evidence, evidence derived from the analysis of Real-World Data, which is data derived from a number of sources that are associated with outcomes in a heterogeneous patient population in real-world settings.
ZIN	Zorg Instituut Nederland, a governments advisory and implementing organisation. It advises the MoH, performs HTA, consults HTD's, insurers, healthcare providers and patients. Responsible for Horizon Scanning Initiative, selection of lock-candidates and advising MoH concerning application of the lock.
ZN	Zorgverzekeraar Nederland, the Dutch Health Insurers Association.
ZN's Clean Team	Joint purchasing group of the Dutch insurers for intramural "open-system" medicine.

Figure 1. Flowchart illustrating the DAP process.

responses on the interview guide, which was included in the data. The interviews were video recorded, and the audio was automatically transcribed using Amberscript, followed by manual editing to 'intelligent verbatim' transcript (removing speech disfluencies such as 'um', filler words such as 'you know' and sentence re-starts) and pseudonymisation. Transcripts were shared with participants upon request. All pseudonymised transcripts were coded using NVivo software (version 15). Thematic analysis was conducted guided by Braun and Clarke's approach [24], with a focus on enablers and challenges that

emerged from the participants' experiences with the DAP programme. Transcripts were re-read by one of the researchers (KV) for a comprehensive understanding of the data. Themes were generated using an inductive thematic analysis approach. . From these common themes, enablers and challenges emerged that are further described in the results section.

Additionally, the DAP process flowchart was adjusted based on the feedback received during the interviews.

Results

In total eight organisations agreed to participate in the interview (with mostly two experts per organisation); the participants represent five MAHs of the products enrolled in the programme (two products were in the early phase and therefore excluded from recruitment), the Dutch payer, the DAP's governance committee and the DAP's study management team.

As shown in Table 1, seven products are included in the DAP programme, comprising nine indications (selpercatinib enrolled four indications), and Figure 1 illustrates the different phases and timelines of the DAP process.

DAP process

The initiation phase (T_0)

T_0 aims at selecting eligible products, which is done by the Dutch Association for Medical Oncology , the Dutch Society of Pulmonology and Tuberculosis and the payer. This process is informed a.o. by the half-yearly results of the Dutch HTA body's Horizon Scan, which provides an overview of medicines expected to come into the market in the upcoming 2 years [25]. For a product to be eligible, it must meet the minimally clinically important difference defined by the Dutch Association for Medical Oncology for indications supported by (a) non-randomised trial(s). These criteria are referred to as the PASKWIL-NRS criteria (Table 2). As evidence from a non-randomised trial is not considered sufficient for regular reimbursement, inclusion in the DAP is mandatory for reimbursement.

Therefore, once a product is selected for a specific indication, negotiations and contracting begin. During the contracting phase (also part of T_0), the MAH negotiates contracts with relevant stakeholders concerning financial terms (with payers), data collection terms (with the Netherlands Cancer Institute / Antoni van Leeuwenhoek hospital) and supply and distribution terms with the selected hospitals. These hospitals are selected by payers, as they meet the requirements to provide care for these rare indications. Contracts are usually signed for a 3-year period.

The implementation phase ($T_{1\text{-}2}$)

After agreement on all terms is reached, the implementation phase is initiated ($T_{1\text{-}2}$). Throughout this phase, the drug is reimbursed based on a personalised reimbursement scheme, with potential additional arrangements between the MAH and payers. Recruitment usually takes 2 years. Data are gathered by a master protocol for each product and a standard electronic Case Report Form (eCRF) for each patient. Sometimes, a product-specific section is added to the protocol, which, for instance, may be relevant for side effect management. In all hospitals, data are monitored, managed and analysed by The Netherlands Cancer Institute / Antoni van Leeuwenhoek hospital , a primary cancer institute for research and care. During the data gathering period, regular updates regarding the number of patients are provided to all stakeholders. Just before the end of the second year, DAP's governance committee and the payer's' Add-on Drugs Assessment Committee assess whether the number of patients recruited and all other publications on the product and indication are expected to deliver the needed level of evidence for a re-assessment or the recruitment phase should be prolonged. When the required number of patients enrolled has been met and/or there are additional evidence available from other studies or registries, recruitment ends after a maximum of 2 years.

Follow-up and the re-assessment phase (T_3)

When recruitment stops, the follow-up period of 6–8 months begins to ensure sufficient follow-up for the last patients recruited. After this, the re-assessment phase (T_3) starts. All new patients who require treatment in this third year will be treated

Table 2. PASKWIL Criteria for Non-Randomised Studies: a product must meet all the requirements listed below to receive a positive opinion.

Requirements	Description
1	The indication for which the treatment is registered is rare.
2	In the related indicated area, either no treatment options with proven clinical benefit exist or all available treatments have been exhausted
3	The patient population can be selected reliably and reproducibly.
4	Preferably, there is a biological rationale for the mechanism of action of the treatment.
5	When assessing clinical value based on the objective response rate (ORR), a combined criterion is used involving the lower bound of the 95% confidence interval (95% CI) of the ORR and the point estimate of the median duration of response (DoR). The treatment is considered clinically relevant and valuable for the target population if: • ORR > 40% **and** DoR > 4 months, **or** • ORR > 30–40% **and** DoR > 8 months, **or** • ORR > 20–30% **and** DoR > 12 months.
6	In a non-randomised study, overall survival (OS) or progression-free survival (PFS) is clinically meaningful if the gain in OS or PFS compared with the implicit or explicit control is more than 16 weeks (lower bound 95% CI).

CI = confidence interval; ORR = Objective Response Rate; DoR = duration of response; OS = overall survival; PFS = progression-free survival

according to the protocol but outside the DAP. This means that no data will be collected for these new patients. Reimbursement, however, will continue to follow the personalised reimbursement scheme and any arrangements between the MAH and payers. This provision is intended to prevent any gap in access during the follow-up and re-assessment phase. The product is re-assessed to make sure that the additional evidence available supports the original clinical trial results. This means that the results of DAP should not differ significantly from the data of the pivotal trial. Because the number of patients may be limited, the final decision considers not only DAP data but also all other published RWE and relevant publications. . If the re-assessment results in a positive outcome, renegotiations with the payer start on the reimbursed price of the product based on the DAP data. DAP data guide the financial arrangements after the DAP so that the drug's regular reimbursement reflects its actual value.

Enablers of participating in the DAP programme

Providing earlier access to patients

Table 3 summarises the main aspects that experts perceive as an enabler or challenge in their participation in the DAP programme.

All participants indicated that a key value of the DAP programme is achieving earlier access for patients to these drugs awaiting reimbursement. This fulfils a high unmet medical need.

However, some concerns exist whether long-term patient access is ensured in all cases. Re-assessment could lead to a negative outcome, ceasing patient access. Moreover, after positive re-assessment, DAP participation could complicate price renegotiations with the payer's negotiation team, leading to a possible halt in access. For instance, MAHs could debate a recoup of their financial investment into the DAP.

Mitigating uncertainty on cost-effectiveness

The majority of MAHs agreed that due to uncertainty in the clinical data, payers face difficulty in predicting real-world effectiveness. This is also linked to the fact that the drugs included in the DAP mostly have an EMA conditional market approval status, as seen in Table 3.

Clear timeframes and roles of stakeholders

Regarding the specific roles of the stakeholders involved, MAHs stated that this was clearly communicated and well defined. As for timeframes, contracts have a clear start and ending date, which can be prolonged if the required number of patients included is not met. However, one MAH argued the process to be incoherent, without any party taking the lead. This absence leads to practical issues and inefficient implementation.

Moreover, MAHs stated to be unbeknownst whether recruitment prolongment is needed until the second year of the study. Also, some MAHs stated that clinicians were not aware of the discontinuation of patient enrolment. This led to MAHs actively reaching out to clinicians in order to stop further patient enrolment. Regarding the managed exit and re-assessment phase, MAHs were uninformed in which manner these procedures would proceed and what the prospected role of the MAH would be during this phase.

Real-world effectiveness in the Netherlands

The health insurer argued that clinical trials by default include patients who do not correspond well with the type of patients expected to receive treatment.

Gathering data from real-world treatment would address these uncertainties and provide some idea about how the treatment performs outside controlled clinical settings. However, MAHs argued that due to the absence of a clear, well-communicated definition of the existing uncertainties, it is challenging to predict whether the RWD collected will effectively address them.

Challenges of participating in the DAP programme

Financial costs of data collection

One of the issues raised was the data management fee paid per patient for preparing the study initiation, collecting data from participating hospitals based on an electronic case report form, monitoring data, providing information to the participating centres and analysing and reporting the data. All MAHs believed that the data management fee was high compared with conventional data collection costs. Unanimously, participants stated it was difficult to obtain clearance within their global company structure for the extra fees of data collection in the Netherlands, as questions were raised regarding the details of the gathered data and what it would yield. Failing to achieve this fair market value assessment almost prohibited DAP participation. In their defence, the DAP's governance committee argues that whereas the study population is small, the infrastructure and personnel costs are spread over a limited number of patients and hence do not offer a valid comparison with conventional data collection costs. Moreover, funding of the data collection could lead to a positive reimbursement decision and thus a return of investment for MAHs.

Rigidity of the financial OB-MEA arrangement

All MAHs argued that the fixed study protocol functions as an indirect selection criteria for products eligible for the DAP. For instance, the rigid cut-off period for the initial 16-week free-of-charge period can be skewed for certain products in terms of costs. For instance, some indications have short prognosis or treatment duration (e.g. gene therapy), or some products have high initial dosing followed by low maintenance doses. Therefore, the characteristics of the scheme itself can be seen as a selection criterion, prohibiting products from entering the programme.

Table 3. Enablers and challenges experienced by participants, concerning participating in the DAP programme.

Enablers	Quotes
Providing earlier access to patients	*'[…] From a pragmatic perspective, we were happy that the DAP was there. We were happy to join. We could get access to patients, and patients get access to this drug two and a half years sooner than in France, for example, where they didn't have such a programme. So we were happy.' [P1]*
Mitigating uncertainty on cost-effectiveness	*'[…] I think the drug access protocol can help us in looking at routes which are beyond the EMA and looking at ways to address uncertainties as well, but also making sure that innovations can really provide value for those patients who need it.' [P3]*
Clear timeframes and roles of stakeholders	*'No. What I would like to do is mention one very positive thing that is the DAP loket [english translation: counter], so the ticket window, the DAP loket. That's a team that's based in the NKI and they do the data collection, they do the inclusion of the patients. They are very responsive. They are proactive. They send us reports, aggregate reports of the inclusion of the patients, start-stop dates and like that. So that's a very positive thing.' [P1]* *'There's nobody really owning any of this, and taking the lead in any of this. We're continuously chasing people to follow these timelines and stop recruitment. We are trying to stop them from recruiting new patients, because this is the evaluation year and the follow up year that we're in right now. We're sharing with cieDAP that they should plan their analysis, that it's time now. So, these [cieDAP] are doctors that have practices and a lot of things on their minds. They're not really owning it and managing it.' [P1]* *'And after [three years of data collection], you don't know what the negotiation will be […]. And when the CieBAG assesses the drug and assesses in a positive way. So the state of practice and science has been established, you don't know upfront what they will do. You can imagine sometimes what they will do, but you don't know what will happen. You can be sent to the Clean Team to make a price deal, or not. You don't know upfront.' [P1]*
Real-world effectiveness in the Netherlands	*'So if the conclusion is that we don't have the time [to wait for EMA required follow-up data], or that it takes too much time, then perhaps we need to decide, yes we go on and we collect this real world data in the Netherlands because patients are waiting, it's too promising, we want to go further with it. And then you can decide that it takes too long and we don't wait, for example.' [P4]*
Challenges	**Quotes**
Financial costs of data collection	*'[…], [assessing the fair market value] took a very long time because they couldn't really provide sufficient arguments for why there should be €X and to provide that this was a fair market value. And I think that is still the issue, also if you want to enter the DAP as a company, that global offices think this is illegal.' [P2]*
Rigidity of the protocol	*'[…] what we experienced is also there is no flexibility in the drug access scheme, how it's set up. So the 16 weeks is fixed. And if you think about the uncertainty and then also the financial conditions linked to such a time point, those are not fit for purpose for every therapeutic area or every drug. And that makes it also more difficult I think, to say if you would agree to such a scheme […]. Because that's a very rigid protocol, which is one size fits or should be a one size fits all, which is actually not the case.' [P5]*
Lack of transparency for MAHs	*'[…] There was no target of patient numbers mentioned in advance. […] In the first two years, we were unclear about what would be the criteria for the drug access protocol to work with. […] That's something where we didn't feel on par with regards to information levels.' [P3]*
Data sharing	*'[…] we would have wanted to be updated on a more regular basis. Also about the number of patients included, but also the number of patients who continued after […] [the free-of-charge phase]. […] you don't know how many patients after four months will continue the treatment. […] I think it would be fair to at least have some information, as guidance for participant or the participating company.' [P3]*
Questions regarding added value of real-world data	*'And what I expect, or what I'm a little bit afraid of, is that during that assessment, after three years, we will come to the conclusion that in more cases, other data bring more weight into the assessment then the collected data in the DAP. And then you could wonder, did we collect the right data, or did we only collect data because we wanted to come to another agreement and we did not want to immediately, fully reimburse the product?' [P4]*
Lack of trust	*'That [re-assessment] should be a criteria to be set in advance. And we have not seen anything for this yet. So I think it should be clear for all stakeholders. If you start managed entry agreements, you need to be clear on the criteria and the outcomes by which you will be measured. And I think this is too much in the open.' [P3]*
Difficulty prescribing product by physicians	*'[…] it did take quite some time for the hospitals to be onboarded. And they needed to hand over data to the AVL [NKI's hospital] of course. Some unclarity about the ordering of the drug, I think also in the beginning. But probably we didn't hear everything to be honest, because that needed to be solved as much as possible by the AVL [NKI's hospital].' [P5]*

Lack of transparency

All MAHs stated that some aspects of the DAP process were unclear to them or poorly communicated. Firstly, eligibility criteria were stated to be not established, changing over time and depending on the person asked. It is unclear how the payer defines 'high unmet medical need' for the products' indications. Moreover, MAHs were not aware if all products receiving market approval based on non-randomised studies are eligible, or whether products authorised on the basis of randomised trials can also be enrolled. The payer argues that these products are permitted for enrolment as well, even as off-label products. Also, MAHs argue it is unknown whether products pending phase III or prolonged phase II results are eligible for the DAP. Furthermore, some MAHs argued that uncertainty in costs and financial motivations are key in the selection of products, which does not emerge from the selection criteria. Likewise, they question whether healthcare budget impact influences the selection of products.

As for 'high unmet medical need', the payer formulated this criterium as a situation where no alternative treatment for the patient population indicated exists (anymore). The payer

remarks that for products to be eligible, a minimum level of the PASKWIL-NRS criteria should be met (Table 1). This means sufficient grounds exist to condone the lack of randomisation, for example, the rarity of an indication. There has been a case where the Dutch Medical Oncology Association was unable to assess the product as the indication was not rare enough. If a product has an ongoing RCT study, there is generally no DAP eligibility, and these results should be awaited to apply for reimbursement. Products authorised based on a non-randomised study could receive reimbursement outside of DAP, provided there are no uncertainties regarding their effectiveness or the uncertainties are addressed in another way.

For DAP, price is not a selection criterium but becomes part of the financial scheme when a drug is included.

Secondly, most MAHs stated that the accrual rate remained unknown to them for a long time during the implementation phase. Also, they were unsure why there was no power calculation conducted to assess for non-inferiority. The payer argues that it is difficult to predict how many patients are expected to enrol during the initial 2 years. The consideration of prolonging the patient recruitment phase can only be undertaken after 2 years of data collection or after the readout of the data cut off after 2.5 to 3 years of the start of implementation. Current competition laws limit contract terms between health insurers and the industry to 3 years.

Thirdly, some MAHs were unsure which specific criteria are used for (re-)assessment and what data are included in the assessment. Moreover, it is unknown how uncertainty regarding (real-world) effectiveness is defined, and consequently, how RWD will solve this uncertainty. The payer states that for re-assessment, PASKWIL-NRS criteria are used, and it is assessed whether the RWD is statistically different from the results of the pivotal trial. The final decision is based on all published data available at that time, for example, other RWE and clinical study reports.

In addition, one company mentioned that the trial organisation could have been more structured, with more active communication towards caregivers and hospital pharmacies. They also noted that support from the DAP's governance committee or medical societies in aligning the different stakeholders would have been appreciated, as for example one hospital pharmacy refused to collaborate with the company.

Data sharing

Data sharing between the different parties involved, such as the Dutch National Cancer Institute and the payer, was mentioned as a difficult point. In addition, MAHs stated the need for information on required number of patients enrolled for both the test phase (first 16 weeks) and the commercial phase of the programme. One explanation for the issue around data sharing could be linked to the fact that there is no contract between the Dutch Cancer Institute and the payer, another reason being that clinicians in partaking hospitals do not always know who to reach out to concerning questions about the DAP programme.

Questions regarding added value of real-world data

MAHs unanimously state their uncertainty as to what extent the RWE will support reimbursement decisions. This uncertainty is linked to the unknown definition of uncertainty and untransparent eligibility criteria. Some MAHs questioned whether their study population was that different from the Dutch patients expected to receive the treatment, and whether gathering RWE is therefore necessary. Also, some MAHs argued that additional data from phase II/IVI trials, whether or not required by conditional market approval, are more valuable for long-term access to these products. The payer confirms that in one case, a DAP-enrolled product received reimbursement after new data publications became available, wherefore in retrospect, the DAP programme had not been needed. Consequently, these products should not be eligible for the DAP.

Lack of trust

An overarching theme that emerged from the interviews is the MAHs' lack of trust in stakeholders (payers and hospitals) and the value of the DAP programme. This challenge is linked to issues in both communication and transparency between stakeholders. Firstly, MAHs resent the lack of a clear definition of uncertainty and the absence of transparent eligibility and re-assessment criteria. MAHs argue that without knowing the origin of uncertainty, they find it difficulty predicting whether the gathered RWD will solve this uncertainty. In the view of MAHs, the data collection aspect of the DAP lacks a clearly defined clinical rationale. Moreover, one MAH stated that the payer can change the DAP's conditions during the implementation phase without consultation with MAHs, as the payer views the field as dynamic.

Secondly, according to some MAHs, the data collection fee is much higher than the typical costs of data collection, rendering suspicion of the fee being a revenue source for hospitals. Moreover, MAHs reckon that financial motivations originating from the payer are factored into the selection of these products.

Thirdly, one MAH pointed out that there is a risk of conflict of interest regarding the double role of certain committee members. Both the selection and exit of products are determined together by members of the DAP's governance committee and members of the Dutch Association for Medical Oncology . In addition, individuals can have occupations in multiple committees, granting these individuals a key role in the programme.

From payer's perspective, trust issues would be mitigated if there would be a better understanding of why the current landscape in the assessment of these products calls for a solution, which the DAP may provide. The underlying idea is that MAHs, payers and the medical society are trying to address the evidence gap. While traditionally, it is the responsibility of the MAH to provide robust evidence in the form of two randomised trials. The payer also hopes that examples of products receiving full reimbursement after participating in DAP, peer-reviewed publications, cohort reports and the annual meeting organised by the DAP team – to inform companies and

address their questions and challenges – would improve trust in the programme.

Difficulty prescribing product by physicians

Several practical challenges surfaced during the implementation phase. The payer usually select specific hospitals with high expertise in treating the indication. MAHs discuss a contract with these hospital on terms of supplying and pricing. The hospitals participating are limited to a selected number of expert centres. Physicians at non-expert centres are not always aware of the existence of this treatment option, leading to lower referrals towards expert centres.

Also, as for the ease of prescribing a product within the DAP for clinicians, there was a clear discrepancy between MAHs. While some MAHs stated clinicians were comfortable using the product within DAP, in contrast, other MAHs argued it was a time-consuming process and an administrative burden for physicians. Furthermore, one MAH stated that physicians did not know how to reach out to the DAP committee or management team and therefore instead opted to reach out to MAHs.

Also, one MAH stated that for their product, some patients had the drug prescribed but were not included in the study. Physicians should send each patient for review to the Dutch Cancer Institute in order to have them enrolled in the study. The payer lacks the ability to monitor for this discrepancy as there is no data exchange in between due to the absence of a contract between the payer and the Dutch Cancer Institute. This discrepancy results in study selection bias and difficulty in the implementation of the financial agreement. [Explanation by DAP-management team: All serious protocol deviations, including the rare cases in which a patient has been mistakenly placed on the medication outside of the DAP, are discussed with the payer of the patient to determine whether the costs can be covered from the healthcare budget or whether a compassionate use request should be submitted to the MAH. A contract between the payer and the Dutch Cancer Institute is legally not allowed due to privacy reasons.]

Discussion

This qualitative study gives insights into the complicated processes of implementing an innovative, clinician-led early access scheme linking evidence generation and reimbursement for tumour-agnostic cancer medicines in the Netherlands. The analysis of the interviews of all involved stakeholders made it clear that while all stakeholders acknowledged several enablers, many challenges still remain for a smooth implementation of the programme. Facilitating patient access and potentially achieving regular reimbursement are key reasons for participating in the programme. However, concerns regarding the lack of clarity, challenges in data sharing and a limited trust can affect the feasibility of the DAP and the willingness of MAHs to participate. Alignment and permission from the corporate headquarters of the MAH seemed to be one of the major challenges for the local branch of the MAH to justify the participation in the DAP.

The study findings align with previous assessments of the implementation of OB-MEAs. Several publications address difficulties in generating evidence, high administrative burdens and time-consuming negotiations [8–10, 26, 27]. Due to this complexity, healthcare decision makers are driven to opt for simpler financial MEAs (e.g. discounts) instead. The requirements needed to make MEAs feasible are well discussed in literature. Among these, a strong alignment of objectives between health decision makers and MAHs is stated [10]. Arguably, in the DAP programme, this alignment could be improved, as highlighted from the identified challenges. As MAHs commit to a long-term agreement that involves high financial (data management fee and free-of-charge clawbacks) and implementation costs (e.g. negotiation time), it is crucial to have upfront guidance on the managed exit or re-assessment phase.

While it has to be acknowledged that DAP provides non-randomised data, the added value of DAP-like registries is that they can reduce health system's uncertainty regarding how the treatment performs in broader, unselected populations, thereby addressing population bias. An additional advantage is that these data can later help payers and companies to make more informed financial arrangements. Representatives of the DAP management argue that concerns about an anticipated unchecked rise in healthcare budget costs make healthcare payers and the Dutch HTA body cautious. This can make the DAP an important decision-making instrument in case of unclear reimbursement recommendations.

The findings of this study have great learning potentials for other countries. Literature suggests that insights into the experiences and interests of stakeholders can be essential in understanding the feasibility of successfully implementing MEA (like-) programmes [27, 28, 29, 30]. This may give healthcare decision-makers the necessary tools to improve these types of agreements and therefore ensure that expenditures of the healthcare system are used efficiently and effectively while also ensuring patient access to these innovative therapies.

However, alike their pivotal trials, RWD gathering faces challenges due to small patient numbers. In multiple cases, the DAP's recruitment phase had to be prolonged in order to collect sufficient data. Implementing the DAP programme in other EU countries could facilitate access and support the joint generation of RWD. A similar programme, the Drug Rediscovery Protocol (DRUP), which is aimed to improve patient access to off-label oncology treatments, makes use of such a collaboration [31]. This collaboration is incorporated in the PRIME-ROSE (Precision Cancer Medicine Repurposing System Using Pragmatic Clinical Trials) consortium, which aggregates data from DRUP-like studies conducted in multiple countries [32, 33]. A similar initiative for DAP-like studies may significantly improve recruitment rates and accelerate evidence building [9, 34, 35, 36, 37].

In a recent evaluation of the Dutch HTA body's coverage with evidence programme as well as the DAP programme, future considerations were mentioned including the consideration of harmonising all different OB-MEA systems in the Netherlands under the umbrella of one. Another point raised was to also adjust the processes to also include diagnostic tests in the

reimbursement process. This originated from the Larotrectinib/Entrectinib case, where the drug was reimbursed after inclusion in the DAP, but the path for the molecular diagnostics at that time was unclear, leading to a low rate of diagnosed patients. Overall, MAHs found the DAP process as more transparent and a quicker process than the other Dutch OB-MEA process by the Dutch HTA body.

While we have to acknowledge that generalisability is the main limitation of this study, we believe that this is at the same time also a strength of the study. We use the DAP protocol from the Netherlands as a case study to describe challenges in implementing early access schemes, which could vastly differ between high- and low-income countries or between single- or multi-payer systems [9]. Also, the Netherlands possesses a good research infrastructure and strong research institutions like the Netherlands Cancer Institute. Fragmentation of healthcare structure can make undertaking MEAs in practice more difficult [10]. However, we believe this case report provides valuable insights from all involved stakeholders on how to practically implement a clinician-led early access scheme, which provides the opportunity for other countries to learn from.

Conclusion

In conclusion, coverage with evidence development programmes like the DAP may be a promising solution to mitigate uncertainty for healthcare payers and simultaneously provide patient access to innovative therapies. Such bottom-up approaches are valuable because they draw on the practical insights of clinicians and payers, aligning access decisions with RWE to ensure they are both practical and sustainable.

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Disclosure statements

The authors report there are no competing interests to declare.

Data availability statement

This study is based information obtained through interviews. Due to privacy protection, the data of the interviews cannot be made publicly available.

Ethics declarations & trial registry information

The research protocol was approved by the Science-Geo Ethics Review Board (SG ERB) of Utrecht University (27/10/2024, 24-0122). Each participant gave oral consent prior to participating in the interview. We ensured the anonymity of the participants and pseudonymised all transcripts by removing information that could be linked to a specific product, company or interviewee. During and after the study, all data were treated confidentially.

Author contributions

CL, AH, KV and SB designed this study. CL, AH, KV and SB planned the quantitative analyses, and KV and CL performed the interviews. KV and CL performed the qualitative analysis. KV and CL were part of drafting the manuscript. All authors reviewed, edited and approved the final manuscript.

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SHORT REPORT

Clinical outcomes of genomically guided trametinib monotherapy across cancer types: results from the IMPRESS-Norway trial

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ABSTRACT

Background and purpose: Molecular profiling guides cancer treatment, by identifying actionable genomic alterations. The IMPRESS-Norway trial (NCT04817956) is a nation-wide precision medicine trial evaluating the efficacy of approved cancer drugs on a novel indication in patients with advanced cancers harbouring potentially actionable alterations. Trametinib, a selective MEK1/2 inhibitor targeting the Mitogen-Activated Protein Kinase (MAPK) signalling pathway, is approved for BRAF V600 mutant melanoma but may also show activity in tumours with other alterations. This sub-study aimed to assess the efficacy of trametinib monotherapy across tumour types with alterations activating the MAPK signalling pathway.

Patient/material and methods: In the IMPRESS-Norway trial patients are screened with the TruSight Oncology 500 panel or circulating tumour DNA profiling. Eligible patients are offered biomarker matched targeted therapies. In this subgroup analysis, we identified patients treated with trametinib monotherapy. Primary endpoints were disease control rate (DCR) after 16 weeks and safety. Secondary endpoints included progression-free survival (PFS) and overall survival (OS).

Results: DCR after 16 weeks of treatment was 39% in 52 response evaluable patients, with four patients (8%) experiencing partial response, and 16 (31%) stable disease. Responses were seen in tumours harbouring BRAF fusions, GNA11, GNAQ, KRAS, NF1, and NRAS alterations, most frequently in low-grade serous ovarian cancer, central nervous system tumours, and uveal melanoma. Forty-eight percent of patients experienced treatment-related adverse events, including two treatment related deaths. Median PFS and OS were 4 and 9 months, respectively.

Interpretation: Trametinib monotherapy achieved a 39% DCR in patients lacking standard options, supporting further studies to confirm efficacy and identify predictive biomarkers for treatment response.

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Introduction

Molecular profiling has become an important part of cancer diagnostics in several cancer types, guiding treatment selection, and identifying emerging therapeutic targets or resistance mechanisms at progression. Additionally, the European Society for Medical Oncology (ESMO) Precision Medicine Working Group recommends multigene sequencing to identify patients eligible for clinical trials [1].

The IMPRESS-Norway study is an ongoing prospective, non-randomised clinical trial evaluating efficacy of off-label, commercially available anti-cancer drugs prescribed for patients with advanced cancer diagnosed with potentially actionable alterations revealed by molecular profiling [2]. Preliminary results have shown an overall disease control rate (DCR) of 40% [3].

One of the available drugs in the IMPRESS-Norway study is trametinib. Trametinib is a reversible and selective inhibitor of MEK1 and MEK2 kinases resulting in MAPK signalling pathway

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inhibition [4]. Trametinib received regulatory approval for unresectable/metastatic melanoma based on the Phase III METRIC trial, which demonstrated significantly improved progression-free survival (PFS) and overall survival (OS) compared with chemotherapy in patients with BRAF V600E/K mutant metastatic melanoma [5]. Trametinib has later become standard treatment in combination with dabrafenib for several tumour types harbouring the BRAF V600 mutations.

Hyperactivation of the MAPK signalling pathway, by activating mutations and fusions of protein kinases and inactivation of tumour suppressor genes, is promoting cell proliferation and tumour growth. Therefore, it is reasonable to assume that trametinib could be effective in the presence of MAPK pathway activating alterations beyond BRAF V600. Earlier studies have shown that trametinib may be effective in tumours harbouring GNAQ**,** NF1**,** KRAS, or NRAS alterations, supporting the rationale to investigate the efficacy of trametinib monotherapy [6–12].

This subgroup analysis aimed to evaluate the efficacy of trametinib monotherapy in patients with alterations in the MAPK signalling pathway enrolled in the IMPRESS-Norway trial.

Patients/material and methods

Study design

IMPRESS-Norway is a prospective, non-randomised, nationwide clinical trial evaluating the efficacy of off-label, commercially available and approved anti-cancer drugs in patients with advanced cancers harbouring potentially actionable genomic alterations. The study employs a combined umbrella and basket design with a Simon two-stage model to assess potentially effective biomarker-drug combinations for specific indications [2].

All patients were screened using the comprehensive genomic profiling panel TruSight Oncology 500 (TSO500, Illumina). For patients with no available tissue, genomic profiling of circulating tumour DNA (ctDNA) using the FoundationOne Liquid CDx assay (Foundation Medicine, Inc.) was performed. A predefined biomarker list was used to allocate patients to treatment with trametinib, and the following potentially actionable alterations were included: BRAF activating fusions, activating mutations in GNAQ, GNA11, GNAS, MAP2K1 or MAP2K2, NF1 mono- or biallelic inactivation (CNS tumours only), NRAS activating mutations or amplification, HRAS and KRAS activating mutations (low grade serous ovarian carcinoma only), and MAP2K4, MAP3K1 or LZTR1 biallelic inactivation. MAP2K1, MAP2K2, MAP2K4, MAP3K1 and LZTR1 were abandoned during the study due to slow accrual and uncertain predictive value of the biomarkers. As of October 2025, trametinib was no longer available in the study.

Study population

Adult patients with advanced solid or haematological malignancies who had progressed on all standard therapies were eligible for inclusion. DNA/RNA profiling had to reveal one of the pre-defined molecular biomarkers for trametinib treatment, adequate performance status and organ function, a life expectancy of at least 3 months, and meet all study and drug-specific inclusion and exclusion criteria.

Patients included in the response-evaluable population used for efficacy analysis had received at least one cycle of trametinib (28 days) and had been evaluated according to protocol. Clinical deterioration and inability to complete per protocol evaluation were considered to be signs of progressive disease at the discretion of the treating physician. All treated patients were included in the safety analysis.

Patients included in this subgroup analysis were enrolled from April 2021 and followed up until data cut-off at September 9, 2025.

Study endpoints

The primary study endpoints were DCR after 16 weeks of treatment and treatment safety. DCR was defined as radiologically confirmed complete response (CR), partial response (PR), or stable disease (SD), after a minimum of 4 weeks. RECIST v1.1 [13] and RANO [14, 15] evaluation criteria were used for solid cancers and primary brain tumours, respectively, while ELN-AML criteria [16] were used for haematological cancers. Patients were evaluated at treatment weeks 8, 16, 24, and every 3 months thereafter.

Toxicity was assessed by the Common Terminology Criteria for Adverse Events v5.0. Treatment-related adverse events (TRAEs) ≥ grade 3 and treatment related serious adverse events of any grade were collected up to 30 days after last treatment dose.

Secondary endpoints were PFS and OS.

Treatment with trametinib

Patients started at a dose level of 2 mg once daily. In cases of toxicity the dose was reduced according to protocol. Left ventricular ejection fraction was evaluated in all patients at baseline, after 1 month and every 3 months thereafter. Patients received treatment until disease progression, unacceptable toxicity, death or withdrawal of any reason. However, treatment beyond progression was permitted in certain cases.

Data collection and statistical analysis

Data included in this analysis were collected from the electronic case report form Viedoc. Stata version 18 was used for statistical analysis. Patient characteristics and tumour responses were summarised using descriptive statistics. DCR was calculated as the proportion of patients with CR, PR, or SD in the response evaluable population. PFS was defined as the time from treatment initiation to the first recorded progression or death of any cause. Event date for progression was defined by the date of CT- or MRI-scan or the date of bone marrow/blood procedure for haematological cancers. Otherwise, in cases of clinical deterioration, the time point of progression was the visit date where the unequivocal progression was recorded. Patients who stopped treatment

due to any cause without recorded progression or death were censored for PFS time at the date of their last visit. OS was defined as the time from treatment initiation to death of any cause, or censored at last date known to be alive, whichever occurred first. PFS and OS were assessed by the Kaplan–Meier method and presented with accompanying 95% confidence intervals (CI).

Results

Patient and tumour characteristics

In total, 65 patients started treatment with trametinib monotherapy. Median age at treatment start was 62 years (range 19–83), and 63% of treated patients were females. The majority of patients had an ECOG performance status of 0–1 (81%) and had received 1–3 prior treatment lines. The most common included tumour types were uveal melanoma and ovarian cancer. Patient characteristics are presented in Table 1.

The most frequently detected actionable alterations among patients who received trametinib were NRAS Q61 H/K/L/R (n = 14), and KRAS G12 D/V (n = 9) identified in different tumour types, GNAQ Q209 P/L (n = 8) identified in uveal melanomas, and NF1 inactivating mutations (n = 8) identified in central nervous system (CNS) tumours. Detailed overview of actionable alterations in treated patients is presented in Supplementary Table 1.

The median time from inclusion to the data-cutoff was 22 months (range 0.4–35).

Table 1. Characteristics of patients treated with trametinib monotherapy, n = 65.

Characteristics	n (%)
Age, years, median (min–max)	62 (19–83)
Sex	
Female	41 (63)
Male	24 (37)
ECOG performance status	
0	23 (35)
1	30 (46)
2	12 (19)
Tumour types	
Ovarian cancer	14 (22)
Uveal melanoma	14 (22)
CNS tumour	10 (16)
Colorectal cancer	7 (11)
Non-small lung cancer	4 (6)
Haematological malignancy	4 (6)
Cholangiocarcinoma	3 (5)
Neuroendocrine carcinoma	2 (3)
Neuroendocrine tumour	2 (3)
Prostate cancer	2 (3)
Mucosal melanoma	1 (1)
Pancreatic cancer	1 (1)
Uterus cancer	1 (1)
Previous treatment lines	
None (radiation/surgery only)	2 (3)
1 line	13 (20)
2 lines	29 (45)
3 lines	10 (16)
4 lines	4 (6)
5 lines	7 (10)

Efficacy assessment

Of the 65 patients who started treatment, 13 were considered not evaluable according to protocol. Among the 52 patients in the response evaluable population, the DCR was 39%; four patients (8%) achieving PR and 16 (31%) SD after 16 weeks of treatment (Figure 1). No CR were observed. Three patients with low-grade serous ovarian cancer (LGSOC) and one with high-grade astrocytoma with piloid features experienced PR. In addition, six patients with LGOSC, one patient with recurrent pilocytic astrocytoma and one patient with diffuse leptomeningeal glioneuronal tumour, six patients with uveal melanoma, one patient with mucosal melanoma and one patient with cholangiocarcinoma had SD. Three of these patients are still on treatment. Three patients received treatment beyond progression.

PR and SD were observed in tumours harbouring BRAF fusions, and GNA11, GNAQ, KRAS, NF1 and NRAS activating or inactivating alterations, whereas no responses were seen in patients with tumours harbouring NRAS amplifications, HRAS activating mutations or MAP2K4 and MAP3K1 biallelic inactivation. A detailed overview over responses according to biomarkers and tumour types are shown in Supplementary Table 1.

In the response evaluable population, the median OS was 9 months (95% confidence interval [CI]: 6–10), median PFS was 4 months (95% CI: 3–6) and 1-year PFS was 14% (95% CI: 6–27) (Figure 2).

Safety

Out of 65 patients treated with trametinib, 31 (48%) experienced TRAEs. In total, 58 TRAEs were reported, with 38 (66%) being serious adverse reactions. The most commonly reported TRAEs were rash, increased liver enzymes, and mucositis. Six suspected unexpected serious adverse reactions (SUSARs) were registered, including myocardial infarction, sepsis, stroke, and thromboembolic event all registered in one patient, and an additional two thromboembolic events in two patients. Two treatment-related deaths were reported, one related to a thromboembolic event, and the other to an intra-abdominal haemorrhage. A total of 14 patients (22%) stopped treatment due to TRAEs. The overview of all reported TRAEs is shown in Supplementary Table 2.

Discussion and conclusion

This subgroup analysis of clinical outcomes in patients treated with trametinib monotherapy in the IMPRESS-Norway trial, demonstrated clinical benefit with a DCR of 39%. The observed responses were seen in patients with LGSOC, CNS tumours, uveal and mucosal melanoma and cholangiocarcinoma harbouring BRAF fusions, and GNA11, GNAQ, KRAS, NF1 and NRAS activating or inactivating mutations.

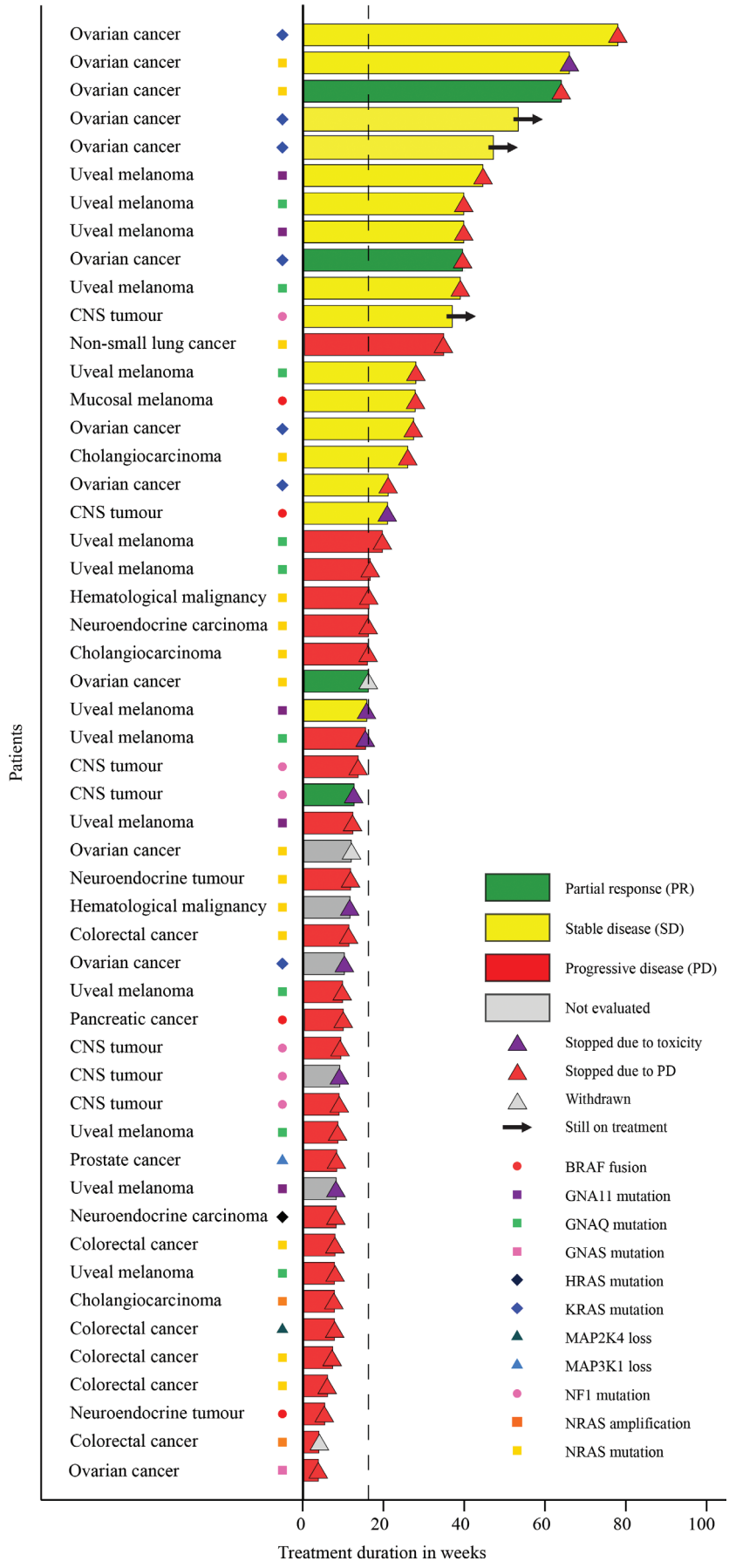

Figure 1. Swimmers plot of 'response evaluable' patients treated with trametinib monotherapy, $n = 52$.

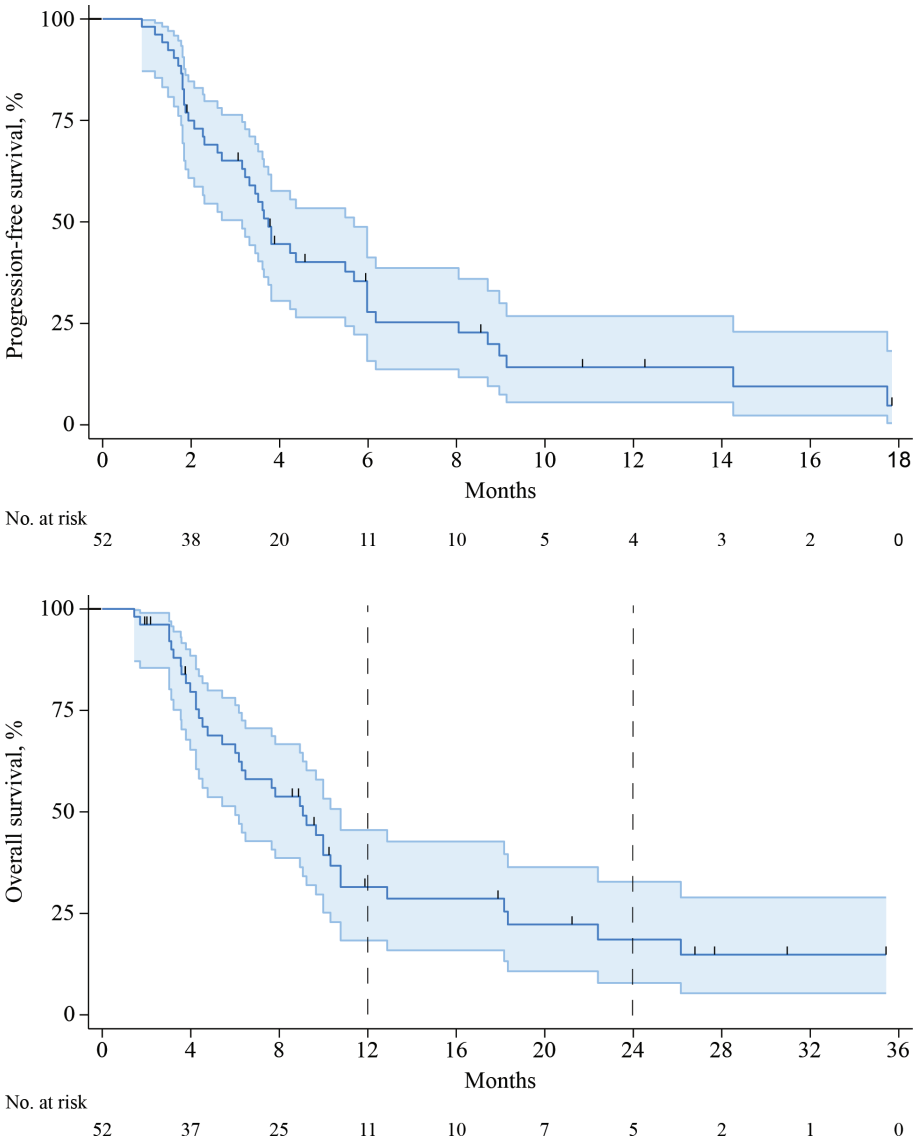

Figure 2. Progression-free survival and overall survival (with 95% CI) of 'response evaluable' patients treated with trametinib monotherapy, *n* = 52. (A) Progression-free survival, (B) Overall survival.

Patients with LGSOC represented the largest subgroup with observed clinical benefit, including both PR and SD. Trametinib monotherapy has been shown to be effective in this patient group in a recurrent setting, regardless of mutational status, although the effect seems to be stronger in those with BRAF/NRAS/KRAS mutations [9]. According to the ESMO guidelines, patients with LGSOC relapse should be considered for treatment with trametinib after platinum failure [17]. This study supports previous findings that this patient group may benefit from trametinib monotherapy. A more detailed analysis of this cohort will be presented in a separate publication.

Patients with metastatic uveal melanoma have limited systemic treatment options. Mutations in GNA11 and GNAQ, which occur in 80–90% of tumours, represent potential molecular targets [18]. A systematic review by Steeb et al. [19] summarises the literature on MEK inhibitors in uveal melanoma. Selumetinib (MEK1/MEK2 inhibitor) was described being the best documented substance, where an effect on PFS was found in a phase II trial [6], but not confirmed in the subsequent phase III- trial [20]. Previous studies on MEK inhibitors have shown only low response rates; however, trametinib remains less well studied [19]. In this study no patients had PR/CR, but several had SD. Metastatic uveal melanoma can follow an indolent course; however, all patients were required to have disease progression before treatment start. Therefore, while part of the disease stabilisation may be due to the indolent nature of metastatic uveal melanoma, a treatment effect cannot be ruled out. The small patient population should also be considered. Thus, these results should be interpreted with caution.

The EANO guidelines recommend testing of NF1 in gliomas, glioneuronal, and neuronal tumours due to the potential efficacy of MEK inhibitors in these patients [21]. This effect was demonstrated in this study, showing both PR and SD in these patients. A more detailed analysis of the CNS patients will be presented in a separate publication.

The overall safety profile of trametinib was, in general, as expected [22]. However, two treatment-related deaths were reported, including one patient with advanced age, and multiple comorbidities, experiencing severe toxicity not previously reported. Out of six reported SUSARs, three were

thromboembolic events, known side effect of trametinib, but still needed to be reported due to regulatory demands. The relatively high treatment toxicity must therefore be balanced against the anticipated benefit, particularly in patients with advanced age and comorbidities.

A limitation of this study is the small number of patients in each biomarker and tumour type. Another limitation is that the two largest groups of patients with effect have tumour biology in which the tumour progression may be slow, potentially influencing the primary endpoint. The strengths of this study include the prospective design and the opportunity to treat and compare results from different types of cancer based on the same molecular target. Furthermore, this trial is conducted in a near real-world setting where heavily pretreated patients with ECOG 0–2 and comorbidities received experimental treatment.

Conclusion

Patients treated with trametinib monotherapy in this biomarker driven study achieved a DCR of 39%, representing a clinically meaningful result in a patient population with no standard treatment options available. However, toxicity profile may be challenging in patients with poor ECOG status and comorbidities. Given these findings, further research is needed to confirm whether this effect persists in a larger cohort and to investigate potential molecular or other predictive factors that may forecast treatment response.

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Conflicts of interest

Katarina Puco: Advisory board or invited speeker: Astellas, Bayer, Bristol-Myers Squibb, Ipsen, MSD, Pfizer, AstraZeneca. Sigmund Brabrand: Invited speaker: Pfizer, Bayer, Ipsen og Astellas. Ingrid Dyvik: Illumina and Roche provided diagnostic tests for research, no personal benefits were received by the author. Egil Blix: Advisory board or invited speaker: AstraZeneca, Daiichi Sankyo, Eli Lilly, Novartis, Pfizer, Roche Åslaug Helland: Research Funding: Roche, AstraZeneca, Novartis, Incyte, Eli Lilly, Bristol-Myers Squibb, Ultimovacs, Merck, GlaxoSmithKline, Illumina, Nanopore, Johnson and Johnson, BeOne. Advisory boards and Honoraria: ABBVIE, Takeda, AstraZeneca, Roche, Pfizer, Janssen, EliLilly, Bristol-Myers Squibb, PierreFabre, Bayer, Merck Sharp & Dome, Novartis, Merck, Sanofi, Medicover. All funds go to Oslo University Hospital. Receipt of honoraria or consultation fees from Astellas, Bayer, Bristol-Myers Squibb, Ipsen, MSD, Pfizer. Participation in a company sponsored speaker's bureau: Bayer, Astellas, AstraZeneca, Ipsen.

Data availability statement

The full clinical dataset consists of de-identified patient-level data obtained from VieDoc. The sponsor and data owner is Oslo University Hospital. Access to full raw patient-level data is limited, but project partners can apply for access through the data and biobank committee of the trial, in accordance with Data Privacy and Ethical Approval for the study project. All authors have full access to complete study data, study analysis performed, tables and figures. The study protocol is available.

Ethics declarations and trial registry information

This study is conducted in accordance with Good Clinical Practice and other relevant research practices, legal requirements and ethical guidelines. The study is approved by the Regional Committees for Medical Research Ethics South East Norway (#200764) and registered at ClinicalTrials.gov (NCT04817956). The study is also approved in CTIS (2023-507894-16-00). Written informed consents were obtained for each patient prior to study inclusion.

Authors' contributions

KSS: Literature review, data analysis, writing the original draft, reviewing and editing the manuscript. KP: Literature review, data analysis, reviewing and editing the manuscript. RSF: Data analysis, statistical analysis, reviewing the manuscript. ID, SB, PN, ESSS, ESB, ÅF, IAO, SM, CFT, HB, KL, AA, SS, KT: Reviewing the manuscript. ÅH: Conceptualisation, study design, methodology, data analysis, project administration, reviewing manuscript.

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ORIGINAL ARTICLE

Targeted therapy in the treatment of lung cancer in Iceland 2010–2023

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ABSTRACT

Background and purpose: Lung cancer is the third most common malignancy in Iceland and remains the leading cause of cancer-related mortality. Lung cancer may harbor driver mutations affecting the function of *Epidermal growth factor receptor (EGFR), Anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1 (ROS1), B-raf proto-oncogene (BRAF), RET proto-oncogene (RET), MET proto-oncogene (MET),* and *NTRK*, which can influence the selection of targeted therapies and treatment outcomes. In Iceland, *EGFR* testing was initiated in 2005, and in 2016, multigene targeted panel became standard for tumor testing. The objective was to determine the uptake of testing and frequency of targeted mutations in lung cancer nationwide, the utilization of targeted therapies, and duration of such treatments.

Patients/material and methods: Data on lung cancer diagnoses and stage at diagnosis were obtained from the Icelandic Cancer Registry, and molecular testing results were retrieved from the Department of Pathology at Landspitali University Hospital. Treatment data and outcomes were obtained from a central prescription/death registry and chart reviews.

Results: From 2010 to 2023, 2,528 patients were diagnosed with lung cancer, and 25% underwent molecular tumor testing, with 90% of stage IV adenocarcinomas tested in 2023. During comprehensive molecular testing in 2016–2023, targeted mutations were detected in 19.3% of tested patients: *EGFR* 9.9%, *BRAF* 2.3%, *MET* 2.7%, *HER2* 1.2%, *ALK* 2.7%, *ROS1* 0.6%, and *RET* 0.2%. Among patients found to have targeted mutations (2010–2023), 61.2% received targeted therapy; 33.8% remained on therapy for ≥ 12 months, and 13.5% for ≥ 24 months.

Interpretation: The use of molecular testing has increased significantly in the last 20 years, and the adaptation of new targeted therapies has been rapid.

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Nonsmall cell lung cancer; next-generation sequencing; precision medicine; epidermal growth factor receptor (EGFR); real-world data

Introduction/Background

Lung cancer remains the leading cause of cancer-related death worldwide and in Iceland [1]. Although the incidence of lung cancer has declined in recent decades due to reduced smoking rates, it continues to represent a major public health burden. In Iceland, lung cancer is the second most common cancer among females and the fourth most common among males, with an average age at diagnosis of 68 years. Smoking rates have decreased significantly in Iceland in the last 30–40 years; in 1991, 31.2% of people in Iceland aged 18–89 smoked daily, compared to 5.7% in 2023 [2, 3].

Over the past two decades, major advances in the molecular understanding of non–small cell lung cancer (NSCLC) have led to the introduction of targeted therapies directed against specific driver mutations such as *EGFR*, B-raf proto-oncogene (*BRAF*), erb-b2 receptor tyrosine kinase (*HER2), KRAS*, MET proto-oncogene. (*MET)*, and RET proto-oncogene. (*RET)* [4]. Adenocarcinomas can harbor oncogenic driver mutations that are more commonly seen in females and nonsmokers, whereas squamous cell carcinomas are more strongly associated with smoking and have fewer targetable mutations [5]. EGFR inhibitors were the first targeted therapy, introduced in the early 2000s [6].

At Landspitali University Hospital, molecular testing of lung cancer samples was first implemented in 2005 using Sanger sequencing on selected *EGFR* exons (see Supplementary Figure 1). In 2014, this method was replaced by Quantitative Polymerase Chain Reaction (qPCR), and by 2016, the TruSight Tumor 15 panel enabled the detection of mutations in 15 cancer-related genes, including *EGFR*, *BRAF*, *HER2, KRAS*, *MET*, *PIK3CA*, and *RET* [7]. Staining for ALK and ROS1 was also implemented in 2016. The TruSight Oncology 500 panel was introduced in 2019, detecting mutations in 523 genes, as well as assessment of microsatellite instability and tumor mutational burden [8]. In 2021, the Archer LungFusionPlex panel was implemented to

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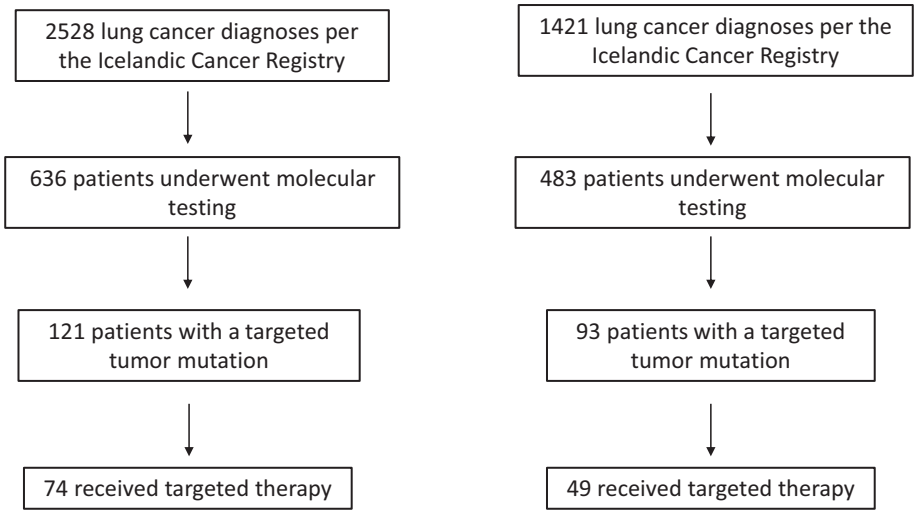

Figure 1. Flowchart for patient selection. Left panel showing testing in 2010–2023, EGFR testing (2010–2023) and multigene panel sequencing (2016–2023). Right panel showing testing in 2016–2023 when multigene panel sequencing was performed.

identify gene fusions across 14 genes [9], and if ALK or ROS1 staining was positive, the samples underwent FISH testing. Since 2023, the VariantPlex Expanded Solid Tumor panel has been used, identifying a wide range of genomic alterations across 76 genes [10].

This rapid evolution of molecular tests has been a key driver of therapeutic advances in NSCLC, improving outcomes not only for patients with advanced-stage disease but also for those with limited-stage tumors [4]. Molecular testing has therefore become an essential part of NSCLC management, guiding treatment decisions and improving survival. The implementation and evolution of molecular testing and targeted therapy in NSCLC in Iceland have not been described before, and it is important to have high coverage of molecular testing for patients. EGFR testing has now been performed for two decades and multigene panel testing for almost a decade, and as all testing is centralized, real-world data analysis are easily accessible.

The aim of this study was to determine the frequency of targeted driver mutations and gene rearrangements in lung adenocarcinoma samples in Iceland from 2010 to 2023, to assess the proportion of patients who received targeted therapy, and to evaluate the duration of these treatments.

Patients/materials and methods

This was a retrospective, population-based cohort study with approval from the central institutional review board (VSN 22-016). All patients diagnosed with NSCLC in Iceland between January 1, 2010 and December 31, 2023 were identified through the Icelandic Cancer Registry**,** which contains comprehensive data on all cancer diagnoses with > 99% accuracy [11]. Information on disease stage at diagnosis was available for cases diagnosed from 2019 to 2023.

Results of molecular testing performed between 2010 and 2023 were retrieved from the Department of Pathology, Landspitali University Hospital, where all molecular analyses for lung cancer in Iceland are centralized (see Figure 1). *EGFR* mutation results were available for the whole period, and from 2016, multiple genes were analyzed for mutations after implementation of multigene next-generation sequencing (NGS) panels; in 2016, the TruSight Tumor 15 (TST15) panel was implemented; in 2019, the TruSight Oncology 500 (TSO500, Illumina, implemented for clinical samples in collaboration with deCODE genetics); in 2021, the ArcherFUSIONPlexLung (IDT); and in 2023, the ArcherVARIANTPlexExpanded Solid Tumor (IDT). With these, mutational testing expanded to include additional actionable genes such as *BRAF, HER2, KRAS, MET, RET, ROS1*, and *NTRK*. For this period (2016–2023), the prevalence of various driver mutations was analyzed, including the distribution of *KRAS* subtypes. The ratio of lung cancer samples that underwent molecular testing each year was analyzed for three groups: all lung cancer cases, adenocarcinoma cases, and stage IV adenocarcinoma cases from 2019 to 2023.

Prescription data on targeted therapies were obtained from the Prescription Medicines Registry, while the cause of death was retrieved from the Causes of Death Registry. Medical records from Landspitali (where 80–90% of patients are treated), as well as Sjukrahusid, Akureyri and Heilbrigdisstofnun Sudurlands hospitals, were reviewed to determine the initiation and duration of targeted therapy.

The primary endpoint was the frequency of actionable driver mutations or gene rearrangements in NSCLC in Iceland. Secondary endpoints included the proportion of patients with a targetable mutation who received targeted therapy and the proportion of treated patients who remained on targeted therapy for ≥ 1 and ≥ 2 years. Statistical analyses were performed using R software (version 4.3.2; R Foundation for Statistical Computing, Vienna, Austria). The software was used for data management, descriptive statistics, and graphical visualization.

Results

Molecular testing

Of 2,528 patients diagnosed with lung cancer in 2010–2023, 636 (25.2%) underwent molecular testing. Patient characteristics are

Table 1. Patient characteristics in the overall group and comparing patients who underwent molecular tumor testing versus those who did not.

	Tested	Not tested	All
	n = 636 (25%)	*n* = 1,892 (75%)	*n* = 2,528
Age, mean (SD), years	68 (±9.8)	71 (±10.6)	70 (±10.4)
Sex			
Females	375 (59%)	999 (53%)	1,374 (54.4%)
Males	261 (41%)	893 (47%)	1,154 (45.6%)
Histology			
Adenocarcinoma	516 (81%)	579 (30.6%)	1,095 (43.3%)
Squamous cell carcinoma	21 (3.3%)	381 (20.1%)	402 (15.9%)
Small cell carcinoma	2 (0.3%)	323 (17.1%)	325 (12.9%)
Other histologies	97 (15.3%)	609 (32.2%)	706 (27.9%)
Diagnosed in			
2010–2014	117 (18.4%)	789 (41.7%)	906 (35.8%)
2015–2019	198 (31.1%)	689 (36.4%)	887 (35.1%)
2020–2023	321 (50.5%)	414 (21.9%)	735 (29.1%)

SD: standard deviation.

shown in Table 1. The ratio of all lung cancer samples that underwent molecular testing rose from 5.8% in 2010 to 59% in 2023. The ratio of lung adenocarcinoma samples that underwent molecular testing was 13.9% in 2010, 50.7% in 2017, and 83.8% in 2023. Among those diagnosed with stage IV lung adenocarcinoma, 41.2% of lung samples underwent molecular testing in 2019, and in 2023, it had reached up to 89.8% (see Figure 2).

Targeted mutations and therapy

During the study period, the frequency of *EGFR* mutations among lung samples that underwent molecular testing was 11.8% (75/636). The distribution of *EGFR* mutations can be seen in Supplementary Figure 2, with almost half carrying exon 19 deletions. From 2016 to 2023, samples from 483 patients underwent molecular testing, and among those, 19.3% (93/483) had a targetable mutation, where *EGFR* mutations had the highest frequency by far. In *KRAS*, a driver gene frequently mutated in lung cancer and an emerging drug target, the most common mutation was G12Cys. The distribution of mutations in *KRAS* can be seen in Supplementary Figure 2. *KRAS* targeted therapy is not yet standard of care in Iceland.

Overall, there were 121 patient samples that were found to have a targetable mutation during the whole study period, 2010–2023 (see Table 2). Among those, 57% (69/121) had *EGFR* mutations, 14% (17/121) had *ALK* translocation, 2.5% (3/121) had *ROS1* translocation, 9.9% (12/121) had *BRAF* V600E mutation, 5.8% (7/121) had *HER2* mutation, 0.8% (1/121) had *RET* mutation, and 11.6% (14/121) had *MET* translocation. No *NTRK* fusions were found. Among those 121 patients, 61.2% (74/121) were treated with targeted therapy; all treated patients had advanced disease.

Targeted therapy uptake varied among different molecular alterations; among patients with *EGFR*-positive tumor, 69.6% (48/69) received targeted therapy, while 82.4% (14/17) of those with *ALK* translocation received therapy. These were followed by 33.3% (1/3) with *ROS1* translocation, 33.3% (4/12) with *BRAF* V600E mutation, and 42.9% (3/7) with *HER2* mutations. The only patient harboring a *RET* translocation received targeted therapy, and 21.4% (3/14) with translocation in the *MET* gene received targeted therapy. The reason that the remaining 32% did not receive targeted therapy was attributed to several factors, such as localized disease at diagnosis, selection of alternative therapy, unavailability of targeted therapy at the time, or death. Among patients who received targeted therapy, 33.8% (25/74) continued therapy for at least 1 year and 13.5% (10/74) for at least 2 years (see Figure 3). The reasons for treatment termination were disease progression, adverse events, or death.

Specifically for the last 5 years of the study period 2019–2023, where data on tumor staging are available, 200 patients were diagnosed with stage IV lung adenocarcinoma in Iceland. The proportion of patients who underwent molecular testing was 71% (142/200), 24.6% (35/142) had targetable mutations, and of those, 74.3% (26/35) received targeted therapy. Nine patients did not receive targeted therapy as they went on palliative therapy (*n* = 5), targeted therapy was not available (*n* = 2), they refused therapy (*n* = 1), or they had not progressed on current therapy (*n* = 1). Among patients harboring *EGFR* mutation, 88.9% (16/18) received targeted therapy, 75% (3/4) with *ALK* translocation, 0% (0/1) with *ROS1* translocation, 100% (2/2) with *BRAF* V600E mutation, 60% (3/5) with *HER2* mutation, 25% (1/4) with *MET* translocation, and 100% (1/1) with *RET* mutation.

Discussion and conclusions

In this study, we show that molecular testing on lung cancer samples has increased dramatically over the past 15 years. In the last 5 years, where data are available specifically for stage IV cancers, 90% underwent molecular testing while the clinical objective is to offer comprehensive molecular analysis for all patients diagnosed with lung adenocarcinoma in Iceland. As driver mutations and gene rearrangements in certain genes can influence treatment choices in advanced lung adenocarcinoma, it is crucial that molecular testing is offered to all patients.

Targeted *EGFR* mutational analysis was first recommended in US guidelines in 2010 and in European guidelines in 2011 for never/former light smokers and tumor with non-squamous histology [12]. In 2013, an evidence-based guideline was

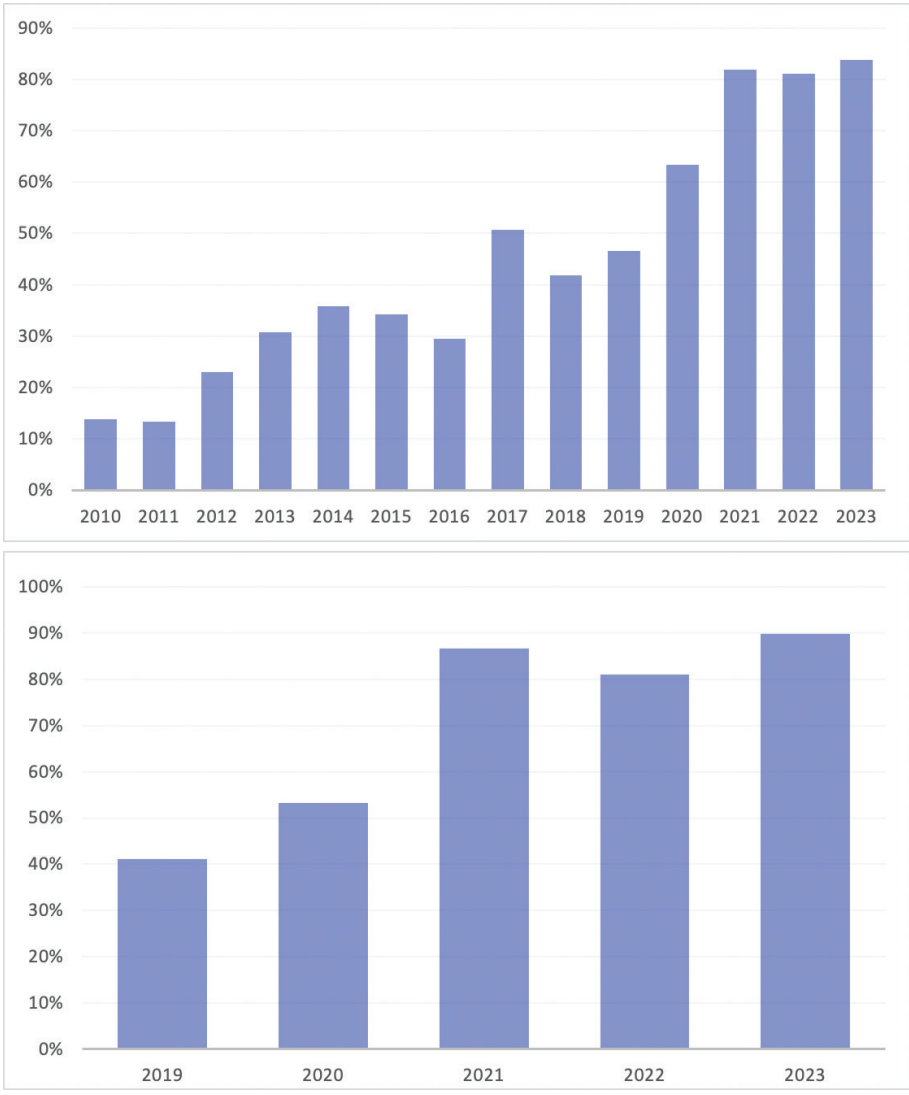

Figure 2. Proportion with molecular testing results examining all adenocarcinoma of the lung (n = 1,229) in 2010–2023 (upper panel) and stage IV adenocarcinoma of the lung (n = 200) in 2019–2023 (lower panel).

published by the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology recommending *EGFR* and *ALK* testing in all advanced NSCLC with an adenocarcinoma component [13]. The guidelines were updated in 2018 to include *ROS1* and *HER2*, *MET*, *BRAF*, *KRAS*, and *RET* testing in laboratories with NGS capabilities [14]. Clinical molecular testing practice in Iceland has followed and at times preceded clinical guideline recommendations.

This rapid increase in molecular testing of lung samples parallels the advancement of targeted therapy development. The driver gene most commonly mutated is *EGFR*, with around 12% of patients testing positive, which is similar to numbers from European cohorts [15]. About half of patients carry an exon 19 deletion. EGFR inhibitors were first approved for treatment of advanced disease around 2004–2005 [16, 17]. Osimertinib was approved as adjuvant therapy for limited disease in Europe in 2021 [18], and as a result, it is important to test all NSCLC cases upfront, and testing of all NSCLC adenocarcinoma cases was implemented in Iceland in year 2021. The proportion of stage IV lung adenocarcinoma samples undergoing molecular testing in Iceland between 2019 and 2023 was similar to that reported in a comparable study from the United States, where 81% of patients with metastatic NSCLC underwent *EGFR* testing [15] and higher than in a Norwegian study where >64% underwent testing in 2017 [19].

Table 2. Proportion of patients with targeted mutations in 2010–2023 receiving targeted therapy.

	EGFR	ALK	ROS1	BRAF	HER2	RET	MET	Total
Targeted mutation	69/636 (10.8%)	17/636 (2.7%)	3/636 (0.9%)	12/636 (1.9%)	7/636 (1.1%)	1/636 (0.16%)	14/636 (2.2%)	121/636 (19%)
Targeted therapy	48/69 (69.6%)	14/17 (82.4%)	1/3 (33.3%)	4/12 (33.3%)	3/7 (42.9%)	1 (100%)	3/14 (21.4%)	74/121 (61.2%)

EGFR: epidermal growth factor receptor; ALK: Anaplastic lymphoma kinase; ROS1: ROS proto-oncogene 1; BRAF: B-raf proto-oncogene; HER2: erb-b2 receptor tyrosine kinase; RET: RET proto-oncogene; MET: MET proto-oncogene.

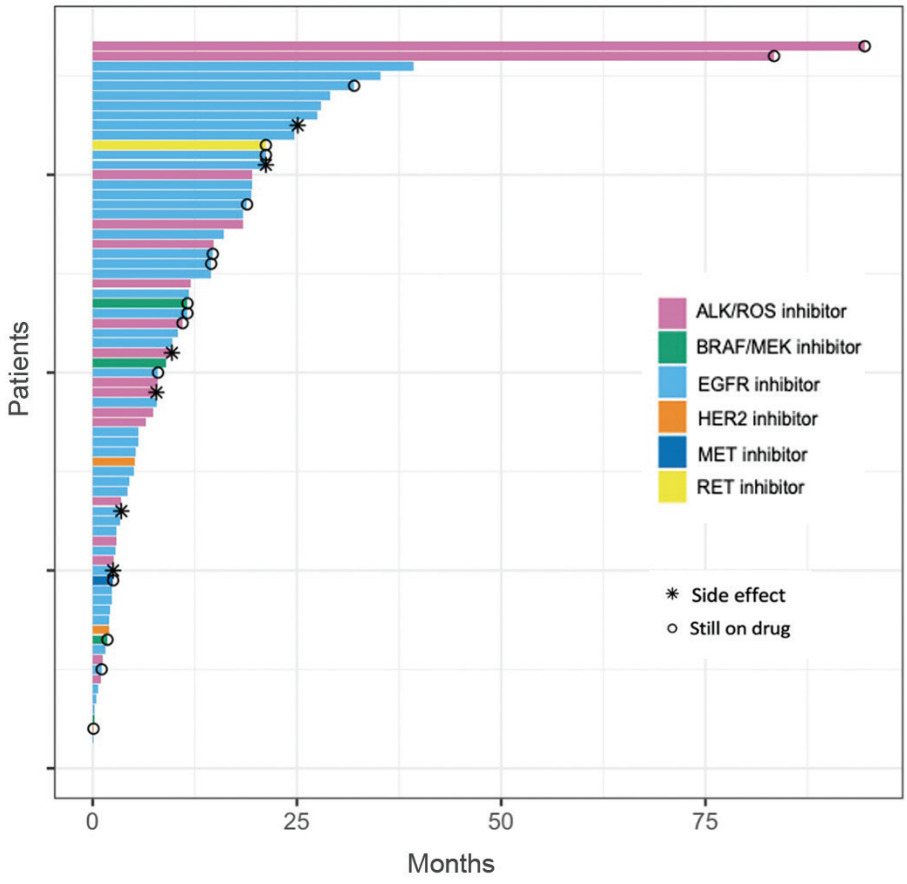

Figure 3. Duration of treatment in months for patients who received targeted therapy 2010–2023 ($n = 74$).

In the last decade, several other targetable gene mutations and gene rearrangements have been identified. *ALK/ROS1* inhibitors were approved for advanced disease driven by *ALK* in the early 2010s [20] and *ROS1* rearrangements around 2016 [21]. Before 2016, testing of targetable mutations was restricted to the *EGFR* gene, and in 2016, 29.5% of lung adenocarcinoma samples, regardless of stage, underwent molecular testing. In the same year, the TST15 sequencing panel was introduced, which detects mutations in 15 genes, including *EGFR*, *KRAS*, *BRAF*, and *HER2*. In 2017, the proportion of samples submitted to sequencing analysis had gone up to 50.7%, and in 2023, 83.8% of lung adenocarcinoma samples underwent molecular testing. In the last 3–5 years, treatments for *BRAF*-driven, *HER2*-driven, *RET*, and *MET*-driven NSCLC have all been approved and adopted, further expanding the armamentarium for this cancer. During the study period, the ratio of patients receiving targeted therapies with targeted mutations has increased. Of the 49 patients diagnosed with stage IV lung adenocarcinoma in 2023, 89.8% (44/49) underwent molecular testing, 18.2% (8/44) had a targeted mutation, and of those, 75% (6/8) received targeted therapy. This is a significant increase compared to 2019, when 34 patients were diagnosed with stage IV lung adenocarcinoma, 41.2% (14/34) underwent molecular testing, 35.7% (5/14) had a targetable mutation, and 100% (5/5) received targeted therapy. A study from Norway found that >85% of patients with EGFR mutations went on targeted therapy in 2010–2017, exhibiting a higher proportion treated [19]. In 2023, patients with stage I–IV lung adenocarcinoma were 99 in Iceland, and 83.8% (83/99) underwent molecular testing. Furthermore in our study, 34% of patients remained on therapy at 1 year [23], which is lower than in the FLAURA first-line trial studying EGFR inhibitors, where 70% remained on osimertinib and 47% remained on a comparator EGFR inhibitor at 1 year. Our study looked at multiple targeted therapies, and therefore, a direct comparison is not possible, but it is not surprising that real-world data show inferior efficacy in comparison with clinical trial data.

Ongoing research continues, and the number of potential therapeutic agents is likely to increase in the future. *KRAS* G12C inhibitors have been approved in the US, and sotorasib received conditional authorization by the EMA, but overall survival benefit is not yet clear [22], and this treatment has not been adopted in the Nordic countries.

The main strength of this study is that this is a population-based study based on comprehensive data from a nationwide cohort. Since molecular analyses are only performed centrally at Landspitali, it is unlikely that any tests performed on patients diagnosed in Iceland were missed. As targeted therapies are given orally, data from the prescription drug registry can easily be accessed and covers the whole country, including treatments prescribed in smaller hospitals.

The main weakness of the study is that there was no comprehensive staging information for the entire study period, and therefore we can only report on stage IV patients for the 2019–2023 period, which are the patients where molecular

testing is critical and targeted therapy appropriately applied. Also, we did not have information on whether targeted therapy was given in the first line or subsequent lines of therapy, and we do not have information on the administration of cytotoxic therapy or immune checkpoint inhibitor therapy.

Targeted drugs were in continuous development during the study period, and new drugs became available for new targets during the period. Therefore, the treatment options are not the same each year of the study. This affected the proportion of those with a targeted mutation who received targeted therapy. Diagnostic technology also changed during the period, initially testing for single gene mutations and then moving to multigene panels. Similar developments occurred in other countries as molecular testing advanced. There are also certain limitations associated with retrospective studies as they are based on past events and older data that were not originally collected for research purposes.

In summary, we conclude that the central testing structure in Iceland has led to high NSCLC testing rates, and adaptation of new targeted therapies has been rapid.

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Disclosure statements

The authors report there are no competing interests to declare.

Data availability statement

The de-identified data that support the findings of this study are available on request from the corresponding author.

Ethics declarations & trial registry information

The Icelandic National Bioethics Committee (VSN22-016) approved this study.

Author contributions

SH, RBB, and BH designed this study. ST, GVS, HB, TG, RBB, and BH worked on data collection. ST, BH, and SH worked on data analysis, and all authors worked on data interpretation. ST and SH drafted the manuscript. All authors reviewed, edited, and approved the final manuscript.

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ORIGINAL ARTICLE

Outcome of resectable distal cholangiocarcinoma in a single-centre Western patient cohort: comparison of the 7th and 8th edition of the UICC/AJCC TNM classification

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ABSTRACT

Background and purpose: Distal cholangiocarcinoma (CCA) is a rare malignancy with poor prognosis, even after surgical resection. Accurate staging is essential for guiding treatment and predicting outcomes. The 8th edition of the Union for International Cancer Control (UICC)/The American Joint Committee on Cancer (AJCC) TNM classification introduced depth of tumour invasion (DOI) as the criterion for T-staging (T1–T3) and a three-tiered lymph node (N) classification. This study evaluates patient stratification and prognostic accuracy of the 8th versus 7th edition in a single-centre Western cohort and discusses difficulties with measuring DOI.

Patient/material and methods: Patients undergoing pancreatoduodenectomy for distal CCA at Oslo University Hospital (2015–2021) were retrospectively analysed. Tumours were restaged according to the 7th and 8th TNM editions. Survival was assessed using Kaplan–Meier estimates and log-rank tests to compare prognostic accuracy.

Results: Seventy-one patients were included. Using the 7th edition, most cancers (94.4%, 67 patients) were categorised as T3. With the 8th edition, stage redistribution was notable: T2 included 45 patients (63.4%) and T3 included 22 (31.0%). Five-year survival was significantly better for T2 (31.8%) than T3 (10.5%) according to the 8th edition, demonstrating improved discrimination. The revised N classification provided better prognostic distinction, with median survival of 30 months for N1 (1–3 nodes) and 23 months for N2 (≥4 nodes).

Interpretation: The 8th edition provides more accurate prognostic stratification of distal CCA compared to the 7th edition but requires meticulous, standardised pathology assessment to ensure accurate prognosis and appropriate post-surgical management.

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KEYWORDS
Distal cholangiocarcinoma; TNM classification; depth of invasion; prognostic stratification

Introduction

Cholangiocarcinoma (CCA) is classified based on the tumour site as intrahepatic, perihilar, and distal; distal CCA accounts for approximately 30% – 40% of the cases [1, 2]. Surgery remains the primary treatment for resectable distal CCA, but even following complete tumour removal, overall survival remains poor [3]. In a recent Western cohort of distal CCA, the median overall survival was 21.9 months following surgery [4]. Systemic treatment results in limited survival benefit, and many patients do not receive adjuvant chemotherapy [4–6]. According to the National Comprehensive Cancer Network® (NCCN) guidelines, observation may be considered after margin-negative and node-negative resections. In contrast, systemic therapy is recommended for patients with margin or regional lymph node involvement [3].

Continuously striving to improve cancer staging, the TNM classification for distal CCA has undergone multiple revisions (Table 1). In 2017, the 8th edition of the TNM classification introduced a new T-staging criterion based on the measurement of the depth of tumour invasion (DOI) with the following threshold: less than 5 mm (T1), 5–12 mm (T2), and > 12 mm (T3) [7, 8]. DOI thus replaced *tumour extent*, which had been the T-staging criterion in the 7th edition. An important reason for this revision was the difficulty with clearly delineating the bile duct wall from the surrounding adjacent pancreas, as the extrahepatic biliary tree lacks a continuous muscle layer, and discrete tissue boundaries may be effaced by inflammatory changes or desmoplastic stromal reaction to invasive cancer [9, 10]. Furthermore, the lymph node classification was also revised in the 8th edition with the introduction of distinct

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N-categories for 1–3 regional lymph node metastases (N1) and metastasis in ≥4 regional lymph nodes (N2) (Table 1). These changes aimed to improve both staging accuracy and prognostic stratification in distal CCA.

Moon et al. paved the way for the new staging system, validating an alternative staging system that closely resembled the 8th edition TNM classification [11]. Two subsequent studies demonstrated the improved prognostic stratification of the 8th edition in Asian cohorts [12, 13]. However, one study [13] reported that DOI was unmeasurable in over 50% of cases, highlighting difficulties in pathology assessment. Indeed, little attention has been paid to the practical execution of the pathology assessment, both by the AJCC/UICC and by national pathology guidelines [14, 15]. This lack of guidance bears the risk of divergent approaches and, consequently, considerable variation among pathology departments. Similar challenges have also been noted in other aspects of pathology examination, including differentiating distal CCA from other periampullary adenocarcinomas [16, 17] and determining margin status, with reported R0 rates for distal CCA ranging from 50% to 90% [18–20]. The lack of standardised pathology assessment, combined with the fact that the updated TNM classification has not been validated in a Western population, highlights the need for further validation. Furthermore, large consensus statements show variation in incidence and mortality between Eastern and Western populations, which are largely attributed to differences in environmental exposures and potentially also to genetic variation [21].

This study aims to compare prognostic stratification and survival prediction according to the 7th versus 8th editions of the AJCC/UICC TNM classification in a single-centre Western cohort of patients with distal CCA. In addition, the study seeks to identify the challenges associated with measurement of DOI in pancreatoduodenectomy (PD) specimens, highlighting the need for standardised pathology assessment. The manuscript was completed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [22].

Patients/material and methods

All patients who underwent pancreatoduodenectomy for histologically confirmed distal CCA at Oslo University Hospital between January 2015 and December 2021 were eligible for inclusion. A multidisciplinary team evaluated all patients before referring them for surgery. Pancreatoduodenectomy with standard lymphadenectomy was performed [23]. No changes in perioperative management were done throughout the study period. Patients with other periampullary or pancreatic head malignancies were excluded. Eligible patients were identified from the institutional surgical database. Follow-up information was obtained from hospital medical records. All patients were followed for a minimum of 2 years, with the last follow-up performed on December 31, 2023. The local hospital data protection officer approved the study, and waived the need for informed consent (case number 2015-13400).

The primary outcome was overall survival (OS), defined as the interval between surgery and death or last follow-up. Exposures of interest included T-stage and N-stage according to the AJCC/UICC 7th and 8th edition TNM classifications. Additional predictors assessed included tumour size, tumour location (intra- vs. extrapancreatic bile duct), resection margin status (R0 vs. R1, with ≤1 mm considered involved), vascular-, lymphatic- and perineural invasion, and severe postoperative complications (Clavien–Dindo grade ≥3a) [24].

Pathology assessment

All specimens had been evaluated by an experienced pancreas pathologist (C.V.), and were retrospectively reclassified

Table 1. Comparing 7th and 8th ed. UICC/AJCC TNM classification and clinical stages.

Category	7th edition	8th edition
Tis	Carcinoma *in situ*	Carcinoma *in situ*/high-grade dysplasia
T1	Tumour confined to the bile duct histologically	T1: DOI ≤ 5 mm
T2	Tumour invades beyond the wall of the bile duct	T2: DOI > 5 mm and ≤ 12
T3	Tumour invades the gallbladder, pancreas, duodenum, or other adjacent organs without involving the celiac axis or the superior mesenteric artery	T3: DOI > 12 mm
T4	Tumour involves the coeliac axis or the superior mesenteric artery	Tumour involves the celiac axis, superior mesenteric artery, and/or common hepatic artery
N0	N0: No regional lymph node metastasis	N0: No regional lymph node metastasis
N1	N1: Regional lymph node metastasis	N1: 1–3 regional lymph node metastases
N2	Not defined	N2: ≥ 4 regional lymph node metastases
Stage	7th edition	8th edition
Stage 0	Tis N0M0	Tis N0M0
Stage 1	Stage 1A: T1N0M0, Stage 1B: T2N0M0	T1N0M0
Stage 2a	T3N0M0	T1N1M0 or T2N0M0
Stage 2b	T1-3N1M0	T2N1M0 or T3N0M0 or T3N1M0
Stage 3a	Stage 3: T4, any N, M0	T1N2M0 or T2N2M0 or T3N2M0
Stage 3b		T4N0M0 or T4N1M0 or T4N2M0
Stage 4	Any T, any N, M1	Any T, any N, M1

according to the AJCC/UICC TNM 7th (2015–2017) and 8th edition (2018–2021) by two experienced pancreas pathologists (C.V., M.B.), who were blinded to the original pathology reports and each other's reviews. All specimens were examined using the same standardised protocols for macroscopic examination and pathology reporting during the entire inclusion period. Standardised specimen dissection was based on serial axial slicing at 3 mm intervals after multicolour-coded inking of the specimens' surfaces, as previously described [25, 26] and recommended by (inter-)national guidelines [15, 27]. The standardised protocol also included detailed photographic documentation and extensive tissue sampling, including complete embedding of the entire common bile duct (CBD), en bloc with the nearest specimen surfaces. In addition to the transection margins of the pancreatic neck, CBD, stomach, and/or duodenum, all circumferential margins (posterior, superior mesenteric vein [SMV], superior mesenteric artery [SMA]) were thoroughly evaluated based on a 1 mm clearance. Of note, the circumferential margin of the extrapancreatic CBD was also included in the evaluation (1 mm clearance). Moreover, the anterior surface was evaluated based on 0 mm clearance.

The DOI was assessed in all tissue sections with a proper cross-section of the CBD to identify the maximum DOI in each case. Measurements were taken from the most superficial part of the tumour to the deepest point of invasion (Figure 1).

Table 2. Demographics and perioperative data in patients undergoing pancreatoduodenectomy for distal bile duct cancer.

Parameters	*n* = 71
Age, years, mean (SD)	69.7 (7.8)
Gender, *n* (%)	
Female	30 (42.3%)
Male	41 (57.7%)
Body mass index, kg/m^2, mean (SD)	25.9 (3.2)
Presence of comorbidity, *n* (%)	57 (80.3%)
Hypertension, *n* (%)	37 (52.1%)
Cardiovascular disease, (%)	19 (26.8%)
Diabetes mellitus, *n* (%)	12 (16.9%)
Total number of comorbidities, median (range)	2 (0–7)
ASA score, *n* (%)	
II	37 (52.1%)
III	34 (47.9%)
Preoperative Ca 19-9, U/mL, median (range)	74 (5–1,102)
Preoperative serum bilirubin level, µmol/L, median (range)	28 (3–469)
Preoperative biliary stent, *n* (%)	53 (74.6%)
Pylorus-preserving procedure, *n* (%)	62 (87.3%)
Vascular reconstruction, *n* (%)	6 (8.5%)
Operative time, min, mean (SD)	336 (73)
Morbidity, *n* (%)	48 (67.6%)
Severe morbidity, *n* (%)	29 (40.8%)
Reoperation, *n* (%)	17 (23.9%)
90-day mortality, *n* (%)	4 (5.6%)
Postoperative stay, days, median (range)	9 (5–86)

Statistical analysis

Continuous data are presented as means (standard deviation [SD]) or medians (range), depending on their distribution, while categorical data are presented as frequencies (percentages). Associations between study parameters and survival outcomes were analysed using the log-rank test, and Kaplan-Meier survival curves were generated. Survival was expressed as median with a 95% confidence interval (CI). A *p*-value of <0.05 was considered statistically significant. Uni- and multivariable Cox regression analyses of prognostic factors for survival were performed. Proportional hazard assumptions were tested by checking on time dependence (time varying covariates) demonstrating the constant effect of the variables on survival over time. Data analyses were performed using Statistical Package for the Social Sciences (SPSS) software (IBM SPSS Statistics, version 18.0).

Results

A total of 745 PDs were performed during the study period. Of these, 674 patients were excluded due to diagnoses other than distal CCA. Hence, 71 patients (9.5%) were included in the analysis. Patient demographics and perioperative details are summarised in Table 2. A preoperative biliary stent was placed in 53 patients (74.6%). Pylorus-preserving PD was the most performed surgical procedure (87.3%). Severe morbidity occurred in 29 patients (40.8%), and the 90-day mortality rate was 5.6% (4 patients).

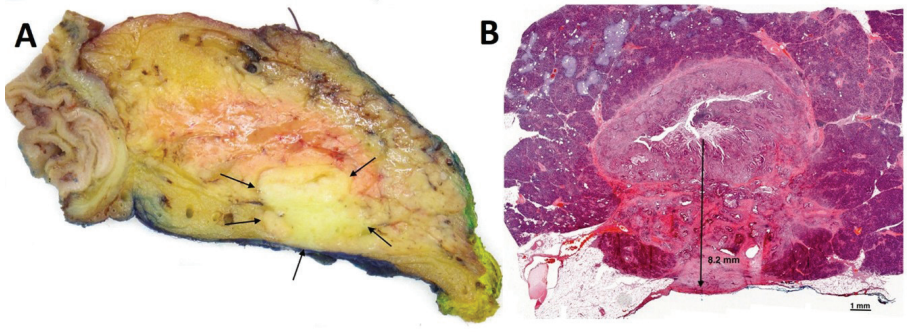

Figure 1. Depth of tumour invasion measured from the luminal surface of the tumour. (a) Axial slice through Whipple specimen (viewed from below, corresponding to CT view). The specimen shows carcinoma of the common bile duct with infiltration into surrounding pancreatic parenchyma(arrows), close to the posterior specimen surface (inked blue), resulting in a slit-like narrowing of the bile duct lumen. (b) H&E section showing maximum depth of tumour invasion (8.2 mm).

Pathology findings

Mean tumour size was 28.1 mm. In 34 patients (47.9%), the cancer involved both the intra- and extrapancreatic parts of the CBD. In 33 patients (46.5%), it was confined to the intrapancreatic CBD while in four patients (5.6%), the tumour was limited to the extrapancreatic portion (Table 3). Using the 7th edition of TNM classification, most cancers (94.4%, 67 patients) were categorised as T3. In contrast, when applying the 8th edition, T2 and T3 accounted for 45 patients (63.4%) and 22 patients (31.0%), respectively. In seven of the 71 cases (10.0%), tangential sectioning rendered measuring of DOI difficult. Lymph node involvement was frequent; according to the 7th edition, 56 patients (78.9%) were classified as N1, while application of the 8th edition criteria resulted in 28 patients (39.4%) being classified as N1 and 28 patients (39.4%) as N2. A high rate of microscopic margin involvement (71.8%) was observed; the three most frequently involved margins were those towards the SMV (36.6%), SMA (33.8%), and the circumferential resection margin of the extrapancreatic CBD (25.4%). Table 4 and Figure 2 illustrate redistribution between the 7th and 8th editions. According to the 7th edition, 56 patients (78.8%) were clinical stage IIB, whereas in the 8th edition, about half of these patients were shifted to clinical stage IIIA (Figure 2).

Table 3. Pathology findings.

Parameters	*n* = 71
Tumour localisation, *n* (%)	
Intrapancreatic	33 (46.5%)
Extrapancreatic	4 (5.6%)
Intra- and extrapancreatic	34 (47.9%)
Tumour size, mm, mean (SD)	28.1 (7.5)
T stage (7th edition)	
T2	4 (5.6%)
T3	67 (94.4%)
T stage (8th edition)	
T1	4 (5.6%)
T2	45 (63.4%)
T3	22 (31%)
Lymph node yield, mean (SD)	18 (6)
Positive lymph nodes, mean (SD)	3 (3)
Lymph node ratio, mean (SD)	16.6 (1.6)
N stage (7th edition)	
N0	15 (21.1%)
N1	56 (78.9%)
N stage (8th edition)	
N0	15 (21.1%)
N1	28 (39.4%)
N2	28 (39.4%)
Grade of differentiation, *n* (%)	
Well	8 (11.3%)
Moderate	28 (39.4%)
Poor	35 (49.3%)
Lymphatic vessel invasion, *n* (%)	59 (83.1%)
Vascular invasion, *n* (%)	39 (54.9%)
Perineural invasion, *n* (%)	66 (93%)
Margin status, *n* (%)	
R0	20 (28.2%)
R1	51 (71.8%)
Positive margins and surfaces, *n* (%)	
Anterior	2 (2.8%)
Posterior	20 (28.2%)
Pancreatic transection margin	9 (12.7%)
Duodenum/stomach	0 (0%)
Bile duct transection margin	7 (9.9%)
Bile duct circumferential margin†	18 (25.4%)
SMV	26 (36.6%)
SMA	24 (33.8%)
Venous resection margin	1 (1.4%)

Survival for T- and N-categories and clinical stages according to 7th and 8th editions

Supplementary Figures S1, S2, and S3 show survival outcomes based on the 7th and 8th editions of the TNM classification. Survival differed significantly for patients classified as T3 with the median survival being 27 months (95% CI: 20.1–33.9) according to the 7th edition compared to 23 months (95% CI: 16.6–29.4) for the 8th edition (Figure S1). For N-classification, median survival was 51 months for N0, 30 months (95% CI: 18.6–41.5) for N1 and 23 months (95% CI: 19.3–26.7) for N2, with the difference between pN0 and pN2 reaching statistical significance (p = 0.019, Figure S2). Regarding the overall TNM-stage (Figure S3), significant differences in median survival were observed between clinical stage IIA (7th edition, 32 months) and clinical stage IIIA (8th edition, 23 months, p = 0.048). Finally, survival differed significantly also between clinical stage IIA and stage IIIA (both 8th edition), with a median survival that was not reached and 23 months, respectively (p = 0.021). No significant survival difference was observed based on tumour location (intrapancreatic: 38 months vs. intra- and extrapancreatic: 24 months, p = 0.12, Figure S4). Independent predictors of poor survival included venous invasion (hazard ratio [HR] 1.84, 95% CI: 1.02–3.29, p = 0.042) and R1-status (HR 3.09, 95% CI: 1.37–6.92, p = 0.007, Table S1, supplementary material).

Discussion and conclusion

This study investigates the outcomes of resectable distal CCA in a single-centre Western cohort, comparing the prognostic impact of the 7th and 8th edition of the UICC/AJCC TNM classification. Our results highlight the major advantage of the 8th edition in that T-staging based on measurement of DOI resulted in a more even distribution of cancers between the categories T2 and T3, compared to the 7th edition. When classified according to the 7th edition, nearly all distal CCA cases in our study were assigned to category T3 (91.5% of cases). This indicates that the vast majority of distal CCA have grown beyond the bile duct wall at the time of resection, and that the extent ('depth') of invasion into the surrounding tissues, that is, the pancreas, is a more distinguishing feature. We believe that the more subtle microanatomical delineation between the bile duct wall and the surrounding tissues is the reason for a much higher proportion of T2 cases in other studies. In addition, 5-year survival rate for T3 tumours according to the 7th edition was 24.4%, illustrating

Table 4. Differences between the 7th and 8th editions of TNM classification – (a) pT stage, (b) pN stage, (c) TNM stage.

(a)

		TNM (8th edition)			Total
		pT1	pT2	pT3	
TNM (7th edition)	pT2	2	1	1	**4**
	pT3	2	44	21	**67**
Total		**4**	**45**	**22**	**71**

(b)

		TNM (8th edition)			Total
		pN0	pN1	pN2	
TNM (7th edition)	pN0	15	0	0	**15**
	pN1	0	28	28	**56**
Total		**15**	**28**	**28**	**71**

(c)

		TNM (8th edition)				Total
		I	IIA	IIB	IIIA	
TNM (7th edition)	IB	1	1	1	0	**3**
	IIA	1	8	3	0	**12**
	IIB	0	2	26	28	**56**
Total		**2**	**11**	**30**	**28**	**71**

the imprecision of the 7th edition in distinguishing survival outcomes among different groups. Patients with cancers classified as T2 according to the 8th edition had a significantly better 5-year survival rate (31.8%) than those classified as T3 (10.5%), demonstrating how DOI is prognostically relevant. This aligns with the findings from Jun et al. [12], who reported similar significant survival differences between T-stages based on DOI, with 5-year survival rates of approximately 42.0% for T2 tumours and 12.0% for T3 tumours.

The changes in N-classification that were introduced in the 8th edition also improve prognostic stratification. According to the 7th edition, patients with nodal involvement were classified as N1, without further distinction reflecting the metastatic burden. In contrast, the 8th edition introduced a three-tiered classification. Moon et al. [11] reported that median survival dropped from 79.2 months in N0 patients to 28.8 months N1 patients, and just 10.9 months in N2 patients. Our study yielded similar results, with median survival of 51, 30 and 23 months for N0, N1 and N2, respectively. Kang et al. [28] also support the improved prognostic accuracy of the 8th edition, reporting 5-year survival rates of 54.4% for N0, 33.6% for N1, and just 4.8% for N2.

The improved staging introduced by the 8th edition of the TNM classification enables clinicians to better identify high-risk patients, such as those with deeply invasive tumours or extensive lymph node involvement, who may benefit from additional therapies or closer post-operative follow-up. While post-operative systemic therapy is not standard of care in some countries [4–6], the NCCN guidelines clearly state that observation only with no further treatment after surgery is an option only for patients with R0/N0 disease, whereas systemic therapy is recommended for R1 or N1/2 disease. Consequently, the clinical effectiveness of this classification depends on careful pathological assessment, in particular accurate measurement of DOI and thorough examination of the lymph nodes and margins. While the latter is extensively discussed for distal CCA and other cancers treated with PD, practical difficulties related to the measurement of DOI have not received much attention. To obtain an accurate measurement of DOI, examining full cross-sections at multiple levels through the entire length of the bile duct cancer is key. In practice, this means that the CBD should be serially sectioned in the perpendicular plane. However, as the bile duct follows a curved course and because current specimen

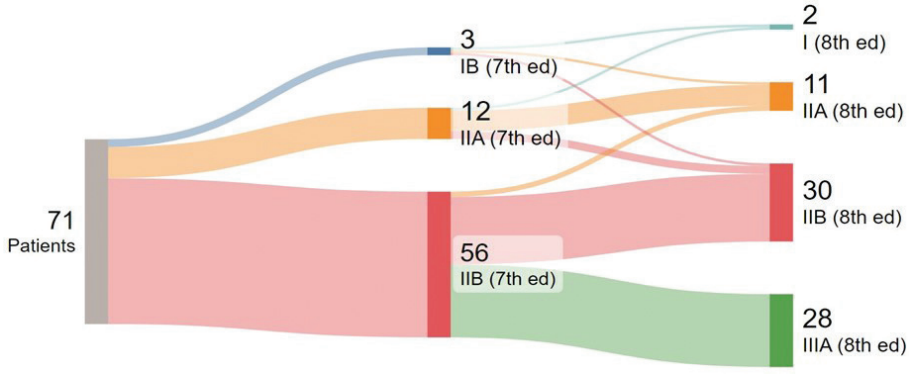

Figure 2. Sankey plot illustrating differences in distribution of clinical stages for TNM 7th and 8th classification systems.

dissection approaches are all based on parallel sectioning (either of the entire or the bivalved head of pancreas), tangential sectioning of a part of the bile duct may occur (Figure 3). If this happens at the level of the tumour, accurate measurement of the DOI may be difficult to achieve. To avoid tangential sectioning, fan-like slicing adapted to the curved shape of the intrapancreatic CBD would be needed. This is practically not feasible, however, as the course and angulation of the bile duct vary considerably between cases. The impracticability of fan-like sectioning is exemplified by Aoyama et al. who reported that their attempt at fan-like sectioning resulted in a near-axial dissection [13]. As such, tangential sectioning cannot be entirely avoided, but fortunately, it renders DOI measurement difficult in only a minority of cases (10%) in our hands. Higher proportions (55%) reported by others (Aoyama) may be due to slicing at thicker intervals (5–7 mm vs. 3 mm according to our grossing protocol), which reduces the number of specimen slices and consequently, the chance of obtaining slices with proper cross-sectioning of the CBD. A further, minor cause for confusion among pathologists is the point from which DOI should be measured. Some authors [9, 10] advocate measuring from the basal membrane of the bile duct epithelium, whereas others have noted that this structure is often fragmented [13]. In practice, this is largely a moot point, as the nonneoplastic/dysplastic epithelial lining usually is absent, either due to cancer infiltration or stent-related ulceration. Thus, in most cases, the practical approach is to measure DOI from the luminal surface of the tumour (Figure 1).

The R1-rate in this study (71.8%) is high in comparison to previously reported rates, which vary from 1.8% to 50.0% [10–13, 18–20]. A likely reason for the substantially higher R1-rate is that – in contrast to other studies – the circumferential margin (also known as the radial margin) of the extrapancreatic bile duct was included in the evaluation and found to be frequently involved (25.4%) in our study. In addition, axial slicing and extensive en bloc sampling of the tumour onto the nearest specimen surfaces also likely contributed to a higher detection rate of microscopic margin involvement. Similarly, high accuracy of the pathology examination procedure is also the likely reason for the higher rate of lymph node metastasis (78.9% N+) than in other studies (31.5% Hong 2007, 33.5% Jun 2019, 40.6% Aoyama 2018, 63.3% Hong 2009).

This study has several limitations. Firstly, it is a retrospective, single-centre study, which may limit the generalisability of our findings. Secondly, the relatively small sample size affects the statistical power of certain analyses. Finally, variations in postoperative treatments, such as chemotherapy, were not accounted for and may have influenced survival outcomes.

Conclusion

In summary, our study confirms in a single-centre Western cohort that the 8th edition of the UICC/AJCC TNM classification provides superior prognostic stratification for distal CCA compared to the 7th edition by using DOI as a criterion for T-stage classification and introducing a 3-tiered N-classification. These refinements improve risk stratification, but rely on meticulous pathology assessment, in particular accurate measurement of DOI and thorough examination of lymph nodes and margins, the latter two variables being independent predictors of poor survival.

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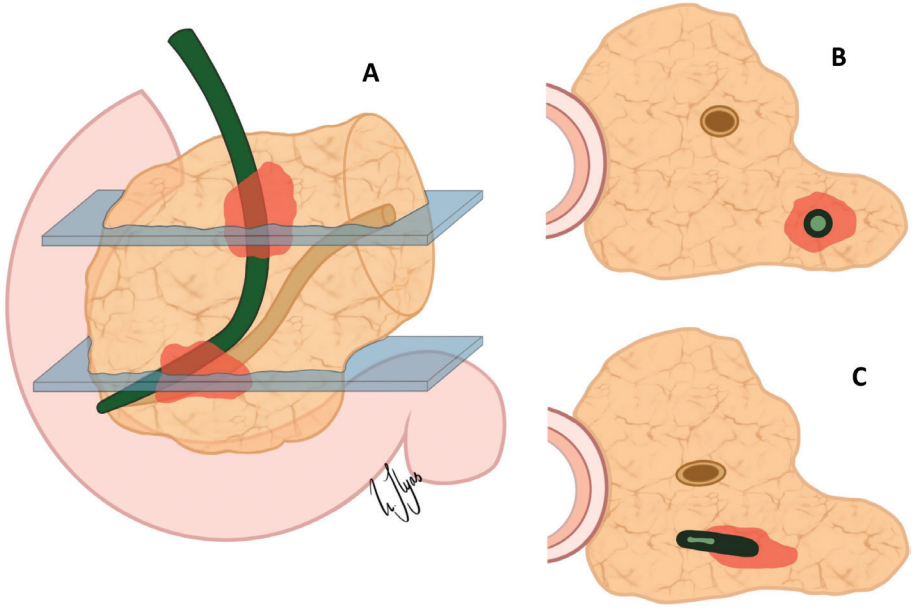

Figure 3. Challenges in pathology assessment – Tangential sectioning of the curved intrapancreatic bile duct.

Challenges in slicing the intrapancreatic bile duct. (a) Different axial sections through the curved bile duct. (b) Proper cross-sectioning enables accurate depth of invasion (DOI) measurement. (c) Tangential sectioning deforms the lumen and may cause over- or underestimation of DOI.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Data availability statement

The data that support the findings of this study are not publicly available, but are available from the corresponding author upon reasonable request.

Ethics declarations & trial registry information

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the institutional data protection officer (No.2015/13400) and individual consent for this retrospective analysis was waived.

Author contributions

(I) Conception and design: DK, CSV, MBH, IPG.
(II) Administrative support: RR, MAS, SB, SY.
(III) Provision of study materials or patients: DK, MBH, CSV, IPG, SY, SB.
(IV) Collection and assembly of data: All authors.
(V) Data analysis and interpretation: All authors.
(VI) Manuscript writing: All authors.
(VII) Final approval of manuscript: All authors.

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ORIGINAL ARTICLE

How does pulmonary function impact QoL in patients with locally advanced NSCLC treated with chemoradiotherapy and durvalumab?

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ABSTRACT

Background: Impaired pulmonary function is common among patients with lung cancer and may negatively affect health-related quality of life (HRQoL). The primary objective of the present sub-study of the DART-trial was to assess the overall quality of life changes during treatment and stratified by the presence of Chronic Obstructive Pulmonary Disease (COPD).

Methods: The investigator-initiated DART trial (NCT04392505) included patients with unresectable stage III non-small cell lung cancer (NSCLC) treated with chemoradiotherapy followed by durvalumab. Baseline pulmonary function was measured by spirometry, and patients were stratified by FEV1/FVC <70% (COPD) or ≥70% (non-COPD). HRQoL was assessed regularly using the EORTC QLQ-C30 and QLQ-LC13 questionnaires at screening and during treatment. A difference in mean score of ≥10 was defined as clinically significant.

Results: A total of 86 patients initiated durvalumab and completed at least one HRQoL assessment; pulmonary function data were available for 64 patients. For the overall cohort, quality of life scores remained stable throughout treatment. Patients with COPD consistently reported lower global health scores than those with preserved lung function. The global health score among patients with COPD was not significantly different at end of treatment compared to baseline, however significantly lower than patients without COPD. Symptom trajectories across QLQ-C30 scales were stable in both groups. Dyspnoea was more prevalent among patients with COPD. In the LC13 module, no clinically significant differences were observed except for dyspnoea, which was consistently higher among patients with COPD.

Interpretation: The HRQoL remained stable during chemoradiotherapy and durvalumab treatment in stage III NSCLC patients. Impaired lung function was associated with modestly lower HRQoL, though larger studies are needed to confirm subgroup effects.

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Cancer; NSCLC; quality of life; COPD; lung

Introduction

Lung cancer is one of the most common malignancies and the leading cause of cancer-related mortality worldwide [1]. In Norway, 3435 new cases were diagnosed in 2024, and 2243 patients died from the disease (Cancer Registry of Norway [https://www.fhi.no/contentassets/1d3cf9facb9747a1b-9148cb23a7f7c54/cancer-in-norway-2024.pdf]). Approximately 20–30% of patients with non-small cell lung cancer (NSCLC) present with stage III, locally advanced disease [2].

For patients with good performance status and unresectable stage III NSCLC without genetic alterations in the genes Epidermal Growth Factor Receptor (EGFR) or Anaplastic Lymphoma Kinase (ALK), the standard of care is radiotherapy given concurrently with platinum-based doublet chemotherapy (chemoradiation), followed by up to 1 year of durvalumab in patients with tumours expressing the protein Programmed Death -Ligand 1 (PD-L1) [3]. This approach, modelled by the PACIFIC trial, achieves cure in a subset of patients, however, the

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median progression-free survival is limited, and only 42% of patients are alive at 5 years [4, 5].

Approximately 40–70% of NSCLC patients also suffer from Chronic Obstructive Pulmonary Disease (COPD) [6–8]. The two diseases share major risk factors such as smoking, environmental pollutants, and occupational carcinogen exposure. Proposed mechanisms linking COPD and lung cancer include genetic predisposition, epigenetic regulation, and chronic local and systemic inflammation [9].

The COPD has been identified as an independent risk factor for mortality in stage III NSCLC, particularly in squamous cell carcinoma [10–12], although some studies report conflicting results [13]. Nevertheless, it's important to note that standard eligibility criteria for concurrent chemotherapy and radiotherapy trials in locally advanced NSCLC typically exclude individuals with advanced COPD and cardiac comorbidities. In addition, tobacco smoking in cancer patients is associated with increased treatment toxicity, higher risk of a treatment failure, and poorer quality of life [14].

The coexistence of COPD complicates diagnosis and management of NSCLC. Overlapping symptoms may delay diagnosis or lead to misinterpretation [15]. Radiotherapy and immunotherapy can further impair pulmonary function due to inflammation, pneumonitis, or fibrosis [16–19]. Baseline pulmonary function parameters, such as Forced Exporatory Volume in 1 Second (FEV1), Forced Vital Capacity (FVC and Diffusing Capasity of the Lungs for Carbon Monoxide (DLCO), may predict risk of radiation pneumonitis [20].

While survival remains a central outcome, health-related quality of life (HRQoL) is increasingly recognized as a critical factor in treatment planning, especially given the substantial symptom burden experienced by these patients, including fatigue, pain, and impaired physical and social functioning. Two systematic reviews – Reale et al. and Marandino et al. – highlight persistent deficiencies in the reporting and integration of HRQoL data in phase III oncology trials [21, 22]. Despite growing awareness, HRQoL outcomes are often under-reported, delayed or omitted, limiting their influence on clinical decision-making [2]. Moreover, the impact of baseline pulmonary function on HRQoL during curative-intent therapy for stage III NSCLC remains poorly understood and there is a need for further studies [22, 23].

In the Durvalumab after RadioTherapy Trial (the Dart Trial), patient well-being is monitored every 6–12 weeks using two validated instruments: the European Organisaton For Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire - 30 (QLQ-C30) (version 3) and the lung cancer-specific QLQ-LC13, capturing physical, emotional, and social dimensions. Here, we report changes in symptoms and functioning according to pre-treatment pulmonary function.

Material and methods

The DART-study

The DART-study is an open-label, multinational, investigator-initiated phase 2 trial aiming to identify biomarkers for stratifying treatment for patients with locally advanced non-small cell lung cancer (NSCLC). The study was conducted at 10 hospitals in Norway, Finland, Lithuania, and Estonia. Inclusion started on May 2020 and ended on December 2023. Patients with unresectable stage III NSCLC were enrolled and treated with curatively intended chemoradiotherapy (CRT), consisting of two cycles of platinum-based doublet chemotherapy every 3 weeks and radiotherapy 60–66 Gy in 30–33 fractions. Patients without disease progression following CRT received durvalumab 1500 mg every 4 weeks, preferably starting within 5 weeks of CRT completion, and continued until progression, intolerable toxicity, or a maximum duration of 12 months independent of PDL1 expression. Participants not starting durvalumab were excluded from further analyses. The follow-up includes a safety follow-up for up to 5 years, and a survival follow-up for up to a total of 10 years. Approval was granted by the Regional Committee for Medical and Health Research Ethics (reference 48665, November 28, 2019). All participants provided written informed consent. The trial is registered at ClinicalTrials.gov (NCT04392505). The primary endpoint in the DART-study was to determine how tumour mutational burden affected hazard ratio, with several secondary and exploratory endpoints, including the HRQoL analyses. The study was powered for the primary endpoint, and no estimation of power for the HRQoL analyses was performed. No specific inclusion requirements were defined regarding lung function, as this was a pragmatic trial with inclusion following clinical practice. For the analyses of HRQoL, we included patients completing at least one questionnaire at screening, and for the analyses related to lung function, we included patients with baseline measurement of lung function.

Quality of life measurements

HRQoL was assessed using the EORTC QLQ-C30 (Version 3) and the lung cancer module LC13 from the screening timepoint (before chemoradiation) and at cycle 3 (6 weeks) and thereafter every 12 weeks during durvalumab treatment. These instruments enable a thorough assessment of the patients' quality of life, encompassing physical, emotional, and social dimensions. QLQ-C30 is a general questionnaire for cancer patients, while QLQ-LC13 incorporates dimensions highly relevant for lung cancer patients.

The primary objective of this study was to assess the overall quality of life changes during treatment and stratified by the presence of COPD. Through this approach, the DART study aims to gather nuanced insights into the experiences and needs of lung cancer patients with clinically relevant comorbidity. The baseline was at inclusion in the study, before starting treatment.

Pulmonary function

Pulmonary function tests, by spirometry, were conducted in adherence to the guidelines outlined by the American Thoracic Society/European Respiratory Society (ATS/ERS) and local standards for participants in the study, prior to study treatment.

Patients were classified according to the severity of airway limitation, as outlined by the latest Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy [24]. Specifically,

individuals with a postbronchodilator FEV1/FVC ratio below 70% as assessed before starting chemoradiation, were identified as having COPD.

Statistical analysis

Scores for the QLQ-C30 and QLQ-LC13 questionnaires were calculated according to the EORTC Scoring Manual, with raw scores standardized by linear transformation to range from 0 to 100 [25]. A higher score represents a better level of functioning and global health status/QoL or greater symptom severity. Clinically meaningful changes were defined as an absolute change (increase or decrease) in score from baseline of ≥10 points [26]. The following items were analysed: Global Health, Emotional functioning, Fatigue, Pain, Dyspnoea, from the QLQ-C30, and Arm/Shoulder pain, Chest pain, Other pain, Cough, Hemoptysis, Dyspnoea from the QLQ-LC13. We have used data from baseline and at cycle 3, 6, 9, and 12 of durvalumab. Scores from patients with and without COPD were compared. Data were reported using descriptive statistics with percentages, means, and standard deviation. We did not perform imputations of missing data. The results are given as the mean values ± one standard deviation unless otherwise stated. R (version 4.5.1) was used to perform calculations and produce graphical figures.

Results

Patients

Of the 123 patients included in the DART-trial, 86 NSCLC patients started treatment with durvalumab. All 86 completed at least one QoL questionnaire and were included in the present analyses. Figure 1 shows a study flowchart illustrating patient enrolment, exclusions, and pulmonary function test availability.

Characteristics of the 86 patients are shown in Table 1. The study cohort consisted of 52 men (60.5%) and 34 women (39.5%), with a median age of 69 years (range 36–85). Pulmonary function was recorded for 64 patients (74.4%) (Table 1), of whom 40 (62.5%) of the patients had FEV1/FVC < 70%, and 24 (37.5%) had FEV1/FVC ≥ 70%. The patients receiving durvalumab received a median of 13 cycles (average 10 cycles). The median Progression Free Survival (PFS) was 18.9 months.

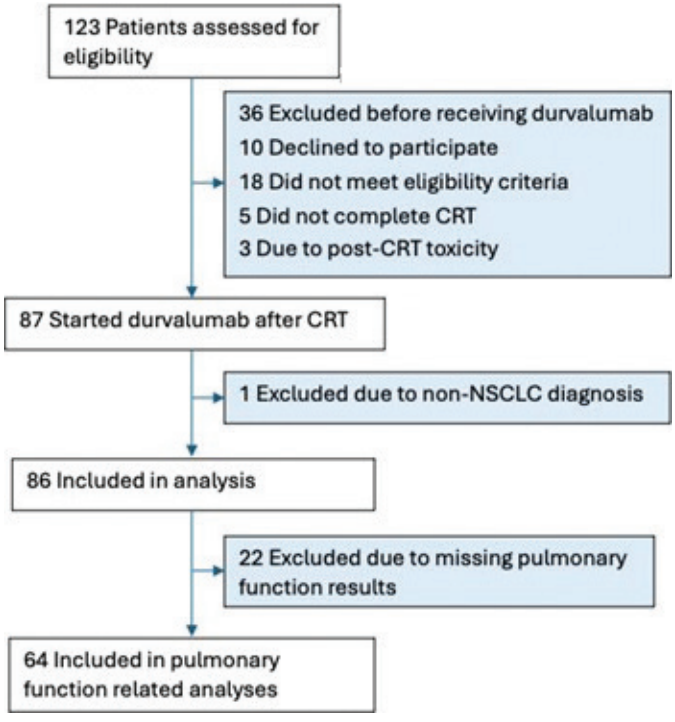

Figure 1. Flowchart.

Baseline Patient Recorded Outcome Measurements (PROMs)

An overview of baseline patient-reported outcome scores stratified by pulmonary function is presented in Table 2. Patients with FEV1/FVC < 0.7 reported lower global health and some symptoms were more severe compared to those with FEV1/FVC ≥ 0.7. Specifically, patients with reduced lung function (FEV1/FVC < 0.7) reported numerically lower (but not significantly different) scores on global health (60.63 ± 18.10 vs. 66.67 ± 17.92) and reported higher levels of dyspnoea (45.83 ± 28.93 vs. 29.17 ± 28.34) in the EORTC QLQ-C30 symptom scale (v3). The emotional function was not significantly different in the two groups. There were no significant differences in the baseline scores as measured by EORTC QLQ-LC13 between patients with or without COPD.

EORTC QLQ-C30 function scale

The mean overall global health (± SD) for all patients who initiated durvalumab treatment, across five time points (V00

Table 1. Clinical characteristics.

Clinical characteristics	*N* = 86 (all)	*N* = 40 (COPD)	*N* = 24 (no-COPD)
Age: median (range)	69 (36–85)	70 (51–80)	67.5 (51–85)
Sex			
Male	52 (60.5%)	22 (55%)	15 (62.5%)
Female	34 (39.5%)	18 (45%)	9 (37.5%)
Smoking			
Current	26 (30.2%)	13 (32.5%)	4 (16.7%)
Former	56 (65.1%)	27 (67.5%)	18 (75%)
Never	4 (4.7%)	0 (0%)	2 (8.3%)
Performance status			
0	34 (39.5%)	11 (27.5%)	12 (50%)
1	52 (60.5%)	29 (72.5%)	12 (50%)
Histology			
Adenocarcinoma	31 (36.0%)	12 (30%)	13 (54.2%)
Squamous cell carcinoma	49 (57.0%)	25 (62.5%)	7 (29.2%)
NSCLC NOS	6 (7.0%)	3 (7.5%)	4 (16.7%)
PD-L1 expression			
Negative (< 1%)	35 (40.7%)	17 (42.5%)	10 (41.2%)
Positive (≥ 1%)	51 (59.3%)	23 (57.5%)	14 (58.3%)
Pulmonary function			
FEV1/FVC < 70%	40 (62.5%)		
FEV1/FVC ≥ 70%	24 (37.5%)		

COPD: Chronic Obstructive Pulmonary Disease; NSCLC: non-small cell lung cancer; NOS: Not Otherwise Specified.

Table 2. PROMs at baseline.

	All patients (*N* = 86)		Patients (*N* = 40) FEV1/FVC < 0.7		Patients (*N* = 24) FEV1/FVC ≥ 0.7	
	N	Score	*N*	Score	*N*	Score
EORTC QLQ-C30 function scale[a]						
Emotional function	83	78.51 ± 20.75	40	78.54 ± 19.60	22	80.30 ± 17.92
Global Health	83	61.95 ± 20.04	40	60.63 ± 18.10	23	66.67 ± 24.10
EORTC QLQ-C30 symptom scale[b]						
Fatigue	82	31.03 ± 24.43	38	36.26 ± 24.60	23	22.22 ± 21.19
Pain	83	16.67 ± 24.00	40	20.83 ± 25.81	23	10.87 ± 19.85
Dyspnoea	86	34.50 ± 28.67	40	45.83 ±28.93	24	29.17 ± 28.34
EORTC QLQ-LC13 symptom scale[b]						
Arm / shoulder pain	86	14.73 ± 25.87	40	15.00 ± 26.09	24	15.28 ± 27.77
Chest pain	85	15.29 ± 23.32	40	14.17 ± 23.74	23	13.04 ± 19.43
Other pain	84	12.30 ± 20.55	39	11.11 ± 20.71	24	13.89 ± 21.80
Cough	86	45.35 ± 26.53	40	47.50 ± 28.13	24	41.67 ± 24.47
Hemoptysis	86	9.30 ± 20.86	40	12.50 ± 24.68	24	9.72 ± 20.80
Dyspnoea	86	26.87 ± 21.04	40	34.44 ± 23.84	24	18.06 ± 15.99

N = number of patients. Scores are presented as mean value ± standard deviation. [a]Higher score indicates higher functioning (scale 0–100), [b]Lower score indicates milder symptoms (scale 0–100).

(Screening), and cycle (C) C3, C6, C9, C12) are shown in Figure 2a. Overall, global health scores remained relatively stable across treatment cycles, with mean values consistently around 60–70. A slight increase was observed around C6, but this was not sustained, and the overall trajectory suggests no significant decline in perceived health status over time.

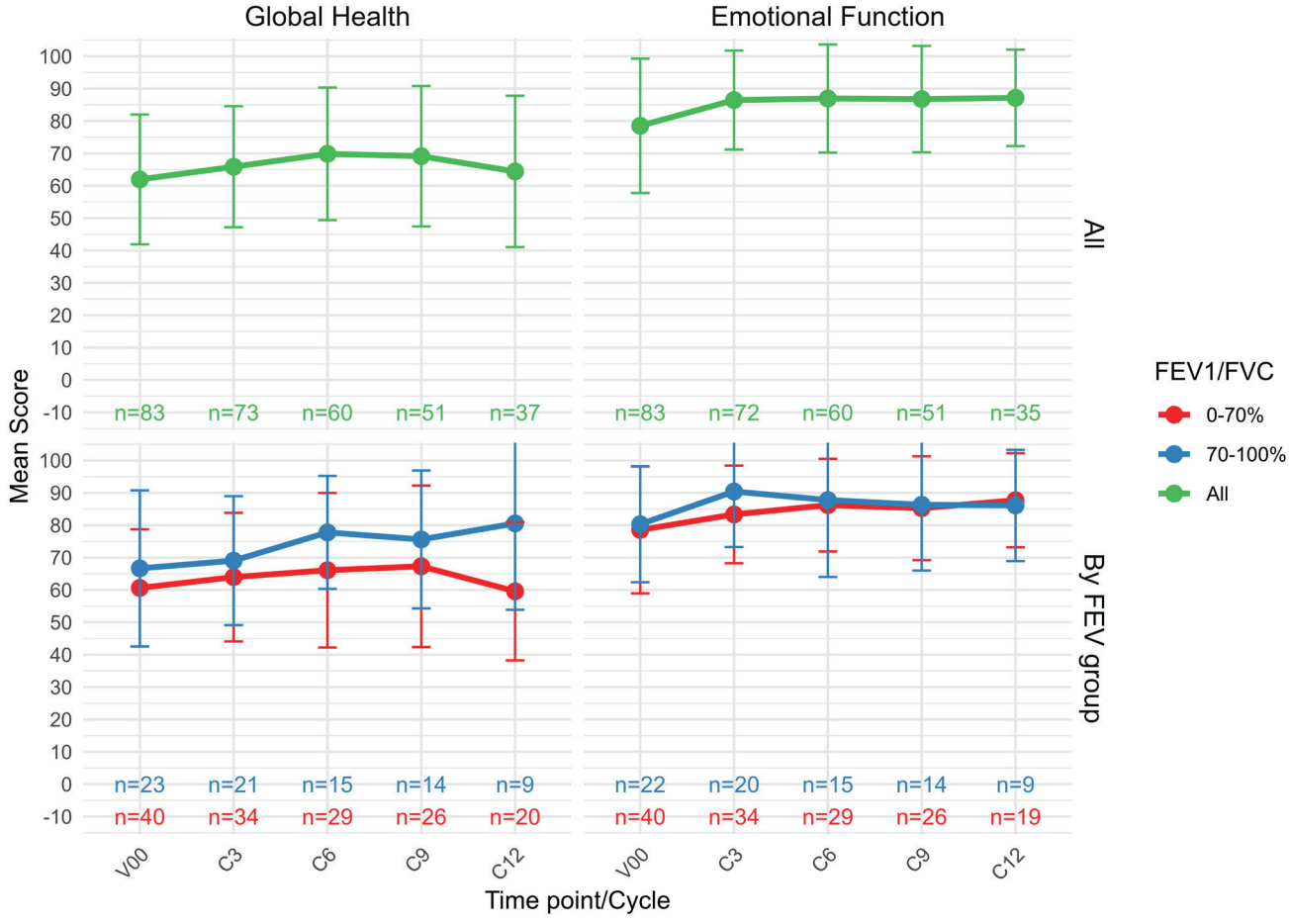

Figure 2. (a) Mean global health function (± SD) for all patients who initiated durvalumab treatment, across five time points (V00, (screening), C3 (cycle 3), C6 (cycle 6), C9 (cycle 9), C12 (cycle 12)). *N** = Number of patients still on treatment. (b) Mean emotional function scores (± SD) for all patients who initiated durvalumab treatment, across five time points (V00, C3, C6, C9, C12). (c) Mean scores for global health for patients treated with durvalumab stratified by FEV1/FVC < or ≥ 0.7 (*N* = 64). (d) Mean scores for emotional function for patients treated with durvalumab stratified by FEV1/FVC group (*N* = 64).

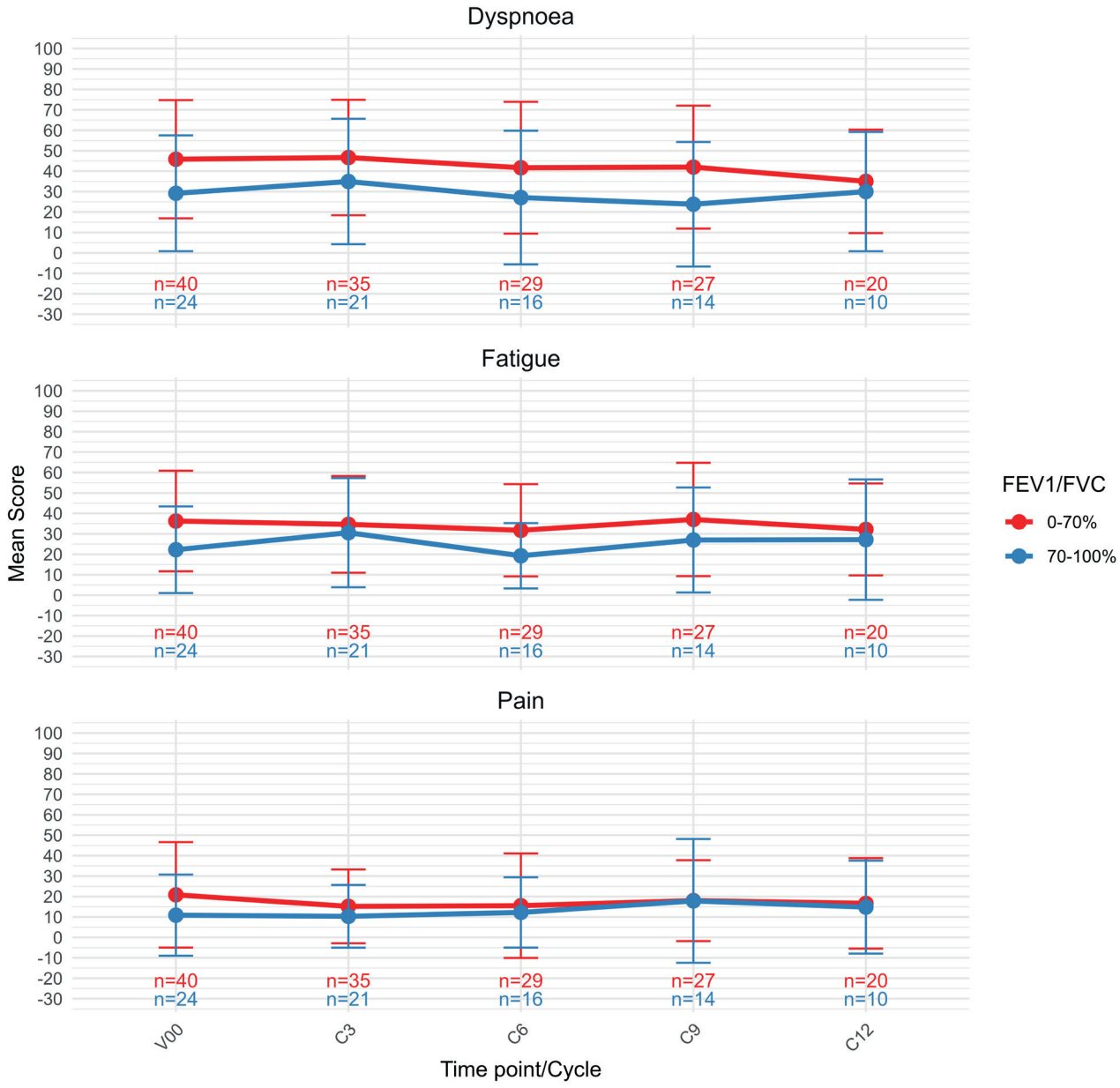

Figure 3. EORTC QLQ-C30 symptoms. A higher score represents more symptoms / higher burden. V00 = screening, C3 = cycle 3, C6 = cycle 6, C9 = cycle 9, C12 = cycle 12.

Figure 2b shows the mean emotional function (± SD) for all patients who initiated durvalumab treatment, revealing a slight non-significant increase in emotional function during the treatment period.

Figure 2c shows mean global health scores stratified by pulmonary function (± SD). Overall, patients without COPD reported higher global health scores than those with COPD (approximately 6–20 points higher). Over the study period, mean global health scores showed a modest but steady increase among patients without COPD whereas those with COPD exhibited a slight initial improvement followed by a decline at the final assessment. Consequently, the difference between the two groups became more pronounced over time (Figure 2c). Importantly, there was no indication of a significant progressive decline in either group during treatment. Figure 2d shows that the emotional function increases non-significantly in both groups.

EORTC QLQ-C30 symptom scale

When stratified by pulmonary function, most QLQ-C30 symptom scores remained broadly stable during treatment, as shown in Figure 3. No clinically significant changes were observed for dyspnoea, fatigue or pain, in either groups, with both groups displaying stable trajectories across treatment cycles. Symptom scores for both fatigues, pain and dyspnoea (QLQ-C30 v3) were consistently higher in the impaired lung function group as compared to the patients with no COPD, although the difference diminished over time for all three symptoms over time.

EORTC QLQ-LC13

Lung cancer specific symptoms were assessed thought EORTC QLQ-LC13. As shown in Figure 4, we see mean scores for six

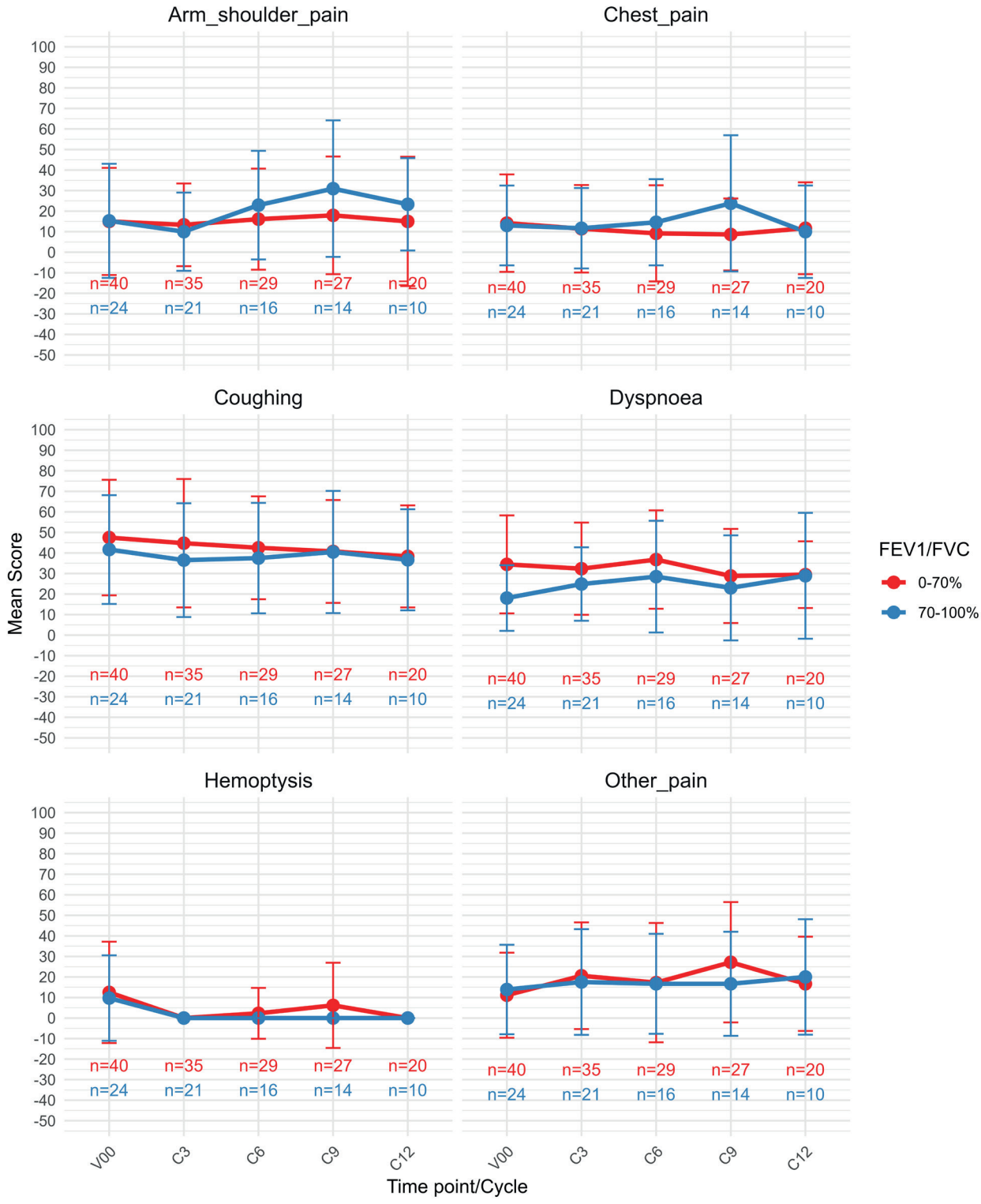

Figure 4. EORTC QLQ-LC13 symptoms. A higher score represents more symptoms / higher burden. V00 = screening, C3 = cycle 3, C6 = cycle 6, C9 = cycle 9, C12 = cycle 12.

common symptoms stratified by FEV1/FVC. Across the LC13 symptom scales, most scores, except dyspnoea were similar between patients with COPD (FEV1/FVC <70%) and without COPD (FEV1/FVC ≥ 70%) at baseline. There was a clinically significant difference at baseline for dyspnoea, but this difference diminished over time, at Cycle 12, there was no significant difference.

Discussion and conclusion

In our study population, over 60% of patients had coexisting COPD, placing them at the higher end of the prevalence range reported in other settings (40–70% among NSCLC patients) [6–8]. The COPD group have more squamous cell carcinoma, more patients with a smoking history and more patients in

Eastern Cooperative Oncology Group (ECOG) Performance Status 1. Generally, the patients with COPD are more frail, and it is important to learn more about how this impacts the treatment tolerability.

Our results show that there was no significant difference over time in overall global health as assessed through the EORTC QLQ-C30, for patients with locally advanced NSCLC treated with chemoradiation and durvalumab, when looking at the whole group (Figure 2a). This aligns well with a previous study in a similar population [27]. Hui and coworkers reported global health status and quality of life remained stable during treatment with chemoradiation ± durvalumab in the PACIFIC trial [27]. This may indicate that patients tolerate the treatment reasonably well and do not experience a decline in quality of life compared to their baseline level. However, when looking at global health in two groups with different pulmonary function (FEV1/FVC < and ≥ 0.7), we see that the patients with COPD showed a steady improvement in global health across all assessments except at Cycle 12, where a significant decline was observed. This deterioration suggests an increased treatment burden in this vulnerable cohort. The fact that one-third of these patients are active smokers may further potentiate treatment-related toxicity, accelerate decline in lung function, and ultimately contribute to poorer quality-of-life outcomes.

We identified clinically significant differences in the QLQ-C30 symptoms Fatigue, Pain and Dyspnoea at baseline, however diminishing difference during the treatment timeline. The number of responders is significantly lower at end of treatment as compared to baseline, and the decline in responders might of course influence the results. Patients with the most severe symptoms might not be represented at Cycle 12.

In the QLQ-LC13 symptom scale, no significant group differences were identified, except for dyspnoea at baseline, where the group with a poor pulmonary function reported higher scores, as would be expected. The two groups differ in several aspects, like smoking history and performance status, which might impact the overall well-being of the patients.

A limitation of this study is the relatively small sample size, and challenges in controlling for other factors impacting the HRQoL, which may reduce the statistical power and limit the generalizability of the findings. As expected, compliance with the questionnaires decrease over time, which partly is related to disease progression and deaths. Moreover, missing data on several items, including DLCO, could have offered further insight into the interplay between lung function and HRQoL, representing an important avenue for future research.

For patients with stage III NSCLC, chemoradiation followed by immunotherapy has significantly improved prognosis [4, 5, 19]. Despite the high prevalence of comorbidities such as COPD, our findings indicate that the treatment is generally well tolerated across patient groups. Although patients with impaired lung function reported lower overall global health scores at end of treatment, no substantial differences were observed in specific QLQ-C30 symptom domains between groups, at end of treatment. These results reinforce the safety and efficacy of this treatment approach, even in patients with compromised pulmonary function, and highlight the importance of individualized monitoring and multidisciplinary care to optimize clinical outcomes.

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Disclosure statements

The study has received an unrestricted research grant from ASTRA Zeneca.

Conflicts of interest

Henrik Horndalsveen: Advisory board: Johnson and Johnson. Honoraria: AstraZeneca, Pfizer, Roche.
Vilde Drageset Haakensen: Advisory board: AstraZeneca, Merck Sharp & Dome, Johnson & Johnson, Novartis, Bristol-Myers Squibb. Honoraria: AstraZeneca, Merck Sharp & Dome, Johnson & Johnson, Novartis, Bristol-Myers Squibb, Pfizer, Takeda.
Tesfaye Madebo: Advisory board: Johnson and Johnson. Honoraria: AstraZeneca, GlaxoSmithKline, Takeda AS, Merck Sharp & Dome.
Bjørn Henning Grønberg: Advisory board: Janssen, Accord, Merck Sharp & Dome, AstraZeneca, Pharmacosmos. Honoraria: AstraZeneca, Pfizer, Accord, Eli Lilly, Merck Sharp & Dome, Gilead, Bristol-Myers Squibb. Research funding: Roche, AstraZeneca.
Tarje Onsøien Halvorsen: Advisory board: AstraZeneca, Sanofi, Immedica. Honoraria: AstraZeneca, Takeda, Merck Sharp & Dome, Pfizer. Research funding: Roche, AstraZeneca
Jussi Koivunen: Honoraria: Roche, AstraZeneca, Johnson and Johnson, Bristol-Myers Squibb, Merck Sharp & Dome, Amgen, Merck KGaA, Novartis, Sanofi and Pfizer. Research Funding: Institutional grants from AstraZeneca and Roche outside of current study. Lecturing: Siemens Healthineers. Employment: Former employee of Faron Pharmaceuticals.
Kersti Oselin: Advisory board: Merck Sharp & Dome, AstraZeneca, Roche. Research Funding: Optellum.
Marianne Aanerud: Honoraria: Bristol-Myers Squibb, Astra Zeneca.
Jarkko Ahvonen: Advisory board: AstraZeneca.
Maria Silvoniemi: Advisory board: AstraZeneca, Merck Sharp & Dome, Johnson and Johnson, Bristol-Myers Squibb, Pfizer, Roche. Honoraria: AstraZeneca, Merck Sharp & Dome, Johnson and Johnson, Bristol-Myers Squibb, Pfizer, Roche, Boehringer-Ingelheim.
Saima Farooqi: Honoraria: Bristol-Myers Squibb.
Åsa Kristina Öjlert: Advisory board: Sanofi.

Åslaug Helland: Research Funding: Roche, AstraZeneca, Novartis, Incyte, Eli Lilly, Bristol-Myers Squibb, Ultimovacs, Merck, GlaxoSmithKline, Illumina, Nanopore, Johnson and Johnson, BeOne. Advisory boards and Honoraria: ABBVIE, Takeda, AstraZeneca, Roche, Pfizer, Janssen, EliLilly, Bristol-Myers Squibb, PierreFabre, Bayer, Merck Sharp & Dome, Novartis, Merck, Sanofi, Medicover. All funds go to Oslo University Hospital.
The remaining authors declare that they have no conflicts of interests.

Data availability statement

Data are available upon request.

Ethics declarations & trial registry information

All research reported here have been conducted in an ethical and responsible manner and is in full compliance with all relevant codes of experimentation and legislation. All patients gave signed an informed consent, and the regional ethics committee has approved the study (#48655). The study is now transferred to CTIS. It is registered in the Clinical.trials.gov: NCT04392505.

Authors' contributions

CRediT authorship contribution

FÅS: Data Curation, Analyses, Visualization, Writing original draft, revising manuscript.
HH: Data Curation, Investigation, Visualization, review editing.
DES: Analyses and visualization.
JK: Investigation, Writing – review editing.
TOH: Investigation Writing – review editing.
BHG: Investigation, Writing – review editing.
MA: Investigation, Writing – review editing.
SC: Investigation, Writing – review editing.
NH: Investigation, Writing – review editing.
JA: Investigation, Writing – review editing.
MS: Investigation, Writing – review editing.
GB: Investigation, Writing – review editing.
MMB: Investigation, Writing – review and editing.
VDH: Data Curation, Methodology, review editing.
ÅKÖ: Investigation, Writing – review editing.
KO: Investigation, Writing – review editing.
ÅH: Conceptualization, Data Curation, Funding Acquisition, Investigation, Methodology, Project Administration, Supervision, Writing – Review editing.
TM: Investigation, Methodology, Supervision, Writing – review editing.

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LETTER

Realising precision oncology through shared real-world data infrastructure

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Oncology in transition

Oncology is in a major transition [1]. The development of targeted therapies has not only expanded treatment options but also introduced new evidence challenges. Precision oncology, characterised by molecularly defined targets and small patient subgroups, has seen a rise in conditional approvals grounded in biological activity and unmet need. Some of these drug approvals rely on small, single-arm basket trials, because the traditional comparative effectiveness approaches are often infeasible due to limited trial feasibility or lack of equipoise [2, 3].

As a result, once new medicines enter clinical practice, uncertainty persists about how they should be positioned within treatment pathways and which patients derive the most benefit. Healthcare systems face increasing pressure, driven by ageing populations, workforce shortages and rising cancer incidence and higher cancer prevalence from improved survival. These factors have placed high demands on health systems [4], amid growing expectations for financial sustainability.

There is a need to generate evidence that not only meets regulatory requirements for benefit–risk assessments but also meets health technology assessment (HTA) requirements for cost-effectiveness and reimbursement decisions. In this context, the secondary use of health data – that is, data generated in routine care but used for purposes beyond the individual patient's treatment – has become critical.

Shift in evidence demands

The pharmaceutical industry, as marketing authorisation holder, is responsible for generating the clinical evidence needed to bring new medicines to market and maintain authorisation. However, with regulatory agencies increasingly relying on conditional approvals, this trend has shifted part of the evidence-generation burden into the post-marketing phase, where secondary use of real-world data (RWD) supports the efforts to address the limitations of clinical trial evidence [2, 5, 6].

This redistribution of *evidence responsibility* has major implications. Although electronic health records (EHRs) systematically capture clinical data, they were built for documentation and administration, not evidence generation. Transforming data into research-ready datasets is complex requiring integration of clinical and data science expertise to ensure data accuracy, completeness and traceability [7]. Moreover, data most critical for oncology, including therapeutic responses, treatment toxicities and disease progression, are predominantly unstructured and therefore challenging to capture, curate and interpret.

This raises a fairness question: if post-approval data collection forms part of the evidence base required for the continued market access of commercial products, should the financial and operational responsibility rest with the public sector? We argue that it should not. Private stakeholders should help fund and maintain RWD infrastructure, ensuring more equitable sharing of the burden of evidence production; in return, it should have access to analyses that align with the industry' evidence needs. For example, the pharmaceutical industry increasingly requires a comprehensive understanding of the evolving biomarker landscape across tumour types and patient populations.

Evidence paradigm in real-world precision oncology

Many potential druggable targets are known, some with therapies approaching regulatory approval and others still in early development. Yet, routine testing for emerging biomarkers is inconsistently implemented and therefore rarely captured in RWD, limiting the ability to evaluate biomarker prevalence, treatment patterns and outcomes at scale.

The master trial concept is traditionally defined as an overarching interventional master protocol designed to evaluate multiple therapeutic hypotheses, such as different treatments, disease subtypes or biomarker-defined populations, within a single coordinated clinical trial framework [8–10] or coordinated trial networks [11]. These designs aim to

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improve efficiency in drug development through shared infrastructure and adaptive evaluation of experimental interventions.

Master observational trials (MOTs) extend this paradigm to a non-interventional, real-world evidence setting that encompasses the entire patient population, including individuals receiving standard-of-care therapies. Rather than assigning treatments, MOTs combine protocol-driven observational rigor with the breadth of RWD to systematically capture molecular diagnostics, therapeutic exposures and outcomes across standard-of-care populations [12]. While informed by the operational principles of master protocols, MOTs differ fundamentally in design and intent, enabling comprehensive biomarker evaluation across the full patient population without experimental intervention.

Copenhagen Master Observational Trial (C-MOT) is part of the Danish OSCAR (One-Stop Shop for Clinical Research) initiative, which exemplifies how public–private collaboration can strengthen data collection, integration and evidence generation [13]. OSCAR is a partnership between healthcare authorities, government, industry stakeholders and patient organisations that aims to improve access to and utilisation of healthcare data. By combining the registry-based RWD, EHR data and whole-genome sequencing (WGS) within a secure governance framework, OSCAR demonstrates shared public–private responsibility for RWD generation. While registries, EHRs and WGS are largely produced within the public healthcare system, sustained private-sector research and innovation are essential to enable scalable, secure and interoperable data infrastructures used in the project.

Looking ahead, the ambition for C-MOT is to evolve into a population-level platform covering all patients in participating clinics. In this model, comprehensive molecular profiling would be embedded into standard clinical pathways and linked with clinical data capture. This could support continuous learning, accelerating the identification, validation and uptake of emerging biomarkers and targeted therapies.

Realising this vision, however, depends on addressing the structural and governance challenges inherent to public–private partnerships. As post-marketing RWD increasingly underpin regulatory and scientific decision-making, the development of research-grade data infrastructures requires sustained investment and time. In the absence of clear alignment on responsibilities, timelines and funding, private-sector involvement may remain transient, potentially undermining the long-term viability of such initiatives.

Building sustainable data ecosystems

Biomarker advances have divided common cancers into rare molecular subtypes, leaving single-site cohorts too small for robust analysis and highlighting the need for multi-site, cross-border data networks [14, 15]. While Denmark and the other Nordic countries maintain some of the most advanced RWD sources, effective linkage for such 'rare cancers' depends on sustained investment in data standardisation, interoperability and analytic capability.

Adopting shared frameworks such as the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM) can facilitate this process [16]. OMOP enables consistent variable definitions across projects and supports federated research models, where data remain local but analytic scripts and aggregated results are exchanged. This approach aligns with GDPR and the forthcoming European Health Data Space (EHDS) regulation, which mandates secure access through authorised data bodies [17].

The OMOP framework supports quality, compliance and multinational research collaborations such as VALO (Value from Nordic Health Data) and FALCON-Lung [18, 19]. These projects use federated analyses to benchmark care quality and treatment outcomes across Nordic countries, illustrating the scalability of OMOP CDM.

Towards a learning oncology system

The increasing use of RWD is a major development in modern oncology. Evidence generation, once largely industry led, is now a shared societal task. As approvals increasingly depend on data generated in the public health system, the sustainable progress requires co-funded, co-governed partnerships aligning commercial interests and public priorities.

Projects such as OSCAR, C-MOT and VALO represent efforts to explore such models in practice. While still evolving, these projects underscore key considerations, including fairness in cost-sharing, transparency in governance, harmonised data standards and the need for sustained investment in technological and analytical capacity. By embracing these principles, the Nordic countries can lead the global transition towards a learning oncology system – one in which evidence generation is embedded in everyday care, ensuring that data from every patient's care translates into faster, safer access to new treatments.

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AF works at Roche.

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Author contributions

All authors contributed to the draft, review, editing and finalisation of the comment.

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LETTER

‘Crossing borders’ in data standardisation: application of OMOP CDM in an international clinical trial network in precision cancer medicine

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Introduction

The PRIME-ROSE initiative is a European collaboration involving 28 countries and 11 national precision cancer medicine (PCM) trials that are ongoing or starting soon [1]. It combines data from trials with similar designs using an umbrella–basket approach and has shown that PCM is feasible and beneficial in European countries [2–4]. Patients with advanced cancer are enrolled into cohorts defined by tumour type, molecular alteration and assigned drug. However, recruitment is slow because these alterations are rare [2].

The PRIME-ROSE main objective is to demonstrate the effectiveness and safety of expanding the indication, and pooling trial data accelerates evidence generation [5].

Several approaches can be applied to standardise the structure of the incoming data within a common framework. Widely used strategies include HL7 Fast Healthcare Interoperability Resources [6], Phenopackets [7] or the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) [8, 9]. The PRIME-ROSE consortium has adopted the OMOP CDM because it reduces variation across multisite data and supports the generation of reliable evidence [9–10, 11,12] in life sciences.

OMOP CDM allows harmonisation of the data from the different PCM clinical trials and retains the original values in the dedicated source fields. Additionally, the standardisation to OMOP CDM supports the usage of various Observational Health Data Sciences and Informatics (OHDSI) tools such as Usagi [13] for semantic mapping or Data Quality Dashboard (DQD) [14, 15] for quality check. Lastly, the standardisation to the OMOP CDM enables federated analysis in large precision oncology networks [16, 17].

The aim is to build an automated extract, transform and load (ETL) pipeline for rapid extraction of statistical outcomes from standardised, aggregated cohort patient data. PRIME-ROSE aims to establish a blueprint for sharing and pooling data between PCM trials.

Methods

Data sharing

Clinical trial data from ongoing trials are uploaded to and shared in the Service for Sensitive Data (TSD) after cohorts are completed. TSD is a secure environment managed by the University of Oslo. The consortium partners have agreed on sharing 41 variables (Table S1) featuring primary and secondary endpoints including progression-free survival [18].

ETL pipeline

Data controllers of each trial submit the respective datasets according to the variables included in the common dataset. Subsequently, these data will be standardised to the OMOP CDM v5.4 using the ETL pipeline (see Figure 1A and Supplementary Material for a detailed description of the pipeline).

ETL implementation and deployment

A pre-processing workflow was developed for sources where eCRF variables must be combined in datasets at the trial level.

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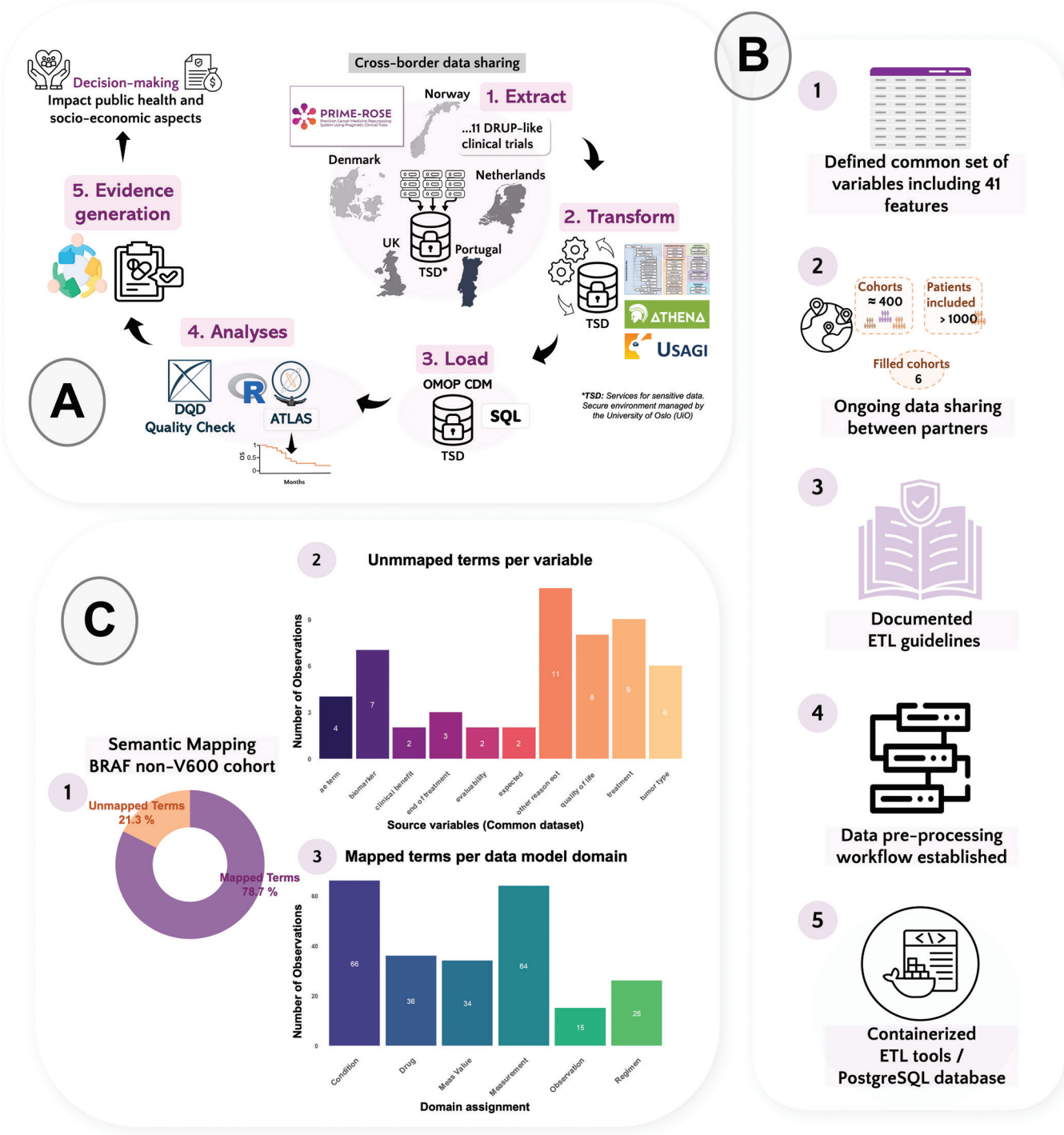

Figure 1. (A) The diagram shows the flow of the data within PRIME-ROSE. Sharing data between countries across Europe and the application of an extract, transform and load (ETL) process for data transformation and statistical analyses are key elements to accelerate the analysis of clinical trial data and evidence generation by enabling rapid patient cohort enrolment. (B) Summary with the major advances of the ETL development in PRIME-ROSE. The common dataset is only shared once the patient cohorts are filled (1 and 2). The ETL logic (3) guides the coding process for transforming the data and connecting the variables to the CDM Database. Currently, a pre-processing step prepares the data acquired from multiple sites (4). A minimal test for setting up software containers in the sensitive area TSD has been developed (5). (C) Semantic mapping was tested with the OHDSI tool Usagi in a BRAF-nonV600 cohort. (1) 306 source observations (terms) were analysed with Usagi and 78.7% (241) were mapped to a standard concept within the OHDSI standardised vocabulary catalogue. (2) The unmapped terms are confided to one of the nine variables displayed in the x axis of the bar plot, refining the semantic mapping process is crucial for the study. (3) Majority of the mapped terms connects to condition_ocurrence or measurement tables within the OMOP CDM version 5.4.

All records are validated against an internal schema and loaded into a harmonised data model. This ensures that downstream modules performing semantic and structural mapping to the OMOP CDM v5.4 target schema receive a consistent input.

For execution within the secure TSD environment, a prototype container-based deployment was tested, comprising a PostgreSQL database container (v15.0) and a separate ETL container with the Python application. Container images were built locally using Docker (v27.5.0) and executed using Podman (v5.6.0) [19].

Results

Common PRIME-ROSE variables

To date, the ongoing data sharing and manual aggregation between the different partners in PRIME-ROSE has led to merging of 396 cohorts with 1133 patients included. Six of the cohorts have been completed, and none has been stopped due to lack of efficacy (Figure 1B). A common dataset with 41 variables has been defined (Table S1).

Mapping to OMOP CDM version 5.4

A first iteration of the ETL logic serves as a reference for mapping the PRIME-ROSE source variables into the OMOP CDM v5.4 structured tables (Figure 1B). Similarly as reported by Ajmal et al. [17], we found that for some of the common PRIME-ROSE variables (e.g. *Concomitant medication* or *Dose delivered)* there is no straightforward mapping to the model and additional relationships should be established.

Semantic mapping challenges

Usagi (v1.4.3) was used to perform a semantic mapping test where source terms from aggregated data were mapped into standard concepts from the OHDSI standardised vocabularies (v5.0 27-FEB-25) (see Table S2). A BRAF-nonV600 cohort (Figure 1C) was selected, consisting of 53 patients recruited in three trials: (1) DRUP (Netherlands), (2) IMPRESS-Norway (Norway), and (3) FINPROVE (Finland).

In total, 306 source terms were processed. From those, 78.7% (241) were successfully mapped (Figure 1C1) to a standard concept within one of the six domains in Figure 1C3. Mostly, the mapped terms belonged to condition_ocurrence or measurement tables within the OMOP CDM v5.4. As shown in Figure 1C1, 21.3% of the terms (*n*=65) remained unmapped, which belonged to one of the nine variables displayed in the plot (Figure 1C2). This can happen in variables where the input is free-text and it contains a misspelling, as seen in one observation for our aggregated dataset. Also, we found that broad terms are employed for defining some of the biomarkers/targets, for example, fusions or BRAF activating mutations. These are not specifically mapped to the OHDSI vocabulary, OMOP Genomic, which contains 289889 concepts. Finally, most of the unmapped terms belonged to the free-text variable *other reasons for end of treatment (eot).*

Discussion and conclusion

Developing an ETL, such as the one presented here, is a dynamic and malleable process that should accommodate the different needs of the partners who are sharing the data. To ease versioning, reproducibility, stabilisation and individualisation of processes, we utilise Docker containers. From our experience, semantic mapping of certain variables such as *biomarker* or even *adverse events* is complex, and probably requires a higher level of data granularity or standard terms to input in the mapping and/or more extensive vocabularies (e.g. more concepts in OMOP genomics OHDSI vocabulary). Also, other variables with free-text observations such as *other reasons end of treatment* are difficult to map, as textual similarity comparisons with Usagi has some limitations. We are refining the process by performing data validation, maintaining multidisciplinary collaboration with experts and investigating alternative approaches, including machine learning-based tools to enhance semantic mapping.

PRIME-ROSE implements FAIR (Findable, Accessible, Interoperable, and Reusable) principles [20]. We are commited to open science, within the limits of sensitive patient data protection, as much as possible, in order to benefit the scientific and public community. FAIRification and standardisation to OMOP CDM prepares PRIME-ROSE for the implementation of the European Health Data Space (EHDS) [21, 22], as a key ecosystem to harbour large-scale evidence networks such as EHDEN [10].

This work with ongoing PCM trials in Europe showcases how standardised and structured data in PCM may facilitate cross-border data sharing to influence the development of PCM, particularly for rare cancer trials. It can serve as a blueprint for similar or expanded initiatives such as Joint Action on Personalised Cancer Medicine (JA PCM) [23]. PRIME-ROSE aims to increase the number of partners, and implementation of standardisation to OMOP CDM is key to enable federated analysis in PCM with similar trials outside of the European consortium.

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work presented at the Nordic Precision Cancer Medicine Symposium 2025 (NPCM2025), taking place in Oslo on the 15th–17th of September 2025. NCPM2025 was financially supported by the Acta Oncologica Foundation.

Conflicts of interest

No competing interests to declare.

Data availability statement

The methodology described in this short report has been developed and tested using: (i) a synthetic dataset created for pipeline development purposes, and (ii) a small patient cohort dataset. Relevant code is publicly available in the GitHub repository https://github.com/pcm-primerose/omop_etl. However, for ethical reasons and in complicance with European GDPR regulations, to protect the patient information, datasets are not publicly available.

Ethics declarations and trial registry information

All aggregated data generated within the PRIME-ROSE are originated from individual datasets shared by partners with on-going DLCTs. All patients have signed informed consent and are informed about the data sharing in the PRIME-ROSE network. Each trial is approved by their ethics committee and registered in CTIS; DRUP study: 2023-509152-33-0. ProTarget: 2023-510527-29-00. IMPRESS-Norway: 2020-004414-35. FINPROVE: 2024-517478-68-01. megaMOST: 2019-001494-88. DETERMINE: NCT05722886.

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Authors' contributions

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Gabriel Bratseth Stav: Conceptualization, Methodology, Software, Investigation, Formal Analysis, Data curation, Writing – Review & Editing.
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Eivind Hovig: Conceptualisation, Methodology, Resources, Supervision, Writing – Review & Editing.
All authors contributed to the article and approved the submitted version.

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LETTER TO EDITOR

The FOCU.SE trial: a nationwide Swedish drug repurposing protocol and research framework

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Introduction

Advances in genomic technologies have transformed cancer classification and treatment selection, enabling more personalized therapeutic strategies [1]. Despite this, many patients with advanced cancer do not benefit from genomic profiling due to regulatory barriers, limited treatment access, and insufficient clinical evidence supporting biomarker-guided therapies [2]. Drug repurposing, using approved drugs based on molecular alterations rather than tumour histology, offers a pragmatic solution, as demonstrated by trials such as Targeted Agent & Profiling Utilization Registry (TAPUR) (USA) and DRUP (Netherlands) [3, 4] Inspired by the Drug Rediscovery Protocol (DRUP), several national precision oncology trials have been launched across Europe, including initiatives in Denmark, Norway, and Finland [5–7].

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In Sweden, the National Life Science Strategy prioritizes equitable access to precision medicine. The MEGALiT trial provided an initial national experience with a DRUP-like approach, while collaborations within Testbed Sweden Precision Health Cancer and European initiatives such as PCM4EU and PRIME-ROSE have paved the way toward a national effort [8, 9]. Building on this groundwork, the FOCU.SE trial was developed as a nationwide platform to support biomarker-driven cancer treatment and integrated data generation.

FOCU.SE leverages national infrastructure through Science for Life Laboratory (SciLifeLab) and Genomic Medicine Sweden (GMS). Beyond the clinical trial component (FOCU.SE-Trial), the platform includes FOCU.SE-Explore, which enables exploratory multi-omics analyses, including whole-genome sequencing (WGS), whole-transcriptome sequencing (WTS), and proteomics. The complementary FOCU.SE-Data framework aims to integrate clinical, molecular, and outcome data into a unified ecosystem to support continuous learning and innovation in precision cancer medicine.

Patients/material and methods

Study design

FOCU.SE is a nonrandomized, pragmatic, phase II exploratory platform trial evaluating biomarker-guided off-label use of European Medical Agency (EMA)-approved targeted therapies. The design combines basket and umbrella trial features, enabling evaluation of targeted treatments across cancer types and biomarkers [10]. Each cohort consists of patients sharing a specific cancer type, molecular alteration, and treatment. A nested biomarker study allows prospective collection of samples irrespective of trial inclusion for exploratory research.

Population

All seven Swedish University Hospitals participate in patient recruitment. Eligible patients are adults (≥18 years) with histologically confirmed locally advanced or metastatic cancer, measurable disease, European Cooperative Oncology Group (ECOG) performance status 0–2, adequate organ function, and no remaining standard treatment options. Key exclusion criteria include rapidly progressive disease, significant cardiac dysfunction, pregnancy, or life expectancy under 6 months.

Screening and biomarker profiling

Patients undergo comprehensive genomic profiling primarily using GMS-developed targeted sequencing panels for solid or hematologic malignancies, supplemented by other validated assays and, when tissue is unavailable, by circulating tumour DNA (ctDNA) analysis. The tissue profiling is performed at each including site as part of the routine diagnostic workflow and is funded by research grants. Analyses of ctDNA and exploratory analyses are centralized with equal access for all sites. The GMS560 panel covers over 500 genes and detects a wide range of genomic alterations, base substitutions (SNVs), insertions and deletions (INDELs), copy-number variations (CNVs), and gene rearrangements (fusions) as well as more complex biomarkers such as microsatellite instability (MSI) and tumour-mutational burden (TMB) [11]. All actionable findings are reviewed by a national Molecular Tumor Board (MTB) using the MTB Portal as a decision-support tool [12]. When multiple actionable alterations are present, treatment prioritization follows predefined criteria. Optional pre-screening is permitted earlier in the disease course.

Exploratory biomarker study (FOCU.SE-Explore)

Tumour tissue and blood samples are systematically collected for exploratory analyses. Baseline proteomics is performed on all available cases, preferably using fresh-frozen tissue but also from Formalin-Fixed Paraffin-Embedded (FFPE) samples. Additional analyses, including WGS, WTS, tissue imaging, long-read sequencing, and spatial omics, are conducted based on treatment rationale and sample availability.

Data integration

FOCU.SE-Data provides harmonized clinical data collection and aims to establish a national, data-driven ecosystem integrating clinical data, biobanking, diagnostics, molecular analyses, and outcomes. The framework supports future development of multimodal diagnostics, artificial intelligence (AI)-driven analytics, and knowledge bases, addressing technical and regulatory challenges in parallel with trial execution.

Treatment assignment

Treatments are selected from a predefined catalog of EMA-approved targeted therapies. Four drugs (olaparib, Poly(ADP-ribose) polymerase [PARP]-inhibitor; tepotinib, targeting proto-oncogene c-MET (MET); amivantamab, targeting Epidermal Growth Factor Receptor (EGFR)/MET; ivosidenib, targeting Isocitrate Dehydrogenase 1 [IDH1]) have been included in the current protocol, but new therapeutical arms will be added as they become available. Initial Assignment is guided by the European Society of Medical oncology (ESMO) Scale for Clinical Actionability of Molecular Targets (ESCAT) [13]. Drugs are administered according to approved dosing, and both monotherapies and previously evaluated combinations are allowed.

Cohort design

Each biomarker–drug–cancer cohort follows a Simon two-stage design with early stopping for futility [14]. In stage 1, eight patients are enrolled; if at least one patient demonstrates clinical benefit (objective response or stable disease at 16 weeks), the cohort proceeds to stage 2 with an additional 16 patients. If five or more patients demonstrate benefit in stage 2, further investigation is supported. Selected cohorts may expand to a

stage 3 with up to 130 additional patients, subject to agreement with sponsors and drug providers.

Statistical considerations

Analyses include descriptive statistics for efficacy and safety, Kaplan–Meier estimates for time-to-event outcomes, and exploratory health economic evaluations. Key outputs include quality-adjusted life years (QALYs), incremental cost-effectiveness ratios (ICERs), and total costs.

Endpoints

Primary endpoints include disease control rate (Complete Response [CR]/Partial Response [PR]/ Stable Disease [SD] at 8 and 16 weeks), proportion of eligible patients accessing recommended therapies, and safety assessed by CTCAE v5.0.

Secondary endpoints include progression-free survival, overall survival, Health-related Quality of Life (measured by European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30, European Quality of Life Five Dimension Five Level Scale (EQ-5D-5L), and Hospital Anxiety and Depression Scale (HADS) questionnaires), and cost-effectiveness.

Exploratory endpoints assess feasibility and yield of multi-omics profiling, serial ctDNA dynamics, and development of predictive biomarkers.

Discussion

FOCU.SE represents a major paradigm shift in the national implementation of precision cancer medicine (PCM) in Sweden by tightly linking biomarker-driven diagnostics, oncology care, and translational research within a single coordinated framework. By integrating molecular diagnostics, structured access to targeted treatments, and standardized data sharing, the platform establishes a sustainable model for real-world evaluation of targeted drug repurposing strategies and substantially lowers the threshold for explorative analyses across treatment cohorts.

Importantly, FOCU.SE reduces regional disparities in access to advanced diagnostics and targeted therapies by enabling that patients throughout Sweden are evaluated using harmonized workflows and evidence-based selection criteria. To monitor nationwide implementation, data on the distribution of included patients across Sweden will be reported to the National Board of Health and Welfare. The platform systematically generates real-world data on treatment effectiveness, safety, and health-economic outcomes, thereby providing robust

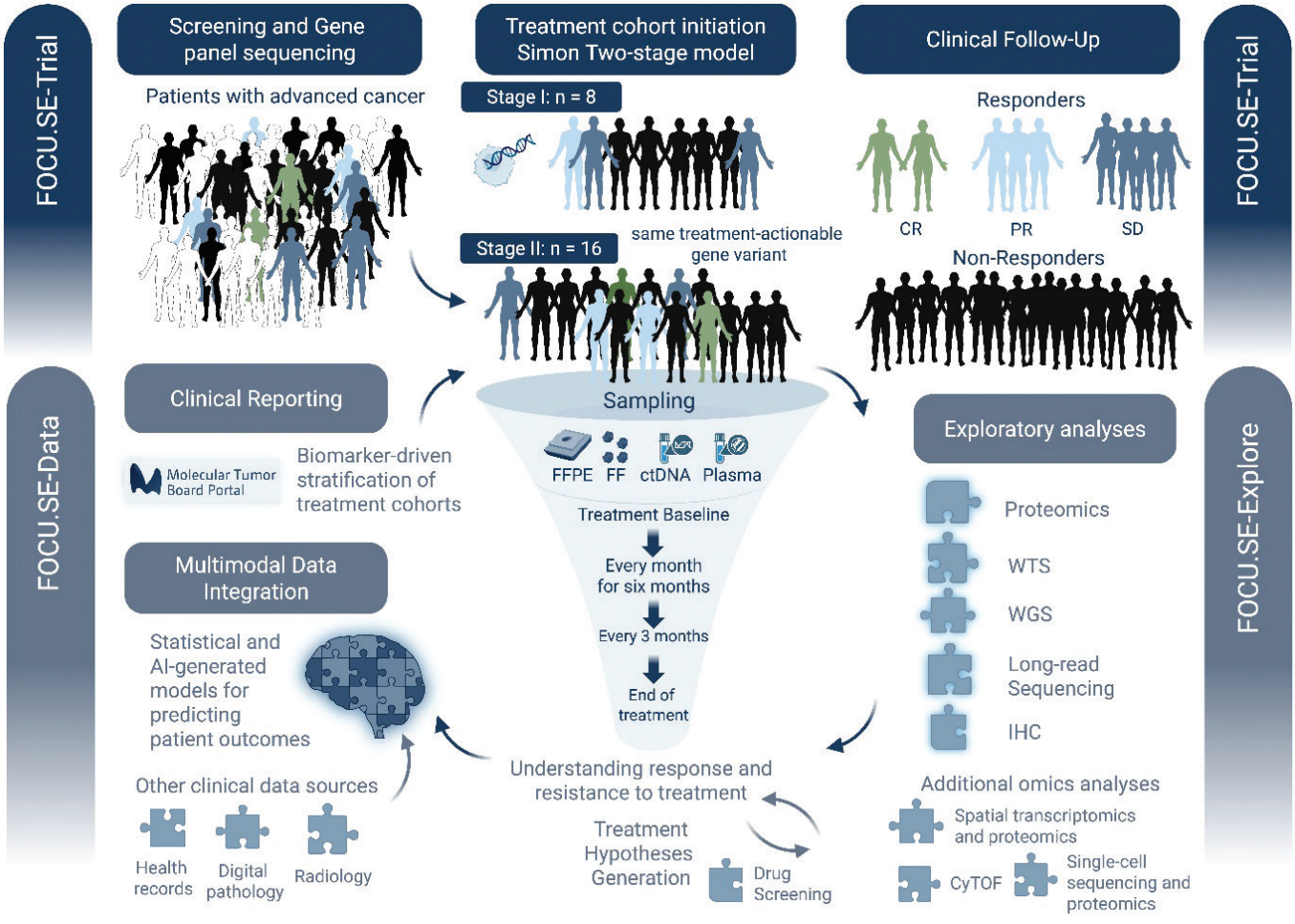

Figure 1. Schematic view of FOCU.SE platform.

Figure 2. Structure of the implementation framework for PCM clinical trials.

data to inform reimbursement decisions, clinical guidelines, and regulatory expansion of targeted therapies. Like in other DRUP-like clinical trials, rare cancers may be overrepresented but more common malignancies will also be included, allowing for potential new indications also for larger patient groups.

The platform's modular structure allows the continuous integration of new drugs and biomarkers within FOCU.SE-Trial and serves as a foundation for advanced multimodal omics profiling through FOCU.SE-Explore. Specifically, all molecularly characterized patients will undergo high-resolution proteomic profiling for assessing whether integration of proteomic and genomic data will improve clinical benefit and patient selection. These efforts aim to deepen the understanding of treatment response mechanisms, while FOCU.SE-Data supports integrated data analysis and secure data accessibility (Figure 1). The national MTB platform will also be able to identify patients for other biomarker-driven clinical trials beyond the present study.

FOCU.SE also exemplifies how clinical trials can function as testbeds for health system readiness in PCM (Figure 2). Beyond evaluating clinical outcomes, the trial addresses organizational, infrastructural, and data-related requirements necessary for large-scale PCM implementation within routine cancer care. By integrating advanced diagnostics, coordinated data flows, and multidisciplinary collaboration, FOCU.SE contributes to understanding how health systems can equitably and sustainably adopt personalized cancer care. Insights from the trial align with emerging implementation frameworks that emphasize early consideration of health system capacity, ensuring that innovations tested in research settings can be translated into real-world clinical practice [15].

Furthermore, as part of the European Horizon Cancer-funded PRIME-ROSE consortium, FOCU.SE contributes to validation of biomarker–drug outcome relationships and to the development of a European PCM infrastructure, strengthening interoperability and scientific exchange across national borders [9]. By harmonizing study design and endpoints to the other trials within PRIME-ROSE, FOCU.SE will add to the structured data sharing enabling aggregation of molecularly defined cohorts. This formalized collaboration between DRUP-like clinical trials has already established itself as a key interface for pharmaceutical companies and has enabled pooling of data from multiple patient cohorts, facilitating substantially faster evidence generation and earlier conclusions on drug effectiveness.

Conclusion

The FOCU.SE trial platform provides a nationwide clinical infrastructure for the implementation of PCM in Sweden. By enabling biomarker-guided use of approved drugs outside of their current indication within a structured clinical trial framework and supporting systematic evaluation of clinical outcomes, the platform aims to accelerate equitable access to personalized cancer therapy across healthcare regions. In parallel, it generates high-quality real-world evidence to support regulatory decision-making and potential expansion of indications for targeted therapies.

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Disclosure statements

MH has received lecture Honoraria from Incyte, Kite Gilead, BMS and participated in advisory board at Incyte, Kyowa Kirin, and Kite Gilead. GL has received honoraria from AstraZeneca, GSK, and MSD. AV has received institutional unrestricted research grant from Roche and MSD unrelated to the current work and institutional payment for lectures from Daiichi-Sankyo, Pfizer, Novartis, MSD, AstraZeneca. RR has received honoraria from AbbVie, AstraZeneca, Illumina, Janssen, Lilly, and Roche. AE has received honoraria from Amgen, AstraZeneca, Bayer, Diaceutics, and Roche. All other authors have no competing interests to declare.

Data availability statement

Data not available yet.

Ethics declarations & trial registry information

The trial is sponsored by Västra Götaland Region and coordinated by Sahlgrenska University Hospital. Planning and development of the trial protocol has been made in close collaboration between the oncology clinics at all seven university hospitals in Sweden and GMS and SciLifeLab. In addition, a separate Patient Council has been formed and has contributed to the protocol and patient informed consents. Ethical approval has been obtained from the European Clinical Trial Information System (CTIS; 2024-516003-16-00) in accordance with the Declaration of Helsinki, ICH-GCP, and GDPR. A Trial Steering Committee will oversee the conduct and progress of the clinical trial with members from all relevant stakeholders mentioned above. The Data Safety and Monitoring Board (DSMB) is responsible for participant safety. All participants will provide written informed consent. Genomics testing on tumour tissue, as basis of inclusion, is performed at each university.

Author contributions

All authors have contributed to the final study protocol. EA, PÖ, EHH, KK, HB, JL, RR, and AE drafted the manuscript. All authors reviewed, edited, and approved the final manuscript.

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LETTER

SPRINTR: Swedish PRecision medicine Initiative for Novel Treatments and Research-towards efficient recruitment to clinical trials for prostate cancer

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Introduction

Precision medicine is key to maximizing the benefits of advanced therapies while reducing costs and side effect moving from risk stratification based on few clinical parameters to ever smaller molecularly defined patient subgroups. This sub-categorization requires screening larger populations to identify cohorts for biomarker-driven trials, necessitating multicenter, structured, clinically integrated workflows for recruitment and biomarker profiling.

Rapid technological advances have enabled development of cancer-specific gene panels, broader RNA sequencing, proteomics and metabolomics, and spatial mapping of -omics and tumor microenvironment at single-cell resolution, greatly advancing the deciphering of signalling pathways and biomarkers [1]. Molecular profiling has still not been integrated into routine diagnostics for prostate cancer, even though profiling efforts show prognostic and/or treatment-predictive potential [2–11].

SPRINTR (Swedish PRecision medicine Initiative for Novel Treatments and Research) is a national research infrastructure for prostate cancer precision medicine with a prospective observational cohort under a broad ethical approval as its backbone. It creates a study-ready population covering research on biomarkers, quality of life, and health economics related to prostate cancer diagnosis and treatment. The SPRINTR concept could be scalable for other cancer forms to facilitate efficient cancer precision medicine trials.

Patients/material and methods

Study design

SPRINTR is designed as a national research infrastructure and enabling platform rather than a fixed clinical study protocol, allowing adaptive integration of biomarker technologies over time. The purpose is to enable multiple studies addressing distinct research questions related to diagnosis, prognosis, treatment prediction, health economics, and quality of life. The SPRINTR study (2024-02263-01 and 2026-01190-01) ethical approval covers research on identifying, comparing, developing, and validating biomarker tools for prostate cancer diagnosis and treatment, as well as co-morbidities, quality of life, and health economic parameters. Participation requires informed consent to be registered in the study database and does not involve biopsies or additional study-specific procedures. Consent includes biomarker profiling of routine tissue samples and optional biobanking of blood and urine. Participants agree to the use of all clinical and research data for trial eligibility matching and centralized invitations. After inclusion, they may have no further contact or be invited to additional studies or trials requiring separate consent.

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Procedures

National participation is important, and sites will be allowed to participate at differing levels. At a minimum this means integration of procedures for information, study invitation and registration of informed consents in medical records. There are no specific exclusion criteria except inability to provide informed consent. All patients entering the diagnostic workflow are therefore eligible, allowing invitation to participate to be systematically integrated into the diagnostic care pathway at participating sites. This enables standardized, low-burden patient inclusion as part of routine clinical workflow without requiring case-by-case eligibility decisions by clinical personnel. An electronic signing module with a unique study-ID connected to the PIN is being implemented. Study staff annotates the consent in medical records. Men not receiving a biopsy-confirmed prostate cancer diagnosis remain registered in the cohort. Baseline data are retained, with limited follow-up restricted to vital status and any subsequent cancer diagnosis.

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A national real-time omics workflow is being implemented in clinical pathology. During standard diagnostic prostate biopsy processing, predefined tissue allocation pathways allow parallel routing of biopsy material for research purposes in addition routine diagnostic procedures. This enables immediate access to representative tissue fractions for the SPRINTR infrastructure. Plasma, buffy coat, and the first portion of urine can be sampled utilizing standardized sampling and freezing protocols through the standard hospital referral systems. Biological samples are handled within the national biobank infrastructure (Biobank Sweden) under a central biobank agreement applicable to all participating regions.

The biomarker workflow builds on this integrated sampling framework, and protocols will be continuously evaluated and updated. Initially, diagnostic biopsy material will undergo H&E staining and immunohistochemical staining for Ki-67, PSA and PTEN, with centralized slide scanning to ensure standardized digital images suitable for AI-based image analysis. In parallel, designated tissue fractions are processed for DNA and RNA extraction, followed by genomic analysis using the GMS560 sequencing panel (Genomic Medicine Sweden [12]) and RNA sequencing for classification according to established models [2, 7, 9–11, 13].

SPRINTR as an open research platform

SPRINTR utilizes centralized data retrieval from national and regional healthcare and quality registers, minimizing manual data entry at participating sites (Figure 1). No study-specific eCRF is required. SPRINTR integrates standardized clinical and registry-based data with molecular data generated through national genomic medicine platforms, including sequencing- and transcriptomics-based profiling of clinical samples. SPRINTR has steering group comprising representatives from all seven medical universities in Sweden and their regional counterparts as well as the Swedish patient organization (Prostatacancerförbundet). It serves as the central coordinating steering group responsible for study approvals, data access, and strategic prioritization, ensuring compliance with ethical permits and transparency for both academic and commercial research proposals. Researchers can submit study proposals to the steering group. Approved studies need to adhere to the open research practices and make the generated data accessible to others.

SPRINTR aims to facilitate and increase the number of biomarker-driven clinical trials in Sweden. Importantly, all participants agree to be contacted for recruitment into other studies or trials based on information in the database, such as genetic alterations, medications, or comorbidities; this feature creates a study-ready population that facilitates nationwide recruitment (Figure 2). The inclusion started at Norrland's University Hospital in Umeå in 2025, and during 2026, 23 additional sites, including all Swedish university hospitals, are preparing to launch – corresponding to ~50% of newly diagnosed prostate cancer patients in Sweden.

Discussion and conclusion

The strength of this study lies in its broad ethical approval including several aspects and research questions in relation to precision medicine combined with a pragmatic participant inclusion procedure integrated into the clinical workflow, a biomarker workflow, automated follow-up data retrieval, and participants' consent to be invited to additional clinical studies or trials based on collected information. In addition, the SPRINTR infrastructure provides a foundation for prostate cancer research, with shared administration, legal agreements, and IT systems. This creates an open research platform to validate and develop diagnostic and treatment-stratifying biomarkers, including AI tools.

Promising biomarkers must be carefully evaluated and compared with studies on quality of life and health economics.

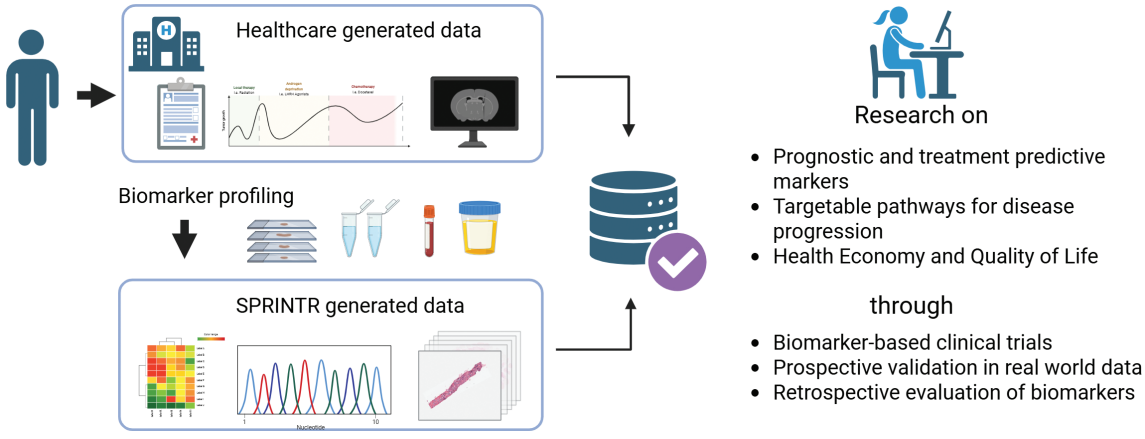

Figure 1. Illustration of the SPRINTR-Real research concept. By accepting participation, a person gives SPRINTR access to healthcare data from medical records, diagnostic images, quality registers and national health related registers, as well as all generated biomarker data from tissue, blood, and urine. Research questions are regulated by a broad ethical permission, including prognostic and predictive biomarkers, co-morbidities, disease progression, quality of life, and health economics. Data include lab parameters, evaluation of physical examinations, magnetic resonance imaging (MRI) and positron emission tomography (PET) imaging as well as regional quality registers and national registers on diagnoses, prescribed drugs, and causes of death. Created in https://BioRender.com

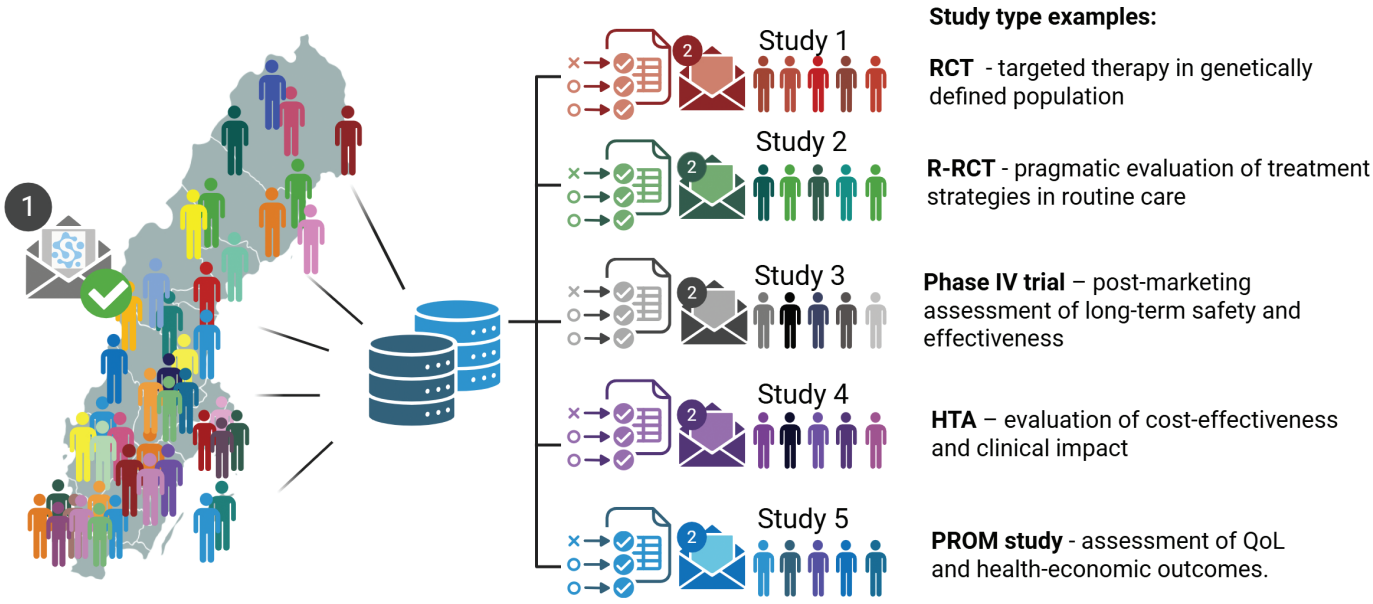

Figure 2. Illustration of the SPRINTR-Real concept for a study-ready population and study examples. Nation-wide invitation (1) and recruitment create a broad dynamic growing well-documented population with automatic follow-up. Built-in modules for selection on inclusion/exclusion criteria enable selected invitations (2) to generate cohorts for different types of studies, within the SPRINTR ethical approval or as add-on trials with separate regulatory frameworks. RCT: randomized controlled trial; R-RCT: register-randomized trial; Phase IV: post-marketing trial; HTA: health technology assessment; QoL: quality of life; PROM: patient-reported outcome measurement. Created in https://BioRender.com

Precision-medicine biomarkers are often evaluated separately in unique settings. SPRINTR enables back-to-back analysis of different biomarkers in a prospective setting, along with health economic assessments across multiple disease stages.

The expanding cohort with long-term follow up, imaging, and stored tissue enables diverse studies. Combined evaluation of MRIs, clinical variables, comorbidities, and tissue- or liquid based omics could support development of multimodal tools to predict early relapse and identify actionable targets.

SPRINTR aims to reduce inequality in patients' access to information about and invitations to clinical trials. Its pragmatic, adaptable site-participation model, with varying involvement levels and a digitalized informed-consent process, enables integration into any diagnostic unit in Sweden. This increases patients' chances of being contacted directly by the central study team based on eligibility, regardless of location, and reduces dependence on individual physicians in recruitment.

All Swedish Universities with medical faculties are part of SPRINTR, and all components are generic and designed for national reuse and scalability across cancer types. SPRINTR is aligned with national precision-medicine initiatives, including Genomic Medicine Sweden [14, 15], Clinical Trials Sweden (national clinical studies network) [16], Biobank Sweden (national biobanking infrastructure) [17], the Swedish Comprehensive Cancer Center network, and precision-medicine centers at university hospitals to achieve synergies molecular diagnostics, data solutions, and competence development. Thereby, SPRINTR aligns with emerging international developments in diagnosis-agnostic precision-medicine infrastructures, including initiatives such as Joint Action on Personalized Cancer Medicine (JA PCM), reflecting a broader transition toward platform-based models for clinical research and biomarker development. Dissemination of the SPRINTR concept will be shared within the EUnetCCC initiative [18].

In summary, the aim is to build a research infrastructure that integrates multimodal biomarker research to accelerate precision-medicine development and clinical implementation. By establishing a broad, well-documented, study-ready population, SPRINTR will increase the number of men invited to clinical studies and trials. SPRINTR supports prognostic and predictive research using multimodal datasets and secure follow-up. Ultimately, SPRINTR seeks to improve survival and quality of life for men with prostate cancer by advancing the clinical use of treatment-predictive biomarkers.

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Conflict of interest

The authors report that there are no competing interests to declare.

Ethics declarations & trial registry information

The SPRINTR study is approved by the Swedish Ethical Review Authority, ref numbers: 2024-02263-01 (amendments 2024-07457-02, 2025-01828-02, 2025-03700-02, 2025-04700-02, 2025-07884-02, 2026-02206-02) and 2026-01190-01.

Authors' contributions

KW and AJ are initiators and PIs for the study. All other authors have contributed with their specific competences in study design, planning of clinical and preclinical research, data handling, regulatory matters, infrastructure, and communication. All authors reviewed, edited, and approved the final manuscript.

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