PharmacoEconomics - Open
https://doi.org/10.1007/s41669-026-00656-9

ORIGINAL RESEARCH ARTICLE

Integrating Structured Expert Elicitation with External Evidence to Inform Earlier Reimbursement Decisions: A Norwegian Case Study of Selpercatinib for Non-Small Cell Lung Cancer

Yancy S. Wu[1] · Emily A. Burger[1,2] · Fredrik Holmboe[3] · Magnus Bangum[3] · Francisco Oteiza[4] · Christoffer Bugge[4] · Erik Magnus Sæther[4] · Eline Aas[1,5]

Received: 2 September 2025 / Accepted: 21 April 2026

Abstract

Background The Norwegian public–private partnership, CONNECT, identified the reimbursement submission case of selpercatinib—a first-line targeted therapy for RET fusion-positive non-small cell lung cancer (NSCLC)—as a unique opportunity to assess the role of structured expert elicitation (SEE) in conjunction with phase II evidence.

Objective This study aims to compare the potential of using SEE and other sources of external evidence with phase III clinical trial results to explore the possibility of facilitating earlier (conditional) reimbursement decisions.

Methods We conducted a series of cost-effectiveness analyses, grouping different sources of evidence (i.e., published clinical evidence and SEE) to estimate the long-term health and economic consequences of selpercatinib versus pembrolizumab plus pemetrexed and platinum-based chemotherapy for patients with advanced RET fusion-positive NSCLC in Norway. We developed a probabilistic partitioned survival model to estimate and compare costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs) associated with evidence potentially available early in the product lifecycle, including SEE, with those using phase III evidence.

Results ICERs consistently ranged between $8257 and $19,819 per QALY gained when we used SEE, either alone or in combination with additional external evidence, or when we used the phase III randomized controlled trial (RCT) evidence.

Conclusions The consistent cost-effectiveness results between pre-submission and post-submission phases support the potential of SEE to complement health technology assessment (HTA) and potentially inform earlier (conditional) reimbursement decisions for this single case study. However, future research should focus on refining SEE protocols for continued methodological development and validation to improve generalizability and applicability.

Key Points for Decision Makers

Structured expert elicitation has the potential to inform survival estimates in health technology assessment when trial evidence is incomplete.

In this case study, reimbursement conclusions based on phase II trial evidence plus structured expert elicitation were similar to those reached after phase III evidence became available.

Structured expert elicitation may potentially support earlier or conditional reimbursement decisions for precision cancer medicines while more evidence is collected.

✉ Yancy S. Wu
yansiw@medisin.uio.no

[1] Department of Health Management and Health Economics, Institute of Health and Society, University of Oslo, Oslo, Norway

[2] Center for Health Decision Science, Harvard T.H. Chan School of Public Health, Boston, MA, USA

[3] AbbVie, Oslo, Norway

[4] Oslo Economics, Oslo, Norway

[5] Division for Health Services, Norwegian Institute of Public Health, Oslo, Norway

Published online: 18 June 2026

1 Introduction

Clinical trials of new drugs and technologies play a critical role in reimbursement decisions of new interventions. In oncology, phase II trials primarily evaluate the efficacy and safety of a new anticancer agent [1], while phase III trials, often conducted as a randomized controlled trial (RCT), provide evidence on the comparative efficacy of a new treatment against existing alternative(s) [1]. Over recent decades, there has been a shift toward accelerated clinical approvals and conditional marketing authorizations, leading to the rise of early-phase trials with uncontrolled study designs, i.e., single-arm trials (SATs) [2–4]. It is particularly challenging to generate robust comparative evidence for interventions targeting small patient populations owing to limited patient availability, reduced statistical power, and difficulties in recruiting sufficiently large and representative study cohorts. Although considered the gold standard, RCTs are notably time-consuming and expensive, and may involve treatment crossover, which can further complicate comparative clinical outcomes, such as overall survival [5]. Consequently, both phase II and III trials may face challenges in providing sufficient and unbiased comparative evidence of clinical benefit.

To address some of the challenges of SATs, published external trial data and real-world evidence (RWE) to inform external control arms are increasingly being used to support health technology assessments (HTA) [6]. More recently, structured expert elicitation (SEE), which relies on clinical experts' quantitative inputs to inform probability distributions on uncertain quantities of interest, continues to gain attention as a potential tool for supporting HTA, especially when the evidence is incomplete, immature, or even absent [7–11].

In recent years, although details of SEE methodologies vary, SEE has been recommended as the preferred method for eliciting expert evidence by several HTA organizations, including the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), the Portuguese National Authority of Medicines and Health Products (INFARMED), and the Dutch National Health Care Institute (Zorginstituut Nederland [Zin]) [12–15]. Moreover, several protocols, frameworks, and technical support documents have been developed to facilitate the application of SEE in HTA, including guidance focused on addressing implementation challenges in real-world decision-making [7–11, 16–18].

In the context of cost-effectiveness analyses, SEE has been used to estimate parameters such as long-term survival probabilities when direct data are lacking [19–21]. However, to our knowledge, no studies have empirically compared the cost-effectiveness findings with and without SEE. The Norwegian public–private partnership, CONNECT (Norwegian Cancer Precision Medicine Implementation Consortium) [22], which includes the Norwegian Medical Products Agency (NOMA), identified the reimbursement submission case of selpercatinib, a first-line monotherapy for advanced RET fusion-positive non-small cell lung cancer (NSCLC), as a unique opportunity to assess the role of SEE in conjunction with the phase II clinical trial evidence. Motivated by the need to accelerate the implementation of precision cancer medicine, this cross-organizational consortium seeks to leverage collective expertise and infrastructure to address key practical barriers (e.g., lack of comparative clinical evidence) and pilot innovative solutions (e.g., SEE).

In Norway, the reimbursement application for selpercatinib, initially evaluated as a second-line treatment, was submitted to NOMA in September 2020 [23]. The clinical evidence was primarily based on the single-arm LIBRETTO-001 trial [24], which provided initial efficacy data for selpercatinib, for both treatment-naïve patients and those who had previously received platinum-based chemotherapy. In March 2022, NOMA rejected the reimbursement of selpercatinib as a second-line treatment [25], stating that the single-arm LIBRETTO-001 trial could not provide an estimate of the relative efficacy of selpercatinib compared with existing alternatives. The reimbursement application was updated in June 2022 to include an indication extension [26], evaluating selpercatinib as a first-line monotherapy, given the expectation of comparative evidence from the then ongoing randomized phase III LIBRETTO-431 trial [25]. In October 2023, the findings from the randomized phase III LIBRETTO-431 trial [27] were published, which evaluated selpercatinib compared with pembrolizumab in combination with pemetrexed and platinum-based chemotherapy as a first-line treatment. The phase III evidence was used to supplement the market access application of selpercatinib as first-line treatment. In October 2024, NOMA approved the reimbursement of selpercatinib as first-line treatment on the basis of the information on the treatment-naïve subpopulation in the updated phase II LIBRETTO-001 trial [28] and information from the phase III LIBRETTO-431 trial [23].

In this stakeholder-initiated case study of SEE, we exploit the timeline delay between the publication of the LIBRETTO-001 phase II and LIBRETTO-431 phase III findings to explore the feasibility of using SEE as additional evidence in cost-effectiveness analyses to potentially support an earlier, phase II-based (conditional) reimbursement decision of selpercatinib compared with the standard of care (SoC) for first-line treatment of advanced RET fusion-positive NSCLC. Owing to availability of external control studies and treatment crossover observed in the phase III LIBRETTO-431 RCT, we also evaluated the impact of supplementing the analysis with other sources of external evidence (i.e., published clinical evidence and RWE). This

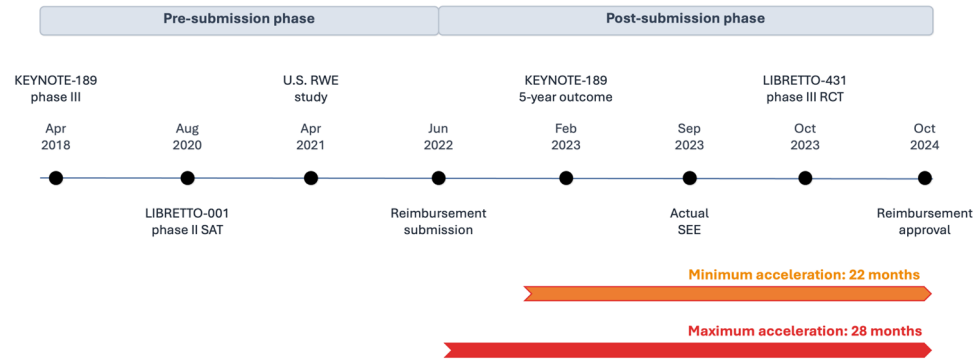

Fig. 1 Timeline impact of SEE on reimbursement. *Note*: The range assumes a hypothetical SEE timepoint before reimbursement submission. The 28-month estimate assumes SEE-informed evidence was available at submission; the 22-month estimate allows for up to 180 days of assessment after submission. *RCT*, randomized controlled trial; *RWE*, real-world evidence; *SAT*, single-arm trial; *SEE*, structured expert elicitation

study contributes to HTA methodology by providing empirical evidence on how SEE can supplement early-phase evidence to support timely cost-effectiveness evaluations.

2 Methods

2.1 Analytical Overview

We used a model-based approach to conduct a series of cost-effectiveness analyses, grouping different sources of evidence (i.e., published clinical evidence and SEE) to estimate the long-term health and economic consequences of selpercatinib versus pembrolizumab plus pemetrexed and platinum-based chemotherapy for patients with advanced RET fusion-positive NSCLC in Norway. Given the June 2022 adjustment of the selpercatinib reimbursement application to extend its indication to the first-line setting, we chose this timepoint as a hypothetical first-line reimbursement submission. We categorized available SoC evidence into either "pre-submission" or "post-submission" phases (Fig. 1), on the basis of their availability relative to this hypothetical submission timepoint. To assess whether incorporating SEE would result in cost-effectiveness findings consistent with those obtained once phase III evidence became available, we compared the cost-effectiveness findings associated with SoC evidence potentially available prior to June 2022 (i.e., "pre-submission evidence"), which includes SEE, with the cost-effectiveness findings using evidence available after June 2022 (i.e., "post-submission evidence"). We evaluated future costs and health outcomes over the remaining lifetime of the cohort, in accordance with Norwegian HTA guidelines [29]. Costs were measured in 2024 Norwegian Kroner and converted to 2024 US dollars (exchange rate 1 USD = 10.7574 NOK) [30]. Costs and health outcomes were discounted at 4% annually, as recommended by the Norwegian guidelines [29]. We adopted an extended healthcare perspective, in line with Norwegian guidelines [29]. Incremental cost-effectiveness ratios (ICERs), calculated as the additional costs per quality-adjusted life-years (QALY) gained, were compared with the Norwegian severity-specific cost-effectiveness threshold, based on the absolute shortfall (see Supplementary Document and Supplementary Table S1), of $46,015 per QALY [31] to indicate a cost-effective intervention. Key model inputs, including long-term survival, health-related quality-of-life (HRQoL) inputs, and cost inputs, are provided in Table 1.

2.2 Target Patient Population

The target patient population was based on the Norwegian reimbursement dossier [23]: Norwegian patients who were aged at least 18 years with pathologically confirmed unresectable stage IIIB, IIIC, or IV metastatic RET-positive nonsquamous NSCLC who had not previously received systemic treatment for metastatic disease, i.e., first-line treatment.

2.3 Interventions

We compared selpercatinib 160 mg twice daily in continuous 21-day cycles with pembrolizumab plus pemetrexed and platinum-based chemotherapy, which represents the current SoC and the relevant comparator for reimbursement decision-making in Norway for first-line treatment of advanced nonsquamous RET fusion-positive NSCLC. Chemotherapy alone is not considered a clinically relevant or reimbursed first-line option in the Norwegian setting and was therefore not included as a comparator. Specifically, the SoC arm received pembrolizumab 200 mg once every 21 days, for up to 35 cycles (24 months), carboplatin (area under the concentration–time curve, 5 mg per milliliter per minute)

Table 1 Key parameter inputs

Parameter	Base-case assumption or value	Source
SEE-based model fit and extrapolation		
"Pre-submission" SoC PFS in analysis 1	Weibull	SEE
"Pre-submission" SoC OS in analysis 1	Weibull	SEE
"Pre-submission" SoC PFS in analysis 2	Log-normal	SEE + KEYNOTE-189 trial [35]
"Pre-submission" SoC OS in analysis 2	Gen Gamma	SEE + KEYNOTE-189 trial [35]
"Pre-submission" SoC PFS in analysis 3	Log-normal	SEE + US RWE study [36]
"Pre-submission" SoC OS in analysis 3	Gen Gamma	SEE + US RWE study [36]
Trial-based model fit and extrapolation		
"Pre-submission" selpercatinib PFS	Gamma (shape: 0.335, rate: −0.474)	LIBRETTO-001 trial [28]
"Pre-submission" selpercatinib OS	Gompertz (shape: 0.387, scale: −2.229)	LIBRETTO-001 trial [28]
"Pre-submission" SoC PFS in analysis 4	Log-logistic (shape: 0.480, scale: −0.338)	KEYNOTE-189 trial [35]
"Pre-submission" SoC OS in analysis 4	Weibull (shape: 0.156, scale: 0.889)	KEYNOTE-189 trial [35]
"Pre-submission" SoC PFS in analysis 5	Log-logistic (shape: 0.347, scale: −0.605)	US RWE study [36]
"Pre-submission" SoC OS in analysis 5	Exponential (rate: −0.720)	US RWE study [36]
"Post-submission" selpercatinib PFS	Gamma (shape: −0.122, rate: −1.267)	LIBRETTO-431 trial [27]
"Post-submission" selpercatinib OS	Gompertz (shape: 0.723, rate: −2.773)	LIBRETTO-431 trial [27]
"Post-submission" SoC PFS	Gamma (shape: −0.025, rate: −0.391)	LIBRETTO-431 trial [27]
"Post-submission" SoC OS in analysis 6	Gompertz (shape: 0.423; rate: −2.322)	LIBRETTO-431 trial [27]
"Post-submission" SoC OS in analysis 7	Log-logistic (shape: 0.319, scale: 0.615)	KEYNOTE-189 5-year outcomes [37]
HRQoL inputs		
PFS	0.84	Nafees et al. [41]
PD	0.17	Nafees et al. [41]
Adverse event HRQoL decrements		
ALT/AST increase	−0.00	Yi et al. [53]
Neutropenia	−0.35	Nafees et al. [41]
Hypertension	−0.03	Nafees et al. [41]
Fatigue	−0.29	Nafees et al. [41]
QT prolongation on ECG	−0.03	Yi et al. [53]; Nafees et al. [41]
Thrombocytopenia	−0.35	Yi et al. [53]; Nafees et al. [41]
Leukopenia	−0.35	Yi et al. [53]; Nafees et al. [41]
Anemia	−0.35	Yi et al. [53]; Nafees et al. [41]
*Costs ($, per 3-week cycle)**		
Selpercatinib	8524	Legemiddelsøk [44]
Pembrolizumab	6180	Legemiddelsøk [44]
Pemetrexed	1926	Legemiddelsøk [44]
Carboplatin	346	Legemiddelsøk [44]
Vitamin B12	5	Legemiddelsøk [44]
Folic acid	3	Legemiddelsøk [44]
Outpatient visit (assumed DRG code 904C)	233	Norwegian Directorate of Health [45]
Best supportive care	4106†	Michel et al. [46]
End of life	15,182†	Michel et al. [46]

Table 1 (continued)

Parameter	Base-case assumption or value	Source
*Adverse event costs ($, one-off cost)**		
AST/ALT increase	22,964	Bilir et al. [48]; Norwegian Directorate of Health [45]
Neutropenia	20,279	Bilir et al. [48]; Norwegian Directorate of Health [45]
Hypertension	12,525	Bilir et al. [48]; Norwegian Directorate of Health [45]
Fatigue	9245	Bilir et al. [48]; Norwegian Directorate of Health [45]
QT prolongation on ECG	12,525	Bilir et al. [48]; Norwegian Directorate of Health [45]
Thrombocytopenia	15,805	Bilir et al. [48]; Norwegian Directorate of Health [45]
Leukopenia	20,279	Bilir et al. [48]; Norwegian Directorate of Health [45]
Anemia	11,034	Bilir et al. [48]; Norwegian Directorate of Health [45]

ALT, alanine aminotransferase; *AST*, aspartate aminotransferase; *ECG*, electrocardiogram; *Gen Gamma*, generalized gamma distribution; *HRQoL*, health-related quality-of-life; *OS*, overall survival; *PD*, progressed disease; *PFS*, progression-free survival; *QT*, QT interval; *RCT*, randomized controlled trial; *RWE*, real-world evidence; *SEE*, structured expert elicitation; *SoC*, standard of care.

*Costs were rounded to the nearest integer

†These cost estimates were initially reported in 2013 Euros, but were converted to Norwegian Kroner using the 2013 average annual exchange rate (1 Euro = 7.8087 NOK) [54], and subsequently inflated to 2024 prices using Norwegian inflation indices (1.39303)[55]

every 21 days for 4 cycles, and pemetrexed (500 mg/m^2) every 21 days.

Patients discontinuing the above first-line treatment continue with second-line treatment. The patients who received selpercatinib continued with pembrolizumab plus pemetrexed and platinum-based chemotherapy, whereas the second-line treatment for patients in the SoC arm was docetaxel (100 mg/m^2) every 21 days for up to ten cycles (7 months). These assumptions reflect a simplified, but representative, second-line treatment for each treatment arm based on Norwegian clinical practice and national guidelines. Although subsequent-line treatment patterns are heterogeneous in real-world clinical practice, this approach was adopted to ensure consistency across analyses. After completion of second-line treatment, patients were assumed to receive best supportive care (BSC) until death.

2.4 Outcomes

The outcomes included long-term survival such as progression-free survival (PFS) and overall survival (OS), extrapolated either from available clinical trials and RWE studies or from SEE. We further leveraged long-term survival to evaluate discounted total costs, quality-adjusted life-years (QALYs), life-years (LYs), and incremental cost-effectiveness ratios (ICERs) to compare the cost-effectiveness of selpercatinib with SoC.

2.5 Model Structure

We developed a partitioned survival model (PSM) in R version 4.2.1 [32, 33] with a 3-week cycle length to probabilistically project expected costs and outcomes over time for first-line treatment of selpercatinib and SoC, based on PFS and OS curves derived from available clinical evidence or SEE. Consistent with standard practice in PSM [34], PFS and OS were modeled as independent survival functions rather than assuming a correlation between treatment effects. As a result, incremental OS benefits are not mathematically derived from PFS, and improvements in PFS do not imply proportional improvements in OS. Instead, time spent in the progressive disease (PD) state is defined by the area between the PFS and OS curves. Therefore, the model consists of three mutually exclusive health states: PFS, PD, and death (D) (Supplementary Fig. S1). The cohort of patients was assumed to start in the PFS state. Over time, the proportion of patients in each health state was determined by the PFS and OS curves, with the time spent in the PD state calculated as the difference in area between these two curves. Accordingly, incremental QALYs may arise not only from differences in OS, but also from differences in the amount of time spent in the PFS and PD states, which are associated with different HRQoL values in the model (Table 1). Patients transitioning from the PFS state to the PD state were assumed to initiate second-line treatment. Upon completion of second-line treatment, patients were assumed to receive BSC until death.

2.6 Clinical Parameters Overview

We derived clinical parameters from two sources: published clinical evidence and SEE. Our primary clinical evidence included PFS and OS curves from the phase II LIBRETTO-001 and phase III LIBRETTO-431 trials. For the post-submission analyses based on LIBRETTO-431, the PFS and OS for the SoC arm were derived from the intention-to-treat (ITT) pembrolizumab population. Although not all patients assigned to this arm ultimately received

Table 2 Progression-free survival (PFS) and overall survival (OS) estimates from structured expert elicitation

	Expert 1			Expert 2			Expert 3		
Time points	1 Year	2 Year	5 Year	1 Year	2 Year	5 Year	1 Year	2 Year	5 Year
PFS									
Alpha	45.41	13.39	3.62	15.96	11.23	–	18.50	12.66	6.24
Beta	75.56	62.40	58.95	14.20	38.31	–	27.68	38.43	48.85
Median	37.50	17.40	5.32	53.00	22.30	–	39.90	24.40	10.90
Lower bound	25.00	5.00	0.00	30.00	10.00	–	25.00	15.00	5.00
Upper bound	50.00	30.00	15.00	75.00	35.00	–	55.00	40.00	20.00
OS									
Alpha	46.55	35.32	13.39	18.99	15.66	–	21.32	37.36	5.97
Beta	20.05	43.13	62.40	12.49	41.04	–	9.23	43.63	22.79
Median	70.10	45.00	17.40	60.60	27.40	–	70.20	46.10	20.10
Lower bound	55.00	30.00	5.00	40.00	15.00	–	50.00	35.00	5.00
Upper bound	85.00	60.00	30.00	80.00	40.00	–	90.00	60.00	35.00

OS, overall survival; *PFS*, progression-free survival

Expert 2 did not provide 5-year PFS or OS estimates during the elicitation; these cells are shown as –

pembrolizumab, the ITT population reflects a predominantly pembrolizumab-based chemo-immunotherapy strategy, consistent with Norwegian first-line practice.

To complement the primary evidence, we also incorporated data from three external studies, two in the "pre-submission" phase and one in the "post-submission" phase (Fig. 1). In addition, to further supplement the evidence for the "pre-submission" SoC, we conducted SEE to gather expert opinions regarding survival probabilities for various time points (Table 2). For long-term projections of PFS and OS, we used parametric regression to extrapolate the values beyond the observed durations.

2.6.1 Published Clinical Evidence

In addition to our primary evidence, two "pre-submission phase" studies were identified to supplement the SoC evidence: (1) the pembrolizumab treatment arm of the phase III KEYNOTE-189 RCT, i.e., SoC in our analysis [35], and (2) a RWE study from the USA, providing the real-world clinical evidence of SoC [36]. Neither of these two studies were specific to the RET fusion-positive NSCLC population. The KEYNOTE-189 RCT included patients with metastatic nonsquamous NSCLC without sensitizing epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutations, while the US RWE study included patients whose tumors tested negative for EGFR and ALK alterations. Although both sources represent RET-unselected populations, in the absence of RET fusion-positive comparator data for pembrolizumab-based chemo-immunotherapy, these studies were considered as the best available external evidence to inform pre-submission SoC effectiveness.

We also identified one additional study to complement the SoC evidence in the "post-submission phase": the 5-year outcomes from the phase III KEYNOTE-189 trial [37]. We reviewed and compared the patient characteristics of these external studies with those of the target patients in the phase II LIBRETTO-001 and phase III LIBRETTO-431 trials (Supplementary Table S2).

2.6.2 Extrapolation of Published Clinical Evidence

We used parametric regression approaches to allow for extrapolation of PFS and OS up to the lifetime horizon. As individual patient data (IPD) were not available for any of the studies, we first reconstructed IPD from the Kaplan–Meier (KM) PFS and OS curves by using the IPDfromKM package in R [38]. Parametric models were then fit to the KM trial data for PFS and OS for extrapolating effectiveness estimates from the short-term trial periods (range 19–42 months) to the remaining lifetime horizon. The survival curve fitting was carried out in line with the Norwegian guidelines [29]. In the base case, we fitted exponential, Weibull, log-normal, log-logistic, Gompertz, gamma, generalized gamma, and Royston–Parmar spline distributions. Model fit was assessed using the Akaike information criterion (AIC) and the Bayesian information criterion (BIC) (Supplementary Table S3), combined with visual inspection and clinical plausibility, to select the best-fitting parametric distributions for the model. Hazard rates over time, estimated nonparametrically from the observed data using kernel-based methods, were compared with hazard rates predicted by each parametric model to assess the long-term extrapolations. Results of the extrapolation are provided in Supplementary Table S4 and Supplementary Figs. S3–S13.

Importantly, for phase III LIBRETTO-431, patients who experienced disease progression were eligible for treatment crossover to selpercatinib [27], leading to uncertainty regarding the survival benefit of the SoC. As current statistical approaches are inadequate for treatment switch adjustments without IPD, we did not adjust the OS treatment effect estimate for treatment crossover. Alternatively, we factored in the costs for the estimated proportion of patients switching from SoC to selpercatinib.

2.6.3 Structured Expert Elicitation

To supplement the pre-submission SoC evidence, we conducted a SEE in September 2023 prior to the phase III LIBRETTO-431 results presented at the European Society for Medical Oncology [39] (Fig. 1). Three Norwegian clinical oncologists with experience in treating advanced lung cancer were identified and shortlisted by NOMA. An evidence dossier summarizing relevant clinical trial data, along with standardized guidance on probabilistic judgements, were provided to the experts in advance. Using a facilitated individual elicitation process, based on the SHELF framework [16], experts provided their probabilistic judgments on the distributions of PFS and OS for three time points (i.e., 1, 2, and 5 years). We aggregated individual estimates from experts using linear pooling and a Bayesian method within the expertsurv package in R [40]. Details about the elicitation procedures can be found in the Supplementary Document and Supplementary Table S5.

2.6.4 SEE Extrapolation

We applied the Bayesian method developed by Cooney and White to fit a range of parametric models [40], including the exponential, Weibull, log-normal, log-logistic, and Royston–Parmar spline distributions, to the SEE-informed estimates to extrapolate long-term survival. We used elicited estimates in two ways as "pre-submission" evidence for SoC, either as the sole source of information or combined with other external published clinical evidence, to investigate their impact. Consistent with our extrapolation approach for published clinical evidence, we evaluated the AIC and BIC, combined with visual inspection and clinical plausibility, to select the best-fitting parametric distributions. We evaluated the long-term plausibility by comparing the projected survival against aggregated expert-elicited uncertainty ranges. Parametric survival curves showing repeated deviations from the expert uncertainty intervals across multiple elicited timepoints were considered less plausible for extrapolation. However, parametric distributions with a single or minor deviation, particularly at later timepoints, were not excluded but would be given lower priority relative to models showing closer agreement. Results of SEE extrapolation can be found in Supplementary Table S6.

2.7 Health-Related Quality of Life (HRQoL) Inputs

As HRQoL data for Norwegian patients with NSCLC are not available, we utilized UK-specific HRQoL values from a published study [41], which employed time trade-off methods to measure HRQoL for NSCLC patients receiving first-line treatment in the UK, Australia, China, France, and Korea (Table 1). We considered adverse events (AEs) of grade 3 or higher with an incidence of 5% or more, on the basis of the phase III LIBRETTO-431 trial (Supplementary Table S7), including aspartate aminotransferase (AST) increase, alanine aminotransferase (ALT) increase, hypertension, fatigue, thrombocytopenia, leukopenia, neutropenia, QT prolongation on electrocardiogram (ECG), and anemia. HRQoL decrements associated with AEs, based on the same HRQoL study [41], were applied (Table 1). We assumed that the decrement of QT prolongation on ECG was the same as hypertension, and the decrements of thrombocytopenia, leukopenia, and anemia were the same as neutropenia.

2.8 Resource Use

Resource use linked to first-line treatment, subsequent treatment, disease management, AE management, clinical tests, and follow-up procedures was derived from official Norwegian guidelines [42], published literature [43], and independent expert opinion (Table 1). Drug prices were derived from the NOMA medicine database [44] of maximum pharmacy purchase price less value added tax. These costs were applied at each infusion up to disease progression or death and limited to dosing schedule reported in LIBRETTO-431 (see "Interventions" section).

We applied outpatient visit costs, based on 2024 diagnosis-related group (DRG) (~ $4857) with DRG weight of 0.048 (DRG code 904 C) [45], to reflect routine disease monitoring and clinical management during active treatment. Patients receiving selpercatinib were assumed to receive an outpatient visit at treatment initiation, at months 2, 4, and 7, and subsequently every 3 months thereafter. Patients receiving pembrolizumab-based chemo-immunotherapy or docetaxel were assumed to have outpatient visits every 3 weeks. As a proxy for BSC costs, we used average healthcare costs incurred in specialist care for cancer patients during the final 2–3 months before death based on Norwegian data. End-of-life costs were applied as a one-off cost at death and were estimated using average primary care and home- or community-based care costs for death of cancer patients. Both BSC and end-of-life costs (Table 1) were based on published literature [46].

Table 3 Source of evidence for selpercatinib and standard of care (SoC) in the pre-submission and post-submission analyses

	Selpercatinib	SoC	
Pre-submission analyses	LIBRETTO-001	Using SEE	(1) SEE (2) SEE + KEYNOTE-189 (3) SEE + US RWE
		Without SEE	(4) KEYNOTE-189 (5) US RWE
Post-submission analyses	LIBRETTO-431	Without external evidence	(6) LIBRETTO-431
		Using external evidence	(7) LIBRETTO-431 + KEYNOTE-189 5-year outcomes

SEE, structured expert elicitation; *RWE*, real-world evidence

Similar to the Canadian Agency for Drugs and Technologies in Health (CADTH) reimbursement review [47], we applied a one-off cost associated with treatment-related AEs at the onset of the model (i.e., in the first cycle) under the assumptions that all identified AEs required hospitalization. The average duration of hospitalization was extracted from a paper [48] that provided the mean length of hospitalization stay of treating grade 3 or 4 AEs associated with metastatic melanoma in the USA (Supplementary Table S7). The hospitalization cost was based on the DRG weight of 0.614 (DRG code 102) and cost of treating lung cancer patients in the Norwegian guideline [45]. We assumed that the cost of managing leukopenia was the same as neutropenia, the cost of managing fatigue was similar to managing nausea, and the cost of QT prolongation on ECG was the same as hypertension.

2.9 Analyses

2.9.1 Analysis Overview

We conducted a total of seven cost-effectiveness analyses (Table 3): five "pre-submission" analyses and two "post-submission" analyses.

First, we conducted three "pre-submission" phase cost-effectiveness analyses that directly incorporated SEE to inform SoC estimates, with selpercatinib data from the phase II LIBRETTO-001 SAT, including using:

(1) Aggregated SEE information alone
(2) Aggregated SEE information, combined with data from the KEYNOTE-189 phase III trial as a prior
(3) Aggregated SEE information, combined with the US RWE data as a prior

We conducted two additional "pre-submission" phase analyses that did not utilize SEE to inform SoC estimates by using:

(4) KEYNOTE-189 phase III alone
(5) US RWE data alone

Finally, in the "post-submission" phase, we conducted two cost-effectiveness analyses that incorporated the phase III LIBRETTO-431 RCT:

(6) Directly applied LIBRETTO-431 phase III trial data for both selpercatinib and SoC, and adjusted treatment costs in the SoC for the proportion of patients (assumed 54%) who switched from SoC to selpercatinib
(7) Adjusted SoC by substituting the OS curves with the KEYNOTE-189 5-year outcomes and maintained the PFS curves from the LIBRETTO-431 phase III

Notably, in the LIBRETTO-431 trial, patients randomized to the SoC arm were permitted to switch to selpercatinib upon disease progression. Several statistical approaches can, in principle, be used to adjust OS estimates for treatment crossover, including rank-preserving structural failure time models, inverse probability of censoring weights, or surrogacy-based adjustment. In addition, assumptions regarding post-progression survival duration according to subsequent treatment received could also be considered. However, these approaches require access to IPD, including information on the timing of crossover, duration of post-progression treatment, and outcomes after switching, or otherwise rely on strong and unverifiable assumptions when only published data are available. As IPD from LIBRETTO-431 were not publicly available, we did not consider these approaches sufficiently robust for the present analysis. Consequently, OS treatment effects were not adjusted for crossover. Instead, we chose to reflect the observed trial design by incorporating the drug costs associated with treatment switching for the estimated proportion of patients who crossed over from SoC to selpercatinib. Our intention was not to redefine the comparator or to assume routine Norwegian practice after progression, but rather to capture the economic consequences of crossover without imposing assumptions about its effect on survival. In doing so, we aimed to preserve an internally consistent, trial-based incremental comparison (and ICER), not to emulate Norwegian practice per se.

2.9.2 Assessing the Predictive Validity of SEE

Within the "pre-submission" phase, we compared Markov traces for PFS and OS derived from SEE-informed SoC estimates versus those obtained from published literature (KEYNOTE-189 and US RWE). Additionally, we also compared Markov traces for PFS derived from SEE-informed SoC estimates in the pre-submission phase with those from the LIBRETTO-431 RCT.

2.9.3 Probabilistic Cost-Effectiveness Analyses

All cost-effectiveness analyses were performed probabilistically through Monte Carlo simulations across 10,000 iterations, jointly sampling key model parameter inputs from their commonly recommended parametric distributions (Table 1).

We compared mean discounted costs, QALYs, and ICERs:

(1) Among three SEE-informed analyses within the pre-submission phase,
(2) Between three SEE-informed analyses and two non-SEE analyses within the pre-submission phase
(3) Across the pre- and post-submission phases

Costs were disaggregated (i.e., first-line treatment, second-line treatment, best supportive care, patient follow-up (including outpatient visits and computed tomography (CT) scans), AE management, and end-of-life costs) to identify key cost drivers across pre- and post-submission analyses.

2.9.4 Scenario Analyses

2.9.4.1 Time Horizon Scenario Analyses To assess the sensitivity of the results to the analytic time horizon, we conducted additional scenario analyses using shorter time horizons of 5 years and 10 years, respectively. The resulting cost-effectiveness estimates were compared with those from the base-case analysis using a remaining lifetime horizon.

2.9.4.2 Parametric Survival Distribution Scenario Analyses To assess the sensitivity of the results to long-term survival extrapolation, we conducted scenario analyses comparing the base-case parametric distributions with alternative parametric distributions for selected survival curves.

First, in the pre-submission analysis using aggregated SEE information alone (i.e., analysis 1 described in Sect. 2.9.1), for the SoC OS curve informed by SEE, we used a Weibull distribution in the base case and an exponential distribution in the scenario analysis.

Second, in the post-submission analysis (i.e., analysis 6 described in Sect. 2.9.1), we explored an alternative distribution for the SoC OS curve in the LIBRETTO-431 RCT. We extrapolated the SoC OS curve from the LIBRETTO-431 RCT using a Gompertz distribution in the base case and a Weibull distribution (shape: 0.077, scale: 1.891) in the scenario analysis.

We compared the cost-effectiveness results from these two scenario analyses with those from the corresponding base-case analyses.

3 Results

3.1 Assessing the Predictive Validity of SEE

Using SEE-informed SoC estimates, either alone or combined with external published literature (i.e., KEYNOTE-189 trial or US RWE study), yielded similar long-term PFS and OS curves as using the external published literature alone (Fig. 2). SEE-informed SoC estimates in the "pre-submission" phase projected lower long-term PFS compared with extrapolating the PFS curve of SoC from the LIBRETTO-431 phase III RCT in the "post-submission" phase (Fig. 2).

3.2 Probabilistic Cost-Effectiveness Analyses

3.2.1 Among Three SEE-Informed Analyses within the Pre-Submission Phase

Within the pre-submission phase, using aggregated SEE information, either alone or combined with data from KEYNOTE-189 trial or US RWE study as a prior, yielded similar outcomes for SoC, with total mean discounted costs ranging from $37,243 (95% credible interval [CrI] $32,656–42,550) to $38,344 (95% CrI $33,444–43,892), and total mean discounted QALYs from 1.00 (95% CrI 0.80–1.23) to 1.29 (95% CrI 0.85–2.84). Selpercatinib, based on LIBRETTO-001 phase II SAT, increased mean discounted costs to $51,994 (95% CrI $42,626–67,800) and total mean discounted QALYs to 1.98 (95% CrI 1.47–2.80), resulting in ICERs ranging from $15,043 to $19,819 per QALY gained (Table 4).

3.2.2 Between Three SEE-Informed Analyses and Two Non-SEE Analyses within the Pre-Submission Phase

Compared with the three SEE-informed analyses above, using either the KEYNOTE-189 trial or the US RWE study alone to inform SoC evidence led to similar total mean discounted costs and slightly lower QALYs (Table 4). For example, using KEYNOTE-189 trial

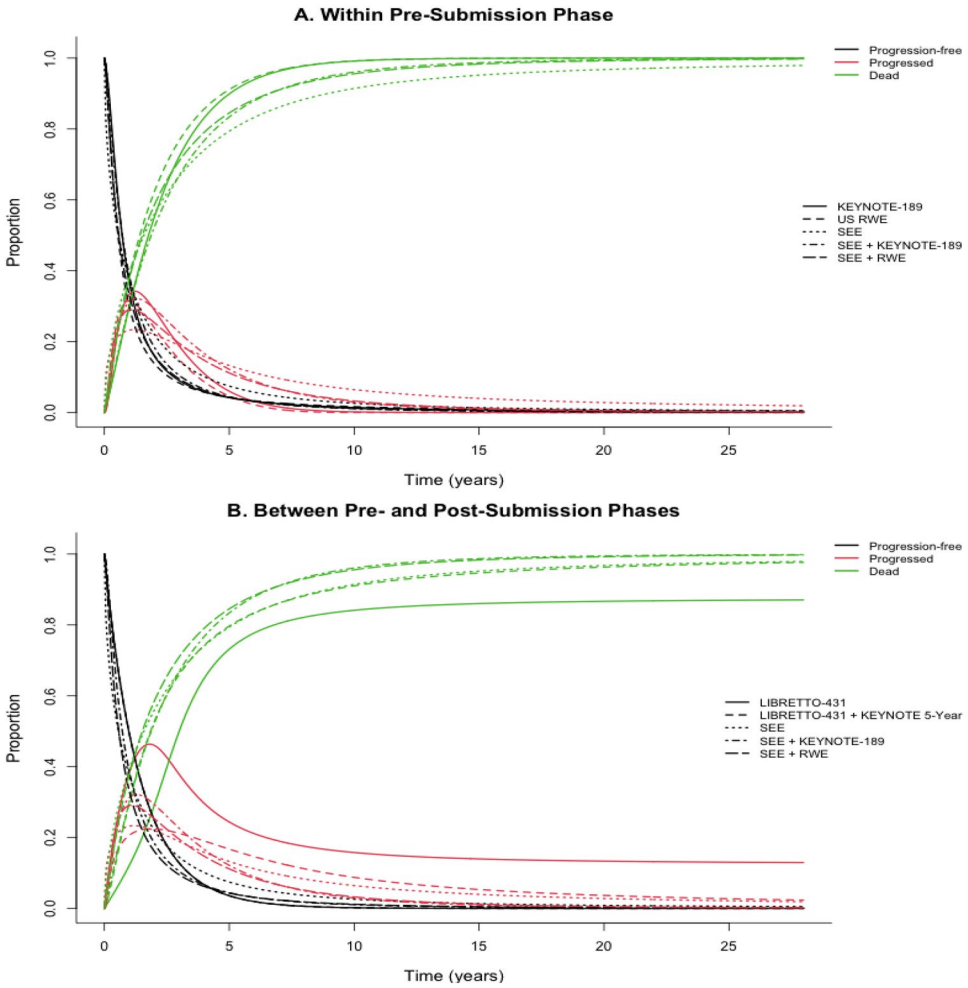

Fig. 2 Mean proportions of SoC patients in progression-free, progressive, and death states within pre-submission phase (**A**) and between pre- and post-submission phases (**B**)

alone resulted in mean discounted costs of $36,912 (95% CrI $32,472–42,056) and mean discounted QALYs of 1.03 (95% CrI 0.83–1.25). Using US RWE alone resulted in mean discounted costs of $35,428 (95% CrI $31,284–40,079) and mean discounted QALYs of 0.92 (95% CrI 0.73–1.13). Compared with these SoC estimates, selpercatinib yielded similar ICERs of $15,909 and $15,570 per QALY gained, respectively. The ICERs were similar to those in the three SEE-informed analyses above.

3.2.3 Across the Pre- and Post-Submission Phase

In the post-submission analysis, using LIBRETTO-431 phase III alone to inform SoC yielded mean discounted costs of $48,467 (95% CrI $35,718–82,526) and mean discounted QALYs of 1.56 (95% CrI 0.90–3.28). When we substituted the SoC OS with the KEYNOTE-189 5-year outcomes data, the mean discounted costs and QALYs were both lower, at $40,926 (95% CrI $34,714–46,825) and 1.27 QALYs (95% CrI 0.96–1.62), respectively. By contrast, selpercatinib, based on LIBRETTO-431 phase III evidence, increased mean discounted costs to $56,047 (95% CrI $45,090–71,821) and mean discounted QALYs to 2.47 (95% CrI 1.79–3.37), yielding ICERs of $8257 per QALY gained when using LIBRETTO-431 phase III alone and $12,576 per QALY gained when using the complementary KEYNOTE-189 5-year outcomes.

Additionally, the relative contribution of cost components remained consistent between the pre- and post-submission phases (Supplementary Table S8). For selpercatinib, first-line treatment was the main driver of total discounted costs, accounting for approximately 41% in the pre-submission analysis and 44% in the post-submission analysis, followed by AE management and end-of-life costs, each contributing approximately 23%. For SoC, end-of-life represented the largest share of total costs across all evidence sources in the pre-submission analyses (34–39%), followed by AE management (28–31%). A similar pattern was observed in the post-submission analyses.

Overall, ICERs from all seven analyses, ranging between $8257 and $19,819 per QALY gained, were consistently below the estimated Norwegian disease severity-specific cost-effectiveness threshold of $46,015 per QALY, indicating that selpercatinib is likely to be cost-effective compared

Table 4 Probabilistic mean (95% credible interval) cost-effectiveness results from 10,000 simulations*

Phases	Strategies	Sources of evidence	Discounted total costs ($)	Discounted total QALYs	Discounted total LYs	ICERs (SoC versus selpercatinib) ($/QALY)	ICERs (SoC versus selpercatinib) ($/LY)
Pre-submission	SoC						
	(1)	SEE	38,220 (31,947–47,728)	1.29 (0.85–2.84)	2.99 (2.03–5.08)	19,819	25,146
	(2)	SEE + KEYNOTE-189	38,344 (33,444–43,892)	1.11 (0.89–1.36)	2.62 (2.15–3.29)	15,593	14,845
	(3)	SEE + US RWE	37,243 (32,656–42,550)	1.00 (0.80–1.23)	2.43 (2.00–2.96)	15,043	13,324
	(4)	KEYNOTE-189	36,912 (32,472–42,056)	1.03 (0.83–1.25)	2.25 (1.87–2.71)	15,909	11,701
	(5)	US RWE	35,428 (31,284–40,079)	0.92 (0.73–1.13)	2.01 (1.75–2.29)	15,570	10,839
	Selpercatinib	LIBRETTO-001	51,994 (42,626–67,800)	1.98 (1.47–2.80)	3.54 (2.48–7.83)	/	/
Post-submission	SoC						
	(6)	LIBRETTO-431	48,467 (35,718–82,526)	1.56 (0.90–3.28)	4.86 (2.00–13.25)	8,257	−6,385
	(7)	LIBRETTO-431 + KEYNOTE 5-year outcomes	40,926 (35,714–46,825)	1.27 (0.96–1.62)	3.15 (2.80–3.52)	12,576	29,207
	Selpercatinib	LIBRETTO-431	56,047 (45,090–71,821)	2.47 (1.79–3.37)	3.67 (2.78–6.41)	/	/

ICER, incremental cost-effectiveness ratio; *LY*, life-year; *QALY*, quality-adjusted life-year; *RWE*, real-world evidence; *SEE*, structured expert elicitation; *SoC*, standard of care

*Costs and ICERs were rounded to the nearest integer; QALYs and LYs were rounded to two decimal places

with SoC. Undiscounted total life-years (LYs) and QALYs are provided in Supplementary Table S9.

3.3 Scenario Analyses

3.3.1 Time Horizon Scenario Analyses

Compared with the base-case analyses using a remaining lifetime horizon, reducing the time horizon to 5 or 10 years lowered mean discounted costs, QALYs, and LYs for both selpercatinib and SoC across all pre- and post-submission analyses (Supplementary Table S10). However, given the Norwegian severity-specific cost-effectiveness threshold of $46,015 per QALY gained, selpercatinib remained cost-effective under the 5-year or 10-year time horizon across both pre- and post-submission analyses.

3.3.2 Parametric Survival Distribution Scenario Analyses

In the pre-submission SEE-only analysis, replacing the base-case Weibull distribution with an Exponential distribution for SoC OS decreased mean discounted costs for SoC from $38,220 to $36,554, mean discounted QALYs from 1.29 to 1.21, and mean discounted LYs from 2.99 to 2.55. Compared with the base-case ICER of $19,819 per QALY gained, the corresponding ICER increased to $20,084 per QALY gained (Supplementary Table S11).

In the post-submission LIBRETTO-431 analysis, replacing the base-case Gompertz distribution with a Weibull distribution increased mean discounted costs for SoC from $48,467 to $50,859, mean discounted QALYs from 1.56 to 1.64, and mean discounted LYs from 4.86 to 5.37. Compared with the base-case ICER of $8,257 per QALY gained, the corresponding ICER decreased to $6,226 per QALY gained (Supplementary Table S11).

Under both alternative extrapolation assumptions, the ICERs remained below the Norwegian severity-specific cost-effectiveness threshold of $46,015 per QALY.

4 Discussion

This study highlights the potential value of SEE in cost-effectiveness analyses, particularly to facilitate quicker and earlier reimbursement decisions when phase III RCT data are limited or immature. When using LIBRETTO-431 phase III RCT, the cost-effectiveness results in the post-submission phase were similar to all five pre-submission phase analyses,

indicating that selpercatinib would likely be considered cost-effective. Specifically, integrating SEE-informed SoC evidence (either alone or combined with other external evidence) with LIBRETTO-001 phase II SAT resulted in ICERs ranging from $15,043 to $19,819 per QALY gained, which are consistently below the severity-specific cost-effectiveness threshold in Norway. Therefore, in this case study, incorporating SEE (alone or combined with external clinical evidence) would have led to a reimbursement conclusion similar to that reached after the LIBRETTO-431 phase III RCT became available for first-line treatment of selpercatinib for patients with NSCLC in Norway.

However, favorable ICERs in this study do not necessarily imply a clear overall survival advantage for selpercatinib. Across the analyses, discounted and undiscounted LYs for selpercatinib and SoC were relatively similar (Table 4 and Supplementary Table S9), yet selpercatinib still generated additional QALYs through increased time spent in the PFS state, which in our model was assigned a higher HRQoL value (0.84) than the PD state (0.17). Thus, even when differences in OS were small, selpercatinib could still yield favorable ICERs. In the post-submission analyses, this interpretation is further complicated by the treatment crossover in the LIBRETTO-431 RCT, contributing to the wide CrI bounds around OS. However, the ICERs could change owing to changes in HRQoL values assigned to the health states. Importantly, these HRQoL assumptions were applied consistently across both the pre-submission and post-submission phases and are therefore expected to have similar impact on the ICERs, which was the main objective of this study.

In our example, an SEE-informed cost-effectiveness analysis could hypothetically have supported a (conditional) reimbursement decision for selpercatinib in first-line RET fusion-positive advanced NSCLC between 22 and 28 months earlier than the actual reimbursement decision (Fig. 1). The upper bound of 28 months reflects a scenario in which an SEE-informed reimbursement decision could hypothetically have been made at the time of the reimbursement submission in June 2022. The lower bound of 22 months allows for up to 180 days of assessment after submission, consistent with the timeline framework for pricing and reimbursement decisions set out in the EU Transparency Directive [49]. However, this estimate should be interpreted as illustrative, because SEE has not been formally used in Norway to generate survival inputs directly for cost-effectiveness analysis and SEE in this study was applied retrospectively rather than being conducted prior to phase II evidence.

This study contributes significantly to the growing evidence supporting SEE, particularly in light of recent ISPOR recommendations advocating for further empirical research and transparent elicitation processes in this area [11]. Our findings suggest that SEE may potentially complement, rather than replace, clinical evidence in HTA, whether used alone or combined with external clinical evidence, to facilitate reimbursement decision-making when randomized evidence is substantially delayed or infeasible owing to practical, ethical, or feasibility constraints. In particular, SEE may be useful in supporting conditional reimbursement decisions, such as managed entry agreements (MEAs), in which uncertainty is explicitly acknowledged and addressed through risk-sharing mechanisms and planned re-evaluation as additional evidence becomes available. The value of SEE may be even greater in rare disease settings, where robust comparative evidence is often unavailable owing to small patient populations and practical challenges of conducting randomized trials. In such circumstances, SEE may play an important role in informing key model inputs by systematically eliciting expert knowledge. Although our case is not a rare disease indication, future research should explore the application of SEE in rare diseases.

Our study has some limitations. First, our analysis assumed pembrolizumab-based chemo-immunotherapy for all patients in the SoC arm and simplified subsequent-line treatment pathways, which may not reflect the heterogeneity observed in real-world clinical practice. However, these assumptions were applied consistently across both pre- and post-submission analyses. As a result, although absolute ICER values may differ under alternative assumptions that more closely reflect real-world treatment patterns, these modeling choices do not affect the primary objective of the study, which was to evaluate whether the use of SEE in the pre-submission phase would have led to reimbursement conclusions consistent with those informed by subsequent phase III evidence.

Moreover, the external evidence used for pre-submission SoC (i.e., KEYNOTE-189 RCT and US RWE study) was not specific to the RET fusion-positive NSCLC population. Both sources excluded patients with EGFR and ALK alterations but did not select patients on the basis of RET fusion status. Survival outcomes and treatment responsiveness may differ across oncogenic subtypes and patient characteristics, including smoking status. In particular, patients with RET fusion-positive NSCLC are typically never-smokers [50], whereas the KEYNOTE-189 and US RWE populations included a substantially higher proportion of current or former smokers (Supplementary Table S1). A higher prevalence of smoking is generally associated with poorer prognosis in NSCLC and may therefore be correlated with shorter survival in the SoC arms of these external studies. As a result, applying survival estimates from higher smoking populations may lead to underestimation of SoC effectiveness, potentially leading to larger estimated incremental benefits for selpercatinib. However, this potential bias would be expected to be consistent across both the pre- and post-submission analyses. Therefore, while differences in smoking status may introduce uncertainty regarding the absolute effectiveness of the SoC

arm, they are unlikely to affect the primary objective of our study. Moreover, RET fusions are generally mutually exclusive with EGFR and ALK alterations [51, 52], making the external comparator populations, which explicitly excluded EGFR- and ALK-positive tumors, biologically closer to the RET fusion-positive population than an entirely unselected NSCLC cohort. At the time of the pre-submission analysis, no RET-specific evidence was available for pembrolizumab-based chemo-immunotherapy. Hence, the external studies used in this analysis represented the best available evidence. Importantly, this evidence gap highlights the type of evidence gap that SEE is intended to address.

A further limitation relates to the handling of treatment crossover in the LIBRETTO-431 trial. Although several statistical and modelling approaches could, in principle, be used to adjust OS for crossover, including surrogacy-based methods or assumptions regarding post-progression survival, these were not implemented because IPD were unavailable and such approaches would have required strong and unverifiable assumptions. We therefore chose a more transparent approach that reflected the economic implications of crossover through treatment costs only. Had we ignored crossover altogether, the SoC arm would have been assigned lower drug costs than those observed in the trial, which could bias the incremental economic comparison in favor of the comparator. Including crossover-related selpercatinib costs, while imperfect from the perspective of Norwegian routine practice, moves the analysis closer to the true incremental economic consequences of selpercatinib versus the LIBRETTO-431 comparator regimen under the observed trial design. Because treatment crossover is likely to continue to occur in phase III oncology trials, future analyses should evaluate the performance and value of SEE in settings where IPD are available, allowing a more definitive validation of SEE.

There are also limitations related to the elicitation procedures. We explicitly compared our elicitation procedures with established SEE frameworks and practical guidance (Supplementary Table S5). This comparison shows that our approach was aligned with several recommended procedural elements, particularly those highlighted in the recently developed Medical Research Council (MRC) and Structured Expert Elicitation Resources (STEER) guidance, including the use of a pre-read evidence dossier, visual feedback during elicitation, formal mathematical aggregation, and fitting distributions to individual judgments prior to aggregation. At the same time, the comparison also identified important limitations, including the absence of behavioral consensus or group discussion, the lack of formal capture of experts' rationales, and the absence of explicit validation procedures.

In addition, our pragmatic elicitation approach involved a relatively small number of Norwegian clinical experts, which may limit the diversity of perspectives and introduce potential bias. However, we expect to continue encountering such limitations in small countries such as Norway, and such constraints reflect the practical real-world challenges the national HTA bodies of these countries may encounter. Additionally, the restriction of the expert panel to Norwegian clinicians was intentional, as the objective was to elicit judgments aligned with Norwegian clinical practice, which may differ substantially across settings.

Another limitation is that experts may be aware of the existing clinical trial evidence for SoC at the time of elicitation. As a result, it is difficult to know the extent to which elicited judgments were driven by experts' personal clinical experience versus published trial data. However, this challenge is difficult to avoid as the clinicians are closely engaged with the evolving trial evidence. Future elicitation may benefit from explicitly asking experts to justify their judgements.

Generally, SEE outputs may be sensitive to panel size and composition, experts' familiarity with probabilistic reasoning, cognitive biases, and the choice of aggregation methods. Future SEE elicitation may benefit from larger and more multidisciplinary panels, enhanced expert training, and, where appropriate, international participation. Importantly, empirical evidence on how these factors influence SEE performance remains limited, highlighting an important area for future SEE methodological research. Additionally, the recent suggestion to integrate hazard ratios guided by clinical experts to revise individual estimates during the elicitation process [18] should also be explored.

HTA agencies should incorporate the considerations above as they produce and revise SEE guidelines, recognizing both the practical constraints of real-world decision-making and the potential sensitivity of SEE outputs to methodological choices. Ongoing SEE methodological refinement and validation are needed to establish more concrete best practices.

Overall, our findings contribute to ongoing policy discussions about balancing the need for prompt patient access with the robustness of economic evaluations, particularly in scenarios characterized by limited or immature clinical evidence, offering a pragmatic solution to accelerate decision-making in precision oncology.

5 Conclusions

For our single case example of selpercatinib in first-line treatment for patients with RET fusion-positive advanced NSCLC, using SEE alone or complementing existing evidence with SEE in a cost-effectiveness analysis, led to results and reimbursement decisions for selpercatinib similar to those reached once phase III evidence became available. We show that incorporating SEE at the time of the phase II single-arm trial could have potentially facilitated an earlier reimbursement decision or conditional approval while

waiting for a phase III trial. However, the generalizability of our results remains uncertain, and further research should explore the precision of SEE in more indications and disease areas to gather empirical evidence needed for SEE development and its role in HTA decision-making.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s41669-026-00656-9.

Acknowledgements We thank the CONNECT network for supporting this work and for providing a valuable platform for discussion of the case study. We also appreciate the feedback received at the 46th Annual Meeting of the Society for Medical Decision Making (SMDM), at ISPOR Europe 2024, and within the CONNECT network, where earlier versions of this paper were discussed and helped improve the manuscript.

Funding Yancy S. Wu, Emily A. Burger, Eline Aas received funding from the ASCERTAIN grant (grant ID 101094938), funded by the European Union. Additional funding was provided by NORCHER (grant ID 296114, Research Council of Norway). The study was also co-funded by CONNECT and Oslo Economics. The funders had no role in the study design, data analysis, manuscript preparation, or decision to publish. Views and opinions expressed are those of the authors only and do not necessarily reflect those of the European Union or the European Health and Digital Executive Agency (HADEA). Neither the European Union nor the granting authority can be held responsible for them.

Declarations

Conflicts of Interest The authors, Fredrik Holmboe and Magnus Bangum, report employment with AbbVie and contributed to this methodological work in an academic capacity. No other competing interests were declared. All remaining authors claimed that there were no conflicts of interest.

Ethics Approval Not applicable. Ethics approval was not required for this study because it was based on publicly available data and structured expert elicitation with clinicians, and did not involve patient-level identifiable data.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Code Availability The R code file is available in the supplementary material of this article.

Authors' Contributions Yancy S. Wu: conceptualization, methodology, software, formal analysis, investigation, writing—original draft, visualization. Emily A. Burger: conceptualization, methodology, writing—review and editing, visualization, supervision, project administration. Fredrik Holmboe: conceptualization, methodology, software, writing—review and editing, supervision. Magnus Bangum: Methodology, software, writing—review and editing. Francisco Oteiza: Data curation, writing—review and editing, funding acquisition. Christoffer Bugge: Conceptualization, data curation, writing—review and editing, funding acquisition. Erik Magnus Sæther: Data curation, writing—review and editing, funding acquisition. Eline Aas: Conceptualization, methodology, writing—review and editing, supervision, project administration, funding acquisition.

References

1. Van Norman GA. Drugs, devices, and the FDA: Part 1. JACC Basic Transl Sci. 2016;1:170–9. https://doi.org/10.1016/j.jacbts.2016.03.002.
2. European Medicines Agency. Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 2016.
3. Huang Y, Xiong W, Zhao J, Li W, Ma L, Wu H. Early phase clinical trial played a critical role in the Food and Drug Administration–approved indications for targeted anticancer drugs: a cross-sectional study from 2012 to 2021. J Clin Epidemiol. 2023;157:74–82. https://doi.org/10.1016/j.jclinepi.2023.03.006.
4. U.S. Food & Drug Administration. Fast track, breakthrough therapy. In Accelerated Approval, Priority Review; 2023.
5. Jönsson L, Sandin R, Ekman M, Ramsberg J, Charbonneau C, Huang X, et al. Analyzing overall survival in randomized controlled trials with crossover and implications for economic evaluation. Value Health. 2014;17:707–13. https://doi.org/10.1016/j.jval.2014.06.006.
6. Patel D, Grimson F, Mihaylova E, Wagner P, Warren J, Van Engen A, et al. Use of external comparators for health technology assessment submissions based on single-arm trials. Value Health. 2021;24:1118–25. https://doi.org/10.1016/j.jval.2021.01.015.
7. O'Hagan A, Buck CE, Daneshkhah A, Eiser JR, Garthwaite PH, Jenkinson DJ, et al. Uncertain judgements: eliciting experts' probabilities. 1st ed. Wiley; 2006. https://doi.org/10.1002/047003312.
8. O'Hagan A. Expert knowledge elicitation: subjective but scientific. Am Stat. 2019;73:69–81. https://doi.org/10.1080/00031305.2018.1518265.
9. Peel A, Jenks M, Choudhury M, Lovett R, Rejon-Parrilla JC, Sims A, et al. Use of expert judgement across NICE guidance-making programmes: a review of current processes and suitability of existing tools to support the use of expert elicitation. Appl Health Econ Health Policy. 2018;16:819–36. https://doi.org/10.1007/s40258-018-0415-5.
10. Bojke L, Soares M, Claxton K, Colson A, Fox A, Jackson C, et al. Developing a reference protocol for structured expert elicitation in health-care decision-making: a mixed-methods study. Health Technol Assess. 2021;25:1–124. https://doi.org/10.3310/hta25370.
11. Soares M, Colson A, Bojke L, Ghabri S, Garay OU, Felli JK, et al. Recommendations on the use of structured expert elicitation protocols for healthcare decision making: a good practices report of an ISPOR task force. Value Health. 2024;27:1469–78. https://doi.org/10.1016/j.jval.2024.07.027.

12. Canada's Drug Agency. Guidelines for the economic evaluation of health technologies: Canada' 2017.
13. Dutch National Health Care Institute. Guideline for economic evaluations in healthcare; 2024.
14. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual; 2022.
15. Perelman J, Soares MO, Mateus C, Duarte AI, Faria R, Ferreira L, et al. Orientações metodológicas para estudos de avaliação económica; 2019.
16. Oakley J. SHELF: Tools to support the sheffield elicitation framework 2015:1.12.0. https://doi.org/10.32614/CRAN.package.SHELF.
17. Jankovic D, Horscroft J, Lee D, Bojke L, Soares M. STEER: open access resources for conducting structured expert elicitation for health care decision making. Med Decis Making. 2025;45:627–39. https://doi.org/10.1177/0272989X251343013.
18. Jeremy EO, Shijie R, Jessica EF, Jogh PG, Kevin W, Nick L, et al. Technical support document 26: expert elicitation for long-term survival outcomes; 2025.
19. Ayers D, Cope S, Towle K, Mojebi A, Marshall T, Dhanda D. Structured expert elicitation to inform long-term survival extrapolations using alternative parametric distributions: a case study of CAR T therapy for relapsed/ refractory multiple myeloma. BMC Med Res Methodol. 2022;22:272. https://doi.org/10.1186/s12874-022-01745-z.
20. Cope S, Ayers D, Zhang J, Batt K, Jansen JP. Integrating expert opinion with clinical trial data to extrapolate long-term survival: a case study of CAR-T therapy for children and young adults with relapsed or refractory acute lymphoblastic leukemia. BMC Med Res Methodol. 2019;19:182. https://doi.org/10.1186/s12874-019-0823-8.
21. Konidaris G, Paul E, Kuznik A, Keeping S, Chen C-I, Sasane M, et al. Assessing the value of cemiplimab for adults with advanced cutaneous squamous cell carcinoma: a cost-effectiveness analysis. Value Health. 2021;24:377–87. https://doi.org/10.1016/j.jval.2020.09.014.
22. CONNECT. Norwegian cancer precision medicine implementation consortium; 2026
23. Nye Metoder. Selpercatinib (Retsevmo); 2024.
24. Drilon A, Oxnard GR, Tan DSW, Loong HHF, Johnson M, Gainor J, et al. Efficacy of selpercatinib in *RET* fusion-positive non-small-cell lung cancer. N Engl J Med. 2020;383:813–24. https://doi.org/10.1056/NEJMoa2005653.
25. Norwegian Medical Products Agency. Rapid health technology assessment for pharmaceuticals funded in the specialist health service: ID2020_076 Selperkatinib (Retsevmo) for the treatment of adults with advanced RET-fusion-positive non-small cell lung cancer requiring systemic therapy after prior treatment with immunotherapy and/or platinum-based chemotherapy; 2022.
26. Nye Metoder. Method Notice: ID2020_076 (ID2022_118) Selperkatinib (Retsevmo) as monotherapy for treating adults with advanced RET-fusion-positive non-small cell lung cancer (NSCLC) who have not previously been treated with a RET inhibitor – New Price;2022.
27. Zhou C, Solomon B, Loong HH, Park K, Pérol M, Arriola E, et al. First-line selpercatinib or chemotherapy and pembrolizumab in RET fusion-positive NSCLC. N Engl J Med. 2023;389:1839–50. https://doi.org/10.1056/NEJMoa2309457.
28. Drilon A, Subbiah V, Gautschi O, Tomasini P, De Braud F, Solomon BJ, et al. Selpercatinib in patients with *RET* fusion-positive non-small-cell lung cancer: updated safety and efficacy from the registrational LIBRETTO-001 phase I/II trial. J Clin Oncol. 2023;41:385–94. https://doi.org/10.1200/JCO.22.00393.
29. Norwegian Institute of Public Health. Guidelines for the submission of documentation for single technology assessment (STA) of pharmaceuticals; 2018.
30. Board of Governors of the Federal Reserve System. Foreign Exchange Rates - G.5A Annual; 2025.
31. Norwegian Ministry of Health and Care Services. Severity of illness and priority setting in Norway; 2015.
32. R Core Team. R: A language and environment for statistical computing; 2021.
33. RStudio Team. RStudio: Integrated Development for R; 2020.
34. Latimer NR. Survival analysis for economic evaluations alongside clinical trials—extrapolation with patient-level data: inconsistencies, limitations, and a practical guide. Med Decis Making. 2013;33:743–54. https://doi.org/10.1177/0272989X12472398.
35. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med. 2018;378:2078–92. https://doi.org/10.1056/NEJMoa1801005.
36. Velcheti V, Hu X, Piperdi B, Burke T. Real-world outcomes of first-line pembrolizumab plus pemetrexed-carboplatin for metastatic nonsquamous NSCLC at US oncology practices. Sci Rep. 2021;11:9222. https://doi.org/10.1038/s41598-021-88453-8.
37. Garassino MC, Gadgeel S, Speranza G, Felip E, Esteban E, Dómine M, et al. Pembrolizumab plus pemetrexed and platinum in nonsquamous non–small-cell lung cancer: 5-year outcomes from the phase 3 KEYNOTE-189 study. J Clin Oncol. 2023;41:1992–8. https://doi.org/10.1200/JCO.22.01989.
38. Liu N, Zhou Y, Lee JJ. IPDfromKM: reconstruct individual patient data from published Kaplan-Meier survival curves. BMC Med Res Methodol. 2021;21:111. https://doi.org/10.1186/s12874-021-01308-8.
39. Loong HHF, Goto K, Solomon BJ, Park K, Pérol M, Arriola E, et al. LBA4 randomized phase III study of first-line Selpercatinib versus chemotherapy and Pembrolizumab in RET fusion-positive NSCLC. Ann Oncol. 2023;34:S1303. https://doi.org/10.1016/j.annonc.2023.10.059.
40. Cooney P, White A. Direct incorporation of expert opinion into parametric survival models to inform survival extrapolation. Med Decis Making. 2023;43:325–36. https://doi.org/10.1177/0272989X221150212.
41. Nafees B, Lloyd AJ, Dewilde S, Rajan N, Lorenzo M. Health state utilities in non–small cell lung cancer: an international study. Asia Pac J Clin Oncol 2017;13. https://doi.org/10.1111/ajco.12477.
42. Norwegian Directorate of Health. Lungekreft, mesoteliom og thymom – handlingsprogram; 2013.
43. Oslo University Hospital. Lunge; 2026.
44. Norwegian Medical Products Agency. Legemiddelsøk; 2026.
45. Norwegian Directorate of Health. Regelverk for innsatsstyrt finansiering 2024 (ISF-regelverket); 2023.
46. Michel YA, Aas E, Augestad LA, Burger E, Thoresen L, Bjørnelv GMW. Healthcare use and costs in the last six months of life by level of care and cause of death. BMC Health Serv Res. 2024;24:688. https://doi.org/10.1186/s12913-024-10877-5.
47. Canadian Agency for Drugs and Technologies in Health. Selpercatinib (Retevmo): CADTH reimbursement review: therapeutic area: RET fusion–positive non–small cell lung cancer; 2022.
48. Bilir SP, Ma Q, Zhao Z, Wehler E, Munakata J, Barber B. Economic burden of toxicities associated with treating metastatic melanoma in the United States. Am Health Drug Benefits. 2016;9:203–13.
49. EU Council Directive (89/105/EEC). Transparency of decisions regulating the prices and reimbursement of medicinal products in European Union Member States; 1988.
50. Feng J, Li Y, Wei B, Guo L, Li W, Xia Q, et al. Clinicopathologic characteristics and diagnostic methods of RET rearrangement in Chinese non-small cell lung cancer patients. Transl Lung Cancer Res. 2022;11:617–31. https://doi.org/10.21037/tlcr-22-202.
51. Tang Z, Zhang J, Lu X, Wang W, Chen H, Robinson MK, et al. Coexistent genetic alterations involving ALK, RET, ROS1

or MET in 15 cases of lung adenocarcinoma. Mod Pathol. 2018;31:307–12. https://doi.org/10.1038/modpathol.2017.109.
52. Lu C, Zhou Q. Diagnostics, therapeutics and RET inhibitor resistance for RET fusion–positive non-small cell lung cancers and future perspectives. Cancer Treat Rev. 2021;96:102153. https://doi.org/10.1016/j.ctrv.2021.102153.
53. Yi H, Cao Y, Shi F, Wei X, Han S. Cost-effectiveness analysis of Selpercatinib versus chemotherapy and Pembrolizumab in the first-line treatment of rearranged during transfection fusion–positive non-small cell lung cancer in the United States. Int J Clin Pharm. 2024;46:1427–35. https://doi.org/10.1007/s11096-024-01800-3.
54. Norges Bank. Valutakurser; 2026.
55. Norges Bank. Price calculator; 2026.