7.02 SELPERCATINIB, Capsule 40 mg, Capsule 80 mg, Retevmo®, ELI LILLY AUSTRALIA PTY LTD.

1 Purpose of submission

1.1 The Standard Re-entry resubmission requested a General Schedule, Authority Required (STREAMLINED) listing for the treatment of advanced or metastatic rearranged during transfection (*RET*) fusion-positive non-small cell lung cancer (NSCLC).

1.2 Listing was requested on the basis of a cost utility analysis versus pembrolizumab in combination with platinum-based doublet chemotherapy (pembrolizumab + PC).

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Adults (ages 18 years or older) with histologically and cytologically confirmed advanced or metastatic NSCLC who are *RET* fusion-positive.
Intervention	Selpercatinib orally administered in *RET* fusion-positive NSCLC patients until disease progression. In patients with bodyweight ≥ 50 kg, the recommended dose of selpercatinib is 160 mg twice daily. In patients with body < 50 kg, the recommended dose of selpercatinib is 120 mg twice daily.
Comparator [a]	Pembrolizumab in combination with platinum-based doublet chemotherapy. [b]
Outcomes	Safety and tolerability of selpercatinib; objective response rate; progression-free survival; overall survival; and health-related quality of life
Clinical claim [c]	In treatment-naïve patients with *RET* fusion-positive advanced or metastatic NSCLC, selpercatinib is superior to pembrolizumab in combination with platinum-based doublet chemotherapy in terms of efficacy and has a different, but clinically manageable, safety profile.

Source: Table 1-1 p27 of the resubmission.
NSCLC, = non-small cell lung cancer; *RET* = rearranged during transfection.
[a] The resubmission did not include docetaxel as a supplementary comparator.
[b] Pemetrexed with either cisplatin or carboplatin.
[c] The resubmission did not include a superiority claim of selpercatinib compared to docetaxel in previously treated patients.

2 Background

Registration status

2.1 Selpercatinib received provisional Therapeutic Goods Administration (TGA) approval on 3 July 2023 for 'the treatment of adult patients with locally advanced or metastatic *RET* fusion-positive non-small cell lung cancer (NSCLC)'.

2.2 The indication section of the TGA Product Information states 'the decision to approve this indication was made on the basis of objective response rate and duration of response from a single arm study. Continued approval of this indication depends on verification and description of benefit in a confirmatory trial'.

2.3 The TGA noted that reports from the LIBRETTO-001 study and LIBRETTO-431 trial should be submitted to the TGA by 2024 and 2026 respectively (the TGA AusPAR).

Previous PBAC consideration

2.4 The PBAC considered selpercatinib for the requested patient population at the July 2023 meeting. Table 2 summarises the outstanding matters of concern.

Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addressed it
Comparative clinical evidence	The PBAC considered the indirect comparisons were associated with a high degree of uncertainty with several transitivity, applicability, and reliability issues. The PBAC advised that the true extent of confounding and the magnitude of the comparative treatment effect of selpercatinib compared with pembrolizumab + PC remained unknown. As such, the PBAC considered that the claim of superior comparative effectiveness was not adequately supported by the data provided (para. 7.7-7.10, selpercatinib, PSD, July 2023 PBAC meeting).	Addressed. Presented evidence from the pivotal head-to-head LIBRETTO-431 trial comparing selpercatinib to platinum-based doublet chemotherapy with or without pembrolizumab in patients with *RET* fusion-positive NSCLC. Patients treated with selpercatinib experienced a statistically significant improvement in PFS compared to patients treated with pembrolizumab + PC arm in the ITT-pembrolizumab population (HR = 0.465; 95% CI: 0.309, 0.699) and the ITT population (HR = 0.482; 95% CI: 0.331, 0.700). The results aligned with the MAIC 2 model presented in the previous submission. However, OS gained was not statistically significant (HR = 0.961; P = 0.9033 in the ITT-pembrolizumab population). OS in the control arm was significantly confounded by treatment cross-over and the comparative treatment effect of selpercatinib was likely underestimated.
Selpercatinib effectiveness relative to docetaxel in previously treated patients	It is anticipated that the predominant use of selpercatinib is as the initial targeted therapy for *RET* fusion-positive advanced NSCLC. The indirect comparison with docetaxel was considered largely uninformative and was not assessed further in the evaluation. The ESC agreed with the evaluation that the indirect comparison with docetaxel was largely uninformative due to the high risk of selection bias (para. 6.9, selpercatinib, PSD, July 2023 PBAC meeting).	A clinical claim of superior efficacy of selpercatinib to docetaxel as a second-line treatment was not proposed in the resubmission.

Component	Matter of concern	How the resubmission addressed it
Economic model	The PBAC considered the economic model unreliable due to the uncertainties in the clinical data from the indirect comparison with pembrolizumab + PC. In addition, the PBAC agreed with the evaluation that the submission made a number of unreasonable or unjustified assumptions and errors in the base case analysis and noted that a re-specified base case was proposed during the evaluation. The pre-PBAC response provided a re-specified base case that differed from that provided during the evaluation in 3 ways: application of the selpercatinib treatment effect derived from the MAIC Model 2; use of a 10 year rather than a 7.5-year time horizon (submission base case time horizon was 20 years); and incorporation of a [redacted]% price reduction for selpercatinib. The PBAC noted the re-specified base case and the price reduction proposed in the pre-PBAC response. However, the PBAC considered the fundamental uncertainty associated with the indirect comparison between poorly transitive studies that formed the basis of the model cannot be resolved by re-specification. As such, the PBAC considered the ICER remained highly uncertain (para. 7.12, selpercatinib, PSD, July 2023 PBAC Meeting). The PBAC considered a resubmission for selpercatinib should address the following issues: The indirect comparisons presented in the submission were associated with a high degree of uncertainty… Provide an economic model that incorporates revised data pertaining to the magnitude of comparative treatment effectiveness (para. 7.15, selpercatinib, PSD, July 2023 PBAC meeting).	Not adequately addressed. The resubmission did not use the clinical outcomes from the LIBRETTO-431 trial in the economic model. Base case comparative efficacy was revised to the MAIC 2 model consistent with the July 2023 pre-PBAC response, rather than the NMA used in the July 2023 submission. The resubmission claimed that this approach was validated with PFS and OS data from the LIBRETTO-431 trial, the KN189 study, the LIBRETTO-001 study January 2023 data, and observational evidence. The results of the LIBRETTO-431 trial would have been more suitable than the MAIC 2 model for the economic evaluation given that it was conducted in the target population and observed and unobserved differences in the patient characteristics were addressed using randomisation. Alternatively, using the more mature data from the LIBRETTO-001 study may have increased certainty around the survival extrapolations. Sensitivity analysis using the LIBRETTO-431 trial data could not be conducted. The survival outcomes in the selpercatinib arm of the MAIC 2 model aligned with the LIBRETTO-001 study (June 2021 and January 2023 data cut) and LIBRETTO-431 trial, providing some external validity for the modelled PFS and OS results in the selpercatinib arm. However, the survival outcomes in the pembrolizumab + PC arm remained uncertain, especially due to crossover in the LIBRETTO-431 trial.
Time horizon	The pre-PBAC response provided a re-specified base case that differed from that provided during the evaluation because it used of a 10 year rather than a 7.5-year time horizon (submission base case time horizon was 20 years) (para. 7.12, selpercatinib, PSD, July 2023 PBAC meeting).	Not adequately addressed. The time horizon was unchanged compared to the July 2023 pre-PBAC response but changed compared to the July 2023 submission, which used 20 years. The resubmission justified using a 10-year time horizon stating that the LIBRETTO-001 study Jan 2023 data cut showed median OS was not reached and 62.3% were alive at median follow-up (3.5 years). The resubmission maintained that a longer time horizon was appropriate given the longer follow-up (median 3.5 years) and greater magnitude of benefit observed in the LIBRETTO-001 study compared with KN-189 when pembrolizumab was considered by the PBAC at the July 2019 meeting.

Component	Matter of concern	How the resubmission addressed it
Financial estimates	The PBAC agreed with the DUSC that the overall financial estimates presented were overestimated. The PBAC considered that the prevalent population was overestimated as a proportion of previously treated patients would be deceased or unable to tolerate further treatment by the time they became eligible for selpercatinib. The PBAC agreed with DUSC that the proportion of prevalent patients eligible for treatment would be between 70% and 80% (para. 7.13, selpercatinib, PSD, July 2023 PBAC meeting).	Addressed. Prevalent patients amended to 80% of the patients from prior 2 years.
Financial estimates	The PBAC also noted that in the LIBRETTO-001 study, 31.9% of patients were treated beyond disease progression, while the proposed restriction stated that patients must not develop disease progression while receiving selpercatinib. The PBAC agreed with DUSC that it may be more appropriate to apply a duration based on the modelled PFS from the trial (32.1 months) (para. 7.13, selpercatinib, PSD, July 2023 PBAC meeting).	Not addressed. Treatment duration was unchanged at 34.7 months, based on the modelled time to treatment discontinuation.

Source: Compiled during the evaluation, based on the resubmission.
CI = confidence interval; DUSC = Drug Utilisation Sub Committee; HR = hazard ratio; ICER = incremental cost effectiveness ratio; ITT = intention to treat; MAIC = matching adjusted indirect comparison; NMA = network meta-analysis; NSCLC = non-small cell lung cancer; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PC = platinum-based doublet chemotherapy; PFS = progression-free survival; PSD = Public Summary Document; *RET* = rearranged during transfection.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
SELPERCATINIB					
Selpercatinib 80 mg capsule, 112	$[redacted] published price $[redacted] effective price	1	112	5	Retevmo, Eli Lilly Australia Pty Ltd
Selpercatinib 80 mg capsule, 56	$[redacted] published price $[redacted] effective price	1	56	5	Retevmo, Eli Lilly Australia Pty Ltd
Selpercatinib 40 mg capsule, 56	$[redacted] published price $[redacted] effective price	1	56	5	Retevmo, Eli Lilly Australia Pty Ltd

Source: Table 1-5, p39 of the resubmission.
DPMQ = dispensed price for maximum quantity; mg = milligram

GENERAL – General Schedule (Code GE)
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (STREAMLINED)
Condition: Non-small cell lung cancer (NSCLC)
Indication: Locally advanced or metastatic non-small cell lung cancer
Clinical criteria:
The condition must have evidence of rearranged during transfection (RET) gene fusion in tumour material – this evidence has been obtained prior to commencing this drug
AND
Clinical criteria:

Patient must have a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score of no higher than 2 at treatment initiation
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this PBS indication.
Treatment criteria:
Patient must be undergoing initial treatment with this drug.
OR
Patient must be undergoing continuing treatment with this drug, with an absence of further disease progression since the last prescription.
Prescribing Instructions:
Administrative Advice: No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.

Source: Table 1-7, pp40-41 of the resubmission.

3.1 The resubmission requested a special pricing arrangement (SPA) for selpercatinib.

3.2 The requested effective ex-manufacturer prices (EMPs) in the resubmission were $ for 80 mg x 112 pack, $ for 80 mg x 56 pack, and $ for 40 mg x 56 pack (9.55% lower than proposed in the July 2023 pre-PBAC response).

3.3 The PBAC previously considered that a line-agnostic listing was appropriate (paragraph 7.4, selpercatinib, public summary document (PSD), July 2023 PBAC meeting). The PBAC previously considered that selpercatinib was most likely to be used as first-line therapy in keeping with international guidelines (paragraph 7.5, selpercatinib PSD, July 2023 PBAC meeting).

3.4 The Secretariat noted that having two different pack sizes for the same strength and for the same 'circumstances' (112 units and 56 units for 80 mg capsule) is not possible within the relevant legislation. For identical restrictions, there can only be one declared maximum quantity. The Secretariat suggested amending the maximum quantity for both listings to 112 units.

3.5 The resubmission proposed flow on changes to the PBS listing of pembrolizumab to enable its use after treatment with selpercatinib for metastatic NSCLC (Stage IV). These proposed flow-on changes were considered reasonable at the July 2023 PBAC meeting (paragraph 3.6, selpercatinib, PSD, July 2023 PBAC meeting).

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 Lung cancer has one of the poorest prognoses of all cancers in Australia. It is the leading cause of cancer-related mortality and accounts for 18% of all cancer-related deaths with an estimated 8,693 lung cancer deaths in 2021.[1] Over half of patients

[1] Australian Institute of Health and Welfare, Cancer in Australia 2021. 2021.

diagnosed with lung cancer die within one year of being diagnosed and the 5-year relative survival rate is 20%. Despite a projected decrease in the mortality rates for lung cancer over the next 20 years, the estimated number of lung cancer deaths is estimated to increase as a result of Australia's growing and ageing population.[2]

4.2 NSCLC accounts for approximately 85%-90% of lung cancers. There are 3 main subtypes of NSCLC: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.

4.3 *RET* fusions are present in 1%-2% of NSCLC patients.[3] At least 45 *RET* gene fusion variants have been identified in lung cancers, the most common being *KIF5B-RET* (70%-90%), followed by *CCDC6-RET* and *NCOA4-RET*. [4] The clinical implications of specific gene fusion partners are currently not well defined.

4.4 The July 2023 submission stated that *RET* fusion status was not an independent prognostic biomarker. At that time, the PBAC considered that *RET* fusion status, as an independent prognostic characteristic for progression-free survival (PFS) or overall survival (OS), was a source of significant uncertainty (paragraph 7.15, selpercatinib, PSD, July 2023 PBAC meeting).

4.5 The target population for treatment with selpercatinib is locally advanced or metastatic *RET* fusion-positive NSCLC patients, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. International guidelines recommend the use of targeted therapies, including selpercatinib, as first-line treatment for advanced or metastatic NSCLC patients with specific oncogenic drivers, as they have been shown to have higher response rates than other therapies, including immune checkpoint inhibitors, and are better tolerated.[5,6]

4.6 The resubmission proposed a line-agnostic indication for selpercatinib to enable access for patients who may have received treatment for their advanced or metastatic disease prior to the listing of selpercatinib or who initiate systemic treatment prior to *RET* fusion status being determined. The PBAC previously considered that a line-agnostic listing was appropriate and that selpercatinib was most likely to be used as first-line therapy in keeping with international guidelines (paragraphs 7.4 and 7.5, selpercatinib, PSD, July 2023 PBAC meeting).

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[2] Luo, Q., et al., Lung cancer mortality in Australia: Projected outcomes to 2040. *Lung Cancer*, 2018. 125: p. 68-76.

[3] Ferrara, R., et al., Clinical and Translational Implications of RET Rearrangements in Non-Small Cell Lung Cancer. *J Thorac Oncol*, 2018. 13(1): p. 27-45.

[4] Novello, S., et al., RET Fusion-Positive Non-small Cell Lung Cancer: The Evolving Treatment Landscape. *The Oncologist*, 2023. oyac264.

[5] ESMO, Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. 2023.

[6] NCCN, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Non-Small Cell Lung Cancer. Version 2.2023. 2023.

4.7 Selpercatinib is an orally available, small molecule inhibitor of the *RET* receptor tyrosine kinase. In *RET* enzyme assays, selpercatinib inhibits the kinase activity of *RET*, *RET*-V804L, *RET*-V804M, *RET*-A883F, *RET*-S904F, and *RET*-M918T.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The resubmission nominated pembrolizumab + PC as the main comparator in the first-line setting. The main argument provided in support of this nomination was that in the absence of PBS-listed treatments for *RET* fusion-positive, advanced or metastatic NSCLC, patients receive therapies within standard of care. Pembrolizumab + PC was considered standard of care for the majority of advanced NSCLC patients with or without *RET* genomic variations. Pembrolizumab + PC as the main comparator for the first-line treatment setting was previously considered reasonable by the PBAC (paragraph 7.5, selpercatinib, PSD, July 2023 PBAC meeting).

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (3) and organisations (3) via the Consumer Comments facility on the PBS website. The comments from the health care professionals described the potential efficacy and quality of life benefits with selpercatinib. It was also stated that selpercatinib was associated with minimal adverse events. The PBAC also recalled that in July 2023 input supporting the listing of selpercatinib was received from an individual and a health care professional.

6.3 Input was again received from Rare Cancers Australia and the Lung Foundation Australia. Rare Cancers Australia highlighted that patients with NSCLC with rare mutations are often faced with an extremely poor prognosis and stated that such patients need treatment options that provide significant improvements in survival. Both organisations noted that selpercatinib is an oral targeted therapy that may allow patients to live a better and healthier life with their condition and commented that an oral medication is more accessible for those in rural and remote areas and those for whom the cost of travel (for infusions) was a barrier to attending treatment.

6.4 The Medical Oncology Group of Australia (MOGA) again expressed its strong support for the selpercatinib submission, categorising it as one of the therapies of "highest priority for PBS listing". The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for

selpercatinib based on the LIBRETTO-431 trial, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)[7].

Clinical trials

6.5 The resubmission was based on one head-to-head trial comparing selpercatinib to pemetrexed plus platinum-based chemotherapy (carboplatin or cisplatin) with or without pembrolizumab (pembrolizumab ± PC) in patients with *RET* fusion-positive advanced (locally advanced or metastatic) non-squamous NSCLC: LIBRETTO-431. This was a new trial presented in the resubmission.

6.6 The resubmission also presented updated data from the LIBRETTO-001 study. This was a phase II, single-arm study of selpercatinib in patients with *RET* fusion-positive advanced (locally advanced or metastatic) non-squamous NSCLC. The July 2023 submission presented data up to 15 June 2021. The resubmission presented updated data up to 13 January 2023 (but did not update the indirect treatment comparisons (ITCs), see discussion below).

6.7 The following clinical evidence from the July 2023 submission was represented and used to inform the ITCs between selpercatinib (LIBRETTO-001 study treatment-naïve cohort) and pembrolizumab + PC (KN-021 (Cohort G) trial and KN-189 trials):

- LIBRETTO-001: As outlined in paragraph 6.6. Data up to 15 June 2021.
- KN-189: A double-blind, randomised, controlled, phase III trial comparing pembrolizumab + PC versus PC in treatment-naïve patients with metastatic non-squamous NSCLC without sensitising *EGFR* or *ALK* mutations.
- KN-021 (Cohort G): An open-label, randomised, controlled, phase II trial comparing pembrolizumab + PC versus PC in treatment-naïve patients with metastatic non-squamous NSCLC without sensitising *EGFR* or *ALK* mutations.

6.8 The ITCs were unchanged from the July 2023 submission and included a network meta-analysis, an anchored ITC, and an unanchored matching-adjusted indirect comparison (MAIC). The MAIC was conducted by matching individual patient data for the single selpercatinib arm of the LIBRETTO-001 study to published summary data for the pembrolizumab + PC arm of the KN-189 trial. Two models were considered: Model 1 matched patients on all prespecified characteristics excluding smoking status (MAIC 1 model); and Model 2 matched patients on all prespecified characteristics including smoking status (MAIC 2 model).

6.9 The resubmission also presented a supplementary study – a retrospective, international, multicenter study on clinical biological features and treatment outcomes for patients with *RET* fusion-positive NSCLC (N=205): RET:MAP.

6.10 Details of the trials and studies presented in the resubmission are provided in Table 3.

[7] Cherny NI, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28:2340-2366, 2017

Table 3: Trials/studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
LIBRETTO-431 NCT04194944	A Multicentre, Randomised, Open-Label, Phase 3 Trial Comparing Selpercatinib to Platinum-Based and Pemetrexed Therapy with or without Pembrolizumab as Initial Treatment of Advanced or Metastatic RET Fusion-Positive Non-Small Cell Lung Cancer	May 2023
	Zhou, C., Solomon, B., Loong, H. H., et al. Investigators, L.-T. First-Line Selpercatinib or Chemotherapy and Pembrolizumab in RET Fusion-Positive NSCLC.	NEJM 2023; 389(20), 1839
LIBRETTO-001 NCT03157128	A Phase 1/2 Study of Oral Selpercatinib (LOXO-292) in Patients with Advanced Solid Tumours, Including RET Fusion-Positive Solid Tumours, Medullary Thyroid Cancer, and Other Tumours with RET Activation	January 2023
	Interim Clinical Study Report (Protocol LOXO-RET-17001): A Study of Selpercatinib (LOXO-292) in Participants With Advanced Solid Tumours, RET Fusion-Positive Solid Tumours, and Medullary Thyroid Cancer.	15 June 2021
	Drilon, A., Subbiah, V., Gautschi, O., 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, 385-394.
	Oxnard, G et al. Clinical Activity of LOXO-292, a Highly Selective RET	J Thorac Oncol, 2018; 13, S349-S350.
	Nishio, M et al. Efficacy and Safety Analysis of Selpercatinib in Patients	Gan To Kagaku Ryoho, 2022; 49, 669-675.
Main comparator: pembrolizumab + pemetrexed + platinum chemotherapy used for an indirect comparison with LIBRETTO-001		
KN-189 NCT03950674	Study of Pemetrexed+Platinum Chemotherapy With or Without Pembrolizumab (MK-3475) in Participants With First Line Metastatic Nonsquamous Non-small Cell Lung Cancer (MK-3475-189/KEYNOTE-189)-Japan Extension Study. NCT03950674	Not reported
	Study of Pemetrexed+Platinum Chemotherapy With or Without Pembrolizumab (MK-3475) in Participants With First-Line Metastatic Nonsquamous Non-small Cell Lung Cancer (MK-3475-189/KEYNOTE-189). NCT02578680	Not reported
	Gandhi L et al. Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer.	N Engl J Med, 2018; 378, 2078-2092
	Horinouchi, H et al. Safety and tolerability of pembrolizumab or placebo plus pemetrexed and platinum as first-line therapy in Japanese patients (PTS) with metastatic non-squamous non-small cell lung cancer (NSCLC) enrolled in the phase III KEYNOTE-189 study.	Annals of Oncology, 2019; 30, ii56-ii57
	Horinouchi, H et al. Pembrolizumab plus pemetrexed-platinum for metastatic nonsquamous non-small-cell lung cancer: KEYNOTE-189	Japan Study. Cancer Sci, 2021; 112, 3255-3265
	Rodríguez-Abreu, D et al. Pemetrexed plus platinum with or without pembrolizumab in patients with previously untreated metastatic nonsquamous NSCLC: protocol-specified final analysis from KEYNOTE-189.	Ann Oncol, 2021; 32, 881-895
KN-021 NCT02039674	A Study of Pembrolizumab (MK-3475) in Combination with Chemotherapy in Participants With Non-small Cell Lung Cancer (MK-3475-021/KEYNOTE-021).	Not reported
	Langer, C et al. Randomized, phase 2 study of carboplatin and pemetrexed with or without pembrolizumab as first-line therapy for advanced NSCLC: KEYNOTE-021 cohort G.	Annals of Oncology, 2016(a); 27, vi582

Trial ID	Protocol title/ Publication title	Publication citation
	Langer, C et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Awad, M et al. Long-Term Overall Survival From KEYNOTE-021 Cohort G: Pemetrexed and Carboplatin With or Without Pembrolizumab as First-Line Therapy for Advanced Nonsquamous NSCLC.	Lancet Oncol, 2016(b); 17, 1497-1508 J Thorac Oncol, 2021; 16, 162-168
Supplementary study		
RET:MAP	Aldea, M., et al., RET-MAP: An International Multicenter Study on Clinicobiologic Features and Treatment Response in Patients With Lung Cancer Harboring a RET Fusion.	J Thorac Oncol, 2023. 18(5): p. 576-586.

Source: Table 2-3of the resubmission; Table 2 of the selpercatinib, PSD, July 2023 PBAC meeting.
Blue shading indicates data previously considered by the PBAC.

6.11 The key features of the direct randomised trial and included evidence are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/duration	Risk of bias	Patient population	Outcomes	Used in modelled evaluation
Selpercatinib vs pembrolizumab +PC						
LIBRETTO-431 [a]	ITT-pembrolizumab population: Selpercatinib: 129 Control: 83 ITT-population: Selpercatinib: 159 Control: 102 Safety-population: Selpercatinib: 158 Control: 98	RCT, OL Median 19.4 months (selpercatinib)	High	Untreated Stage IIIB to Stage IV, *RET* fusion-positive NSCLC	PFS by BICR, PFS by investigator, ORR, DOR, DCR, OS, EORTC QLQ-C30.	No
LIBRETTO-001	Selpercatinib: 69 (treatment naïve [b]) Previously treated with platinum-based chemotherapy: 247	Single arm, OL Median 25.2 months (15 June 2021 data-cut) Median 31.1 months (13 January 2023 data-cut)	High	Treatment naïve [b] Stage IIIB or Stage IV, *RET* fusion-positive advanced NSCLC	ORR, PFS, OS, TTD	Yes (15 June 2021 data-cut)
Indirect comparison						
KN-021 (Cohort G)	Pembrolizumab + PC: 60 PC alone: 63	RCT, OL Median 49.4 months	High	Untreated NSQ Stage IV, *EGFR* and *ALK* negative NSCLC	ORR, PFS, OS	Yes
KN-189	Pembrolizumab + PC: 410 Placebo + PC: 206	RCT, DB Median 31.0 months	High	Untreated NSQ Stage IV, *EGFR* and *ALK* negative NSCLC	ORR, PFS, OS	Yes
Supplementary study						
RET:MAP	*RET* inhibitor: 145 No *RET* inhibitor: 60	Retrospective Median OS 50.6 months Median PFS 16.2 months	High	Advanced *RET* fusion-positive NSCLC who received treatment with *RET* inhibitors	OS, ORR	No

Source: Section 2 of the resubmission; section 2 of the July 2023 submission; Table JZJC.8.11, p195 of the LIBRETTO 431 CSR.
ALK = anaplastic lymphoma kinase; BICR = blinded independent central review; DB = double blind; DCR = duration of complete response; DOR = duration of response; *EGFR* = epidermal growth factor receptor (not reported for LIBRETTO-001); EORTC QLQ-C30 = the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; ITT = intention to treat; NSQ = non-squamous; NSCLC = non-small cell lung cancer; OL = open label; ORR = overall/objective response rate; OS = overall survival; PC = pemetrexed plus platinum (cisplatin or carboplatin) chemotherapy; PFS = progression-free survival; RCT = randomised controlled trial; *RET* = rearranged during transfection; TTD = time to treatment discontinuation
[a] 1 May 2023 data cutoff.
[b] No prior cancer treatment for metastatic or advanced stage NSCLC.
Italics added during the evaluation.
Blue shading indicates data previously considered by the PBAC.

6.12 The LIBRETTO-431 trial was a global, multicentre, randomised, open-label, controlled, phase III study comparing selpercatinib to pemetrexed plus platinum-based

chemotherapy (carboplatin or cisplatin) with or without pembrolizumab in patients with advanced or metastatic, *RET* fusion-positive NSCLC. The LIBRETTO-431 trial commenced on 19 March 2020 and is ongoing.

6.13 In the LIBRETTO-431 trial, patients were randomly assigned 2:1 (initially 1:1 with protocol amended June 2020) to the selpercatinib arm or the pembrolizumab + PC arm, stratified based on:

- Geography (East Asia versus non-East Asia),
- Brain metastases per investigator assessment (presence versus absence or unknown), and
- Whether the investigator intended to treat the participant with or without pembrolizumab (decision was made before treatment allocation).

6.14 The LIBRETTO-431 trial had a high risk of bias as:

- The trial was open-label, and so there was a high risk of bias for patient-reported outcomes such as quality of life. To minimise bias, key primary and secondary endpoints were determined based on the assessment of a blinded independent central review (BICR).
- Overall, 75% of patients who discontinued treatment crossed over from the control arm to selpercatinib treatment or a commercially available selective *RET* inhibitor (see paragraph 6.19). Consequently, OS in the control arm was significantly confounded and likely to underestimate the comparative treatment effect of selpercatinib.

6.15 The resubmission only presented the ITT-pembrolizumab population (patients where the investigator intended to treat the patient with pembrolizumab if allocated to the pembrolizumab ± PC arm) and not the ITT-population (all patients whether or not they received pembrolizumab). The resubmission explained that this was because pembrolizumab + PC is considered the standard of care in many geographies. While the ITT-pembrolizumab population was most relevant given the proposed comparator, the ITT-population would also capture the efficacy of selpercatinib in patients who would not have been treated with pembrolizumab. Furthermore, this decreased the total available sample size for analysis from 261 to 212, and increased uncertainty in the results. The evaluation included the ITT-population for PFS and OS. The pre-PBAC response stated that as pembrolizumab + PC was considered the appropriate comparator in July 2023, the results of the ITT-pembrolizumab population were considered the pivotal evidence. Further, the pre-PBAC response noted that LIBRETTO-431 was powered to investigate outcomes in the ITT-pembrolizumab population.

Comparative effectiveness

LIBRETTO-431

6.16 The survival outcomes PFS and OS for the ITT-pembrolizumab population and the ITT-population are summarised in Table 5**.** The corresponding Kaplan-Meier curves are presented in Figure 1 and Figure 2.

Table 5: Summary of survival outcomes in LIBRETTO-431 trial

	Selpercatinib	Pembrolizumab ± PC	Absolute difference	Hazard ratio (95% CI) P value
Progression-free survival assessed by BICR				
ITT-pembrolizumab population (+PC)				
Events, n (%)	49/129 (37.9%)	49/83 (59.0%)	-	**0.465** [a] (0.309,0.699) [b] P=0.0002 [c]
Median PFS, months (95% CI)	24.84 (16.89, NE)	11.17 (8.77, 16.76)	13.67 months	
% not progressed at 6 months	87.2 (80.0, 92.0)	72.1 (60.8, 80.7)	15.1 (3.6, 26.6)	
% not progressed at 30 months	49.7 (36.6, 61.4)	NE	NE	
ITT-population (±PC)				
Events, n (%)	61/159 (38.4%)	57/102 (55.9%)	-	**0.482** [a] (0.331, 0.700) [b] P=0.0001 [c]
Median PFS, months (95% CI)	24.84 (17.31, NE)	11.17 (8.77, 16.76)	13.67 months	
% not progressed at 6 months (95% CI)	87.0 (80.6, 91.4)	69.8 (59.5, 78.0)	17.2 (6.6, 27.8)	
% not progressed at 30 months (95% CI)	48.5 (36.9, 59.1)	16.3 (4.0, 36.0)	32.2 (11.8, 52.5)	
Overall survival				
ITT-pembrolizumab population (+PC)				
Deaths, n/N (%)	25/129 (19.4%)	15/83 (18.1%)	-	0.961 [a] (0.503,1.835) [b] P=0.9033 [c]
Median months OS (95% CI)	NE	NE	NE	
% Alive at 6 months (95% CI)	95.3 (89.9, 97.9)	95.1 (87.4, 98.1)	0.3 (-5.7, 6.2)	
% Alive at 24 months (95% CI)	75.2 (65.0, 82.8)	79.0 (67.3, 86.9)	-3.8 (-16.9, 9.3)	
% Alive at 30 months (95% CI)	75.2 (65.0, 82.8)	79.0 (67.3, 86.9)	-3.8 (-16.9,9.3)	
ITT-population (±PC)				
Deaths, n/N (%)	32/159 (20.1%)	18/102 (17.6%)	-	1.042 [a] (0.578, 1.879) [b] P=0.8905 [c]
Median months OS (95% CI)	33.05 (33.05, NE)	NE	NE	
% Alive at 6 months (95% CI)	94.9 (90.1, 97.4)	96.0 (89.6, 98.5)	-1.0 (-6.2, 4.1)	
% Alive at 24 months (95% CI)	74.1 (64.7, 81.4)	80.0 (69.4, 87.2)	-5.8 (-18.0, 6.3)	
% Alive at 30 months (95% CI)	74.1 (64.7, 81.4)	75.5 (61.2, 85.2)	-1.4 (-15.9, 13.1)	

Source: Table 2-23of the resubmission; Tables JZJC.5.1, JZJC.5.2, JZJC.5.3, JZJC.8.77, JZJC.8.79, and 14.2.1.1.2, pp102-103 of the LIBRETTO-431 CSR.

BICR = blinded independent central review; CI = confidence interval; HR = hazard ratio; ITT = intention to treat; IWRS = interactive web response system; NE = not estimable; OS = overall survival; PC = platinum-based doublet chemotherapy; PFS = progression-free survival.

[a] Stratified by Geography (East Asian versus non-East Asian) – IWRS, Brain metastases (presence or absence/unknown) – IWRS.

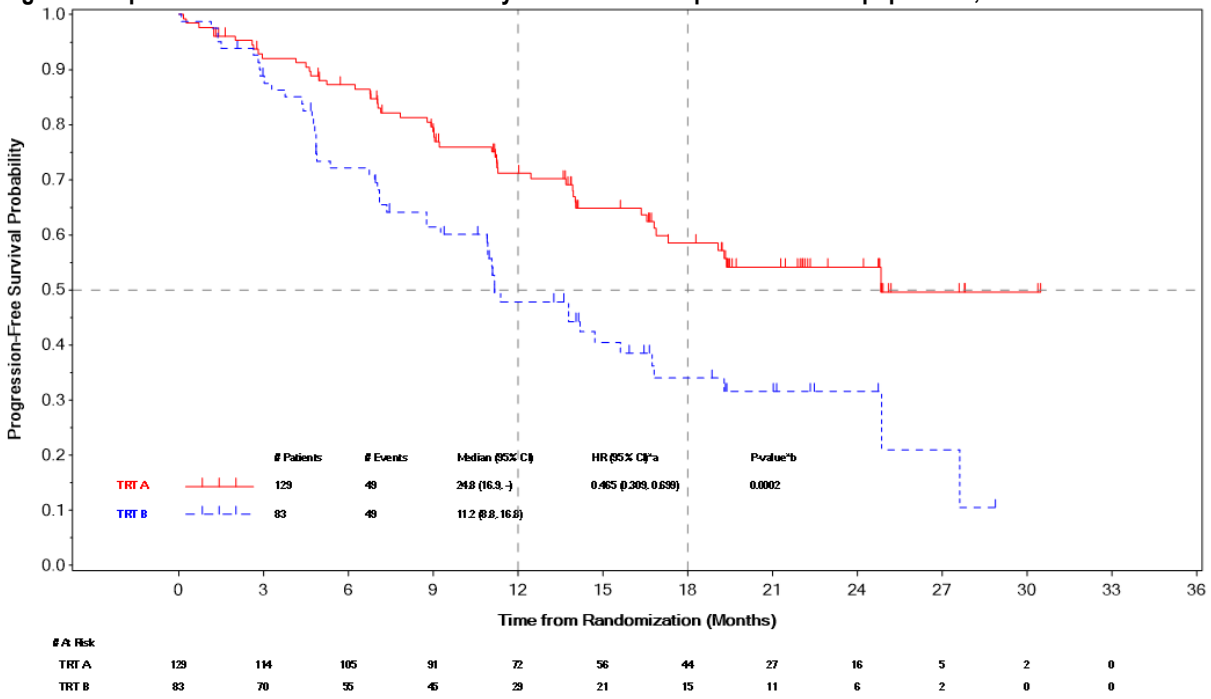
[b] 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation.

[c] p-values are computed based on comparator carboplatin or cisplatin + pemetrexed + pembrolizumab.

Note: ITT-pembrolizumab population were those that received pembrolizumab as decided by the study investigator intention to treat (no less than 80%); ITT-population included the ITT-pembrolizumab population and those that did not receive pembrolizumab as decided by the study investigator intention to treat (no more than 20%).

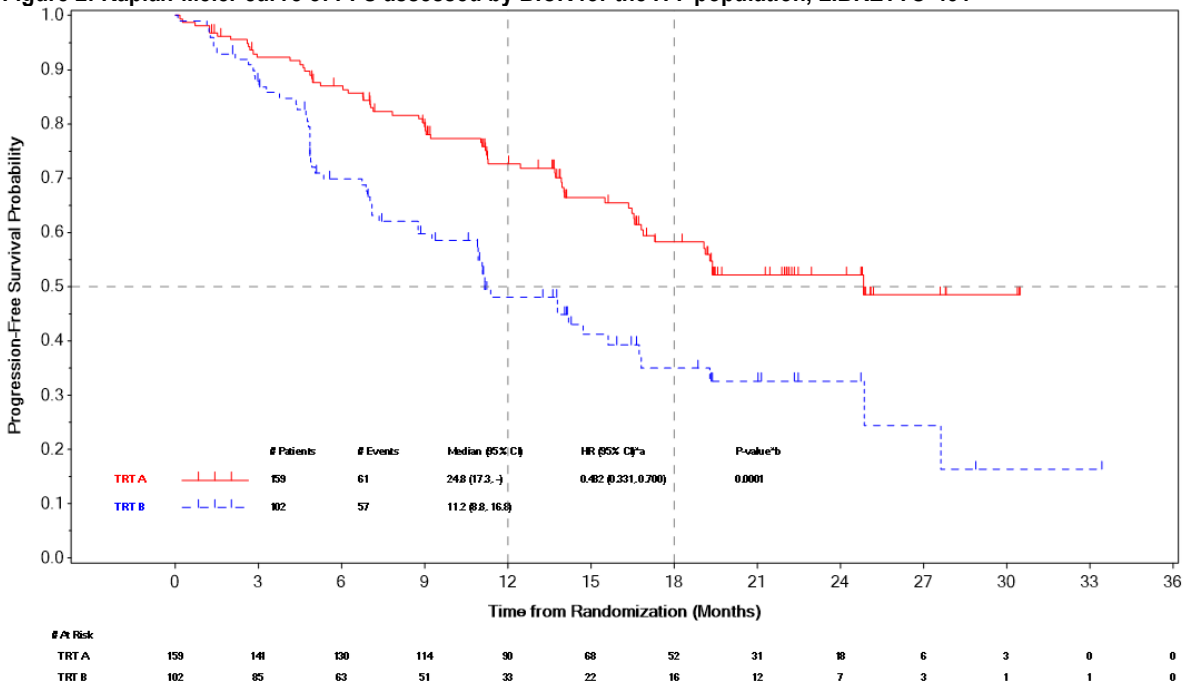
Bold indicates statistically significant results.

Figure 1: Kaplan-Meier curve of PFS assessed by BICR for the ITT-pembrolizumab population, LIBRETTO-431



Source: Figure 2-5, p70 of the resubmission.
BICR = blinded independent central review; CI, confidence interval; HR = hazard ratio; ITT = intent-to-treat; IWRS = interactive web response system; PFS = progression-free survival; TRT A = selpercatinib; TRT B = carboplatin or cisplatin + pemetrexed + pembrolizumab.
[a] HR – IWRS stratified hazard ratio from Cox proportional hazard model and 95% CI of TRT A versus TRT B.
[b] Log-rank IWRS stratified p-value (2-sided) for comparison of TRT A versus TRT B.

Figure 2: Kaplan-Meier curve of PFS assessed by BICR for the ITT-population, LIBRETTO-431



Source: Figure JZJC.5.2, p104 of the LIBRETTO-431 CSR.
BICR = blinded independent central review; CI, confidence interval; HR = hazard ratio; ITT = intent-to-treat; IWRS = interactive web response system; PFS = progression-free survival; TRT A = selpercatinib; TRT B = carboplatin or cisplatin + pemetrexed ± pembrolizumab.
[a] HR – IWRS stratified hazard ratio from Cox proportional hazard model and 95% CI of TRT A versus TRT B.
[b] Log-rank IWRS stratified p-value (2-sided) for comparison of TRT A versus TRT B.

6.17 Patients treated with selpercatinib experienced a statistically significant improvement in PFS compared to patients treated with pembrolizumab + PC arm in the ITT-pembrolizumab population (HR = 0.465, 95% CI: 0.309, 0.699) and the ITT-population (HR = 0.482, 95% CI:0.331, 0.700). The median incremental PFS was 13.67 months in both analysis populations.

6.18 The OS data were immature. As at the 1 May 2023 data cutoff, in the ITT-pembrolizumab population, 19.4% of patients in selpercatinib arm and 18.1% of patients in the pembrolizumab + PC arm had died.

6.19 As of the 01 May 2023 data cutoff date, 56 patients from the ITT-pembrolizumab population randomised to the control arm (including 3 patients who were randomised but did not receive treatment) had discontinued treatment. Of these, 36 patients (64.3%) crossed over and received selpercatinib on-study. In addition, 6 other patients who discontinued study treatment (10.7%) received a commercially available selective *RET* inhibitor after discontinuation from the study. The effective crossover rate was 75% of patients who discontinued treatment in the control arm[8]. The OS in the control arm was confounded by treatment cross-over and the comparative treatment effect

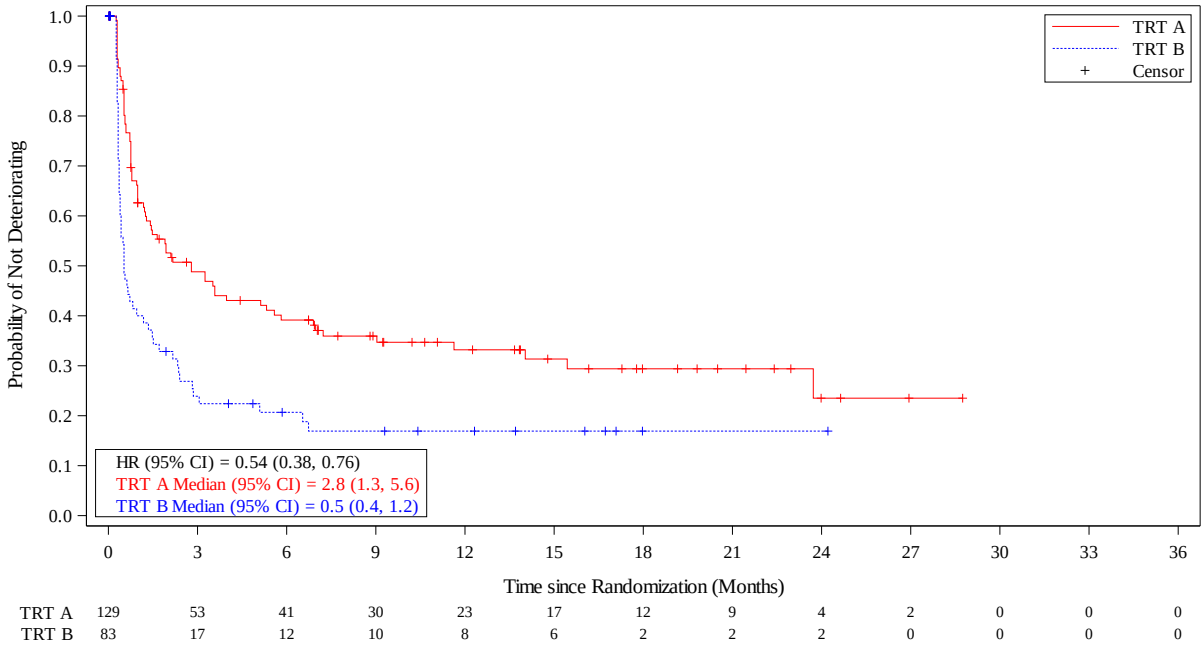
[8] 42/56 = 75%

of selpercatinib was likely underestimated. The resubmission did not present any adjustment for crossover. The ESC agreed with the Pre-Sub-Committee Response (PSCR) that given the immaturity of the OS data from LIBRETTO-431, none of the crossover adjustment methods would have provided a reliable estimate of OS. The PBAC noted that 50%[9] of patients randomised to the pembrolizumab + PC arm crossed over to a *RET* inhibitor.

6.20 Objective Response Rate (ORR) was significantly higher in the selpercatinib (83.7%) versus the pembrolizumab + PC arm (65.1%) in the ITT-pembrolizumab population (odds ratio, OR = 2.7; 95% CI: 1.4, 5.1; p=0.0028). A similar result was found in the ITT-population (OR = 2.9; 95% CI: 1.6, 5.2; p = 0.0003).

6.21 The LIBRETTO-431 trial collected patient-reported health related quality of life using the European Organisation for Research and Treatment QLQ-C30 (Figure 3).

Figure 3: EORTC IL19 physical functioning Kaplan-Meier plots of time to confirmed deterioration, ITT-pembrolizumab population



Source: Figure JZJC.8.49, p2159 of the LIBRETTO-431 CSR.
CI = confidence interval; EORTC IL19 = European Organisation for Research and Treatment Item Library 19; HR = hazard ratio; PRO = patient-reported outcome; TRT A = selpercatinib; TRT B = carboplatin or cisplatin + pemetrexed + pembrolizumab.
The time to confirmed PRO deterioration was calculated using all on-treatment visits prior to disease progression and was defined as the time from randomization until first assessment with a deterioration in PRO score meeting or exceeding the responder definition threshold (5) confirmed at the next subsequent assessment.
Patients without a PRO deterioration event were censored at the date of their last PRO assessment; patients with no data or no baseline data were censored at Day 1. Patients with no post-baseline data were censored at Day 2.

[9] 42/83 = 50%

6.22 Time to confirmed deterioration was defined as the time from the date of randomization to the date of the first increase (≥ 5 points of the EORTC QLQ-C30 Physical Functioning score) and confirmed at the next subsequent assessment.

6.23 The median time to confirmed deterioration of physical function in the ITT-pembrolizumab population was 2.8 months (95% CI: 1.3, 5.6) in the selpercatinib arm versus 0.5 months (95% CI: 0.4, 1.2) in the pembrolizumab + PC arm (HR = 0.54, 95% CI: 0.38, 0.76). The results were similar for the ITT-population. The ESC, noting the open-label nature of the trial, considered that the quality-of-life outcomes were likely biased as they did not reflect the adverse event (AE) profile of selpercatinib.

6.24 Subgroup analyses were performed based on age, Eastern Cooperative Oncology Group (ECOG) performance status, disease state, brain metastasis, liver metastasis, gender, race, region, smoking status, *RET* specimen type, *RET* fusion results, and PD-L1 expression by both BICR and investigator assessment for all the primary and secondary outcomes. Subgroup analyses of PFS and OS were generally consistent with the PFS and OS for the overall population.

LIBRETTO-001

6.25 At the 13 January 2023 data cutoff, 115 (32.3%) advanced *RET* fusion-positive NSCLC patients (including treatment-naïve population [N=19] and the population previously treated with platinum-based chemotherapy [N=83]) in LIBRETTO-001 remained on treatment with at least 4.5 years of follow-up from the first dose of selpercatinib.

6.26 Table 6 summarises the efficacy results from LIBRETTO-001 study for the 13 January 2023 and the June 2021 data cut.

Table 6: Summary of efficacy results for the advanced *RET* fusion-positive NSCLC population in LIBRETTO-001

	January 2023 data cut		June 2021 data cut (included in ITC)	
	Treatment-naïve cohort (N=69)	**Previously treated with platinum-based chemotherapy cohort (N=247)**	**Treatment-naïve cohort (N=69)**	**Previously treated with platinum-based chemotherapy cohort (N=247)**
ORR assessed by IRC [a]				
Events, n (%)	57 (82.6)	152 (61.5)	58 (84.1)	151 (61.1)
95% CI [b]	71.6, 90.7	55.2, 67.6	73.3, 91.8	54.7, 67.2
PFS assessed by IRC [a]				
Median PFS, months (95% CI) [c, d]	22.0 (16.5, 24.9)	26.2 (19.3, 35.7)	22.0 (13.8, NE)	24.9 (19.3, NE)
OS				
Median OS, months (95% CI) [c, d]	NE (37.8, NE)	47.57 (35.9, NE)	NE (27.9, NE)	NE (33.5, NE)

Source: Table 2-38, p88 of the resubmission and Table 4, Table 5, and para. 6.16 selpercatinib, PSD, July 2023 PBAC meeting.
CI = confidence interval; IRC = independent review committee; NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.
[a] ORR was defined as the proportion of patients with best overall response of confirmed complete or partial response. Response was confirmed by a repeat assessment ≥28 days.
[b] 95% CI was calculated using the Clopper-Pearson method.
[c] Estimate based on the Kaplan-Meier method.
[d] 95% CI was calculated using the Brookmeyer and Crowley method.

6.27 Objective response rate by independent review committee assessment in treatment-naïve patients treated with selpercatinib was 82.6% (95% CI: 71.6, 90.7) for the January 2023 data cut, compared to 84.1% (95% CI: 73.3, 91.8) for the June 2021 data cut.

6.28 PFS by independent review committee assessment in treatment-naïve patients treated with selpercatinib was 22.0 months (95% CI: 16.5, 24.9) for the January 2023 data cut. This was consistent with the PFS for the June 2021 data cut.

6.29 Median OS was not reached for the treatment-naïve population at the January 2023 data cut. Median OS was 47.6 months (95% CI: 35.9, NE) for patients previously treated with platinum-based chemotherapy.

Indirect comparisons

6.30 The ITCs were unchanged from the July 2023 submission; the updated data from the LIBRETTO 001 study were not incorporated in the comparisons. The PBAC previously considered the indirect comparisons were associated with a high degree of uncertainty with several transitivity, applicability, and reliability issues (paragraph 7.10, selpercatinib, PSD, July 2023 PBAC meeting).

6.31 Table 7 presents a comparison of the PFS from the indirect analysis to that of the LIBRETTO-431 trial. Figure 4 presents an overlay of Kaplan-Meier curves of PFS from the indirect analyses of LIBRETTO-001 and KN-189/KN-021 (Cohort G) MAIC 2 model and the LIBRETTO-431 trial.

Table 7: Summary of PFS reported in the indirect comparisons and in LIBRETTO-431

Indirect comparisons LIBRETTO-001 versus KN-189/KN-021 (Cohort G)	**Median PFS, months (95% CI)**	
	LIBRETTO-001 Selpercatinib (N=69) (15 June 2021)	**KN-189/KN-021 (Cohort G) (N=60) Pembrolizumab plus platinum-based chemotherapy (carboplatin or cisplatin) plus pemetrexed**
NMA	NR	NR
Median HR (95% CI)	0.391 (0.202, 0.759)	
Bucher	21.9 (13.8, NR)	9.0 (8.2, 10.5)
HR (95% CI); p-value	0.40 (0.23, 0.71); 0.002	
Unadjusted (non-matching)	21.9 (13.8, NR)	9.0 (8.2, 10.5)
HR (95% CI); p-value	0.46 (0.32, 0.66); <0.001	
Adjusted Model 1[a]	21.9 (11.5, NR)	9.0 (8.2, 10.5)
HR (95% CI); p-value	0.44 (0.29, 0.67); <0.001	
Adjusted Model 2[b]	21.9 (NR, NR)	9.0 (8.2, 10.5)
HR (95% CI); p-value	0.48 (0.27, 0.84); 0.01	
Direct comparison presented in LIBRETTO-431 (ITT-pembrolizumab)	**Selpercatinib (N=129)**	**Pembrolizumab + PC (N=83)**
Stratified [c]	24.84 (16.89, NE)	11.17 (8.77, 16.76)
HR (95% CI); p-value	0.465 (0.309, 0.699); 0.0002	

Source: Table 2-33, p79 of the resubmission.

CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; ITC = indirect treatment comparison; IWRS = interactive web response system; MAIC = matching-adjusted indirect comparison; NMA = network meta-analysis; NR = not reported; PFS = progression-free survival; PS = performance score

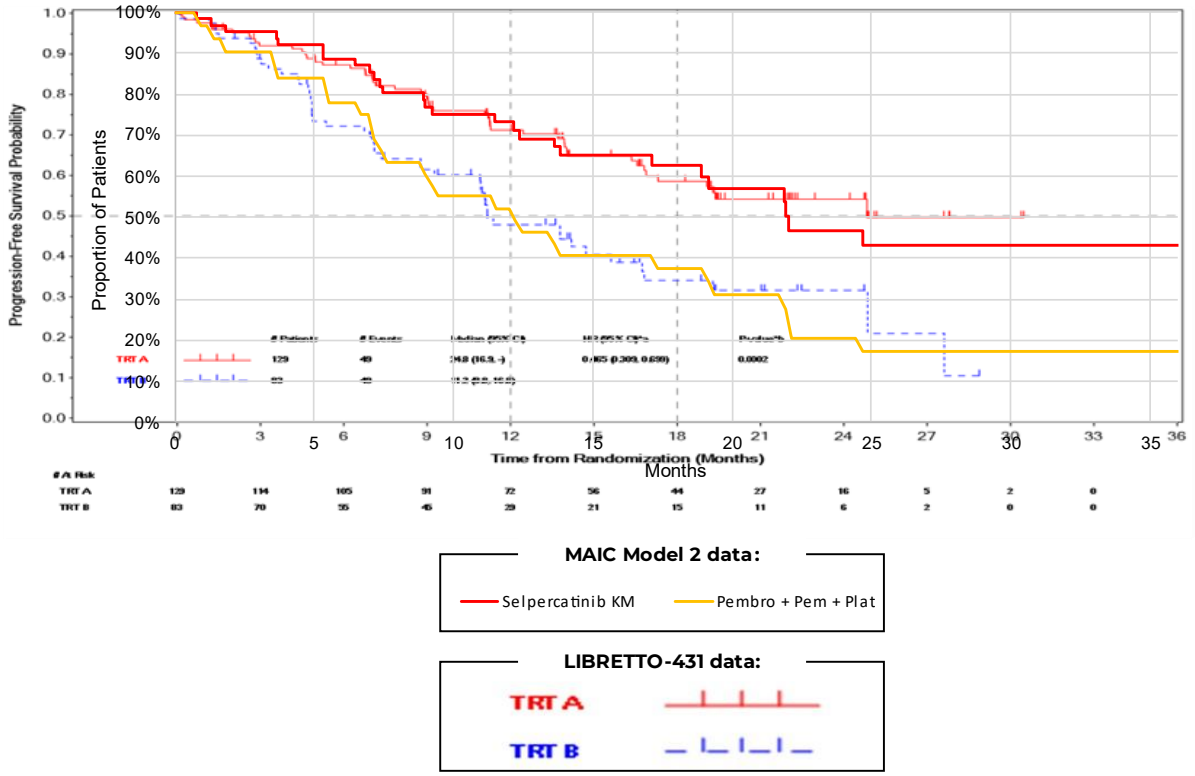
[a] MAIC Model 1 adjusted for age, sex, ECOG PS and presence of brain metastases.

[b] MAIC Model 2 adjusted for age, sex, ECOG PS, presence of brain metastases and smoking status.

[c] Stratified by Geography (East Asian versus non-East Asian) – IWRS, Brain metastases (presence or absence/unknown) – IWRS.

Blue shading indicates data previously considered by the PBAC.

Figure 4: Overlay of Kaplan-Meier curves of PFS comparing selpercatinib to pembrolizumab plus platinum-based chemotherapy (carboplatin or cisplatin) plus pemetrexed in MAIC Model 2[a] vs LIBRETTO-431



Source: Figure 2-7, p80 of the resubmission.
BICR = blinded independent central review; CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; IWRS = interactive web response system; KM = Kaplan-Meier; PFS = progression-free survival; TRT A = selpercatinib; TRT B = carboplatin or cisplatin + pemetrexed + pembrolizumab
[a] MAIC Model 2 using PFS from the indirect analyses of LIBRETTO-001 and KN-189/KN-021 (Cohort G).
Note: Solid red and yellow lines represent MAIC 2 modelled data while the broken red and blue lines are from LIBRETTO-431 (ITT-pembrolizumab population).

6.32 The MAIC 2 model adjusted for sex, age, ECOG PS, presence of brain metastases and smoking status. While this model was the most conservative among all the presented ITCs, the sample size in the selpercatinib arm in the LIBRETTO-001 trial was reduced to 22 patients, potentially reducing the statistical power of this model to predict PFS and OS.

6.33 The resubmission claimed that the PFS results for the direct head-to-head comparison from the LIBRETTO-431 trial were consistent with the results of the ITC of the LIBRETTO-001 study and the KN-189/KN-021 (Cohort G) trial using the MAIC 2 model presented in the July 2023 submission. The resubmission further argued that the comparability across results from LIBRETTO-431 and the indirect comparisons provided more certainty regarding the effectiveness of selpercatinib. This is discussed further in paragraphs 6.65 to 6.71.

Comparative harms

6.34 The Safety-Overall Population (N=256) was presented from the LIBRETTO-431 trial. The Safety-Overall Population included all randomised patients who received at least one dose (including a partial dose) of study treatment.

6.35 Table 8 summarises the key adverse events in the LIBRETTO-431 trial.

Table 8: Summary of key adverse events in LIBRETTO-431 (Safety-Overall population)

	Selpercatinib (N=158) n with event/N (%)	Pembrolizumab ± PC (N=98) n with event/N (%)
Median time on treatment, months	16.7	9.8
Any TEAE, n (%)	158 (100)	97 (99.0)
Related to study treatment [b]	149 (94.3)	92 (93.9)
Grade ≥3 TEAE, n (%)	111 (70.3)	56 (57.1)
Related to study treatment [a]	89 (56.3)	41 (41.8)
Frequently occurring (≥5%) Grade ≥3 TEAEs		
ALT increased	35 (22.2)	3 (3.1)
Anaemia	2 (1.3)	10 (10.2)
AST increased	20 (12.7)	1 (1.0)
ECG QT prolonged	14 (8.9)	0
Fatigue	5 (3.2)	5 (5.1)
Hypertension	32 (20.3)	3 (3.1)
Leukopenia	2 (1.3)	7 (7.1)
Neutropenia	3 (1.9)	27 (27.6)
Thrombocytopenia	5 (3.2)	7 (7.1)
Any SAE, n (%)	55 (34.8)	23 (23.5)
Related to study treatment [a]	30 (19.0)	14 (14.3)
Frequently occurring SAEs, n (%)		
Pleural effusion	7 (4.4)	0 (0)
Abnormal hepatic function	4 (2.5)	0 (0)
Pneumonia	3 (1.9)	2 (2.0)
Anaemia	0	2 (2.0)
Intestinal obstruction	1 (0.6)	2 (2.0)
Neutropenia	0	2 (2.0)
Decreased platelet count	1 (0.6)	2 (2.0)
Pneumonia	3 (1.9)	2 (2.0)
Pyrexia	2 (1.3)	2 (2.0)
Spinal cord compression	0	2 (2.0)
AE leading to permanent treatment discontinuation	16 (10.1)	2 (2.0)
Related to study treatment [a]	11 (7.0)	2 (2.0)
SAE leading to permanent treatment discontinuation [c]	8 (5.1)	1 (1.0)
Related to study treatment [a]	4 (2.5)	1 (1.0)
Fatal AEs [b]	7 (4.4)	0
Fatal AE on-study treatment	6 (3.8)	0
Related to study treatment [c]	2 (1.3)	0
Fatal AE within 30 days of last dose	1 (0.6)	0

Source: Tables 2-29 to 2-31, pp75-77 of the resubmission and Table JZJC.8.158, p1075 of the LIBRETTO-431 CSR.

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ECG = electrocardiogram; PC = platinum-based chemotherapy; SAE = serious adverse events; TEAE = treatment-emergent adverse event

[a] Included events that were considered related to study treatment as judged by the Investigator.

[b] Deaths on therapy and within 30 days of last dose date were included. Deaths were also included as SAEs and discontinuations due to adverse events.

[c] Sudden death and malnutrition.

6.36 The frequency of AEs, including events with fatal outcomes, was higher in the selpercatinib arm than in the pembrolizumab ± PC arm. The pre-PBAC response noted that patients in the selpercatinib arm were exposed to treatment for substantially longer that those in the pembrolizumab ± PC arm (median time on treatment 16.7 months vs 9.8 months respectively).

6.37 A greater proportion of patients in the selpercatinib arm (n=111) experienced Grade ≥3 treatment-emergent adverse events (TEAEs) versus the pembrolizumab ± PC arm (n=56) (70.3% versus 57.1%, respectively).

6.38 The most reported (≥5%) Grade ≥3 AEs in the selpercatinib arm were increased alanine aminotransferase (22.2%), hypertension (20.3%), increased aspartate aminotransferase (12.7%) and electrocardiogram QT prolonged (8.9%).

6.39 A greater proportion of patients experienced serious adverse events (SAEs) in the selpercatinib arm (34.8%) compared to the pembrolizumab ± PC arm (23.5%). The pre-PBAC response stated that when the incidence rate of SAEs was adjusted to per 100 patient years at risk, the rates were more comparable: 31.3% (95% CI: 23.6, 4.8) for the selpercatinib arm and 26.7% (95% CI: 16.9, 40.0) for the pembrolizumab ± PC arm. The most commonly reported SAEs in the selpercatinib arm were pleural effusion (4.4%) and abnormal hepatic function (2.5%).

6.40 Seven patients (4.4%) in the selpercatinib arm experienced fatal AEs. Most deaths (6 deaths, 3.8%) occurred while receiving treatment and 2 deaths (1.3%) were assessed to be related to selpercatinib (sudden death and malnutrition). No fatal AEs were reported in the pembrolizumab arm.

6.41 The TGA Product Information states that fatal haemorrhagic events occurred in patients treated with selpercatinib. The TGA advises permanently discontinuing selpercatinib in patients with severe or life-threatening haemorrhage (the TGA Product Information). In the LIBRETTO-431 trial, there were no Grade ≥ 3 TEAE haemorrhagic events in the selpercatinib arm and 2 (2.0%) in the pembrolizumab ± PC arm (Table JZJC.8.152, p1028 of the LIBRETTO-431 CSR).

Benefits/harms

6.42 A summary of the comparative benefits and harms for selpercatinib versus pembrolizumab ± PC is presented in Table 9.

Table 9: Summary of comparative benefits and harms for selpercatinib and pembrolizumab + PC

Benefits				
Progression free survival assessed by BICR for the ITT-pembrolizumab population in the LIBRETTO-431 trial (median duration of follow up 19.38 months)				
Event	**Selpercatinib (N=129)**	**Pembro + PC (N=83)**	**Absolute difference**	**HR (95% CI) P value**
Progressed, n (%)	49/129 (38%)	49/83 (59%)	-	**0.465** [a] (0.309, 0.699) [b] P=0.0002 [c]
Median PFS, months (95% CI)	24.84 (16.89, NE)	11.17 (8.77, 16.76)	13.67	
% not progressed at 6 months (95% CI)	87.2	72.1	15.1 (3.6, 26.6)	
% not progressed at 24 months (95% CI)	54.2	31.6	22.6 (6.9, 38.4)	
% not progressed at 30 months (95% CI)	49.7	NE	NE	
Overall survival for the ITT-pembrolizumab population in the LIBRETTO-431 trial (median duration of follow up 21.65 months)				
Deaths, n/N (%)	25/129 (19.4%)	15/83 (18.1%)	-	0.961 [a] (0.503, 1.835) [b] P=0.9033 [c]
Median OS, months (95% CI)	NE	NE	NE	
% Alive at 6 months (95% CI)	95.3 (89.9, 97.9)	95.1 (87.4, 98.1)	0.3 (-5.7, 6.2)	
% Alive at 24 months (95% CI)	75.2 (65.0, 82.8)	79.0 (67.3, 86.9)	-3.8 (-16.9, 9.3)	
% Alive at 30 months (95% CI)	75.2 (65.0, 82.8)	79.0 (67.3, 86.9)	-3.8 (-16.9, 9.3)	

Harms (Safety population)						
	Selpercatinib (N=158)	**Pembro ± PC (N=98)**	**RR**	**Event rate/100 patients**		**RD**
				Selpercatinib	**Pembro ± PC**	
Grade ≥3 TEAE related to study treatment	89/158	41/98	1.3	56.3	41.8	14.5
Grade ≥3 TEAEs, ALT increased	35/158	3/98	7.2	22.2	3.1	19.1
Grade ≥3 TEAEs, AST increased	20/158	1/98	12.4	12.7	1.0	11.7
Grade ≥3 TEAEs, Hypertension	32/158	3/98	6.6	20.3	3.1	17.2
Grade ≥3 TEAEs, ECG QT prolonged	14/158	0/98	NE	8.9	0	8.9

Source: Tables JZJC.5.1 and 14.2.1.1.1, pp98-99; Table JZJC.5.3., pp106-107 of the LIBRETTO-431 CSR.

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; ECG = electrocardiogram; HR = hazard ratio; ITT = intention to treat; IWRS = interactive web response system; NE = not estimable; PC = platinum-based chemotherapy; Pembro = pembrolizumab; PFS = progression-free survival; RD = risk difference; RR = risk ratio; TEAE = treatment-emergent adverse event.

[a] Stratified by Geography (East Asian versus non-East Asian) – IWRS, Brain metastases (presence or absence/unknown) – IWRS

[b] 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation.

[c] p-values were computed based on comparator carboplatin or cisplatin + pemetrexed + pembrolizumab.

ITT-population included the ITT-pembrolizumab population and those that did not receive pembrolizumab as decided by the study investigator intention to treat (no more than 20%)

6.43 On the basis of the direct evidence from the LIBRETTO-431 trial presented by the resubmission, for every 100 patients treated with selpercatinib in comparison with pembrolizumab ± PC:

- Approximately 23 patients will remain progression free after 24 months.
- Approximately 15 additional patients will experience an adverse event from the treatment.
- Approximately 19 additional patients will experience Grade ≥ 3 increases in alanine aminotransferase (an enzyme elevated in the blood caused by liver damage).
- Approximately 12 additional patients will experience a Grade ≥ 3 increase in aspartate aminotransferase (an enzyme elevated in the blood caused by liver damage).

- Approximately 17 additional patients will experience Grade ≥ 3 hypertension (high blood pressure).
- Approximately 9 additional patients will experience Grade ≥ 3 prolonged electrocardiogram QT (indicating an irregular heart rhythm).

Clinical claim

6.44 The resubmission described selpercatinib as superior in terms of effectiveness compared with pembrolizumab + PC in patients with advanced *RET* fusion-positive NSCLC based on the new head-to-head LIBRETTO-431 trial data. In July 2023, the PBAC could not support the claim of superior efficacy as the ITCs presented were associated with a high degree of uncertainty (paragraph 7.1, selpercatinib PSD, July 2023 PBAC meeting).

6.45 Patients from the LIBRETTO-431 trial treated with selpercatinib demonstrated a statistically significant ($p<0.05$) improvement in PFS when compared to patients in the pembrolizumab + PC arm in the ITT-pembrolizumab population and ITT-population (incremental PFS = 13.67 months).

6.46 However, OS gained was not statistically significant in either analysis population. OS in the control arm was confounded as 75% of patients in the ITT-pembrolizumab population who discontinued treatment crossed over to receive selpercatinib treatment or a commercially available selective *RET* inhibitor after disease progression. This resulted in the comparative treatment effect of selpercatinib being underestimated.

6.47 Overall, the PBAC agreed with ESC in considering that in terms of PFS, the claim of superior efficacy was supported and in terms of OS, the claim of superior efficacy was uncertain due to the high rate of crossover in the LIBRETTO-431 trial.

6.48 The resubmission described selpercatinib as having a different, but clinically manageable, safety profile compared with pembrolizumab + PC in patients with advanced *RET* fusion-positive NSCLC. The PBAC previously considered the claim that selpercatinib has a different, but manageable, safety profile compared to pembrolizumab + PC was reasonable (paragraph 6.67, selpercatinib, PSD, July 2023 PBAC meeting).

6.49 Overall, the ESC considered that selpercatinib had an inferior safety profile compared to pembrolizumab ± PC, as evidenced by the higher rate of TEAEs, SAEs and fatal AEs.

6.50 The PBAC considered that the claim that selpercatinib has a different, but clinically manageable, safety profile was reasonable.

Economic analysis

6.51 The resubmission presented a stepped economic evaluation of selpercatinib compared with pembrolizumab + PC as first-line therapy for the treatment of *RET* fusion-positive, locally advanced or metastatic NSCLC based on an indirect comparison

of the treatment-naïve cohort of the LIBRETTO-001 study (June 2021 data cut) and the pembrolizumab trials KN-189 and KN-021 (Cohort G). The base case economic analysis was based on the primary indirect comparison using the MAIC 2 model approach.

6.52 The type of economic evaluation presented was a cost-effectiveness analysis and a cost-utility analysis. The resubmission presented a partitioned survival model, which was the same basic model structure as the July 2023 submission.

6.53 The key differences from the July 2023 submission base case were:

- The source of the treatment effect changed from the network meta-analysis to the MAIC 2 model.
- The time horizon was reduced from 20 years to 10 years.
- *RET* fusion testing was excluded.
- No dose reductions for pembrolizumab were applied.
- The TTD for later-line pembrolizumab therapy was doubled from 5.65 treatment cycles in the July 2023 submission to 11.31 cycles in the resubmission.
- The drug acquisition costs for pembrolizumab, pemetrexed, carboplatin and docetaxel were recalculated according to the Efficient Funding of Chemotherapy (EFC) Program.

6.54 The key differences outlined above were consistent with the respecified base case model provided in the July 2023 pre-PBAC response (paragraph 6.88, selpercatinib PSD, July 2023 PBAC meeting). The PBAC previously noted the respecified base case provided in the pre-PBAC response differed from that provided during the evaluation in three ways: application of the selpercatinib treatment effect derived from the MAIC Model 2; use of a 10 year rather than a 7.5 year time horizon; and incorporation of a % price reduction for selpercatinib (paragraph 7.12, selpercatinib PSD, July 2023 PBAC meeting).

6.55 Further details regarding the key components of the economic evaluation used in the resubmission, along with the key differences with the July 2023 submission and the pre-PBAC response are described in Table 10.

Table 10: Summary of model structure, key inputs and differences between the July 2023 submission, the pre-PBAC response and the current resubmission

Component	July 2023 submission	July 2023 pre-PBAC response	July 2024 resubmission
Time horizon	20 years	10 years	10 years
Methods to generate results	Partitioned survival model	Unchanged	Unchanged
Health states	3 health states: PFS, PD and death	Unchanged	Unchanged
Allocation to health states	Health state allocation over time in the selpercatinib arm was derived from the KM curves of PFS and OS from treatment-	Health state allocation over time in the selpercatinib arm: unchanged	Unchanged from July 2023 pre-PBAC response

Component	July 2023 submission	July 2023 pre-PBAC response	July 2024 resubmission
	naïve cohort of the LIBRETTO-001 study (June 2021 data cut) until median follow-up (21.9 months for PFS and 25.2 months for OS), after which PFS and OS were extrapolated using parametric functions. Health state allocation over time in the pembrolizumab + PC arm was determined by applying HRs generated from the NMA to the selpercatinib arm (HR for OS= 0.931 (95% CI: 0.202, 0.759); HR for PFS= 0.337 (95% CI: 0.166, 0.687)). The NMA involved generating a synthetic pseudo-control PC arm by matching (using PSM) the PC arm of KN-189 to the IPD in the LIBRETTO-001 study. PFS was extrapolated using a Gompertz parametric function in both treatment arms. OS was extrapolated using a Spline Knot 1 parametric function in both arms.	Health state allocation over time in the pembrolizumab + PC arm was based on applying the HRs generated from the MAIC 2 model to the selpercatinib arm (HR for OS = 0.43 (95% CI: 0.21, 0.89); HR for PFS = 0.48 (95% CI: 0.27, 0.84)). Extrapolation functions: Unchanged	
TTD for later-line pembrolizumab	July 2023 submission: 5.65 x 3-weekly treatment cycles (i.e. 16.95 weeks)	11.31 x 3-weekly cycles (i.e. 33.93 weeks)	Unchanged from July 2023 pre-PBAC response
Utilities	PFS = 0.776 PD = 0.714	Unchanged	Unchanged

Source: Table 3-2, and Sections 3.2-3.6 of the resubmission.
CI: confidence interval; HR = hazard ratio; IPD = individual patient data; KM = Kaplan- Meier; Lys = life years; MAIC = matching adjusted indirect comparison; NMA = network meta-analysis; OS = overall survival; PC = platinum-based doublet chemotherapy; PD = progressed disease; PFS = progression-free survival; PSM = propensity score matching; TTD = time to treatment discontinuation
Blue shading indicates data previously considered by the PBAC.

6.56 The time horizon in the model (10 years) was long compared to the duration of follow-up in the LIBRETTO-001 study June 2021 data cut (median 2.1 years) and the duration of follow-up in the LIBRETTO-431 trial (median 1.8 years). The PBAC previously accepted a 7.5-year time horizon for pembrolizumab chemotherapy as first-line therapy for advanced NSCLC (paragraph 6.70. selpercatinib, PSD, July 2023 PBAC meeting). The ICER increased from $75,000 to < $95,000 per quality-adjusted life year (QALY) gained to $75,000 to < $95,000 per QALY gained when a time horizon of 7.5 years was applied. The ESC considered that a 7.5-year time horizon was reasonable. The pre-PBAC response reiterated that a 10-year time horizon was reasonable, stating that given the superiority in PFS demonstrated by selpercatinib a greater OS could be inferred. In addition, the pre-PBAC response noted that the January 2023 data cut from LIBRETTO-001 reported 52.3% of patients were alive 5 years after receiving their

first dose of selpercatinib in the first-line setting. The PBAC recalled it had accepted a 10-year time horizon for larotrectinib (paragraph 7.12, larotrectinib PSD, March 2024 PBAC meeting).

6.57 Health state allocation over time in the selpercatinib arm was derived from the Kaplan-Meier curves of PFS and OS from treatment-naïve patients from the LIBRETTO-001 study (June 2021 data cut) until median follow-up (21.9 months for PFS and 25.2 months for OS), after which PFS and OS were extrapolated using parametric functions. This was unchanged compared to the July 2023 submission. Allocation of patients to health states (and thus efficacy) in the pembrolizumab + PC arm was based on PFS and OS calculated by applying the PFS and OS hazard ratios from the MAIC 2 model to the selpercatinib arm in the LIBRETTO-001 study. Sensitivity analysis could not be conducted using the 95% confidence intervals of the hazard ratios for PFS and OS.

6.58 In July 2023, the PBAC considered the re-specified base case using the MAIC 2 model provided in the pre-PBAC response; however, considered the fundamental uncertainty associated with the ITC between poorly transitive studies that formed the basis of the model could not be resolved by re-specification. As such, the PBAC considered the ICER remained highly uncertain (paragraph 7.12, selpercatinib, PSD, July 2023 PBAC Meeting). The approach used in the current resubmission was the same as that used in the July 2023 pre-PBAC response.

6.59 The resubmission did not use the data from the LIBRETTO-431 trial to populate the economic model. Instead, the resubmission claimed comparability of PFS estimates between the trial (HR = 0.47; 95% CI: 0.31, 0.70) and the ITC using the MAIC 2 model (HR = 0.48, 95% CI: 0.27, 0.84). The MAIC 2 model adjusted for sex, age, ECOG PS, presence of brain metastases and smoking status. While this model was the most conservative among all the presented ITC (see Table 7), the evaluation noted the sample size in the selpercatinib arm in the LIBRETTO-001 study was reduced to 22 patients, potentially reducing the statistical power of this model to predict PFS and OS.

6.60 The PSCR stated that due to the immaturity and the high rate of crossover in the LIBRETTO-431 trial the data would not meaningfully inform the economic model. The PSCR stated that given the maturity of the data in LIBRETTO-001 and the very high consistency of results between LIBRETTO-431 and the ITCs the current model was reliable to inform the cost effectiveness of selpercatinib compared with pembrolizumab + PC. The ESC considered that using the results of the LIBRETTO-431 trial would have been more suitable than the MAIC 2 model given that it was conducted in the target population (i.e., *RET*-fusion positive) and observed and unobserved differences in the patient characteristics were addressed using randomisation.

6.61 The resubmission did not update the model to use the most recent data cut of the LIBRETTO-001 study (January 2023), which had a longer median follow-up

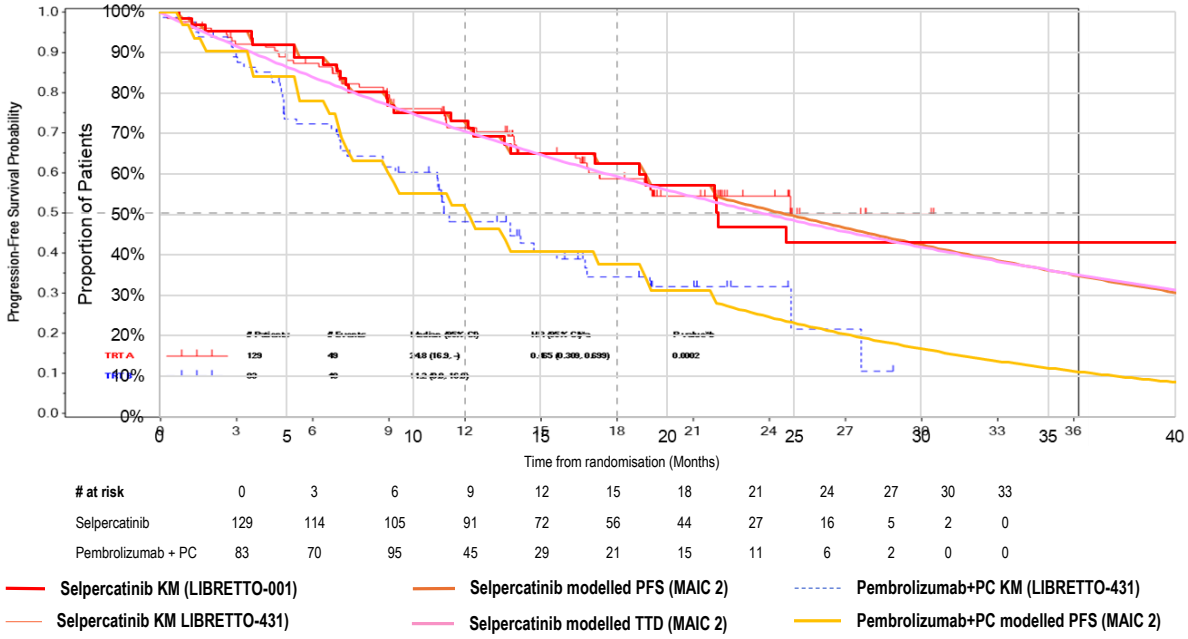
(38.9 months for PFS and 41.9 months for OS) than the June 2021 data cut (21.9 months for PFS and 25.2 months for OS). The resubmission claimed that the modelled OS in the selpercatinib arm based on the LIBRETTO-001 June 2021 data cut, was consistent with the observed OS from the LIBRETTO-001 January 2023 data cut. Additionally, the PSCR stated that the modelled OS for the selpercatinib arm tracked below the more mature LIBRETTO-001 data (from the January 2023 data) and the modelled pembrolizumab + PC arm tracked above that in KN-189, suggesting that the modelled scenario presented in the resubmission was conservative. The ESC considered that incorporation of the more mature data from the LIBRETTO-001 study would allow its impact on survival extrapolations to be appropriately assessed. The pre-PBAC response provided an economic model based on the MAIC 2 model using updated LIBRETTO-001 data. The PBAC noted the ICER was lower than that provided in the resubmission base case; however, this model and the updated MAIC 2 analysis had not been evaluated.

6.62 The resubmission extrapolated PFS using the Gompertz function and OS using the spline knot 1 function. Statistically (based on the AIC and BIC) these parametric functions had the poorest fit to the data. The resubmission claimed that the survival estimates from the selected parametric functions aligned well with those provided for selpercatinib by the clinical experts. The validity of the estimates from clinicians could not be assessed as the resubmission did not supply information on how these clinicians were selected, nor provide PFS or OS estimates from individual clinicians or the basis of their estimates.

6.63 The ICER was not sensitive to changing the extrapolation function applied for PFS (ICER with Gompertz function = $75,000 to < $95,000per QALY gained versus ICERs for other functions: $55,000 to < $75,000 per QALY gained to $75,000 to < $95,000 per QALY gained). For OS, although the lognormal and loglogistic functions had better statistical fit than the spline knot 1, they resulted in more patients alive at 10 years (22.7% and 19.1% versus 15.7%, respectively). The PSCR argued that all the parametric functions had similar statistical fit and that the spline-knot 1 function was chosen as it supported the proportional hazards assumption and predicted consistently higher OS in the pembrolizumab + PC arm compared with KN-189. The ESC considered the gamma function may be more appropriate noting the function had better AIC and BIC statistics and reported 10.0% of patients alive at 10 years. The ESC noted that use of the gamma function resulted in an ICER of $75,000 to < $95,000 per QALY gained.

6.64 The PFS and OS generated by the selpercatinib and pembrolizumab + PC arms over 40 months compared to the LIBRETTO-431 trial are presented in Figure 5 and Figure 6, respectively.

Figure 5: Overlay of modelled PFS (MAIC 2 model) with the LIBRETTO-431 trial

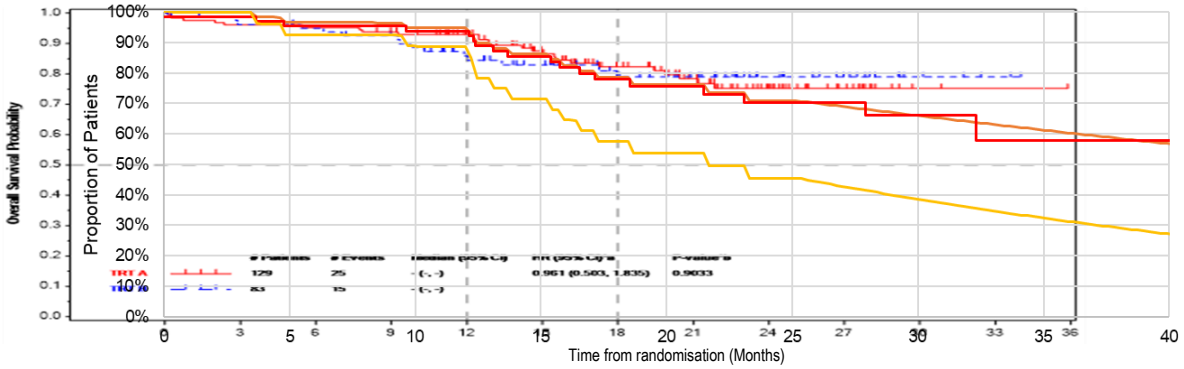


Source: Figure 3-12, p138 of the resubmission.
KM = Kaplan-Meier; MAIC = matching-adjusted indirect comparison; PC = platinum-based doublet chemotherapy; PFS = progression-free survival; TTD = time to treatment discontinuation.
Thick red line denoted the trial-based KM curve of the selpercatinib arm from the LIBRETTO-001 study (June 2021 data cut).
Thin orange line denoted the trial-based KM curve of the selpercatinib arm from the LIBRETTO-431 trial.
Thick orange line denoted the modelled selpercatinib PFS curve based on the MAIC 2 model.
Thick yellow line denoted the modelled pembrolizumab + PC PFS curve based on the MAIC 2 model.
Thin blue line denoted the trial-based KM curve of the pembrolizumab + PC arm from the LIBRETTO-431 trial.

6.65 The resubmission claimed that the modelled selpercatinib PFS curve using the MAIC 2 model (thick orange line) aligned with the trial-based selpercatinib Kaplan-Meier curve from the LIBRETTO-431 trial (thin orange line). This was reasonable for the Kaplan-Meier curve prior to 22 months (median follow-up at June 2021 data cut). Beyond 22 months, the LIBRETTO-431 trial Kaplan-Meier curve was consistently higher than that of the MAIC 2 model. This difference may be inconsequential given the small number of patients remaining progression-free at 22 months.

6.66 The resubmission claimed that the modelled pembrolizumab + PC PFS curve using the MAIC 2 model (thick yellow line) aligned with the trial-based pembrolizumab + PC Kaplan-Meier curve from the LIBRETTO-431 trial (thin blue line). The modelled median PFS for pembrolizumab + PC was higher in the MAIC 2 model (12.43 months) compared to the LIBRETTO-431 trial (11.17 months), and the modelled incremental gain in median PFS was lower than in the LIBRETTO-431 trial (12.19 months versus 13.67 months, respectively).

Figure 6: Overlay of modelled OS (MAIC 2 model) with the LIBRETTO-431 trial



# at risk	0	3	6	9	12	15	18	21	24	27	30	33	36
Selpercatinib	129	124	123	119	106	88	70	53	32	16	3	1	0
Pembrolizumab + PC	83	78	76	71	59	51	40	33	20	13	5	2	0

Selpercatinib KM (LIBRETTO-001) **Selpercatinib modelled OS (MAIC 2)** **Pembrolizumab+PC KM (LIBRETTO-431)**
Selpercatinib KM LIBRETTO-431) **Pembrolizumab+PC modelled OS (MAIC 2)**

Source: Figure 3-13, p139 of the resubmission.
KM = Kaplan-Meier; MAIC = matching-adjusted indirect comparison; OS = overall survival; pembro+pem+plat = pembrolizumab plus pemetrexed plus platinum-based doublet chemotherapy
Thick red line denoted the trial-based KM curve of the selpercatinib arm from the LIBRETTO-001 study (June 2021 data cut).
Thin orange line denoted the trial-based KM curve of the selpercatinib arm from the LIBRETTO-431 trial.
Thick orange line denoted the modelled selpercatinib OS curve based on the MAIC 2 model.
Thick yellow line denoted the modelled pembrolizumab + PC OS curve based on the MAIC 2 model.
Thin blue line denoted the trial-based KM curve of the pembrolizumab + PC arm from the LIBRETTO-431 trial.

6.67 The resubmission claimed that the modelled selpercatinib OS curve using the MAIC 2 model (thick orange line) aligned with the trial-based selpercatinib Kaplan-Meier curve from the LIBRETTO-431 trial (thin orange line). The trial-based Kaplan-Meier curve from the LIBRETTO-431 trial was consistently higher than the modelled selpercatinib OS curve.

6.68 The trial-based Kaplan-Meier curve from the LIBRETTO-431 trial was consistently higher than the modelled pembrolizumab + PC OS curve. This can be explained by the high level of cross-over of patients from the pembrolizumab + PC arm to the selpercatinib arm in the LIBRETTO-431 trial. Overall, the OS estimates remain uncertain.

6.69 The resubmission did not provide TTD data for selpercatinib from the LIBRETTO-431 trial or from the later data cut of the LIBRETTO-001 study. The TTD for selpercatinib applied in the economic model remained the same as the July 2023 submission and was based on the LIBRETTO-001 study (June 2021 data cut).

6.70 The resubmission doubled the TTD for later-line pembrolizumab therapy, from 5.65 treatment cycles to 11.31 cycles. This aligned with the re-specified base case proposed during the evaluation of the July 2023 submission (paragraph 6.82, selpercatinib, PSD, July 2023 PBAC meeting).

6.71 Overall, the evaluation noted the survival outcomes (PFS and OS) in the selpercatinib arm of the MAIC 2 model aligned with the LIBRETTO-001 study (June 2021 and January 2023 data cut) and the LIBRETTO-431 trial. Alignment with the LIBRETTO-001 study

was anticipated given that the selpercatinib population in the MAIC 2 model was derived from the LIBRETTO-001 study. The alignment with the LIBRETTO-431 trial provides some external validity for the modelled PFS and OS results for the selpercatinib population. In contrast, the survival outcomes in the pembrolizumab + PC arm remain uncertain. The MAIC 2 model was estimated using the KN-189 trial in which the *RET* fusion status was unknown. Comparing OS outcomes for the pembrolizumab + PC arm with the LIBRETTO-431 trial was not possible due to crossover in the LIBRETTO-431 trial.

6.72 The key drivers of the model are outlined in Table 11.

Table 11: Key drivers of the economic model

Description	Method/Value	Impact Base case: $[1]/QALY gained
Extrapolation parametric function for OS	Spline knot 1. Statistically (based on the AIC and BIC), the spline knot 1 function did not have a good fit to the data (AIC ranked 10th, BIC ranked 11thand 1.97% alive at 20 years). The gamma function may have been a better alternative function statistically and in terms of clinical plausibility (AIC ranked 5th, BIC ranked 4th and 0.63% alive at 20 years).	Moderate, likely favoured selpercatinib. The ICER with a gamma function was $[redacted]1/QALY gained.
Time horizon	10 years. The PBAC previously accepted a 7.5-year time horizon for pembrolizumab as first-line chemotherapy for advanced NSCLC (para 6.70. selpercatinib, PSD, July 2023 PBAC meeting).	Moderate, favoured selpercatinib. The ICER with a 7.5-year time horizon was $[redacted]1/QALY gained.
KM data source	LIBRETTO-001 study June 2021 data cut. The PBAC had anticipated that the results of the LIBRETTO-431 trial may address much of the uncertainty associated with the indirect comparison used to inform estimates of comparative effectiveness in this submission (para. 7.14, selpercatinib, PSD, July 2023 PBAC meeting).	Data from the LIBRETTO-431 might affect the ICER, but the magnitude cannot be predicted using the data provided.

Source: Compiled during the evaluation.
AIC = Akaike information criterion; BIC = Bayesian information criterion; ICER = incremental cost-effectiveness ratio; KM = Kaplan Meier; NSCLC = non-small cell lung cancer; OS = overall survival; QALY = quality adjusted life years.
The redacted values correspond to the following ranges:
1 $75,000 to < $95,000

6.73 Table 12 presents the results of the economic evaluation (using the assumed effective price of pembrolizumab).

Table 12: Results of the stepped economic evaluation

	Cost	Incremental cost	Effectiveness	Incremental effectiveness	ICER
Step 0 (cost per LY – Trial based analysis)					
Selpercatinib	$[redacted]	$[redacted]	3.438	1.081	$[redacted][1]/LY
Pembrolizumab + PC	$163,453		2.358		
Step 1 (cost per LY – MAIC 2 model[a] over 10-year time horizon)					
Selpercatinib	$[redacted]	$[redacted]	4.771	2.151	$[redacted][2]/LY
Pembrolizumab + PC	$168,692		2.620		
Step 2 (cost per LY – 5% discounting)					
Selpercatinib	$[redacted]	$[redacted]	4.057	1.687	$[redacted][2]/LY
Pembrolizumab + PC	$159,603		2.370		
Step 3 (cost per QALY)					
Selpercatinib	$[redacted]	$[redacted]	3.043	1.270	**$[redacted][1]/QALY**
Pembrolizumab + PC	$159,603		1.773		
July 2023 submission					
Step 3 (cost per QALY)					
Selpercatinib	$[redacted]	$[redacted]	3.289	1.852	$[redacted][2]/QALY
Pembrolizumab + PC	$169,401		1.437		
July 2023 pre-PBAC response					
Step 3 (cost per QALY)					
Selpercatinib	NR	NR	NR	NR	$[redacted][2]/QALY
Pembrolizumab + PC	NR		NR		

Source: Table 3-34 of the resubmission, and Table 21 and para.6.88, selpercatinib, PBAC PSD, July 2023 PBAC meeting.
ICER = incremental effectiveness ratio; LY = life year; MAIC= matching adjusted indirect comparison; NR = not reported; PC = pemetrexed + carboplatin; QALY = quality-adjusted life year.
[a] Transcription error in the resubmission specified using the network meta-analysis results in the table.
Blue shading indicates data previously considered by the PBAC.
The redacted values correspond to the following ranges:
1 $75,000 to < $95,000
2 $55,000 to < $75,000

6.74 Over a 10-year model horizon, the resubmission reported that selpercatinib was associated with incremental costs of $[redacted] per patient, 1.687 life years gained and 1.270 QALYs gained (discounted). The ICER estimated in the resubmission's base case was $75,000 to < $95,000 per QALY gained. The PBAC noted the ICER using the effective price of pembrolizumab.

6.75 Table 13 presents a step wise analysis of the changes to the July 2023 submission, and the July 2023 pre-PBAC response, that resulted in the ICER presented in the resubmission. The ICER was higher in the resubmission compared with the July 2023 pre-PBAC response because of decreased unit cost of pembrolizumab and increased per-cycle costs of pembrolizumab.

Table 13: Step-wise analysis of the changes to the July 2023 submission, and the pre-PBAC response

Change in inputs from the July 2023 submission to the pre-PBAC response and resubmission (incremental inputs)	ICER (cost per QALY gained)	% change vs ICER in previous step
Base case in July 2023 submission	[redacted]1	
Source of the treatment effect changed from the NMA to the MAIC 2 model	[redacted]2	[redacted]%
Time horizon decreased from 20 to 10 years	[redacted]2	[redacted]%
Decreased EMP of selpercatinib (1.5%)	[redacted]2	[redacted]%
Increased dose of pembrolizumab in Cycle 2+ (from 166.72 mg to 200 mg), and decreased drug acquisition cost pembrolizumab in Cycle 1, Cycle 2 and subsequent cycles (from $7,876.91 to $7,829.19)	[redacted]1	-[redacted]%
Increase in time on treatment on pembrolizumab in subsequent cycle from 16.96 to 33.92 weeks (doubled number of cycles)	[redacted]2	[redacted]%
Decreased drug acquisition cost of pemetrexed and carboplatin in Cycle 1, Cycle 2, and subsequent cycles	[redacted]3	[redacted]%
Decreased drug acquisition cost of docetaxel in subsequent cycles, from $272.31 to $149.06	[redacted]3	[redacted]%
Removal of *RET* testing cost	[redacted]1	-[redacted]%
Base case in July 2023 pre-PBAC response	[redacted]1	
Decreased EMP of selpercatinib (9.5%)	[redacted]1	-[redacted]%
Decreased drug acquisition cost of pembrolizumab based on [redacted]% rebate (AEMP per 100 mg vial from $3,938 to $[redacted]) and EFC-based costs, resulting in decreased costs in Cycle 1 and Cycle 2 (from $7,829.19 to $[redacted])	[redacted]2	[redacted]%
Increased drug acquisition cost of carboplatin and decreased drug acquisition costs of pemetrexed and other therapies, based on updated EFC costs	[redacted]2	[redacted]%
Decrease in cost of adverse events and use of latest life tables to estimate life expectancy.	[redacted]2	[redacted]%
Base case in resubmission	[redacted]2	-

Source: tabulated during the evaluation by changing the inputs step wise, to the July 2023 economic model.

AEMP = approved ex-manufacturer price; EFC = Efficient Funding of Chemotherapy program; EMP = ex-manufacturer price; ICER = incremental cost-effectiveness ratio; MAIC = matching adjusted indirect comparison; NMA = network meta-analysis; QALY = quality-adjusted life year; *RET* = rearranged during transfection

The redacted values correspond to the following ranges:

1 $55,000 to < $75,000

2 $75,000 to < $95,000

3 $95,000 to < $115,000

6.76 Table 14 presents the life years and QALYs gained in each health state.

Table 14: Disaggregated summary of health outcomes for selpercatinib vs pembrolizumab + PC

Health state	Selpercatinib	Pembrolizumab + PC	Incremental outcome	% of total incremental outcome
LYs (discounted)				
Progression-free	2.399	1.341	1.058	62.7%
Progressed disease	1.658	1.029	0.629	37.3%
Total LYs	**4.057**	**2.370**	**1.687**	**100%**
Lys (undiscounted)				
Progression-free	2.664	1.424	1.240	57.6%
Progressed disease	2.107	1.197	0.910	42.3%
Total LYs	**4.771**	**2.621**	**2.150**	**100%**
QALYs (discounted)				
Progression-free	1.859	1.041	0.821	64.6%
Progressed disease	1.184	0.735	0.449	35.4%
Total QALYs	**3.043**	**1.776**	**1.270**	**100%**
QALYs (undiscounted)				
Progression-free	2.067	1.105	0.962	59.7%
Progressed disease	1.504	0.854	0.650	40.3%
Total QALYs	**3.571**	**1.959**	**1.612**	**100%**

Source: Table 3-36, p144 of the resubmission, and 'Attachment 5.1 Selpercatinib Section 3 Workbook'.
LY = life year; PC = Pemetrexed + carboplatin; QALY = quality-adjusted life year.

6.77 QALYs gained accumulated in both the progression-free (59.7%) and progressed disease (40.3%) health states. The QALYs gained in the progression-free health state may be reasonable given the similarities across the MAIC 2 model and the LIBRETTO-431 trial in terms of hazard ratios. However, the QALYs gained in the progressed disease health state are uncertain due to cross-over in the LIBRETTO-431 trial and the extrapolation approach.

6.78 The undiscounted incremental life years gained of 2.15 years appeared optimistic considering the advanced disease stage of NSCLC of the target population.

6.79 The results of key univariate sensitivity analyses are summarised in Table 15.

Table 15: Results of the one-way sensitivity analyses

Description	Incremental cost ($)	Incremental QALYs	ICER (cost per QALY gained)	% change from base case ICER
Base case	[redacted]	**1.27**	[redacted][1]	[redacted]%
Time horizon (base case: 10 years)				
7.5 years	[redacted]	1.06	[redacted][1]	[redacted]%
Discount rate (costs and outcomes) (base case: 5%)				
0%	[redacted]	1.61	[redacted][1]	[redacted]%
3.5%	[redacted]	1.36	[redacted][1]	[redacted]%
Utilities in PD and PF states (base case, PD = 0.714, PF =0.776)				
Utility in PD state=0.691 and PF = 0.766[a]	[redacted]	1.25	[redacted][1]	[redacted]%
Indirect comparison method (base case= MAIC 2 model)				
MAIC 1 model	[redacted]	1.42	[redacted][1]	[redacted]%
Survival curve extrapolation functions for OS[b] (base case: Spline Knot= 1)				
Lognormal for selpercatinib arm (1st best fit)	[redacted]	1.34	[redacted][1]	[redacted]%
Loglogistic for selpercatinib arm (2nd best fit)	[redacted]	1.29	[redacted][1]	[redacted]%
Gamma for selpercatinib arm (3rd best fit)	[redacted]	1.17	[redacted][1]	[redacted]%
Survival curve extrapolation functions for TTD (base case: exponential)				
Gompertz extrapolation for TTD (2nd best fit)	[redacted]	1.270	[redacted][2]	[redacted]%
Weibull extrapolation for TTD (3rd best fit)	[redacted]	1.270	[redacted][1]	[redacted]%
Inclusion of terminal care cost (base case: yes)				
No[c]	[redacted]	1.270	[redacted][1]	[redacted]%
Multivariate sensitivity analyses				
Time horizon = 7.5 years + gamma function for selpercatinib OS	[redacted]	1.02	[redacted][1]	[redacted]%

Source: Sensitivity analyses performed during the evaluation, Table 3-39of the resubmission.

ICER = incremental cost-effectiveness ratio; MAIC = matching-adjusted indirect comparison; OS = overall survival; PC = platinum-based doublet chemotherapy; PD = progressed disease; PF = progression free; QALY = quality-adjusted life year; TTD = time to treatment discontinuation

[a] Health state utilities in the PC arm of the July 2019 pembrolizumab model (pembrolizumab PSD, July 2019 PBAC meeting). The sensitivity analysis, as noted in the July 2023 commentary, was replicated by using the health state utilities in the PC arm of the July 2019 pembrolizumab model (0.766 for PFS and 0.691 for PD).

[b] Extrapolation functions applied to both pembrolizumab + arm and selpercatinib arms resulted in the same ICER as changing extrapolation function only in selpercatinib arm (pembrolizumab PSD, July 2019 PBAC meeting). It is difficult to say which function was the best for OS, given the uncertainty in data on the proportion alive beyond 5 years available from the trials. Considering the advanced stage of lung cancer in the cohort, few patients are expected to live longer than 10 years. Observing the number of patients alive at 10 years and 20 years, one of the plausible alternatives was the gamma function where 10% were alive at 10 years, and 0.6% alive at 20 years. The gamma function was also the 3rd best fit, statistically. Other functions with small numbers alive beyond 10 years were Gompertz (0.08% and 0% at 10 and 20 years, respectively), Stratified Weibull (4.1% and 0.02% at 10 and 20 years, respectively), Stratified Gamma (7.5% and 0.3% at 10 and 20 years, respectively), and Weibull (8.7% and 0.3% at 10 and 20 years, respectively).

[c] Change the cost of terminal care from $42,370.93 to $0 (F1377, 'Country-Specific Data 1L NSCLC', "A5.1_Selpercatinib Section 3 Workbook")

The redacted values correspond to the following ranges:

1 $75,000 to < $95,000

2 $55,000 to < $75,000

6.80 The ESC noted that a multivariate sensitivity analysis which incorporated a 7.5-year time horizon and the gamma function for selpercatinib OS resulted in an ICER of $75,000 to < $95,000 per QALY.

6.81 The evaluation considered it was difficult to predict the magnitude of the change in the ICER if data from the LIBRETTO-431 trial were used. However, the evaluation considered:

- The modelled median PFS of selpercatinib may be reasonable given the similarities across the LIBRETTO-001 study and the LIBRETTO-431 trial in terms of hazard ratios (HR from the MAIC 2 model = 0.48 (95% CI: 0.27, 0.84) versus HR from LIBRETTO-431 = 0.465 (95% CI: 0.309, 0.699) and median PFS estimates (21.9 months versus 24.8 months, respectively).
- The modelled OS for selpercatinib may be conservative, given that the proportion of patients alive at 24 months at the June 2021 data cut from the LIBRETTO-001 study (69.3%) was less than that from the January 2023 data cut (74.3%) and the LIBRETTO-431 trial (75.2%). A similar comparison regarding the modelled OS for pembrolizumab + PC was not possible due to cross-over in the LIBRETTO-431 trial.
- The relative dose intensity (RDI) of selpercatinib was similar across the LIBRETTO-001 study (June 2021 data cut), LIBRETTO-001 study (January 2023 data cut) and the LIBRETTO-431 trial (83.4% vs 82.50 vs 83.7%, respectively).

Drug cost/patient/course

6.82 Table 16 presents the drug costs per patient for selpercatinib and pembrolizumab + PC.

Table 16: Drug cost per patient for selpercatinib and pembrolizumab + PC

	Selpercatinib			Pembrolizumab + PC		
	Trial dose and duration	**Model**	**Financial estimates**	**Trial dose and duration**	**Model**	**Financial estimates**
Mean dose	LIBRETTO-431: 21-day cycles 1,875 mg/week =268 mg/day LIBRETTO-001: 28-day cycles 1,855 mg/week = 265 mg/day	28-day cycles Cycle 1: 293.3 mg/day Cycles 2+: 251.1 mg/day[a]	252.19 mg/day[b]	21-day cycles Pembrolizumab: 63.5 mg/week Carboplatin: 1.5 mg*min/ml/week Cisplatin: 22.9 mg/m^2/week Pemetrexed: 148 mg/m^2/week	21-day cycles Pembrolizumab: Cycle 1: 200 mg every 3 weeks Cycle 2+: 200 mg every 3 weeks Carboplatin: Cycle 1: 15mg/mL AUC (=490 mg/day) Cycle 2+: 4.17mg/mL*min (=408 mg/day) Pemetrexed: Cycle 1: 905 mg/day Cycle 2+: 416.8mg/m^2 (=754 mg/day)	NA
Mean duration	LIBRETTO-431: Mean = 16.6 months Median = 16.7 months LIBRETTO-001 (January 2023): Median = 24.6 months	36.8 x 28 day-cycles = 33.8 months	37.7 x 28-day cycles[c] =34.7 months	9.8 months (median, any drug) 10.9 months (mean, any drug)	19.89 cycles =13.7 months	NA
Cost/patient /cycle	–	28-day cycles Cycle 1: $[redacted] Cycles 2+: $[redacted]	28-day cycles Cycle 1: $[redacted] Cycles 2+: $[redacted][d]	–	21-day cycles Pembrolizumab: Cycle 1: $[redacted] Cycles 2+: $[redacted] Carboplatin: Cycle 1: $170.65 Cycles 2-4: $143.87 Cycles 5+: $0 Pemetrexed: Cycle 1: $169.01 Cycles 2+: $158.30	NA
Cost/patient /course	–	$[redacted]	$[redacted][e]	–	$[redacted]	NA

Source: Table compiled during the evaluation, based on "Attachment 2.3 LIBRETTO-431 CSR", "Attachment 2.1 LIBRETTO-001 CSR", "Attachment 5.1_Selpercatinib Section 3 Workbook" and "Attachment 6.1_ Selpercatinib Cost and utilisation model" of the resubmission.
AUC = area under the curve; NA = not applicable; PC = platinum-based doublet chemotherapy.

[a] Cycle 2 onwards the dose is lower because the model considered potential dose reductions to account for toxicity and adverse events (the resubmission).

[b] The daily dose used in the financial analysis was the weighted mean of 293.3 mg/day for the first 28-day treatment cycle and 251.1 mg/day for the remaining 36.7 cycles.

[c] Based on 150.91 weeks of treatment received in LIBRETTO-001 (cell 'F173' in tab '3a. Scripts- proposed' in 'Attachment 6.1_ Selpercatinib Cost and utilisation model'). Data not presented in the main resubmission document. In the resubmission, patients were assumed to receive treatment with selpercatinib for an average of 34.71 months or 2.8925 years. In line with this, each patient received treatment for 10.71 months (89.25% of the year) in their third year of treatment.

[d] Costs calculated during the evaluation by multiplying effective cost of selpercatinib by dose/pack size (Table 3-24, of the submission), with the proportion of patients on each dose regimens in Cycle 1 and Cycles 2+ described in Sheet 3a. Scripts – proposed (cells E178:H183).

[e] Cost during the evaluation based on cost/patient/cycle across 37.7 cycles.

Estimated PBS usage & financial implications

6.83 This resubmission was not considered by DUSC. The July 2023 submission was considered by the DUSC. The submission utilised an epidemiological approach to determine the number of eligible patients in the first 6 years of listing.

6.84 The key inputs utilised to determine the number of eligible patients and financial estimations, and the differences between the July 2023 submission and resubmission are summarised in Table 17.

Table 17: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value	Source	Comment
Eligible population			
Incident patients with lung cancer	Yr 1: 14,840 Yr 2: 15,133 Yr 3: 15,414 Yr 4: 15,686 Yr 5: 15,943 Yr 6: 16,182	AIHW, Cancer in Australia 2021	This data source was the same as the July 2023 submission and was considered reasonable by DUSC (Table 26, selpercatinib, PSD, July 2023 PBAC meeting).
Prevalent patients with lung cancer	Yr 1: 28,833 Yr 2-6: Not used	AIHW, Cancer in Australia 2021. The prevalent pool was estimated by totalling the incidence of lung cancer for the past 2 years.	This data source was the same as the July 2023 submission and was reasonable given the proportion of prevalent patients eligible to receive treatment outlined below.
Additional parameters utilised to estimate the number of eligible patients			
Proportion of patients who have NSCLC	86.6%	Mitchell et al. (2013)	This data source was the same as the July 2023 submission and was considered reasonable by DUSC (Table 26, selpercatinib PSD, July 2023 PBAC meeting).
Proportion of patients who are NSQ/NOS	74.2%	Paragraph 6.46, nivolumab, PSD, March 2016 PBAC meeting.	This data source was the same as the July 2023 submission and was considered reasonable by DUSC (Table 26, selpercatinib PSD, July 2023 PBAC meeting). The PBAC noted the restriction criteria does not limit by histology but recalled the occurrence of *RET* fusions is rare in squamous NSCLC (Table 26, selpercatinib PSD, July 2023 PBAC meeting).
Proportion of patients who are ECOG PS: 0-2	96.8%	Hess et al. (2021)	This data source was the same as the July 2023 submission and was reasonable. The DUSC noted that this proportion was reasonable for incident patients, but likely to be overestimated in 2L+ patients (Table 26, selpercatinib, PSD, July 2023 PBAC meeting).
Proportion of patients who are *RET* fusion-positive	1.5%	Kohno et al. (2012), Ferrara et al. (2018)	This data source was the same as the July 2023 submission. The DUSC noted that this proportion was uncertain and impacted the estimates significantly but agreed the estimate of 1.5% was likely reasonable (Table 26, selpercatinib, PSD, July 2023 PBAC meeting).
Eligible patients			
Proportion of patients diagnosed at Stage IIIB/IV	65.5%	Mitchell et al. (2013) and the Erlotinib and Gefitinib DUSC report.	This data source was the same as the July 2023 submission and was reasonable.

Data	Value	Source	Comment
Proportion of patients, diagnosed at Stage I-IIIA who progress to Stage IIIB/IV within a year	30%	Mitchell et al. (2013).	This data source was the same as the July 2023 submission and was considered reasonable by DUSC (Table 26, selpercatinib PSD, July 2023 PBAC).
Proportion of pre-treated (prevalent) Stage IIIB/IV patients alive and eligible to receive selpercatinib	80%	Assumption	The July 2023 submission assumed 100% of patients were eligible. This reduction was consistent with July 2023 PBAC advice that the proportion of prevalent patients eligible for treatment would be between 70 - 80% (para.7.13, selpercatinib PSD, July 2023 PBAC meeting).
Treatment utilisation			
Uptake rate	Yr 1-6: 100%	Assumption	This was the same as the July 2023 submission. The PBAC and DUSC considered a 100% uptake rate appropriate (para.7.13, selpercatinib PSD, July 2023 PBAC meeting).
Treatment duration	34.71 months	Modelled TTD based on the LIBRETTO-001 study (June 2021 data cut). This data was not presented in the resubmission.	The PBAC advised to apply a shorter duration (32.1 months) based on PFS from the LIBRETTO-001 trial (para. 7.13, selpercatinib, PSD, July 2023 PBAC meeting). The resubmission did not change the TTD from the July 2023 submission. The DUSC also advised to use a shorter treatment duration in the prevalent population compared with the incident population (Table 26, selpercatinib PSD, July 2023 PBAC meeting). The resubmission applied the same duration to all populations citing consistency of TTD across treatment-naïve and pre-treated cohorts. The PBAC noted the resubmission did not provide any additional TTD data (see paragraph 6.69).
Scripts dispensed	13.04 per patient per year	Assuming 53%, 43% and 19% for the following dose/size packs: 80 mg (112 capsules pack), 80 mg (56 capsules pack) and 40 mg (56 capsules pack).	This was the same as the July 2023 submission.
Costs			
Selpercatinib 80 mg x 112 pack 80 mg x 56 pack 40 mg x 56 pack	$ $ $	Requested effective DPMQs	The effective DPMQs were lower than the July 2023 submission and the July 2023 pre-PBAC response for each strength x pack size combination: 80 mg x 112 pack: 10.7% and9.3% lower, respectively 80 mg x 56 pack: 10.4% and 9.1%, respectively. 40 mg x 56 pack: 10.5% and 9.2% respectively.
Patient co-payment	PBS: $15.27 RPBS: 7.28[b]	Services Australia PBS item statistics PBS item numbers: 11492W, 11494Y, 12119W, 12121Y	-

Data	Value	Source	Comment
PBS/RPBS Split	PBS: 97.01% RPBS: 2.99%	Services Australia PBS item statistics PBS item numbers: 11492W, 11494Y, 12119W, 12121Y	-
MBS costs			
RET fusion testing	$0	Assumed	The July 2023 submission included RET fusion testing costs for all eligible patients, and the pre-PBAC response in July 2023 applied test costs to 34% of prevalent patients. The resubmission argued that RET fusion testing was not required in the financial estimates because the test was a part of the standard diagnostic pathway for NSCLC patients in Australia. The MBS item was listed in November 2023, so the prevalent pool of patients eligible for selpercatinib in 2025 would have had access to the test.
ECG	$25.60 per service. 2024 MBS fee was $1.00 higher ($26.65).	MBS item 11714, 80% rebate	The July 2023 submission assumed 2.4 ECG services per year. In line with DUSC advice (Table 26, selpercatinib PSD, July 2023 PBAC meeting), the resubmission assumed 7 ECG services in the first year. Using the updated fee, the cost to MBS over 6 years increased by $4,838.

Source: Tabulated during evaluation from Sections 4.1-4.3 of the resubmission.
2L+ = second-line and beyond; AIHW = Australian Institute of Health and Welfare; DPMQ = dispensed price for maximum quantity; DUSC = Drug Utilisation Sub-Committee; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; MBS = Medicare Benefits Schedule; NSCLC = non-small cell lung cancer; NSQ/NOS = non-squamous/not otherwise specified; PS = performance status; PBS = Pharmaceuticals Benefits Scheme; PFS = progression free survival; *RET* = rearranged during transfection; RPBS = Repatriation Pharmaceuticals Benefits Scheme; TTD = time to treatment discontinuation; Yr = year
[a] The median time on treatment with selpercatinib was 24.6 months according to the LIBRETTO-001 January 2023 data cut (Table JZJA.4.19, p94 of 'Attachment 2.1 LIBRETTO-001 CSR January 2023' of the resubmission). The median time on selpercatinib was 16.72 months in the LIBRETTO-431 trial (Figure 8.19, p 998, of 'Attachment 2.3 LIBRETTO-431 CSR May 2023' of the resubmission).
Blue shading indicates data previously considered by the PBAC.

6.85 The key differences between the July 2023 submission and resubmission were:

- The reduction in the assumption that 100% of prevalent patients are eligible for treatment to 80%.
- An approximate % reduction in the effective DPMQ of selpercatinib.
- The exclusion of *RET* fusion testing. The July 2023 submission included testing costs for all eligible patients, and the pre-PBAC response in July 2023 that applied test costs to 34% of prevalent patients.
- Increasing the number of ECG services in the first year of selpercatinib treatment from 2.4 to 7.

6.86 The total number of patients treated with selpercatinib in Year 1 was estimated to be < 500. This included < 500 prevalent patients from the prior 2 years in addition to 1< 500 incident patients. The prevalent patients included < 500 grandfathered patients enrolled to an early patient familiarisation program. The eligible prevalent population comprised 80% of all the pre-treated Stage IIIB/IV patients, reduced from 100% in the

July 2023 submission. This reduction was consistent with July 2023 PBAC advice that the proportion of prevalent patients eligible for treatment would be between 70 - 80% (paragraph 7.13, selpercatinib PBAC PSD, July 2023 PBAC meeting).

6.87 The net cost to the PBS/RPBS and the healthcare budget are described in Table 18.

Table 18: Estimated use and financial implications (at proposed effective prices of selpercatinib)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	1	1	1	1	1	1
Number of scripts dispensed	2	3	3	2	2	2
Estimated financial implications of selpercatinib						
Cost to PBS/RPBS less copayments	4	5	6	5	5	5
Estimated financial implications for other medicines						
Cost to PBS/RPBS less copayments	7	7	7	7	7	7
Net financial implications						
Net cost to PBS/RPBS	4	5	6	5	5	5
Net cost to MBS	7	7	7	7	7	7
Net cost to PBS/RPBS/MBS	3	5	6	5	5	5
Previous submission: July 2023						
Number of patients treated	1	1	1	1	1	1
Number of scripts dispensed	2	3	3	2	2	2
Net cost to PBS/RPBS	5	6	6	5	5	5

Source: tabulated during evaluation from Table 4-5of the resubmission; Sheet "3a. Scripts – proposed" from the "Attachment 6.1_ Selpercatinib Cost and utilisation model" of the resubmission.
MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme
Blue shading indicates data previously considered by the PBAC.
The redacted values correspond to the following ranges:
1 < 500
2 500 to < 5,000
3 5,000 to < 10,000
4 $10 million to < $20 million
5 $20 million to < $30 million
6 $30 million to < $40 million
7 $0 to < $10 million

6.88 The total cost to the PBS/RPBS of listing selpercatinib was estimated to be $10 million to < $20 million in Year 1, increasing to $20 million to < $30 million in Year 6, and totalling $100 million to < $200 million over the first 6 years of listing. These costs did not incorporate any cost offsets as the resubmission assumed that selpercatinib will displace later lines rather than replace other therapies, including pembrolizumab. The resubmission claimed that this was a conservative assumption. This was previously considered reasonable (Table 26, selpercatinib PSD, July 2023 PBAC meeting).

6.89 In comparison, in the July 2023 resubmission the net cost to the PBS/RPBS was estimated to be $100 million to < $200 million in the first 6 years of selpercatinib listing. The key reasons for a reduction in net cost to the PBS/RPBS in the resubmission were:

- Inclusion of smaller proportion of pre-treated patients eligible to receive selpercatinib than in the July 2023 submission (80% versus 100%, respectively).

- A lower effective DPMQ for selpercatinib.

6.90 The total cost to the PBS/RPBS of listing selpercatinib was most sensitive to the estimated prevalence of RET fusion-positive patients. Assuming a prevalence of 1% and 3.2% (upper and lower bounds for international estimate of 1.5%) resulted in a total cost over the first 6 years of listing to the PBS/RPBS of $90 million to < $100 million and $200 million to < $300 million, respectively.

6.91 The resubmission applied the following assumptions to calculate the cost to the MBS:

- 7 ECGs in the first year of treatment for all incident patients. This aligned with DUSC advice (Table 26, selpercatinib PSD, July 2023 PBAC meeting).
- Exclusion of *RET* fusion testing costs. The resubmission argued that the costs associated with *RET* fusion testing were not required in the financial estimates as the test is part of the standard diagnostic pathway for NSCLC patients in Australia. The pre-PBAC response for the July 2023 submission applied test costs to 34% of prevalent patients (paragraph 6.90, selpercatinib, PSD, July 2023 PBAC meeting). The MBS item was listed in November 2023, so the prevalent pool of patients eligible for selpercatinib in 2025 would have had access to the test.

6.92 The resubmission estimated the total cost to the Australian Government (MBS/PBS/RPBS) over 6 years to be $100 million to < $200 million.

Quality Use of Medicines

6.93 The Quality Use of Medicines (QUM) section acknowledges that this is a new medicine with potential unknown safety and includes a QUM plan involving education for providers, risk minimization strategies and post marketing surveillance.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC recommended Authority Required (Streamlined) listing for selpercatinib for the treatment of advanced or metastatic rearranged during transfection (*RET*) fusion-positive non-small cell lung cancer (NSCLC). The PBAC considered that the additional clinical evidence presented in the resubmission supported the claim that selpercatinib was superior to pembrolizumab plus platinum-based doublet chemotherapy (PC) in terms of progression free survival (PFS) but that the magnitude of any overall survival (OS) benefit remained uncertain. The PBAC considered that applying a more conservative extrapolation function to OS in the economic model would be appropriate. The PBAC considered selpercatinib would be cost effective with an incremental cost effectiveness ratio (ICER) of less than $75,000 to < $95,000 per QALY gained (using the effective price of pembrolizumab), consistent with other targeted therapies for NSCLC.

7.2 The PBAC noted the input from health care professionals, the Lung Foundation

Australia and Rare Cancers Australia which highlighted the clinical need for effective treatment options for these patients. In addition, the PBAC noted the Medical Oncology Group of Australia's support for the listing of selpercatinib. The PBAC acknowledged the clinical need for effective treatments for patients with this condition.

7.3 The PBAC noted that pembrolizumab + PC was nominated as the comparator in the first-line setting. The PBAC recalled that it had previously considered that this was appropriate.

7.4 The PBAC noted that the resubmission presented new clinical data from the LIBRETTO-431 trial, a randomised controlled trial which compared selpercatinib with pembrolizumab ± PC. The PBAC noted that the resubmission presented results for the ITT-pembrolizumab population which included patients who investigators intended to treat with pembrolizumab prior to treatment allocation. The PBAC noted that it would have been more appropriate to present data from the ITT population (i.e., all patients), but noted that the ITT-pembrolizumab population accounted for 80% of the ITT population and results were similar between both populations.

7.5 The PBAC noted that selpercatinib was associated with improved PFS outcomes compared to pembrolizumab + PC in both the ITT-pembrolizumab population (HR = 0.465; 95% CI: 0.309, 0.699) and the ITT population (HR = 0.482; 95% CI: 0.331, 0.700).

7.6 The PBAC noted that the OS results were not statistically significant (HR = 0.961; 95% CI: 0.503, 1.879 in the ITT-pembrolizumab population). The PBAC noted that the OS results in the pembrolizumab + PC arm were confounded as 75% of patients who discontinued treatment (50% of patients randomised to the ITT population) crossed over to receive selpercatinib or a commercially available selective *RET* inhibitor. Given the immaturity of the OS data (19.4% of patients in selpercatinib arm and 18.1% of patients in the pembrolizumab + PC arm had died) the PBAC considered that crossover adjustment would not have provided a reliable estimate of OS.

7.7 The PBAC noted that the resubmission also presented updated data from the January 2023 data cut from the single arm LIBRETTO-001 study. The PBAC recalled that data from the June 2021 data cut were presented in the July 2023 submission. The PBAC noted that the updated PFS result for treatment-naïve patients who received selpercatinib (median = 22.0 months; 95% CI: 16.5, 24.9) was consistent with that presented in the previous submission (median = 22.0 months; 95% CI: 13.8, NE).

7.8 Overall, the PBAC considered that the resubmission's claim that selpercatinib demonstrated superior efficacy compared to pembrolizumab + PC was supported in terms of PFS. In terms of OS, the PBAC considered that the magnitude of the benefit was uncertain due to the immaturity of the LIBRETTO-431 trial and the high rate of crossover in the pembrolizumab + PC treatment arm.

7.9 The PBAC noted that selpercatinib was associated with a higher frequency of adverse events compared to pembrolizumab ± PC in the LIBRETTO-431 trial. However, the

PBAC acknowledged that selpercatinib patients were exposed to treatment for a longer duration (median time on treatment 16.7 months vs 9.8 months). Overall, in terms of safety, the PBAC noted that the data from the LIBRETTO-431 trial supported its previous decision that selpercatinib had a different, but clinically manageable safety profile compared with pembrolizumab ± PC.

7.10 The PBAC noted that the resubmission represented indirect treatment comparisons (ITCs) from the July 2023 submission which compared selpercatinib (from LIBRETTO-001) with pembrolizumab + PC (from the KN-189 and KN-021 studies), as these formed the basis of the economic analysis. The PBAC noted that the updated data from LIBRETTO-001 were not incorporated into the ITCs.

7.11 The PBAC recalled that it had previously anticipated that the results of the LIBRETTO-431 trial would be used to inform the economic model and that they would address many of the uncertainties associated with the use of ITCs to inform the estimates of comparative effectiveness. The PBAC noted that the resubmission stated that due to the immaturity and high rate of crossover in the LIBRETTO-431 trial, the data would not meaningfully inform the economic model. Instead, the resubmission noted that the maturity of the data in the LIBRETTO-001 study and the comparability of the PFS estimates between the LIBRETTO-431 trial (HR = 0.47; 95% CI: 0.31, 0.70) and the ITC using the MAIC 2 model (HR = 0.48; 95% CI: 0.27, 0.84) (see Figure 5) meant that the original model was reliable to inform the cost effectiveness of selpercatinib compared with pembrolizumab + PC. The PBAC considered that it would have been more appropriate to apply the results of the LIBRETTO-431 trial given that it was conducted in the target population and observed and unobserved differences in the patient characteristics were addressed using randomisation. The PBAC acknowledged that the data from the LIBRETTO-431 trial provided some external validity for the modelled PFS results and for OS in the selpercatinib arm, but the OS in the pembrolizumab + PC arm, and therefore the incremental OS benefit, remained highly uncertain.

7.12 The PBAC noted that a 10-year time horizon was applied to the base case economic model. The PBAC noted the ESC considered a 7.5-year time horizon would be more appropriate and the ICER was sensitive to the time horizon (see paragraph 6.56). The PBAC noted the arguments in the pre-PBAC response supporting a 10-year time horizon and considered that, on balance, a 10-year time horizon was likely to be reasonable.

7.13 The PBAC noted that the resubmission applied a spline knot 1 function to extrapolate OS in the selpercatinib arm which resulted in 15.7% of patients remaining alive at 10 years. The PBAC considered the use of the spline knot 1 function to extrapolate OS was not adequately justified, particularly given it had the worst statistical fit (paragraph 6.62). The PBAC considered that applying the gamma function was more appropriate and resulted in a more conservative estimate of the proportion of patients alive at 10 years (10.0%). The PBAC noted the ICER using the gamma function (and the assumed effective price of pembrolizumab) was $75,000 to < $95,000 per QALY gained. The PBAC considered selpercatinib would be cost effective with an ICER

of <$55,000 to < $75,000 per QALY gained (using the effective price of pembrolizumab), consistent with other targeted therapies for NSCLC (paragraph 7.5, osimertinib PSD, July 2020 PBAC meeting; paragraph 7.8, mobocertinib PSD, July 2023 PBAC meeting).

7.14 The PBAC considered that the utilisation estimates provided in the resubmission were appropriate. The PBAC noted that the resubmission applied an estimated prevalence of *RET* fusion-positive patients of 1.5% and considered that this was reasonable. However, the PBAC noted some uncertainty remained regarding the treatment duration for selpercatinib (see Table 17). The PBAC considered a risk sharing arrangement with expenditure caps based on the financial estimates (incorporating a revised price) with % rebate over the caps would be reasonable to manage the risk that the duration of treatment is longer than estimated.

7.15 In terms of the proposed restriction, the PBAC considered that the line-agnostic restriction was appropriate. The PBAC agreed with the Secretariat suggestion regarding maximum quantities (see paragraph 3.4) and advised a prescribing instruction should be added to direct prescribers on prescribing the sufficient quantities according to their patient's need. The PBAC advised it would be appropriate to remove the administrative note "No increase in the maximum quantity or number of units may be authorised" from the 40 mg listing to allow clinicians to prescribe sufficient quantity for dose titration. The PBAC noted that the restriction wording will provide for initial, continuing and grandfather treatment in one treatment phase.

7.16 The PBAC noted that flow on changes to the PBS listing of pembrolizumab would be required to enable its use after selpercatinib. The PBAC considered that the amendment of the pembrolizumab clinical criterion 'the condition must have progressed after treatment with tepotinib' to 'the condition must have progressed after treatment with only one of: (i) tepotinib, (ii) selpercatinib' was reasonable and should apply to pembrolizumab PBS item numbers: 11492W, 11494Y, 12119W and 12121Y.

7.17 The PBAC requested that future data from the LIBRETTO-431 be provided to the PBAC should it become available.

7.18 The PBAC advised that selpercatinib was not suitable for prescribing by nurse practitioners.

7.19 The PBAC advised that selpercatinib should not be treated as interchangeable with any other drugs.

7.20 The PBAC advised that selpercatinib should not be exempt from the Early Supply rule.

7.21 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not] met. Specifically, the PBAC found that in the circumstances of its recommendation for selpercatinib:

a) The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy, over alternative therapies, given the magnitude of OS benefit is highly uncertain.

b) The treatment is not expected to address a high and urgent unmet clinical need as other therapies for this condition are available on the PBS;

c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

7.22 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
SELPERCATINIB					
selpercatinib 40 mg modified release capsule, 56	NEW 1 MP	1	56	5	Retevmo
					Safety Net rule penalty applies? Yes
Restriction Summary [new 1] / Treatment of Concept: [new 1.1]					
Concept ID – for internal use only	**Category / Program:** GENERAL – General Schedule (Code GE)				
	Prescriber type: ☒Medical Practitioners				
	Restriction type: ☒Authority Required – Streamlined *(new code 1)*				
	Administrative Advice: No increase in the maximum number of repeats may be authorised				
	Administrative Advice: Special pricing arrangements apply				
	Indication: Locally advanced or metastatic non-small cell lung cancer				
	Clinical criteria:				
	The condition must have evidence of rearranged during transfection (RET) gene fusion in tumour material – this evidence has been obtained prior to commencing treatment with this drug				
	AND				
	Clinical criteria:				
	Patient must have a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score of no higher than 2 at treatment initiation				
	AND				
	Clinical criteria:				
	The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this PBS indication.				
	Treatment criteria:				

	Patient must be initiating treatment with this drug; or
	Patient must be continuing treatment with this drug, with an absence of further disease progression while being treated with this drug
	Prescribing instructions: Medical practitioners must prescribe the appropriate quantities of appropriate strength(s) to provide sufficient drug, based on the weight of the patient, adequate for 4 weeks, according to the specified dosage in the Therapeutic Good Administration Approved Product Information. A separate authority prescription form must be completed for each strength requested.

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
SELPERCATINIB					
selpercatinib 80 mg modified release capsule, 56	NEW 2 MP	2	112	5	Retevmo
selpercatinib 80 mg modified release capsule, 112	NEW 3 MP	1	112	5	Retevmo
					Safety Net rule penalty applies? Yes

Restriction Summary [new 2] / Treatment of Concept: [new 2.1]		
Concept ID – for internal use only		**Category / Program:** GENERAL – General Schedule (Code GE)
		Prescriber type: ☒Medical Practitioners
		Restriction type: ☒Authority Required – Streamlined (new code 2)
		Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
		Administrative Advice: No increase in the maximum number of repeats may be authorised
		Administrative Advice: Special pricing arrangements apply
		Indication: Locally advanced or metastatic non-small cell lung cancer
		Clinical criteria:
		The condition must have evidence of rearranged during transfection (RET) gene fusion in tumour material – this evidence has been obtained prior to commencing treatment with this drug
		AND
		Clinical criteria:
		Patient must have a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score of no higher than 2 at treatment initiation
		AND
		Clinical criteria:
		The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this PBS indication.
		Treatment criteria:
		Patient must be initiating treatment with this drug; or
		Patient must be continuing treatment with this drug with an absence of further disease progression while being treated with this drug
		Prescribing instructions: Medical practitioners must prescribe the appropriate quantities of appropriate strength(s) to provide sufficient drug, based on the weight of the patient, adequate for 4 weeks per dispensing, according to the specified

	dosage in the approved Therapeutic Goods Administration (TGA) Product Information (PI). A separate authority prescription form must be completed for each strength requested.
	Prescribing instructions: Medical practitioners may prescribe selpercatinib 80 mg with a quantity of up to 56 units where the dose doesn't exceed 120 mg twice daily (i.e., in combination with selpercatinib 40 mg). Selpercatinib 80 mg with a quantity of 112 units must be prescribed only where the dose is 160 mg twice daily to provide 28 days of treatment per dispensing. Prescribers should refer to the TGA PI for dosing and dose adjustments' regimens.

8.2 Flow on changes to pembrolizumab to enable its use after selpercatinib (the full restrictions haven't been populated below, only the changes have been marked in *italics)*

MEDICINAL PRODUCT **Form**	**PBS item code**	**Max. Amount**	**№.of Rpts**
PEMBROLIZUMAB Injection	11494Y (Public) 11492W (Private) MP	200 mg	6
Available brands			
Keytruda (pembrolizumab 100 mg/4 ml injection, 4 ml vial)			
Edit of Restriction Summary 13430 / ToC: 13431: Authority Required: Streamlined			
Concept ID for internal use only	**Category / Program:** Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals		
	Prescriber type: ☒Medical Practitioners		
	Restriction type: ☒Authority Required – Streamlined		
	Indication: Stage IV (metastatic) non-small cell lung cancer (NSCLC)		
	Treatment Phase: Initial treatment - 3 weekly treatment regimen		
	Clinical criteria:		
	Patient must not have previously been treated for this condition in the metastatic setting; or		
	The condition must have progressed after treatment with *only one of (i)* tepotinib, *(ii) selpercatinib*		

MEDICINAL PRODUCT **Form**	**PBS item code**	**Max. Amount**	**№.of Rpts**
PEMBROLIZUMAB Injection	12121Y (Public) 12119W (Private) MP	400mg	3
Available brands			
Keytruda (pembrolizumab 100 mg/4 ml injection, 4 ml vial)			
Edit of Restriction Summary 13444 / ToC: 13436: Authority Required: Streamlined			
Concept ID for internal use only	**Category / Program:** Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals		
	Prescriber type: ☒Medical Practitioners		
	Restriction type: ☒Authority Required – Streamlined		
	Indication: Stage IV (metastatic) non-small cell lung cancer (NSCLC)		
	Treatment Phase: Initial treatment - 6 weekly treatment regimen		
	Clinical criteria:		
	Patient must not have previously been treated for this condition in the metastatic setting; or		
	The condition must have progressed after treatment with *only one of (i)* tepotinib, *(ii) selpercatinib*		

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.