For public – No ACIC information

Selpercatinib for untreated RET fusion-positive advanced non-small-cell lung cancer

HST committee 15 March 2023

Chair: Peter Jackson

Lead team: Jonathan Ives, Annett Blochberger and Ed Wilson

External assessment group: Kleijnen Systematic Reviews (KSR) in collaboration with Erasmus University Rotterdam and Maastricht University Medical Centre

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Company: Eli Lilly

Selpercatinib for untreated RET fusion-positive advanced non-small-cell lung cancer

- ✓ **About**
- ❑ Clinical evidence
- ❑ Modelling
- ❑ Key issues
- ❑ ICERs
- ❑ Other considerations: severity, managed access, equality, innovation
- ❑ Summary

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Background on RET fusion-positive advanced non-small-cell lung cancer

The condition

- A malignant disorder which begins in the cells of the lung

Epidemiology

- In 2019, 40,168 new lung cancer cases in the UK of which 80-85% are NSCLC
- 1–2% of NSCLC cases have a RET fusion-positive mutation
- Typically affects people under 60 years old, females, and non-smokers

Symptoms

- Symptoms are non-specific and may be disregarded leading to advanced cancer diagnosis

Prognosis

- In 2019, 70% of NSCLC diagnoses were in advanced stages (III/IV)
- Estimated 5-year survival for advanced stages were 2.9%
- Advanced lung cancer frequently metastasise to the central nervous system (brain metastasis)

Abbreviations: NSCLC: non-small cell lung cancer; RET: rearranged during transfection

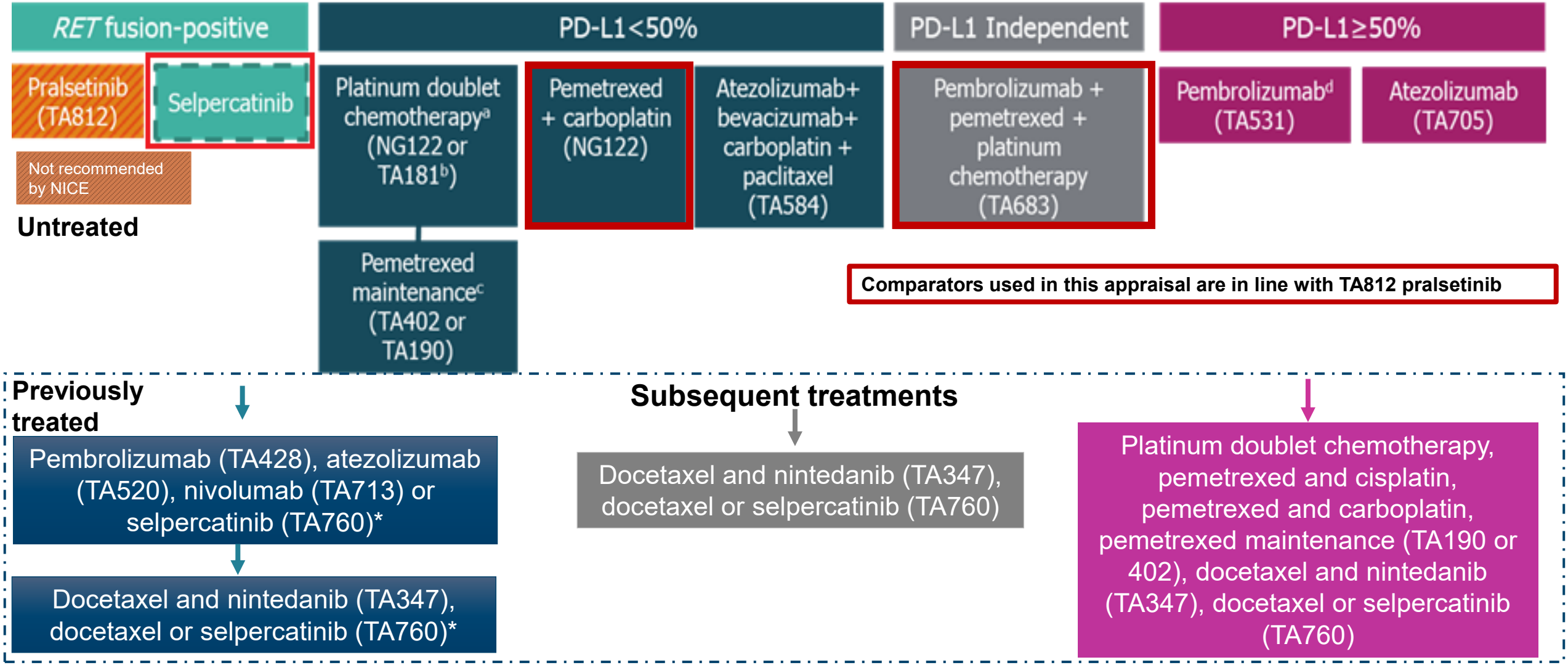
Selpercatinib (Retsevmo, Eli Lilly)

Technology details

Marketing authorisation	• Retsevmo as monotherapy is indicated for the treatment of adults with advanced RET fusion-positive NSCLC not previously treated with a RET inhibitor. • MHRA approved • Granted; September 2022
Mechanism of action	• Highly selective small molecule inhibitor of fusion, mutant and wild-type products involving the proto-oncogene RET tyrosine kinase receptor. Inhibits cell growth in tumour cells that exhibit increased RET activity.
Administration	• 160 mg (2 x 80mg oral capsules) twice daily.
Price	• List price per 60 hard capsules pack of 80 mg is £4,680.00 and £2,340.00 for a 40mg pack. • List price for 28-day cycle is £8,736.00 • PAS discount available from established NHS arrangement of selpercatinib in pre-treated setting.

Abbreviations: MHRA: Medicines and Healthcare products Regulatory Agency; NSCLC: non-small cell lung cancer; PAS: patient access scheme; RET; rearranged during transfection

Non-squamous NSCLC treatment pathway and positioning of selpercatinib



Source: Adapted from Company submission, Document B, Figure 1 and NICE guideline 122

[a] Platinum doublet chemotherapy may include: platinum-based chemotherapy (carboplatin/cisplatin) + paclitaxel, docetaxel, gemcitabine or vinorelbine; or cisplatin + pemetrexed. [b] TA181 (pemetrexed + cisplatin) and TA347 (nintedanib + docetaxel) recommend technologies in adenocarcinoma and large cell carcinoma, respectively. [c] Pemetrexed maintenance is only permitted after pemetrexed + cisplatin (not carboplatin). [d] Pembrolizumab monotherapy is subject to a 2-year stopping rule

*Selpercatinib (TA760) available for previously treated RET-fusion positive NSCLC through managed access.

Abbreviations: PD-L1: programmed death-ligand; NG: NICE guidelines; NSCLC: non-small cell lung cancer; RET: rearranged during transfection; TA: technology appraisal.

Patient perspectives

Submissions from Roy Castle Lung Cancer Foundation

- People with RET alterations tend to be younger and with few comorbidities so tend to be diagnosed later as they do not fit the typical lung cancer patient profile.
- Systemic treatment with a combination of chemotherapy and immunotherapy is currently available to manage untreated RET fusion positive NSCLC. For the treated population, selpercatinib through CDF(NICE TA760) is available.
- Selpercatinib is the first therapy available specifically targeting RET fusion positive lung cancer.
- Oral therapy is an advantage over in-hospital intravenous treatments. Reducing hospital attendance is preferable during COVID-19 times.

Abbreviations: CDF: cancer drugs fund; COVID-19: coronavirus disease; NSCLC: non-small cell lung cancer; RET: rearranged during transfection; TA: technology appraisal.

Clinical perspectives

The Royal College of Pathologists
Pathology: the science behind the cure

Submissions from the Royal College of Pathologists

- Response from RET fusion positive NSCLC to targeted treatment is associated with high quality of life.
- Evidence show that RET positive NSCLC responds poorly to immunotherapy→ associated with more side effects than targeted therapy.
- Currently, people with RET fusion positive NSCLC must endure chemotherapy and immunotherapy (less well tolerated and potentially less effective) before becoming eligible for their ideal therapy.
- The introduction of this technology would have an impact on a few centres which do not currently test for RET mutation in first line→ extra resource implications lead to delayed results.
- Absence of central funding for tissue preparation for genomic testing by pathology laboratories mean RET testing will never be as quick as it can be.

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Abbreviations: NSCLC: non-small cell lung cancer; RET: rearranged during transfection

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Key clinical trial-LIBRETTO-001

LIBRETTO-001 is currently ongoing (final completion date expected September 2024)

Trial name	LIBRETTO-001 (NCT03157128)
Design	Phase 2 , multicentre, open-label, single arm study, non-randomised
Population	>12 years old with locally advanced or metastatic solid tumours, including *RET* fusion-positive solid tumours, *RET*-MTC and other tumours with RET activation who: - who progressed on or were intolerant to standard therapy - no standard therapy exists - would be unlikely to have clinical benefit from standard therapy - declined standard therapy and have ECOG ≤2
Intervention	Selpercatinib 160mg twice daily (69)
Duration	25.2 months for OS and 21.9 months for PFS (latest data cut 15th June 2021)
Primary outcome	ORR
Secondary outcomes	BOR, DOR, CBR, CNS ORR, CNS DOR, PFS, OS and AE
Locations	85 investigational study sites across 16 countries worldwide including UK

Abbreviations: AE: adverse event; BOR: best overall response; CNS: central nervous system; DOR: duration of response; ECOG: Eastern cooperative oncology group; MTC: medullary thyroid cancer; NSCLC: non-small cell lung cancer; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; RET: rearranged during transfection

Clinical trial: LIBRETTO-001 patient cohorts
Clinical effectiveness informed from SAS1 dataset

Source: Adapted from Company submission, Document B, Figure 4

Abbreviations: BID: twice daily; IAS: integrated analysis set; MTC: medullary thyroid cancer; N: number of patients; NSCLC: non-small cell lung cancer; PAS: primary analysis set; QD: once daily; RET: Rearranged during Transfection; SAS: supplemental analysis set.

LIBRETTO-001 clinical trial results: response rate, PFS and OS

	(SAS1, treatment-naïve) N=69
ORR (Complete response + Partial response) n (%), (95% CI)	58 (84.1), (73.3–91.8)
Median PFS, months (95% CI)	22 [redacted]
Median OS, months (95% CI)	[redacted]
Number of events, progressed (%)	29 (42.0)

- SAS1 a subset from LIBRETTO-001
- SAS1 included people with untreated RET fusion positive NSCLC
- Latest data cut 15 June 2021
- SAS1 data used for cost effectiveness modelling and ITC/NMA

PFS Kaplan-Meier plots for treatment naïve RET fusion positive NSCLC (SAS1)

Source: EAG report, efficacy results, figure 3.1. Latest data cut: 15 June 2021.

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Abbreviations: CI: confidence interval; ITC; indirect treatment comparison; N: number of patients; NE: not estimated; NMA: network meta-analysis; NSCLC: non-small cell lung cancer; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; SAS1: supplemental analysis set 1.

Indirect treatment comparison results between selpercatinib and pemetrexed plus platinum-based chemotherapy

- LIBRETTO-001 single-arm trial → company did an ITC to connect selpercatinib to the NMA
- Used IPD for selpercatinib arm (LIBRETTO-001) and IPD for pemetrexed plus platinum chemotherapy arm (RCT KEYNOTE-189)
- PSM methodology to account for differences in baseline characteristics across trials known to have an impact on prognosis (age, ECOG performance, sex, smoking status, race and cancer stage)

Indirect treatment comparison results

Outcome	Hazard ratio (95% CI)	P value
PFS	[redacted]	[redacted]
OS	[redacted]	[redacted]

Source: EAG report, indirect treatment comparison, table 3.38

EAG comment:

- Unclear how baseline characteristics were selected as potential treatment effect modifiers→ See issue 7
- In line with NICE TSD 17, other methods of control arm adjustment were explored→ See issue 8

Abbreviations: CI: confidence interval; ECOG: Eastern cooperative oncology group; IPD: individual patient data; OS: overall survival; PFS: progression free survival; PSM: propensity score matching; RCT: randomised control trial; TSD: Technical support document.

Network meta-analysis results comparing selpercatinib with pemetrexed plus platinum-based chemotherapy and pembrolizumab plus pemetrexed plus platinum-based chemotherapy

- Random effects model used in base-case as it best fitted data

Relative treatment effect estimates of comparative efficacy between selpercatinib and comparators

Treatment	Objective response rate Pairwise OR (95% CrI) of comparators versus selpercatinib	Progression-free survival Median HR (95% CrI) of comparators versus selpercatinib	Overall survival Median HR (95% CrI) of comparators versus selpercatinib
Pemetrexed plus platinum-based chemotherapy	[redacted]	[redacted]	[redacted]
Pembrolizumab plus pemetrexed plus platinum-based	[redacted]	[redacted]	[redacted]

Source: EAG report, network meta-analysis, table 3.46-3.48

Abbreviations: CI: credible interval; HR: Hazard ratio; OR: Odds ratio

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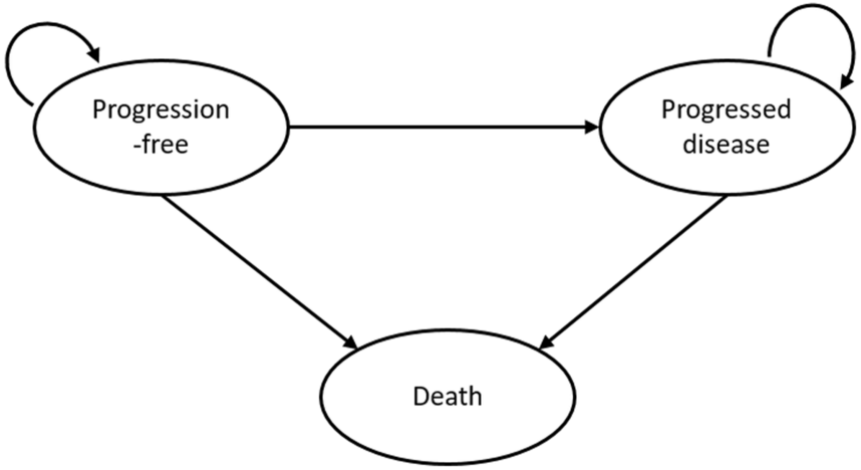
Company's economic model

Partitioned survival model comprising 3 mutually exclusive health states:
progression-free state, progressed disease, and death



Parameter	Assumption and evidence source
Selpercatinib	LIBRETTO-001
Comparators	KEYNOTE-189, KEYNOTE-189 Japan, KEYNOTE-021.
Time horizon; Cycle length	Lifetime horizon (25 years); weekly cycles
Discount rate	3.5% per annum
Utility values	Health state utility, LIBRETTO-001, TA654
Costs and resource use	PSSRU, NHS reference costs, BNF, Eli Lilly and company, electronic market information tool and assumption in previous appraisals

Abbreviations: BNF: British national formulary; PSSRU: Personal Social Services Reference Unit; TA: technology appraisal

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Key issues after technical engagement

Key Issues identified prior to technical engagement	Impact	Status
1) Population: no evidence has been provided for squamous histology		Not resolved
2) Comparators: mismatch to NICE scope and NICE guideline, which might undermine the validity of any effectiveness or cost-effectiveness estimates. Comparators used by the company: pembrolizumab + pemetrexed + platinum chemotherapy and pemetrexed + platinum chemotherapy		Not resolved
3) Subsequent therapy: possible bias resulting from mismatch between LIBRETTO-001 and NHS clinical practice		No – for discussion
4) Lack of comparative evidence in the correct population, which might mean treatment effect of selpercatinib overestimated and ICERs underestimated		No – for discussion
5) Applicability: there is no information on the characteristics of the UK target population, meaning that comparability between trial and target population cannot be assumed		Not resolved
6) Adverse events: there are no specific adverse event data for the treatment naïve sub-set (SAS1 dataset) in LIBRETTO-001, or the equivalent subset of the LIBRETTO-321.		Resolved
7) ITC: choice of trial data (KEYNOTE-189) might have biased comparison with all comparators		Partially resolved
8) ITC: methods of adjustment for confounding might have biased comparison with all comparators		No – for discussion
9) NMA: heterogeneity in trials to inform pembrolizumab plus pemetrexed plus platinum chemotherapy versus pemetrexed plus platinum chemotherapy		Resolved

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Abbreviations: ITC: indirect treatment comparison; NMA: network meta-analysis; NSCLC: non-small cell lung cancer; RET: rearranged during transfection; SAS1: supplemental analysis set 1

Key: Model driver; Unknown impact; Small/moderate impact

Key issues after technical engagement

Key Issues identified prior to technical engagement	Impact	Status
10) No NMA or comparative analysis was carried out for adverse events, preventing a rigorous assessment of benefits and harms		Not resolved
11) Lack of an STM to assist in verifying the plausibility of PSM extrapolations and to address uncertainties in the extrapolation period		Not resolved
12) Immaturity of the data obtained from the LIBRETTO-001 trial for OS and PFS, adding substantial uncertainty to the extrapolated survival data in the economic model		No – for discussion
13) The company's choice of survival curves for the modelling of treatment effectiveness was not transparent		No – for discussion
14) Waning of the selpercatinib treatment effect was not explored		No – for discussion
15) Potential underestimation of PFS pemetrexed plus platinum chemotherapy and hence an overestimation of the increments versus selpercatinib		No – for discussion
16) Utility values were higher than the ones used in other TAs, only slightly lower than the UK general population, and had a relatively small decrement between PF and PD state		Partially resolved
17) The plausibility of the company's choices for the modelling of subsequent treatments - See key issue 3		Partially resolved

Abbreviations: NMA: network meta-analysis; NSCLC: non-small cell lung cancer; OS: overall survival; PD: progressed disease; PF: progression free; PFS: progression-free survival; RET: rearranged during transfection; STM: state transition model; TA: technology appraisal

NICE

Key:
Model driver;  Unknown impact;  Small/moderate impact 

Issues not resolved after technical engagement and contributing to uncertainty

The issues below have been reviewed by the chair and lead team and will not be discussed during the committee meeting. This is because conclusions have been made in previous appraisals or were not resolved at technical engagement.

Issue 1: Population: uncertainty as to whether include squamous histology for which no evidence has been provided

Issue 2: Comparators: mismatch to NICE scope and NICE guideline

Issue 5: Applicability: there is no information on the characteristics of the UK target population

Issue 10: No NMA or comparative analysis was carried out for adverse events

Issue 11: Lack of an STM to assist in verifying the plausibility of PSM extrapolations and to address uncertainties

Issue 16: Utility values higher than other TAs, slightly lower than UK general population and relative small decrement between PF and PD states

Abbreviations: NMA: network meta-analyses; PD: progressed disease; PF: progression free; PSM: partitioned survival model; STM: state transition model

Key issue 3: Subsequent therapy: possible bias resulting from mismatch between LIBRETTO-001 and NHS clinical practice - linked to key issue 17

Background

- Differences between subsequent therapies in LIBRETTO-001 and UK clinical expert opinion → could lead to bias
- Economic model costing should align with subsequent therapies used in LIBRETTO-001
- Subsequent therapies provided by company do not align with NG122 (key issue 17)

Company

- Selpercatinib currently not provided as first line so no evidence on subsequent treatments available
- Sample size of people receiving subsequent therapy is low ([redacted])→ informed by prior TAs
- Updated base-case after TE→ subsequent treatment provided by UK clinical experts
- Scenario analyses using 1) subsequent treatment distribution from SAS1; 2) subsequent treatments regardless of NHS reimbursement and 3) omitting therapies not reimbursed by NHS

EAG comments

- LIBRETTO-001 data should be used to inform subsequent therapy distribution in economic model → only empirical source and correlated with estimates of effectiveness from the trial
- EAG would like to see a scenario analysis of LIBRETTO-001 trial data where treatments not reimbursed by the NHS were omitted and which is consistent with the NG122 care pathway for people with RET fusion positive NSCLC

Should the model consider subsequent therapies from LIBRETTO-001 or UK clinical expert opinion? What subsequent treatments are expected to follow after selpercatinib in the NHS?

Abbreviations: NG: NICE guideline; TE: technical engagement

Key issue 4: Lack of comparative evidence in the correct population, which might mean treatment effect of selpercatinib overestimated and ICERs underestimated

Background

- Clinical evidence relies on single arm study (LIBRETTO-001)
- Pemetrexed plus platinum chemotherapy compared through ITC using KEYNOTE-189
- Pembrolizumab with pemetrexed plus platinum chemotherapy compared through NMA using KEYNOTE-189, KEYNOTE-189 Japan and KEYNOTE-021 (largely non-RET fusion positive population)

Company

- RET-fusion positive NSCLC is rare; only 2% of all lung cancers → absence of comparative evidence
- IPD only available from KEYNOTE-189 trial; preferred over population data → using MAIC as suggested in NICE DSU18 would introduce greater bias and methodological difficulties
- Population adjustment method would reduce LIBRETTO-001 dataset size (n=69)→ increased uncertainty
- IPD adjustment methods match patients based on individual patient characteristics→ essential: population is younger, healthier and largely non-smokers
- RET fusion status is not a prognostic factor
- Previous NICE appraisals of RET fusion-positive indications, TA760 and TA812, did not adjust for RET status in NMAs

Abbreviations: DSU: decision support unit; IPD: individual patient data; ITC: indirect treatment comparison; MAIC: matched adjusted indirect comparison; NSCLC: non-small cell lung cancer; RET: rearranged during transfection; SAS1: supplemental analysis set 1

Key issue 4: Lack of comparative evidence in the correct population, which might mean treatment effect of selpercatinib overestimated and ICERs underestimated

EAG comments

- RET fusion positive NSCLC might affect prognosis
- Hess et al (2021) RET mutation increases mortality hazard compared to those without it; HR 1.52 (0.95-2.43) p=0.08. Although not statistically significant implies a worse prognosis which might favour the comparator
- Drilon et al (2016) study reported PFS for pemetrexed higher in RET fusion positive than KEYNOTE-189; 19 months versus 9 months

Abbreviations: HR: hazard ratio; NSCLC: non-small cell lung cancer; RET: rearranged during transfection

Key issue 7: ITC: choice of trial data (KEYNOTE-189) might have biased comparison with all comparators

Background

- EAG suggests other sources for pemetrexed plus platinum chemotherapy would have yielded different overall NMA results

Company

- KEYNOTE-189 only comparable trial with IPD available. Patient matching is essential for a representative ITC so IPD preferred over AD → allows patient matching based on baseline characteristics
- IPD methods more robust given that available sample size from LIBRETTO-001 is only n=69
- Baseline characteristics of patients in KEYNOTE-189 were well-matched to the patients in other treatment arms of other trials included in the NMA

EAG comments

- IPD useful in constructing pseudo-comparator arm;
- Baseline characteristics in KEYNOTE-189 not comparable to selpercatinib data, even after PSM adjustment (smoking status covariate was considerably different between arms)
- Prefers to see all alternative studies for pemetrexed plus platinum chemotherapy (with baseline characteristics data) as that would have ensured a closer match to the selpercatinib cohort

Are other sources for pemetrexed plus platinum chemotherapy needed to inform decision making?
Is the ITC for the comparison of pemetrexed plus platinum chemotherapy robust for decision making?

Abbreviations: AD: aggregated data; IPD: individual patient data; ITC: indirect treatment comparison; NMA: network meta-analysis

Key issue 8: ITC: methods of adjustment for confounding might have biased comparison with all comparators

Background

- Array of methods explored by the company were limited; other methods may have yielded results less favourable to selpercatinib than those from the PSM approach

Company

- Different methods explored for adjusting for confounding in NMA include: genetic matching, PSW using a generalised boosted model, and PSW using a logistic regression model
- TMLE method explored to address EAG concerns

EAG comments

- PSM in base-case led to most conservative results supporting this method
- No justification for using TMLE method and not mentioned in TSD17; results do not seem implausible
- Studies in the literature report higher survival than CS e.g., Drilon (2016) PFS 19 months → reiterates problem of lack of comparative evidence in RET fusion positive NSCLC
- TMLE method highlights uncertainty and possibility of treatment effect for selpercatinib vs pemetrexed plus platinum chemotherapy might be potentially overestimated in company's base-case

Abbreviations: NMA: network meta-analyses; PSM: propensity score matching; PSW: propensity score weighting; TMLE: Targeted minimum loss-based estimation; TSD: technical support documents

Key issue 8: ITC: methods of adjustment for confounding might have biased comparison with all comparators

Comparison of median PFS and median OS generated through different adjustment methods to the observed values from KEYNOTE-189 for the pemetrexed plus platinum chemotherapy arm

Adjustment method	mPFS (months)	mOS (months)
PSM (base-case)	[redacted]	[redacted]
Genetic matching	[redacted]	[redacted]
PSW using generalised booster model	[redacted]	[redacted]
PSW using logistic regression	[redacted]	[redacted]
TMLE	[redacted]	[redacted]
KEYNOTE-189 (observed)	4.9	10.6

Source: Company TE response, Issue 8, table 4.

Has the method of adjustment used in the base-case yielded valid results for decision making?

Abbreviations: mOS: median overall survival; mPFS: median progression free survival; PSM: propensity score matching; PSW: propensity score weighting; TMLE: Targeted minimum loss-based estimation

Key issue 12: Data immaturity from LIBRETTO-001 trial for OS and PFS, adding substantial uncertainty to the extrapolated survival data in the economic model

Background

- Because data from LIBRETTO-001 trial for OS and PFS are immature, the survival extrapolations from the economic model are uncertain.

Company

- Latest data-cut show consistent trend of improving PFS and OS estimates compared to previous data-cuts
- Recruitment stopped in [redacted] further data cuts will only validate latest data cut (June 2021) in CS
- Results from interim-cut from LIBRETTO-431 trial is anticipated in [redacted]
- Urge committee to consider recommending selpercatinib through CDF
- NMA demonstrated selpercatinib is likely to be superior to pemetrexed plus platinum chemotherapy and most other treatment options

EAG comments

- Maturity of data should be considered in interpretation of economic model
- Current interim analysis highly promising; further data cuts over course of [redacted]

Is the data from LIBRETTO-001 (SAS1) robust for decision making?

Abbreviations: CDF: cancer drugs fund; CS: company submission; NMA: network meta-analysis OS: overall survival; PFS: progression free survival; SAS1:supplemental analysis set 1

Key issue 12: Data immaturity from LIBRETTO-001 trial for OS and PFS, adding substantial uncertainty to the extrapolated survival data in the economic model

PFS and OS results from LIBRETTO-001- RET fusion positive NSCLC (SAS1) arm data-cuts

	17June 2019	16 December 2019 (additional 6 months follow-up)	30 March 2020 (additional 9.5 months follow-up)	15 June 2021 (additional 24 months follow-up)
N	[redacted]	[redacted]	[redacted]	[redacted]
No. of eligible patients*	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free survival (months)				
Median, (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Rate of progression-free survival (%)				
≥12 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Overall survival (months)				
Median (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Rate (%) of overall survival				
≥12 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

*Eligible patients include all patients in the analysis set who have the opportunity to be followed for at least 6 months from the first dose of selpercatinib.

Source: Company response to technical engagement, Issue 12, table 7.

Abbreviations: CI: confidence interval; N:number; OS: overall survival; PFS: progression free survival; RET: rearranged during transfection; SAS1:supplemental analysis set 1

Key issue 13: The company's choice of survival curves for the modelling of treatment effectiveness was not transparent

Background

Data immaturity

- EAG did scenario analyses to explore plausible PFS and OS curves → wide range of NMBs, confirms uncertainty

Curve selection

- EAG requested detail and justification concerning the choice of parametric survival curves
  a) Choice of considering complex survival curve
  b) Plots were not provided in clarification response
  c) Choice between survival curves in detail
  d) Mismatch between PFS and OS in CS and values used in economic model

Company

Data immaturity

- Acknowledges uncertainty surrounding NMB of the intervention in EAG scenario analyses. Contests external validity of the stratified Gompertz curve → did updated scenario analysis; Gamma curve → more conservative. OS curve selection is not a considerable model driver

Curve selection

a) Spline knot 1 distribution for OS chosen based on external validation [clinical experts and Tan et al study (2020)]
b) Plots for standard normal quantiles versus log time and log survival odds versus log time have been provided in response to technical engagement
c) Gompertz distribution chosen to model PFS as it aligned with estimates from trials in other targeted areas (ALTA-1L and ALEX) as well as clinical expert opinion
d) PFS and OS have been updated after technical engagement

Key issue 13: The company's choice of survival curves for the modelling of treatment effectiveness was not transparent

EAG comments

Data immaturity

- Regardless of curve choice there is uncertainty given immaturity from LIBRETTO-001 trial

Curve selection

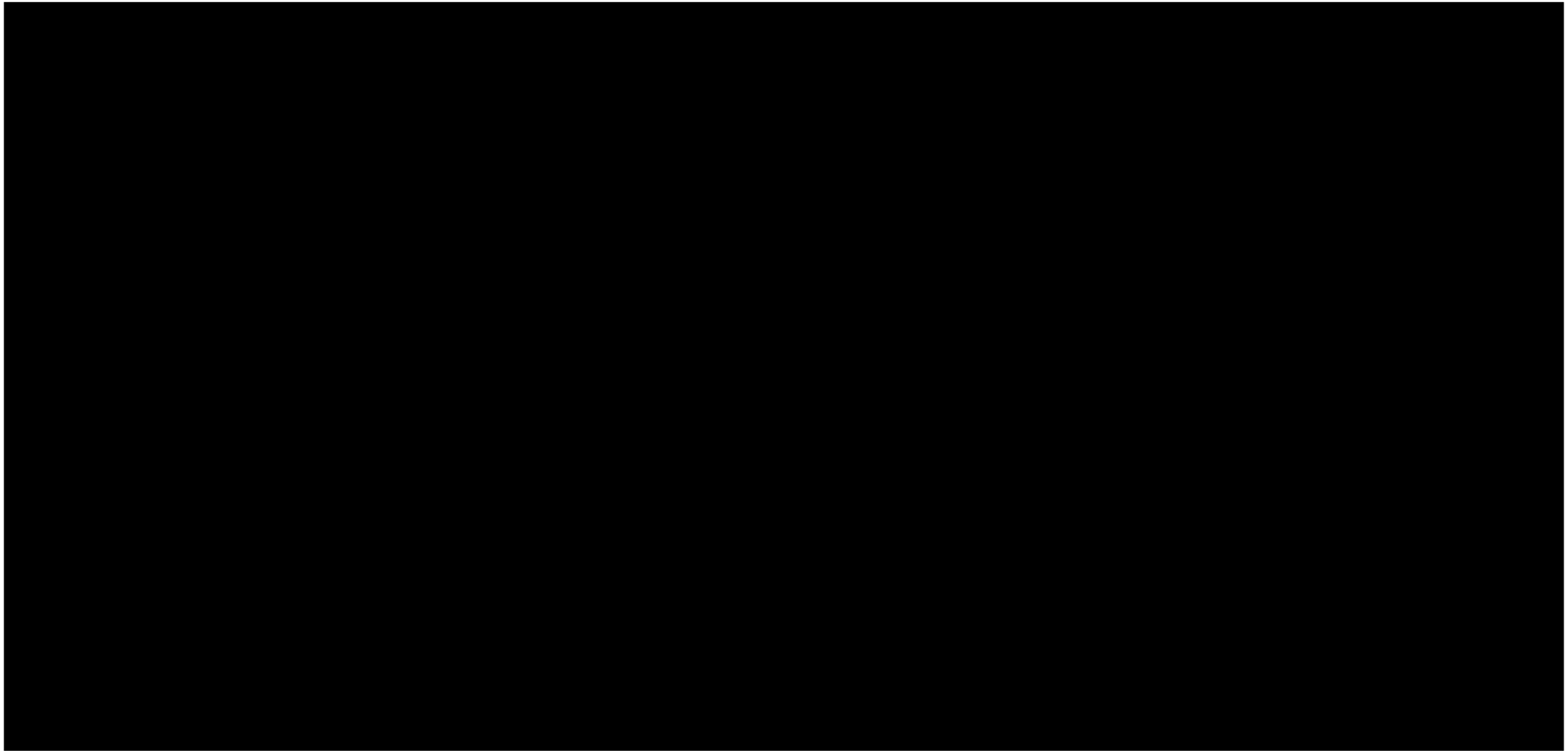
a) NICE DSU TSD 21 states complex curves should be considered when hazard functions are observed or expected in longer-term to have complex shapes → further justification needed to use spline knot 1 model
b) Generally agrees with company's interpretation about curves but visual examination cannot justify the suitability for using log-normal and log-logistic curves for modelling PFS and OS
c) Agrees with company that Gompertz curve yields conservative estimates for PFS
d) A mismatch still appears between reported numbers after technical engagement and values in economic model

Are the company's choice of survival curves appropriate for decision making?

Abbreviations: OS: overall survival; PFS: progression free survival; TSD: technical support document

Issue 13: Modelling of treatment effectiveness

Selpercatinib PFS parametric survival function extrapolations



Source: Company submission, document B, progression free survival, figure 20.

Abbreviations: PFS: progression free survival

Issue 13: Modelling of treatment effectiveness

Pemetrexed plus platinum chemotherapy PFS parametric survival function extrapolations

Source: Company submission, document B, progression free survival, figure 21.

Abbreviations: PFS: progression free survival

Issue 13: Modelling of treatment effectiveness

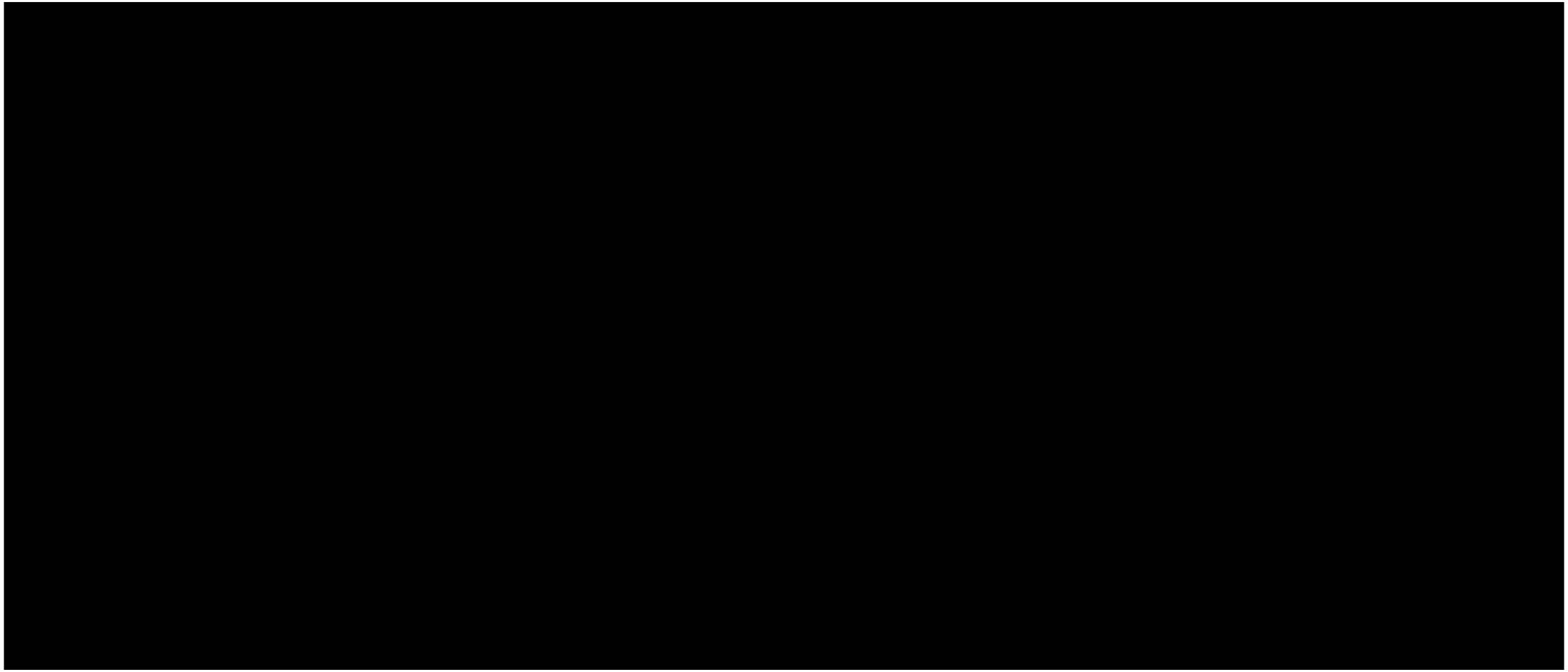
Selpercatinib OS parametric survival function extrapolations

Source: Company submission, document B, overall survival, figure 22.

Abbreviations: OS, overall survival

Issue 13: Modelling of treatment effectiveness

Pemetrexed plus platinum chemotherapy OS parametric survival function extrapolations



Source: Company submission, document B, overall survival, figure 23.

Abbreviations: OS, overall survival

Issue 13: Survival at landmark timepoints

Technology	Curve	3-yr	5-yr	10-yr	20-yr
Company: overall survival					
Selpercatinib	Spline 1-knot	60.68%	41.88%	15.74%	1.97%
Pemetrexed plus platinum chemotherapy	Spline 1-knot	9.46%	1.64%	0.02%	0.00%
Pembrolizumab combination therapy	Spline 1-knot-HR from NMA applied to pemetrexed plus platinum based chemo	23.78%	8.18%	0.49%	0.00%
Company: progression-free survival					
Selpercatinib	Gompertz	35.20%	15.15%	0.95%	0.00%
Pemetrexed plus platinum chemotherapy	Gompertz	0.51%	0.01%	0.00%	0.00%
Pembrolizumab combination therapy	Gompertz- HR from NMA applied to pemetrexed plus platinum based chemo	6.50%	0.72%	0.00%	0.00%

Source: Company's technical engagement response, appendix G, table 20 and 21.

EAG comment:

- Given uncertainty from data immaturity in LIBRETTO-001 and lack of transparency in survival curve choice, EAG had no preference so uses same curves as company's base-case.
- Note: Caution recommended as small mismatch between landmark values and model values→ Impact on ICER potentially small

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Abbreviations: HR: hazard ratio; ICER: ; Incremental cost-effectiveness ratio; NMA: network meta analyses; yr: year

Issue 13: EAG scenario analysis, curves and survival at landmark timepoints

Technology	Curve	3-yr	5-yr	10-yr	20-yr
EAG scenario: PFS					
Selpercatinib	Gompertz†	35.20%	15.15%	0.95%	0.00%
	Exponential *	37.08%	19.14%	3.66%	0.13%
Pemetrexed plus platinum chemotherapy	Exponential *	0.81%	0.03%	0.00%	0.00%
	Gompertz†	0.51%	0.01%	0.00%	0.00%
Pembrolizumab combination therapy	Exponential*	8.26%	1.57%	0.02%	0.00%
	Gompertz†	6.50%	0.72%	0.00%	0.00%
EAG scenario: OS					
Selpercatinib	Spline 1-knot	60.68%	41.88%	15.74%	1.97%
	Exponential*	61.97%	45.05%	20.29%	4.12%
	Stratified Gompertz†	56.25%	21.65%	0.00%	0.00%
Pemetrexed plus platinum chemotherapy	Stratified lognormal	17.58%	8.64%	2.57%	0.56%
	Lognormal	18.16%	9.11%	2.81%	0.65%
	Exponential*	13.36%	3.49%	0.12%	0.00%
	Loglogistic	15.57%	7.90%	2.95%	1.07%
	Spline knot 2	5.45%	0.23%	0.00%	0.00%
	Stratified Gompertz†	11.06%	1.80%	0.00%	0.00%
Pembrolizumab combination therapy	Exponential*	29.34%	12.95%	1.68%	0.03%
	Spline knot 2	16.98%	2.49%	0.00%	0.00%
	Stratified Gompertz†	26.15	8.65	0.20	0.00

Source: Company's technical engagement response, appendix G, table 20 and 21 and EAG report section 6.1.2.1

Abbreviations: OS: overall survival; PFS: progression free survival; yr: year

*EAG exploratory analyses: survival curves with the highest NMB
† EAG exploratory analyses: survival curves with the lowest NMB

Key issue 14: Waning of the selpercatinib treatment effect was not explored

Background

- The company did not explore waning of selpercatinib treatment effect

Company

- Lack of clinical data to suggest selpercatinib's efficacy would decrease over time
- HR plots overtime for PFS and OS for selpercatinib versus pemetrexed plus platinum chemotherapy and pembrolizumab combination are >1 in all instances→ selpercatinib showed reduced risk for disease progression and death (Immature data, not a robust conclusion)
- Treatment waning implicitly captured in survival curves, correcting them without evidence→ double counting
- Treat-to-progression treatment so population is unlikely to experience waning of selpercatinib efficacy

EAG comments

- No compelling new evidence nor arguments provided
- Although agrees HR plots overtime for PFS and OS are all >1, the decreasing trend in OS and PFS HR plots versus pemetrexed plus platinum chemotherapy towards a HR of 1 suggests potential treatment waning effect.
- Given immature data, an updated model and scenario analyses exploring treatment waning is needed

Should treatment waning be explored in the modelling?

Abbreviations: HR: hazard ratio; OS: overall survival; PFS: progression free survival

Key issue 15: Potential underestimation of PFS pemetrexed plus platinum chemotherapy and hence an overestimation of the increments versus selpercatinib

Background

- Observed PFS for pemetrexed plus platinum chemotherapy (based on 1-1.5-year time horizon) is larger than the modelled PFS based on a lifetime horizon→ suggests estimate underestimation which potentially overestimates selpercatinib

Company

- Accuracy of RMST linked to extrapolation curves; complexity when associated with incomplete data
- RMST provides an average survival at 1-1.5 year timepoints and derived from KM (non-parametric method)
- Liao et al (2020) suggest not to calculate RMST too far away from study follow up to avoid long extrapolation
- Disagrees with EAG's comparison study - Drilon et al (2016) - where PFS for pemetrexed plus platinum chemotherapy was 19 months given that 12 patients had bevacizumab combination therapy which is a drug with a distinct molecular target than comparators used in company submission
- Company predicted median PFS was [redacted] months for pemetrexed plus platinum chemotherapy, while median PFS was 4.9 months in KEYNOTE-189 → if misaligned then may be overestimated in model
- Provided scenario analyses using different curves; results in alignment with analyses presented in main submission with no major impact on ICER

NICE Abbreviations: OS: overall survival; PFS: progression free survival; RMST: restricted mean survival time

Key issue 15: Potential underestimation of PFS pemetrexed plus platinum chemotherapy and hence an overestimation of the increments versus selpercatinib

EAG comments

- Require further information on economic model mechanism and plausibility about why large majority of PF gains are accumulated beyond observed data period
- Besides alternative PFS curves, provide information on plausibility of why observed mean PFS for pemetrexed plus platinum chemotherapy (based on 1 or 1.5-year time horizon) is larger than modelled mean PFS based on a life time horizon.

Is the estimate for PFS for pemetrexed plus platinum chemotherapy underestimated?

NICE Abbreviations: PFS: progression free survival

Selpercatinib for untreated RET fusion-positive advanced non-small-cell lung cancer

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- ❑ Clinical evidence
- ❑ Modelling
- ❑ Key issues
- ✓ ICERs
- ❑ Other considerations: severity, managed access, equality, innovation
- ❑ Summary

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Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts. The EAG has provided the following scenario analyses:

1. Using survival curves with highest NMB
2. Using survival curves with lowest NMB

Company and EAG base case assumptions

Comparison of company base case and EAG base case to the £20,000 to £30,000 threshold

Deterministic results

Using a willingness to pay threshold of £20,000-30,000 per QALY

Base case and scenarios	Incremental costs (£) versus comparator	Incremental QALYs versus comparator	ICER (£) versus comparator	ICER position with respect to threshold
Company base case				Above threshold
EAG base case	↑	=	↑	Above threshold

Source: EAG response to technical engagement

Arrow indicates direction of change in costs, QALYs or ICER **compared to a willingness to pay threshold of £20,000-30,000 per QALY**

Abbreviations: ICER: Incremental Cost Effectiveness Ratio; LY: life years; QALY: Quality Adjusted Life Year

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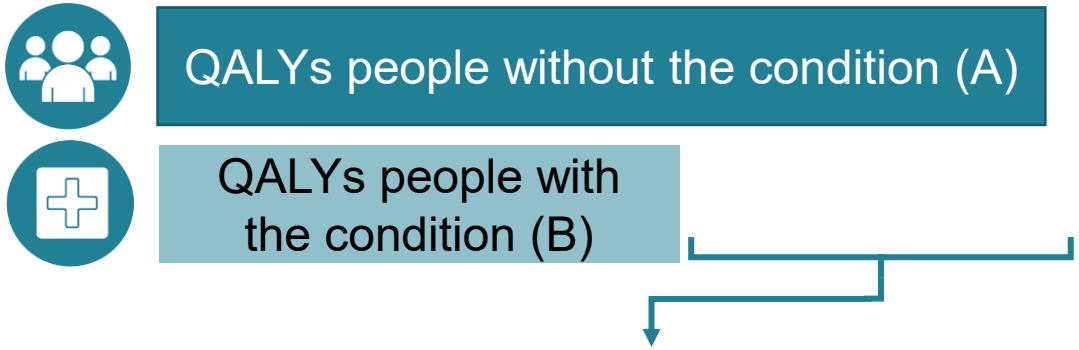
QALY weightings for severity

New severity modifier calculations and components:



Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A
- *Note: The QALY weightings for severity are applied based on **whichever of absolute or proportional shortfall implies the greater severity**. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply

QALY weight	Absolute shortfall (AS)	Proportional shortfall (PS)
1	Less than 12	Less than 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

- All analyses resulted in a QALY modifier of 1.2, which was applied to the willingness to pay threshold (£24,000-36,000 per QALY) in its base-case
- The EAG reproduced the reported absolute and proportional QALY shortfall and the 1.2 x QALY weight

Abbreviations: QALY: quality-adjusted life year

QALY weightings for severity

Summary of QALY shortfall analysis

HRQoL norms source	Expected remaining QALYs in general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
Base case: Hernandez Alava et al., EQ-5D-5L mapped to 3L plus HSE 2017–2018	[redacted]	Pembrolizumab combination: [redacted]	10.28	87.05%	X1.2
Base case: Hernandez Alava et al., EQ-5D-5L mapped to 3L plus HSE 2017–2018	[redacted]	Pemetrexed plus platinum based chemotherapy: [redacted]	10.81	91.53%	X1.2
Van Hout et al., EQ-5D-5L mapped to 3L plus HSE 2017–2018	[redacted]	Pembrolizumab combination: [redacted]	10.36	87.13%	X1.2
Van Hout et al., EQ-5D-5L mapped to 3L plus HSE 2017–2018	[redacted]	Pemetrexed plus platinum based chemotherapy: [redacted]	10.89	91.59%	X1.2
VH EQ-5D-3L value set plus health state profiles	[redacted]	Pembrolizumab combination: [redacted]	10.26	87.03%	X1.2
MVH EQ-5D-3L value set plus health state profiles	[redacted]	Pemetrexed plus platinum based chemotherapy: [redacted]	10.79	91.52%	X1.2
MVH EQ-5D-3L value set + HSE 2012–2014	[redacted]	Pembrolizumab combination: [redacted]	10.59	87.38%	X1.2
MVH EQ-5D-3L value set + HSE 2012–2014	[redacted]	Pemetrexed plus platinum based chemotherapy: [redacted]	11.12	91.75%	X1.2

Source: Company submission, severity, table 67

Abbreviations: EQ-5D-3/5L: Euro-Quality of life questionnaire 5 Dimensions 3/5 levels; HRQoL: Health related quality of life; QALY:quality-adjusted life year

Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.

- LIBRETTO-431 (NCT04194944) randomised, open label, phase 3 trial comparing selpercatinib versus pemetrexed platinum chemotherapy with or without pembrolizumab for first line treatment of advanced RET-fusion positive NSCLC. Results expected in December 2023.
- SIREN international, multicentre, RWE study observing efficacy of selpercatinib in 50 patients in this population. Current data immature (median follow up 10 months) further data collection is planned.
- If selpercatinib was to be recommended for managed access, data would be collected from LIBRETTO-001, LIBRETTO-431 and SIREN.

Clinical trials continue until 2023/2025
Is this timeframe enough to resolve the uncertainties regarding PFS and OS?

Abbreviations: NSCLC: non small cell lung cancer; RET: rearranged during transfection; RWE: real world evidence

Other considerations

Equality considerations

(Professional organisation response)

- The absence of funding of pathology departments means individual trust need to fund the preparation for genomic testing. Patients at trusts that lack this funding do not have access to comprehensive testing and instead receive targeted testing which may not include RET. The lack of funding from NHSE will continue to create inequity of access to diagnostic tests between trusts.*

Innovation

(Professional organisation response)

- Targeted therapy for a specific mutation like RET is the most appropriate treatment in terms of tolerability and efficacy.

*The cost for RET fusion testing is considered to be absorbed by the healthcare system in this appraisal. However, a proportional cost associated with the detection of *RET* fusion status was included in the model for pre-treated population in line with selpercatinib (TA760)

Abbreviations: RET: rearranged during transfection

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Key issues after technical engagement

Key Issues identified prior to technical engagement	Impact	Status
1) Population: no evidence has been provided for squamous histology		Not resolved
2) Comparators: mismatch to NICE scope and NICE guideline, which might undermine the validity of any effectiveness or cost-effectiveness estimates. Comparators used by the company: pembrolizumab + pemetrexed + platinum chemotherapy and pemetrexed + platinum chemotherapy		Not resolved
3) Subsequent therapy: possible bias resulting from mismatch between LIBRETTO-001 and NHS clinical practice		No – for discussion
4) Lack of comparative evidence in the correct population, which might mean treatment effect of selpercatinib overestimated and ICERs underestimated		No – for discussion
5) Applicability: there is no information on the characteristics of the UK target population, meaning that comparability between trial and target population cannot be assumed		Not resolved
6) Adverse events: there are no specific adverse event data for the treatment naïve sub-set (SAS1 dataset) in LIBRETTO-001, or the equivalent subset of the LIBRETTO-321.		Resolved
7) ITC: choice of trial data (KEYNOTE-189) might have biased comparison with all comparators		Partially resolved
8) ITC: methods of adjustment for confounding might have biased comparison with all comparators		No – for discussion
9) NMA: heterogeneity in trials to inform pembrolizumab plus pemetrexed plus platinum chemotherapy versus pemetrexed plus platinum chemotherapy		Resolved

NICE

Abbreviations: ITC: indirect treatment comparison; NMA: network meta-analysis; NSCLC: non-small cell lung cancer; RET: rearranged during transfection; SAS1: supplemental analysis set 1

Key:
Model driver;  Unknown impact;  Small/moderate impact 

Key issues after technical engagement

Key Issues identified prior to technical engagement	Impact	Status
10) No NMA or comparative analysis was carried out for adverse events, preventing a rigorous assessment of benefits and harms		Not resolved
11) Lack of an STM to assist in verifying the plausibility of PSM extrapolations and to address uncertainties in the extrapolation period		Not resolved
12) Immaturity of the data obtained from the LIBRETTO-001 trial for OS and PFS, adding substantial uncertainty to the extrapolated survival data in the economic model		No – for discussion
13) The company's choice of survival curves for the modelling of treatment effectiveness was not transparent		No – for discussion
14) Waning of the selpercatinib treatment effect was not explored		No – for discussion
15) Potential underestimation of PFS pemetrexed plus platinum chemotherapy and hence an overestimation of the increments versus selpercatinib		No – for discussion
16) Utility values were higher than the ones used in other TAs, only slightly lower than the UK general population, and had a relatively small decrement between PF and PD state		Partially resolved
17) The plausibility of the company's choices for the modelling of subsequent treatments - See key issue 3		Partially resolved

Abbreviations: NMA: network meta-analysis; NSCLC: non-small cell lung cancer; OS: overall survival; PD: progressed disease; PF: progression free; PFS: progression-free survival; RET: rearranged during transfection; STM: state transition model; TA: technology appraisal

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Thank you.