NICE National Institute for Health and Care Excellence

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Slides for public

Selpercatinib for RET fusion-positive advanced non-small-cell lung cancer [ID3743]

Lead team presentation

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Chair: Peter Jackson

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Company: Eli Lilly

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NSCLC: Disease overview

- ≥47,000 people are diagnosed with lung cancer each year in the UK, and there are over 35,000 deaths
- 48% of lung cancers in England are stage 4 (metastatic) at diagnosis. 5-year survival at stage 4 is around 3%
- 80 to 85% of lung cancer cases are non-small cell lung cancer (NSCLC). There are 2 major histological subtypes of NSCLC:
  - Squamous cell carcinoma (25 to 30% of cases)
  - Non-squamous cell carcinoma: comprises adenocarcinoma (40% of cases) and large cell carcinoma (10 to 15% of cases)
- Several biomarkers used in the NHS, including PD-L1, EGFR, ALK and ROS1. PD-L1 has a continuum of expression levels. ~70% of people with NSCLC have a PD-L1 tumour proportion score (TPS) <50%
- Rearranged during transfection (RET) gene fusions are rare and occur in 1-2% of NSCLC
- NICE treatment recommendations for untreated stage 4 or recurrent NSCLC without an EGFR or ALK mutation vary depending on both histology and PD-L1 level (<50% versus greater than or equal to 50%)

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Key: ALK = Anaplastic lymphoma kinase; EGFR = Epidermal growth factor receptor; PD-L1 = Programmed death-ligand 1; ROS1 = C-ros oncogene 1

Selpercatinib (Retsevmo, Eli Lilly)

Marketing authorisation	Granted by MHRA in February 2021. From MHRA: “Retsevmo as monotherapy is indicated for the treatment of adults with advanced RET fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy”
Mechanism of action	Selpercatinib is a first-in-class, orally available, highly selective small molecule inhibitor of fusion, mutant and wild-type products involving the proto-oncogene RET tyrosine kinase receptor. Selpercatinib inhibits cell growth in tumour cells that exhibit increased RET activity
Administration	Oral capsule
Dosing	Oral 160 mg (2 x 80 mg capsules), twice daily (BID). 40 mg capsules are also available for patients who require dose adjustments
Price	List price: £4,680.00 for 60 hard capsule pack of 80 mg, £2,340.00 for 60 hard capsule pack of 40 mg. The cost of a 28-day cycle of selpercatinib is approximately £8,736.00. A Patient Access Scheme is in place with confidential discount

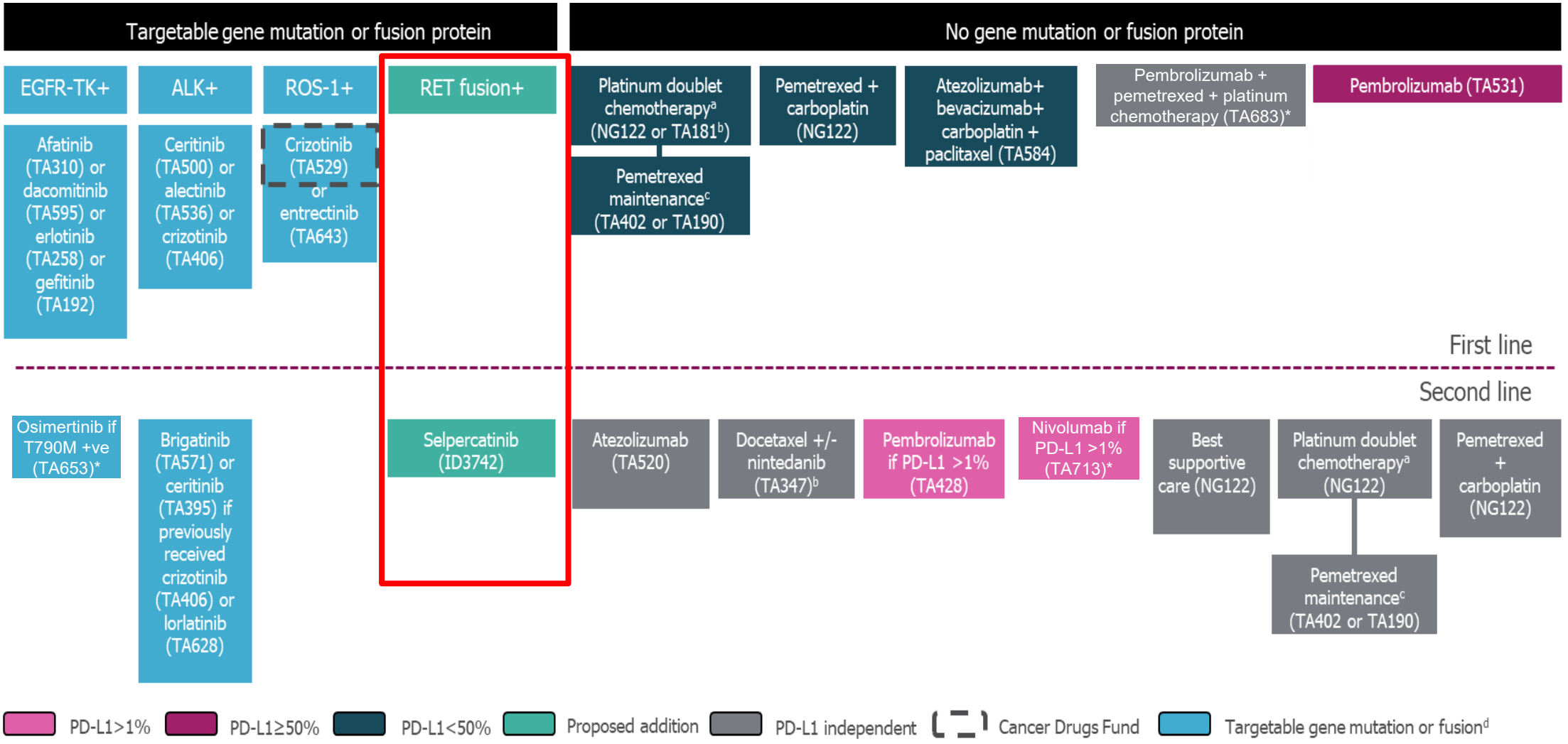
Company decision problem

- Company updated decision problem after submission:

	Scope wording	Company focus
Population	Patients with advanced *RET*+ NSCLC who require systemic therapy	Patients with advanced, **non-squamous**, **pre-treated** *RET*+ NSCLC who require systemic therapy

- Company noted that *RET* fusions occur rarely in tumours with squamous histology
- Majority of people in company's pivotal trial had non-squamous histology
- Therefore company have restricted population in submission to non-squamous histology only to reflect patients in pivotal trial

Treatment pathway and positioning of selpercatinib



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

Note: * signifies product in CDF at time of ID3743 submission (October 2020)

Patient and clinical expert submissions

Kings College London; Roy Castle Lung Cancer Foundation

- National Lung Cancer Audit: 1-year survival for lung cancer is 37%
- Symptoms (breathlessness, cough, weight loss) are hard to treat
- RET rearrangement is rare (1-2%) but detectable in non-squamous NSCLC, the commonest histological subtype. It is overrepresented in never-smokers, and associated with a high prevalence of CNS metastases, a devastating complication in this disease
- Few standard treatments in common use in the NHS, typical treatments are untargeted chemotherapy and immunotherapy
- Selpercatinib:
  - "first therapy available specifically targeted at RET fusion positive lung cancer"
  - High response rate especially for first line patients (84%)
  - Systemic and intracranial response
  - Oral treatment: preferred by patients, fewer hospital visits in Covid times
  - Some side-effects: "specialist lung cancer oncology team is important"

Selpercatinib Trial

	LIBRETTO-001/LOXO-RET 17001 (NCT03157128)
Study design	Phase I (dose escalation) / II (dose expansion) Multi-centre, multi-indication, open-label, single-arm Duration of study: selpercatinib continued in 28 day cycles until disease progression
Population	Patients ≥12 years old with locally advanced or metastatic solid tumours, including RET fusion-positive solid tumours (e.g. NSCLC, thyroid, pancreas or colorectal), RET-mutant MTC and other tumours with RET activation, who progressed on/were intolerant to standard therapy, or would/could not have standard therapy, and have Eastern Cooperative Oncology Group (ECOG) score ≤2 or Lansky Performance Score (LPS) ≥40%
Number of participants	[redacted] patients enrolled. N=329 enrolled with NSCLC, N=184 in second-line (including 105 in primary analysis set)
Intervention(s)	Selpercatinib
Comparator(s)	None
Outcomes	Primary: ORR; Secondary: PFS, OS; HRQoL: EORTC QLQ-C30

Source: Company submission, Document A, Table 3
Key: ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questions C-30; LPS: Lansky Performance Score; MTC: medullary thyroid cancer; ORR: objective response rate; OS: overall survival; PFS: progression free survival; RET: rearranged during transfection

Selpercatinib Trial Results

	Primary analysis set (PAS), N=105	Integrated analysis set (IAS), N=184
ORR n (%)	67 (63.8)	[redacted]
Median PFS (95% CI), months	16.53 (13.7 to NE)	[redacted]
Median OS (95% CI), months	[redacted]	[redacted]
Number of events, deaths (%)	[redacted]	[redacted]

- PAS a subset of IAS
- PAS included first 105 *RET* fusion-positive patients previously treated with platinum-based chemotherapy
- IAS included the PAS population plus all further eligible patients enrolled before the cut-off point (16th December 2019)
- **IAS used for cost effectiveness modelling and NMAs**

[redacted]

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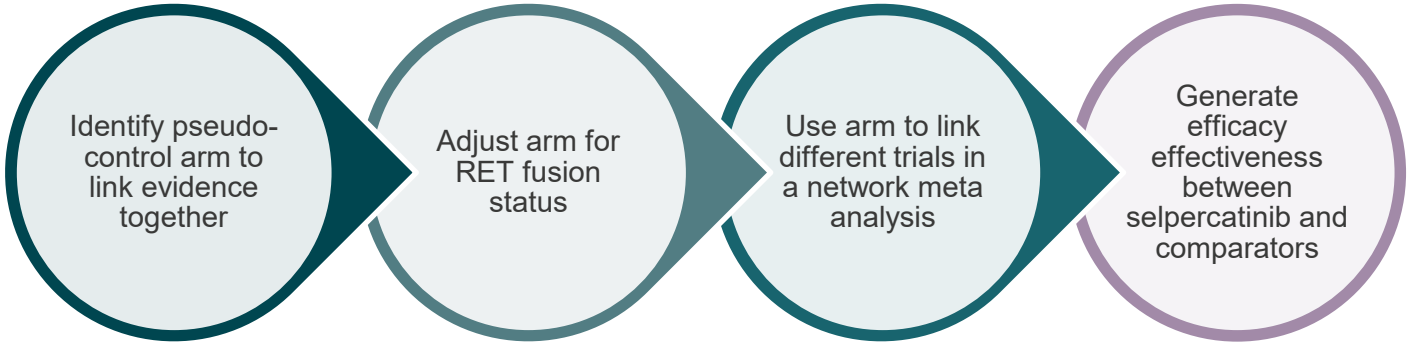
Key: DOR: duration of response; IAS: integrated analysis set; PAS: primary analysis set; ORR: objective response rate; OS: overall survival; PFS: progression free survival

Indirect treatment comparison

- LIBRETTO-001 is a single-arm trial → no comparator available from the trial
- Trials identified in literature review were used to provide comparator data
  - REVEL RCT was used to generate pseudo-control docetaxel + placebo
    - REVEL compared 628 patients allocated ramucirumab + docetaxel and 625 patients who received docetaxel + placebo in advanced NSCLC
  - Pseudo-control acts as a common comparator, allowing LIBRETTO-001 results to be linked with other trials, even though it was not present in LIBRETTO-001
  - Docetaxel + placebo arm was extracted from REVEL RCT and adjusted to account for *RET* fusion status using data from Flatiron clinic-genomic database (CGDB)

The CGDB is a linked, de-identified, longitudinal database which connects comprehensive genomic profiling data from Foundation Medicine to clinical data curated from Flatiron Health's EHR database. Find out more on the CGDB website. Flatiron Health is a real-world evidence organisation focussed on oncology data.

- Network meta-analyses (NMAs) were used to compare selpercatinib to the identified comparators



Pseudo-control generation is an uncertain process

- Several steps are taken in generating, adjusting and applying the pseudo-control in order to include selpercatinib in the networks
- ERG has said each step has complexity and possible uncertainty in conclusions
- Company approach was updated following technical engagement (TE):
  - Original approach used targeted minimum loss-based estimation (TMLE) to adjust the pseudo-control for *RET* status
  - After Technical Engagement, this was replaced with propensity score matching, using multivariable regression to adjust the pseudo-control based on characteristics of the trial populations:
    - Age, gender, race, smoking history, histology (non-squamous %), ECOG performance, history of prior surgery, stage at diagnosis (% stage IV), time since diagnosis to start of trial, sum of longest diameters of tumours, metastatic sites
- It was not possible to control for *RET* status in other trials in the networks (*RET* was not tested for in these trials), meta-regression methods were used to mitigate heterogeneity in trials

Company's updated network meta analyses results: drug versus docetaxel+placebo

Second-line population	Drug	ORR OR (95% CrI)	PFS HR (95% CrI)	OS HR (95% CrI)
All non-squamous NSCLC	Selpercatinib	[redacted]	[redacted]	[redacted]
	Atezolizumab	No data available	No data available	[redacted]
	Nintedanib+docetaxel	[redacted]	[redacted]	[redacted]
Non-squamous NSCLC and PD-L1≥1%	Nivolumab	[redacted]	[redacted]	[redacted]
	Pembrolizumab	No data available	[redacted]	[redacted]

- Green cells indicate statistical significance, i.e. drugs showing a statistically significant advantage over the docetaxel + placebo pseudo-control are:
  - Selpercatinib and nivolumab for all outcomes
  - Pembrolizumab for PFS and OS
  - Atezolizumab for OS

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Key: CrI: credible interval; HR: hazard ratio; OR: odds ratio; ORR: objective response rate; OS: overall survival; PD-L1: programmed death-ligand 1; PFS: progression-free survival

Economic Model

- Company presented a cohort-based partitioned survival model comprising 3 mutually exclusive health states: progression-free, progressed and death
- The modelled population is adults with advanced RET+ non-squamous NSCLC who require systemic therapy
- Company updated model at technical engagement to include only the following comparators:
  - nintendanib plus docetaxel
  - docetaxel monotherapy.

Parameter	Source
Selpercatinib	From LIBRETTO-001 (IAS)
Comparators	Pseudo-control based on REVEL RCT data and evidence from NMAs
Time horizon, cycle length	Lifetime horizon of 25 years, 1-week cycle consistent with other NICE NSCLC appraisals
Utility values	HSUVs from previous NICE NSCLC appraisals treated as relevant source (e.g. TA621, TA484, TA520)
Patient characteristics	Derived from LIBRETTO-001 (IAS) and TA520
Costs and resource use	PSSRU and NHS reference costs

Key: HSUV: Health state utility value; IAS: integrated analysis set; PSSRU: Personal Social Services Reference Unit

Key model outcomes

- Following technical engagement, the company and ERG presented survival estimates for selpercatinib and comparators from the model
- Figure shows K-M plots with company base case and ERG fitted curves

[redacted]

Intervention	Median PFS (months)	Mean PFS (months)	Median OS (months)
Selpercatinib	[redacted]	[redacted]	[redacted]
Docetaxel monotherapy	[redacted]	[redacted]	[redacted]
Nintedanib + docetaxel	[redacted]	[redacted]	[redacted]

Source: Adapted from revised company base case estimates reported in TE response to issue 12 (Table 12) (table) and ERG Report Figure 7, extrapolated PFS (chart)

Key issues

	Issue	ICER impact	Status
1	Trial data demonstrating the clinical effectiveness of selpercatinib are only available from the LIBRETTO-001 trial	N/A	No
2	LIBRETTO-001 trial survival events and length of follow-up		No
3	Prior treatments received by the LIBRETTO-001 trial population do not reflect NHS clinical practice	N/A	No
4	Relevant comparator treatments	N/A	Partially
5	The relevance of population participating in the trials that provided comparator evidence for the company NMAs	N/A	No
6	Uncertainty associated with the pseudo-control (reference) arm used to connect selpercatinib for network meta-analysis	N/A	No
7	The company modelling of survival for patients receiving selpercatinib		No
8	The company modelling of survival for patients receiving nintedanib+docetaxel		No
9	Progressive disease health state utility value		Partially
10	Costing of treatment with selpercatinib		No
11	Cost of testing for *RET* fusions		Resolved
12	NICE End of Life criteria may not be met	N/A	No
13	Absence of data for subgroups of patients listed in the final scope issued by NICE		No

Issue 1: Clinical effectiveness data are only available from LIBRETTO-001

Data for clinical effectiveness of selpercatinib only available from the LIBRETTO-001	
ERG: • LIBRETTO-001 is a single-arm trial • Does not compare versus any comparator treatment	**Company response at TE:** • Company acknowledges ERG concerns • No comparative trial currently exists • Further consideration has been given to network meta-analyses (NMAs)

Refer to **issues 5** and **6** for additional detailed response from company and ERG

Issue 2: LIBRETTO-001 trial survival events and length of follow-up

Small number of trial survival events and short median follow-up mean there is considerable uncertainty

ERG:

- LIBRETTO-001 reported a small number of trial survival events ([redacted]) and short median follow up times ([redacted]) mean that
- There is considerable uncertainty around the impact of selpercatinib on survival

Company response at TE:

- Data immature, company has provided further data cut from 30th March 2020 with [redacted] additional eligible efficacy patients
- Revised PFS and OS estimates are consistent with original submission, e.g. OS: [redacted] of patients in the IAS (N=184) alive as of the 30th March 2020 data cut
- Updated results consistent and support selpercatinib benefit

ERG views after TE:

- ERG agrees additional data are consistent with the results presented in the original CS
- Both PFS and OS data remain immature, median OS has not been reached in the IAS
- ERG notes additional data **not** used within the revised NMAs and economic model to reduce uncertainty in OS and PFS projections for selpercatinib and provide the most up-to-date NMA results and ICERs

Issue 3: Prior treatments received by the LIBRETTO-001 population do not reflect NHS practice

Company has not provided separate results for patients who have *only* received prior chemotherapy or for patients who have *only* received prior immunotherapy

ERG:

- [redacted] patients in LIBRETTO-001 had received prior platinum chemotherapy [redacted]
- [redacted] had also received an anti-PDL1 therapy [redacted]
- [redacted] had received an MKI* XXXXX

Company response at TE:

- Excluding MKI, prior treatments mirror therapy regimens recommended by NICE in first-line
- Company has analyses for a subset excluding patients who had received MKI treatment (N=[redacted])
- In MKI-naïve group:
  - Median PFS was [redacted]
  - Median OS was [redacted] months vs [redacted]
- Results are consistent with IAS overall, therefore LIBRETTO-001 results are generalisable to the UK

Clinical experts: Overall, the trial population is not very different from NHS patients who might be treated as part of this TAG indication

ERG views after TE:

- This would be post-hoc analysis, not pre-specified sub-group analysis
- ERG agrees with the company that the PFS and OS results for the IAS MKI-naïve subgroup are consistent with the results for the IAS analysis set overall

*MKI; multi-kinase inhibitor. Not used for RET fusion positive NSCLC

Issue 4: Relevant comparator treatments

Comparators used do not reflect clinical advice to ERG on relevant 2nd line treatments

ERG:

- Company compared selpercatinib vs pembrolizumab, nivolumab, atezolizumab & nintedanib+docetaxel
- Clinical advice to ERG: comparators in 2nd line: nintedanib+docetaxel, docetaxel, pemetrexed+carboplatin & platinum doublet chemotherapy
- Most patients receive first-line immunotherapy, not offered at second-line

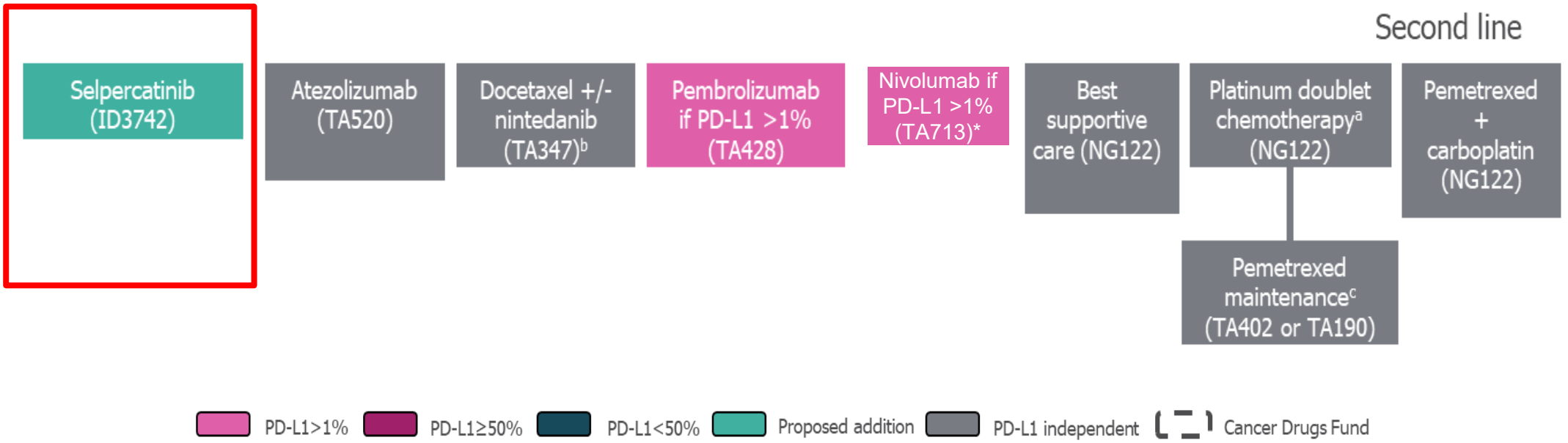
Company response at TE:

- Company agrees immunotherapies are not relevant
- Pemetrexed + carboplatin and platinum doublet chemotherapy used rarely at 2nd line
- Following further clinical advice, company agrees comparators are:
  - Docetaxel monotherapy
  - Nintedanib plus docetaxel
- NMA and cost effectiveness results have been updated to reflect this

Clinical experts: These unattractive options [docetaxel with/without nintedanib] are the only "standard" therapies available in this setting

Question to committee:
Should atezolizumab be considered a comparator for selpercatinib in second-line NSCLC, notwithstanding the ERG and company arguments?

Treatment pathway reminder and positioning of selpercatinib



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

Note: * signifies product in CDF at time of ID3743 submission (October 2020)

Issue 5: Relevance of populations participating in the trials providing comparator evidence for NMAs

Comparator evidence may include very few *RET*+ patients

ERG:

- Trials used in NMAs (other than LIBRETTO-001) did not test for *RET*+ fusion status
- Populations likely included small numbers of patients with *RET*+ NSCLC (1-2% of all NSCLC cases)
- Networks were not adjusted for prognostic factors associated with *RET*+ NSCLC

Company response at TE:

- ERG's argument is acknowledged and is a limitation of the data
- Pseudo-control arm (docetaxel+placebo) was adjusted for effect of *RET* on survival using data from Flatiron CGDB
- Further prognostic factors were taken into account in LIBRETTO-001
- Meta-regression used to establish no significant impact of *RET* status on survival outcomes between trials
- Company simulated a relevant population within confines of available data

Clinical experts: the result of the indirect comparisons of selpercatinib with docetaxel and docetaxel+nintedanib are clinically plausible

Issue 6: Uncertainty associated with the use of a pseudo-control arm

Uncertainty associated with the use of a pseudo-control arm to connect selpercatinib for network meta-analysis (NMA)

ERG:

- Pseudo-control arm (docetaxel+placebo) connects selpercatinib (via LIBRETTO-001) to comparators to enable a network meta-analysis to estimate OS and PFS
- Originally unclear how this was done
- Requested further detail on use of (targeted minimum loss-based estimation) TMLE method
  - *Note: company no longer use this approach*

Company response at TE:

- ERG's argument acknowledged, methodology has been updated to improve robustness by using propensity score matching to estimate treatment effects
- Pseudo-control arm (docetaxel+placebo) was adjusted for effect of *RET* on survival using data from Flatiron CGDB
- Results of adjustment for *RET* fusion are to improve OS for docetaxel with little effect on selpercatinib
- OS may be overestimated in pseudo-control arm
- Revised results incorporated into cost effectiveness results

Issue 6: Uncertainty associated with the use of a pseudo-control arm (2)

ERG views after TE:

- Some uncertainties resolved by use of propensity score matching, but other uncertainties and issues remain:
  - Propensity score matching usually results in some individuals effectively being present in multiple populations. Company does not show it has accounted for overlap between trial populations
  - Propensity score matching carried out using logistic regression model and generalised boosted model. ERG considers it is not clear which approach was used
  - Rationale for the model choices and assessments of the model also not presented
  - Fewer patients were included in the propensity score matching approach than in other analyses
- Additional data raised in issue 2 were not used within revised NMAs
- ERG does not consider definite conclusions on the direction and magnitude of the relative effect of selpercatinib vs comparators can be made

Issue 7: Company modelling of survival for people having selpercatinib

Company selection of distribution for survival modelling is open to bias

ERG:

- Company has ignored its Akaike information criterion (AIC) and Bayesian information criterion (BIC*) rankings of distributions
- Company's selection made on clinical advice considering most important was that the relative advantage of selpercatinib over the pseudo-control should be maintained across whole model time horizon
- ERG is concerned about bias in this approach
- ERG's alternative approach significantly increases the ICER against both comparators

Company response at TE:

- Detailed response made combining issues 7 and 8

*AIC compares the quality of the models fitted, a lower AIC implies a better chance the model fits the data well than a higher AIC.
BIC serves the same purpose, depending more on known prior information and penalising model complexity more heavily. Lower BIC implies a better chance the model accurately fits the truth.

Refer to **issue 8** for company response details and further ERG comments

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Issue 8: Company modelling of survival for people having comparator treatments

ERG considers that uncertainties mean OS and PFS projections for all comparators are unreliable

ERG:

- ERG considers NMAs uncertain, therefore projections based on these are unreliable
- ERG approach is to assume
  - Survival of patients receiving docetaxel is equivalent to pseudo-control arm
  - An additional QALY gain represents added benefit of nintedanib+docetaxel compared to docetaxel

Company response at TE:

- Implementing ERG's preferred modelling of OS in company model leads to high survival rates
- NMAs were revised in resolving **issue 6**,
- Most selected fitted curves produced predicted PFS medians [redacted] months, similar to LIBRETTO-001 observed PFS [redacted] months

Issue 7/8: Overall survival extrapolations after technical engagement

	Median PFS (months)	Median OS (months)	5-year	10-year	25-year
Gompertz – highlighted by ERG as closest to clinical advice					
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Weibull – highlighted by company					
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline/Knot 1 – used in updated company base case					
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gamma – highlighted by company					
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- **Company** explored various extrapolations including others not included here
- **Company** believes **Spline/knot 1** extrapolation fits most closely to clinical expert advice
- **ERG** believes there is insufficient data to determine the best fit, but Gompertz appears close to clinical advice

NICE **Source:** Adapted from Company TE response, Table 9

Issues 7/8: Survival extrapolations after technical engagement (2)

Other Stakeholders:

- Roche noted ERG approach to modelling docetaxel+nintedanib by adding 0.140 QALYs to docetaxel monotherapy arm as per NICE TA347
    - ERG showed in TA347 that docetaxel+nintedanib added 0.140 QALYs (and 0.224 life years) compared to docetaxel alone
- Roche queries whether this simple additive approach is seen as a valid approach for decision making, especially given the differing patient populations and modelling approaches
- Would be useful for transparency if ERG were to outline if any more robust approaches were explored/attempted and the reasons why these were rejected

ERG views after TE:

- Model estimates for OS and 5-year survival with selpercatinib are higher than clinical expert estimates
- ERG still believes company modelling choices driven by clinical opinion
- ERG unable to justify one model choice over another, but using Gompertz fits closest to clinical expert estimates. Change increases ICER

Issues 7/8: Survival extrapolations after technical engagement (3)

Selpercatinib OS parametric survival function extrapolations, illustrating the impact of using different extrapolations

Source: Company TE response Figure 17

Issue 9: Progressive disease health state utility value

Inconsistency in using key information from other appraisals

ERG:

- Utility values used in company model are taken from NICE TA484*
- However, the **Progressed disease (PD) health state utility value** (0.688) does not match NICE TA484 (0.569)
  - I.e. someone with progressed disease has higher utility by company's calculation than expected from TA484
- Using the NICE TA484 preferred PD health state utility value increases the ICER per QALY gained for selpercatinib versus nintedanib+docetaxel

Company response at TE:

- Company acknowledges ERG's consistency point and preference for PD value from TA484 (PD=0.569)
- Company gathered European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 data in LIBRETTO-001 (PD=0.688)
- Company mapped EQ-5D-3L to EORTC using method in Young *et al.* (2015) to calculate new PD=[redacted]
- Revised value appears high and may be uncertain
- Company elected to use a compromise PD between ERG and company base cases of 0.628 (midpoint) for the updated model

ERG views after TE:

- ERG considers that the PFS and PD health state utility values preferred by the NICE TA484 are the most relevant values available
- Using the TA484 preferred utility values increases the company base case ICER per QALY gained

Issue 10: Costing of treatment with selpercatinib

Company has used LIBRETTO-001 trial Progression free survival data as basis for costing treatment with selpercatinib

ERG:

- Company originally used progression free survival data to calculate treatment costs
- ERG prefers to use time to discontinuation (TTD) data to calculate treatment costs
- Using TTD increased ICER for selpercatinib

Company response at TE:

- Model has been updated with a conservative TTD model rather than PFS

Other Stakeholders:

- Roche agreed this approach was appropriate and aligned with other NICE appraisals

ERG views after TE:

- In original company model it was possible to model cost of treatment using extrapolated LIBRETTO-001 trial TTD data → **Option no longer available in revised model**
- Modelling TTD with exponential distribution (best fit) significantly increased cost of selpercatinib
- ERG preferred approach remains using TTD data from the LIBRETTO-001 trial
- ERG used exponential distribution fitted to the LIBRETTO-001 trial TTD data from original company model in revised company model. Change increases ICER

Issue 11: Cost of testing for RET fusions

RET fusions are not routinely tested for in the NHS and a national NHS Genomic Medicine Service to provide next generation sequencing (NGS) has yet to be established

ERG:

- Until NGS is established for *RET* fusions, testing costs should be included in cost-effectiveness estimates
- Excluding testing costs would exert downwards pressure on the ICER

Company response at TE:

- NGS at genetic hubs will become testing method in the NHS. Multiple parallel screening is cost-effective
- Since routine screening is expected to be implemented across the UK, this cost should not be included in the economic assessment
- Company recognises uncertainty in timing of routine NGS implementation
- Company has added a cost for *RET*-fusion portion of multi-gene testing NGS panel in the updated model
- [redacted] per test recommended by NHS England

Clinical experts: *RET* testing will be available as part of lung cancer screening, from that point will not represent additional expense

Other Stakeholders:

- Roche agreed with the company that NGS will test for *RET*-fusion NSCLC and therefore implementation of selpercatinib as standard of care on the cost of testing will be budget neutral

Issue 12: NICE end-of-life criteria may not be met

ERG does not agree with company estimates for survival for comparator treatment

ERG:

- Company calculates:
  - Median and mean OS for patients receiving nintedanib+docetaxel are [redacted] and [redacted] months respectively
  - Median and mean OS for patients receiving selpercatinib are [redacted] and [redacted] months, respectively
- ERG calculates:
  - nintedanib+docetaxel generates mean OS of [redacted] months (median not evaluable)
  - OS gain for selpercatinib is uncertain, may exceed 3 months

Company response at TE:

- ERG mean OS estimate for nintedanib+docetaxel of [redacted] months is a substantial overestimate of survival, supported by clinical advice to company
- Company updated its estimates for survival based on issue 6, producing revised figures:

Intervention/comparator	Median PFS (months)	Median OS (months)
Selpercatinib	[redacted]	[redacted]
Docetaxel monotherapy	[redacted]	[redacted]
Nintedanib + docetaxel	[redacted]	[redacted]

- Targeted literature review supported the view that ERG (and original company base case) figures were overestimates
- Company has re-stated its belief selpercatinib meets end-of-life criteria
- All models >2 life years gained from ERG and company

Issue 12: NICE end-of-life criteria may not be met (2)

Clinical experts:
"Median PFS with docetaxel with or without nintadenib in this setting is 3 months, and OS 10 months in this context (Reck et al., Lancet Oncology 2014). I would expect selpercatinib to exceed these numbers (PFS in LIBRETTO-001 was 18 months)."

ERG views after TE:

- Company evidence indicates it is **plausible** life expectancy for patients with *RET*-fusion positive NSCLC extends beyond 2 years
- OS gain for selpercatinib could exceed 3 months
- OS gain is highly uncertain without more robust comparative OS data

Issue 12: NICE end-of-life criteria may not be met (3)

Recap on 'life-extending treatment at the end of life', from NICE Guide to the Methods of Technology Appraisal 2013

Section 6.2.10:
In the case of a 'life-extending treatment at the end of life', the Appraisal Committee will satisfy itself that all of the following criteria have been met:

- the treatment is indicated for patients with a short life expectancy, normally less than 24 months and
- there is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared with current NHS treatment.

In addition, the Appraisal Committees will need to be satisfied that:

- the estimates of the extension to life are sufficiently robust and can be shown or reasonably inferred from either progression-free survival or overall survival (taking account of trials in which crossover has occurred and been accounted for in the effectiveness review) and
- the assumptions used in the reference case economic modelling are plausible, objective and robust.

Issue 13: Absence of data for squamous disease

Company did not provide any clinical or cost effectiveness evidence for patients with squamous disease (any setting)

ERG:

- In original submission, selpercatinib was indicated for both squamous and non-squamous NSCLC
- Company did not provide data to support use of selpercatinib in squamous NSCLC
- Company followed clinical advice to limit their submission to non-squamous NSCLC only

Company response at TE:

- Eli Lilly and Company agree with the clinical advice that it is reasonable to exclude patients with advanced squamous cell NSCLC, because *RET* fusions are extremely rare in this population

NICE technical team note:
While squamous NSCLC is very rare, it would not be impossible to encounter a patient with *RET*-positive NSCLC. Squamous disease is within the marketing authorisation of selpercatinib

Other Considerations

- Company perspective on innovation
  - First *RET*-fusion targeted treatment, clinical benefit of selpercatinib is demonstrated
  - Oral administration is an advantage over chemotherapies and immunotherapies
- Equality issues
  - None identified at scoping
- Cancer drugs fund (CDF)
  - Would it be of benefit to recommend selpercatinib be reimbursed through the CDF?
  - LIBRETTO-431 expected to complete in 2025
  - A Multicenter, Randomized, 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

Cost effectiveness results

Company's revised probabilistic base case cost effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	ICER pairwise selpercatinib vs comparator (£/QALY)
Docetaxel monotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-	74,809
Nintedanib + docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£105,775	69,220
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	74,809	-

Analyses including confidential commercial arrangements for subsequent or comparator treatments will be considered in the private session of the appraisal committee meeting

NICE **Sources:** Company TE response

ERG amendments to company base case

- The ERG made the following amendments to the company base case analysis following technical engagement:
  - used the NICE TA484 committee preferred progressed health state utility values (**issue 9**)
  - Changed cost of treatment with selpercatinib using LIBRETTO-001 trial time to discontinuation data (**issue 10**)
- Ran a scenario on a different OS extrapolation (Gompertz) for patients receiving selpercatinib, nintedanib + docetaxel and docetaxel (**issues 7 & 8**)

Sources: Adapted from ERG report, Page 90

ERG's base-case cost-effectiveness results for selpercatinib versus nintedanib+docetaxel

- **Deterministic** - using PAS price for selpercatinib and list prices for nintedanib+docetaxel (please note nintedanib+docetaxel has a confidential PAS. Results using this are presented in the confidential part 2 session)

Scenarios	Incremental			ICER (£/QALY gained)
	Cost	Life Years	QALYs	
Company base case	[redacted]	[redacted]	[redacted]	£69,411
B3 TA484 committee preferred utility values	[redacted]	[redacted]	[redacted]	£76,140
B4 Use of TTD to model treatment duration of selpercatinib	[redacted]	[redacted]	[redacted]	£106,468
Alternative ERG base case (B3+B4)	[redacted]	[redacted]	[redacted]	**£116,790**
S1 Use of Gompertz distribution to extrapolate OS	[redacted]	[redacted]	[redacted]	£91,570
Alternative ERG scenario (S1+B3+B4)	[redacted]	[redacted]	[redacted]	£156,013

ERG's base-case cost-effectiveness results for selpercatinib versus docetaxel

- Deterministic - using PAS price for selpercatinib and list prices for docetaxel:

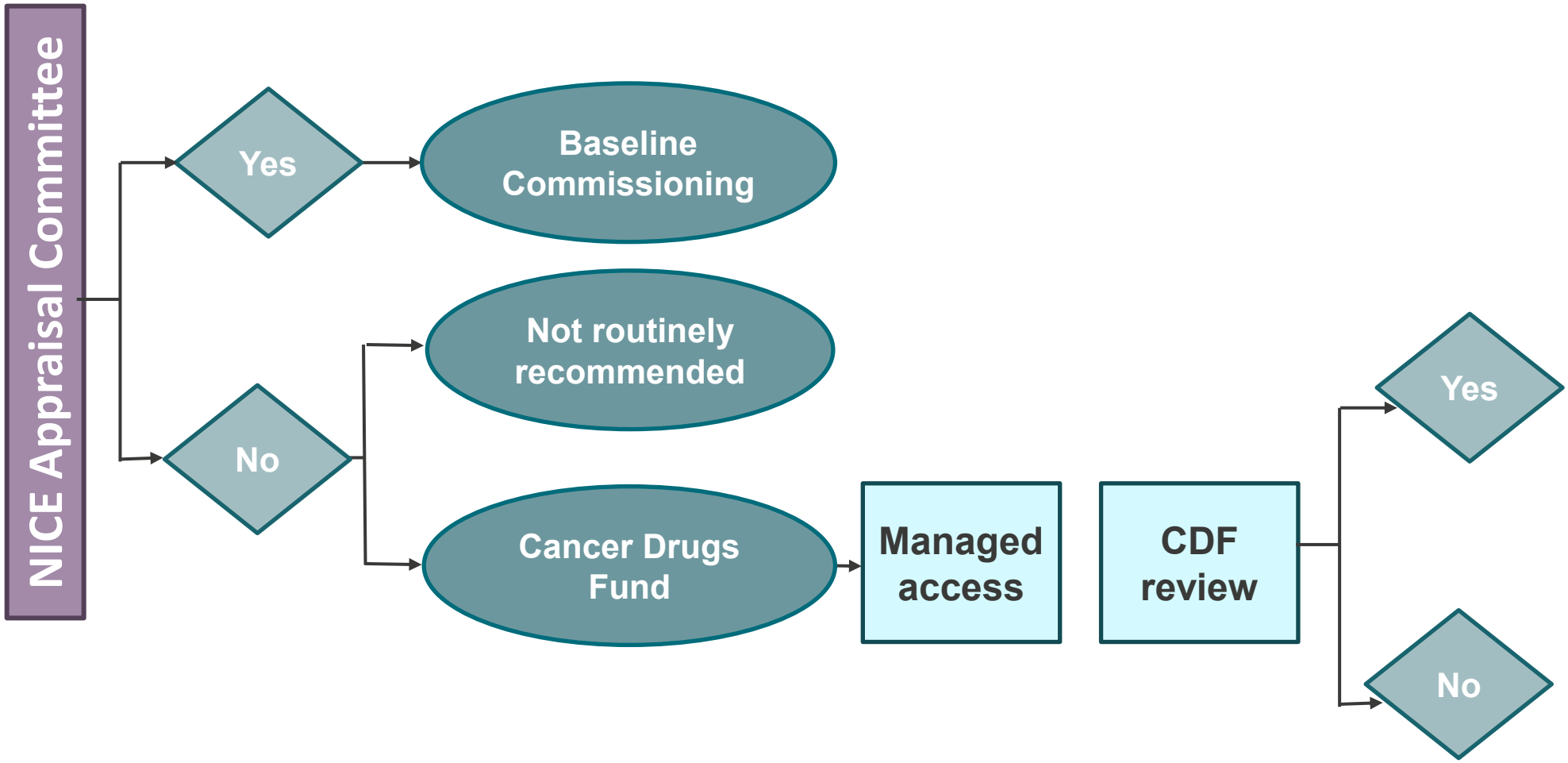
Scenarios	Incremental			ICER (£/QALY gained)
	Cost	Life Years	QALYs	
Company base case	[redacted]	[redacted]	[redacted]	£74,833
B3 TA484 committee preferred utility values	[redacted]	[redacted]	[redacted]	£82,105
B4 Use of TTD to model treatment duration of selpercatinib	[redacted]	[redacted]	[redacted]	£106,084
Alternative ERG base case (B3+B4)	[redacted]	[redacted]	[redacted]	**£116,393**
S1 Use of Gompertz distribution to extrapolate OS	[redacted]	[redacted]	[redacted]	£97,537
Alternative ERG scenario (S1+B3+B4)	[redacted]	[redacted]	[redacted]	£153,075

Key issues

	Issue	ICER impact	Status
1	Trial data demonstrating the clinical effectiveness of selpercatinib are only available from the LIBRETTO-001 trial	N/A	No
2	LIBRETTO-001 trial survival events and length of follow-up		No
3	Prior treatments received by the LIBRETTO-001 trial population do not reflect NHS clinical practice	N/A	No
4	Relevant comparator treatments	N/A	Partially
5	The relevance of population participating in the trials that provided comparator evidence for the company NMAs	N/A	No
6	Uncertainty associated with the pseudo-control (reference) arm used to connect selpercatinib for network meta-analysis	N/A	No
7	The company modelling of survival for patients receiving selpercatinib		No
8	The company modelling of survival for patients receiving nintedanib+docetaxel		No
9	Progressive disease health state utility value		Partially
10	Costing of treatment with selpercatinib		No
11	Cost of testing for *RET* fusions		Resolved
12	NICE End of Life criteria may not be met	N/A	No
13	Absence of data for subgroups of patients listed in the final scope issued by NICE		No

Additional supporting slides

Cancer drugs fund option for technology appraisals



Committee decision making