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Chair's presentation

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

2nd Appraisal Committee meeting – 15 September 2021

HST Committee

Chair: Peter Jackson

Technical team: Stephen Norton, Nicola Hay, Jasdeep Hayre

ERG: Liverpool Reviews and Implementation Group (LRiG)

Company: Eli Lilly

NICE

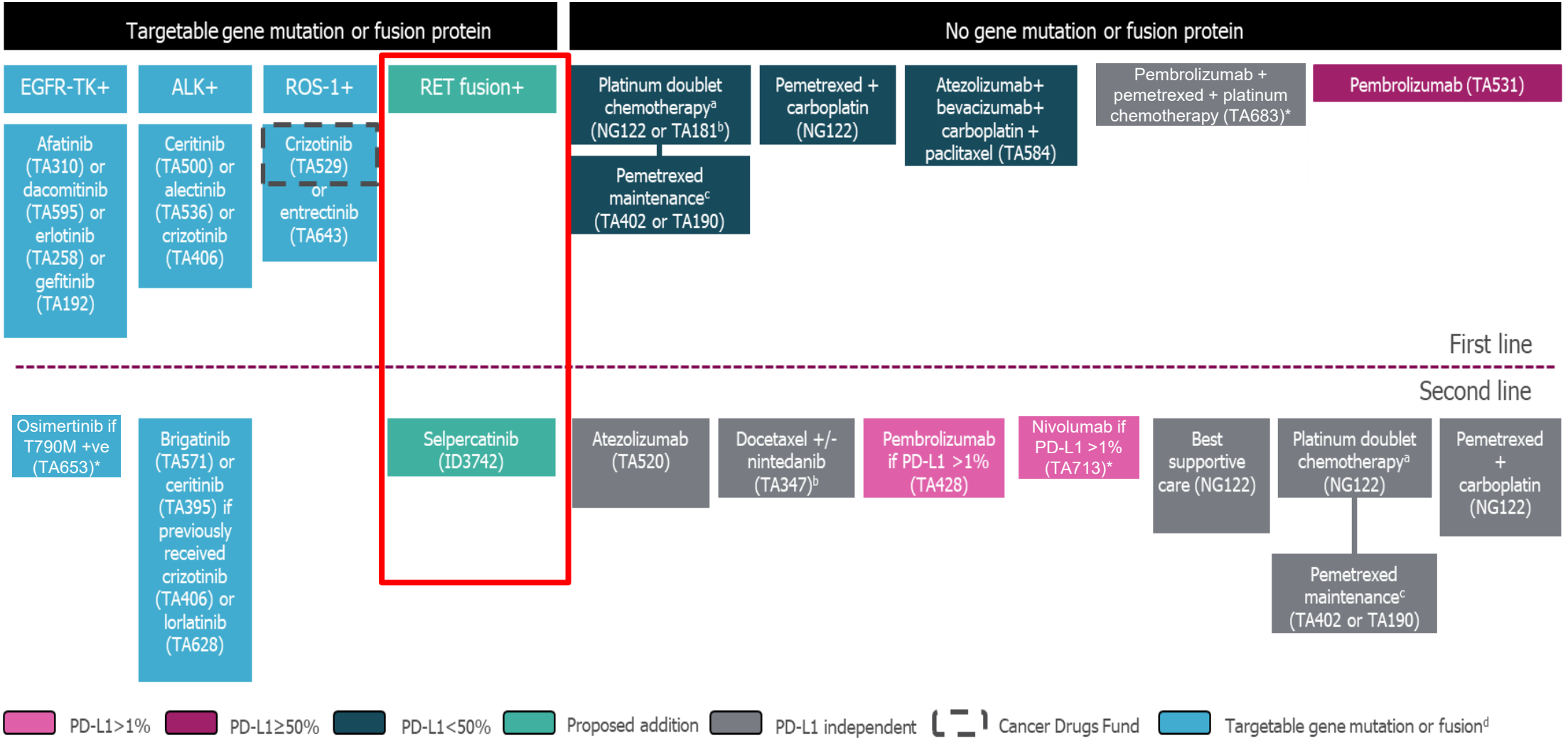
Key issues

- Is the generation of the pseudo-control (docetaxel) arm robust?
- Are estimates of OS and PFS robust?
- What is the correct method for calculating cost of selpercatinib?
- Does selpercatinib meet the NICE end of life criteria?
- Would entry in to the cancer drugs fund (CDF) be appropriate?

ACM1 recap: Selpercatinib (Retsevmo, Eli Lilly)

Marketing authorisation	Granted by MHRA in February 2021. “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

ACM1 recap: 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)

ACM1 recap: 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**

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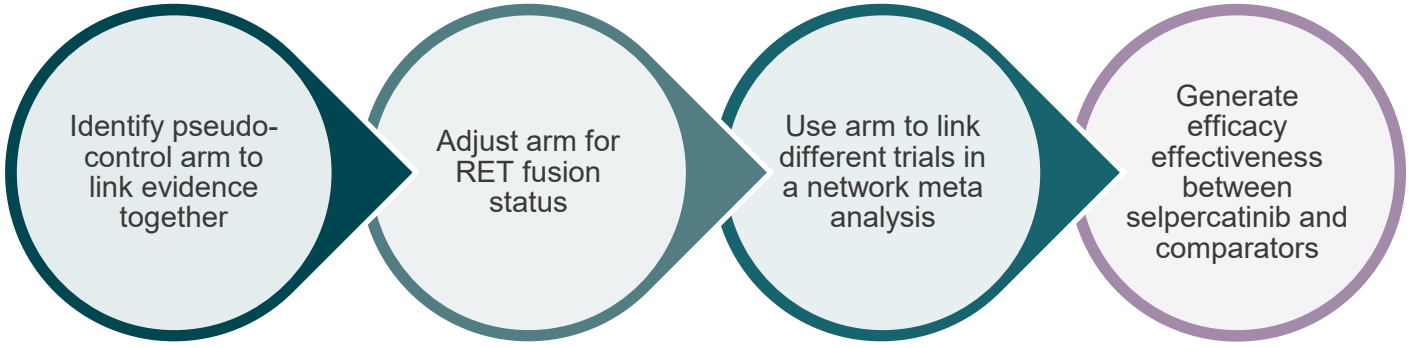
Key: DOR: duration of response; IAS: integrated analysis set; PAS: primary analysis set; ORR: objective response rate; OS: overall survival; PFS: progression free survival

ACM1 recap: 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



ACM1 recap: Company's network meta analyses results at TE: 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

ACM1 recap: ACD preliminary recommendation

Selpercatinib is not recommended, within its marketing authorisation, for treating RET fusion-positive advanced non-small-cell lung cancer (NSCLC) in adults who need systemic therapy after immunotherapy or platinum-based chemotherapy.

ACM1 recap: ACD considerations (1)

Issue	Committee's considerations
Clinical evidence (ACD section 3.3)	Evidence for selpercatinib is uncertain as it depends solely on LIBRETTO-001, a single-arm study.
Trial generalisability (ACD section 3.4)	LIBRETTO-001 included people who had also had chemotherapy. Some people had also had immunotherapy, and some had also had multikinase inhibitory therapy. The committee concluded that the LIBRETTO-001 population is generalisable to NHS clinical practice and is appropriate for decision making.
Tumour pathology (ACD section 3.5)	Although the company did not present data for squamous NSCLC, the committee agreed its recommendations should apply to squamous and non-squamous NSCLC.
ITC trial usage (ACD section 3.6)	The company carried out indirect treatment comparison (ITC) by network meta-analysis (NMA). Populations in the trials selected for the ITC were not tested for RET fusion status but were relevant for use in the ITC.

ACM1 recap: ACD considerations (2)

Issue	Committee's considerations
NMA control (ACD section 3.7)	The company's simulated pseudo-control arm depended on an independent cancer database. Results obtained for the control arm were uncertain, did not appear feasible, and relied on several complex statistical steps. The committee concluded that this control was not robust.
Economic model (ACD section 3.8)	The economic model design is consistent with other NICE appraisals for NSCLC therapies.
Economic model results (ACD section 3.9)	Modelled OS and PFS were not robust. A wide range of extrapolations could be made from the trial data, and the ERG was unable to make a preferred selection due to uncertainty. Survival estimates for selpercatinib and the pseudo-control may have been overestimated. Further data was needed to refine estimates for OS and PFS of selpercatinib, and a more robust control arm was needed to establish OS and PFS for the control.
Economic model costs (ACD section 3.10)	Most costs used in the model were appropriate, however the cost of selpercatinib was calculated using PFS. The committee agreed that using time to discontinuation (TTD) was more accurate.

ACM1 recap: ACD considerations (3)

Issue	Committee's considerations
Genetic testing costs (ACD section 3.11)	It is appropriate to include the costs of testing for RET fusion status into the economic model as this is not included in routine NSCLC genetic testing at the time of this appraisal.
Utility values (ACD section 3.12)	The company calculated its utility value for progressed disease from health-related quality of life (HRQoL) data gathered in LIBRETTO-001. This was inconsistent with other utility values obtained from a previous NICE appraisal for NSCLC. In the absence of more robust data, the committee agreed the value used by the company was acceptable.
End of life (ACD section 3.13)	It was feasible from the presented evidence that selpercatinib may extend life compared to docetaxel with or without nintedanib. However, the evidence was not robust enough to determine if end of life criteria were met. There were particular concerns with the control, and OS and PFS estimates for both control and selpercatinib arms.
Cost-effectiveness (ACD section 3.14)	No ICERs presented by the company were in the range normally considered cost-effective. Neither the ERG nor the committee defined a preferred ICER due to the uncertainty discussed in the earlier sections.

Consultation comments

ACD consultation responses

- **Commentator comments from:**
  - Roche Products Ltd
- **Consultee comments from:**
  - Eli Lilly (company)
- **Web comments:**
  - None
- **Other developments:**
  - Company has provided an increased PAS discount following ACM1

Consultation comments

Commentator comments: Roche

- The company is inconsistent in using LIBRETTO-001 data to model OS and PFS but stating TTD would be too immature. A consistent approach across OS, PFS and TTD is needed
- Use of TTD to inform treatment costs is appropriate (as per committee preference)
- Given the expected upcoming roll-out of widespread next generation sequencing testing for various forms of NSCLC, if a cost of testing is to be included in the economic model, the cost of testing attributed to selpercatinib should represent a percentage of overall testing costs. This percentage should represent the short term additional uptake in testing over and above what the expected testing roll-out would have been.

ACD consultation comments

Consultee comments: Eli Lilly (company)

ACD section	Areas of uncertainty	Reason for uncertainty	Company response
3.7	The generation and use of the simulated pseudo-control arm in NMAs is not robust	Excessive survival due to overestimating effect of RET mutation	New analysis Removed adjustment for RET status from process to generate docetaxel control arm Revised adjustment process in control arm used in NMAs
3.9	The modelled results of OS and PFS are not robust	A wide range of extrapolations could be made from the trial data	New analysis PFS and OS extrapolations updated based on updated NMA.
3.10	Method for calculating the cost of selpercatinib was incorrect	Company used PFS to calculate treatment costs, committee agreed time to discontinuation (TTD) was more appropriate	Narrative Clarified that its approach was a modified PFS New analysis Added scenario analyses for TTD approach, base case unaltered
3.13	Whether selpercatinib meets end of life criteria	Uncertainty in OS estimates reduced robustness in end of life criteria	New analysis Updated OS extrapolations from revised adjustment process in control arm were used to suggest that selpercatinib fulfils EOL criteria

New analysis: removal of RET adjustment for pseudo-control arm and updated NMAs

RET status adjustment of pseudo-control arm caused uncertainty, new evidence showed it was not required

- Hess *et al.* show increased survival for people with RET fusion mutations that was not statistically significant
- Therefore, company presented pseudo-control (docetaxel) survival results without adjustment for RET status
  - Revised pseudo-control median OS: [redacted]

Relative treatment effects expressed as HRs versus docetaxel plus placebo (with 95% CrI) for PFS and OS in pre-treated advanced non-squamous RET fusion-positive NSCLC patients from company response to ACD:

Treatment	Median HR (95% CrI) versus docetaxel + placebo
Fixed effects	
Selpercatinib (PFS)	[redacted]
Nintedanib + docetaxel (PFS)	[redacted]
Selpercatinib (OS)	[redacted]
Nintedanib + docetaxel (OS)	[redacted]

New analysis: removal of RET adjustment for pseudo-control arm and updated NMAs

ERG comment

- Appropriate and informative to present generation of pseudo-control without adjustment for RET status
- Cited Hess *et al.* study specifically not designed to establish if RET status is prognostic
- Study limitations are: authorship includes Eli Lilly staff, only 46 patients were included, different chemotherapy regimes were permitted, results are not conclusive (there may be statically significant prognostic effect of RET status)
- Results demonstrated statistically significant advantages for selpercatinib versus docetaxel+placebo, and for nintedanib with docetaxel versus docetaxel+placebo
- Smaller hazard ratios (HRs) for selpercatinib versus docetaxel+placebo after the revision compared with those presented at technical engagement imply larger advantages for selpercatinib in the revised results
- Not possible to mitigate all uncertainty in estimation of treatment effects
- Issues with data and methods in NMAs remain, such as different definitions of PFS in various data sources, trial used in NMAs not representing a RET+ population, formal checks of overlap of covariate distribution not done (or not reported), and fewer patients included in the propensity score matching approach than in original approach

New analysis: extrapolations based on updated NMAs generated new survival estimates

Updated extrapolations generated clinically plausible survival estimates

- Curve fitting re-run after revised pseudo-control generated
- AIC and BIC indicated Gamma and Weibull extrapolations were best fits for PFS
- Company maintained view from technical engagement that stratified Gompertz was most appropriate PFS extrapolation for selpercatinib and docetaxel arms due to clinical advice
  - PFS fixed by applying stratified Gompertz
- Company noted Gompertz and stratified Weibull extrapolations as most conservative, clinically plausible curves for selpercatinib OS, and Gompertz for docetaxel

	Median PFS (months)	Median OS (months)	5-year survival (%)	10-year survival (%)	25-year survival (%)
Gompertz – company choice for selpercatinib and docetaxel OS					
Docetaxel	[redacted]	[redacted]	2.2	0.0	0.0
Selpercatinib	[redacted]	[redacted]	38.8	8.5	0.0
Stratified Weibull – alternative company choice for selpercatinib OS					
Docetaxel	[redacted]	[redacted]	3.2	0.1	0.0
Selpercatinib	[redacted]	[redacted]	36.1	9.9	0.1

New analysis: extrapolations based on updated NMAs generated new survival estimates

- Figure shows company revised base case OS extrapolations (stratified Gompertz) following updated pseudo-control generation
- A wide range of extrapolations can be fitted to the Kaplan-Meier (K-M) curves
- The range of possible extrapolations is an uncertainty
- Choice of extrapolation is key to determining OS and PFS

ERG comment

- Company has succeeded in reducing survival estimates for pseudo-control which were high at ACM1, but limited data still means the true survival for this group is uncertain
- Based on this figure and the current K-M curve, survival for selpercatinib appears to be overestimated
- Company ICERs are therefore likely to be optimistic for selpercatinib versus chemotherapy

Narrative comment and new evidence: clarification on treatment costs calculation

Company clarified its modified PFS approach to calculating costs of selpercatinib and provided scenario analysis for TTD approach

- Mean time from progression to discontinuation measured in LIBRETTO-001: [redacted] days
- This was applied by simple addition to the PFS curve, therefore modelling time on treatment is not solely dependent on PFS
- Analyses of extrapolations of time to discontinuation (TTD) appear to overestimate time on treatment (see next slide) to longer than PFS, especially in long-term survivors
- Therefore costs of selpercatinib in the company model are based on PFS (with applied time from progression to discontinuation) rather than TTD

ERG comment

- Company has not presented new evidence to support their alternative approach to modelling time on treatment
- Company considers that using a distribution fitted to TTD is flawed, producing unrealistically high TTD estimates
- More TTD data than OS data exist from LIBRETTO-001 and the company believes fitting distributions to the OS data produces robust results
- TTD is the usual value used as the basis for calculating costs in NICE appraisals

Narrative comment and new evidence: TTD extrapolations overestimate time on treatment

Analysis of time on treatment for modified PFS compared to TTD extrapolations, from company response to ACD.

Time (yrs)	PFS: Stratified Gompertz (%)	On Treatment (based on TTD curves)							
		Exponential (%)	Weibull (%)	Lognormal (%)	Loglogistic (%)	Gompertz (%)	Gamma (%)	Spline Knot 1 (%)	Spline Knot 2 (%)
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

New analysis: update in pseudo-control arm may resolve uncertainty around end of life criteria

Revised approach to generating the control arm may mean selpercatinib meets end of life criteria

- Uncertainty in OS for docetaxel made establishing end of life status for selpercatinib unworkable
- Update in generation of docetaxel (pseudo-control) arm resulted in clinically feasible median OS ([redacted]) and extrapolations (below)

Revised survival outcomes (PFS and OS) and clinical outcomes from company response to ACD					
Intervention/ comparator	**Median PFS (months)**	**Mean PFS (months)**	**Median OS (months)**	**Discounted LYs**	**Undiscounted LYs**
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nintedanib + docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- I.e. docetaxel and docetaxel+nintedanib are estimated to have OS less than 24 months and selpercatinib OS is estimated to be greater than 24 months
- Company believes these revisions have overcome uncertainty in the docetaxel arm
- Therefore, company believes OS gains observed in selpercatinib are more robust and selpercatinib now meets end of life criteria

New analysis: update in pseudo-control arm may resolve uncertainty around end of life criteria

ERG comment

The company has not addressed the uncertainty around the reliability of model OS estimates for patients who had selpercatinib and, therefore, the ERG considers that the evidence remains insufficiently robust to conclude that treatment with selpercatinib meets the NICE End-of-Life criteria.

Cost-effectiveness analysis

- Because of confidential prices for comparator treatments, the cost-effectiveness analyses are presented in Part 2

- Part 2 slides will discuss:
  - The company's updated base case
  - ERG's alternative base case

Company's updated base case

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]	-	-	-	-	**55,119**
Nintedanib + docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	118,952	**48,800**
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	55,119	-

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

Company's scenario analyses for selpercatinib costs

Company conducted scenario analyses for various fixed time between PFS and stopping treatment with selpercatinib based on LIBRETTO-001 data

Scenario	Pairwise ICER vs. docetaxel (£)	Pairwise ICER vs. nintedanib + docetaxel (£)
Base case	55,199	48,800
Alternative stopping assumptions: [redacted](mid-point of lower limit of 95% CI and mean [redacted] for mean time between PFS and treatment discontinuation in LIBRETTO-001)	54,006 (-2.16%)	47,577 (-2.51%)
Alternative stopping assumptions: [redacted](mid-point of upper limit of 95% CI and mean [redacted] for mean time between PFS and treatment discontinuation in LIBRETTO-001)	56,596 (+2.53%)	50,423 (+3.33%)
Alternative stopping assumptions: [redacted](upper limit of 95% [redacted] for mean time between PFS and treatment discontinuation in LIBRETTO-001)	59,540 (+7.86%)	53,659 (+9.96%)

ERG's updated alternative base case for selpercatinib versus nintedanib+docetaxel

- **Deterministic** - using updated 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)

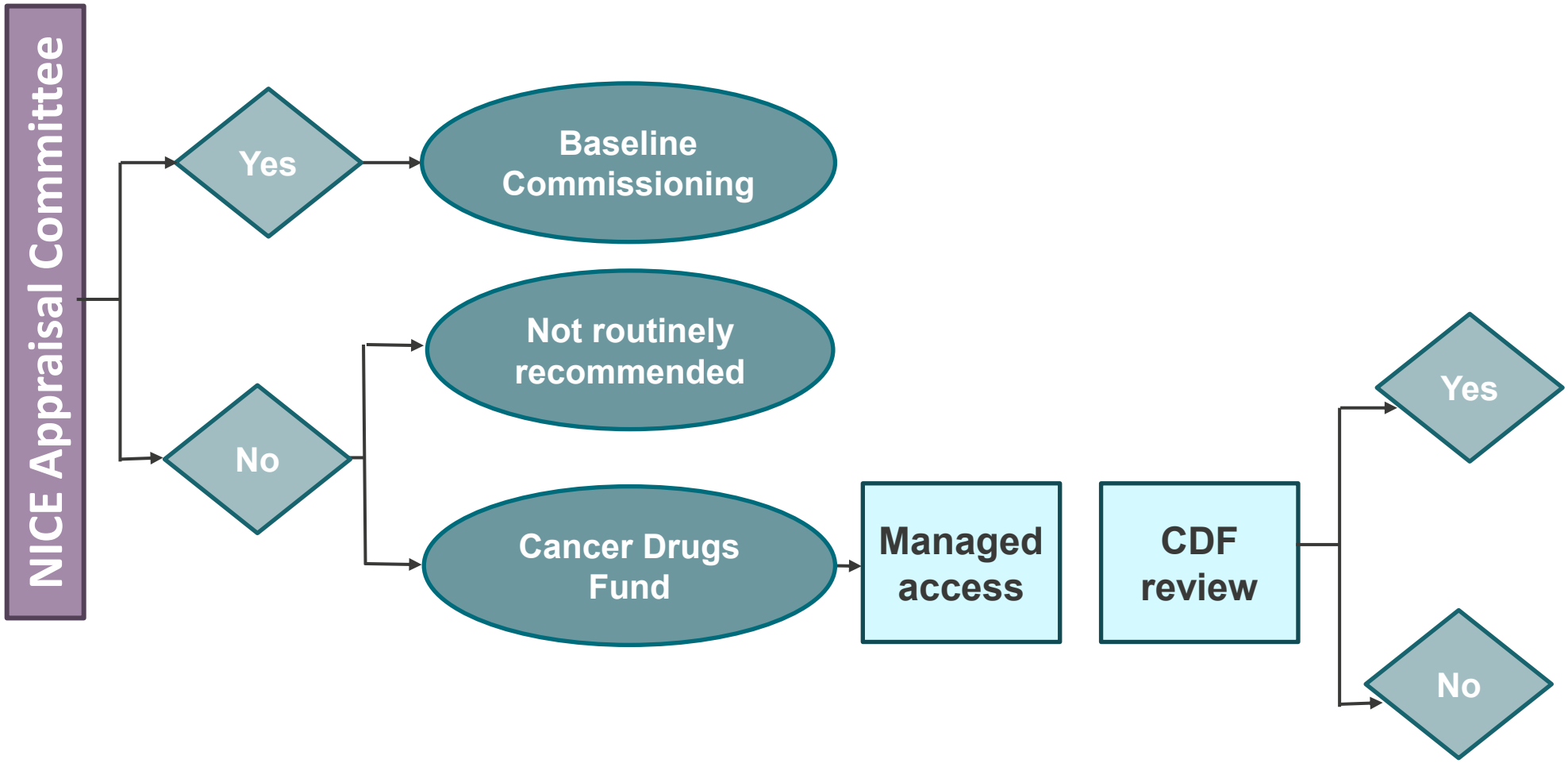
Scenarios	Incremental			ICER (£/QALY gained)
	Cost	Life Years	QALYs	
Company base case	[redacted]	[redacted]	[redacted]	£48,800
Alternative ERG base case: Use of TTD to model treatment duration of selpercatinib	[redacted]	[redacted]	[redacted]	£71,978

ERG's preferred base-case results for selpercatinib versus docetaxel

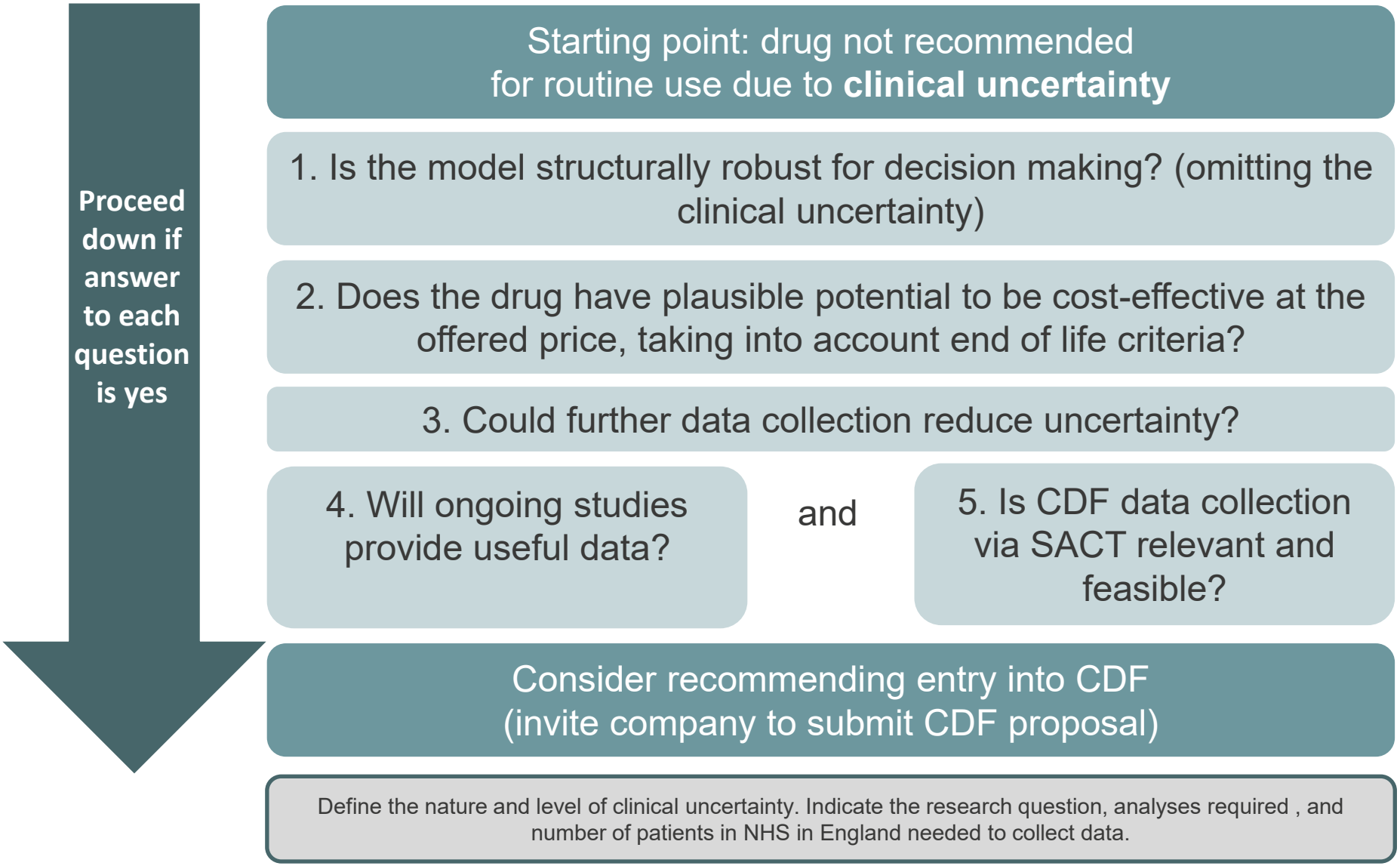
- Deterministic - using updated PAS price for selpercatinib and list prices for docetaxel:

Scenarios	Incremental			ICER (£/QALY gained)
	Cost	Life Years	QALYs	
Company base case	[redacted]	[redacted]	[redacted]	£55,119
ERG preferred base case: Use of TTD to model treatment duration of selpercatinib	[redacted]	[redacted]	[redacted]	£76,210

Cancer drugs fund option for technology appraisals



Committee decision making



Supplementary slide: ERG TTD extrapolation

- Extrapolation made by ERG following original submission to illustrate difference in approach
- ERG said: “At 12 months, the LIBRETTO-001 trial data show that [redacted] of patients are progression-free but [redacted] are still on treatment. The ERG is aware that during the first months of a trial some patients will stop treatment with the study drug due to intolerability but patients who tolerate treatment may remain on treatment beyond progression if clinicians believe these patients are still deriving benefit from treatment.”