NICE National Institute for Health and Care Excellence

For public: ACIC data redacted

Cemiplimab for treating metastatic or locally advanced cutaneous squamous cell carcinoma (CSCC)

Lead team presentation

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Company: Sanofi
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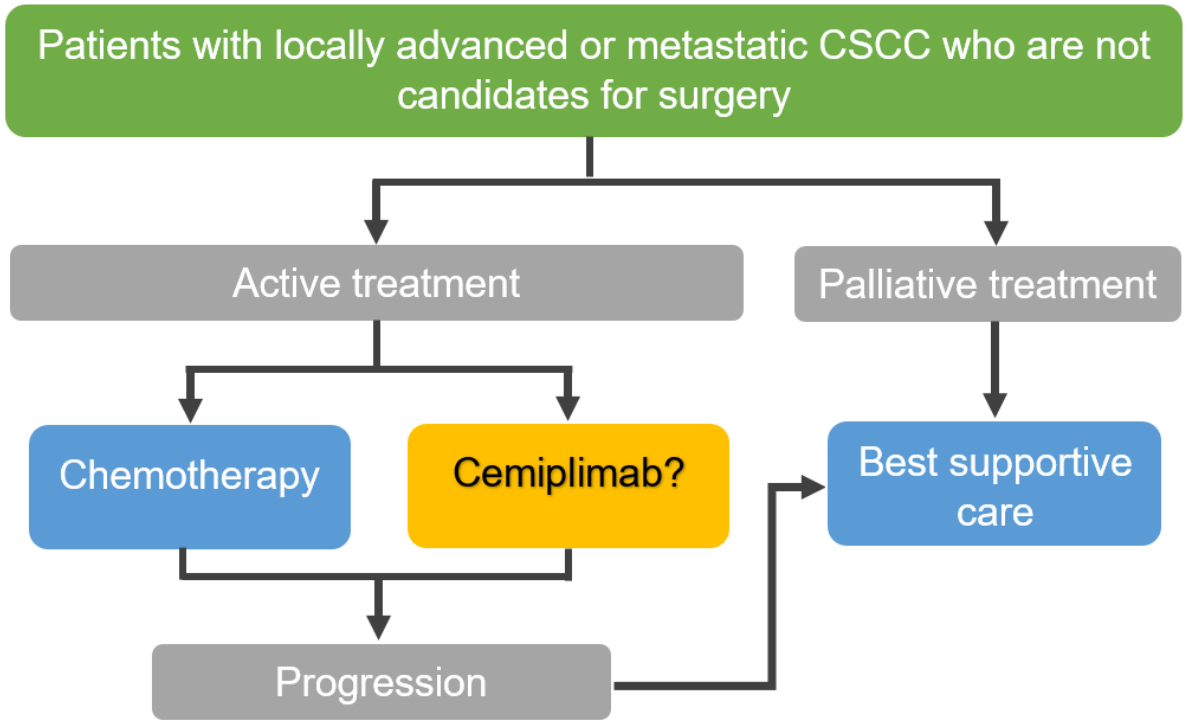
Key issues

1. The clinical evidence for cemiplimab is promising but immature and the quality of the comparator data is very low
2. Because of this, the estimates of relative clinical and cost effectiveness are very uncertain
3. The base case and key scenario ICERs are all outside the range normally considered to be a cost effective use of NHS resources (20-30K) so cemiplimab can only be recommended if the end of life criteria are considered to apply
4. If the current estimates of extension to life/assumptions used in the modelling are too uncertain, and the CDF criteria are met, then a CDF recommendation could be considered

Cutaneous squamous cell carcinoma (CSCC)



[redacted]

- CSCC is a distinct disease (separate to both melanoma and other SCCs such as head and neck squamous cell carcinoma (HNSCC)
- Major risk factors: exposure to UV radiation, advanced age and immunosuppression
- CSCC is cured in the majority of patients but a small proportion reach incurable advanced state
- Advanced patients are often older and have a poor prognosis
- As the disease progresses, lesions may grow quite large and spread to different parts of the body
- Patients with disfigurement due to CSCC and its treatments have been shown to have a reduced QoL, affecting physical and psychological health and social relationships

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Patient and carer perspectives

The following points were provided by a carer of a patient with advanced CSCC

Living with unresectable or advanced SCC is challenging – the disease can often be visible and can result in patients isolating themselves from social interaction

Patients are often older and may have other conditions that impact on their ability to manage their condition

Palliation can be difficult and progression of disease is unpredictable leaving patients feeling like they are living on borrowed time never knowing when the disease might progress.

Physically it can result in unpleasant foul smelling wounds requiring sometimes multiple daily dressings, depending on the location of the disease it can also cause pain

In the younger population patients are often very well except for their skin cancer but the visual nature of their disease often results in them retreating from their normal daily lives

Caring for a relative with this condition can be physically and emotionally draining

Cemiplimab (Libtayo)

Monoclonal antibody that binds to PD-1 (a protein on the surface of T-cells) enabling the immune system to recognise and act against cancer cells

Anticipated marketing authorisation	Cemiplimab as monotherapy is indicated for the treatment of patients with metastatic cutaneous squamous cell carcinoma or locally advanced cutaneous squamous cell carcinoma who are not candidates for surgery	
Administration	IV infusion over 30 minutes through an IV line containing a sterile, in-line or add-on filter (0.2 micron to 5 micron pore size)	
Anticipated licenced dose	350mg every three weeks until initial measurable disease progression, symptomatic disease progression or unacceptable toxicity	
CAA price	**CAA (for CDF only)**	**List**
	£[redacted] per 350mg vial	£[redacted] per 350mg vial

Summary of clinical evidence for cemiplimab (1)

The evidence for cemiplimab was limited to two, single arm trials

The Phase I trial

N=26 mCSCC and laCSCC receiving weight-based dose (3 mg/kg) every 2 weeks for up to 48 weeks; median age 71 years (range 38-96)

Median follow-up	11.1 months
Best Overall Tumour Response, n (%)	
Complete Response	0
Partial Response	13 (50.0)
Stable Disease	[redacted]
Progressive Disease	[redacted]
Objective Response Rate [95% CI]	13 (50.0) [56.4 to 91.0]

Data reported here reflect table 7 of original CS - the updated phase 1 data that informed the company's revised model (supplied at technical engagement) were not reported

Summary of clinical evidence for cemiplimab (2)

The evidence for cemiplimab was limited to two, single arm trials

The Phase II trial

Group 1: mCSCC N=59 receiving weight-based dose (3 mg/kg) every 2 weeks for up to 96 weeks

Group 2: laCSCC N=64 weight-based dose (3 mg/kg) every 2 weeks) for up to 96 weeks

Group 3: mCSCC N=44 receiving fixed dose 350 mg every 3 weeks for up to 54 weeks

	Group 1 (med f/u **** months)	Group 2 (med f/u *** months	Group 3 (med f/u *** months
Best Overall Tumour Response, n (%)			
Complete Response	********	********	*
Partial Response	********	********	********
Stable Disease	********	********	********
Progressive Disease	********	********	********
Objective Response Rate [95% CI]	******** * **********	******** * **********	******** * **********

Data cut-off as of **********, patients who had had the opportunity for at least 3 response assessments only; Mean age of updated study population was NR

Licensed dose/regimen but 54 week stopping rule not included in anticipated MA wording

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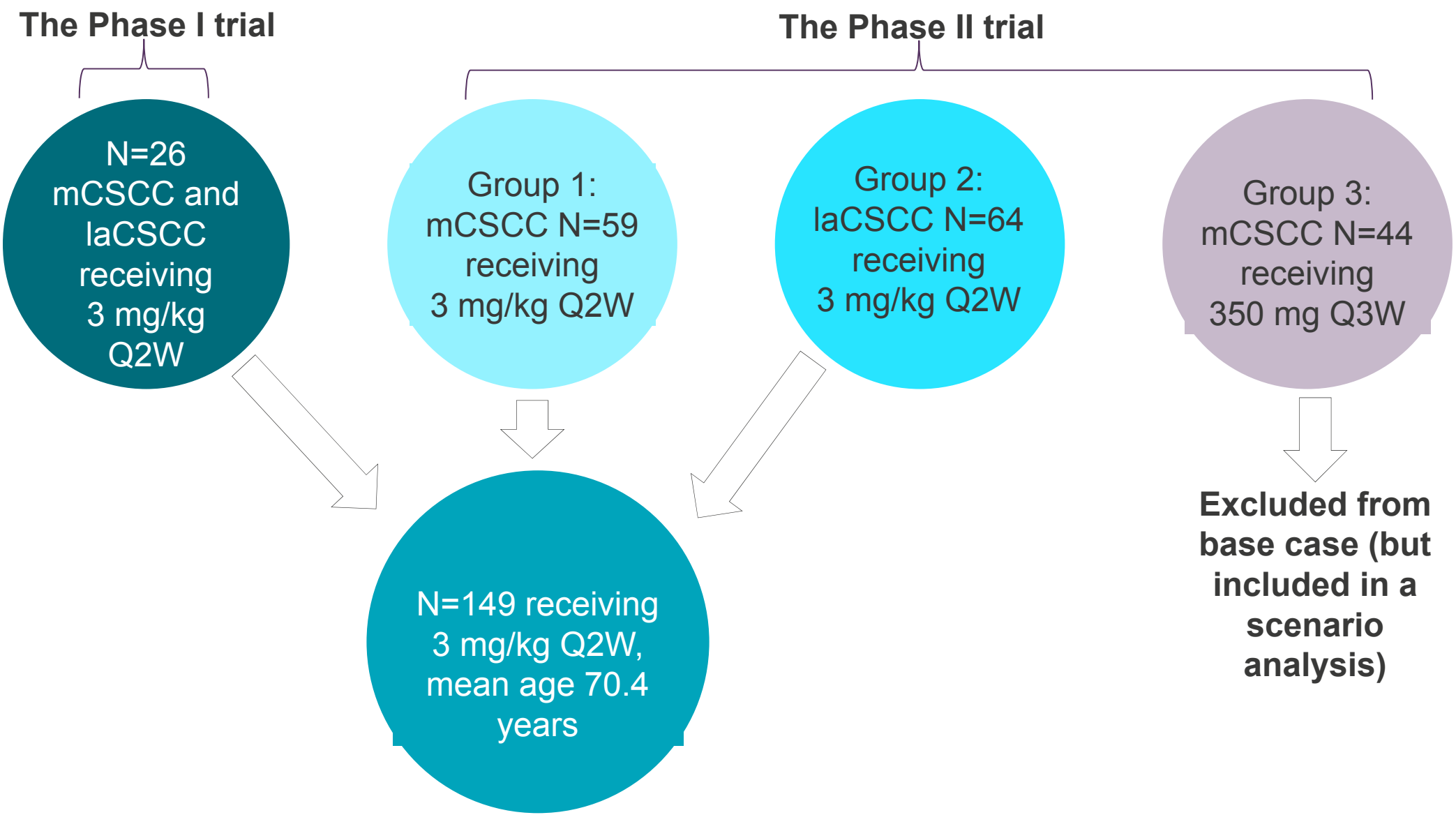
Summary of clinical evidence for cemiplimab (3)



The company's final integrated analysis for base case
(median duration of f/u NR)

Cemiplimab evidence: Limitations

Generalisability of the trial data to UK clinical practice

- Clinical experts believe patients much older than 70 may benefit from cemiplimab treatment > age of patients in base case integrated analysis is 70.4 years
- Licensed dose and regimen is likely to be 350mg every three weeks > patients in base case integrated analysis got weight-based dose every 2 weeks and not currently possible to assess if this dose/regimen is associated with better or worse OS
- Some clinicians believe implementing a treatment stopping rule for patients who have not progressed would be difficult in practice > both cemiplimab trial protocols included stopping rules and the company's updated base case assumes patients will be treated to progression (TTP) or up to maximum of 24 months (~104 weeks)

Lack of a comparator arm

- Relative effectiveness cannot be assessed > base case relies on ITC (more details to follow) and due to unproven efficacy of comparators, no RCTs likely to become available in future

Immaturity of data

- Median OS not reached, at most recent data cut more than [redacted] of the patients that were included from the phase II trial were still alive > survival estimates based on extrapolation of very few observed events; in company base case PFS and OS hazards equal to those for chemotherapy after 3 years, this assumption is not evidence-based

Summary of clinical evidence for the comparators

Used in company base case for both chemotherapy and BSC	
Sub-set of patients who received platinum-based chemotherapy from a non-UK retrospective chart review by Jarkowski et al. 2016 N=18; median f/u 42.8 months [range 11.5 to 62 months]; median age of sub-set of interest was NR but the median age of the whole cohort was 66 years (range: 39-85)	Median OS: 10.9 months (95% CI: 5.3 to 21.3) 3-year OS: 22%
Potential alternative data sources for BSC	
Sub-set of patients immunocompetent patients with unresectable lesions from a non-UK retrospective review by Sun et al. 2019 N=20; median age of sub-set of interest was NR but the median age of the N=36 patients with unresectable lesions was 73 years	Median OS: 5.0 months; (95% CI: 2.6 to 14.4 months)
4 pooled EGFR inhibitor studies N=146; median f/u NR, age range across all studies 32-95 years	Only reported in figure - see next slide
Potential alternative data source for both chemotherapy and BSC	
UK patients in Sanofi's ongoing retrospective chart review N=106; med f/u NR; mean age [redacted] years (SD [redacted])	Not available until [redacted]

Overlaid survival curves for visual inspection

Key	Source	Used in economic analysis?
	Integrated analysis of Phase I/II cemiplimab trials	Base case for cemiplimab
	Plat. chemotherapy patients from Jarkowski 2016	Base case for chemo/BSC
	Alt. source for BSC: Sun et al. 2019	Not used in economic analysis
	Alt. source for BSC: Pooled EFGR studies	Scenario analysis in original CS (not updated at TE)

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Comparator evidence: Limitations

Generalisability of the data to UK clinical practice

- Jarkowski 2016 > non-UK study, all patients received platinum chemotherapy (may be healthier than patients who are currently receiving BSC and would be potentially eligible for treatment with cemiplimab). Median OS was10.9 months
- Sun et al. 2019 > non-UK, only included patients with CSCC on the head and neck. Median OS was 5 months
- Pooled EGFR inhibitor studies > EGFR inhibitor treatments not used in UK

Study design

- All data sources are retrospective and at risk of selection bias

Sample size

- All currently available data sources are limited by small sample size > company base case estimates are based on N=18 patients

Note: the comparator data will be used to determine whether patients have a short life expectancy (less than 24 months) under current treatment

Summary of the company's indirect treatment comparisons using current data

- As the only available evidence was from two single-arm studies, it was necessary to conduct an indirect treatment comparison (ITC)
- Comparator data was taken from a retrospective chart review by Jarkowski 2016 – the same data was used for both chemotherapy and BSC
- The company explored three ITC methods
  - a naïve comparison (where survival extrapolations were fitted directly to the observed data from the available sources)
  - a simulated treatment comparison (STC)
  - a matching-adjusted indirect comparison (MAIC).
- Both STC and MAIC involve adjusting the observed results from the cemiplimab studies to reflect the results that would be expected had the study been conducted in the Jarkowski 2016 study population

Data sources used in the company's final ITC	
Cemiplimab	Chemotherapy/BSC
Integrated analysis of patients who received a weight-based dose of cemiplimab in the two single arm trials (N= 149; med f/u NR)	Sub-set of patients who received platinum-based chemotherapy from a retrospective chart review by Jarkowski et al. (N=18; med f/u 42.8 months [range 11.5 to 62 months])

ITC results

Unadjusted and population adjusted Kaplan–Meier curves for OS

Unadjusted and population adjusted Kaplan–Meier curves for PFS

Key	Observed/ predicted	Source	Used in economic analysis?
	Observed	Integrated analysis of Phase I/II cemiplimab trials	Base case for cemiplimab
	Observed	Naïve comparison (based on plat. chemotherapy patients from Jarkowski 2016)	Base case for chemo/BSC
	Predicted	Simulated treatment comparison	Scenario analysis
	Predicted	Matching-adjusted indirect comparison	Not used in economic analysis

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Key considerations with the current ITC results

	Pros	Cons
Naïve	• Provides the most conservative estimate of relative effectiveness	• Results highly likely to be confounded by population differences between the studies • Results for chemotherapy/BSC based on Jarkowski 2016 patients who may not representative of relevant UK patient group
STC/ MAIC	• Analysis generally well reported and consistent with NICE DSU guidance • Results adjusted for differences in study populations' disease stage and location	• Only 2 out of 12 prognostic factors could be adjusted for due to data limitations • Cemiplimab data are adjusted to reflect Jarkowski 2016 patients who are not representative of relevant UK patient group • Results for chemotherapy/BSC based on Jarkowski 2016 patients who are not representative of relevant UK patient group • Specific limitation of MAIC: Reweighting the cemiplimab patients in the MAIC lowered the expected sample size (ESS) on an already small study

Summary of cost effectiveness evidence (1)

- **Population**
  - As per NICE scope and proposed marketing authorisation
  - Characteristics obtained from the integrated analysis of the Phase I and II studies
  - Mean age=70.4 years; 85% male
- **Intervention**
  - Cemiplimab fixed dose regimen (as per proposed marketing authorisation)
    - Clinical outcomes from Phase I and II studies, where all patients received the weight-based dose.
    - Costed as per fixed dose regimen.
- **Comparators**
  - Chemotherapy
    - Cost and clinical outcomes from Jarkowski et al
    - Relate to cisplatin + 5-fluorouracil chemotherapy regimen
  - Best Supportive Care (BSC)
    - Clinical outcomes using data for chemotherapy (from Jarkowski et al) or EGFR inhibitors as a proxy for BSC
    - Costs relate to packages of routine care, palliative surgery and radiotherapy

Summary of cost effectiveness evidence (2)

- The company decided to update their base case at technical engagement so that latest data from the cemiplimab trials could be included
- At this stage they also updated some assumptions based on the technical team's preliminary scientific judgements that were included in the draft technical report
- The details below reflect the updated model, not the original

Model	Partitioned survival model. 3 health states: pre-progression, post-progression, death. 30 year time horizon; 30.4 day cycles w/ half-cycle correction
Extrapolation	Log normal curves fitted to observed data, treatment benefit limited to 3 years (cemiplimab PFS and OS hazards set equal to chemotherapy hazards 3 years from baseline)
Duration of treatment	Cemiplimab: until progression or up to max 24 months in non-progressed patients. Chemotherapy: 3 three-week cycles
Adverse events	One-off utility decrements and costs for grade 3 and 4 events with ≥5% incidence for any study
Utility data source	EORTC-QLQ C30 values from phase II cemiplimab study mapped to EQ-5D-3L using Longworth algorithm

Survival curves

Progression-free survival extrapolations for cemiplimab: original and updated company base case (KM and selected extrapolations)

Overall survival extrapolations for cemiplimab: original and updated company base case (KM and selected extrapolations)

Summary of cost effectiveness results

Discounted base case results versus chemotherapy with the proposed commercial access agreement price for cemiplimab ([redacted] data)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Chemotherapy	[redacted]	[redacted]	[redacted]	_	_	_	
Cemiplimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	45,693

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Discounted base case results versus best supportive care with the proposed commercial access price for cemiplimab ([redacted] data)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	_	_	_	
Cemiplimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	47,463

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Summary of key scenario analyses

Age of patients at baseline	70.4 years[a]	71.67 years[b]	80 years[c]
ICER vs. chemotherapy (£/QALY gained)	**45,693**	46,506	55,931
ICER vs. BSC (£/QALY gained)	**47,463**	48,324	58,323

Bold text indicates company's base case ICERs. [a]mean age of patients in cemiplimab trials; [b]mean age of UK patients in Sanofi's ongoing retrospective chart review; [c]mid-point in plausible age range for most potential treatment candidates according to clinical experts

Data informing the model	Integrated analysis = phase I + II groups 1 & 2	Integrated analysis = phase I + II groups 1 & 2 with fixed-dose option applied	Integrated analysis = phase I + II groups 1, 2 & 3
ICER vs. chemotherapy (£/QALY gained)	**45,693**	42,779	44,695
ICER vs. BSC (£/QALY gained)	**47,463**	44,463	46,465

Bold text indicates company's base case ICERs

Treatment stopping rule[a]	TTP in all patients		TTP or up to a maximum of 24 months		TTP or up to a maximum of 22 months	
Assumed duration of treatment benefit	3 years	5 years	**3 years**	5 years	3 years	5 years
ICER vs. chemotherapy (£/QALY gained)	62,332	60,764	**45,693**	39,589	43,979	38,214
ICER vs. BSC (£/QALY gained)	64,146	62,215	**47,463**	40,996	45,745	39,618

Bold text indicates company's base case ICERs. [a]3 chemotherapy cycles assumed in all scenarios

Committee decision making: Clinical plausibility of the overall survival estimates and EoL (1)

- The base case and key scenario ICERs are all above the threshold normally considered to be a cost effective use of NHS resources
- The company have argued that the committee should take account of the end of life criteria

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.

Committee decision making: Clinical plausibility of the overall survival estimates and EoL (2)

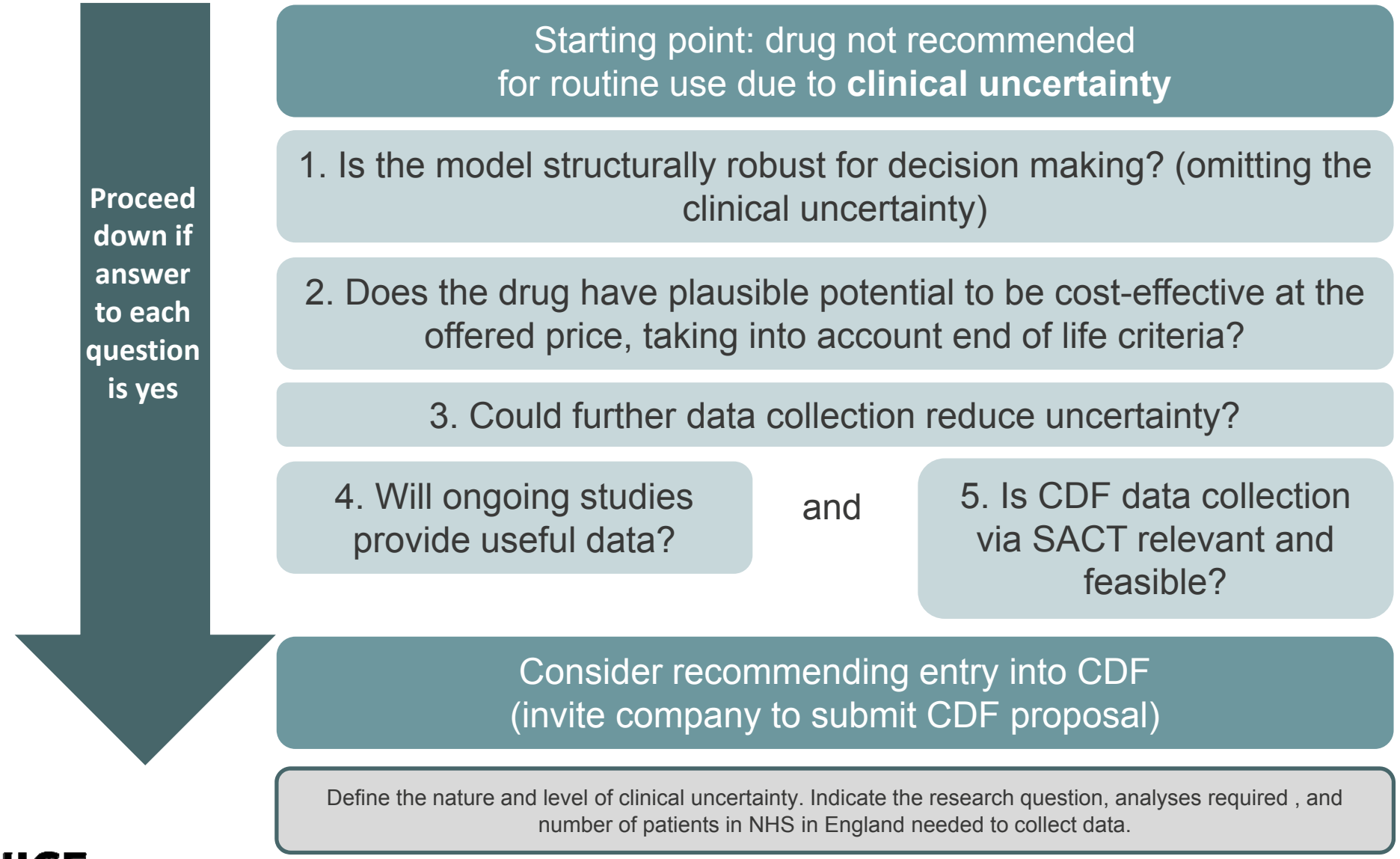
- The ERG described the company's approach to extrapolation as 'well-structured' and the company's choice of base case PFS and OS distributions as 'reasonable'
  - But they noted that other functions had similar goodness of fit and predicted 5-year survival between [redacted] (vs [redacted] in the base-case)
- There is consensus that life expectancy with current treatment is likely the be less than 2 years but the current survival estimates (shown below) do not reflect this.
  - Stakeholders believe the chemotherapy/BSC extrapolations are are optimistic (meaning the cost effectiveness results are likely to be conservative if cemiplimab extrapolation is accurate)
- It is unclear whether the estimates of the extension to life are sufficiently robust because of the limitations with the underlying data and un-adjusted ITC
  - Stakeholders believe the cemiplimab extrapolations are plausible and there is a strong likelihood of >3 month survival benefit

Base case survival estimates (undiscounted)

Technologies	Total life years	Incremental life years gained
Chemotherapy/BSC	[redacted]	-
Cemiplimab	[redacted]	[redacted]

Question: Can the EoL criteria be applied?

Committee decision making: CDF recommendation criteria



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What data is in pipeline and when will it become available?

Cemiplimab

Long term OS and PFS data for all three cohorts of the Phase II trial:

- Group 1: mCSCC on 3mg/kg q2w
- Group 2: laCSCC on 3mg/kg q2w
- Group 3: mCSCC on 350mg q3w

Key dates: ******** data cut (could be fully incorporated into ITCs and the economic model by **********)

Baseline characteristics and efficacy data through SACT for UK patients receiving cemiplimab

Key dates: ******** assuming a 2 year CDF data collection period

Chemotherapy/BSC

Data from an ongoing retrospective chart review by Sanofi

Key dates:

- UK patients' efficacy data will be available in ********* (with data fully incorporated in the economic model in **********)
- Europe and the US patients' efficacy data will be available in ********* (with data fully incorporated in the economic model in **********)

Impact of further data on uncertainty in ITC

Using Sanofi's retrospective chart review instead of the Jarkowski 2016 study would reduce uncertainty in estimates of relative effectiveness to some extent:

- Individual patient data for N=106 UK patients (compared N=18 non-UK patients)

But results will still be limited by the following:

- Any differences between the UK cohort and the population who are likely to receive treatment (ERG note that the study is likely to be subject to selection bias)
- ERG have noted only 5/12 prognostic variables could potentially be controlled for in a future STC or MAIC analysis > still leaves 7 variables unadjusted, unclear how much uncertainty would remain
- Major limitation of any STC or MAIC of single arm studies is assumption that all prognostic and effect modifying variables are accounted for – this assumption is implausible. Moreover, the level of uncertainty arising from the inability to adjust for unidentified prognostic/effect modifying variables is difficult to quantify. Of concern for this analysis because:
  - of limitations in the evidence used to identify the original 12 prognostic variables
  - difference in the study designs (single-arm controlled intervention studies vs. retrospective observational study) increases the likelihood of unknown prognostic variables being an issue

Impact of further data on key areas of uncertainty

Additional data	Generalisability of clinical data	Outcomes of ITC	Extrapolation
Long term OS & PFS data for cemiplimab [redacted]	Some more data on patients who received fixed dose	No impact	More mature data to inform OS and PFS extrapolations
Baseline characteristics & outcomes data through CDF SACT [redacted]	Baseline data could inform model inputs and help committee understand whether Sanofi's chart review is representative of real-life cemiplimab population	No impact	Due to limited length of f/u usefulness for extrapolation is probably limited
Ongoing retrospective chart review by Sanofi [redacted]	Will provide a much larger sample of UK-based patients (no need to rely on Jarkowski 2016 data)	More variables could be adjusted for which would reduce some uncertainty in results (see previous slide)	Unclear – length of f/u NR

Question: Are the criteria for inclusion in the CDF met?

Key issues

1. The clinical evidence for cemiplimab is promising but immature and the quality of the comparator data is very low
2. Because of this, the estimates of relative clinical and cost effectiveness are very uncertain
3. The base case and key scenario ICERs are all outside the range normally considered to be a cost effective use of NHS resources (20-30K) so cemiplimab can only be recommended if the end of life criteria are considered to apply
4. If the current estimates of extension to life/assumptions used in the modelling are too uncertain, and the CDF criteria are met, then a CDF recommendation could be considered