Slides for projector (AiC)

NICE National Institute for Health and Care Excellence

Cemiplimab for treating cutaneous squamous cell carcinoma (CDF review of TA592)

Lead team presentation

Lead team: David Maudgil (clinical/lay), Hugo Pedder (cost), Jane Adam (chair)
ERG: Southampton Health Technology Assessments Centre (SHTAC)
Technical team: Lizzie Walker, Joanna Richardson, Janet Robertson
Company: Sanofi
Tuesday 12 April 2022

Key clinical issues

- What proportion of people with locally advanced or metastatic CSCC would receive platinum-based chemotherapy versus best supportive care (BSC) in the UK?
- How does the stopping rule compare to use of cemiplimab in the EMPOWER-CSCC 1 trial?
- Is the clinical trial evidence more appropriate than the real world data from SACT?
- Is the clinical trial evidence generalisable to UK clinical practice?
- Does the committee accept the uncertainty surrounding the clinical effectiveness of BSC and chemotherapy?
- Does the committee accept the uncertainty surrounding the indirect treatment comparison (ITC) approaches and results, given the lack of reliable data on comparators?

Cemiplimab (Libtayo, Sanofi)

Marketing authorisation Conditional marketing authorisation – July 2019 Full marketing authorisation – [redacted]	Monotherapy for people with metastatic or locally advanced CSCC who are not candidates for surgery
Mechanism of action	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
Administration and dose	IV infusion over 30 minutes 350 mg every 3 weeks until disease progression or unacceptable toxicity
List price	£4,650 per 350 mg vial Confidential patient access scheme approved (simple discount)

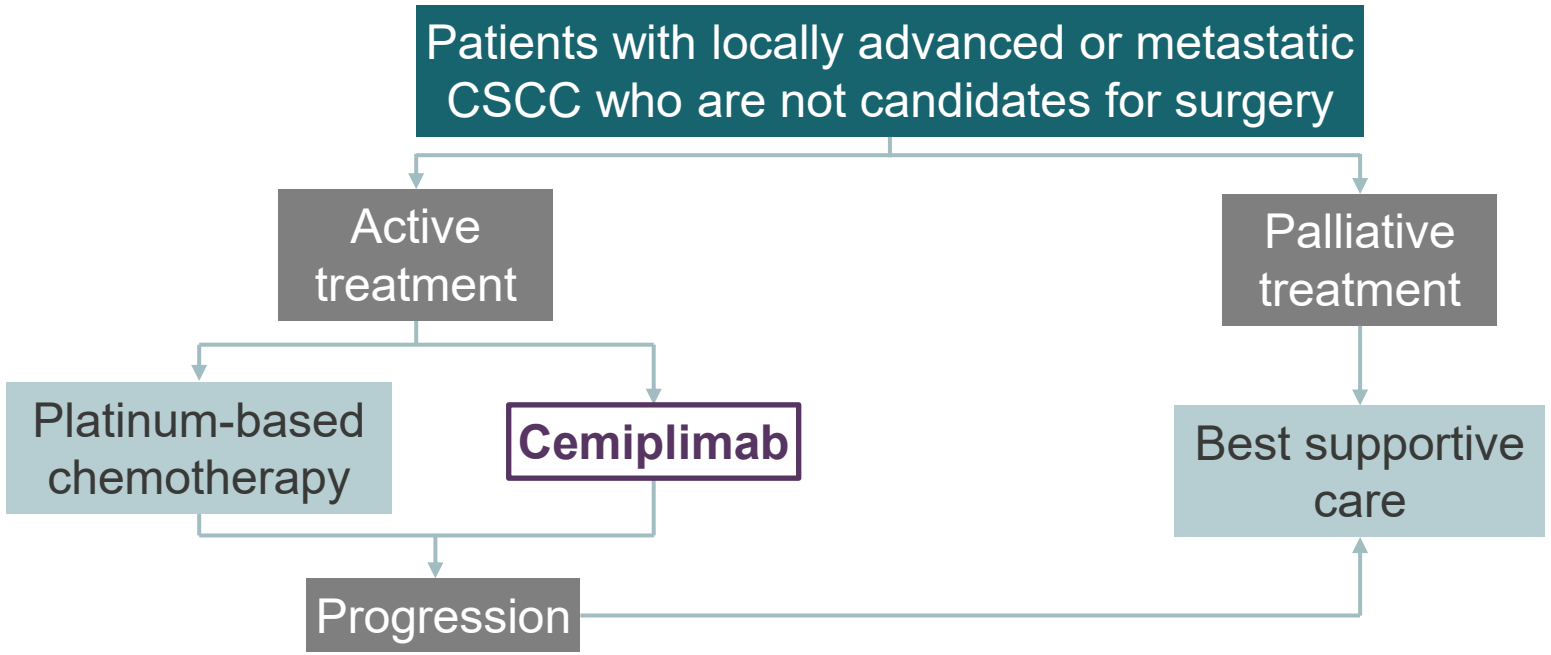
NICE CSCC, cutaneous squamous cell carcinoma; IV, intravenous

Disease background

- CSCC is a distinct disease, separate to melanoma and other SCCs
- **Major risk factors:** exposure to UV radiation, advanced age and immunosuppression
- CSCC is cured in most 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 a reduced quality of life, affecting physical and psychological health and social relationships

NICE CSCC, cutaneous squamous cell carcinoma; SCC, squamous cell carcinoma

Treatment pathway



Clinical expert: "Very few patients would be eligible for chemotherapy and even when they were, responses were rare and very short lived. In my own practice I might use chemotherapy on less than one patient per year. This compares with cemiplimab which I will start on approximately 20 new patients annually."

Professional organisation response to technical engagement: "Many more patients are likely to benefit from immunotherapy than chemotherapy as the use of platinum containing chemotherapy is limited to only the fittest patients with adequate renal function."

What proportion of people with locally advanced or metastatic CSCC would have platinum-based chemotherapy versus BSC in the UK?

BSC, best supportive care; CSCC, cutaneous squamous cell carcinoma

Patient and professional perspectives

Comments received from: British Association of Dermatologists and a clinical expert during this appraisal, and a carer of a patient with advanced CSCC during TA592 (no new patient perspectives were received for this appraisal)

Impact of CSCC

CSCC is often very visible, with unpleasant foul smelling wounds, which can result in people with CSCC isolating themselves from social interaction

Palliation can be difficult and progression the disease is unpredictable, leaving people feeling like they are living on borrowed time

Caring for a relative with CSCC can be physically and emotionally draining

People would like an effective targeted treatment option:

- Any tumour reduction that alleviates pain
- Prevention of tumour progression

Current treatment

Before cemiplimab, no treatment was available for most patients and they were referred back to general practice or hospices for terminal care

Cemiplimab

Cemiplimab is a well-tolerated, effective treatment that improves survival and quality of life for people with advanced CSCC

Cemiplimab has changed the treatment paradigm for people with advanced CSCC

Cemiplimab provides effective tumour control for a significant proportion of patients with minimal toxicity – some patients remain alive and well more than 2 years after starting treatment

CSCC, cutaneous squamous cell carcinoma

CDF recommendation (TA592 published May 2019)

Cemiplimab recommended in the CDF for adults with locally advanced or metastatic CSCC when curative surgery or radiotherapy is not appropriate
Treatment should be continued until disease progression or up to 24 months (whichever is sooner)

The key sources of uncertainty are:

- Baseline characteristics of patients in the model and generalisability to UK clinical practice
- Long-term treatment benefit of cemiplimab, particularly size of continued benefit after stopping rule
- Lack of reliable comparative evidence that is generalisable to UK clinical practice
- Whether end-of-life criteria are met

Further data collection requirements:

Data source	Use
Further follow-up from EMPOWER-CSCC 1	Provide longer-term survival data and reduce uncertainty about the treatment effect duration
Ongoing retrospective UK chart review	Provide an additional comparative data source and evidence on whether cemiplimab meets end-of-life criteria on short life expectancy
SACT data	Support the generalisability of the trials, provide data on OS and treatment duration and provide baseline characteristics to inform the model

How does the stopping rule compare to use of cemiplimab in the EMPOWER-CSCC 1 trial?

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CDF, Cancer Drugs Fund; CSCC, cutaneous squamous cell carcinoma; OS, overall survival; SACT, systemic anti-cancer therapy

CDF review (TA592) – terms of engagement

Subject	Committee preferred assumption in TA592	ERG comments on company's CDF review submission
Population	Adults with metastatic or locally advanced CSCC, not eligible for curative local therapy	✓
Comparators	Chemotherapy or best supportive care	✓
Generalisability of trial	Use SACT data to demonstrate generalisability of trial evidence	? SACT data indicated differences between trial data and NHS practice
Survival outcomes	Use updated EMPOWER-CSCC 1 data and fully explore most appropriate survival extrapolations. Validate using SACT data	? Survival extrapolations with updated trial data were explored, but not informed by SACT data
Comparator data	Use UK chart review and any additional data to inform comparator arms	? UK chart review data was used, but uncertainties remain due to methodological limitations
Relative effectiveness	Fully explore most appropriate treatment comparison method using any newly available data	? Results of ITC remain uncertain because of uncertainty in comparator data
Treatment effect duration	Use updated EMPOWER-CSCC 1 data and fully explore the impact of a 24-month stopping rule on long-term outcomes	✓
End of life	Demonstrate whether end-of-life criteria are met	? Uncertainty whether end-of-life criteria are met vs chemotherapy

Company trials

Two single-arm studies, study 1423 and EMPOWER-CSCC 1, were pooled for the company's base case analysis

	Study 1423 (N=26)	EMPOWER-CSCC 1 (N=193)
Design	Phase I, non-comparative, multicentre study	Phase II, non-comparative, multicentre study
Population	Adults with mCSCC or laCSCC with ECOG PS 0-1	Adults with mCSCC or laCSCC with ECOG PS 0-1
Intervention	Cemiplimab 3 mg/kg IV every 2 weeks for up to 48 weeks	• Cemiplimab 3 mg/kg IV every 2 weeks for up to 96 weeks in one group with laCSCC and one group with mCSCC • Flat dose cemiplimab 350 mg IV every 3 weeks for up to 54 weeks (people with mCSCC **only**)
Outcomes collected	ORR, DoR, PFS (new data 2019), OS (new data 2019), safety	OS (new data July 2021), PFS (new data July 2021), treatment duration, safety (new data July 2021), HRQoL (EORTC QLQ-C30; new data October 2020)

CSCC, cutaneous squamous cell carcinoma; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life questionnaire; HRQoL, health-related quality of life; laCSCC, locally advanced CSCC; mCSCC, metastatic CSCC; IRC, independent review group; IV, intravenous; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PS, performance status

Comparison of baseline patient characteristics

People in the SACT dataset were slightly older and had higher ECOG scores than in the company trials, and a lower proportion had metastatic disease versus locally advanced disease

		Pooled study 1423/ EMPOWER-CSCC 1 (N=219)	SACT dataset (N=352)
Disease severity	laCSCC	[redacted]	172 (49)
	mCSCC	[redacted]	180 (51)
Age, median (range)		[redacted]	77
Gender, n (%)	Male	[redacted]	262 (74)
ECOG PS >1, n (%)		[redacted]	**ECOG = 2:** 14 (4) **Missing:** 51 (15)

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CSCC, cutaneous squamous cell carcinoma; ECOG, Eastern Cooperative Oncology Group; laCSCC, locally advanced CSCC; mCSCC, metastatic CSCC; PS, performance status; SACT, systemic anti-cancer therapy

Results from company trials

After a median follow-up of [redacted], overall survival was [redacted] and median survival [redacted]

Summary of results from study 1423 (2019 DCO) and EMPOWER CSCC-1 (July 2021 DCO)

	Study 1423 (N=26)	EMPOWER-CSCC 1 (N=193)
Objective response, n (%)	[redacted]	[redacted]
Complete response, n (%)	[redacted]	[redacted]
Stable disease, n (%)	[redacted]	[redacted]

Summary of survival data from study 1423 (2019 DCO) and EMPOWER CSCC-1 (July 2021 DCO)

	Study 1423 (N=26)		EMPOWER-CSCC 1 (N=193)		
	PFS	OS	ToT	PFS	OS
Study follow-up, median (95% CI)	[redacted]			[redacted]	
Median, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NICE CI, confidence interval; DCO, data cut-off; NE, not estimated; NR, not reported; OS, overall survival; PFS, progression-free survival; ToT, time on treatment

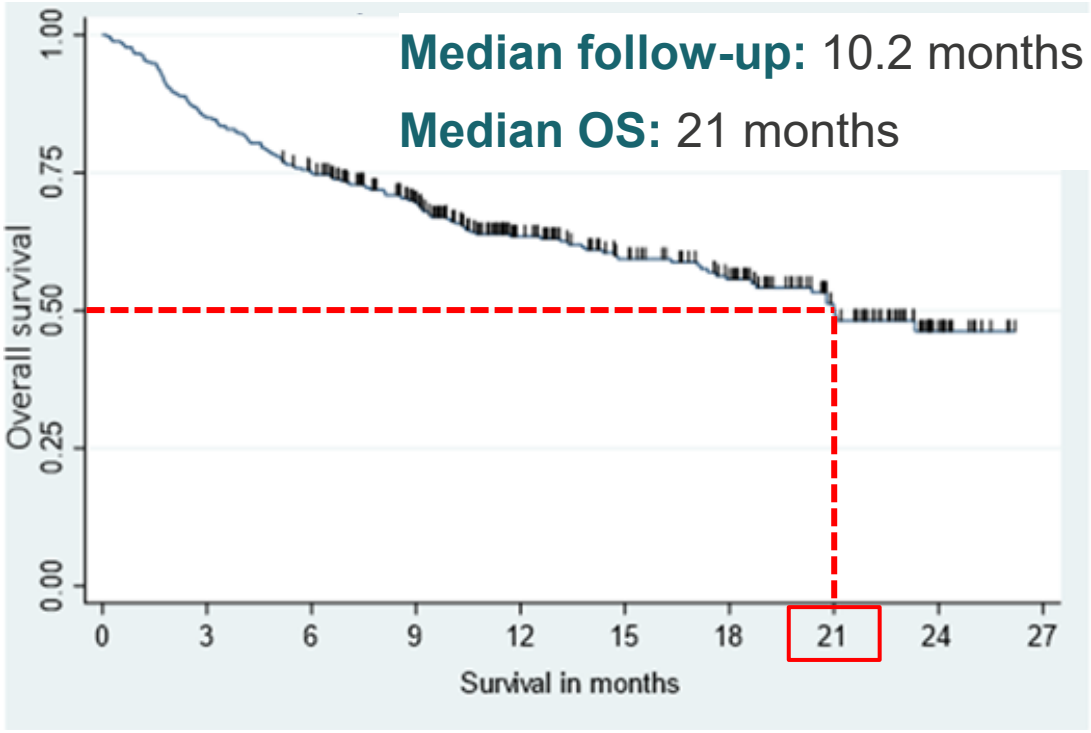
Comparison of overall survival - trial vs SACT

OS in the SACT population is substantially lower than in the company trials

Kaplan-Meier curve from EMPOWER-CSCC 1 and fitted OS curve for cemiplimab from the company model

[redacted]

Kaplan-Meier curve for cemiplimab from the SACT database



Please note that the scales differ between the two Kaplan-Meier plots

NICE NR, not reached; OS, overall survival; SACT, systemic anti-cancer therapy

Use of company trial data vs SACT data

ERG:

- SACT is reflective of current clinical practice and indicates that an older population can be treated with cemiplimab, but with lower overall survival
- Company use the SACT data to validate outcomes of the cemiplimab trials but did not digitise the SACT OS Kaplan-Meier data for comparison against results from the company's trials and modelled extrapolations

Company:

- SACT data set is immature compared with EMPOWER-CSCC 1 (SACT median follow-up of 10.2 months vs EMPOWER-CSCC 1 median follow-up of [redacted] months and maximum follow-up of [redacted] months), therefore use of the longer-term trial data is preferred
- Data from SACT is in some instances incomplete and contains a number of uncertainties compared to EMPOWER-CSCC 1 (unknown impact of COVID-19 pandemic, limited information on patient characteristics and missing data)

Is the clinical trial evidence more appropriate than the real world data from SACT? Is trial data more appropriate due to the longer follow-up?

ECOG, Eastern Cooperative Oncology Group; OS, overall survival; PS, performance status; SACT, systemic anti-cancer therapy

Generalisability of clinical trial evidence to UK clinical practice

ERG:

- SACT dataset suggests the clinical trials lack generalisability to UK clinical practice. However, SACT dataset has limitations due to few population characteristics collected and impact of COVID-19 pandemic

Company:

- Data shows that older and sicker patients who historically would have received BSC, would now be treated with cemiplimab in clinical practice
- Due to limitations of SACT data (unknown impact of COVID-19 pandemic, limited information on patient characteristics and missing data), difficult to definitively conclude on generalisability of trials to UK practice using the SACT dataset

Clinical expert:

- SACT data likely to be representative of UK practice, however, SACT data may not be comparable with trial data because trial patients generally younger and fitter, SACT data was collected during COVID-19 pandemic and SACT data includes patients treated in the learning curve of immunotherapy

Is the clinical trial evidence generalisable to UK clinical practice?

Clinical evidence for the comparators

	UK Retrospective Chart review study (new data) ([redacted])	Jarkowski 2016 (used in NICE TA592) (n=18 [sub-set of interest])	Sun 2019 (new publication identified during TA592) (n=20 [sub-set of interest])
Used in CS	Chemotherapy (OS)	Chemotherapy (OS and PFS)	Best supportive care (OS)
Study design and eligibility	Retrospective chart review in people with laCSCC and mCSCC in UK	Retrospective chart review in people with mCSCC in the US	Retrospective chart review in people with lacSCC or mCSCC in the US
Results	**Median OS: [redacted] months** Median PFS: not reported	**Median OS: 15.1 months** Median PFS: 9.8 months	Median OS: 5.0 months (95% CI 2.6 to 14.4 months) Median PFS: not reported

NICE CI, confidence interval; CSCC, cutaneous squamous cell carcinoma; laCSCC, locally advanced CSCC; mCSCC, metastatic CSCC; OS, overall survival; PFS, progression-free survival

Uncertainty in the clinical effectiveness of BSC and chemotherapy

ERG:

- There are major limitations with the three comparator studies. None of the included studies provide a reliable estimate of the effects of chemotherapy or BSC in the UK
  - The UK chart review has poor face-validity – the population characteristics and results are highly uncertain
  - The Jarkowski and Sun studies are both very small (N≤20) and were conducted in the US, therefore are of questionable reliability and relevance to UK clinical practice
- The uncertainties in the comparators have not been reduced compared to TA592

Company:

- Sanofi have invested in developing the comparative evidence base for CSCC. Whilst there is remaining uncertainty, further analyses or data collection will not resolve this

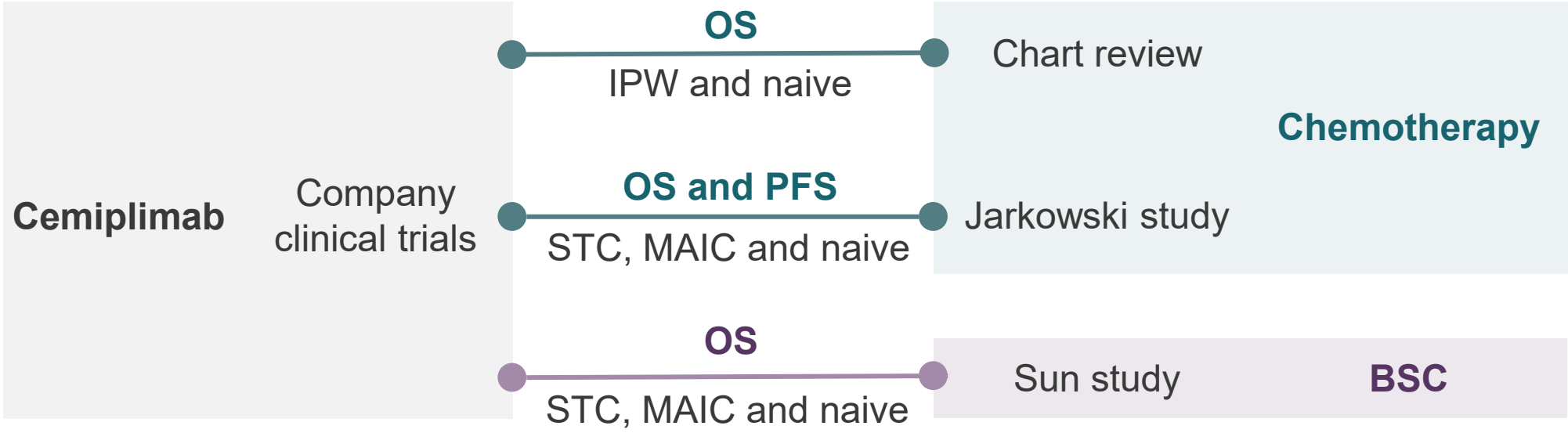
Clinical expert:

- There is an almost complete lack of data on survival in patients with advanced CSCC, partly due to the lack of treatment options meaning that patients were not followed up in the hospital setting

Does the committee accept the uncertainty surrounding the clinical effectiveness of BSC and chemotherapy?

Indirect treatment comparisons

- No studies directly comparing cemiplimab against chemotherapy or best supportive care are currently available, therefore the company conducted an indirect treatment comparison (ITC)
- Three methods of ITC were used: inverse probability of treatment weighting (IPW), simulated treatment comparison (STC) and matched-adjusted indirect comparison (MAIC)
- Three comparisons were conducted:



NICE BSC, best supportive care; ITC, indirect treatment comparison; IPW, inverse probability of treatment weighting; MAIC, matched-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; STC, simulated treatment comparison

Uncertainty in the clinical effectiveness of cemiplimab compared with BSC and chemotherapy

ERG:

The results of the ITC analyses are highly uncertain due to:

- High uncertainty in the population characteristics and results of the comparator studies
- In the IPW approach, the models could not balance all measured prognostic covariates
- In the STC and MAIC approaches, there is not enough data to allow sufficient prognostic covariates to be modelled

Company:

- Sanofi have followed best practice guidance for conducting ITCs from NICE DSU TSDs
- Remaining uncertainty is from heterogeneity in evidence base and limited number of covariates reported by included studies
- Alternative approaches/analyses are unlikely to have a significant impact on cost-effectiveness results

Does the committee accept the uncertainty surrounding the ITC approaches and results, given the lack of reliable data on comparators?

NICE

BSC, best supportive care; DSU TSD, Decision Support Unit Technical Support Document; ITC, indirect treatment comparison; IPW, inverse probability of treatment weighting; MAIC, matched-adjusted indirect comparison; OS, overall survival; STC, simulated treatment comparison

Key clinical issues

- What proportion of people with locally advanced or metastatic CSCC would receive platinum-based chemotherapy versus best supportive care (BSC) in the UK?
- How does the stopping rule compare to use of cemiplimab in the EMPOWER-CSCC 1 trial?
- Is the clinical trial evidence more appropriate than the real world data from SACT?
- Is the clinical trial evidence generalisable to UK clinical practice?
- Does the committee accept the uncertainty surrounding the clinical effectiveness of BSC and chemotherapy?
- Does the committee accept the uncertainty surrounding the indirect treatment comparison (ITC) approaches and results, given the lack of reliable data on comparators?

Cost-effectiveness evidence

Key cost issues

- **Does the committee accept the uncertainty surrounding the extrapolations of treatment effectiveness for cemiplimab, BSC and chemotherapy in the model?**
  - SACT dataset suggests that the OS and PFS extrapolations based on trial data are likely to be more favourable than in UK clinical practice
  - Results of the ITCs are all highly uncertain, therefore there is uncertainty over the comparability of the extrapolations for cemiplimab vs comparators
  - Different sources are used to model OS and PFS for chemotherapy, and for BSC all patients are assumed to start in 'post-progression' health state
- **Does metastatic or locally advanced CSCC meet the short life criterion?**
  - It is uncertain whether patients receiving chemotherapy have a life expectancy of less than 24 months

BSC, best supportive care; CSCC, cutaneous squamous cell carcinoma; ERG, evidence review group; ITC, indirect treatment comparison; OS, overall survival; PFS, progression-free survival; SACT, systemic anti-cancer therapy

Base case assumptions

Key issue	Company's base case post-technical engagement		ERG comments
Model	3-state partitioned survival model, monthly cycle, lifetime horizon		No comments
Population baseline characteristics	Mean age (77 years) and gender (74% male) from SACT dataset (updated post-technical engagement)		ERG prefer use of baseline characteristics from SACT dataset
Survival extrapolations			
	OS	PFS	High degree of uncertainty due to limitations in data for comparators. ERG use the same survival extrapolations as the company in base case and explored a range of alternative extrapolations in scenario analyses.
Cemiplimab	Trial data updated to July 2021 (no change to log-normal survival function)	Trial data updated to July 2021, fractional polynomial (p1=0, p2=-1) survival function	
Chemotherapy	UK Chart Review, ATT model 1 trimmed, log-logistic survival function	No change to data source (Jarkowski et al. 2016) or survival function (Weibull).	
BSC	Sun et al. 2019, STC analysis with log-logistic survival function	Patients start in post-progression state	

Base case assumptions

Key issue	Company's base case post-technical engagement	ERG comments
Treatment waning	Duration of cemiplimab relative effects extended to 60 months (no change to 2-year stopping rule)	Consistent with TA592, with a longer assumed advantage for cemiplimab
Adverse event rates	Cemiplimab rates updated to July 2021 trial data, exclusion of adverse events with <5% incidence	Changes have minimal impacts on cost-effectiveness results
Utilities	Updated EORTC QLQ-C30 from company trials with October 2020 data cut (mapped to EQ-5D-3L using Longworth et al. mapping algorithm), correction to cap for age-related utility decrement for PFS health state, and inclusion of multiplicative option	Small changes in utilities, the ERG agree with the correction
Resource use and costs	Updated cemiplimab PAS price discount and updated unit costs	No comments

NICE

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life questionnaire; EQ-5D-3L, EuroQol Five Dimensions, Three Levels ERG, evidence review group; PAS, patient access scheme; PFS, progression-free survival

Uncertainty in extrapolations of treatment effectiveness for cemiplimab, BSC and chemotherapy in model

ERG:

- Company's approach to selecting distributions for the survival extrapolations appears reasonable
- SACT dataset suggests that the OS and PFS extrapolations based on trial data are likely to be more favourable than in UK clinical practice
- Results of the ITCs are all highly uncertain, therefore there is uncertainty over the comparability of the extrapolations for cemiplimab vs comparators

Company:

- Sanofi have followed guidance for conducting survival extrapolations from NICE DSU TSDs
- Alternative parametric approaches do not significantly impact the ICERs
- Clinical experts have suggested the results are an underestimation of the expected benefits of cemiplimab

Does the committee accept the uncertainty surrounding the extrapolations of treatment effectiveness for cemiplimab, BSC and chemotherapy in the model?

BSC, best supportive care; DSU TSD, Decision Support Unit Technical Support Document; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; OS, overall survival; PFS, progression-free survival; SACT, systemic anti-cancer therapy

End-of-life criteria (1/3)

TA592
"The evidence on life expectancy with current treatments and how long life might be prolonged with cemiplimab is very uncertain. Because of this it is not known whether the end-of-life criteria apply"
"However, if more mature data become available from an ongoing trial of cemiplimab, and more data on life expectancy with current treatments are obtained, this could confirm the expectation that end-of-life criteria apply"

End-of-life criteria

- Both criteria must be met:
  1. **Treatment is indicated for patients with a short life expectancy, normally less than 24 months**
  2. Sufficient evidence to indicate that treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment
- In addition, committee should be satisfied that:
  - estimates are robust
  - assumptions used in the reference case economic modelling are plausible, objective and robust

End-of-life criteria (2/3)

ERG:

- The company's economic modelling confirms that cemiplimab extends life for more than 3 months compared with chemotherapy or BSC
- However, in the base case economic model, the mean OS for patients receiving chemotherapy is greater than 24 months. Mean OS for patients receiving BSC is less than 24 months
- This suggests that end-of-life criteria is only met for patients receiving BSC, and not chemotherapy

Life expectancy without cemiplimab

Life expectancy	Chemotherapy	BSC
Literature sources	Median OS: [redacted] months (chart review) Median OS: 15.1 months (Jarkowski et al. 2016)	Median OS: 5.0 months (Sun et al. 2019)
Economic model	**Mean OS: 2.65 life years (31.8 months)** (company/ERG base case, using chart review data)	Mean OS: 1.42 life years (17.04 months) (company/ERG base case, using Sun data)

NICE BSC, best supportive care; ERG, evidence review group; OS, overall survival

End-of-life criteria (3/3)

Company:

- All available data suggest that, without cemiplimab, survival is less than 24 months
- Modelled mean survival based on the chart review is above 24 months for chemotherapy, but this is considered an overestimate by clinicians and is heavily influenced by the tail of the curve
- Only a small proportion of patients who receive cemiplimab would be eligible for chemotherapy
- Clinical experts would not expect any patients receiving chemotherapy to be alive after 2 to 3 years
- Conducting a restricted mean survival analysis, where survival is restricted to 3 years in line with clinical opinion, results in a mean survival of less than 24 months

ERG technical report:

- The validity of the restricted mean survival approach is uncertain and it is unclear whether and how this modification would impact on the cost-effectiveness results

Clinical expert:

- No data available in the UK, but clinical experience is that survival is less than 12 months

Professional organisation response to technical engagement:

- Median survival of 15 months for chemotherapy is longer than expected

Does metastatic or locally advanced CSCC meet the short life criterion?

Company base case and scenario analyses

The company accepted the ERG's preferred analysis post-technical engagement

Deterministic results (PAS price)

Technologies	Incremental		ICER (£/QALY)
	QALYs	Costs (£)	
Cemiplimab vs BSC	[redacted]	[redacted]	30,952
Cemiplimab vs chemotherapy	[redacted]	[redacted]	37,775

Company scenario analyses

Scenario	ICER vs BSC	ICER vs chemo
Base case	**30,952**	**37,775**
Survival for comparator arms from Jarkowski 2016	42,179	38,930
Use of ATC propensity score model 1	NA	41,021
Full ATT propensity score model	NA	38,531
No waning of treatment benefit (continuation of hazard trend)	26,738	29,276
Treatment waning applied between 60 and 96 months	27,475	33,942

NICE

ATC, average treatment effect of the comparator; ATT, average treatment effect of the treated; BSC, best supportive care; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year

ERG scenario analyses

The ERG conducted a number of additional scenario analyses:

- **Versus chemotherapy:** ICERs ranged between **£33,195** (Scenario: PFS for chemotherapy extrapolated using Gompertz) and **£43,233** (Scenario: Treatment waning at 42 months)
- **Versus BSC:** ICERs ranged between **£28,859** (Scenario: without applying population adjusted indirect comparison for efficacy) and **£32,646** (Scenario: Patient demographic with mean age of 81 years and 80% male, based on the population in an Italian cemiplimab cohort reported by Strippoli et al.)

ERG:
These analyses do not capture the underlying uncertainties related to generalisability of the trial data and weaknesses in the evidence base for the indirect comparisons

Key cost issues

- **Does the committee accept the uncertainty surrounding the extrapolations of treatment effectiveness for cemiplimab, BSC and chemotherapy in the model?**
  - SACT dataset suggests that the OS and PFS extrapolations based on trial data are likely to be more favourable than in UK clinical practice
  - Results of the ITCs are all highly uncertain, therefore there is uncertainty over the comparability of the extrapolations for cemiplimab vs comparators
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