Nivolumab in combination with chemotherapy for previously untreated unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥1% [ID2712]

Technology appraisal committee A [13th September 2022]

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Company: Bristol Myers Squibb

NICE National Institute for Health and Care Excellence

Background and decision problem

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Key decision problem and clinical issues

- Is pembrolizumab with chemotherapy now considered standard of care in clinical practice?
- If pembrolizumab and nivolumab were both available, would the clinician's choice of drug be made first, then the relevant PD-L1 test done, or both tests done in a search for which product (or whether both) might be applicable?
- The comparison of nivolumab with pembrolizumab depends on an indirect comparison. Are the populations in the trials used to compare nivolumab and pembrolizumab in the ITC suitably comparable to determine superiority of one treatment over another? OR
- Should each be compared separately with chemotherapy because of differences in definition of the threshold value for PD-L1 expression?

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Abbreviations: ITC, indirect treatment comparison; PD-L1, programmed death-ligand 1

Disease overview – oesophageal cancer

- Oesophageal cancer can occur at any point in the oesophagus (gullet)
- Squamous cell carcinoma mostly occurs in the upper oesophagus and accounts for ~1/3 of UK cases
- Adenocarcinoma mostly occurs in the lower oesophagus and accounts for ~2/3 of UK cases
- The most common symptoms are difficulty swallowing, food regurgitation, nausea or vomiting, unexplained weight loss and persistent indigestion or cough[1]
- 7,680 new cases of oesophageal cancer diagnosed in England, between 2016-2018
- Around 40% of oesophageal cancers develop in people aged 75 and over
- Incidence is higher in men
- On average 70-80% are diagnosed at stage 3 (locally advanced) or 4 (metastatic)[2]
- Advanced OSCC is associated with high mortality, the median overall survival is less than a year[3]

 Abbreviations: OSCC, oesophageal squamous cell carcinoma

Nivolumab

Table 1: Nivolumab (OPDIVO) overview

Aspect	Description
Mechanism of action	Anti-programmed cell death 1 antibody; blocks interaction with PD-L1 and PD-L2 ligands and reactivates T-cell anti-tumour activity
Marketing authorisation	Indicated for first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with **tumour cell PD-L1 expression ≥1%**
Administration & dose	Nivolumab: IV, 240 mg, on day 1 every 2 weeks for up to 24 months (stopping rule) Plus platinum and fluoropyrimidine based chemotherapy: Fluorouracil IV, 800 mg/m^2 per day on days 1 to 5, and cisplatin IV, 80 mg/m^2 on Day 1, of a 4-week cycle
List price	Nivolumab is £2,633 per 240mg vial, the cost of a single administration is £2,633. Confidential PAS discount also in place

NICE Abbreviations: IV, intravenous; mg, milligram; PAS, patient access scheme; PD-L1, programmed death-ligand 1; TC, tumour cells

Recent NICE appraisals in oesophageal cancer

Pembrolizumab recommended in PD-L1 CPS ≥10 expressing tumours
Current appraisal: nivolumab earlier in the pathway as per pembrolizumab but with a different definition of eligibility

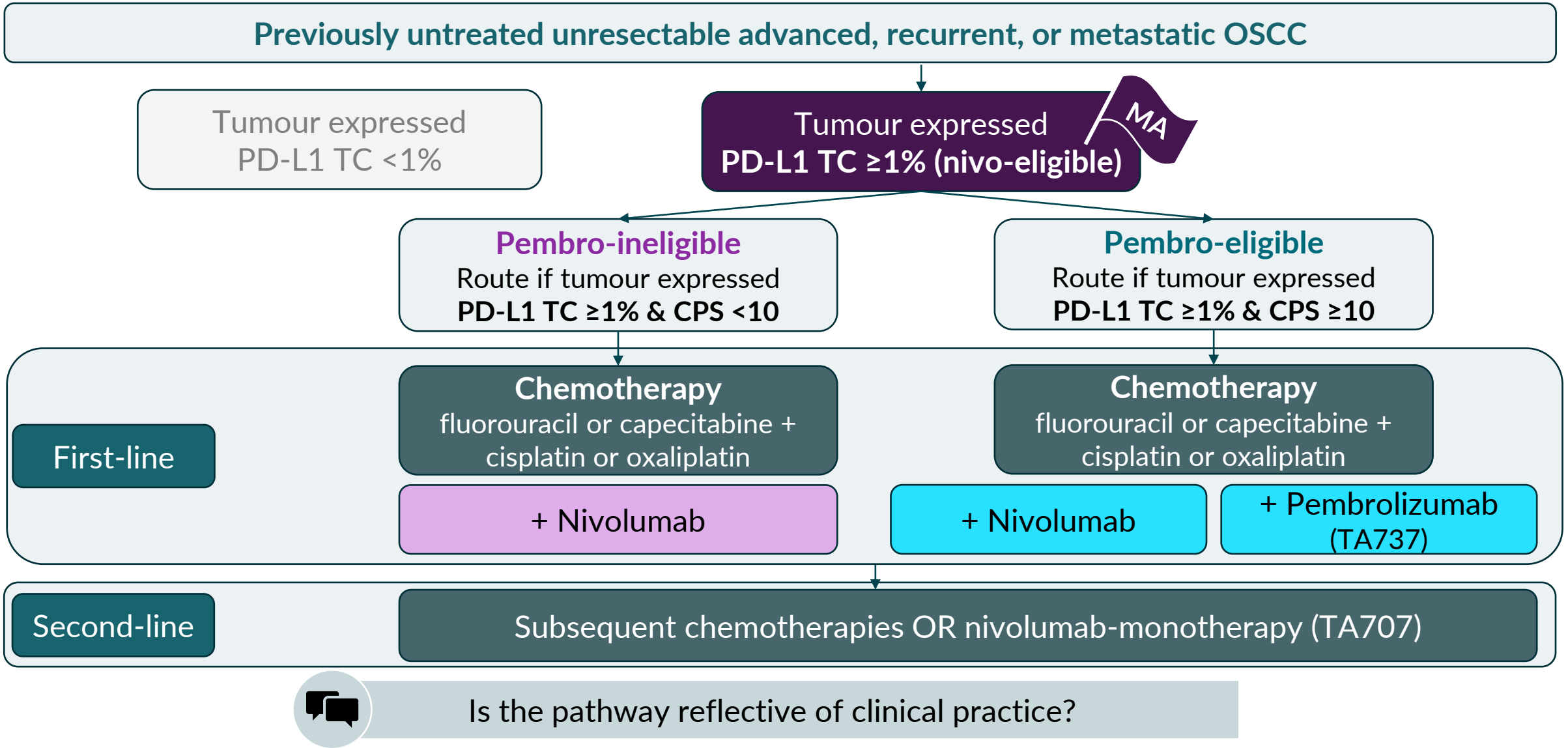
Table 2: Recent NICE appraisals in oesophageal cancer

Technology appraisal	Drug	Recommendation
NICE TA737 (November 2021)	Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy	Untreated locally advanced unresectable or metastatic carcinoma of the oesophagus or HER2-negative gastro-oesophageal junction adenocarcinoma in adults **whose tumours express PD-L1 CPS ≥10**
NICE TA707 (May 2021)	Nivolumab	Unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma in adults **after fluoropyrimidine and platinum-based therapy**

Abbreviations: CPS, combined positive score; HER2, human epidermal growth factor receptor 2; PD-L1, programmed death-ligand 1

Treatment pathway

Figure 1: Treatment pathway



Abbreviations: CPS, combined positive score; MA, market authorisation; PD-L1, programmed death-ligand 1; TC, tumour cell

Two different tools are used to measure PD-L1 expression

Background: PD-L1 status is measured differently in the nivo and pembro MA, requiring further examination

PD-L1 measurement	Tumour cell (TC)	Combined positive score (CPS)
Expressed as	Percentage (%)	Whole number
Threshold in licence for PD-L1 positivity	≥1%	≥10
Therapy/trial/assay (manufacturer)	Nivolumab CheckMate-648/ IHC 28-8 pharmDx (Dako)	Pembrolizumab KEYNOTE-590/ 22C3 pharmDX (Dako)

Figure 2: % of CheckMate-648 ITT (n=645) that meet the nivo MA (TC ≥1%)

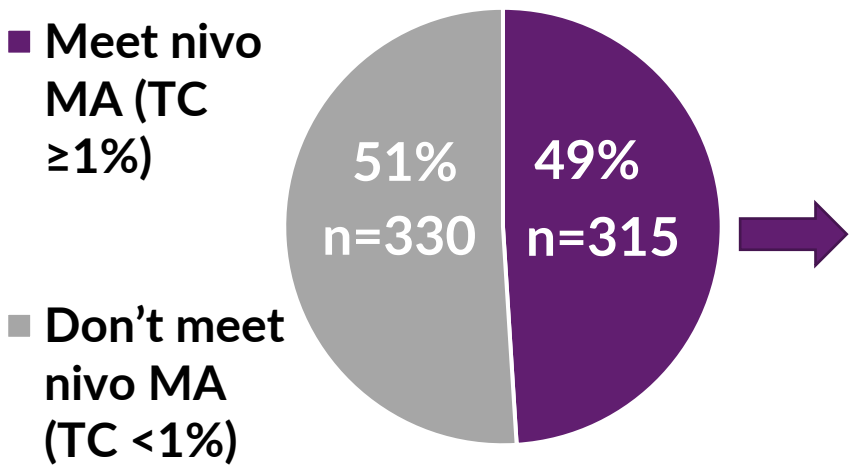
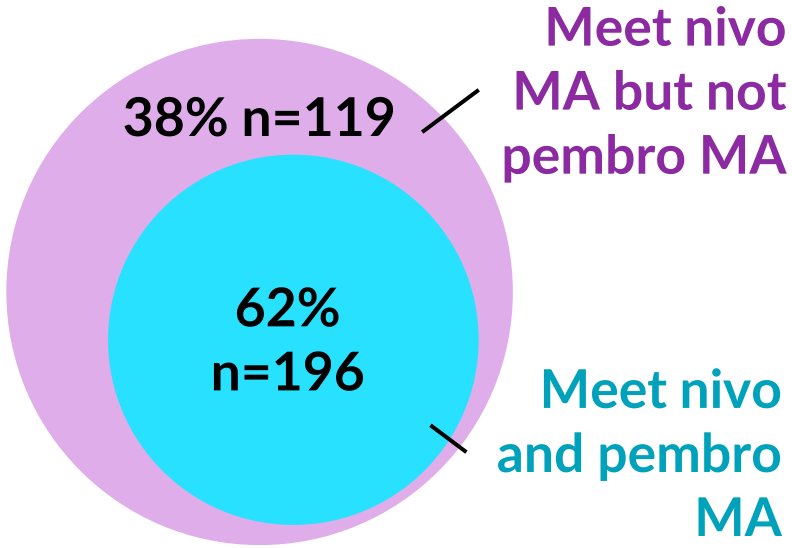


Figure 3: % overlap of pembro MA within nivo MA (n=315)



Clinical trials

- In CheckMate-648 there is an overlap in CPS ≥10 and TC ≥1%, but the measures are not completely comparable
- In KEYNOTE-590, 52% of tumours were CPS >10. TC status or TC outcomes were not reported

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Abbreviations: CPS, combined positive score; ITT, intention-to-treat; MA, marketing authorisation; nivo, nivolumab; PD-L1, programmed death-ligand 1; TC, tumour cell

Patient perspectives: living with the condition

Patient expert submission from Guts UK:

- These cancers are less survivable cancers, for which there are no screening tools to identify them which are widely used and they are frequently diagnosed late, when the treatment options are limited
- People with lived experience of these cancers strive to maintain fitness and gain control of their situation and their suffering is associated with symptoms and treatment side effects, which massively affects their quality of life, social experience and relationships with family and carers
- With a life limited condition it is extremely important that people living with these cancers enjoy time with their family and this treatment could help people participate and provide them with valuable time
- This treatment works by a different mechanism and offers another option for treatment where there are currently few options available
- Patients will always look for hope in new treatments, or trials for themselves and others

Clinical perspectives on treatment options:

In the absence of clinical expert submissions, the following points were provided in engagement with Dr Elizabeth Smyth and Dr Was Masoor:

- Pembrolizumab is embedded as an option for treating OSCC tumours expressing PD-L1 CPS ≥10
- The correct comparator for nivo + chemo is chemotherapy and cross-comparing PD-L1 positive patients across antibodies and datasets is a risky proposition in terms of validity
- There is little to no difference separating nivolumab and pembrolizumab efficacy outcomes in treating OSCC (e.g. in terms of response or survival)
- Clinicians are likely to make decisions on prescribing either nivolumab and pembrolizumab based on their prior experience of using each immunotherapy
- Clinicians will be willing to conduct both TC and CPS tests because they will want to give immunotherapies to their patients
- Uptake on conducting both tests (TC and CPS) may be slow, but its likely the clinician would conduct both tests

Abbreviations: CPS, combined positive score; OSCC, oesophageal squamous carcinoma cancer; PD-L1, programmed death-ligand; TC, tumour cell

Key issue 1: Comparators

What is the additional benefit of introducing nivo for first-line OSCC?

Company

- Pembro + chemo was recommended too recently to be standard of care for patients with PD-L1 CPS ≥10
- In clinical practice, clinicians will request either nivolumab or pembrolizumab based on preference, and then be given the test relevant to the chosen treatment
- Treatment choices will not be based on TC and CPS expression collectively. The two tests for assessing PD-L1 are independent of each other. There is no perceived linear relationship in expression levels
- Testing is time and resource intensive, in clinical practice one test would be conducted for PD-L1 positivity

ERG response

- Pembro + chemo is the most appropriate comparator for patients with PD-L1 TC ≥1% and CPS ≥10 expression based on the (NICE TA737 recommendation)
- Chemo is a relevant comparator for patients with PD-L1 TC ≥1% expression
- Chemo is the only comparator in PD-L1 TC ≥1% and CPS <10 subgroup
- There is uncertainty around the expectation of testing and treatment eligibility in clinical practice

Is pembrolizumab with chemotherapy now considered standard of care in clinical practice?
If pembrolizumab and nivolumab were both available, would the clinician's choice of drug be made first, then the relevant PD-L1 test done, or both tests done in a search for which, or whether both, might be applicable?

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Abbreviations: chemo, chemotherapy; CPS, combined positive score; ERG, Evidence Review Group; nivo, nivolumab; PD-L1, programmed death-ligand 1; OSCC, oesophageal squamous cell carcinoma; pembro, pembrolizumab; TC, tumour cell

Clinical effectiveness

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Pivotal trial design and outcomes: CheckMate-648

Around half CheckMate-648 patients meet the TC ≥1% nivo MA criteria

Table 4: CheckMate-648 trial design and outcomes

	Description	
Trial design	Phase III, randomised, open-label trial across 25 countries	
Population	Adults with unresectable advanced, recurrent or metastatic, previously untreated OSCC	
Intervention	Nivolumab + fluorouracil + cisplatin (n=321) up to 24 months	
Comparators*	Fluorouracil + cisplatin (n=324)	
Proportion TC ≥1%	Nivo + chemo: 49.2% (n=158); chemo: 48.5% (n=157)	
Outcomes	**Primary** • Overall survival • Progression free survival	**Secondary** • Objective response rate • Adverse effects of treatment • Health-related quality of life
Stratification factors	• Geographic region • Histology • ECOG performance score • Number of organs with metastasis	• Disease status • Age category • Sex • PD-L1 TC and CPS subgroups

*Nivolumab + ipilimumab + chemotherapy trial arm is not included in the decision problem

Abbreviations: chemo, chemotherapy; CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; MA, marketing authorisation; nivo, nivolumab; OSCC, oesophageal squamous cell carcinoma; PD-L1, programmed death-ligand 1; TC, tumour cell

Summary of available evidence to inform comparisons

Nivo-eligible
Tumour expressed: **PD-L1 TC ≥1%**

MA

Chemotherapy fluorouracil or capecitabine + cisplatin or oxaliplatin	+ Nivolumab

Pembro-ineligible
Tumour expressed: **PD-L1 TC ≥1% & CPS <10**

Chemotherapy fluorouracil or capecitabine + cisplatin or oxaliplatin	+ Nivolumab

Pembro-eligible
Tumour expressed: **PD-L1 TC ≥1% & CPS ≥10**

Chemotherapy fluorouracil or capecitabine + cisplatin or oxaliplatin	+ Pembrolizumab (TA737)
	+ Nivolumab

Economic model: base case

CheckMate 648 nivolumab
Nivo + Chemo vs Chemo
PD-L1 TC ≥1% N=315

MA

Economic model: scenario pembro-ineligible

CheckMate 648 nivolumab
Nivo + chemo vs Chemo
PD-L1 TC ≥1% & CPS <10
N=119 (subgroup pembro-ineligible)

Economic model: scenario pembro-eligible

Indirect comparison:
Nivo + chemo vs Pembro + chemo
CheckMate 648 nivo, **PD-L1 TC ≥1% & CPS ≥10**
N=196 (subgroup nivo- & pembro-eligible)
KEYNOTE-590 pembrolizumab, **PD-L1 CPS ≥10**
N=383 (subgroup pembro-eligible)

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Nivo + chemo versus chemo (CheckMate 648 PFS)

Nivolumab extends PFS in PD-L1 TC ≥1%

	Nivolumab + chemo (n=158)	Chemo (n=157)
PD-L1 TC ≥1% median PFS, months (95% CI)	[redacted]	[redacted]
PD-L1 TC ≥1% Proportion with PFS events (%)	[redacted]	[redacted]

PFS HR (95% CI) p nivo + chemo vs. chemo	
PD-L1 TC ≥1%	[redacted]

PFS rate at X Months (95% CI)	Nivolumab + chemo (n=158) %	Chemo (n=157) %
12 Months	[redacted]	[redacted]
18 Months	[redacted]	[redacted]

[redacted]

Figure 4 PFS KM analysis PD-L1 TC ≥1% patients

[redacted]

Abbreviations: chemo, chemotherapy; CI, confidence interval, CPS, combined positive score; nivo, nivolumab; OSCC, oesophageal squamous cell carcinoma; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TC, tumour cell

Nivo + chemo versus chemo (CheckMate 648 OS)

Nivolumab extends OS in PD-L1 TC ≥1%

	Nivolumab + chemo (n=321)	Chemo (n=324)
PD-L1 TC ≥1% median OS, months (95% CI)	[redacted]	[redacted]
PD-L1 TC ≥1% Proportion with OS events (%)	[redacted]	[redacted]

OS HR (95% CI) p nivo + chemo vs. chemo	
PD-L1 TC ≥1%	[redacted]

OS rate at X Months (95% CI)	Nivolumab + chemo (n=321) %	Chemo (n=324) %
12 Months	[redacted]	[redacted]

[redacted]

Figure 3 OS KM analysis PD-L1 TC ≥1% patients

[redacted]

Abbreviations: chemo, chemotherapy; CI, confidence interval, CPS, combined positive score; nivo, nivolumab; OS: overall survival, OSCC, oesophageal squamous cell carcinoma; PD-L1, programmed death-ligand 1; TC, tumour cell

Nivo versus chemo comparison

Chemo comparison is in pembro ineligible population: TC ≥1% & CPS <10

Background

- The company presented clinical evidence for OSCC PD-L1 ≥1% TC patients

ERG

- A clinical and cost-effectiveness comparison with chemo should be presented by the company in the pembro ineligible population: PD-L1 TC ≥1% and CPS <10

Company response

CheckMate-648 was not powered for the analysis. Only [redacted] nivo + chemo and [redacted] chemo patients in the trial meet ≥1% TC and <10 CPS criteria

- Following technical engagement the company presented:
  - CheckMate-648 clinical effectiveness results (PFS, OS and ToT) for patients with ≥1% TC & <10 CPS
    - **ERG:** did not comment on the effectiveness of nivo + chemo vs. chemo in this subgroup
  - Cost-effectiveness results for patients with ≥1% TC and <10 CPS as a scenario analysis
    - In the company model, nivo + chemo vs. chemo ICER was slightly higher
    - **ERG comment:** unable to critique analysis on this subgroup

Abbreviations: chemo, chemotherapy; CPS, combined positive score; ICER, incremental cost-effectiveness ratio; nivo, nivolumab; OS, overall survival; OSCC, oesophageal squamous cell carcinoma; PD-L1, programmed death-ligand 1; pembro, pembrolizumab; PFS, progression-free survival; TC, tumour cell, ToT, time on treatment

Nivo + chemo vs pembro + chemo: Indirect treatment comparison

The ITC was limited by the data available from KEYNOTE-590

Table 5 Clinical trial designs and outcomes of trials used in the ITC

	CheckMate-648, nivolumab	KEYNOTE-590, pembrolizumab
Design	Phase III, triple-arm, open-label	Phase III, double-arm, double-blind
Population	**OSCC**	**Squamous cell carcinoma or adenocarcinoma, located in either the oesophagus or the gastroesophageal junction**
Intervention	Nivolumab + chemotherapy	Pembrolizumab + chemotherapy
Comparator	Chemotherapy	Chemotherapy
Follow-up	11.2 months	10.8 months

Background

- An ITC was conducted with pembrolizumab + chemotherapy using the pembrolizumab MA population (CPS ≥10) in KEYNOTE-590 trial, in the absence of nivolumab MA population (TC ≥1%) efficacy outcomes

Clinical expert comments (at expert engagement)

- Expect the patients in the trials to be comparable based on the OSCC survival, observed in both control arms
- There is little clinical understanding of how outcomes may differ by TC and CPS status, or also in the broader oesophageal cancer population and by PD-L1 expression (through either TC or CPS)

Are the populations in the trials used in the ITC suitably comparable?

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Abbreviations: CPS, combined positive score; MA, market authorisation; OSCC, oesophageal squamous cell carcinoma; PD-L1, programmed death-ligand 1; TC, tumour cell

Key issue: Comparability of trials used in the ITC

Proportion of Asian and metastatic disease patients differed among trials

Background

- Assessment of comparability in the ITT populations showed more patients in CheckMate-648 were Asian and less had metastatic disease compared to KEYNOTE-590. TC percentage was not reported in KEYNOTE-590

Table 6 Key differences in ITT baseline characteristics across CheckMate-648 and KEYNOTE-590

	CheckMate-648, nivolumab		KEYNOTE-590, pembrolizumab	
Treatment arm	Nivo + chemo (n=321)	Chemo (n=324)	Pembro + chemo (n=286)	Chemo (n=376)
Asian	70%	70%	53%	52%
Metastatic disease	57%	58%	92%	90%
PD-L1 CPS ≥10	42%	45%	50%	52%

Company at technical engagement

- Presented a comparison of some baseline characteristics in patients with PD-L1 CPS ≥10 from both trials

ERG response

- Agree that PD-L1 CPS ≥10 patients appear comparable to the ITT populations in trials (in Table 6)
- But conclusions are limited as only characteristics presented were: age, Asian (%), ECOG and metastatic disease and these were only available for both arms of the KEYNOTE-590, combined

Are the populations in the trials used in the ITC suitably comparable?

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Abbreviations: chemo, chemotherapy; CPS, combined positive score; ITC, indirect treatment comparison; ITT, intention-to-treat; nivo, nivolumab; OSCC, oesophageal squamous cell carcinoma; PD-L1, programmed death-ligand 1; pembro, pembrolizumab; TC, tumour cell

Key issue: Uncertainty in nivo vs pembro comparison

Company ITC:

- Conducted various PFS and OS analyses. The base case model used the overlap ITC analysis and estimated the pembro + chemo survival using chemo as the baseline

ERG

- Understood arguments for using the overlap analysis, but use the primary analysis in the base case, as it maintains more comparability between trials. Used nivo + chemo as the baseline to estimate the pembro + chemo survival in the base case, in the absence of relevant data

Analysis	Trial	Population	Outcome	Conclusions
Primary analyses **(populations used in the ERG base case)**	CheckMate-648 (nivo + chemo)	OSCC CPS ≥10	PFS & OS	[redacted]
	KEYNOTE-590 (pembro + chemo)	Mixed histology oesophageal, CPS ≥10	PFS	
		OSCC CPS ≥10	OS	
Overlap analyses **(populations used in company base case)**	CheckMate-648 (nivo + chemo)	OSCC CPS ≥10 & TC ≥1%	PFS & OS	[redacted]
	KEYNOTE-590 (pembro + chemo)	Mixed histology oesophageal, CPS ≥10	PFS	
		OSCC CPS ≥10	OS	

Given the uncertainty, what conclusions can be made around the relative effectiveness of nivo versus pembro in PD-L1 expressing tumours?

Abbreviations: chemo, chemotherapy; CPS, combined positive score; CrI, credible interval; ITC, indirect treatment comparison; ITT, intention-to-treat; nivo, nivolumab; NR, not reported; PD-L1, programmed death-ligand 1; pembro, pembrolizumab; TC, tumour cell

Cost effectiveness

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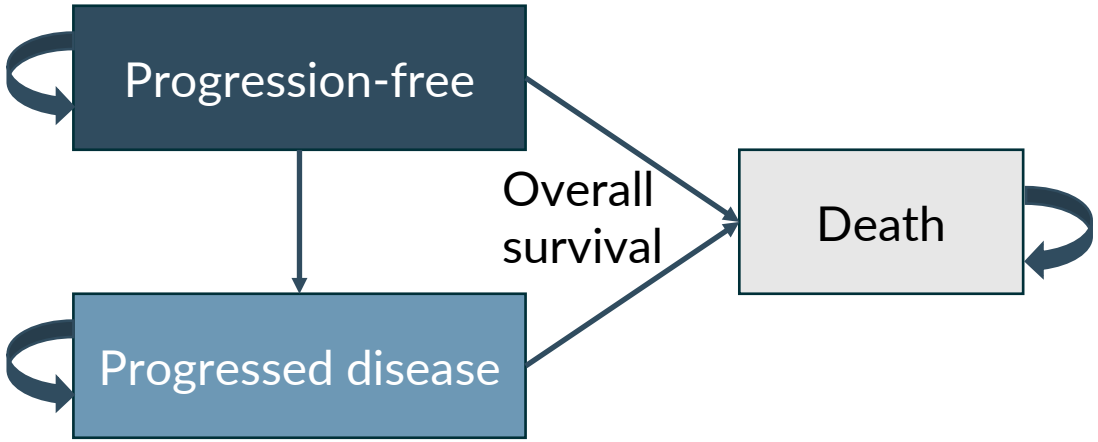
Key cost-effectiveness issues

- Survival modelling in the comparison with chemotherapy:
  - Is a parametric or semi-parametric extrapolation approach more appropriate for modelling OS?
  - Should OS be adjusted for switching to another therapy, as observed in CheckMate-648?
  - What treatment waning assumptions are appropriate for nivolumab?
- Should all-cause mortality be incorporated in the model?
- Are treatment-specific progression-based utility values appropriate?
- What is the most appropriate method for adjusting for delayed or missed doses?

Company's model overview

A three-state partitioned survival model was used

Figure 5 Model structure



Background: The NICE TA737 committee found this model structure acceptable for decision making

ERG comments: Model structure concerns relate to modelling of subsequent therapy [see next slides]

- Nivolumab + chemo affects **costs** by:
  - Increasing PFS and thus increasing time in the lower cost health state as well as reducing the rate of relatively expensive subsequent immunotherapy
  - Increasing OS and thus increasing time alive and delaying terminal care
- Nivolumab + chemo affects **QALYs** by:
  - Increasing OS and thus increasing time alive and delaying terminal care
  - Increasing PFS and thus increasing time in the higher utility health state
- Assumptions with greatest **ICER** effect:
  - Choice of OS curve
  - How subsequent treatment is modelled in terms of type, effectiveness and cost

Abbreviations: chemo, chemotherapy; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year

How company incorporated evidence into model
Evidence from CheckMate-648, an ITC and previous NICE TAs

Input	Assumption and evidence source	
	Versus chemotherapy	**Versus pembrolizumab + chemotherapy**
Baseline characteristics	CheckMate-648 **nivo-eligible (PD-L1 TC ≥1%)** population	
Intervention efficacy	CheckMate-648 **Nivo-eligible (PD-L1 TC ≥1%)**	Indirect comparison in CheckMate-648 **Nivo- and pembro-eligible patients (PD-L1 CPS ≥10 &TC ≥1%)**
Comparator efficacy	CheckMate-648 **Nivo-eligible (PD-L1 TC ≥1%)**	Indirect comparison in KEYNOTE-590 **Pembro-eligible patients (PD-L1 CPS ≥10)**
Treatment discontinuation	CheckMate-648 time-on-treatment Kaplan Meier	CheckMate-648 and KEYNOTE-590 time-on-treatment Kaplan Meier
Utilities	Progression-based EQ-5D-3L values collected from CheckMate-648	
Costs	NHS reference costs; BNF; eMIT; Published literature	
Resource use	Health state costs from NICE TA737	
Adverse event incidence	Nivo + chemo and chemo: CheckMate-648	Nivo + chemo: CheckMate-648 Pembro + chemo: KEYNOTE-590

Abbreviations: BNF, British National Formulary; chemo, chemotherapy; CPS, combined positive score; ITC, indirect treatment comparison; nivo, nivolumab; PD-L1, programmed death-ligand 1; pembro, pembrolizumab; TC, tumour cell

ICER impact: **Major**

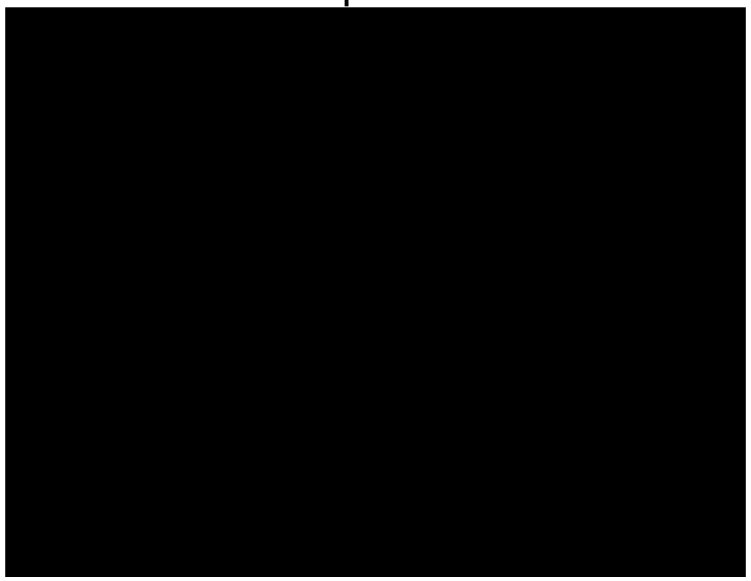
OS extrapolation for nivo + chemo vs chemo in nivo-eligible

Base case	OS extrapolation	Switching adjustment	Treatment waning
Company	Semi-parametric, 6.9 month KM cut-off	None	None
ERG	Parametric	None (but preferred)	Nivo treatment waning: 2.5-4 yrs

Figure 4 CheckMate-648 TC ≥1% OS log-log plot: nivo+chemo vs. chemo

Figure 5 CheckMate-648 TC ≥1% OS smoothed hazard plot: nivo+chemo

Figure 6 CheckMate-648 TC ≥1% OS smoothed hazard plot: chemo



NICE TA737 precedence

- Company modelled semi-parametric, 40-week KM cut-off. The ERG considered this to be broadly acceptable.
- No switching analysis was requested by the ERG. Treatment waning omitted by company, ERG preferred treatment waning effect from 5–7yrs. Committee did not conclude whether treatment waning was appropriate

NICE

Abbreviations: chemo, chemotherapy; CPS, combined positive score; ERG, external review group; FAD, final appraisal document; ICER, incremental cost-effectiveness ratio; KM, Kaplan Meier; nivo, nivolumab; OS, overall survival; PD-L1, programmed death-ligand 1; TC, tumour cell

ICER impact: **Major**

OS extrapolation for nivo + chemo vs chemo in nivo-eligible

Table 8 Company-preferred OS assumptions and justification

Preferred assumption	Justification
Semi-parametric extrapolation	• Approach better reflects changing OS hazards after 20 months observed in both arms. • Clear inflexion point in chemo arm OS hazards at around 6 months • **Choice of fully parametric or semi-parametric extrapolation has a large impact on the ICER**
No switching adjustment	• Low numbers of patients switching to an anti-PD-L1 in CheckMate-648 • Switching adjustment analysis places large demands placed on limited data • **Switching scenario analysis (using NICE DSU TSD 16 methods) has a large impact on the ICER**

Table 9 ERG-preferred OS assumptions and justification

Preferred assumption	Justification
Parametric extrapolation	• No inflexion point was observed in nivo + chemo smoothed OS hazard plot and no well-founded justification for the 6.9 month KM cut off • Reasonable correspondence of CheckMate-648 with parametric OS landmark analysis

Switching adjustment, using NICE TSD 16 methods	• In CheckMate-648,
	  • [redacted]% of nivo+chemo and [redacted]% of chemo received a subsequent systemic therapy
	  • [redacted]% of nivo+chemo and [redacted]% of chemo received an anti-PD-L1
	• The decreasing OS hazard profile for chemo after 24 months is implausible and suggests that survival was prolonged by a switch to an anti PD-L1
	• Switching scenarios demonstrate that without adjustment ICER is underestimated

Clinical expert: In-trial switching to an anti-PD-L1 may introduce some bias, but its impact on the overall OS is likely to be small

Abbreviations: chemo, chemotherapy; CPS, combined positive score; KM, Kaplan Meier; nivo, nivolumab; OS, overall survival; PD-L1, programmed death-ligand 1; TC, tumour cell

ICER impact: **Major**

Waning of nivolumab treatment effect

Including treatment waning has a substantial impact on cost-effectiveness

Company base case: No treatment waning

- Evidence of robust and durable treatment effect after discontinuing an immunotherapy
- Waning does not begin until 5 years, in line with the ongoing gastro-oesophageal cancer appraisal (ID1465)
- Did not find any clear justification for the ERG's preferred treatment waning assumptions

ERG base case: 2.5 – 4.0 years treatment waning

- OS HRs over time for nivo + chemo versus chemo, show that for some parametric functions, the nivo + chemo treatment effect increased over time. This is considered implausible
- Treatment waning was considered acceptable by the committee in NICE TA737
- Model application: treatment effect for OS diminishes from 2.5 years (6 months after all patients have finished nivo + chemo). By year 4.0 the OS HR for nivo + chemo vs chemo reaches 1
- Unconvinced waning occurs later (e.g. 4 to 10 years)
- **Including treatment waning impacts the ICER substantially**

Clinical expert: Some treatment waning is possible and is more likely in those who discontinue therapy earlier

Abbreviations: chemo, chemotherapy; nivolumab; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival

ICER impact: **Major**

Key issue: OS assumptions in nivo-eligible comparison

Figure 7 Company base case OS extrapolations

Figure 8 ERG base case OS extrapolations + waning

Table 8: OS landmark analysis in TC ≥1% patients

Time, months	Nivo + chemo			Chemo		
	CheckMate-648	Company model	ERG model	CheckMate-648	Company model	ERG model
12	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
24	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
36	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Median OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Which OS extrapolation approaches and assumptions are more appropriate?

Abbreviations: chemo, chemotherapy; CPS, combined positive score; ERG, external review group; KM, Kaplan Meier; nivo, nivolumab; OS, overall survival; PD-L1, programmed death-ligand 1; TC, tumour cell

Key issue: Handling implausible OS hazards

Many OS extrapolations generated implausibly low OS hazards

Background

- CheckMate-648 demonstrated a hazard of mortality which was similar to that of background mortality, which is considered implausible
- Conclusions over the handling of implausibly low hazards were not made by the NICE TA737 committee

Company

- Modelled all-cause mortality (ACM) to enforce minimum rate of mortality additional to predicted OS mortality
- The impact applying all-cause mortality on the results is minimal

ERG

- The company's approach double counts mortality
- Base case includes ACM, but unconvinced the approach is the most appropriate method
- **Removing ACM decreases the ICER slightly**
- Prefer an alternative approach to prevent implausibly low mortality with any OS extrapolation

Should all-cause mortality be included in the model?

Abbreviations: ACM, all-cause mortality; OS, overall survival; nivo, nivolumab; pembro, pembrolizumab; QALY, quality-adjusted life-year;

ICER on impact: **Minor**

Key issue: Appropriate health state utilities

Background

- In CheckMate-648, the EQ-5D-3L scores were consistently higher for chemo compared to nivo + chemo
- In NICE TA737, the committee concluded a preference for progression-based utilities, although considered interaction-based approaches may appropriate in some circumstances

Company base case: treatment-independent pre-progression, post-progression and terminal care utilities

ERG base case: treatment-specific pre-progression, post-progression and terminal care utilities

- The ERG requested an interaction-based analysis using clinically relevant covariates: health state, treatment and time-to-death. Company did not present analysis, concluding the analysis produced similar results
- **Using the ERG's utilities increases the ICER slightly**

Table 10 Health state utility values applied in each model base case

	Arm	Pre-progression	Post-progression	Terminal care
Company	Nivo+chemo	[redacted]	[redacted]	[redacted]
	Chemo	[redacted]	[redacted]	[redacted]
ERG	Nivo+chemo	[redacted]	[redacted]	[redacted]
	Chemo	[redacted]	[redacted]	[redacted]

Clinical expert comment:

- Expect better QoL in nivo + chemo as these patients are likely to have better disease control

Are treatment-specific progression-based utility values appropriate?

Abbreviations: chemo, chemotherapy; Inc., incremental; nivo, nivolumab; QALY, quality-adjusted life-year; QoL, quality of life

Key issue: Adjustment for delayed / missed doses

A small proportion of patients delayed or missed dose in CheckMate-648

NICE TA737 precedence

- Relative dose intensity (RDI) was applied in both arms in NICE TA737, using data from KEYNOTE-590. The FAD does not conclude over the appropriateness of the company and ERG assumptions.

Company

- Applied dose modification to calculate lower treatment costs. Adjustment is based on mean RDI weighted by time-on-treatment (ToT) in CheckMate-648. Nivo + chemo RDI assumed equal to pembro + chemo

	Arm	Company base case	ERG base case
Nivo + chemo	Nivolumab	[redacted]	[redacted]
	Fluorouracil	[redacted]	[redacted]
	Cisplatin	[redacted]	[redacted]
Chemo	Fluorouracil	[redacted]	[redacted]
	Cisplatin	[redacted]	[redacted]

ERG comments

- Is uncertain why the dose of medication needs to be reweighted by ToT
- Base case uses RDI, omits ToT weighting
- **The ICER is notably higher using the ERG approach (removal of ToT weighting)**

What is the most appropriate method for modelling missed or delayed doses of therapy

Abbreviations: chemo, chemotherapy; ERG, external review group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; nivo, nivolumab; pembro, pembrolizumab; QoL, quality of life; RDI, relative dose intensity; ToT, time-on-treatment.

End-of-life criteria

Criteria appears to be met versus chemotherapy but not versus pembro

Criteria	Nivo-eligible (TC ≥1%)	Pembro-ineligible (TC ≥1% & CPS <10)	Nivo- and pembro-eligible (TC ≥1% & CPS ≥10)
Life expectancy less than 24 months	**Appears to be met:** • [redacted]month OS in patients with PD-L1 TC ≥1% status in CheckMate-648	**Appears to be met:** • Median OS is not reported in CheckMate-648 for chemo in TC ≥1% & CPS <10 • In all extrapolations median OS modelled in TC ≥1% & CPS <10 for chemo exceeded 24 months	**Appears to be met:** • [redacted]month median OS for pembro + chemo in patients with TC ≥1% & CPS ≥10
Technology extends life by at least 3 months	**Appears to be met:** • 6 month longer OS for nivo-chemo vs. chemo ([redacted]-[redacted]), as observed in CheckMate-648 • The mean OS gain modelled is greater than 3 months in the Company ([redacted] years) and ERG ([redacted] years) base case	**Appears to be met:** • The mean OS gain modelled is greater than 3 months in the Company base case ([redacted] years)	**Not met:** • Nivo + chemo median OS is [redacted]month longer than pembro + chemo ([redacted]-14.0) in the PD-L1 CPS ≥10 population • The mean OS gain modelled is less than 3 months in the Company ([redacted] months or [redacted] years) • The ERG modelled OS (mean) is shorter for nivo + chemo versus pembro + chemo

NICE

Abbreviations: chemo, chemotherapy; CPS, combined positive score, ERG, quality-adjusted life-year; ICER, incremental-cost effectiveness ratio; LY, life year; nivo, nivolumab; OS, overall survival; PD-L1, programmed death-ligand 1; QALY, quality-adjusted life-year; TC: tumour cell;

Costs presented in Part 2

Summary

Nivo-eligible
Tumour expressed: **PD-L1 TC ≥1%**

MA

Chemotherapy
fluorouracil or capecitabine + cisplatin or oxaliplatin

+ Nivolumab

Pembro-ineligible
Tumour expressed: **PD-L1 TC ≥1% & CPS <10**

Chemotherapy
fluorouracil or capecitabine + cisplatin or oxaliplatin

+ Nivolumab

Nivo- and pembro-eligible
Tumour expressed: **PD-L1 TC ≥1% & CPS ≥10**

Chemotherapy
fluorouracil or capecitabine + cisplatin or oxaliplatin

+ Pembrolizumab (TA737)

+ Nivolumab

MA

Economic model: base case

Nivo + chemo meets the end-of-life criteria and results in QALY [redacted] versus chemo in the company and ERG base case

Economic model: scenario pembro ineligible

Nivo + chemo meets the end-of-life criteria and results in QALY [redacted] versus chemo in the company and ERG base case

Economic model: scenario pembro eligible

Indirect comparison:
Nivo + chemo does not meet the end-of-life criteria and results in [redacted] QALYs

NICE

Other considerations

Equality considerations

- **Company:** no known equality issues have been identified relating to the use of nivolumab with chemotherapy in patients with advanced untreated OSCC
- **Patient experts:** people in the most deprived areas are more likely to be diagnosed with oesophageal cancer later than other areas

Innovation

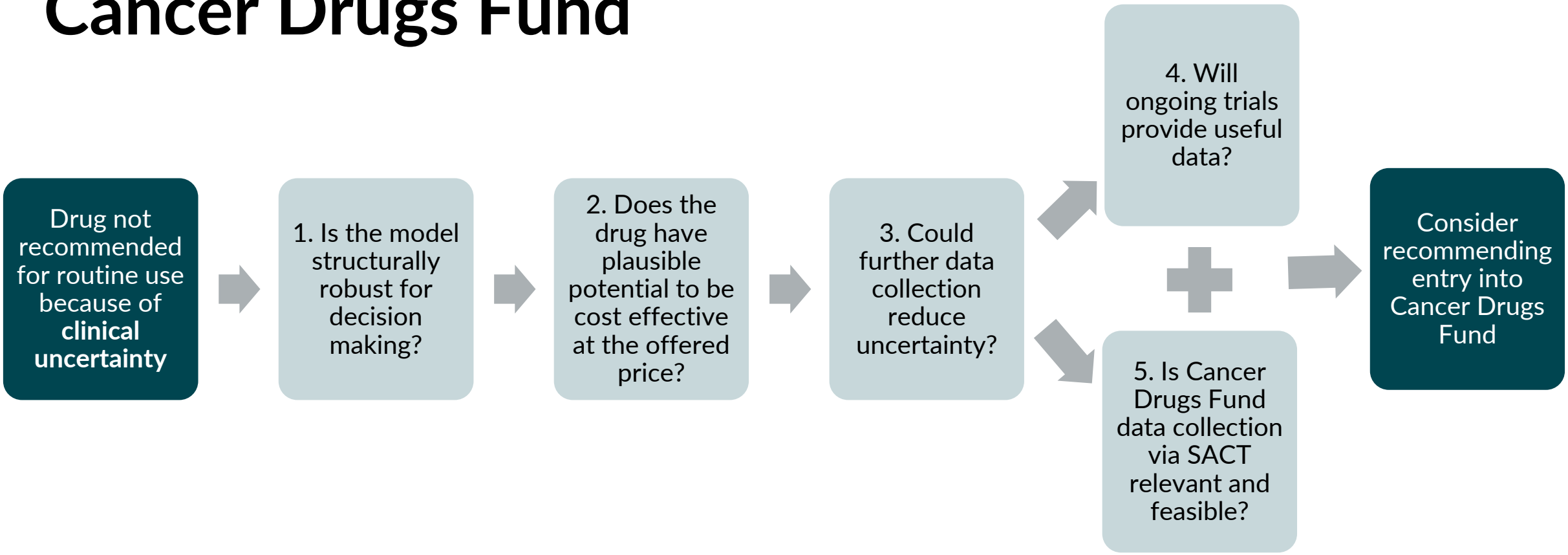
- **Company:** the benefits of nivolumab + chemotherapy include: improved efficacy outcomes versus standard of care, maintained quality of life, acceptable safety profile and provide an additional treatment option for patients with high unmet need

Abbreviations: OSCC, oesophageal squamous cell carcinoma

NICE National Institute for Health and Care Excellence

Thank you.

Cancer Drugs Fund



Define the nature and level of clinical uncertainty. Indicate the research question, analyses needed, and number of patients in the NHS in England needed to collect data.

Abbreviations: SACT, systemic anti-cancer therapy