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 [8 November 2022]

Chair: Radha Todd

Evidence assessment group: Kleijnen Systematic Reviews

Technical team: Owen Harrison, Carl Prescott, Henry Edwards

Company: Bristol Myers Squibb

Key issues: ACM1 conclusions

Optimised recommendation: nivolumab plus chemotherapy is recommended as an option for untreated unresectable advanced, recurrent, or metastatic OSCC in adults whose tumours express **PD-L1 at a level of 1% or more** and **when pembrolizumab plus chemotherapy is not suitable**

Issue (ACD section)	Committee conclusion
Relevant comparators (3.4)	Chemo alone is the relevant comparator when only nivo is suitable (PD-L1 TC ≥1% & CPS <10) Pembro + chemo is the relevant comparator when only nivolumab and pembrolizumab are suitable (PD-L1 TC ≥1% & CPS ≥10)
PD-L1 testing (3.3)	Uncertain whether both tests would be done sequentially or concurrently. But sequential testing most likely
Indirect treatment comparison (3.7 - 3.8)	Uncertainty in whether trials are suitably comparable No clear evidence of superiority of one treatment over the other
OS assumptions (3.10 - 3.12)	Committee aware of uncertainty around OS modelling, concluded: • The most appropriate model for estimating OS was not clear • In-trial switching may have impacted OS, but its effect is uncertain • Waning treatment effect is expected, but its impact on OS is unclear
Utilities (3.14)	The committee considered treatment-specific utilities to be inappropriate
End of life (3.16)	Criteria met vs chemotherapy Criteria not met vs pembrolizumab

Abbreviations: chemo, chemotherapy; CPS, combined positive scored; ERG, Evidence Review Group; nivo, nivolumab; ICER, incremental cost-effectiveness ratio; OS, overall survival; OSCC, oesophageal squamous cell carcinoma; PD-L1, programmed death-ligand 1; pembro, pembrolizumab; TC, tumour cell.

Cost-effectiveness: ACM1 conclusions

The committee concluded that compared with:

- **Pembrolizumab plus chemotherapy**,
  - Nivolumab was dominated by pembrolizumab in the company and ERG base case
  - The uncertainty around the relative treatment effect was acknowledged
  - **Concluded: nivolumab is unlikely to be cost effective compared with pembrolizumab**

- **Chemotherapy**
  - In the company's base case nivolumab is cost-effectiveness when considering the end of life criteria
  - In the ERG's base case nivolumab is not cost-effectiveness when considering the end of life criteria. However nivolumab was cost-effective when treatment-specific utilities, which the committee deemed as inappropriate, were removed from the ERG's analyses and when considering end of life criteria
  - **Concluded**: **nivolumab is likely to be cost effective compared with chemotherapy**

Optimised recommendation: nivolumab plus chemotherapy is recommended as an option for untreated unresectable advanced, recurrent, or metastatic OSCC in adults whose tumours express **PD-L1 at a level of 1% or more** and **when pembrolizumab plus chemotherapy is not suitable**

Abbreviations: ACM, appraisal committee meeting; ERG, Evidence Review Group; nivo, nivolumab; OSCC, oesophageal squamous cell carcinoma; PD-L1, programmed death-ligand 1; TC, tumour cell.

RECAP: Background, decision problem and clinical effectiveness

NICE National Institute for Health and Care Excellence

Background on oesophageal cancer

Epidemiology

- 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
- 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

Diagnosis and classification

- On average 70-80% are diagnosed at stage 3 (locally advanced) or 4 (metastatic)[1]

Symptoms and prognosis

- The most common symptoms are difficulty swallowing, food regurgitation, nausea or vomiting, unexplained weight loss and persistent indigestion or cough[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 (OPDIVO, Bristol Myers Squibb)

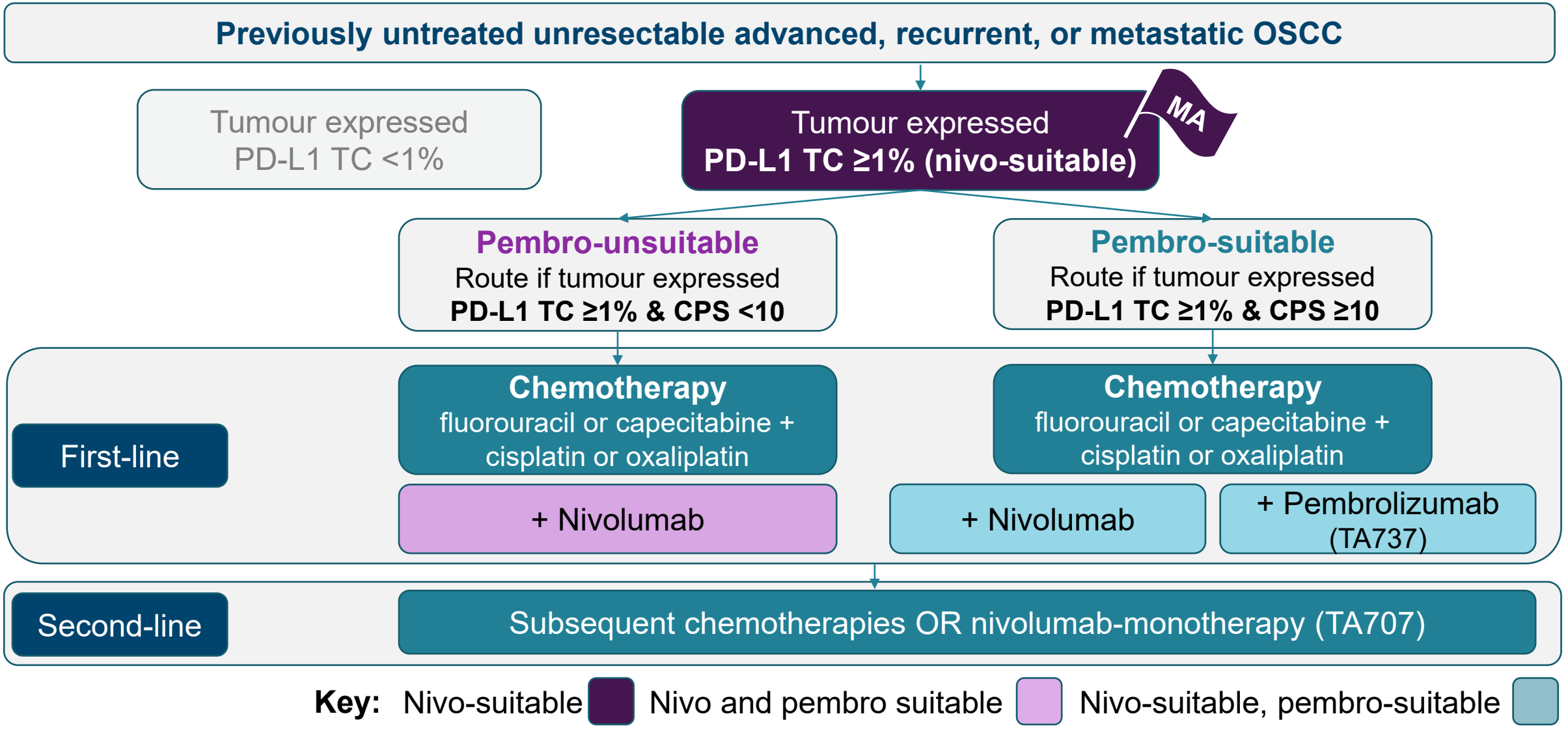
Table 1 Nivolumab (OPDIVO) overview

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%**
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
Administration	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/m2 per day on days 1 to 5, and cisplatin IV, 80 mg/m2 on Day 1, of a 4-week cycle
Price	Nivolumab is £2,633 per 240mg vial, the cost of a single administration is £2,633. Confidential PAS discount also in place

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

Treatment pathway

Figure 1: Treatment pathway



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

Treatment pathway

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

PD-L1 measurement	Tumour cell (TC)	Combined positive score (CPS)
Expressed as	Percentage (%)	Whole number
Threshold in licence for PD-L1 positivity	≥1%	≥10

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

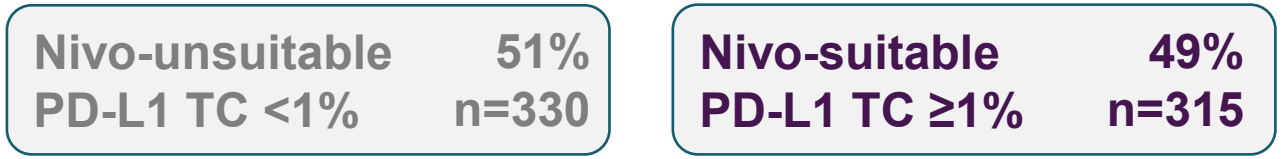
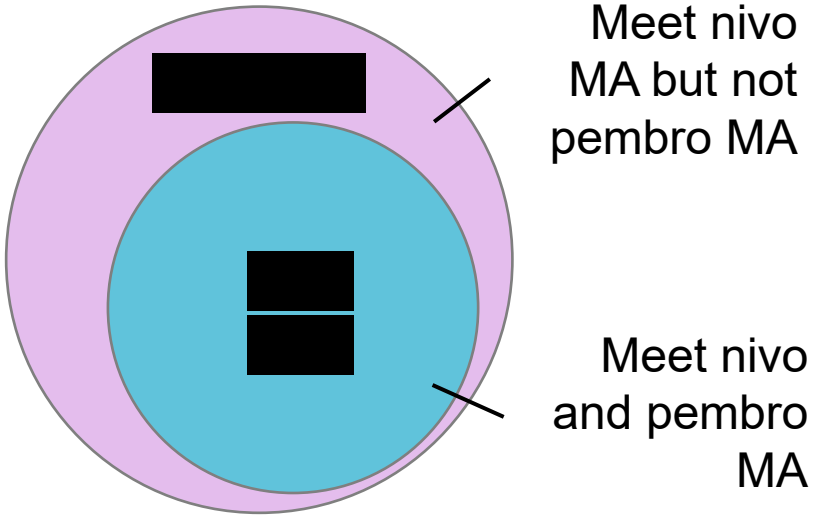


Figure 3: % overlap of pembro MA within nivo MA (n=315)



The committee concluded:

- Chemo alone is a relevant comparator when only nivolumab is suitable
- Pembro + chemo is a relevant comparator when nivo and pembro are suitable

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

Patient and clinical perspectives at ACM1

Patient experts

- Some people do not have pembrolizumab plus chemotherapy despite its suitability
- There is an unmet need in people for whom treatment with pembrolizumab plus chemotherapy is not suitable

Clinical experts

- Pembrolizumab plus chemotherapy is widely used when it is suitable
- Clinicians would value an additional treatment option where both immunotherapies were suitable and there may be circumstances were nivolumab is preferred over pembrolizumab
- Testing is time and resource intensive.
    - The 2 tests (TC and CPS) should be done concurrently, rather than sequentially, to determine nivo or pembro suitability
- There was uncertainty on whether both tests would be done sequentially or concurrently

Committee concluded that **patients and clinicians would welcome a new treatment** for untreated unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma **whose tumours express PD-L1 at a level of 1% or more** and **when pembrolizumab plus chemotherapy is unsuitable**.

And that sequential testing was more likely option in clinical practice for defining nivo and pembro suitability.

Abbreviations: CPS, combined positive scored; nivo, nivolumab; OSCC, oesophageal squamous cell carcinoma; pembro, pembrolizumab; TC, tumour cell.

RECAP

Nivo vs pembro indirect treatment comparison

ITC background

- An ITC was conducted with pembrolizumab + chemotherapy in the absence of direct trial evidence
- Uncertainty was apparent in the:
  - **Comparability of the trial populations** – lack of evidence from KEYNOTE-590 prevent a thorough assessment of comparability between the two trials (CheckMate-648 and KEYNOTE-590)
  - **Relative treatment-effect (PFS and OS)** – comparing the estimated HRs from the company and ERG base case ITC settings do not give clear evidence of superiority of one treatment over the other

Clinical expert opinion

- The effectiveness of nivo and pembro is almost the same in other cancers and this effect is expected to be consistent in treating OSCC tumours
- Comparing nivo and pembro across different definitions of PD-L1 positivity and trial datasets was 'risky' in terms of validity

The committee:

- Acknowledged the complexity of calculating a reliable relative treatment-effect in the comparison of nivolumab and pembrolizumab, based on the available evidence
- Agreed with the clinical experts, company, ERG and committee that no definitive evidence of superiority of one treatment over the other had been demonstrated in the ITC

Abbreviations: chemo, chemotherapy; CI, confidence interval, CPS, combined positive score; ERG, external review group; HR, hazard ratio; ITC, indirect treatment comparison; nivo, nivolumab; OSCC, oesophageal squamous cell carcinoma; PD-L1, programmed death-ligand 1; pembro, pembrolizumab; PFS, progression-free survival; TC, tumour cell

RECAP

Key cost-effectiveness issues: ACM1 conclusions

Cost-effectiveness issue at committee	Discussed during ACM1
OS assumptions	Uncertain which assumptions were appropriate
Utilities	Treatment specific utilities are inappropriate
Implausible mortality	Minimal impact on the cost-effectiveness
Relative dose intensity	Uncertain which assumptions were appropriate
End of life	Criteria met vs chemotherapy Criteria not met vs pembrolizumab

The committee concluded that compared with:

- Chemotherapy, the end of life criteria was met
- Pembrolizumab plus chemotherapy, the end of life criteria was not met, as there was no evidence nivolumab extends life by 3-months compared with pembrolizumab

NICE

Abbreviations: ACM, appraisal committee meeting; ERG, Evidence Review Group; overall survival.

RECAP

Cost-effectiveness: ACM1 conclusions

The committee concluded that compared with:

ICERs are confidential and cannot be shown here

- **Chemotherapy**
  - Company base case: nivolumab is cost-effectiveness when considering the end of life criteria
  - ERG base case: nivolumab is not cost-effectiveness when considering the end of life criteria. However nivolumab was cost-effective when treatment-specific utilities, which the committee deemed as inappropriate, were removed from the ERG's analyses and when considering end of life criteria
  - **Concluded**: **nivolumab is likely to be cost effective compared with chemotherapy**

- **Pembrolizumab plus chemotherapy**,
  - Nivolumab was dominated by pembrolizumab in the company and ERG base case
  - The uncertainty around the relative treatment effect was acknowledged
  - **Concluded: nivolumab is unlikely to be cost effective compared with pembrolizumab**

Optimised recommendation: nivolumab plus chemotherapy is recommended as an option for untreated unresectable advanced, recurrent, or metastatic OSCC in adults whose tumours express **PD-L1 at a level of 1% or more** and **when pembrolizumab plus chemotherapy is not suitable**

NICE

Abbreviations: chemo, chemotherapy; CPS, combined positive scored; ERG, Evidence Review Group; nivo, nivolumab; ICER, incremental cost-effectiveness ratio; OS, overall survival; OSCC, oesophageal squamous cell carcinoma; PD-L1, programmed death-ligand 1; pembro, pembrolizumab; TC, tumour cell.

ACD consultation comments

Comments received from:

- **BMS** (company)
- **UK and Ireland Oesophago-gastric Cancer Group (UKIOG)** (clinical group)
- **NCRI-ACP-RCP-RCR** (clinical research groups)
- **2 UK clinicians**

Two key issues were raised at consultation were the:

- **Appropriate comparator**
- **Testing implementation**

NICE National Institute for Health and Care Excellence

Consultees comment: appropriate comparator

Consultee comments:

- Suggest broadening draft guidance to remove the ‘where pembrolizumab is unsuitable” wording
    - Pembrolizumab is not yet standard of care – slow uptake
    - Complexities relating to capacity in NHS services and testing for pembrolizumab suitability has impacted uptake of the treatment
    - Chemotherapy should be considered standard of care

At ACM1 clinical and patient experts explained:

- Pembrolizumab plus chemotherapy is widely used when it is suitable, but uptake of pembrolizumab has been lower than anticipated

Does the committee maintain that pembrolizumab is a relevant comparator? What factors have affected the uptake of pembrolizumab?

Abbreviations: ACM, appraisal committee meeting

Consultees comment: testing and implementation

At ACM1 clinical experts explained:

- It is preferrable that the 2 tests (TC and CPS) to determine nivolumab and pembrolizumab suitability would be conducted concurrently, rather than sequentially
- Testing is time and resource intensive
- Treatment decisions are often guided by local health service protocols which may determine a standardised approach
- The TC test may be more accessible to clinicians than testing for PD-L1 expression through CPS, meaning this test was more likely to be requested first if sequential testing occurred
- The clinical experts did not agree on whether sequential testing would occur in practice

At ACM1 the committee concluded:

- There was uncertainty on whether both tests would be done sequentially or concurrently, but concluded sequential testing was the more likely option in clinical practice

Note: combined positive scored (CPS) test used to determine pembrolizumab-suitability; tumour cell (TC) test used to determine nivolumab-suitability

Consultees comment: testing and implementation

Consultee comments:

- There is low availability of CPS tests, with only 7 centres in England offering the test
- Requesting tests externally can mean a long wait time, CPS test results can take up to 2 weeks or more. The TC test can be done in house, saving time for treatment decisions
- Treatment with the most effective treatment early is critical, the time taken to conduct the two biomarker tests will delay treatment initiation impacting patient wellbeing and disadvantage people who need quick response associated with immunotherapy
- The requirement for testing PD-L1 using both the CPS and TC test
  - introduces a significant risk that patients may not have sufficient tissue for both tests. In these cases invasive biopsies may be required which carry safety concerns
  - will result in additional complexity and workload for diagnostic services and double the testing cost needed

Note: combined positive scored (CPS) test used to determine pembrolizumab-suitability; tumour cell (TC) test used to determine nivolumab-suitability

Consultees comment: testing and implementation

Consultee comments:

- The guidance recommendation wording should be amended to either :
  - "… it is recommended where pembrolizumab plus chemotherapy is not suitable, or where access to CPS testing will delay combined treatment with immunotherapy"
  - OR "… it is recommended where pembrolizumab is not suitable or if a CPS test result is not readily available"

Note

- Marketing authorisations each require a different tests
  - Committee's remit is to evaluate technologies *within* their marketing authorisation
- Nivolumab was dominated by pembrolizumab in both the company and ERG base case analysis, as such nivolumab is not considered a cost-effective option when pembrolizumab is suitable

How is the suitability of pembrolizumab decided?
Does use of a potentially cost-ineffective treatment outweigh implementation challenges?

Other considerations

ACM1

Equality considerations

- Acknowledged people in the most deprived areas may be more likely to be diagnosed with oesophageal cancer
- Committee noted this issue but it is unable to be addressed in a technology appraisal.

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
    - However, no uncaptured benefits were noted

Does use of an alternative test constitute an uncaptured benefit?

Abbreviations: OSCC, oesophageal squamous cell carcinoma

NICE National Institute for Health and Care Excellence

Thank you

NICE National Institute for Health and Care Excellence

Backup slides

Clinical perspectives at expert engagement

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 clinicians would conduct both tests

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

CheckMate 648 results

Table 1: Survival results from CheckMate 648 in PD-L1 TC ≥1% (n=315), [redacted]

	Nivolumab + chemo (n=158)	Chemo (n=157)
Progression free-survival		
Median PFS, months (95% CI)	[redacted]	[redacted]
Proportion with PFS events (%)	[redacted]	[redacted]
PFS HR (95% CI) p nivo + chemo vs. chemo	[redacted]	
Proportion PF at 12 months (95% CI)	[redacted]	[redacted]
Proportion PF at 18 months (95% CI)	[redacted]	[redacted]
Overall survival		
Median OS, months (95% CI)	[redacted]	[redacted]
Proportion with OS events (%)	[redacted]	[redacted]
OS HR (95% CI) p nivo + chemo vs. chemo	[redacted]	
Proportion alive at 12 months (95% CI)	[redacted]	[redacted]

The committee concluded that:

- PD-L1 TC ≥1% survival outcomes results are appropriate for decision making in this appraisal
- Nivolumab improves PFS and OS compared with chemotherapy alone

NICE

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