NICE National Institute for Health and Care Excellence

**For public: Contains no confidential information [Fully redacted]**

# Nivolumab for adjuvant treatment of oesophageal or gastroesophageal junction cancer [ID1676]

## Lead team presentation

**Lead team**: Min Ven Teo, Brian Shine
**Chair:** Jane Adam
**ERG:** ScHARR, University of Sheffield
**Technical team:** Summaya Mohammad, Lorna Dunning, Janet Robertson
**Company:** Bristol-Myers Squibb Pharmaceuticals
7th September 2021 – virtual meeting

# Key clinical issues

- Is nivolumab expected to be equally effective for adenocarcinoma and squamous cell carcinoma?
- Is CheckMate 577 generalisable to NHS practice?
- CheckMate 577 had specific inclusion criteria. Is this reflected in the MA?
  - Completed pre-operative chemo-radiotherapy followed by surgery
  - No residual disease after surgery (with clear margins)
  - Residual pathologic disease in the resected specimen
- Some people have chemotherapy not chemoradiotherapy in clinical practice in the NHS, are they excluded from the MA/this appraisal?
- Some people do not have surgery in clinical practice in the NHS, are they excluded from the MA/this appraisal?
- Only disease-free survival data is available from CheckMate 577, no overall survival data. What does the available evidence show in relation to potential disease cure both on current watch and wait, and with nivolumab?

# Disease background

## Two main types, diagnosis often at late stage with palliative treatment

**Definition:** Malignant tumour from cells lining oesophagus

- Squamous cell carcinoma → usually upper/middle oesophagus
- Adenocarcinoma → usually lower oesophagus including gastroesophageal junction

**Prevalence**

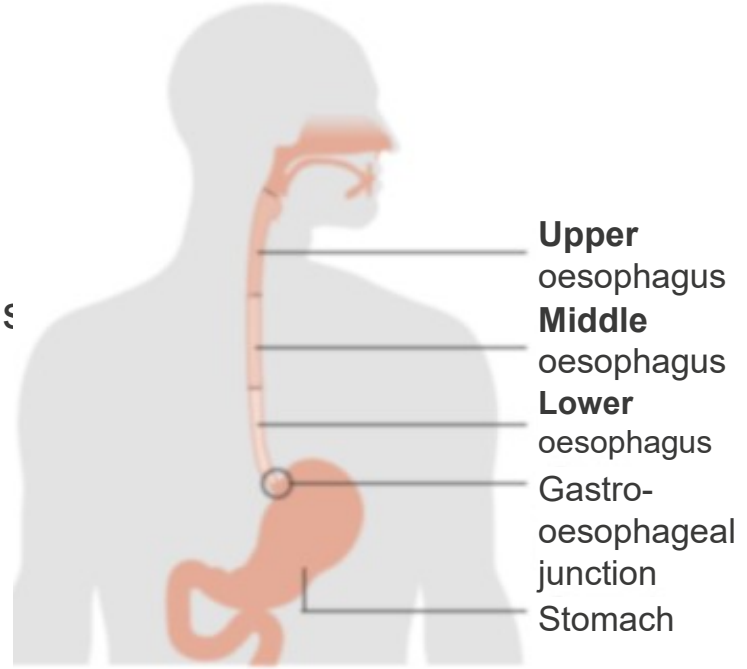
- 7,500 new oesophageal cancer diagnosis (England, 2017)
- Most common type of OC in the UK is adenocarcinoma
- 70-80% diagnosed at stage 3 (locally advanced) or 4 (metastatic)

**Symptoms**

- Initial symptoms: vague/similar to other stomach conditions leads to late diagnosis due to subtle/missed symptoms
- Advanced symptoms: lack of appetite, weight loss, fluid in abdomen, blood in stool

**Survival**

- 5 year survival 16.3% for stage 3
- Median survival post-recurrence reported as being less than six months in the Netherlands




*Adapted from Cancer Research UK*

Is nivolumab likely to be equally effective in both histological types?

# Patient organisation perspective

## Oesophageal cancer

- Early symptoms are vague, leading to late diagnosis and poor prognosis
- No treatment to delay/prevent cancer recurrence in this population
- Fear around lack of treatment and potential recurrence affects mental wellbeing
- Extremely difficult for carers and friends who have concerns about nutrition

## What people would like from treatment

- Current treatment options affect wellbeing and quality of life
- Improved quality and length of life
- Preventative option would be beneficial, knowing that treatment may increase outcomes
- More time with families

## Nivolumab

- Significant psychological benefit and health benefits
- Well tolerated, but patients to consider, any increased risk with COVID and long-term effects
- Treatment can increase own immune system to reduce rates of recurrence

# Clinical expert perspective

## Unmet need

- No recommended maintenance treatments after surgery
- Aim of treatment is cure, but 3-year survival only 57.4% after curative surgery
- Outcomes poor despite intense chemo/radiotherapy and surgery
- **CROSS trial:** Progression in 32% cases after neoadjuvant chemoradiation and surgery; better outcomes likely in complete response; 50-60% with residual disease likely to progress

## Nivolumab clinical trial

- CheckMate 577 trial representative of population having treatment in NHS
- Smaller eligible population
- Clinically meaningful benefit in disease free survival from nivolumab treatment
- Overall Survival data not available – but would be most important outcome

## Nivolumab in clinical practice

- Treatment well tolerated with no adverse effect on quality of life; toxicity is acceptable
- Consider additional hospital visits and management of serious adverse events via blood tests and CT scans
- Capacity of oncology units to be considered

# Nivolumab (Opdivo, Bristol-Myers Squibb)

| | |
|---|---|
| **Positive CHMP opinion EMA (June 21)** | Nivolumab as monotherapy is indicated for the adjuvant treatment of adult patients with oesophageal or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy |
| **Mechanism of action** | Human, monoclonal immunoglobulin antibody (IgG4) that acts as a checkpoint inhibitor of PD-1 |
| **Administration** | • 240 mg intravenous (IV) every 2 weeks over 30 mins<br>Or<br>• 480 mg every 4 weeks over 30 mins for 16 weeks<br>Followed by:<br>• 480 mg every 4 weeks over 30 mins |
| **Stopping rule** | • For adjuvant therapy, the maximum treatment duration with nivolumab is 12 month |
| **List price** | • £3,159.60 per 240 mg (24 ml) vial; £1,316.40 per 100 mg (10 ml) vial; £526.80 per 40 mg (4 ml) vial<br>• **Cost per dose:** £3,159.60 per 240 mg; £6,319.20 per 480 mg |

Does the MA align precisely with CheckMate 577 inclusion criteria, including requirement for surgical resection?

# Decision problem

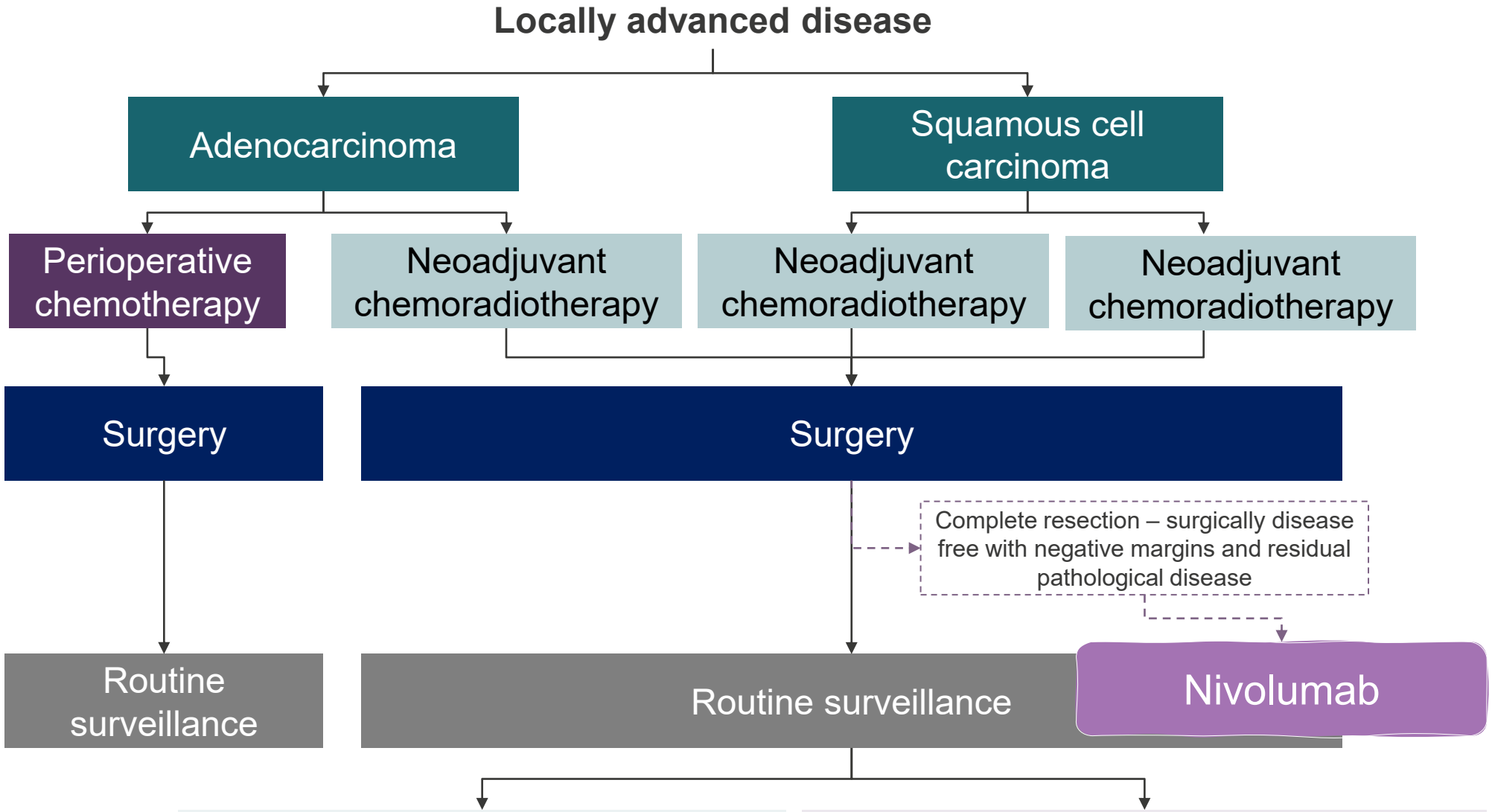
*Population aligned with key trial (CheckMate 577); overall survival excluded*

| | Final NICE scope | Company approach |
|---|---|---|
| **Population** | Adults with resected oesophageal cancer or gastroesophageal junction cancer | Adjuvant treatment of adult patients with resected oesophageal, or gastro-oesophageal junction cancer with residual pathologic disease following prior neoadjuvant chemoradiotherapy<br>More in line with CheckMate 577 |
| **Intervention** | Nivolumab | As final scope |
| **Comparators** | Routine surveillance | As final scope |
| **Outcomes** | • Overall survival (OS)<br>• Disease free survival (DFS)*<br>• Adverse effects of treatment<br>• Health-related quality of life | All except overall survival<br>➢ OS data not available at time of submission due to immature data<br>**ERG:** DFS up to 51 months was accepted as reasonable for modelling purposes |
| **Subgroups** | None | As final scope |

**ERG:**

- Differing evidence supporting DFS as surrogate outcome for OS – more data beneficial
- Some evidence suggests DFS not a good surrogate for OS in neoadjuvant treatment of GEJC, but sufficient follow-up means DFS is appropriate for modelling

# Treatment pathway



# Current treatments

- Depend on size, location and cancer stage
- Recent technology appraisals: NICE TA707 Nivolumab for previously treated unresectable advanced/recurrent oesophageal cancer (June 2021)
- **NICE clinical guideline [NG83]: Oesophago-gastric cancer: assessment and management in adults:**
  - Localised (gastro)oesophageal adenocarcinoma: chemotherapy before or before & after surgery **or** chemoradiotherapy before surgery
  - Squamous cell oesophageal carcinoma: chemoradiotherapy alone or before surgery
- **Advanced** (gastro)oesophageal cancer treatment aim: mainly palliative, prevent progression, extend survival and relieve symptoms

*Common chemotherapy agents: fluorouracil, capecitabine, cisplatin, epirubicine, docetaxel*

# Professional organisation input: variation in current practice

**Trial: very specific patient group** – post neoadjuvant chemoradiotherapy, complete resection after surgery, residual pathological disease in the specimen

- Expected in approx. 70% adenocarcinoma, 50% squamous cell carcinoma

- **Squamous:** difference in opinion between NHS professionals whether neoadjuvant chemoradiotherapy followed by surgery or **definitive chemoradiotherapy*** is preferred - broadly considered to be equivalent choices
- **Adenocarcinoma** of gastroesophageal junction: surgical based treatment is considered standard of care. Both neoadjuvant chemoradiotherapy followed by surgery and **peri-operative FLOT chemotherapy*** are considered acceptable

*** not included in CheckMate 577**

# Professional organisation: Non-trial patient eligibility

1) **Excludes:** Patients (SCC) with definitive chemoradiotherapy & no surgery. But suggest if have residual disease on re-staging endoscopy without metastatic disease on imaging could be equivalent

→ **Suggest Include**

2) **Excludes:** Patients with FLOT chemotherapy before surgery (adenocarcinoma gastro-oesophageal junction) instead of chemoradiotherapy – proportion of patients with residual disease post FLOT is slightly higher than chemoradiotherapy. Could be comparable

→ **Suggest Include**

3) **Excludes:** Patients with pre-op chemotherapy (Cisplatin-capecitabine or ECX) – complete path response is <10%, so >90% of the patients will have residual disease → higher than with chemoradiotherapy, so unlikely to be comparable groups (cannot be extrapolated)

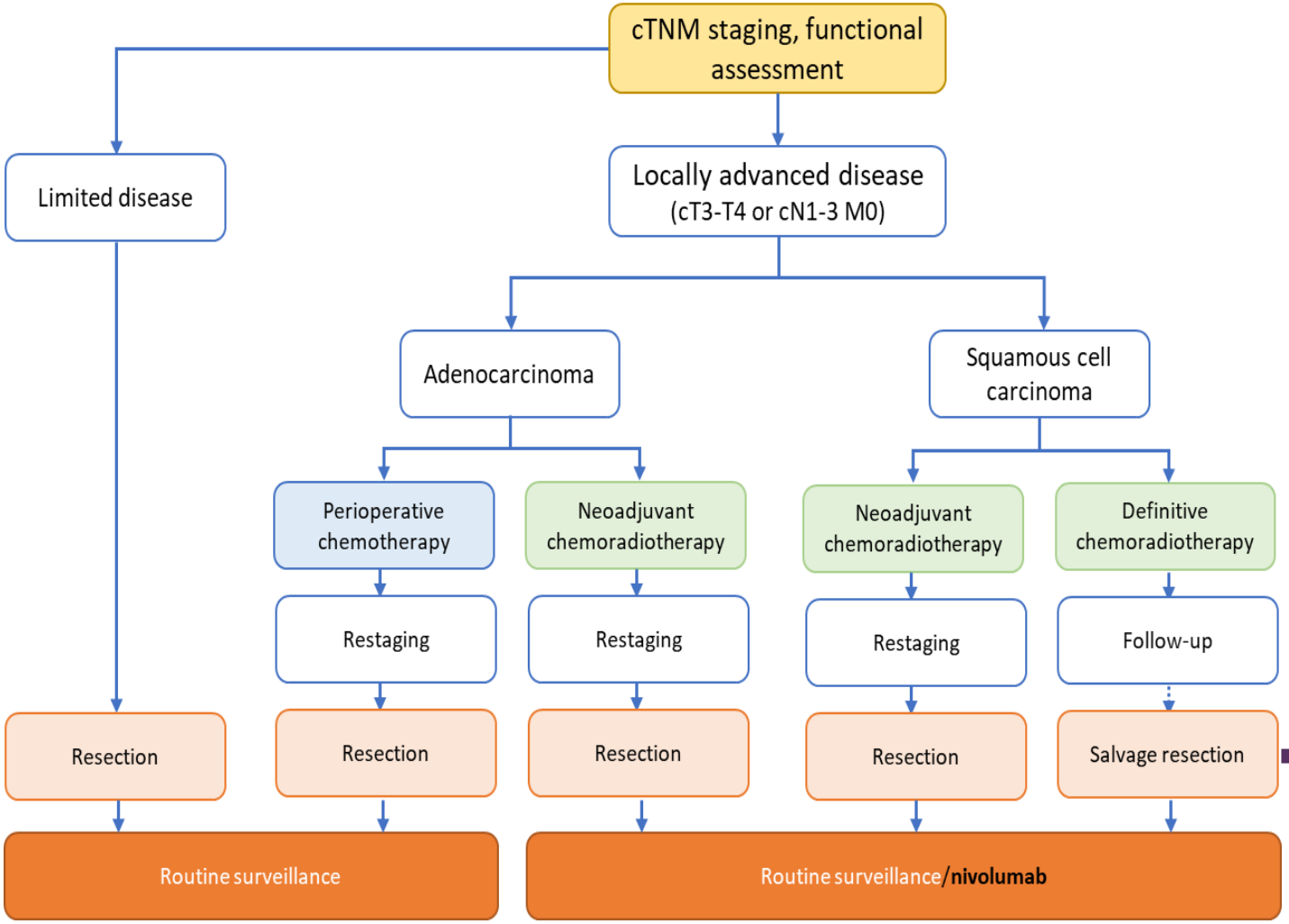
→ **Exclude**

**SmPC:**

- Baseline performance score ≥ 2, without concurrent chemoradiotherapy prior to surgery, with stage IV resectable disease, active autoimmune disease or medical conditions needing systemic immunosuppression, excluded from clinical study in oesophageal and gastroesophageal junction cancer
- Absence of data: Use nivolumab with caution in these populations after considering individual potential benefit/risk

Do alternative treatments exclude people from nivolumab treatment?

# Company treatment pathway




**Clinical experts:**
Salvage resection offered if:

1. Persistent disease after chemoradiotherapy (similar to CheckMate 577 cohort)
2. No evidence of disease after chemoradiotherapy but later develop locally recurrent disease (not evaluated in CheckMate 577) – unknown benefit of nivolumab

Eligibility for nivolumab may need to differentiate between (1) and (2)

# Clinical effectiveness evidence

# Key clinical trial: CheckMate 577

*CheckMate 577 identified as only relevant randomised controlled trial*

| | CheckMate 577 (in economic model as direct comparative evidence) |
|---|---|
| **Study design** | Phase III, multicentre, randomised, double blind, placebo-controlled study [redacted] |
| **Population** | Adults with stage II or III oesophageal or gastroesophageal junction carcinoma, after pre-operative chemoradiotherapy followed by surgery<br>➢ Complete resection with negative margins and residual tumour in the removed specimen |
| **Intervention** | Nivolumab monotherapy, 240mg intravenously (IV) every 2 weeks for 16 weeks. Then, 480 mg IV every 4 weeks, for 1 year or until disease recurrence, toxicity, withdrawal<br>➢ Some people had longer than 1 year treatment duration (due to delayed dose) |
| **Comparator** | Placebo |
| **1º outcome** | Disease free survival (time between randomisation and recurrence or death) |
| **2º outcomes** | OS (time from randomisation to death), OS rates at 1, 2 and 3 years |
| **Exploratory outcomes** | Adverse events and safety outcomes<br>Health-related quality of life |
| **Follow up** | 24.4 months (median), July 2020 primary analysis, further data cut February 2021 |

**ERG:** Good methodological quality of trial but only interim analyses available (ongoing trial) with immature overall survival data at time of submission

# CheckMate 577 baseline characteristics

*Generalisable to UK population with likely differences in age, sex and ethnicity*

| Baseline characteristic | | Nivolumab | Placebo |
|---|---|---|---|
| **Cohort size, n** | | 532 | 262 |
| **Median age (range), years** | | 62 (26-82) | 61 (26-86) |
| **Sex, n (%)** | Male | 449 (84.4) | 222 (84.7) |
| **Ethnicity, n (%)** | White | 432 (81.2) | 216 (82.4) |
| | Asian | 83 (15.6) | 34 (13) |
| **Location, n (%)** | US/Canada, Europe | 369 (69.4) | 189 (72.1) |
| | Asia | 77 (14.5) | 29 (11.1) |
| | Rest of world | 86 (16.2) | 44 (16.8) |
| **Histology, n (%)** | Adenocarcinoma | **376 (70.7)** | **187 (71.4)** |
| | Squamous cell | **155 (29.1)** | **75 (28.6)** |
| **Initial diagnosis, n (%)** | Oesophageal | 320 (60.2) | 155 (59.2) |
| | Gastroesophageal | 212 (39.8) | 107 (40.8) |
| **Baseline PD-L1, n (%)** | ≥ 1% | 89 (16.7) | 40 (15.3) |
| | < 1% | 374 (70.3) | 196 (74.8) |

**ERG: CheckMate 577 generalisability to UK:**

- UK population may be older
- Lower percentage of males in UK eligible population
- Ethnic balance unlikely to affect clinical efficacy

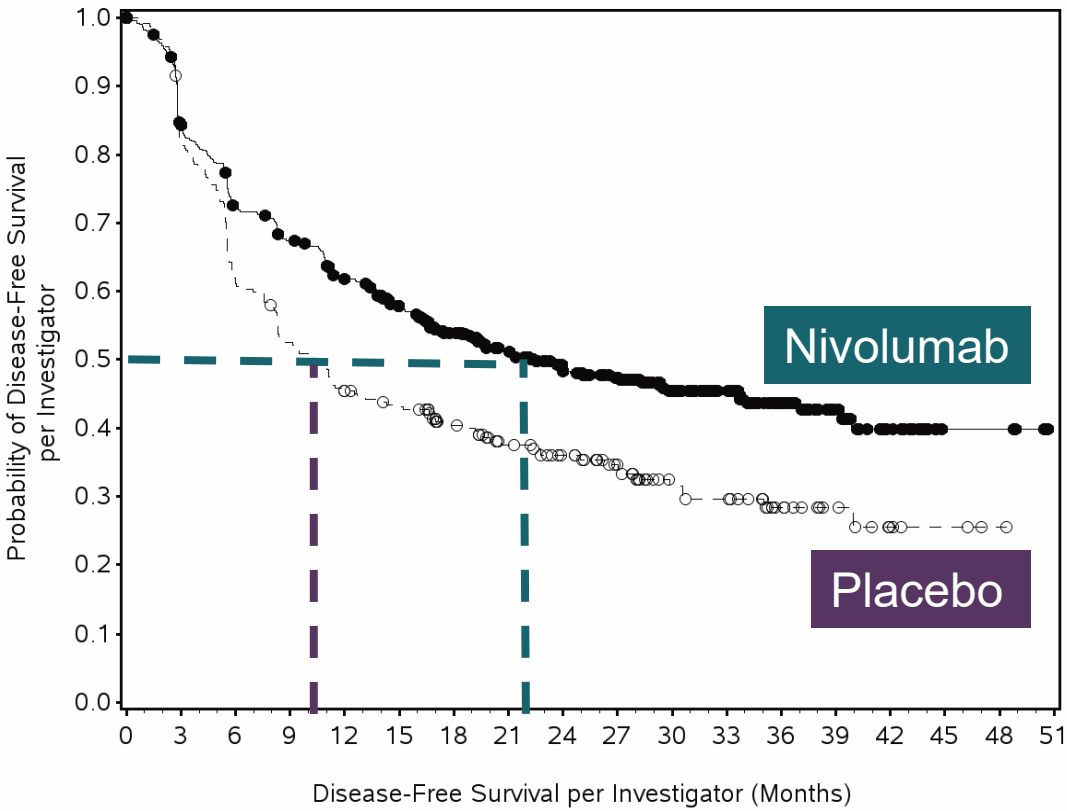
Is the balance of people with adenocarcinoma/ squamous cell cancer reflective of NHS population?

- Does the committee think CheckMate 577 is generalisable to population seen in NHS?

# CheckMate 577 Disease-free survival Kaplan-Meier plot

*Updated base case use new disease-free survival data with greater survival in nivolumab*

- Company updated base case to recently available Feb 2021 data – ERG agrees with change




Sustained plateau from July 2020 data

| | Nivolumab | Placebo |
|---|---|---|
| **Event, n (%)** | 268 (50.4) | 171 (65.3) |
| **Median, months (95% CI)** | 22.41 (16.95, 33.64) | 10.35 (8.31, 13.93) |
| **HR (95% CI)** | 0.67 (0.55, 0.81) | |

**Clinical experts:**

- At curve plateau, more patients are disease-free in nivolumab compared to placebo
- Some patients cured with lifelong benefit expected (maximum 26% according to 1 clinical expert)
- Most recurrences occur within 3 years.

What is committee's view on the clinical efficacy of nivolumab for adjuvant treatment of oesophageal or gastroesophageal junction cancer?

# CheckMate 577 subgroup DFS results

*Hazard ratios <1 for pre-specified subgroups*

Hazard ratio (95% CI) calculated using the stratified Cox method with treatment, subgroup, and treatment*subgroup interaction.

| | | Hazard Ratio (95% CI) nivolumab vs placebo |
|---|---|---|
| Histology | Squamous cell carcinoma | [redacted] |
| | Adenocarcinoma | [redacted] |
| Pathologic lymph node status | Positive | [redacted] |
| | Negative | [redacted] |
| PD-L1 status | PD-L1 ≥ 1% | [redacted] |
| | PD-L1 < 1% | [redacted] |
| | Indeterminate/non-evaluable | [redacted] |

**ERG:**
Although not powered to test for an interaction between treatment and subgroups, subgroup analyses unadjusted for randomisation stratification factors showed a hazard ratio (HR) <1 for almost all pre-specified subgroups

# Adverse events

*Similar frequency of overall adverse events and total serious adverse events in nivolumab and placebo*

| | | Nivolumab (N=532) | Placebo (N=260) |
|---|---|---|---|
| ***Safety event: Any grade, n (%)*** | | | |
| Adverse events | Overall all-cause | 510 (95.9) | 243 (93.5) |
| | Treatment-related | 376 (70.7) | 119 (45.8) |
| Serious adverse events | Total | 158 (29.7) | 78 (30.0) |
| | Treatment-related | 40 (7.5) | 7 (2.7) |
| Discontinuation | All-cause events | 68 (12.8) | 20 (7.7) |
| | Treatment-related | 48 (9.0) | 8 (3.1) |

**Most frequent adverse events** (any grade):

- Nivolumab and placebo: diarrhoea, fatigue, nausea, cough, vomiting

**Serious adverse event:** (fatal, life-threatening, hospitalisation, disability, birth defect, infection)

- Nivolumab: pneumonia, malignant neoplasm progression, pneumonia aspiration, pneumonitis, dysphagia
- Placebo: malignant neoplasm progression, pneumonia, dysphagia, pleural effusion, pneumothorax, dyspnoea, diaphragmatic hernia, oesophageal stenosis

# Key clinical issues

- Is nivolumab expected to be equally effective for adenocarcinoma and squamous cell carcinoma?
- Is CheckMate 577 generalisable to NHS practice?
- CheckMate 577 had specific inclusion criteria. Is this reflected in the MA?
  - Completed pre-operative chemo-radiotherapy followed by surgery
  - No residual disease after surgery (with clear margins)
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- Only disease-free survival data is available from CheckMate 577, no overall survival data. What does the available evidence show in relation to potential disease cure both on current watch and wait, and with nivolumab?

# Cost-effectiveness evidence

# Key cost issues

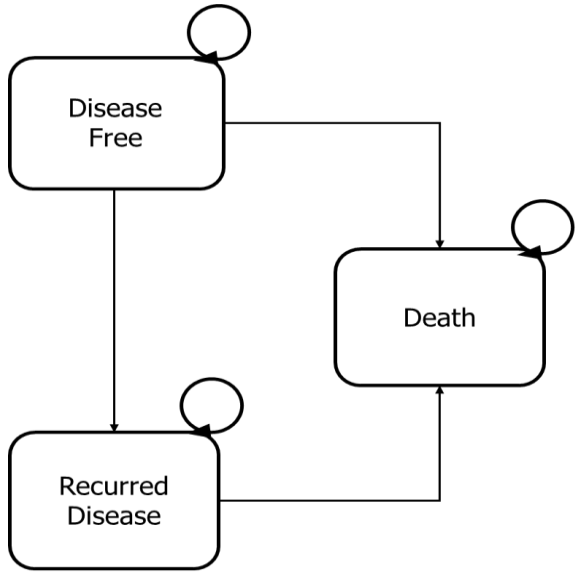
- Is the model appropriate for decision making?
- At what duration of DFS can a ‘cure’ be assumed?
- Does cure imply, not just no recurrence of the cancer, but QoL and life expectancy equivalent to the whole population despite previous chemotherapy and surgery?
- Is the replacement of a stopping rule at 12 months by dose modifier appropriate?

# Company's economic model

*Semi-Markov model with 3 health states*

| | |
|---|---|
| **Model type** | Semi-Markov model – 3 health states<br>• Allows dependency between events rather than priori assumptions |
| **Time horizon** | Lifetime (up to 40 years) |
| **Model cycle** | Weekly |
| **Population** | CheckMate 577 patient-level data |
| **Intervention** | Adjuvant nivolumab treatment |
| **Comparators** | Routine surveillance (CheckMate 577 placebo arm) |
| **Utility values** | • EQ-5D-3L data from CheckMate 577<br>• Utility post-recurrence from TA707: revised post TE to use age adjusted utilities from Ara and Brazier (2010) as data missing from CheckMate 577<br>• Disutilites associated with nivolumab included |
| **Stopping rule** | 1 year → removed post TE: dose modifier added, agreed by ERG |

**Company:** Partitioned survival model not possible because unavailable overall survival data




**ERG:** No half-cycle correction is not a limitation because of weekly time cycles

Does the committee think that the model is appropriate?

# Outstanding issues after technical engagement

| Key issues | Company | ERG | Updated company base case |
|---|---|---|---|
| **Data used in fitting Disease-free survival (DFS)** | DFS data used at submission (June 2020) | More recently available DFS data (Feb 2021) | Yes – More recently available DFS data (Feb 2021) |
| **Distribution used to model DFS** | Lognormal 1 knot spline distribution | Generalised F-distribution | Yes – Generalised F-distribution |
| **'Cure' point during DFS** | 3 years* | 5 years* | No – 3 years* |
| **Average age of patients treated in UK** | 60.5 years (CheckMate 577) | Audit data | Yes – 62.7 years used from adjusted trial data |
| **Utility data** | Source: Szende et al. | Source: Ara and Brazier | Yes – Ara and Brazier and factor age-related utility |
| **Underestimation of costs** | 12 months duration of treatment | 63 weeks duration of treatment (CheckMate 577) | Yes – No stopping rule but dose modifier added |

# Disease-free survival 'cure' point

*Company maintain 3 year 'cure' point, considered appropriate by clinical experts*

**'Cure' point:** patients in disease-free state have mortality risk associated with general population

**Company:**
- Cure point at **3 years DFS appropriate**
- Low risk of DFS events after ~2 years
- Feb 2021 data showed [redacted] events after 36m – from [redacted] patients at risk in nivolumab arm and [redacted] in placebo
- Clinical advice: all patients considered disease-free after resection but hazard may not converge to general population for 3-5 years
- Provided scenario analysis up to 3 years

**ERG:**
- Cure points at **5 years DFS preferred**
- Some DFS events occur after 3 years
- Longer duration can better estimate timepoint of no further events
- Cured patients means death only due to background mortality – data from company indicate rates greater than general population aged around 66 years
- Limited impact on ICER

**Clinical experts: 3 years is an appropriate cure point**
- Most events occur within 3 years
- Studies including CROSS trial (basis for current standard of care) and CheckMate 577 show flattening of curve after 3 years.
- This patient group is relatively worse off where events are expected earlier
- Few relapses occur between 3-5 years, some can occur after 5 years but 3 years is reasonable

Which 'cure' point does the committee prefer?

# Return to general population mortality estimates after ‘cure’ point

**Company:**

- Assume that all patients who were alive at 3 years and did not have progressed disease were ‘cured’, and returned to general population mortality rates from this time point

‘Cure’

- No recurrence
- Quality of life and life expectancy aligned to a person who has not had the disease

People who had Nivolumab would have received: chemoradiotherapy, surgery and immunotherapy
Risk factors for this condition may pre-dispose for increased background mortality

**ERG:**

- ERG provide a scenario where after 5 years, the mortality rate of ‘cured’ patients was higher than that of the general population.
- Modelled survival using an uplifted general population mortality rate (standardised mortality ratio of 1.1). Probability of death was increased by an arbitrary 10% for all patients aged 68 years and over.
- Resulted in a deterministic ICER of £17,105 (+£500)
- Indicates the results robust to assumptions regarding increased mortality compared with the general population after ‘cure’.

Is the mortality of ‘cured’ patients likely to be higher than the general population?

# Underestimation of costs

*Stopping rule removed, dose modifier included which results in decrease in ICER*

**Company:**
- Capped the duration of Nivolumab treatment at 12 months
- Longer treatment due to dose delays not incorporated in model

**ERG:**
- Patients in CheckMate 577 had treatment for up to 63 weeks
- Benefit may be incorporated in disease-free survival, costs should reflect benefits

**After Technical Engagement:**
- Company removed 12 month stopping
- Dose modifier included for dose delays (with updated CheckMate 577 data)
- ICER largely unchanged from base case.

**ERG:**
- Agree with adding dose modifier

**Clinical experts:**
- Dose delays can be due to toxicity/scheduling
- Total intended infusions in trial = [redacted] – suggest as cap instead of 63 weeks

**Potential overestimation of costs:**
- Not all patients will complete 1 year treatment, eligible population limited to residual disease after resection (not all resection cases)
- Cap of 63 weeks for patient not delayed leads to 5 further infusions and added costs

What is committee's view on the dose modifier and removal of stopping rule?

# Issues resolved after Technical Engagement

# Disease-free survival distributions: agreed

*Generalised F-distribution and lognormal are appropriate, with generalised F-distribution giving the lowest AIC and BIC values, accepted by company post TE*

Nivolumab

**Lognormal:**
**AIC:** [redacted], **BIC:** [redacted], **Median:** [redacted]
**Generalised F-distribution:**
**AIC:** [redacted], **BIC:** [redacted], **Median:** [redacted]

Placebo

**Lognormal:**
**AIC:** [redacted], **BIC:** [redacted], **Median:** [redacted]
**Generalised F-distribution:**
**AIC:** [redacted], **BIC:** [redacted], **Median:** [redacted]

**Company:**

- Only generalised F-distribution and log-normal splines with 1 or 2 knots were appropriate
- Log-normal splines with 1 knot led to a high mean survival, but in the model, after 3 years mortality risk is associated with average age- and sex-matched member of the general population

# Model inputs agreed post TE

**Utilities:**

- Company updated model to use **Ara and Brazier (2010) data and factor age-related utility**
- Amendment decreases original ICER from £22,766 to £22,112

**Age:**

- Company original submission: mean age 60.5 years from CheckMate 577
- ERG noted UK population expected to be older than CheckMate 577 trial population and ICER sensitive to average age
- After TE company present adjusted CheckMate 577 age using NCRAS/CRUK data, average age **62.66 years used as model input**
- Clinical experts noted trial likely to represent UK population and reflects audit data from NHS clinical trust (average age 63 years)
- Amendment increases original ICER from £22,766 to £24,714
- 62.66 agreed by ERG

# Cost effectiveness results

# Summary of assumptions in updated base case post TE

| | Company | ERG |
|---|---|---|
| **Data source** | Feb 2021 data cut | Feb 2021 data cut |
| **Age** | 62.66 years<br>(Adjusted from trial) | 62.66 years<br>(Adjusted from trial) |
| **Extrapolation of DFS** | Generalised F-distribution | Generalised F-distribution |
| **Cure** | **3 years** | **5 years** |
| **Utilities** | Age adjusted Ara and Brazier (2010) | Age adjusted Ara and Brazier (2010) |
| **Stopping rule** | No stopping rule, but with dose modification | No stopping rule, but with dose modification |

# Cost-effectiveness results post TE

| | Treatment | Costs (£) | QALYs | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|
| **Company base case (probabilistic)** | Nivolumab | [redacted] | [redacted] | [redacted] | [redacted] | £17,511 |
| | Routine surveillance | [redacted] | [redacted] | | | |
| **Company base case (deterministic)** | Nivolumab | [redacted] | [redacted] | [redacted] | [redacted] | £16,668 |
| | Routine surveillance | [redacted] | [redacted] | | | |
| **ERG base case (probabilistic)** | Nivolumab | [redacted] | [redacted] | [redacted] | [redacted] | £17,613 |
| | Routine surveillance | [redacted] | [redacted] | | | |

# Scenario analyses

| Scenario | Source base case | Incremental costs (£) | Incremental QALYS | ICER (£/QALY) |
|---|---|---|---|---|
| Company base case (deterministic) | | [redacted] | [redacted] | £16,668 |
| ERG base case (deterministic) | | [redacted] | [redacted] | £16,611 |
| Mean age 65 years | ERG | [redacted] | [redacted] | £18,574 |
| Mortality rate of 'cured' patients higher than general population (standard mortality rate [SMR] 1.1) | ERG | [redacted] | [redacted] | £17,105 |
| Mean age 65 years with SMR 1.1 for 'cured' patients | ERG | [redacted] | [redacted] | £19,169 |

# Equalities

No equality issues raised during scoping, submission or technical engagement

# Key cost issues

- Is the model appropriate for decision making?
- At what duration of DFS can a ‘cure’ be assumed?
- Does cure imply, not just no recurrence of the cancer, but QoL and life expectancy equivalent to the whole population despite previous chemotherapy and surgery?
- Is the replacement of a stopping rule at 12 months by dose modifier appropriate?