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NICE National Institute for Health and Care Excellence

Nivolumab in combination with chemotherapy for untreated advanced gastric, gastro-oesophageal junction cancer or oesophageal adenocarcinoma

Lead team presentation
G.J. Melendez-Torres, Khalida Ismail, Richard Ballerand

ERG: Liverpool Reviews & Implementation Group
Technical team: Jane Adam, Marcela Haasova, Cara Gibbons, Mary Hughes, Janet Robertson
Company: Bristol-Myers Squibb

ACM1: 3rd August 2021

Key clinical issues

- Note: CHMP decision not expected at time of first committee meeting.
  - The anticipated wording of CHMP decision has changed since technical engagement to: [redacted].

- **Comparators:**
  - Is XELOX the key comparator for this appraisal?
- **Generalisability of trial data:**
  - Is the CheckMate 649 trial generalisable to NHS practice?
- **Long-term remission:**
  - The trial data is approximately 70% complete for PFS and OS. Does lack of progression at 30 months = being cured? What is the evidence that advanced gastric, gastro-oesophageal junction and oesophageal adenocarcinoma can be cured? If people survive will their rate of death be the same as the general population?

Gastric, gastro-oesophageal junction or oesophageal adenocarcinoma: disease background

- **Gastric adenocarcinoma:** originates in the cells of the stomach
- **Gastro-oesophageal junction adenocarcinoma:** the centre of the tumour is less than 5cm above or below where the oesophagus meets the stomach.
- **Oesophageal adenocarcinoma:** originates from cells lining the oesophagus.
  - Can be collectively referred to as **gastroesophageal adenocarcinoma**.

Note: Ninety-five percent of cancers of the stomach are adenocarcinomas. Adenocarcinoma arises in the glandular tissue. In oesophageal or gastro-oesophageal junction cancer, adenocarcinoma is mostly found in the lower oesophagus and accounts for ~2/3 of UK cases.

Diagnosis is often at an advanced stage. The 5-year survival for people with gastroesophageal adenocarcinoma between 2013 and 2017 was between 17-22%.

- In the UK between 40-50% of all new cases of gastroesophageal adenocarcinoma are diagnosed in people aged 75 years and over.

Nivolumab with chemotherapy

Mechanism	Fully human, monoclonal immunoglobulin antibody (IgG4) that acts as a checkpoint inhibitor of PD-1.
Anticipated marketing authorisation	[redacted].
Anticipated administration as per marketing authorisation	Nivolumab + fluoropyrimidine- and platinum-based chemotherapy intravenously over 30 minutes: 1. 360 mg nivolumab + chemotherapy every 3 weeks or 2. 240 mg nivolumab + chemotherapy every 2 weeks. ➢ Nivolumab is given first, followed by chemotherapy. ➢ Treatment until disease progression or unacceptable toxicity. ➢ Maximum treatment duration for nivolumab is 24 months.
Price	• 10 mg/ml concentration for solution for infusion: 4, 10 and 24 ml vials: 240 mg = £2,633 & 360 mg= £3,950. • Confidential PAS for nivolumab is in place.

Patient and carer perspectives

Guts UK

- These cancers are frequently diagnosed late so treatment options are limited.
- Nivolumab + chemotherapy offers a different mechanism of action and another option where there are currently few available.
- This treatment could help people with life limiting conditions to enjoy valuable time with family and participate in daily living.
- Symptoms such as fatigue, pain and appetite loss have an impact on quality of life and affect social activities such as eating with family, enjoyment of food and attending social events.
- Fewer are diagnosed with these cancers compared to other cancers, so any population differences should not prevent patients access to nivolumab.

Clinician perspectives on treatment options

NCRI-ACP-RCP-RCR (National Cancer Research Institute, Association of Cancer Physicians, Royal College of Physicians, Royal College of Radiologists)

- The standard first line treatment is platinum based chemotherapy (oxaliplatin/cisplatin) plus a fluoropyrimidine (infused fluorouracil or capecitabine tablets).
- In this population, current treatment does not lead to long term remissions or cures:
  - There is a significant unmet need.
  - Survival for patients with advanced gastro-oesophageal adenocarcinoma is poor.
  - More research and better treatments are required to improve outcomes.
- CheckMate 649 is a large, well powered global trial which shows a significant and meaningful survival benefit for nivolumab plus chemotherapy in advanced gastroesophageal cancer with a PD-L1 CPS score of ≥5.
- Although adding nivolumab to chemotherapy does lead to higher levels of toxicity, patients did not stop treatment as a results of these side effects.

PD-L1 = programmed death ligand 1; CPS, combined positive score.

Advanced gastric, gastro-oesophageal junction (GOJ) or oesophageal adenocarcinoma

1st line

NG 83 Palliative chemotherapy:

- **Doublet chemotherapy**: fluorouracil or capecitabine + cisplatin or oxaliplatin
  - fluorouracil + oxaliplatin: (FOLFOX = fluorouracil + folinic acid + oxaliplatin)
  - XELOX = capecitabine + oxaliplatin
  - cisplatin + fluorouracil
  - cisplatin + capecitabine
- **Triplet chemotherapy**
  - doublet treatment with epirubicin and best supportive care
- **NB: company considers FOLFOX/XELOX to be established NHS practice**

Trastuzumab with cisplatin + capecitabine or fluorouracil for **HER2-positive** metastatic adenocarcinoma of the **GOJ** - TA208

Gastric cancer: Capecitabine + platinum-based regimen TA191

Proposed: Nivolumab + chemotherapy (FOLFOX or XELOX) for **gastric**, **GOJ and oesophageal adenocarcinoma** ID1465

Note proposed: pembrolizumab + platinum-based chemotherapy for **HER2-negative GOJ (adenocarcinoma) and oesophageal (squamous cell or adenocarcinoma) PD-L1 CPS >10 cancer** ID3741

2nd line

Palliative chemotherapy and best supportive care (NG83)

Decision problem

	Scope	Company
Population	Adults with untreated locally advanced or metastatic gastric or gastro-oesophageal junction or oesophageal adenocarcinoma.	Expected MA: [redacted].
Intervention	Nivolumab + chemotherapy.	Nivolumab + XELOX or FOLFOX.
Comparators	Chemotherapy without nivolumab: • Doublet treatment = fluorouracil or capecitabine plus cisplatin or oxaliplatin. • Triplet treatment = doublet treatment plus epirubicin. For people with HER2-positive status: • Trastuzumab with cisplatin plus capecitabine or fluorouracil.	**PD-L1 with CPS ≥5 population:** • XELOX or FOLFOX (direct evidence). + Cost-effectiveness scenario analyses based on ITT population (using NMA): - fluorouracil+cisplatin - capecitabine+cisplatin
Outcomes	• Overall survival; progression-free survival; response rate; adverse effects of treatment; health-related quality of life.	

Abbreviations: XELOX, capecitabine + oxaliplatin; FOLFOX, fluorouracil + folinic acid + oxaliplatin; PD-L1, programmed death ligand 1; CPS, combined positive score; HER2, human epidermal growth factor receptor 2

Clinical effectiveness evidence

Pivotal trial: CheckMate 649

Trial design	Phase 3 trial, open-label, randomised, multi-centre trial: • 175 centres across 29 countries - 38 patients from 5 UK centres
Population	Untreated and inoperable, advanced or metastatic (regardless of PD-L1 status): – gastric ([redacted]), – gastro-oesophageal junction ([redacted]), – or oesophageal adenocarcinoma ([redacted]) • ≥18 years; ECOG performance status 0 or 1; patients with known HER2-positive status and patients with untreated CNS metastases were excluded.
Intervention	Nivolumab + chemotherapy (n=789): XELOX ([redacted]) or FOLFOX ([redacted]).
Comparator	Chemotherapy (n=792): XELOX ([redacted]) or FOLFOX ([redacted]).
Primary Outcomes	PFS by BICR and OS in PD-L1 CPS ≥5 participants.
Stratification factors	PD-L1 CPS expression levels (≥1% vs <1%); Region (Asia vs North America vs Rest of world); ECOG performance status (0 vs 1); XELOX vs FOLFOX.

Abbreviations: CNS = central nervous system, XELOX = capecitabine+oxaliplatin, FOLFOX = fluorouracil+folinic acid+oxaliplatin, OS = overall survival, PFS = progression-free survival, BICR = blinded independent central review, PD-L1 = programmed death ligand 1, CPS = combined positive score, HER2 = human epidermal growth factor receptor 2

Patient baseline characteristics

	PD-L1 CPS ≥5 (n = 955)		All (n = 1581)	
	Nivo+chemo (n = 473)	Chemo (n = 482)	Nivo+chemo (n = 789)	Chemo (n = 792)
Mean age, years	[redacted]	[redacted]	[redacted]	[redacted]
Gender, male (%)	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS 1 (%)	[redacted]	[redacted]	[redacted]	[redacted]
Initial diagnosis (%) Gastric Cancer	[redacted]	[redacted]	[redacted]	[redacted]
Gastro-oesophageal junction Cancer	[redacted]	[redacted]	[redacted]	[redacted]
Oesophageal Adenocarcinoma	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 (%) ≥5	[redacted]	[redacted]	[redacted]	[redacted]
Region (%) US	[redacted]	[redacted]	[redacted]	[redacted]
Asia	[redacted]	[redacted]	[redacted]	[redacted]
Rest of the world	[redacted]	[redacted]	[redacted]	[redacted]

CheckMate 649: PFS results – approximately [redacted] events have occurred

		Nivolumab+Chemotherapy	Chemotherapy
All randomised patients with PD-L1 CPS ≥5 (n = 955) – primary outcome			
Median Months (95% CI)	**July 20**	7.69 (7.03 to 9.17)	6.05 (5.55 to 6.90)
	[redacted]	[redacted]	[redacted]
Events: n (%)	**July 20**	[redacted] **events**	[redacted] **events**
	[redacted]	[redacted] **events**	[redacted] **events**
HR (CI)	**July 20**	**0.68 (98% CI: 0.56 to 0.81)**	
	[redacted]	[redacted]	

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Note: July 2020 data in model. Limited [redacted] data submitted post TE - supportive evidence only.

CheckMate 649: OS results– approximately [redacted] events have occurred

		Nivolumab+Chemotherapy	Chemotherapy
All randomised patients with PD-L1 CPS≥5 (n = 955) – primary outcome			
Median Months (95% CI)	**July 20**	14.39 (13.11 to 16.23)	11.10 10.02 to 12.09)
	[redacted]	[redacted]	[redacted]
Events: n (%)	**July 20**	[redacted] **events**	[redacted] **events**
	[redacted]	[redacted] **events**	[redacted] **events**
HR (CI)	**July 20**	**0.71 (98.4% CI: 0.59 to 0.86)**	
	[redacted]	[redacted]	
All randomised patients (n = 1581)			
Median Months (95% CI)	**July 20**	13.83 (12.55 to 14.55)	11.56 (10.87 to 12.48)
	[redacted]	[redacted]	[redacted]
HR (CI)	**July 20**	**0.80 (99.3% CI: 0.68 to 0.94)**	
	[redacted]	[redacted]	

Note: All randomised data shown because ERG critique of plausibility of modelled overall survival relates to this population (company updated its intended MA after technical engagement). July 2020 data in model. Limited [redacted] data submitted post TE - supportive evidence only.

Issue: Comparators

Background:

Company:

- XELOX and FOLFOX are the key comparators & same clinical effectiveness assumed for XELOX and FOLFOX.
- Base case: nivolumab + XELOX/ FOLFOX vs XELOX/ FOLFOX (CheckMate 649).
- Scenario cost-effectiveness analyses for:
  - fluorouracil + cisplatin.
  - capecitabine + cisplatin using indirect evidence from an NMA.
  - number of comparators not included.

ERG:

- XELOX/FOLFOX are key comparators.
- 80% of NHS patients will have XELOX.

Clinical expert:

- Preferred regimens: XELOX, FOLFOX, cisplatin + fluorouracil, cisplatin + capecitabine.
- Assuming similar clinical effectiveness is reasonable.
- Oxaliplatin is preferred to cisplatin as it is safer and has a shorter infusion time.
- Triplet treatment is uncommon.
- Confirm XELOX/FOLFOX are the key treatments.

Company in response to ERG report:

- Direct evidence available in CheckMate 649.

ERG: direct CheckMate 649 evidence used in base case.

Is XELOX the key comparator for this appraisal?

Issue: Generalisability of CheckMate 649

Background:

- Trial mean age was [redacted] years and ([redacted]) were under 65.
- At baseline, all patients in the trial had an ECOG of 0 or 1.

ERG:

- CheckMate 649 trial population is younger and fitter than seen in NHS practice (including patients with ECOG 2).
- Age is lower than average age reported by:
  - ERG's clinical advisor (70 to 75 years).
  - Cancer Research UK (mean 64.15 years).
  - The Royal Marsden Hospital Trust data (median 66 years).

Clinical expert:

- Mean trial age is expected to be younger than NHS population.
- No evidence in CheckMate 649 that treatment is less effective in older patients.
- Treatment should be based on patient fitness and co-morbidities, regardless of age and performance status.

Company in response to ERG report:

- Age aligned with UK data sources.
- Limited evidence to suggest outcomes differences between different ECOG performance scores.

ERG post engagement: No new evidence presented by company at technical engagement.

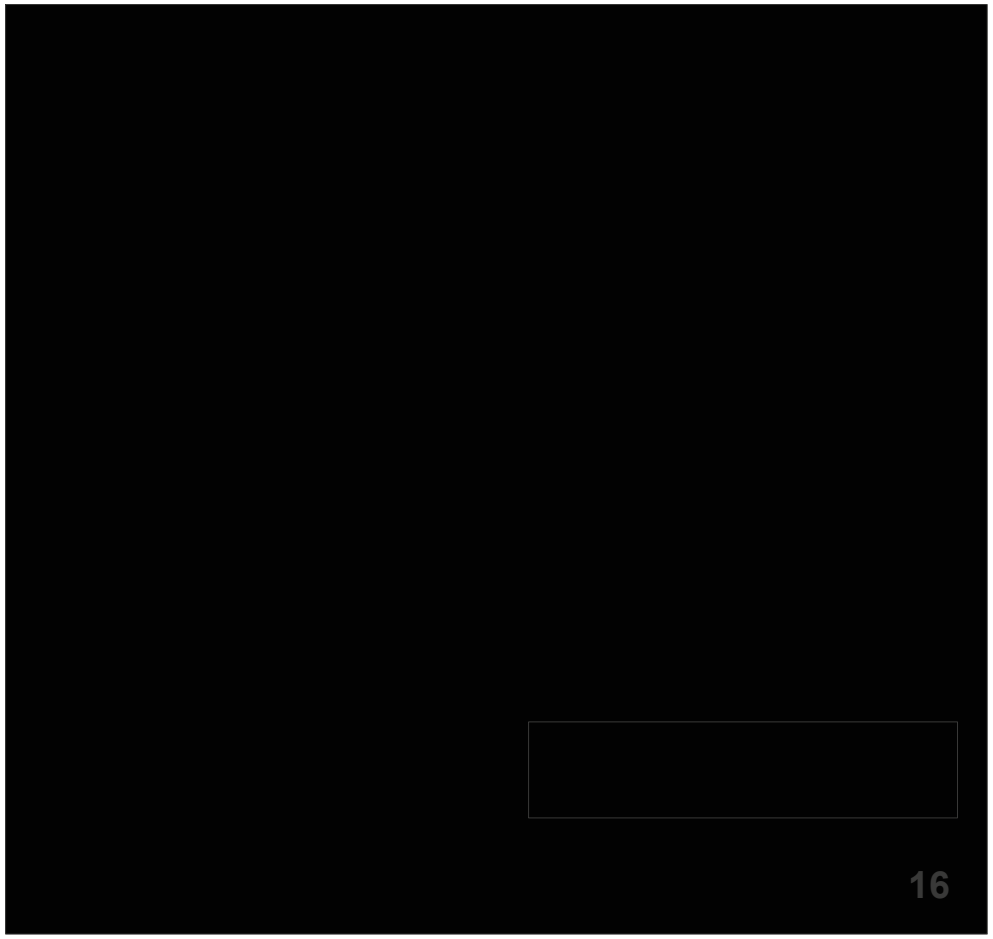
Is the CheckMate 649 trial generalisable to NHS practice?

Abbreviations: ECOG = Eastern Cooperative Oncology Group

Issue: long term remission/cure 1/2

Company: hazard of progression or death among patients who had not yet progressed decreases over time and plateaus at 30 months. OS hazard estimated to reduce to approximately match the general population.

ERG: Company assumes people who have not progressed by 30 months have same risk of dying as general population = are cured. Cure assumption not supported by evidence: low numbers at risk.



Issue: Long-term remission/cure 2/2

Company: CheckMate 649 (July 2020 ITT data), the proportion of patients with prolonged survival is increased in NIVO+CHEMO arm: OS at one year was 55.0% (versus 47.9% for CHEMO), [redacted] at two years (versus [redacted] for CHEMO) and [redacted] at three years (versus [redacted] for CHEMO).

- Long term remission (LTR) supported by data from number of trials (COUGAR-02, ATTRACTION-2, Chau 2009, CheckMate 649, Royal Marden Hospital data).

ERG: Company's assumption of cure at 30 months is not supported by evidence:

- Company's model: based on CheckMate 649 ITT data [redacted] of patients on nivolumab + chemotherapy and [redacted] on chemotherapy are cured. Of patients alive at 5 years, [redacted] of nivolumab + chemotherapy & [redacted] on chemotherapy are in LTR and cured.
- Number at risk on PFS at 18 months are low – uncertain results.
- Clinical advice: only about 1% of patients can achieve LTR.
- Other clinical evidence: COUGAR-02: only 5 patients at risk at 18 months etc…

Clinical expert:

- LTR is likely, this has been seen with immunotherapy.
- ATTRACTION-2: patients with chemorefractory gastroesophageal adenocarcinoma responding to nivolumab monotherapy had median OS of ~ 2 years.

Does lack of progression at 30 months = cure? What is the evidence that advanced gastroesophageal adenocarcinoma can be cured and that people will have the same risk of death as the general population?

Key clinical issues

- Note: CHMP decision not expected at time of first committee meeting.
  - The anticipated wording of CHMP decision has changed since technical engagement to: [redacted].
- **Comparators:**
  - Is XELOX the key comparator for this appraisal?
- **Generalisability of trial data:**
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- **Long-term remission:**
  - The trial data is approximately 70% complete for PFS and OS. Does lack of progression at 30 months = being cured? What is the evidence that advanced gastric, gastro-oesophageal junction and oesophageal adenocarcinoma can be cured? If people survive will their rate of death be the same as the general population?

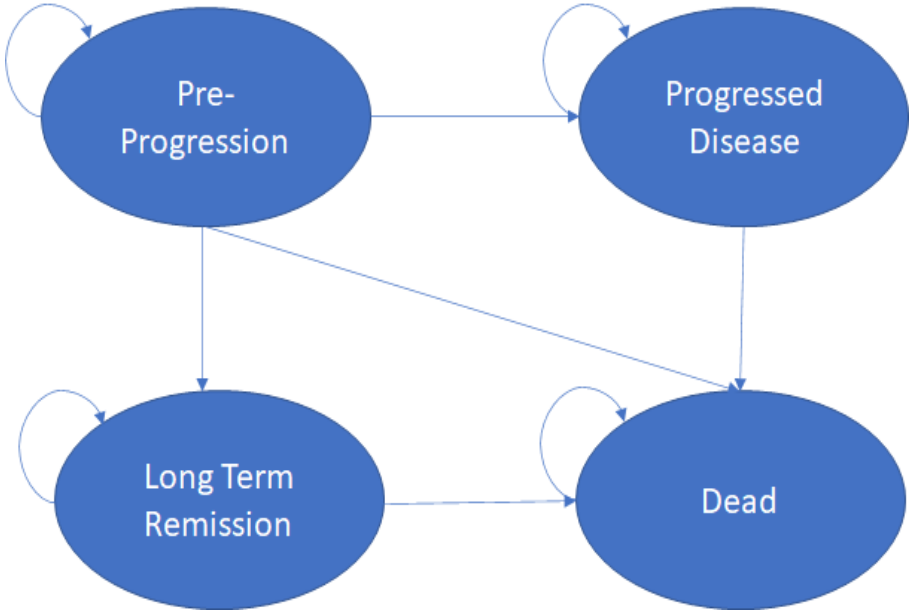
Cost-effectiveness evidence

Key cost-effectiveness issues

- **Overall survival modelling**
  - The trial data is approximately 70% complete for PFS and OS. ERG considers the company's model unnecessarily complicated. CheckMate 649 OS data are not directly used in the model which is based on projecting OS from PFS data.
  - The model estimates for OS at 12-month are higher than the trial.
  - Is the company's method for estimating OS suitable for decision making?
- **Long-term remission (LTR) state**
  - ERG removed LTR state from the model. **This has a large impact on ICER.** Should the LTR state be included in the model? If so, how it should be modelled?
- **End of life:** Are end of life criteria met?
- **PD-L1 testing:** Are there any potential issues with implementing PD-L1 and CPS assessments in practice? Should the cost of PD-L1 testing be included?
- After technical engagement company and ERG use the same inputs for: a) Utilities: based on CheckMate 649, b) Baseline age: 64.15 years (Cancer Research UK) rather than [redacted] (CheckMate 649), c) Adjustment of costs for missed doses.

Model summary

- Cohort-based semi-Markov with 4-states: long-term remission state used as it may occur in a small proportion of patients.
- Model differs from the 3-state partitioned survival model frequently used in NICE oncology technology appraisals (e.g. TA208, TA483, TA484).



Time horizon	Up to 50 years
Model cycle	2 weeks
Discount rates	3.5%
Population	Adults with previously untreated advanced or metastatic, HER2-negative, gastric or gastro-oesophageal junction or oesophageal adenocarcinoma. Model baseline age 64.15 years based on Cancer Research UK mean age. • Company's scenario based on CheckMate 649 ([redacted] years).
Intervention	Nivolumab + XELOX or FOLFOX
Comparators	XELOX or FOLFOX
Outcomes	Progression-free survival and post-progression survival

Issue: OS modelling 1/2

Background:

Company:

- Survival indirectly modelled through PFS (measures people whose disease has progressed or have died before progression). Modelled the probability a PFS event was death over time. Progression risk was calculated by subtracting mortality risk from the composite PFS risk.

ERG report:

- Company's model is unnecessarily too complicated.
- CheckMate 649 OS data are not directly used in the model.
- Estimates for first 12-months are higher than CheckMate 649 data.
- Model does not reflect trial survival estimates, therefore long-term OS estimates and cost-effectiveness results lack confidence and reliability.

Company response to ERG report:

- Death on progression recalculated based on BICR (blinded independent central review) - this suggests that investigator values were used pre technical engagement which is unclear.
- The new calculation offers a better match with trial data.

Issue: OS modelling 2/2

ERG (after technical engagement):

- Better fit but results still do not match trial data and are overly optimistic: long-term estimates and cost-effectiveness results remain uncertain.
- Unable to provide more accurate estimates of OS and uses the updated modelling in revised base case.

	OS ITT data: % survived						
Time, months	Nivolumab + chemotherapy			Chemotherapy			
	CheckMate 649	Pre TE model	Post TE model	CheckMate 649	Pre TE model	Post TE model	Royal Marsden Hospital
6	[redacted]	[redacted]	**83.17%**	[redacted]	[redacted]	**79.18%**	74%
12	54.96%	60.40%	**58.21%**	47.94%	52.84%	**50.46%**	44%
18	[redacted]	[redacted]	**39.42%**	[redacted]	[redacted]	**30.77%**	16%

Is the company's method for estimating OS suitable for decision making?

CheckMate 649 & long-term remission state

Model progression and mortality rates over time for nivolumab + chemotherapy:

- mortality rates drop in the model at 30 months.
- all patients who have not progressed by 30 months are cured and are assumed to have background mortality.

CheckMate 649 mortality hazards in PFS health state for nivolumab + chemo: wide credible intervals, no distribution robustly model mortality hazard after 2 years.

- **ERG:** R-P spline, the most plausible distribution, plateaus well above background mortality.
- population still at risk at 18 months is low (nivolumab+chemo n=83; chemo n=38).

Issue: Long-term remission (LTR)

Company:

- Long-term remission is clinically plausible, mortality plateaus between 3-5 year & few mortality events between 5-10 years.

ERG:

- Company's model (ITT): [redacted] of patients on nivolumab + chemotherapy and [redacted] on chemotherapy are cured, but only 1% expected to achieve LTR.

Clinical experts:

- LTR is likely, this has been seen with immunotherapy.
- Company's LTR assumption is reasonable – with a caveat: rarely some people can relapse.

Company (response to ERG report):

- Royal Marsden Hospital data shows low hazards of deaths observed from 36 months; Al Bartan 2008: data plateaued from 3 years; Chau 2009: LTR benefit maintained in 4 RCTs…
- CheckMate 649 [redacted] ITT data: [redacted]
- Acknowledges uncertainty of the mortality of this population due to short follow-up: presents scenario analysis with a standardised mortality ratio of 1.5 in LTR.

ERG: Still no substantive evidence to support cure: no new evidence presented by company.

- Scenario with mortality for LTR of 1.5 times the background rate is arbitrary.
- Removes LTR from updated base case.

Should long-term remission be included in the model?
If so, how it should be modelled?

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Issue: End of Life

Criterion	Company evidence	ERG
The treatment is indicated for patients with a short life expectancy *(normally less than 24 months)*	• CheckMate 649 chemotherapy arm median OS = [redacted] months (ITT) and [redacted] months (PD-L1 CPS >5). • Royal Marsden Hospital data median OS 11.5 months.	Agree
Evidence to indicate that the treatment offers an extension to life *(normally at least an additional 3 months compared with current NHS treatment)*	CheckMate 649 OS median gain ([redacted] data) • PD-L1 CPS >5: ***** months. Model predicted OS gain (discounted LY) in PD-L1 CPS >5: • Company: [redacted] years ([redacted] months). • ERG = [redacted] years ([redacted] months).	Met for PD-L1 CPS ≥5 subgroup.

Clinical expert:

- Agree with ERG: OS gain >3 months expected in PD-L1 CPS ≥5 subgroup.

Does the committee agree the End of Life criteria have been met?

Abbreviations: OS = overall survival

Issue: PD-L1 subgroups and testing

Company

- Cost-effectiveness results provided for PD-L1 CPS ≥1 and ≥5 subgroups.
- Cost of PD-L1 testing is not included.

ERG:

- Cost-effectiveness results for PD-L1 CPS <1 & <5 subgroups are missing.

Technical team:

- Testing cost should be included in as PD-L1 testing is not routine in gastroesophageal adenocarcinoma.

Clinical expert:

- If recommended for a subgroup, integration of PD-L1 testing into clinical pathway will be required. This is needed to allow nivolumab use in the beginning of the treatment instead of only when and if tests are available.

Company:

- No cost-effectiveness data for PD-L1 CPS <1 and <5 subgroups due to small sample sizes (insufficiently powered to detect differences).
- Cost of PD-L1 testing not included.

Are there any potential issues with implementing PD-L1 and CPS assessments in practice?

Should the cost of PD-L1 testing be included?

ERG identified issues – Resolved post technical engagement:

Issue	Summary of the post technical engagement change
Adjustment of modelled cost	Company updated adjustment of costs for missed doses that now include both chemotherapy and nivolumab in both arms. • Company & ERG used the updated adjustment in its updated base case
Model baseline age	Company changed model baseline age from CheckMate 649 mean of [redacted] years to 64.15 years (Cancer Research UK). • Company & ERG used 64.15 years in its updated base case.
Utilities	• Company used CheckMate 649 data: mean PFS: [redacted], PD: [redacted], time-to death disutility [redacted] applied 6 months before death (if death < 6 months, disutility was adjusted accordingly), age dependent disutility (Janssen 2014) and disutility for adverse events. • ERG considered the values high compared to population norm (0.799 for 60 year old) and other appraisals and used TA208 trastuzumab HER2- positive gastric cancer values instead (PFS: 0.7292, PD: 0.577). • Company explained that time-to-death disutility of [redacted] needs to be removed when TA208 utilities are used. When the disutility is removed, both TA208 and CheckMate 649 utilities provide similar results. • Company & ERG used CheckMate 649 utilities in its updated base case.

Innovation and equalities

Innovation

- **Company:** addition of nivolumab to chemotherapy would provide an opportunity to make a significant and substantial impact on health-related benefits and address a current unmet need in the management of this life-threatening condition.

Equalities

- **Company:** no equality issues have been identified or are anticipated.
- **Guts UK:** there may be a culture of some community groups not utilising primary care and going to their GP, people in this situation often present late. Also, inequalities in health in respect to cancer mean that people from the most deprived areas are more likely to be diagnosed later as people have reduced ability and opportunity to access healthcare. This is particularly true of stomach cancer.

Delays to diagnosis in some groups is not considered to be an equality issue because it is not anticipated that committee's recommendations can have different impact on people protected by the equality legislation and on people experiencing health inequalities arising from socioeconomic factors than on the wider population.

Company: Deterministic results for PD-L1 CPS≥5

- **Note: cost of PD-L1 testing is not included in PD-L1 CPS≥5 results.**
- **No probabilistic results for this subgroup provided.**
- PAS discount applied to nivolumab, list prices for other treatments:

Treatment	Total		Incremental		ICER (£/QALY gained)
	Costs	QALYs	Cost	QALYs	
vs FOFLOX					
Nivolumab+FOLFOX	[redacted]	[redacted]	-	-	-
FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	£40,659
vs XELOX					
Nivolumab+XELOX	[redacted]	[redacted]	-	-	-
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	£37,229

Note: company did not run scenario analyses in PD-L1 CPS ≥5 population

- number of scenario analyses was included for ITT population:
  - e.g. standardised mortality ratio of 1.5 in the LTR state.

ERG:
Scenario analyses for PD-L1 CPS≥5

- **Note: cost of PD-L1 testing is not included in PD-L1 CPS≥5 results.**
- PAS discount applied to nivolumab, list prices for other treatments.

	Inc. cost	Inc. QALYs	ICER
vs FOFLOX			
A. Company base case	[redacted]	[redacted]	**£40,659**
1. Removal of long term remission	[redacted]	[redacted]	£77,329
B. ERG base case = scenario 1	[redacted]	[redacted]	**£77,329**
vs XELOX			
A. Company base case	[redacted]	[redacted]	**£37,229**
1. Removal of long term remission	[redacted]	[redacted]	£71,014
B. ERG base case = scenario 1	[redacted]	[redacted]	**£71,014**

Company and ERG: assumptions after technical engagement

	Company	ERG
PAS	New increased PAS for nivolumab is applied.	
Long-term remission	Patients who remain in pre-progression health state after 30 months move to long-term remission health state. • New company scenario assuming 1.5 mortality risk in long-term remission.	Long-term remission health state removed from the model.
Death on progression	Updated and based on BICR (blinded independent central review) • ERG: results are still overly optimistic and long term results are uncertain.	
Age	Model baseline age 64.15 years based on Cancer Research UK mean age. Company's scenario based on CheckMate 649 ([redacted] years).	
Cost	Updated post TE adjustment of costs for missed doses that includes both chemotherapy and nivolumab in both arms.	
Utilities	CheckMate 649 utilities with time-to-death disutility ([redacted]; is applied to all patients who survived for at least 6 months during the 6 months before death). • Company's new scenario: disutility removed when utilities are based on TA208.	

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Abbreviations: PFS = progression-free survival, PD = progressed disease, TTDD = time to death disutility

Key cost-effectiveness issues

- **Overall survival modelling**
  - The trial data is approximately 70% complete for PFS and OS. ERG considers the company's model unnecessarily complicated. CheckMate 649 OS data are not directly used in the model which is based on projecting OS from PFS data.
  - The model estimates for OS at 12-month are higher than the trial.
  - Is the company's method for estimating OS suitable for decision making?
- **Long-term remission (LTR) state**
  - ERG removed LTR state from the model. **This has a large impact on ICER.** Should the LTR state be included in the model? If so, how it should be modelled?
- **End of life:** Are end of life criteria met?
- **PD-L1 testing:** Are there any potential issues with implementing PD-L1 and CPS assessments in practice? Should the cost of PD-L1 testing be included?
- After technical engagement company and ERG use the same inputs for: a) Utilities: based on CheckMate 649, b) Baseline age: 64.15 years (Cancer Research UK) rather than [redacted]
- (CheckMate 649), c) Adjustment of costs for missed doses.