NICE National Institute for Health and Care Excellence

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

3rd Committee Meeting

Chair: Jane Adam
ERG: Liverpool Reviews & Implementation Group
Technical team: Anne Murray, Mary Hughes, Janet Robertson
Company: Bristol-Myers Squibb
ACM3: 12 July 2022

Key issues

- The company and ERG have different approaches to model overall survival but these give similar results.
- Previously the committee considered some treatment effect waning plausible. Assuming treatment waning increases the ICER. The company suggests a scenario using 6.5 years as a cut off for treatment effect waning which differs to the ERG scenario using a 5 year cut-off.
- The company has agreed an increased patient access scheme for nivolumab.
- End of life criteria apply, does the committee consider that the ICER with the new PAS can be considered cost effective?

Draft recommendation

Nivolumab with platinum- and fluoropyrimidine-based combination chemotherapy is not recommended for untreated HER2-negative, advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma in adults whose tumours express PD-L1 with a CPS of 5 or more.

History of appraisal

First meeting
- August 2021
- Company model not appropriate for decision making →new model requested.
- Not recommended

2nd meeting
- February 2022
- New model considered
- Unresolved disagreement between company and ERG about implementation of company's modelling approach; company had not had chance to fully respond to ERG critique ahead of meeting.
- Further information requested from company to resolve.
- Not recommended

Today's meeting
- July 2022
- Increased patient access scheme.
- Requested information from company provided.
- Consultation comments

Abbreviations: CPS: Combined positive score; ERG: Evidence review group; HER 2: Human epidermal growth factor; PD-L1: programmed death-ligand 1.

Recap: 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: 95% of cancers of the stomach are adenocarcinomas. In the oesophagus adenocarcinoma is mostly found in the lower oesophagus and accounts for ~2/3 of UK cases.

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

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

Recap: nivolumab with chemotherapy

MA October 2021	Nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of advanced or metastatic HER2- negative gastric, gastro-oesophageal junction or oesophageal adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 5.
Adminis-tration	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. ➢ Treatment until disease progression or unacceptable toxicity. ➢ **Maximum treatment duration for nivolumab is 24 months.**
Price	Patient access scheme has been updated since 2nd committee meeting.

Abbreviations: CHMP**:** Committee for Medicinal Products for Human use; CPS: Combined positive score; HER 2: Human epidermal growth factor;IG4: Immunoglobulin G4; MA: Marketing authorisation; PD-1: PD-L1: programmed death-ligand 1.

Recap: treatment pathway and unmet need

- Alternative treatment options are dual chemotherapies XELOX and FOLFOX with most people using XELOX as it is better tolerated and has shorter infusion time.
- Pembrolizumab is also a treatment option, but for a narrower population than nivolumab because people with gastric cancer and people with a PDL1 CPS ≥5 and <10 would only be eligible for nivolumab.
- Pembrolizumab is not a comparator in this appraisal (its guidance, TA737, published during course of this appraisal).
- Committee concluded XELOX is key comparator (ACD 3.3)

Abbreviations: ACD: appraisal consultation document**;** CPS: combined positive score; FOLFOX: fluorouracil, folinic acid and oxaliplatin; PD-L1: programmed death ligand 1;TA: technology appraisal; XELOX: capecitabine and oxaliplatin.

Recap: treatment pathway and unmet need

Different populations covered by the marketing authorisation of nivolumab and pembrolizumab

		Nivolumab + chemo	Pembrolizumab + chemo
Tumour site	Oesophageal adenocarcinoma	Y	Y
	Oesophageal squamous cell	N	Y
	Gastro-oesophageal junction	Y	Y
	Gastric	Y	N
PDL1 combined positive score	≥ 5	Y	N
	>10	Y	Y

NICE **Abbreviations:** Chemo: chemotherapy; PD-L1: programmed death ligand 1.

Recap: pivotal trial-CM 649.

Data from subgroup with PD-L1 CPS ≥5

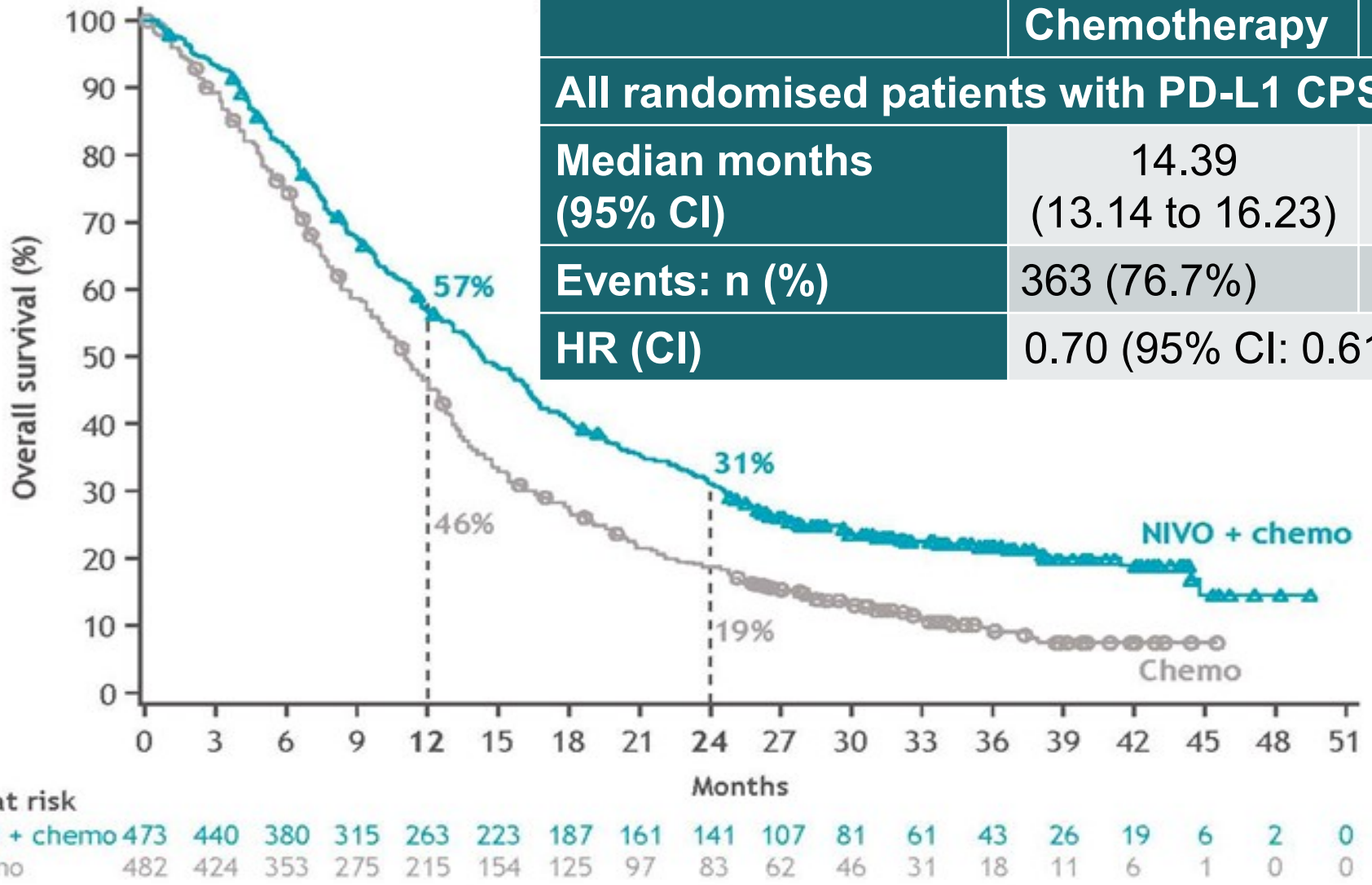
Population	Untreated and inoperable, advanced or metastatic (regardless of PD-L1 status): – gastric ([redacted]), – gastro-oesophageal junction ([redacted]), – or oesophageal adenocarcinoma ([redacted]) Data from subgroup with PD-L1 CPS ≥5 used in this appraisal
Intervention	Nivolumab + chemotherapy (n=468) The chemotherapy combined with nivolumab was XELOX ([redacted]) or FOLFOX ([redacted])
Comparator	Chemotherapy (n=465) XELOX ([redacted]) or FOLFOX ([redacted])
Primary outcomes	PFS by BICR and OS
Key results	[redacted]Data were mature >70% had events for both outcomes in both arms. PFS HR: 0.70 (95% CI: 0.60 to 0.81) OS HR: 0.70 (95% CI: 0.61 to 0.81)

Abbreviations: CM: CheckMate; BICR: blinded independent central review; CPS: combined positive score; FOLFOX: fluorouracil, folinic acid and oxaliplatin; OS: overall survival, PFS: progression-free survival, PD-L1: programmed death ligand 1; XELOX: capecitabine and oxaliplatin.

Recap: CheckMate 649-updated OS results

Note: data taken from [redacted] database lock. Used in the updated model.

	Nivolumab + Chemotherapy	Chemotherapy
All randomised patients with PD-L1 CPS ≥5 (n = 955)		
Median months (95% CI)	14.39 (13.14 to 16.23)	11.10 (10.05 to 12.25)
Events: n (%)	363 (76.7%)	416 (86.3%)
HR (CI)	0.70 (95% CI: 0.61 to 0.81)	



Abbreviations: CI: Confidence intervals; CPS: combined positive score; HR: hazard ratio; N: number; OS: overall survival, PFS: progression-free survival, PD-L1: programmed death ligand 1.

Recap: End of Life criteria met

Criterion	Company evidence
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.
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: [redacted] months. Model (1st meeting) predicted OS gain (discounted LY) in PD-L1 CPS >5: • Company: [redacted] years ([redacted] months). • ERG = [redacted] years ([redacted] months).

Abbreviations: CI: Confidence intervals; CPS: combined positive score; ERG: Evidence review group; HR: hazard ratio; ITT; Intention to treat; LY: life years; OS: overall survival, PFS: progression-free survival, PD-L1: programmed death ligand 1.

Modelling approach: overall survival

Company and ERG suggested different approaches to extrapolate overall survival. Both agreed that mortality hazard (risk of dying) would never be lower in people who had the condition compared with general population.

- Both use Kaplan Meier data used to 6.44 months then parametric extrapolation.
- ERG used Gompertz and generalised gamma; company's base case used Gompertz.
- Different approaches to ensure mortality hazards were never lower than general population:
- Company added excess mortality of the condition to general population mortality
- ERG adjusted extrapolation so mortality hazards were not below those from the general population.
- ERG considered company's approach potentially good but did not had the full information to assess modelling approach and thought the company had implemented it incorrectly.
- Committee: company had not had chance to formally respond to ERG's comments on its modelling, committee had not been able to fully compare the modelled OS outcomes with both approaches.

Please note company has now provided a full explanation on how it implemented its modelled overall survival and ERG agree it has been correctly done.

Abbreviations: ERG: evidence review group; OS: overall survival.

Treatment effect waning

Company:

- There is a 2-year stopping rule in CheckMate 649 and in summary of product characteristics for nivolumab.

ERG:

- Considered that a scenario should be explored whereby any treatment effect from NIVO+XELOX compared to XELOX is not maintained for life.
- In line with previous nivolumab submissions, the ERG produced a scenario whereby the mortality hazard for those treated with NIVO+XELOX is equal to that of those treated with XELOX at 5 years (i.e., 3 years after treatment with nivolumab has stopped for all patients).
- Noted the scenario is not evidence-based and does not form part of the ERG preferred base case. The results are presented with the ERG cost-effectiveness results.

Committee conclusions: Treatment effect waning should be considered.

Abbreviations: ERG: evidence review group; NIVO: nivolumab; XELOX: capecitabine and oxaliplatin.

Modelled overall survival: predicted % alive

Based on the evidence available at the time, the ERG approach using Gompertz with treatment waning gave long term survival estimates which experts considered plausible of 3.1% at 20 years.

Distribution	5-year	10-year	20-year
Company base case (Gompertz)	[redacted]		
ERG approach using Gompertz	13.6%	9.2%	5.9%
ERG approach using Gompertz + waning assumption	13.4%	5.3%	3.1%
ERG generalised gamma	10.6%	2.8%	0.5%
XELOX % alive			
Company base case (Gompertz)	[redacted]		
ERG correction to company Gompertz	3.8%	1.5%	0.9%
ERG generalised gamma	2.9%	0.3%	0.2%
Royal Marsden	4.0%	-	-

Committee conclusions: ERG approach using Gompertz with waning assumption in nivolumab arm gave plausible results. Deterministic ICER using this assumption: £49,840.

Abbreviations: ERG: evidence review group; ICER: Incremental cost effectiveness ratio; XELOX: capecitabine and oxaliplatin.

Conclusions from 1st and 2nd meetings

Issues raised in previous meetings	Committee conclusions
Unmet need	Nivolumab has different mechanism to chemotherapy Nivolumab has broader MA than pembrolizumab TA737 There remains an unmet need in people with gastric cancer and a PDL1 CPS of between 5 and 10 who cannot have pembrolizumab.
Comparator	XELOX key comparator for appraisal.
Clinical effectiveness	Direct evidence nivolumab + XELOX vs XELOX. Data mature. Nivolumab + XELOX improves PFS and OS vs. XELOX
End of life	End of life met.

Conclusions from 1st and 2nd meetings

Issues raised in previous meetings	Committee conclusions
Model	The company's updated 3 state partitioned survival model for second meeting appropriate. No issues with PFS modelling.
Plausibility of modelled overall survival	Different parametric distributions result in markedly different OS in nivolumab + XELOX arm after 5 years. A 3% survival with ERG approach using Gompertz and applying 5 year treatment waning plausible, but highly uncertain.
Acceptable ICER	Given uncertainty around long term modelled OS and long term OS benefits with nivolumab + XELOX an acceptable ICER would be comfortably under £50,000- most plausible ICER at second meeting (£49,840) was not. Committee noted it did not have probabilistic ICERs which could have been higher.

The Committee requested additional explanation and analyses following ACM2

The company should provide:

- Explanation on why company's modelling approach should be considered correct.
- OS estimates at 5,10 and 20 years using company's base case with and without treatment waning.
- Cost-effectiveness estimates for a scenario including treatment waning assumption.

ACD consultation responses

Responses received from:

- Experts: 1 clinical expert (Professor Was Mansoor)
- Web comments
- Company: Bristol-Myers Squibb
  - Company responded to committee's request and provided clarification on its methods, long term survival predictions and treatment waning scenarios.

ACD response: clinical expert (Professor Was Mansoor)

- **Inequity of care and unmet need**
  - Nivolumab + chemotherapy is the global standard of care for non resectable gastric and gastro-oesophageal cancer → Inequity in care in UK
  - UK would struggle to attract multi-national studies that use this treatment as their standard arm.
  - Anatomical inequity: Oesophageal cancer can receive immunotherapy, but gastric cancer cannot.
- **Survival advantage**
  - Given EOL is met, survival advantage would be lost for people denied this treatment.
  - After treatment, the immune system provides protection against cancer beyond the last dose as opposed to chemotherapy alone.

ACD response: clinical expert (Professor Was Mansoor)

- **Emphasis on long term survival**
  - There is absence of long term data on survival and waning effect in this population.
  - Models usually used for chemotherapies are dubious (for immunotherapy), especially waning effect (because they do not work past its last administration).
  - Condition prognosis is <18 months; only a minor cohort of people would benefit past 5 years.
  - Consideration should be made on benefits at 18-24 months which are relevant to the majority of people.

ACD response: web comments

- **Inequity of care and unmet need**
  - UK unable to participate in trials that use this global standard of care
  - Lack of equity in access to immunotherapy between oesophageal and gastric cancer.
  - Disparity in treatment options available in Europe and UK →Health inequalities and poorer outcomes
  - Would welcome a treatment for CPS score >5; currently a CPS score >10 is required to receive immunotherapy.
  - Provides an additional option for a condition that has limited options.

ACD response: web comments

- **Emphasis on small proportion of long-term survivors**
  - General prognosis <18 months, more consideration to outcome benefits should be considered.
  - Negative recommendation based heavily on long term remission/ cure which only represents a small proportion of the population.
- **Implications for the NHS**
  - This population have higher burden of care throughout their treatment journey. Improvement in ORR → improvements in quality of care and reduce burden on NHS (reduced inpatient care)

Company's response: Clarification of methods

Company:

- Provided explanation of how it had implemented its methods in the model.
- **ERG**:
- Concluded that the company had implemented appropriately.
- Long-term overall survival estimates associated with treatment with nivolumab remain uncertain. Agreed with company that both the ERG's model and the company's model generate similar overall survival estimates.

Company's response: Treatment waning

Company:

- Notes lack of evidence of treatment waning in relation to immunotherapies and lack of guidance in how treatment waning should be considered in technology appraisals.

Comments on whether treatment effect waning expected after stopping nivolumab

- Nivolumab stimulates an antitumour response from immune system→ biologically plausible treatment effect continues even after stopping it.
- CM649, nivolumab treatment stopped at 2 years and at maximum follow up 49.5 months no evidence of treatment waning.
- CM649 time from randomisation to progression on second treatment, starting 3rd treatment or death (PFS2)→ 25% reduction in nivolumab arm (HR 0.75%, 95% CI 0.67-0.84). Company suggests PFS benefit of nivolumab persists.

Abbreviations: CI: Confidence interval; CM: check mate; HR: Hazard ratio; NSCLC: non small cell lung cancer; TA: technology appraisal.

Company's response: Treatment waning

Comments on whether treatment effect waning expected after stopping nivolumab

- Evidence in other solid tumours show long term benefit with nivolumab→ CM067 (melanoma), CM057 (non-squamous NSCLC) and KEYNOTE-006 (pembrolizumab advanced melanoma) showed mortality hazards not increasing after stopping treatment.

Use of 5 year cut-off in ERG scenario pessimistic

- Company suggested 6.5 year treatment waning assumption based on longest available follow-up data CM067(melanoma) and in line with TA737 Pembrolizumab with chemotherapy for oesophageal and gastro-oesophageal cancer (7 years treatment waning).

ERG: Company's approach of applying a treatment effect waning at 6.5 years is not implausible.

OS and mortality hazard estimates in nivolumab arms of lung cancer, melanoma and gastro-oesophageal cancer trials

- Company suggest that mortality hazards do not increase after stopping treatment with nivolumab supporting no treatment waning.
- Company did not provide comparator arm data for the lung cancer or melanoma trial.

Source: Company response to ACD2, 3.

CM057: Nivolumab versus docetaxel in previously treated non–small-cell lung cancer.

CM067: Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab in patients with advanced melanoma.

CM649: Nivolumab plus ipilimumab or nivolumab plus chemotherapy versus chemotherapy alone on untreated advanced gastric or gastroesophageal junction cancer.

Abbreviations: OS: Overall survival, CM: checkmate.

Company's response: Long term overall survival projections

- The company and ERG approaches give similar overall survival projections.
- Assumptions on treatment waning have a bigger impact.

Technology	Percent alive at each time point			
	Company base case		ERG approach with Gompertz	
	5 yrs	20 yrs	5 yrs	20 yrs
Without waning				
NIVO+XELOX	XXXX	[redacted]	[redacted]	[redacted]
XELOX	[redacted]	[redacted]	[redacted]	[redacted]
With waning at 5 years				
NIVO+XELOX	[redacted]	[redacted]	[redacted]	[redacted]
With waning at 6.5 years				
NIVO+XELOX	[redacted]	[redacted]	[redacted]	[redacted]

Source: Company response to ACD2, table 12.

ERG:

- Long-term OS estimates associated with treatment with nivolumab remain uncertain.
- Both the ERG's model and the company's model generate similar OS estimates.

Abbreviations: NIVO: Nivolumab; OS: Overall survival; XELOX: Capecitabine and oxaliplatin; Yrs: Years

Cost effectiveness estimates with revised PAS

ERG approach with Gompertz with waning was committee's preferred of the ERG scenarios presented in the 2nd meeting and the deterministic ICER for this before the PAS increase was £49,840.

		Deterministic			Probabilistic		
		Inc. life years	Inc. QALYs	ICER (£/QALY)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Company base case	Without waning	[redacted]	[redacted]	£43,889	[redacted]	[redacted]	£46,221
	With waning at 6.5 years	[redacted]	[redacted]	£47,137	[redacted]	[redacted]	£49,365
ERG approach with Gompertz	Without waning	[redacted]	[redacted]	£40,418	[redacted]	[redacted]	£41,527
	With waning at 5 years	[redacted]	[redacted]	£47,988	[redacted]	[redacted]	£49,869

Company base case with treatment waning at 5 years:

- Deterministic ICER £49,784
- Probabilistic ICER £51,331

Abbreviations: ICER: Incremental cost effectiveness ratio; Inc.:incremental; PAS: patient access scheme; QALY:quality adjusted life years.

Key issues

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- The company has agreed an increased patient access scheme for nivolumab.
- End of life criteria apply, does the committee consider that the ICER with the new PAS can be considered cost effective?