NICE National Institute for Health and Care Excellence

SLIDES FOR PUBLIC

Nivolumab for previously treated unresectable advanced oesophageal cancer

Chair's presentation

2nd Appraisal Committee Meeting (Committee B)

Chair: Jane Adam

ERG: Peninsula Technology Assessment Group (PenTAG)

NICE technical team: Farhaan Jamadar, Ellie Donegan, Janet Robertson

Company: Bristol-Myers Squibb (BMS)

5th January 2021

History

First committee meeting October 2020

- Company advised of additional 36-month data day before committee
- Based on 24-month follow-up data, nivolumab improved survival vs taxanes in people who survived 3 months (higher risk of death in first 3 months)
- Company and ERG cost-effectiveness estimates for nivolumab higher than what NICE considers to be a cost-effective use of NHS resources
- Committee requested further justification of several model assumptions

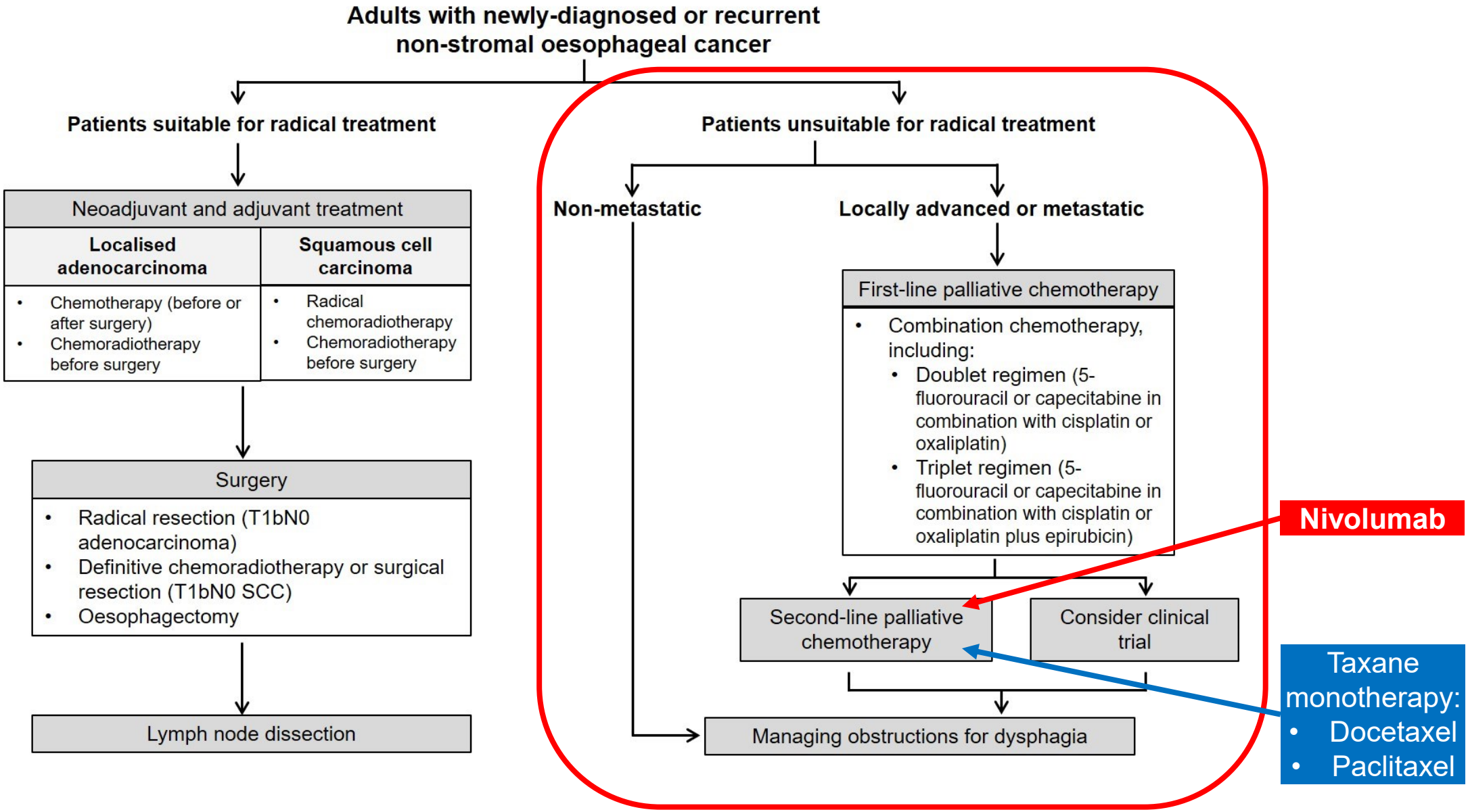
Nivolumab was not recommended, within its anticipated marketing authorisation, for treating unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma in adults after prior fluoropyrimidine and platinum-based therapy.

Additional information received during consultation (November 2020):

- Company submitted 36-month data from ATTRACTION-3 trial
- Company submitted revised cost-effectiveness analysis and economic model, justifying some of its model assumptions following committee discussion
- ERG critiqued company's ACD response and additional analysis

No other consultation responses were received from stakeholders

Treatment pathway (derived from NICE NG83)



NICE

Nivolumab (Opdivo, Bristol-Myers Squibb)

Marketing authorisation	Nivolumab monotherapy for the treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine and platinum-based combination chemotherapy
Mechanism of action	Nivolumab: human monoclonal antibody targets the PD-1 checkpoint-inhibitor on the surface of lymphocytes and blocking its activity may promote an anti-tumour immune response.
Administration	Intravenous administration over 30 minutes at 2-week intervals, dosage of 240 mg. **Treatment continued until disease progression**

Key issues

- What is the clinical view on the higher death rate seen with nivolumab in first 3 months?
- Given the additional 36-month data, are the parameters and extrapolation methods used for OS and ToT appropriate for both treatment arms?
- Are the post-progression utility values clinically plausible?
- Have medical resource use costs, particularly hospitalisation costs, been calculated accurately and justified adequately?
- Is the source for costs of treatment now reflective of average prices paid by NHS trusts?
- Have the end of life criteria been met?

Committee's comments and company response

Issue	Committee comments (preference/request)	ERG comments on company response	Resolved/ uncertain?
Longer term OS not provided in time for first committee meeting	The committee requested to see the 36-month data at second committee meeting	Both the company and ERG base-case analyses underestimated OS at 36-months	
Extrapolation of OS	Need to see 36-month data, including exploration of different cut points and methods of extrapolation	• Alternative cut points not provided • Nivolumab arm is a good fit but taxane arm is not	
Extrapolation of PFS	Need to see effect of 36-month data	Extrapolation has little effect on the ICER	
Extrapolation of TOT	Need to see effect of 36-month data	Uncertainty over model for both arms	
Utility values	• Higher nivolumab pre-progression utility plausible • Inadequate justification provided for long-term difference in post-progression utility	• Utility values were not updated following 36-month data • Exploratory analyses stratified utility values were based on treatment status (vs progression status)	
Hospitalisation cost	Inadequate justification for estimating costs based on stay of 1 bed day	Greater justification and detail needed for company estimate of hospitalisation cost	
Treatment costs	eMIT should be used as source of costs, company used MIMS	Treatment costs have now been updated to reflect committee and ERG preference	
End-of-life criteria	Likely that EOL criteria was met, wanted to see 36-month data effect	Additional follow-up resolves some uncertainty (but extrapolation unresolved)	

Key: Issue resolved

Issue remains uncertain

Clinical trial information: ATTRACTION-3

Trial design	Randomised, open-label study (Phase III)
Intervention	Nivolumab – 240 mg every 2 weeks, intravenous infusion (N = 210)
Comparators	Docetaxel – 75mg/m^2 every 3 weeks (N = 65) Paclitaxel – 100mg/m^2 weekly for 6 weeks, then 2-week drug holiday (N = 144)
Outcomes of interest	• Overall survival • Progression-free survival • Overall response rate • Adverse events • Patient reported outcomes
Eligibility criteria	• Adult patients with histologically proven unresectable advance or recurrent oesophageal cancer, refractory or intolerant to combination therapy with fluoropyrimidine and platinum-based drugs • **ECOG Performance Status 0 or 1** • **Life expectancy of at least 3 months**
Baseline characteristics	• **All participants had oesophageal squamous-cell carcinoma** • Median age 65 years (33-87) • 87% male and 13% female • 96% participants Asian, 4% White • 50% ECOG PS 0 and 50% ECOG PS 1

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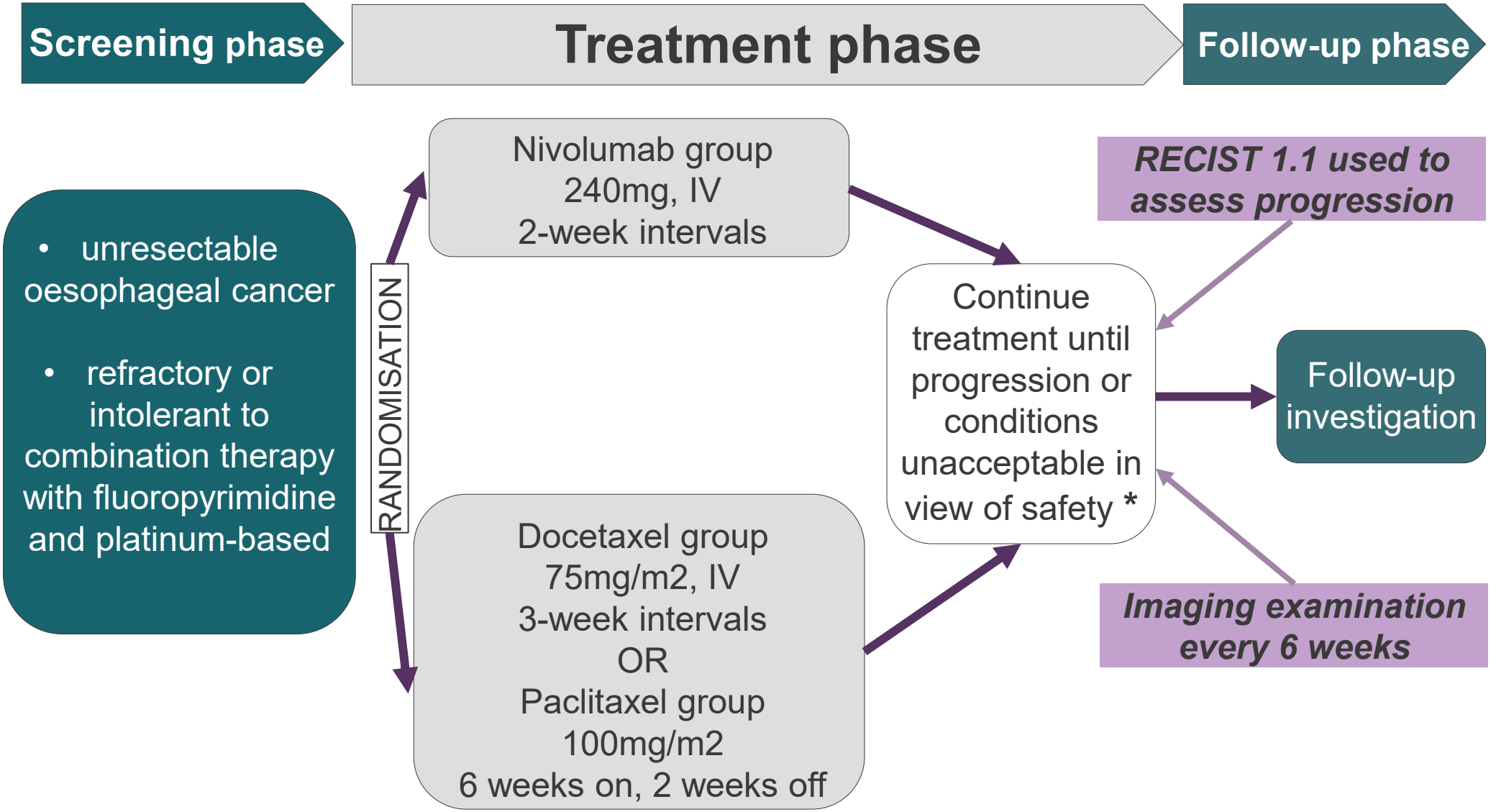
NB. Only ATTRACTION-3 trial results used to inform economic model

ATTRACTION-3 study design



* *"Patients were permitted to continue treatment beyond initial disease progression in both treatment arms based on the investigators' judgement", Lancet, Kato K et al. (2019)*

Recap of first appraisal committee meeting (October 2020)

Clinical effectiveness data – Overall survival

	Nivolumab	Total (control)
Evaluable patients	210	209
Median, months	10.91 (9.23, 13.34)	8.38 (7.20, 9.86)
Hazard Ratio	0.77 (0.62, 0.96)	
No. of events (n/N)	160 / 210	173 / 209
3 months	[redacted]	[redacted]
6 months	[redacted]	[redacted]
9 months	[redacted]	[redacted]
12 months	46.9% (39.9, 53.5)	34.4% (27.8, 40.9)
24 months	[redacted]	[redacted]

Overall survival defined as the time from randomisation until death from any cause.

[redacted]

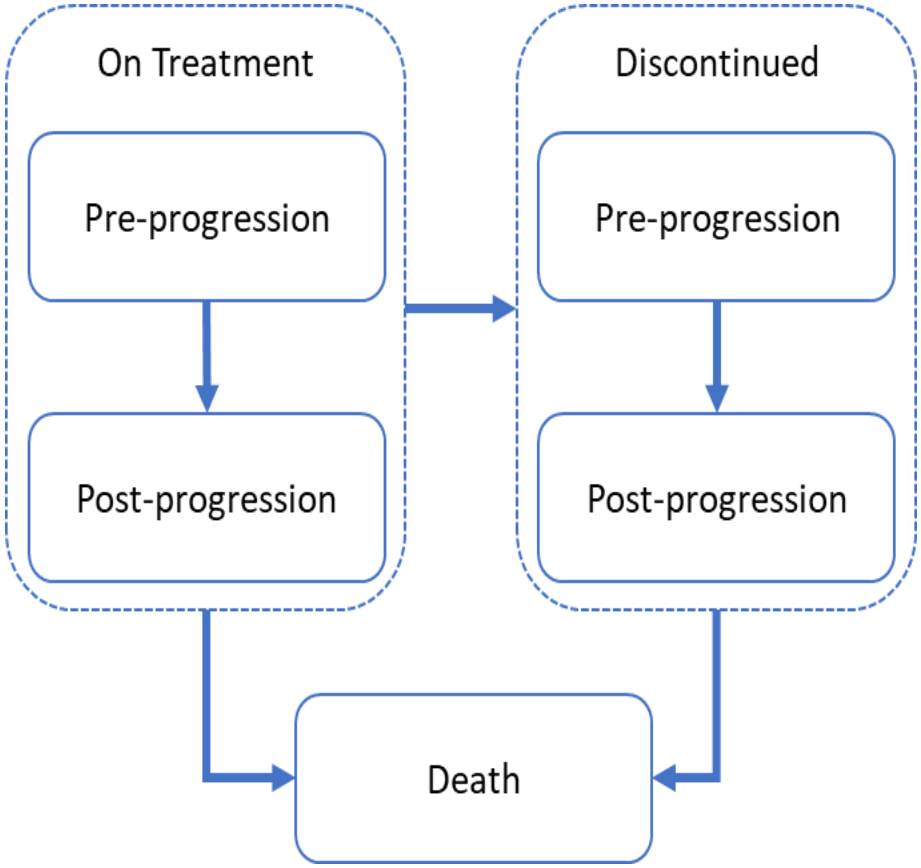
Economic model used in company base-case

De-novo partitioned survival model, informed by data from ATTRACTION-3.

Intervention: nivolumab monotherapy

Comparator: taxane (docetaxel/paclitaxel)

- Cycle length: 7 days.
- Time horizon: 40 years.
- 3.5% discount rate.
- Mean age: 63.8
- 86.9% male, 13.1% female



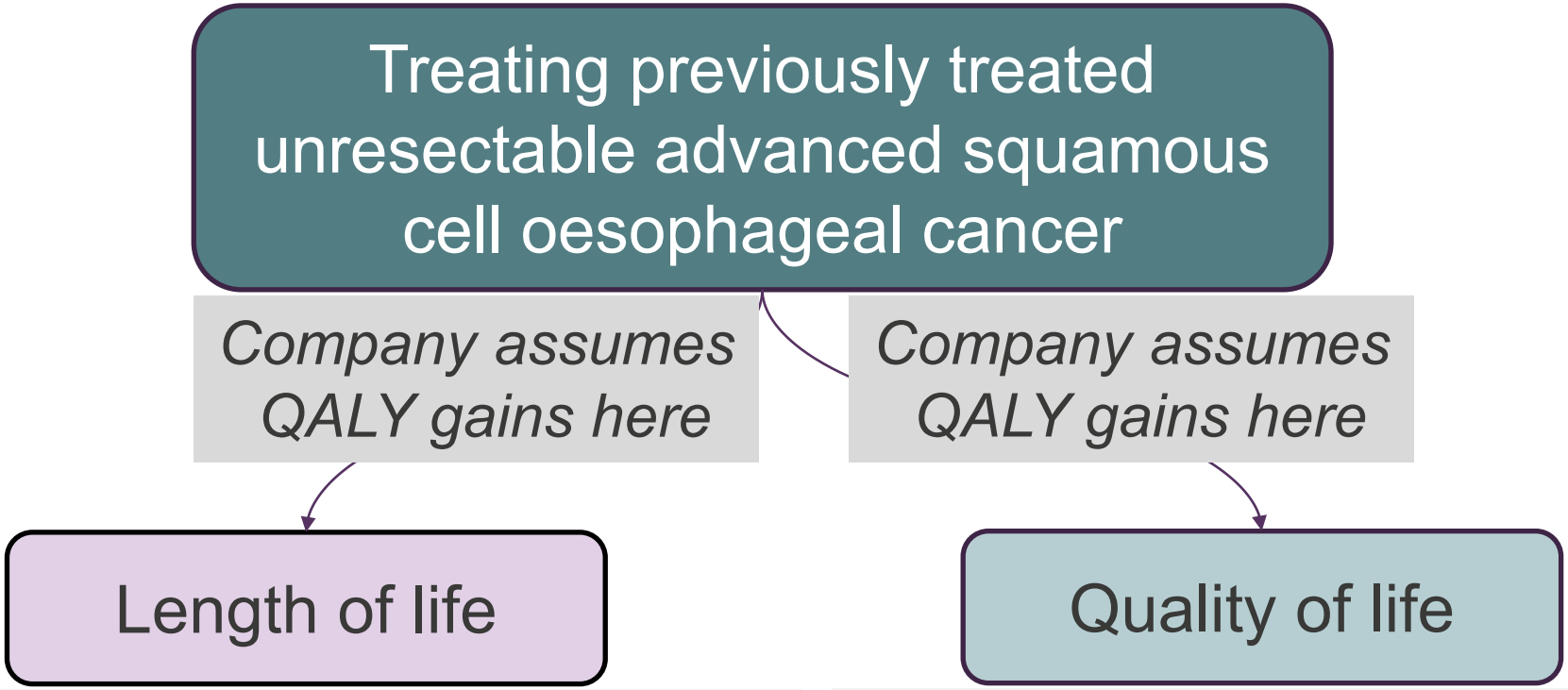
Adverse events included by using constant weekly probabilities of each AE

Utility values based on EQ-5D data from trial

	Nivolumab	Taxanes
Pre-progression	[redacted]	[redacted]
Post-Progression	[redacted]	[redacted]

Approach to obtain utility values for model based on imputation of ATTRACTION-3 EQ-5D data "missing at random", as opposed to fitting a regression model

Where do gains come from in company's model?



- Improved OS for nivolumab in patients who survive first 3 months
- **Company ACD comment:** nivolumab activates the immune system, providing OS and PFS benefit versus taxane chemotherapy

- Nivolumab is associated with better tolerability and reduced adverse events compared with taxane chemotherapy
- Benefits of nivolumab treatment continue into the post-progression phase and after stopping treatment

Original company and ERG base-case results

	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Company base-case (deterministic)							
Taxane	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	20,842	0.536	0.458	**45,491**
ERG base-case (deterministic)							
Taxane	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	27,845	0.302	0.221	**125,984**

Cost of taxanes and subsequent therapy

- *Company used MIMS (Monthly Index of Medical Specialities), ERG used eMIT (Electronic Market Information Tool) provides estimates reflective of average prices paid by NHS trusts.*
- *When using eMIT as cost source, company ICER increased to **£53,459 per QALY***

Hospitalisation costs

- *Company cost hospitalisation as £534.07 (1 day bed stay), ERG preferred estimate is £3,379.73 (full length of hospitalisation unadjusted for length of stay)*
- *When using ERG medical resource use costs, pairwise ICER increased to **£62,092 per QALY***

Description of company's updated results and base-case analysis

ATTRACTION-3 updated results (OS and PFS)

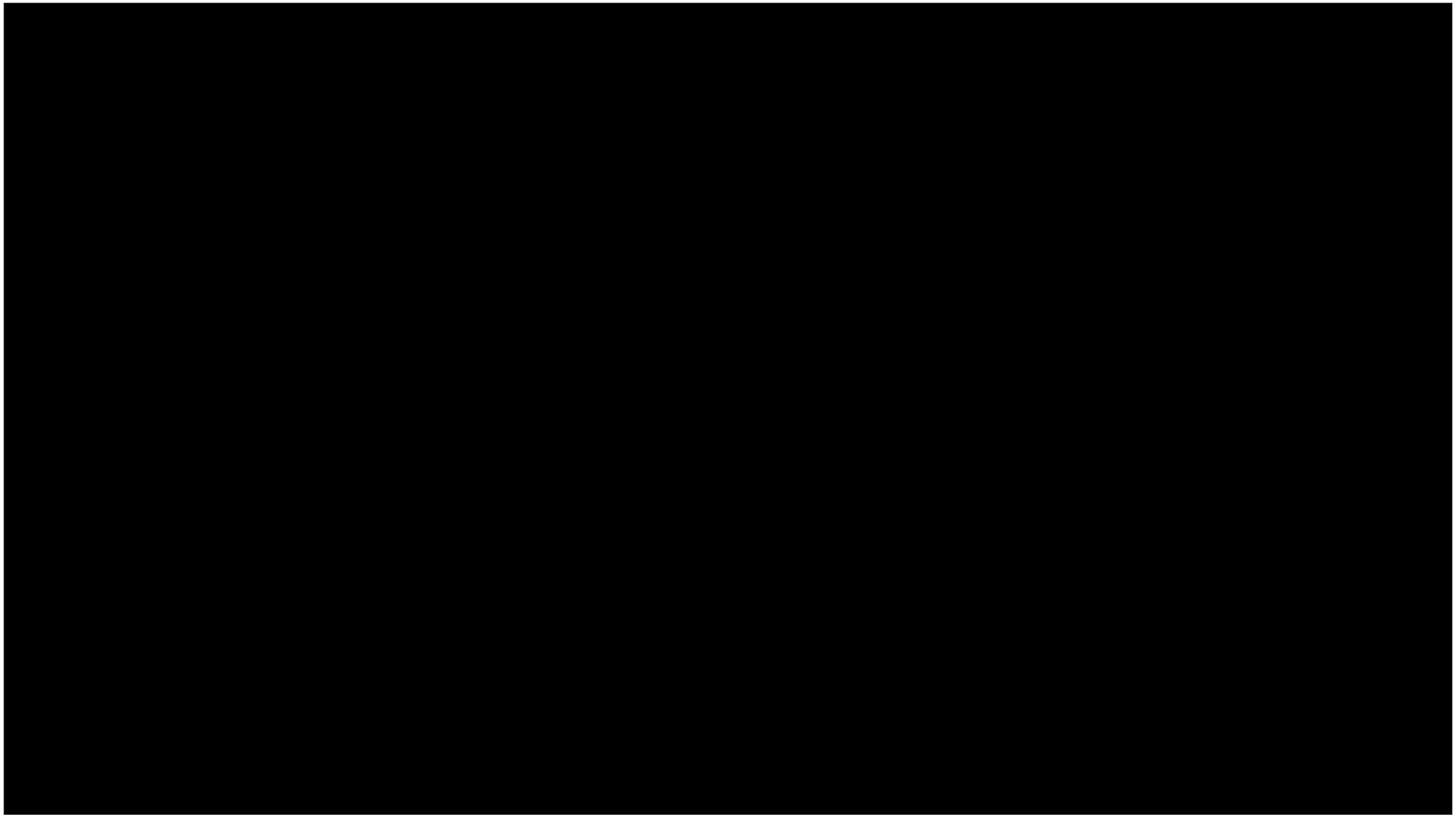
Additional data from ATTRACTION-3 provided, with 36 month follow-up until May 2020.

ACD response Table 1. ATTRACTION-3 updated outcomes

Endpoint	Nivolumab	Control
Number evaluable	210	209
Overall Survival (95% CI)		
Median, months	[redacted]	[redacted]
HR	[redacted]	
12-month	[redacted]	[redacted]
24-month	[redacted]	[redacted]
36-month	[redacted]	[redacted]
Investigator-assessed Progression-free Survival (95% CI)		
Median, months	[redacted]	[redacted]
HR	[redacted]	
12-month	[redacted]	[redacted]
24-month	[redacted]	[redacted]
36-month	[redacted]	[redacted]

Company: 36-month results consistent with primary analysis presented
ERG: Kaplan-Meier curve can be considered reasonably stable up to 36-months (in context of trial)

Updated Kaplan-Meier plot of OS



Updated extrapolation of overall survival

Nivolumab arm: KM data to 25 weeks, then log-logistic distribution

Taxane arm: KM data to 25 weeks, then Weibull distribution

ACD Response Table 2: Comparison of predicted versus observed OS outcomes

OS Rates (%)		24 months	36 months
Nivolumab	Observed	[redacted]	[redacted]
	Company base-case	21.3	12.3
	Updated base-case	22.2	13.9
	ERG base-case	20.7	10.2
Taxane	Observed	[redacted]	[redacted]
	Company base-case	11.1	3.3
	Updated base-case	15.1	7.0
	ERG base-case	12.2	4.4

ERG noted that Kaplan-Meier curve for OS not equivalent to 'true survival' curve (given it is based on finite sample, generalisability issues etc.)
The ERG base-case referred to above was from the previous committee meeting, rather than an update of current preferences in line with the new data

Updated extrapolation of overall survival continued

ERG comments on cut-point used for Kaplan-Meier data (OS, PFS, ToT)

- Company chose previous ERG preferred cut-off point (5.75 months), no alternatives provided.
- ERG preference may have changed based on updated data
- The company estimate OS at 5 years to be [redacted] in the nivolumab group and [redacted] in the taxanes group ([redacted] and [redacted], respectively at 10 years)

ERG comments on choice of OS extrapolation for taxane arm

The company stated models predicting OS >104 weeks (2 years) in the taxane arm were considered clinically implausible, but no equivalent upper limit was specified for nivolumab. Clinical plausibility was used to justify the chosen extrapolation model for the taxane arm.

- The ERG considered their previous extrapolation to provide a better visual fit to the taxane arm within the short term, but commented that the company's updated model provided more suitable estimates in the longer term
- Log-logistic had the lowest AIC/BIC scores (provided but not discussed); insufficient justification to its exclusion

Based on ACD response, company choice of model for taxane arm is likely sub-optimal (further exploration necessary)

Updated extrapolation of time on treatment

Nivolumab arm: KM data to 25 weeks, then Weibull distribution.
Taxane arm: KM data to 25 weeks, then log-logistic distribution.

ERG

Company selected model with: - long tail for OS, but not ToT **(nivolumab)**
- long tail for ToT, but not OS **(taxanes)**

Nivolumab: selection of any of the other 3 models caused the ICER to increase. For example, mean difference of less than [redacted] between Weibull ([redacted]) and generalised-gamma ([redacted]) distributions caused ICER to increase by >£1,000.

Taxanes: unclear why log-logistic mean ToT ([redacted]) considered 'clinically plausible' but other models with a range from [redacted] were not. Weibull distribution has better AIC/BIC scores and similar estimate to other plausible models.

The extrapolation selected is advantageous for nivolumab

Utility values

At ACM1, the committee considered it plausible for **pre-progression utility** to be higher for nivolumab compared with taxane arm, based on differences in tolerability and adverse events.

Also concluded company had not provided adequate justification for long-term difference in **post-progression utility**.

	Nivolumab	Taxanes
Pre-progression	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]

Utility values applied to company's original base-case were unchanged in updated model

Company (ACD response – justification for higher nivolumab post-progression utility)

- Utility in oncology is a function of time to death. As most of OS benefit from nivolumab was after progression, appropriate to reflect this benefit in post-progression utility value.
- Patients in nivolumab arm frequently continued receiving initial treatment after progression, any beneficial impact associated with nivolumab continued for these patients.
- Pooling post-progression quality of life data for the two arms assumes patients in the taxane arm receive benefit equivalent to patients receiving nivolumab.

ERG

- Concerns from ERG report remain: control arm baseline utility lower at screening (unadjusted for), mean utility in progression-free state higher than age-matched UK population mean utility
- ERG preferred utilities remain unchanged, values still subject to substantial uncertainty

Cost inputs to updated economic model

Administration costs

Company: Treatment administration costs are the same as original base-case.

ERG: Taxanes expected to have higher administration costs due to longer time of administration

Company assumed treatment would be in outpatient rather than day-case setting

Hospitalisation costs

- In original model, mean of 0.095 hospitalisations per week assumed based on clinicians' survey. So each patient incurs a cost of 9.5% of a hospital stay per week.
- Costs derived from NHS National Cost Collection, converting long-stay costs to cost per day (using weighted average from £1,907 for 3 days and £8,986 for 19 days).
- Hospitalisation costed as £534.07 (i.e. cost of 1 day), as per original company model.

ERG perspective on hospitalisation costs

- Greater justification and detail required for using cost equivalent to length of stay of 1 day.
- Based on the description provided by the company, the ERG calculated the weighted average for hospitalisation costs as £3,379.73.
- At ACM1, updated MRU costs increased the ICER from £45,491 to £62,092 per QALY.

End of life

Company and ERG agreed that life expectancy is <24 months (first end of life criterion)

Extension to life with nivolumab (ACM1)

Observed data: 2.58 months (median)

Company base-case model: 7.8 months (modelled mean)

ERG base-case model: 4.0 months (modelled mean)

Company

Additional follow-up sufficient to demonstrate extension to life criteria was met (3.14 months)

Restricted mean OS: [redacted] months for nivolumab, [redacted] months for taxanes

Updated base-case (cost effectiveness)

	Nivolumab	Taxanes
Costs (with PAS)		
Health state costs	XXXXX	XXXXX
Treatment costs	XXXXX	XXXXX
BSC costs	XXXXX	XXXXX
Average AE costs per patient	XXX	XXXXX
Total costs	XXXXX	XXXXX
Health benefits		
Total QALYs	XXXX	XXXX
Total life years (undiscounted)	XXXX	XXXX
ICER		
Cost/QALY	-	£48,205

Company's updated base-case with ERG preferred assumptions

It was not possible for the ERG to change survival models to reflect their preferences. Therefore, preferred utility values, administration and hospitalisation costs were applied to the company's updated base-case.

Technology	Total			Incremental			ICER (£/QALY)
	Costs (£)	QALYs	LYs	Costs (£)	QALYs	LYs	
Nivolumab	XXXXX	XXXX	XXXX	-	-	-	
Taxanes	XXXXX	XXXX	XXXX	31,554	0.411	0.567	**76,701**

Company scenario analysis: Alternative extrapolations of OS

Scenario			Incremental QALYs	Incremental Costs (£)	ICER (£/QALY)
OS: Semi-parametric with Kaplan-Meier to 5.75 months	Nivolumab	*Exponential*	*0.316*	*£22,563*	***£71,365***
		Generalised Gamma	0.413	£23,551	**£56,959**
		Gompertz	*0.666*	*£26,435*	***£39,690***
		Log-logistic	0.512	£24,665	**£48,205**
		Log-normal	0.506	£24,605	**£48,583**
		Weibull	0.344	£22,826	**£66,451**
	Taxanes	*Exponential*	*0.521*	*£24,795*	***£47,557***
		Generalised Gamma	0.494	£24,418	**£49,462**
		Gompertz	*0.364*	*£22,650*	***£62,246***
		Log-logistic	0.409	£23,263	**£56,875**
		Log-normal	0.414	£23,336	**£56,347**
		Weibull	0.512	£24,665	**£48,205**

*Implausible extrapolations are in **grey italics**, these are defined using the two criteria outlined: extrapolations exceed 95% confidence intervals of Kaplan-Meier data, or mean survival considered implausible*

Company scenario analysis: Alternative extrapolations of ToT

Scenario			Incremental QALYs	Incremental Costs (£)	ICER (£/QALY)
Time on treatment: Semi-parametric with Kaplan-Meier to 5.75 months	Nivolumab	*Exponential*	*0.512*	*£24,595*	***£48,069***
		Generalised Gamma	0.512	£25,232	**£49,314**
		Gompertz	*0.512*	*£28,261*	***£55,235***
		Log-logistic	0.512	£28,289	**£55,289**
		Log-normal	0.512	£26,967	**£52,705**
		Weibull	0.512	£24,665	**£48,205**
	Taxanes	Exponential	0.512	£24,810	**£48,490**
		Generalised Gamma	0.512	£24,814	**£48,497**
		Gompertz	*0.512*	*£24,797*	***£48,464***
		Log-logistic	0.512	£24,665	**£48,205**
		Log-normal	0.512	£24,682	**£48,240**
		Weibull	0.512	£24,813	**£48,495**

Implausible extrapolations are in grey italics, these are defined using the two criteria outlined: extrapolations exceed 95% confidence intervals of Kaplan-Meier data, or mean survival considered implausible

Company scenario analysis: utility values

ACD response Table 6. Impact of alternative utilities on base-case analyses

Scenario	Pre-progression	Post-progression	Incremental QALYs	Incremental costs (£)	ICER (£/QALY)
Base case analysis CS values					
Nivolumab	0.832	0.658	0.512	£24,665	**£48,205**
Taxanes	0.747	0.555			
Base case analysis ERG values					
Nivolumab	0.820	0.6055	0.411	£24,665	**£59,955**
Taxanes	0.763				
ERG values with non-pooled post-progression values					
Nivolumab	0.820	0.650	0.485	£24,665	**£50,850**
Taxanes	0.763	0.561			

ERG individual and cumulative ICER updates

Technology	Total			Incremental			ICER £/QALY
	Costs (£)	QALYs	LYs	Costs (£)	QALYs	LYs	
Change 1: ERG's preferred administration costs							
Nivolumab	[redacted]	[redacted]	[redacted]				
Taxanes	[redacted]	[redacted]	[redacted]	23,551	0.512	0.567	**46,030**
Change 2: ERG's preferred utility values							
Nivolumab	[redacted]	[redacted]	[redacted]				
Taxanes	[redacted]	[redacted]	[redacted]	24,665	0.411	0.567	**59,955**
Change 3: ERG's preferred hospitalisation cost							
Nivolumab	[redacted]	[redacted]	[redacted]				
Taxanes	[redacted]	[redacted]	[redacted]	32,667	0.512	0.567	**63,846**
Change 1 + 2							
Nivolumab	[redacted]	[redacted]	[redacted]				
Taxanes	[redacted]	[redacted]	[redacted]	23,551	0.411	0.567	**57,249**
Change 1 + 3							
Nivolumab	[redacted]	[redacted]	[redacted]				
Taxanes	[redacted]	[redacted]	[redacted]	31,554	0.512	0.567	**61,670**
Change 2 + 3							
Nivolumab	[redacted]	[redacted]	[redacted]				
Taxanes	[redacted]	[redacted]	[redacted]	32,667	0.411	0.567	**79,407**
Change 1 + 2 + 3							
Nivolumab	[redacted]	[redacted]	[redacted]				
Taxanes	[redacted]	[redacted]	[redacted]	31,554	0.411	0.567	**76,701**