NICE National Institute for Health and Care Excellence

SLIDES FOR PUBLIC

Nivolumab for previously treated unresectable advanced oesophageal cancer [ID1249]

Lead team presentation

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Company: Bristol-Myers Squibb (BMS)

13th October 2020

Overview of oesophageal cancer

- Oesophageal cancer affects the oesophagus, the muscular tube through which food passes from the throat to the stomach
- Over 95% of oesophageal cancers are either **squamous cell carcinoma** (arising in mucosal lining, usually the upper 2/3) or **adenocarcinoma** (arising from glandular cells of the submucosa, usually lower 1/3)
- This appraisal covers only squamous cell carcinoma
- Common symptoms: difficulty swallowing (dysphagia), indigestion/heartburn, weight loss and pain in throat or behind the breastbone

Epidemiology

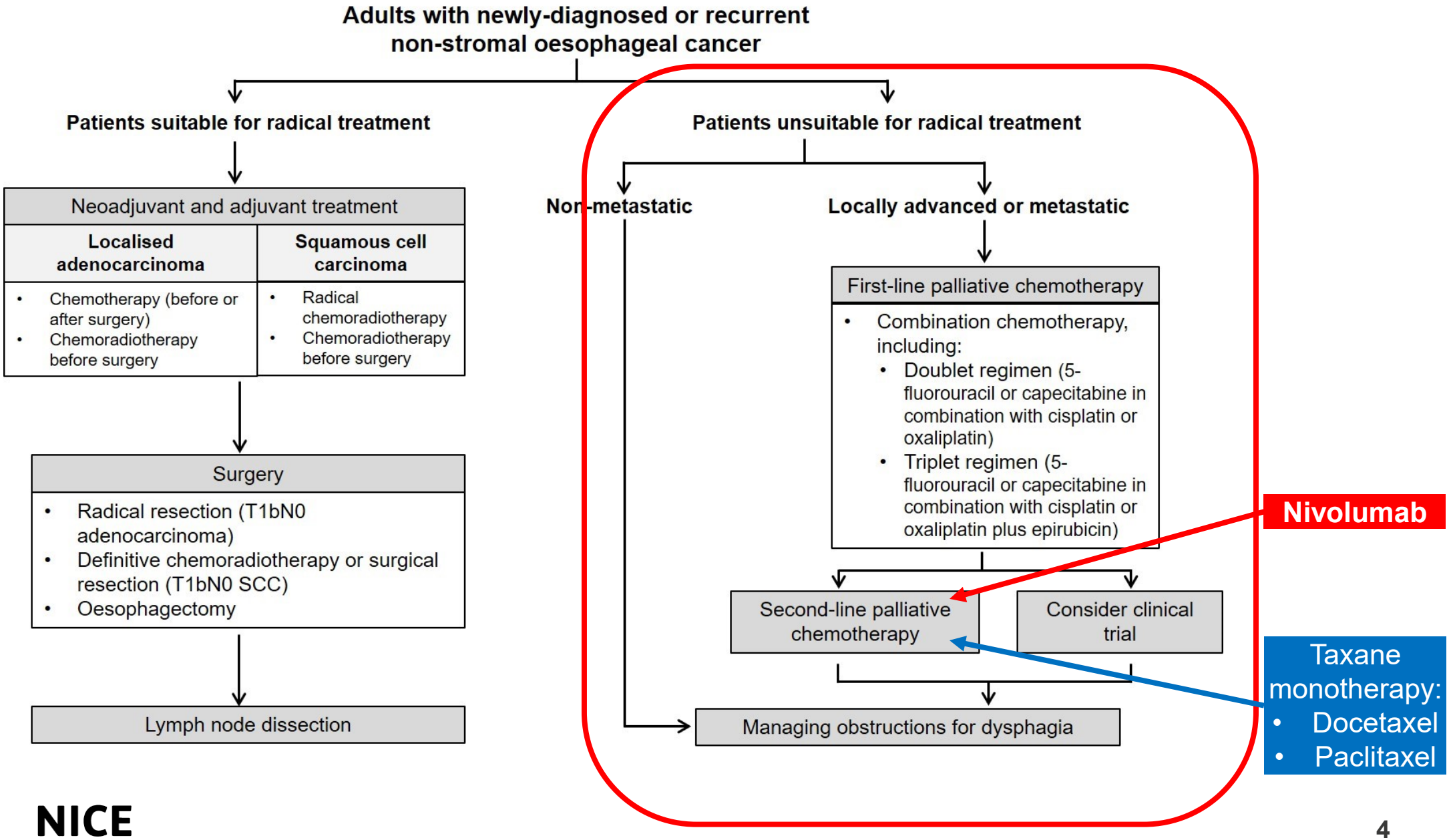
- >8,000 oesophageal cancers diagnosed annually in UK (70% males, 30% females)
- 40% of new cases in people aged 75 or over
- In England, 42% of patients remain alive at 12 months
- Rates of oesophageal cancer are higher amongst white males and females, compared with those of Asian or African-Caribbean family origin
- Although oesophageal cancer is uncommon, it is a common cause of cancer death

Nivolumab (Opdivo, Bristol-Myers Squibb)

Anticipated marketing authorisation	[redacted]*
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 240mg. **Treatment continued until disease progression**

CHMP opinion expected to be received by company on 15th October

Treatment pathway (derived from NICE NG83)



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Summary of technical report issues

- **Issue 1:** risk benefit profile of nivolumab
- **Issue 2:** is BSC a relevant comparator
- **Issue 3:** generalisability of ATTRACTION-3
- **Issue 4:** safety data for nivolumab
- **Issue 5:** adjusting efficacy for beneficial effects of 3rd line therapy
- **Issue 6:** differential use of taxanes
- **Issue 7:** model time horizon
- **Issue 8:** alternative extrapolations for overall survival
- **Issue 9:** exploratory analysis of utility values
- **Issue 10:** alternative extrapolations of time on treatment
- **Issue 11:** costs of comparator treatment, administration and MRU
- **Issue 12:** does nivolumab meet criteria for end of life?

Key issues: clinical effectiveness

- How does the side effect profile and treatment experience differ between nivolumab and taxanes?
- Is efficacy in ATTRACTION-3 generalisable to clinical practice in the NHS given the predominantly Asian, particularly Japanese trial population, open label design, and inclusion and exclusion criteria?
- How would nivolumab treatment be selected for patients? Is BSC a reasonable comparator and is the indirect comparison robust?
- How is the taxane chosen, and what is the perceived relative effectiveness, and relative usage of paclitaxel and docetaxel the UK?
- Disease progression was faster on nivolumab than taxanes up to 3 months; and survival was less at 2 months, equal at 4 months and greater at 6 months. Why is this?
- How long would people stay on treatment? Might people stay on treatment after progression?
- The model shows more survival benefit occurs post-progression than pre-progression. Is this due to more post-progression treatments being given in the nivolumab arm in ATTRACTION-3, people continuing on nivolumab post-progression and it slowing the disease, or carry-over effect post stopping nivolumab?

Patient and carer perspectives

- Distressing and debilitating symptoms include dysphagia, which leads to nutritional compromise, pain, and deterioration of quality of life.
- Poor prognosis and poor survival have a significant impact on health & wellbeing.
- 42% people with unresectable oesophageal cancer remain alive at 12 months in England; 15% of people with oesophageal cancer survive for five years or more.
- Incidence of oesophageal cancer strongly correlated to age: elderly people, especially females, have poorer outcomes than younger people.

Currently there are very limited treatment options in the second-line setting

- Older patients, who cannot tolerate chemotherapy, have even more limited options and are more likely to receive Best Supportive Care (BSC).
- BSC has limited or no impact on symptoms, quality of life, progression and survival.
- Huge unmet need for a treatment that provides long term benefit with low toxicity compared to chemotherapy and also improves quality of life.

Clinical trial information: ATTRACTION-3

Trial design	Randomised, open-label study (Phase III)
Intervention	Nivolumab – 240mg 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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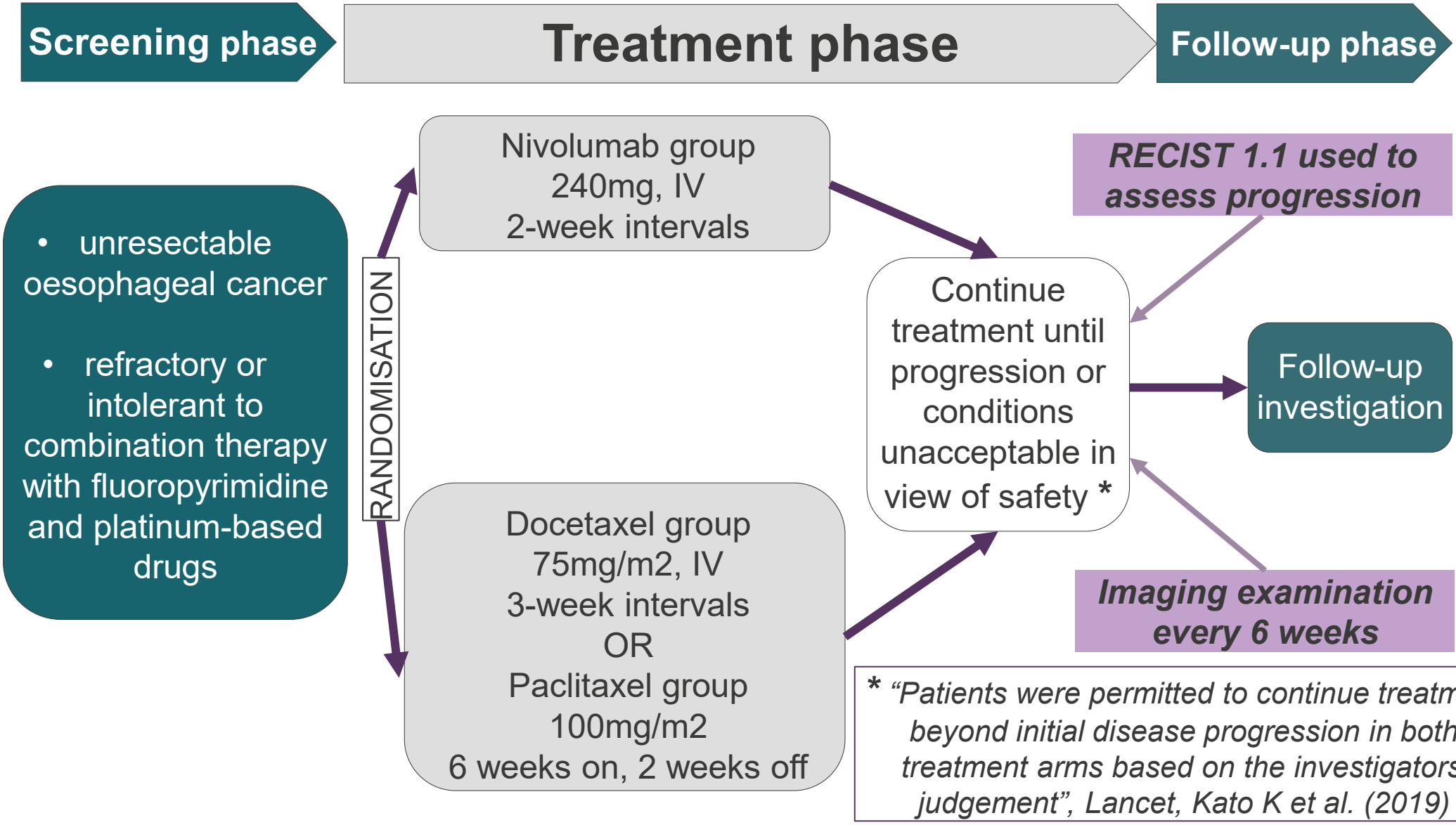
NB. Only ATTRACTION-3 trial results used to inform economic model

ATTRACTION-3 study design



Are patients likely to remain on treatment after progression?

Issue 3: Generalisability of ATTRACTION-3

- 96% of ATTRACTION-3 participants were Asian (2/3 Japanese).
- Patients had Eastern Cooperative Oncology Group (ECOG) performance scores 0-1
- Treatment follows pan-Asian adapted European Society for Medical Oncology guidelines
- Although the relative efficacy of nivolumab compared with taxane is similar in the Japanese and ROW population, absolute OS benefit is greater in Japanese population. Japanese patients on taxanes had superior OS than the Rest of the World (ROW) patients on nivolumab ([redacted]*)
- **Company –** OSCC more prevalent in Asian population with Treatment guidelines based on evidence predominantly using outcomes in Asian population. Clinical experts agree that biology of OSCC comparable between Asian and Western patients. ATTRACTION-3 showed overall differences in efficacy for nivolumab versus taxanes, rather than specifically in ROW population.
- **Clinical expert –** Underlying biology of oesophageal cancer is the same in different regions of the world. There is no reason to assume efficacy will be lower in people with PS 0-1 in NHS.
- **ERG** - there are substantial limitations in the generalisability of treatment pathways in ATTRACTION-3 to a UK context. Using the ROW subgroup is unlikely to completely resolve this issue.

Questions

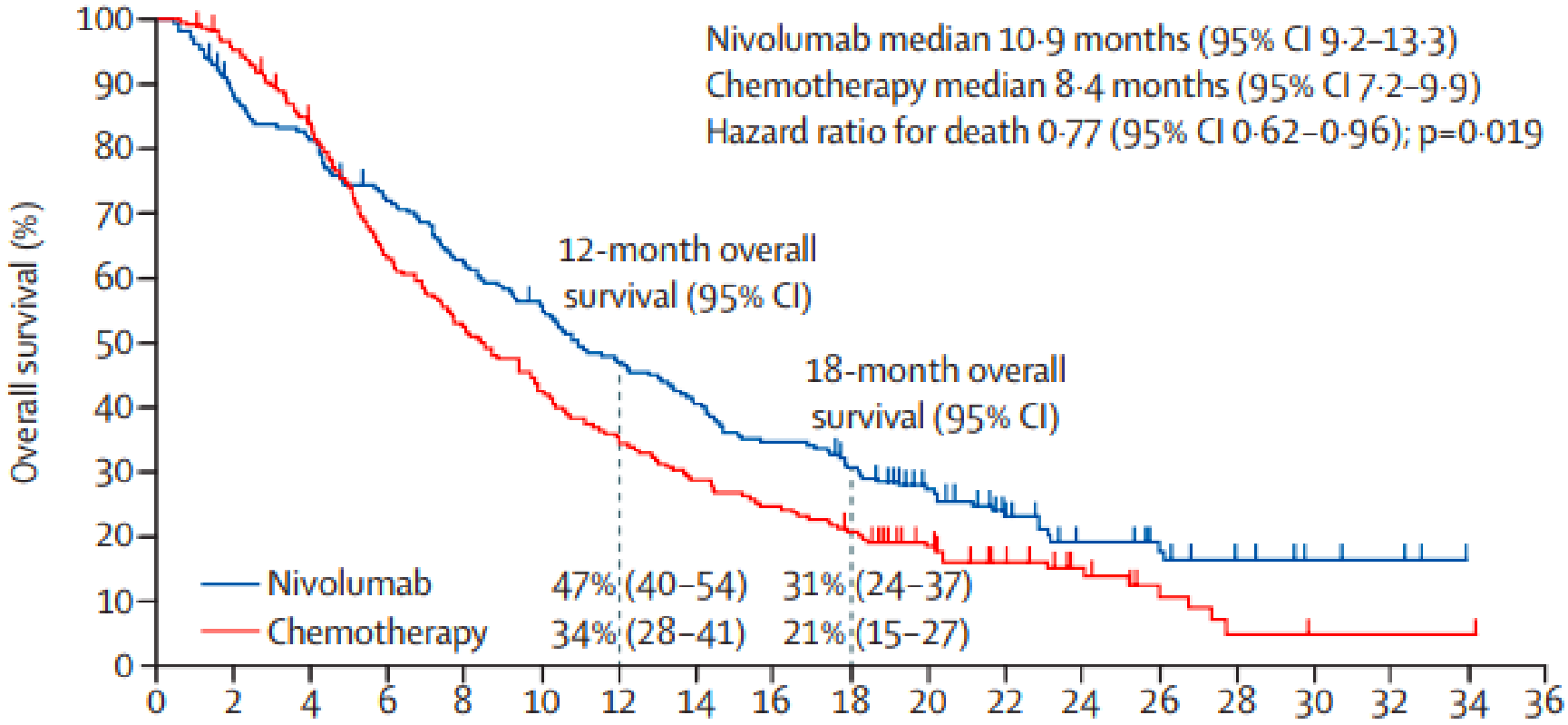
- **Is efficacy of nivolumab in NHS practice likely to be similar to ATTRACTION-3?**

Primary outcome – Overall survival

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

	Nivolumab	Total control (D + P)
Evaluable patients	210	209
Median, months (95% CI)	10.91 (9.23, 13.34)	8.38 (7.20, 9.86)
Hazard Ratio (95% CI)	0.77 (0.62, 0.96)	0.77 (0.62, 0.96)
Number of events, n/N	160 / 210	173 / 209
3 months, % (95% CI)	[redacted]	[redacted]
6 months, % (95% CI)	[redacted]	[redacted]
9 months, % (95% CI)	[redacted]	[redacted]
12 months, % (95% CI)	46.9% (39.9, 53.5)	34.4% (27.8, 40.9)
24 months, % (95% CI)	[redacted]	[redacted]

Primary outcome – Overall survival



Number at risk (number censored)

Nivolumab	210	182	167	147	126	111	95	82	70	60	43	25	17	13	7	4	3	0	0
	(0)	(4)	(4)	(5)	(5)	(6)	(6)	(6)	(6)	(8)	(19)	(31)	(35)	(38)	(43)	(46)	(47)	(50)	(50)
Chemotherapy	209	196	169	126	105	84	68	57	49	40	27	17	12	6	2	1	1	1	0
	(0)	(3)	(7)	(8)	(8)	(9)	(9)	(9)	(9)	(10)	(19)	(26)	(30)	(33)	(34)	(35)	(35)	(35)	(36)

ATTRACTION-3: Kaplan-Meier plot of overall survival in patients receiving nivolumab or docetaxel/paclitaxel

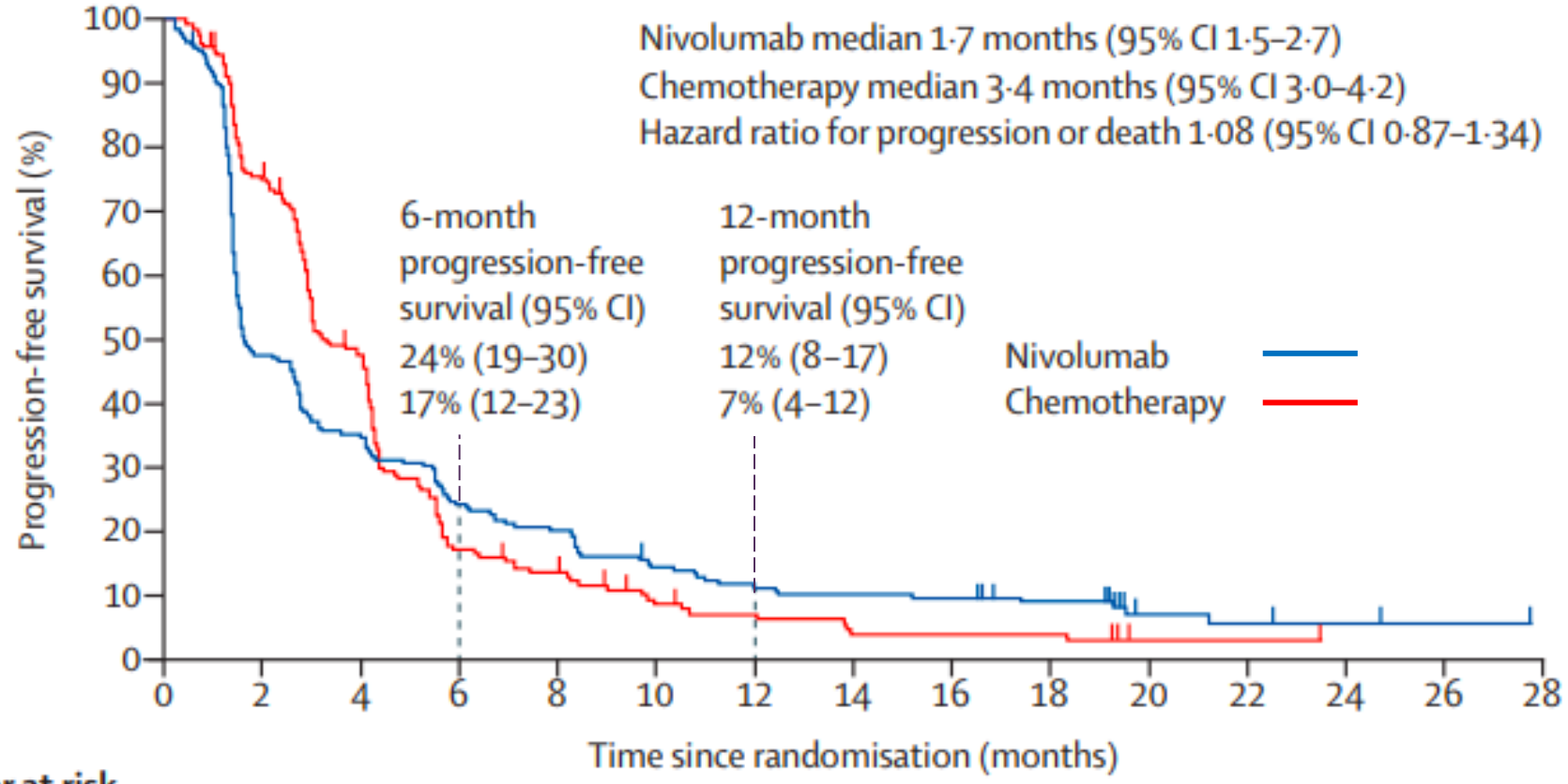
Progression-free survival

Progression-free survival calculated from following equation: “time from date of randomisation until either the overall response was assessed as progressive disease or patient died of any cause, whichever was earlier” + 1 / 30.4375

(converted from days into months)

	Nivolumab	Total control (D + P)
Evaluable patients	210	209
Median, months (95% CI)	1.68 (1.51, 2.73)	3.35 (2.99, 4.21)
Hazard Ratio (95% CI)	1.08 (0.87,1.34)	1.08 (0.87,1.34)
Number of events, n/N	167 (79.5)	162 (77.5)
3 months, % (95% CI)	[redacted]	[redacted]
6 months, % (95% CI)	24.2% (18.6, 30.3)	17.2% (12.1, 23.1)
9 months, % (95% CI)	[redacted]	[redacted]
12 months, % (95% CI)	11.9% (7.8, 16.8)	7.2% (3.8, 12.0)
18 months, % (95% CI)	[redacted]	[redacted]

Secondary outcome – Progression-free survival



Number at risk (number censored)

Nivolumab	210	96	71	48	40	27	22	19	18	13	5	4	3	1	0
	(0)	(6)	(6)	(7)	(7)	(9)	(9)	(9)	(9)	(13)	(19)	(19)	(20)	(22)	(23)
Chemotherapy	209	147	89	29	22	12	9	5	5	5	1	1	0	0	0
	(0)	(12)	(19)	(24)	(25)	(28)	(29)	(29)	(29)	(29)	(32)	(32)	(33)	(33)	(33)

ATTRACTION-3: Kaplan-Meier plot of progression-free survival in patients receiving nivolumab or docetaxel/paclitaxel

Response rate

Objective response rate (ORR) % either complete response (CR) or partial response (PR)

Complete response (CR): disappearance of all target lesions

Partial response (PR): at least 30% decrease in sum of diameters of target lesions

Stable disease (SD): no significant change

Progressive disease (PD): 20% or more increase in sum of diameters of target lesions

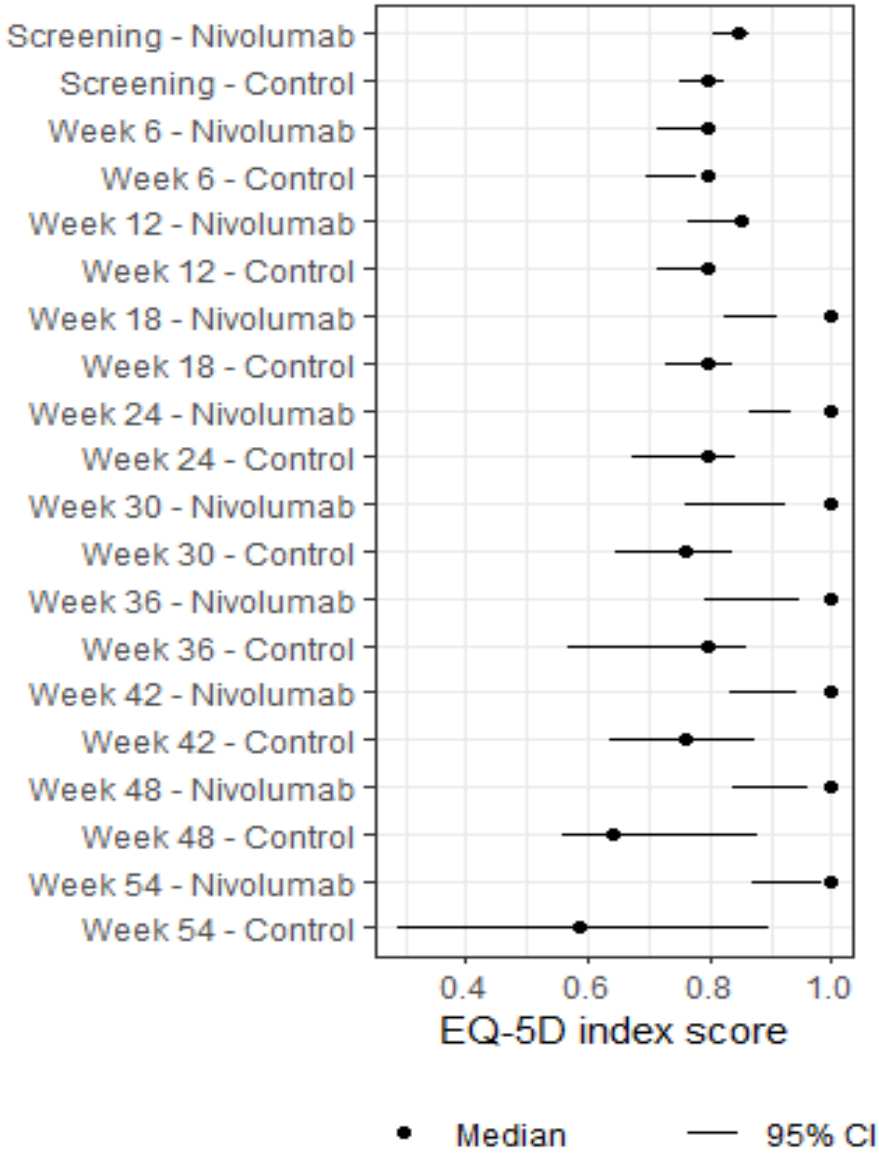
Endpoint	Nivolumab	Total control (D + P)
Evaluable patients	171	158
ORR (%) [95% CI]	19.3% [13.7, 26.0]	21.5% [15.4, 28.8]
CR (%)	0.6%	1.3%
PR(%)	18.7%	20.3%
SD (%)	18.1%	41.1%
PD (%)	55.0%	32.3%

RECIST 1.1 criteria was used.

EQ-5D data

ATTRACTION-3 collected patient reported outcomes through the EQ-5D questionnaire. Summary of EQ-5D index scores at each timepoint in the trial up to 54 weeks is shown in the figure on the right.

- In nivolumab arm, no meaningful changes in proportion of patients reporting QoL-related problems were observed during the treatment period in any EQ-5D category
- In control arm, proportion of patients reporting QoL-related problems in mobility, self-care and usual activities categories after commencing chemotherapy increased by >10% compared with at screening stage



Safety data (adverse events with incidence >5%)

Frequency of patients experiencing drug-related adverse events with incidence rate >5%

	Nivolumab	Control arm
Total	**137 (65.6)**	**198 (95.2)**
Hypothyroidism	17 (8.1)	1 (0.5)
Decreased appetite	16 (7.7)	56 (26.9)
Fatigue	15 (7.2)	43 (20.7)
Malaise	9 (4.3)	45 (21.6)
Anaemia	5 (2.4)	49 (23.6)
Stomatitis	5 (2.4)	25 (12.0)
Nausea	4 (1.9)	34 (16.3)
Alopecia	3 (1.4)	98 (47.1)
Arthralgia	3 (1.4)	21 (10.1)
White blood cell count decreased	2 (1.0)	72 (34.6)
Neutropenia	1 (0.5)	40 (19.2)
Peripheral sensory neuropathy	1 (0.5)	47 (22.6)
Vomiting	1 (0.5)	14 (6.7)
Febrile neutropenia	0	22 (10.6)

Safety data (drug-related adverse events)

	Nivolumab arm (N =209)		Control arm (N =208)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Number of patients with drug-related-AEs	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients with drug-related AEs leading to discontinuation of study treatment	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients with drug-related AEs leading to dose-delay	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients with drug-related AEs leading to dose reduction	[redacted]	[redacted]	[redacted]	[redacted]

Issue 1: Disease progression on nivolumab

- Most of the overall survival benefit from nivolumab in ATTRACTION-3 is in the post-progression phase. No PFS benefit associated with nivolumab (median PFS was 1.68 months for nivolumab group and 3.35 months in control group).
- Furthermore, there was little difference in overall response rate between nivolumab and taxane therapy (19.3% versus 21.5% with an odds ratio of 0.88 [0.51, 1.50])

Is the risk of death within first 3 months with initial nivolumab treatment worth an additional 2.58 months overall survival, as reported in the trial?

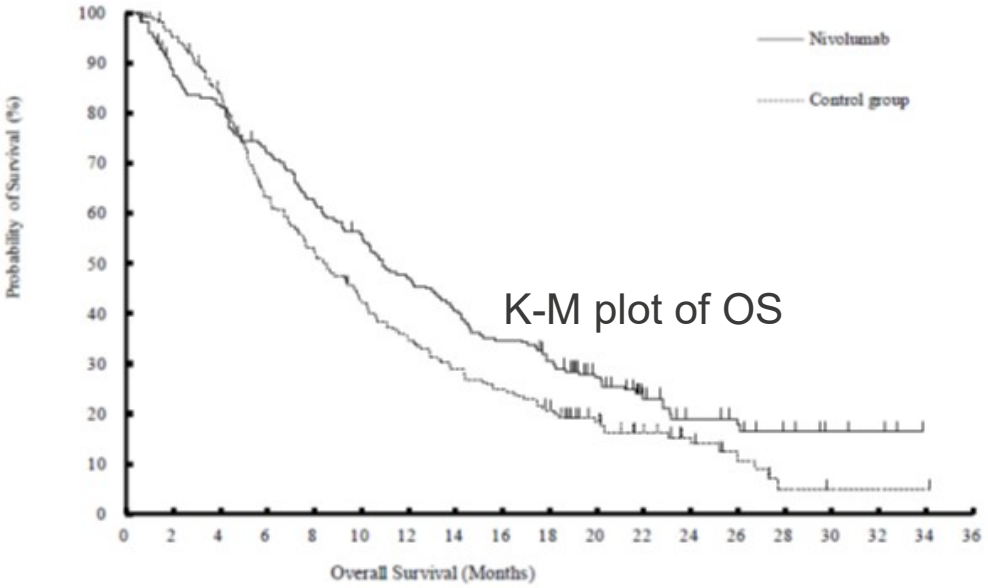
OS remains higher on nivolumab at all time points after six months. An additional 2.58 months is significant as median OS for standard of care is 8.38 months.

Clinical expert: Progression free survival is not an accurate metric to measure the efficacy of immunotherapy as benefit is in long-term.

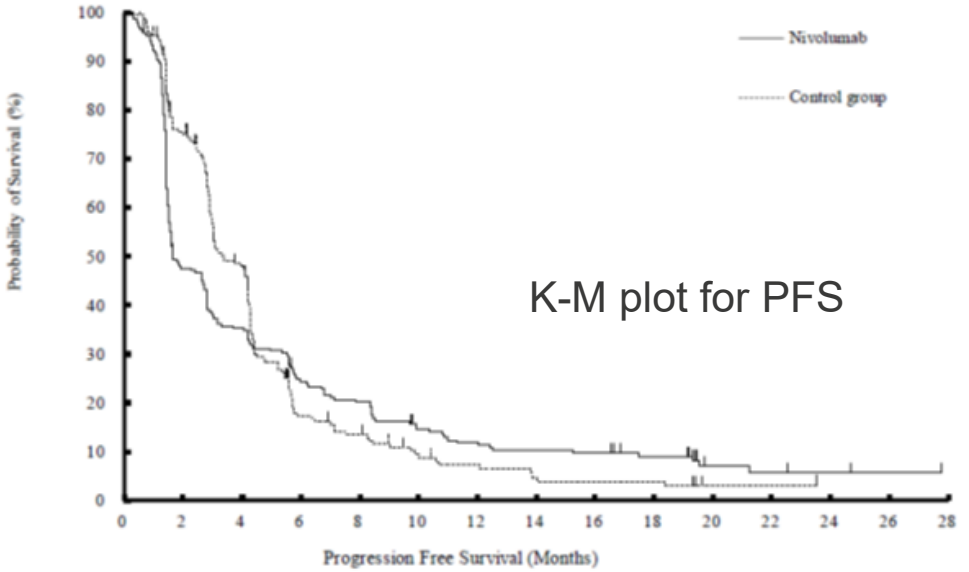
ERG: Presence of response on imaging may be delayed for immunotherapies versus taxanes, due to pseudo-progression and differences in trajectory of benefit. PFS as an outcome is not a good predictor of efficacy in the context of immunotherapies.

Issue 1: relative treatment effect constant over time (1)

- Cox proportional hazards model to estimate hazard ratios and 95% CI's for OS and PFS.
- ERG: proportional hazard assumption was violated (treatment curves crossed for OS+PFS)



K-M plot of OS



K-M plot for PFS

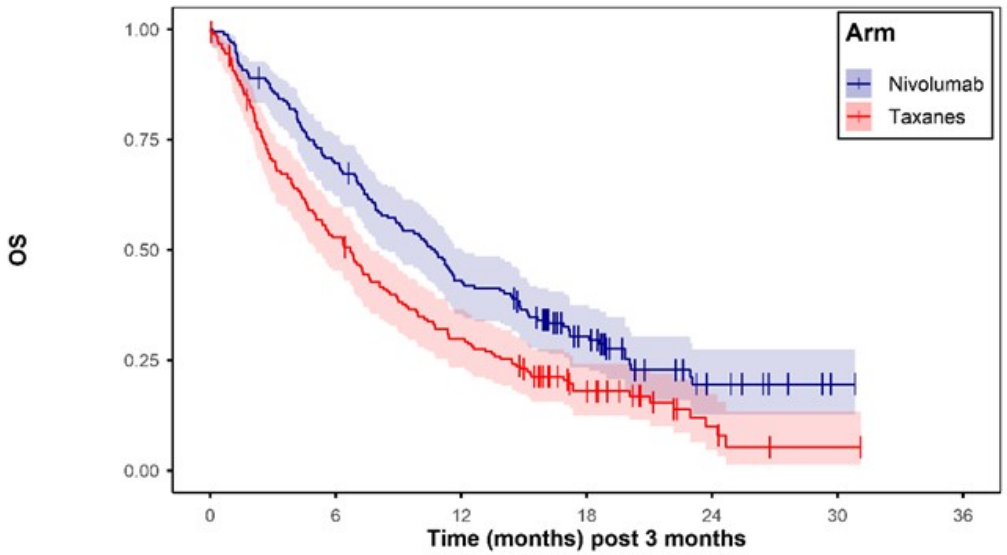
Clinical expert – benefit increases over time (different trajectory of immunotherapy vs chemotherapy). **ERG** considers this to be plausible

Company

- Efficacy is not likely to be constant over time (diverging efficacy in the model).
- Kaplan-Meier data for conventional chemotherapies has a lower initial hazard followed by increasing hazard over time. Kaplan-Meier curves for nivolumab monotherapy demonstrate a high initial hazard, followed by decreasing hazard over time.

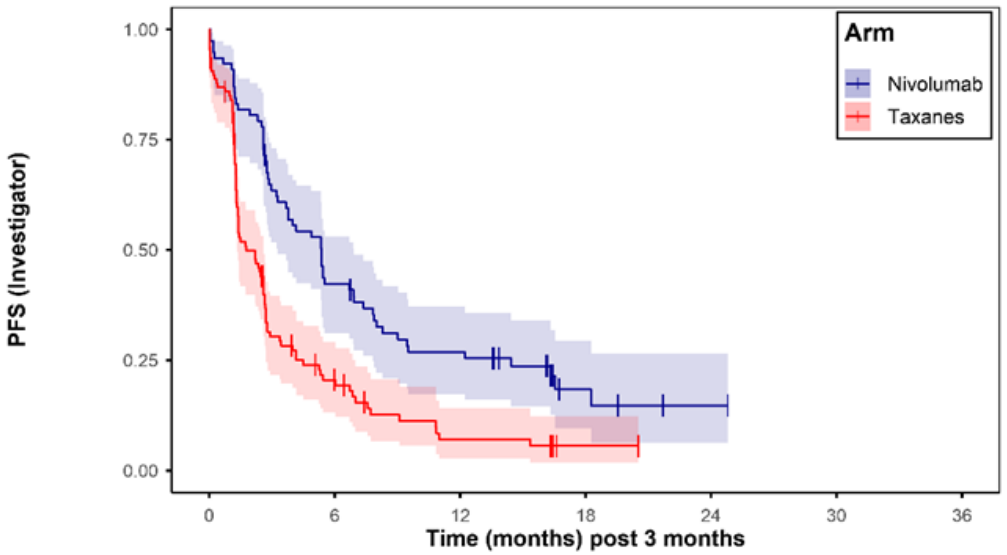
Issue 1: relative treatment effect constant over time (2)

Landmark analysis of ATTRACTION-3 on patients alive at three months.



NAR (Cumulative Events)

Nivolumab	172 (0)	119 (52)	73 (97)	38 (117)	8 (126)	1 (126)	0 (126)
Taxanes	183 (0)	95 (85)	53 (126)	21 (145)	5 (150)	1 (152)	0 (152)



NAR (Cumulative Events)

Nivolumab	77 (0)	32 (44)	19 (55)	5 (59)	1 (60)	0 (60)	0 (60)
Taxanes	107 (0)	18 (80)	5 (90)	1 (91)	0 (91)	0 (91)	0 (91)

Company: Outcomes are improved for those in the nivolumab arm for both PFS and OS, which remain significantly higher across the observed data.

Hazard rates observed in ATTRACTION-3 are in line with clinical knowledge about how the mechanism of action may result in a slightly delayed response from immunotherapies

Benefit profile comparable to that observed for all immuno-oncology therapies assessed in indications where survival is short, and evidence is versus an active comparator

Issue 4: Safety data for nivolumab

Although the safety profile of nivolumab is favourable compared with taxanes, ERG noted higher 'on treatment' death rate [redacted]

Company – In the first 3 months of treatment there were more deaths in the nivolumab compared with the taxane arm [redacted] There is initial crossover of treatment arms but beneficial OS and PFS from 6 months with nivolumab, patients alive at 3 months have a better prognosis (Landmark analysis). There is significant evidence for a class effect seen in all immunotherapies.

Clinical expert – agrees with company that delayed response is common with immunotherapies. Some people with advanced oesophageal cancer have poor prognosis regardless of treatment. These patients can often be identified in clinic as those with very advanced disease (e.g. large volume metastases)

ERG - ERG's main concern is 'deaths in the first three months' (not 'on treatment deaths') but acknowledges clinical expert opinion that this to be because of the different trajectory of immunotherapy

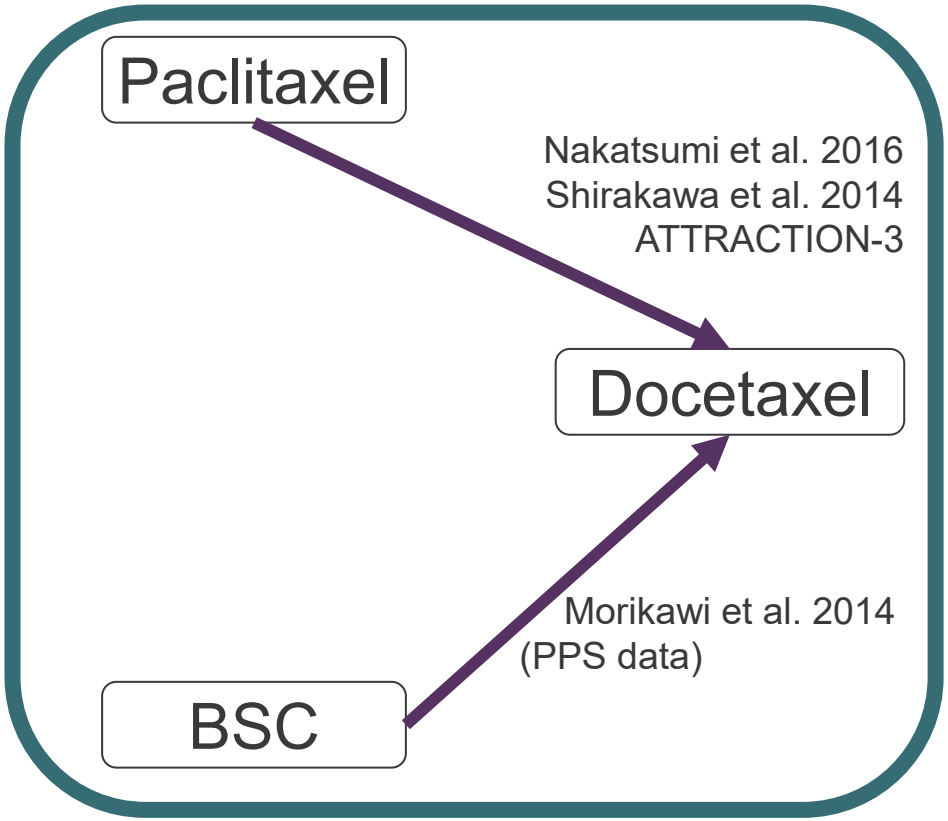
Questions

- **Is the pattern of mortality with nivolumab consistent with its mode of action and comparable to responses seen with other immunotherapies?**
- **Can patients at most risk of death in first 3 months be identified?**

Issue 2: Best supportive care as a comparator

Company provided exploratory indirect treatment comparison (ITC), outlined its limitations.

BSC is questioned as a relevant comparator (pivotal trial was in taxane-eligible patients)



Clinical expert – In clinical practice nivolumab will only be used in taxane eligible.

Company – BSC is a relevant comparator (in patients who are not eligible for taxanes). Patients may be considered healthy enough for nivolumab but not healthy enough to tolerate taxane.

ERG – several flaws in the ITC: non-randomised studies, lack of adjustment for differences in baseline characteristics & other inconsistencies. Generalisability of ITC results to NHS practice questioned as all studies except ATTRACTION-3 used Japanese-only populations, who have better survival outcomes.

Some patients who are not fit enough for taxanes may be eligible for nivolumab. **However**, this group is not represented in ATTRACTION-3 and it is uncertain whether the efficacy is generalisible.

Questions

- **Is BSC is a relevant comparator, are the results of the ITC robust?**

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Issue 6: Combined taxane arm, is the mixture of paclitaxel and docetaxel important?

Company assumed 50:50 mix of paclitaxel and docetaxel in the comparator arm. Provided a subgroup analysis by taxane therapy but noted that ATTRACTION-3 was not powered to detect differences by taxane therapy.

- ICER slightly higher vs. docetaxel than paclitaxel

Clinical expert and company: some clinicians prefer to use paclitaxel because it is better tolerated, others prefer docetaxel because it is administered less frequently (i.e. once every three weeks instead of once per week).

- The clinical expert considered it reasonable to assume a class effect for taxanes
- No evidence for paclitaxel or docetaxel preferred population

ERG:

- Clinical advisers to the ERG preferred docetaxel to paclitaxel (regional differences compared with the experts/ clinical advisers to the company?).
- ERG considers it reasonable to assume a class effect for taxanes

Key issues: clinical effectiveness

- How does the side effect profile and treatment experience differ between nivolumab and taxanes?
- Is efficacy in ATTRACTION-3 generalisable to clinical practice in the NHS given the predominantly Asian, particularly Japanese trial population, open label design, and inclusion and exclusion criteria?
- How would nivolumab treatment be selected for patients? Is BSC a reasonable comparator and is the indirect comparison robust?
- How is the taxane chosen, and what is the perceived relative effectiveness, and relative usage of paclitaxel and docetaxel the UK?
- Disease progression was faster on nivolumab than taxanes up to 3 months; and survival was less at 2 months, equal at 4 months and greater at 6 months. Why is this?
- How long would people stay on treatment? Might people stay on treatment after progression?
- The model shows more survival benefit occurs post-progression than pre-progression. Is this due to more post-progression treatments being given in the nivolumab arm in ATTRACTION-3, people continuing on nivolumab post-progression and it slowing the disease, or carry-over effect post stopping nivolumab?

Key issues: cost effectiveness

- Is the model structure appropriate for estimating the cost effectiveness of nivolumab?
- Which of the company's or ERG's method to extrapolate OS is most appropriate?
- Should the efficacy of nivolumab in the model be adjusted for potential benefits of 3rd line therapy?
- How should time on treatment be modelled?
- Should pre- and post-progression utilities be treatment independent or differ by treatment?
- Are the ERG or company costs most relevant to NHS practice?
- Does nivolumab provide at least a 3-month extension to life, and hence meet the criteria for end of life consideration?

Economic model used in company base-case

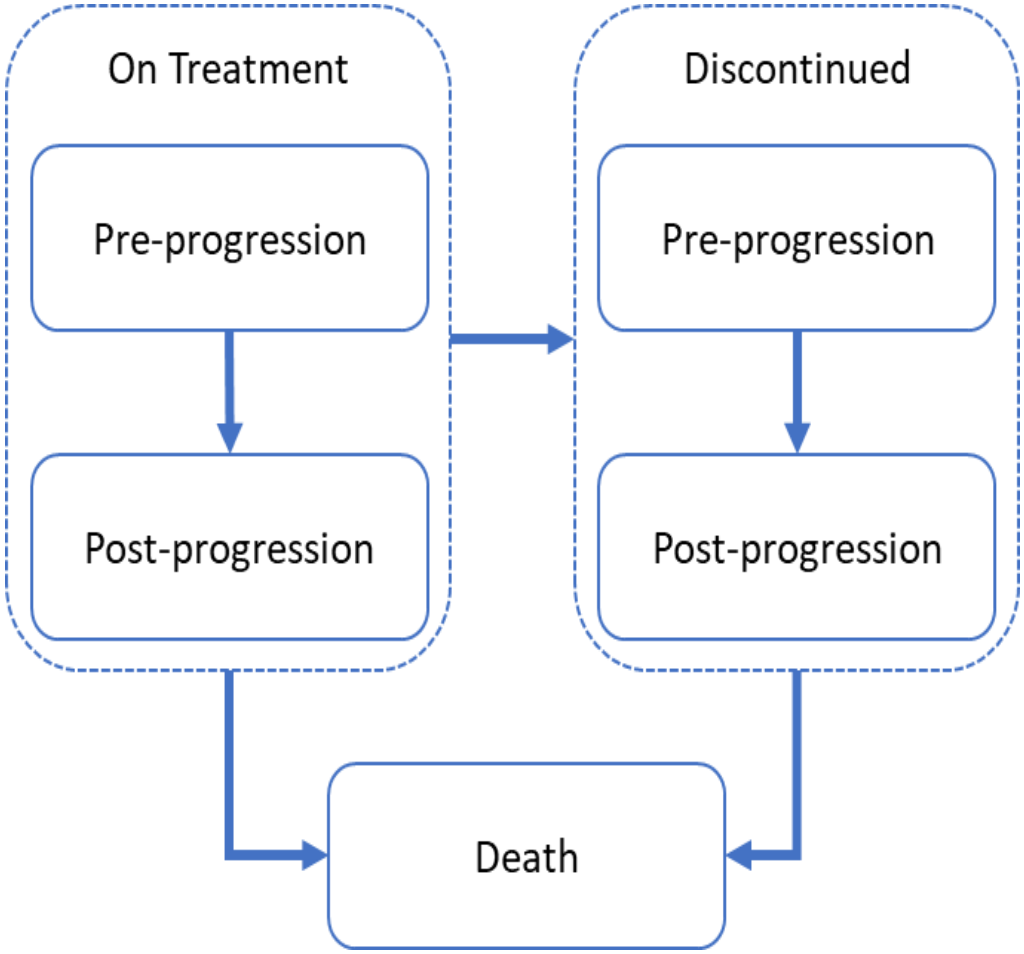
De-novo partitioned survival model, informed by data from ATTRACTION-3.

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% men.



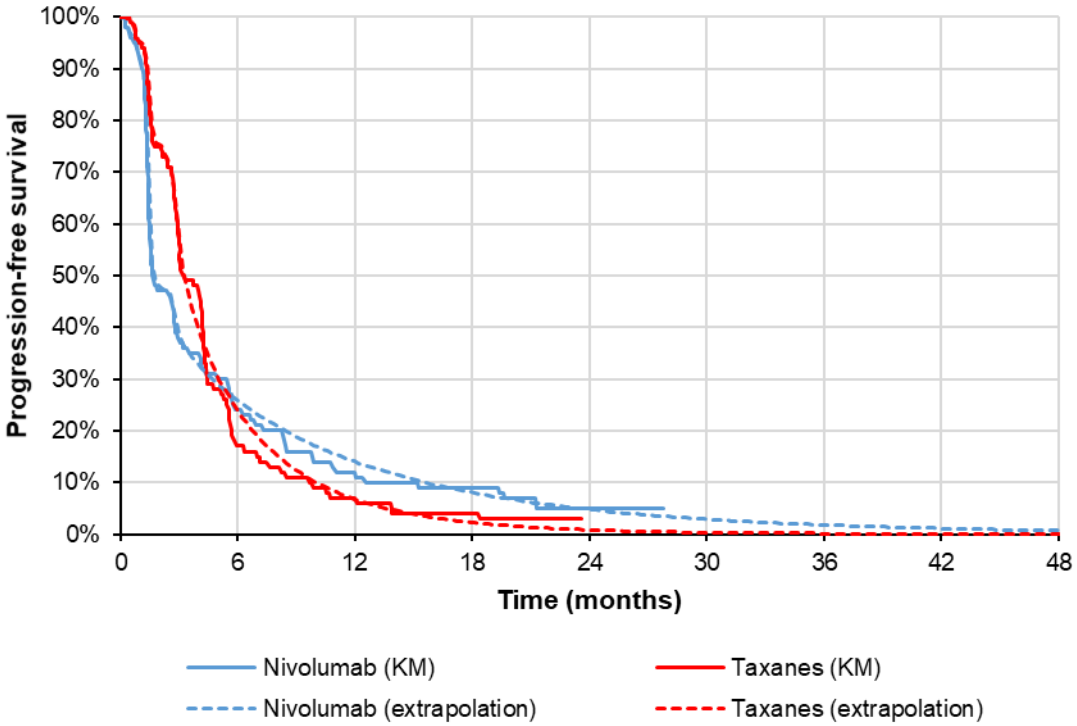
Progression-Free and Overall Survival

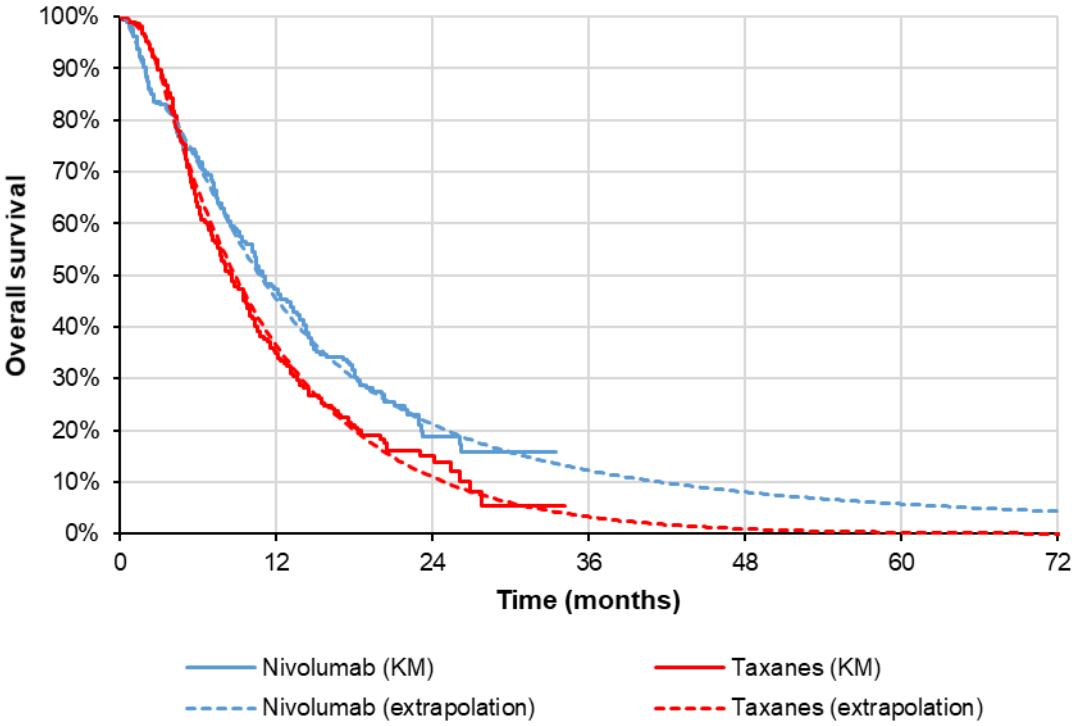
Semi-parametric approach:

- Kaplan-Meier curves up to 2.99 months
- Extrapolation using parametric model

	Progression-free survival	Overall survival
Nivolumab		
Median	1.68 months	10.91 months
Extrapolation	Weibull	Log-logistic
Median (from extrapolation)	1.68 months	10.87 months
Mean (from extrapolation)	5.78 months	24.33 months
Taxane		
Median	3.35 months	8.37 months
Extrapolation	Weibull	Exponential
Median (from extrapolation)	3.27 months	8.90 months
Mean (from extrapolation)	4.79 months	11.96 months

Progression-Free and Overall Survival





Semi-parametric approach

- Kaplan-Meier curves up to 2.99 months
- Extrapolation using parametric model

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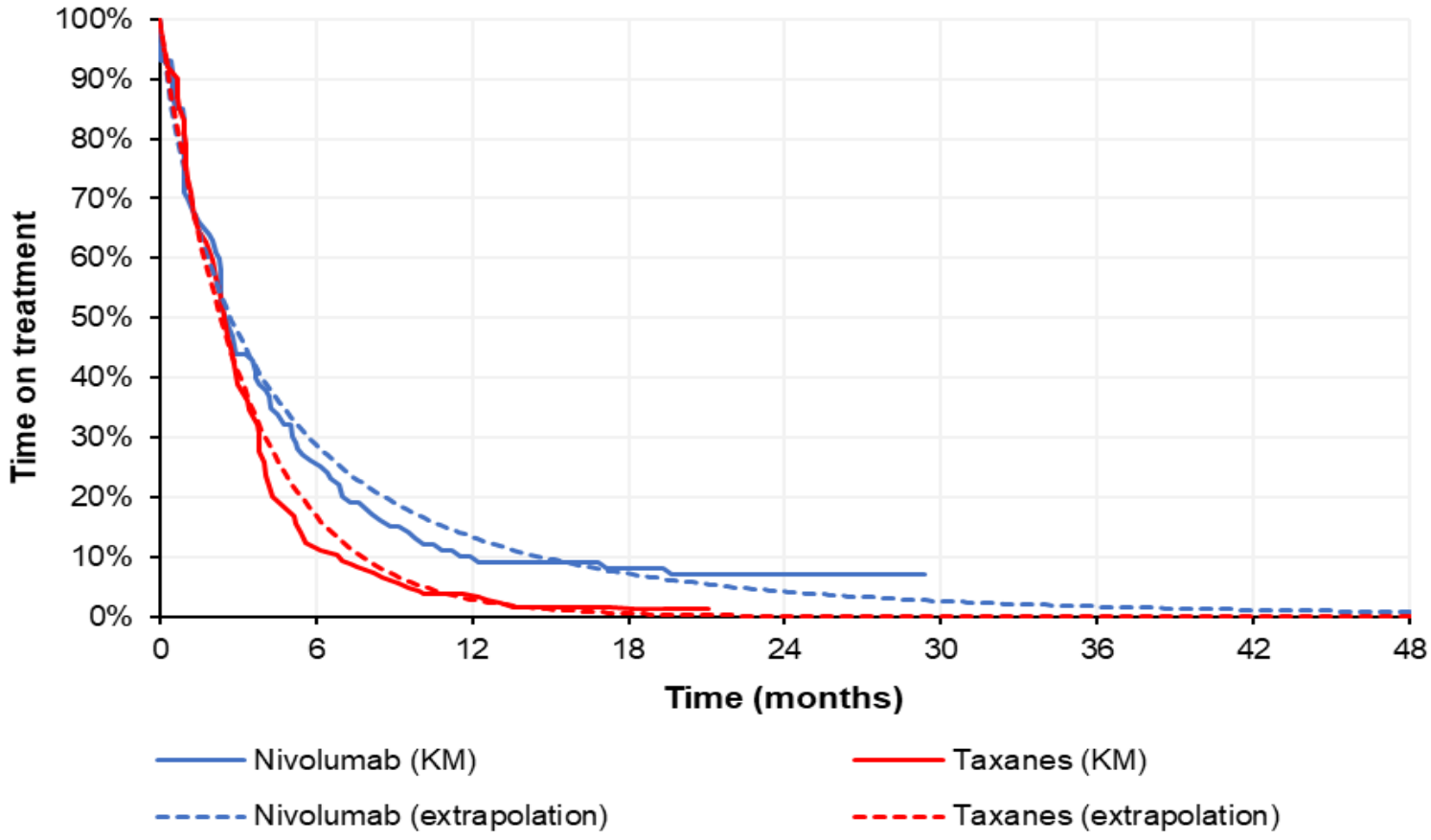
Time on treatment

Semi-parametric approach not considered, as company considered that the criteria for a fully parametric model were satisfied.

Nivolumab: generalised gamma

Taxanes: exponential



Utilities and adverse events

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

- Based on EQ-5D data from ATTRACTION-3, with imputation of missing data under assumption that values were Missing At Random.
- Higher pre-progression utility on nivolumab due to more favourable safety profile.
- Grades 3-4 AEs and other clinically relevant AEs included in the analysis, using constant weekly probabilities of each AE, estimated from ATTRACTION-3 separately for nivolumab and taxanes.

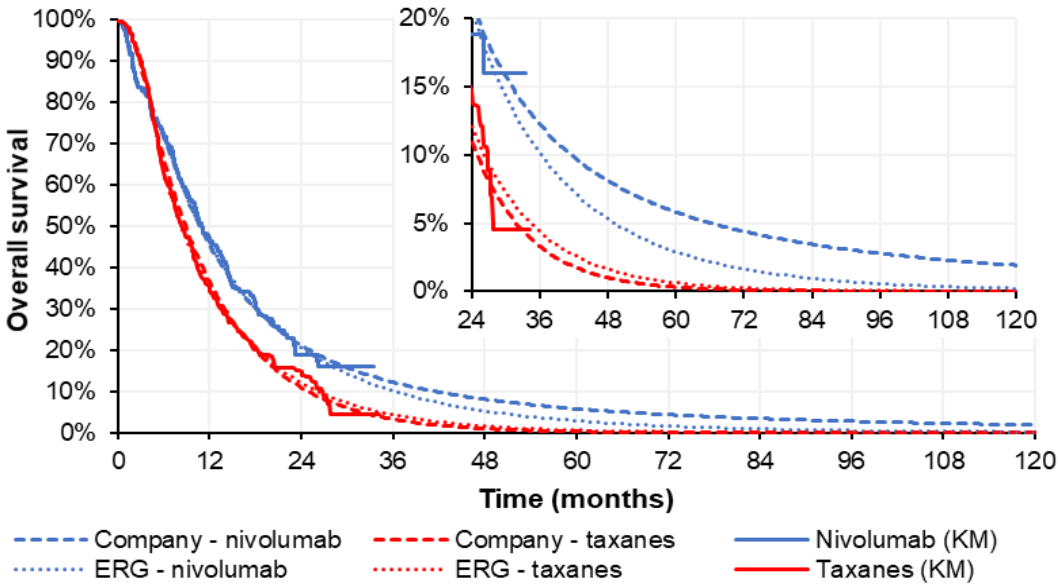
Company base-case results

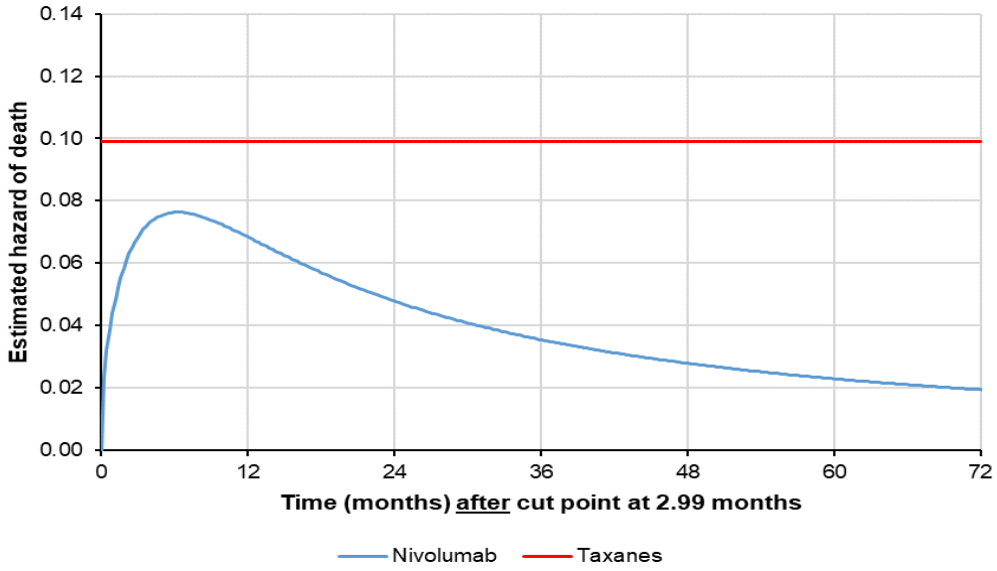
Technology	Total costs (£)	Total life years	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Nivolumab	[redacted]	[redacted]	[redacted]	£21,210	0.547	0.468	£45,278
Taxane	[redacted]	[redacted]	[redacted]	-	-	-	

Issue 8: Extrapolation of overall survival

	Company		ERG	
Description	SP log-logistic (nivolumab) or exponential (taxanes) with cut-point at 2.99 months		SP generalised gamma (both arms) with cut-point at 5.75 months	
Time (years)	**Nivolumab**	**Taxanes**	**Nivolumab**	**Taxanes**
1	45.61%	36.57%	46.07%	35.40%
2	21.27%	11.06%	20.70%	12.20%
5	5.84%	0.30%	2.93%	0.63%
10	1.92%	0.00%	0.20%	0.01%

Similar outputs at 2 years but after that nivolumab survival worse and taxane survival better in ERG model.





Issue 8 continued: Extrapolation of overall survival

ERG:

- Company's log-logistic extrapolation (nivolumab) assumes hazard of death changes over time, with a peak and then a steady decline
- Company's exponential extrapolation (taxanes) assumes a constant hazard of death over time, does not look a good visual fit to Kaplan-Meier curve
- In semi-parametric models, extrapolation can be sensitive to the 'cut-point' i.e. time from which parametric function is used rather than Kaplan-Meier curve

Company:

- ERG model predicts clinically implausible outcomes: longer mean OS for taxanes than nivolumab, but ToT is extended compared with company model
- Modelling of OS should be considered alongside other model inputs, not in isolation

ERG critique of the company response to technical engagement:

- ERG model predicts 0.968 mean life-years for taxane group, 1.288 for nivolumab
- Choice of models should be based on evidence to assess their suitability, including visual fit to Kaplan-Meier curve, goodness of fit statistics and clinical plausibility
- Comparing ERG model outputs with those from company is not a sufficient justification for considering ERG's analysis to be clinically implausible
- Most appropriate choice of cut-point and extrapolation model both highly uncertain

Which of the company's or ERG's method to extrapolate OS is most appropriate?

Issue 5: 3rd line treatments

Patients continuing initial treatment after progression in ATTRACTION-3:

- [redacted] of nivolumab group for [redacted]
- [redacted] of taxanes group for [redacted]

Patients receiving subsequent therapy after progression in ATTRACTION-3:

- 57% of nivolumab group (53.3% received subsequent pharmacotherapy)
- 55% of taxanes group (47.4% received subsequent pharmacotherapy)

Clinical expert: approximately 15% of patients receive 3rd line treatment in UK.

ERG: Uncertainty surrounding the composition of third-line treatment in NHS practice.

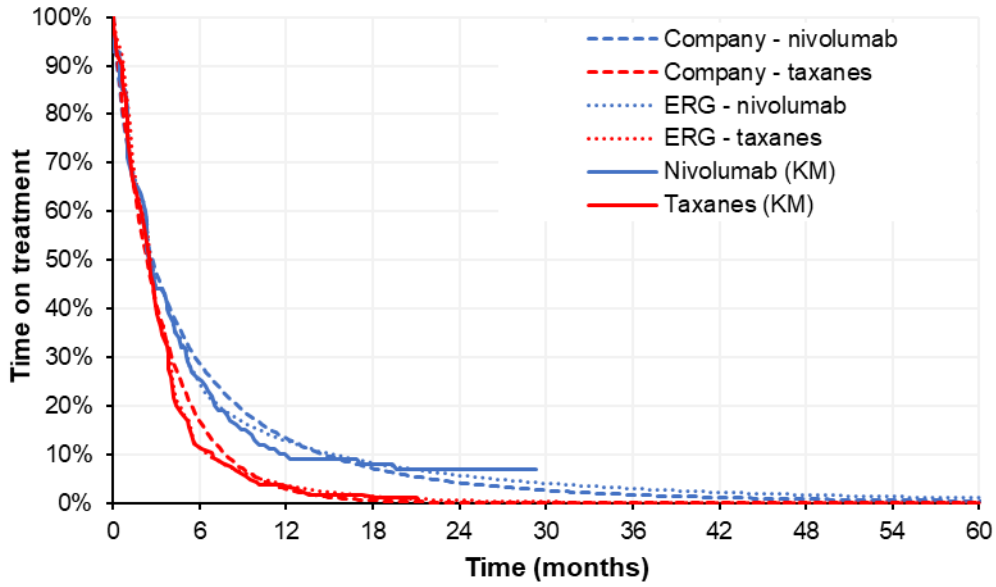
It is difficult to understand how costs and outcomes may be robustly adjusted to reflect the differences between the ATTRACTION-3 and NHS patient populations.

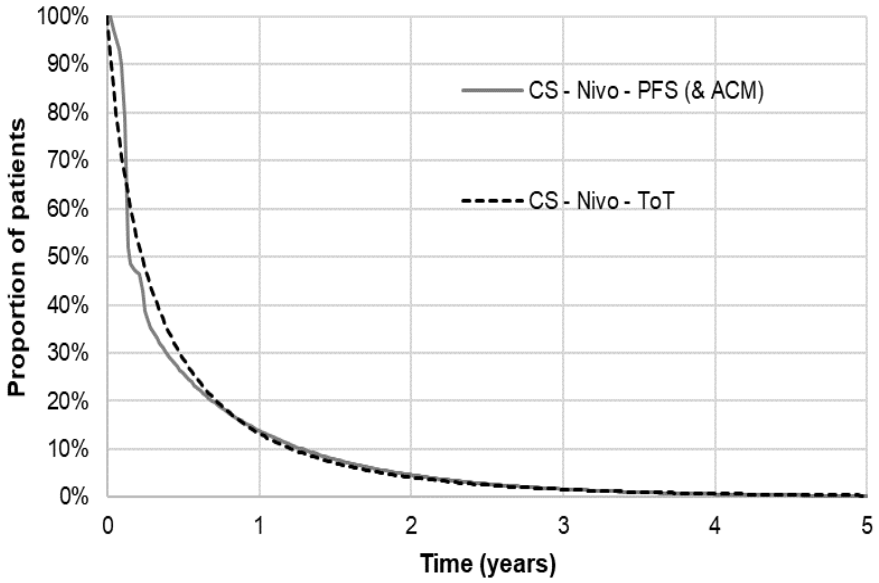
Any scenario analyses to adjust for the impact of 3rd line treatment (adding costs of 3rd line treatment both treatment arms and reducing efficacy) would be highly uncertain.

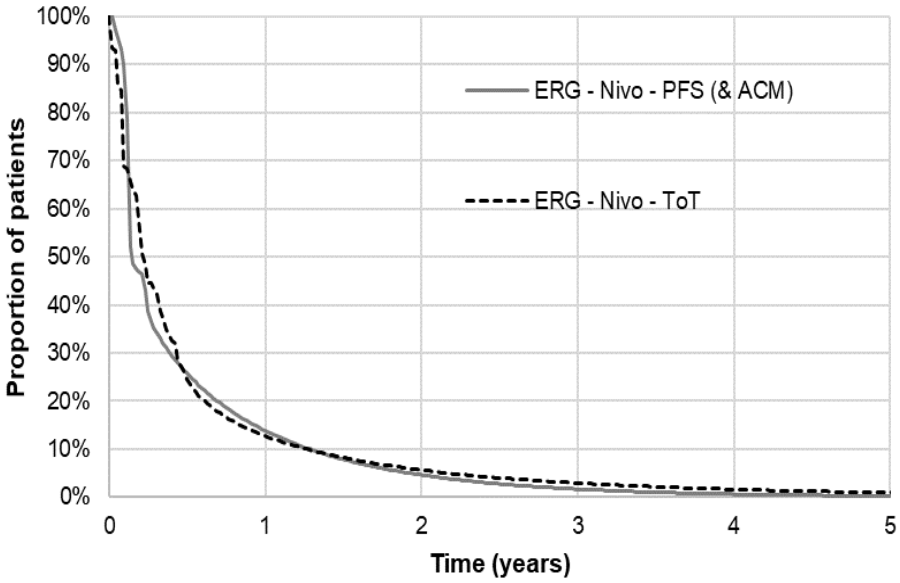
Could the results seen in ATTRACTION-3 be influenced by the administration of treatment after progression in either arm?

Issue 10: Extrapolation of time on treatment

	Company		ERG	
Method	**Fully-parametric generalised gamma**		**Semi-parametric Weibull with cut-point at 5.75 months**	
Time (years)	Nivolumab	Taxanes	Nivolumab	Taxanes
1	13.36%	2.90%	12.80%	3.68%
2	4.19%	0.08%	5.69%	0.51%
3	1.67%	0.00%	2.96%	0.08%
4	0.76%	0.00%	1.66%	0.01%
5	0.38%	0.00%	0.98%	0.00%







Issue 10 continued: Extrapolation of time on treatment

ERG:

- Disagreed with company that fully-parametric models are appropriate, given poor visual fit to Kaplan-Meier curves
- Preferred semi-parametric Weibull model with cut-point at 5.75 months for both nivolumab and taxanes

Company:

- Not appropriate to extend time on treatment (relative to company model) while reducing OS for nivolumab and assuming no post-progression utility differential

ERG critique of company response to technical engagement:

- Re-iterated that mean life-years on OS are higher on nivolumab than on taxanes
- Suitability of its model should be considered against evidence available, not by comparison with the company's model

How should time on treatment be modelled?

Issue 9: Utility values

ERG critique: (prefers use of treatment independent utilities)

- not appropriate for pre-progression utility with nivolumab (0.832) to be higher than mean age-adjusted utility in the UK general population (0.8041).
- large difference in post progression utility ([redacted] for nivolumab vs [redacted] for taxane patients) lacks face validity.

Company response: (utility difference between nivolumab and taxanes supported by following)

- large post-progression survival benefit compared with taxanes in ATTRACTION-3
- safety profile of nivolumab compared with taxanes
- published utility values for taxanes in gastric cancer (pre-progression 0.738, post-progression 0.588) similar to those used in company model (0.747, 0.555)
- ERG assumption of equal utility in the progressed disease state can be considered illogical given the extended post-progression survival.

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

Issue 11: Costs

Company: **MIMS (Monthly Index of Medical Specialities)** list price of taxanes and subsequent treatment.

- Probability of adverse events each week determined by company; these are used to calculate the costs for resolving adverse events for each arm independently.
- Administration costs for taxanes were higher compared with nivolumab due to the expected time of administration for each treatment.

ERG: **eMIT (Electronic Market Information Tool)** provides price estimates reflective of average prices paid by NHS trusts, considered to be standard for NICE appraisals.

Queried unit costs for outpatient consultation using company's references:

- Per patient cost of nerve block is overestimated (£26.62 instead of £2.66)
- Cost of hospitalisation substantially underestimated at £534.07 (1 day) instead of £3379.73 (full length of hospitalization unadjusted for the length of stay).

Are costs calculated by the company or ERG most relevant to NHS practice?

Is MIMS or eMIT most reflective of the prices paid by NHS trusts?

ERG's preferred model assumptions (Table 25 ERG report)

Preferred assumption	Pairwise ICER £/QALY	Cumulative ICER £/QALY
Company base-case	45,491	45,491
SP generalised gamma (5.75) OS models	62,440	62,440
SP Weibull (5.75) ToT models	49,463	68,343
Correction of taxanes costs	53,459	80,614
ERG's preferred administration costs	43,255	77,198
ERG's preferred utility values	57,372	106,643
Update of unit costs for MRU	62,092	125,984

Company and ERG base-case results (Table 26 ERG report)

	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

Issue 12: End of life

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

Extension to life with nivolumab

- Observed data: 2.58 months (median)
- Company base-case model: 7.8 months (modelled mean)
- ERG base-case model: 4.0 months (modelled mean)

ERG: limited follow-up data from ATTRACTION-3 means extrapolation is subject to substantial uncertainty. Estimated OS was at least 3 months in both the company and ERG model. However, potential issue of generalising from predominantly Asian to UK population.

Further data from ATTRACTION-3 on OS and TOT may resolve some uncertainty but there remains uncertainty in the utility and taxane split

Company response to technical engagement: ATTRACTION-3 is an ongoing study; additional data will be provided when possible in order to inform long-term survival estimates.

Improvement in OS with nivolumab must be considered alongside the increased risk of death associated with nivolumab use within the first 3 months.

Clinical expert: selecting correct patients for nivolumab treatment likely to lead to meaningful improvement in quality of life.

Key issues: cost effectiveness

- Is the model structure appropriate for estimating the cost effectiveness of nivolumab?
- Which of the company's or ERG's method to extrapolate OS is most appropriate?
- Should the efficacy of nivolumab in the model be adjusted for potential benefits of 3rd line therapy?
- How should time on treatment be modelled?
- Should pre- and post-progression utilities be treatment independent or differ by treatment?
- Are the ERG or company costs most relevant to NHS practice?
- Does nivolumab provide at least a 3-month extension to life, and hence meet the criteria for end of life consideration?

Equality issues

No subgroups were identified in which nivolumab is expected to have a different clinical effect.

Unmet need of older patients who are not fit enough for taxane therapy:

- 41% of new cases in the UK between 2014 to 2015 were diagnosed in those over 75 years old (2014-15).
- Five-year net survival of oesophageal cancer patients aged 70 years (15% in males and 16.5% in females) and overall survival (18.1% in males and 27.7% in females) is notably poorer compared with younger patients, particularly in female patients.
- Treatment options for these older patients may be extremely limited due to their reduced ability to tolerate chemotherapy and therefore more likely to receive BSC which has no impact on symptoms.

Utility values explored by ERG (Table 21 ERG report)

	Nivolumab		Taxanes		ICER (£/QALY)
	PF	PP	PF	PP	
Company base-case	[redacted]	[redacted]	[redacted]	[redacted]	45,491
Average PP value	[redacted]	[redacted]	[redacted]	[redacted]	55,449
Minimum PP value	[redacted]	[redacted]	[redacted]	[redacted]	59,215
Custom small benefit (both states)	[redacted]	[redacted]	[redacted]	[redacted]	58,830
Custom moderate benefit (both states)	[redacted]	[redacted]	[redacted]	[redacted]	56,119
Custom large benefit (both states)	[redacted]	[redacted]	[redacted]	[redacted]	53,646

Abbreviations: PF progression-free utility, PP post-progression utility

ERG additional clinical and economic analyses (Table 22 ERG report)

Analysis description	ICER £/QALY
Company base-case	45,491
Remove AE costs	47,671
ERG background mortality	42,749
Remove background mortality	42,299
Pragmatic ToT estimation (1% at 3 years)	41,501
Pragmatic ToT estimation (1% at 4 years)	45,323
Pragmatic ToT estimation (1% at 5 years)	49,034
ATTRACTION-3 taxane split	44,703
100% docetaxel	47,578
Average PP value	55,449
Minimum PP value	59,215
Custom small benefit (both states)	58,830
Custom moderate benefit (both states)	56,119
Custom large benefit (both states)	53,646
Change clinician consultation cost	45,575
Change hospitalisation cost	62,008
Change both	62,092