NICE National Institute for Health and Care Excellence

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Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma [ID1609]

Lead team presentation

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Committee B

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1st committee meeting 4 August 2021 virtual

Key issues: clinical

Key trial and NHS practice:

- Does NHS practice make treatment decisions based on histology or programmed death-ligand (PD-L1) status?
- Is trial population representative of NHS patients with relation to potential effect modifiers, for example, histology?
- Does nivolumab's fixed dosing and weight-based dosing used in trial have similar efficacy and safety?
- Does use of carboplatin and cisplatin in trial represent UK practice?
- Do 2nd line treatments in trial reflect NHS practice?
- Does progression-free survival have clinical relevance?
- Is the interim analysis likely to overestimate the effect on overall survival?

2nd line treatments

- Which, if any, 2nd line treatments reflect NHS practice?

Stopping rule:

- Does a 2-year stopping rule reflect the trial?

Key issues: cost effectiveness

Validation of extrapolating survival curves:

- Given the proportion of life years the model predicts beyond observed trial period, should the company develop another model for validation?

Survival extrapolations:

- **Overall survival**: which extrapolation is most appropriate for the comparator?
- **Progression free survival**: which extrapolations are more appropriate?

Treatment effect waning:

- Will treatment effect of nivolumab with ipilimumab wane over time?

Subsequent treatments:

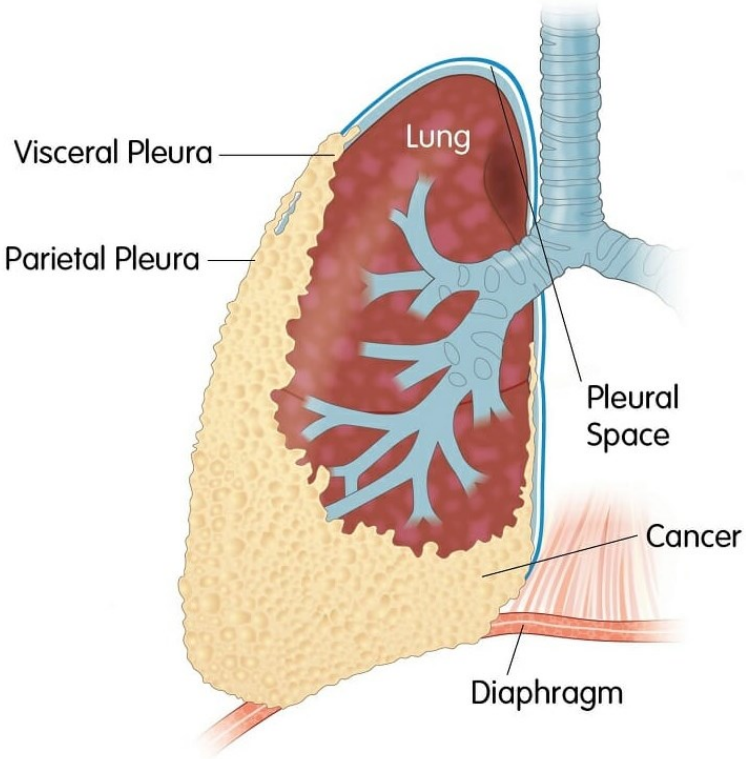
- Which 2nd line treatment scenarios reflect NHS practice?

End of life criteria:

- Does nivolumab with ipilimumab meet end-of-life criteria?

Background: malignant pleural mesothelioma

- Aggressive cancer of pleura affecting membranes lining lungs and chest wall
- 94% linked to asbestos
- Asbestos banned in UK 1999 but UK now experiencing peak in cases since presents around 40 years after exposure (*Source: company submission*)
- Symptoms: breathlessness, chest pain, fatigue and lethargy, weight loss, cough *(Source: Mesothelioma UK)*
- Incidence: 6,551 cases in England in 2016-2018 *(Source: UK National Mesothelioma Audit, company submission)*
- Survival: 8-10% alive after 3 years
  (*Source: UK National Mesothelioma Audit and UK Cancer Analysis System Registry in England 2013-2017, company submission)*

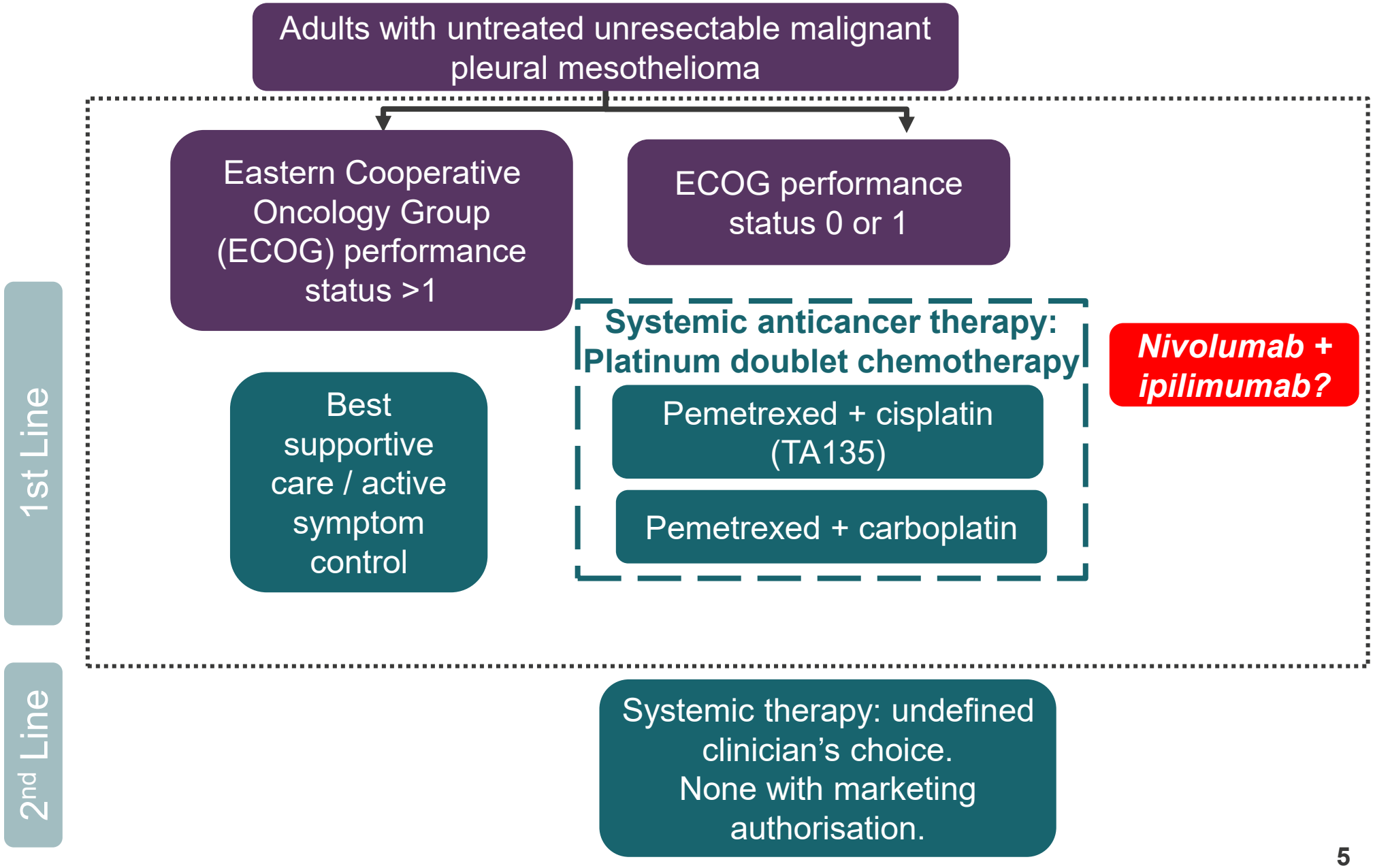


Source: Mesothelioma UK

◉ *Survival in the UK at 5 and 10 years?*

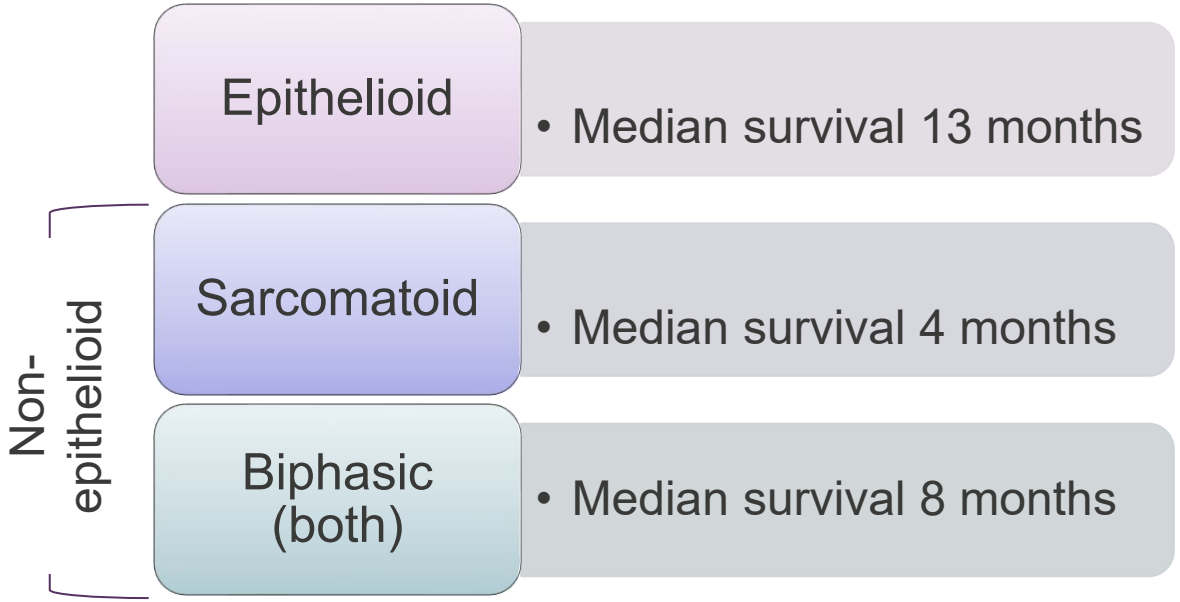
Treatment pathway and position of technology

Company propose nivolumab + ipilimumab replace platinum doublet chemotherapy as new 1st-line standard of care



Histologic types + programmed death-ligand

Epithelioid subtype better prognosis; non-epithelioid responds poorly to chemotherapy
Some 1 in 3 unknown or unspecified histology



- *Are patients routinely tested for histological subtypes in the NHS? For PD-L1?*
- *Are these likely to be effect modifiers?*
- *Would clinicians expect recommendations based on histology? PD-L1?*

- Testing for programmed death-ligand PD-L1 not routine
- Thresholds, scoring methods, and antibodies used not standardised
  - wide variation in threshold cut offs (1%, 5%, 20%, 25%, 50%) and rates of expression in clinical studies (20% to 70% of specimens tested PD-L1-positive).
- Some evidence that PD-L1 expression associated with poorer survival, but may be because non-epithelioid tumours more often express PD-L1

Patient perspective

Limited treatment options and unmet need

Diagnosis challenging:

- People visit GP several times before being referred for tests which requires frequent visits to hospital.

Limited treatment options for those eligible for 1st line systemic therapy:

- Limited chemotherapy options available.
- Chemotherapy associated with adverse effects of nausea and vomiting, sore mouth, and alopecia.
- Some people not eligible for chemotherapy if too frail or unable to travel for treatment
- No cure for untreated unresectable disease.

New technology:

- CheckMate 743 (trial for nivolumab with ipilimumab): broke new ground for untreated patients with chemotherapy-free regimen. Suggests improvement in *non-epithelioid* mesothelioma which is most aggressive form with high symptom burden, few effective treatment options and shorter prognosis.
- Side effects minimal compared with chemotherapy but expertise required for planning, treating and monitoring for side effects (including pancreatic side effects).

"advantage of being offered immunotherapy over other treatments …gave me a great source of immediate comfort following my diagnosis…Receiving nivo and ipi is giving me hope "

Nivolumab with ipilimumab

Opdivo and Yervoy, Bristol-Myers Squibb

Marketing authorisation	1st-line treatment of adult patients with unresectable malignant pleural mesothelioma.
Mechanism of action	• **Nivolumab:** antibody that targets and blocks PD-1 receptor, to promote an anti-tumour immune response • **Ipilimumab:** antibody that blocks effects of the anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) to enhance T-cell mediated immune response to tumour cells
Administration & dose	**Nivolumab**: intravenous infusion (IV) of 360 mg every 3 weeks (n.b. trial used weight based dosing) **Ipilimumab**: IV infusion 1 mg/kg ipilimumab every 6 weeks
Stopping rule	24 months or if disease progresses earlier, stop
List price	• Per dose: **nivolumab,** £3,950; **ipilimumab,** £7,500. • Separate Patient Access Scheme (PAS discount) approved by Department of Health for both nivolumab and ipilimumab

Note: Treatment currently available through Early Access to Medicine Scheme

Slide amended/corrected after the meeting

Decision problem

Company submission limited to patients with ECOG status 0-1 which reflects trial but which is not specified in marketing authorisation, and excludes 2 comparators from scope

	NICE final scope	Company submission
Population	Adults with untreated unresectable malignant pleural mesothelioma	As scope with Eastern Cooperative Oncology Group (ECOG) performance status 0-1
Intervention	Nivolumab with ipilimumab	
Comparators	1. Pemetrexed with cisplatin 2. Pemetrexed with carboplatin (for people for whom treatment with cisplatin is unsuitable) 3. Raltitrexed with cisplatin (for people for whom treatment with pemetrexed is unsuitable) 4. Best supportive care.	1. Pemetrexed with cisplatin 2. Pemetrexed with carboplatin **Exclude:** **Raltitrexed**: not licensed for indication and not commonly used in the UK. **Best supportive care**: not appropriate for fit patients **ERG**: agree with exclusions.
Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects • Health-related quality of life	• As in scope.

Clinical expert: Some patients with ECOG 0-1 may not be suitable for or chose not to have chemotherapy.

◉ What is committee's view on ECOG? Excluded comparators? Is best supportive care relevant?

Decision problem – subgroups

Company presented subgroup analysis for clinical effectiveness but not cost effectiveness

	NICE final scope	Company submission
Subgroups (if evidence allows)	• Histologic subtype (epithelioid, sarcomatoid, biphasic) • Level of programmed death-ligand 1 (PD-L1) expression.	Clinical effectiveness by: • Histology: epithelioid and non-epithelioid • PD-L1 expression: ≥ 1% and < 1%. (no subgroup analyses used in model) No cost effectiveness analyses by subgroup

◉ *Would NHS patients be tested for histology and PD-L1 status subtypes to receive treatment? Would clinicians expect NICE recommendations based on histology? PD-L1 expression?*

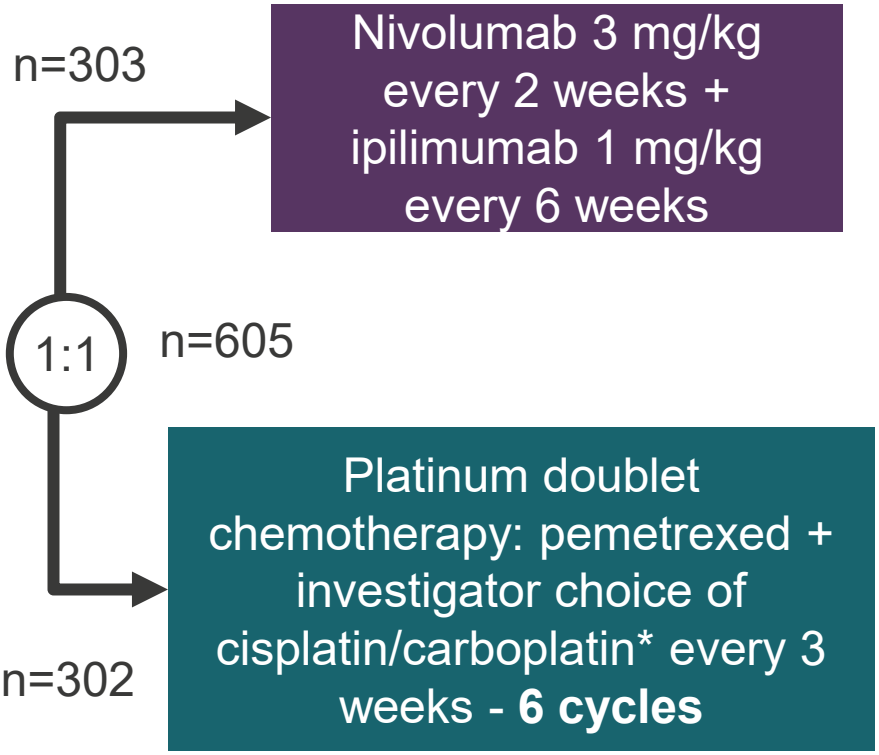
Clinical effectiveness

Pivotal trial: CheckMate-743

Ongoing international randomised controlled trial; weight-based dosing not in model

Eligibility criteria:
- Adults with histologically confirmed disease epithelioid or non-epithelioid
- Disease not amenable to surgery
- No previous chemotherapy - previous palliative radiotherapy permitted
- ECOG PS 0-1

Stratification by:
- Sex
- Epithelioid vs non-epithelioid



Duration of treatment until:
1. disease progression or
2. unacceptable toxicity, **or**
3. **2 years of treatment for NIVO+ IPI arm or 6 cycles for chemotherapy**

Outcomes		In model?
1º	Overall survival	✓
Key 2º	Progression-free survival (PD-L1 expression as predictive biomarker but not used in model)	✓
Exploratory	Adverse events, health-related quality of life (EQ-5D-3L)	✓

Abbreviations: ECOG, Eastern Cooperative Oncology Group

Slide amended/corrected after the meeting

CheckMate-743 statistical plan

Results reflect planned interim analysis

Primary endpoint	Overall survival
Targeted power	90%
Target hazard ratio	0.72
Alpha (α)	0.05 2-sided, 0.03 at interim analysis, 0.041 at final analysis
Sample size	606
Expected number of events for interim analysis (% of target event, at about 38 months)	**Planned**: 403 (85%); **Actual**: 419 (89%), at April 2020 data cut**; median follow-up 29.7 months
Target number of events	473
Expected duration	56 months*

Source: Table 5-1, CSR appendix 1.11; *Study completion planned April 2023 as per clinicaltrial.gov (4-year overall survival update planned); ** 98.3% of patients on nivo + ipi and 100% of those on chemotherapy have stopped treatment as of data cut

◉ Are the results from an interim analysis likely to overestimate effect?

Baseline demographics

	Nivolumab + ipilimumab (n = 303)	Platinum-based doublet chemotherapy (n = 302)
Eastern Cooperative Oncology Group (ECOG) performance status, N (%)		
0	114 (38)	128 (42)
1	189 (62)	173 (57)
Histology, N (%)		
Epithelioid	229 (76)	227 (75)
Non-epithelioid*	74 (24)	75 (25)
PD-L1 quantifiable at baseline, n (%)	289 (95)	297 (98)
< 1%**, N (%)	57 (20)	78 (26)
≥ 1%**, N (%)	232 (80)	219 (74)

*47-48% sarcomatoid, 52-3% mixed/other in both arms; ** Based on PD-L1 quantifiable at baseline

6% (38/605) of patients randomised were from the UK

◉ ***Is the trial population representative of NHS patients?***

Unknown impact on ICER

Fixed vs weight-based dosing of nivolumab

Company uses fixed dosing as in marketing authorisation, trial weight-based dosing

Background

- CheckMate-743 used weight-based dosing - 3 mg/kg every 2 weeks for up to 2 years
- Fixed dosing (360 mg every 3 weeks) used in model aligning with license
- Company provided evidence (Tsao et al. 2020) showing treatment effect does not vary by weight

ERG

- Tsao et al. (2020) provides no evidence in people treated with high or low doses
- Effectiveness and safety of fixed dosing uncertain

Company response

- Dosing regimens similar; fixed dosing accepted in NICE appraisals
- [redacted]

Clinical expert

- Fixed dose is standard practice
- Fixed and weight-based dosing has similar treatment effect in other cancers

◉ Which dosing should be used in the health economic model?

Unknown impact on ICER

Comparator: cisplatin and carboplatin in NHS practice

Comparator in trial pemetrexed + cisplatin or carboplatin per 'investigator's choice'

Comparator in scope	***Company submission***
Pemetrexed with cisplatin OR Pemetrexed with carboplatin, when cisplatin unsuitable	Pemetrexed with cisplatin or carboplatin investigator's choice

Source of data and comparability with trial	Pemetrexed + carboplatin (%)	Pemetrexed + cisplatin (%)
CheckMate-743	66 (209/302)*	34 (104/302)
UK National Mesothelioma Audit 2020	48	20
Cancer Analysis System registry (n=3159 received unresected first line systemic anti-cancer therapy)	[redacted]	[redacted]
EU cross-sectional study (248 UK patients)	[redacted]	[redacted]

NICE

*includes 29 patients who switched from cisplatin

Unknown impact on ICER

Trial comparator and NHS practice

ERG: unclear if carboplatin and cisplatin use in trial represents clinical practice; Clinical expert: carboplatin often chosen for practical reasons

ERG

- British Thoracic Society guideline recommends carboplatin but only when cisplatin contraindicated
- Trial results not reported separately by cisplatin or carboplatin

Clinical expert

- Carboplatin cheaper and less toxic
  - Carboplatin given in 30 minutes to 1 hour; cisplatin up to 8 hours
  - Cisplatin may have less dose intensity but evidence lacking
- Choice between the 2 depends on practical reasons including unit capacity and safety; not scientific or clinical justification or patient eligibility
- Some evidence of similar treatment effect between carboplatin and cisplatin in other indications

◉ Does carboplatin or cisplatin added to pemetrexed in CheckMate-743 reflect UK clinical practice?

2nd-line treatments – reflect NHS practice?

Use varied between arms; NHS will not offer immunotherapy twice

2nd-line treatments CheckMate 743 - % (n)	Nivolumab + ipilimumab (n = 303)	Chemo-therapy (n = 302)
Immunotherapy	3% (10)	20% (61)
Chemotherapy	43% (131)	32% (95)
Experimental therapies	0.7% (2)	4% (12)
Total	44% (134)	41% (123)

Company:

- Offering a 2nd-line treatment with different mode action is standard clinical practice - 35% and 30% expected in clinical practice
- National cancer analysis system (CAS) registry supports trial's representativeness to UK: 44% received chemotherapy, 19% in clinical trial, 24% vinorelbine

NHS England: Despite use during pandemic, immunotherapy not routinely available in 2nd line

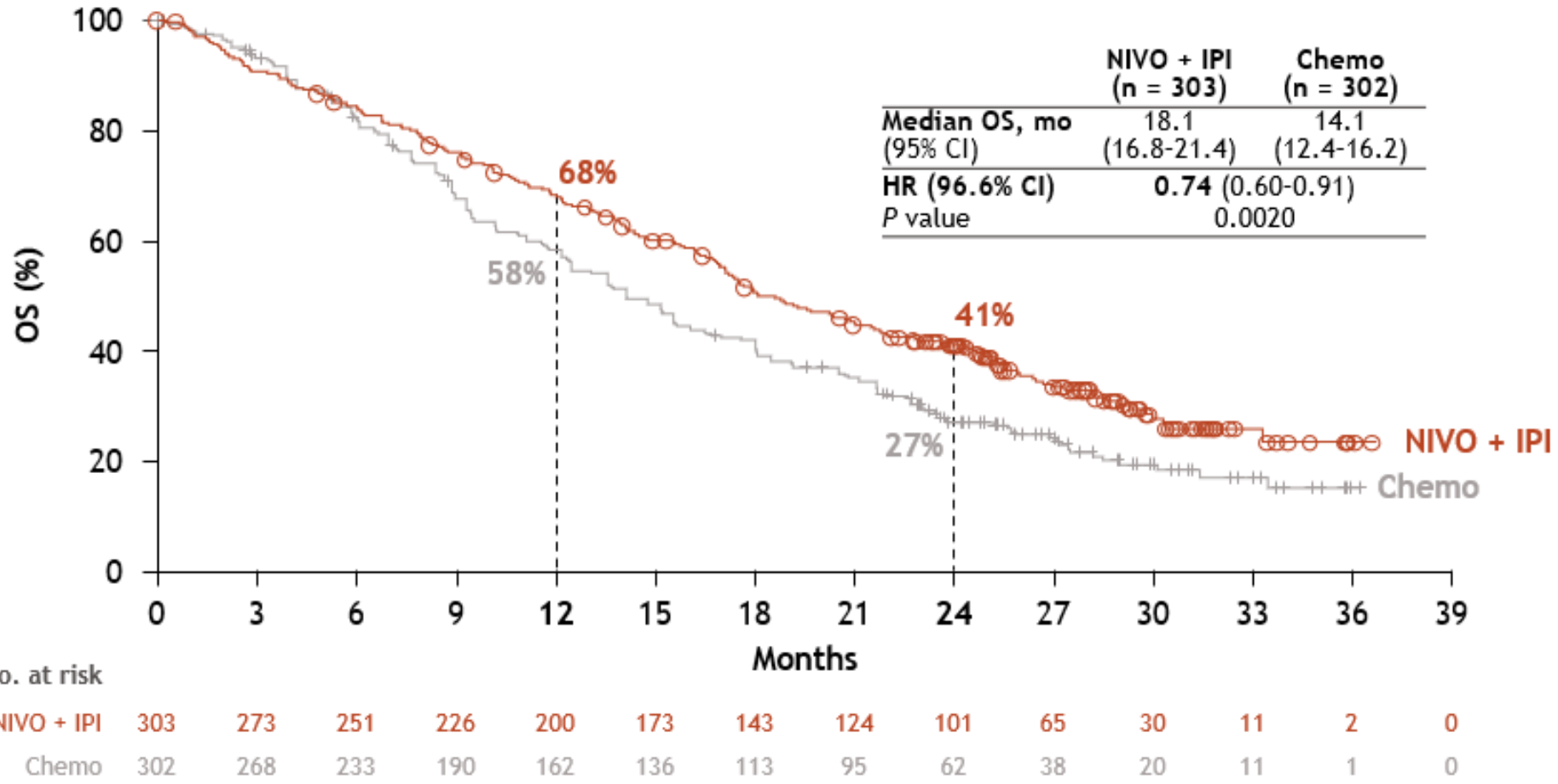
ERG: registry values differ from trial: 16% received pemetrexed and 8% vinorelbine

◉ ***Do 2nd line treatments in trial reflect NHS practice? If not, how to adjust for this?***

CheckMate-743: Overall survival interim analysis

Nivolumab with ipilimumab reduced risk of death compared with chemotherapy

Median follow-up: 29.7 months (April 2020 data cut)



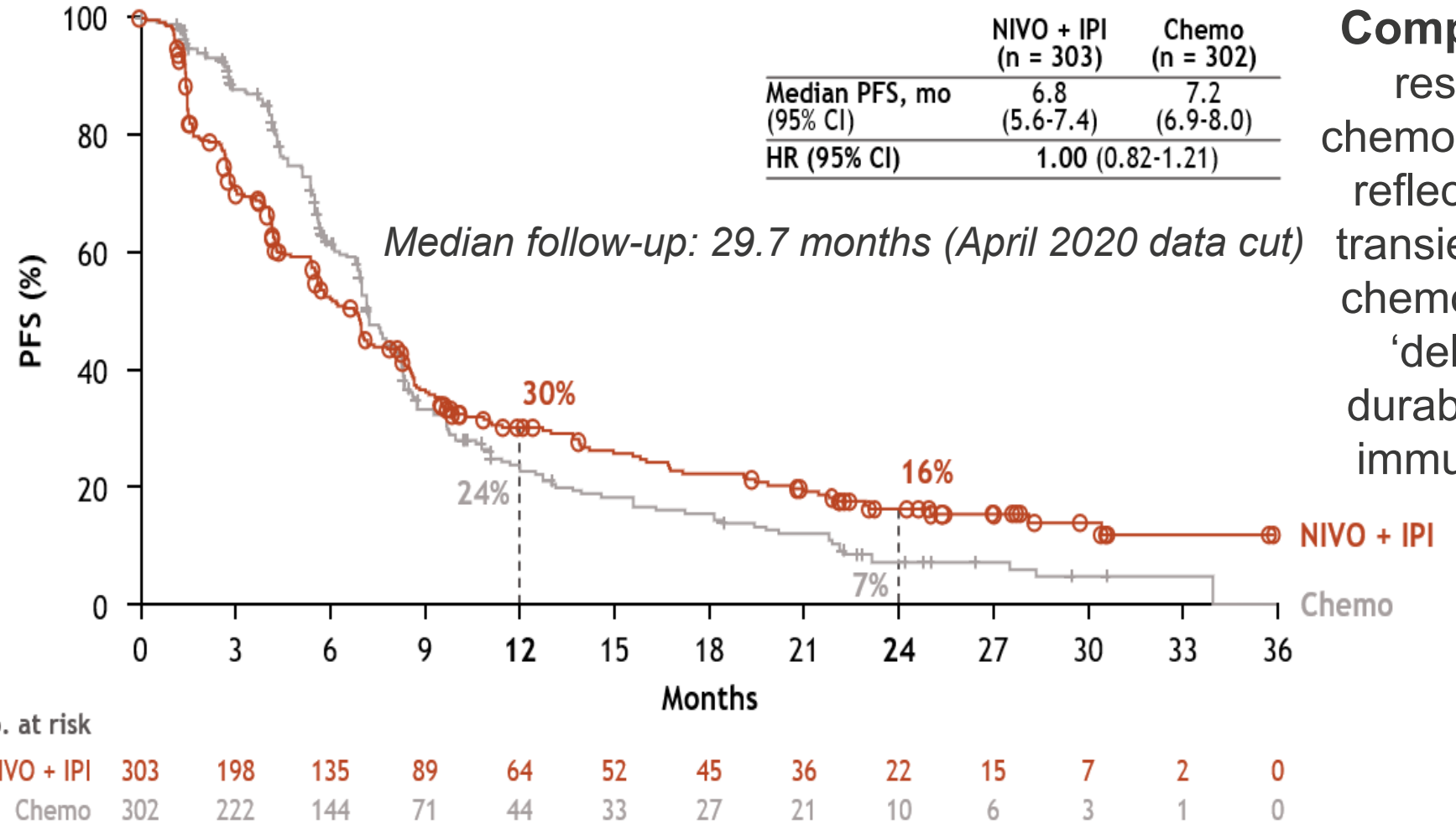
	NIVO + IPI (n = 303)	Chemo (n = 302)
Median OS, mo (95% CI)	18.1 (16.8-21.4)	14.1 (12.4-16.2)
HR (96.6% CI)	**0.74** (0.60-0.91)	
P value	0.0020	

Overall survival defined as time from randomisation to the date of death from any cause. Overall survival was censored at the date of randomisation for patients who were randomised but had no follow-up. For withdrawals, OS was censored on the last date a patient was known to be alive; Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival

◉ Might trial results overestimate effect reflecting early positive reporting?

CheckMate-743: Progression-free survival

At interim analysis no difference between 2 arms in PFS;
Company: PFS not reliable endpoint in mesothelioma



	NIVO + IPI (n = 303)	Chemo (n = 302)
Median PFS, mo (95% CI)	6.8 (5.6-7.4)	7.2 (6.9-8.0)
HR (95% CI)	1.00 (0.82-1.21)	

Median follow-up: 29.7 months (April 2020 data cut)

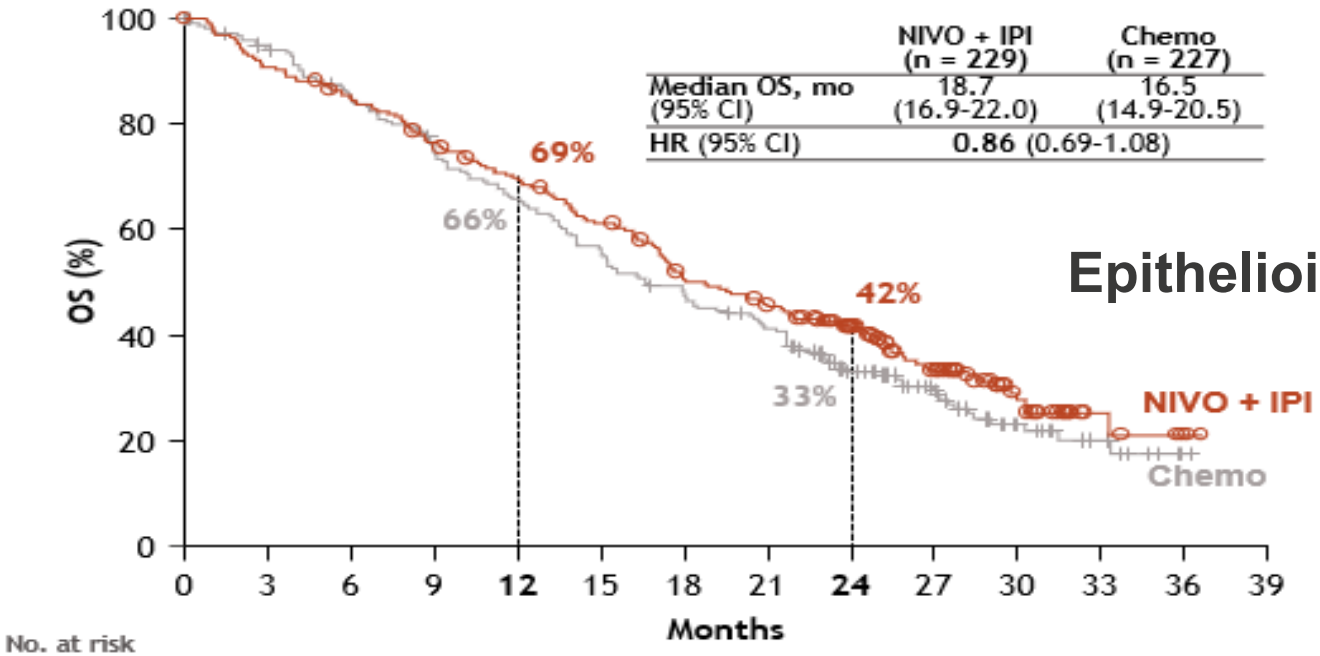
Company: initial response of chemotherapy may reflect 'early but transient' effect of chemotherapy vs 'delayed but durable' effect of immunotherapy

PFS by blinded independent central review using adapted mRECIST and/or RECIST v1.1 criteria.
Abbreviations: CI, confidence interval; HR, hazard ratio; PFS, progression-free survival

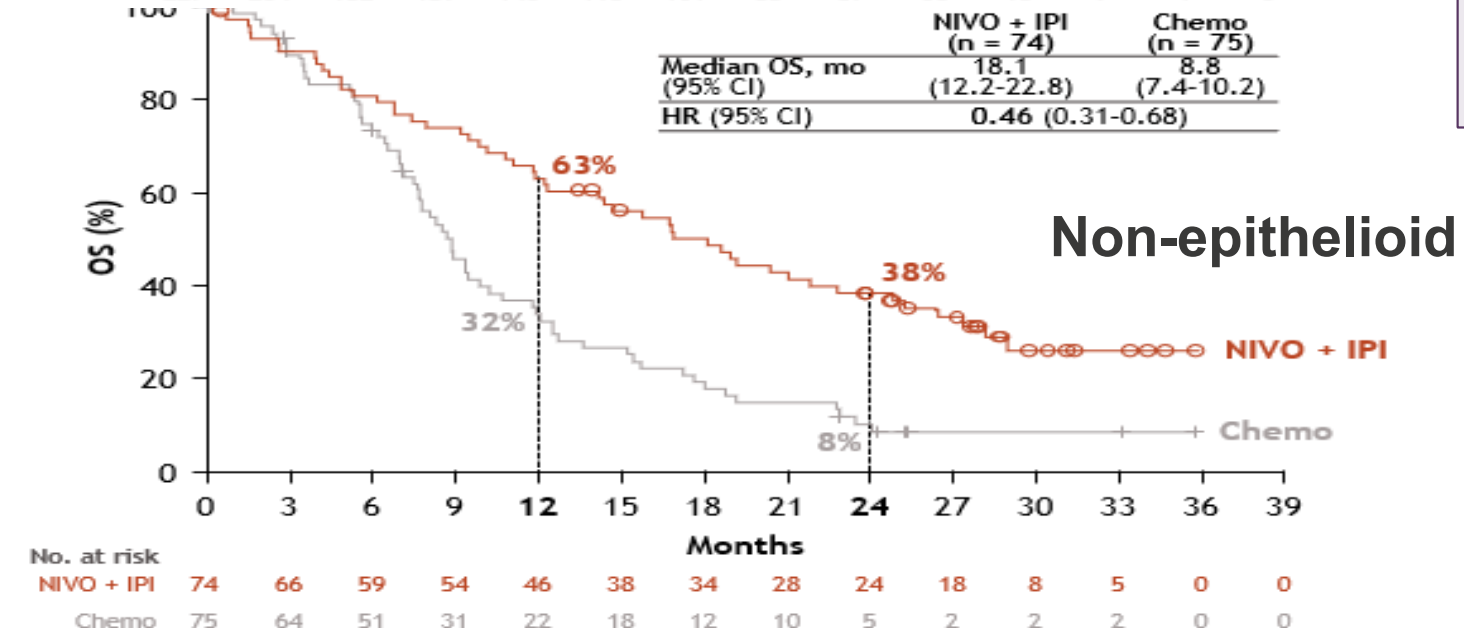
◉ *Does progression free survival have clinical relevance in practice + modelling?*

Overall survival by histology

Committee must look across marketing authorisation



Epithelioid



Non-epithelioid

ERG: confidence intervals for hazard ratio of epithelioid disease includes 1

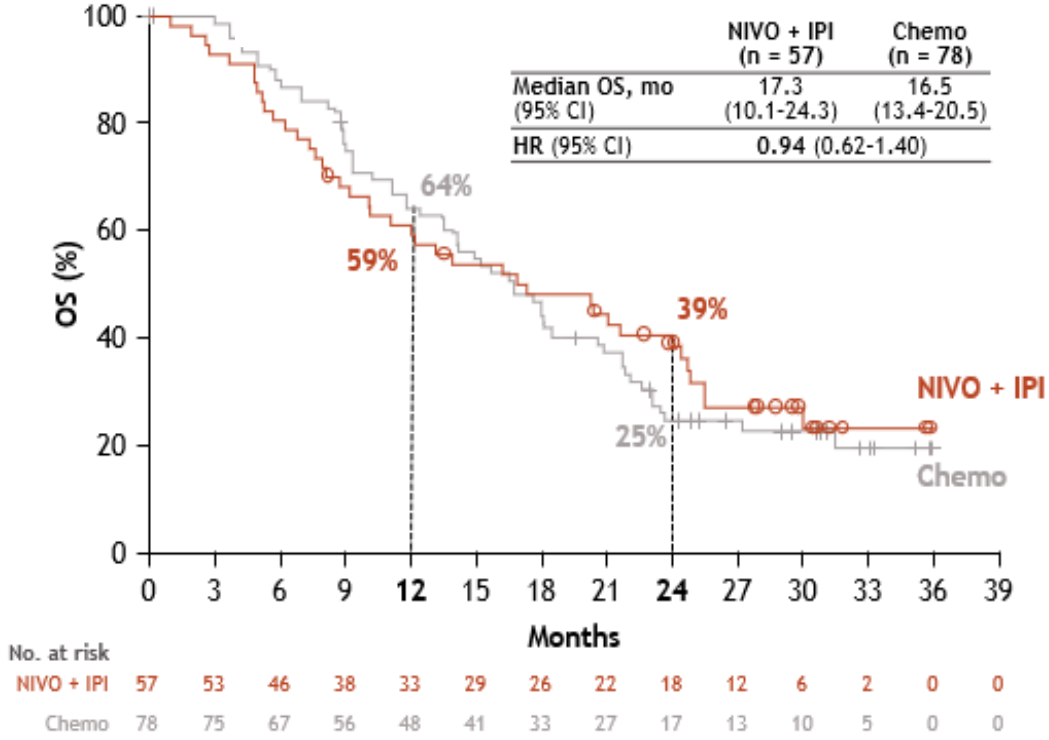
◉ *Does evidence suggest treatment effect of nivolumab with ipilimumab vs. chemotherapy on overall survival differ by histological subtype?*

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival

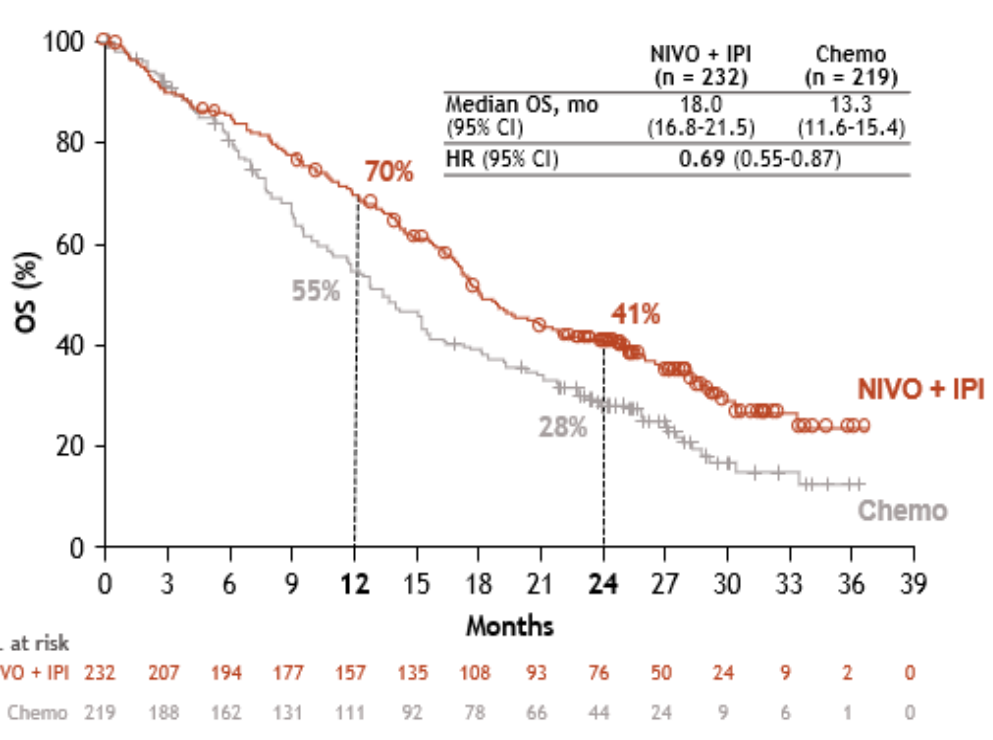
Overall survival by PD-L1 subgroup

Possible effect modification

PD-L1 < 1%



PD-L1 ≥ 1%



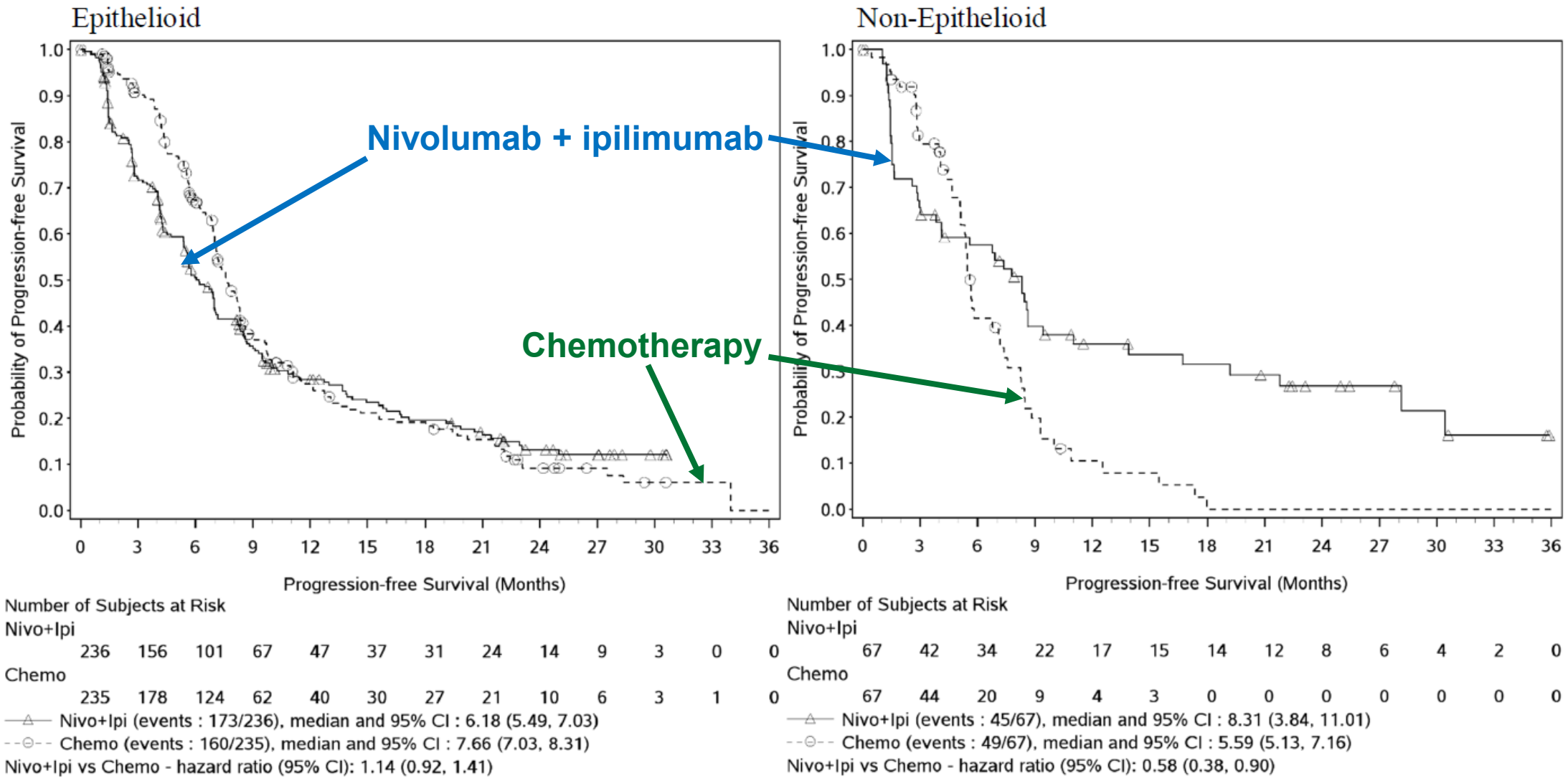
Median follow-up: 29.7 months (April 2020 data cut)

◉ *Proportional hazards? Does evidence suggest treatment effect of nivolumab with ipilimumab vs. chemotherapy on overall survival differ by PD-L1 status?*

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival

Progression-free survival by histology

Nivolumab with ipilimumab associated with PFS benefit in non-epithelioid disease but chemotherapy associated with PFS benefit in epithelioid disease



NICE Abbreviations: CI, confidence interval; PFS, progression-free survival

Unknown impact on ICER

Subgroups by histology and PD-L1 status

Treatment effect varies by subgroup

Company did not perform cost-effectiveness analyses by subgroups

Company

- Histology stratification factor in trial.
- Histological unspecified in 34.5% of NHS patients between 2013 and 2017 (CAS registry data).
- PD-L1 testing for people with malignant pleural mesothelioma not routinely conducted in NHS
- PD-L1 not a stratification factor in trial, subgroup analysis by PD-L1 descriptive in nature
- Trial not powered for subgroup analyses, differences in efficacy results may be chance

ERG

- Scope pre-specified subgroup analyses
- Potential interaction between histology and PD-L1 status, both clinically relevant subgroups, but no data

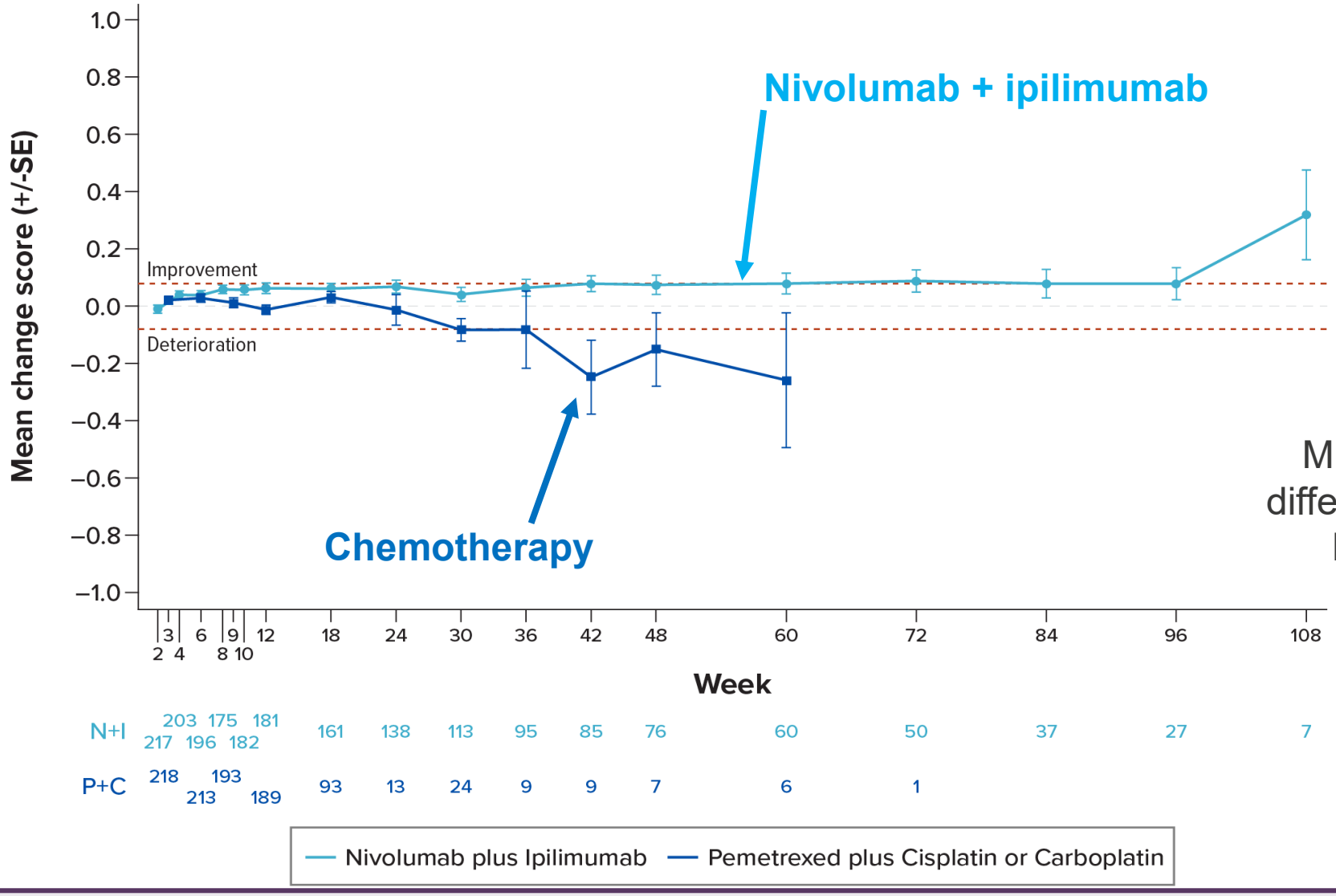
NHSE:

- Separate epithelioid from non-epithelioid on a biopsy relatively straightforward in mesothelioma; Checkmate -743 trial stratified histology subtypes for randomisation.
- PD-L1 testing possible but inconsistent evidence on its predictability in oncology

◉ *Does evidence suggest treatment effect of nivolumab with ipilimumab differ by subgroup? Would cost-effectiveness analyses by subgroup be informative for decision making?*

Health-related quality of life: EQ-5D-3L utility index

Clinically meaningful reduction in mean score from baseline at week 72 with nivolumab and ipilimumab; clinically meaningful deterioration at week 30 with chemotherapy



Minimally important difference: change from baseline of 0.08

◉ What is the committee's interpretation of the evidence?

Adverse events

More adverse events with nivolumab + ipilimumab compared with chemotherapy

- In nivolumab with ipilimumab arm:
  - diarrhoea and pruritus most common adverse events; respiratory tract infections more common than with chemotherapy
  - more people stopped treatment because of drug toxicity
- Most treatment-related events and immune-mediated adverse events resolved at time of database lock, but not endocrine-related events

Safety parameters, n (%)	Nivolumab with ipilimumab (n=300)		Chemotherapy (n=284)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
All-causality severe adverse events	164 (55)	103 (34)	72 (25)	54 (19)
Treatment-related severe adverse events	64 (21)	46 (15)	22 (8)	17 (6)
All-causality adverse events leading to discontinuation	88 (29)	59 (20)	58 (20)	28 (10)
Treatment-related adverse events leading to discontinuation	69 (23)	45 (15)	45 (16)	21 (7)
All-causality adverse events	299 (100)	159 (53)	277 (98)	121 (43)
Treatment-related adverse events	240 (80)	91 (30)	233 (82)	91 (32)

% rounded to nearest integer

ERG: higher death rate with chemotherapy, but 3 patients died due to drug toxicity in nivolumab + ipilimumab arm: pneumonitis, encephalitis and heart failure

Unknown impact on ICER

24 month stopping rule in trial and model

Stopping rule not adhered to in trial; ERG concerned

- Checkmate-743 trial protocol stipulated a 24-month stopping rule with nivolumab + ipilimumab but [redacted] on treatment at 25 months

ERG
- When patients continue on treatment, effectiveness and ICER may increase
- Implications if it occurs with remaining patients in trial or in clinical practice
- Rule may need to be relaxed in the model

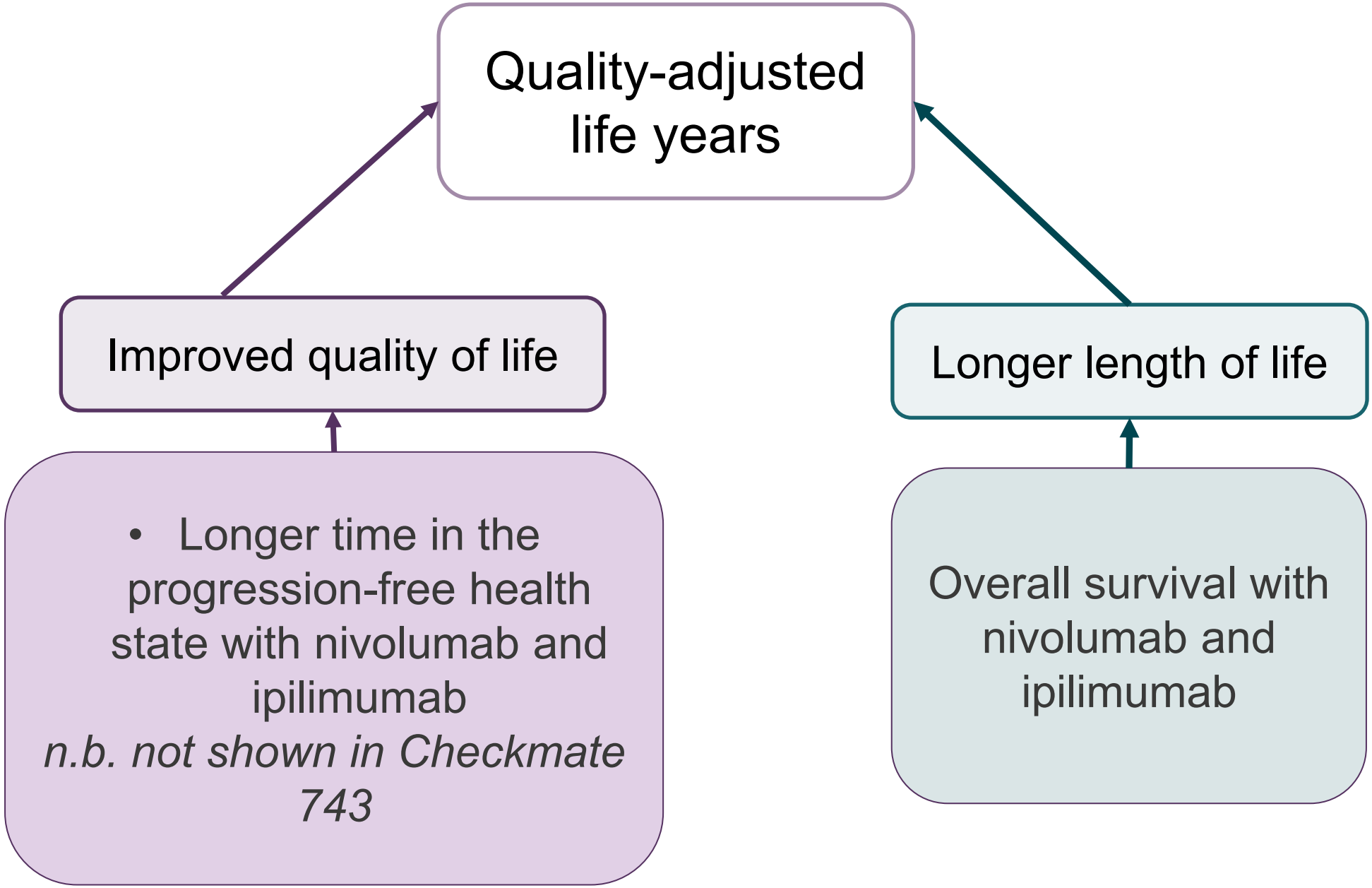
Company
- Stopping rules routinely used in multiple indications across immunotherapies
- Patients remaining on therapy after 24 months in CheckMate-743 have minimal impact on cost effectiveness

Clinical experts
- Clinical practice would adhere

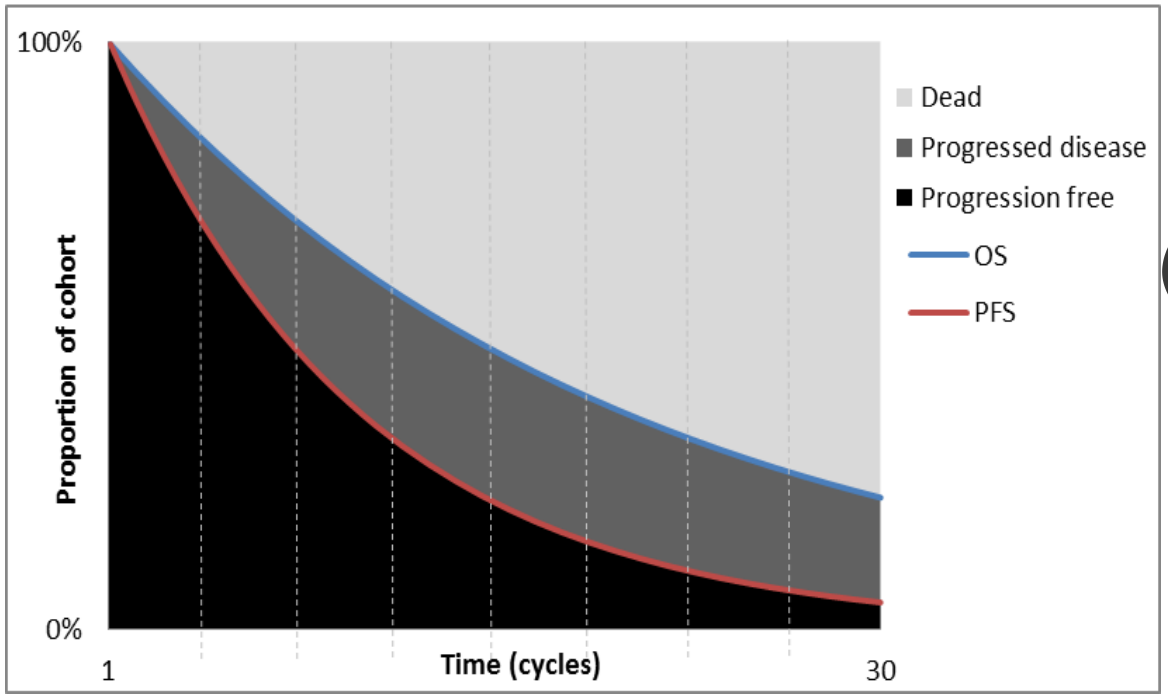
◉ Would the 24-month stopping rule be used in NHS practice for nivolumab and ipilimumab and would only 6-cycles be used for chemotherapy?

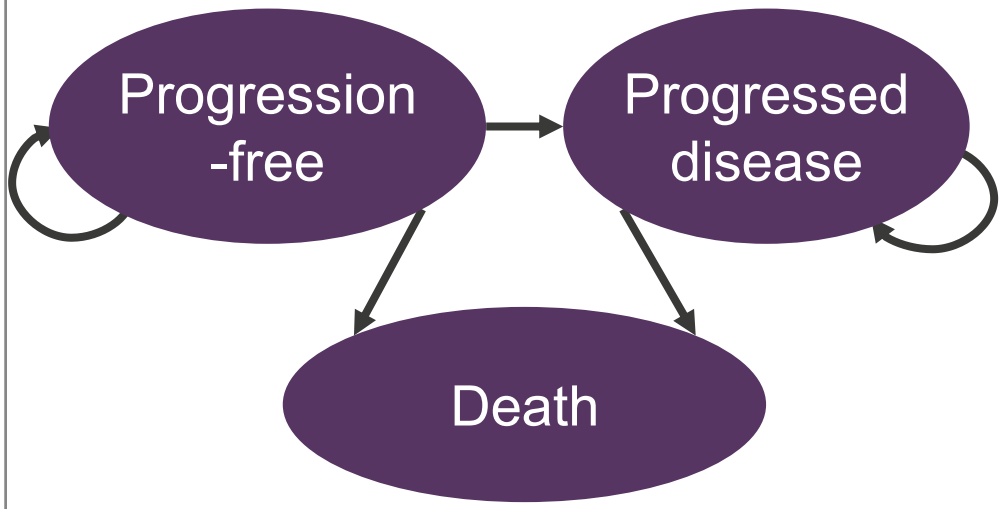
Cost effectiveness

Overview: how quality-adjusted life years accrue



Company: 3-state partitioned survival model





Patients enter in progression-free health state

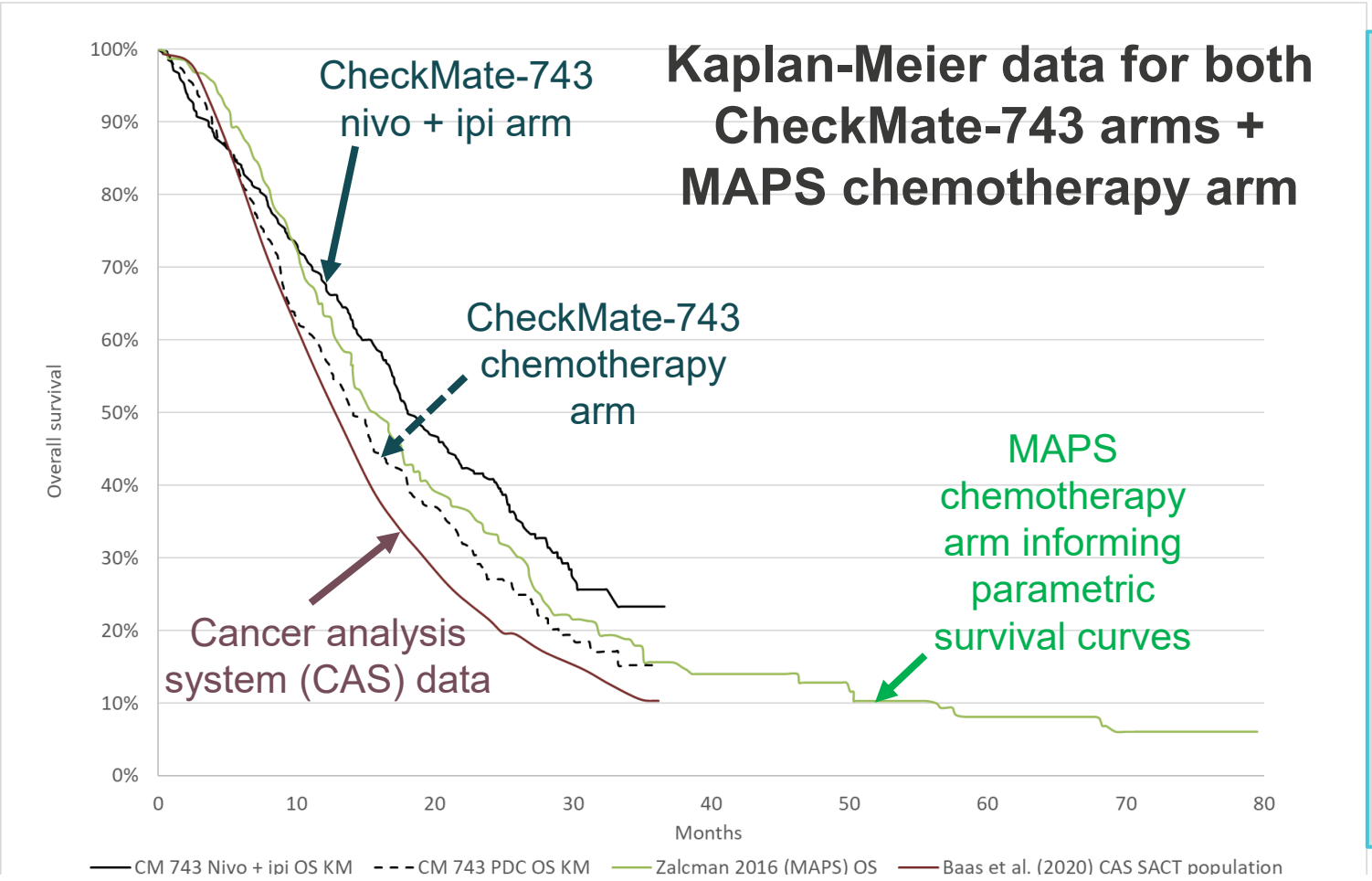
Structure	3-state partitioned survival model
Time horizon	20 years
Cycle length	1 week
Half-cycle correction	Yes
Duration of treatment effect	Lifetime
Stopping rule	• Nivolumab with ipilimumab: stop treatment after 2 years; • Chemotherapy: after 6 cycles (21 days each cycle)
Discount rate	3.5% for utilities and costs
Perspective	NHS and Personal social services

Model inputs: extrapolations and assumptions

Model inputs	Company	ERG	Impact on ICER per ERG
Overall survival	**Nivolumab + ipilimumab**: log-logistic **Chemotherapy**: 2 knots spline normal	Log-logistic distribution for both treatments	**Increases ICER**
Progression-free survival	**Nivolumab + ipilimumab:** generalised gamma **Chemotherapy**: log-logistic	Same as company, note significant uncertainty since most progression-free life years accrue beyond observed data	**Increases ICER**
Duration of treatment	2 year maximum, using trial Kaplan-Meier data	2-year max, spline models for time to treatment discontinuation from company scenario	**Minimal ICER impact**
Duration treatment benefit	Model lifetime (20 years)	Waning from 5 years onwards	**Increases ICER**
2nd line treatment duration and costs	Treatments used in CheckMate-743; treatment duration 1.7 months for all	Treatments used and treatment duration do not reflect clinical practice	**Minimal ICER impact**
Subgroups	No subgroups presented	Presentation of subgroups preferred, given variations in treatment effect	**Unknown ICER impact**

Extrapolating overall survival

Company: non-proportional hazards and models fitted separately for nivo + ipi and chemotherapy; uses long-term follow-up in Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS) (median 39 months) to choose chemotherapy curve



MAPS: ongoing trial of bevacizumab + chemotherapy vs. chemotherapy

Using MAPS to validate CheckMate-743:

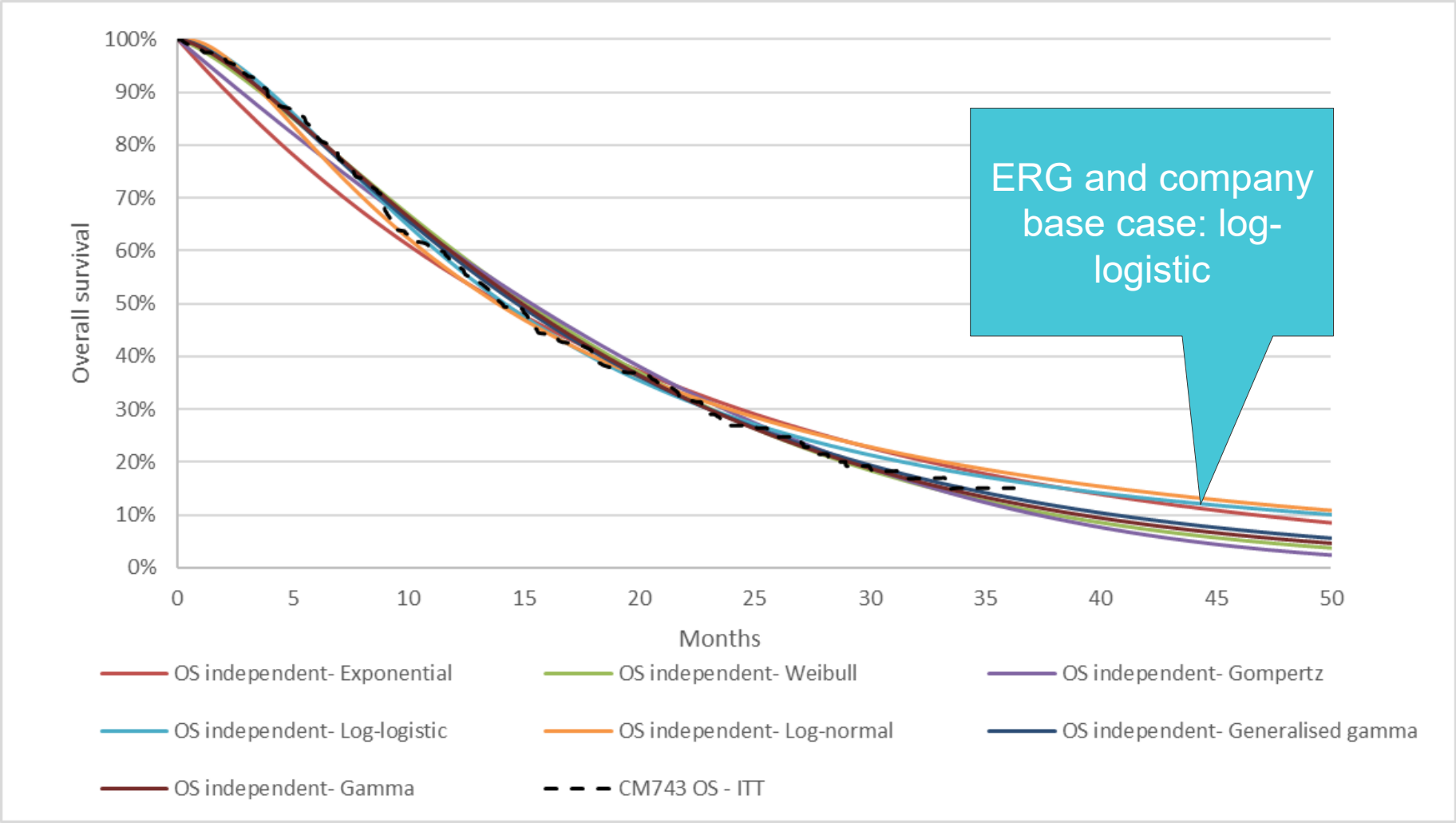
- Both arms: modelled hazard function should initially increase then decrease over time
- *Nivolumab with ipilimumab*: survival probabilities better than in either arm of MAPs
- *Chemotherapy:* long-term survival below survival observed in MAPS

Abbreviations: CAS, Cancer Analysis System; CM, CheckMate; KM, Kaplan-Meier; Nivo + ipi, nivolumab + ipilimumab; OS, overall survival; SACT, systemic anticancer therapy.

◉ *In current clinical practice, what is the best estimate of proportion of patients with malignant pleural mesothelioma expected alive at 5 and 10 years?*

Extrapolating overall survival: nivolumab + ipilimumab

Company and ERG agree on log-logistic distribution



Abbreviations: CM, CheckMate; ITT, intent to treat; OS, overall survival.

◉ *What is committee's view on most appropriate distribution for overall survival for the nivolumab and ipilimumab arm?*

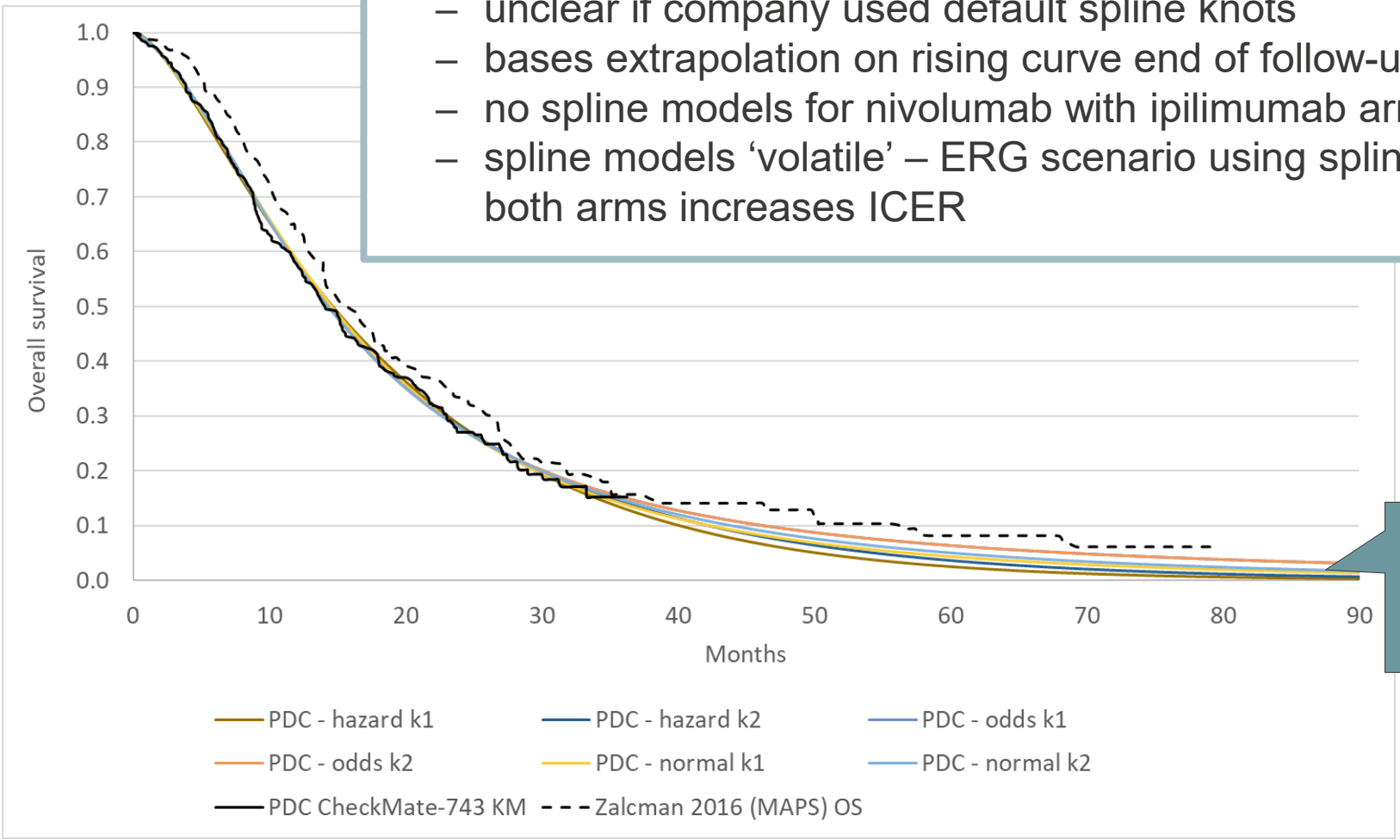
Increases ICER

Extrapolating overall survival: chemotherapy (1/3)

Company use spline 2-knot normal model in updated base-case; ERG disagrees

ERG

- Company focus on within-trial fit rather than plausibility of the extrapolation
- Spline models valid but:
  - unclear if company used default spline knots
  - bases extrapolation on rising curve end of follow-up based on few events
  - no spline models for nivolumab with ipilimumab arm
  - spline models 'volatile' – ERG scenario using spline 2-knot normal model for both arms increases ICER



Company base case: spline 2-knot normal model

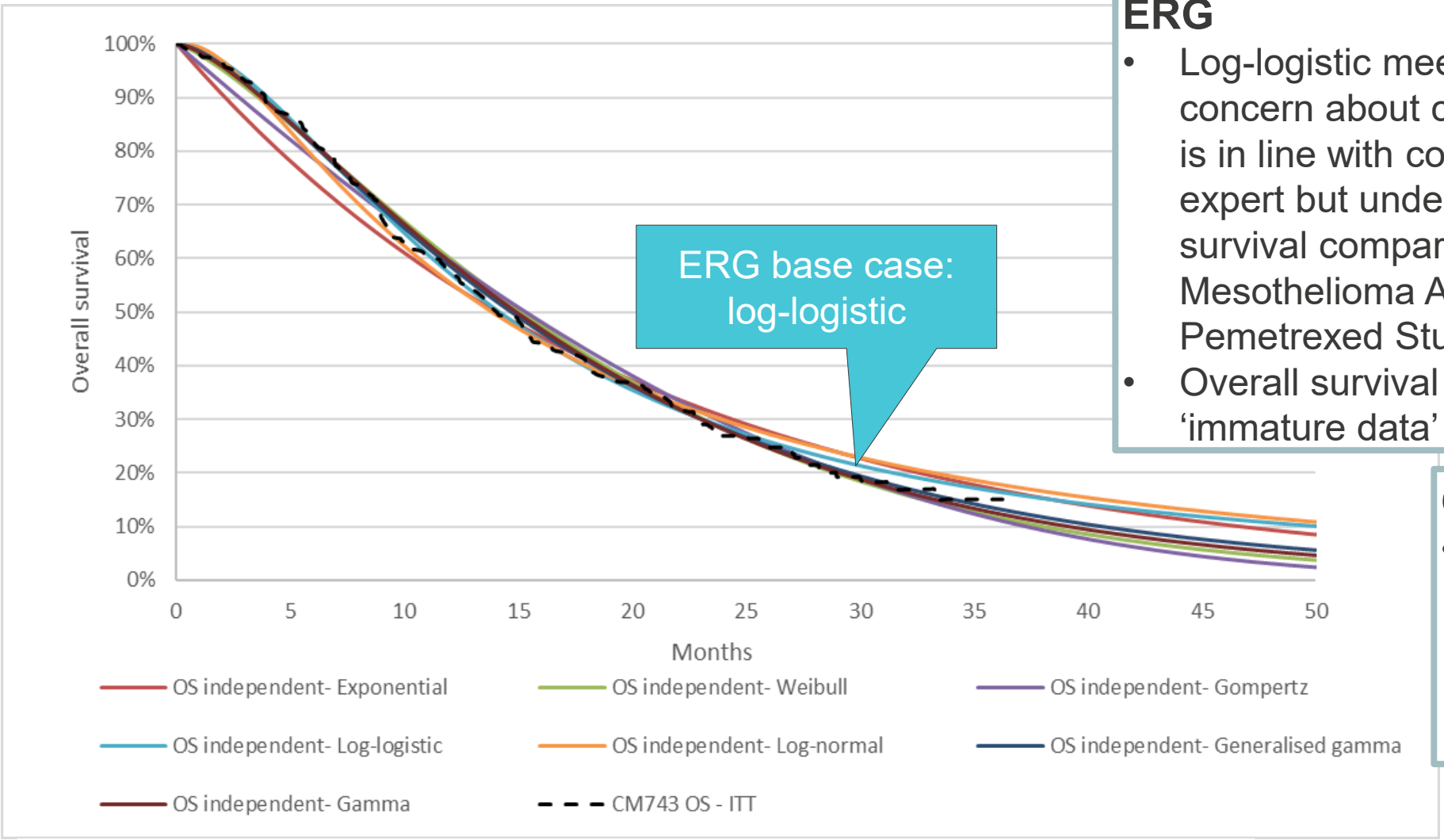
Abbreviations: CM, CheckMate (Kaplan-Meier data); ITT, intent to treat; MAPS, Mesothelioma Avastin Cisplatin Pemetrexed Study (Kaplan-Meier data); OS, overall survival

Slide amended/corrected after the meeting

Increases ICER

Extrapolating overall survival: chemotherapy (2/3)

ERG prefer log-logistic model instead of company's spline 2-knot model



ERG

- Log-logistic meets all criteria but concern about clinical plausibility: is in line with company's clinical expert but underestimates survival compared with Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS) data
- Overall survival uncertain: 'immature data'

Company

- Log-logistic model overestimates survival for chemotherapy

Abbreviations: CM, CheckMate; ITT, intent to treat; OS, overall survival.

◉ *What is the most appropriate method for extrapolating overall survival for chemotherapy?*

Slide amended/corrected after the meeting

Overall survival predictions in chemotherapy arm (3/3)

Overall survival predictions in chemotherapy arm	5 years (%)	7.5 years (%)	10 years (%)
Log-logistic - *ERG base case*	7.5	Unknown	2.4
Spline 2-knots normal - *company base case*	3.6	Unknown	0
MAPS trial	8.1	n/a	n/a
Another company estimate	5.0	2.0	0
Exponential	5.1	n/a	0.3

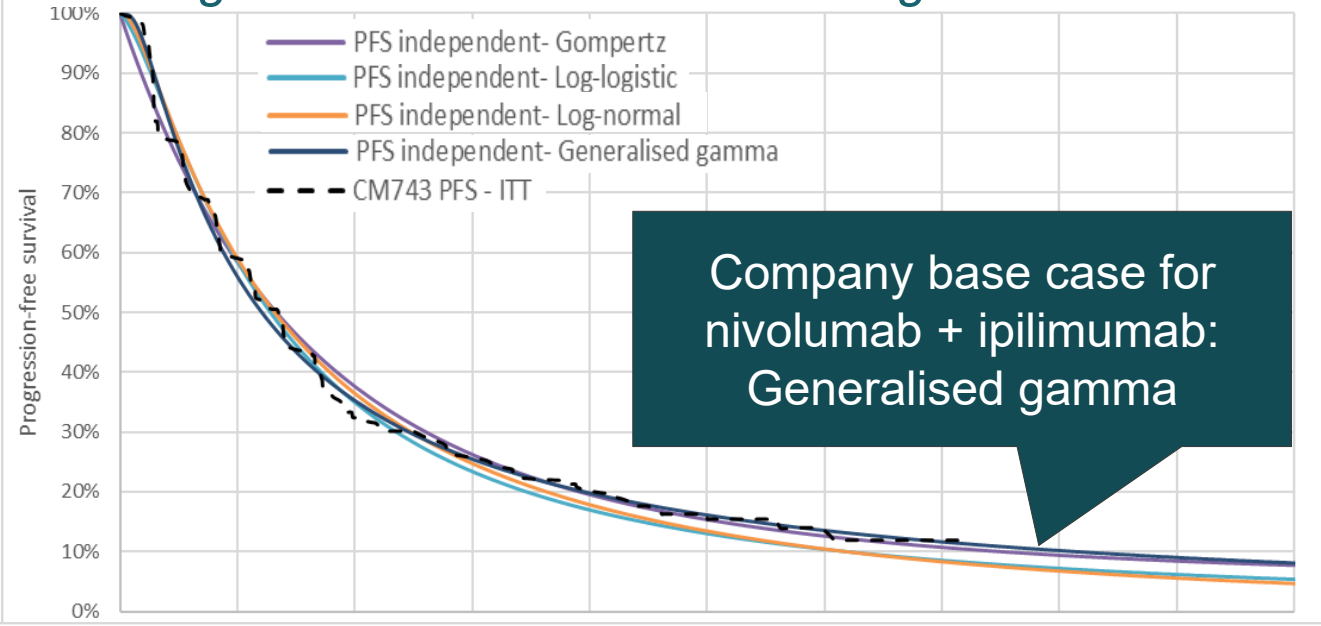
Abbreviations: MAPS, Mesothelioma Avastin Cisplatin Pemetrexed Study (Kaplan-Meier data)

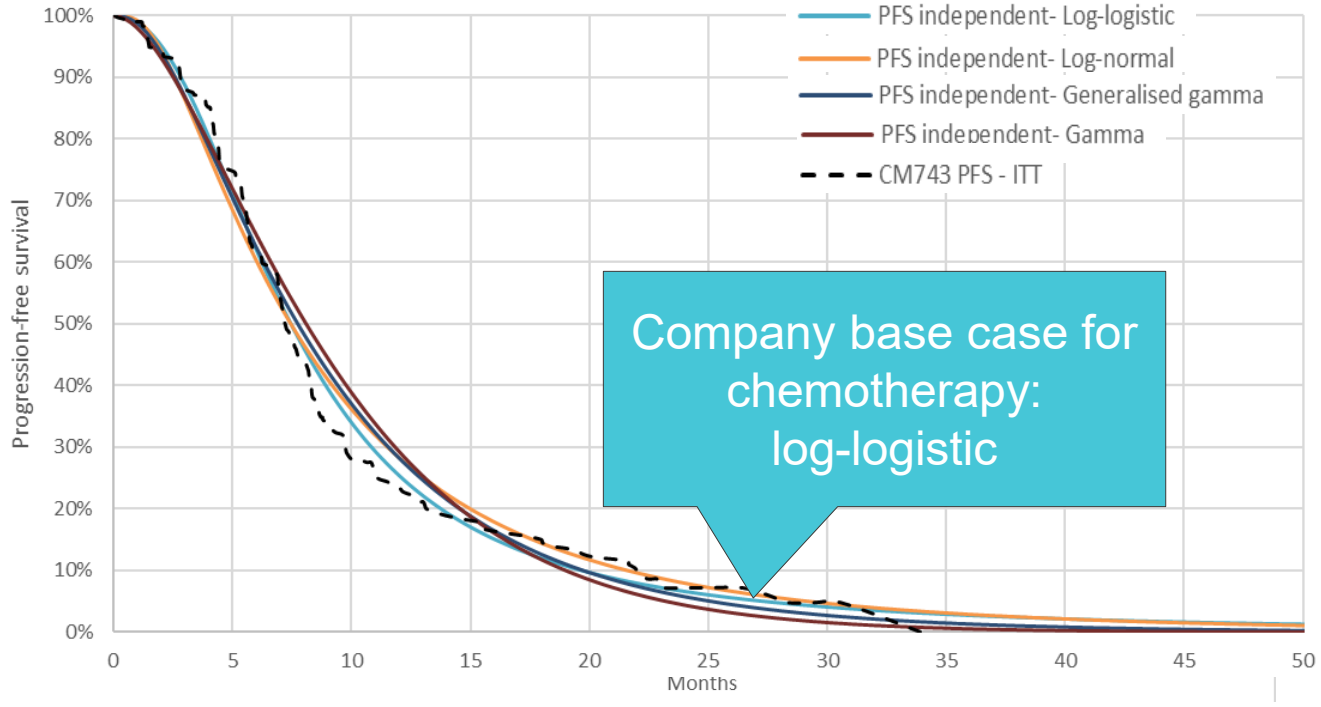
◉ *Which model best reflects clinical practice in terms of the proportion of patients with malignant pleural mesothelioma expected alive at 5, 7.5 and 10 years?*

Extrapolating progression-free survival

Increases ICER

Company: different distributions for each arm justified by different mechanism of action; ERG agree with distributions. Both agree validation of long-term extrapolation limited.





Company:

- MAPS to validate extrapolating chemotherapy up to 5 years (0.3 and 0.1% survival, respectively) but not appropriate for nivolumab + ipilimumab arm – few patients at end of both trials and issues with PFS for immunotherapies.

ERG:

- Concern with validation since majority of progression-free life years accumulated **after** observed period.
- 2 scenario analyses increased ICER:
  - 1) log-logistic both arms
  - 2) generalised gamma both arms

◉ *Does modelling reflect Checkmate 743 trial? Is progression-free survival relevant? Which function appropriate to extrapolate progression-free survival?*

Unknown impact on ICER

Model structure and validating extrapolation

ERG: concerned partitioned survival model not validated with state transition model given 'data immature'

Company approach

Partitioned survival model

+ State transition model validation

Company:

- State transition models not recommended over partitioned models.
- Unreasonable to also present state transition model; requires clinical validation of all analyses.
- Choice of model unlikely impact cost effectiveness because post-progression treatments had short duration.

ERG:

- Impact of partitioned survival model limitations unclear i.e. assuming structural independence between endpoints – relevant given high level of uncertainty with large proportion of extrapolated life years.
- Unclear why company argue short-duration post-progression treatment relevant.

◉ *Is a second model required for validation?*

Relative treatment effect duration - 'waning'

Increases ICER

Company assumes no waning of benefit for 20-year horizon after stopping 2-year treatment

Company

- Long-term benefit in advanced previously treated non-small-cell lung cancer.
  - *N.b. committee for ID1566 assumed no effect after 5 years*
- Durable treatment effect in melanoma

Clinical expert

- Appears response maintained up to 24 months, but few survivors at 5 years
- Data in renal cell carcinoma and melanoma effect to 10 years

ERG

- True long-term treatment effect unknown
- To assume no waning not plausible based on only 3 patients at risk at 36 months.
- Company argument based on company's experts – but how company chose experts and results unclear
- Later data cut may help
- As with nivolumab for previously treated head and neck cancer (ID1585) ERG uses waning from 5 years for base-case; notes 5 years 'arbitrary'

◉ *Is treatment benefit likely to persist unabated after 2 years of treatment? Is one type of cancer generalisable to another particularly given possible effect modification by histology? What waning assumption most appropriate, if any?*

Slide amended/corrected after the meeting

2nd-line treatment costs

- Minimal impact on ICER

Company chooses same treatment length for all 2nd-line treatments
Immunotherapies not offered 2nd line in NHS

Company

- Checkmate-743: 44% nivo + ipi, 41% chemotherapy;
- **1.7 months** duration for all treatments from median duration in Waterhouse et al. (2019) poster (mean 2.5 months)
- Conservative as immunotherapies longer and more in chemotherapy arm
- In relapsed disease, CONFIRM trial results: median 2.8 months duration after nivolumab (n = 221) 1.4 months after placebo (n = 111). (Fennell et al., 2021).
- Company's clinical expert input: anticipate treatment duration 1-3 months
- Vinorelbine expected to be next line after chemotherapy
- Any confounding of overall survival from 2nd-line treatments biased in favour of chemotherapy.

Clinical experts

- Treatment duration differs between treatments and 1.7 months is not long enough. Should be ≥4 months for pemetrexed and vinorelbine

ERG

- Same treatment duration for different treatments not plausible.
- Large variation in duration in Waterhouse (interquartile range 1-11.9 months).
- Unable to change treatment duration per arm in model – model needs to change.
- ERG scenario: 2nd-line treatment costs for **3 months both arms**.
- Even though small impact on ICER, company model does not reflect practice.

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How to model duration of 2nd line treatments?

Additional issues with minor or unclear impact

Issue	Why issue important	Impact on ICER
Potentially missing cost studies	• ERG concerned company filtered NHS Economic Evaluation Database which compromised finding potentially relevant cost studies	Unclear
Adverse events in model	• ERG noted fewer adverse events in the model with nivolumab with ipilimumab compared with chemotherapy whereas company submission suggests more with nivolumab with ipilimumab	Minor

◉ ***Do these issues affect decision?***

Issues resolved at technical engagement

Issue	Summary	Company response	ERG	In updated base case?
Treatment cost calculation	ERG concerned company treatment cost calculation using mean number of doses in CheckMate-743 biased. ERG prefer parametric model using trial dose intensity to reflect delayed or missed doses	Scenario with parametric methods. Note as the scenario did not use dose intensity, likely to overestimate compared to clinical practice	Adopt company scenario in ERG base-case	Company scenario ✓ ERG base-case ✓
Utility benefit beyond treatment	Company assumes comparative utility benefits maintained over time horizon. ERG question plausibility; ERG base cases uses treatment-dependent effects to 3 years and then treatment-independent effects after. Selected 3 years because only 3 patients at risk	ERG approach	N/A	Company ✓ ERG base-case ✓

◉ ***Why assumptions preferred?***

End-of-life criteria

Company: end-of-life criteria likely met

Criteria 1 – treatment indicated for patients with a short life expectancy - normally <24 months	**Company:** Most patients treated with chemotherapy die < 2 years - median survival 13 months **ERG:** • CheckMate-743: median overall survival 14 months with chemotherapy • Company base-case: mean overall survival 1.7 years • ERG base-case could be up to exactly 2 years (upper estimate).
Criteria 2 – sufficient evidence to indicate that treatment offers an extension to life normally >= 3 months compared to current NHS treatment	**Company:** CheckMate-743 **interim** results: median 4-month survival benefits for nivolumab + ipilimumab (18.1 months) versus chemotherapy (14.1 months), in median follow-up: 29.7 months. **ERG** supports survival gain of > 3 months

◉ *Taking into account mean values does nivolumab with ipilimumab meet criteria?*

Slide amended/corrected after the meeting

Equality issues

- '…preventable, occupational-related disease caused by asbestos exposure…incidence rates vary across England…higher rates in areas of heavy industry (e.g., the northeast and southern England). Patients … often old and diagnosed at a late stage … can be too frail to travel for treatment, which may limit their treatment options.' *Company submission*

- 'Patients not able to self fund or pay for treatment from funding from a compensation claim are at a disadvantage. If the technology only becomes available in the setting of private / self-funding an inequality will be generated..' *Mesothelioma UK*

- 'Mesothelioma is an industrial disease …therefore typically patients would be in lower socioeconomic groups compared to other cancer types. It has been long recognised that people from lower socioeconomic backgrounds experience health inequality and fare less well with most diseases including malignancy.' *Clinician*

◉ *Do these relate to protected characteristics or unequal access to care were nivolumab + ipilimumab recommended?*

Innovation

- **Company – treatment is innovative**
  - No new therapies in last 2 decades and no new drugs on horizon
  - Nivolumab + ipilimumab: 1st-in-class immunotherapy
    - complementary modes of action
    - step change
- **Clinical experts:**
  - 'Step-change': biggest advance in over a decade of research
  - QALY calculation may not capture anger towards the occupational disease

◉ *Is nivolumab innovative? Can committee identify unaccounted benefits?*

Cancer Drugs fund ‘CDF’

Committee decision-making criteria

Starting point: treatment not recommended for routine use because of **clinical uncertainty**

1. Is the model structurally robust for decision making?

2. Does treatment have plausible potential to be cost-effective at the price company chooses to charge?

3. Could further data collection reduce uncertainty?

4. Will ongoing studies provide useful data?

and

5. Is CDF data collection via systemic anti-cancer therapy data relevant and feasible?

Consider recommending entry into CDF (invite company to submit CDF proposal)

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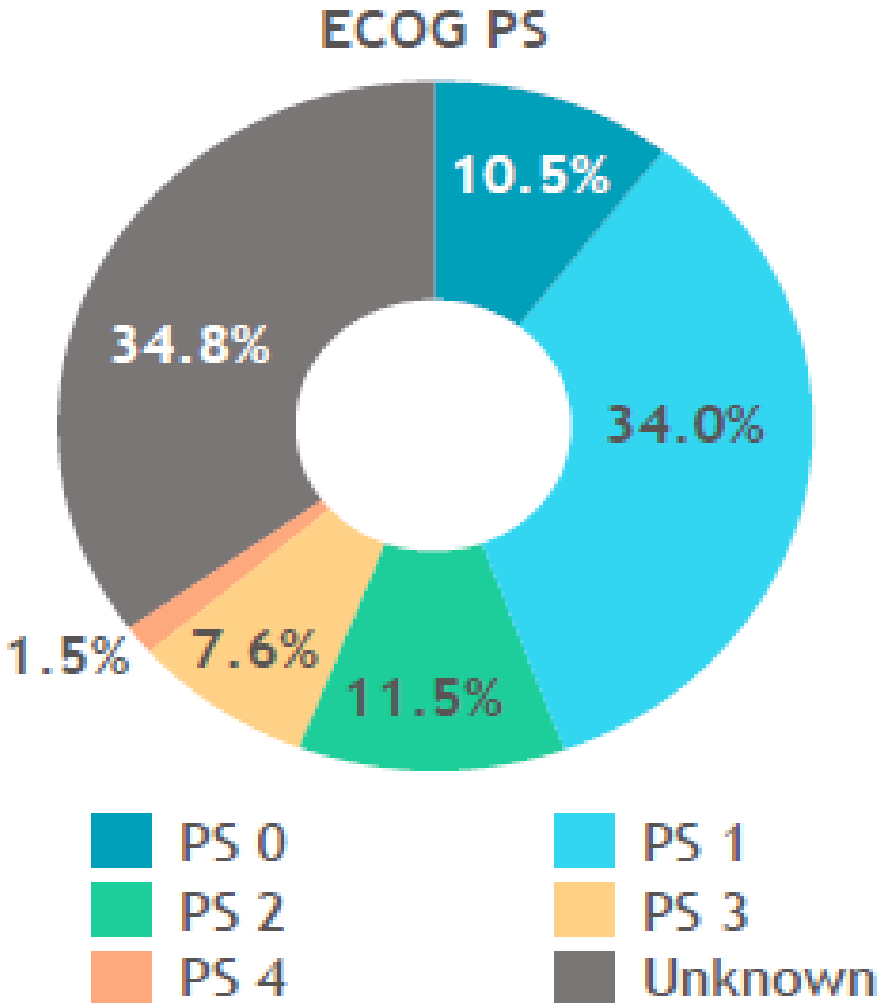
Back-up slides / slides for info

Distribution of patients by Eastern Cooperative Oncology Group (ECOG) status



Cancer Analysis System Registry in England, 2013-2017

Progression-free survival by PD-L1 subgroup

Chemotherapy associated with PFS benefit for patients with PD-L1 <1%; for patients with PD-L1≥ 1%, nivolumab with ipilimumab had PFS benefit but the difference not significant

	Nivolumab + ipilimumab	Chemotherapy
PD-L1 negative (< 1%)	n=57	n=78
Median progression-free survival, months (95% confidence interval)	4.1 (2.7-5.6)	8.3 (7.0-11.1)
Hazard ratio (95% confidence interval)	**1.79 (1.21-2.64)**	
PD-L1 positive (≥ 1%)	n=232	n=219
Median progression-free survival, months (95% confidence interval)	7.0 (5.8-8.5)	7.1 (6.2-7.6)
Hazard ratio (95% confidence interval)	**0.81 (0.64-1.01)**	

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Abbreviation: PFS, progression-free survival

Subgroups by PD-L1 status and histology

ERG consider cost effectiveness should be presented by subgroup because of differences in effectiveness and scope pre-specification

ERG:

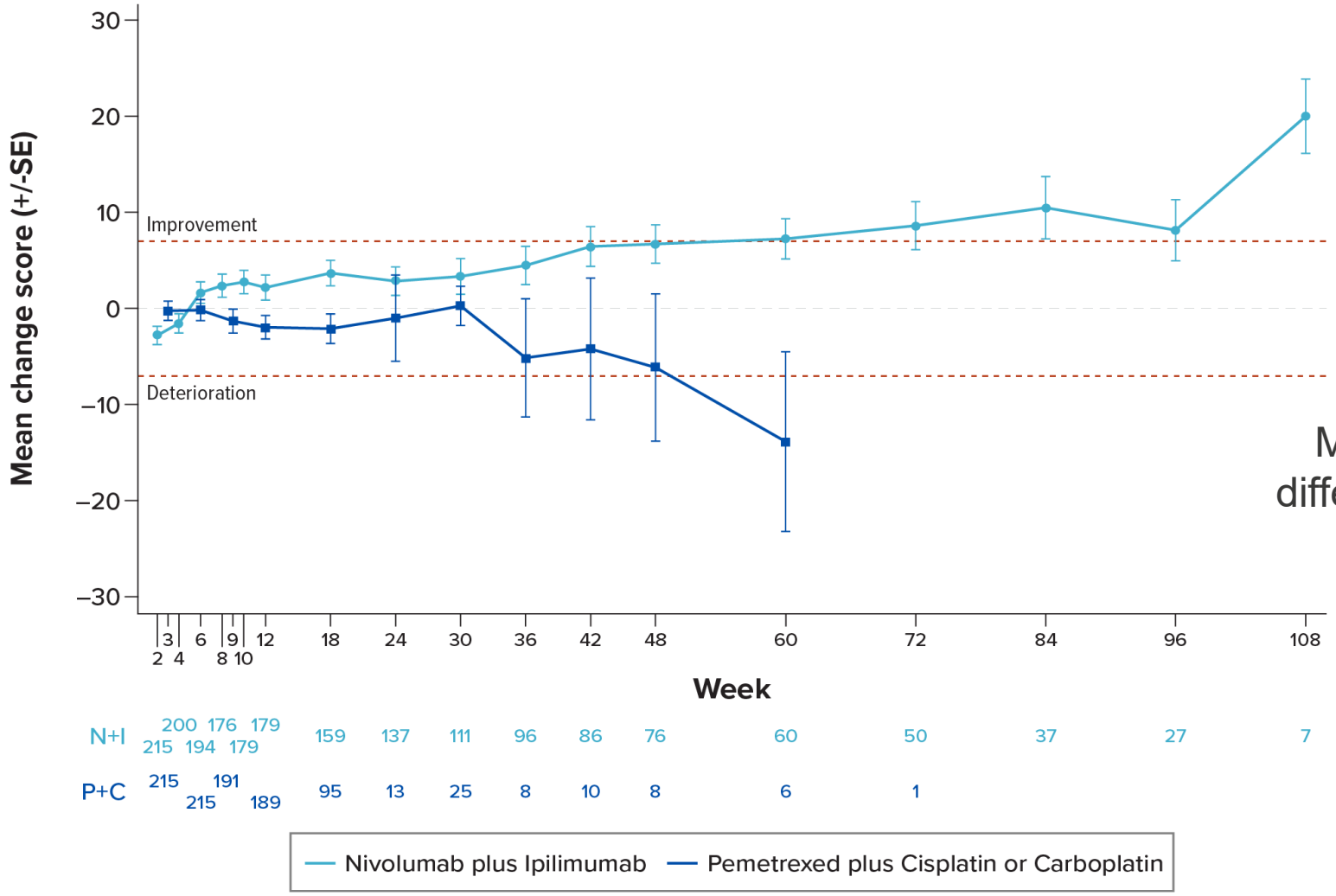
- Potential interaction between PD-L1 status and histology, both clinically relevant subgroups, but no data.
- Uncertainty would be reduced by:
  - analysing combined PD-L1 status and histology subgroups
  - more complete results i.e. at a later data-cut.

Company:

- Inherent issues in subgroup analyses by both PD-L1 and histology, mean analyses that combine these two subgroups would also be inappropriate and increased uncertainty.
- Clinical expert input during technical engagement:
  - unmet need for new treatments for all patients with the disease, determining access to nivolumab + ipilimumab based on subgroups would exclude patients who would benefit from it.
  - level of overall survival benefit in the entire intention-to-treat population not seen in other studies in this disease.

Health-related quality of life: EQ-5D-3L Visual analogue scale

Clinically meaningful reduction in mean score from baseline to week 60 and 72 with nivolumab and ipilimumab; chemotherapy reductions show clinically meaningful deterioration



Minimally important difference: change from baseline 7

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Overall survival estimates for nivolumab + ipilimumab with treatment effect waning scenarios

Scenario	Absolute Survival (%)	
	Year 5	Year 10
Modelled without treatment waning	14.6	5.7
ERG proposed treatment waning from year 5	14.6	2.2
Constant treatment effect from Year 5	14.6	5.2

Second-line treatments used in model

Rates of second-line treatments were based on CheckMate-743

Company's model	Second-line therapy (%)	
	Nivo + ipi	PDC
Nivolumab	2.2	17.5
Ipilimumab	0.6	1.3
Pembrolizumab	0.6	7.3
Bevacizumab	6.2	3.4
Carboplatin	27.7	16.7
Cisplatin	12.5	3.4
Pemetrexed	37.7	20.5
Gemcitabine	7.8	19.2
Vinorelbine	4.7	10.7