Pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3907]

For projector – contains NO confidential information

Technology appraisal committee D [7th August 2024]

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Pembrolizumab for treating adjuvant treatment of resected non-small-cell lung cancer

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Background on resected non-small-cell lung cancer (NSCLC)

Causes

- Lung cancer is characterised by malignant cells forming in the tissue of the lungs
- Main risk factors: older age and cigarette smoking. Risk increases for men and with deprivation score

Epidemiology

- In the UK, lung cancer is the 3rd most common cancer and NSCLC constitutes 85 - 88% of all cases

Diagnosis and classification

- NSCLC staged from 1A to 4B, based on size and extent of primary tumour, location of involved lymph nodes and presence of distant metastases

Symptoms and prognosis

- Early stages may be asymptomatic, later symptoms include fatigue, cough, chest pain
- Curative intent surgery often used for stage 1 to 3 NSCLC but recurrence is common
  - 41% with stage 1-3 with complete resection develop recurrence within 23 months
- Life expectancy depends on several factors such including stage at diagnosis, sex and performance status
  - 1-year survival: stage 1 (88%), stage 2 (76%), stage 3 (53%)
  - 5-year survival: stage 1 (68%), stage 2 (49%), stage 3 (25%)

Patient and clinical perspectives

Patient submissions from Roy Castle Lung Cancer Foundation

- People with lung cancer face many challenges, including difficulties associated with post-surgery symptoms and the mental and emotional impacts associated with diagnosis of a potentially fatal illness
- Symptoms of recurrent disease, such as breathlessness, cough and weight loss are often difficult to treat, without active anti-cancer therapy and can be distressing for loved ones to observe
- Relapse after surgery means that further potentially curative therapy is unlikely - patients and their carers have continual anxiety that the lung cancer will come back
- Adjuvant treatment shown to be of benefit in the management of patients with early-stage NSCLC
- No other immunotherapies available for people with PD-L1 TPS <50%
- A need to develop therapy options to improve outcomes and reduce the risk of recurrence after surgery

Clinical submissions from Royal College of Pathologists; British Thoracic Oncology Group, National Cancer Research Institute and Royal College of Physicians

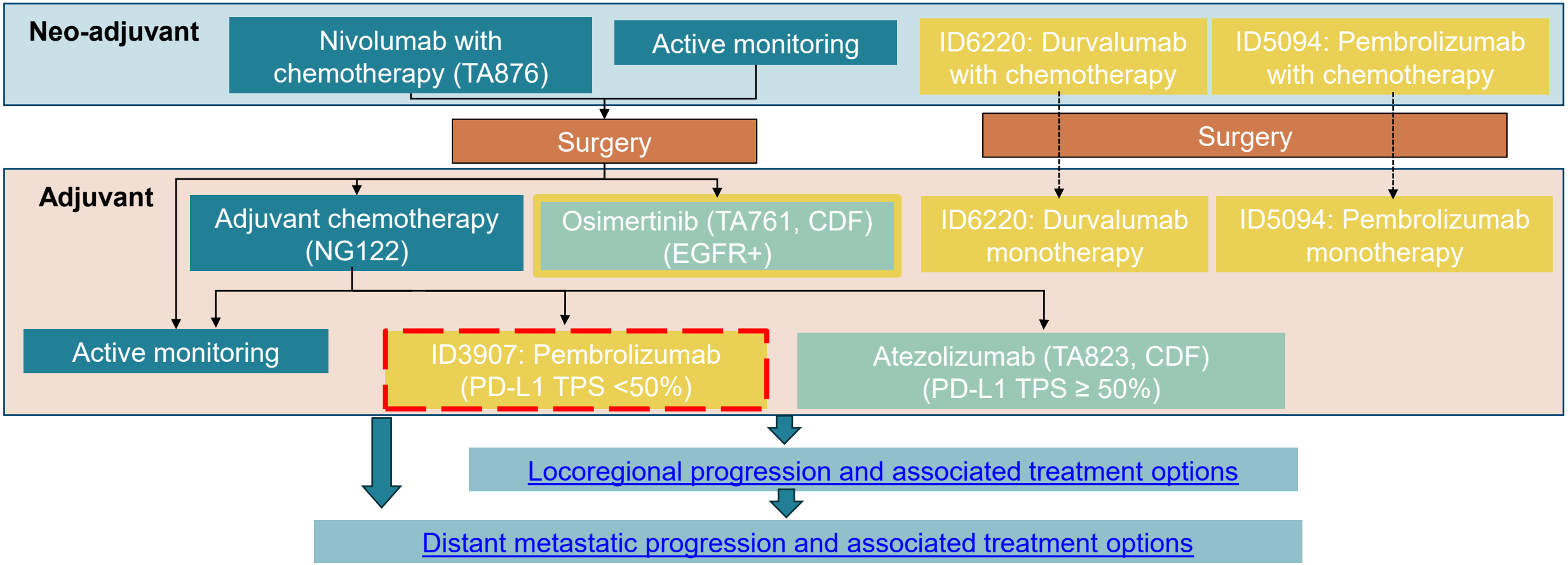
- Treatment aims to reduce risk of recurrence following surgery for people with potentially curable NSCLC
- NSCLC (especially in UK) has a very poor prognosis - most cases present late and are incurable
- Survival gains will likely come from early detection or a higher cure rate in the few suitable for surgery
- Most UK centres do PD-L1 testing at diagnosis of all NSCLC, so most people undergoing surgery will already have a PD-L1 score available, so no additional testing needed

Abbreviations: NSCLC, non-small-cell lung cancer; PD-L1, programmed death-ligand 1; tumour proportion score

Treatment pathway (resectable NSCLC)

Link to decision problem

Ongoing appraisal | NICE recommended / current practice | In the CDF | Ongoing CDF review



Population	Adults with NSCLC, had complete surgical resection, adjuvant chemotherapy and tumours has PD-L1 TPS <50%	Company restricted the population: • Most clinical benefit and highest unmet need
Comparator	Active monitoring	Other treatments not standard care (ongoing appraisal), in the CDF, or not in same population

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Abbreviations: NSCLC, non-small-cell lung cancer; CDF, cancer drugs fund; PD-L1, programmed death-ligand 1; TPS, tumour proportion score; EGFR, epidermal growth factor receptor

Pembrolizumab (KEYTRUDA, Merck Sharp & Dohme)

Marketing authorisation	Pembrolizumab as monotherapy is indicated for the adjuvant treatment of adults with NSCLC who are at high risk of recurrence following complete resection and platinum-based chemotherapy • MHRA approved December 2023
Mechanism of action	Pembrolizumab is a monoclonal antibody, which binds to the PD-1 receptor, thereby potentiating an immune response to tumour cells.
Administration	Either 200 mg every 3 weeks (Q3W) or 400 mg every 6 weeks (Q6W) administered as an intravenous infusion over 30 minutes
Testing	Testing for PD-L1 tumour expression level, measured by the TPS which consists of the proportion of PD-L1–positive tumour cells relative to the total number of viable tumour cells
Price	• List price per pack: £2,630 per 100 mg • There is a confidential commercial arrangement in place

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Abbreviation: NSCLC, non-small cell lung cancer; PD-1, programmed death 1; TPS, tumour proportion score; MHRA, Medicines and Healthcare products Regulatory Agency

Key issues

Issue	ICER impact
PD-L1 TPS <50% subgroup data • The clinical evidence supporting the company submission relies on a *post-hoc* subgroup of the KEYNOTE-091 trial	N/A
Model baseline age • The baseline age from the trial, used in the model, is too low compared to the target population in clinical practice	Small
DFS models • Better fitting DFS curves are available and should be used • Evidence of treatment waning justifies using different curves for each treatment arm	Large
Uncertainty in LR and DM health state transitions • Significant uncertainty in the trajectory of patient's post-recurrence due to limitations of the model structure and lack of available trial data	Unknown

Abbreviations: PD-1, programmed cell death 1; TPS, tumour proportion score; DFS, disease free survival; ICER, incremental cost-effectiveness ratio; N/A, not applicable; DM, distant metastases; LR, local recurrence

Pembrolizumab for treating adjuvant treatment of resected NSCLC

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Key clinical trial results

Disease free survival (DFS)

Treatment	N	Events (%)	Median DFS (Months) (95% CI)	vs. Placebo	
				Hazard Ratio (95% CI)	p-Value
PD-L1 TPS < 50% Subpopulation					
Pembrolizumab	363	168 (46)	52 (39, 70)	0.72 (0.58, 0.89)	0.001
Placebo	363	199 (55)	35 (23, 46)	---	---
Prior Adjuvant Chemotherapy Population (License Population)					
Pembrolizumab	506	225 (44.5)	54 (46, 70)	0.76 (0.64, 0.91)	0.002
Placebo	504	262 (52.0)	41 (33, 47)	---	---
Overall population (KEYNOTE-091 Population)					
Pembrolizumab	590	264 (45)	54 (46-67)	0.81 (0.68, 0.96)	0.008
Placebo	587	297 (51)	43 (35-52)	---	---

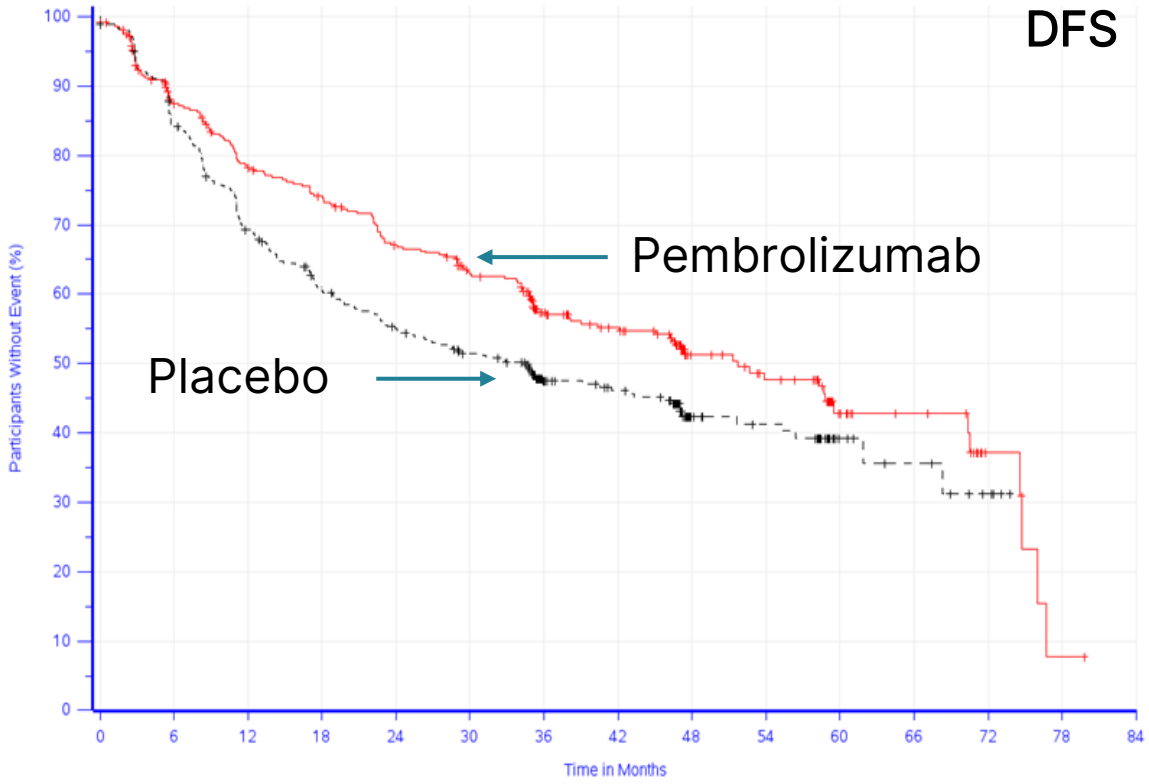
Overall survival (OS)

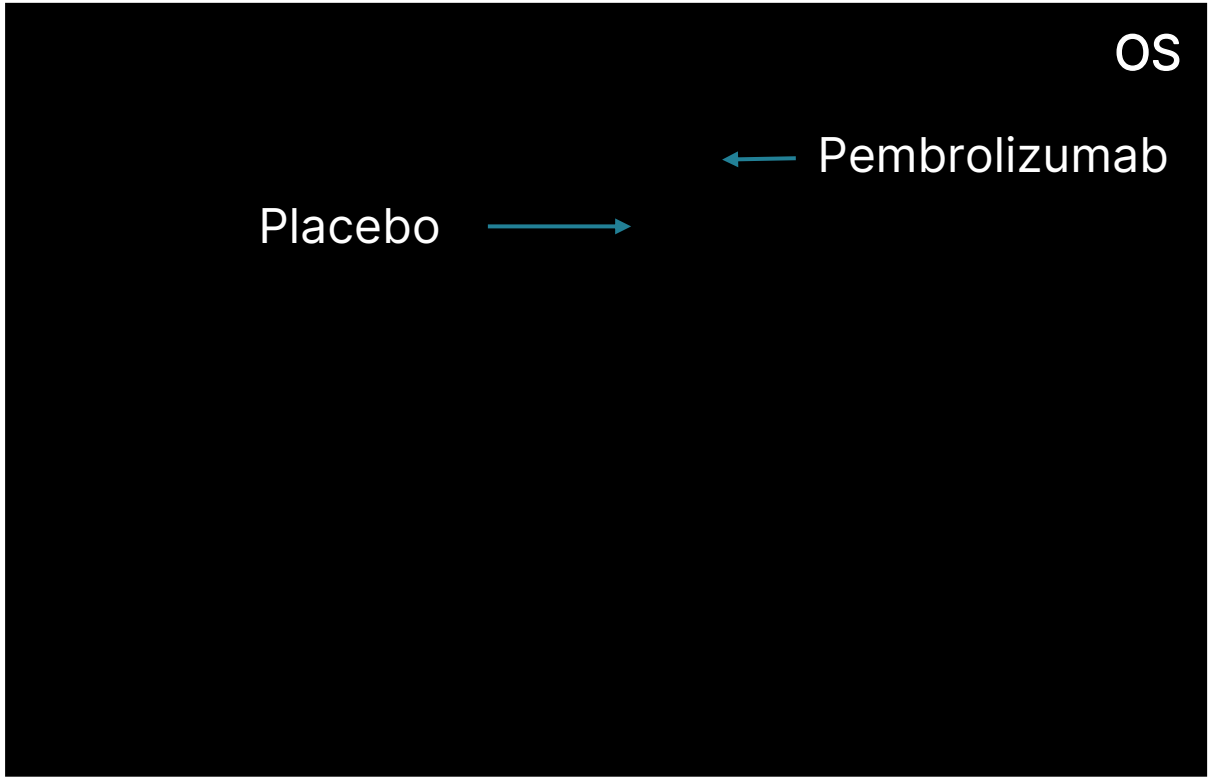
Treatment	N	Events (%)	Median OS (Months) (95% CI)	vs. Placebo	
				Hazard Ratio (95% CI)	p-Value
PD-L1 TPS < 50% Subpopulation					
Pembrolizumab	363	84 (23)	NR	0.73 (0.55, 0.97)	0.016
Placebo	363	110 (30)	NR	---	---
Prior Adjuvant Chemotherapy Population (License Population)					
Pembrolizumab	506	113 (22)	NR (NR-NR)	0.79 (0.62, 1.01)	0.032
Placebo	504	138 (27)	NR (NR-NR)	---	---
Overall population (KEYNOTE-091 Population)					
Pembrolizumab	590	136 (23)	NR [redacted]	0.87 (0.69-1.10)	0.118
Placebo	587	154 (26)	NR [redacted]	---	---

Abbreviations: PD-1, programmed death 1; TPS, tumour proportion score; CI, confidence interval; NR, not reached

Key clinical trial results – KEYNOTE-091 (PD-L1 TPS <50%)

Pembrolizumab (n=363) improves DFS and OS compared to placebo (n=363)





Median (months)	Pembrolizumab: 52; Placebo: 35
Events (%)	Pembrolizumab: 168 (46) Placebo: 199 (55)
HR (95% CI; p-value)	0.72 (0.58-0.89; 0.001)

Median (months)	Pembrolizumab: NR; Placebo: NR
Events (%)	Pembrolizumab: 84 (23) Placebo: 110 (30)
HR (95% CI; p-value)	0.73 (0.55-0.97; 0.016)

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Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; DFS, disease free survival; PD-L1, Programmed death-ligand 1; TPS, tumour proportion score; NR, not reached

- Link to trial characteristics

Key issues: PD-L1 TPS <50% subgroup data [1]

Link to decision problem

Background: Company's proposed positioning narrower than licensed population and relies on *post-hoc* subgroup

Stage IB (T2a ≥4 cm), Stage II, or Stage IIIA NSCLC (based on AJCC 7th edition) confirmed after complete surgical resection (resected-R0) with or without adjuvant chemotherapy → **KEYNOTE-091 trial population** (overall population, n=1,177)

Adjuvant treatment of adults with NSCLC who are at high risk of recurrence following complete resection (resected-R0) and platinum-based chemotherapy → **Licensed population** (prior adjuvant chemotherapy population, n=1,010)

Adults with NSCLC who are at high risk of recurrence following complete resection (resected-R0) and platinum-based chemotherapy and whose tumours express PD-L1 TPS <50% → **Proposed population** (*post-hoc subgroup*: PD-L1 TPS <50%, n=726)

Company

PD-L1 TPS <50% (proposed population)

- Positioning consistent with KEYNOTE-091 results – pembrolizumab significantly reduces risk of recurrence / death compared with placebo in this subpopulation
- Subgroup has highest unmet need and can benefit most from additional adjuvant option given lack of treatments

PD-L1 TPS ≥50% (excluded from proposed population)

- Clinical feedback: pembrolizumab not expected to become preferred treatment in PD-L1 TPS ≥50% subpopulation due to efficacy uncertainties compared to atezolizumab (currently in CDF)
- Company's UK advisory boards: KEYNOTE-091 PD-L1 TPS ≥50% results contradict clinical expectations
  - Established evidence that PD-1 inhibitors have greater efficacy in ≥50% group → control arm overperformed
  - Long-term follow-up data could clarify efficacy, but limited unmet need for pembrolizumab to address

Abbreviations: NSCLC: Non-small cell lung cancer; PD-L1: programmed death-ligand 1; TPS: tumour proportion score; CDF, cancer drugs fund

Key issues: PD-L1 TPS <50% subgroup data [2]

EAG comments

- Focus on PD-L1 TPS <50% subgroup is appropriate, but was not pre-specified in KEYNOTE-091 - focus *post-hoc* subgroup could be a data-driven decision and could be at risk of bias and Type I error
  - Potentially overestimates effectiveness as population reflects where pembrolizumab has most benefit
  - Smaller sample = power reduced = prevents reliable conclusion and a risk of Type I error (due to chance)
    - ↳ Company: focus on subpopulation not data-driven but reflects population with high unmet need
    - ↳ Company: no substantial imbalances in baseline characteristic between treatment arms, except for smoking, ECOG, histology and ALK status which were also imbalanced in overall trial population
- EAG clinical experts: PD-L1 TPS ≥50% results contradict current knowledge on immunotherapies where magnitude of benefit is generally correlated to the level of PD-L1 expression
  - Mechanism underpinning greater clinical benefit in PD-L1 TPS <50% subgroup is not yet understood
  - Company: likely to be due to an ‘’overperforming’’ control arm in PD-L1 TPS >50% subpopulation
    - ↳ Results better than expected and do not reflect other trials in adjuvant setting
    - ↳ Besides overperformance, cannot rule out results being due to an imbalance in unknown factors
- EAG: no evidence supporting “overperformance” over, e.g., control arm underperforming in PD-L1 TPS <50%

Is the KEYNOTE PD-L1 TPS <50% *post-hoc* subgroup appropriate to use?

Abbreviations: PD-L1: programmed death-ligand 1; TPS: tumour proportion score; ECOG, eastern cooperative oncology group; ALK, anaplastic lymphoma kinase

Key issues: Baseline age [1]

Background

- Company's model baseline age: 64.3 years (KEYNOTE-091 overall population mean age)
  - ↳ KEYNOTE-091 PD-L1 TPS <50% subgroup mean age: [redacted] years – decision problem population
- EAG: model baseline age is too low compared to the target population in UK clinical practice

Company

- Must be fit enough for surgery and to complete adjuvant chemo – likely younger than average NSCLC patient
- Median lung cancer diagnosis age (England): 73 years – but includes all lung cancer stages
  - E.g., stage 4 - people older due to late diagnosis. Younger people likely diagnosed at early stage
- UK / England-specific evidence on age distribution by stage is sparse and based on single-centre studies
- Other early-stage NSCLC trials for different treatment types have shown similar age distribution
- Treatment effect does not differ across age groups in PD-L1 TPS <50% DFS subgroup analysis - no evidence to suggest age may be a treatment effect modifier in decision problem population

Trial / study name (NSCLC literature presented by company and EAG)	Median Age (range), years
KEYNOTE-091 (adjuvant) (PD-L1 TPS <50% population)	[redacted]
KEYNOTE-091 (overall population)	65 (31 to 87)
Jessica et al. 2024 (resected stage 2 and 3 NSCLC)	62 (42 to 74)
Ugolini et al. 2023 (underwent surgical resection)	70 (45 to 81)
Escriu et al. 2023 (resectable early-stage NSCLC)	70 (44 to 92)
Trevelyan et al. 2024 (NSCLC underwent curative treatment with surgery)	70 (not reported)
Belcher et al. 2021 (operative patients)	70.4 (18.1 to 87.7)
EAG BASE CASE - Belot et al. 2019 (NSCLC patients who received surgery)	68.4 (mean)

Abbreviations: NSCLC, non-small-cell lung cancer; PD-L1: programmed death-ligand 1; TPS: tumour proportion score; DFS, disease free survival

Key issues: Baseline age [2]

EAG comments

- Clinical experts: KEYNOTE-091 trial population is younger than clinical practice in England
  - Clinical practice: 68 years (registry data from people with NSCLC having surgery in England 2012)
  - SEER-Medicare cohort (early-stage NSCLC) baseline age at surgery: 74 years (had min age of 65)
    - ↳ Age is significant risk factor - would expect higher number having NSCLC with increasing age
    - ↳ Company: significant number of people aged <65 have surgery in UK clinical practice and only 41% had adjuvant chemotherapy in SEER so serious generalisability concerns using this to inform UK age
- Expect similar median age in other NSCLC trials - often select people younger than general patient population
- Concerned over generalisability of trial age to clinical practice and potential impact on effectiveness results:
  - Higher starting age = higher mortality rates - limits treatment benefit of pembrolizumab over placebo
  - Age is a potential treatment effect modifier - lower tolerability of pembrolizumab in older individuals
  - Clinical experts: cure rate likely higher in younger population compared to older population
- EAG base case: baseline age of 68 years; conservative scenario: use SEER-Medicare age 74 years

Other considerations

- ID5120 (adjuvant osimertinib, EGFR+ NSCLC): model starting age should be 70 years to reflect NHS practice (based on SACT data)

NICE Which baseline age is most appropriate – 64 years (company), 68 years (EAG) or other?

Abbreviations: NSCLC, non-small-cell lung cancer; PD-L1, Programmed death-ligand 1; EGFR, epidermal growth factor receptor; SACT, Systemic Anti-Cancer Therapy

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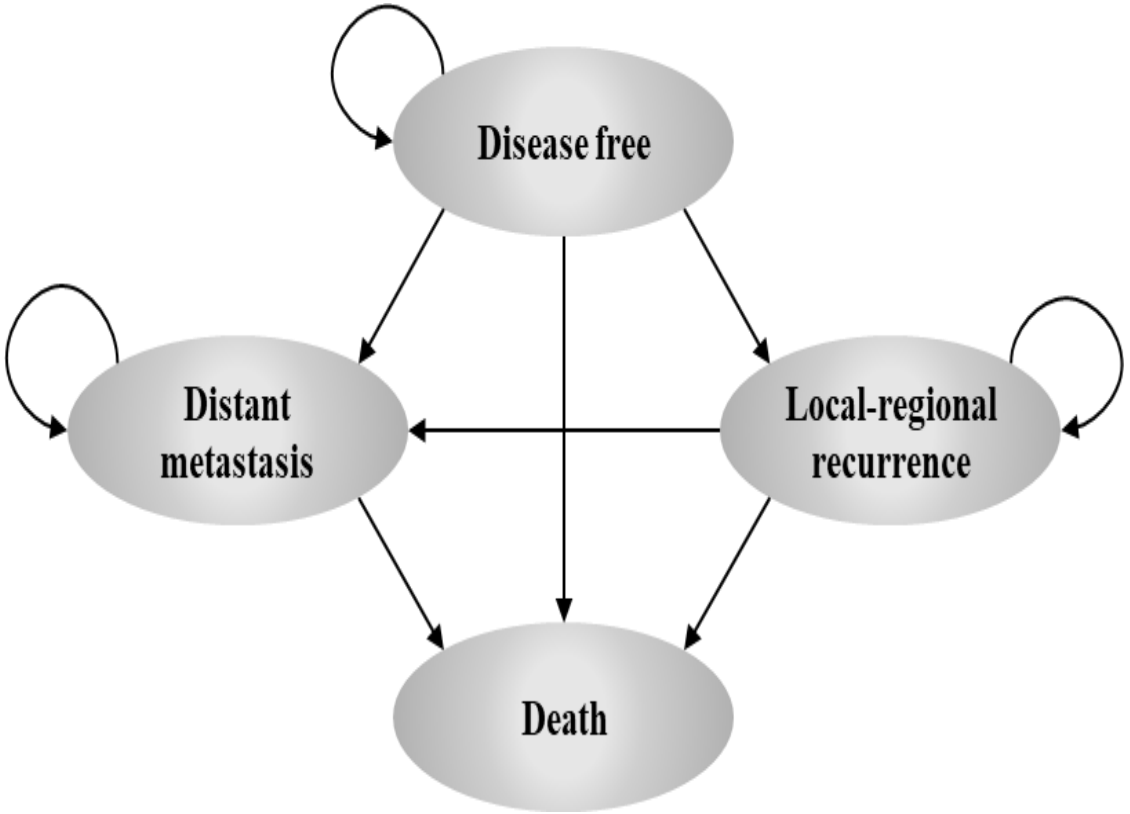
Company's model overview

Model structure



Markov structure implies modelled survival is primarily a function of DFS

- Improved DFS results in improved OS
- OS is the primary driver of modelled benefits

Cure assumption

- A cure assumption was applied among people who achieve long-term DFS
- Base case assumes a cure point of 5 – 7 years.
- After 5 years, risk of recurrence reduces linearly to maximum of 95%
- Modelled patients therefore have a long-term residual risk of recurrence
- Proportion of people reaching the cure point, as determined by DFS curve, is the primary factor influencing the magnitude of incremental QALY benefits

- Evidence informing the model
- Impacts of pembrolizumab on costs, QALYs, ICERs

Abbreviations: DFS, disease free survival; OS, overall survival; QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio

Key Issue: DFS models [1]

Company and EAG approaches to modelling DFS reflect 2 alternative interpretations of the data

Background:

- Company: pembrolizumab increases proportion of people cured and benefits are sustained across time horizon
  - ↳ Applied log-normal curve to both treatment arms and both transitions from DF to LR and DM
- EAG: pembrolizumab benefits represent a delay in recurrence and are not sustained throughout time horizon
  - ↳ Used different DFS curves for each arm and transition to account for treatment waning and to better fit data

Company

- No treatment effect waning applied, 5-year KEYNOTE-091 data shows sustained DFS and OS curve separation
- Clinical Advisory Board: expect continued DFS curve separation → pembrolizumab increases probability of long-term cure rather than just delaying recurrence = rejected models trending towards early convergence of DFS/OS
- Cure assumption is conservative, clinical feedback = narrower period with 100% risk reduction equally plausible
  - KEYNOTE-091: hazards declining and plateau towards end of follow-up - imply proportion cured increasing

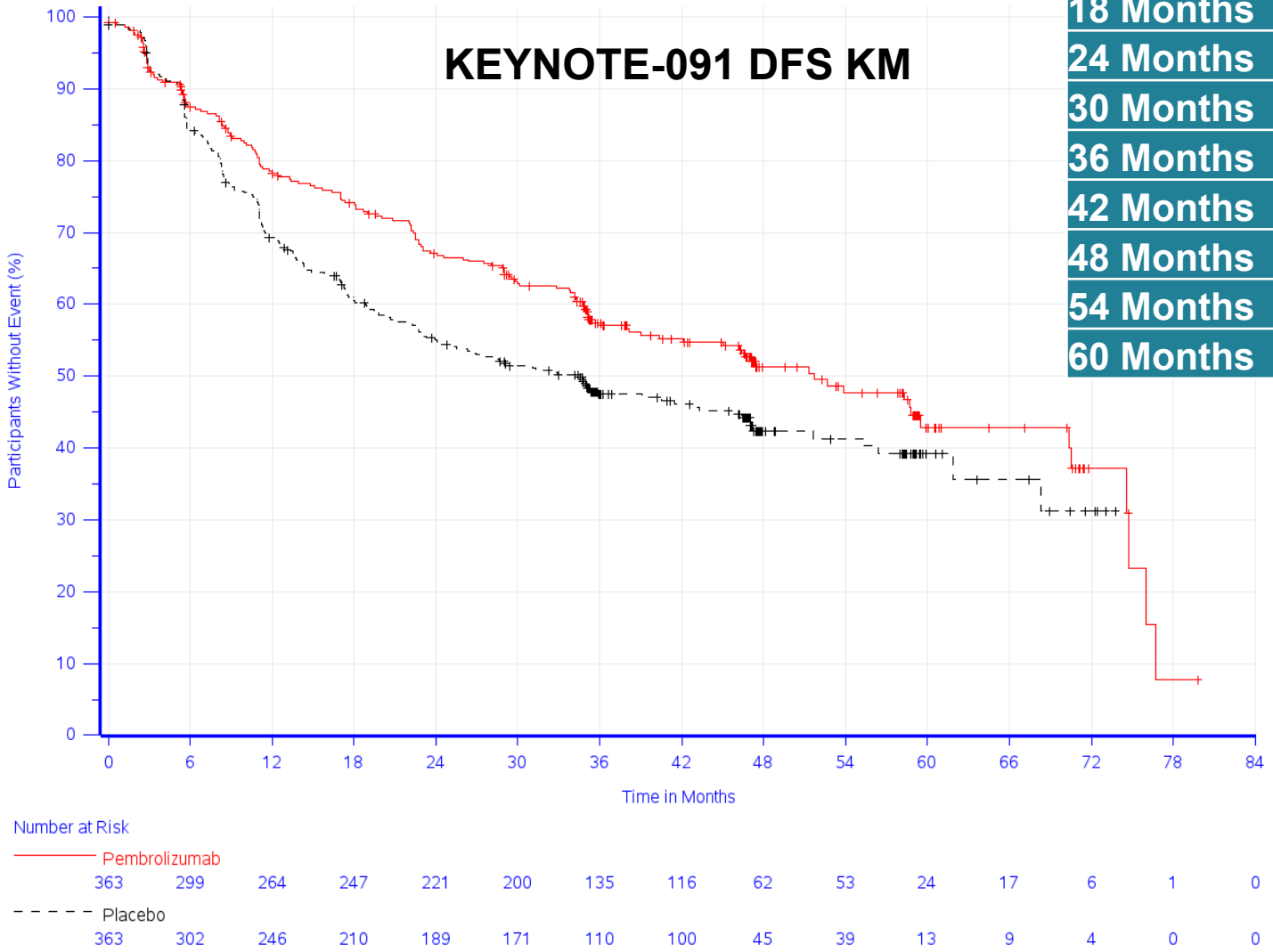
EAG comments

- Evidence of treatment waning from KEYNOTE-091 observed DFS (see next slide)
- TA761/TA823 used differential cure points to address long-term uncertainty – similar impact to differential curves
- 95% from TA569 (breast cancer): used to match curve to literature ultra-late recurrence rate (not clinically valid)
  - Company: did not update cure rate, model ultra-late recurrences (0.73%) align with NSCLC literature (0.8%)

Abbreviation: NSCLC, non-small-cell lung cancer; DF, disease free; DFS, disease free survival; LR, local recurrence; DM, distant metastases, OS, overall survival

Key Issue: DFS models [2]

EAG: pembrolizumab treatment benefit consistently declines every timepoint from 18 months



DFS probability (95% CI)	Pembrolizumab (N=363)	Placebo (N=363)	Difference
12 Months	[redacted]	[redacted]	[redacted]
18 Months	[redacted]	[redacted]	[redacted]
24 Months	[redacted]	[redacted]	[redacted]
30 Months	[redacted]	[redacted]	[redacted]
36 Months	[redacted]	[redacted]	[redacted]
42 Months	[redacted]	[redacted]	[redacted]
48 Months	[redacted]	[redacted]	[redacted]
54 Months	[redacted]	[redacted]	[redacted]
60 Months	[redacted]	[redacted]	[redacted]

Difference in DFS probability

[redacted]

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Abbreviations: CI, confidence interval; DFS, disease free survival; KM, Kaplan-Meier

Key Issue: DFS models [3]

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- Link to full company / EAG comments

Company response to EAG DFS curves selection

- Need stronger evidence to use differential distributions, suggest alternative: generalised gamma / log-normal
- Inappropriate to conclude evidence of treatment waning based on limited data - gap meaningfully narrows after 4 years, but at this point 2/3rds censored and only 19 events
- Exponential curve (constant hazards in pembro arm) and Gompertz curve (0 hazards soon after follow-up in placebo arm) likely inappropriate to project recurrences in adjuvant setting, particularly in only one arm
- EAG models no curative advantage of pembrolizumab (only delayed recurrence)

EAG response to company

- Sufficient treatment waning evidence – DFS advantage meaningfully decreases between years 2-4 ([redacted]% - [redacted]%)
- Exponential best fits observed data and cure period - constant hazards plausibly explained by treatment waning
- Long-term recurrences underpredicted due to combination of assumptions, not from by curve choice (gompertz)
  - 95% reduction in hazards is arbitrary - 75% reduction in hazards needed to match NSCLC literature
- Plausible that pembrolizumab leads to higher proportion cured but does not align with best fit DFS projection
  - Significant uncertainty in cure point and reduction in hazards

DFS curves summary	DF → LR		DF → DM	
	Pembrolizumab	Placebo	Pembrolizumab	Placebo
Company	Log-normal	Log-normal	Log-normal	Log-normal
EAG	Exponential	Generalised gamma	Log-normal	Gompertz
Company alternative	Generalised gamma	Generalised gamma	Log-normal	Log-normal

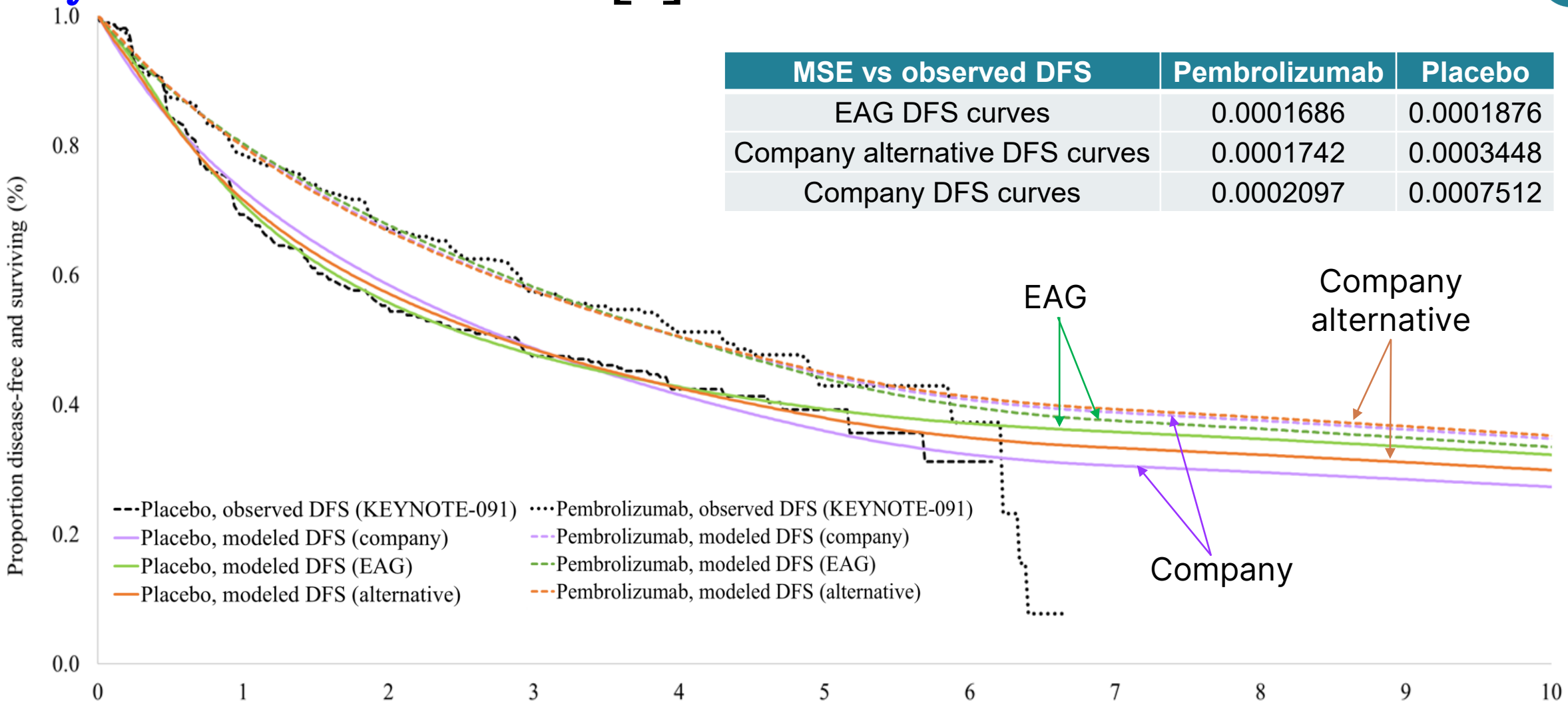
TSD14 guidance - fit the same model type in both arms unless there is strong evidence to contrary

Abbreviation: DF, disease free; DFS, disease free survival; LR, local recurrence; DM, distant metastases; TSD, technical support document

Key Issue: DFS models [4]

- DFS curves extrapolated over 50 years

MSE vs observed DFS	Pembrolizumab	Placebo
EAG DFS curves	0.0001686	0.0001876
Company alternative DFS curves	0.0001742	0.0003448
Company DFS curves	0.0002097	0.0007512



Numbers at risk

363	264	221	135	62	24	6	0	Pembrolizumab
363	246	189	110	45	13	4	0	Placebo

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Abbreviations: DFS, disease free survival; MSE, mean squared error

Key Issue: DFS models [5]

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Time (years)	Pembrolizumab				Placebo			
	Observed DFS	Modelled DFS			Observed DFS	Modelled DFS		
		Company base case	EAG base case	Company alternative		Company base case	EAG base case	Company alternative
1	[redacted]	80.1%	80.3%	79.9%	[redacted]	73.2%	71.0%	71.7%
1.5	[redacted]	73.0%	73.6%	72.7%	[redacted]	65.0%	62.1%	63.3%
2	[redacted]	67.1%	67.8%	66.8%	[redacted]	58.6%	55.8%	57.2%
5	[redacted]	44.7%	44.1%	45.0%	[redacted]	36.0%	39.4%	38.0%
6	[redacted]	40.8%	39.7%	41.2%	[redacted]	32.3%	37.1%	34.9%
10	-	34.8%	33.5%	35.2%	-	27.3%	32.3%	29.9%
20	-	16.0%	15.2%	16.3%	-	12.5%	15.2%	13.9%
30	-	1.4%	1.3%	1.5%	-	1.1%	1.4%	1.3%
40	-	0.0%	0.0%	0.0%	-	0.0%	0.0%	0.0%
45	-	0.0%	0.0%	0.0%	-	0.0%	0.0%	0.0%

Note: Red boxes highlight modelled DFS that is closest to observed DFS

Abbreviations: DFS, disease free survival

Key Issue: Uncertainty in LR and DM health state transitions

Background

- Appropriate KEYNOTE-091 data unable to inform transition probabilities from LR and DM health states to death.
- Use external data - LR: SEER-Medicare; DM: subsequent treatment trial data = model with exponential curves

Company

- Using external data in pembrolizumab arm results in significantly different OS than trial and real-world data
- To closer match OS to trial results, simultaneously apply multiplier to all recurrence transitions in both arms
- 2023 Clinical Advisory Board: plausible that some residual pembrolizumab benefit not fully captured in DFS
  - ↳ Immunotherapy may fundamentally alter disease trajectory – may slow disease progression or enable recurrence at stages more amenable to radical treatment
  - ↳ Immunotherapy may enhance sensitivity to chemotherapy and the effectiveness of subsequent treatments

EAG comments

Company rely on 3 modelling assumptions = stacking all assumptions → significant uncertainty in transition rates:

1. Exponential curves provide reasonable fit to external data → EAG cannot validate goodness of fit without IPD
2. Relative transition rates derived are accurate (i.e. ratio of LR → DM versus DM → death)
   - ↳ Evidence of treatment waning - unlikely same distribution and relative transition rates applies to both arms
3. To match trial results, single universal multiple used to alter all values in each arm
   - ↳ Assuming a single multiplier, for each treatment arm, applies to all transitions equally seems unlikely

- No alternative approach with time constraints – cost-effectiveness uncertain and no clear direction of bias
  - ↳ Partitioned survival model or adapting model to allow for time-dependent transitions in recurred patients would allow different modelling methods and further investigation of IPD used to inform transitions

Are the transitions from LR and DM health states to death appropriate for decision-making?

Abbreviation: LR, local recurrence; DM, distant metastases; OS, overall survival; IPD, individual patient data; DFS, disease free survival

Summary of company and EAG base case assumptions and results

Cost-effectiveness results are heavily reliant on assumptions around DFS

Assumption	Company base case	EAG base case
Baseline age	64 years (overall KEYNOTE-091 population)	68 years
DFS curves (DF-LR) / (DF-DM)	Both arms: log-normal / log-normal	○ Pembrolizumab: exponential / log-normal ○ Placebo: generalised gamma / gompertz

Scenario (applied to both base cases)	Inc costs (£)	Inc QALYs	ICER (£/QALY)
Company base case	See part 2	See part 2	Under £30,000
Baseline age: 68 years	↓	↓	Under £30,000
Baseline age: 74 years (SEER)	↓	↓	Over £30,000
EAG base case DFS curves	↑	↓	Over £30,000
Generalised gamma / log-normal (company alternative DFS curves)	↑	↓	Over £30,000
EAG base case	See part 2	See part 2	Over £30,000
Generalised gamma / log-normal (company alternative DFS curve)	↓	↑	Over £30,000

Note: results include confidential prices

NICE Abbreviations: DF, disease free; DFS, disease free survival; LR, local recurrence; DM, distant metastases; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Pembrolizumab for treating adjuvant treatment of resected NSCLC

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ Other considerations
  - ↳ Severity / equality / innovation / uncaptured benefits not raised
- ❑ Summary

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- ✓ **Summary**

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Decision making framework

What are committee's preferred assumptions?	Options
Baseline age	64 (company), 68 (EAG), other e.g., 74 years

DFS curves (DF->LR / DF->DM transition)	• Company base case:
	  ○ Both arms: log-normal/log-normal
	• Company alternative:
	  ○ Both arms: generalised gamma/log-normal
	• EAG base case:
	  ○ Pembrolizumab: exponential / log-normal
	  ○ Placebo: generalised gamma / gompertz

What is committee's preferred ICER threshold?	£20,000 / £30,000 per QALY gained / other
What is committee's preferred ICER?	If a range, lower, upper, or midpoint
Is the ICER below preferred ICER threshold?	Yes / No
If yes, recommend for routine commissioning?	Yes / No (consider uncertainty, inequalities, innovation etc - may impact decision if close to threshold)
Could key uncertainties be sufficiently resolved during period of managed access? If so, see slide:	Yes / No – note, no managed access proposal made.
What, if any, are the key remaining uncertainties?	*Post-hoc* subgroup? Treatment waning? Cure rate / cure point? Recurrence transitions?

Abbreviations: DF, disease free; DFS, disease free survival; LR, local recurrence; DM, distant metastases; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Managed access decision making framework

What are committee's preferred assumptions?	Options
• Has company made a managed access proposal? Is this considered feasible? • Are any updates or amendments required to the managed access proposal? • Has committee answered the questions in NICE's feasibility assessment? • What is committee's preferred threshold for managed access? • Which ICERs/assumptions represent committee's lower/upper end of uncertainty?	*Company has not made a managed access proposal
If not, is chair's action appropriate?	Yes / No

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**

KEYNOTE-091: Final OS analysis ~[redacted]- analyses event-driven, so timelines subject to change. Currently at [redacted] and [redacted] of numbers needed. Expect slow accrual rate of OS events

Does committee want the company to submit a managed access proposal? If yes, what key uncertainties would it like the proposal to address?

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Abbreviations: OS, overall survival; PD-L, Programmed death-ligand; ICER, incremental cost-effectiveness ratio

Thank you

NICE

Supplementary appendix

NICE National Institute for Health and Care Excellence

Decision problem

Link back to PD-L1 subgroup data issue and treatment pathway

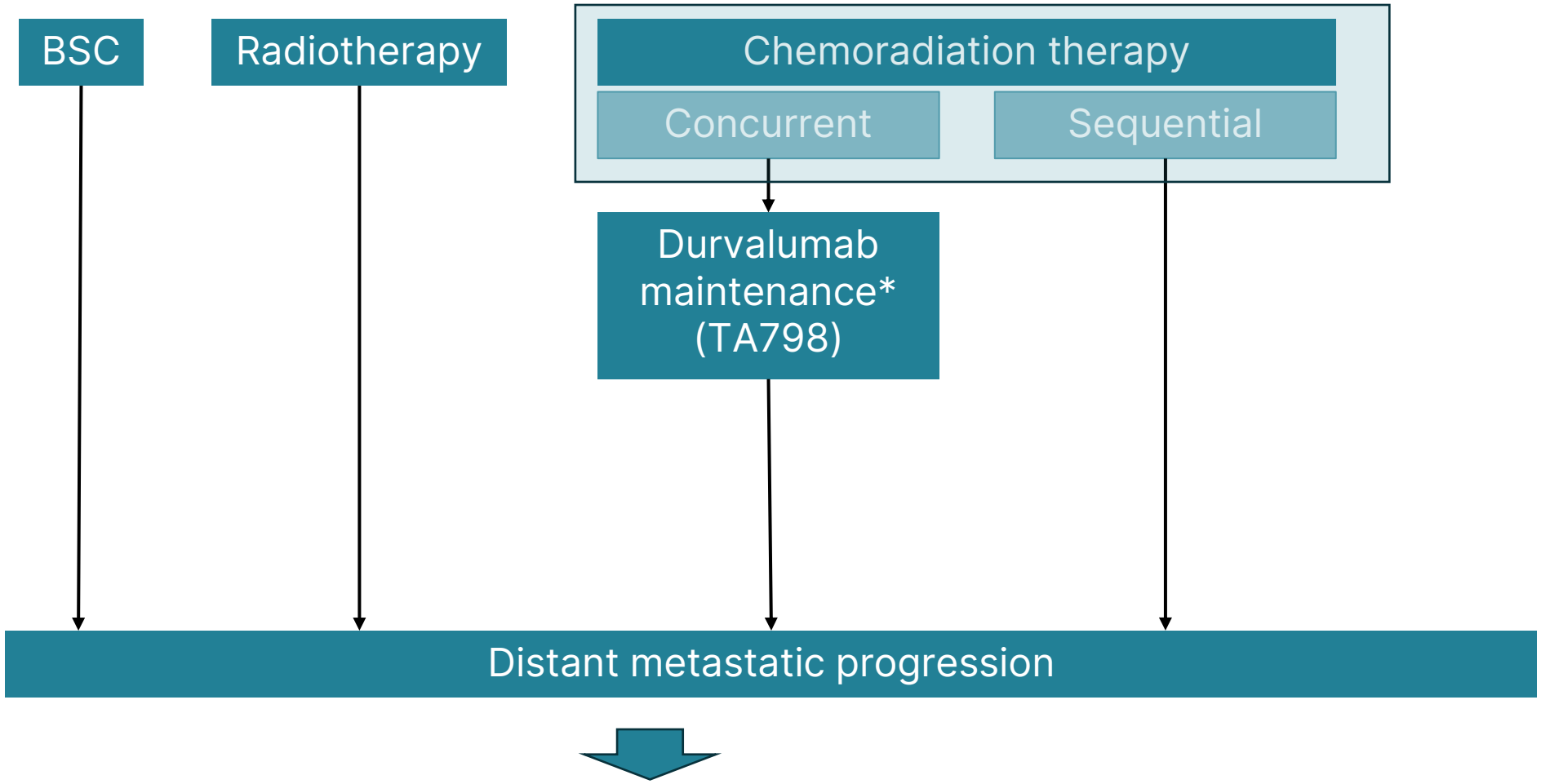
	Final scope	Company	EAG comments
Population	Adults with NSCLC who have undergone complete surgical resection with or without adjuvant chemotherapy	Adults with NSCLC who have undergone complete surgical resection after adjuvant chemotherapy and whose tumours have PD-L1 biomarker expression <50% • Higher unmet need - benefit most from extra treatment • Clinicians' feedback: pembrolizumab likely not used in PD-L1 TPS ≥50% subpopulation	Reasonable to narrow the population
Intervention	Pembrolizumab		
Comparators	• Established clinical management without pembrolizumab • Platinum doublet chemo Subject to NICE appraisal: • Durvalumab / osimertinib / atezolizumab	Established clinical management without pembrolizumab (active monitoring) • Eligible population will have had prior chemotherapy • Durvalumab - ongoing appraisal so not SoC. Trial did not include neoadjuvant immunotherapies • Atezolizumab (PD-L1 TPS <50%) and osimertinib (EGFR) available under CDF and not same population	Agree with company
Outcomes	Disease-free survival, event-free survival, overall survival, AE of treatment, HRQoL • Company: all except event free survival (not relevant for adjuvant treatment) • EAG: company model includes time on treatment		
Subgroups	If evidence allows: • disease stage • level of PD-L1 expression	No subgroups considered • Submission focuses on PD-L1 TPS <50% • Separate subgroups by stage should not be considered	Further subgroups of PD-L1 TPS <50% subpopulation could result in very small sample = prevents reliable conclusion

Abbreviations: NSCLC, non-small-cell lung cancer; PD-L1, Programmed death-ligand 1; TPS, tumour proportion score; EGFR, epidermal growth factor receptor; CDF, cancer drugs fund

Treatment pathway

Unresectable locally advanced

Back to main treatment pathway



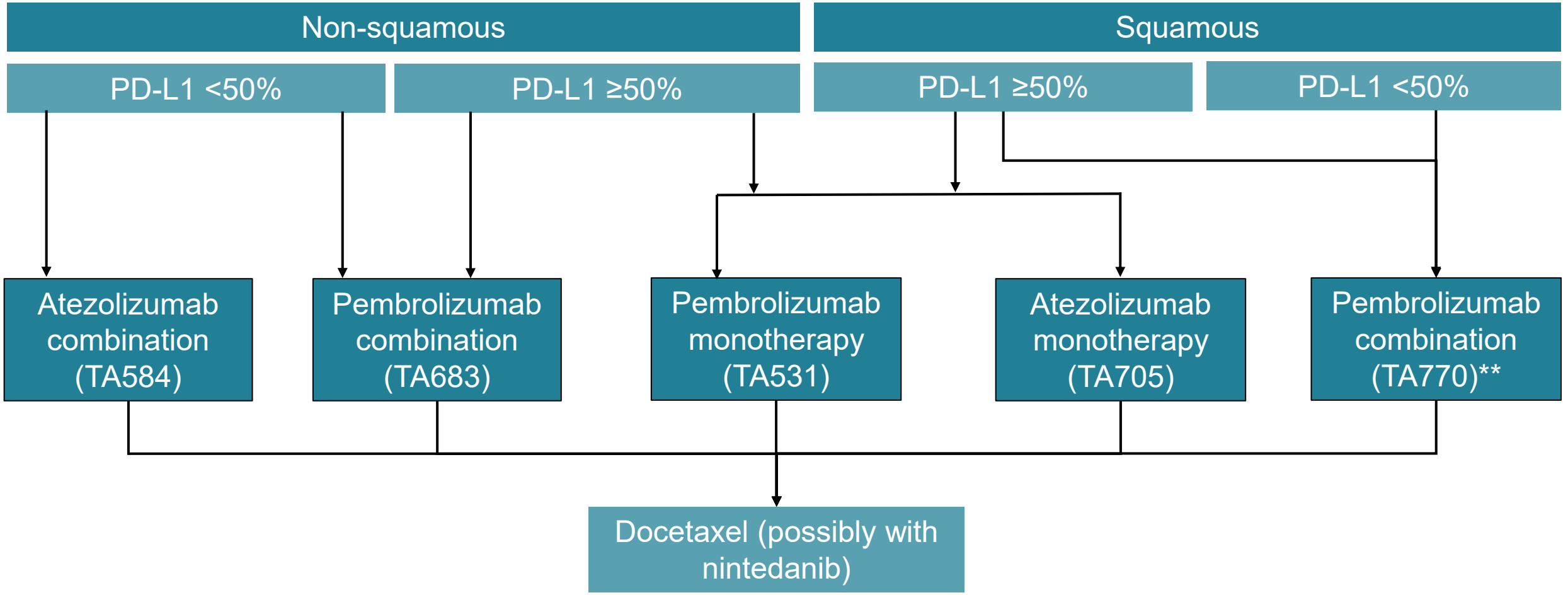
*Durvalumab maintenance recommended for PD-L1 positive NSCLC

Abbreviations: BSC, best supportive care; PD-L1, Programmed death-ligand 1; NSCLC, non-small-cell lung cancer

Treatment pathway (active treatments*)

Back to main treatment pathway

Advanced/metastatic



*Chemotherapy only regimens or BSC is also offered where immunotherapy or active treatment is not suitable or preferred

** Only where urgent clinical intervention is required

Abbreviations: PD-L1, Programmed death-ligand 1; BSC, best supportive care

Key clinical trial

Main slide set results

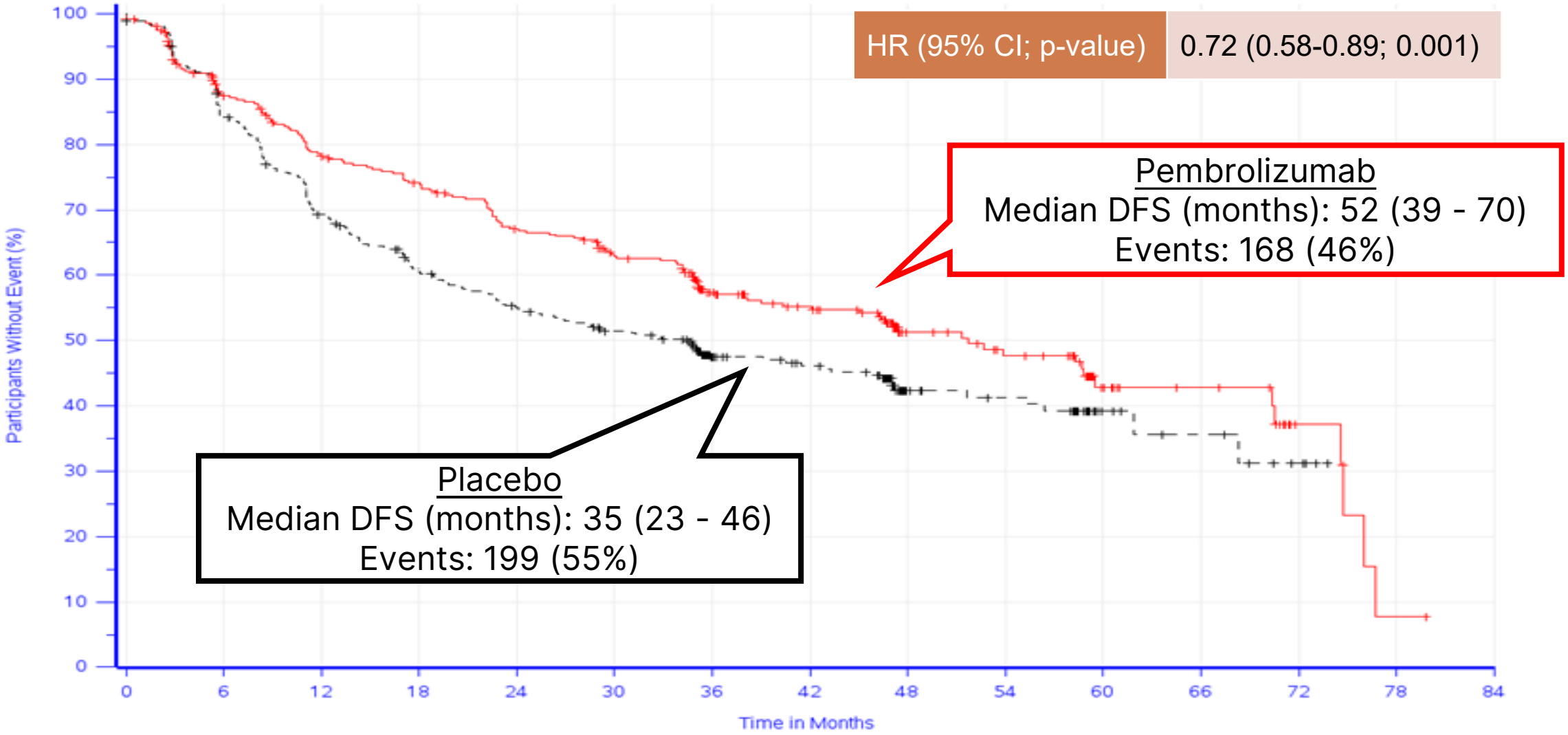
Clinical trial design and outcomes

	KEYNOTE-091 / PEARLS
Design	Phase 3, randomised, triple-blinded, placebo controlled, multicentre study
Population	Adults with Stage IB (T2a ≥4 cm), Stage II, or Stage IIIA NSCLC confirmed after complete surgical resection. Adjuvant chemotherapy was not mandatory* but considered for patients Stage IB and strongly recommended for Stage II and IIIA. *Marketing authorisation: people who had prior adjuvant chemotherapy following complete resection
Intervention	Pembrolizumab - 200 mg every 3 weeks (Q3W) for 18 cycles (1 year)
Comparator(s)	Placebo - Q3W for 18 cycles (1 year)
Duration	Follow up duration: [redacted] months (ITT population – prior adj chemo)
Primary outcome	Disease free survival
Key secondary outcomes	Overall survival, adverse events, health-related quality of life
Locations	206 centres, 29 countries includes 53 people from UK across 14 sites
Used in model?	Yes

Abbreviations: NSCLC, non-small-cell lung cancer; ITT, intention to treat

Key clinical trial results – KEYNOTE-091 (PD-L1 TPS <50%)

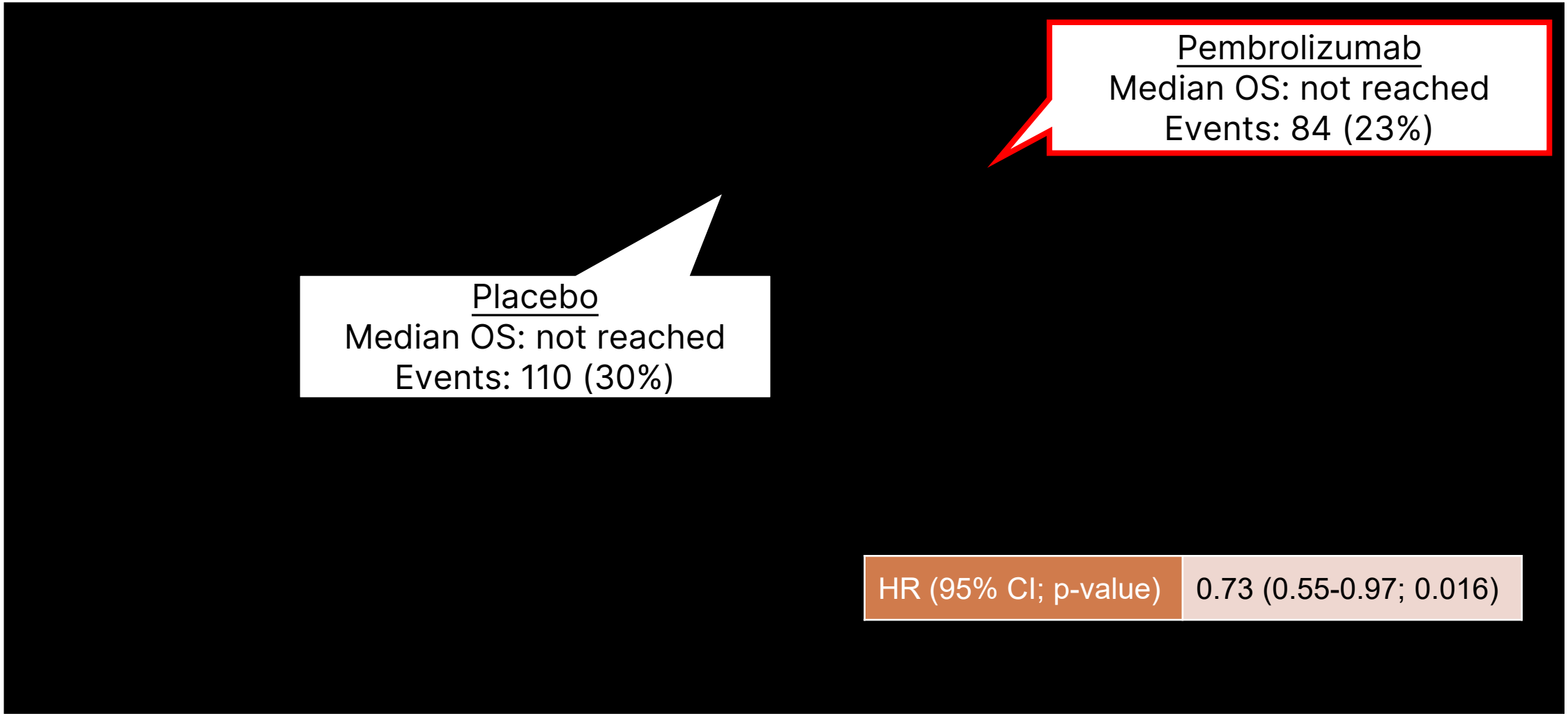
Pembrolizumab (n=363) improves DFS compared to placebo (n=363)



Abbreviations: CI, confidence interval; HR, hazard ratio; DFS, disease free survival; PD-L1, Programmed death-ligand 1; TPS, tumour proportion score

Key clinical trial results – KEYNOTE-091 (PD-L1 TPS <50%)

Pembrolizumab (n=363) improves OS compared to placebo (n=363)



Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; PD-L1, Programmed death-ligand 1; TPS, tumour proportion score

Impact of technology on model costs, QALYs and ICERs

Technology affects **costs** by:

- Decreasing rate of transition from DF to health states with different healthcare costs: LR, DM recurrence, and death, (increasing their DFS);
- Decreasing rate of transition to from LR to DM recurrence and death
- Decreasing mortality of patients who experience a DM recurrence;
- Decreasing mortality rate = end of life costs accrued later in life though patients cease to incur costs;
- Increasing rates of AE/hospitalisations due to AE.
- Increasing treatment costs for first year;
- Different makeup of subsequent treatments due to I/O ineligibility in some adjuvant pembrolizumab patients.

Technology affects **QALYs** by:

- Decreasing patients rate of transition from DF to health states with poorer QoL: LR, DM recurrence, and death, (increasing their DFS);
- Decreasing rate of transition from LR to dm recurrence and death;
- Decreasing mortality of patients who experience a DM recurrence;
- Increasing rates of AE.

Assumptions with greatest **ICER** effect:

- Estimation of DFS curves;
- Cost of intervention;
- Cost/makeup of subsequent treatments.

Back to model structure slide

Abbreviations: DF, disease free; DM, distant metastases; LR, local recurrence; QALYs, quality-adjusted life years; I/O, immunotherapy; AE, adverse events; QoL, quality of life; ICER, incremental cost-effectiveness ratio

How company incorporated evidence into model

Input	Assumption and evidence source
Model structure	Markov model, 4 health states (disease free, local recurrence, distant metastases, death), lifetime horizon, 3.5% discount rate
Baseline characteristics	KEYNOTE-091 PD-L1 <50% subpopulation baseline characteristics • Start age: overall KEYNOTE-091 population (64.3 years)
DFS (to LR, DM and death)	• Transition probabilities: KEYNOTE-091 • Extrapolation: log-normal (to LR and DM); exponential (to death) • Cure point: 5–7-year period, maximum risk reduction 95%
Recurrence (from LR and DM states)	• Transition probabilities: RWE (LR), published trials (DM) • Extrapolation: all transitions modelled with exponential distribution • Calibration applied to transitions to match OS to trial results ○ Calibrate up to 5 years, not applied to immunotherapy ineligible patients
Dosing	Every 6 weeks for 75% of pembrolizumab patients, every 3 weeks for 25%
Utilities	DFS / LR : KEYNOTE-091; DM: utility data in pivotal metastatic trials
Costs	PD-L1 testing included, End of life costs based on PSSRU
Resource use	• Elicited from UK advisory board • Full Kaplan-Meier used for time on treatment and relative dose intensity calculations

NICE

Abbreviations: RWE, real-world evidence; OS overall survival; PD-L1, Programmed death-ligand 1; DM, distant metastases; LR, local recurrence; DFS, disease free survival

Key Issue: DFS models

• Back to DFS discussion

Company comments about EAG DFS modelling	EAG response
Exponential curve (constant hazards) likely inappropriate to project recurrences in adjuvant setting, particularly when only applied to one arm • Hazards should decrease as proportion cured increases	Best fitting curve to observed data and cure period • Constant hazards plausibly explained by treatment waning • As more people recur, there is greater proportion of people cured but, in pembrolizumab arm only, there is also several people who have treatment waning
Gompertz curve (0 hazards soon after follow-up) likely inappropriate to model recurrences in adjuvant setting, particularly when only applied to one arm 1. Know ultra-late recurrences occur in early NSCLC 2. EAG ultra-late recurrences ([redacted]) not aligned with literature (0.8%)	Discrepancy in long-term recurrences predictions is due to combination of assumptions applied, not caused by choice of curve • 95% reduction in hazards is arbitrary - from breast cancer topic • Need 75% reduction in hazards to match literature recurrence
Exact cure point in early NSCLC is unknown • If use 5-8 years cure period in EAG model, pembrolizumab DFS lower than placebo = clinically implausible	Agree pembrolizumab overall DFS shouldn't decline below placebo • Significant uncertainty in cure point **and** reduction in hazards ↳ Reduction in hazards depends on rate of decline predicted by DFS curve and ultra-late recurrence rate • If only change reduction in hazards, cannot expect model to continue to provide plausible outcomes given both cure rate and cure point in combination are unknown
OS HR favours placebo arm for most of time horizon (years 5-26), after which HR=1 → clinically implausible	HR driven by higher recurrence rate in pembrolizumab after year 3 • If recurrence higher between year 3-5, plausible that higher pembrolizumab HR delayed until after year 5

Abbreviations: NSCLC, non-small-cell lung cancer; HR, hazard ratio; DFS, disease free survival; OS, overall survival

Key Issue: DFS models

• Back to DFS discussion

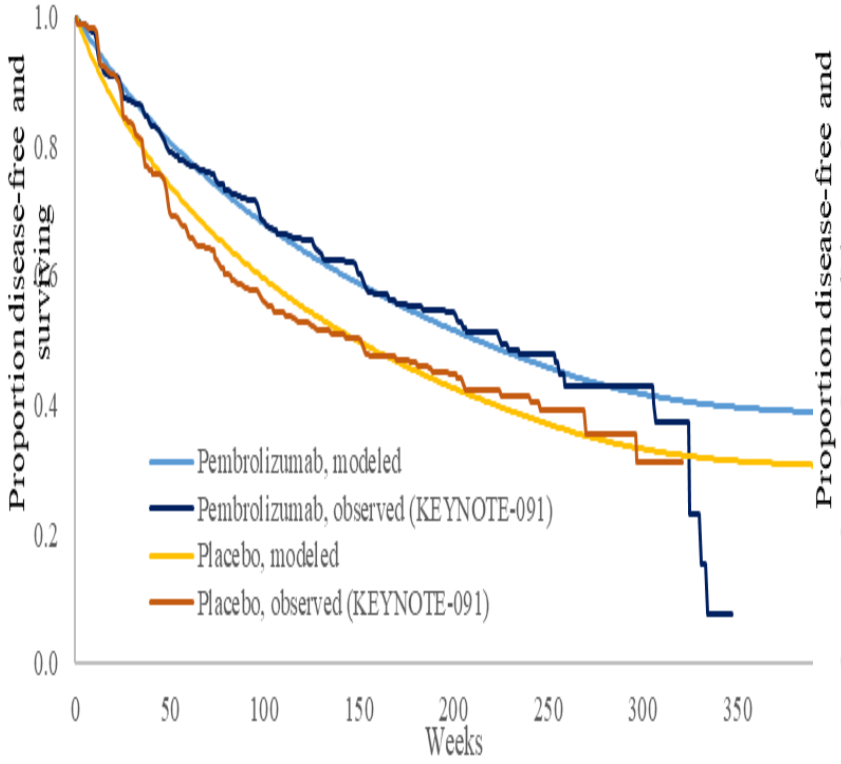
Company comments about EAG DFS modelling	EAG response
Inappropriate to conclude evidence of treatment waning based on limited data • DFS curve separation: year 1 ([redacted]%), 2 ([redacted]%), 3 ([redacted]%), 4 ([redacted]%) • Small increase in year 2 but otherwise relatively consistent • Gap only meaningfully narrows after 4 years, but at this point 2/3rds censored and only 19 events	Disagrees that decrease in DFS advantage from [redacted]% to [redacted]% (year 2-4) is not meaningful • Limited year 5 data available, but no other data to inform modelling • TA830 (waning accepted) - similar trial data limitations in final year
No curative advantage of pembrolizumab modelled (only delayed recurrence) Contrary to clinical expectation: • Extrapolations showing improved cure rate considered plausible • 5-year cure point reasonable – do not use differential cure points by arm • Expect adjuvant therapy to improve cure probability, not delay recurrence	Clinically plausible that pembrolizumab leads to higher proportion cured but does not align with best fit DFS projection
Differential distributions contrary to TSD14 – need stronger evidence Alternative: generalised gamma / log-normal: • Follows TSD14, good visual/statistical fit and clinically plausible projection • Can examine alternative cure points without curves crossing • No clinically unexpected early convergence of DFS curves • OS HR converge by 10 years (no long-term benefit in non-cured patients) • Reasonable ultra late recurrences (placebo: 0.4%; pembrolizumab: 0.6%) • Only limitation vs base case: greater underestimation of observed OS	Sufficient treatment waning evidence to justify differential distributions • If waning accepted, likely an allowable exception to TSD14 • Acknowledge alternative curves provide significantly better fit than company base case. If waning rejected, use these curves

Abbreviation: DFS, disease free survival; TSD, technical support document; OS, overall survival; HR, hazard ratio

Key Issue: Modelled DFS

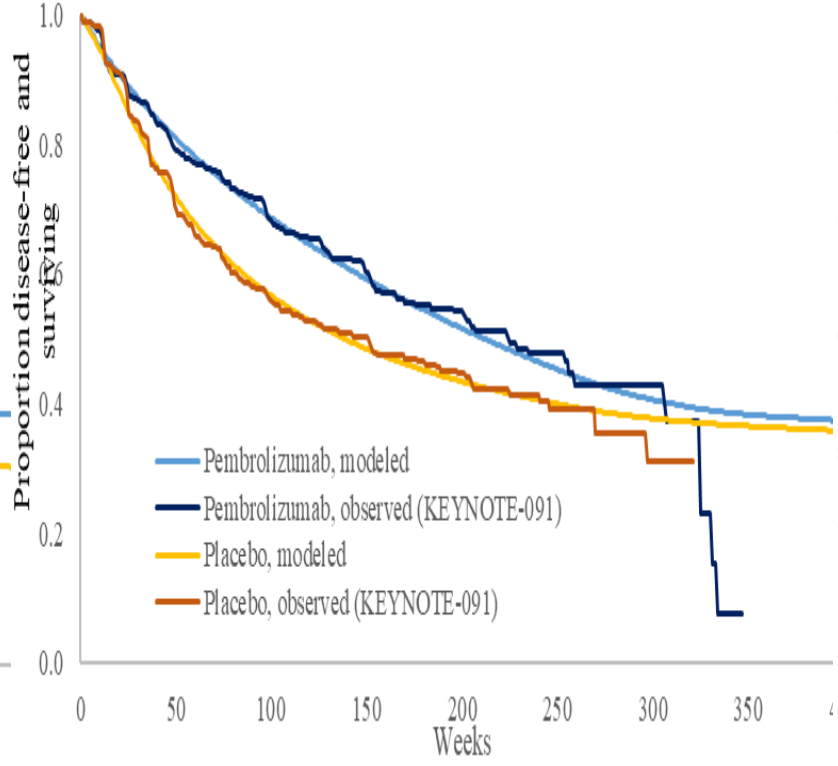
Company

Placebo: log-normal / log-normal
Pembrolizumab: log-normal / log-normal



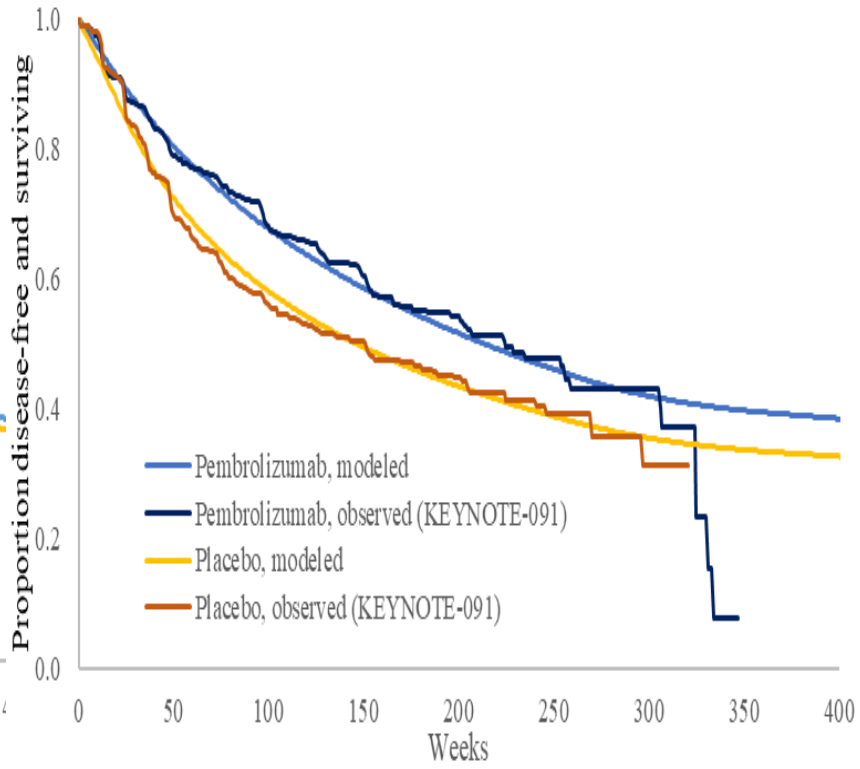
EAG

Placebo: generalised gamma / gompertz
Pembrolizumab: exponential / log-normal



Alternative

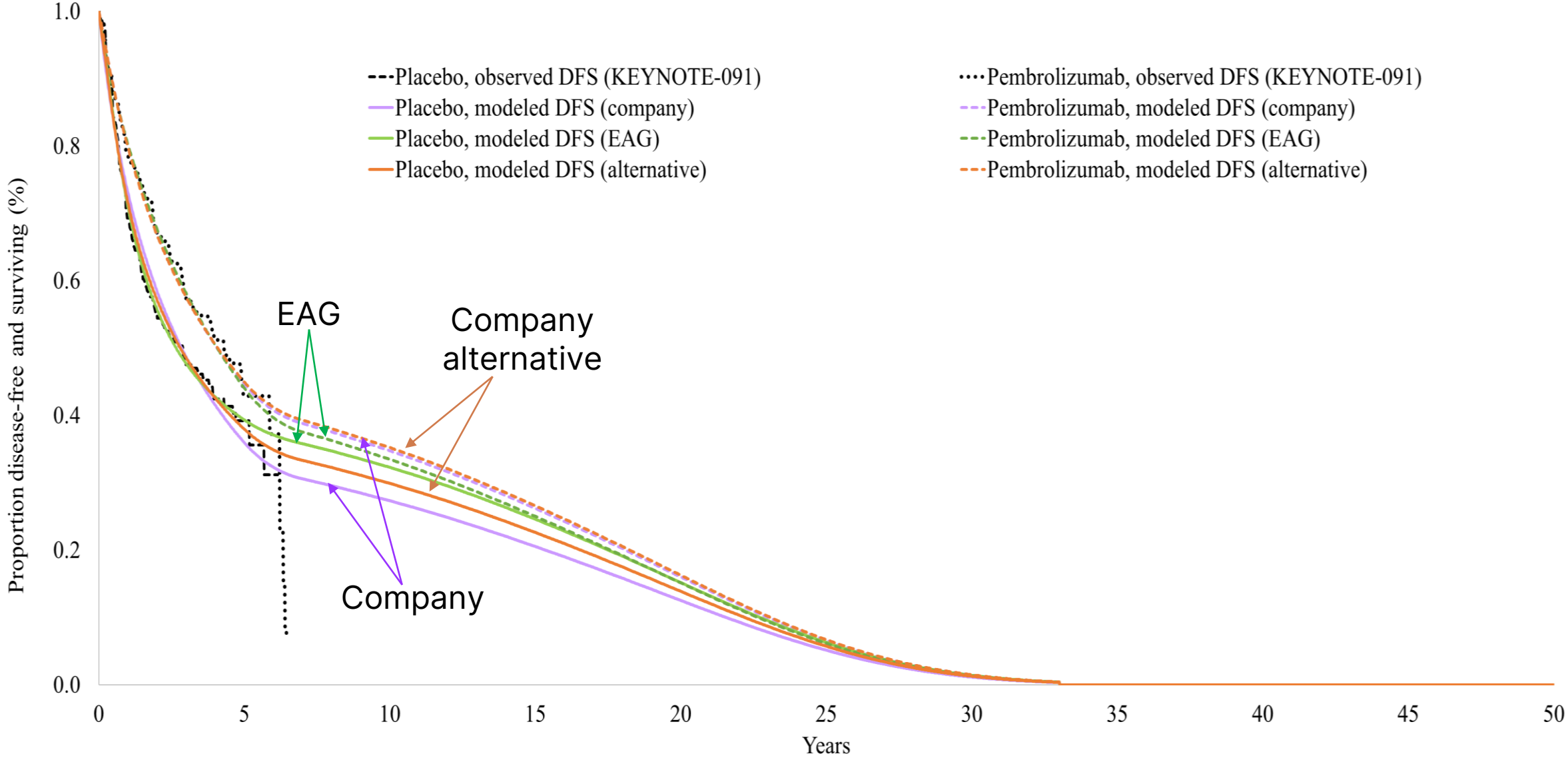
Placebo: generalised gamma / log-normal
Pembrolizumab: generalised gamma / log-normal



Abbreviations: DFS, disease free survival

Key Issue: DFS models

- Back to 10-year DFS extrapolation

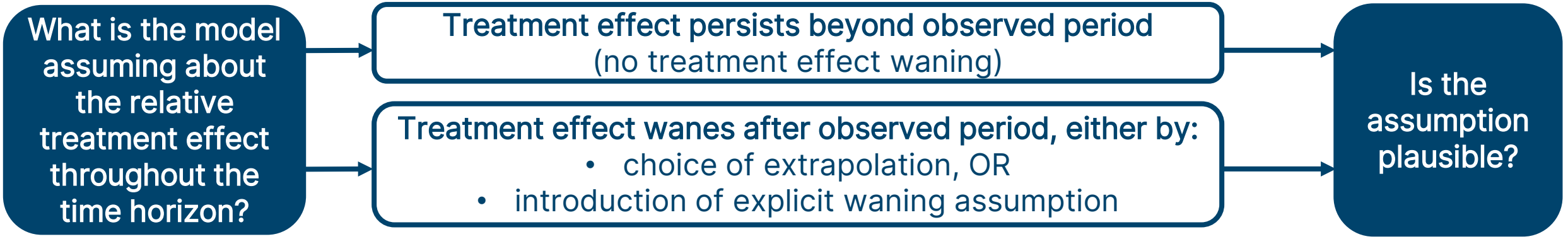


Abbreviations: DFS, disease free survival

Life years gained from each model assumption

LYG (years)	Pembrolizumab	Placebo	Incremental	Difference between start ages
Starting age: 64.3 years				
Company (base case)	9.11	8.01	1.10	-
Alternative DFS curves	9.15	8.21	0.94	-
EAG	9.03	8.42	0.61	-
Starting age: 68.4 years				
Company	8.55	7.57	0.98	-0.12
Alternative DFS curves	8.58	7.74	0.87	-0.7
EAG (base case)	8.50	7.88	0.62	+0.1

Abbreviations: LYG, life years gained



Consider:

1. Is the modelled treatment effect consistent with the observed data?
2. Is clinical trial follow-up long enough to provide estimate of treatment effect waning (also consider observational and real-world data)?
3. Is there evidence to support a sustained treatment effect or effect waning from another technology with same or similar mechanism of action?
4. Does a stopping rule apply? Is treatment effect likely to continue following stopping treatment?
5. Are the hazard rates of key clinical inputs plausible? Consider the plots of smoothed empirical time-varying hazard ratios from pivotal trial or MAIC
6. Are the model outputs plausible? Are they supported by clinical expert opinion?
7. What impact do scenarios of different treatment effect waning assumptions have?

Treatment effect waning (TEW) may be captured in a model by either:

- Make explicit TEW assumption (i.e. HR converges to 1 over a period of time)
- Implicitly include TEW through selected parametric survival models (i.e. accounted for in survival estimates)

NICE **Do not consider:**

Committee's preferred assumptions from previous appraisals (evidence base varies between each evaluation – consistency with precedent is not required)