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NICE National Institute for Health and Care Excellence

Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation (CDF review of TA578)

Lead team presentation

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ERG: Kleijnen Systematic Reviews

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Company: AstraZeneca

Date 07/04/2022

Issues remaining after technical engagement

Issue	Description	ICER Impact	Resolved?
PACIFIC generalisability (PD-L1 status)	Restriction of PACIFIC trial cohort to PD-L1 1% or more may limit its generalisability. In SACT cohort 12% had unknown status		Partially resolved
PACIFIC generalisability (dosing)	PACIFIC trial used weight-based dosing, which no longer reflects clinical practice and may [redacted] (ERG view)		Partially resolved
No QoL data update	No new QoL data was collected in PACIFIC. Model uses utility values from 2-year data cut		Unable to resolve
Durvalumab survival predictions	Inconsistency between OS observed in PACIFIC and that predicted by the model		No
Treatment effect duration	Uncertainty about whether treatment waning should be applied		No
Effect of non-NHS subsequent treatments	People in PACIFIC had immunotherapy after durvalumab, which does not reflect current NHS practice and could bias outcomes		No

PD-L1, programmed cell death ligand 1; OS, overall survival; ICER, incremental cost effectiveness ratio; QoL, quality of life; SACT, systemic anti-cancer therapy

Key: Large impact  Small/moderate impact  Unknown impact 

Summary of original appraisal (TA578) and CDF Review

TA578 Recommendation: Durvalumab monotherapy is recommended for use within CDF as an option for treating locally advanced unresectable NSCLC in adults whose tumours express PD-L1 on at least 1% of tumour cells and whose disease has not progressed after platinum-based chemoradiation only if:

- they have had concurrent platinum-based chemoradiation
- the conditions in the managed access agreement are followed

In a Cancer Drugs Fund (CDF) review:

- The comparators are the same as those in the original scope
- Key assumptions and issues listed in the managed access agreement to be revisited.
- Other key assumptions not addressed during managed access remain unchanged

Durvalumab (IMFINZI, AstraZeneca)

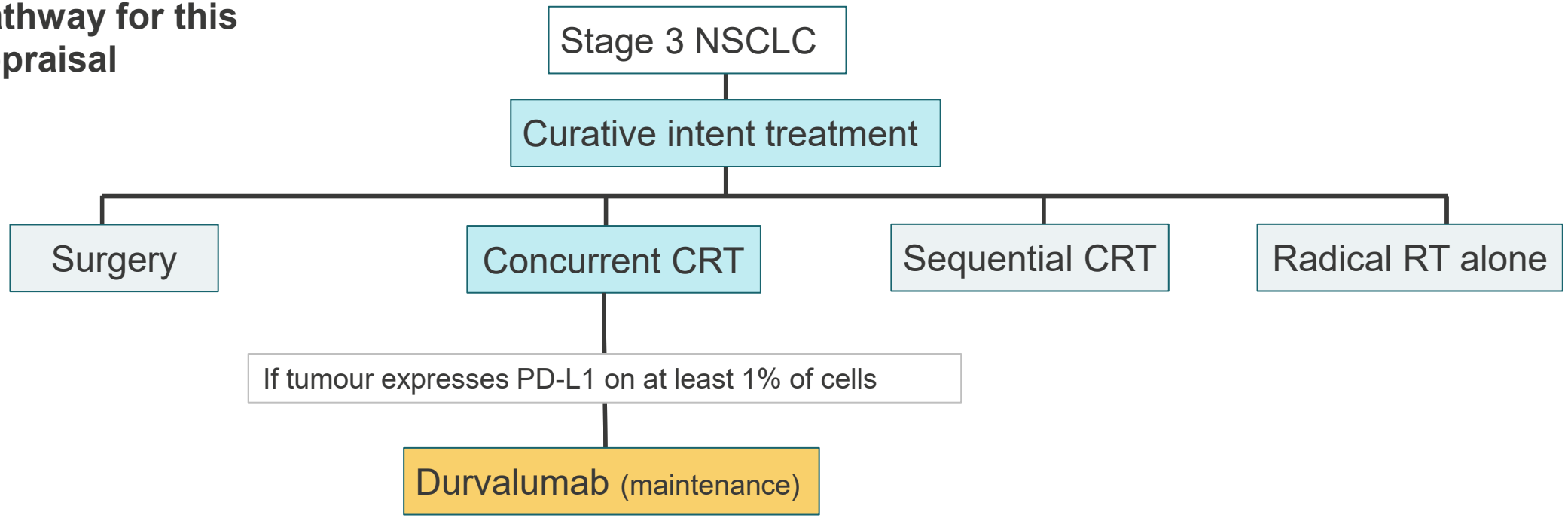
Marketing authorisation	Durvalumab as monotherapy is indicated for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults: • whose tumours express PD-L1 on at least 1% of tumour cells, and • whose disease has not progressed following platinum-based chemoradiation therapy
Mechanism of Action	Human monoclonal antibody that targets the 'programmed death ligand-1' (PD-L1) protein. Durvalumab blocks PD-L1 interaction with both PD-1 and CD80 on T cells, countering the tumour's immune-evading tactics and activating the immune system to attack the cancer.
Administration	• 10mg/kg every 2 weeks (weight-based dose), or • 1500mg every 4 weeks (fixed dose) • People with a body weight of 30kg or less must have weight-based dosing • Durvalumab is given until disease progression, unacceptable toxicity or for up to 12 months
List price	• £592 per 120mg vial • £2,466 per 500mg vial • Total mean cost of treatment (Q4W dose): [redacted] • There is a patient access scheme in place for durvalumab

PD-L1, programmed cell death ligand 1; Q4W, every four weeks

Disease background and treatment pathway

- Non-small-cell lung cancer (NSCLC) makes up around 85-90% of lung cancer, and 35,000 people were estimated to be diagnosed with NSCLC in 2018
- Most lung cancers are diagnosed at an advanced stage, when the cancer has spread to lymph nodes and other organs in the chest (stage 3) or to other parts of the body (stage 4)
- This appraisal focuses on stage 3 NSCLC, before metastatic disease develops and where treatment intent is usually curative
- Almost 15% of people with stage 3 NSCLC will survive for 5 years or more after diagnosis[1]

Pathway for this appraisal



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CRT, chemoradiation therapy; PD-L1, programmed cell death ligand 1; RT, radiotherapy

[1] Cancer survival in England: adult, stage at diagnosis and childhood-patients followed up to 2018 (2019) Office for National Statistics. Accessed November 2021

Patient and carer perspectives – Roy Castle Lung Cancer Foundation & National Lung Cancer Forum for Nurses (TA578)

- Lung cancer is a distressing condition, with complex symptoms and co-morbidities which affect performance status and quality of life
- People with lung cancer and their carers welcome new treatments which improve symptoms and survival without having a negative impact on quality of life
- Side effects and quality of life are important but especially so when a cure is not possible
- Durvalumab is well tolerated, reduces recurrent disease in this population and also has a significant survival benefit
- The significant survival benefit is important for this patient group where overall survival has not improved despite advances in chemotherapy and radiotherapy

"Patients have more chance of cure and of delayed recurrence. This marks a step change in the treatment of this disease"

"Treatments for lung cancer remain very limited; it is refreshing to see these new technologies being considered"

Clinician perspectives – Royal College of Radiologists, British Thoracic Oncology Group, 2 clinical oncologists

- There are no alternative adjuvant maintenance treatments in this setting. Since its introduction in the CDF, durvalumab has become the standard of care
- Older patients with more comorbidities and lower performance status have sequential CRT. The introduction of durvalumab has led to more people having concurrent CRT which is associated with better outcomes than SCRT, although there remains wide variation in clinical practice
- Durvalumab has increased cure rates for the first time in NSCLC. 5-year outcomes from PACIFIC trial show very clinically meaningful overall survival improvement – would expect durvalumab to improve patient quality of life
- Durvalumab is generally well tolerated, although a significant proportion of people had grade 3 or 4 toxicities in PACIFIC (e.g., pneumonitis). Patients should be fully informed of the risks, well enough to undergo treatment and have no contraindications to immunotherapy
- Increased monitoring requirements for durvalumab compared with chemotherapy due to wide range of potential toxicities

"The expertise of delivering immunotherapy (durvalumab) is already business as usual for all oncology units"

"Beginning to believe that this [durvalumab] may be better than surgery for stage 3 patients"

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SCRT, sequential chemoradiation therapy; CCRT, concurrent chemoradiation therapy; NSCLC, non-small-cell lung cancer; CDF, cancer drugs fund

Recap: Clinical effectiveness – PACIFIC trial (NCT02125461)

- Adults with locally-advanced unresectable stage 3 NSCLC, whose disease has not progressed following at least 2 cycles of concurrent platinum-based chemoradiation
- WHO performance status score 0 or 1
- Estimated life expectancy of 12 weeks or more
- Any PD-L1 status
  - Only the PD-L1 1% or more cohort was used to inform this appraisal

The PACIFIC trial included 8 UK patients across 3 centres

N=713, 2:1 randomisation stratified by age, sex and smoking history

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Durvalumab 10mg/kg Q2W for up to 12 months
- N=476 (any PD-L1 status)
- **N=212 (PD-L1 1% or more)**

Key outcomes collected
- OS
- PFS
- TTP
- HRQoL
- Subsequent treatments

Matching placebo Q2W for up to 12 months
- N=237 (any PD-L1 status)
- **N=91 (PD-L1 1% or more)**

Retreatment for patients who experienced disease control at the end of 12 months treatment, but progressed during follow-up. Alternatively, additional treatment upon disease progression.

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Q2W, every two weeks; OS, overall survival; PFS, progression free survival; TTP, time to progression HRQoL, health related quality of life; NSCLC, non-small-cell lung cancer; PD-L1, programmed cell death ligand 1

Recap: Decision problem

	Decision problem (original scope)	Committee preference
Population	Adults with locally advanced, unresectable non-small cell lung cancer whose disease has not progressed after platinum-based chemoradiation therapy	Committee heard that those undergoing concurrent CRT may be healthier and have better responses than those getting sequential CRT. It optimised the population to only those having concurrent CRT as the PACIFIC trial only included people having concurrent CRT Also only those with PD-L1 1% or more were considered after regulatory approval was granted
Comparators	Best supportive care	Defined as surveillance every 6 months for 2 years and a chest CT scan at least every year
Outcomes	• OS • PFS • Response rates • Adverse effects • HRQoL	Company to collect updated overall survival and subsequent treatment data from the trial, and overall survival from the SACT cohort, during the CDF period

PD-L1, programmed cell death ligand 1; OS, overall survival; PFS, progression free survival; HRQoL, health-related quality of life

Recap: Key uncertainties from CDF entry

Uncertainties in TA578		Committee preference
Uncertainty in long-term survival benefit	Data immaturity and few patients at end of Kaplan-Meier curve meant durvalumab PFS extrapolations were uncertain	Preferred log-normal but accepted scenario analysis with generalised gamma pending long-term trial data
Treatment effect duration uncertainty	Long-term treatment effect after stopping treatment is plausible but its duration is uncertain	A 3- to 5-year treatment effect duration is plausible but highly uncertain. Further data would reduce this uncertainty
Uncertainty about effect on cure rates	Durvalumab is a potentially curative treatment. Cure rate models need mature data	PACIFIC data were too immature for a cure model to be robust, 5-year data could inform cure rate decisions

CDF Data collection agreement

- 5-year PFS and OS data from PACIFIC should resolve clinical uncertainty regarding the longer term survival benefit of durvalumab versus standard of care
- Data on subsequent therapies from PACIFIC will also be collected to update the frequency, duration and costs in the economic model
- Data will be collected via Public Health England's routine population-wide datasets, including SACT, to support data collected in PACIFIC

OS, overall survival; PFS, progression free survival; SACT, systemic anti cancer therapy

Summary of key clinical evidence

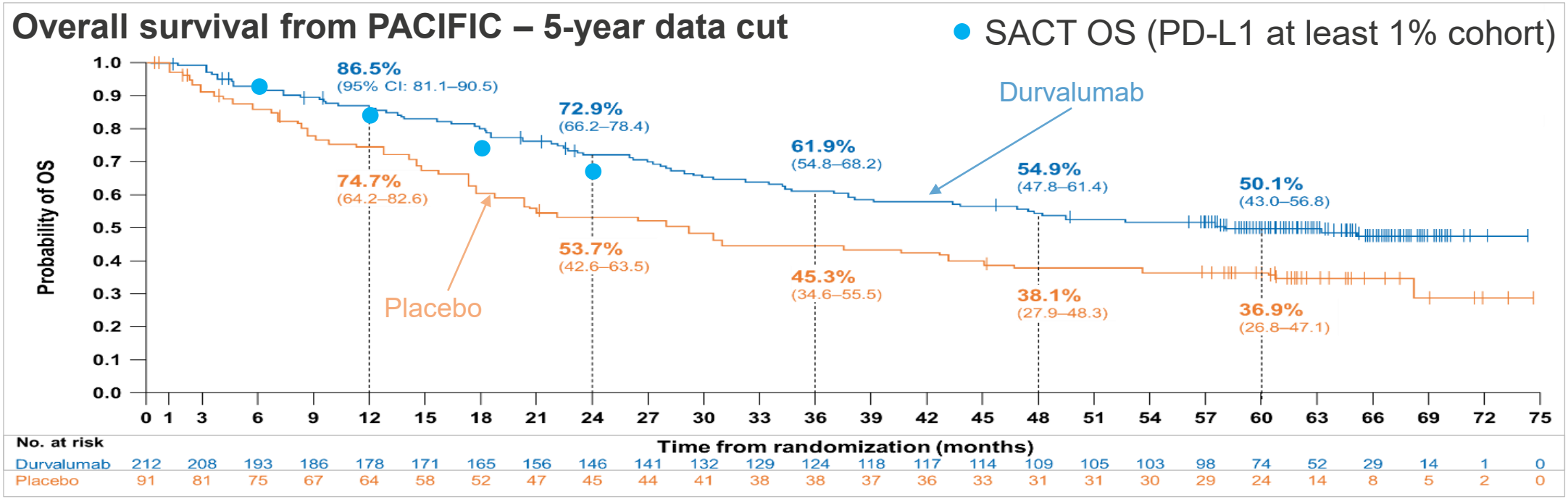
	Original appraisal		Updated outcomes after CDF		
	PACIFIC (Mar 2018)		**PACIFIC (Jan 2021)**		**SACT***
Outcome	Durvalumab (n=212)	Placebo (n=91)	Durvalumab (n=212)	Placebo (n=91)	Durvalumab (n=522)
Median follow up (months)	26.9	21.1	34.2		14.3
Median PFS, months (95% CI)	23.9 (17.2, NR)	5.6 (3.6, 11.0)	24.9 (16.9, 38.7)	5.5 (3.6, 10.3)	Not collected
PFS hazard ratio (95% CI)	0.44 (0.31, 0.63)		0.47 (0.35, 0.64)		
OS rate at 12 months (95% CI)	86.5% (81.1, 90.5)	74.7% (64.2, 82.6)	86.5% (81.1, 90.5)	74.7% (64.2, 82.6)	85% (82, 88)
OS rate at 24 months (95% CI)	72.8% (66.2, 78.4)	53.6 (42.5, 63.4)	72.9% (66.2, 78.4)	53.7 (42.6, 63.5)	68% (62, 74)
Median OS, months (95% CI)	NR (NR, NR)	29.1 (17.7, NR)	63.1 (43.7, NE)	29.6 (17.7, 44.7)	NR
OS hazard ratio (95% CI)	0.54 (0.35, 0.81)		0.61 (0.44, 0.85)		N/A

NE, not estimable; NR, not reached

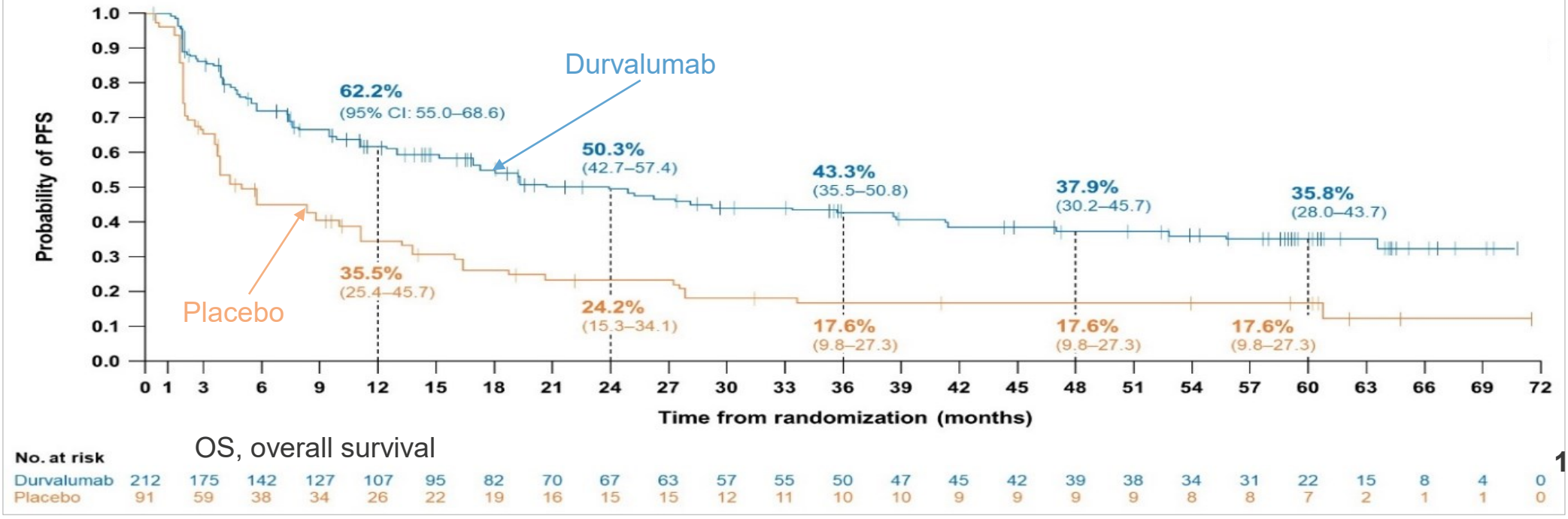
* Data presented here is for the "SACT PD-L1 1% or more" restricted cohort (PD-L1 unknown, not possible or unquantifiable removed)

Kaplan-Meier curves

Overall survival from PACIFIC – 5-year data cut



Progression-free survival from PACIFIC – 5-year data cut



OS, overall survival

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Clinical Effectiveness

Issue: Generalisability of PACIFIC dataset to clinical practice - PD-L1 status

Background: 12% of SACT cohort were PD-L1 unknown. Blueteq criteria allow durvalumab use if PD-L1 score unavailable despite reasonable attempt. Unlikely to change post-CDF review

- All patients in PACIFIC cohort of interest had tumours with PD-L1 of 1% or more; PD-L1 unknowns were excluded
- Durvalumab's marketing authorisation (MA) is limited to PD-L1 of 1% or more. NICE appraises within the MA, but the generalisability of the evidence to clinical practice should be assessed

Company: OS rates are similar between the full and restricted SACT cohorts and PACIFIC. OS at 24 months: 67% (SACT full cohort), 68% (SACT cohort restricted to PD-L1 of 1% or more), 73% (PACIFIC)

- Key experts stated around 5% of people having durvalumab have unknown PD-L1 status
- The PD-L1 unknown population is not covered by the NICE scope for this appraisal
- PD-L1 testing was not mandated in PACIFIC: PD-L1 unknowns cannot be used in the analysis

Clinical experts: the actual PD-L1 status of "unknown" patients will likely reflect the overall NSCLC population: 25-30% would be PD-L1 less than 1% and may derive less benefit from durvalumab

ERG: still a risk that patients who do not have tumours that express PD-L1 will experience reduced effectiveness, and this may have an unknown impact on cost-effectiveness

SACT, systemic anti cancer therapy; PD-L1, programmed cell death ligand 1; OS, overall survival,

Issue: Generalisability of PACIFIC to UK practice - Dosing

Background: the PACIFIC trial only used weight-based dosing (10mg/kg, Q2W)

- An unreported number of people in the SACT cohort had a fixed dose (1500mg, Q4W)
- Fixed dose is company base case after company key experts stated it is now clinical practice
- **ERG:** PACIFIC may [redacted] (where fixed dose is used) as heavier patients having fixed dose may have lower durvalumab serum concentrations

Company: cited EMA concluding statements "[redacted]" and "there are no anticipated clinically significant differences in efficacy and safety [between weight based and fixed dosing]"

- Provided scenario analysis showing that choice of dosing has minimal ICER impact
- Mean body weight in PACIFIC durvalumab arm was 72.6kg, at 10mg/kg this would correspond to a dose of 1,452mg Q4W dose, very close to the fixed dose (1,500mg)
- Company cited previous appraisals where weight-based dosing was switched to longer treatment interval fixed dose, for example:
  - Avelumab maintenance for urothelial cell cancer (ID3735): ERG concluded they were not concerned with difference between weight-based and fixed dose
  - Avelumab in combination with axitinib for renal cell carcinoma (TA645): Shift from weight based (used in trial) to fixed dose. Committee accepted comparable effectiveness

Q2W, every 2 weeks; Q4W, every 4 weeks; NSCLC, non-small-cell lung cancer; ERG, external research group

Issue: Generalisability of PACIFIC to UK practice - Dosing

Clinical experts: most UK centres use fixed dose to a) increase convenience b) alleviate capacity issues in day units

- Patients below 30kg are extremely rare in adult oncology practice
- "In line with our experience of other PD-L1 [or] PD-1 inhibitors I do not think the efficacy of durvalumab is likely to be affected by this dosing regimen"

ERG: does not question the conclusions of the EMA that the fixed dose is an acceptable alternative to the weight-based dosing

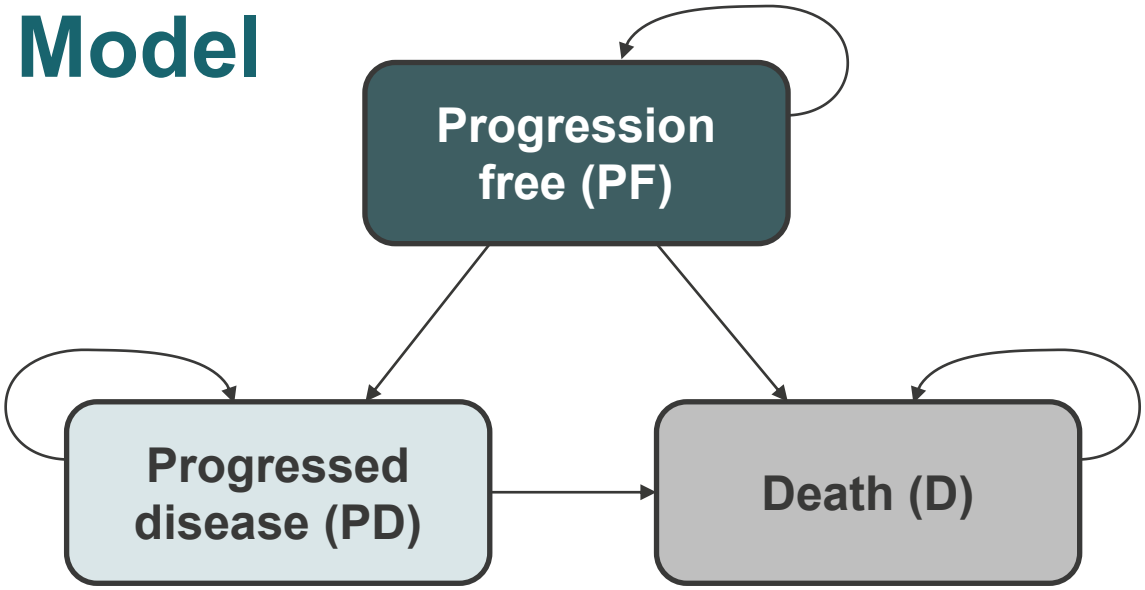
- However, the EMA report indicates [redacted]
- This could have implications for cost-effectiveness in comparison with standard care

NICE Tech Team: In TA713, nivolumab for advanced NSCLC, a similar situation arose with a weight-based to fixed dose move accepted by the committee despite the lack of direct evidence

Is the fixed dose likely to be used in clinical practice?
If so, is the PACIFIC dataset generalisable to NHS clinical practice?

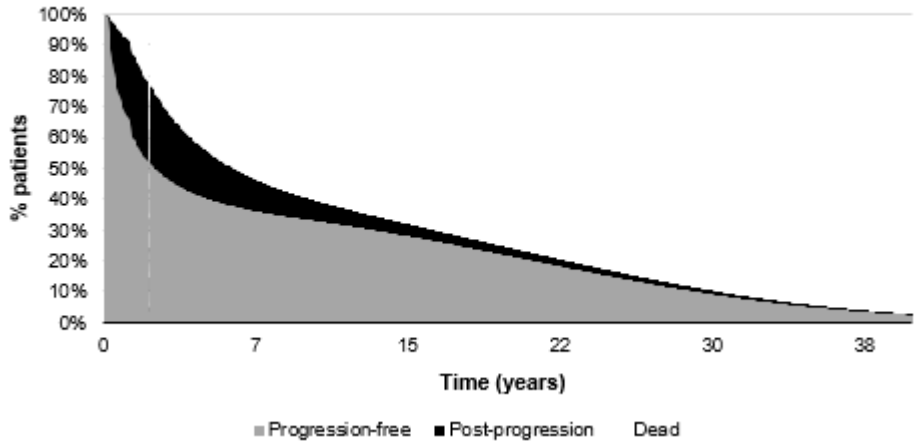
Cost Effectiveness

Cost-effectiveness model structure – Semi-Markov Model

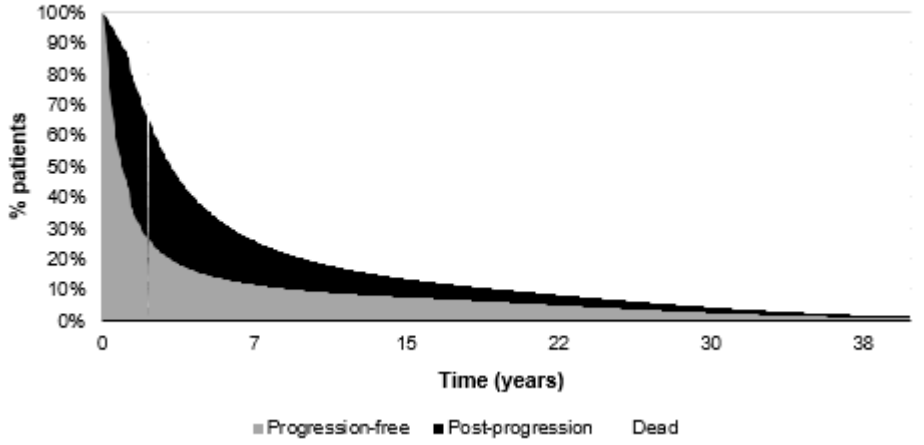


Health State or Parameter	Data Source (PACIFIC 5-year data unless otherwise stated)
PF → PF transition probability	PFS extrapolation (generalised gamma for both arms)
PF → PD transition probability	TTP extrapolation (generalised gamma for both arms)
PD → D transition probability	PPS extrapolation (log-logistic, arms pooled)
PF → D probability	Difference between PFS and TTP
Utility	PACIFIC 2-year data

Durvalumab – Company base case - Markov Trace (proportion of cohort in each state)



Standard of care – Company base case – Markov Trace (proportion of cohort in each state)



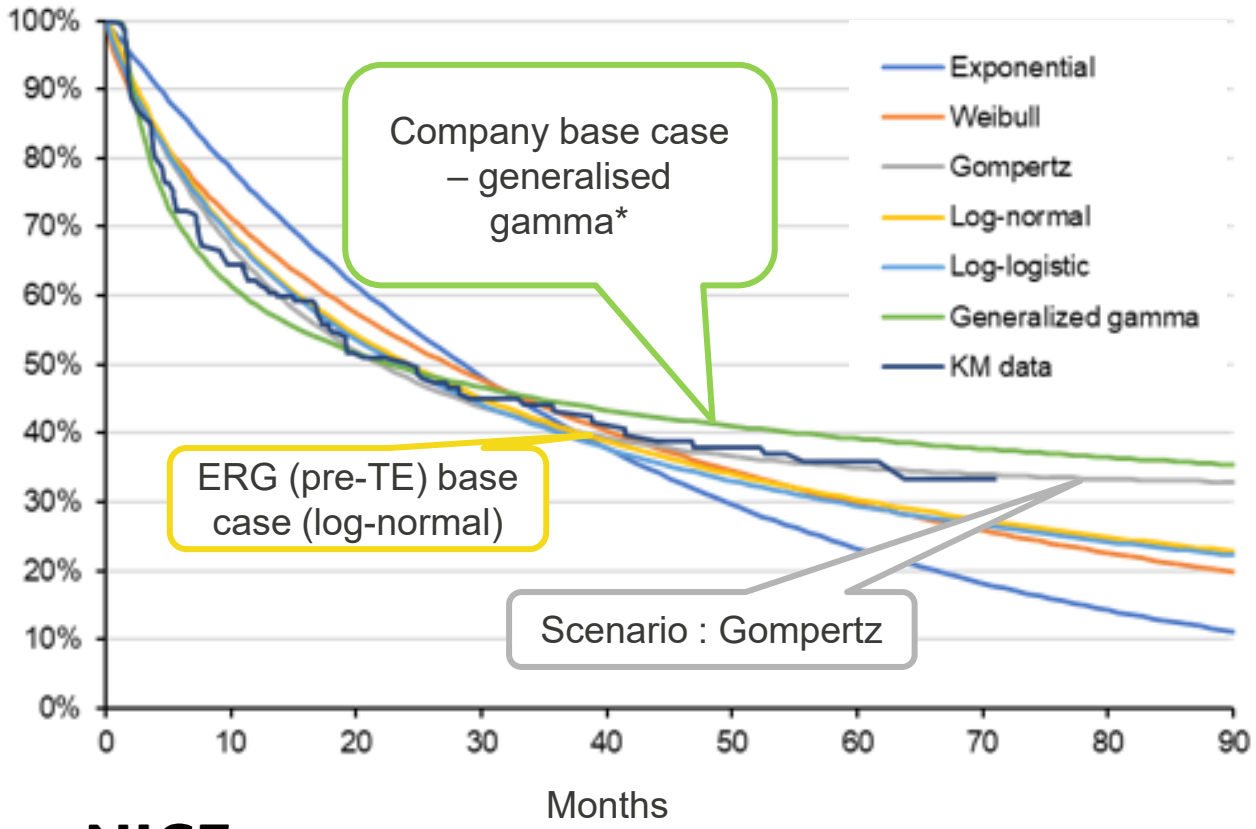
NICE PFS, progression free survival; TTP, time to progression; PPS, post progression survival

Issue: Durvalumab survival predictions

Background: company modelled estimates for OS in durvalumab arm exceed PACIFIC. OS primarily driven by PFS extrapolations in the model. Generalised gamma is company base case

- ERG prefers generalised gamma for durvalumab PFS with 3 or 5 year treatment effect waning
- Company's modelled estimates placebo arm OS were lower than in PACIFIC, but the company's generalised gamma PFS distribution had the best internal consistency. ERG therefore did not select alternative PFS distribution for placebo arm

Durvalumab progression-free survival extrapolations



Company: log-normal is pessimistic, especially considering patients progression free at 5 years are "no longer considered at risk. . ." (Company key experts)

- 5 UK clinical oncologists preferred generalised gamma or Gompertz distributions to extrapolate PFS
- Long-term OS estimates from model generally comparable with PACIFIC
- Chosen curves reflect small chance of progression after 5 years PFS

OS, overall survival; PFS, progression free survival *Note: The generalised gamma was also used in the ERG base case, but with additional treatment effect waning that is not show on this graph

Issue: Durvalumab survival predictions

Trial observed and modelled PFS, effect of PFS distribution

Scenario	PFS Distribution*	3yr PFS	5yr PFS	10yr PFS	15yr PFS	20yr PFS
PACIFIC Trial**	-	43%	36%	-	-	-
Company Base Case	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG Scenario	Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG/Company Scenario	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Trial observed and modelled OS, effect of PFS distribution

Source	PFS Distribution*	3yr OS	5yr OS	10yr OS	15yr OS	20yr OS
PACIFIC Trial**	-	62%	50%	-	-	-
Company Base Case	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG Scenario	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG/Company Scenario	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

OS, overall survival; PFS, progression free survival

* These tables show effect of PFS distribution on progression free survival and overall survival as predicted by the model

** The survival rates shown for the PACIFIC trial are derived from the PD-L1 1% or more cohort of interest

Issue: Durvalumab survival predictions

ERG: a remaining concern is the underestimation of placebo OS and slight overestimation of durvalumab OS toward the end of the trial data

- The choice of lognormal for durvalumab PFS was not regarded as clinically plausible by experts but it highlights the possible impact of long-term uncertainty around PFS on the ICER
- Further uncertainty comes from lack of detail on estimation of time-to-progression (TTP) (i.e what is the justification for setting TTP extrapolation in line with PFS – time-to-event analysis is needed)
- The full impact of the uncertainty around extrapolating PFS and modelling OS is not explored

OS, overall survival; PFS, progression free survival; ICER, incremental cost effectiveness ratio

Which extrapolation does committee prefer for PFS in the durvalumab arm?

Issue: Treatment waning

Background: company did not apply treatment waning effect in base case

- ERG questioned this, as the hazard ratios seen in the PACIFIC trial for OS and PFS approach 1 (no treatment effect) at around 60 months

Company: chosen extrapolations already incorporate any treatment waning effect

- People who are progression free at 5-years are at very low risk of progression
- Kaplan-Meier curves for durvalumab and placebo remain separate at 60 months - it would be inappropriate to apply treatment waning at 5 years after treatment starts
- Did scenario analyses showing effect of waning 7.5 and 10 years after starting treatment

Clinical experts: would expect to see either no or only minor waning of treatment effect of durvalumab 2 years after stopping treatment

ERG: requested graphs plotting the model implied hazard ratios (HR) over time were not provided

- Company's smoothed hazard ratio plots [redacted] Unclear whether the chosen distributions capture this
- Explored treatment waning scenarios (PFS and TTP, 3 and 5 years after treatment start); these have significant effect on ICER, implying waning not captured in company distributions
- 3 years might be overly conservative, but 5 years potentially biased in favour of durvalumab

OS, overall survival; PFS, progression free survival; ICER, incremental cost effectiveness ratio

Treatment waning – recent NSCLC precedents

Intervention (TA #)	NSCLC Population	Length of treatment	Committee preferred waning assumption
Pembrolizumab (TA770)	Untreated metastatic squamous	2 years	5 years for OS and PFS after stopping treatment
Nivolumab (TA724)	Untreated metastatic	2 years	3 to 5 years for OS after stopping treatment
Nivolumab (TA713)	Locally advanced or metastatic non-squamous (PD-L1 positive)	2 years	3 years after stopping treatment
Atezolizumab (TA705)	Untreated metastatic (PD-L1 50% or more)	No stopping rule	Range of scenarios (including 3, 5 and 10 years after starting treatment)
Pembrolizumab (TA683)	Untreated metastatic non-squamous	2 years	Gradually decreasing treatment effect from 3 to 5 years

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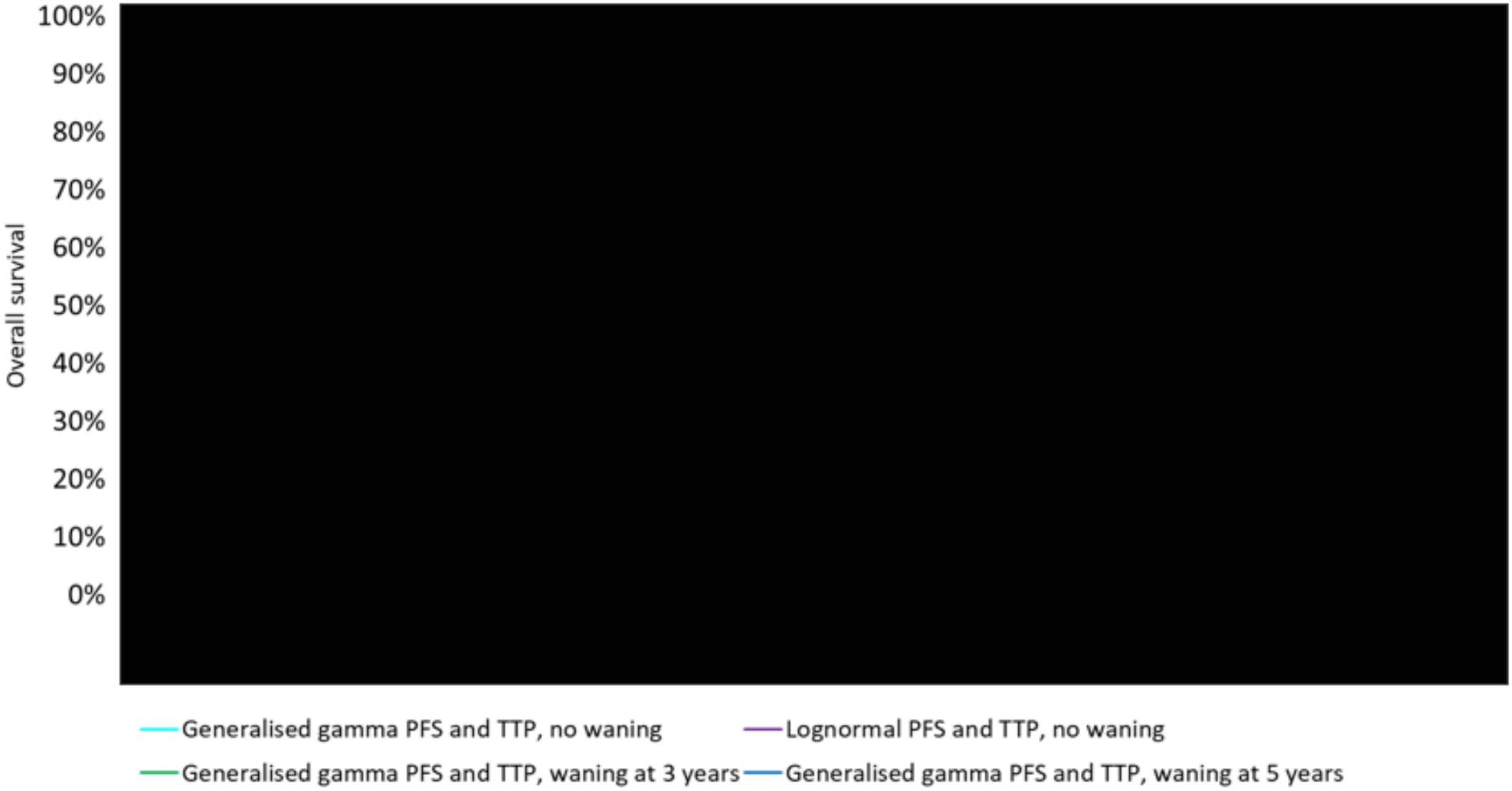
What are committee conclusions on a treatment waning effect in this appraisal?

Summary of impact of durvalumab PFS and waning assumptions

Impact of durvalumab PFS and TTP curves and waning assumptions on modelled OS



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Issue: Subsequent treatments

Background – Some patients had immunotherapy (IO) after durvalumab discontinuation in PACIFIC; does not reflect current NHS practice: (NHSE have stated this may change in near future)

- **ERG:** Effect of subsequent immunotherapy could bias outcomes in favour of durvalumab

Company: fewer patients in the durvalumab arm had subsequent immunotherapy, and for less time

- RPSFTM and M2SM treatment switching analyses showed little effect of subsequent IOs
- Removing subsequent immunotherapies from the durvalumab arm would not significantly impact OS but would reduce costs, so base case with no adjustment is conservative

PACIFIC: Proportion of people having subsequent treatment

	PACIFIC 5-year data	
	Durvalumab	Placebo
Subsequent treatment, n (%)	[redacted]	[redacted]
Immunotherapy, n (%)	[redacted]	[redacted]
Mean duration (months)	[redacted]	[redacted]

Switching analyses

Dataset	HR (95% CI)
Primary ITT*	0.68 (0.53-0.87)
RPSFTM*	0.70 (0.55-0.88)
M2SM*	0.69

Clinical experts: majority of patients in UK would not be eligible for a second immunotherapy. Other malignancies have evidence base for using subsequent immunotherapies however in lung cancer trials are ongoing and the potential benefit is hard to quantify

ERG: reasonable that the most plausible treatment effect likely in practice is not far from the ITT value, perhaps slightly higher as few durvalumab patients would benefit from subsequent treatment

- Did exploratory scenario analyses removing subsequent immunotherapy costs from both arms

RPSFTM, rank preserving structural failure time model; M2SM, modified two stage method; NHSE, NHS England

* The treatment adjusted analyses include includes all patients, regardless of PD-L1 status

Innovation and Equalities

Innovation:

- “Durvalumab is the first and only immunotherapy option that is available in the locally-advanced stage 3 setting, for treatment with curative intent” – Company submission TA578 (2019)
- “Durvalumab may be innovative. However, all relevant benefits of the technology are captured in the QALY.” – FAD for TA578

Equality issues:

- “No relevant equality issues were found” – FAD for TA578
- No equality issues were reported in professional organisation or clinical expert submissions for this appraisal

Cost Effectiveness Results

Scenario	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER* (£/QALY)
1. Company base case: Generalised gamma for durvalumab PFS					
Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	11,507
Standard of Care	[redacted]	[redacted]			
2. Company base case: Generalised gamma for durvalumab PFS - probabilistic					
Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	13,231
Standard of Care	[redacted]	[redacted]			
3. ERG base case 1: Company base case with treatment waning for PFS & TTP at 3 years					
Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	20,345
Standard of Care	[redacted]	[redacted]			
4. ERG base case 1: (Probabilistic)					
Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	21,718
Standard of Care	[redacted]	[redacted]			
5. ERG base case 2: Company base case with treatment waning for PFS and TTP at 5 years					
Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	15,871
Standard of Care	[redacted]	[redacted]			
6. ERG base case 2: (Probabilistic)					
Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	17,041
Standard of Care	[redacted]	[redacted]			

*These are not decision making ICERs and do not include comparator/subsequent treatment confidential discounts which could make the ICERs substantially higher or lower. Note: All ICERs are deterministic unless otherwise stated
PFS, progression free survival; QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio

Cost Effectiveness Results – Scenario Analyses

Scenario	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER* (£/QALY)
7. ERG Scenario: Lognormal for durvalumab PFS					
Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	21,676
Standard of Care	[redacted]	[redacted]			
8. ERG Scenario: Gompertz for durvalumab PFS					
Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	12,577
Standard of Care	[redacted]	[redacted]			
9. Company scenario: Company base case with Q2W weight-based dosing					
Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	11,903
Standard of Care	[redacted]	[redacted]			
10. Company Scenario: Alternative utility values (Progressed disease utility of 0.713)					
Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	11,180
Standard of Care	[redacted]	[redacted]			
11. Company modified base case (with IO therapy costs removed)					
Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	23,427
Standard of Care	[redacted]	[redacted]			
12. ERG base case 1, (Company BC, 3 year treatment waning, IO therapy costs removed)					
Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	36,868
Standard of Care	[redacted]	[redacted]			
13. ERG base case 2, (Company BC, 5 year treatment waning, IO therapy costs removed)					
Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	29,915
Standard of Care	[redacted]	[redacted]			

NICE *These are not decision making ICERs and do not include comparator/subsequent treatment confidential discounts which could make the ICERs substantially higher or lower. ICERs on this slide are deterministic

Supplementary Slides

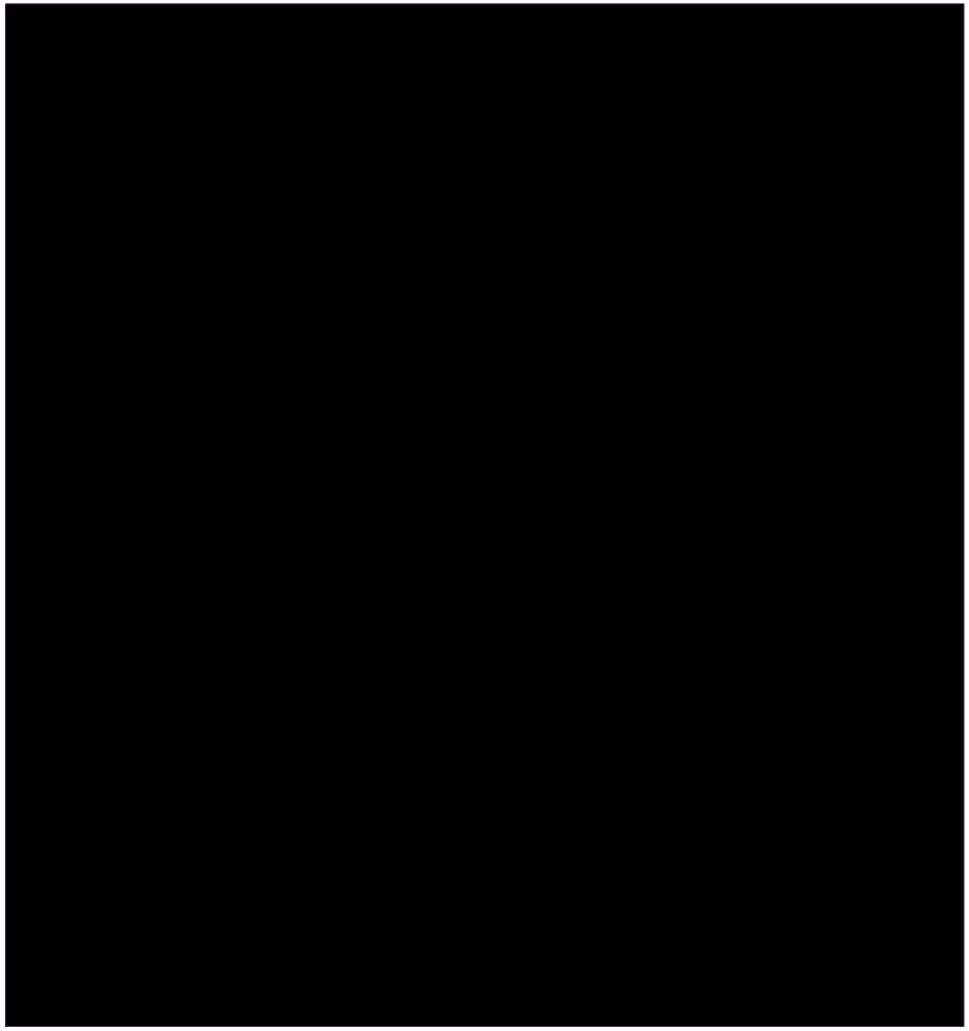
Cost Effectiveness Results – Waning Scenarios

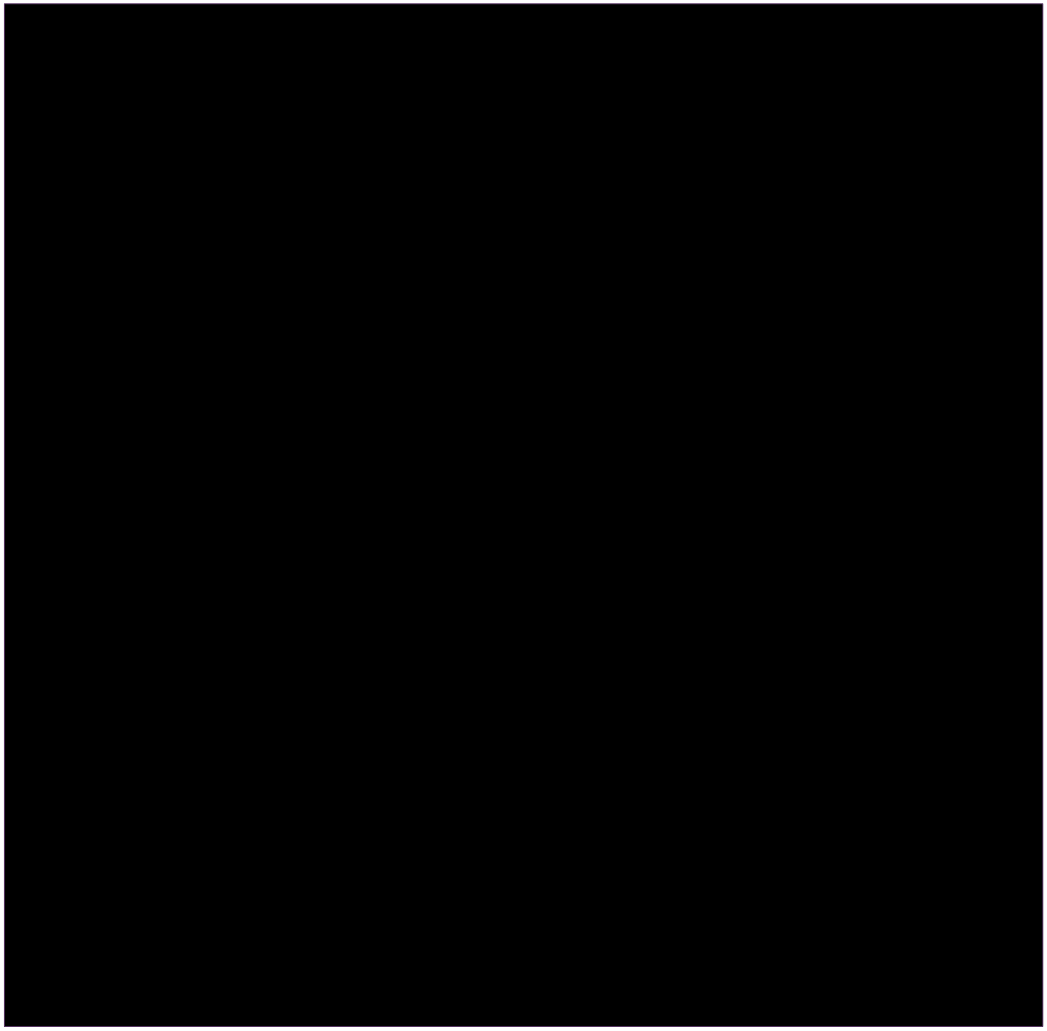
PFS Distribution	Waning starts	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Company base case (generalised gamma)	N/A	[redacted]	[redacted]	11,507
Generalised Gamma	3 years*	[redacted]	[redacted]	20,345
	5 years**	[redacted]	[redacted]	15,871
	7.5 years	[redacted]	[redacted]	13,442
	10 years	[redacted]	[redacted]	12,139
Gompertz	3 years	[redacted]	[redacted]	22,029
	5 years	[redacted]	[redacted]	18,032
	7.5 years	[redacted]	[redacted]	14,773
	10 years	[redacted]	[redacted]	13,246
Lognormal	3 years	[redacted]	[redacted]	21,806
	5 years	[redacted]	[redacted]	21,676
	7.5 years	[redacted]	[redacted]	
	10 years	[redacted]	[redacted]	

PFS, progression free survival; QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio
*ERG base case 1 **ERG base case 2

NICE Note: Waning is the return to the hazards of the standard of care arm. Treatment waning at 7.5 and 10 years had no effect on the ERG base case with lognormal durvalumab PFS extrapolation

PFS and OS smoothed hazard ratios





PFS, progression free survival; OS, overall survival; KM, Kaplan-meier

Issue: No additional QoL data collected in CDF

Background: company did not collect updated utility data from the PACIFIC trial for the 5-year data cut. This was in the CDF terms of engagement

Company: further data collection not listed in the CDF data collection agreement

- Impractical for patients to continue collecting QoL data for extended periods
- Company's approach to applying HSUs in the base case is conservative given the significant and proven long-term PFS benefit demonstrated with durvalumab at five years
- The same utility value is applied to both arms following progression which is also conservative.
- Conducted a scenario analysis using an alternative HSU (0.713) for progressed disease from TA713 (locally advanced or metastatic squamous NSCLC), which reduced the ICER

ERG: satisfied that the company sufficiently explored the impact of alternative utility values in the model

Utility values used in company base case model

Health state	Durvalumab	Placebo
Progression-free	0.803	0.827
Progressed	0.793	0.793

NICE HSU, health state utility; CDF, cancer drugs fund; PFS, progression free survival; QoL, quality of life; ICER, incremental cost effectiveness ratio

Model structure

Background: ERG would have preferred that company explore a partitioned survival model (PSM) approach, to fully explore the most appropriate survival method

- ERG: Company's semi-Markov model needs more assumptions than PSM, e.g., that post-progression survival (PPS) is same in both arms. Unclear if this is appropriate

Company: All plausible distributions for OS and PFS crossed which created a logical inconsistency preventing use of a PSM (figures below)

- The terms of the CDF prohibit development of new modelling approaches
- Pooling PPS data is conservative, scenario analysis provided to show effect of extrapolating from stratified PPS (each arm separately) and this reduces ICER minimally

ERG: the company explanation for the choice of model is valid, but seeing the results from a partitioned survival analysis would have reassured that no bias was introduced by the company's modelling approach

Recap: CDF Terms of engagement

Parameter	Terms of engagement -	Addressed in submission? (ERG opinion)
Population	Adults with locally advanced, unresectable non-small cell lung cancer whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed after concurrent platinum based chemoradiation.	Yes
Comparators	Durvalumab compared to standard care (agreed in TA578 as 6 monthly surveillance and annual chest CT scan)	Yes
Survival Outcomes	Use updated survival data from the PACIFIC trial and fully explore the most appropriate method to extrapolate survival outcomes	Partly
Assumption of cure	Use updated survival data to explore appropriateness of a cure assumption.	No
Treatment effect duration	Use updated survival data to explore the treatment effect after stopping treatment.	Yes
Utility values	Use more mature quality of life data to inform health state utilities	No
ICERs	The model should be able to replicate the key results from CDF entry, incorporate data collected during the CDF period and run key sensitivity and scenario analysis.	Yes