NICE National Institute for Health and Care Excellence

Part 1
[CIC] and [AIC] redacted

Atezolizumab monotherapy for untreated advanced non-small-cell lung cancer

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Company: Roche

ACM 1 11th March 2021

Key issues

- What duration of treatment effect should be used for pembrolizumab and atezolizumab?

Disease background

Overview of NSCLC

- Lung cancer is third most common cancer in the UK (~13% of all cancer)
- Around 80 to 85% of lung cancers are non-small cell lung cancer (NSCLC)
- More than 47,000 people are diagnosed with lung cancer each year in the UK, and there are over 35,000 deaths
- Prognosis is often poor due to late diagnosis

Subgroups and staging

- Molecular testing for EGFR mutations, ROS1 mutations, ALK rearrangements, or PD-L1 expression is recommended in all patients with NSCLC. PD-L1 testing is routinely offered to patients with NSCLC
- Determination of PD-L1 expression is used to judge suitability for checkpoint inhibitor therapy. A global study estimated that 22% of patients have high PD-L1 expression[1]
- The extent of disease is evaluated by staging. In 2017, around 65% of patients diagnosed with lung cancer in the UK had stage IIIb or IV disease.

This appraisal focuses on people with stage IV metastatic non-squamous or squamous NSCLC with high PD-L1 tumour expression and without EGFR- or ALK-positive mutation

NICE

1. Company submission

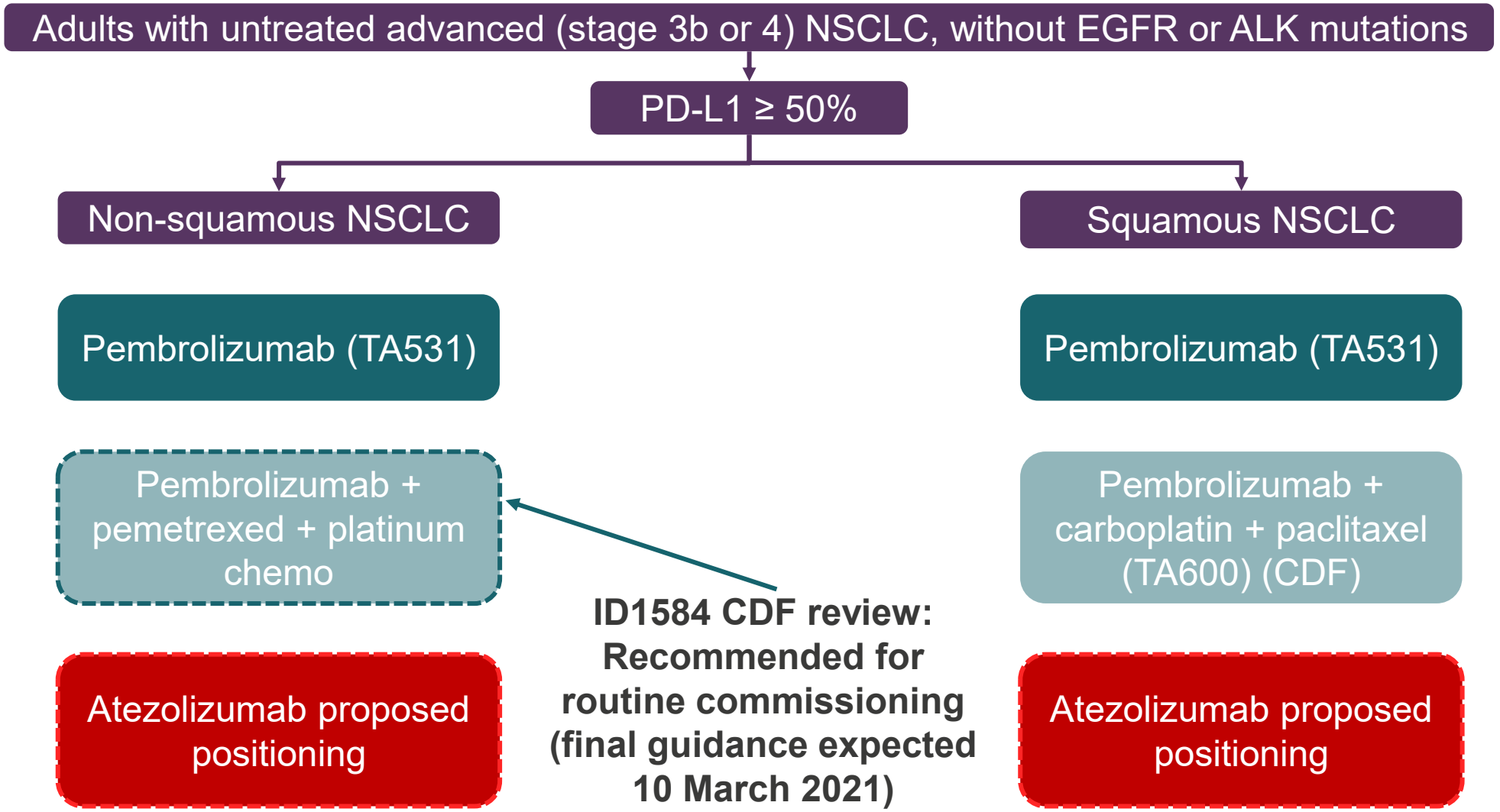
Clinical expert opinion

- Although survival is improving for patients with advanced NSCLC, there is still unmet need:
  - There is currently only one immunotherapy agent (pembrolizumab) available for this indication in patients with high PD-L1 expressing NSCLC
  - Although outcomes and toxicity are similar, choice and competition in the market is valuable for the NHS
- The majority of patients with advanced NSCLC with PD-L1 ≥50% are treated with single agent pembrolizumab
  - A smaller proportion are treated with histology specific chemotherapy combined with pembrolizumab (ID1584* and TA600**). This treatment would be considered in those with bulky disease or disease impinging on critical central structures e.g. main airways
- Atezolizumab is very similar to pembrolizumab, with no robust differences in toxicity or efficacy (given limitations of cross trial comparisons)
- First-line immunotherapy is innovative, however atezolizumab itself could not be considered innovative in this setting (as there is already pembrolizumab available in this indication)

*Previously Cancer Drugs Fund; recommended for routine commissioning (expected final guidance publication 10 March 2021); **Currently in Cancer Drugs Fund

Due to resource constraints associated with the COVID-19 pandemic, no patient organisations were able to provide a statement on patient and carer perspectives

Treatment pathway

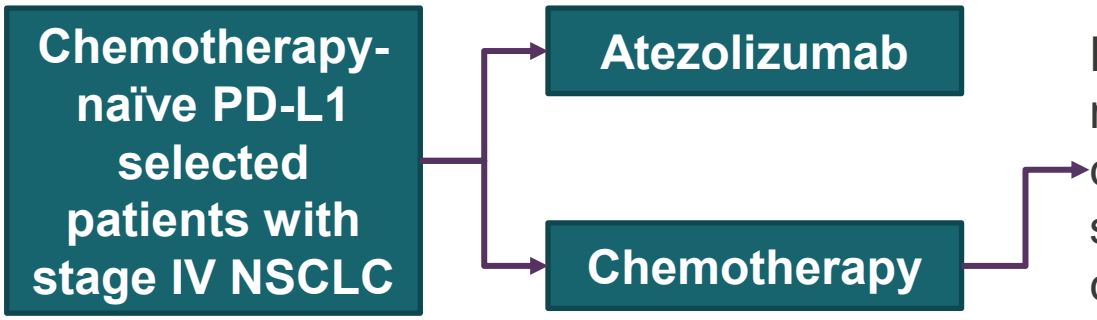


Atezolizumab (Tecentriq, Roche)

Marketing authorisation	[redacted]
Mechanism of action	IgG1 monoclonal antibody, binds directly and selectively to PD-L1 preventing it from binding to PD-1 and B7.1
Administration, dose	The recommended dose of atezolizumab is: • 840 mg administered intravenously every two weeks, or • 1,200 mg administered intravenously every three weeks, or • 1,680 mg administered intravenously every four weeks.
List price	£3,807.69 per 20 ml vial (1,200 mg); £2,665.38 per 14 ml vial (840mg)
PAS	Confidential simple discount PAS has been approved and is currently operational in the NHS

NICE PAS: patient access scheme

Clinical evidence: IMpower110



Patients with non-squamous disease received pemetrexed in combination with cisplatin or carboplatin. Patients with squamous disease received gemcitabine in combination with cisplatin or carboplatin.

Study design	Open-label, randomised, multi-centre
Stratification	By sex, ECOG status, histology and PD-L1 expression (see next slide)
Crossover	Not allowed
Continuation of atezolizumab	Patients who received atezolizumab and showed clinical benefit were allowed to continue treatment after progressed disease (specific criteria applied)

NICE ECOG: Eastern Cooperative Oncology Group

Clinical evidence: populations

Definitions of PD-L1 expression using SP142 assay

TC	% of PD-L1 expression on tumour cells	PD-L1 expression
TC1/2/3	≥1%	Any
TC2/3	≥5%	Medium or high
TC3	**≥50%**	**High**
IC	**% tumour area with PD-L1 expressing immune cells**	**PD-L1 expression**
IC1/2/3	≥1%	Any
IC2/3	≥5%	Medium or high
IC3	**≥10%**	**High**

In scope

- The trial population included people with all levels of PD-L1 expression (TC1/2/3 and IC1/2/3). However, only the TC3 and IC3 populations (high PD-L1 expression) are in scope of this appraisal
- PD-L1 expression of eligible patients was tested using the SP142 assay. 2 additional assays were used to assess assay comparability: SP263 and 22C3
- 22C3 assay is the most commonly used assay in NHS clinical practice. High PD-L1 expression using the 22C3 assay is defined as a tumour proportion score (TPS) of ≥50%

NICE IC: immune cells; TC: tumour cells

Clinical evidence: IMpower110

Results for IC3 and TC3 populations only

	Key outcomes	Atezolizumab vs. chemotherapy	Hazard ratio (95% CI)	P-value
Primary analysis	Median OS (months)	20.2 vs. 13.1	0.59 (0.41, 0.89)	0.0106
	Median PFS (months)	8.1 vs. 5.0	0.63 (0.45, 0.88)	0.007*
	Objective response rate (%)	38.3 vs. 28.6	-	-
	Duration of response (months)	Not estimable vs. 6.7	-	-
Exploratory analysis	Median OS (months)	[redacted]	[redacted]	[redacted]
	Median PFS (months)	[redacted]	-	-
	Objective response rate (%)	[redacted]	-	-
	Duration of response	[redacted]	-	-

- Conducted at a median follow-up of [redacted]
- Exploratory analysis conducted for TC3 and IC3 populations at the same time as the final analysis of OS for the TC2/3 or IC2/3, and TC1/2/3 or IC1/2/3 subpopulations

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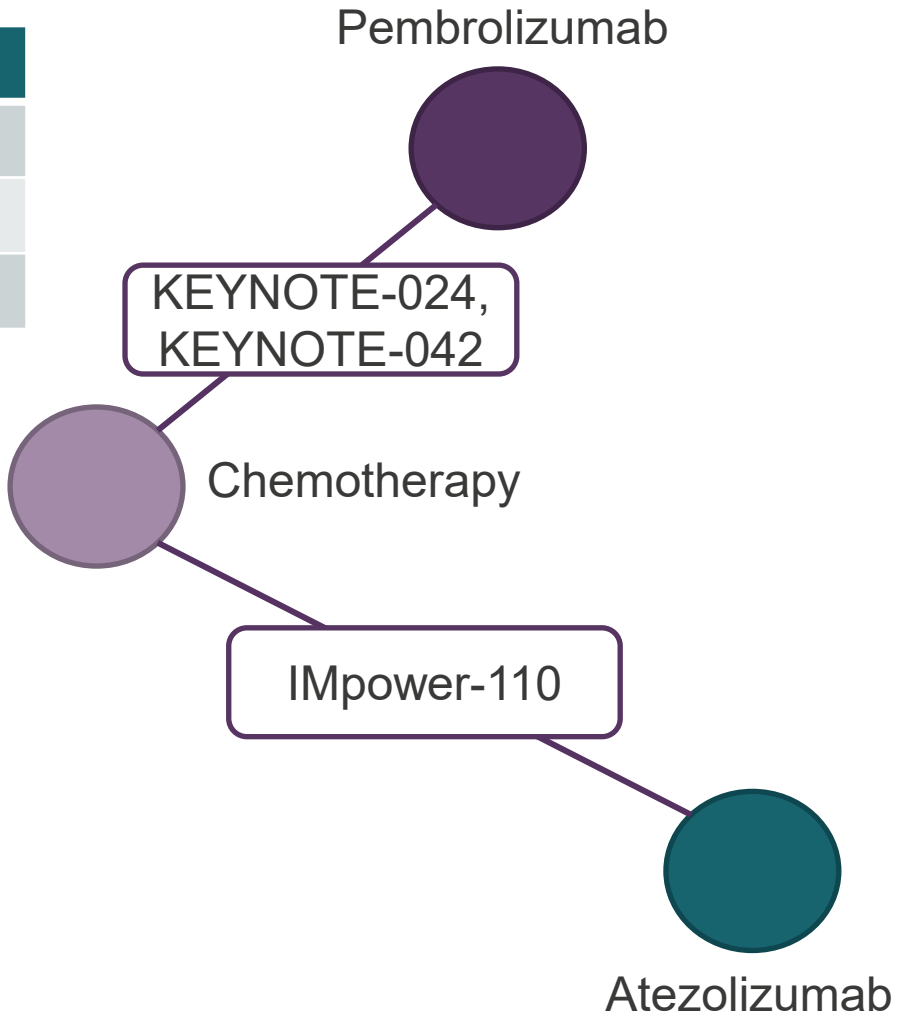
CI: confidence intervals; OS: overall survival; PFS: progression free survival
*p-value is descriptive only

Network meta-analysis approach

Trials included

Trial	N	ATZ	Chemo	PEMB
IMpower110	205	107	98	-
KEYNOTE-024	305	-	151	154
KEYNOTE-042	599	-	300	299



Approach

- For aggregate hazard ratio data, a network meta-analysis using a Normal distribution was used
- A fractional polynomial model was also used for overall survival and progression free survival to account for an assumption of non-proportional hazard ratios

Company network meta-analysis results

Overall survival and progression free survival results

	Analysis	Hazard ratio (CI)
OS	**Primary analysis**	
	NMA	[redacted] (n/s)
	Exploratory analysis	
	NMA	[redacted] (n/s)
	FP-NMA	
	3 months	[redacted] (n/s)
	6 months	[redacted] (n/s)
	12 months	[redacted] (n/s)
PFS	**NMA**	[redacted] (n/s)
	FP-NMA	
	3 months	[redacted] (n/s)
	12 months	[redacted] (n/s)

Summary

- Indirect comparisons from both the standard and the FP-NMA for overall survival and progression free survival imply no statistically significant differences between atezolizumab and pembrolizumab

Results 2 years+

- Overall survival:
  - Trend towards favouring pembrolizumab continues with time but with widening credible limits and small sample sizes indicating they may be less reliable
  - The company and ERG agree this may be influenced by differences in long-term follow-up between studies (see slide 15)
- Progression free-survival
  - Point estimates favour pembrolizumab but sample sizes are small

FP-NMA: fractional polynomial network meta-analysis; NM: network meta analysis; n/s: statistically non-significant

Issues resolved after technical engagement

	Summary	Tech engagement response	Technical team
1	**Population:** company use SP142 assay, but 22C3 is more commonly used in clinical practice and does not measure PD-L1 expression on immune cells (ICs)	• [redacted] of TC3/IC3 population is IC3 only. [redacted] of PD-L1 high patients identified by SP142 were also detected as high by the 22C3 • Overall survival and PFS benefit is [redacted] across IC3 and TC3 subgroups	IC3 only subgroup is too small to inform alternative comparison. Acceptable for recommendations to cover IC3 and TC3
5	**Pembrolizumab ToT:** assumed to follow progression free survival up to stop rule at 2-years. PEMB costs may be overestimated	• Submitted 3 revised approaches (2 using KEYNOTE-042 extrapolations and 1 using a weighted average approach using KEYNOTE-042 and KEYNOTE-024 data)	New approaches using KEYNOTE-042 extrapolations are plausible
6	**Resource frequencies:** ERG considered number of GP home visits and occupational therapist visits to be overestimated (26 annually)	• Company: agreed with ERGs suggestions of reducing estimations by 50% to 13 annually for each • Clinical expert estimations are lower. GP visits: 5 annually, OT: 2 annually	Reduce estimations to be consistent with clinical expert feedback

NICE PEMB: pembrolizumab; ToT: time on treatment

Outstanding issues after technical engagement

	Company position	ERG	Question for committee
4	Duration of treatment effect: 5-year duration for pembrolizumab and life-time duration for atezolizumab is acceptable based on previous appraisals and literature	More than one scenario should be considered	Which duration of treatment effect is suitable for decision-making?

Additional areas of uncertainty that cannot be resolved. Committee should be aware these when making its recommendations

	Company position	ERG
2	Effect over time: FP-NMA results increasingly favour pembrolizumab because of bias introduced by different lengths of long-term follow-up	• Company have given a fair account and taken a conservative approach in base case • Bias associated with issue 2 favours pembrolizumab • Bias associated with issue 3 favours atezolizumab • Lack of evidence to support a meaningful difference in progression free survival or overall survival cannot rule out the possibility that one exists
3	Assays comparability: additional sensitivity and scenario analyses using 22C3 assay show atezolizumab generates more QALYs than pembrolizumab	

NICE FP-NMA: fractional polynomial network meta-analysis

Issue 4: duration of treatment effect

Treatment effect		QALY difference*
PEMB	Base-case: 2-year stopping rule, 5-year treatment effect	-
ATZ	Base-case: life time treatment effect, **no stopping rule**	0.08
	Sensitivity analysis: 8-years (overall survival curves converge and overlap from 90-months onward, considered "worst-case" by company)	0.14
	Sensitivity analysis: 5-years (implies no additional benefit for treating >2-years, considered implausible by company)	0.2

Company technical engagement response

- Precedent from previous appraisals: 5-year treatment effect with 2-year stopping rule
- No justification for revision of the treatment effect cap at 5-years with a 2-year stopping rule
- Literature shows continuous treatment is associated with a trend towards improved overall survival

ERG: issue is central to QALY estimates, so >1 scenario should be considered

- Fundamental issue (lack of long-term pembrolizumab data) cannot be resolved
- NSCLC specific appraisals do not consistently use a 5-year treatment effect (see slide 21)
- Interpretation of correlation of treatment duration and overall survival is questionable

Which duration of treatment effect is suitable for decision-making?

*All favour pembrolizumab

ATZ: atezolizumab; PEMB: pembrolizumab

Additional areas of uncertainty: issue 2, atezolizumab effect over time

Summary: company's base-case fractional polynomial network meta-analysis hazard ratios increasingly favour pembrolizumab over time

Company's technical engagement response: duration of follow-up and rechallenge in KEYNOTE-024 may have biased results in favour of pembrolizumab.

- Larger pembrolizumab trials only have follow-up data in line with the earlier IMPOWER110 data cut
- Longer follow-ups of IMPOWER110 show plateauing in the chemotherapy arm (potentially due to subsequent lines of cancer immunotherapies) reducing the HR for atezolizumab
- Using small pembrolizumab study with longer follow-up data, improves HRs slightly for atezolizumab (highlights importance of follow-up duration)
- KEYNOTE-024 allowed pembrolizumab re-challenge in patients after stopping at 2-years. This would not be allowed in NHS clinical practice

Overall, all sensitivity analyses conducted improved hazard ratios in favour of atezolizumab

ERG: company base-case reflects the most conservative approach from options available

- Agrees that the above factors may have biased results
- Substantial uncertainty remains in network meta-analysis comparison: lack of evidence to support a meaningful difference in PFS or OS cannot rule out the possibility that one exists

Additional areas of uncertainty: issue 3, assays comparability

Summary: IMpower110 used assay SP142 to select IC3 or TC3 patients, while KEYNOTE trials used assay 22C3 to select patients with a tumour proportion score ≥50%

Company's technical engagement response

- Conducted sensitivity analyses using the 22C3 TPS ≥50% subgroup of IMpower110 to inform the network meta-analysis
- These changes were incorporated into an alternative base-case, with a full set of scenarios around it. In all additional scenarios informed by the 22C3 TPS >50% subgroup, atezolizumab generated more QALYs and potentially dominated pembrolizumab

ERG: company base-case reflects most conservative approach from options available

- Company have provided a fair account of data and there is potential for bias to work in both directions in the network meta-analysis (issues on previous slide may favour pembrolizumab, while lower sensitivity SP142 and the 22C3 TPS >50% subgroup being double-selected could bias in favour of atezolizumab)
- Lack of evidence to support a meaningful difference in progression free survival or overall survival cannot rule out the possibility that one exists
- Uncertainties cannot be fully resolved without long-term comparative data on patients selected on the same assay. Should be noted that clinical opinion supports comparability of drugs

Decision-making with south west quadrant ICERs

- South-west quadrant ICERs are presented as costs saved per QALY lost.
- The higher the ICER, the more cost is saved per QALY lost, so high ICERs are better here and the commonly assumed decision rule of accepting ICERs below a given threshold is reversed
- This is reflected in decision making in previous appraisals with south-west quadrant ICERs (e.g. TA433, TA561).
- Positive recommendations are made when the costs saved are sufficient to cover the QALY loss.
- Usually, south-west quadrant ICERs have led to positive recommendations when ICERs are substantially above £30,000 per QALY lost.
- As with other decision-making, more certainty is needed the closer to the margins of cost-effectiveness the ICERs are.

Decision-making with net-health benefit

	Equation	Output	Meaning
ICERs	$\frac{\text{Incremental costs(£)}}{\text{Incremental benefits (QALYS)}}$	ICER value	Extra cost per extra unit of benefit
Net health benefit	$\text{Incremental benefits} - \frac{\text{Incremental costs}}{\text{threshold}}$	QALYs	Value of an intervention in health terms at a given willingness-to-pay threshold

- Net health benefit can be presented as an additional consideration to support decision-making in appraisals involving south-west quadrant ICERs
- Positive net health benefit implies that the overall population health would be increased as a result of the new intervention
- Negative net health benefit implies that the health benefits of the new intervention are not sufficient to outweigh the health losses that would arise of the new intervention being recommended

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential PAS discounts

Key issues

- What duration of treatment effect should be used for pembrolizumab and atezolizumab?

Innovation, equality and CDF

Innovation

- The company considers atezolizumab to be innovative
  - The technical team considers that all relevant benefits associated with atezolizumab are adequately captured in the model.

Equality

- The company submission does not identify any specific equalities considerations.

Cancer Drugs Fund

- The company submission does not include CDF proposal
- CDF should be considered if:
  - Model is structurally robust for decision-making
  - There is plausible potential to be cost-effective
  - Further data collection would reduce clinical uncertainty.

Appendix slide: issue 4

Treatment effect precedent with NSCLC appraisals*

TA	Treatment effect
TA520	Unlikely to be more than 5-years from when treatment is stopped
TA584	3-years from when treatment is stopped
TA531	3- and 5-year scenarios taken into account
TA428	3, 5 and 10-year scenarios presented. Committee noted a lack of evidence to agree in a single clinically plausible scenario
TA577	Between 3 and 5 years from the start of treatment
TA655	At least 3 years after treatment stopped

- Company also submitted evidence from previous appraisals in urothelial cancer, small cell lung cancer, breast cancer and head and neck squamous cell carcinoma
- Both ERG and technical team agree that:
  - To avoid generalising across cancers, focus should be on previous NSCLC appraisals
  - Previous appraisal demonstrate that treatment effect has not always been 5-years (e.g. 3-years and 10-years have also been used)

NICE *All include 2-year stopping rules