NICE National Institute for Health and Care Excellence

Slides for public - redacted

Nivolumab with ipilimumab and chemotherapy for untreated advanced non-small-cell lung cancer [ID1566]

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Company: Bristol-Myers Squibb

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Key unresolved issues

- **Issue 1:** Should the population in the decision problem be split into 3 separate sub-populations?
- **Issues 6 and 7:** What composition of PDC best reflects UK clinical practice?
- **Issue 8:** Should separate survival curves be applied based on histology and PD-L1 status?
- **Issue 9:** Which approach to modelling survival is most appropriate for patients having PDC?
- **Issue 10:** Should the duration of treatment effect for nivolumab plus ipilimumab plus limited PDC be restricted (e.g. to 3 or 5 years after starting treatment)?
- **Issue 12:** Should utilities be based on progression status or proximity to death?
- **Issue 13:** Should the relative dose intensity adjustment be applied to the acquisition cost, or the expected required treatment dose?
- **Issues 14 and 15:** What proportion of patients have subsequent anticancer treatment, and what composition of subsequent treatment best reflects clinical practice?
- **Issue 16:** Does nivolumab plus ipilimumab plus limited PDC meet the requirements to be considered as an end of life therapy?
- **Issue 17:** Should nivolumab plus ipilimumab plus limited PDC be entered into the CDF?

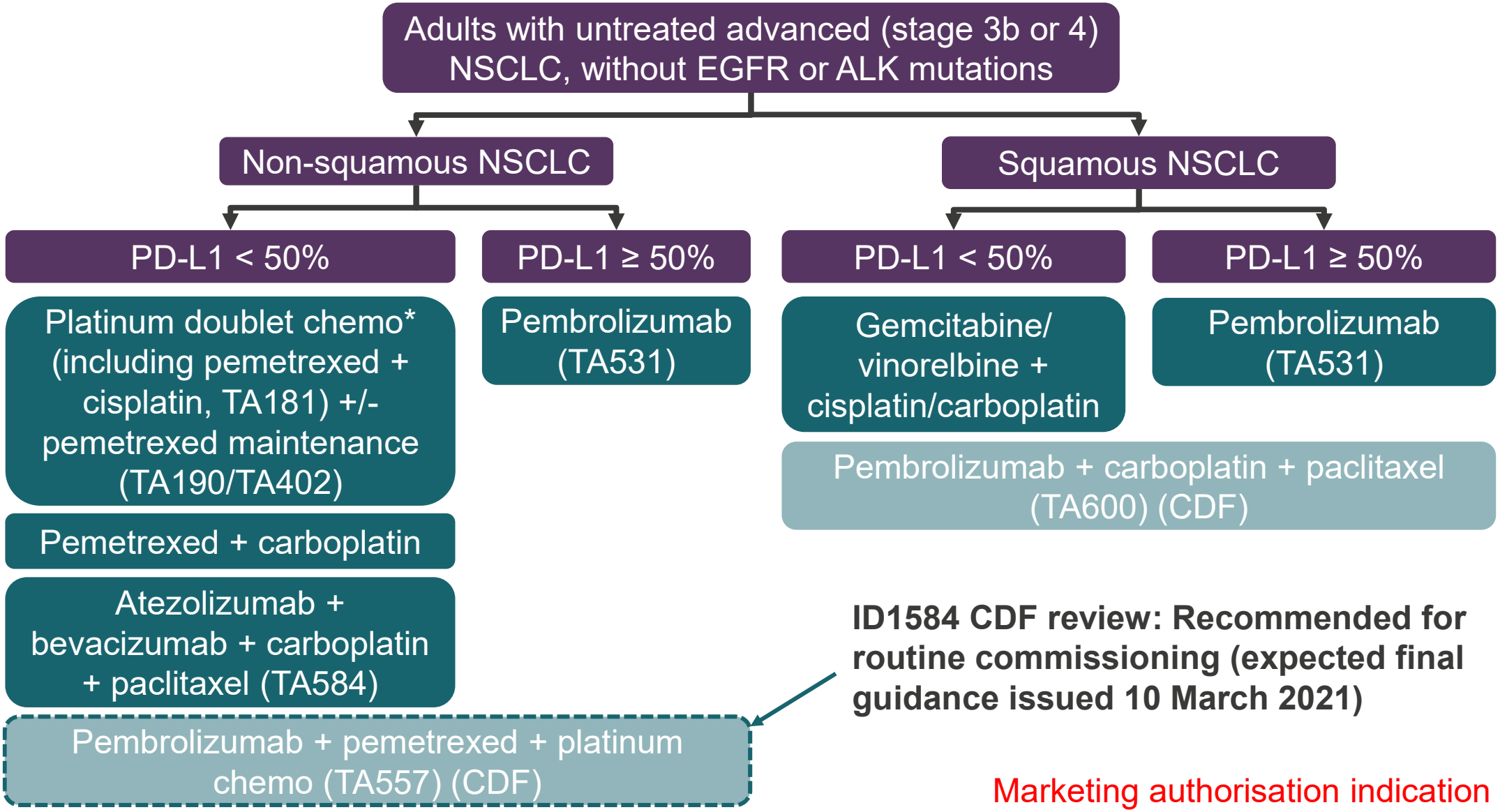
CDF = Cancer Drug Fund; PDC = Platinum doublet chemotherapy; PFS = Progression-free survival

NSCLC: Disease overview

- More than 47,000 people are diagnosed with lung cancer each year in the UK, and there are over 35,000 deaths
- 48% of lung cancers in England are stage 4 (metastatic) at diagnosis. 5-year survival for people diagnosed at stage 4 is around 3%
- Around 80 to 85% of lung cancer cases are non-small cell lung cancer (NSCLC). There are 2 major histological subtypes of NSCLC:
  - Squamous cell carcinoma (25 to 30% of cases)
  - Non-squamous cell carcinoma: comprises adenocarcinoma (40% of cases) and large cell carcinoma (10 to 15% of cases)
- Several biomarkers are used in UK clinical practice, including PD-L1, EGFR, ALK and ROS1. PD-L1 has a continuum of expression levels. Around 70% of people with NSCLC have a PD-L1 tumour proportion score (TPS) less than 50%
- NICE treatment recommendations for untreated stage 4 or recurrent NSCLC without an EGFR or ALK mutation vary depending on both histology and PD-L1 level (less than 50% versus greater than or equal to 50%)

ALK = Anaplastic lymphoma kinase; EGFR = Epidermal growth factor receptor; PD-L1 = Programmed death-ligand 1; ROS1 = C-ros oncogene 1

Positioning in treatment pathway



* Platinum doublet chemotherapy = carboplatin/cisplatin plus pemetrexed/paclitaxel/gemcitabine/vinorelbine

Nivolumab plus ipilimumab (Opdivo and Yervoy, Bristol-Myers Squibb)

Marketing authorisation	Nivolumab plus ipilimumab plus 2 cycles of platinum-based chemotherapy for the first-line treatment of metastatic NSCLC in adults whose tumours have no sensitising EGFR mutation or ALK translocation
Mechanism of action	• **Nivolumab:** antibody that targets blocks the programmed death 1 (PD-1) receptor, to promote an anti-tumour immune response • **Ipilimumab:** antibody that blocks the effects of the anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) to enhance T-cell mediated immune response to tumour cells • A limited dose of platinum doublet chemotherapy (PDC) may mitigate risk of early disease progression and achieve initial disease control
Administration and dose	Intravenous infusion • 360 mg nivolumab every 3 weeks, plus • 1 mg/kg ipilimumab every 6 weeks, plus • 2 cycles of chemotherapy every 3 weeks (non-squamous: pemetrexed plus cisplatin/carboplatin; squamous: paclitaxel plus carboplatin)
Cost (list price)	• Per dose: nivolumab: £3,950; ipilimumab: £7,500; PDC: £634.10 • Average cost per treatment course: [redacted] • There are simple discount patient access schemes for nivolumab and ipilimumab applicable for this appraisal

Background (1/2)

Comparators (NICE scope)	**Non-squamous NSCLC:** • Pemetrexed plus carboplatin/cisplatin, with or without pemetrexed maintenance (cisplatin regimens only) • Chemotherapy (docetaxel, gemcitabine, paclitaxel, vinorelbine) plus carboplatin/cisplatin, with or without pemetrexed maintenance • PD-L1 < 50%: atezolizumab plus bevacizumab, carboplatin and paclitaxel (ABCP) • PD-L1 ≥ 50%: pembrolizumab **Squamous NSCLC:** • Chemotherapy (docetaxel, gemcitabine, paclitaxel, vinorelbine) plus carboplatin/cisplatin • PD-L1 ≥ 50%: pembrolizumab
Main clinical trial	**CheckMate-9LA:** Phase 3, randomised, controlled, open-label trial of nivolumab plus ipilimumab plus limited PDC (nivo+ipi+PDC) compared with PDC in patients with stage 4 or recurrent NSCLC with no prior systemic therapy and no EGFR or ALK mutations
Key results	**Median OS:** 15.6 months vs 10.9 months. HR 0.66 (95% CI 0.55 to 0.80) **Median PFS:** 6.7 months vs 5.0 months. HR 0.68 (95% CI 0.57 to 0.82) **Objective response rate:** 38.2% vs 24.9%. OR 1.9 (95% CI 1.4 to 2.6)

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CI = Confidence interval; HR = Hazard ratio; OR = Odds ratio;
OS = Overall survival; PFS = Progression-free survival

Background (2/2)

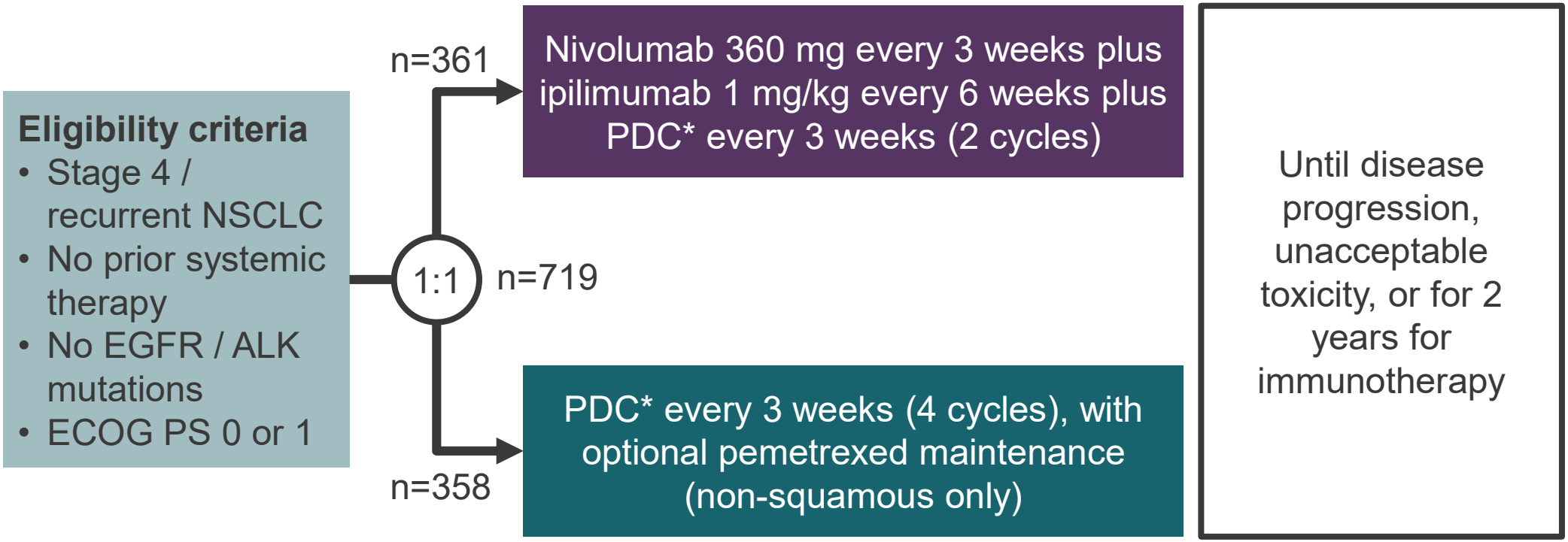
Indirect treatment comparisons (including CheckMate-227)	**1. Patients with mixed histology, PD-L1 ≥ 50%:**
	• vs pembrolizumab:
	  • OS at 48 months: HR [redacted] (95% CI [redacted] to [redacted])
	  • PFS at 36 months: HR [redacted] (95% CI [redacted] to [redacted])
	2. Patients with non-squamous histology, PD-L1 < 50%:
	• vs ABCP:
	  • OS (constant HR): HR [redacted] (95% CI [redacted] to [redacted])
	  • PFS at 24 months: HR [redacted] (95% CI [redacted] to [redacted])

Model structure	Partitioned survival model with 3 health states: progression-free, progressed disease and death
Company base case deterministic ICERs*	• **All patients:** £36,380 vs PDC • **Non-squamous, PD-L1 < 50%:** £36,380 vs PDC; Dominant vs ABCP • **PD-L1 ≥ 50%:** £36,380 vs PDC; £315,308 vs pembrolizumab (south west ICER)
ERG base case deterministic ICERs*	• **Squamous, PD-L1 < 50%:** £47,872 vs PDC • **Non-squamous, PD-L1 < 50%:** £38,451 vs PDC; Dominant vs ABCP • **Mixed histology, PD-L1 ≥ 50%:** £41,160 vs PDC; £85,350 vs pembrolizumab (south west ICER)

* Includes confidential PASs for nivolumab and ipilimumab. Does not include confidential discounts for atezolizumab, pembrolizumab, bevacizumab or pemetrexed

ABCP = Atezolizumab plus bevacizumab, carboplatin and paclitaxel; ICER = Incremental cost-effectiveness ratio

Company's main clinical evidence: CheckMate-9LA



* For non-squamous NSCLC: PDC = pemetrexed plus cisplatin/carboplatin;
For squamous NSCLC: PDC = paclitaxel plus carboplatin

Primary outcome	Overall survival
Key secondary outcomes	Progression-free survival, objective response rate, safety
Locations	103 sites across 19 countries. [redacted] patients from the UK

ECOG = Eastern Cooperative Oncology Group

Company's supporting clinical evidence

	CheckMate-227	CheckMate-568
Design	Randomised, controlled, open-label	Non-randomised, single-arm, open-label
Population	• Adults with stage 4 / recurrent NSCLC • No previous systemic treatment • ECOG PS 0 or 1 • No EGFR mutations / ALK translocations • Stratified by PD-L1 status	• Adults with stage 4 / recurrent NSCLC • No previous systemic treatment • ECOG PS 0 or 1 • No EGFR mutations / ALK translocations • PD-L1 all-comers
Interventions	Nivolumab plus ipilimumab	Nivolumab plus ipilimumab plus PDC
Comparator	PDC Q3W for up to 4 cycles	None
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	• Dose-limiting toxicities • Safety and tolerability • Overall survival • Progression-free survival • Objective response rate
Use in submission	Used for the revised fractional polynomial NMA, and the long-term survival analyses	Provides evidence on safety of nivolumab plus ipilimumab. Does not inform economic model

HRQoL = Health-related quality of life; NMA = Network meta-analysis

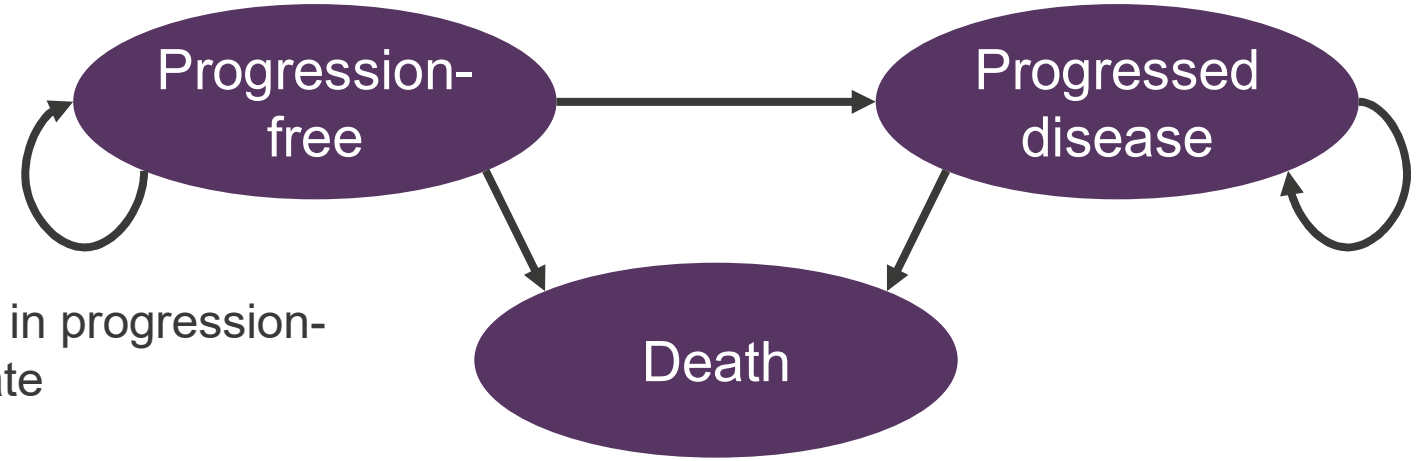
Patient and carer perspective

- Views from Roy Castle Lung Cancer Foundation and the Manchester University NHS Foundation Trust
- Patients with stage 4 lung cancer have a particularly poor outlook. *"Studies which show improvements in survival are of obvious importance to patients"*
- Symptoms such as breathlessness, cough and weight loss are difficult to treat. *"These are symptoms which can be distressing for loved ones to observe"*
- Unmet need is highest in patients whose NSCLC does not have a treatable target (e.g. EGFR / ALK)
- Nivolumab plus ipilimumab plus limited chemotherapy is the first dual immunotherapy regimen for NSCLC. Long-term survival benefits have been shown in other cancers: *"offers hope to patients"*
- Provides another treatment option, with similar efficacy and tolerability to existing chemo-immunotherapy treatments
- 2 cycles of chemo (rather than 4, as standard), is preferable to patients

Clinical perspective

- Views from 2 consultants in medical oncology
- Unmet need for treatments that extend survival; only a small number of patients achieve long-term survival on immunotherapy. A clinically significant response would be an overall survival improvement of 2-6 months
- Toxicity with existing chemo-immunotherapy regimens restricts their use to fitter patients. *"Immunotherapy toxicity can occur over 2 years of treatment (and indeed in the year after while not on treatment) and can be irreversible"*
- The current care pathway is well defined and follows NICE guidelines (NG122, TA557, TA584, TA600)
- Nivolumab plus ipilimumab plus limited chemotherapy is not a step change, but provides another first-line treatment option
  - *"Survival is likely to be similar to other first-line chemo-immunotherapy combinations"*
- Nivolumab plus ipilimumab is already widely used in other indications, with established toxicity management algorithms. *"There should be no major barriers to use within the NHS in terms of resources and training"*

Model structure: 3-state partitioned survival



Patients enter in progression-free health state

Structure	3-state partitioned survival model
Time horizon	Lifetime (25 years)
Cycle length	1 week for first 28 weeks; 4 weeks after this point
Half-cycle correction	Yes
Duration of treatment effect	Lifetime
Stopping rule	2 years
Discount rate	3.5%
Perspective	NHS and Personal social services

Issues resolved after technical engagement

	Summary	Stakeholder responses	Technical team consideration
2 (P)	Trial populations may be healthier and younger than UK clinical practice, with few ([redacted]) patients from the UK	Experts: age unlikely to impact outcomes. ECOG PS 2 excluded in other IO trials	Expert feedback suggests that trial populations are appropriate
3 (P)	Trials in indirect treatment comparisons (ITCs) had notable differences in patient characteristics/design. [redacted]	Experts: reasonable to consider results of ITCs. Crossover rates/use of subsequent IO important	ITC analyses appropriate, though likely subject to underlying bias
4	Agreement that fractional polynomial NMA including CheckMate-227 is appropriate. ERG generally satisfied with validation of company models	Some uncertainty incorporating CheckMate-227 due to trial design. Adds confidence in long-term outcomes	CheckMate-227 data should be included in the NMA
5	Nivo+ipi+PDC failed to demonstrate a significant benefit in certain subgroups (e.g. elderly and non-smokers)	Experts: lack of efficacy based on age/site not concerning. Subgroups not pre-specified, low patient numbers	Expert feedback suggests that nivo+ipi+PDC likely to be effective in all subgroups
11	Company agreed with ERG's revised approach to modelling DoT for ABCP using data from IMPower150. However, still some uncertainty as to DoT for nivo+ipi+PDC	None	ICER impact from any uncertainty is likely to be minimal

P = Partially resolved

DoT = Duration of treatment; IO = Immuno-oncology therapy; PS = Performance status

Outstanding issues after technical engagement

Issue	Impact	Slides
Issue 1: Splitting decision problem into subpopulations		15-16
Issues 6 and 7: PDC composition		17-19
Issue 8: Separate survival curves for subpopulations		20-22
Issue 9: PDC survival modelling		23-25
Issue 10: Duration of treatment effect		26-28
Issue 12: Utilities		29-31
Issue 13: Relative dose intensity adjustment		32
Issues 14 and 15: Subsequent treatment		33-34
Issue 16: End of life	N/A	35-36
Issue 17: Cancer Drug Fund	N/A	37-38


Model driver

Unknown impact

Small/Moderate impact

Issue 1: Decision problem (1/2)

- **Scope population:** Adults with untreated metastatic NSCLC without sensitising EGFR mutations or ALK fusions. *If evidence allows, subgroup analysis by level of PD-L1 expression will be considered*
- Company considered the scope population as a single decision problem, although presented results separately vs pembrolizumab in subgroup with PD-L1 ≥ 50% NSCLC, and vs ABCP in subgroup with non-squamous, PD-L1 < 50% NSCLC

ERG comments:

- 3 separate decision problems should be modelled: 1) Non-squamous, PD-L1 < 50%; 2) Squamous, PD-L1 < 50%; 3) Any histology, PD-L1 ≥ 50%
- Considering only the broad population may risk unnecessarily restricting access, or recommending an intervention that is not cost-effective
- Relative treatment effects and prognosis may differ based on PD-L1 expression and histology
- Available treatments (including chemotherapy regimens) are different in each subpopulation. Precedent for histology-specific decisions (TA557 and TA600)
- Data from CheckMate-9LA and CheckMate-227 suggest that the efficacy of nivo+ipi+PDC may differ by subgroup
- End of life criteria may only apply in certain subpopulations

Issue 1: Decision problem (2/2)

Company response at technical engagement:

- Data from CheckMate-9LA suggest that histology and PD-L1 expression are not effect modifiers for nivo+ipi+PDC
- Combining 3 different mechanisms of action expected to reduce some of the differences in efficacy by histology / PD-L1 status seen with other regimens
- Subgroup data for comparators are preferred where they suggest that histology or PD-L1 expression are effect modifiers

Experts and technical team:

- **Experts:** Current treatment strongly driven by previous NICE appraisals, which are histology/PD-L1-dependent
- **Technical team:** Comparators/end of life considerations differ by subgroup
- In ID1584 (TA557 CDF review), committee considered cost-effectiveness results separately for 2 populations: 1) Non-squamous NSCLC regardless of PD-L1 level (vs pemetrexed with carboplatin/cisplatin); 2) Non-squamous NSCLC, PD-L1 ≥ 50% (vs pembrolizumab monotherapy). Atezolizumab not a relevant comparator as it was recommended after publication of TA557
- Complex algorithm may necessitate separation of decision problem
- In practice, has limited ICER impact as in ERG base case only the distribution of PDC regimens differs by subgroup. However, impacts consideration of other issues (e.g. end of life, and rationale for applying separate survival curves by subgroup)

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Question: Should the population in the decision problem be split into 3 separate subpopulations?

Issues 6 & 7: PDC composition (1/3)

- Company based distribution of PDC agents in model on CheckMate-9LA. Average PDC treatment cost applied across all subgroups, based on distribution of regimens in all-comer population of CheckMate-9LA:

PDC regimen	Nivolumab plus ipilimumab plus PDC	PDC
Carboplatin plus paclitaxel	[redacted]	[redacted]
Carboplatin plus pemetrexed	[redacted]	[redacted]
Cisplatin plus pemetrexed	[redacted]	[redacted]
Pemetrexed maintenance	[redacted]	[redacted]

ERG comments:

- Distribution of PDC regimens in CheckMate-9LA may not represent UK clinical practice. Model omits some chemotherapy agents in scope, e.g. gemcitabine
- Applying a single weighted PDC regimen to all populations in the model does not reflect heterogeneity in PDC regimens by histology
- Although PDC regimens can generally be considered to have equal efficacy, there are differences in acquisition and administration costs, and potentially HRQoL
- ERG prefers to model PDC separately by subgroup, using market share distributions from TA557 and TA600. ERG also applies subgroup-specific duration of treatment, using data from CheckMate-9LA

Issues 6 & 7: PDC composition (2/3)

Company response at technical engagement:

- Agrees that PDC distribution in CheckMate-9LA does not reflect clinical practice
- Updated the PDC distributions for patients with non-squamous and squamous NSCLC separately based on clinical input
- Retained weighted average distribution across all patients, rather than using subgroup-specific distributions – more robust to use totality of trial data

ERG comments on response:

- Using an average distribution results in inclusion of regimens not available in practice (e.g. carboplatin plus gemcitabine in patients with non-squamous NSCLC)
- Citing robustness as an argument to use the weighted average approach is misleading. Neither the updated company or ERG base cases use the data from CheckMate-9LA to derive the PDC distributions

Experts:

- Carboplatin plus pemetrexed most widely used PDC regimen in general
- Carboplatin plus gemcitabine most common regimen in squamous patients as chemo alone; carboplatin plus paclitaxel more common when used in combo with immunotherapies

Issues 6 & 7: PDC composition (3/3)

Comparison of PDC regimen distributions

Submission	Carboplatin plus:				Cisplatin plus:		Pem maint.
	Pem	Pac	Gem	Vin	Gem	Pem	
Company original, **all patients**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG, **squamous (SQ)**	0%	0%	69%	0%	31%	0%	0%
ERG, **non-squamous (NSQ)**	34%	0%	3%	0%	19%	44%	[redacted]
ERG, **mixed histology**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical expert 1, **all patients**	45%	5%	30%	10%	0%	10%	-
Clinical expert 2, **plus IO, NSQ**	55%	35%	4%	5%	0%	1%	-
Company clinical expert after TE (**SQ**)	0%	20%	60%	20%	0%	0%	-
Company clinical expert after TE (**NSQ**)	80%	0%	0%	0%	0%	20%	-
Company average after TE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* PDC arm only. IO = Immuno-oncology therapy

Technical team: Company updated base case after technical engagement appears to reflect feedback from clinical experts

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Question: Which PDC distribution best reflects UK clinical practice? Should separate distributions for each subgroup be used, or a weighted average?

Issue 8: Survival curves for subpopulations (1/3)

- Company used the all-comers data from CheckMate-9LA and CheckMate-227 to derive the survival curves for all subpopulations, regardless of histology or PD-L1 expression
- On basis that a consistent efficacy benefit was observed in CheckMate-9LA across all subgroups, including those based on histology and PD-L1 expression

ERG comments:

- A systematic review suggests that immunotherapy has a larger relative treatment effect in patients with higher PD-L1 expression levels
- In TA557, clinical experts noted that 5-year survival is lower for people with non-squamous versus squamous tumours
- Data from CheckMate 9-LA suggest that the effectiveness of nivo+ipi+PDC differs across subpopulations:
  - [redacted]
  - [redacted]
- [redacted]

Issue 8: Survival curves for subpopulations (2/3)

Company response at technical engagement (in addition to Issue 1):

- ITT data from CheckMate-9LA are more appropriate than data from subgroups, which were not pre-specified, have low patient numbers and may lead to less robust survival estimates
- Fewer external clinical data available to validate curves – greater reliance on clinical opinion
- However, provided clinically validated survival models for OS and PFS fitted to the subgroup data at technical engagement

ERG comments on response:

- Unclear whether histology/PD-L1 expression are effect modifiers. Base case uses ITT data

Experts and technical team:

- **Experts:** Biggest distinction is patients with very low or high PD-L1 level – affects suitability for single-agent immunotherapy. Otherwise, similar benefits anticipated in all subgroups
- **Technical team:** Clinical expert feedback suggests that using ITT data for all subgroups is clinically appropriate. Benefit of larger patient numbers – more robust
- In TA600, committee concluded that extrapolations should be based on ITT data, rather than subgroups based on PD-L1 level. Subgroup analysis not robust enough for decision-making
- In ID1584, company applied survival curves derived from ITT population of KEYNOTE-189 (non-squamous NSCLC, regardless of PD-L1 level) to subgroup with PD-L1 ≥ 50%. Committee concluded that subgroup OS estimates were uncertain, but sufficient to conclude that pembrolizumab plus pemetrexed and platinum chemo was cost-effective

Issue 8: Survival curves for subpopulations (3/3)

Comparison of survival landmarks for company selected models by subgroup

Subgroup	Distribution	Year				
		1	2	3	5	10
Overall survival						
All comers	Spline on probit link 2 knots	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Squamous, PD-L1 < 50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-squamous, PD-L1 < 50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mixed histology, PD-L1 ≥ 50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free survival						
All comers	Spline on odds 2 knots	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Squamous, PD-L1 < 50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-squamous, PD-L1 < 50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mixed histology, PD-L1 ≥ 50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NICE

Question: Should separate survival curves be applied based on histology and PD-L1 status?

Issue 9: PDC survival modelling (1/3)

- Company modelled survival (OS and PFS) for PDC using hybrid approach. Observed survival data from CheckMate-9LA were used up to 13 months. A parametric curve was fitted to more mature data from CheckMate-227 after this point
- Company considered the hybrid approach more clinically plausible than extrapolations based only on CheckMate-9LA

ERG comments:

- Median overall survival for patients having PDC lower in CheckMate-9LA (10.7 months) versus CheckMate-227 (13.9 months)
- Difference could be because fewer patients had subsequent treatment in CheckMate-9LA than CheckMate-227. ERG considers CheckMate-227 better reflects clinical practice in this regard (Issues 14 and 15)
- Presents scenario in which survival for patients having PDC is modelled using data from CheckMate-227 alone, and the relative effects for nivo+ipi+PDC are used from the indirect treatment comparison

Company response at technical engagement:

- Company hybrid approach ensures consistency between treatment arms
- Clinical experts feel that CheckMate-9LA is representative of UK clinical practice

Issue 9: PDC survival modelling (2/3)

Comparison of overall survival curves for patients having PDC

OS survival curve	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 5 (%)	Year 10 (%)
Hybrid CM-9LA plus CM-227	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CM-227 only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Issue 9: PDC survival modelling (3/3)

ERG comments on response:

- Survival of patients having PDC in CheckMate-9LA is pessimistic
- Company's clinical experts did not comment on the representativeness of subsequent treatments in CheckMate-9LA
- Company has not provided compelling evidence as to why survival is different between the 2 trials
- Data from CheckMate-227 may be more appropriate, as it reflects greater use of subsequent treatments

Technical team:

- In previous appraisals, 5-year overall survival of 5% to 11% for patients having standard of care has been considered reasonable. Both the company base case curve and the ERG scenario curve fall within this range
- Clinical expert input for Issue 14, and previous appraisals, suggest that around 50% of patients having first-line PDC have subsequent treatment. Higher than in CheckMate-9LA, suggesting that more optimistic curve may be more appropriate

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Question: Which approach to modelling overall survival is more appropriate for patients having PDC?

Issue 10: Duration of treatment effect (1/3)

- Company assumed that nivo+ipi+PDC has lifetime duration of effect
- Based on study using 4-year overall survival data pooled from 4 clinical studies of nivolumab in previously treated NSCLC

ERG comments:

- Lifetime treatment effect inconsistent with previous NICE appraisals (e.g. TA600, TA531, TA584), in which it was considered implausible. Scenarios based on 3- and 5-year effect after starting treatment considered plausible by committee
- All patients having nivo+ipi+PDC in CheckMate-9LA discontinued treatment by 2 years – company model therefore assumes that OS effect lasts long after discontinuation
- Study referenced by company of limited relevance. It considers nivolumab as a monotherapy in second line, and 4-year data is not long enough to support a lifetime benefit
    - Large degree of censoring in nivolumab arm after 4 years – relative difference versus docetaxel uncertain
- ERG provides scenarios with 1-, 3- and 5-year duration of treatment effect after discontinuation, modelled by reverting the hazard rate to that in the PDC arm

Issue 10: Duration of treatment effect (2/3)

Company response at technical engagement:

- Agrees that this is an area of uncertainty
- Disagrees that supporting reference should be disregarded. Remains most robust and relevant available evidence – draws on data from patients with NSCLC treated with nivolumab
- Evidence suggests robust and durable treatment benefit beyond discontinuation

ERG comments on response:

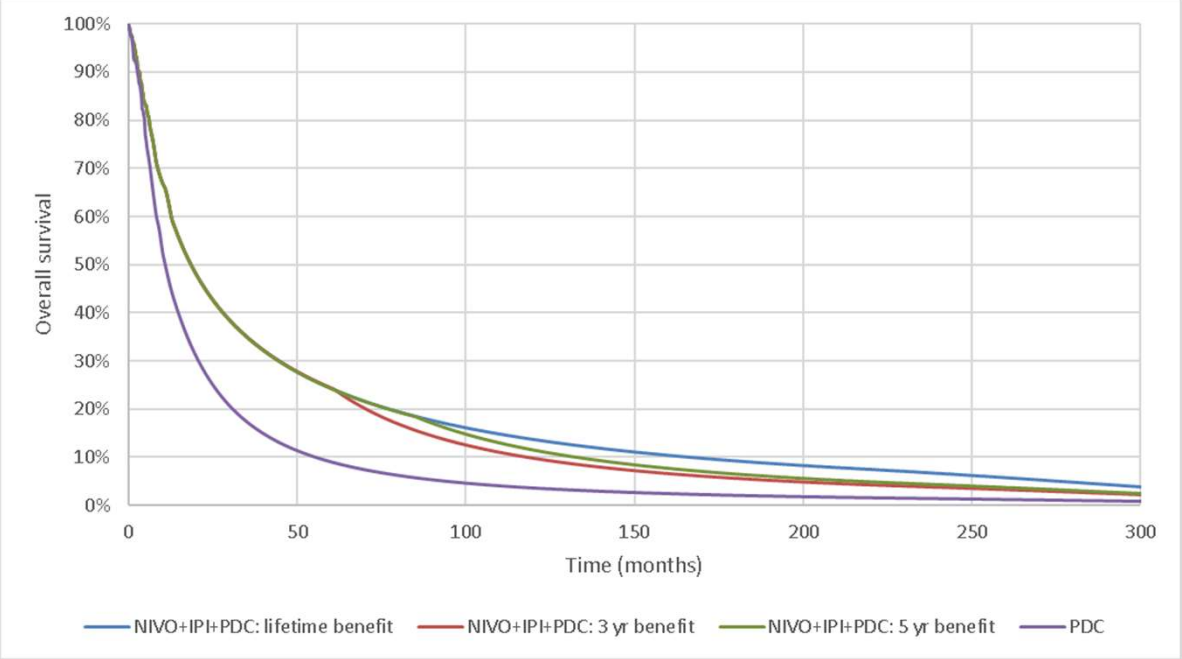
- Company did not provide any new analyses or evidence to support assumption of lifetime benefit
- ERG prefers 5-year treatment effect after discontinuation as base case

Experts:

- Duration of benefit may depend on reason for stopping. If due to toxicity / stopping rule, benefit may be long-lasting. On average, 3 months treatment benefit beyond disease progression can be assumed for immunotherapy
- Would expect around 30% of patients to relapse in the first year after stopping treatment

Issue 10: Duration of treatment effect (3/3)

Comparison of overall survival curves by duration of treatment effect



Technical team:

- A duration of treatment effect of 3- or 5- years after starting treatment is consistent with previous appraisals. A lifetime benefit has not been accepted by committee
- In ID1584, committee accepted ERG scenario with a gradually decreasing treatment effect between 3 and 5 years after starting treatment (to match the comparator arm treatment effect at 5 years)

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Question: Should the duration of treatment effect for nivo+ipi+PDC be restricted (e.g. to 3 or 5 years after starting treatment)?

Issue 12: Utilities (1/3)

- The company used time-to-death (TTD) utilities, derived from CheckMate-9LA (below). A TTD utility approach was accepted in TA531 and TA584

Time to death	Utilities (SE)
More than 52 weeks	[redacted]
27 to 52 weeks	[redacted]
5 to 26 weeks	[redacted]
4 weeks or less	[redacted]

ERG comments:

- Difficult to verify company's approach due to lack of detail
- In previous appraisals, rationale for TTD approach was it being a better statistical fit than progression-based utilities. No statistical difference between pre- and post-progression utilities, and lack of long-term data to inform post-progression state
- Here, there were 1,004 post-progression observations from 353 patients. Around one third were observed 6 months after progression. Conversely, only 114 observations informing '4 weeks or less' utility
- ERG also has conceptual concerns – TTD likely a proxy for disease severity
- ERG preferred progression-based utilities provided by company as scenario

Issue 12: Utilities (2/3)

Company response at technical engagement:

- Maintains that TTD approach enables model to better capture variation in HRQoL between progression and death
- Progression-based utilities provide only a snapshot of HRQoL. Expected to be biased upwards because of fewer observations in more severe patients
- TTD approach is more clinically plausible

ERG comments on response:

- Disagrees that insufficient data points informed progressed disease state
- The difference between the progressed-free utility ([redacted]) and progressed diseased utility ([redacted]) is large enough to adequately capture progression
- Progression remains a statistically and conceptually superior approach than TTD

Technical team:

- Purely TTD-based approach rejected in TA600 and TA557. In TA557, clinical experts noted that progression status was important to consider for HRQoL
- Progression-based approach appears robust, as it is based on large number of post-progression data points

Issue 12: Utilities (3/3)

- Company-proposed TTD utilities are somewhat comparable to those accepted in TA584, although the utility for 4 weeks or less is lower in the current appraisal. Times to death are also different between the 2 appraisals
- TA584 utilities applied for all patients (non-squamous NSCLC) and treatment arms
- TTD utilities in TA557 and TA600 marked as academic in confidence and cannot be shown for comparison

Proposed company TTD utilities		TTD utilities accepted in TA584	
Time to death	**Utilities (SE)**	**Time to death**	**Utilities**
More than 52 weeks	[redacted]	More than 30 weeks	0.73
27 to 52 weeks	[redacted]	15 to 30 weeks	0.7
5 to 26 weeks	[redacted]	5 to 11 weeks	0.59
4 weeks or less	[redacted]	5 weeks or less	0.52

NICE

Question: Should utilities be based on progression status or proximity to death?

Issue 13: Relative dose intensity adjustment

- Company incorporated mean relative dose intensity (RDI) into model. Applied to drug acquisition costs, after these had been estimated from number of vials

ERG comments:

- More appropriate to apply RDI to expected required treatment dose, and then estimate treatment cost from the adjusted expected dose. In some cases, the number of vials required may not be reduced, so costs would not change
- Company's approach may underestimate drug acquisition costs

Company response at technical engagement:

- RDI accounts for number of doses (cycles of treatment) received compared with number of planned doses, not a reduced dose per se
- Each dose delivered will still be based on prescribed dose and number of vials
- ERG's approach will not reflect the impact that RDI would have on costs

ERG comments on response:

- RDI for chemotherapy represents reductions in total doses and size of doses, which may not be associated with a reduction in required vials
- Impact of RDI likely lies between the company and ERG assumptions

NICE

Question: Should the relative dose intensity adjustment be applied to the acquisition cost, or the expected required treatment dose?

Issues 14 & 15: Subsequent treatment (1/2)

- Company assumed the following proportion of patients have subsequent treatment, based on the data from CheckMate-9LA:
  - Nivo+ipi+PDC: 31%. Also used for other immunotherapy regimens
  - PDC: 40%
- All patients having first-line immunotherapy in the model have docetaxel second line. 85% of patients having PDC have immunotherapy in second line; 15% had docetaxel

ERG comments:

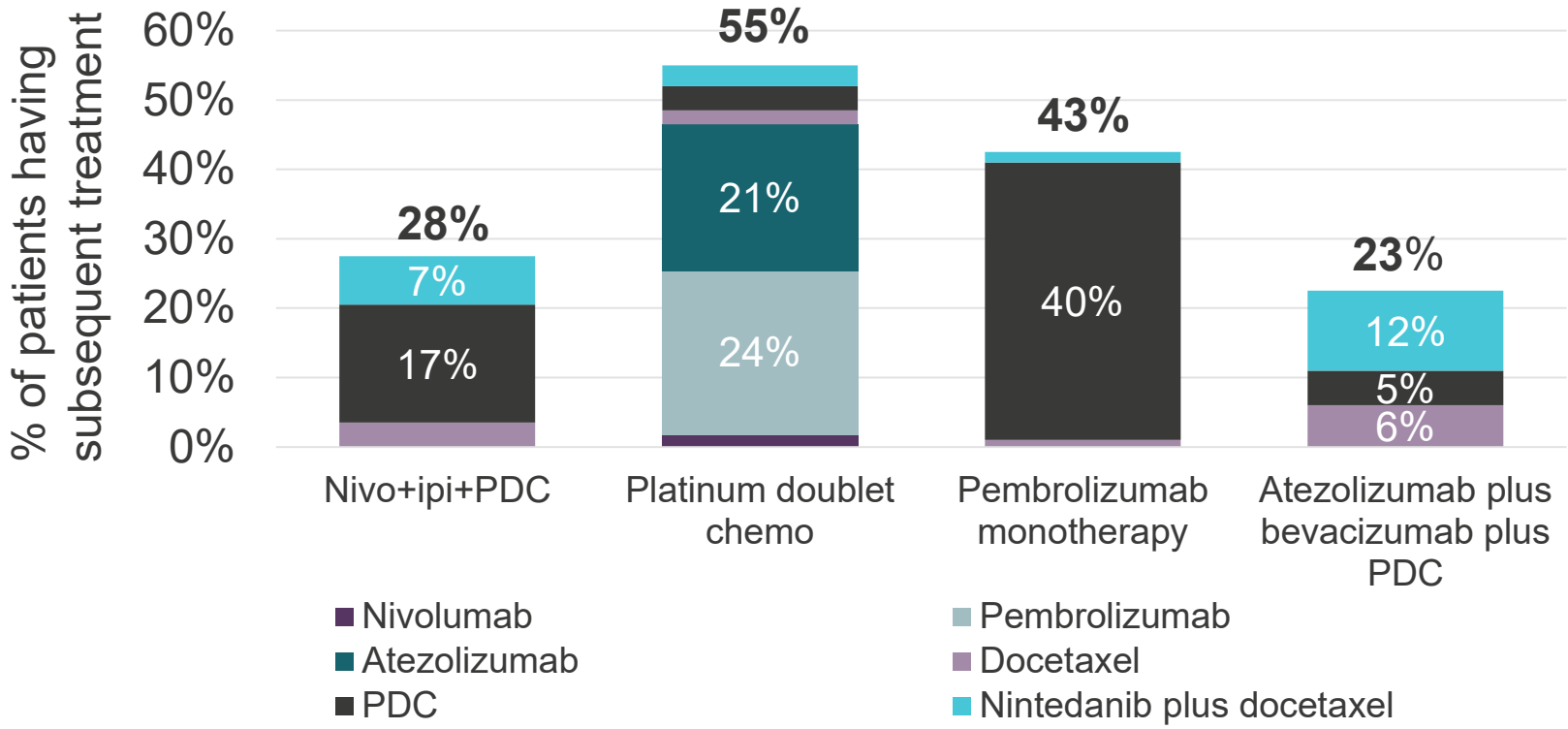
- Subsequent therapies after nivo+ipi+PDC in CheckMate-9LA not reflective of clinical practice: 5% had immunotherapy and 5% had targeted therapy
- Subsequent treatment after nivo+ipi+PDC likely underestimated. Based on immature data
- 40% may be too low for PDC. Clinical opinion in TA584 and TA600 suggests that around 50% of patients would have immunotherapy after progression on PDC
- ERG prefers rates from CheckMate-227 (45% for nivo+ipi+PDC, 61% for PDC). Aligned with clinical practice and use of CheckMate-227 data to model long-term survival
- Patients having first-line PDC would not have docetaxel in second-line

Company response at technical engagement:

- Agrees that subsequent treatment in CheckMate-9LA was lower than expected in trial setting, but reflects clinical practice
- Agreed to remove docetaxel following PDC

Issues 14 & 15: Subsequent treatment (2/2)

Clinical expert feedback on distribution of subsequent treatment



Technical team:

- Clinical expert feedback supports company's estimate for the % of patients having subsequent treatment after nivo+ipi+PDC. However, also suggests that using the same assumption for all immunotherapies may not reflect clinical practice
- Removing docetaxel as a second-line option after PDC appears appropriate

NICE

Question: What % of patients have subsequent treatment after each first-line regimen? Is it appropriate to assume no patients have docetaxel after PDC?

Issue 16: End of life criteria (1/2)

- Company considered that end of life (EoL) criteria are not met for the all-comer population

ERG comments:

- EoL criteria should be considered separately for each subgroup
- The criteria are met in squamous population with PD-L1 < 50%. Undiscounted mean life years from model: [redacted] years for patients having PDC. Nivo+ipi+PDC has survival benefit greater than 3 months (undiscounted mean life years: [redacted] years across all subgroups)

Company response at technical engagement:

- Agrees that EoL criteria are met in patients with squamous NSCLC, PD-L1 < 50%

Experts:

- Life expectancy for patients with squamous NSCLC likely to be less than 2 years
- PD-L1 ≥ 50% does not meet end of life criteria. PD-L1 1 to 49% more likely to meet criteria in squamous NSCLC

Technical team: Expert feedback suggests nivo+ipi+PDC meets EoL criteria in subgroup with squamous NSCLC, PD-L1 < 50%

- Observed data from CheckMate-9LA suggest that EoL criteria are met in patients with squamous NSCLC:
  - **Median OS nivo+ipi+PDC:** 15.6 months (ITT population); 14.5 months (squamous)
  - **Median OS PDC:** 10.9 months (ITT population); 9.1 months (squamous)

Issue 16: End of life criteria (2/2)

End of life conclusions in recent appraisals in NSCLC

Appraisal	Population	Life expectancy <24m*	Life extension ≥3m
ID1584 *(Mar 21)*	Non-squamous, any PD-L1	✓ (pemetrexed plus chemo)	✓
	Non-squamous, PD-L1>50%	✗ (pembrolizumab)	✗
TA600 *(Sep 19)*	Squamous, any PD-L1	✓ (chemo/pembrolizumab, depending on PD-L1 level)	✓

* Comparator in brackets ✓ = Criteria met ✗ = Criteria not met

Life expectancy in model for current appraisal, and clinical expert feedback on criteria

Population	Life expectancy in model	Expert feedback: life expectancy
Full population	[redacted] years (PDC)	Close to non-squamous NSCLC, as this is the largest subgroup
Squamous, PD-L1 <50%	[redacted] years (PDC)	Less than 2 years
Non-squamous, PD-L1 < 50%	[redacted] to [redacted] years (ABCP)	Around 2.5 years may be realistic
Mixed histology, PD-L1 ≥ 50%	[redacted] to [redacted] years (pembrolizumab)	Around 2.8 years

NICE

Question: Does nivo+ipi+PDC meet NICE's end of life criteria? In which patient subgroups?

Issue 17: Cancer Drugs Fund (1/2)

Committee decision-making criteria:

Proceed down if answer to each question is yes

Starting point: drug not recommended for routine use due to **clinical uncertainty**

1. Is the model structurally robust for decision making? (omitting the clinical uncertainty)

2. Does the drug have plausible potential to be cost-effective at the offered price, taking into account end of life criteria?

3. Could further data collection reduce uncertainty?

4. Will ongoing studies provide useful data?

and

5. Is CDF data collection via SACT relevant and feasible?

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

Define the nature and level of clinical uncertainty. Indicate the research question, analyses required, and number of patients in NHS in England needed to collect data.

Issue 17: Cancer Drugs Fund (2/2)

- **Company:** Recognises data from CheckMate-9LA are immature. Considers nivo+ipi+PDC a CDF candidate
- Nivolumab for previously treated NSCLC was recommended for the CDF (TA483 and TA484). Original OS modelling consistent with longer term data from clinical trials, suggesting that OS can be plausibly modelled

ERG comments:

- Minimum follow-up of CheckMate-9LA is currently 12.7 months
- A key model driver is the duration of treatment effect. The data may not be sufficiently mature at the of the data collection period to determine this parameter

Technical team: Nivo+ipi+PDC may have plausible potential to be cost effective. CDF entry would reduce some areas of uncertainty:

- Survival modelling, although as the ERG states, the key uncertainty is the duration of treatment effect – this may not be resolved via the CDF
- Time on treatment for nivo+ipi+PDC
- Proportion of patients having subsequent treatment ([redacted] of patients in the nivo+ipi+PDC arm of CheckMate-9LA were still on treatment)

CDF team: Nivo+ipi+PDC is not a suitable candidate for the CDF

NICE

Question: Should nivo+ipi+PDC be entered into the CDF?

Additional areas of uncertainty

Issue	Why issue is important	Impact on ICER
Progression-free survival model selection	• Company PFS model for nivo plus ipi plus limited PDC may be too optimistic • Company PFS model for PDC not best statistical fit	Small increase in ICER with revised ERG curves
CheckMate-9LA and -227 open-label study design	• Increases risk of selection bias and performance bias	Unknown
More outcomes measured than reported in CheckMate-9LA	• High risk of outcome reporting bias	Unknown
Unclear if ITT population used in CheckMate-227	• Risk of attrition bias	Unknown
Fixed effects models used in NMA	• Analysis should be interpreted with caution due to possibility of imbalance in covariates	Unknown
Single duration of treatment curve used for nivo+ipi+PDC	• Patients can discontinue nivolumab and ipilimumab separately • Likely overestimates treatment costs	Overestimates ICER, though degree unknown
Toxicities of nivolumab plus ipilimumab not fully captured	• Serious long-term toxicities may not be fully captured • Threshold for treatment-related adverse events excludes some events	Unknown

Summary of company and ERG base cases

Summary of key differences between company and ERG base cases

Issue	Company base case	ERG base case
Issue 1: Decision problem	Single decision problem	3 decision problems
Issues 6 & 7: PDC regimen distribution	• Weighted distribution for all comers based on clinical input • Same DoT for all histologies	• Separate distributions by histology based on TA557/TA600 • Different DoT by histology
Issue 10: Duration of treatment benefit	Lifetime	5 years from stopping treatment
Issue 12: Utilities	Time-to-death approach	Progression-based approach
Issue 13: Relative dose adjustment	Applied to drug acquisition costs	Applied to expected required treatment dose
Issues 14 & 15: Subsequent treatment	• Following nivo+ipi+PDC: 31% have subsequent treatment • Following PDC: 40% have subsequent treatment	• Following nivo+ipi+PDC: 45% have subsequent treatment • Following PDC: 61% have subsequent treatment
PFS models (additional area of uncertainty)	**Nivo+ipi+PDC:** Spline on odds 2 knots **PDC:** Spline on normal link 2 knots	**Both arms:** Spline on hazards 2 knots

DoT = Duration of treatment

Cost-effectiveness results

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