Part 1 slides for public - redacted

NICE National Institute for Health and Care Excellence

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

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Company: Bristol-Myers Squibb

ACM2 12 May 2021

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] • Simple discount patient access schemes for nivolumab and ipilimumab applicable for this appraisal

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ALK = Anaplastic lymphoma kinase; EGFR = Epidermal growth factor receptor; NSCLC = Non-small-cell lung cancer

Background

Comparators (updated scope)	**Non-squamous (NSQ) NSCLC:** • Pemetrexed plus carboplatin/cisplatin, with or without pemetrexed maintenance • Chemotherapy (docetaxel, gemcitabine, paclitaxel, vinorelbine) plus carboplatin/cisplatin, with or without pemetrexed maintenance • **NEW:** *Pembrolizumab plus pemetrexed and platinum chemotherapy* • PD-L1 < 50%: atezolizumab plus bevacizumab, carboplatin and paclitaxel (ABCP) • PD-L1 ≥ 50%: pembrolizumab **Squamous (SQ) 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
Model structure	Partitioned survival model, 3 health states: progression-free, progressed disease, death

Recap: clinical evidence at ACM1

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)

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 NSQ 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])

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ACM= Appraisal Committee meeting; ABCP = Atezolizumab plus bevacizumab, carboplatin and paclitaxel; CI = Confidence interval; HR = Hazard ratio; OR = Odds ratio; OS = Overall survival; PD-L1 = Programmed death-ligand 1; PFS = Progression-free survival

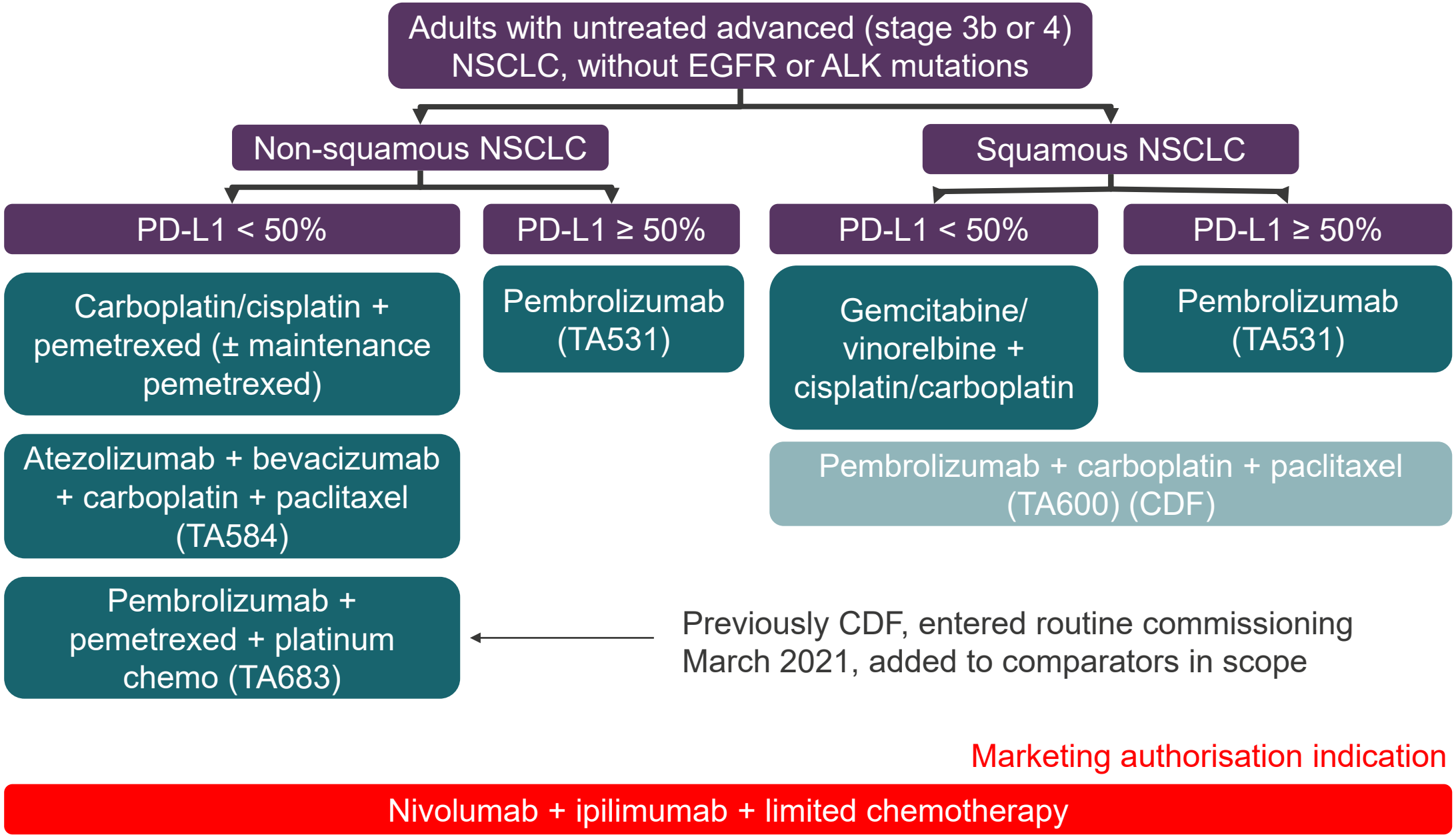
Recap: cost-effectiveness at ACM1

Company base case deterministic ICERs*	• **All patients:** £36,380 vs PDC • **NSQ, PD-L1 < 50%:** £36,380 vs PDC; Dominant vs ABCP • **PD-L1 ≥ 50%:** £36,380 vs PDC; £315,308 vs pembrolizumab (south west quadrant ICER)
ERG base case deterministic ICERs*	• **SQ, PD-L1 < 50%:** £47,872 vs PDC • **NSQ, 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)
ICERs with committee preferred assumptions	• **Nivolumab combination not cost effective in any subgroup** (values cannot be shown here because they include confidential PAS discounts)

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

ABCP = Atezolizumab plus bevacizumab, carboplatin and paclitaxel; ICER = Incremental cost-effectiveness ratio; PD-L1 = Programmed death-ligand 1

Positioning in treatment pathway



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

ACD preliminary recommendation: Not recommended

Committee's views at ACM1
Considering 3 separate subgroups based on histology and PD-L1 TPS: • people with NSQ NSCLC, whose PD-L1 TPS is below 50% • people with SQ NSCLC, whose PD-L1 TPS is below 50% • people with NSCLC of either histology, whose PD-L1 TPS is at least 50%
2-year treatment stopping rule acceptable
Applying separate survival curves for each subgroup
Modelling survival for people having platinum-doublet chemotherapy using CheckMate-227 data alone
Treatment effect lasting 3 to 5 years after starting treatment
Utility values based on disease progression rather than time to death
Applying separate platinum-doublet chemotherapy distributions for each subgroup, using UK market share data from TA557 and TA600
Subsequent treatment rates based on CheckMate-227 data
Nivolumab combination only likely to meet NICE's end of life criteria for SQ NSCLC with a PD-L1 TPS below 50%
Unlikely that collecting more data in Cancer Drugs Fund (CDF) would resolve uncertainty in modelling, nivolumab combination could not be recommended within CDF

TPS = Tumour Proportion Score

Key uncertainties in ACD

- Duration of treatment effect
- Whether it was appropriate to use the same survival curves for all 3 subgroups
- Unclear whether people having nivolumab combination live longer depending on their PD-L1 TPS and the type of NSCLC they have

ACD consultation

- Only response/comments received were from company, none from other stakeholders or consultees

TPS = Tumour Proportion Score

Key issues after consultation

- Comparison with pembrolizumab+pemetrexed+platinum chemotherapy
- Data collection and Cancer Drugs Fund
- Tolerability of nivolumab combination
- Appropriateness of using the same survival curves for all 3 subgroups
- Modelling survival for people having platinum-doublet chemotherapy
- Duration of treatment effect
- End of life

Comparison with pembrolizumab plus pemetrexed and platinum chemotherapy

ACD	*'Nivolumab combination has not been compared with pembrolizumab plus pemetrexed and platinum chemotherapy, which is widely used in the NHS'* • Final guidance for pembrolizumab+pemetrexed+platinum chemo for NSQ NSCLC published day before ACM1 for this topic. Went from CDF to routine commissioning, so now an appropriate comparator in NSQ
Company response	Have included pembrolizumab+pemetrexed+platinum chemo for NSQ in updated model Cost-effectiveness result in company's updated modelling: • Pembrolizumab+pemetrexed+platinum chemo **dominated** (for NSQ PD-L1 < 50%, and NSQ all comers)

ACM= Appraisal Committee meeting; CDF= Cancer Drugs Fund; Chemo = Chemotherapy

Comparison with pembrolizumab plus pemetrexed and platinum chemotherapy (cont.)

ERG view	• Revised NMA excluded pembrolizumab monotherapy as a comparator • No comparative evidence for pembrolizumab monotherapy vs pembrolizumab+PDC in NSQ PD-L1 > 50% population • None of the updated NMAs included [redacted] • Hazard ratio from CM-9LA for nivo+ipi+PDC vs PDC [redacted]; uncertain to what extent this will impact relative treatment effect estimated from NMAs • No access to data used in new NMAs, insufficient time to validate all fractional polynomial model choices. Company stated methods for model choice were same as in original CS which were appropriate • Some Kaplan-Meier and fitted curve plots seemed inconsistent, some corrections from company which couldn't be fully validated in time*

Questions: Has the comparison between the nivolumab combination and pembrolizumab+pemetrexed+platinum chemotherapy been carried out appropriately for decision making?

*Company confirmed that this did not affect numerical analysis results which were correctly incorporated in model.
CM = CheckMate; CS= Company submission; NMA= Network meta analysis

Data collection and Cancer Drugs Fund

ACD	*'It is unlikely that collecting more data in the Cancer Drugs Fund would resolve the uncertainty in the modelling'* • CM-9LA and CM-227 ongoing, further data likely insufficient to reduce key uncertainties affecting cost-effectiveness results (duration of treatment effect, whether it was appropriate to use same survival curves for all 3 subgroups)
Company response	• Uncertainty in modelling from lack of long-term follow-up and anticipated long-term treatment effect • Provided most up to date landmark OS and PFS results for CM-9LA versus CM-227, in NSQ (PD-L1 < 50%; all-comers) and SQ (PD-L1 < 50%; all-comers), confidential so cannot be shown here.* • Demonstrate that outcomes [redacted] • Additional database locks planned for both trials — reduce uncertainty, increase confidence in analyses, facilitate comparison of long-term outcomes across currently approved IO regimens

*Committee, please see pages 3 and 4 of company's ACD response for values

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CM= CheckMate; OS= Overall survival; PFS = Progression-free survival

Data collection and Cancer Drugs Fund (cont.)

Company response (cont.)	• Nivolumab combination meets criteria for inclusion in CDF - collection of further data would reduce uncertainty and facilitate long-term comparison

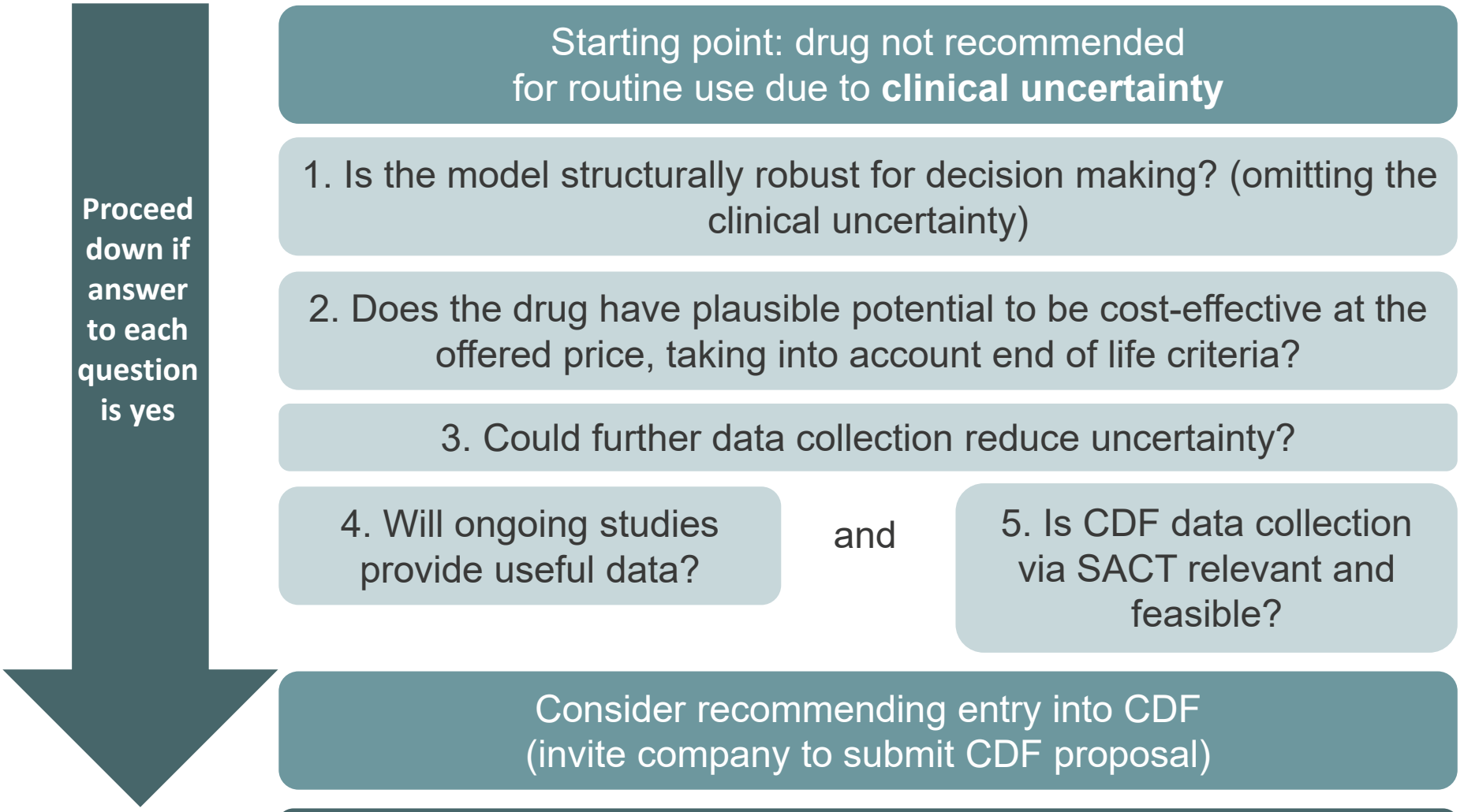
ERG view	• Number of issues regarding resolution of uncertainty, including from original report
	  • Even with CDF data collection, maximum duration of treatment benefit that could be observed is 5 years from point of treatment initiation as per upper limit of committee's preference. It was the uncertainty around this key issue of lifelong duration of benefit (i.e. cure in some patients) that was deemed unresolvable with up to 2 years of further data collection
	  • Company provided results from [redacted] ERG agree that these data support a [redacted] for nivo+ipi compared to PDC. **But** as these data were not included in new ITCs including pembrolizumab+ PDC, efficacy of nivo+ipi in long-term, compared to other immunotherapy combination therapies, is uncertain
	  • Any CDF long term outcomes data would be influenced by subsequent therapies received in CM-9LA which aren't in line with UK practice

Questions: Would further data collection address remaining uncertainties?
Do any of the subgroups meet the criteria for inclusion into the Cancer Drugs Fund?

CDF = Cancer Drugs Fund; IO = Immuno-oncology; ITC = Indirect treatment comparison; Nivo+ipi = nivolumab+ipilimumab

Cancer Drugs Fund

Committee decision-making criteria:



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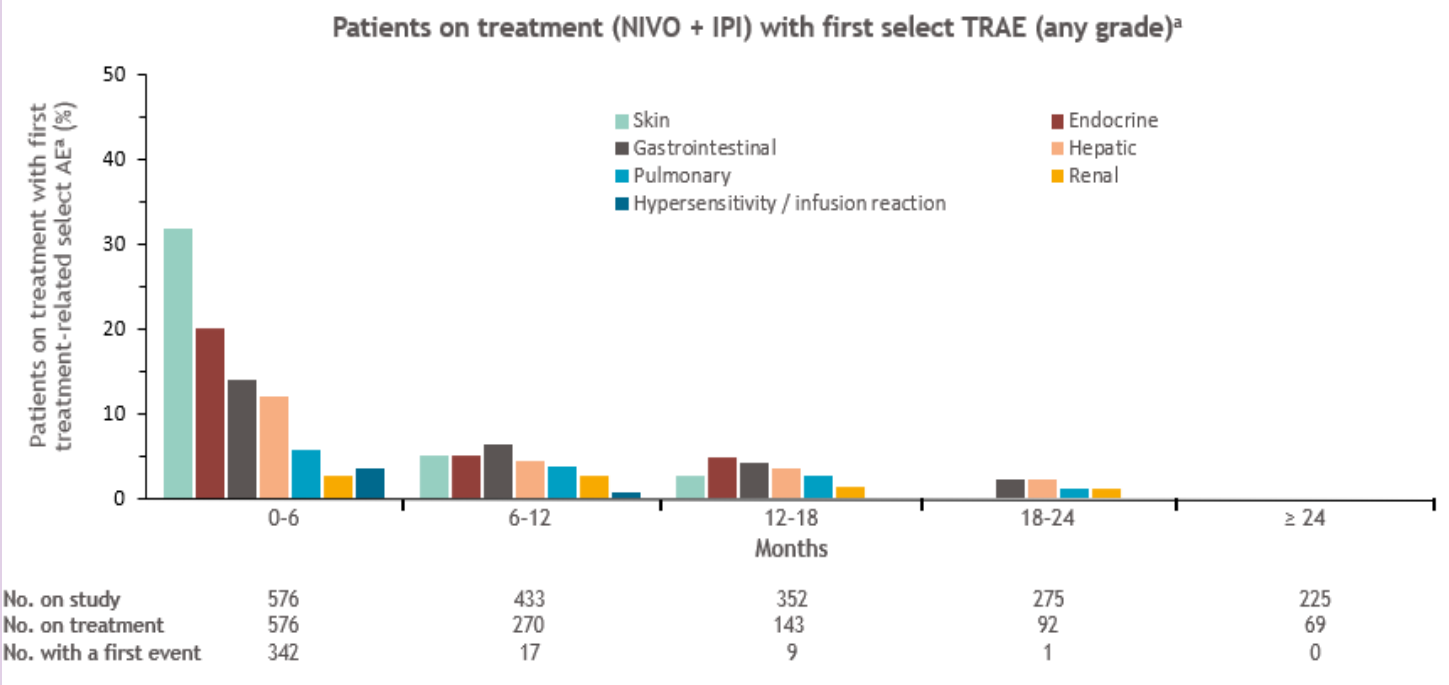
SACT = Systemic Anti-Cancer Therapy

Tolerability of nivolumab combination

ACD	*'It concluded that nivolumab combination was likely to be less well tolerated than other chemo-immunotherapy combinations, so more specialist management would be needed to address severe toxicities'* • Clinical experts - rare but unpleasant, and potentially serious, adverse events likely more common for nivolumab combination (2 different immunotherapies) than current chemo-immunotherapy combinations (only 1 immunotherapy)
Company response	• Disagree that tolerability of nivolumab combination will require more specialist management than other options • Limited course of chemo means AEs typically associated with chemo are less prevalent with this combination. CM-227 data (next slide) — AEs with nivo+ipi combination tend to occur early in treatment, managed effectively, reduce with later cycles • ITC of AEs for nivo+ipi+chemo and pembrolizumab+chemo regimens in 1L. No statistically significant differences in odds of AEs leading to discontinuation of study drug (any drug within regimen), either for grades 3/4/5 or grade 1-5 AEs

Tolerability of nivolumab combination (cont.)

Company response (cont.)



Select AEs were events with a potential immunological cause that required frequent monitoring/intervention; percentages were for patients who had events of any grade reported between first dose and 30 days after last dose of study treatment. Source: Ramalingham et al., 2020

ERG view

- Further details and results of these ITCs not available to ERG, so cannot comment further
- Unclear how company's plot of treatment-related AEs over time should be interpreted, in light of treatment discontinuations that will also occur over time

Question: Does the evidence the company has presented on tolerability necessitate a change to related wording in the guidance?

AE = Adverse event; ITC = Indirect treatment comparison

Appropriateness of using the same survival curves for all 3 subgroups

ACD	*'The committee agreed that there was uncertainty about the validity of applying survival curves derived from the ITT data across all the subgroups. It concluded that survival curves should be modelled separately for each subgroup.'*

Company response	• Have provided analyses using OS data for separate histology and PD-L1 subgroups
	• Scenario analysis using histology-specific PD-L1 all-comers data, to be consistent with decision-making data in recent CDF-exit for pembrolizumab+chemo in non-squamous (TA683)
	• CM-9LA not stratified or powered for analyses of combined histology/PD-L1 subgroups
	  • Histology was stratification factor — some rationale for analysing by histology subgroup, but not for combined histology and PD-L1 subgroups (not pre-specified, low patient numbers)
	  • PD-L1 not effect modifier due to mechanism of action for combination, as seen in trial data — further rationale supporting analyses for histology subgroups but not combined histology/PD-L1 subgroups

ERG view	• Company's updated base case implements survival curves for separate histology and PD-L1 subgroups (originally provided during technical engagement, based on 1-year data cut for CM-9LA and 3-year data-cut for CM-227. [redacted])

AE = Adverse event; CDF = Cancer Drugs Fund; Chemo= Chemotherapy; CM = CheckMate; Nivo+ipi = nivolumab+ipilimumab

Appropriateness of using the same survival curves for all 3 subgroups (cont.)

ERG view

- Company did scenario analysis where histology-specific, PD-L1 all-comers data used to model survival, for consistency with pembrolizumab+chemo in NSQ NSCLC (TA683). Did not provide details of curve fitting process for these 2 subgroups so ERG couldn't validate approach
- ERG generated OS plots extrapolated over model time horizon using company's model (survival up to 1 year informed by observed CM-9LA data, thereafter informed from survival models fit to data from CM-227; assumes there is a treatment benefit duration for immunotherapies for 5 years after discontinuing treatment):

OS in NSQ (generated from company model)

OS in SQ (generated from company model)

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OS = Overall survival

Appropriateness of using the same survival curves for all 3 subgroups (cont.)

ERG view

Landmark OS for company-selected parametric models – nivolumab + ipilimumab + limited PDC
(adapted from economic model)

	Distribution	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 5 (%)	Year 10 (%)
NSQ PD-L1 < 50%	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SQ PD-L1 < 50%	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SQ	Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NSQ	Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Landmark PFS for company-selected parametric models – nivolumab + ipilimumab + limited PDC
(adapted from economic model)

	Distribution	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 5 (%)	Year 10 (%)
NSQ PD-L1 < 50%	Spline Odds 1 Knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SQ PD-L1 < 50%	Spline Normal 1 Knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SQ	Spline Odds 2 Knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NSQ	Spline Odds 1 Knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Question: Are the company's analyses, using OS data for separate histology and PD-L1 subgroups, appropriate for decision making?

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OS = Overall survival; PDC= Platinum-doublet chemotherapy

Modelling survival for people having PDC

ACD	*'The committee concluded that the survival curves for people having platinum-doublet chemotherapy should be based on the CheckMate-227 data alone'* • Median OS PDC longer in CM-227 than in CM-9LA • Rate of subsequent immunotherapy in CM-227 likely closer to NHS practice
Company response	• Prefer original approach aligned with that of nivo+ipi+PDC arm: CM-9LA used up to 13 months, then conditional survival from CM-227 applied • CM-9LA is registrational trial, most appropriate for estimation of survival benefit of patients on PDC, preserve benefits of comparing between arms of randomised controlled trial • Using CM-227 naïvely to inform absolute survival for chemo arm would disregard data from registrational trial; using CM-227 alone is choosing 'worst case' comparator data available • Limited UK real-world evidence suggests OS seen in clinical practice for patients treated with chemo lower than in CM-9LA and less than half that in CM-227 • [redacted]

1L = First line; ALK = Anaplastic lymphoma kinase; EGFR = Epidermal growth factor receptor; PDC = Platinum-doublet chemotherapy

Modelling survival for people having PDC (cont.)

Company response (cont.)	• Median OS for CM-9LA within range recently reported in other phase 3 1L NSCLC studies, which had similar populations
	• Systematic lit review and NMA of 1L therapies for advanced NSCLC in patients without sensitising EGFR mutations or ALK translocations.
	  • Median OS for chemo arm of CM-9LA above overall median, similar to medians for both KeyNote-189 and 407, median OS for CM-227 substantially higher. Median PFS for chemo arms of CM-9LA, Keynote-189 and KeyNote-407 similar, with CM-227 slightly higher
	• Inappropriate to use survival estimate from chemo arm of CM-227 in this appraisal as these seem to be outliers. CM-9LA is registrational trial, chemo survival estimates well aligned with those from other trials (particularly KeyNote-189 and -407, considered representative of UK in other recent NICE appraisals)
	  • Inconsistent for committee to assume higher OS for patients treated with PDC in comparison with nivolumab combination, than was considered valid in similar appraisal of pembrolizumab+chemo (TA683), published last month

ERG view	• Model predicts 10.5% 5-year survival for PDC in CM-227 alone; 9% in hybrid approach using CM-9LA followed by CM-227 — both fall in range considered in previous STAs (5-11% in TA531; 9-12% in TA584 though committee considered these results with reference to in TA531; 5-11% in TA683)

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NMA= Network meta analysis; OS = Overall survival; PDC= Platinum-doublet chemotherapy; PFS = Progression-free survival; STA = Single technology appraisal

Modelling survival for people having PDC (cont.)

ERG view

- PDC arm in CM-227 better for NHS decision making compared to CM-9LA, due to subsequent therapy (numerically lower in CM-9LA, proportion with subsequent therapy in CM-227 closer to anticipated proportion in NHS)
- Company suggest committee-preferred scenario of using PDC survival from CM-227 and relative effects from fractional polynomial NMA naively informs absolute survival for PDC arm. **Incorrect interpretation** - analysis not conducted naively, relative treatment effects estimated from the NMA are applied to baseline survival curve, maintaining randomised nature of relative treatment effects
- ERG have not seen search strategies or extracted data for company's lit review, difficult to comment on how comparable results are
- REAL-O analysis —shows survival below that in CM-227, but no access to database or opportunity to scrutinise the analysis, so difficult to comment on how comparable the results are. ERG agrees with company that limited real world evidence from UK is available
- **ERG agrees with committee — PDC arm in CheckMate-227 appears to be better for decision making in NHS**

Question: Should the company's original approach to modelling survival in the platinum-doublet chemotherapy arm be used, instead of using CheckMate-227 data alone?

OS = Overall survival; PDC= Platinum-doublet chemotherapy

Duration of treatment effect

ACD	*'The committee concluded that a treatment effect lasting **3 to 5 years after starting treatment** was appropriate for decision making, for consistency with previous immunotherapy appraisals in NSCLC.'*
Company response	• CM-227 3-year data cut show clear continued treatment effect beyond 2-year treatment stop • Evidence from nivolumab in 2L NSCLC demonstrates robust, durable treatment effect of IO therapy in patients with NSCLC • Growing evidence across other tumour types that dual IO therapy will have a robust treatment effect beyond discontinuation when compared to single-IO therapy (advanced melanoma, RCC) • 5-year treatment effect duration after discontinuation in updated analyses
ERG view	• Company's updated economic analysis considers a treatment effect duration of 5 years **after stopping** treatment (i.e. 7 years after starting treatment, given a maximum 2 year treatment duration for nivolumab) — **more optimistic assumption than was preferred by Committee**
Technical team	• Company should have provided analyses for 3 and 5 year treatment effect duration **from the start of treatment**. Committee should consider ERG's scenario analyses with a 3-year and 5-year effect from the start of treatment.

Questions: Is 5-year treatment effect duration sufficient for decision making? Should 3-year values also be considered?

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2L = Second line; IO = Immuno-oncology; RCC = Renal cell carcinoma

End of life

ACD	Committee '*understood that the company and ERG agreed that nivolumab combination did not meet the criteria for end of life treatments for:* • *non-squamous NSCLC and a PD-L1 TPS below 50%* • *NSCLC of either histology and a PD-L1 TPS of 50% or more'* Nivolumab combination likely to meet criteria for end of life treatment in single subgroup with SQ NSCLC and PD-L1 TPS below 50%
Company response	Need for additional treatment options in 1L, end-of-life (EOL) criteria apply across all populations in this appraisal (median OS less than 24 months, anticipated survival benefit greater than 3 months following nivolumab combination) Trial OS for IO+chemo combinations not reflected in clinical practice, **median OS less than 24 months in all subgroups**: • Waterhouse et al (2021), stage IIIB/IV NSCLC retrospective study in Flatiron database, IO+chemo (pembrolizumab+chemo used in over 98%) • Median OS SQ/NSQ NSCLC (10.6 / 12 months) lower than for SQ/NSQ (17.1 / 22 months) in KeyNote-407&KeyNote-189 trials CDF-exit reviews for nivolumab in **2L** NSCLC (TA655 and GID-TA10513): SACT data OS reflects that in trials; longer follow-up in trials showed predicted long-term OS achieved in practice (Popat et al., 2021)

CDF = Cancer Drugs Fund;; IO = Immuno-oncology; OS = Overall survival; PD-L1 = Programmed death-ligand 1; RCT = Randomised control trial; SACT = Systemic Anti-Cancer Therapy

End of life (cont.)

ERG view

- Immunotherapy+chemo combinations — patients in observational dataset had more severe performance status, were older, more likely to have unstable brain metastases. Treated in USA (different treatment patterns to UK), substantially fewer patients went on to 2L treatment compared to trials
  - Uncertain whether observational dataset more reflective of UK population that may receive nivolumab for untreated, advanced NSCLC. In recent TA683 (pembrolizumab+chemo), clinical advisers considered that population of KeyNote-189 generalisable to UK population, end of life criteria judged on mean survival predicted by model (informed by KeyNote-189 data)
- Currently very little long-term observational evidence for survival of patients on 1L nivolumab to demonstrate whether 3 month survival extension would be observed in practice
  - Company cited Popat et al. Possible there is similar efficacy decline for nivolumab in practice when patients with more severe characteristics are treated when compared to corresponding trial, and that 3 month life extension may not be observed —consider this **uncertain, not yet supported by evidence**
- **Both median and mean survival considered when judging whether end of life criteria apply**. Median typically lower than mean estimate — median OS 22.0 months for pembrolizumab+PDC in KeyNote-189 likely had associated mean greater than 24 months

End of life (cont.)

ERG view (cont.)

- Company's analysis of cost-effectiveness in NSQ PD-L1 < 50% population predicts mean (undiscounted) life years gained for all immunotherapies are greater than 24 months:

Mean (undiscounted) life years predicted by company analysis

	NSQ, PD-L1 < 50%	NSQ	SQ, PD-L1 < 50%	SQ
24 months survival?	ABPC: 2.61 PDC: 2.15 Pembro+PDC: 2.77	PDC: 2.38 Pembro+PDC: 3.24	PDC: 1.26	PDC: 1.29
3 month extension to survival?	Nivo+Ipi+PDC: 3.56	Nivo+Ipi+PDC: 4.17	Nivo+Ipi+PDC: 2.48	Nivo+Ipi+PDC: 2.80
Meets EOL conditions?	No, survival is > 24m	No, survival is > 24m	Yes	Yes

- Evidence not sufficiently compelling to demonstrate EOL criteria met in NSQ PD-L1 < 50%. EOL criteria not met in PD-L1 ≥ 50% subgroups where pembrolizumab monotherapy is a comparator, with greater than 24 months mean survival
- EOL criteria only met in SQ PD-L1 < 50%, where only comparator to nivo+ipi+PDC is PDC (similar conclusion made in recent appraisal of pembrolizumab+PDC [TA683] regarding EOL criteria in each NSQ subgroup)

Question: Are NICE's end of life criteria met for any of the populations in this appraisal?

ERG's other comments – Subsequent therapies

- Nivo+ipi+PDC CM-9LA survival data captures effects of subsequent immunotherapies and targeted therapies not in line with current NHS practice. Survival benefits of subsequent therapies inherently included in cost-effectiveness of nivolumab combination
- **Despite benefits being included, company's model does not include cost of these therapies** — cost of docetaxel applied, assumed 100% of patients having subsequent therapy had docetaxel (as would happened in NHS practice)
  - More consistent approach would be to apply costs of subsequent immunotherapies used in CM-9LA and/or CM-227
  - Though resulting costs may be less generalisable to NHS practice, there is consistency in applying relevant costs of all therapies used to match observed effects of these therapies, prevent under/overestimation of cost-effectiveness
  - Similar issue highlighted in recent appraisal of pembrolizumab for urothelial carcinoma after platinum-containing chemotherapy (TA692), committee found it inconsistent to include potential benefits of retreatment without the costs, concluding that both should either be included or excluded.

Assumptions in company's updated analyses

	Company's interpretation of Appraisal Committee's preferred assumption in ACD	Company's interpretation of their assumptions in ACD response economic analysis	Notes
Survival curves by subgroups	Apply separate survival curves by histology (NSQ and SQ) and PD-L1 status	Apply separate survival curves by histology (NSQ and SQ) and PD-L1 status	
PDC Survival Modelling	Survival for people having PDC should be modelled using CheckMate-227 data alone	Model survival for people having PDC based on CheckMate-9LA followed by CheckMate-227	Not in line with committee preference
Treatment effect duration	3 – 5 years	5 years as per the ERG and Appraisal Committee's preferred assumption	Not in line with committee preference
Utility values	Progression-based utility values	Progression-based utility values	
Composition of PDC	Separate chemotherapy regimen distributions should be used	Separate chemotherapy regimen distributions are used	
Proportion of subsequent therapy	Subsequent therapy proportion should be based on CheckMate-227	Subsequent therapy based on CheckMate-227	
Relative dose intensity	Minimal impact on ICER results and likely to lie between company and ERG approach	Retained company-preferred approach	

Key issues after consultation

Issue at ACM2	Questions for committee
Comparison with pembrolizumab+pemetrexed+ platinum chemotherapy	• Has the comparison between the nivolumab combination and pembrolizumab+pemetrexed+platinum chemotherapy been carried out appropriately for decision making?
Data collection and Cancer Drugs Fund	• Would further data collection address remaining uncertainties? • Do any of the subgroups meet the criteria for inclusion into the Cancer Drugs Fund?
Tolerability of nivolumab combination	• Does the evidence the company has presented on tolerability necessitate a change to related wording in the guidance?
Appropriateness of using the same survival curves for all 3 subgroups	• Are the company's analyses, using OS data for separate histology and PD-L1 subgroups, appropriate for decision making?
Modelling survival for people having platinum-doublet chemotherapy	• Should the company's original approach to modelling survival in the platinum-doublet chemotherapy arm be used, instead of using CheckMate-227 data alone?
Duration of treatment effect	• Is 5-year treatment effect duration sufficient for decision making? • Should 3-year values also be considered?
End of life	• Are NICE's end of life criteria met for any of the populations in this appraisal?

Cost-effectiveness results

All decision making ICERs were discussed in part 2 slides because they included confidential comparator PAS discounts