NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission** from Bristol-Myers Squibb
2. **Clarification questions and company responses**
3. **Patient group, professional group and NHS organisation submission** from:
   a. Roy Castle Lung Cancer Foundation
4. **Evidence Review Group report** prepared by Centre for Reviews Dissemination and Centre for Health Economics – York
5. **Evidence Review Group – factual accuracy check**
6. **Technical engagement response** from Bristol Myers-Squibb
   a. Technical engagement response form
   b. Appendix A: Fractional Polynomial Heuristic Description
   c. Appendix B: Curve selection for subgroups
7. **Expert personal perspectives and technical engagement responses from experts:**
   a. Dr Alastair Greystoke, Consultant Oncologist – clinical expert, nominated by Bristol Myers Squibb
   b. Professor Mary O'Brien, Consultant Oncologist and Professor of practice (medical oncology) – clinical expert, nominated by Royal College of Physicians
   c. Peter Barton, Lung Cancer Specialist Nurse – patient expert, nominated by Lung Cancer Nurse UK
8. **Evidence Review Group critique of company response to technical engagement** prepared by Centre for Reviews Dissemination and Centre for Health Economics - York

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Single technology appraisal

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

Document B

Company evidence submission

Submitted by Bristol Myers Squibb Pharmaceuticals, Ltd.

4 December 2020

File name	Version	Contains confidential information	Date
ID1566 Nivolumab + ipilimumab + PDC in 1L NSCLC Document B 4 Dec 20 [Redacted]	2.0	No	4 December 2020

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B.1 Decision problem, description of the technology and clinical care pathway

B.1.1Decision problem

The European Medicines Agency (EMA) marketing authorisation application is for nivolumab with ipilimumab and limited chemotherapy (hereafter referred to as *nivolumab + ipilimumab + limited platinum doublet chemotherapy [PDC]*) for adults with untreated metastatic non-small cell lung cancer (NSCLC). This submission covers the technology's full marketing authorisation for this indication. Nivolumab + ipilimumab + limited PDC has demonstrated efficacy in the pivotal CheckMate-9LA trial,[1] and will provide patients with an additional chemotherapy-limited treatment option. In the United Kingdom (UK), patients with non-squamous histology are treated with either pemetrexed in combination with a platinum therapy (NICE technology appraisal [TA] guidance 181[2]); atezolizumab with bevacizumab, carboplatin, and paclitaxel (for people whose tumours express programmed death-ligand 1 [PD-L1] with < 50% tumour proportion score [TPS]; NICE TA guidance 584[3]); or pembrolizumab (for people whose tumours express PD-L1 ≥ 50% TPS; NICE TA guidance 531[4]). Patients with squamous histology are treated with PDC (NICE guideline 122[5]); those whose tumours express PD-L1 ≥ 50% TPS are treated with pembrolizumab (NICE TA guidance 531[4]).

The company submission is consistent with the final National Institute for Health and Care Excellence (NICE) scope and the NICE reference case (Table 1).

Table 1. The decision problem

	Final scope issued by NICE[6]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with untreated metastatic NSCLC without sensitising EGFR mutations or ALK fusions	Adults with untreated stage IV or recurrent NSCLC without sensitising EGFR mutations or ALK fusions	
Intervention	Nivolumab with ipilimumab and standard chemotherapy	Nivolumab (Opdivo®) with ipilimumab (Yervoy®) and standard chemotherapy	
Comparator(s)	For adults with non-squamous histology: • Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) (for people with adenocarcinoma or large cell carcinoma only) – With (following cisplatin-containing regimens only) or without pemetrexed maintenance treatment • Chemotherapy (docetaxel, gemcitabine, paclitaxel, or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) – With or without pemetrexed maintenance treatment • Atezolizumab with bevacizumab, carboplatin, and paclitaxel (for people whose tumours express PD-L1 with < 50% TPS) • Pembrolizumab (for people whose tumours express PD-L1 with ≥ 50% TPS) For adults with squamous histology: • Chemotherapy (docetaxel, gemcitabine, paclitaxel, or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin)	For adults with non-squamous histology: • Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) (for people with adenocarcinoma or large cell carcinoma only) – With (following cisplatin-containing regimens only) or without pemetrexed maintenance treatment • Chemotherapy (docetaxel, gemcitabine, paclitaxel, or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) – With or without pemetrexed maintenance treatment • Atezolizumab with bevacizumab, carboplatin, and paclitaxel (for people whose tumours express PD-L1 with < 50% TPS) • Pembrolizumab (for people whose tumours express PD-L1 with ≥ 50% TPS) For adults with squamous histology: • Chemotherapy (docetaxel, gemcitabine, paclitaxel, or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin)	

	Final scope issued by NICE[6]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Pembrolizumab (for people whose tumours express PD-L1 with ≥ 50% TPS)	• Pembrolizumab (for people whose tumours express PD-L1 with ≥ 50% TPS)	
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	The outcome measures considered include: • Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life-year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be conducted. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be considered. If appropriate, the economic modelling should include the costs associated with diagnostic testing for biological markers (e.g., PD-L1) in people with NSCLC who	We present a cost-effectiveness analysis in line with the reference case.	

	Final scope issued by NICE[6]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.		
Other considerations	If evidence allows, subgroup analysis by level of PD-L1 expression will be considered. Guidance will only be issued according to the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	We present the CheckMate-9LA trial ITT population as the base case. The overall survival benefit of nivolumab + ipilimumab + limited PDC was consistent across subgroups in CheckMate-9LA; therefore, histological and PD-L1 subgroups will only be considered to align with positioning of the in-scope comparators.	
Special considerations including issues related to equity or equality		BMS are not aware of specific equality issues for this appraisal.	

Abbreviations: ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; ITT = intention to treat; NHS = National Health Service; NSCLC = non-small cell lung cancer; PDC = platinum doublet chemotherapy; PD-L1 = programmed death-ligand 1; TPS = tumour proportion score.

Sources: NICE (2020)[6]; NICE (2020)[7]

B.1.2Description of the technology being appraised

As summarised in Section B.1.1, this appraisal is for nivolumab + ipilimumab + limited PDC for adults with untreated stage IV or recurrent NSCLC. Nivolumab (Opdivo®; Bristol Myers Squibb) is a fully human immunoglobulin G4 (IgG4) monoclonal antibody that targets and blocks the programmed death-1 (PD-1) receptor to promote an antitumour immune response. It is administered intravenously.[8-12] Ipilimumab (Yervoy®; Bristol Myers Squibb) is a recombinant human anti–cytotoxic T-lymphocyte antigen-4 (CTLA-4) monoclonal antibody that blocks the effects of CTLA-4 to enhance T-cell–mediated immune responses to tumour cells. Ipilimumab is administered intravenously.[13-17]

The mechanisms of action of ipilimumab and nivolumab are distinct and complementary, with ipilimumab working early in the immune response by potentiating antigen presentation to naive T-cells in the lymph nodes and nivolumab working later in the immune response on the tumour-specific effector T-cells.[8,13] Therefore, the combination of the two immuno-oncology (IO) therapies is expected to result in improved efficacy versus a single IO agent. Adding a limited course (2 cycles) of chemotherapy to nivolumab + ipilimumab may help to mitigate the risk of early disease progression and to achieve initial disease control while minimising the toxicity associated with a prolonged course of chemotherapy. Further, this combination may preserve PDC as a later-line treatment option.

Nivolumab + ipilimumab + limited PDC for untreated metastatic NSCLC does not currently have a marketing authorisation in the UK. It has been studied in the CheckMate-9LA clinical trial compared with PDC (pemetrexed or paclitaxel, with platinum therapy) alone in adults with untreated metastatic NSCLC without epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutations (Table 2).[1,6]

Table 2. Technology being appraised

UK approved name and brand name	Ipilimumab (Yervoy®) and nivolumab (Opdivo®) + 2 cycles of PDC
Mechanism of action	Ipilimumab and nivolumab are both fully human, monoclonal immunoglobulin antibodies (IgG1k and IgG4 human monoclonal antibodies, respectively) that act as checkpoint inhibitors of CTLA-4 and PD-1 at their distinct, yet complementary, positions within the T-cell response pathway[8,13]: • Ipilimumab switches off the negative regulation of the immune response (by blocking CTLA-4 [expressed on T-cells] signalling), thus allowing further activation and expansion of the early T-cell response and increasing the number of antigen-specific activated T-cells surrounding the tumour.[13-17] • Nivolumab blocks PD-1, an inhibitory receptor expressed on activated T-cells, thus reversing immune suppression and increasing T-cell activation. Therefore, nivolumab allows active T-cells to infiltrate and destroy the tumour, promoting antitumour immunity.[8-12] The mechanisms of action of ipilimumab and nivolumab are distinct and complementary, with ipilimumab working early in the immune response by potentiating the presentation of antigens to naive T-cells in the lymph nodes and nivolumab working later in the immune response to increase tumour-specific effector T-cells.[18] Therefore, nivolumab + ipilimumab potentiates immune-mediated tumour destruction, stimulating the patient's own immune system to directly fight cancer cells (in the same way that it would any other foreign cell), which results in destruction of the tumour through pre-existing,

	intrinsic processes. Adding a limited course of chemotherapy to this combination may help to mitigate the risk of early disease progression and to achieve initial disease control while minimising the toxicity associated with a prolonged course of chemotherapy.
Marketing authorisation/ CE mark status	A marketing authorisation application has been filed in the UK for [redacted]. It has been studied in a clinical trial (CheckMate-9LA) compared with chemotherapy (pemetrexed or paclitaxel, with platinum therapy) alone in adults with untreated metastatic NSCLC without EGFR or ALK mutations.[1] [redacted]
Indications and any restriction(s) as described in the SmPC	[redacted]
Method of administration and dosage	Intravenous infusion of 360 mg nivolumab every 3 weeks + 1 mg/kg ipilimumab every 6 weeks + 2 cycles of chemotherapy every 3 weeks (non-squamous: pemetrexed + cisplatin or carboplatin; squamous: paclitaxel + carboplatin).
Additional tests or investigations	No additional tests or investigations outside current practice are expected.
List price and average cost of a course of treatment	Nivolumab list price per dose: £3,950 Ipilimumab list price per dose: £7,500 PDC list price per dose: £634.10 Average cost of a course of treatment at list price: [redacted][a]
Patient access scheme (if applicable)	There is a simple discount PAS for nivolumab and ipilimumab approved by the Department of Health that is applicable to this appraisal. [redacted]

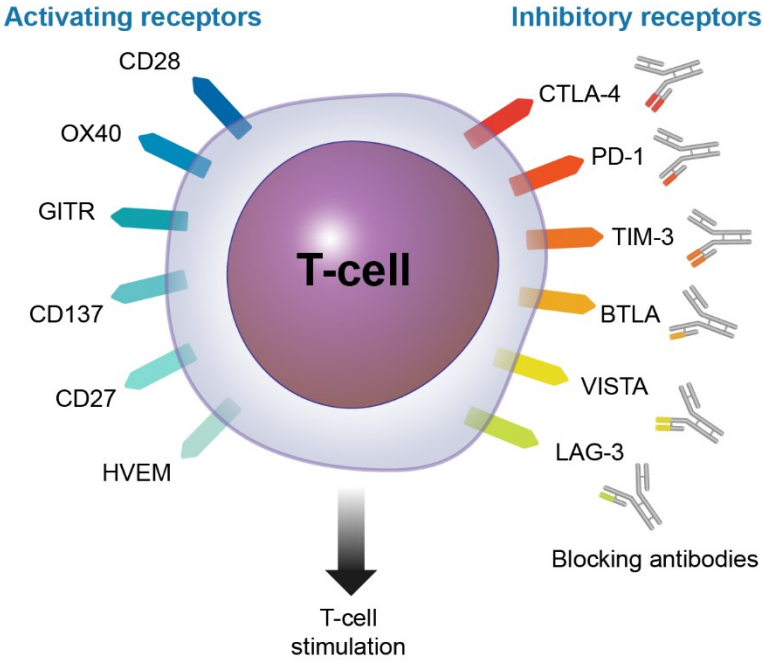
Abbreviations: ALK = anaplastic lymphoma kinase; BMS = Bristol Myers Squibb; CDF = Cancer Drugs Fund; CHMP = Committee for Medicinal Products for Human Use; CTLA-4 = cytotoxic T-lymphocyte antigen-4; EGFR = epidermal growth factor receptor; IgG = immunoglobulin G; NSCLC = non-small cell lung cancer; PAS = patient access scheme; PD-1 = programmed death-1; PDC = platinum doublet chemotherapy; SmPC = summary of product characteristics; UK = United Kingdom.

[a] Cost of a course of nivolumab + ipilimumab + limited PDC at list price based on duration of treatment and dose intensity in the CheckMate-9LA trial.

Immunotherapy has been at the forefront of therapeutic development in oncology since the discovery that cancer cells evade destruction by exploiting the signalling pathways that control the immune system.[8,13] Neoantigens are novel peptide sequences found on tumour cells that mark them as “non-self” to the immune system; these neoantigens are then identified as “non-self” by circulating antigen-presenting cells (e.g., dendritic cells) and used to generate an immune response against the foreign cells. The typical immune response to foreign cells in the body is the activation of antigen-specific T-cells that can eradicate them. Discrete populations of T-cells (effectors and regulators) proliferate and differentiate through various pathways, with T-cell activation regulated through a complex balance of positive and negative signals provided by costimulatory receptors on the T-cell surface (Figure 1).[13] Healthy, non-foreign cells (“self-cells”) avoid T-cell destruction by stimulating and displaying inhibitory receptors known as *checkpoints* to suppress the effector T-cell response; cancer cells can use

these same inhibitory receptors to escape the immune response. Blocking antibodies designed to bind to these checkpoints (so-called *checkpoint inhibitors*) can prevent tumour-driven T-cell suppression, as depicted in Figure 1, and increase immune activity against cancer cells.[8,13]

Figure 1. Receptors involved in the regulation of the T-cell immune response



Abbreviations: BTLA = B- and T-lymphocyte attenuator; CD27 = cluster of differentiation 27; CD28 = cluster of differentiation 28; CD137 = cluster of differentiation 137; CTLA-4 = cytotoxic T-lymphocyte antigen-4; GITR = glucocorticoid-induced tumour necrosis factor receptor; HVEM = herpes virus entry mediator; OX40 = tumour necrosis factor receptor superfamily, member 4; LAG3 = lymphocyte-activation gene 3; PD-1 = programmed death-1; TIM3 = T-cell immunoglobulin and mucin-domain containing-3; VISTA = V-domain immunoglobulin suppressor of T-cell activation.

Source: Mellman et al. (2011)[13]

Nivolumab is a human IgG4 monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with programmed death-ligand 1 (PD-L1) and PD-L2. The PD-1 checkpoint is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed on antigen-presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation.[8,13] Nivolumab potentiates T-cell responses, including antitumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands.[8,13]

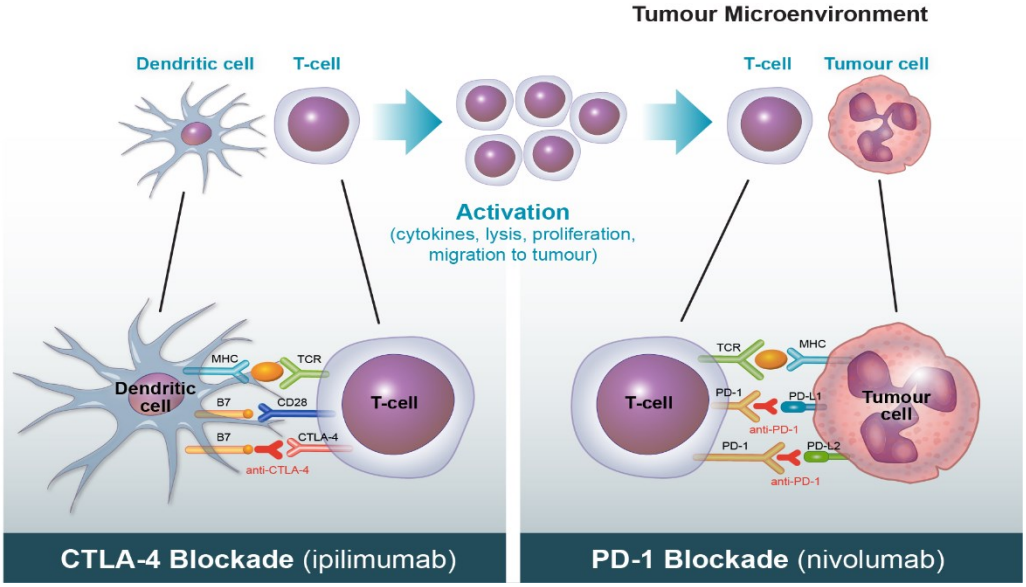
CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a monoclonal antibody that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumour-infiltrating T-effector cells.[8,13] Inhibition of CTLA-4 signalling can also reduce T-cell regulatory function, which may contribute to a general increase in T-cell responsiveness, including the antitumour immune response.

The mechanisms of action of ipilimumab and nivolumab are distinct and complementary, with ipilimumab working early in the immune response by potentiating the presentation of antigens

to naive T-cells in the lymph nodes and nivolumab working later in the immune response on the tumour-specific effector T-cells.[18] Therefore, nivolumab + ipilimumab potentiates immune-mediated tumour destruction, stimulating the patient's own immune system to directly fight cancer cells (in the same way that it would any other foreign cell), which results in destruction of the tumour through pre-existing, intrinsic processes (Figure 2).

Figure 2. Nivolumab and ipilimumab: mechanism of action for dual immune checkpoint blockade

Ipilimumab (anti–CTLA-4)	Nivolumab (anti–PD-1)
Induces de novo antitumour T-cell responses[9,11]	Restores antitumour T-cell function[14,15]
Enables adaptation to evolving tumour[11,12] Promotes emergence of memory T-cells[10] Causes compensatory increase in tumour PD-L1[11]	Enhances pre-existing T-cell response[14] Increases cytokine production[17]



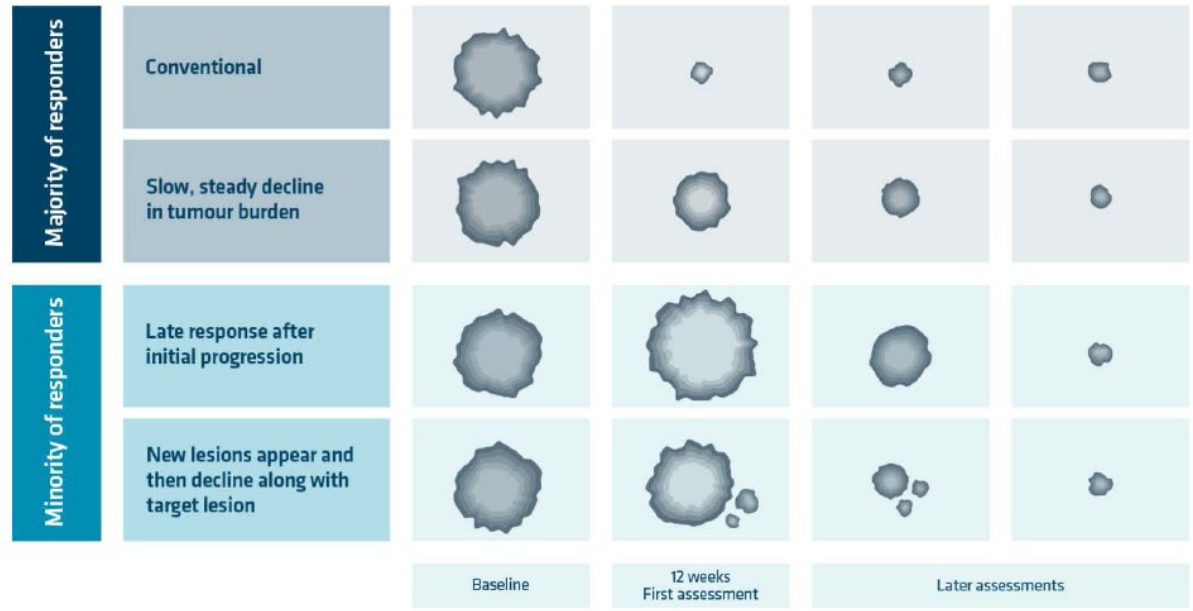
Abbreviations: CD28 = cluster of differentiation 28; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; MHC = major histocompatibility complex; PD-1 = programmed death-1; PD-2 = programmed death-2; PD-L1 = programmed death-ligand 1; PD-L2 = programmed death-ligand 2; TCR = T-cell receptor.
Sources: Mellman et al. (2011)[13];Guo et al. (2017)[8]

The combined mechanism of action of nivolumab + ipilimumab, which involves the complementary inhibition of CTLA-4 and PD-1, results in increased antitumour activity and may offer the potential of long-term survival to patients with advanced NSCLC.[19,20] Adding a limited course of chemotherapy to this combination may help to mitigate the risk of early disease progression and to achieve disease control.

It is important to recognise the key differences between IO therapies and standard anticancer therapies; these differences arise from the novel mechanisms of action of IO therapies. First, varying patterns of response can be observed with IO therapies such that patients who ultimately achieve a positive clinical outcome may have tumours that appear to have enlarged when assessed in the early stages of treatment. This is due to increased T-cell activity that makes the tumour appear larger (pseudoprogression) (Figure 3). It is anticipated that adding a limited course of chemotherapy to the IO-IO combination may provide initial disease control and may be sufficient to provide an additive effect to nivolumab and ipilimumab by increasing

tumour antigen release and reducing inhibitory signal with a net effect of activating the host immune system.[21] This effect has been observed with other IO plus chemotherapy combinations that have been launched or are in late-stage development trials. However, such combinations use 4 cycles of chemotherapy, with the potential for much higher levels of chemotherapy-related toxicities compared with limited chemotherapy with 2 cycles.

Figure 3. Typical patterns of response observed with immuno-oncology therapies



Second, IO therapies should not be considered targeted therapies. Although they target specific pathways in the immune system, this is not the same as targeting an abnormal protein resulting from a tumour-specific DNA mutation.

B.1.3Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease background

B.1.3.1.1 Introduction

Lung cancer is the third most common cancer in the UK and has the highest mortality of any cancer.[22,23]

B.1.3.1.2 Histology and biomarkers

There are two major groups of lung cancer that differ based on histology: NSCLC (80%-85%) and small cell lung cancer (10%-15%).[24]

NSCLC is divided into three main histological subtypes: squamous cell carcinoma (~25%-30%), adenocarcinoma (~40%), and large cell carcinoma at (~10%-15%).[24,25] A few other subtypes of NSCLC, such as adenosquamous carcinoma and sarcomatoid carcinoma, are much less common.[24] Together, adenocarcinoma and large cell carcinoma are referred to as *non-squamous NSCLC*.

A better understanding of lung disease has led to the development of new treatment options and the identification of subgroups of patients who can most benefit from them. These biomarkers include EGFR, ALK, ROS proto-oncogene 1 (ROS1), B-Raf proto-oncogene (BRAF), and, more recently, PD-L1.[26-35]

Unlike the molecular biomarkers (EGFR, ALK), which clearly identify tumours with a specific mutation or translocation that may respond to a given targeted therapy, PD-L1 is a protein biomarker that has a continuum of expression levels with no clear cutoff point,[36] and many health care professionals view this biomarker as an inadequate selection tool. Prevalence of PD-L1 expression in metastatic NSCLC has been assessed in a pooled analysis of seven clinical trials of nivolumab (Table 3).[37]

Table 3. Prevalence of PD-L1 expression in pooled analysis of seven nivolumab trials in metastatic NSCLC

PD-L1 expression	Percentage of patients (N = 4,972)
≥ 50%	29.8
≥ 1% to 49%	34.8
< 1%	35.4

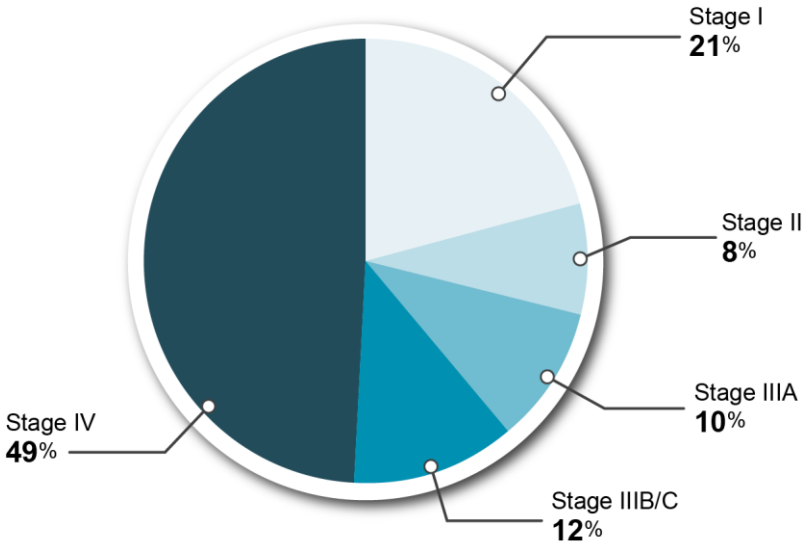
Abbreviations: NSCLC = non-small cell lung cancer; PD-L1 = programmed death-ligand 1.
Source: Krigsfeld et al. (2017)[37]

In some cancers, there is evidence that anti–PD-1/L1 IO therapies show a greater likelihood of benefit in patients whose tumours have higher levels of PD-L1 expression.[37] Nevertheless, PD-L1 is not an exclusionary biomarker, and durable responses and long-term survival in response to anti–PD-1/L1 treatment have been observed in patients with low or no PD-L1 expression across different tumours, lines of therapy, and agents.[38,39]

B.1.3.2 Diagnosis

Most lung cancers are diagnosed at an advanced stage when the cancer has spread to lymph nodes and other organs in the chest (locally advanced disease and unresectable locally advanced disease; stages IIIA and IIIB) or to other parts of the body (metastatic disease; stage IV). Of all lung cancer cases, 49% are diagnosed at stage IV (metastatic) (Figure 4).[40]

Figure 4. Stage distribution of lung cancer for 2018 in the United Kingdom



Note: data are missing for 4% of the sample (not presented).

Source: Royal College of Physicians (2020)[40]

B.1.3.3 Prevalence and incidence

In 2018, approximately 33,207 people were diagnosed with NSCLC in England and 1,941 in Wales. Approximately 57% had stage IIIB or IV disease in both England and Wales.[41]

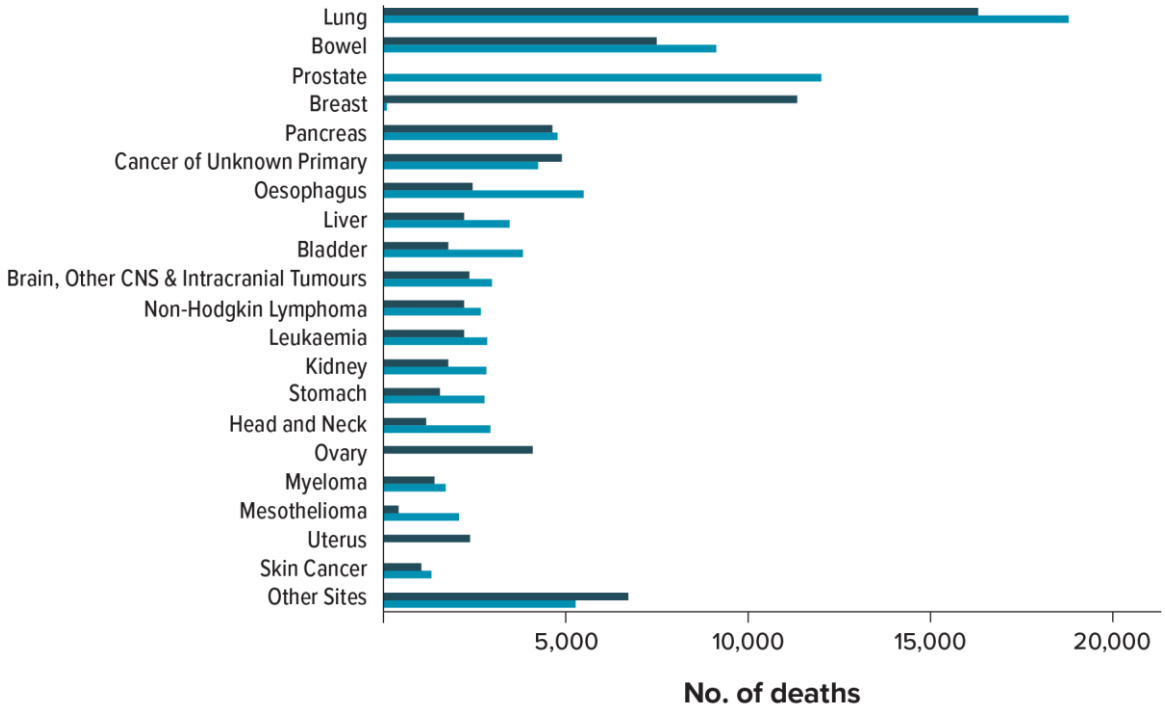
B.1.3.4 Mortality and survival

Patients with advanced or metastatic NSCLC have limited life expectancy, and long-term survival remains poor. National Lung Cancer Audit data from the UK suggest the 1-year relative survival rate for NSCLC in 2016 (by stage at diagnosis) was 81.7%, 64.1%, 42.5%, and 15.5% for stage I, II, III, and IV disease, respectively.[42] The 1-year survival for all patients with lung cancer in the UK was 38.9% in 2018 (England, 38.7%; Wales, 40.4%).[40] In England only, 21.1% of patients with lung cancer survived at 2 years, and 11.3% at 3 years.[i] In the UK, the 5-year survival rates for lung cancer overall were 35%, 20%, and 6% for stages I, II, and III, respectively.[43] The 5-year survival rates for stage IV lung cancer were estimated to be 2.9% in 2017.[44]

In 2017, lung cancer was the most common cause of cancer death in the UK (Figure 5).[45]

[i] Different cohort of patients, including those in the 2014-2017 annual reports.

Figure 5. Causes of cancer deaths, United Kingdom, 2017



Note: Males = light blue; females = dark blue.

Source: Cancer Research UK (2017)[45]

A review published in 2013 (when PDC was the standard of care for advanced NSCLC without specific biomarkers) found that, despite aggressive PDC therapy, 30% of patients who presented with locally advanced disease were expected to relapse with incurable disease.[46] Even among patients with early-stage NSCLC who underwent surgery with curative intent, at least 30% relapsed, primarily at distant metastatic sites.[46]

B.1.3.5 Morbidity

Approximately 90% of patients with advanced NSCLC experience two or more disease-related symptoms, such as cough, dyspnoea, pain, anorexia, or fatigue.[47] These symptoms, in turn, can cause psychological distress and may negatively affect a patient's health-related quality of life (HRQOL). High degrees of psychological distress influence emotional well-being in both patients and their families.[47,48]

B.1.3.6 Clinical pathway of care

For most people with metastatic NSCLC, the aims of treatment are to prolong survival and improve quality of life. The current treatment landscape is complex, with treatment choices influenced by the presence of biological markers (e.g., EGFR mutation, ALK translocation, or PD-L1 expression status), histology (squamous or non-squamous), clinical factors (e.g., patient fitness and comorbidities), and previous treatment experience.[5]

Despite recent advances, available IO monotherapy or IO + PDC options have improved overall survival (OS), but long-term durability requires further improvements. In newly diagnosed metastatic NSCLC, there is a need for a more durable and limited chemotherapy-based treatment option that offers the chance for long-term survival for more patients and avoids the detriment of long-term chemotherapy side effects from ongoing treatment.

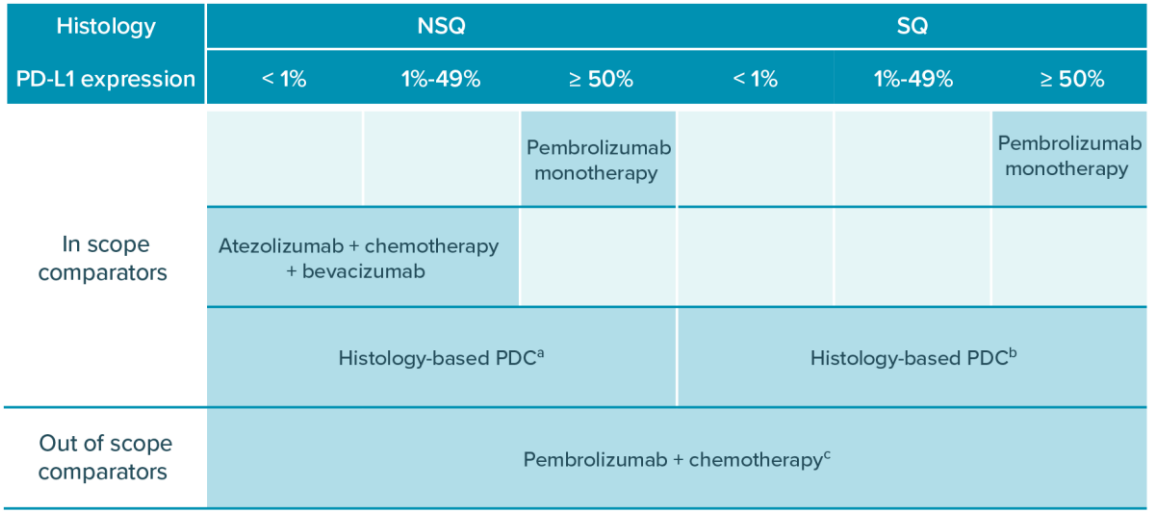
For patients without EGFR or ALK mutations, several treatments are available. Figure 6 presents an overview of first-line treatment of NSCLC in clinical practice in England that are included in the NICE scope as well as those that are out of scope for this appraisal but are used in England.

For patients with previously untreated squamous stage III or IV NSCLC and good performance status, NICE guideline 122 recommends platinum combination chemotherapy (i.e., cisplatin or carboplatin, and either gemcitabine or vinorelbine) as an option.[5] Pembrolizumab with carboplatin and paclitaxel is also recommended as an option for metastatic untreated squamous NSCLC via the Cancer Drugs Fund (CDF; NICE TA guidance 600).[49] However, pembrolizumab with chemotherapy is not an in-scope comparator for this appraisal.[6]

For patients with non-squamous NSCLC (adenocarcinoma or large cell carcinoma), patients may receive pemetrexed in combination with cisplatin (NICE TA guidance 181).[2] NICE TA guidance 584 recommends atezolizumab + bevacizumab + carboplatin + paclitaxel as an option for untreated NSCLC if the tumour expresses PD-L1 with < 50% tumour proportion score.[3] For non-squamous NSCLC that has not progressed immediately after initial therapy with a NICE-recommended platinum-based chemotherapy regimen, maintenance treatment with pemetrexed is recommended as an option (NICE TAs 190 and 402).[50,51]

Pembrolizumab monotherapy may be used as an option for untreated PD-L1–positive metastatic NSCLC if the tumour expresses PD-L1 with at least 50% tumour proportion score and has no EGFR or ALK mutations, regardless of histology (NICE TA guidance 531).[4] Pembrolizumab combination therapy is recommended for use within the CDF as an option for untreated metastatic NSCLC if the tumour has no EGFR or ALK mutations, again, regardless of histology (NICE TA guidance 557)[52]; it is not an in-scope comparator for this appraisal.[6]

Figure 6. Treatments used for the first-line treatment of NSCLC in clinical practice in England



Abbreviations: NSCLC = non-small cell lung cancer; NSQ = non-squamous; PDC = platinum doublet chemotherapy; PD-L1 = programmed death-ligand 1; SQ = squamous.

[a] In NSQ, PDC = chemotherapy (docetaxel, gemcitabine, paclitaxel, or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin); for those with adenocarcinoma or large cell carcinoma, pemetrexed in combination with a platinum drug with or without pemetrexed maintenance treatment.

[b] In SQ, PDC = chemotherapy (gemcitabine or vinorelbine) in combination with a platinum drug.

[c] Currently funded via the Cancer Drugs Fund and not included in the NICE scope.

B.1.4Equality considerations

No equality issues are foreseen.

B.2 Clinical effectiveness

SUMMARY OF CLINICAL EFFECTIVENESS

Two randomised controlled trials (RCTs) of relevance to the decision problem were identified in the systematic literature review (SLR): CheckMate-9LA and CheckMate-227.[53] CheckMate-9LA includes nivolumab + ipilimumab + limited PDC and is the key trial supporting this indication. CheckMate-227 part 1 (hereafter referred to as *CheckMate-227*) provides supporting evidence for the efficacy and safety of nivolumab + ipilimumab in this setting. An additional phase 2, single-arm, open-label study of nivolumab + ipilimumab + limited PDC in patients with stage IV or recurrent NSCLC that was not previously treated with chemotherapy is also presented (CheckMate-568 part 2; hereafter referred to as *CheckMate-568*).

CheckMate-9LA

- CheckMate-9LA met its primary objective, demonstrating a statistically significant and clinically meaningful survival benefit for nivolumab + ipilimumab + limited PDC versus PDC.
  - At the interim analysis (minimum follow-up of 8.1 months for OS), nivolumab + ipilimumab + limited PDC demonstrated improved OS compared with PDC irrespective of tumour PD-L1 expression or histology, with a hazard ratio (HR) of 0.69 (96.71% confidence interval [CI], 0.55-0.87).
  - The additional 4.6 months of follow-up from the updated analysis (minimum follow-up of 12.7 months) demonstrated that more follow-up is required to show the full benefit of nivolumab + ipilimumab + limited PDC and supports the proposed entry of nivolumab + ipilimumab + limited PDC into the CDF:
    - HR, 0.66; 95% CI, 0.55-0.80[1,21]
    - 1-year OS: 62.9% versus 46.9% for PDC
    - Median OS: 15.64 months (95% CI, 13.93-19.98 months) versus 10.91 months (95% CI, 9.46-12.55 months)
    - Separation of the Kaplan-Meier curves favouring nivolumab + ipilimumab + limited PDC occurred early, with no crossing of the curves and continued separation at all time points
  - With 12.7 months of minimum follow-up, nivolumab + ipilimumab + limited PDC demonstrated improved progression-free survival (PFS) compared with PDC with an HR of 0.68 (95% CI, 0.57-0.82).[1,21] Median PFS was longer with nivolumab + ipilimumab + limited PDC compared with PDC: 6.74 (95% CI, 5.55-7.75) versus 4.96 (95% CI, 4.27-5.55) months. One-year PFS was higher with nivolumab + ipilimumab + limited PDC compared with PDC (32.9% vs. 17.6%).
  - Objective response rate (ORR) was higher with nivolumab + ipilimumab + limited PDC than with PDC: 38.2% (95% CI, 33.2%-43.5%) versus 24.9% (95% CI, 20.5%-29.7%).[1,21]
    - The median duration of response (DOR) was more than double for all confirmed responders treated with nivolumab + ipilimumab + limited PDC than with PDC, with non-overlapping CIs (DOR, 11.30 months vs. 5.59 months).
  - A consistent efficacy benefit was also observed across subgroups, including PD-L1 and histology.
- Nivolumab + ipilimumab + limited PDC demonstrated a manageable safety profile in CheckMate-9LA, with no new safety signals observed.[1] Consistent with the limited cycles of PDC, several toxicities typically related to chemotherapy were less frequently reported with nivolumab + ipilimumab + limited PDC compared with full courses of PDC.

- The combination of nivolumab + ipilimumab + limited PDC is a durable treatment option that is expected to result in initial disease control (from 2 cycles of PDC) followed by the long-term benefit from the IO-IO combination.

CheckMate-227 and CheckMate-568

- Among all trial participants in CheckMate-227, the median duration and rate of OS were higher among patients who received nivolumab + ipilimumab than among those who received chemotherapy (17.1 months vs. 13.9 months, respectively). Progression-free survival rates were also higher in patients treated with nivolumab + ipilimumab versus PDC (32% and 20% at 1 and 2 years, respectively, vs. 17% and 6%). The ORR and median DOR with nivolumab + ipilimumab were 33.1% and 19.6 months, respectively, versus 27.8% and 5.8 months with PDC.
- In the CheckMate-568 study, nivolumab + ipilimumab + limited PDC showed encouraging clinical activity. Median OS was 19.4 months, and median PFS was 10.8 months. The ORR was 47%, and the median DOR was 12.7 months.

Indirect treatment comparison

- In the absence of head-to-head trial evidence of nivolumab + ipilimumab + limited PDC versus relevant comparators of interest in the UK, an indirect treatment comparison (ITC) was necessary to enable a comparison for this submission. A fractional polynomial network meta-analysis was conducted because the treatment effect of nivolumab + ipilimumab + limited PDC over PDC is not constant over time.
- The results of this analysis suggested that there is a benefit in terms of OS for nivolumab + ipilimumab + limited PDC over both pembrolizumab monotherapy and atezolizumab plus bevacizumab and chemotherapy.

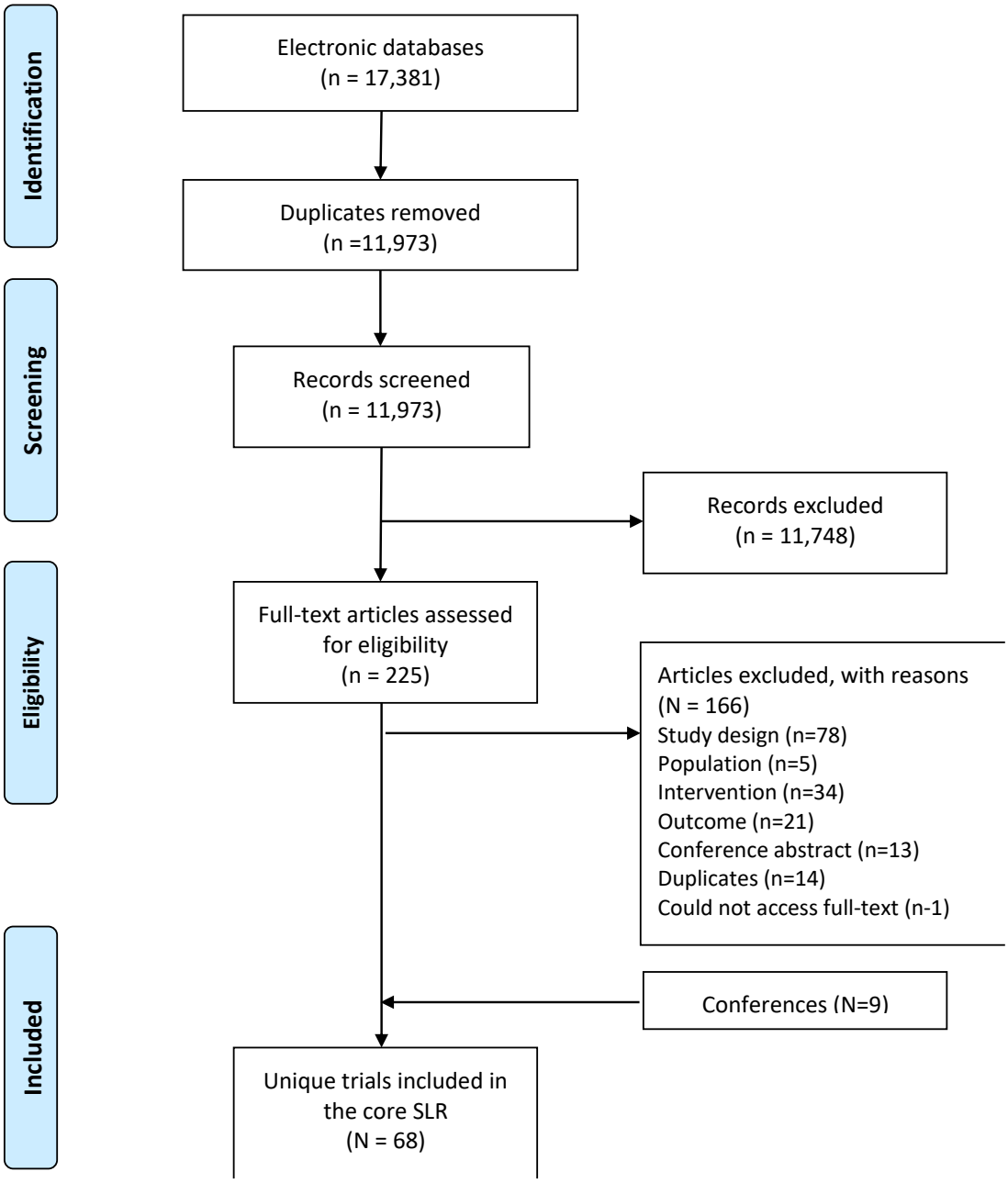
B.2.1Identification and selection of relevant studies

An SLR was conducted (main review) to identify all RCTs comparing relevant therapies in the first-line treatment of advanced NSCLC and is described in detail in Appendix D.[53]

The NICE decision problem for this submission, as stated in Section B.1.1, is a patient population, aligned with the anticipated EMA marketing authorisation, defined as adults with untreated stage IV or recurrent metastatic NSCLC. Randomised controlled trials involving nivolumab (with or without ipilimumab and PDC) and relevant comparators (i.e., IOs), targeted therapies, PDC, non–platinum-based chemotherapy, monotherapies, and best supportive care for the first-line treatment of advanced and recurrent NSCLC were included in the SLR.[53]

The SLR was first conducted in 2016 with the final updated searches conducted in MEDLINE, Embase, and the Central Register of Controlled Trials (CENTRAL) in March 2020. To complement the search of published trials, an electronic search of conference proceedings and registers were searched for unpublished RCTs.[53] A Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow diagram showing the number of studies included and excluded at each stage of the systematic review is presented in Figure 7 and further details are provided in Appendix D.[53] A total of 68 trials for core comparators were identified in the SLR.

Figure 7. Consolidated PRISMA diagram for all search updates for the identification of the core comparators



Abbreviations: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analysis; SLR = systematic literature review; WHO = World Health Organization.

The core comparator SLR included 68 unique trials. Among the 68 studies, 13 involved an IO in one of the arms, either as an IO monotherapy (i.e., nivolumab, pembrolizumab, atezolizumab, or durvalumab), IO combination with another IO (i.e., nivolumab + ipilimumab, durvalumab + tremelimumab), IO combination with a targeted agent (i.e., bevacizumab), or IO combination with chemotherapy (i.e., pembrolizumab + chemotherapy, atezolizumab + chemotherapy, or camrelizumab + chemotherapy).[53]

Two RCTs of relevance to the decision problem were identified in the SLR: CheckMate-9LA and CheckMate-227.[53] CheckMate-9LA includes nivolumab + ipilimumab + limited PDC and

is the key trial in support of this indication. CheckMate-227 provides supporting evidence for the efficacy and safety of nivolumab + ipilimumab in this setting and is described in Section B.2.2.2.

B.2.2List of relevant clinical effectiveness evidence

B.2.2.1 CheckMate-9LA

One relevant RCT that evaluated nivolumab + ipilimumab + limited PDC in a first-line metastatic NSCLC patient population was identified in the clinical SLR: CheckMate-9LA (Table 4).[1,53] This is the key study relevant to the decision problem described in Section B.1.1.

Table 4. Clinical effectiveness evidence: CheckMate-9LA

Study	**NCT03215706; Reck et al. (2020)[1]**				
Study design	Phase 3, randomised, controlled, open-label trial				
Population	Adults with stage IV or recurrent NSCLC not previously treated with chemotherapy				
Intervention(s)	Nivolumab (360 mg Q3W) + ipilimumab (1 mg/kg Q6W) + 2 cycles of PDC (Q3W)				
Comparator(s)	PDC				
Indicate if trial supports application for marketing authorisation	Yes	x	**Indicate if trial used in the economic model**	Yes	x
	No			No	
Rationale for use/non-use in the model	As the key study that is relevant to the decision problem, CheckMate-9LA is the basis of the economic model.				
Reported outcomes specified in the decision problem[a]	• **Overall survival** • **Progression-free survival** • Response rate • Adverse effects of treatment • **Health-related quality of life**				
All other reported outcomes	Duration of response				

Abbreviations: NSCLC = non-small cell lung cancer; PDC = platinum doublet chemotherapy; Q3W = every 3 weeks; Q6W = every 6 weeks.

[a] Outcomes marked in bold are incorporated into the model.

Source: Reck et al. (2020)[1]

CheckMate-9LA is the pivotal phase 3, randomised, open-label study of nivolumab + ipilimumab + limited PDC versus PDC in patients with stage IV NSCLC.[1]

NICE guidelines recommend that patients with NSCLC with no EGFR tumour mutations or ALK translocations can be offered PDC, which is a combination of a third-generation chemotherapy (gemcitabine, or vinorelbine) plus a platinum drug (either carboplatin or cisplatin); pemetrexed + cisplatin is an option for patients with non-squamous histology only.[5] Therefore, PDC is listed as a key comparator in the NICE decision problem (see Section B.1.1). CheckMate-9LA provides a direct comparison of nivolumab + ipilimumab + limited PDC with PDC.

B.2.2.2 Supporting studies

One RCT evaluating nivolumab + ipilimumab versus PDC in patients with stage IV or recurrent NSCLC was identified in the SLR (CheckMate-227) and is described further in Section B.2.2.2.1. An additional non-RCT (CheckMate-568) that was not identified in the SLR of RCTs is also included here, as it was considered relevant to the appraisal (see Section B.2.2.2.2 for further details).

B.2.2.2.1 CheckMate-227

CheckMate-227 is a phase 3, global, randomised, open-label, multipart study of nivolumab + ipilimumab versus PDC in patients with stage IV or recurrent NSCLC who were not previously treated with chemotherapy (Table 5). CheckMate-227 consists of three parts, of which CheckMate-227 part 1 (1a and 1b) is relevant to this submission (hereafter referred to as *CheckMate-227*).

Table 5. Clinical effectiveness evidence: CheckMate-227

Study	**NCT02477826; Hellmann et al. (2019)[54]**			
Study design	Phase 3, randomised, controlled, open-label trial Only part 1 is described here			
Population	Adults with untreated stage IV or recurrent NSCLC			
Intervention(s)	**Part 1a:** • Nivolumab 3 mg/kg IV Q2W + ipilimumab 1 mg/kg IV Q6W • Nivolumab monotherapy 240 mg Q2W **Part 1b:** • Nivolumab 3 mg/kg IV Q2W + ipilimumab 1 mg mg/kg IV Q6W • Nivolumab monotherapy 360 mg Q3W + PDC Q3W for up to 4 cycles followed by nivolumab 360 mg Q3W			
Comparator(s)	PDC Q3W for up to 4 cycles			
Indicate if trial supports application for marketing authorisation	Yes		Indicate if trial used in the economic model	Yes x
	No x			No
Rationale for use/non-use in the model	CheckMate-227 was included in the economic model to provide longer-term overall survival data for the nivolumab + ipilimumab combination			
Reported outcomes specified in the decision problem[a]	• **Overall survival** • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life			
All other reported outcomes	• Duration of response			

Abbreviations: IV = intravenously; NSCLC = non-small cell lung cancer; PDC = platinum doublet chemotherapy; Q2W = every 2 weeks; Q3W = every 3 weeks; Q6W = every 6 weeks.

[a] Outcomes marked in bold are incorporated into the model.

B.2.2.2.2 CheckMate-568

CheckMate-568 was a phase 2, single-arm, global, non-randomised, open-label study that consists of two parts. Part 1 evaluated nivolumab (3 mg/kg every 2 weeks) + ipilimumab (1 mg/kg every 6 weeks) in patients with stage IV or recurrent NSCLC that was not previously treated with chemotherapy, and part 2 evaluated nivolumab + ipilimumab + 2 cycles of PDC in the same population; only part 2 is described here (Table 6).[55-57] CheckMate-568 was not used to populate the economic model because it does not include a relevant comparator, but it is included in Sections B.2.2 to B.2.6, as part 2 provides evidence on the safety of nivolumab + ipilimumab. Only CheckMate-568 part 2 is described in this submission (hereafter referred to as *CheckMate-568*).

Table 6. Clinical effectiveness evidence: CheckMate-568

Study	**NCT02659059; Gainor et al. (2020)[57]**			
Study design	Open-label, phase 2, single-arm clinical trial Only part 2 is described here			
Population	Adults with stage IV or recurrent NSCLC that was not previously treated with systemic therapy			
Intervention(s)	Nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W + 2 cycles of PDC (Q3W)			
Comparator(s)	Not applicable			
Indicate if trial supports application for marketing authorisation	Yes x No		Indicate if trial used in the economic model	Yes No x
Rationale for use/non-use in the model	CheckMate-568 was not used in the model, as data from CheckMate-9LA are considered more appropriate			
Reported outcomes specified in the decision problem	• Dose-limiting toxicities • Safety and tolerability • Overall survival • Progression-free survival • Objective response rate			

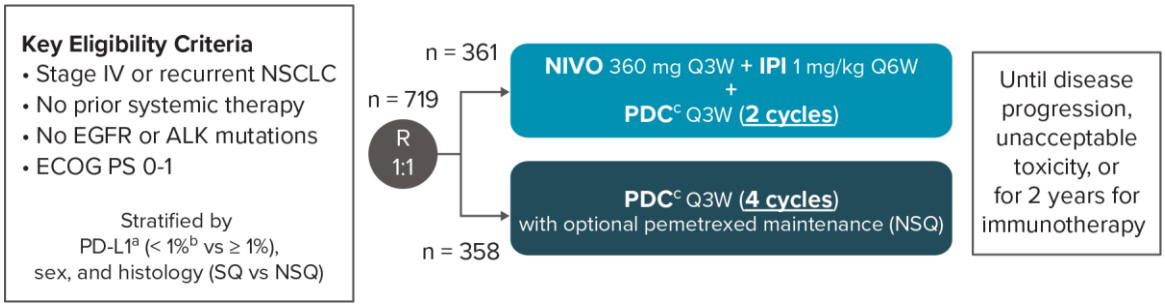
Abbreviations: NSCLC = non-small cell lung cancer; Q2W = every 2 weeks; Q3W = every 3 weeks; Q6W = every 6 weeks.

B.2.3Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 CheckMate-9LA methodology

As stated in the decision problem (see Section B.1.1), the main comparator for nivolumab + ipilimumab + limited PDC in this patient population is PDC. CheckMate-9LA provides clinical data for a direct comparison of nivolumab + ipilimumab + limited PDC with PDC. It is an open-label, phase 3 study with 719 randomised patients with non-squamous and squamous histologies that evaluated nivolumab + ipilimumab + limited PDC versus PDC in patients with first-line advanced NSCLC (Figure 8).[1]

Figure 8. CheckMate-9LA study design



Abbreviations: ALK = anaplastic lymphoma kinase; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; IPI = ipilimumab; NIVO = nivolumab; NSCLC = non-small cell lung cancer; NSQ = non-squamous; PD-L1 = programmed death-ligand 1; PDC = platinum doublet chemotherapy; Q3W = every 3 weeks; Q6W = every 6 weeks; R = randomised; SQ = squamous.

Notes: Interim database lock: October 3, 2019; minimum follow-up: 8.1 months for OS and 6.5 months for all other endpoints.

Updated database lock: March 9, 2020; minimum follow-up: 12.7 months for OS and 12.2 months for all other endpoints.

[a] Determined by the PD-L1 immunohistochemistry 28-8 pharmDx assay (Dako).

[b] Patients unevaluable for PD-L1 were stratified to PD-L1 < 1% and capped to 10% of all randomised patients.

[c] NSQ: pemetrexed + cisplatin or carboplatin; SQ: paclitaxel + carboplatin.

Source: Reck et al. (2020)[1]

A prespecified interim analysis of CheckMate-9LA was performed (database lock 3 October 2019; minimum follow-up of 8.1 months for OS and 6.5 months for all other data) as well as an updated analysis (database lock 9 March 2020; minimum follow-up of 12.7 months for OS and 12.2 months for all other data).[21] The additional 4.6 months of follow-up available in the updated analysis suggest that additional follow-up will further demonstrate the long-term benefit anticipated with the dual IO of nivolumab and ipilimumab (as demonstrated in CheckMate-227). Additional maturity of OS data would further reduce current uncertainty; thus, a period in the CDF would be beneficial.

CheckMate-9LA was conducted at 103 sites in 19 countries. The trial enrolled adults aged ≥ 18 years with stage IV or recurrent NSCLC and an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 who had not been previously treated with systemic therapy and had no sensitising EGFR mutations or known ALK translocations.

A total of 719 patients were randomised 1:1 to treatment with nivolumab + ipilimumab + limited PDC (n = 361) or PDC (n = 358). 707 patients were treated: 358 with nivolumab + ipilimumab + limited PDC and 349 with PDC.

The stratification factors for randomisation were PD-L1 level (≥ 1% vs. < 1%), histology (squamous vs. non-squamous), and gender (male vs. female). Patients whose PD-L1 status was “not quantifiable” were stratified as “PD-L1 < 1%”; the total number of PD-L1 “not quantifiable” patients was capped to not exceed 10% of the total randomised population. Before randomisation, the investigator decided if a patient with non-squamous histology would receive cisplatin therapy, based on cisplatin eligibility criteria.[21]

Nivolumab + ipilimumab + limited PDC arm: Nivolumab (360 mg Q3W) was administered intravenously (IV) with ipilimumab (1 mg/kg Q6W), plus 2 cycles of histology-based chemotherapy (Q3W) as follows:

- Squamous histology: carboplatin area under the concentration time curve (AUC) 6 + paclitaxel 200 mg/m^2 (or 175 mg/m^2 as per local institutional practice)
- Non-squamous histology: carboplatin AUC 5 or 6 + pemetrexed 500 mg/m^2 or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2

After 2 cycles of PDC, treatment with nivolumab and ipilimumab (hereafter, nivolumab + ipilimumab) could continue for up to 24 months, or until Response Evaluation Criteria in Solid Tumours (RECIST) v1.1–defined disease progression, unacceptable toxicity, or other reasons specified in the protocol. Treatment beyond initial investigator-assessed RECIST v1.1-defined progression was permitted up to 24 months in the treatment arm only if the investigator believed the patient was receiving clinical benefit from treatment and was tolerating nivolumab + ipilimumab. Patients who received nivolumab + ipilimumab beyond investigator-assessed progression were also to continue tumour assessments until further progression at subsequent tumour assessment.[21]

PDC arm[ii]: Histology dependent, platinum-based doublet chemotherapy was selected by the investigator and administered on day 1 Q3W for 4 cycles. After 4 cycles, patients with non-squamous histology could continue to receive optional maintenance therapy with 500 mg/m^2 pemetrexed alone on day 1 every 3 weeks until disease progression or unacceptable toxicity.

Histology-based PDC was one of the following:

- Squamous histology: carboplatin AUC 6 + paclitaxel 200 mg/m^2 (or 175 mg/m^2 as per local institutional practice)
- Non-squamous histology: carboplatin AUC 5 or 6 + pemetrexed 500 mg/m^2 or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2

The primary endpoint was OS, and secondary endpoints included blinded independent central review (BICR)–assessed PFS and ORR. Efficacy (ORR, PFS, and OS) by PD-L1 expression and tumour mutational burden (TMB) levels (tissue TMB and blood TMB) were also evaluated as secondary endpoints. Exploratory objectives included biomarker analysis and their association with clinical outcomes (ORR, PFS, and OS), pharmacokinetics, and health care resource utilisation.[21]

[ii] The PDC combination in the trial is not that used in clinical practice in the UK (see Section B.1.3.6).

Table 7 presents a methodological overview of CheckMate-9LA.

Table 7. Summary of CheckMate-9LA trial methodology

Trial number	NCT03215706; Reck et al. (2020)[1]; Bristol Myers Squibb data on file (2020)[21]
Location	103 sites in the following 19 countries: Argentina, Australia, Belgium, Brazil, Canada, Chile, China, France, Germany, Ireland, Italy, Japan, Mexico, Poland, Romania, Russian Federation, Spain, United Kingdom, and United States
Trial design	Phase 3 RCT. Patients were randomised 1:1 to treatment with nivolumab + ipilimumab + chemotherapy or chemotherapy. The stratification factors for randomisation were PD-L1 expression level (≥ 1% vs. < 1%), histology (SQ vs. NSQ), and gender (male vs. female).
Eligibility criteria for participants (inclusion criteria)	Both male and female adults (aged ≥ 18 years) with ECOG PS 0-1, histologically confirmed stage IV NSCLC of SQ or NSQ histology, and no prior systemic anticancer therapy (including EGFR and ALK inhibitors) given as primary therapy for advanced or metastatic disease.
Eligibility criteria for participants (exclusion criteria)	Patients with known EGFR mutations or ALK translocations sensitive to targeted inhibitor therapy or with untreated central nervous system metastases were also excluded.
Trial drugs Permitted and disallowed concomitant medication	• Nivolumab + ipilimumab + limited PDC arm: nivolumab (360 mg Q3W) administered IV with ipilimumab (1 mg/kg Q6W) plus 2 cycles of histology-based PDC • PDC arm[a]: administered on day 1 Q3W for 4 cycles
Primary outcomes (including scoring methods and timings of assessments)	• OS: time from randomisation to the date of death from any cause. OS was censored on the last date a patient was known to be alive. Survival follow-up was to be conducted every 3 months after patient's off-treatment date. • PD-L1 expression: the percentage of tumour cell membrane staining in a minimum of 100 evaluable tumour cells as per the validated PD-L1 immunohistochemistry 28-8 pharmDx assay (Dako). PD-L1 expression was classified as PD-L1 < 1%, ≥ 1%, and not quantifiable.
Other outcomes used in the economic model/ specified in the scope	• PFS (primary definition): time from the randomisation date to the date of the first documented tumour progression based on BICR assessment (per RECIST v1.1), or death from any cause. Patients who died without a reported prior progression were considered to have progressed on the date of their death. Patients who had not progressed or died were censored on the date of their last evaluable tumour assessment. Patients who did not have any on-study tumour assessments were censored on the randomisation date. Patients who started any palliative local therapy or subsequent anticancer therapy without a prior reported progression were censored at the last evaluable tumour assessment before initiation of the palliative local therapy or subsequent anticancer therapy, whichever procedure occurred first. • ORR: the number of patients with a best overall response of CR or PR per RECIST v1.1, divided by the number of randomised patients. – DOR and TTR were evaluated for patients who achieved confirmed PR or CR. DOR was defined as the date of the first documented BICR-assessed tumour progression (per RECIST v1.1), or death from any cause, whichever occurred first. Patients who started subsequent therapy (including palliative local therapy) without a prior reported progression were censored at the last evaluable tumour assessments before initiation of the subsequent anticancer therapy (including palliative local therapy). Patients who died without a reported prior progression were considered

Trial number	NCT03215706; Reck et al. (2020)[1]; Bristol Myers Squibb data on file (2020)[21]
	to have progressed on the date of their death. For patients who neither progressed nor died, DOR was censored on the date of their last evaluable tumour assessment. DOR was evaluated for responders (confirmed CR or PR) only. – TTR: time from randomisation to the date of the first confirmed documented response (CR or PR), as assessed by BICR. TTR was evaluated for responders (confirmed CR or PR) only. • Safety: Safety assessments were based on the frequency of deaths, serious AEs, AEs leading to discontinuation or dose modification, overall AEs, select AEs, immune-mediated AEs, and other events of special interest.
Preplanned subgroups	• PD-L1 expression: the percentage of tumour cell membrane staining in a minimum of 100 evaluable tumour cells per validated PD-L1 immunohistochemistry 28-8 pharmDx assay (Dako). PD-L1 expression was classified as PD-L1 < 1%, ≥ 1%, and not quantifiable.

Abbreviations: AE = adverse event; ALK = anaplastic lymphoma kinase; BICR = blinded independent central review; CR = complete response; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; IV = intravenously; NSCLC = non-small cell lung cancer; NSQ = non-squamous; ORR = objective response rate; OS = overall survival; PDC = platinum doublet chemotherapy; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; PR = partial response; PS = performance status; Q3W = every 3 weeks; Q6W = every 6 weeks; RCT = randomised controlled trial; RECIST = Response Evaluation Criteria in Solid Tumours; SQ = squamous; TTR = time to response.

[a] PDC in the trial is not that used in clinical practice in the United Kingdom.

B.2.3.2 CheckMate-9LA baseline characteristics

Baseline characteristics in all randomised patients were balanced between the nivolumab + ipilimumab + limited PDC and the PDC arms and were representative of a systemic treatment-naive recurrent or metastatic NSCLC population (Table 8).[1]

Table 8. CheckMate-9LA: baseline characteristics

Characteristic	NIVO + IPI + limited PDC (n = 361)	PDC (n = 358)
Age, median (range), years	65 (35-81)	65 (26-86)
Female, %	30	30
ECOG PS,[a] %		
0	31	31
1	68	68
Smoking status, %		
Never smoker	13	14
Current/former smoker	87	86
Histology, %		
Squamous	31	31
Non-squamous	69	69
Metastases, %		
Bone	27	31
Liver	19	24
Central nervous system	18	16

Characteristic	NIVO + IPI + limited PDC (n = 361)	PDC (n = 358)
Tumour PD-L1 expression,[b,c] %		
< 1%	40	39
≥ 1%	60	61
1%-49%	38	32
≥ 50%	22	29

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; IPI = ipilimumab; NIVO = nivolumab; PDC = platinum doublet chemotherapy; PD-L1 = programmed death-ligand 1.

[a] ECOG PS was not reported for 1 patient (0.3%) in each of the NIVO + IPI + limited PDC and PDC arms.

[b] Six percent and 7% of patients in the NIVO + IPI + limited PDC and PDC arms, respectively, were unevaluable for PD-L1.

[c] Calculated as a percentage of quantifiable patients.

Source: Reck et al. (2020)[1]

B.2.3.3 CheckMate-227 and CheckMate-568 methodology

Table 9 summarises the methodology of the key supporting studies for this submission, CheckMate-227 part 1 and CheckMate-568 part 2, which are then described in more detail in Sections B.2.3.3.1 and B.2.3.3.2. A summary of the methodology for additional supporting trials relating to the second-line treatment of patients with metastatic NSCLC (CheckMate-017 and CheckMate-057) is presented in Appendix L.

Table 9. Comparative summary of trial methodology: supporting studies

Trial name	CheckMate-227[54,58]	CheckMate-568[57,59]
Location	Part 1: 239 sites in 32 countries (Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Colombia, Czech Republic, Finland, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Japan, Korea, Lebanon, Mexico, Netherlands, Peru, Poland, Romania, Russian Federation, South Africa, Spain, Switzerland, Taiwan, United Kingdom, and United States)	Part 2: 12 sites in the US
Trial design	Global, phase 3, two-part, randomised, open-label trial. Patients were randomised in a 1:1:1 ratio and stratified by PD-L1 status (≥ 1% vs. < 1%), histology (SQ vs. NSQ), and gender (male vs. female). Part 1 evaluated nivolumab + ipilimumab and nivolumab monotherapy and is described further in this submission.	Global, phase 2, two-part, open-label, single-arm, non-randomised trial. Part 2 evaluated nivolumab + ipilimumab combined with 2 cycles of chemotherapy (part 2 described further in this submission).
Eligibility criteria for participants (inclusion criteria)	Adults (aged ≥ 18 years) with histologically confirmed stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer Classification) SQ or NSQ histology with no prior systemic anticancer therapy (including EGFR and ALK inhibitors) given as primary therapy for advanced or metastatic disease. Patients must have had ECOG PS ≤ 1. In part 1a, patients were required to have PD-L1 ≥ 1% expression; in part 1b, patients were required to have PD-L1 < 1% expression.	Men and women aged ≥ 18 years who met the following criteria: • Diagnosed with stage IV NSCLC • Diagnosed with recurrent stage IIIB NSCLC and previous concurrent chemoradiation failure with no further curative options • ECOG PS ≤ 1 • PD-L1 all-comers
Eligibility criteria for participants (exclusion criteria)	Exclusion criteria: • Patients with known EGFR mutations or ALK translocations that were sensitive to available targeted inhibitor therapy	Exclusion criteria: • Patients with an autoimmune disease or known EGFR mutations or ALK translocations • Patients with untreated CNS metastases • Patients with carcinomatous meningitis

Trial name	CheckMate-227[54,58]	CheckMate-568[57,59]
		• Patients with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of first treatment.
Trial drugs Permitted and disallowed concomitant medication	**Interventions** Part 1a: • Nivolumab 240 mg IV over 30 minutes Q2W given for up to 24 months in the absence of disease progression or unacceptable toxicity. • Nivolumab 3 mg/kg IV over 30 minutes Q2W + ipilimumab 1 mg/kg IV over 30 minutes Q6W given for up to 24 months in the absence of disease progression or unacceptable toxicity. • PDC IV in 3-week cycles for a maximum of 4 cycles or until disease progression or unacceptable toxicity (whichever came first). For patients with NSQ histology, pemetrexed maintenance was allowed until disease progression or unacceptable toxicity after 4 cycles of chemotherapy. The choice of PDC regimen depended on NSCLC histology: • For SQ: gemcitabine (1,000 or 1,250 mg/m^2, administered on days 1 and 8 of each cycle) with cisplatin (75 mg/m^2); or gemcitabine (1,000 mg/m^2, administered on days 1 and 8 of each cycle) with carboplatin (AUC). • For NSQ: pemetrexed (500 mg/m^2) with cisplatin (75 mg/m^2) administered on day 1 of each cycle; or pemetrexed (500 mg/m^2) with carboplatin (AUC 5 or 6) administered on day 1 of each cycle. Part 1b: • Nivolumab 3 mg/kg IV over 30 minutes Q2W + ipilimumab 1 mg/kg IV over 30 minutes Q6W given for up to 24 months in the absence of disease progression or unacceptable toxicity. • PDC IV in 3-week cycles for a maximum of 4 cycles or until disease progression or unacceptable toxicity (whichever comes first). For patients with NSQ histology, pemetrexed maintenance was allowed until disease progression or unacceptable toxicity after 4 cycles of chemotherapy.	**Intervention** Nivolumab IV at 3 mg/kg Q2W combined with ipilimumab IV at 1 mg/kg Q6W (n = 288) until disease progression, unacceptable toxicity, or 2 years' maximum treatment

Trial name	CheckMate-227[54,58]	CheckMate-568[57,59]
	• Nivolumab 360 mg IV over 30 minutes combined with IV PDC Q3W for a maximum of 4 cycles. Patients who have not experienced disease progression were to receive nivolumab 360 mg Q3W until the progression of disease, discontinuation due to toxicity, withdrawal of consent, or up to 24 months. For patients with NSQ histology, pemetrexed maintenance was allowed until disease progression or unacceptable toxicity after 4 cycles of chemotherapy. The choice of PDC regimens depended on NSCLC histology: • SQ: nivolumab 360 mg IV over 30 minutes, followed by gemcitabine (1,000 or 1,250 mg/m^2) with cisplatin (75 mg/m^2). • Nivolumab 360 mg IV over 30 minutes, followed by gemcitabine (1,000 mg/m^2) with carboplatin (AUC 5). • NSQ: Nivolumab 360 mg IV over 30 minutes, followed by pemetrexed (500 mg/m^2) with cisplatin (75 mg/m^2) administered on day 1 of each cycle, or nivolumab 360 mg IV over 30 minutes, followed by pemetrexed (500 mg/m^2) with carboplatin (AUC 5 or 6) administered on day 1 of each cycle. Patients must not have received prior anticancer therapy (including EGFR and ALK inhibitors) except prior adjuvant or neoadjuvant chemotherapy (if the last administration of the prior regimen occurred at least 6 months before enrolment and prior definitive chemoradiation for locally advanced disease if the last administration of chemotherapy or radiotherapy, whichever was given last, occurred at least 6 months before enrolment). Patients with adequately treated CNS metastases were to be either off corticosteroids or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) for at least 2 weeks before randomisation. Patients with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomisation were to be excluded. However, inhaled or topical steroids and adrenal replacement steroids > 10 mg daily prednisone equivalent were permitted in the absence of active autoimmune disease	

Trial name	CheckMate-227[54,58]	CheckMate-568[57,59]
Primary outcomes (including scoring methods and timings of assessments)	• In patients with PD-L1 ≥ 1%: OS • In patients with TMB ≥ 10 mutations per megabase): PFS by BICR	• ORR by BICR in patients with PD-L1 ≥ 1% and < 1%
Other outcomes used in the economic model/ specified in the scope	NA	NA
Preplanned subgroups	PD-L1 hierarchy: • PFS per BICR for nivolumab + PDC vs. PDC in patients with PD-L1 < 1% • OS per BICR for nivolumab + PDC vs. PDC in patients with PD-L1 < 1% • OS for nivolumab vs. PDC in patients with PD-L1 ≥ 50% TMB hierarchy: • PFS per BICR for nivolumab vs. PDC in patients with PD-L1 ≥ 1% • OS for nivolumab + ipilimumab vs. PDC in patients who are TMB high • OS for nivolumab vs. PDC in patients with PD-L1 ≥ 1% and who are TMB high	NA

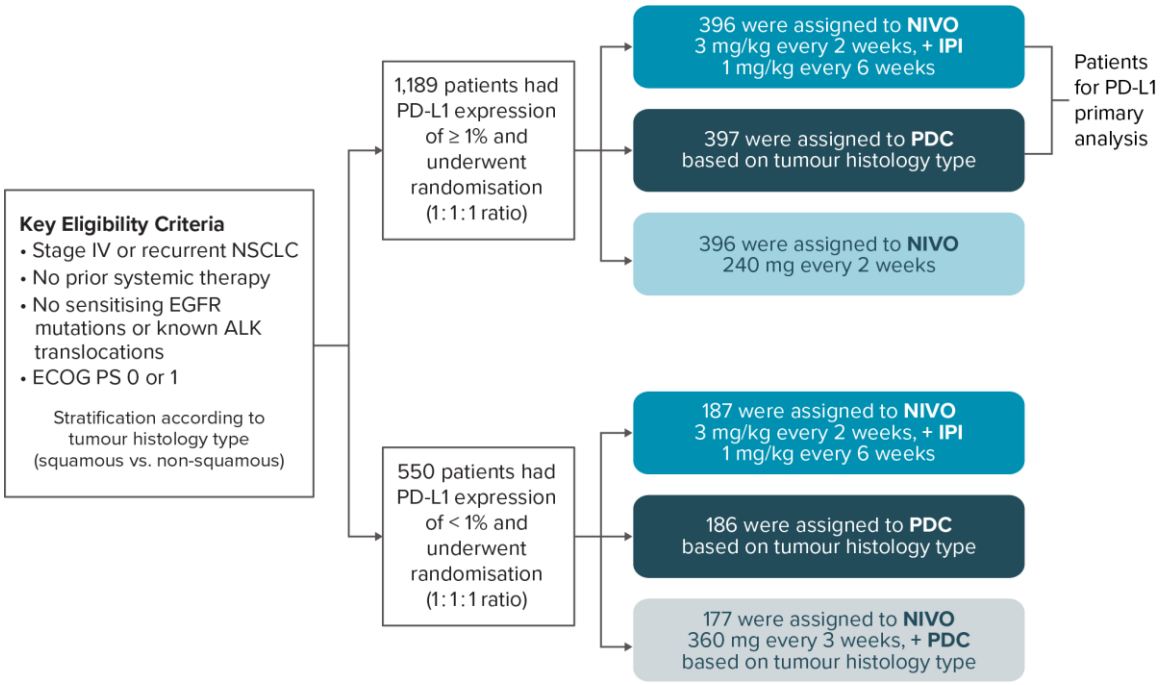
Abbreviations: ALK = anaplastic lymphoma kinase; AUC = area under the curve; BICR = blinded independent committee review; CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; IV = intravenously; NA = not applicable; NSCLC = non-small cell lung cancer; NSQ = non-squamous; ORR = objective response rate; OS = overall survival; PDC = platinum doublet chemotherapy; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; Q12W = every 12 weeks; Q2W = every 2 weeks; Q3W = every 3 weeks; Q6W = every 6 weeks; SQ = squamous; TMB = tumour mutational burden; UK = United Kingdom; US = United States.

B.2.3.3.1 CheckMate-227 methodology

CheckMate-227 provides clinical data for a direct comparison of nivolumab + ipilimumab with PDC. A methodological overview of CheckMate-227 is presented in Table 7.

The CheckMate-227 trial programme consists of three parts: 1a, 1b, and 2, of which parts 1a and 1b are relevant to this submission and included 1,739 patients. It is an open-label, multipart, randomised phase 3 trial in patients with non-squamous and squamous histologies, evaluating nivolumab-based regimens versus PDC in patients with first-line advanced NSCLC.[54] Part 1a evaluates nivolumab + ipilimumab and nivolumab monotherapy versus PDC among chemotherapy-naive patients with NSCLC whose tumours express PD-L1 (PD-L1 ≥ 1%). Part 1b evaluates nivolumab + ipilimumab and nivolumab + PDC versus PDC among chemotherapy-naive patients with NSCLC whose tumours do not express PD-L1 (PD-L1 < 1%) (Figure 9).

Figure 9. CheckMate-227: part 1 study design (NCT02477826)



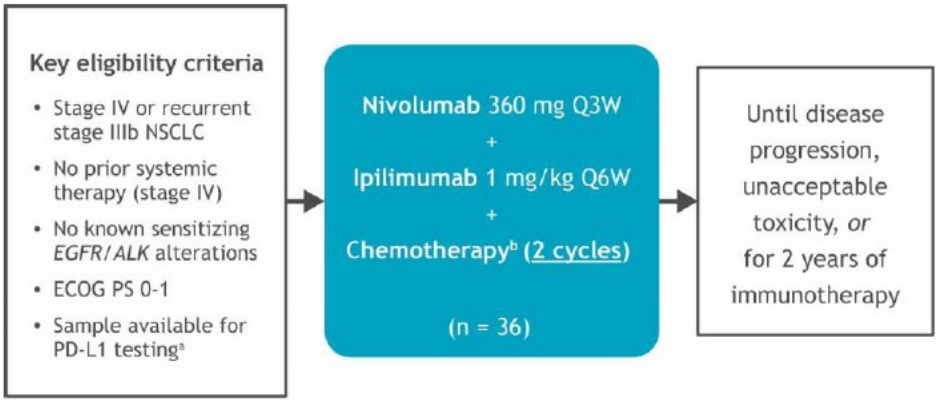
Abbreviations: ALK = anaplastic lymphoma kinase; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancerPD-L1 = programmed death-ligand 1.

Source: Hellmann et al. (2019)[54]

B.2.3.3.2 CheckMate-568 methodology

Figure 10 presents the study design for CheckMate-568 part 2. At database lock, 35 of 36 patients (97%) had completed 2 cycles of PDC. All 36 patients discontinued treatment: 16 owing to disease progression, 9 owing to study drug toxicity, 4 owing to an unrelated adverse event (AE), 4 owing to completion of 2 years of immunotherapy per protocol, and 1 patient each owing to death, withdrawal of consent, or other reasons. The median (range) number of doses was 10 (1-35) for nivolumab, 4 (1-18) for ipilimumab, and 2 (1-2) for chemotherapy. Median (range) duration of therapy was 6.4 (0-24.0) months for nivolumab and 4.2 (0-23.9) months for ipilimumab.[57]

Figure 10. CheckMate-568 part 2: study design



Abbreviations: ALK = anaplastic lymphoma kinase; AUC = area under the curve; EGFR = epidermal growth factor receptor; ECOG PS = Eastern Cooperative Oncology Group performance status; NSCLC = non-small cell lung cancer; PD-L1 = programmed death-ligand 1; Q3W = every 3 weeks; Q6W = every 6 weeks.

[a] Treatment may have been initiated before PD-L1 testing.

[b] Histology-based platinum doublet chemotherapy in 3-week cycles. Squamous: carboplatin AUC6 + paclitaxel 200 mg/m^2; non-squamous: carboplatin AUC5 or 6 + pemetrexed 500 mg/m^2 or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2.

Note *Chemotherapy* refers to platinum doublet chemotherapy.

Source: Gainor et al. (2020)[57]

B.2.3.4 CheckMate-227 and CheckMate-568 baseline characteristics

Baseline characteristics for CheckMate-227 part 1 and CheckMate-568 part 2 are presented in the following sections. Baseline characteristics for the additional trials relating to the second-line treatment of patients with metastatic NSCLC (CheckMate-017 and CheckMate-057) are presented in Appendix L.

B.2.3.4.1 CheckMate-227 baseline characteristics

A total of 2,876 patients were screened in CheckMate-227 part 1; of these, 1,739 underwent randomisation. The main reason for exclusion was not meeting the trial criteria. Of the 1,189 patients who had a PD-L1 expression level of ≥ 1%, 396 were assigned to receive nivolumab + ipilimumab, 396 to receive nivolumab monotherapy, and 397 to receive PDC. Of the 550 patients with a PD-L1 < 1%, 187 were assigned to receive nivolumab + ipilimumab, 177 to receive nivolumab + PDC, and 186 to receive PDC. The characteristics of the patients were balanced across the treatment groups at baseline (Table 10).[54]

Table 10. Characteristics of participants in CheckMate-227 across treatment groups

	PD-L1 ≥ 1%			All Patients	
Patient characteristics	**NIVO+IPI (n = 396)**	**NIVO monotherapy (n = 396)**	**PDC (n = 397)**	**NIVO+IPI (n = 583)**	**PDC (n = 583)**
Age, median (range), years	64 (26-84)	64 (27-85)	64 (29-87)	64 (26-87)	64 (29-87)
Category, n (%)					
< 65 years	199 (50.3)	210 (53.0)	207 (52.1)	306 (52.5)	305 (52.3)
≥ 65 to < 75 years	157 (39.6)	129 (32.6)	149 (37.5)	219 (37.6)	223 (38.3)
≥ 75 years	40 (10.1)	57 (14.4)	41 (10.3)	58 (9.9)	55 (9.4)
Sex, n (%)					
Male	255 (64.4)	272 (68.7)	260 (65.5)	393 (67.4)	385 (66.0)
Female	141 (35.6)	124 (31.3)	137 (34.5)	190 (32.6)	198 (34.0)
ECOG PS, n (%)[a]					
0	135 (34.1)	142 (35.9)	134 (33.8)	204 (35.0)	191 (32.8)
1	260 (65.7)	252 (63.6)	259 (65.2)	377 (64.7)	386 (66.2)
Other score or missing data	1 (0.3)	2 (0.5)	4 (1.0)	2 (0.3)	6 (1.0)
Smoking status, n (%)					
Never smoked	56 (14.1)	50 (12.6)	51 (12.8)	79 (13.6)	78 (13.4)
Current/former smoker	334 (84.3)	342 (86.4)	340 (85.6)	497 (85.2)	499 (85.6)
Missing data	6 (1.5)	4 (1.0)	6 (1.5)	7 (1.2)	6 (1.0)
Histology, n (%)					
Squamous	117 (29.5)	117 (29.5)	116 (29.2)	163 (28.0)	162 (27.8)
Non-squamous	279 (70.5)	279 (70.5)	281 (70.8)	419 (71.9)	421 (72.2)
Missing data	0	0	0	1 (0.2)	0
Tumour PD-L1 expression, n (%)[b]					
< 1%	NA	NA	NA	187 (32.1)	186 (31.9)
≥ 1%	396 (100.0)	396 (100.0)	397 (100.0)	396 (67.9)	397 (68.1)
1%-49%	191 (48.2)	182 (46.0)	205 (51.6)	191 (32.8)	205 (35.2)

Patient characteristics	PD-L1 ≥ 1%			All Patients	
	NIVO+IPI (n = 396)	NIVO monotherapy (n = 396)	PDC (n = 397)	NIVO+IPI (n = 583)	PDC (n = 583)
≥ 50%	205 (51.8)	214 (54.0)	192 (48.4)	205 (35.2)	192 (32.9)
Tumour mutational burden, n (%)[c]					
Patients evaluated	240 (60.6)	228 (57.6)	242 (61.0)	330 (56.6)	349 (59.9)
≥ 10 mut/Mb	101 (42.1)	102 (44.7)	112 (46.3)	139 (42.1)	160 (45.8)
< 10 mut/Mb	139 (57.9)	126 (55.3)	130 (53.7)	191 (57.9)	189 (54.2)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; IPI = ipilimumab; mut/Mb = mutations per megabase; NA = not applicable; NIVO = nivolumab; PDC = platinum doublet chemotherapy; PD-L1 = programmed death-ligand 1.

[a] Study treatment only in PD-L1 ≥ 1% population.

[b] Using PD-L1 immunohistochemistry 28-8 pharmDx assay (Dako).

[c] Using the FoundationOne CDxTM assay.

Source: Hellmann et al. (2019)[54]

B.2.3.4.2 CheckMate-568 baseline characteristics

In part 2 of CheckMate-568, 36 patients were treated; Table 11 presents baseline characteristics for these patients.

Table 11. Baseline characteristics for patients in CheckMate-568 part 2

Patient characteristic	NIVO+IPI
Age, median (range), years	70 (35-90)
Male, n (%)	23 (64)
Smoking status, n (%)	
Current smoker	6 (17)
Former smoker	26 (72)
Never smoked	4 (11)
ECOG PS, n (%)	
0	13 (36)
1	23 (64)
Disease stage, n (%)	
Recurrent stage IIIB	2 (6)
Stage IV	34 (94)
Histology, n (%)	
Adenocarcinoma	23 (64)
Squamous cell carcinoma	12 (33)
Large cell carcinoma	1 (3)
PD-L1 expression	
Quantifiable, n	30
< 1%, n (%)	18 (60)
≥ 1%, n (%)	12 (40)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; IPI = ipilimumab; NIVO = nivolumab; PD-L1 = programmed death-ligand 1.

Source: Gainor et al. (2020)[57]

B.2.4Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 CheckMate-9LA

Table 12 summarises the statistical analyses in CheckMate-9LA. It was estimated that a sample of approximately 700 randomised patients with 402 deaths would provide 81% power to detect an HR of 0.75 with a 5% type 1 error (2-sided).[60]

Table 12. Summary of the statistical analyses of CheckMate-9LA

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management and patient withdrawals	Missing data
To compare the efficacy and safety of NIVO + IPI + limited PDC vs. PDC in participants with histologically confirmed stage IV NSCLC	PFS (primary definition adjusting for subsequent therapy) was compared between the treatment arms via a stratified log-rank test among all randomised patients. The stratification factors were histology (SQ vs. NSQ), sex (male vs. female), and PD-L1 level (≥ 1% vs. < 1% or not quantifiable). HRs of OS and PFS between the treatment arms (NIVO + IPI + limited PDC vs. PDC) and corresponding 2-sided 95% CIs were estimated using a stratified Cox proportional hazards model, with treatment arm as a single covariate. OS and PFS were estimated using the KM product-limit method and were displayed graphically. A 2-sided 95% CI for median OS and PFS in each treatment arm was computed via the log-log transformation method. OS and PFS rates at fixed time points were presented along with their associated 95% CIs. These estimates were derived from the KM estimate, and the corresponding CIs were derived based on the Greenwood formula for variance derivation and on log-log transformation applied on the survivor function. The number and percentage of patients in each category of BOR per BICR (CR, PR, SD, PD, or unable to determine) were presented by treatment arm.	It was estimated that a sample of approximately 700 randomised patients with 402 deaths would provide 81% power to detect an HR of 0.75 with a 5% type 1 error (2-sided).	The study was performed at the Guardant Health Clinical Laboratory Improvement Amendments laboratory following Good Clinical Laboratory Practice, in compliance with the diagnostic study protocol. OS was censored on the last date a patient was known to be alive. For PFS, patients who died without a reported prior progression were considered to have progressed on the date of their death. Patients who had not progressed or died were censored on the date of their last evaluable tumour assessment. Patients who did not have any on-study tumour assessments were censored on the randomisation date. Patients who started any palliative local therapy or subsequent anticancer therapy without a prior reported progression were censored at the last evaluable tumour assessment before initiation of the palliative local therapy or subsequent anticancer therapy, whichever procedure occurred first. DOR was defined as the date of the first documented BICR-assessed tumour progression (per RECIST v1.1) or death from any cause, whichever occurred first. Safety assessments were based on	If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management and patient withdrawals	Missing data
	Estimates of response rate, with its exact 2-sided 95% CI based on the Clopper and Pearson method, are presented by treatment arm. A 2-sided 95% CI was calculated for the odds ratio of response between the treatment arms and for the difference in response rates between treatment arms. Similar analyses were repeated based on the investigator's assessment of ORR. The DOR for each treatment arm was estimated using the KM product-limit method for patients who achieved PR or CR and included median values, 2-sided 95% CIs, and range.		the frequency of deaths, serious AEs, AEs leading to discontinuation or dose modification, overall AEs, select AEs, immune-mediated AEs, and other events of special interest.	

Abbreviations: AE = adverse event; BICR = blinded independent central review; BOR = best overall response; CI = confidence interval; CR = complete response; DOR = duration of response; HR = hazard ratio; IPI = ipilimumab; KM = Kaplan-Meier; NIVO = nivolumab; NSCLC = non-small cell lung cancer; NSQ = non-squamous; ORR = objective response rate; OS = overall survival; PD = progressive disease; PDC = platinum doublet chemotherapy; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SD = stable disease; SQ = squamous.

Source: Bristol Myers Squibb data on file (2020)[21]; [60]

B.2.4.2 Supporting studies

Table 13 summarises the planned statistical analyses in CheckMate-227 part 1 and CheckMate-568 part 2. Planned statistical analyses for additional trials relating to second-line treatment of patients with metastatic NSCLC (CheckMate-057 and CheckMate-017) are presented in Appendix L.

Table 13. Summary of the statistical analyses of CheckMate-227 and CheckMate-568

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management and patient withdrawals
CheckMate-227[a]			
To determine whether NIVO+IPI vs. PDC improves survival in patients with stage IV or recurrent NSCLC who were not previously treated with chemotherapy	OS: based on a 2-sided stratified log-rank test stratified by histology. HRs of OS and corresponding 2-sided CIs (97.5% and 95%) were estimated using a stratified Cox proportional hazard model, with treatment arm as a single covariate. KM product-limit methodology was used to estimate OS curves, OS medians with 95% CIs, and OS rates at 6, 12, 18, and 24 months with 95% CIs. PFS: HRs of PFS and corresponding 2-sided 97.5% CIs were estimated using a Cox proportional hazard model, with treatment arm as a single covariate. KM product-limit methodology was used to estimate PFS curves, PFS medians with 95% CIs, and PFS rates at 6, 12, 18, and 24 months with 95% CIs. BICR-determined ORR in part 1 was estimated by treatment arm; corresponding 95% exact 2-sided CIs were calculated using the Clopper-Pearson method. The unweighted differences in ORR between the 2 treatment groups and corresponding 95% 2-sided CIs using the method of	OS of NIVO+IPI vs. PDC in part 1a: calculated under a 2-sided 0.0249 type 1 error with 90% power consideration for PD-L1 ≥ 1% patients. Note that an alpha of 0.0001 (2-sided) was spent for an interim analysis of ORR for part 1a. The number of events was estimated assuming an exponential distribution for OS in each arm.	OS was censored on the last date a patient was known to be alive. For PFS, patients who died with no reported progression were considered to have progressed on the date of death. Patients who did not progress or die were censored on the date of their last evaluable tumour assessment. Patients who did not have any on-study tumour assessments and did not die were censored on their date of randomisation. Patients who had palliative local therapy or initiated anticancer therapy without a prior reported progression were censored on the date of their last evaluable tumour assessment on or before the initiation of subsequent anticancer therapy or palliative local therapy. For DOR, patients who did not progress or die were censored on the date of their last evaluable tumour assessment.

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management and patient withdrawals
	Newcombe were provided. BOR as determined by BICR was summarised by response category for each treatment group. Summary statistics of time to objective response were provided for each treatment arm for patients who achieved PR or CR. DOR in each treatment arm was estimated using KM product-limit method for patients who achieved PR or CR, including median values, 2-sided 95% CIs, and range. A forest plot by baseline subgroups of the BICR-determined unweighted differences in ORR (between NIVO-containing arms and chemotherapy arm) and corresponding 95% CIs using the method of Newcombe were provided.		
CheckMate-568			
To determine the incidence of DLTs within 9 weeks after the first dose in patients with stage IV or recurrent stage IIIB NSCLC treated with NIVO + IPI + limited PDC as first-line therapy	Descriptive statistics of safety are presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 by treatment group. All on-study AEs, drug-related AEs, SAEs, drug-related SAEs, IMAEs, select AEs, and OESIs are tabulated using worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term. On-study laboratory parameters including haematology, chemistry, liver function and renal function are summarised using worst grade per NCI CTCAE v 4.0 criteria. ORR (based on investigator assessments using RECIST v1.1 criteria with	The sample size was targeted at 22 DLT evaluable subjects within 28 subjects who initiated treatment assuming 20% of subjects would not complete the 9-week DLT evaluation period for reasons other than DLTs. With a sample size of 22 DLT evaluable subjects with a safety event incident rate as 10%, there was above 90% probability to observe 1 or more cases of this safety event in this group. The goal was to identify safe regimens for future development, and safe is defined as 25% evaluated subjects or less exhibit DLTs (i.e., 5 or less subjects with such events out of 22 subjects). With 22 evaluable subjects, the false rejection rate	The status of subjects who were censored in the PFS KM analysis were tabulated using the following categories: censored at the first dose date, censored on date of last tumour assessment on-study or last assessment prior to subsequent anti-cancer therapy, on-study (on treatment, in follow-up), and off-study (lost to follow-up, withdrew consent, other reason). The status of subjects who were censored in the OS KM analysis were tabulated using the following categories: on-study (on-treatment and not progressed, on-treatment progressed, in follow-up) and off-study (lost to follow-up, withdraw consent, etc.)

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management and patient withdrawals
	requirement for response confirmation) was summarised by a binomial response rate and its corresponding 2-sided 95% exact CIs using Clopper-Pearson method. BOR was also summarised by response category. Investigator-assessed ORR was summarised for the following subsets within PD-L1 ≥ 1%, PD-L1 < 1%, and all treated population: baseline histology (SQ, NSQ) and TMB subgroup. The duration of response and time to response per investigator was summarised similarly for subjects who achieve confirmed PR or CR. OS and PFS were also summarised by PD-L1 and TMB. Time-to-event distributions of PFS (based on investigator assessments) and OS were estimated using KM techniques. Median PFS and median OS along with 95% CI were constructed based on a log transformed CI for the survivor function. Rates at fixed time points (3, 6, 9, 12 months) for PFS and OS were derived from the KM estimate and corresponding CIs were derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function.	is 10% if the true toxicity rate is 15%, the false acceptance rate is 16% if the true toxicity rate is 35%. The false rejection and false acceptance rates were deemed acceptable.	

Abbreviations: BICR = blinded independent central review; BOR = best overall response; CI = confidence interval; CR = complete response; DLT = dose-limiting toxicity; DOR = duration of response; HR = hazard ratio; IPI = ipilimumab; KM = Kaplan-Meier; NIVO = nivolumab; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PDC = platinum doublet chemotherapy; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; PR = partial response.

Note: Information on missing data not available for either study.

[a] An analysis in patients who were tumour mutational burden–high was also planned but not discussed here, as the focus is the intention-to-treat population.

B.2.5Quality assessment of the relevant clinical effectiveness evidence

Table 14 presents the quality assessment for CheckMate-9LA. Quality assessments for the supporting studies, CheckMate-227 part 1 and CheckMate-568 part 2, are presented in Table 15 and Table 16, respectively. CheckMate-568 is a non-randomised study; therefore, the Critical Appraisal Skills Programme (CASP) quality assessment tool is used (Table 16). Quality assessments for the supporting studies in second-line NSCLC are presented in Appendix L.

Table 14. Quality assessment of CheckMate-9LA

Was randomisation carried out appropriately?	Yes, randomisation was by an interactive web response system which grouped by PD-L1 status and randomised in a 1:1 ratio, stratified by histology, gender and PD-L1 level
Was the concealment of treatment allocation adequate?	No; open-label
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes; baseline characteristics of all randomly assigned patients were similar and balanced between treatment groups
Were the care providers, participants, and outcome assessors blind to treatment allocation?	No; open-label
Were there any unexpected imbalances in dropouts between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes
How closely does the RCT(s) reflect routine clinical practice?	Not clear; PDC is standard of care in England, but there are some differences in regimen vs. those in the trial

Abbreviations: PDC = platinum doublet chemotherapy; RCT = randomised controlled trial.

Table 15. Quality assessment of CheckMate-227 (part 1)

Was randomisation carried out appropriately?	Yes, randomisation was by an interactive voice response system which grouped by PD-L1 status and randomised in a 1:1:1 ratio, stratified by histology and gender
Was the concealment of treatment allocation adequate?	No; open-label
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes; baseline characteristics of all randomly assigned patients were similar and balanced between treatment groups
Were the care providers, participants, and outcome assessors blind to treatment allocation?	No; open-label
Were there any unexpected imbalances in dropouts between groups?	No; consort
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Modified intention to treat; not clear
How closely does the RCT(s) reflect routine clinical practice?	Not clear; PDC is standard of care in England, but there are some differences in regimen vs. those in the trial

Abbreviations: PDC = platinum doublet chemotherapy; RCT = randomised controlled trial.

Table 16. Quality assessment of CheckMate-568

Did the study address a clearly focused issue?	Yes
Did the authors use an appropriate method to answer their question?	Yes
Was the cohort recruited in an acceptable way?	Yes
Was the exposure accurately measured to minimise bias?	Yes
Was the outcome accurately measured to minimise bias?	Yes
Have the authors identified all important confounding factors?	Yes, all known confounding factors addressed
Have they taken account of the confounding factors in the design and/or analysis?	Yes, study inclusion and exclusion criteria helped to reduce confounding and stratification and sub-group analyses accounted for others (e.g. histology, PD-L1 expression, gender)
Was the follow-up of subjects complete enough?	Yes
Was the follow-up of subjects long enough?	Yes
What are the results of this study?	See Sections B.2.6.2.2 and B.2.10.2.1
How precise are the results?	Appropriate
Do you believe the results?	Yes

Did the study address a clearly focused issue?	Yes
Can the results be applied to the local population?	Yes
Do the results of this study fit with other available evidence?	Yes
Did the authors of the study publication declare any conflicts of interest?	Not reported
Does the trial reflect routine clinical practice in England?	Yes

B.2.6Clinical effectiveness results of the relevant trials

B.2.6.1 CheckMate-9LA

As detailed in Section B.2.4.1, on 9 March 2020, the clinical database was locked for the planned updated analysis of OS.[21] Based on the interim analysis for OS (minimum follow-up of 8.1 months for OS and 6.5 months for all other data), the Data Monitoring Committee recommended that the trial continue.[1] Overall survival results based on both the 3 October 2019 database lock and the 9 March 2020 database lock (minimum follow-up of 12.7 months) are presented here. For all other endpoints, results are based on the database lock of 9 March 2020.

Table 17 presents a summary of treatment and exposure in CheckMate-9LA.

Table 17. CheckMate-9LA treatment and exposure

Treatment and exposure	NIVO + IPI + limited PDC (n = 358)	PDC (n = 349)
Duration of therapy, median (range), months	[redacted]	[redacted]
Number of doses, median (range)		
NIVO	[redacted]	Not applicable
IPI	[redacted]	
Treatment discontinuation, n (%)		
IPI	19[a] (5)	Not applicable
NIVO+IPI	265 (74)	
Cycles of chemotherapy received, n (%)		
1	25 (7)	23 (7)
2	333 (93)	49 (14)
3	Not applicable	17 (5)
4	Not applicable	260 (74)
Patients receiving pemetrexed maintenance therapy, n (%)	Not applicable	158[b] (45)
Patients still on treatment, n (%)	74 (21)	28 (8)

Abbreviations: IPI = ipilimumab; NIVO = nivolumab; PDC = platinum doublet chemotherapy.

[a] Includes 3 patients who discontinued IPI but were still on treatment with NIVO.

[b] 66% of patients with non-squamous histology.

Source: Reck et al. (2020)[1]

Results presented in this section represent all patients relevant to NICE's decision problem. Subgroup analyses, including analysis by PD-L1 expression level, are presented in Section B.2.7.

B.2.6.1.1 Primary outcome

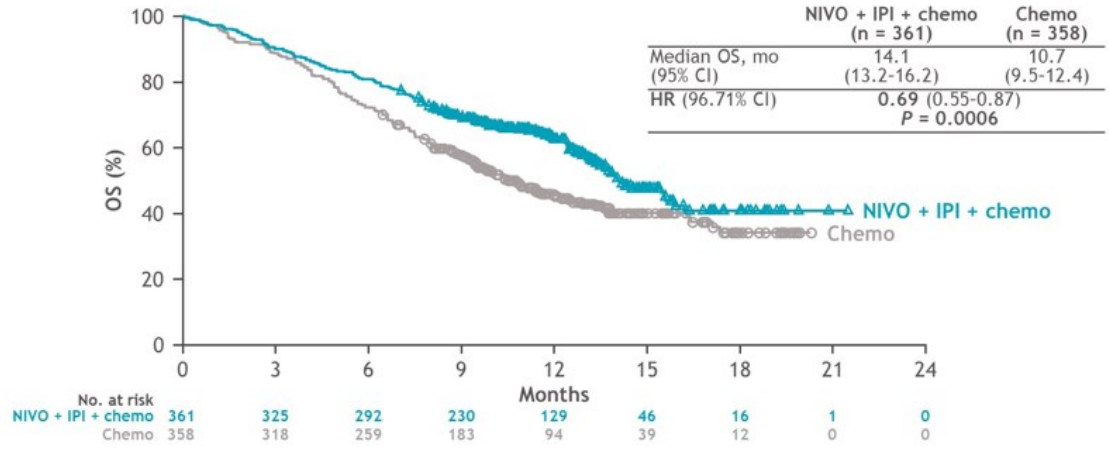
Overall survival

CheckMate-9LA is ongoing, and OS results presented here are from the interim analysis based on the 3 October 2019 database lock (minimum follow-up of 8.1 months for OS and 6.5 months for all other data) and the updated analysis based on the 9 March 2020 database lock (minimum follow-up of 12.7 months for OS and 12.2 months for all other data). Overall survival results are still maturing. The additional 4.6 months of follow-up available from the interim analysis (8.1 months of follow-up) and the updated analysis (12.7 months of follow-up) demonstrate that additional follow-up is required to show the full benefit of nivolumab + ipilimumab + limited PDC.

The combination of nivolumab + ipilimumab + limited PDC is a durable treatment option that is expected to result in initial disease control (from 2 cycles of PDC) followed by long-term benefit from the IO-IO combination.

The OS benefit of nivolumab + ipilimumab + limited PDC versus PDC is statistically significant and clinically meaningful; at the interim analysis, nivolumab + ipilimumab + limited PDC demonstrated improved OS compared with PDC irrespective of patients' PD-L1 expression, with an HR of 0.69 (96.71% CI, 0.55-0.87) (Figure 11).

Figure 11. CheckMate-9LA interim analysis: Kaplan-Meier of overall survival in all randomised patients



Abbreviations: CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; NIVO = nivolumab; OS = overall survival.

Note: *Chemo* refers to platinum doublet chemotherapy.

Source: Reck et al. (2020)[1]

The OS benefit was also seen in the updated (minimum follow-up, 12.7 months) analysis. Nivolumab + ipilimumab + limited PDC demonstrated a clinically meaningful survival benefit versus PDC, with an HR of 0.66 (Table 18).[1,21] Median OS was longer in the nivolumab + ipilimumab + limited PDC arm compared with the PDC arm: 15.64 months versus 10.91 months. Overall survival rates were higher in the nivolumab + ipilimumab + limited PDC arm compared with the PDC arm: 80.9% versus 72.6% at 6 months and 62.9% versus 46.9% at 12 months. The updated analysis demonstrated increased benefit, with clear separation of the curves; increased median OS versus PDC; and improved HR compared with the interim analysis.

Table 18. CheckMate-9LA updated analysis: summary of overall survival results from all randomised patients

OS	NIVO + IPI + limited PDC (n = 361)	PDC (n = 358)
Events, n (%)	190 (52.6)	242 (67.6)
Hazard ratio (95% CI)[a]	0.66 (0.55-0.80)	
Median survival, months (95% CI)[b]	15.64 (13.93-19.98)	10.91 (9.46-12.55)
OS rate at 6 months (95% CI)[a]	80.9 (76.4-84.6)	72.6 (67.7-76.9)
OS rate at 12 months (95% CI)[a]	62.9 (57.7-67.6)	46.9 (41.6-51.9)

Abbreviations: CI = confidence interval; IPI = ipilimumab; NIVO = nivolumab; OS = overall survival; PDC = platinum doublet chemotherapy.

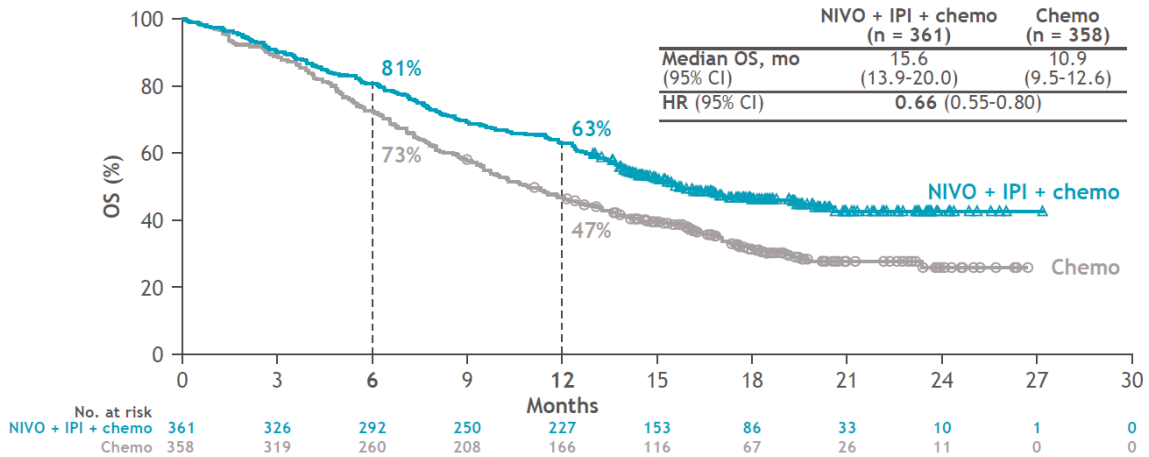
[a] Stratified Cox proportional hazards model. Hazard ratio is NIVO + IPI + limited PDC over PDC.

[b] Based on Kaplan-Meier estimates.

Sources: Reck et al. (2020)[1]; Bristol Myers Squibb data on file (2020)[21]

Separation of the Kaplan-Meier curves favouring nivolumab + ipilimumab + limited PDC occurred early, with no crossing of the curves and continued separation at all time points (Figure 12), showing rapid disease control. This benefit was seen across histologies and PD-L1 subgroups, as described in detail in Section B.2.7.

Figure 12. CheckMate-9LA updated analysis: Kaplan-Meier overall survival in all randomised patients



Abbreviations: CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; NIVO = nivolumab; OS = overall survival.

Note: *Chemo* refers to platinum doublet chemotherapy.

Source: Reck et al. (2020)[1]

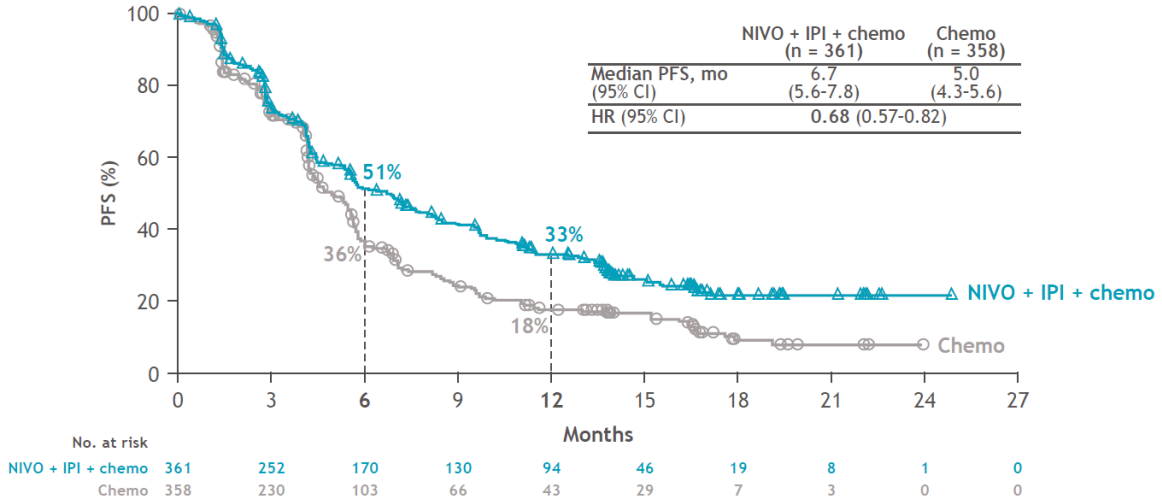
B.2.6.1.2 Secondary outcomes

Progression-free survival

Results for PFS are based on the 9 March 2020 database lock (minimum follow-up, 12.7 months). Nivolumab + ipilimumab + limited PDC demonstrated improved PFS per BICR compared with PDC with an HR of 0.68 (Figure 13).[1,21] Median PFS was longer with nivolumab + ipilimumab + limited PDC compared with PDC: 6.74 versus 4.96 months (Table 19). Progression-free survival rates were higher with nivolumab + ipilimumab + limited PDC compared with PDC: 51.3% versus 35.7% at 6 months and 32.9% versus 17.6% at 12 months.

Separation of the Kaplan-Meier curves favouring nivolumab + ipilimumab + limited PDC over PDC occurred early at approximately 4 months, grew rapidly, and was maintained thereafter.

Figure 13. CheckMate-9LA: Kaplan-Meier progression-free survival in all randomised patients



Abbreviations: CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; NIVO = nivolumab; PFS = progression-free survival.

Note: *Chemo* refers to platinum doublet chemotherapy.

Source: Reck et al. (2020)[1]

Table 19. CheckMate-9LA: summary of progression-free survival results from all randomised patients

PFS	NIVO + IPI + limited PDC (n = 361)	PDC (n = 358)
Events, n (%)	249 (69.0)	265 (74.0)
Hazard ratio for progression or death (95% CI)[a]	0.68 (0.57-0.82)	

PFS	NIVO + IPI + limited PDC (n = 361)	PDC (n = 358)
Median, months (95% CI)[b]	6.74 (5.55-7.75)	4.96 (4.27-5.55)
PFS rate at 6 months (95% CI)[a]	51.3 (45.9-56.5)	35.7 (30.3-41.1)
PFS rate at 12 months (95% CI)[a]	32.9 (27.8-38.0)	17.6 (13.4-22.2)

Abbreviations: CI = confidence interval; IPI = ipilimumab; NIVO = nivolumab; PDC = platinum doublet chemotherapy; PFS = progression-free survival.

[a] Stratified Cox proportional hazards model. Hazard ratio is NIVO + IPI + limited PDC over PDC.

[b] Based on Kaplan-Meier estimates.

Sources: Reck et al. (2020)[1]; Bristol Myers Squibb data on file (2020)[21]

Objective response rate

Results for ORR are based on the 9 March 2020 database lock (minimum follow-up, 12.7 months). In all randomised patients, BICR-assessed ORR was higher with nivolumab + ipilimumab + limited PDC than with PDC: 38.2% (95% CI, 33.2%-43.5%) versus 24.9% (95% CI, 20.5%-29.7%) (Table 20).[1,21] A numerically higher proportion of patients had a best overall response of complete response (CR; 2.2% vs. 1.1%) or partial response (PR; 36.0% vs. 23.7%), and a numerically lower proportion of patients had a best overall response of progressive disease (PD; 8.9% vs. 12.6%).

A higher proportion of patients in the nivolumab + ipilimumab + limited PDC arm compared with the PDC arm had a CR or PR within the first 3 months (27.7% vs. 19.6%), 6 months (34.1% vs. 23.5%), or 12 months (38.0% vs. 24.9%). Further, a higher percentage reduction from baseline in the sum of diameter of target lesions was observed in the nivolumab + ipilimumab + limited PDC arm compared with the PDC arm.

Table 20. CheckMate-9LA: summary of objective response rate results from all randomised patients

Response	NIVO + IPI + limited PDC (n = 361)	PDC (n = 358)
Objective response rate, n (%)	138 (38)	89 (25)
Odds ratio (95% CI)	1.9 (1.4-2.6)	
Best overall response, n (%)		
Complete response	8 (2)	4 (1)
Partial response	130 (36)	85 (24)
Stable disease	164 (45)	185 (52)
Progressive disease	32 (9)	45 (13)
Disease control rate, n (%)	302 (84)	274 (76)

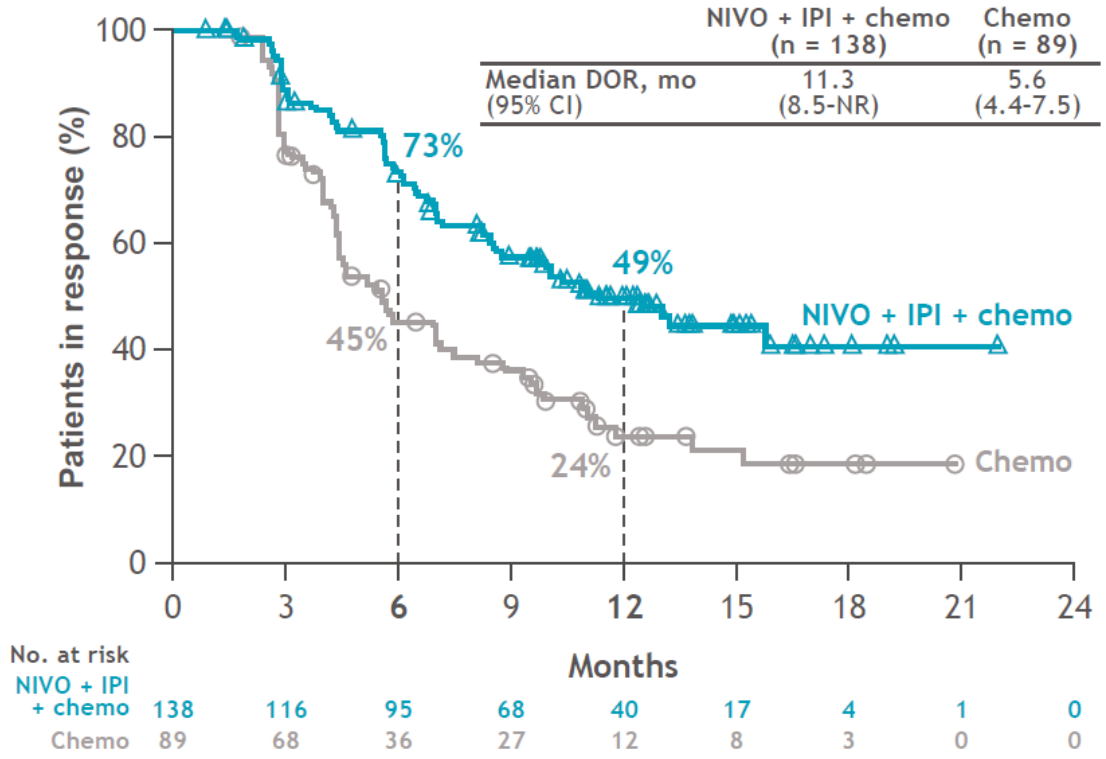
Abbreviations: CI = confidence interval; IPI = ipilimumab; NIVO = nivolumab; PDC = platinum doublet chemotherapy.

Sources: Reck et al. (2020)[1]; Bristol Myers Squibb data on file (2020)[21]

For all confirmed responders, median time to response (TTR) per BICR was 2.56 months in the nivolumab + ipilimumab + limited PDC arm and 1.54 months in the PDC arm.[1,21] The median DOR

was more than double for all confirmed responders treated with nivolumab + ipilimumab + limited PDC than with PDC, with non-overlapping CIs (DOR, 11.30 vs. 5.59 months). In the nivolumab + ipilimumab + limited PDC and PDC arms, 49.0% and 24.0% of responders, respectively, had a DOR of at least 12 months. Separation of the Kaplan-Meier curves for DOR favouring nivolumab + ipilimumab + limited PDC over PDC occurred at approximately 3 months with continued separation at all time points (Figure 14).

Figure 14. CheckMate-9LA: Kaplan-Meier DOR in all randomised patients



Abbreviations: CI = confidence interval; DOR = duration of response; IPI = ipilimumab; NIVO = nivolumab; NR = not reported.

Note: *Chemo* refers to platinum doublet chemotherapy.

Source: Reck et al. (2020)[1]

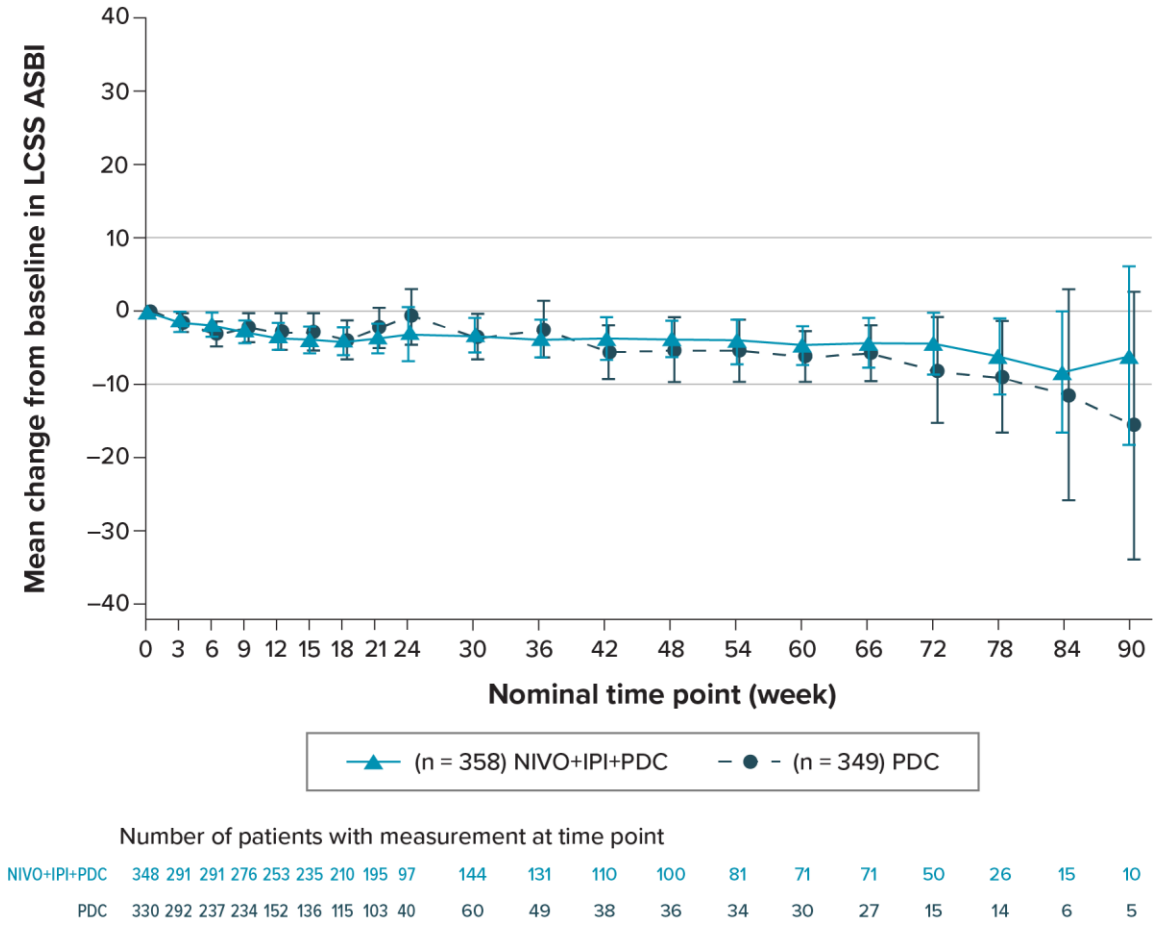
B.2.6.1.3 Exploratory outcomes

Patient-reported outcomes

In CheckMate-9LA, patient-reported outcome results were generally similar between the nivolumab + ipilimumab + limited PDC arm and the PDC arm, showing steady on-treatment improvements from baseline, as measured by the Lung Cancer Symptom Scale (LCSS) Average Symptom Burden Index (ASBI), EQ-5D visual analogue scale (VAS), and EQ-5D 3-Level (EQ-5D-3L) Utility Index.[21]

Mean LCSS ASBI scores generally improved in both arms during the treatment period; however, the mean changes from baseline in both arms did not meet the minimally important difference (MID) of 10 at any time (Figure 15).

Figure 15. CheckMate-9LA: mean change in LCSS ASBI from baseline, all treated patients

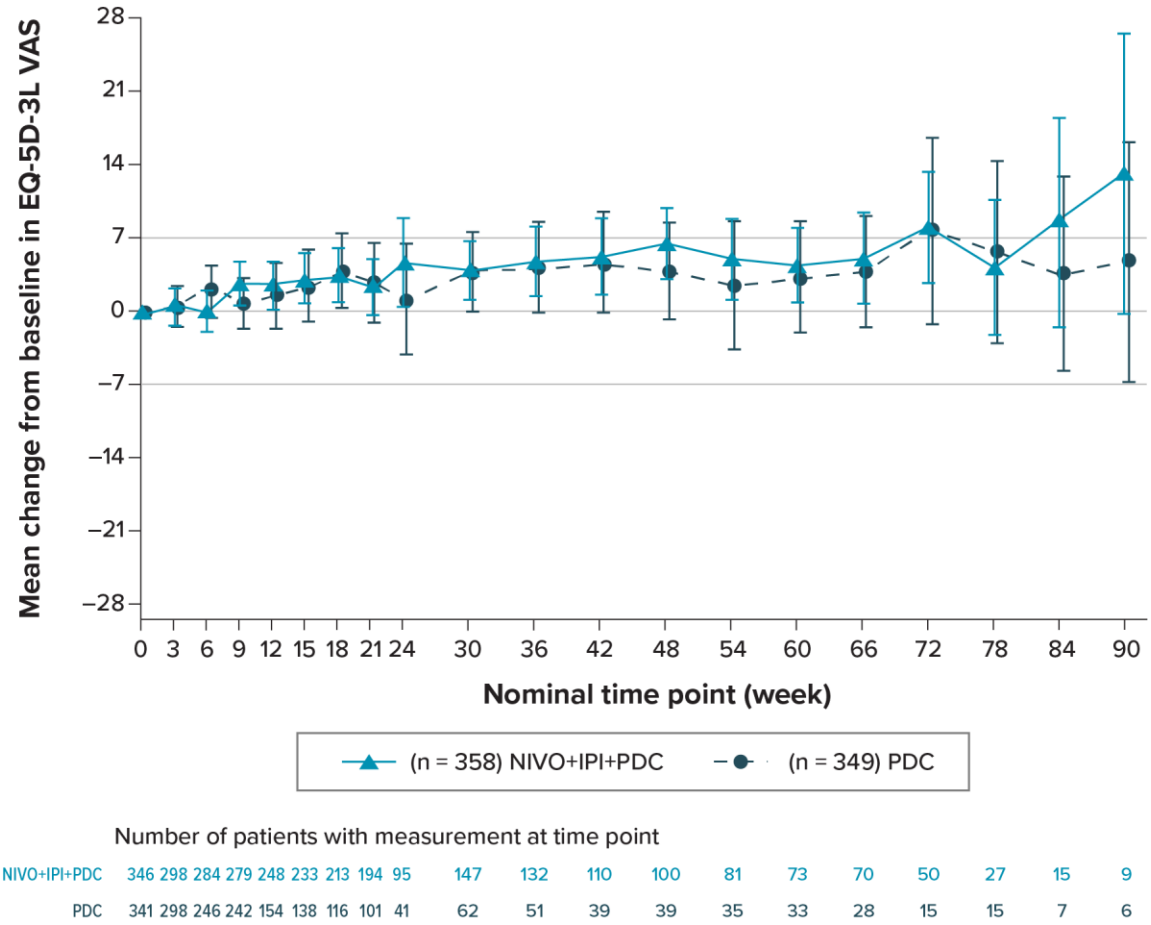


Abbreviations: ASBI = Average Symptom Burden Index; IPI = ipilimumab; LCSS = Lung Cancer Symptom Scale; NIVO = nivolumab; PDC = platinum doublet chemotherapy.

Source: Bristol Myers Squibb data on file (2020)[21]

For both arms, there were steady improvements in the EQ-5D VAS during the treatment period. Patients in both arms had numerically increased (improved) mean EQ-5D VAS scores from baseline at all on-treatment assessments with sufficient data, and mean changes from baseline exceeding the MID of 7 at weeks 72 and 84 for the nivolumab + ipilimumab + limited PDC arm and at week 72 for the PDC arm (Figure 16). For the nivolumab + ipilimumab + limited PDC arm, mean scores did not reach the UK general population norm (82.8) at any point; mean scores for the PDC arm reached the UK general population norm at weeks 72 and 78.

Figure 16. CheckMate-9LA: mean changes in overall self-rated health status in EQ-5D-3L VAS score from baseline, all treated patients

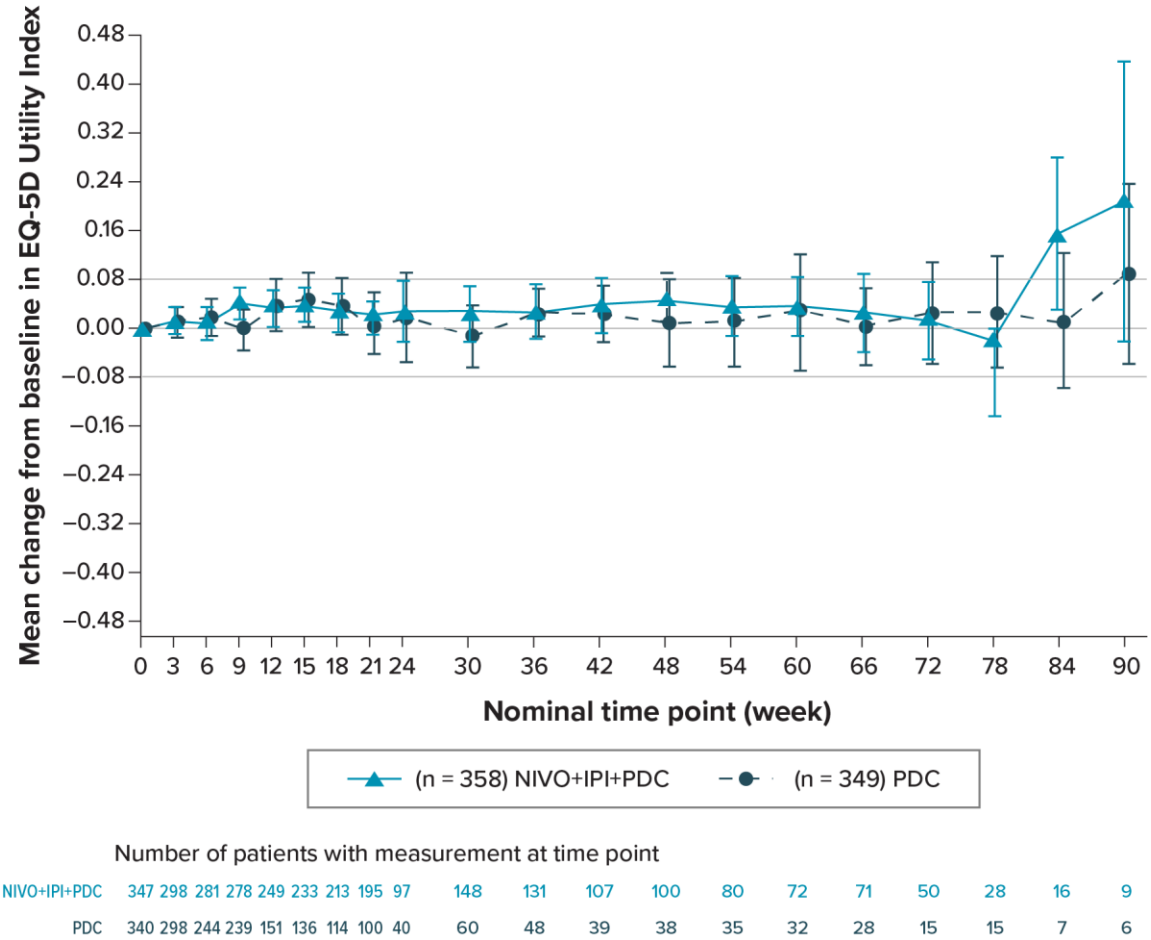


Abbreviations: IPI = ipilimumab; NIVO = nivolumab; PDC = platinum doublet chemotherapy; VAS = visual analogue scale.

Source: Bristol Myers Squibb data on file (2020)[21]

Mean EQ-5D Utility Index scores generally improved in both arms during the treatment period; however, improvements in both arms did not reach the UK general population norm (0.86) at any time (Figure 17). The mean changes from baseline exceeded the MID of 0.08 for the nivolumab + ipilimumab + limited PDC arm at week 84 only and did not meet the MID of 0.08 for the PDC arm at any time.

Figure 17. CheckMate-9LA: mean changes in EQ-5D Utility Index score from baseline, all treated patients



Abbreviations: IPI = ipilimumab; NIVO = nivolumab; PDC = platinum doublet chemotherapy; UI = Utility Index.
Source: Bristol Myers Squibb data on file (2020)[21]

B.2.6.2 Supporting studies

B.2.6.2.1 CheckMate-227

Efficacy of nivolumab + ipilimumab versus PDC

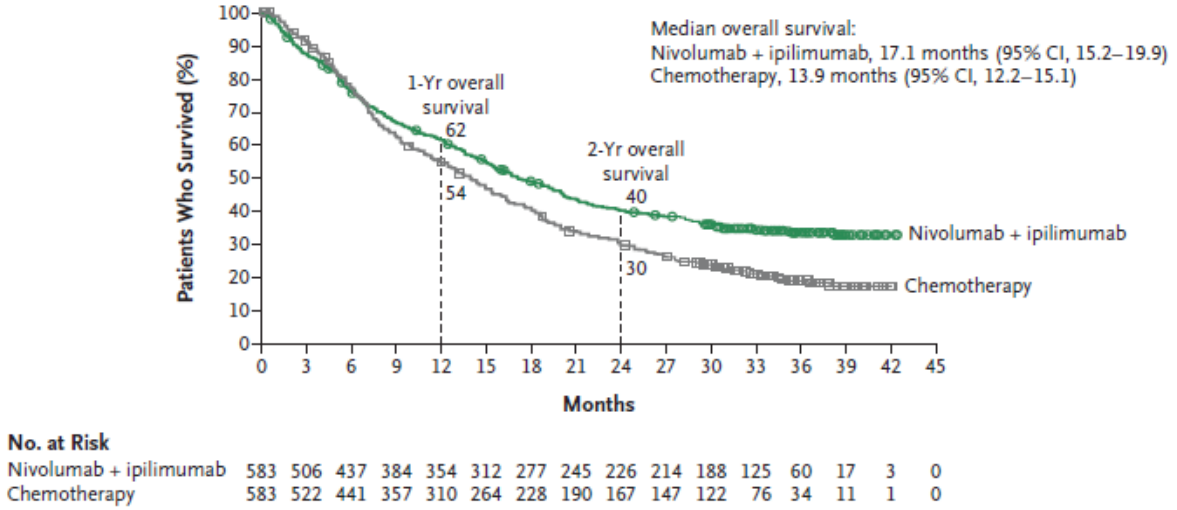
Overall survival

Results for CheckMate-227 part 1 presented here are based on the final analysis of OS with nivolumab + ipilimumab, as compared with PDC, as of the database lock of 2 July 2019 (minimum follow-up, 29.3 months).[54] A 3-year update analysis with a minimum follow-up of 37.7 months (database lock of 28 February 2020) has also been conducted, and results are presented here.

Although the primary analyses of this study evaluated patients with a PD-L1 expression of ≥ 1%, the results for all trial participants are relevant to this submission and presented in this section. Please see Section B.2.7.2 for subgroup analyses.

Among all trial participants, regardless of PD-L1 expression level, the median duration and rate of OS were higher among the patients who received nivolumab + ipilimumab than among those who received PDC. Overall survival was 17.1 months and 13.9 months, respectively, and the rate of OS at 2 years was 40.1% and 29.7%, respectively (Figure 18); the OS benefit was consistent across most subgroups.

Figure 18. CheckMate-227: overall survival in all patients



No. at Risk

Nivolumab + ipilimumab	583	506	437	384	354	312	277	245	226	214	188	125	60	17	3	0
Chemotherapy	583	522	441	357	310	264	228	190	167	147	122	76	34	11	1	0

Abbreviation: CI = confidence interval.

Note: *Chemotherapy* refers to platinum doublet chemotherapy.

Source: Hellmann et al. (2019)[54]

[redacted][61]

Figure 19. CheckMate-227 part 1: Kaplan-Meier estimates of overall survival with nivolumab + ipilimumab versus PDC in all patients (minimum follow-up, 37.7 months)

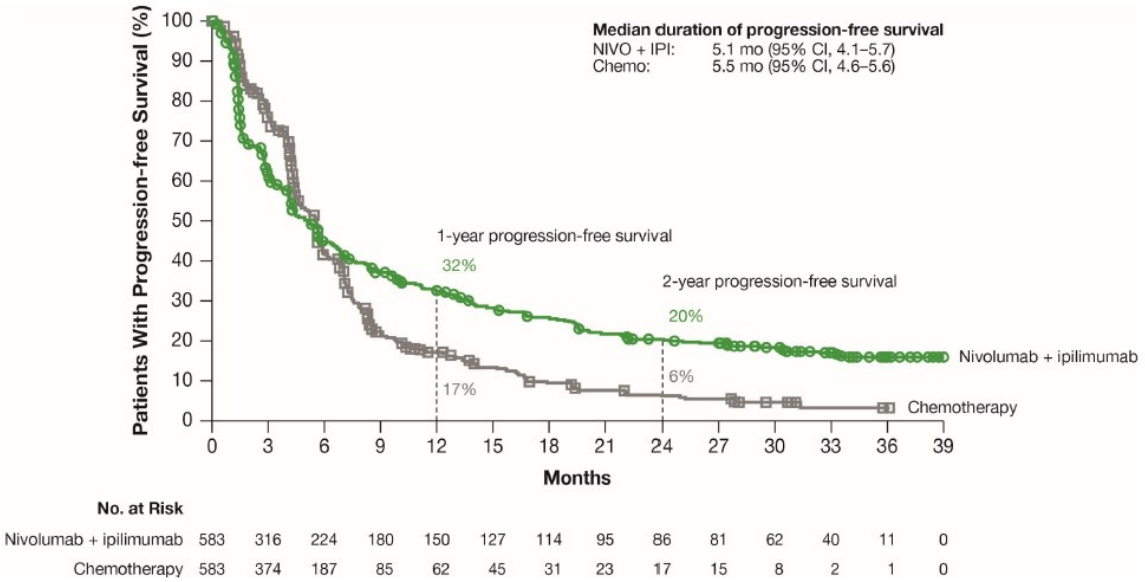
Abbreviations: CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; NIVO = nivolumab; PDC = platinum doublet chemotherapy.

Source: Bristol Myers Squibb data on file (2020)[61]

Progression-free survival

Progression-free survival in all patients treated with nivolumab + ipilimumab was 32% and 20% at 1 and 2 years, respectively, versus 17% and 6% in patients treated with PDC (Figure 20).

Figure 20. CheckMate-227: progression-free survival in all patients



Abbreviations: CI = confidence interval; IPI = ipilimumab; NIVO = nivolumab.

Note: *Chemotherapy* refers to platinum doublet chemotherapy.

Source: Hellmann et al. (2019)[54]

Response

Table 21 presents efficacy outcomes of ORR, DOR, and TTR for all patients.

Table 21. CheckMate-227: ORR, DOR, and TTR for all patients

	NIVO+IPI (n = 583)	PDC (n = 583)
Objective response rate,[a] n (%)	193 (33.1)	162 (27.8)
95% CI	29.3-37.1	24.2-31.6
Best overall response,[a] n (%)		
Complete response	27 (4.6)	9 (1.5)
Partial response	166 (28.5)	153 (26.2)
Stable disease	189 (32.4)	287 (49.2)
Progressive disease	135 (23.2)	74 (12.7)
Could not be determined	66 (11.3)	60 (10.3)
Median time to response, months	2.7	1.6
Duration of response, months		
Median (95% CI)	19.6 (16.1-28.6)	5.8 (5.4-6.9)
Patients with a response who had ongoing responses (%)		
At 1 year	66	28
At 2 years	47	9

Abbreviation: CI = confidence interval; IPI = ipilimumab; NIVO = nivolumab; PDC = platinum doublet chemotherapy.

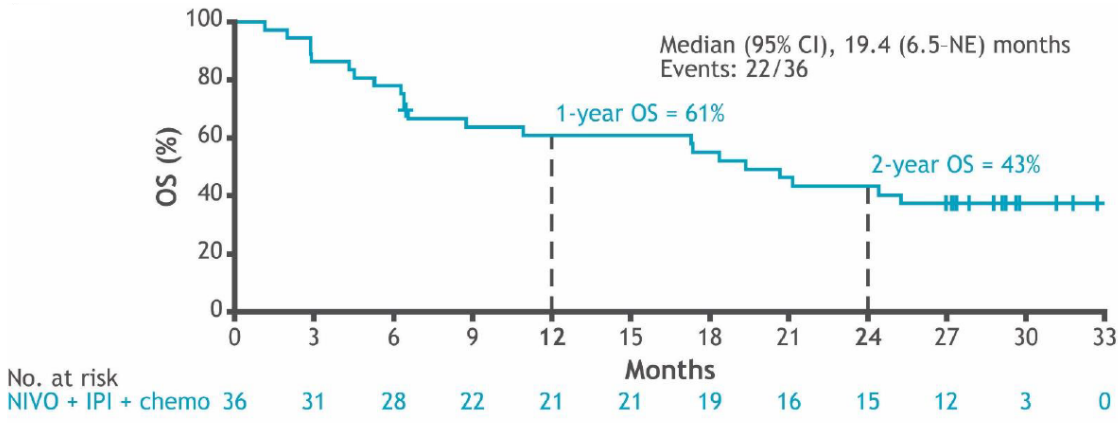
[a] Minimum follow-up was 28.3 months.

Source: Hellmann et al. (2019)[54]

B.2.6.2.2 CheckMate-568

In CheckMate-568 part 2, nivolumab + ipilimumab + limited PDC showed encouraging clinical activity. Median OS was 19.4 months (Figure 21), and median PFS per investigator was 10.8 months (Figure 22).[57] The ORR was 47%, with 89% achieving disease control (stable disease or better); the median DOR was 12.7 months (Table 22).[57]

Figure 21. CheckMate-568: overall survival in all patients treated with nivolumab + ipilimumab + limited PDC

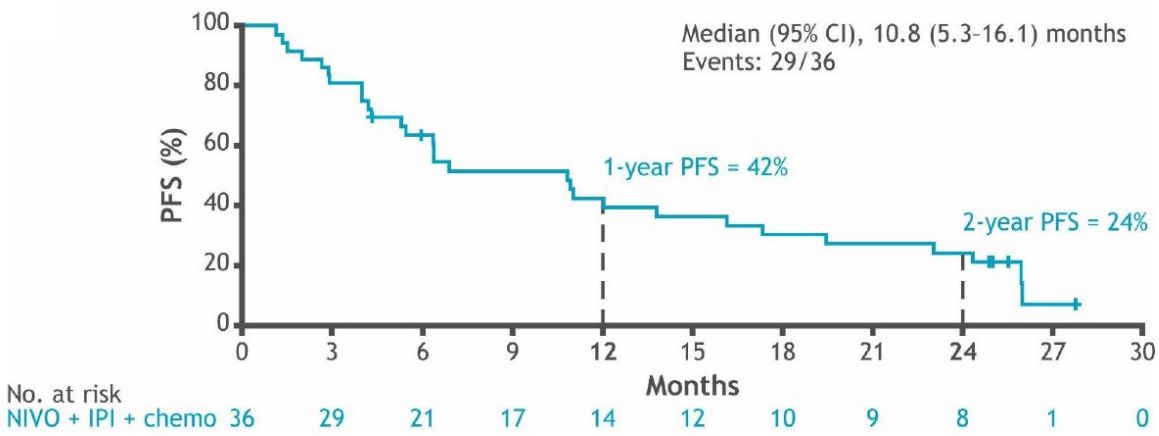


Abbreviations: CI = confidence interval; IPI = ipilimumab; NE = not estimable; NIVO = nivolumab; OS = overall survival; PDC = platinum doublet chemotherapy.

Note: *Chemo* refers to platinum doublet chemotherapy.

Source: Gainor et al. (2020)[57]

Figure 22. CheckMate-568: progression-free survival per BICR in all patients treated with nivolumab + ipilimumab + limited PDC



Abbreviations: BICR = blinded independent central review; CI = confidence interval; IPI = ipilimumab; NIVO = nivolumab; PDC = platinum doublet chemotherapy; PFS = progression-free survival.

Note: *Chemo* refers to platinum doublet chemotherapy.

Source: Gainor et al. (2020)[57]

Table 22. CheckMate-568: response in all patients treated with nivolumab + ipilimumab + limited PDC

Response	All treated (n = 36)
Objective response rate	
n (%)	17 (47)
95% CI	30-64
Best overall response, n (%)	
Complete response	2 (6)
Partial response	15 (42)
Stable disease	15 (42)
Progressive disease	2 (6)
Not available	2 (6)
Disease control rate, n (%)	32 (89)
Duration of response, median (95% CI), months	12.7 (5.6 to NE)

Abbreviations: CI = confidence interval; NE = note estimable; PDC = platinum doublet chemotherapy.

Source: Gainor et al. (2020)[57]

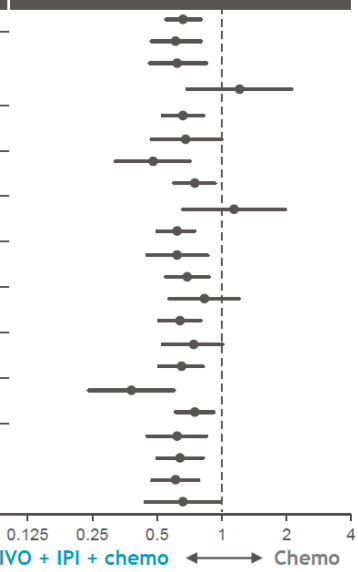
B.2.7Subgroup analysis

B.2.7.1 CheckMate-9LA

A consistent efficacy benefit was observed across subgroups, including PD-L1 and histology (Figure 23), suggesting that histology and PD-L1 are not effect modifiers for nivolumab + ipilimumab + limited PDC in this indication.[1]

Figure 23. CheckMate-9LA: overall survival subgroup analysis in all randomised patients

Subgroup	Median OS, mo		Unstratified HR
	NIVO + IPI + chemo n = 361	Chemo n = 358	
All randomized (N = 719)	15.6	10.9	0.66[a]
< 65 years (n = 354)	15.6	10.7	0.61
65 to < 75 years (n = 295)	19.4	11.9	0.62
≥ 75 years (n = 70)	8.5	11.5	1.21
Male (n = 504)	14.1	9.8	0.66
Female (n = 215)	19.4	15.8	0.68
ECOG PS 0 (n = 225)	NR	15.4	0.48
ECOG PS 1 (n = 492)	13.6	9.7	0.75
Never smoker (n = 98)	14.1	17.8	1.14
Smoker (n = 621)	15.6	10.4	0.62
Squamous (n = 227)	14.5	9.1	0.62
Non-squamous (n = 492)	17.0	11.9	0.69
Liver metastases (n = 154)	10.2	8.1	0.83
No liver metastases (n = 565)	19.4	12.4	0.64
Bone metastases (n = 207)	11.9	8.3	0.74
No bone metastases (n = 512)	20.5	12.4	0.65
CNS metastases (n = 122)	NR	7.9	0.38
No CNS metastases (n = 597)	15.4	11.8	0.75
PD-L1 < 1% (n = 264)	16.8	9.8	0.62
PD-L1 ≥ 1% (n = 407)	15.8	10.9	0.64
PD-L1 1-49% (n = 233)	15.4	10.4	0.61
PD-L1 ≥ 50% (n = 174)	18.0	12.6	0.66



Minimum follow-up: 12.7 months.
[a]Stratified HR; unstratified HR was 0.67 (95% CI, 0.55-0.81).

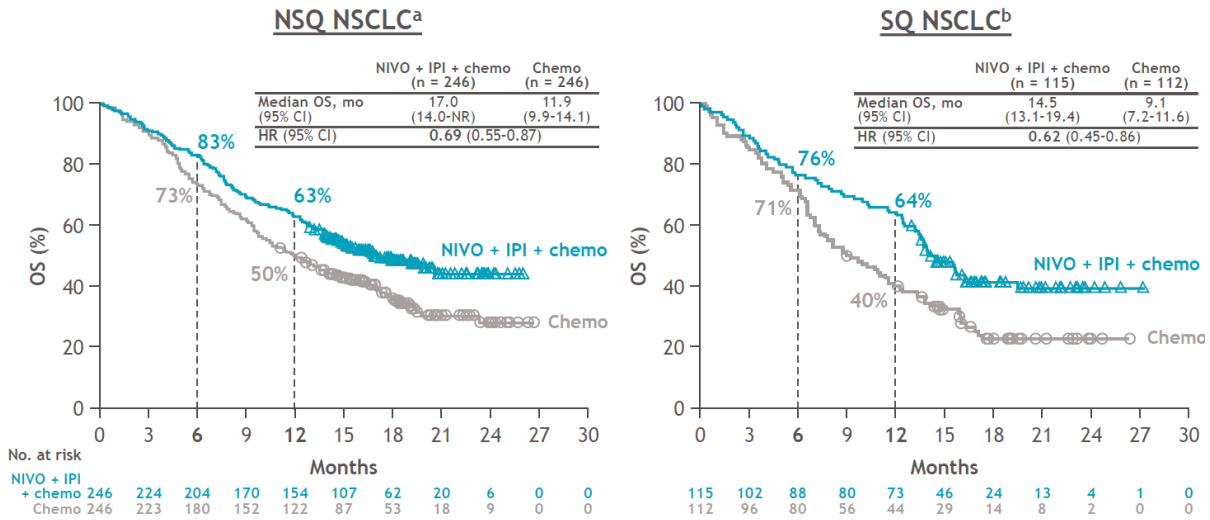
Abbreviations: CI = confidence interval; CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; IPI = ipilimumab; NIVO = nivolumab; OS = overall survival; PD-L1 = programmed death-ligand 1.

Note: *Chemo* refers to platinum doublet chemotherapy.

Source: Reck et al. (2020)[1]

The efficacy benefit of nivolumab + ipilimumab + limited PDC treatment versus PDC was observed in both squamous and non-squamous subgroups (Figure 24).[1]

Figure 24. CheckMate-9LA: overall survival by histology



Abbreviations: CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; NIVO = nivolumab; NSCLC = non-small cell lung cancer; NSQ = non-squamous; OS = overall survival; PDC = platinum doublet chemotherapy; SQ = squamous.

Note: *Chemo* refers to platinum doublet chemotherapy.

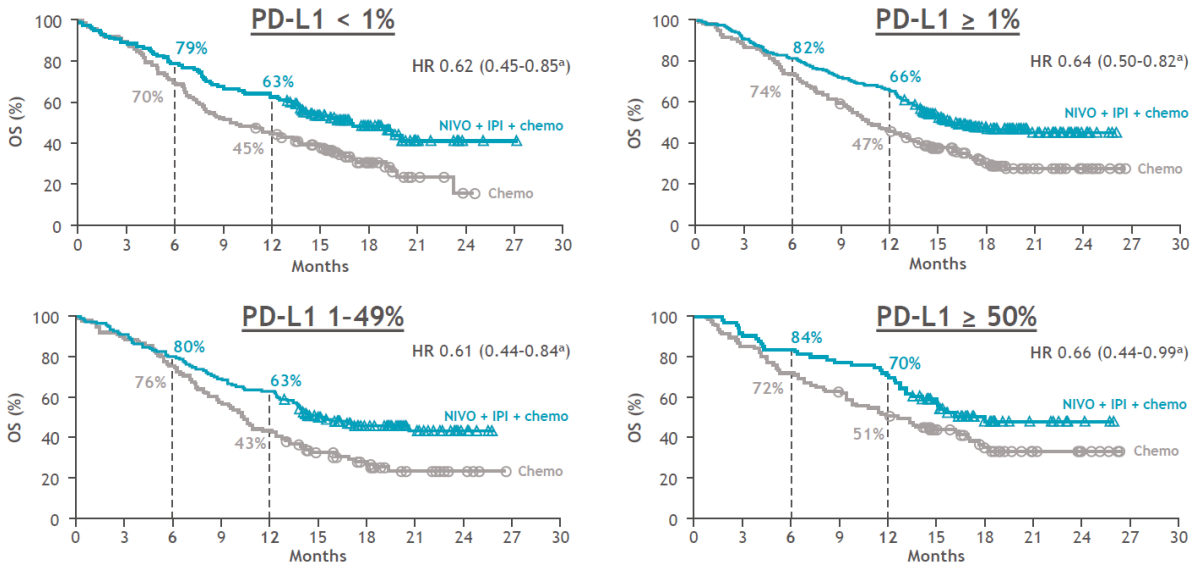
[a] Subsequent systemic therapy was received by 30% of patients in the NIVO + IPI + limited PDC arm and 39% of patients in the PDC arm; subsequent immunotherapy was received by 6% and 28% and subsequent chemotherapy by 29% and 22%, respectively.

[b] Subsequent systemic therapy was received by 31% of patients in the NIVO + IPI + limited PDC arm and 44% of patients in the PDC arm; subsequent immunotherapy was received by 4% and 35% and subsequent chemotherapy by 30% and 24% of patients, respectively.

Source: Reck et al. (2020)[1]

The efficacy benefit of nivolumab + ipilimumab + limited PDC versus PDC was observed regardless of PD-L1 status (< 1%, ≥ 1%, 1%-49%, and ≥ 50%) or histology, and across all efficacy endpoints (OS, PFS, ORR) (Figure 25).[1]

Figure 25. CheckMate-9LA: overall survival by PD-L1 expression level



Abbreviations: HR = hazard ratio; IPI = ipilimumab; NIVO = nivolumab; OS = overall survival; PD-L1 = programmed death-ligand 1.

Note: *Chemo* refers to platinum doublet chemotherapy.

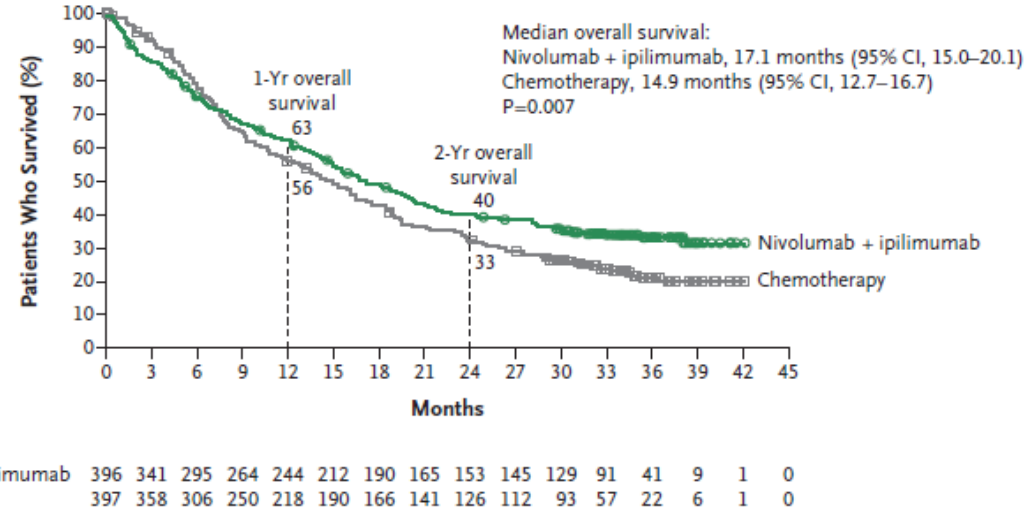
[a] 95% confidence interval.

Source: Reck et al. (2020)[1]

B.2.7.2 CheckMate-227

The primary population of CheckMate-227 part 1 included patients with a PD-L1 expression level of ≥ 1%. In these patients, the median duration of OS was 17.1 months with nivolumab + ipilimumab and 14.9 months with PDC ($P = 0.007$) (Figure 26). Overall survival rates at 1 year and 2 years were 62.6% and 40.0%, respectively, with nivolumab + ipilimumab compared with 56.2% and 32.8% with PDC. The rate of OS was significantly higher among patients who received nivolumab + ipilimumab than among those who received PDC, but the proportional hazards assumption was not met; the HR for death was 0.79 (97.72% CI, 0.65-0.96), which, although providing an overall estimate of benefit, should be interpreted in the context of the shape of the curves. These are characterised by the transient initial survival benefit seen with PDC, followed by a later separation of the curves as the long-term benefit of nivolumab + ipilimumab is seen.[54]

Figure 26. CheckMate-227: overall survival in patients with PD-L1 ≥ 1%



No. at Risk

Nivolumab + ipilimumab	396	341	295	264	244	212	190	165	153	145	129	91	41	9	1	0
Chemotherapy	397	358	306	250	218	190	166	141	126	112	93	57	22	6	1	0

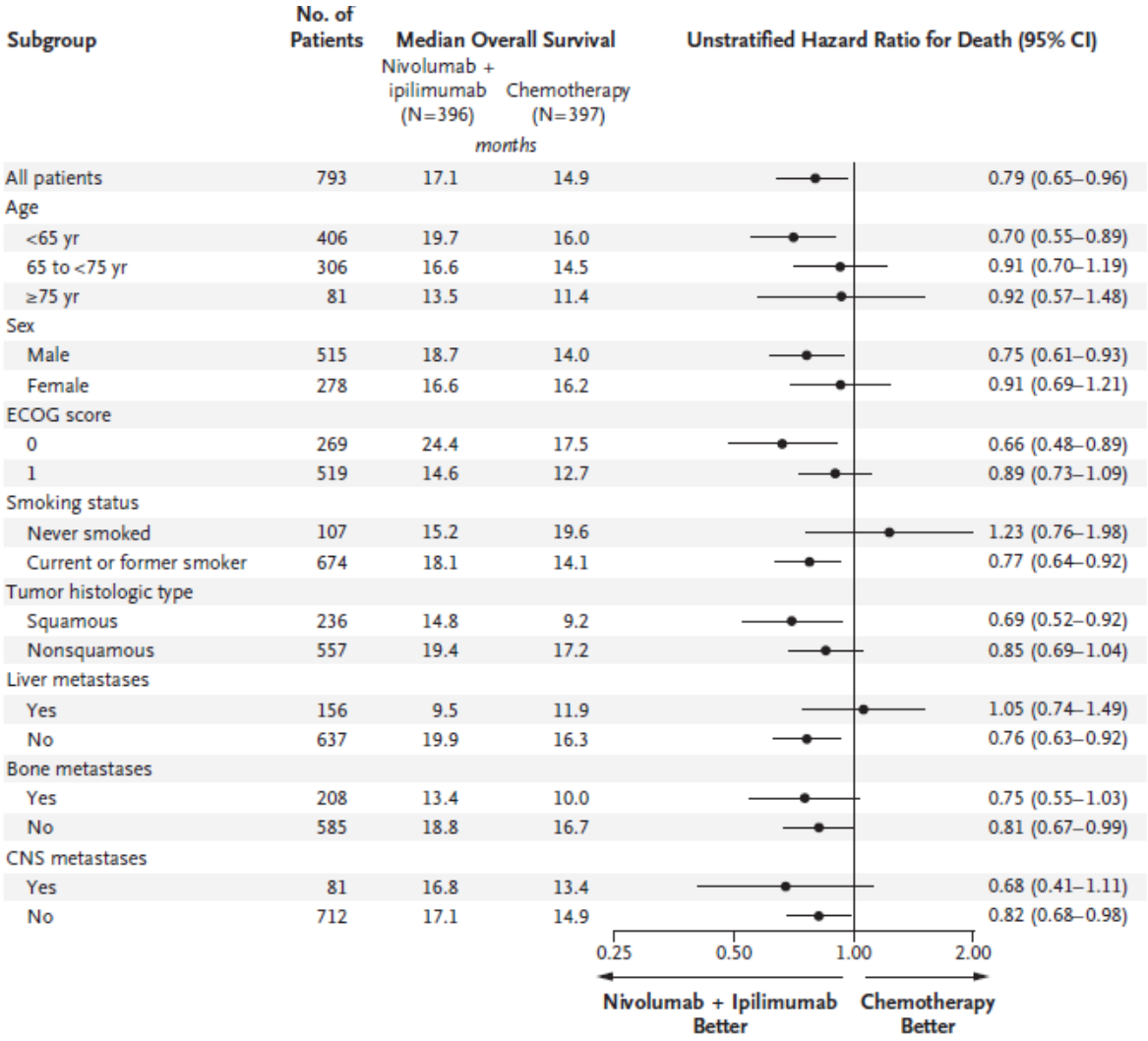
Abbreviations: CI = confidence interval; PD-L1 = programmed death-ligand 1.

Note: *Chemotherapy* refers to platinum doublet chemotherapy.

Source: Hellmann et al. (2019)[54]

Overall survival in most subgroups favoured nivolumab + ipilimumab (Figure 27) except in patients with liver metastases and those who had never smoked. The results of the analysis of PFS also favoured nivolumab + ipilimumab over PDC.[54]

Figure 27. CheckMate-227: overall survival in patients in prespecified subgroups



Abbreviations: CI = confidence interval; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group.

Note: *Chemotherapy* refers to platinum doublet chemotherapy.

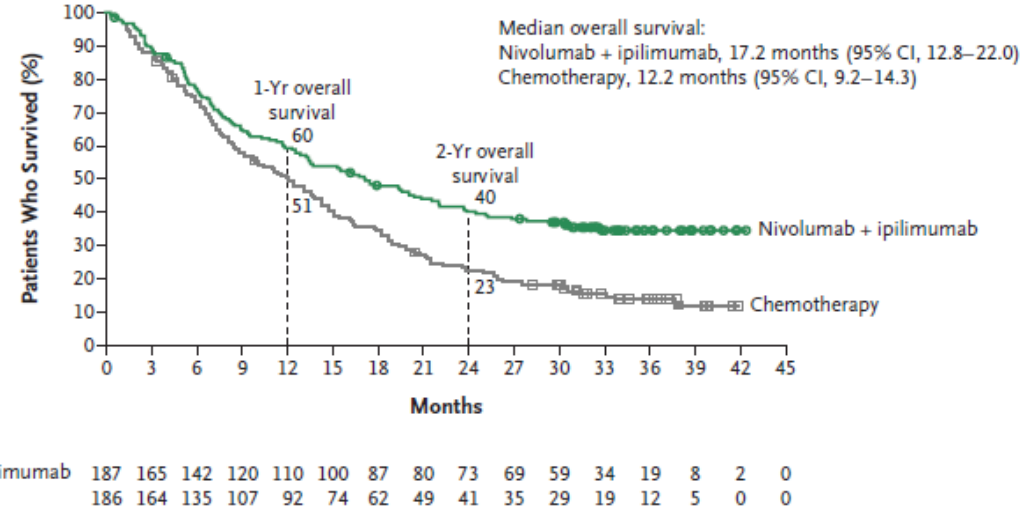
Source: Hellmann et al. (2019)[54]

The ORR was 35.9% (95% CI, 31.1%-40.8%) with nivolumab + ipilimumab (with 5.8% of patients having a CR) versus 30.0% (95% CI, 25.5%-34.7%) with PDC (with 1.8% of patients having a CR). The median DOR was 23.2 months (95% CI, 15.2-32.2 months) with nivolumab + ipilimumab and 6.2 months (95% CI, 5.6-7.4 months) with PDC. The proportion of patients with an ongoing response was also higher with the combination therapy than with PDC (64.2% vs. 27.9% at 1 year and 49.5% vs. 11.0% at 2 years).[54]

Nivolumab + ipilimumab, as compared with PDC, was also evaluated in a prespecified descriptive analysis of patients with a PD-L1 expression level of < 1% and in all trial participants. In patients with a PD-L1 < 1%, the median duration of OS was longer with nivolumab + ipilimumab than with PDC, with an HR for death of 0.62 (95% CI, 0.48-0.78) (Figure 28). This benefit was observed

across most subgroups. The 2-year OS rates were 40.4% for nivolumab + ipilimumab and 23.0% for PDC.[54]

Figure 28. CheckMate-227: overall survival in patients with PD-L1 < 1%



Abbreviations: CI = confidence interval; PD-L1 = programmed death-ligand 1.

Note: *Chemotherapy* refers to platinum doublet chemotherapy.

Source: Hellmann et al. (2019)[54]

Among the patients with a PD-L1 expression level of < 1%, the rate of PFS was significantly higher with nivolumab + PDC than with PDC alone (10.5% vs. 4.6% at 2 years; HR for disease progression or death, 0.73; 97.72% CI, 0.56-0.95; *P* = 0.007). The median duration of OS was 15.2 months (95% CI, 12.3-19.8 months) with nivolumab + PDC and 12.2 months (95% CI, 9.2-14.3 months) with PDC alone. However, the between-group difference did not meet the nominal significance level of 0.023 (HR for death, 0.78; 97.72% CI, 0.60-1.02, *P* = 0.035). Thus, formal statistical testing of the one remaining secondary endpoint was not conducted.[54]

An OS benefit with nivolumab + ipilimumab, as compared with PDC, was observed regardless of the subgroup of PD-L1 expression level. Exploratory analysis of additional PD-L1 expression thresholds that are currently used for selection of anti–PD-1 monotherapy showed more variable benefit.

The contribution of ipilimumab was evaluated in an analysis of nivolumab + ipilimumab versus nivolumab monotherapy in patients with a PD-L1 expression level ≥ 1% and in those with PD-L1 ≥ 50% (minimum follow-up, 29.3 months).

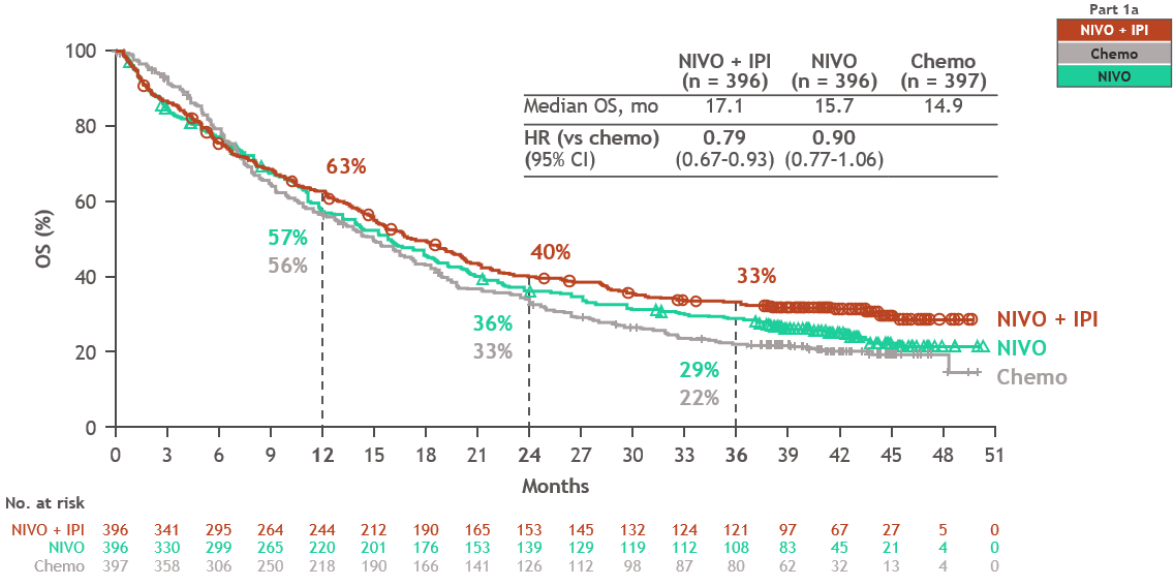
In patients with a PD-L1 expression level ≥ 1%, the rates of OS at 2 years were 40.0% with nivolumab + ipilimumab and 36.2% with nivolumab monotherapy. In patients with PD-L1 ≥ 50%, the 2-year OS rates were 48.1% and 41.9%, respectively. The percentage of patients who had a CR with nivolumab + ipilimumab, as compared with nivolumab monotherapy, was 5.8% and 3.0%, respectively, among the patients with PD-L1 ≥ 1% and 8.8% and 4.7% among those with PD-L1 ≥ 50%. The median DOR was 23.2 months (95% CI, 15.2-32.2 months) with nivolumab +

ipilimumab and 15.5 months (95% CI, 12.7-23.5 months) with nivolumab monotherapy among the patients with PD-L1 > 1%; among those with PD-L1 ≥ 50%, the median DOR was 31.8 months (95% CI, 18.7 months to not reached) and 17.5 months (95% CI, 13.5-31.0 months), respectively.[54]

The benefit of nivolumab + ipilimumab, as compared with nivolumab + PDC, was also evaluated in patients with a PD-L1 expression level ≤ 1% (minimum follow-up, 29.3 months). The ORR was 27.3% with nivolumab + ipilimumab and 37.9% with nivolumab + PDC. At 2 years, the OS rate was 40.4% and 34.7%, respectively. The median DOR was longer with nivolumab + ipilimumab than with nivolumab + PDC (18.0 months vs. 8.3 months).[54]

A 3-year update analysis with a minimum follow-up of 37.7 months (database lock of 28 February 2020) has been conducted, which also includes a landmark analysis of OS by response status at 6 months.[62] In the updated OS analysis, nivolumab + ipilimumab demonstrated a 21% reduction in the risk of death compared with PDC alone in patients with PD-L1 ≥ 1% (HR, 0.79; 95% CI, 0.67-0.93; Figure 29). The median OS was 17.1 months in the nivolumab + ipilimumab group and 15.7 months in the nivolumab monotherapy group compared with 14.9 months in the PDC group; 3-year OS rates were 33%, 29%, and 22%, respectively.[62]

Figure 29. CheckMate-227 part 1a: Kaplan-Meier estimates of overall survival with nivolumab + ipilimumab versus PDC in patients with PD-L1 ≥ 1% (minimum follow-up, 37.7 months)



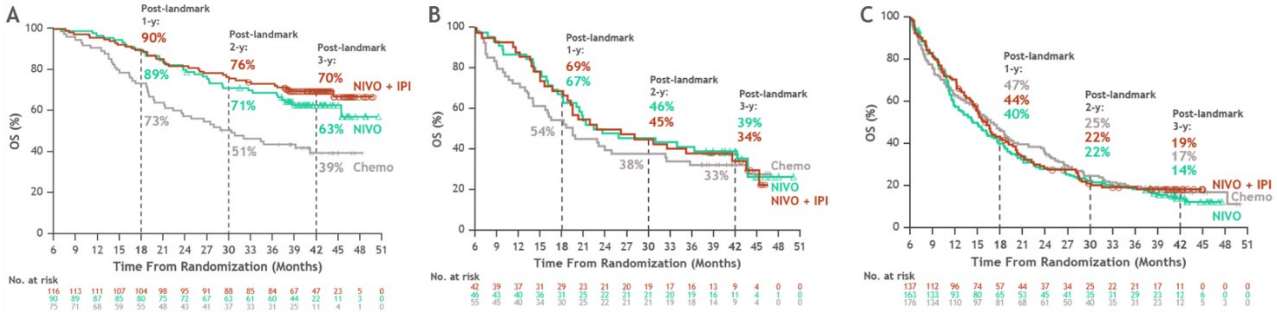
Abbreviations: CI = confidence Interval; HR = hazard ratio; IPI = ipilimumab; NIVO = nivolumab; OS = overall survival; PD-L1 = programmed cell death-ligand-1; PDC = platinum doublet chemotherapy.

Note: *Chemo* refers to PDC.

Source: Ramalingam et al. (2020)[62]

Of the PD-L1 ≥ 1% patients who achieved CR or PR at 6 months while treated with nivolumab + ipilimumab, 70% were still alive at 42 months (post-landmark 3 years) compared with 39% of patients treated with PDC (Figure 30).[62]

Figure 30. CheckMate-227 part 1a: post-landmark overall survival in patients with PD-L1 ≥ 1% with (A) complete response or partial response, (B) stable disease, and (C) progressive disease at 6 months (minimum follow-up, 37.7 months)



Abbreviations: CI = confidence Interval; CR = complete response; IPI = ipilimumab; NIVO = nivolumab; OS = overall survival; PD = progressive disease; PDC = platinum doublet chemotherapy; PR = partial response; SD = stable disease.

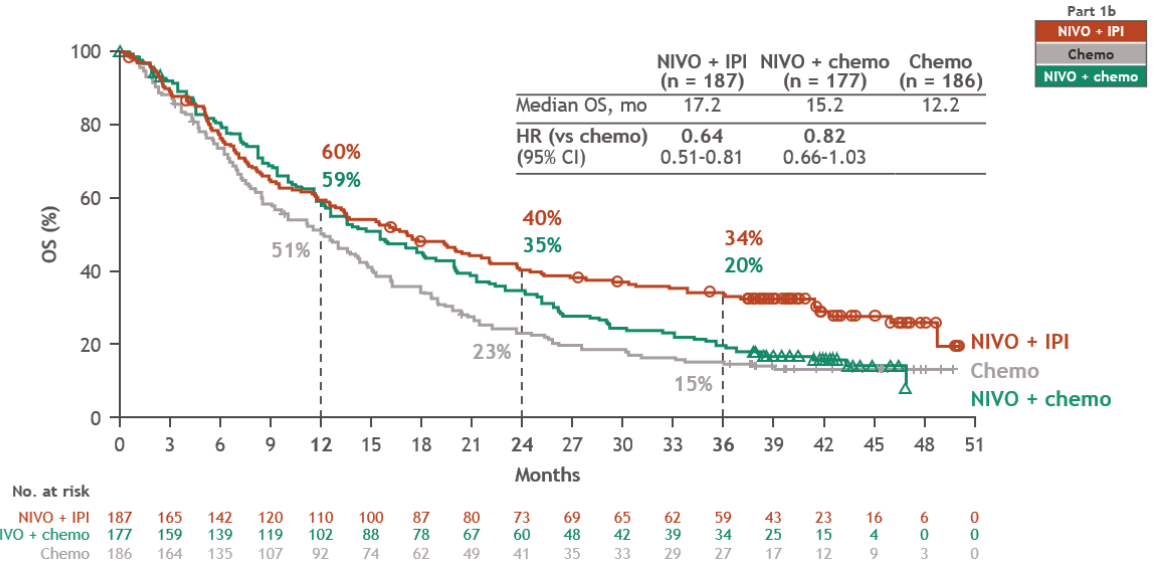
Notes: CheckMate-227 was powered to compare NIVO+IPI vs. PDC. The trial was not powered to compare NIVO+IPI vs. NIVO monotherapy; any such comparisons should be considered exploratory and results should be interpreted with caution.

Chemo refers to PDC.

Source: Ramalingam et al. (2020)[62]

With a minimum follow-up of 37.7 months, nivolumab + ipilimumab demonstrated a clinically meaningful 36% reduction in the risk of death compared with PDC alone, in patients with PD-L1 expression < 1% (HR, 0.64; 95% CI, 0.51-0.81; Figure 31).[63]

Figure 31. CheckMate-227 part 1b: Kaplan-Meier estimates of overall survival with nivolumab + ipilimumab versus PDC in patients with PD-L1 < 1% (minimum follow-up, 37.7 months)



Abbreviations: CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; NIVO = nivolumab; OS = overall survival; PD-L1 = programmed death-ligand 1; PDC = platinum doublet chemotherapy.

Notes: CheckMate-227 was powered to compare NIVO+IPI vs. PDC in part 1a patients (PD-L1 ≥ 1%). The trial was not powered to compare NIVO+IPI vs. PDC in part 1b patients (PD-L1 < 1%), nor was it designed to compare NIVO+IPI vs. NIVO + PDC. Any such comparisons should be considered exploratory and results should be interpreted with caution.

Chemo refers to PDC.

Source: Ramalingam et al. (2020)[62]

B.2.8Meta-analysis

Only one RCT (CheckMate-9LA) was identified via SLR that has investigated the efficacy and safety of nivolumab + ipilimumab + limited PDC. As such, a meta-analysis could not be conducted; thus, an ITC was considered to be most appropriate (see Section B.2.9) to enable comparisons for the comparators considered in the decision problem addressed in this submission.

B.2.9Indirect and mixed treatment comparisons

In the absence of head-to-head trial evidence of nivolumab + ipilimumab + limited PDC versus all UK relevant comparators of interest, an ITC was necessary to enable a comparison for this submission. Specifically, the comparison with atezolizumab + bevacizumab + PDC in PD-L1 < 50% non-squamous patients and pembrolizumab in PD-L1 ≥ 50% had to be informed by the ITC.

B.2.9.1 Evidence base

An SLR was conducted to identify relevant studies to inform indirect comparisons between the interventions of interest (see Section B.2.1). The search strategy was prespecified in terms of

population, interventions, comparisons, outcomes, and study design and is outlined in Appendix G.

B.2.9.1.1 Comparators included

The comparators of interest included in the SLR reflect the comparators considered in the decision problem addressed in this submission. The comparators of interest presented in Table 23 were included for the current evidence submission in patient populations aligned with their marketing authorisation and reimbursement from NICE.

Table 23. Included comparators

Comparator	Patient population
NIVO + IPI + limited PDC	All patients regardless of PD-L1 expression and histology
PDC	All patients regardless of PD-L1 expression and histology
Atezolizumab + bevacizumab+ PDC	Non-squamous patients and PD-L1 < 50%
Pembrolizumab	PD-L1 ≥ 50%

Abbreviations: IPI = ipilimumab; NIVO = nivolumab; PDC = platinum doublet chemotherapy PD-L1 = programmed death-ligand 1.

B.2.9.1.2 Criteria used in trial selection

The inclusion and exclusion criteria and the study selection process are described in Appendix N. Table 24 summarises the data sources used in the ITC.

Table 24. Summary of data sources

Trial	Endpoint	Reference
CM-9LA	OS	Bristol Myers Squibb data on file (2020)[64]
	PFS	
KN-024	OS	Reck et al. (2016)[65]
	PFS	
KN-042	OS	Mok et al. (2019)[66]
	PFS	
ERACLE	OS	Galetta et al. (2015)[67]
	PFS	
PRONOUNCE	OS	Zinner et al. (2015)[68]
	PFS	
IMpower-150	OS	Socinski et al. (2018)[69]
	PFS	

Abbreviations: CM = CheckMate; KN = KeyNote; OS = overall survival; PFS = progression-free survival.

B.2.9.1.3 Histology-specific considerations

The trials involving IO-based regimens were conducted in histology all-comer populations, and non-squamous–only populations.

The CheckMate-9LA RCT involved all histologies, which aligned with the comparator RCTs for pembrolizumab. For the comparison between CheckMate-9LA and atezolizumab + bevacizumab + PDC for non-squamous–only populations, we used data from the CheckMate-9LA ITT population to preserve study design and power given that the effect size for nivolumab + ipilimumab + limited PDC relative to PDC was the same across squamous and non-squamous histologies. This assumption was based on the findings that the relative effect sizes did not differ substantially, as well as practical reasons related to sample size (see Section B.2.7.1).

B.2.9.1.4 PD-L1–related considerations

In the main analyses, the comparator RCTs were restricted to the relevant target populations: PD-L1 all-comers for nivolumab + ipilimumab + limited PDC, PD-L1 < 50% for atezolizumab + bevacizumab + carboplatin + paclitaxel, and PD-L1 ≥ 50% for pembrolizumab monotherapy. CheckMate-9LA was stratified for PD-L1 ≥ 1% and < 1% (not ≥ 50% and < 50% as IMpower-150 and KEYNOTE-042) and the relative effect sizes were similar across PD-L1–defined categories (see Section B.2.7.1); hence, to preserve the RCT design and maximise sample size, the PD-L1 all-comer population was used in the indirect comparisons with IO monotherapies under the assumption that PD-L1 expression levels do not modify treatment effect for dual IO (specifically, the combination of PD-1 inhibitors plus CTLA-4 inhibitors as suggested by data from both CheckMate-9LA and CheckMate-227).

B.2.9.2 Network meta-analysis method assessment

In line with recent technology assessments in NSCLC, the first step in the feasibility assessment of suitable ITC methods was investigating if the proportional hazards assumption was violated. This proportional hazards assessment was conducted using the following tests:

- Visually inspecting the KM curve (ensuring the re-created curve accurately matches the original curve in absence of individual patient-level data).
- Assessing Schoenfeld residual plots with Schoenfeld residuals global tests to assess slope in generalised linear regression of Schoenfeld residuals (Table 25).
- Examining a log-cumulative hazard plot of the patient-level data for each pair of curves, examining to see if lines are close to parallel, diverging over time, or crossing (Figure 32 to Figure 35).

The results of the first two steps are presented in Appendix N.

Table 25. Assessment of proportional hazards assumption with Schoenfeld residuals global test across included trials

Study	Histology	Endpoint	PD-L1 status	[redacted]
CM-9LA IPD (database lock March 2020)	Mixed	OS	PD-L1 all-comers	[redacted]
		PFS	PD-L1 all-comers	[redacted]
KN-024	Mixed	PFS	PD-L1 ≥ 50%	[redacted]
		OS	PD-L1 ≥ 50%	[redacted]
KN-042	Mixed	PFS	PD-L1 ≥ 50%	[redacted]
		OS	PD-L1 ≥ 50%	[redacted]
IMpower-150	NSQ	OS	PD-L1 < 50%	[redacted]
		PFS	PD-L1 < 50%	[redacted]

*Significantly different from proportional hazards based Schoenfeld residuals global test, to assess slope in generalised linear regression of Schoenfeld residuals.

Abbreviations: CM = CheckMate; IPD = individual patient-level data; KN = KeyNote; NSQ = non-squamous; OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = progression-free survival.

Figure 32. Log-cumulative hazard plot for nivolumab + ipilimumab + limited PDC versus PDC for CheckMate-9LA: overall survival (left) and progression-free survival (right)

[redacted]

Abbreviations: NIVO + IPI + limited PDC = nivolumab + ipilimumab combined with limited platinum doublet chemotherapy; OS = overall survival; PDC = platinum doublet chemotherapy.

Figure 33. Log-cumulative hazard plot and Schoenfeld residuals plot for pembrolizumab versus PDC for KeyNote-024: overall survival (left) and progression-free survival (right)

[redacted]

Abbreviations: PEMBRO = pembrolizumab; OS = overall survival; PDC = platinum doublet chemotherapy.

Figure 34. Log-cumulative hazard plot and Schoenfeld residuals plot for pembrolizumab versus PDC for KeyNote-042: overall survival (left) and progression-free survival (right)

Abbreviations: PEMBRO = pembrolizumab; PDC = platinum doublet chemotherapy.

Figure 35. Log-cumulative hazard plot and Schoenfeld residuals plot for atezolizumab + bevacizumab + platinum paclitaxel vs. bevacizumab + platinum paclitaxel for IMpower-150: overall survival (left) and progression-free survival (right)

[redacted]

For completeness, an ITC assuming proportional hazards using a frequentist approach and the Bucher method[72] for time-to-event outcomes (OS, PFS) is provided in Appendix N, although not considered in the current economic analyses.

B.2.9.2.1 Summary of fractional polynomials network meta-analysis method

[redacted] The methodology followed the approach outlined by Jansen (2011)[73]. Specifically, after reconstruction of individual patient-level data (IPD) based on digitised Kaplan-Meier curves was completed, using the methodology described by Guyot et al. (2012)[74], the log hazards of OS and PFS from eligible RCTs were fit as a function of time using parametric models in the following form:

$$\log \text{hazard} = \mu 1 + \mu 2\ tP1 + \mu 3\ tP2,$$

where *μ1* represents the scale parameter, *μ2* and *μ3* represent shape parameters, t represents time, and *P1* and *P2* are powers from the set {−1,−0.5, 0, 0.5, 1}, where t0 = ln(t), and when P1 = P2. The model is structured as a repeated powers model (see Jansen (2011)[73]). Differences, *d1*, *d2*, and/or *d3*, were then added to μs within each term to capture treatment effects; these *d*s were then meta-analysed.

$$\log \text{hazard} = (\mu 1 + d1) + (\mu 2 + d2)\ tP1 + (\mu 3 + d3)\ tP2$$

[redacted]

B.2.9.3 Results of fractional polynomials network meta-analysis

The full results of the NMA is reported in Appendix N. The results used for the base-case analysis is reported in this section.

B.2.9.3.1 Overall survival in patients with PD-L1 ≥ 50%

Table 26 shows the RCTs included in the NMA of OS for the target population of mixed histology and PD-L1 ≥ 50% in first-line advanced NSCLC.

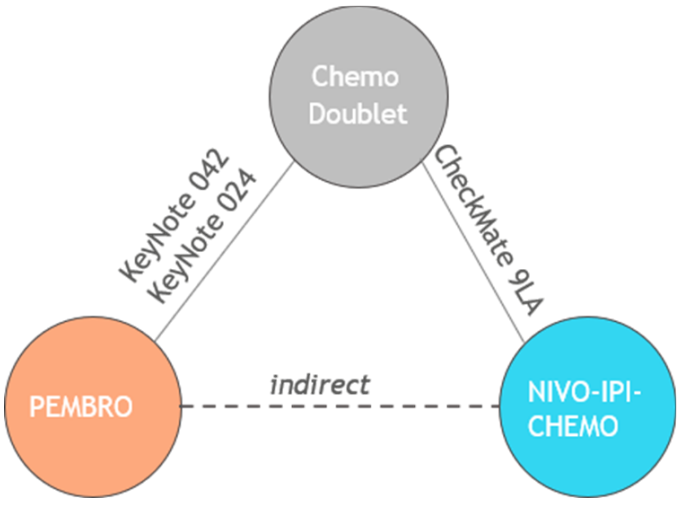
Table 26. Included randomised controlled trials for target population of mixed histology and PD-L1 ≥ 50%

Study	PD-L1	Histology	Treatment 1	Treatment 2	HR (95% CI)
KN-024	≥ 50%	Mixed	PEMBRO	PDC	[redacted]
KN-042	≥ 50%	Mixed	PEMBRO	PDC	[redacted]
CM-9LA	All-comers	Mixed	NIVO + IPI + limited PDC	PDC	[redacted]

Abbreviations: CI = confidence interval; CM = CheckMate; HR = hazard ratio; IPI = ipilimumab; KN = KeyNote; NIVO = nivolumab; PDC = platinum doublet chemotherapy; PD-L1 = programmed death-ligand 1; PEMBRO = pembrolizumab.

Figure 36 shows the network diagram for OS for the target population of mixed histology and PD-L1 ≥ 50% in first-line advanced NSCLC. Table 115 in Appendix N shows the model fit statistics for OS for the target population of mixed histology and PD-L1 ≥ 50% in first-line advanced NSCLC.

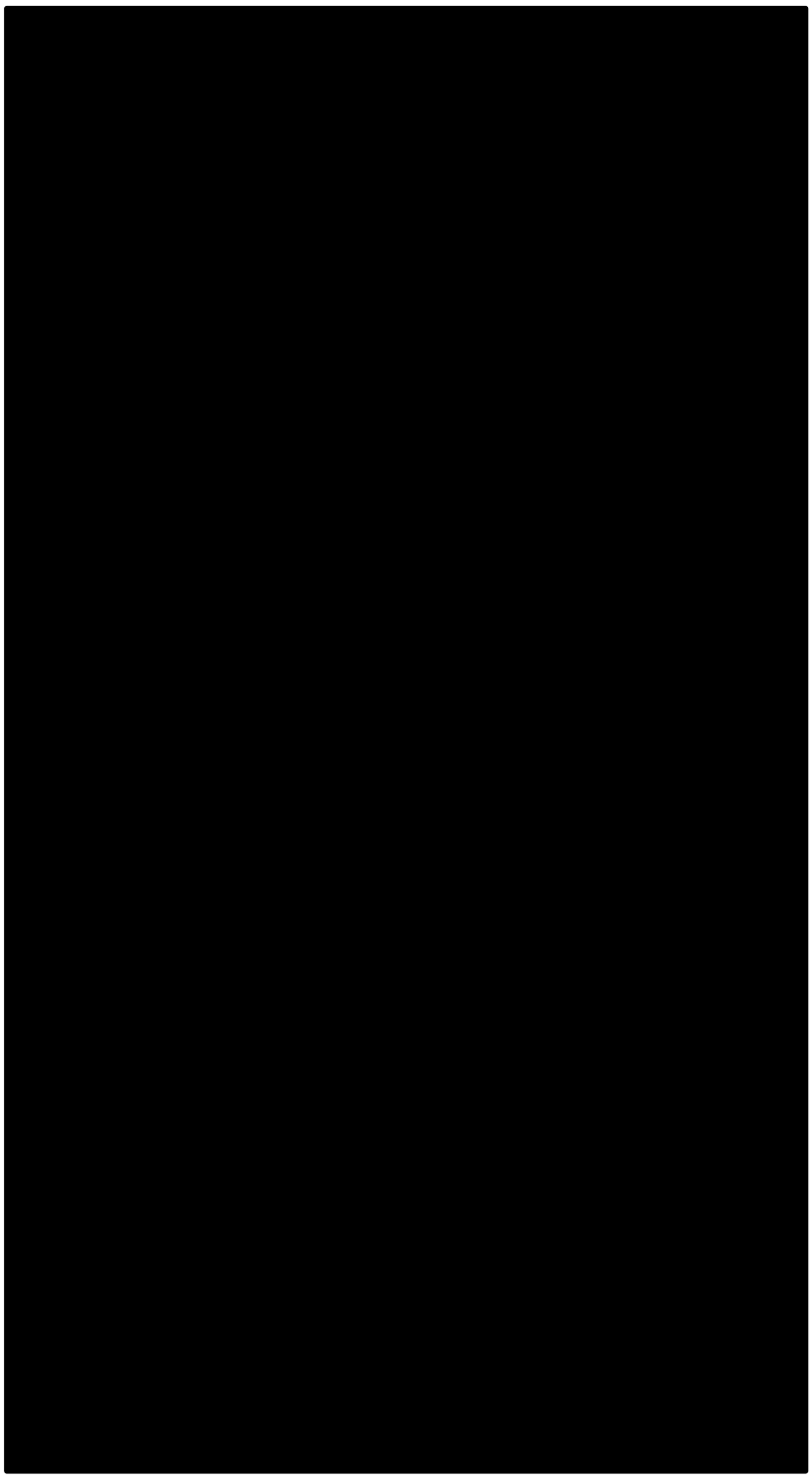
Figure 36. Network diagram for overall survival for target population of mixed histology and PD-L1 ≥ 50%



Abbreviations: IPI = ipilimumab; NIVO = nivolumab; PEMBRO = pembrolizumab.

[redacted]

Figure 37. Comparison of fractional polynomial model fit to Kaplan-Meier curves of contributing randomised controlled trials for overall survival for the target population of mixed histology and PD-L1 ≥ 50% in first-line advanced NSCLC



Abbreviations: CM = CheckMate; IPD = individual patient-level data; IPI = ipilimumab; KM = Kaplan-Meier; NIVO = nivolumab; NSCLC = non-small cell lung cancer; PD-L1 = programmed death-ligand 1; PEMBRO = pembrolizumab.

[redacted]

Table 27. Hazard ratios of nivolumab + ipilimumab + limited PDC versus comparators over 4 years for overall survival in patients with PD-L1 ≥ 50%

NIVO + IPI + limited PDC vs.	Time point (months)	HR (95% CrI)
PDC	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
Pembrolizumab	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]

Abbreviations: CrI = credible interval; HR = hazard ratio; IPI = ipilimumab; NIVO = nivolumab; PD-L1 = programmed death-ligand 1; PDC = platinum doublet chemotherapy.

Note: Estimates obtained from the following model: p1 p1; treatment effect on scale, 1st shape.

B.2.9.3.2 Overall survival in patients with non-squamous histology and PD-L1 < 50%

[redacted]

Table 28. Included randomised controlled trials for target population of non-squamous histology and PD-L1 < 50%

Study	PD-L1	Histology	Treatment 1	Treatment 2	HR (95% CI)
ERACLE Galetta et al. (2015)[67]	All-comers	NSQ	PLAT+PEMX	BEV+PDC	[redacted]
PRONOUNCE Zinner et al. (2015)[68]	All-comers	NSQ	PLAT+PEMX	BEV+PDC	[redacted]
IMpower-150[69]	< 50%	NSQ	ATEZO+BEV+ PDC	BEV+PDC	[redacted]
CheckMate-9LA	All-comers	All-comers	NIVO+IPI+ PLAT+PEMX*	PLAT+PEMX*	[redacted]

Abbreviations: ATEZO = atezolizumab; BEV = bevacizumab; CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; NIVO = nivolumab; NSQ = non-squamous; PD-L1 = programmed death-ligand 1; PDC = platinum doublet chemotherapy; PEMX = pemetrexed; PLAT = platinum.

* This is the NSQ regimen in the CheckMate-9LA trial.

Figure 38 shows the network diagram for OS for the target population of mixed histology and PD-L1 < 50% in first-line advanced NSCLC.

Figure 38. Network diagram for overall survival for target population of non-squamous histology and PD-L1 < 50%

[redacted]

Abbreviations: ATEZO = atezolizumab; BEV = bevacizumab; CARB = carboplatin; IPI = ipilimumab; NIVO = nivolumab; NSQ = non-squamous; PEMX = pemetrexed; PLAT = platinum; TAX = paclitaxel.

* This is the NSQ regimen within CheckMate-9LA.

Appendix N shows the model fit statistics for OS for the target population of non-squamous histology and PD-L1 < 50% in first-line advanced NSCLC.

[redacted]

[redacted]

[redacted]

Figure 39. Comparison of fractional polynomial models fit to Kaplan-Meier curves of contributing randomised controlled trials for overall survival for the target population of non-squamous histology and PD-L1 < 50% in first-line advanced NSCLC

Abbreviations: ATEZO = atezolizumab; BEV = bevacizumab; CARB = carboplatin; IPI = ipilimumab; KM = Kaplan-Meier; NIVO = nivolumab; NSCLC = non-small cell lung cancer; PD-L1 = programmed death-ligand 1; PLAT = platinum; TAX = paclitaxel.

Table 29 shows the base-case HRs of nivolumab + ipilimumab + limited PDC for OS for the target population of non-squamous histology and PD-L1 < 50%.

Table 29. Hazard ratios of nivolumab + ipilimumab + limited PDC versus comparators over time for overall survival

NIVO + IPI + limited PDC vs.	Time point (months)	HR (95% CrI)
PDC	Constant HR	[redacted]
BEV+PLAT+TAX	Constant HR	[redacted]
ATEZO+BEV+PLAT+TAX	Constant HR	[redacted]

Abbreviations: ATEZO = atezolizumab; BEV = bevacizumab; CrI = credible interval; HR = hazard ratio; IPI = ipilimumab; NIVO = nivolumab; PDC = platinum doublet chemotherapy; PLAT = platinum; TAX = paclitaxel.
Note: Estimates obtained from the following models: p1 p1, treatment effect on scale, and 1st shape.

B.2.9.3.3 Progression-free survival in patients with PD-L1 ≥ 50%

The RCTs included in the NMA of PFS for the target population of mixed histology and PD-L1 ≥ 50% in first-line advanced NSCLC were the same as those used for OS (Table 30).

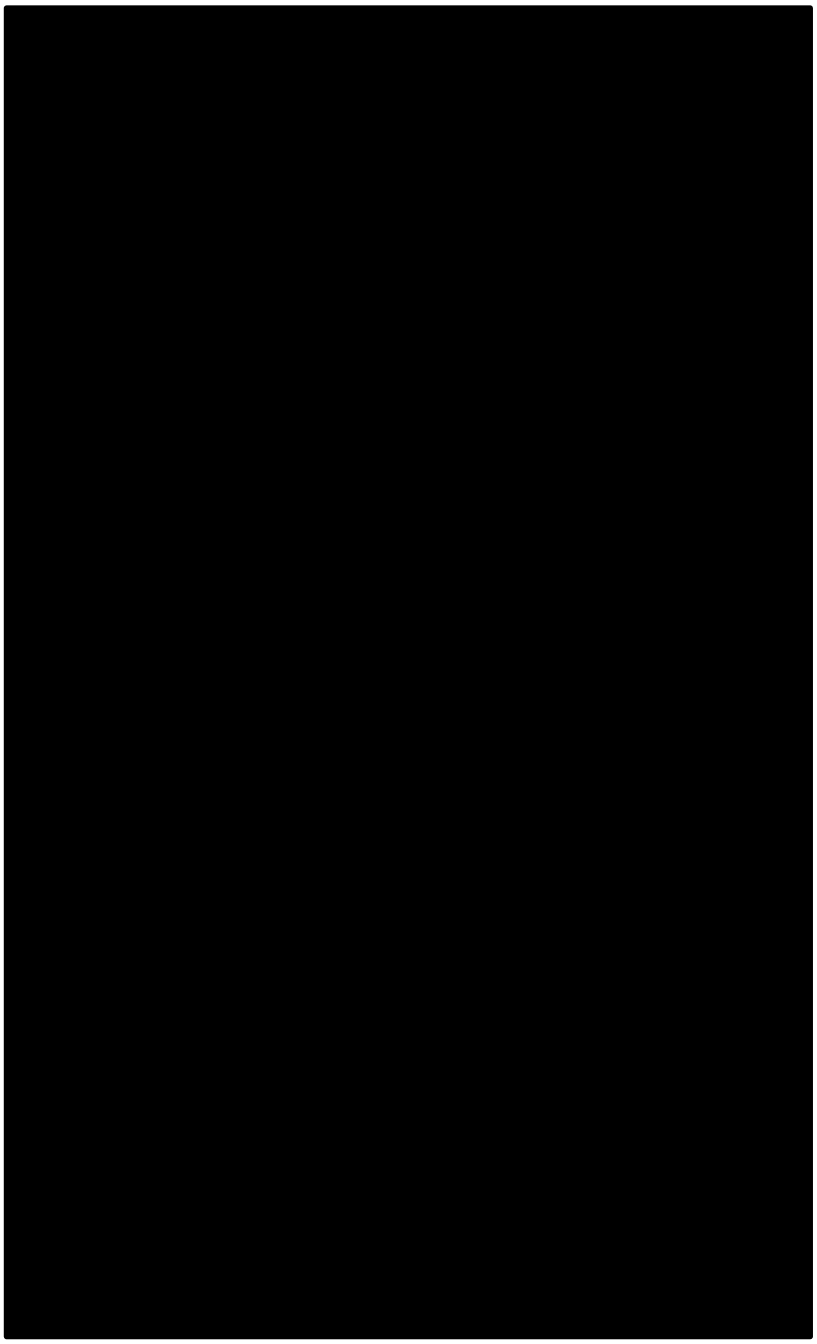
Table 30. Randomised controlled trials included in the network meta-analysis of progression-free survival for the target population of mixed histology and PD-L1 ≥ 50%

Study	PD-L1	Histology	Treatment 1	Treatment 2	HR (95% CI)
KN-024	≥ 50%	Mixed	PEMBRO	PDC or PLAT+PEMX	[redacted]
KN-042	≥ 50%	Mixed	PEMBRO	PDC or PLAT+PEMX	[redacted]
CM-9LA	All-comers	Mixed	NIVO + IPI + limited PDC	PDC or PLAT+PEMX	[redacted]

Abbreviations: CI = confidence interval; CM = CheckMate; HR = hazard ratio; IPI = ipilimumab; KN = KeyNote; NIVO = nivolumab; NSCLC = non-small cell lung cancer; PDC = platinum doublet chemotherapy; PD-L1 = programmed death-ligand 1; PEMBRO = pembrolizumab; PEMX = pemetrexed; PLAT = platinum.

[redacted]

Figure 40. Comparison of fractional polynomial model fit to Kaplan-Meier curves of contributing randomised controlled trials for progression-free survival for the target population of mixed histology and PD-L1 ≥ 50%



Abbreviations: CM = CheckMate; IPD = individual patient-level data; IPI = ipilimumab; KM = Kaplan-Meier; NIVO = nivolumab; NSCLC = non-small cell lung cancer; PD-L1 = programmed death-ligand 1; PEMBRO = pembrolizumab.

Note: mu parameters are study specific, whereas d parameters are meta-analysed. From model: p0 p1; treatment effect on scale, and 1st shape.

Data sources: CheckMate-9LA[64]; KeyNote-024[65]; KeyNote-042[66]

Table 31. Hazard ratios of nivolumab + ipilimumab + limited PDC versus comparators over time for progression-free survival for the target population of mixed histology and PD-L1 ≥ 50%

NIVO + IPI + limited PDC versus	Time point (months)	HR (95% CrI)
PDC	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
Pembrolizumab	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]

Abbreviations: CrI = credible interval; HR = hazard ratio; IO = immuno-oncology; IPI = ipilimumab; NIVO = nivolumab; NSCLC = non-small cell lung cancer; PD-L1 = programmed death-ligand 1; PDC = platinum doublet chemotherapy; RCT = randomised controlled trial.

Notes: NIVO + IPI + limited PDC becomes a projection and not an observed finding after 18 months of follow-up.

Estimates obtained from the following models: p0 p1, treatment effect on scale, and 1st shape.

B.2.9.3.4 Progression-free survival in patients with non-squamous histology and PD-L1 < 50%

The RCTs included in the NMA of PFS for the target population with non-squamous histology and PD-L1 < 50%in first-line advanced NSCLC were the same as those used for OS (Table 32).

Table 32. Randomised controlled trials included in the network meta-analysis of progression-free survival for the target population of non-squamous histology and PD-L1 < 50% in first-line advanced NSCLC

Study	PD-L1	Histology	Treatment 1	Treatment 2	HR (95% CI)
ERACLE Galetta et al. (2015)[67]	All-comers	NSQ	PLAT+PEMX	BEV+PDC	[redacted]
PRONOUNCE Zinner et al. (2015)[68]	All-comers	NSQ	PLAT+PEMX	BEV+PDC	[redacted]
IMpower-150[69]	< 50%	NSQ	ATEZO+BEV +PDC	BEV+PDC	[redacted]
CheckMate-9LA	All-comers	All-comers	NIVO+IPI+ PLAT+PEMX[a]	PLAT+PEMX[a]	[redacted]

Abbreviations: ATEZO = atezolizumab; BEV = bevacizumab; CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; NIVO = nivolumab; NSCLC = non-small cell lung cancer; NSQ = non-squamous; PD-L1 = programmed death-ligand 1; PDC = platinum doublet chemotherapy; PEMX = pemetrexed; PLAT = platinum; RCT = randomised controlled trial.

[a] This is the NSQ regimen within CheckMate-9LA.

Figure 41. Comparison of fractional polynomial model fit to Kaplan-Meier curves of contributing randomised controlled trials for progression-free survival for the target population of non-squamous histology and PD-L1 < 50% in first-line advanced NSCLC

Abbreviations: ATEZO = atezolizumab; BEV = bevacizumab; CM = CheckMate; IPD = individual patient-level data; IPI = ipilimumab; KM = Kaplan-Meier; NIVO = nivolumab; NSCLC = non-small cell lung cancer; PD-L1 = programmed death-ligand 1; PEMBRO = pembrolizumab; PLAT = platinum; TAX = paclitaxel.

Note: mu parameters are study specific, whereas d parameters are meta-analysed. From models: p0 p0, treatment effect on scale, and 1st shape.

Data sources: CheckMate-9LA[64]; ERACLE[68]; IMpower-150[69]; PRONOUNCE[67]

Table 33. Hazard ratios of nivolumab + ipilimumab + limited PDC versus comparators over time for progression-free survival for the target population of non-squamous histology and PD-L1 < 50% in first-line advanced NSCLC

NIVO + IPI + limited PDC vs.	Time point (months)	HR (95% CrI)
PDC	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
BEV+PLAT+TAX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
ATEZO+BEV+PLAT+TAX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]

Abbreviations: ATEZO = atezolizumab; BEV = bevacizumab; CrI = credible interval; HR = hazard ratio; IPI = ipilimumab; NIVO = nivolumab; NSCLC = non-small cell lung cancer; PDC = platinum doublet chemotherapy; PD-L1 = programmed death-ligand 1; PLAT = platinum; RCT = randomised controlled trial; TAX = paclitaxel.

Notes: NIVO + IPI + limited PDC becomes a projection and not an observed finding after 18 months of follow-up. Estimates obtained from the following models: p0 p0, treatment effect on scale, and 1st shape.

B.2.9.4 Uncertainties in the indirect and mixed treatment comparisons

[redacted]

[redacted]

B.2.10 Adverse reactions

The safety data from CheckMate-9LA (see Section B.2.10.1) are of most relevance to the decision problem, with CheckMate-568 providing supporting information (see Section B.2.10.2.1). No other trials evaluated the combination of nivolumab + ipilimumab + limited PDC; therefore, the other supporting studies are not discussed here.

B.2.10.1 CheckMate-9LA

Nivolumab + ipilimumab + limited PDC demonstrated a manageable safety profile in CheckMate-9LA, with no new safety signals observed (Table 34).[1] Consistent with the limited cycles of PDC, several toxicities typically related to chemotherapy were less frequently reported with nivolumab + ipilimumab + limited PDC compared with full courses of PDC (Figure 42).

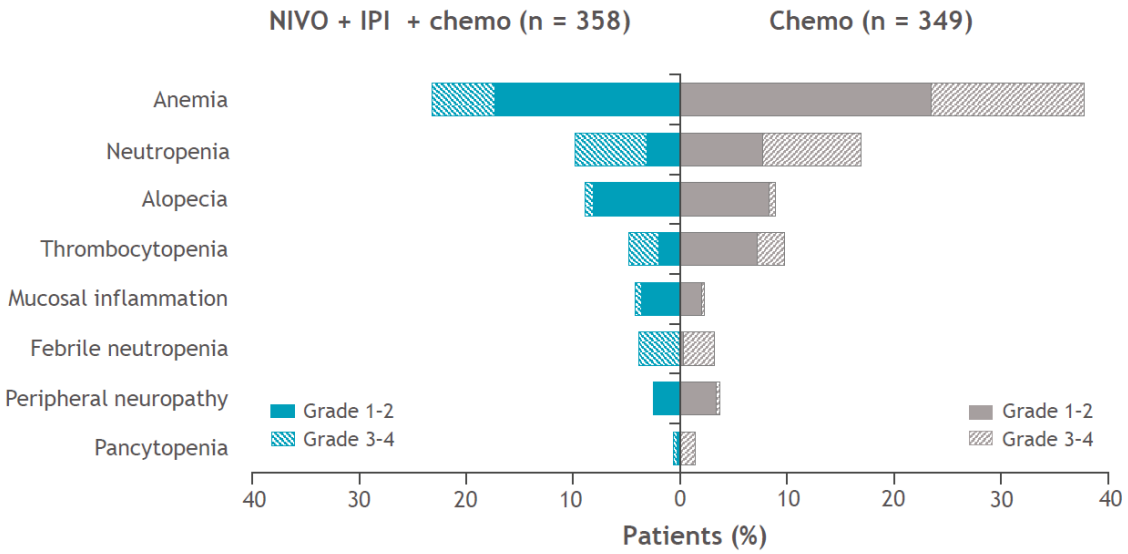
Table 34. CheckMate-9LA: summary of safety results from all randomised patients

	NIVO + IPI + limited PDC (n = 358)		PDC (n = 349)	
Event, % of patients	**Any grade**	**Grade 3-4**	**Any grade**	**Grade 3-4**
Any AE	99.4	68.4	98.0	53.9
Any SAE	60.1	47.2	42.7	32.1
Any TRAE	91.6	446.9	87.7	37.8
Nausea	26.8	1.4	35.8	0.9
Anaemia	23.2	5.9	37.8	14.3
Asthenia	20.9	0.8	17.8	2.3
Diarrhoea	20.9	3.9	11.7	0.6
Pruritus	20.9	0.8	1.7	0
Rash	18.7	1.7	3.2	0
Fatigue	17.0	2.2	10.9	0.6
Decreased appetite	16.5	1.1	15.8	1.1
Neutropenia	9.8	6.7	16.9	9.2
TRAEs leading to discontinuation of any component of the regimen	19.3	16.2	7.4	4.6
Serious TRAEs	29.6	25.4	17.8	14.6
Treatment-related deaths	2.0		1.7	

Abbreviations: AE = adverse event; IPI = ipilimumab; NIVO = nivolumab; PDC = platinum doublet chemotherapy; SAE = serious adverse event; TRAE = treatment-related adverse event.

Sources: Reck et al. (2020)[1]; Bristol Myers Squibb data on file (2020)[21]

Figure 42. Treatment-related adverse event typically associated with PDC



Abbreviations: IPI = ipilimumab; NIVO = nivolumab; PDC = platinum doublet chemotherapy.

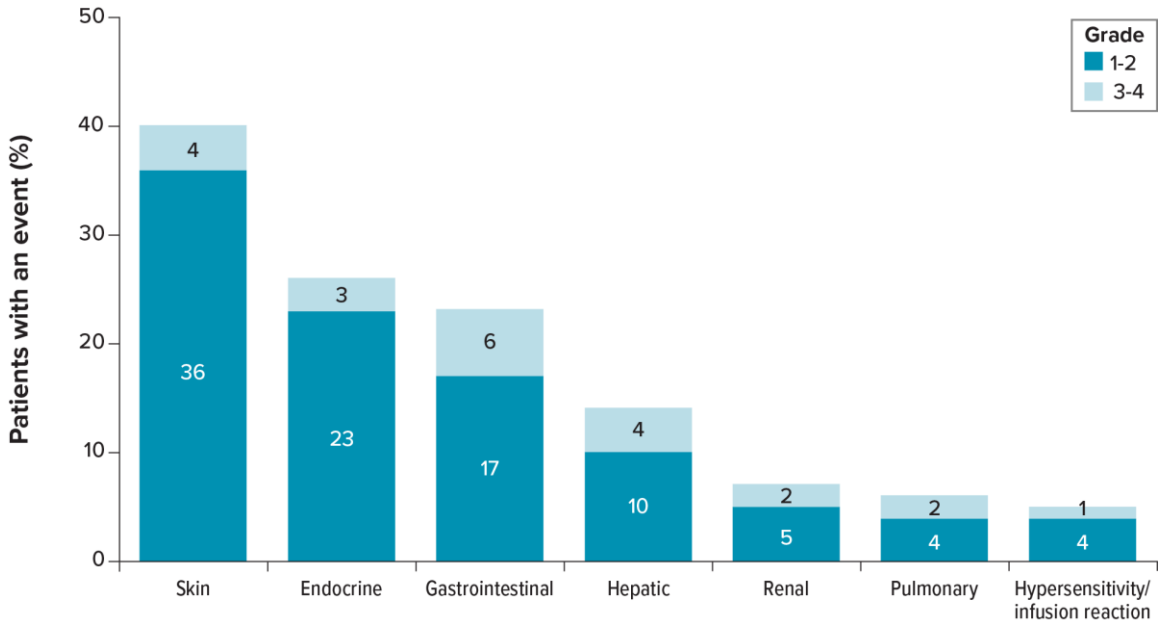
Note: *Chemo* refers to PDC.

Source: Reck et al. (2020)[1]

The most common any-grade TRAEs (≥ 15%) were nausea, anaemia, asthenia, and diarrhoea. Figure 43 presents treatment-related select AEs with nivolumab + ipilimumab + limited PDC.

The frequency of deaths attributed to study drug toxicity was similar between the nivolumab + ipilimumab + limited PDC (2.0%) and PDC arms (1.7%).

Figure 43. Treatment-related select adverse events with nivolumab + ipilimumab + limited PDC



Abbreviation: PDC = platinum doublet chemotherapy.

Source: Reck et al. (2020)[1]

Overall, most immune-mediated AEs were grade 1-2. The most frequently reported immune-mediated AEs (any grade) were as follows in each treatment arm[79]:

- Nivolumab + ipilimumab + limited PDC: rash (16.2%), hypothyroidism/thyroiditis (15.9%), hyperthyroidism (8.1%), pneumonitis (5.3%), and hepatitis (5.0%)
- PDC: hypothyroidism/thyroiditis (0.9%).

B.2.10.2 Supporting studies

B.2.10.2.1 CheckMate-568

In CheckMate-568 part 2, the addition of 2 cycles of PDC to nivolumab + ipilimumab was tolerable, with no new safety signals in patients with untreated advanced NSCLC.

During the first 9 weeks, 1 patient experienced a DLT and asymptomatic grade 3 aspartate aminotransferase (AST) and alanine transaminase (ALT) elevation, which resolved within 2 weeks. Adverse events of any cause were reported in all 36 patients; 27 patients (75%) experienced grade 3-4 events. Four grade 5 events (that led to death within 24 hours) occurred, unrelated to treatment. Serious AEs (SAEs) were reported in 26 patients (72%), and AEs leading to discontinuation were reported in 9 patients (25%). Overall, 21 patients (58%) experienced a grade 3-4 TRAE (Table 35). The most common TRAEs were pruritus, fatigue, and rash. There were no treatment-related deaths. In total, 22 deaths (61%) occurred, 13 (36%) due to disease progression, 6 (17%) due to other reasons, and 3 (8%) due unknown reasons.[57]

Table 35. CheckMate-568: treatment-related adverse events

	All treated (n = 36)	
Event, n (%) of patients	**Any grade**	**Grade 3-4**
All TRAEs	33 (92)	21 (58)
TRAE in ≥ 15% of patients		
Pruritus	12 (33)	0
Fatigue	10 (28)	0
Rash	9 (25)	1 (3)
Diarrhoea	7 (19)	0
Nausea	7 (19)	0
Anaemia	7 (19)	2 (6)
Hypothyroidism	6 (17)	1 (3)
Maculo-papular rash	6 (17)	1 (3)
Lipase increased	6 (17)	6 (17)
Treatment-related SAE	13 (36)	12 (33)
TRAEs leading to discontinuation	8 (22)	7 (19)
Treatment-related deaths	0	0

Abbreviations: SAE = serious adverse event; TRAE = treatment-related adverse event.

Source: Gainor et al. (2020)[57]

The most common treatment-related select AEs (with a potential immunologic cause) were in the skin, endocrine, and gastrointestinal categories and were typically grade 1-2 (Table 36).

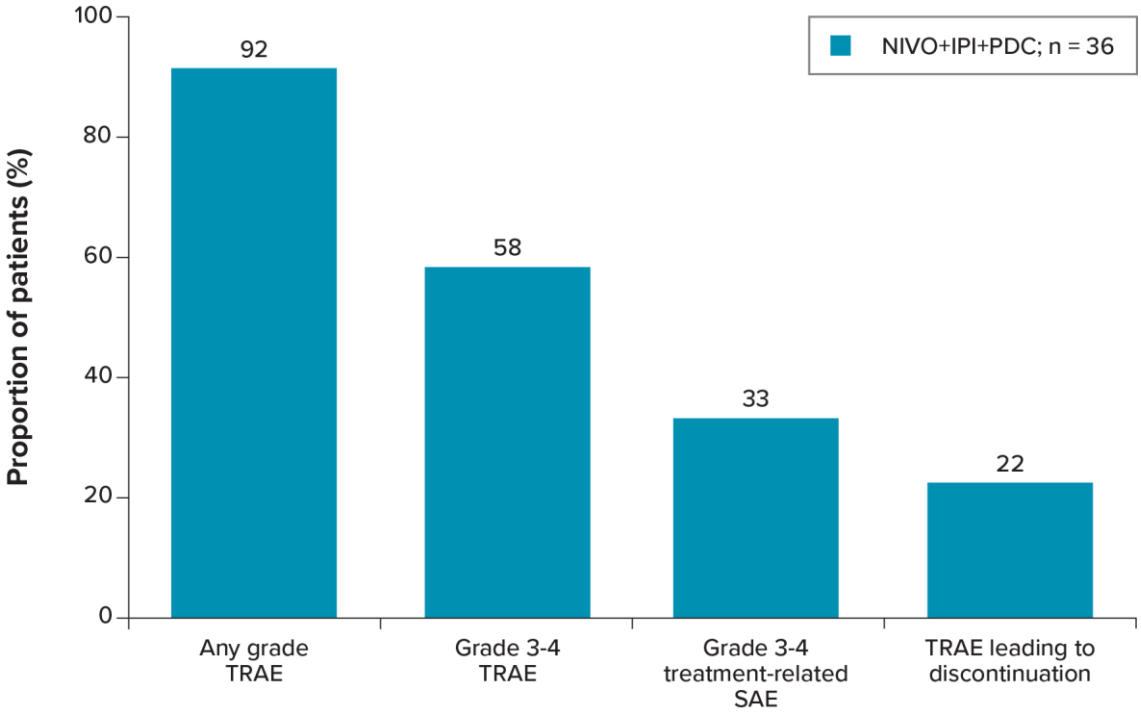
Table 36. CheckMate-568: treatment-related select adverse events

	All treated (n = 36)	
Select adverse event category, n (%)	**Any grade**	**Grade 3-4**
Skin	18 (50)	2 (6)
Endocrine	11 (31)	3 (8)
Gastrointestinal	11 (31)	2 (6)
Hepatic	5 (14)	1 (3)
Pulmonary	3 (8)	2 (6)
Hypersensitivity/infusion reaction	2 (6)	0
Renal	2 (6)	1 (3)

Source: Gainor et al. (2020)[57]

Figure 44 presents frequencies of TRAEs with nivolumab + ipilimumab + limited PDC. Results should be interpreted with caution owing to differences in patient numbers and nivolumab dosing and a lack of a randomised comparison.

Figure 44. Treatment-related adverse events reported with nivolumab + ipilimumab + limited PDC



Abbreviations: IPI = ipilimumab; NIVO = nivolumab; PDC = platinum doublet chemotherapy; SAE = serious adverse event; TRAE = treatment-related adverse event.

Source: Gainor et al. (2020)[57]

B.2.11 Ongoing studies

[redacted]

Table 37. Additional data anticipated from CheckMate trials in the next 12 months

Trial	Next anticipated publication	Analyses anticipated
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: OS = overall survival; PDC = platinum doublet chemotherapy; TBC = to be confirmed.

In addition, real-world data could be collected through the Systemic Anti-Cancer Therapy (SACT) and other real-world data sets during the CDF data collection period. BMS plan to leverage secondary data from I-O Optimise, a pan-European evidence platform that brings together real-word data sources under independent scientific guidance. Data analyses are ongoing with continuous creation of new cohorts to capture changes over time. This includes the analysis of UK registry data.

B.2.12 Innovation

Nivolumab + ipilimumab is the first dual immunotherapy approved in NSCLC and represents the fourth tumour type in which dual checkpoint blockade with nivolumab + ipilimumab has demonstrated significantly increased OS, durable benefit, and improved HRQOL in a phase 3 trial, while offering a predictable and tolerable safety profile.[54,80,81]

The mechanisms of action of ipilimumab and nivolumab are distinct and complementary, with ipilimumab working early in the immune response by potentiating antigen presentation to naive T-cells in the lymph nodes and nivolumab working later in the immune response on the tumour-specific effector T-cells.[8,13] Combining nivolumab and ipilimumab in NSCLC, renal cell carcinoma, melanoma, and mesothelioma produces durable responses and survival benefits, establishing a robust body of evidence for the durability of this regimen.

Building on the benefits of nivolumab + ipilimumab in NSCLC, renal cell carcinoma, melanoma, and mesothelioma, it was hypothesised that adding limited cycles of chemotherapy (2 cycles) would provide initial disease control, complementing the durability of nivolumab + ipilimumab seen in NSCLC and other tumours.

As nivolumab, ipilimumab, and PDC each have non-overlapping anticancer mechanisms, they may have complementary and/or added activity as combination therapy. Two cycles of chemotherapy added during induction may be sufficient to provide an additive effect to nivolumab + ipilimumab by increasing tumour antigen release and reducing inhibitory signal

with a net effect of activating the host immune system. Furthermore, other IO plus PDC combinations that have been launched or are in late-stage development trials use 4 cycles of chemotherapy, with the potential for much higher levels of chemotherapy-related toxicities compared with limited chemotherapy with 2 cycles.

B.2.13 Interpretation of clinical effectiveness and safety evidence

In the updated analysis of CheckMate-9LA, a clinically meaningful and statistically significant benefit in terms of OS was seen for nivolumab + ipilimumab + limited PDC–treated patients compared with PDC-treated patients (database lock 9 March 2020; see Section B.2.6.1.1).[1] The median OS was 15.64 months (95% CI, 13.93-19.98 months) for nivolumab + ipilimumab + limited PDC versus 10.91 months (95% CI, 9.46-12.55 months) for PDC. The HR also favoured nivolumab + ipilimumab + limited PDC (HR, 0.66; 95% CI, 0.55-0.80). Considering these data include a minimum follow-up of 12.7 months and are thus immature, additional analyses will be conducted over the next few years as more follow-up data accrue. These analyses will provide further evidence of the long-term benefit associated with nivolumab + ipilimumab + limited PDC over current standard of care and reduce uncertainty in the longer-term outcomes. Therefore, BMS consider nivolumab + ipilimumab + limited PDC to be a candidate for entry into the CDF.

No new safety concerns or toxicities with nivolumab + ipilimumab + limited PDC were identified in CheckMate-9LA.[1] The safety profiles of nivolumab + ipilimumab + limited PDC and PDC were considered to be similar (see Section B.2.10).

In the patient population of CheckMate-9LA, NICE's end-of-life criteria are not met. Patients with advanced or metastatic NSCLC are expected to have a life expectancy of more than 24 months if treated with IO therapies; however, treatment pattern data have shown that this is not true for all eligible patients (Table 38).

Table 38. End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally < 24 months	Patients with advanced or metastatic NSCLC have a life expectancy of > 24 months with IO therapy	N/A
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Nivolumab + ipilimumab + limited PDC does not offer an additional 3 months of extension to life when compared with IO or IO + chemotherapy	B2.9.3

Abbreviation: IO = immuno-oncology; NSCLC = non-small cell lung cancer; PDC = platinum doublet chemotherapy.

Source: Reck et al. (2020)[1]

B.3 Cost-effectiveness

SUMMARY OF COST-EFFECTIVENESS

A de novo partitioned survival model was developed to assess the cost-effectiveness of nivolumab + ipilimumab + limited PDC for adults with untreated stage IV or recurrent NSCLC with no known EGFR mutation or ALK translocation. This is consistent with the study population of CheckMate-9LA compared with PDC, pembrolizumab monotherapy, and atezolizumab + bevacizumab + carboplatin + paclitaxel.

The primary data source for modelling the nivolumab + ipilimumab + limited PDC and PDC arms in the economic model is the data derived from the CheckMate-9LA trial. At the March 2020 database lock of CheckMate-9LA, the minimum follow-up for all patients was 12.7 months for OS and 12.2 months for the other endpoints. To estimate OS and PFS over the 25-year model time horizon, survival beyond the study time horizon had to be informed by extrapolation. As the current survival data from CheckMate-9LA are relatively immature, it is anticipated that long-term extrapolations based only on these data would not fully capture the short-term treatment response and long-term survival that are unique for the dual IO being investigated. More mature survival data are available from CheckMate-227 part 1, which includes patients with similar characteristics and treatments to those in CheckMate-9LA. Therefore, following recommendations from the Decision Support Unit (DSU) at NICE[82] to use external data to guide extrapolations and following more recent methods described by Jackson et al. (2017)[83] to formally include external data, if available, into the survival extrapolations, survival analyses of the CheckMate-227 data were also performed.

To determine the most plausible extrapolations to be used for OS, the distributions identified to provide the best fit to the CheckMate-9LA and CheckMate-227 clinical data were assessed against long-term external data. For the piecewise approach using a combination of CheckMate-9LA and CheckMate-227 clinical data, a break point was set to 13 months (a minimum follow-up with the lowest censoring) from which to switch from CheckMate-9LA KM data to the CheckMate-227 part 1 parametric curves. For the parametric extrapolation of CheckMate-227 part 1, a spline normal 2 knots distribution was selected for the OS extrapolation for nivolumab + ipilimumab + limited PDC while a log-logistic model was selected for PDC. For PFS, spline odds 2 knots was used for nivolumab + ipilimumab + limited PDC and spline normal 2 knots for PDC.

The primary data source for modelling of the pembrolizumab and atezolizumab + bevacizumab + PDC was an ITC with time-varying hazards. Quality-adjusted life-years (QALYs) were estimated per health state (allocated by time to death and pooled across treatment arms). Adverse event disutilities were identified from the literature. Cost and resource use for drug acquisition, AEs, and subsequent treatment were all incorporated to align with recent NICE submissions in NSCLC. Time on treatment used to estimate treatment costs was based on duration of therapy as observed in CheckMate-9LA or PFS for comparators not included in that study.

The results of the cost-effectiveness analysis showed improved survival for patients treated with nivolumab + ipilimumab + limited PDC, resulting in an increase of [redacted] QALYs versus PDC. [redacted] resulted in an incremental cost-effectiveness ratio (ICER) of £29,139 per QALY. Compared with pembrolizumab monotherapy, nivolumab + ipilimumab + limited PDC was dominant as it generated [redacted] incremental QALYs and [redacted] incremental LYGs, and had lower total lifetime costs. Compared with atezolizumab + bevacizumab + carboplatin + paclitaxel, nivolumab + ipilimumab + limited PDC was dominant because it generated [redacted] incremental QALYs and [redacted] incremental LYGs and had lower total lifetime costs. The ICERs were generally most sensitive to changes in the assumptions around OS extrapolation and the utility applied to the health state of > 52 weeks to death.

In conclusion, nivolumab + ipilimumab + limited PDC offers an innovative, clinically effective, and plausibly cost-effective treatment option in the first-line NSCLC setting, building on the value of nivolumab in the pretreated metastatic NSCLC setting.

B.3.1Published cost-effectiveness studies

An SLR was undertaken to identify all cost-effectiveness studies relevant to the decision problem from the published literature. A total of 38 studies reported economic evidence: 19 conducted cost-utility analysis; 13 conducted cost-effectiveness analysis; 2 conducted budget-impact analysis; and 1 each conducted cost-minimisation, costing study, cost-benefit, and microsimulation analysis. Most studies reported a health care or payer perspective (34 studies), one study reported a societal perspective, and three studies did not report perspective. Full details of the search strategy, study selection process, and results are presented in Appendix G.

B.3.2Economic analysis

B.3.2.1 Patient population

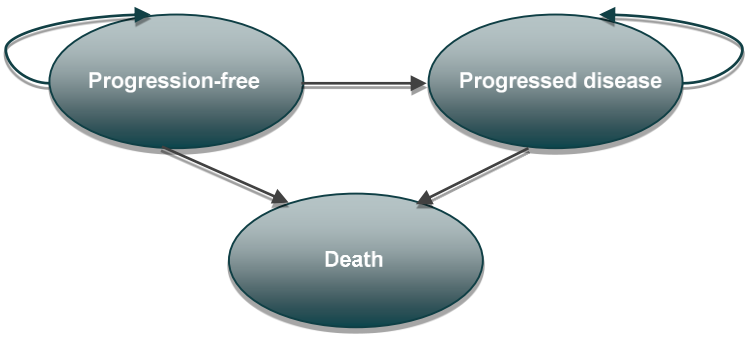
The economic evaluation considers adults with untreated stage IV or recurrent NSCLC with no known EGFR mutation or ALK translocation; this is consistent with the study population of CheckMate-9LA and the decision problem presented in Section B.1.1.

B.3.2.2 Model structure

A three-health-state cohort–based partitioned survival model was developed to evaluate the incremental cost-effectiveness of nivolumab + ipilimumab + limited PDC versus alternative therapy options in patients with previously untreated stage IV or recurrent NSCLC. The model was developed in Microsoft Excel and programmed using standard Excel functions wherever possible.

Figure 45 shows the standard three-health-state model structure. The three health states represent the primary stages of disease in advanced or metastatic NSCLC: progression free (PF) with first-line treatment, progressed disease (PD), and death. These health states correspond to the primary and secondary endpoints in the CheckMate-9LA trials and other key trials for nivolumab + ipilimumab + limited PDC as outlined in Section B.2.3.1. This model structure is also consistent with the approaches adopted in previous published economic evaluations and technology appraisals within NSCLC (TA428, TA531, TA483, TA484).[70,71,84,85]

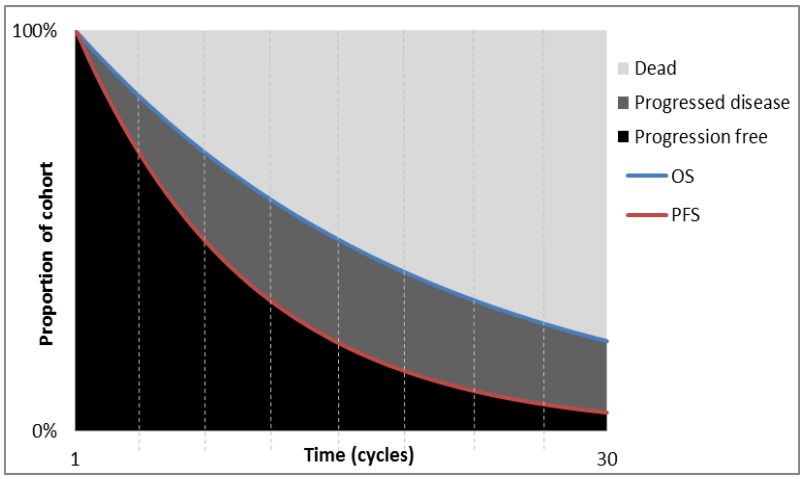
Figure 45. Overview of the standard three-health-state model



Source: Bristol Myers Squibb (2018)[86]

The number of patients in each health state was estimated using the partitioned survival method. The partitioned survival approach allows for modelling of OS and PFS based on study-observed events, which is expected to reflect disease progression and the long-term expected survival profile of patients treated with nivolumab in combination with ipilimumab. The proportion of patients in the PD health state is calculated as the difference between OS and PFS. Figure 46 presents the partitioned survival method.

Figure 46. Overview of the partitioned survival method



Abbreviations: OS = overall survival; PFS = progression-free survival.
Source: Bristol Myers Squibb (2018)[86]

Patients enter the model in the PF health state and are treated with either nivolumab + ipilimumab or PDC. At the end of each cycle, the proportion of patients in PF, PD, and death is estimated from PFS and OS. A restriction is that patients cannot transition to an improved health state, which is consistent with previous economic modelling in NSCLC (TA428, TA531, TA483, TA484).[70,71,84,85]

Costs and health-related utilities are allocated to each health state and multiplied by state occupancy to calculate the weighted costs and QALYs per cycle. A 1-week cycle length is used for the first 28 weeks of the model to allow for more flexible modelling of the initial treatment administration. From week 28 onwards, four-weekly model cycles are used. A half-cycle correction is implemented to mitigate bias.

A 2-year treatment stopping rule is applied to the nivolumab + ipilimumab regimen, consistent with the CheckMate-9LA clinical trial design and in alignment with the recent NICE appraisal of untreated NSCLC (TA531).[85] Comparators are treated according to administration recommendations or until disease progression. Treatment costs include costs of drug acquisition, administration, and monitoring. Costs and disutilities associated with AEs are estimated per episode and are applied once at the beginning of the simulation based on the proportion of patients in each treatment arm experiencing each AE.

Table 39 presents a summary of the core elements of the economic model.

Table 39. Features of the economic analysis

Factor	Previous appraisals				Current appraisal	
	Pemetrexed first line (TA181)[2]	Pemetrexed maintenance (TA402)[51]	Pembrolizumab (TA531)[4]	Atezolizumab (TA584)[3]	Chosen values	Justification
Time horizon	Lifetime (6 years)	Lifetime (equivalent to 15.99 years; range, 6-20 years)	Lifetime (20 years)	Lifetime (20 years)	25 years	Considered to be appropriate as the lifetime of patients with advanced or metastatic NSCLC accounting for typical age at diagnosis and advanced nature of disease; consistent with previous NICE STAs in this disease area and validated by expert clinical opinion
Cycle length	3 weeks	3 weeks	1 week	1 week	1-week cycles for initial 28 weeks of model; 4-week cycles after 28 weeks	Initial 1-week cycle length to accommodate the administration cycles of the included therapies. From week 28 onwards, 4-weekly model cycles are used.
Half-cycle correction	A half-cycle correction appeared to have been disabled for costs and used incorrectly for outcomes	Yes	Yes	Yes	Yes	For consistency with previous submissions, midcycle estimates are used.
Were health effects measured in QALYs? If not, what was used?	Yes	Yes	Yes	Yes	Yes	According to the NICE reference case[87]

	Previous appraisals				Current appraisal	
Factor	**Pemetrexed first line (TA181)[2]**	**Pemetrexed maintenance (TA402)[51]**	**Pembrolizumab (TA531)[4]**	**Atezolizumab (TA584)[3]**	**Chosen values**	**Justification**
Discount of 3.5% for utilities and costs	The "in-trial" analysis did not use discounting on either costs or outcomes, despite trial follow-up extending to > 2 years for some patients. The ERG stated that this was an important omission because much of the survival gain occurred after the first 12 months and therefore would likely be affected by discounting.	Yes	Yes Direct health effects related to patients were considered, but the impact on carers has not been considered owing to the unavailability of data to incorporate this into the model.	Yes	Yes	According to the NICE reference case[87]
NHS perspective?	Yes	Yes	Yes	Yes	Yes	According to the NICE reference case[87]
Duration of treatment effect	Not mentioned	The committee considered comments from a clinical expert mentioning that continued benefit of pemetrexed over best supportive care after disease progression was difficult to explain,	Considered in NICE Committee decision making.	Considered in base case and different cutoffs explored in scenario analyses.	Lifetime treatment effect of nivolumab + ipilimumab + limited PDC.	There is now long-term evidence of a robust and durable treatment effect lasting beyond discontinuation for immuno-oncology therapies.[88] Alternative assumptions around duration of effect are explored in scenarios.

Factor	Previous appraisals				Current appraisal	
	Pemetrexed first line (TA181)[2]	Pemetrexed maintenance (TA402)[51]	Pembrolizumab (TA531)[4]	Atezolizumab (TA584)[3]	Chosen values	Justification
		but no further analyses seemed to have been conducted to assess the impact of this assumption.				
Source of utilities	Nafees et al. (2008)[89], which was a study commissioned by the manufacturer on second-line treatment of NSCLC.	PARAMOUNT EQ-5D individual patient data.	KeyNote-024 EQ-5D individual patient data.	IMPower-150 EQ-5D individual patient data	CheckMate-9LA EQ-5D individual patient data	According to the NICE reference case[87]
Source of costs	Patient-level data from the clinical trial and resource use events from the JMDB clinical trial database	Resource use data from PARAMOUNT.	Published literature, resource utilisation, and costs accepted in previous NICE submissions.	Published literature, resource utilisation, and costs accepted in previous NICE submissions.	Published literature, resource utilisation, and costs accepted in previous NICE submissions.	These reflect resource utilisation and costs accepted in previous NICE submissions.[4]

Abbreviations: ERG = evidence review group; NHS = National Health Service; NSCLC = non-small cell lung cancer; QALY = quality-adjusted life-year; STA = single technology appraisal.

B.3.2.3 Intervention technology and comparators

The current analysis investigates the cost-effectiveness of nivolumab + ipilimumab + limited PDC compared with PDC, pembrolizumab monotherapy, and atezolizumab + bevacizumab + carboplatin + paclitaxel, which are included based on the scope of the decision problem.[6] The availability of these comparators in UK clinical practice is discussed in Section B.1.3.6.

In CheckMate-9LA, the PDC regimen received by patients with non-squamous NSCLC consisted of carboplatin + pemetrexed or carboplatin + cisplatin, while patients with squamous NSCLC received carboplatin + paclitaxel. Pemetrexed maintenance therapy was offered to non-squamous patients who had not progressed after the initial 4 treatment cycles of PDC. This is in line with the clinical study report (CSR) for CheckMate-9LA.[21] Comparators external to CheckMate-9LA are pembrolizumab monotherapy and atezolizumab + bevacizumab + carboplatin + paclitaxel. Indirect treatment comparisons with pembrolizumab monotherapy and atezolizumab + bevacizumab + carboplatin + paclitaxel are presented in Section B.2.9.

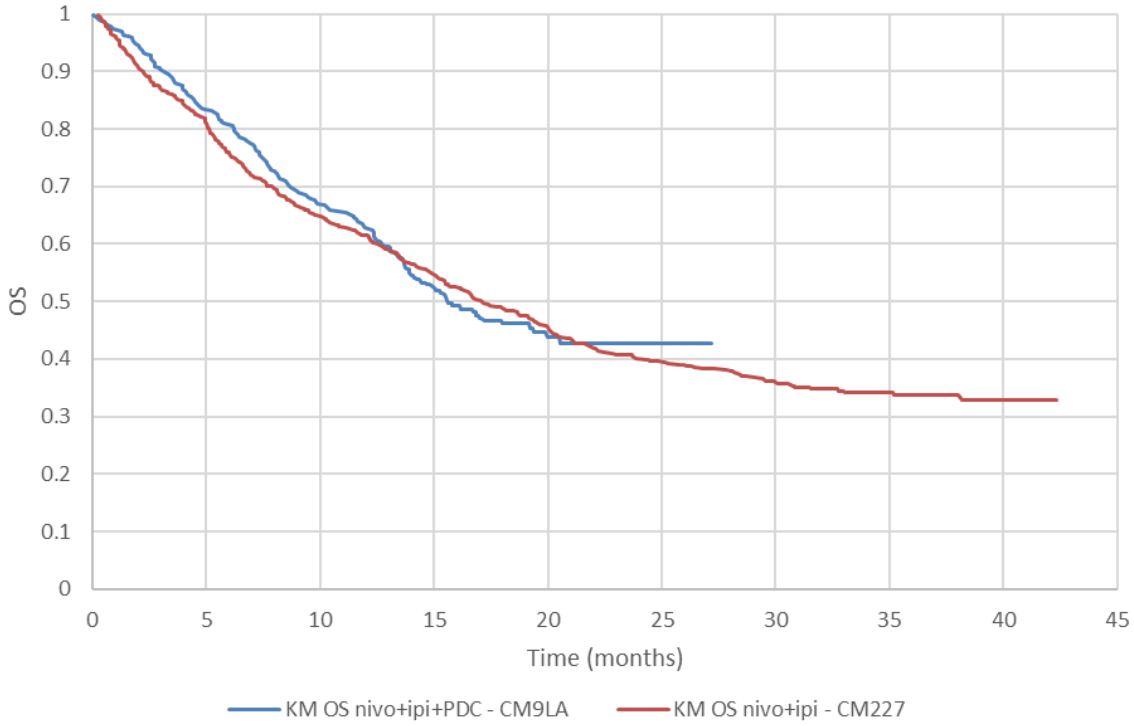
B.3.3Clinical parameters and variables

B.3.3.1 Methods for modelling survival

B.3.3.1.1 Data used for survival modelling

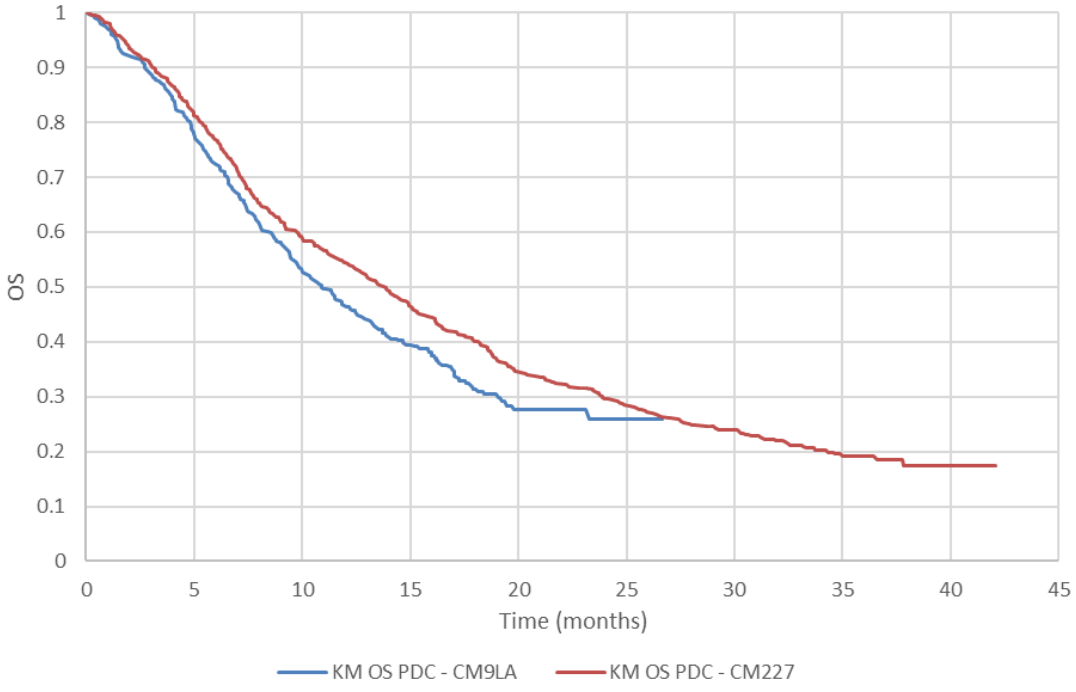
The primary data source for modelling the nivolumab + ipilimumab + limited PDC and PDC arms in the economic model is the CheckMate-9LA trial. At the March 2020 database lock of CheckMate-9LA, the minimum follow-up for all patients was 12.7 months for OS and.2 months for the other efficacy endpoints. Both follow-up periods are shorter than the time horizon of the economic analysis (a lifetime of up to 25 years), and a substantial number of patients will still be alive with expected ongoing benefit from nivolumab + ipilimumab + limited PDC and PDC. To estimate the OS and PFS over the 25-year model time horizon, survival beyond the study time horizon had to be informed by extrapolation. It is common for oncology economic evaluations developed to support HTA submissions to only use parametric survival analysis fitted to data derived from pivotal trials for the interventions of interest and extrapolated over the full model time horizon. As the current survival data from CheckMate-9LA are relatively immature (see Section B.3.3.1.4), it is anticipated that long-term extrapolations based only on these data would not fully capture short-term treatment response and long-term survival that are unique for the dual IO being investigated. As presented in Section B.2.6.2.1, more mature survival data are available from CheckMate-227 part 1, which includes patients with similar characteristics and treatments to those in CheckMate-9LA. Therefore, following recommendations from the DSU at NICE[82] to use external data to guide extrapolations and following more recent methods described by Jackson et al. (2017)[83] to formally include external data, if available, in the survival extrapolations, survival analyses of the CheckMate-227 data were also performed. This was to explore the potential to use the CheckMate-227 data in combination with the CheckMate-9LA data for informing long-term survival. As shown in Figure 47 to Figure 50, the trajectories of both PFS and OS for CheckMate-9LA and CheckMate-227 are similar. Thus, using long-term survival hazards following a break point (a piecewise approach) in the CheckMate-9LA data based on survival analysis of the CheckMate-227 data would be anticipated to improve the validity of the long-term survival extrapolation until longer-term survival data become available through the continued data collection as part of the CDF.

Figure 47. Comparison of overall survival for immuno-oncology in CheckMate-227 part 1 versus CheckMate-9LA



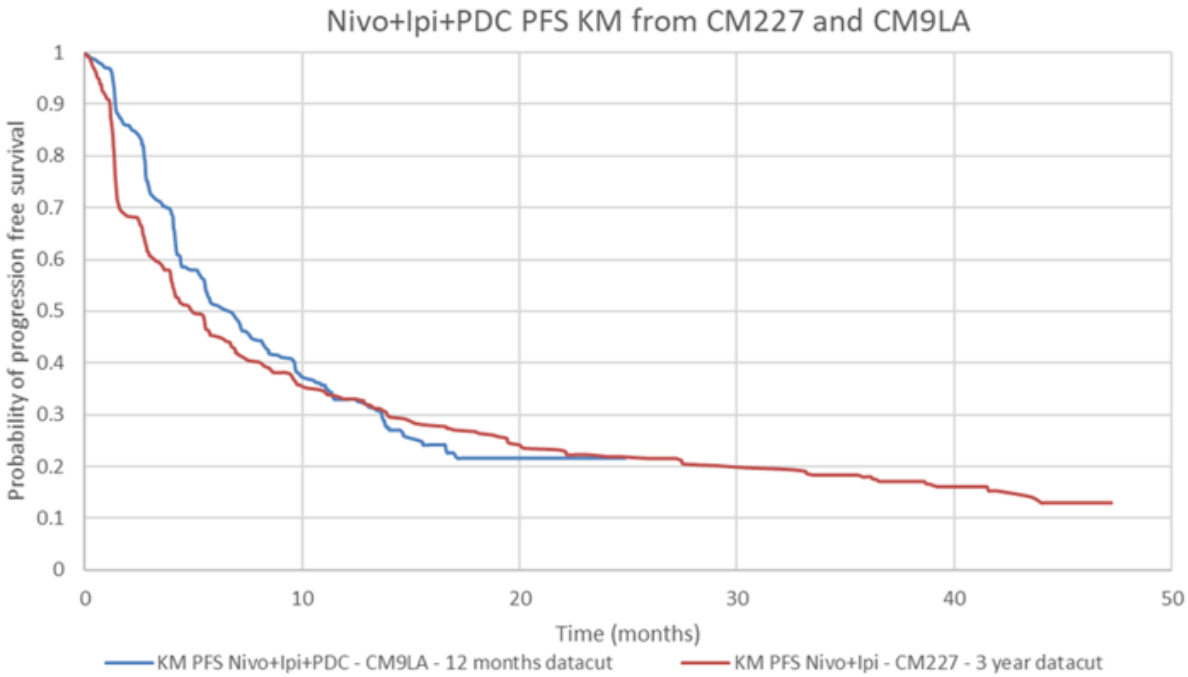
Abbreviations: CM = CheckMate; IPI = ipilimumab; KM = Kaplan-Meier; NIVO = nivolumab; PDC = platinum doublet chemotherapy; OS = overall survival.

Figure 48. Comparison of overall survival for the PDC control group in CheckMate-227 part 1 versus CheckMate-9LA



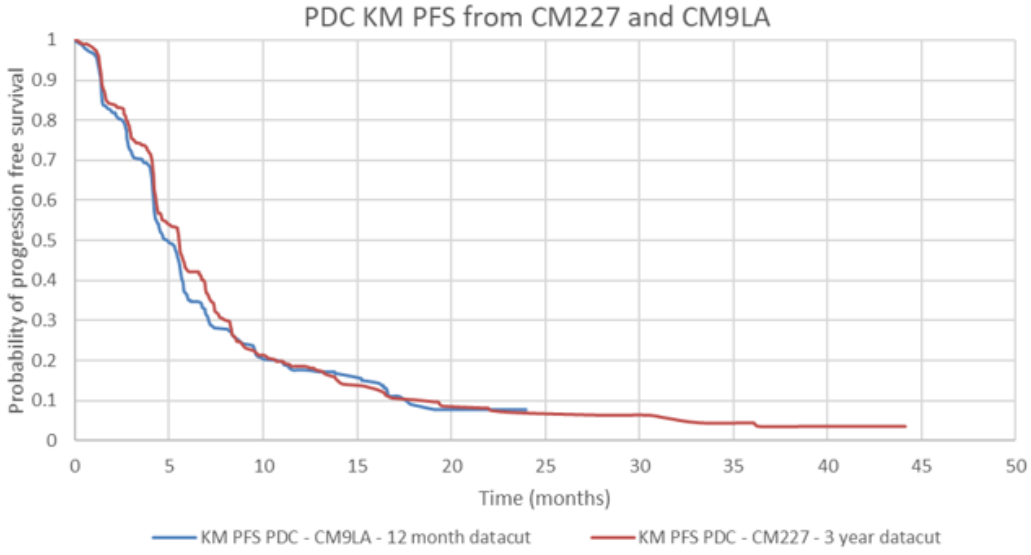
Abbreviations: CM = CheckMate; IO = immuno-oncology; KM = Kaplan-Meier; PDC = platinum doublet chemotherapy; OS = overall survival.

Figure 49. Comparison of progression-free survival for immuno-oncology in CheckMate-227 part 1 versus CheckMate-9LA



Abbreviations: CM = CheckMate; IPI = ipilimumab; NIVO = nivolumab; KM = Kaplan-Meier; NIVO = nivolumab; PDC = platinum doublet chemotherapy; PFS = progression-free survival.

Figure 50. Comparison of progression-free survival for PDC control group in CheckMate-227 part 1 versus CheckMate-9LA



Abbreviations: CM = CheckMate; KM = Kaplan-Meier; PDC = platinum doublet chemotherapy; PFS = progression-free survival.

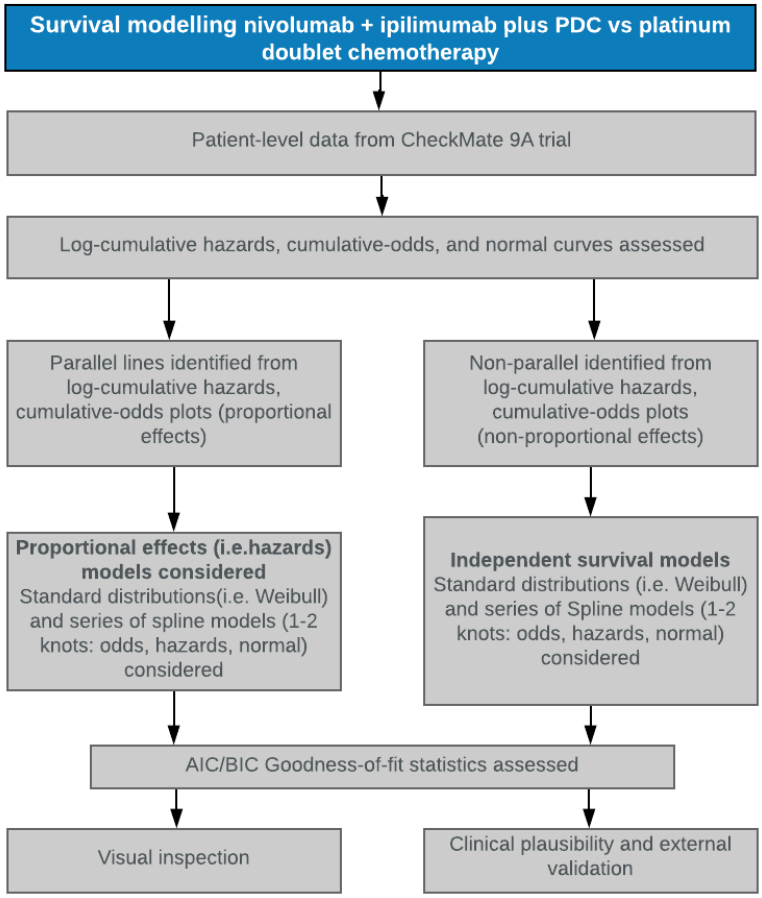
Overall survival for comparators within the NICE scope[6] that are not included in the CheckMate-9LA and CheckMate-227 trials are informed by applying the relative treatment effect from the fractional polynomial NMA (see Section B.2.9) to the selected base-case curve for nivolumab + ipilimumab + limited PDC.

B.3.3.1.2 Process for fitting survival models

The process for fitting survival models to patient-level data was based on methods guidance from the DSU at NICE.[82] Figure 51 presents the process for identifying the survival model for both PFS and OS. The steps required to determine the most appropriate curve fits in the model included the following:

- Testing the proportional effects assumption: The log-cumulative hazards, log-cumulative odds, and standardised normal curve plots were assessed to determine if the data indicate proportional effects. This assessment was done both by testing the significance of the Grambsch-Therneau correlation test between Schoenfeld residuals and log of time as well as visual inspection to determine if the survival curves of each arm were parallel.
- Based on the assessment of proportional hazards, survival models fitted to the data from the clinical trial either as dependent models with a treatment effect or independently to each treatment arm were explored and assessed.
- Within the various survival models, the Akaike information criterion (AIC) and Bayesian information criterion (BIC) goodness-of-fit statistics were assessed to identify differences in statistical fit among the survival models.
- The choice of survival model used for the base-case economic model was based on the following:
  - The AIC and BIC statistics of the survival models, which provide goodness of fit to the Kaplan-Meier data
  - Visual fit compared with the Kaplan-Meier data
  - Identifying a common functional form of survival model for both arms that most closely fit the data overall as recommended in the DSU guidelines
  - Clinical plausibility and external validation of the extrapolated survival compared with real-world survival data and input from UK clinicians

Figure 51. Identifying the parametric survival curves for the economic model



Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; PDC = platinum doublet chemotherapy.

B.3.3.1.3 External data used for curve selection and validation

For validation of the extrapolation towards external data, different external data were used for the validation of the nivolumab + ipilimumab + limited PDC and PDC arms.

Platinum doublet chemotherapy

In 2013, the National Lung Cancer Audit (NLCA) reported the 5-year survival rates for stage IV lung cancer to be 5%.[90] However, because IO therapy has recently become standard of care in the second-line setting, survival rates are expected to have improved since 2013. Therefore, the survival estimates for standard of care in previous NICE submissions (TA447, TA557) were used to validate long-term survival in the PDC arm.[52,91] In TA447, the ERG-preferred survival curves for PDC that resulted in a survival of 9.6% and 1.5% at 5 and 10 years, respectively, in a PD-L1–positive population. It is expected that an all-comers population, such as those in CheckMate-9LA, would have lower survival probability compared with a PD-L1–positive population because an all-comers population includes PD-L1 non-expressor patients. In TA557, the NICE committee stated that a 5-year survival of 5% to 11% for PDC was considered realistic.

Nivolumab + ipilimumab + limited PDC

There is no current long-term data available for validating the survival extrapolation of the nivolumab + ipilimumab + limited PDC arm of CheckMate-9LA. Thus, to validate and guide selection of approach for extrapolation of OS in the nivolumab + ipilimumab + limited PDC arm, the following data and approaches were used:

- CheckMate-227 part 1 data
- Surveillance, Epidemiology, and End Results (SEER) data
- Swedish and Norwegian registry data (primarily chemotherapy)
- CheckMate-017 and CheckMate-057 pooled data

Table 40 presents the conditional survival, defined as the percentage of patients alive in year X who will survive to year Y, for each of the sources mentioned. This was used to construct a curve to predict long-term OS for first-line patients with NSCLC receiving nivolumab + ipilimumab + limited PDC. This curve was constructed using a step-wise approach with each successive step adopting data that most closely related to CheckMate-9LA (Figure 52 and Figure 53). The constructed curve was produced in five steps:

1. The absolute survival at year 1 was derived from the nivolumab + ipilimumab + limited PDC arm in CheckMate-9LA. The minimum follow-up of the CheckMate-9LA data used was 12.7 months.
2. To predict OS at 2 and 3 years, the conditional survival from year 1 to 2 and from year 2 to 3 observed in CheckMate-227 was applied, as CheckMate-227 part 1 is considered the best source of external evidence to predict survival for patients in CheckMate-9LA receiving nivolumab + ipilimumab + limited PDC.
3. As there are no trials involving patients with NSCLC taking nivolumab + ipilimumab as first-line treatment, conditional survival from year 3 to 5 was derived from the pooled analysis of CheckMate-017 and CheckMate-057 (data reflecting long-term OS in patients with NSCLC treated with IO in the second line) and used to predict OS at 5 years.
4. Because no relevant trial data are available for this patient population with a follow-up longer than 5 years, registry data were used to predict survival at 10 years. A Nordic patient population was considered an appropriate proxy for the patient population of interest. Norwegian registry data were available for up to 10 years and were used to estimate OS at 10 years based on the conditional survival between 5 and 10 years.
5. The registry with the longest follow-up data available to us when we developed the constructed OS curve was the SEER registry. SEER registry data were leveraged to predict OS at 15 years using the conditional survival between 10 and 15 years. Using this approach, a survival of [redacted] is predicted at 15 years.

Table 40. Validation of base-case parametric models for overall survival compared with SEER data and other trials (conditional survival)

	Curve	Conditional survival (%)					
	Start year	Yr 1	Yr 2	Yr 3	Yr 4	Yr 5	Yr 10
Data set	End year	Yr 2	Yr 3	Yr 4	Yr 5	Yr 10	Yr 15
SEER	OS stage IIIB-IV (1998 cohort)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Swedish registry	OS NSCLC stage IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Norwegian registry	OS lung cancer stage IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Norwegian registry 2	OS lung cancer stage IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled CM-017 and CM-057	OS NIVO 3 mg/kg pretreated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CM = CheckMate; NIVO = nivolumab; NSCLC = non-small cell lung cancer; OS = overall survival; SEER = Surveillance, Epidemiology, and End Results.

[a] Years 3-5.

Figure 52. Constructed overall survival curve for nivolumab + ipilimumab + limited PDC in CheckMate-9LA: validation of long-term survival

Abbreviations: CM = CheckMate; OS = overall survival; PDC = platinum doublet chemotherapy; SEER = Surveillance, Epidemiology, and End Results.

Figure 53. Constructed Kaplan-Meier overall survival curves for nivolumab + ipilimumab + limited PDC in CheckMate-9LA

Abbreviations: CM = CheckMate; PDC = platinum doublet chemotherapy; SEER = Surveillance, Epidemiology, and End Results.

Long-term OS rates predicted with these constructed curves can be considered a conservative estimate, given that they were derived using data from pretreated trials and registries, which largely represent chemotherapy before IO therapies were available. However, using conditional survival allows us to use the shape of the curve from previous trials or registry data as an indication of the long-term shape of the OS curve for nivolumab + ipilimumab + limited PDC. However, it can be expected that survival curves for IO therapies are flatter compared with those from data reflecting mainly chemotherapy. Therefore, the tail of the constructed survival curve could be considered conservative, and the 15-year OS for nivolumab + ipilimumab + limited PDC will likely be above the estimated [redacted]

B.3.3.1.4 Analyses of overall survival

Overall survival analysis using CheckMate-9LA data

Using the process for selection of parametric curves shown in Figure 51, parametric extrapolation analyses were conducted for OS using CheckMate-9LA data. Additional information on the analyses conducted is provided in Appendix M. As presented in Section B.2.9, the assumption of non-proportional hazards was deemed the most plausible considering analyses of both current trial data and long-term treatment effect IO therapies such as nivolumab + ipilimumab + limited PDC. As such, independent models were considered to be the most appropriate method and thus reported here for the base case. For completeness, Appendix M includes dependent survival models.

Goodness-of-fit indicators for the independent OS models are shown in Table 41 and Table 42 for nivolumab + ipilimumab + limited PDC and PDC, respectively.

Table 41. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to overall survival data for nivolumab + ipilimumab + limited PDC

Independent model	AIC	BIC
Log-logistic	1,598	1,606
Spline on odds 1 knot	1,599	1,611
Gamma	1,600	1,607
Weibull	1,600	1,608
Exponential	1,600	1,604
Generalised gamma	1,601	1,613
Spline on probit link of survival 2 knots	1,601	1,617
Spline on odds 2 knots	1,601	1,617
Spline on hazards 1 knot	1,602	1,613
Gompertz	1,602	1,610
Spline on hazards 2 knots	1,602	1,618
Lognormal	1,610	1,618

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; PDC = platinum doublet chemotherapy.

Table 42. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to overall survival data for PDC

Independent model	AIC	BIC
Log-logistic	1,836	1,844
Spline on odds 1 knot	1,838	1,850
Spline on odds 2 knots	1,839	1,854
Spline on hazards 2 knots	1,839	1,854
Spline on probit link of survival 2 knots	1,839	1,855
Spline on probit link of survival 1 knot	1,839	1,851
Generalised gamma	1,841	1,852
Spline on hazards 1 knot	1,841	1,853
Gamma	1,842	1,850
Weibull	1,844	1,852
Lognormal	1,845	1,853
Exponential	1,850	1,853

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; PDC = platinum doublet chemotherapy.

Figure 54 shows the independent parametric models for nivolumab + ipilimumab + limited PDC with the best statistical fit based on AIC over a longer time horizon. The curves fit the within-trial period reasonably well but result in different long-term survival predictions.

Figure 54. Independent parametric models overlaying the overall survival Kaplan-Meier data for nivolumab + ipilimumab + limited PDC

Abbreviations: KM = Kaplan-Meier; PDC = platinum doublet chemotherapy.

Figure 55 shows the independent parametric models for PDC with the best statistical fit based on AIC.

Figure 55. Independent parametric models overlaying the overall survival Kaplan-Meier data for PDC

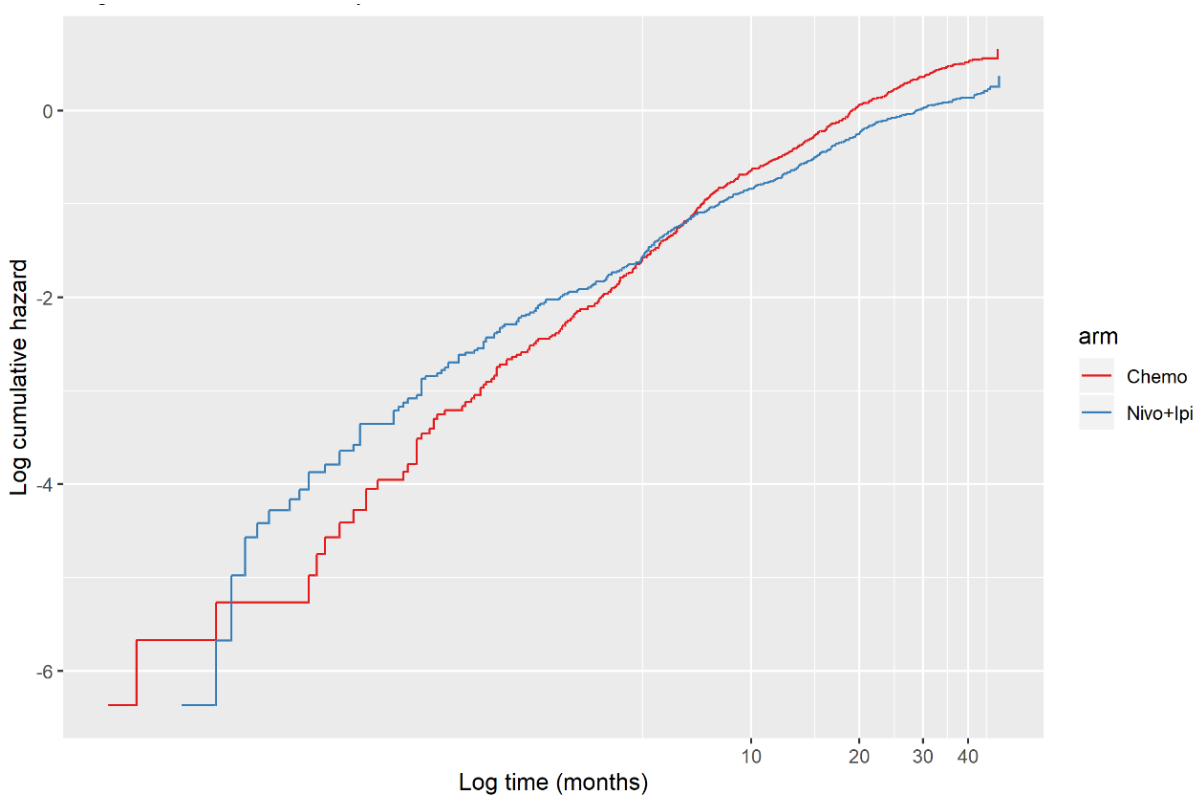
Abbreviations: KM = Kaplan-Meier; PDC = platinum doublet chemotherapy.

Overall survival analysis using CheckMate-227 data

As described in Section B.3.3.1, survival analyses were conducted on the CheckMate-227 part 1 ITT population to investigate whether using the more mature survival data from CheckMate-227 could inform the long-term survival extrapolation for CheckMate-9LA. The CheckMate-227 data used for the analyses were that from the 28 February 2020 database lock of CheckMate-227 (after a minimum and median follow-up for OS of 37.7 months and 43.1 months, respectively). Although the predicted hazards from the CheckMate-227 data will be appended from a breakpoint for the CheckMate-9LA data, the complete 3-year data set from CheckMate-227 part 1, starting from baseline until the end of patient follow-up, was used to derive parametric survival curves. The inclusion of early data in this approach prevents the loss of information and avoids the problem of fitting models to low numbers of patients at risk.

As presented in Figure 56 and Figure 57, the proportional hazards assumption was clearly violated with the log-cumulative hazard plots crossing and Schoenfeld residuals plot, which indicates that the hazards were not constant over time. The Grambsch-Therneau test also showed that the hazards were significantly different from proportional hazards (P = 0.0002). Therefore, only independent models were investigated for the CheckMate-227 part 1 data.

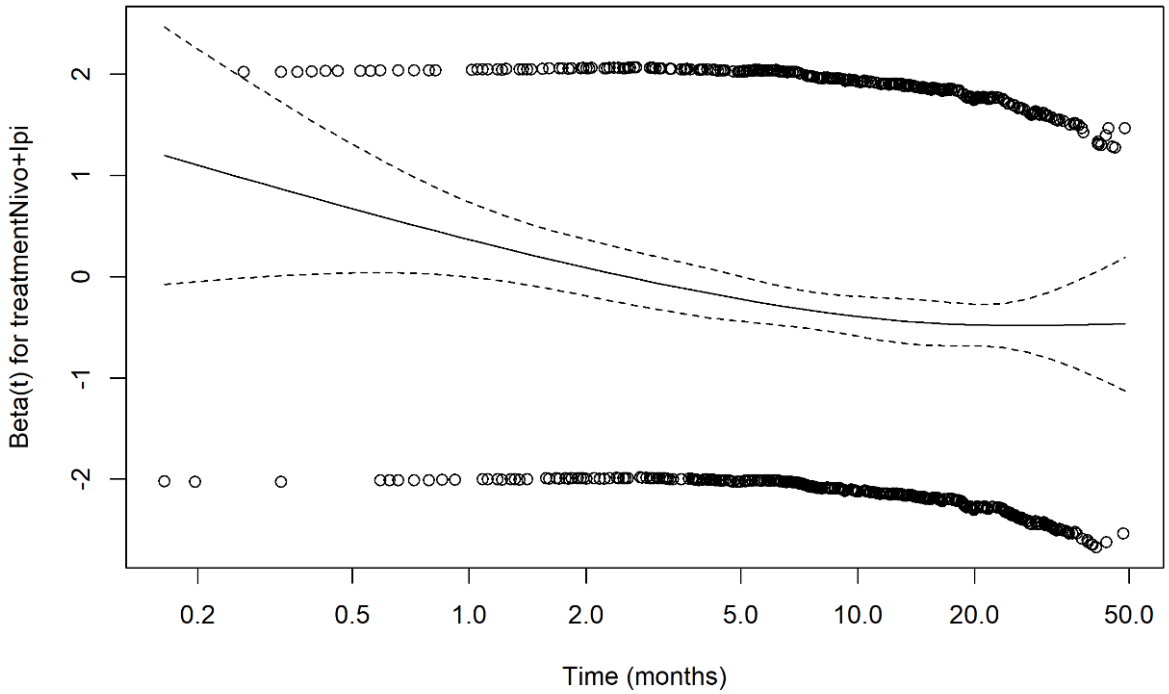
Figure 56. Log-cumulative hazard plot for nivolumab + ipilimumab versus PDC for CheckMate-227 part 1



Abbreviations: Nivo+ipi = nivolumab + ipilimumab; PDC = platinum doublet chemotherapy.

Note: *Chemo* refers to PDC.

Figure 57. Schoenfeld residuals plot for nivolumab + ipilimumab versus PDC for CheckMate-227 part 1



Abbreviation: PDC = platinum doublet chemotherapy.

Table 43 presents goodness-of-fit statistics for the parametric curves based on data from the nivolumab + ipilimumab arm of CheckMate-227 part 1. The lognormal and generalised gamma are statistically the best-fitting distributions, followed by spline models. For AIC, distributions with a difference of less than 4 to the distribution with the lowest AIC were considered appropriate based on the Burnham and Anderson rule of thumb.[92] This suggests that not all models would provide a reasonable fit to the data because the range of values observed is much larger.

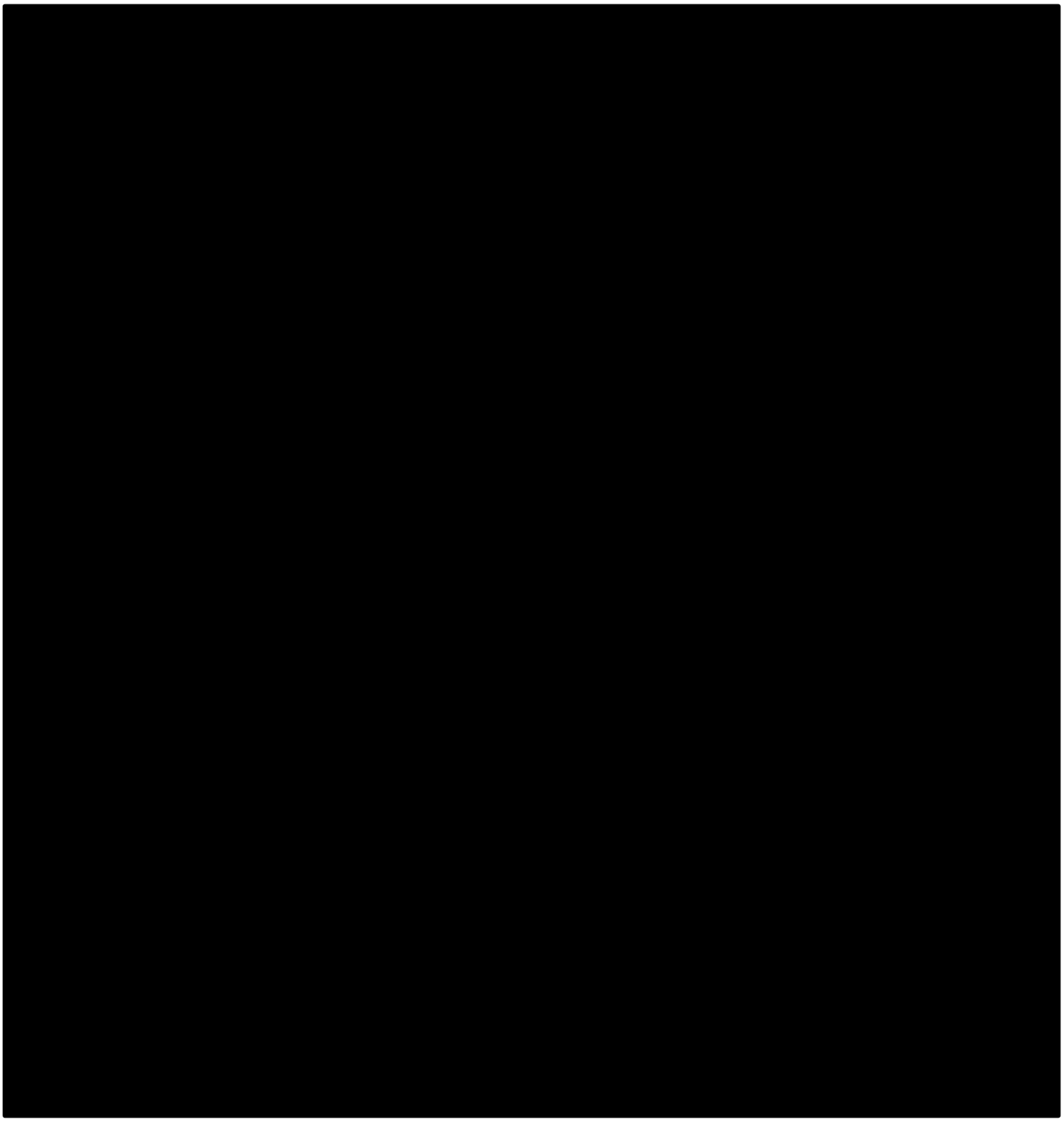
Table 43. Statistical goodness-of-fit indicators (AIC/BIC) values for independent parametric models fitted to overall survival data for nivolumab + ipilimumab for CheckMate-227 part 1

Independent model	AIC	BIC
Lognormal	3,483	3,492
Generalised gamma	3,485	3,498
Spline on normal, 1 knot	3,485	3,498
Spline on normal, 2 knots	3,486	3,503
Spline on odds, 1 knot	3,486	3,500
Spline on hazards, 1 knot	3,488	3,501
Spline on hazards, 2 knots	3,488	3,506
Spline on odds, 2 knots	3,488	3,506
Gompertz	3,488	3,497
Log-logistic	3,489	3,498
Weibull	3,515	3,524
Gamma	3,522	3,531
Exponential	3,535	3,539

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion.

Figure 58 shows the independent parametric models for nivolumab + ipilimumab with the best statistical fit based on AIC. As shown, all curves fit the KM data reasonably well within the trial period.

Figure 58. Independent parametric models overlaying the CheckMate-227 part 1 overall survival Kaplan-Meier data for nivolumab + ipilimumab



Abbreviation: Nivo+ipi = nivolumab + ipilimumab.

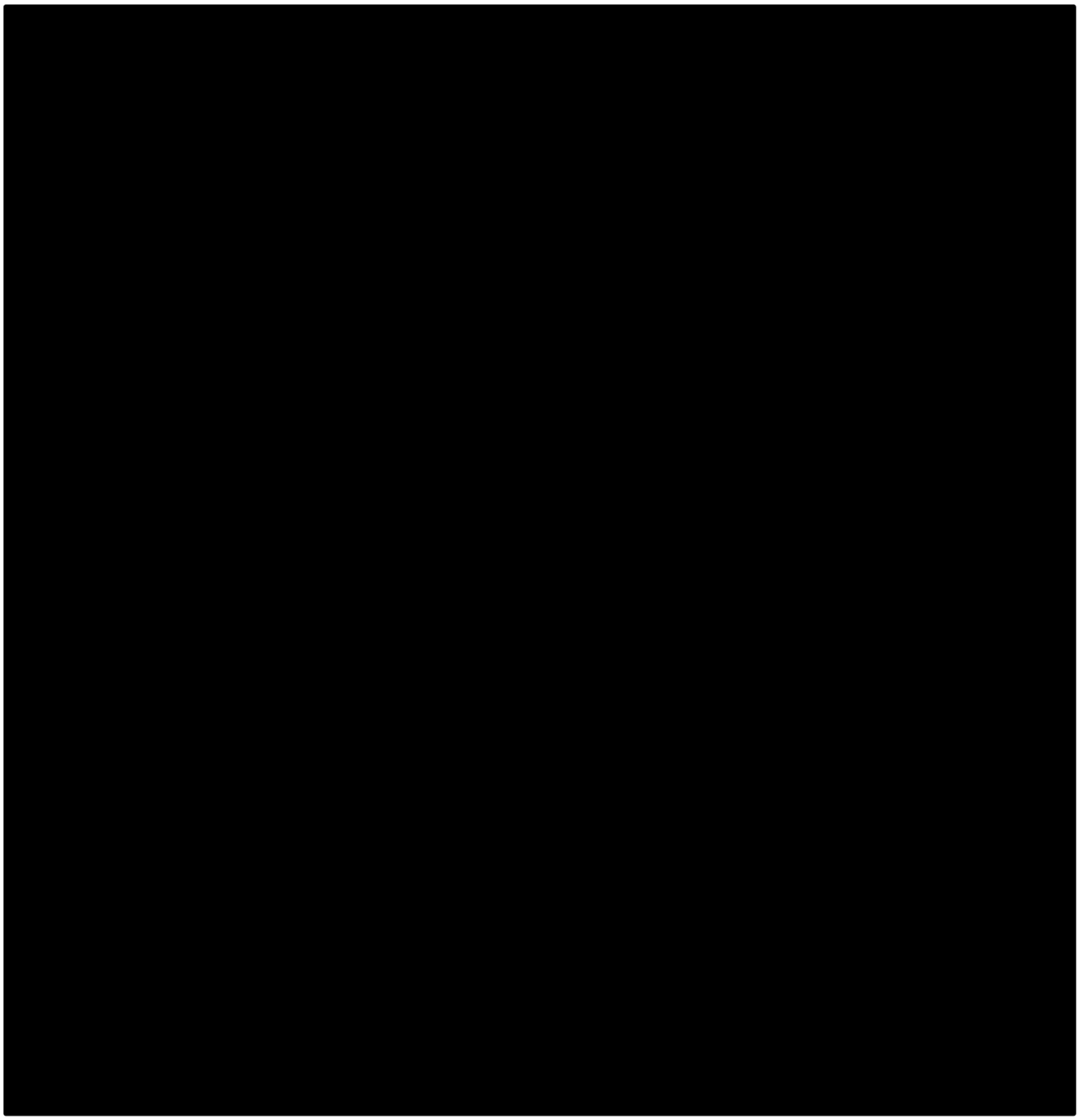
Table 44 presents the goodness-of-fit statistics for the parametric models fitted to the data from the PDC arm of CheckMate-227. The log-logistic was the best-fitting distribution by AIC and BIC criteria. Figure 59 shows the curves with the best statistical fit to the CheckMate-227 data. As shown, all curves fit the KM data reasonably well within the trial period.

Table 44. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to overall survival data for PDC from CheckMate-227 part 1

Independent model	AIC	BIC
Log-logistic	3,775	3,783
Spline on odds, 1 knot	3,775	3,788
Spline on odds, 2 knots	3,776	3,794
Spline on probit link of survival, 2 knots	3,777	3,795
Spline on hazards, 2 knots	3,778	3,795
Spline on hazards, 1 knot	3,779	3,792
Lognormal	3,780	3,789
Spline on probit link of survival, 1 knot	3,781	3,794
Generalised gamma	3,781	3,794
Gompertz	3,806	3,815
Exponential	3,815	3,819
Gamma	3,815	3,823
Weibull	3,816	3,825

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; PDC = platinum doublet chemotherapy.

Figure 59. Independent parametric models overlaying the CheckMate-227 part 1 overall survival Kaplan-Meier data for PDC



Abbreviation: PDC = platinum doublet chemotherapy.

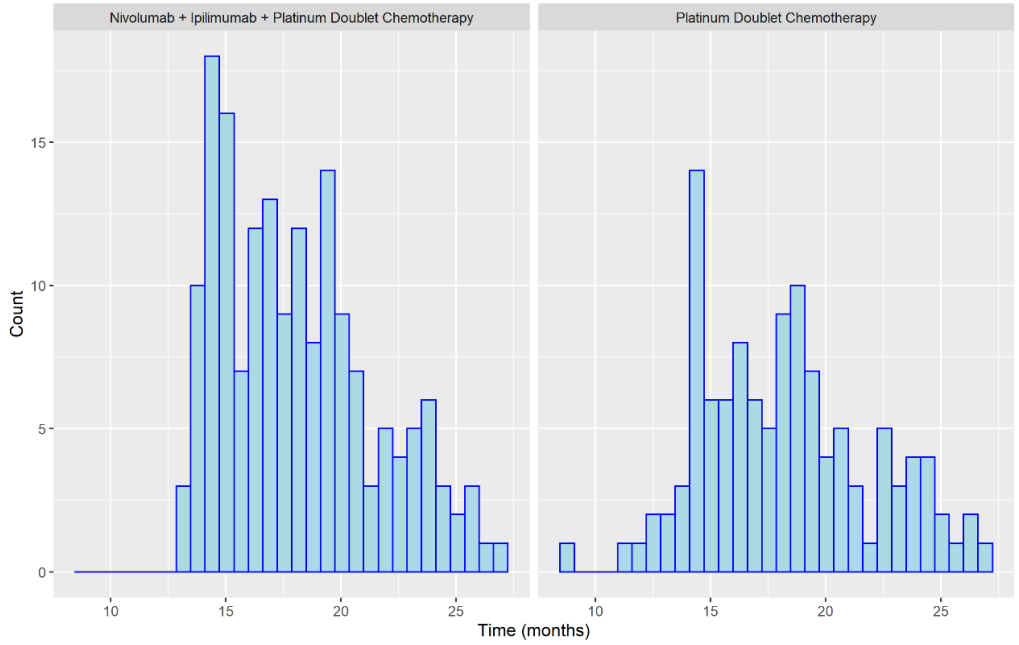
Note: *Chemo* refers to PDC.

Selection of overall survival base-case extrapolations

To determine the most plausible extrapolations to be used for OS, the distributions identified to provide the best fit to the CheckMate-9LA and CheckMate-227 clinical data were assessed against long-term external data as outlined in Section B.3.3.1. However, for the piecewise approach using a combination of CheckMate-9LA and CheckMate-227 clinical data, a break point from which to switch from CheckMate-9LA KM data to the CheckMate-227 part 1 parametric curves first had to be selected. For the base-case analysis, this break point was set to 13 months. Although minimum patient follow-up was approximately 13 months at the database lock of CheckMate-9LA, the primary reason for selecting this specific time point was

because a large degree of censoring occurred after 13 months in the OS data in both CheckMate-9LA treatment arms (Figure 60). Bagust and Beale (2014)[93] warn of the risk of bias that can be introduced by censoring patients (often visually evident as sudden downward movements in the KM plot at the end of the observed data). Further, Latimer (2014)[94] highlights that the selection of a time point for switching from KM curve to extrapolation becomes increasingly arbitrary as the effective sample size decreases.[94] Therefore, selecting a time point before large censoring occurs maintains a suitable sample size from which to apply the extrapolation. However, the impact of selecting an alternative break point was tested in a scenario analysis (see Section B.3.8.3).

Figure 60. CheckMate-9LA time to overall survival censoring



Survival extrapolation for the nivolumab + ipilimumab + limited PDC arm

Table 45 presents the predicted landmark survival for patients treated with nivolumab + ipilimumab + limited PDC from the analyses performed on the CheckMate-9LA data, the hybrid approach using the combined CheckMate-9LA and CheckMate-227 data, and the constructed KM curves based on external data used for validation (see Section B.3.3.1). All extrapolations based on the CheckMate-9LA data resulted in significantly underestimated long-term survival predicted form external sources. Even the most optimistic distributions (log-logistic and spline on odds 1 knot) underpredicted the anticipated survival in the 2- to 5-year time frame.

For the hybrid approach, most distributions have a 10-year survival estimate that is more conservative than the 13.2% or 13.8% predicted for the constructed KM curves. However, they provide a better fit to the constructed KM data in the 2- to 5-year period compared with models only fitted to CheckMate-9LA data. This improved comparison with the external data is believed to be due to the more mature CheckMate-227 data better reflecting the anticipated long-term effect of IO treatments compared with the relatively immature CheckMate-9LA data.

Thus, the most appropriate method for extrapolation of OS was determined to be the hybrid modelling approach encompassing data from both CheckMate-9LA and CheckMate-227. Based on this approach, the spline on normal link 2 knots distribution fitted to the

CheckMate-227 data was deemed to be the most appropriate to use. This was primarily driven by the 5-year OS predictions, which, for all other models (excluding spline on normal link 2 knots), substantially underestimated OS at 5 years compared with the two constructed curves. The selected model—spline on normal link 2 knots—still presents an estimate that is more conservative than OS predicted by the constructed curves from 1 and 2 years. At 10 years, OS at 13.7% is comparable with those estimates derived from the constructed curves. Based on these justifications, the spline on normal link 2 knots distribution was selected for the base case for nivolumab + ipilimumab + limited PDC.

Table 45. Overall survival at different landmark points with the best-fitting distributions using multitrial approach in the nivolumab + ipilimumab + limited PDC arm

	Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 5 (%)	Year 10 (%)
CM-9LA–only approach	Log-logistic	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline on odds 1 knot	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gamma	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Exponential	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hybrid approach	Lognormal	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline on probit link 1 knot	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline on probit link 2 knots	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline on odds 1 knot	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline on hazards 1 knot	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Validation data	CM-9LA KM data		[redacted]				
	CM-227 part 1 KM data		[redacted]	[redacted]	[redacted]		
	Constructed KM OS curve (1-year CM-9LA data)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Constructed KM OS curve (2-year CM-9LA data)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; KM = Kaplan-Meier; OS = overall survival; PDC = platinum doublet chemotherapy.

Survival extrapolation for the PDC arm

Table 46 presents the survival estimates at different landmark points for the best-fitting distributions (based on AIC criteria) for OS in the PDC arm from the analyses performed on the CheckMate-9LA data and the hybrid approach using the combined CheckMate-9LA and CheckMate-227 data. In addition, Table 46 presents the external data used for validation. The survival extrapolations based on the CheckMate-9LA data only result in clinically implausible long-term survival predicting 10-year survival similar to what would be considered plausible at

year 5. Thus, because of this and to be consistent across the two arms, the hybrid approach was considered to be the best approach for extrapolation. All of the best-fitting distributions are within the range of 5% to 11%, which is considered the plausible range for 5-year survival for standard of care in TA557.[52] Considering that the all-comers population would have lower survival compared with a PD-L1–positive population, the 5-year survival should likely be below 9.6%, which was considered to be the preferred estimate for standard of care by the ERG in NICE TA447.[91] The first, fourth, and sixth best-fitting distributions meet this criterion. To be conservative, log-logistic resulting in the highest 10-year OS therefore has been selected as the distribution for the base case.

Table 46. Overall survival at different landmark points with the best-fitting distributions using multitrial approach

	Distribution	Rank (AIC)	Year 1, %	Year 2, %	Year 3, %	Year 5, %	Year 10, %
CM-9LA only	Log-logistic	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline on odds 1 knot	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline on odds 2 knots	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline on hazards 2 knots	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline on probit link of survival 2 knots	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline on probit link of survival 1 knot	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hybrid approach	Log-logistic	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline on odds 1 knot	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline on odds 2 knots	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline on probit link 1 knot	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline on hazards 2 knots	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline on hazards 1 knot	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Validation data	CM-9LA KM data		[redacted]				
	CM-227 part 1 KM data		[redacted]	[redacted]	[redacted]		
	ERG-preferred estimate for SOC from NICE TA 447					[redacted]	[redacted]

Distribution	Rank (AIC)	Year 1, %	Year 2, %	Year 3, %	Year 5, %	Year 10, %
NICE committee estimated range of 5-year survival for SOC in TA557					[redacted]	
Insinga et al. (2018)[95]					[redacted]	[redacted]

Abbreviations: AIC = Akaike information criterion; CM = CheckMate; ERG = Evidence review group; KM = Kaplan-Meier; SOC = standard of care; TA = technology appraisal.

Summary of base-case overall survival extrapolations used for all comparators

Based on the curve selection above, Figure 61 presents the resulting nivolumab + ipilimumab + limited PDC versus PDC survival curves for OS used in the base case.

Figure 61. Overall survival: nivolumab + ipilimumab + limited PDC versus PDC

Abbreviations: KM = Kaplan-Meier; PDC = platinum doublet chemotherapy.

As presented in Section B.3.3.1, the survival for comparators not included in the CheckMate-9LA trial was informed by the survival predictions for CheckMate-9LA and the fractional polynomial NMA. Because both pembrolizumab monotherapy and atezolizumab + bevacizumab + carboplatin + paclitaxel are IO therapies, it was deemed most appropriate to model both treatments as a function of the nivolumab + ipilimumab + limited PDC survival estimates rather than the PDC estimates. Figure 62 presents the resulting pembrolizumab monotherapy survival curve for OS, and Figure 63 presents the resulting atezolizumab + bevacizumab + carboplatin + paclitaxel survival curve for OS used in the base case.

Figure 62. Overall survival: pembrolizumab monotherapy versus nivolumab + ipilimumab + limited PDC

Abbreviations: KM = Kaplan-Meier; PDC = platinum doublet chemotherapy.

Figure 63. Overall survival: atezolizumab combination versus nivolumab + ipilimumab + limited PDC

Abbreviations: KM = Kaplan-Meier; PDC = platinum doublet chemotherapy.

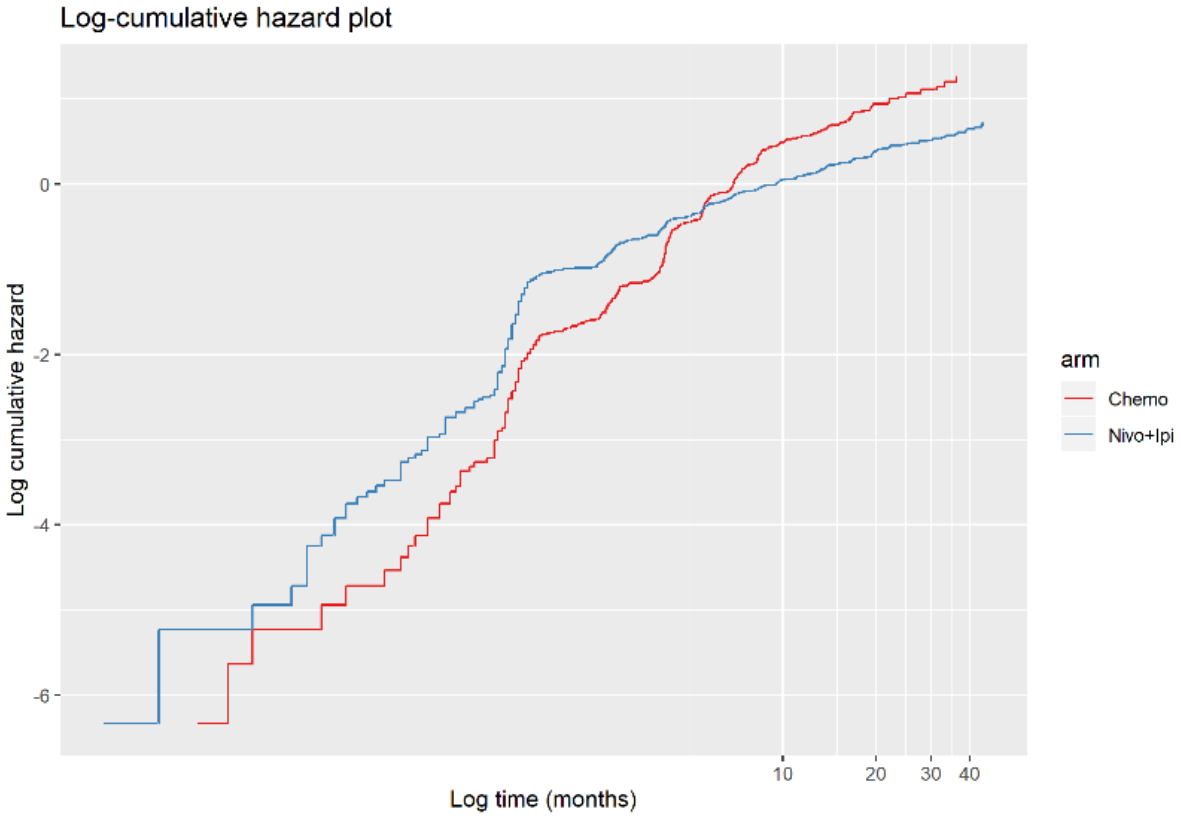
B.3.3.1.5 Analyses of progression-free survival

For consistency with the approach to the modelling of OS, a piecewise approach combining CheckMate-9LA and CheckMate-227 part 1 data was also deemed most appropriate for PFS and is presented in this section. However, for completeness, parametric survival analysis was also conducted for PFS only based on CheckMate-9LA and is presented in Appendix M.

The March 2020 database lock for CheckMate-9LA had a minimum follow-up of 12.7 months for OS and 12.2 months for all other data.[21] A piecewise approach (combining CheckMate-9LA KM data up to 13 months with CheckMate-227 part 1 extrapolations based on the full data set) was again used for the base-case analysis, which is consistent with the modelling approach for OS.

As presented in Figure 56 and Figure 57, the proportional hazards assumption was clearly violated with the log-cumulative hazard plots crossing and Schoenfeld residuals plot, which indicates that the hazards were not constant over time. The Grambsch-Therneau test also showed that the hazards were significantly different from proportional hazards ($P = 0.00$). Therefore, only independent models were investigated for the CheckMate-227 part 1 data.

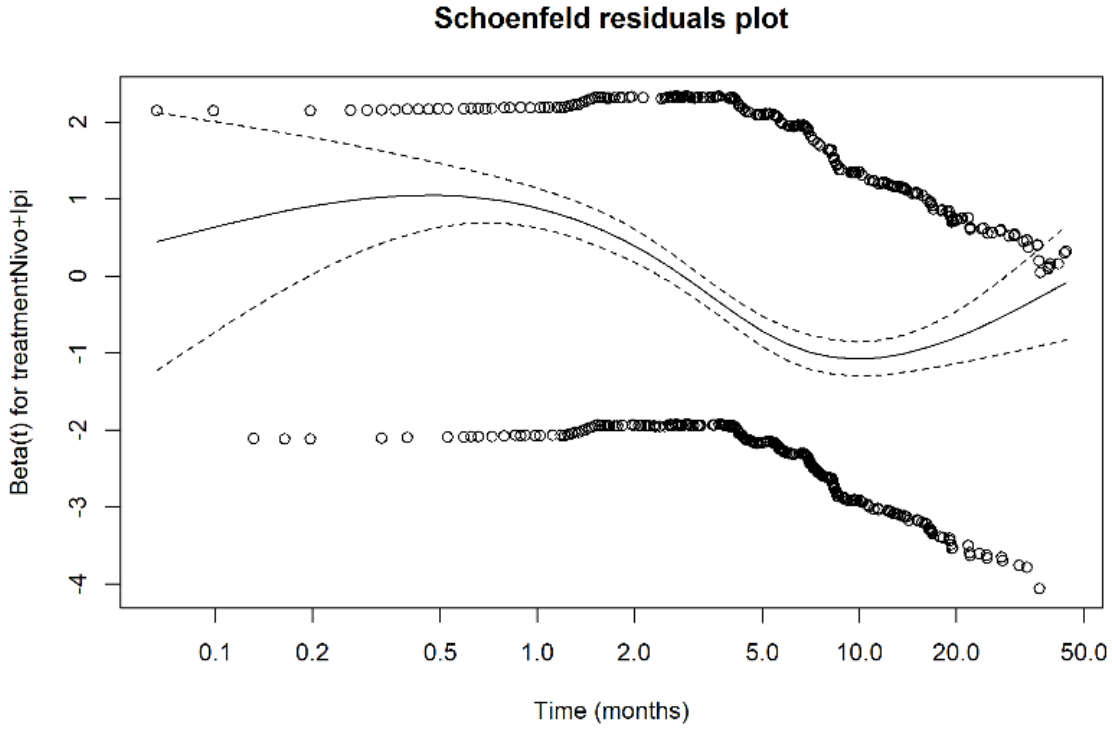
Figure 64. Log-cumulative hazard plot for nivolumab + ipilimumab versus PDC for CheckMate-227 part 1



Abbreviations: Nivo+ipi = nivolumab + ipilimumab; PDC = platinum doublet chemotherapy.

Note: *Chemo* refers to PDC.

Figure 65. Schoenfeld residuals plot for nivolumab + ipilimumab versus PDC for CheckMate-227 part 1



Abbreviation: PDC = platinum doublet chemotherapy.

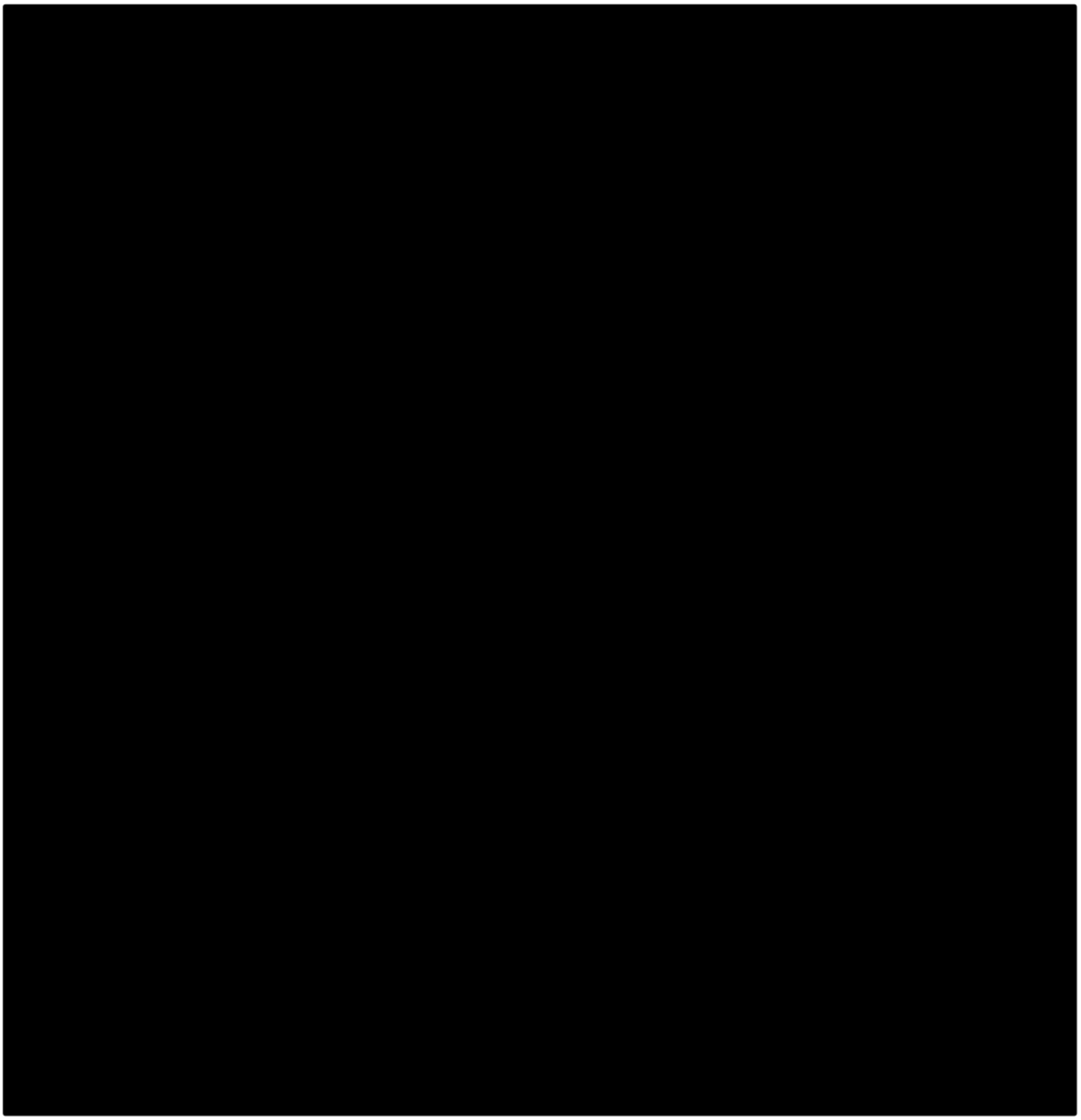
Table 47 presents the goodness-of-fit statistics for parametric distributions fitted to the CheckMate-227 data for nivolumab + ipilimumab. Figure 66 shows the resulting curves with the best statistical fit. The lognormal and generalised gamma distributions produced a conservative PFS compared with the spline models.

Table 47. Statistical goodness-of-fit indicators (AIC/BIC) values for independent parametric models fitted to progression-free survival data for nivolumab + ipilimumab for CheckMate-227 part 1

Independent model	AIC	BIC
Spline on hazards 2 knots	2,872	2,890
Spline on odds 2 knots	2,873	2,890
Spline on odds 1 knot	2,881	2,894
Spline on normal 1 knot	2,882	2,896
Spline on hazards 1 knots	2,884	2,897
Spline on normal link 2 knot	2,885	2,902
Generalised gamma	2,891	2,904
Lognormal	2,915	2,924
Log-logistic	2,929	2,938
Gompertz	2,939	2,947
Weibull	3,015	3,024
Gamma	3,048	3,057
Exponential	3,114	3,119

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion.

Figure 66. Independent parametric models overlaying the progression-free survival Kaplan-Meier data for nivolumab + ipilimumab



Abbreviation: Nivo+ipi = nivolumab + ipilimumab.

Table 48 presents PFS at different landmark points using the five best-fitting distributions taken from the piecewise approach (based on AIC/BIC) in the nivolumab + ipilimumab + limited PDC arm. The three best-fitting distributions were the 2-knot spline hazard, the 2-knot spline odds, and the 1-knot spline odds. To validate the PFS extrapolations, PFS at 5 years was predicted by deriving the conditional survival (defined as the percentage of patients in PFS at year X who will be in PFS at year Y) from years 2 to 5 from the pooled analysis of CheckMate-017 and CheckMate-057[96] (59.7%) and applying it to the 2-year PFS from CheckMate-227 part 1 (20.2%). The pooled CheckMate-017 and CheckMate-057 data had the longest follow-up for PFS at the time of the validation. Because the data reflect second-line IO therapy, PFS from CheckMate-017 and CheckMate-057 can be considered a conservative estimate for the first-line population evaluated in this analysis.

Using this approach, the predicted 5-year PFS was 12.9%. Both the second and third best-fitting distributions were close to the 5-year predicted estimate (< 1.5% difference). To be conservative, the second best-fitting distribution (2-knot spline odds), which has a 5-year estimate of 11.7%, was selected for the base case.

Table 48. Progression-free survival at different landmark points with the best-fitting distributions using the hybrid approach for the nivolumab + ipilimumab + limited PDC arm

Dependent model	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 5 (%)	Year 10 (%)
Spline on hazards 2 knots	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline on odds 2 knots	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline on odds 1 knot	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline on probit link 1 knot	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline on hazards 1 knot	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CM-9LA KM data		[redacted]				
CM-227 part 1 KM data (3-year database lock)		[redacted]	[redacted]	[redacted]		
Estimated 5-year PFS based on CM-227 3-year estimate and conditional PFS from 3-5 years pooled from CM-057 and CM-017						[redacted]

Abbreviations: AIC = Akaike information criterion; CM = CheckMate; KM = Kaplan-Meier; PDC = platinum doublet chemotherapy; PFS = progression-free survival.

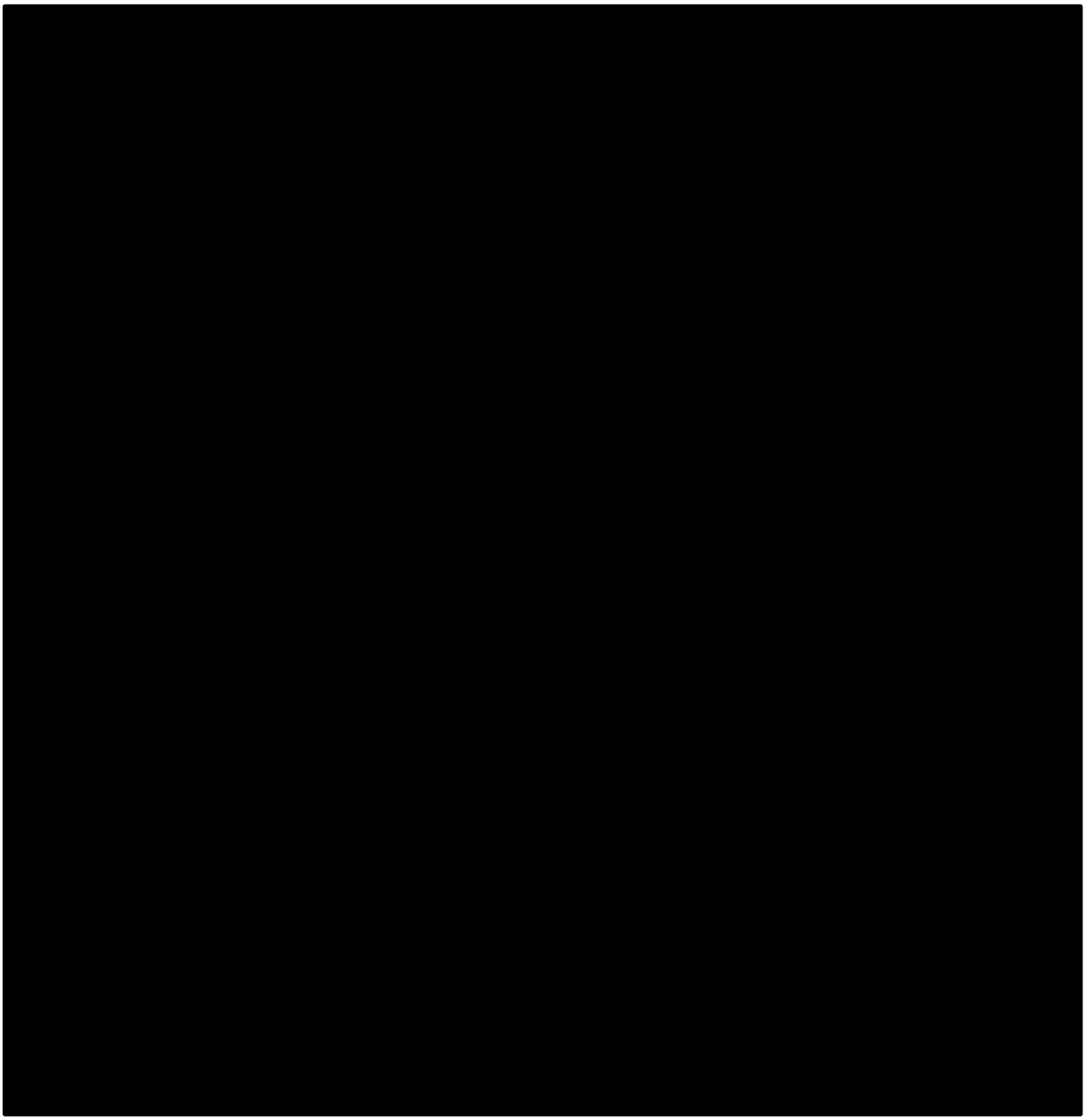
Table 49 presents the goodness-of-fit statistics for parametric models fitted to the PDC arm of the CheckMate-227 data, and Figure 67 shows the resulting curves with the best statistical fit. The long-term PFS for the different distributions is consistent, with the spline on hazards 2 knots and spline on normal 2 knots being the most optimistic curves for PDC.

Table 49. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to progression-free survival data PDC for CheckMate-227 part 1

Independent model	AIC	BIC
Spline on hazards 2 knots	2,614	2,632
Spline on normal link 2 knots	2,618	2,635
Log-logistic	2,618	2,627
Spline on odds 2 knots	2,619	2,636
Spline on odds 1 knot	2,620	2,633
Spline on hazards 1 knot	2,628	2,641
Spline on normal link 1 knot	2,633	2,646
Lognormal	2,633	2,642
Generalised gamma	2,634	2,647
Gamma	2,680	2,689
Weibull	2,698	2,707
Gompertz	2,708	2,717
Exponential	2,710	2,714

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; PDC = platinum doublet chemotherapy.

Figure 67. Independent parametric models overlaying the progression-free survival Kaplan-Meier data for PDC



Abbreviation: PDC = platinum doublet chemotherapy.
Note: *Chemo* refers to PDC.

Table 50 presents PFS at different landmark points for the five best-fitting distributions in the PDC arm based on the hybrid approach. Given the maturity of PFS for PDC, the extrapolated curves result in only marginal differences in long-term PFS. Therefore, it was considered appropriate to select the best-fitting distribution (2-knot spline on normal link) based on goodness-of-fit statistics in the base-case analysis.

Table 50. Progression-free survival at different landmark points with the best-fitting distributions using hybrid approach in the PDC arm

Dependent model	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 5 (%)	Year 10 (%)
Spline on hazards 2 knots	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline on normal link 2 knots	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline on odds 2 knots	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline on odds 1 knot	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CM-9LA KM data		[redacted]				
CM-227 part 1 KM data (3-year database lock)		[redacted]	[redacted]	[redacted]		
Estimated 5-year PFS based on CM-227 3-year estimate and conditional PFS from 3-5 years pooled from CM-057 and CM-017					[redacted]	[redacted]

Abbreviations: AIC = Akaike information criterion; CM = CheckMate; KM = Kaplan-Meier; PDC = platinum doublet chemotherapy; PFS = progression-free survival.

Summary of base-case progression-free survival extrapolations used for all comparators

Based on the curve selection above, Figure 68 presents the resulting nivolumab + ipilimumab + limited PDC versus PDC survival curves for OS used in the base case.

Figure 68. Progression-free survival: nivolumab + ipilimumab + limited PDC versus PDC

Abbreviations: KM = Kaplan-Meier; PDC = platinum doublet chemotherapy.

In line with the approach taken for OS extrapolations, it was deemed most appropriate to model PFS for both pembrolizumab monotherapy and atezolizumab + bevacizumab + carboplatin + paclitaxel as a function of the nivolumab + ipilimumab + limited PDC survival estimates rather than the PDC arm. Figure 69 presents the resulting pembrolizumab monotherapy survival curve for PFS, and Figure 70 presents the resulting atezolizumab + bevacizumab + carboplatin + paclitaxel survival curve for PFS used in the base case.

Figure 69. Progression-free survival: pembrolizumab monotherapy versus nivolumab + ipilimumab + limited PDC

Abbreviations: KM = Kaplan-Meier; PDC = platinum doublet chemotherapy.

Figure 70. Progression-free survival: atezolizumab combination versus nivolumab + ipilimumab + limited PDC

Abbreviations: KM = Kaplan-Meier; PDC = platinum doublet chemotherapy.

B.3.3.2 Subsequent treatment

After failure with first-line treatment, a proportion of patients from the initial randomised cohort will go on to a subsequent treatment. Given the advanced nature of the disease and the lack of data on multiple lines of therapy beyond second-line treatment, only one line of subsequent therapy is modelled. The proportion of patients receiving subsequent treatment was 31% for nivolumab + ipilimumab + limited PDC and 40% for PDC, as reported in the CheckMate-9LA CSR.[21] The proportion of patients receiving subsequent treatment after first-line treatment with pembrolizumab and atezolizumab regimens is assumed to be the same as nivolumab + ipilimumab + limited PDC. As assumed in previous technology appraisals, all patients receiving IO therapy first line will receive docetaxel second line.[3]

These patients are assumed to receive a subsequent systemic anticancer therapy in the second line of therapy. Table 51 presents the distribution of the nine most common subsequent treatments received by treatment arm and the distribution of subsequent therapies received by initial treatment. The percentage of patients on each treatment is based on the CheckMate-9LA CSR.[21]

Table 51. Distribution of subsequent treatments applied in the base-case model

Drug	NIVO + IPI + limited PDC	PDC	Pembrolizumab	Atezolizumab
Nivolumab		34%		
Pembrolizumab		34%		
Atezolizumab		17%		
Docetaxel	100%	15%	100%	100%

Abbreviations: IPI = ipilimumab; NIVO = nivolumab; PDC = platinum doublet chemotherapy.

Source: NICE (2019)[3]

Table 52 presents the average time on subsequent treatment dependent on the subsequent treatment received that is reflective of UK clinical practice and has been used in a previous submission.[3]

Table 52. Distribution of subsequent treatments applied in the base-case model

Drug	Average treatment duration (weeks)	Source
Nivolumab	26.52	NICE (2019)[3]
Pembrolizumab	21.59	
Atezolizumab	35.80	
Docetaxel	18	

B.3.4Measurement and valuation of health effects

B.3.4.1 Health-related quality of life data from clinical trials

Health-related quality of life data were collected in CheckMate-9LA using the EQ-5D preference-based health-state utility questionnaire (EQ-5D Utility Index) (see Section B.2.6.1.3). Utility scores were based on a UK value set.[97]

Table 53 presents the EQ-5D assessment schedule for CheckMate-9LA. Assessments were taken every treatment cycle (every 3 weeks) on day 1 for the first 6 months of the study for nivolumab, PDC, and ipilimumab, and then every 2 treatment cycles (every 6 weeks) up to 2 years thereafter. For PDC, assessments were taken every 3 weeks for the first 6 months and every 6 weeks up to 2 years thereafter. Additional assessments were made at follow-up visits 1 and 2 and then every 3 months for the remainder of the study period for both treatment arms.

Table 53. EQ-5D assessment schedule in CheckMate-9LA

	On-study assessment			
EQ-5D assessment schedule	Every 3 weeks for the first 6 months	Every 6 weeks after the initial 6 months	Follow-up assessment (visits 1 and 2)[a]	Survival follow-up[b]
NIVO + IPI + limited PDC	✓	✓	✓	✓
PDC	✓	✓	✓	✓

Abbreviations: IPI = ipilimumab; NIVO = nivolumab; PDC = platinum doublet chemotherapy.

[a] Follow-up visit 1 within 35 days from last dose; follow-up visit 2 to occur within 80 days of follow-up visit 1.

[b] Every 3 months from follow-up visit 2.

Patient-level utility data from CheckMate-9LA (12 months of data) were used to derive utility values for the PF and PD health states using a UK value set. An analysis was conducted to assess model fit using utilities based on models with or without treatment. The *P* values for utilities based on progression (*P* = 0.009) and time to death (TTD; *P* = 0.001) together with the AIC/BIC values for each model show that the model with treatment has a better fit (Table 54).

Table 54. Utilities based on progression and time to death, UK value set

	Model without treatment		Model with treatment		
Model	**AIC**	**BIC**	**AIC**	**BIC**	***P* value**
Progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; UK = United Kingdom.
Source: Bristol Myers Squibb (2020)[98]

Table 55 presents the overall and treatment-specific utilities by health state derived using a UK value set. Utility in the dead state was set to zero.

Table 55. Treatment-specific utilities by health state, UK value set

Treatment	Mean utility (SE)	95% CI	Reference
Progression free			
Overall	[redacted]	[redacted]	Bristol Myers Squibb (2020)[98]
NIVO + IPI + limited PDC	[redacted]	[redacted]	
PDC	[redacted]	[redacted]	
Progressed disease			
Overall	[redacted]	[redacted]	Bristol Myers Squibb (2020)[98]
NIVO + IPI + limited PDC	[redacted]	[redacted]	
PDC	[redacted]	[redacted]	

Abbreviations: CI = confidence interval; IPI = ipilimumab; NIVO = nivolumab; PDC = platinum doublet chemotherapy; SE = standard error; UK = United Kingdom.

In addition to the health state–specific utilities, time-to-death utilities are estimated from the CheckMate-9LA trial using UK value set.[97] Table 56 presents the overall and treatment-specific TTD utilities derived using a UK value set.

Table 56. Treatment-specific utilities by time to death, UK value set

Time to death	Overall utilities, mean (SE)	NIVO + IPI + limited PDC, mean (SE)	PDC, mean (SE)	Reference
> 52 weeks	[redacted]	[redacted]	[redacted]	Bristol Myers Squibb (2020)[98]
27-52 weeks	[redacted]	[redacted]	[redacted]	
5-26 weeks	[redacted]	[redacted]	[redacted]	
≤ 4 weeks	[redacted]	[redacted]	[redacted]	

Abbreviations: IPI = ipilimumab; NIVO = nivolumab; PDC = platinum doublet chemotherapy; SE = standard error; UK = United Kingdom.

B.3.4.2 Mapping

Utility values were implemented using EQ-5D data collected directly from patients in CheckMate-9LA, which aligns with the NICE reference case and negates the need for mapping.

B.3.4.3 Health-related quality of life studies

An SLR to identify HRQOL studies was performed as part of the SLR described in Section B.3.1 using the inclusion and exclusion criteria and search strategy defined in Appendix G.

A total of 48 studies were identified that met the eligibility criteria for the review; however, none of the studies evaluated nivolumab + ipilimumab + limited PDC or used EQ-5D in an appropriate population. Therefore, HRQOL data from CheckMate-9LA were used in this submission.

B.3.4.4 Adverse reactions

The incidence of AEs was taken from CheckMate-9LA and relevant studies for comparators (Table 57). The inclusion criterion for AEs in the economic model was any-grade 3 or 4 AE with ≥ 5% incidence in either treatment arm.

Table 57. Incidence of grade 3/4 adverse events

	NIVO + IPI + limited PDC		Pembrolizumab monotherapy		Atezolizumab + bevacizumab + carboplatin + paclitaxel		PDC	
Adverse event	**Incidence**	**Source**	**Incidence**	**Source**	**Incidence**	**Source**	**Incidence**	**Source**
Anaemia	5.87%	Bristol Myers Squibb (2020)[79]	0.89%	Weighted: [99,100]	6.40%	NICE (2019)[3]	14.3%	Bristol Myers Squibb (2020)[79]
Lipase increased	6.15%		0.00%		0.00%		9.2%	
Febrile neutropenia	0.00%		0.00%		8.40%		0.0%	
Neutrophil count decreased	0.00%		0.00%		8.70%		0.0%	
Thrombocytopenia	2.79%		0.13%		4.30%		2.58%	
Platelet count decreased	0.00%		0.00%		5.10%		0.0%	
White blood cell count decreased	0.00%		0.00%		3.30%		0.0%	
Neutropenia	6.7%		0.13%		14.00%		0.0%	
Fatigue	2.23%		0.63%		3.30%		0.57%	

Abbreviations: IPI = ipilimumab; NIVO = nivolumab; PDC = platinum doublet chemotherapy.

B.3.4.5 Health-related quality of life data used in the cost-effectiveness analysis

Time-to-death utilities have been used and accepted in recent oncology submissions to NICE[85] and thus have been used for the base-case analysis in the current submission. Table 58 presents the overall treatment-independent TTD utilities used in the economic model. Alternative utility selections are tested in scenario analyses.

Table 58. Summary of pooled utilities by health state used in the economic model

Time to death	Utilities (SE)	Reference
> 52 weeks	[redacted]	Bristol Myers Squibb (2020)[98]
27-52 weeks	[redacted]	
5-26 weeks	[redacted]	
≤ 4 weeks	[redacted]	

Abbreviation: SE = Standard error.

To account for the impact of AEs on quality of life, utility decrements from published literature are applied in the model to adjust for quality of life losses associated with AEs (Table 59). Decrements are applied in the model as a one-off decrement based on the incidence of AEs per treatment and corresponding utility decrement.

Table 59. Disutility of grade 3/4 adverse events

Adverse event	Disutility	Reference
Anaemia	−0.125	Lloyd et al. (2008)[101]
Neutropenia	−0.46	Nafees et al. (2008)[89]
Fatigue	−0.41	Nafees et al. (2008)[89]
Lipase increased	0	Assumption
Thrombocytopenia	−0.184	Attard et al. (2014)[102]
Neutrophil count decreased	−0.46	Nafees et al. (2008)[89]
Platelet count decreased	0	Assumption
White blood cell count decreased	−0.46	Nafees et al. (2008)[89]
Febrile neutropenia	−0.5	Nafees et al. (2008)[89]

B.3.5Cost and health care resource use identification, measurement, and valuation

The types of costs considered in the economic model included drug and administration costs related to the intervention and comparators (see Sections B.3.5.1 and B.3.5.1.2), administration costs (see Section B.3.5.2), management of the disease (see Section B.3.5.4), costs related to terminal care (see Table 67), and costs related to AEs (see Section B.3.5.5).

An SLR was conducted to identify costs and resource use in the treatment and ongoing management of patients with advanced NSCLC from a UK perspective as described in Appendix I.

B.3.5.1 Intervention and comparators' costs and resource use

Table 60 presents the drug acquisition costs per treatment, with the unit costs for comparators taken from the electronic market information tool and the British National Formulary. [redacted]. It appears, based on NICE appraisals of the comparator treatments included, that such arrangements are also in place for most of the other therapies. Given that these discounts are unknown to the company, the current analyses are provided based on the information available to us. Thus, discounted prices have been used for nivolumab and ipilimumab and list prices used for all other treatments.

Table 60. Drug unit costs by first-line therapy

Treatment	Dose/unit	Strength (mg)	Dose frequency (days)	Cost per pack	Source
Nivolumab	360 mg	40	21	£439.00	Joint Formulary Committee (2020)[103]
		100		£1,097.00	
Ipilimumab	1 mg/kg	50	42	£3,750.00	Joint Formulary Committee (2020)[103]
		200		£15,000.00	
Pembrolizumab	200 mg	100	21	£2,630.00	Joint Formulary Committee (2020)[103]
		50		£1,315.00	
Cisplatin	75 mg/m^2	10	21	£2.64	Department of Health and Social Care (2020)[104]
		50		£4.12	
		100		£6.66	
Carboplatin	400 mg/m^2	50	21	£3.75	Department of Health and Social Care (2020)[104]
		150		£11.14	
		450		£27.90	
		600		£28.22	
Pemetrexed	500 mg/m^2	100	21	£150.00	Joint Formulary Committee (2020)[103]
		500		£450.00	
Docetaxel	75 mg/m^2	20	21	£4.61	Department of Health and Social Care (2020)[104]
		80		£12.50	
Paclitaxel	200 mg/m^2	30	21	£4.69	Department of Health and Social Care (2020)[104]
		100		£23.06	
		300		£39.32	
Bevacizumab	15 mg/m^2	100	21	£242.66	Joint Formulary Committee (2020)[103]
		400		£924.40	
Atezolizumab	1,200 mg	1,200	21	£3,807.69	Joint Formulary Committee (2020)[103]

B.3.5.1.1 Nivolumab + ipilimumab + limited PDC regimen

As per the anticipated licence, the model uses a 360 mg dose of nivolumab administered as a 30-minute intravenous infusion Q3W, a 1 mg/kg dose of ipilimumab administered by intravenous infusion Q6W, and 2 cycles of PDC. The list prices of a 100-mg vial of nivolumab and a 200-mg vial of ipilimumab are £1,097 and £15,000, respectively. Table 61 presents the proportion of patients treated with each PDC regimen in the model in the nivolumab + ipilimumab + limited PDC arm.

Table 61. Proportion of patients treated with each PDC in the nivolumab + ipilimumab + limited PDC arm

Treatment	Intended therapy before randomisation	Source
Paclitaxel + carboplatin	[redacted]	Bristol Myers Squibb data on file (2020)[21]
Pemetrexed + cisplatin	[redacted]	
Pemetrexed + carboplatin	[redacted]	

Abbreviation: PDC = platinum doublet chemotherapy.

B.3.5.1.2 Comparators

Table 62 presents the distribution between the different PDCs applied in the cost-effectiveness model. The proportion of patients receiving each PDC is based on the proportion intended to receive each treatment in CheckMate-9LA at randomisation.

Table 62. Proportion of patients treated with each PDC in the PDC arm

Treatment	Intended therapy before randomisation	Source
Paclitaxel + carboplatin	[redacted]	Bristol Myers Squibb data on file (2020)[21]
Pemetrexed + cisplatin	[redacted]	
Pemetrexed + carboplatin	[redacted]	

Abbreviation: PDC = platinum doublet chemotherapy.

B.3.5.1.3 Extent of exposure to study treatment

Mean relative dose intensity information is applied in the model to reflect the extent of exposure to study treatment observed in the clinical trials of each treatment. Relative dose intensities for comparator treatments were taken from previous NICE submissions and are shown in **Error! Reference source not found.**.

Table 63. Relative dose intensity of all treatments applied in the model

Treatment	Relative dose intensity	Source
Nivolumab	[redacted]	Bristol Myers Squibb (2020)[105]
Ipilimumab	[redacted]	
Cisplatin (nivolumab + ipilimumab + limited PDC arm)	[redacted]	
Carboplatin cisplatin (nivolumab + ipilimumab + limited PDC arm)	[redacted]	

Treatment	Relative dose intensity	Source
Paclitaxel cisplatin (nivolumab + ipilimumab + limited PDC arm)	[redacted]	
Pemetrexed cisplatin (nivolumab + ipilimumab + limited PDC arm)	[redacted]	
Cisplatin (PDC arm)	[redacted]	
Carboplatin (PDC arm)	[redacted]	
Paclitaxel (PDC arm)	[redacted]	
Pemetrexed (PDC arm)	[redacted]	
Pembrolizumab	99.21%	NICE (2018)[4]
Atezolizumab	94.00%	NICE (2019)[3]
Bevacizumab	93.80%	

Abbreviation: PDC = platinum doublet chemotherapy.

B.3.5.2 Administration costs

Combination administrations were costed as a complex parenteral chemotherapy administration, and monotherapy administrations were costed as a simple parenteral chemotherapy administration (Table 64).

Table 64. Administration costs by treatment

Treatment	Cost per administration per dose	Note
Combination therapy	£259.08	Deliver more complex parenteral chemotherapy at first attendance (National Schedule of NHS Costs 2019 - SB14Z)
Monotherapy	£183.54	Deliver simple parenteral chemotherapy at first attendance (outpatients) (National Schedule of NHS Costs 2019 - SB12Z)

B.3.5.3 Modelling of duration of treatment

Various assumptions can be made about the duration of treatment (DOT) in the economic model. In oncology models, it is often assumed that PFS can be used as a proxy for DOT. Nevertheless, patients may stop treatment before progression (e.g., owing to intolerability or AEs) or continue treatment beyond disease progression. In CheckMate-9LA, both PFS and DOT were measured directly, and KM curves are available for both endpoints. Thus, at least for nivolumab + ipilimumab + limited PDC and PDC, DOT KM data can be directly used to inform treatment duration in the model.

Figure 71 presents the PFS and DOT KM curves from CheckMate-9LA. The PFS KM curve for nivolumab + ipilimumab + limited PDC lies above the KM DOT curve, indicating that a proportion of patients may have discontinued treatment before disease progression. A steep drop in the DOT curve can also be seen at 24 months, which reflects the 2-year stopping rule included in the study protocol.

Figure 72 shows that the DOT KM curve for PDC is also below the PFS KM curve. This reflects that patients with squamous histology discontinue treatment after 4 cycles of chemotherapy but could also reflect early discontinuation due to toxicity. Only patients with non-squamous

histology were allowed pemetrexed maintenance until disease progression or unacceptable toxicity.

Figure 71. CheckMate-9LA duration of treatment and progression-free survival Kaplan-Meier curves for nivolumab + ipilimumab + limited PDC

Abbreviations: CM = CheckMate; DOT = duration of therapy; IPI = ipilimumab; KM = Kaplan-Meier; NIVO = nivolumab; PDC = platinum doublet chemotherapy; PFS = progression-free survival.

Figure 72. CheckMate-9LA duration of treatment and progression-free survival Kaplan-Meier curves for PDC

Abbreviations: CM = CheckMate; DOT = duration of therapy; KM = Kaplan-Meier; PDC = platinum doublet chemotherapy; PFS = progression-free survival.

In the base case, the model uses the DOT KM curve for nivolumab + ipilimumab + limited PDC to more accurately reflect treatment use in the clinical trial. For PDC, treatment costs are also modelled according to the DOT curve in the base-case analysis to reflect that chemotherapy is discontinued after 4 cycles of treatment after which non-squamous patients who have not progressed can continue on pemetrexed maintenance therapy. Both nivolumab + ipilimumab + limited PDC and PDC KM curves for DOT are very close to 0 at end of follow-up. Hence, it was considered appropriate to use the DOT KM curve (rather than a parametric extrapolation) for treatment cost calculations for both arms in the base-case analysis.

Duration of treatment for comparators that are not included in the CheckMate-9LA trial was estimated by using PFS curves a proxy for DOT, given lack of access to individual patient data on which to base the DOT for other comparators. The impact of this was explored in scenario analyses by using PFS as a proxy for all comparators, including nivolumab + ipilimumab + limited PDC and PDC, to assess results when using a consistent method of modelling DOT across all comparators.

B.3.5.4 Health-state unit costs and resource use

There is limited published literature that explores in detail the resource use associated with patients with NSCLC previously untreated. Consequently, the main source of resource utilisation per health state used in this submission is the resource use previously assessed by NICE in TA531 for pembrolizumab in previously untreated NSCLC. The health-state costs in the model include monitoring and disease management costs. Monitoring is included in health-state costs based on the pembrolizumab submission.

There are three health states included in the model—progression-free (PF), progressed (PD), and death. Table 65 and Table 66 present health state–related costs.

Patients incur disease management costs for as long as they remain on treatment, and potentially longer. The unit costs of treatment are consistent over cycle lengths; however, the frequency of resource consumption per cycle varies depending on the health state.

Table 65. List of health states and associated resource use in the economic model

Health state	Items	Frequency	Unit	Reference
Progression free	Outpatient visit	9.61	Per annum	NICE (2018)[4]
	Chest radiography	6.79	Per annum	
	CT scan (chest)	0.62	Per annum	
	CT scan (other)	0.36	Per annum	
	Electrocardiogram	1.04	Per annum	
Progressed	Outpatient visit	7.91	Per annum	NICE (2018)[4]
	Chest radiography	6.5	Per annum	
	CT scan (chest)	0.24	Per annum	
	CT scan (other)	0.42	Per annum	
	Electrocardiogram	0.88	Per annum	
	General practitioner home visit	26.09	Per annum	
	Therapist visit	26.09	Per annum	

Abbreviation: CT = computed tomography.

Table 66. List of health states (progression free and progressed disease) and associated costs in the economic model

Items	Value	Reference
Outpatient visit	£142.58	NHS Improvement (2018/19)[106]
Chest radiography	£28.36	NICE (2018)[4]
CT scan (chest)	£103.61	NHS Improvement (2018/19)[106]
CT scan (other)	£115.19	NHS Improvement (2018/19)[106]
ECG	£143.86	NHS Improvement (2018/19)[106]
Community nurse visit	£131.00	Curtis (2019)[107]
Clinical nurse specialist	£113.00	Curtis (2019)[107]
GP home visit	£89.76	Curtis (2019)[107]
Therapist visit	£48.00	Curtis (2019)[107]

Abbreviations: CT = computed tomography; GP = general practitioner; ECG = electrocardiogram.

A one-off cost was applied to patients at the moment of dying to reflect the cost of terminal care. The resource consumption reflected treatment received in various care settings and was based on the resource use frequency and cost values used in the NICE submission for pembrolizumab (TA531) and validated by clinical experts. These costs were assumed to be the same for all treatments and are shown in Table 67.

Table 67. Terminal care costs used in the economic model

Item	Value	Proportion of patients	Reference for cost value	Reference for proportion
Community nurse visit	£131	27%	Curtis (2019)[107]	NICE (2018)[4]
GP home visit	£89.76	27%	Curtis (2019)[107] (p.120 including direct care staff £39 costs per patient contact lasting 9.22 minutes + 12 minutes travelling time)	
Macmillan nurse	£87.38	27%	NICE (2018)[4]assumed to be 66.7% of community nurse cost	
Drugs and equipment	£283.16	27%	Brown et al. (2013)[108] (Marie Curie report figure [2013/14] of £240, inflation adjusted to 2020)	
Terminal care in hospital	£3,833.61	56%	NICE (2018)[4], inflated to current price year	
Terminal care in hospice	£4,792.01	17%	NICE (2018)[4]. Assumed to be 25% increase on hospital inpatient care	
Weighted total cost for end-of-life care	£5,377.51	100%	Calculated	

Abbreviation: GP = general practitioner.

B.3.5.5 Adverse event costs

The AEs included in the economic model are described in Section B.3.5.5. Frequency of grade ≥ 3 AEs experienced by ≥ 5% of patients in CheckMate-9LA are included in the analysis and are detailed in Table 68. Costs of AEs were taken from previous NICE technology appraisals and inflated to the current price year (Table 68).

Table 68. Treatment-related adverse events included in the economic model by treatment

AE type	Cost of AE	Reference
Anaemia	£2,835.66	NICE (2018)[4]
Lipase increased	£0	Assumption, Laboratory value not requiring hospitalisation
Febrile neutropenia	£7,385.81	Brown et al. (2013)[108]
Neutrophil count decreased	£199.55	TA428 NICE (2017)[109]
Thrombocytopenia	£419.00	NHS Improvement (2018/19)[106]
Platelet count decreased	£0.00	Assumed to be £0 as in NICE (2018)[4]
White blood cell count decreased	£621.49	NICE (2017)[109]
Neutropenia	£634.19	Brown et al. (2013)[108]
Fatigue	£2,993.20	Brown et al. (2013)[108]

Abbreviation: AE = adverse event.

B.3.5.6 Miscellaneous unit costs and resource use

There are no additional costs included in the model except those outlined in the previous sections.

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

Table 69 presents a summary of the key variables.

Table 69. Summary of variables applied in the economic model

Area	Variable	Value	Reference to section in submission
General	Patient population	Adults with untreated stage IV or recurrent NSCLC that (with no known EGFR- or ALK-positive tumour mutations)	Section B.3.2.1
	Time horizon	5 years	Section B.3.2.2
	Model cycle length	1-week cycles for initial 28 weeks of model; 4-week cycles after 28 weeks	
	Discount rate	3.5% for both costs and outcomes	
	Simple administration (monotherapy)	£259.08	Section B.3.5.2
	Complex administration (combination therapy)	£183.54	Section B.3.5.2
Health-state costs	PF cost per 4 weeks	£139.86	Section B.3.5.4
	PD cost per 4 weeks	£392.78	Section B.3.5.4
End-of-life cost	Terminal care	£5,377.51	Section B.3.5.4
AE costs	Anaemia	£2,835.66	Section B.3.5.5
	Lipase increased	£0	Section B.3.5.5
	Neutropenia	£634.19	Section B.3.5.5
	Neutrophil count decreased	£199.55	Section B.3.5.5
	Platelet count decreased	£0.00	Section B.3.5.5
	Thrombocytopenia	£419.00	Section B.3.5.5
	Fatigue	£2,993.20	Section B.3.5.5
	White blood cell count decrease	£621.49	Section B.3.5.5
	Febrile Neutropenia	£7,385.81	Section B.3.5.5
AEs for nivolumab + ipilimumab	Anaemia	5.87%	Section B.3.4.4
	Lipase increased	6.15%	Section B.3.4.4
	Febrile neutropenia	0.00%	Section B.3.4.4
	Neutrophil count decreased	0.00%	Section B.3.4.4
	Thrombocytopenia	2.79%	Section B.3.4.4
	Platelet count decreased	0.00%	Section B.3.4.4
	White blood cell count decreased	0.00%	Section B.3.4.4
	Neutropenia	6.7%	Section B.3.4.4
	Fatigue	2.23%	Section B.3.4.4
AEs for PDC	Anaemia	14.3%	Section B.3.4.4
	Lipase increased	9.2%	Section B.3.4.4
	Febrile neutropenia	0.0%	Section B.3.4.4
	Neutrophil count decreased	0.0%	Section B.3.4.4

Area	Variable	Value	Reference to section in submission
	Thrombocytopenia	2.58%	Section B.3.4.4
	Platelet count decreased	0.0%	Section B.3.4.4
	White blood cell count decreased	0.0%	Section B.3.4.4
	Neutropenia	0.0%	Section B.3.4.4
	Fatigue	0.57%	Section B.3.4.4
AEs for Pembrolizumab monotherapy	Anaemia	0.89%	Section B.3.4.4
	Lipase increased	0.00%	Section B.3.4.4
	Febrile neutropenia	0.00%	Section B.3.4.4
	Neutrophil count decreased	0.00%	Section B.3.4.4
	Thrombocytopenia	0.13%	Section B.3.4.4
	Platelet count decreased	0.00%	Section B.3.4.4
	White blood cell count decreased	0.00%	Section B.3.4.4
	Neutropenia	0.13%	Section B.3.4.4
	Fatigue	0.63%	Section B.3.4.4
AEs for ATEZO + BEV +chemo	Anaemia	6.40%	Section B.3.4.4
	Lipase increased	0.00%	Section B.3.4.4
	Febrile neutropenia	8.40%	Section B.3.4.4
	Neutrophil count decreased	8.70%	Section B.3.4.4
	Thrombocytopenia	4.30%	Section B.3.4.4
	Platelet count decreased	5.10%	Section B.3.4.4
	White blood cell count decreased	3.30%	Section B.3.4.4
	Neutropenia	14.00%	Section B.3.4.4
	Fatigue	3.30%	Section B.3.4.4
Utilities	> 52 weeks	0.758 (0.009)	Section B.3.4.5
	27-52 weeks	0.730 (0.011)	Section B.3.4.5
	5-26 weeks	0.633 (0.010)	Section B.3.4.5
	≤ 4 weeks	0.409 (0.020)	Section B.3.4.5

Abbreviations: AE = adverse event; ALK = anaplastic lymphoma kinase; ATEZO = atezolizumab; BEV = bevacizumab; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; PD = progressed disease; PDC = platinum doublet chemotherapy; PF = progression free.

B.3.6.2 Assumptions

Table 70 presents a list of the main parameters and assumptions used in the economic analysis.

Table 70. Key assumptions in the economic model

Parameter	Base-case assumption	Justification
Comparator	PDC Pembrolizumab monotherapy Atezolizumab in combination with bevacizumab + chemotherapy	In line with the decision problem, based on UK clinical practice[6]
Time horizon	25 years	Lifetime equivalent consistent with NICE reference case[87]
Survival: OS	NIVO + IPI + limited PDC: Spline on normal link 2 knots using CM-9LA + CM-227 PDC: Log-logistic using CM-9LA + CM-227	Choice of extrapolation model was based on statistical goodness of fit, visual fit, clinical plausibility, and validation with real-word evidence
Survival: PFS	NIVO + IPI + limited PDC: Spline on odds 2 knots using CM-9LA + CM-227 PDC: Spline on normal link 2 knots using CM-9LA + CM-227	Choice of extrapolation model was based on statistical goodness of fit, visual fit, clinical plausibility, and validation with real-word evidence
Survival: DOT	KM data were used to model DOT for NIVO + IPI + limited PDC and PDC PFS used as a proxy for DOT for comparators not included in CM-9LA	KM data provides the most accurate reflection of DOT and is mature enough to use directly from CM-9LA. PFS used as proxy due to lack of access to DOT for comparators.
HRQOL	Based on EQ-5D data collected in CM-9LA. Utility values are allocated by time to death and pooled across treatment arms.	Consistent with NICE recommendations[87]
Safety	Grade ≥ 3 adverse events experienced by ≥ 5% of patients in CM-9LA are included in the analysis	Conservative approach given safety profile of nivolumab
Subsequent treatment	Treatment type is based on UK clinical practice, and duration of therapy is taken from previous NICE submission[3]	Applied as a one-off cost for all patients moving out of the progression-free health state to account for any treatment costs following first-line therapy

Abbreviations: CM = CheckMate; DOT = duration of treatment; HRQOL = health-related quality of life; IPI = ipilimumab; KM = Kaplan-Meier; NIVO = nivolumab; OS = overall survival; PDC = platinum doublet chemotherapy; PFS = progression-free survival; UK = United Kingdom.

B.3.7Base-case results

The results of the model are presented for nivolumab + ipilimumab + limited PDC versus PDC, pembrolizumab monotherapy, and atezolizumab + bevacizumab + carboplatin + paclitaxel.

B.3.7.1 Base-case incremental cost-effectiveness analysis results

Table 71 presents total costs, life-years gained (LYGs), QALYs, and incremental cost per QALY for nivolumab + ipilimumab + limited PDC versus PDC, pembrolizumab monotherapy, and atezolizumab + bevacizumab + carboplatin + paclitaxel.

Compared with PDC, nivolumab + ipilimumab generated [redacted] incremental QALYs and [redacted] incremental LYGs, and the nivolumab + ipilimumab + limited PDC–treated cohort had higher total lifetime costs. The ICER was £29,139 per QALY gained.

Compared with pembrolizumab monotherapy, nivolumab + ipilimumab was dominant, as it generated [redacted] incremental QALYs and [redacted] incremental LYGs, and had lower total lifetime costs.

Compared with atezolizumab + bevacizumab + carboplatin + paclitaxel, nivolumab + ipilimumab + limited PDC was dominant because it generated [redacted] incremental QALYs and [redacted] incremental LYGs and had lower total lifetime costs.

Table 71. Base-case results: PDC (all-comers) comparison

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Nivolumab + ipilimumab + limited PDC	[redacted]	[redacted]	[redacted]				
PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29,139

Abbreviations: ICER = incremental cost-effectiveness ratio; LYG = life-year gained; PDC = platinum doublet chemotherapy; QALY = quality-adjusted life-year.

Table 72. Base-case results: pembrolizumab monotherapy (PD-L1 ≥ 50%) comparison

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Nivolumab + ipilimumab + limited PDC	[redacted]	[redacted]	[redacted]				
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ICER = incremental cost-effectiveness ratio; LYG = life-year gained; PDC = platinum doublet chemotherapy; PD-L1 = programmed death-ligand 1; QALY = quality-adjusted life-year.

Table 73. Base-case results: atezolizumab +bevacizumab + carboplatin + paclitaxel (non-squamous histology and PD-L1 < 50%) comparison

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Nivolumab + ipilimumab + limited PDC	[redacted]	[redacted]	[redacted]				
Atezolizumab +bevacizumab + carboplatin + paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ICER = incremental cost-effectiveness ratio; LYG = life-year gained; PDC = platinum doublet chemotherapy; PD-L1 = programmed death-ligand 1; QALY = quality-adjusted life-year.

B.3.8Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

A second-order Monte-Carlo simulation was run for 1,000 iterations. A 10% standard error was assumed for all parameters when no data were available related to statistical uncertainty of the parameter.

B.3.8.1.1 Results of the probabilistic sensitivity analysis on the base-case model

The results of the probabilistic sensitivity analysis (PSA) are presented in Table 74, which also shows results from the deterministic analysis for comparisons.

Figure 73 presents the cost-effectiveness acceptability curve. The cost-effectiveness acceptability curve shows that nivolumab + ipilimumab + limited PDC has a 0%, 5%, and 69% probability of being cost-effective at a willingness-to-pay threshold of 20,000, 30,000, and 50,000 per QALY, respectively.

Figure 73. Cost-effectiveness acceptability curve versus PDC

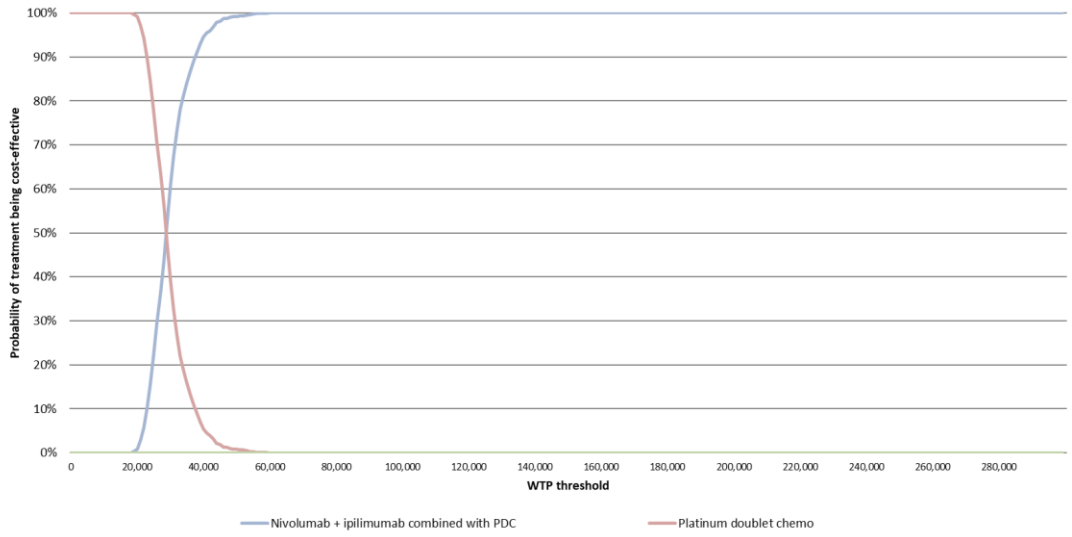
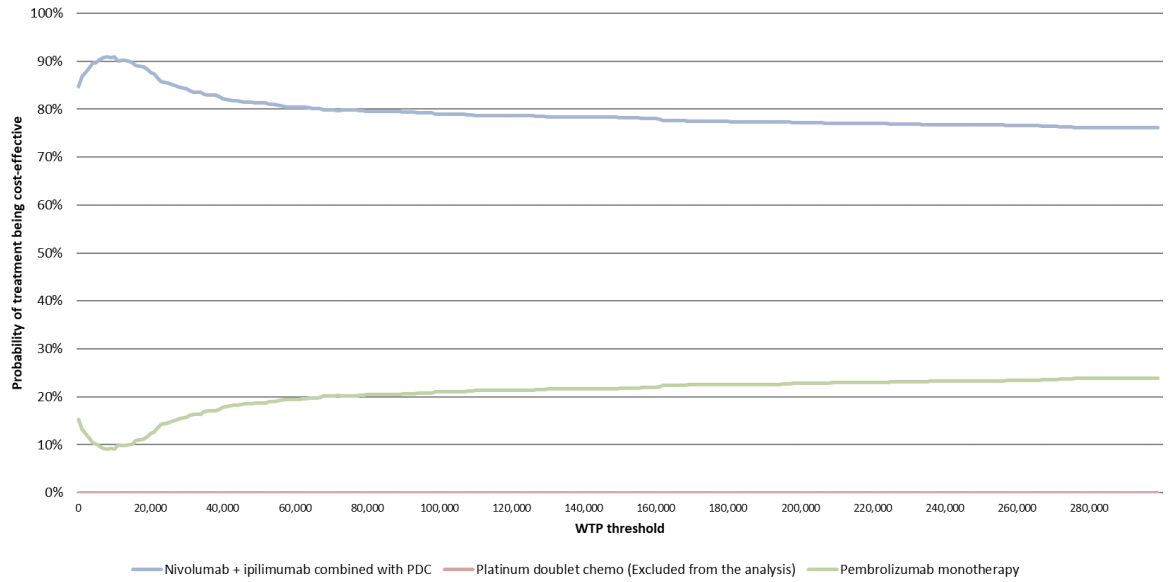
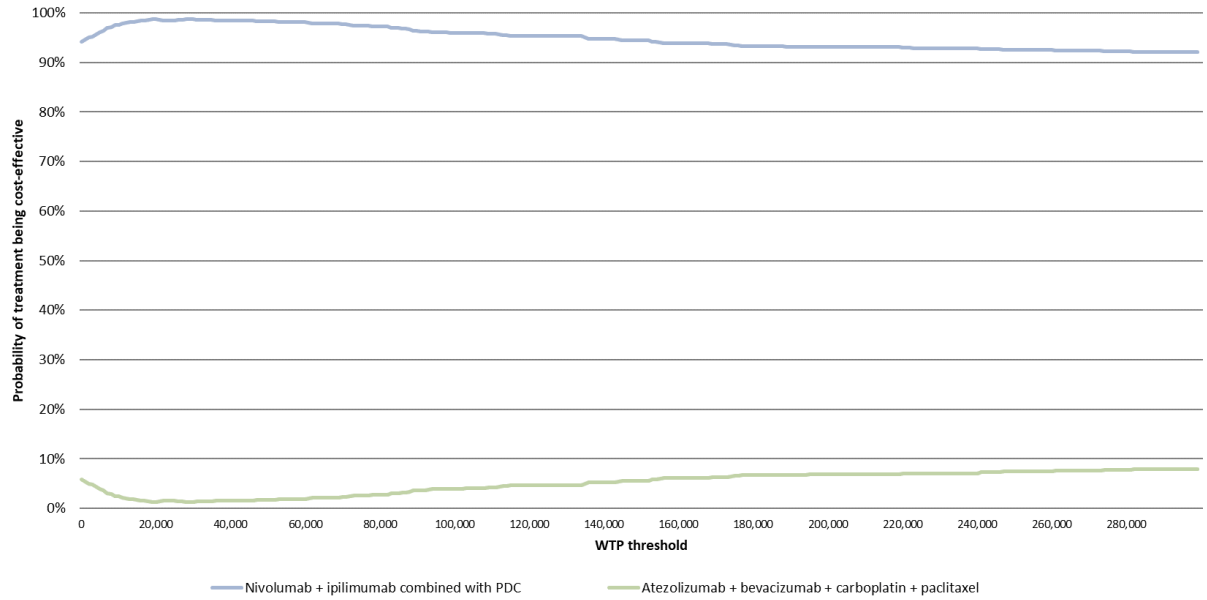


Figure 74. Cost-effectiveness acceptability curve versus pembrolizumab



Abbreviations: PDC = platinum doublet chemotherapy; WTP = willingness to pay.

Figure 75. Cost-effectiveness acceptability curve versus PDC and atezolizumab + bevacizumab + PDC



Abbreviations: PDC = platinum doublet chemotherapy; WTP = willingness to pay.

Figure 76 presents the cost-effectiveness plane, which shows that most of the 1,000 iterations ended up in the northeast quadrant. This means that nivolumab + ipilimumab + limited PDC resulted in more QALYs and higher costs compared with PDC alone.

Figure 76. Cost-effectiveness plane versus PDC

Abbreviations: ICER = incremental cost-effectiveness ratio; PDC = platinum doublet chemotherapy; QALY = quality-adjusted life-year.

Figure 77. Cost-effectiveness plane versus pembrolizumab

Abbreviations: ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Figure 78. Cost-effectiveness plane versus atezolizumab + bevacizumab + PDC

Abbreviations: ICER = incremental cost-effectiveness ratio; PDC = platinum doublet chemotherapy; QALY = quality-adjusted life-year.

Results of the PSA are shown in Table 74, which also shows results from the deterministic analysis for comparison. The probabilistic ICER versus PDC was £28,531 per QALY gained compared with £29,139 per QALY gained in the deterministic analysis. The uncertainty in the ICER appears to be driven by the variation in treatment efficacy, resource utilisation, body weight, and utility weights, given the high impact they have overall on the results of the model.

Table 74. Results of the probabilistic sensitivity analysis for PDC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Deterministic results					
PDC	[redacted]	[redacted]	[redacted]	[redacted]	29,139
Nivolumab + ipilimumab	[redacted]	[redacted]			
Probabilistic results					
PDC	[redacted]	[redacted]	[redacted]	[redacted]	28,531
Nivolumab + ipilimumab	[redacted]	[redacted]			

Abbreviations: ICER = incremental cost-effectiveness ratio; PDC = platinum doublet chemotherapy; QALY = quality-adjusted life-year.

Table 75. Results of the probabilistic sensitivity analysis for pembrolizumab monotherapy

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Deterministic results					
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Nivolumab + ipilimumab	[redacted]	[redacted]			
Probabilistic results					
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Nivolumab + ipilimumab	[redacted]	[redacted]			

Abbreviations: ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Table 76. Results of the probabilistic sensitivity analysis: atezolizumab + bevacizumab + PDC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Deterministic results					
Atezolizumab + bevacizumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Nivolumab + ipilimumab	[redacted]	[redacted]			
Probabilistic results					
Atezolizumab + bevacizumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Nivolumab + ipilimumab	[redacted]	[redacted]			

Abbreviations: ICER = incremental cost-effectiveness ratio; PDC = platinum doublet chemotherapy; QALY = quality-adjusted life-year.

B.3.8.2 Deterministic sensitivity analysis

Table 77 summarises the deterministic sensitivity analysis for nivolumab + ipilimumab versus PDC. In the deterministic sensitivity analysis important parameters were changed with ± 20% to study the impact on the ICER. Table 77 and Figure 79 show that, across most scenarios tested, the ICER for nivolumab + ipilimumab versus PDC did not change significantly.

Figure 79 shows that the ICER was most sensitive to the TTD > 52 weeks utility weight, discount rate on QALYs, and average body weight. All other variables had minimal impact on the ICER. The sensitivity analyses versus pembrolizumab monotherapy are presented in Table 78 and Figure 80 and those versus atezolizumab + bevacizumab + carboplatin + paclitaxel in Table 79 and Figure 81.

Table 77. Deterministic sensitivity analysis of nivolumab + ipilimumab + limited PDC versus PDC

Parameter	Base-case value	Analysis	Values for DSA	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Base-case analysis						
Average body weight, kg	72.32	Lower	57.86	[redacted]	[redacted]	29,517
		Higher	86.79	[redacted]	[redacted]	28,574
Costs						
Cost, PF state	139.85	Lower	111.88	[redacted]	[redacted]	28,786
		Higher	167.82	[redacted]	[redacted]	29,493
Cost, PD state	392.78	Lower	314.22	[redacted]	[redacted]	28,814
		Higher	471.33	[redacted]	[redacted]	29,465
Terminal cost	4,946.46	Lower	3,957.17	[redacted]	[redacted]	29,193
		Higher	5,935.75	[redacted]	[redacted]	29,085
Administration cost, nivolumab + ipilimumab	259.08	Lower	207.26	[redacted]	[redacted]	28,634
		Higher	310.90	[redacted]	[redacted]	29,644
Administration cost, PDC	82.40	Lower	65.92	[redacted]	[redacted]	29,179
		Higher	98.88	[redacted]	[redacted]	29,100
Outcomes						
Utility TTD (> 52 weeks)	0.758	Lower	0.740	[redacted]	[redacted]	30,294
		Higher	0.776	[redacted]	[redacted]	28,070
Utility TTD (27-52 weeks)	0.730	Lower	0.708	[redacted]	[redacted]	29,276
		Higher	0.752	[redacted]	[redacted]	29,004
Utility TTD (5-26 weeks)	0.633	Lower	0.613	[redacted]	[redacted]	29,277
		Higher	0.653	[redacted]	[redacted]	29,003
Utility TTD (≤ 4 weeks)	0.409	Lower	0.370	[redacted]	[redacted]	29,195
		Higher	0.448	[redacted]	[redacted]	29,084

Abbreviations: DSA = deterministic sensitivity analysis; PD = progressed disease; PDC = platinum doublet chemotherapy; PF = progression free; QALY = quality-adjusted life-year; TTD = time to death.

Table 78. Deterministic sensitivity analysis of nivolumab + ipilimumab + limited PDC versus pembrolizumab monotherapy

Parameter	Base-case value	Analysis	Values for DSA	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Base-case analysis						
Average body surface area	1.847	Lower	1.48	[redacted]	[redacted]	Dominant
		Higher	2.22	[redacted]	[redacted]	Dominant
Costs						
Cost, PF state	139.85	Lower	111.88	[redacted]	[redacted]	Dominant
		Higher	167.82	[redacted]	[redacted]	Dominant
Cost, PD state	392.78	Lower	314.22	[redacted]	[redacted]	Dominant

Parameter	Base-case value	Analysis	Values for DSA	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
		Higher	471.33	[redacted]	[redacted]	Dominant
Terminal cost	4,946.46	Lower	3,957.17	[redacted]	[redacted]	Dominant
		Higher	5,935.75	[redacted]	[redacted]	Dominant
Administration cost, nivolumab + ipilimumab	259.08	Lower	207.26	[redacted]	[redacted]	Dominant
		Higher	310.90	[redacted]	[redacted]	Dominant
Administration cost, pembrolizumab monotherapy	183.54	Lower	146.83	[redacted]	[redacted]	Dominant
		Higher	220.25	[redacted]	[redacted]	Dominant
Outcomes						
Utility TTD (< 52 weeks)	0.758	Lower	0.740	[redacted]	[redacted]	Dominant
		Higher	0.776	[redacted]	[redacted]	Dominant
Utility TTD (27-52 weeks)	0.730	Lower	0.708	[redacted]	[redacted]	Dominant
		Higher	0.752	[redacted]	[redacted]	Dominant
Utility TTD (5-26 weeks)	0.633	Lower	0.613	[redacted]	[redacted]	Dominant
		Higher	0.653	[redacted]	[redacted]	Dominant
Utility TTD (≤ 4 weeks)	0.409	Lower	0.370	[redacted]	[redacted]	Dominant
		Higher	0.448	[redacted]	[redacted]	Dominant

Abbreviations: DSA = deterministic sensitivity analysis; PD = progressed disease; PDC = platinum doublet chemotherapy; PF = progression free; QALY = quality-adjusted life-year; TTD = time to death.

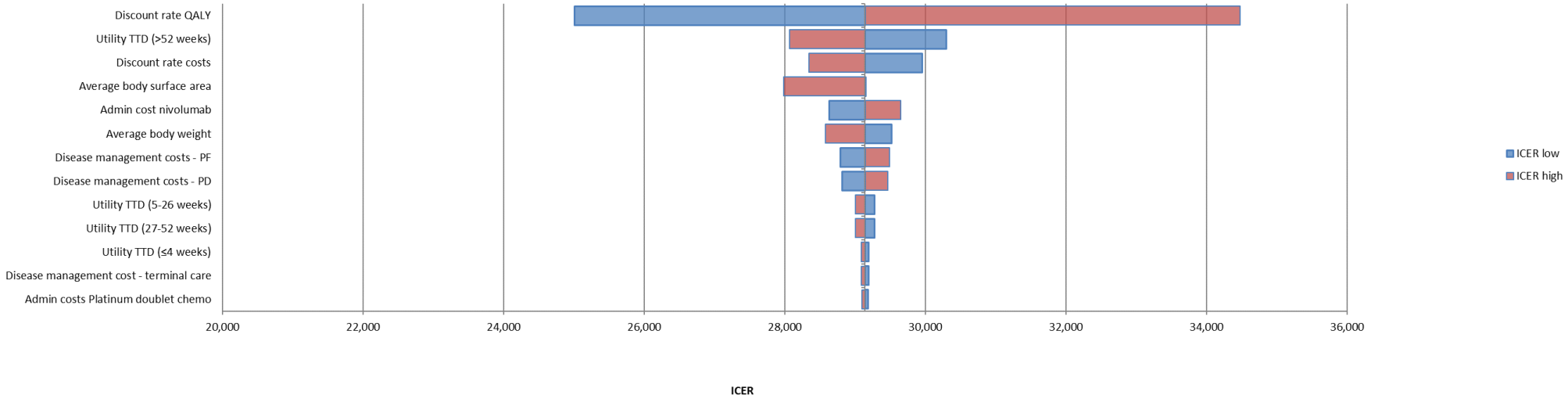
Table 79. Deterministic sensitivity analysis of nivolumab + ipilimumab + limited PDC versus atezolizumab + bevacizumab + carboplatin + paclitaxel

Parameter	Base-case value	Analysis	Values for DSA	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Base-case analysis						
Average body weight, kg	72.32	Lower	57.86	[redacted]	[redacted]	Dominant
		Higher	86.79	[redacted]	[redacted]	Dominant
Costs						
Cost, PF state	139.85	Lower	111.88	[redacted]	[redacted]	Dominant
		Higher	167.82	[redacted]	[redacted]	Dominant
Cost, PD state	392.78	Lower	314.22	[redacted]	[redacted]	Dominant
		Higher	471.33	[redacted]	[redacted]	Dominant
Terminal cost	4,946.46	Lower	3,957.17	[redacted]	[redacted]	Dominant
		Higher	5,935.75	[redacted]	[redacted]	Dominant
Administration cost, nivolumab + ipilimumab	259.08	Lower	207.26	[redacted]	[redacted]	Dominant
		Higher	310.90	[redacted]	[redacted]	Dominant
Outcomes						
Utility TTD	0.758	Lower	0.740	[redacted]	[redacted]	Dominant

Parameter	Base-case value	Analysis	Values for DSA	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
(< 52 weeks)		Higher	0.776	[redacted]	[redacted]	Dominant
Utility TTD (27-52 weeks)	0.730	Lower	0.708	[redacted]	[redacted]	Dominant
		Higher	0.752	[redacted]	[redacted]	Dominant
Utility TTD (5-26 weeks)	0.633	Lower	0.613	[redacted]	[redacted]	Dominant
		Higher	0.653	[redacted]	[redacted]	Dominant
Utility TTD (≤ 4 weeks)	0.409	Lower	0.370	[redacted]	[redacted]	Dominant
		Higher	0.448	[redacted]	[redacted]	Dominant

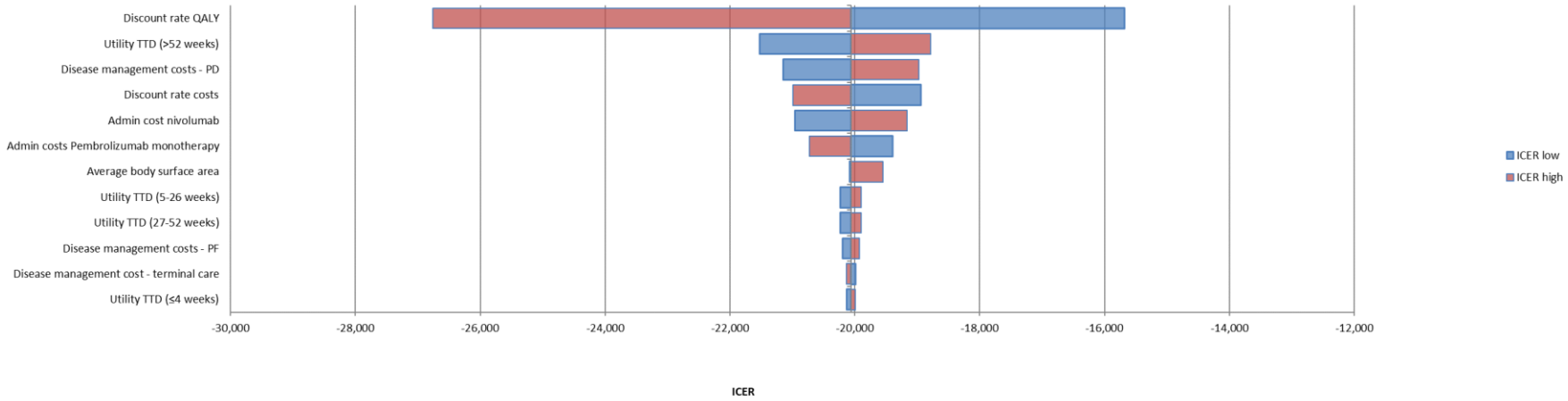
Abbreviations: DSA = deterministic sensitivity analysis; PD = progressed disease; PDC = platinum doublet chemotherapy; PF = progression free; QALY = quality-adjusted life-year; TTD = time to death.

Figure 79. Tornado diagram for the deterministic sensitivity analysis of nivolumab + ipilimumab versus PDC showing impact on the ICER



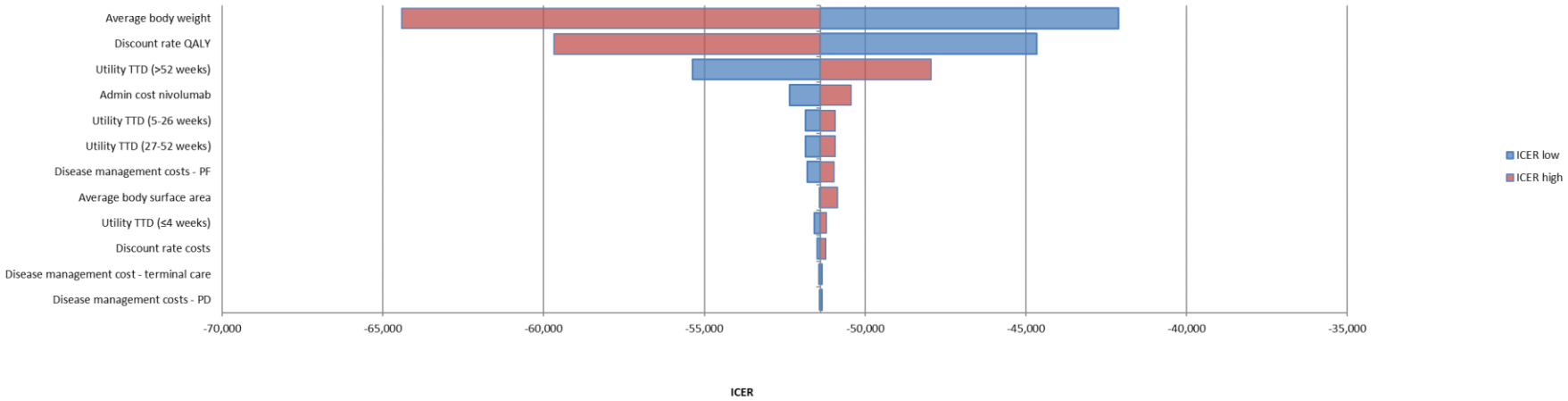
Abbreviations: Admin = administration; ICER = incremental cost-effectiveness ratio; PD = progressed disease; PDC = platinum doublet chemotherapy; PF = progression free; PFS = progression free survival; QALY = quality-adjusted life-year; TTD = time to death.

Figure 80. Tornado diagram for the deterministic sensitivity analysis of nivolumab + ipilimumab versus pembrolizumab monotherapy showing impact on the ICER



Abbreviations: Admin = administration; ICER = incremental cost-effectiveness ratio; PD = progressed disease; PF = progression free; PFS = progression free survival; QALY = quality-adjusted life-year; TTD = time to death.

Figure 81. Tornado diagram for the deterministic sensitivity analysis of nivolumab + ipilimumab versus atezolizumab + bevacizumab + carboplatin + paclitaxel showing impact on the ICER



Abbreviations: Admin = administration; ICER = incremental cost-effectiveness ratio; PD = progressed disease; PF = progression free; PFS = progression free survival; QALY = quality-adjusted life-year; TTD = time to death.

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B.3.8.3 Scenario analysis

Table 80 presents the scenario analyses undertaken to investigate the effect of certain model inputs on costs and outcomes. Different approaches to the modelling of OS were explored, first by altering the point at which the extrapolations based on CheckMate-227 begin following the CheckMate-9LA data. The use of CheckMate-9LA data was also considered in a scenario analysis.

Further, Table 80 shows that using a later cut-point to move to CheckMate-227 extrapolations led to a small increase in the ICER. The use of CheckMate-9LA data only to extrapolate OS led to a substantial increase in the ICERs for all comparisons.

Table 80. Scenario analyses: nivolumab + ipilimumab + limited PDC versus PDC

Scenario	Treatment	Base case	Parameter value in scenario	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
1	Base case			[redacted]	[redacted]	**29,139**
3	Switch to using CM-227 data for OS	13 months	18-months	[redacted]	[redacted]	31,903
4	Use CM-9LA data only for OS	CM-9LA and CM-227	CM-9LA: Log-logistic distribution for NIVO + IPI + limited PDC and PDC	[redacted]	[redacted]	47,643
5	Use CM-9LA data only for OS	CM-9LA and CM-227	CM-9LA: Spline on odds 1 knot distribution for NIVO + IPI + limited PDC and PDC	[redacted]	[redacted]	53,280
6	Use CM-9LA data only for PFS	CM-9LA and CM-227	CM-9LA: Spline on odds 2 knots distribution for NIVO + IPI + limited PDC and PDC	[redacted]	[redacted]	30,587
7	Utilities	Time-to-death approach, pooled	Progression-based utilities	[redacted]	[redacted]	32,150
8	Utilities	Time-to-death approach, pooled	Time-to-death approach, treatment-specific	[redacted]	[redacted]	30,133
9	DOT	TTD KM for CM-9LA comparators, PFS as proxy for others	PFS as proxy for all comparators: Spline on odds 2 knots distribution for NIVO + IPI + limited PDC and PDC PFS	[redacted]	[redacted]	33,344
10	Duration of treatment effect	Lifetime	3 years after end of IO therapy	[redacted]	[redacted]	35,149

Abbreviations: AIC = Akaike information criterion; DOT = duration of treatment; NICE = National Institute for Health and Care Excellence; OS = overall survival; PDC = platinum doublet chemotherapy; PFS = progression-free survival; QALY = quality-adjusted life-year; UK = United Kingdom.

Table 81. Scenario analyses: nivolumab + ipilimumab + limited PDC versus pembrolizumab monotherapy

Scenario	Treatment	Base case	Parameter value in scenario	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
1	Base case			[redacted]	[redacted]	**Dominant**
3	Switch to using CM-227 data for OS	13-months	18-months	[redacted]	[redacted]	Dominant
4	Use CM-9LA data only for OS	CM-9LA and CM-227	CM-9LA: Log-logistic distribution for NIVO + IPI + limited PDC and PDC	[redacted]	[redacted]	Dominant
5	Use CM-9LA data only for OS	CM-9LA and CM-227	CM-9LA: Spline on odds 1 knot distribution for NIVO + IPI + limited PDC and PDC	[redacted]	[redacted]	Dominant
6	Use CM-9LA data only for PFS	CM-9LA and CM-227	CM-9LA: Spline on odds 2 knots distribution for NIVO + IPI + limited PDC and PDC	[redacted]	[redacted]	Dominant
7	Utilities	Time-to-death approach, pooled	Progression-based utilities	[redacted]	[redacted]	Dominant
8	Utilities	Time-to-death approach, pooled	Time-to-death approach, treatment-specific	[redacted]	[redacted]	Dominant
9	DOT	TTD KM for CM-9LA comparators, PFS as proxy for others	PFS as proxy for all comparators: Spline on odds 2 knots distribution for NIVO + IPI + limited PDC and PDC PFS	[redacted]	[redacted]	Dominant
10	Duration of treatment effect	Lifetime	3 years after end of IO therapy	[redacted]	[redacted]	Dominant

Abbreviations: CM = CheckMate; DOT = duration of treatment; IO = immuno-oncology; IPI = ipilimumab; KM = Kaplan-Meier; NIVO = nivolumab; OS = overall survival; PDC = platinum doublet chemotherapy; PFS = progression-free survival; QALY = quality-adjusted life-year; TTD = time to death.

Table 82. Scenario analyses: nivolumab + ipilimumab + limited PDC versus atezolizumab + bevacizumab + carboplatin + paclitaxel

Scenario	Treatment	Base case	Parameter value in scenario	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
1	Base case			[redacted]	[redacted]	**Dominant**
3	Switch to using CM-227 data for OS	13-months	18-months	[redacted]	[redacted]	Dominant
4	Use CM-9LA data only for OS	CM-9LA and CM-227	CM-9LA: Log-logistic distribution for NIVO + IPI + limited PDC and PDC	[redacted]	[redacted]	Dominant
5	Use CM-9LA data only for OS	CM-9LA and CM-227	CM-9LA: Spline on odds 1 knot distribution for NIVO + IPI + limited PDC and PDC	[redacted]	[redacted]	Dominant
6	Use CM-9LA data only for PFS	CM-9LA and CM-227	CM-9LA: Spline on odds 2 knots distribution for NIVO + IPI + limited PDC and PDC	[redacted]	[redacted]	Dominant
7	Utilities	Time-to-death approach, pooled	Progression-based utilities	[redacted]	[redacted]	Dominant
8	Utilities	Time-to-death approach, pooled	Time-to-death approach, treatment-specific	[redacted]	[redacted]	Dominant
9	DOT	TTD KM for CM-9LA comparators, PFS as proxy for others	PFS as proxy for all comparators: Spline on odds 2 knots distribution for NIVO + IPI + limited PDC and PDC PFS	[redacted]	[redacted]	Dominant
10	Duration of treatment effect	Lifetime	3 years after end of IO therapy	[redacted]	[redacted]	Dominant

Abbreviations: CM = CheckMate; DOT = duration of treatment; IO = immuno-oncology; IPI = ipilimumab; KM = Kaplan-Meier; NIVO = nivolumab; OS = overall survival; PDC = platinum doublet chemotherapy; PFS = progression-free survival; QALY = quality-adjusted life-year; TTD = time to death.

B.3.8.4 Summary of sensitivity analyses results

As shown in Section B.3.8, the results of the sensitivity analyses are generally robust, but results are sensitive to some key parameters, including the selection of the most appropriate method of modelling OS.

B.3.9 Subgroup analysis

No subgroup analyses were performed.

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

B.3.10.1.1 Validating the model against clinical data

As discussed in Section B.3.3, model predictions using the base-case survival extrapolations were checked extensively against relevant external data sources to ensure that they are clinically plausible.

B.3.10.1.2 External expert validation

Throughout the development of the economic model and submission, clinical and economic expert advice was sought to ensure both clinical and economic validity.

A UK advisory workshop was held 21 July 2020 and attended by two UK health economists and one UK clinician, reflecting practice in the UK. The primary purpose of this workshop was to help validate the key inputs within the economic model and determine the base-case scenario for NICE.

The discussions during the advisory boards and subsequent interviews focused on the following:

- Model structure
- Comparator and subsequent treatments for NSCLC in the second-line setting
- Validation of resource use and costs included in the economic model
- Use of survival analysis models for OS
  - Clinical experts reviewed the survival curves for the best-fitting models for OS for nivolumab + ipilimumab + limited PDC and identified those that they considered to be clinically plausible as well as those that they considered were too optimistic or pessimistic.
  - The considerations of the experts were used as part of the validation process, described in Section B.3.3, to identify the most appropriate survival models to use in the economic model.

B.3.11 Interpretation and conclusions of economic evidence

This is the first economic evaluation undertaken for nivolumab + ipilimumab + limited PDC in a previously untreated NSCLC population; therefore, there are no published economic analyses with which to compare.

Generalisability of the results to clinical practice in England and relevance to all patients as identified in the decision problem

The analysis is likely to be directly applicable to clinical practice in England as follows:

- The patient population in CheckMate-9LA and CheckMate-227 and the economic analysis reflect patients with previously untreated NSCLC treated in the UK. Therefore, the clinical outcomes (PFS and OS) are likely to be applicable to the patient population in England.
- The economic model structure is in line with other oncology models and previous NSCLC submissions to NICE.[4,70,84]
- The resource use and costs in the analysis have been validated by UK clinicians and were sourced from UK-based publications (e.g., NHS Reference Costs and British National Formulary) and previous NICE technology appraisals.[4,70,84]

The economic evaluation is relevant to all adults with untreated stage IV or recurrent NSCLC, with no known EGFR mutations or ALK translocations, who would currently be considered for treatment with PDC, pembrolizumab monotherapy, or atezolizumab + bevacizumab + chemotherapy.

Strengths and weaknesses of the evaluation

The economic model is underpinned by patient-level data from CheckMate-227 and CheckMate-9LA, which included efficacy (including OS), treatment patterns, and quality of life of both nivolumab + ipilimumab + limited PDC and the key UK comparators. Because of shorter follow-up in the clinical trial than the model time horizon, survival extrapolation was essential to quantify the survival benefit beyond the study period. A robust and comprehensive approach was followed to ensure the survival extrapolation methods were statistically sound but also clinically plausible and reflective of real-world clinical practice. In terms of resource utilisation, all inputs were validated and aligned with previous NICE technology appraisals and identified from UK sources.

B.3.11.1 Further analyses that could be conducted

The cost-effectiveness analysis is based on early immature OS data from CheckMate-9LA and CheckMate-227. Therefore, longer-term OS data will be important to confirm the survival extrapolations included in the current economic analysis. BMS recognise this uncertainty in the extrapolation of long-term OS and therefore have proposed that this appraisal is a candidate for the CDF to allow for more data to be collected.

In the NICE technology appraisals of nivolumab for previously treated NSCLC (TA483 and TA484), there was uncertainty in the long-term OS extrapolation, and the company extrapolations were seen to be too optimistic at time of submission.[70,84] Therefore, the recommendation was to use nivolumab within the CDF to enable further evidence of long-term treatment effect to be collected. Since these appraisals, the pivotal trials CheckMate-017 and CheckMate-057 have reported (observed) 5-year OS data that are similar to the 5-year OS modelled by BMS (Table 83).[110] This gives BMS confidence in their ability to plausibly model long-term OS and thus establish the cost-effectiveness of nivolumab + ipilimumab in treating NSCLC.

Table 83. Comparison of long-term trial data versus modelled survival for previously treated NSCLC

	Proportion alive at each year						
Data source	**1**	**2**	**3**	**4**	**5**	**10**	**15**
Squamous							
CheckMate-017	42.2%	23.0%	15.6%	[redacted]	[redacted]		
BMS model estimates for nivolumab OS in TA483	42.34%	23.53%	16.08%	12.17%	9.77%	4.90%	3.26%
Non-squamous							
CheckMate-057	50.7%	28.7%	17.7%	[redacted]	[redacted]		
BMS model estimates for nivolumab OS in TA484	46.78%	27.78%	18.75%	13.61%	10.35%	3.83%	1.93%

Abbreviations: BMS = Bristol Myers Squibb; NSCLC = non-small cell lung cancer; OS = overall survival.
Sources: Bristol Myers Squibb data on file (2019)[110]; NICE (2017)[70]; NICE (2017)[84]

As previously noted, BMS plan to use data from I-O Optimise, a pan-European evidence platform that brings together real-word data sources under independent scientific guidance. Data collection is ongoing with continuous enrolment of new cohorts to capture changes over time. This includes collection of UK registry data. Further, entry into the CDF will allow for further data to be presented from both CheckMate-227 and CheckMate-9LA to validate current extrapolations.

B.3.11.2 Concluding the economic analyses

In CheckMate-9LA, nivolumab + ipilimumab + limited PDC showed improved OS versus PDC in patients with systemic therapy–naive metastatic NSCLC, regardless of histology and PD-L1 expression (HR, 0.66; 95% CI, 0.55-0.80).

In the cost-effectiveness model, the improved survival for patients treated with nivolumab + ipilimumab + limited PDC resulted in an increase of [redacted] QALYs versus PDC when modelled over 25 years. [redacted], this resulted in an ICER of £29,139 per QALY. Compared with pembrolizumab monotherapy, the intervention generated [redacted] incremental QALYs and compared with atezolizumab + bevacizumab + carboplatin + paclitaxel, the intervention generated [redacted] incremental QALYs. In comparisons with pembrolizumab monotherapy and atezolizumab + bevacizumab + carboplatin + paclitaxel, total lifetime costs of the nivolumab + ipilimumab + limited PDC–treated cohort was lower. Thus nivolumab + ipilimumab + limited PDC was dominant compared with both comparators. The direct generalisability of these results is limited due to treatments in both the pembrolizumab and atezolizumab regimens having confidential discounts that we could not account for in the current analyses. However, even when these discounts are applied it is believed that nivolumab + ipilimumab + limited PDC offers an innovative, clinically effective, and plausibly cost-effective treatment option in the first-line NSCLC setting, building on the value of nivolumab in the pretreated metastatic NSCLC setting.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Clarification questions

4 December 2020

File name	Version	Contains confidential information	Date
ID1566 nivolumab clarification letter responses 4 Dec 20 [redacted]	2	No	4 December 2020

Section A: Clarification on effectiveness data

Nivolumab clinical effectiveness

A1. PRIORITY Please confirm how many UK patients were in each treatment arm of the CheckMate-9LA and CheckMate-227.

The number of patients in both trials and those from the UK are presented in Table 1. For CheckMate-227 only the nivolumab + ipilimumab and platinum doublet chemotherapy (PDC) arms are included, additional UK patients were randomised to nivolumab monotherapy and nivolumab + chemotherapy, which are not relevant to this appraisal.

Table 1. Number of patients in CheckMate-9LA and CheckMate-227

Study	Nivolumab + ipilimumab (± PDC) arm (n)	PDC arm (n)	Total[a] (n)
CheckMate-9LA total	361	358	719
CheckMate-9LA UK	[redacted]	[redacted]	[redacted]
CheckMate-9LA Europe	[redacted]	[redacted]	[redacted]
CheckMate-227 Part 1 total	583	583	1,166
CheckMate-227 Part 1 UK	[redacted]	[redacted]	[redacted]
CheckMate-227 Part 1 Europe	[redacted]	[redacted]	[redacted]

[a] Total in arms relevant to the decision problem, in total across all arms [redacted] UK patients were included in part 1

Sources: Bristol Myers Squibb (2020); Bristol Myers Squibb (2019)

A2. Using all the information available (e.g., from study protocols etc.), please clarify the domains labelled as 'not clear' in tables 14, 15 and 16.

Risk of bias was previously completed based on publications. Tables 14, 15, and 16 have been updated also using the protocols.

Table 14 in the Company Submission. Quality assessment of CheckMate-9LA

Was randomisation carried out appropriately?	Yes; randomisation was by an interactive web response system which grouped by PD-L1 status and randomised in a 1:1 ratio, stratified by histology, gender and PD-L1 level
Was the concealment of treatment allocation adequate?	No; open-label
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes; baseline characteristics of all randomly assigned patients were similar and balanced between treatment groups
Were the care providers, participants, and outcome assessors blind to treatment allocation?	No; open-label

Were there any unexpected imbalances in dropouts between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes
How closely does the RCT(s) reflect routine clinical practice?	Not clear; PDC is standard of care in England, but there are some differences in regimen vs. those in the trial

Abbreviations: PD-L1 = programmed death-ligand 1; PDC = platinum doublet chemotherapy; RCT = randomised controlled trial.

Table 15 in the Company Submission. Quality assessment of CheckMate-227 (part 1)

Was randomisation carried out appropriately?	Yes; randomisation was by an interactive voice response system which grouped by PD-L1 status and randomised in a 1:1:1 ratio, stratified by histology and gender
Was the concealment of treatment allocation adequate?	No; open-label
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes; baseline characteristics of all randomly assigned patients were similar and balanced between treatment groups
Were the care providers, participants, and outcome assessors blind to treatment allocation?	No; open-label
Were there any unexpected imbalances in dropouts between groups?	No; consort
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Modified intention to treat; not clear
How closely does the RCT(s) reflect routine clinical practice?	Not clear; PDC is standard of care in England, but there are some differences in regimen vs. those in the trial

Abbreviations: PD-L1 = programmed death-ligand 1; PDC = platinum doublet chemotherapy; RCT = randomised controlled trial.

Table 16 in the Company Submission. Quality assessment of CheckMate-568

Did the study address a clearly focused issue?	Yes
Did the authors use an appropriate method to answer their question?	Yes
Was the cohort recruited in an acceptable way?	Yes
Was the exposure accurately measured to minimise bias?	Yes
Was the outcome accurately measured to minimise bias?	Yes

Have the authors identified all important confounding factors?	Yes, all known confounding factors addressed
Have they taken account of the confounding factors in the design and/or analysis?	Yes, study inclusion and exclusion criteria helped to reduce confounding and stratification and subgroup analyses accounted for others (e.g., histology, PD-L1 expression, gender)
Was the follow-up of subjects complete enough?	Yes
Was the follow-up of subjects long enough?	Yes
What are the results of this study?	See Sections in Document B
How precise are the results?	Appropriate
Do you believe the results?	Yes
Can the results be applied to the local population?	Yes
Do the results of this study fit with other available evidence?	Yes
Did the authors of the study publication declare any conflicts of interest?	Not reported
Does the trial reflect routine clinical practice in England?	Yes

Abbreviations: PD-L1 = programmed death-ligand 1.

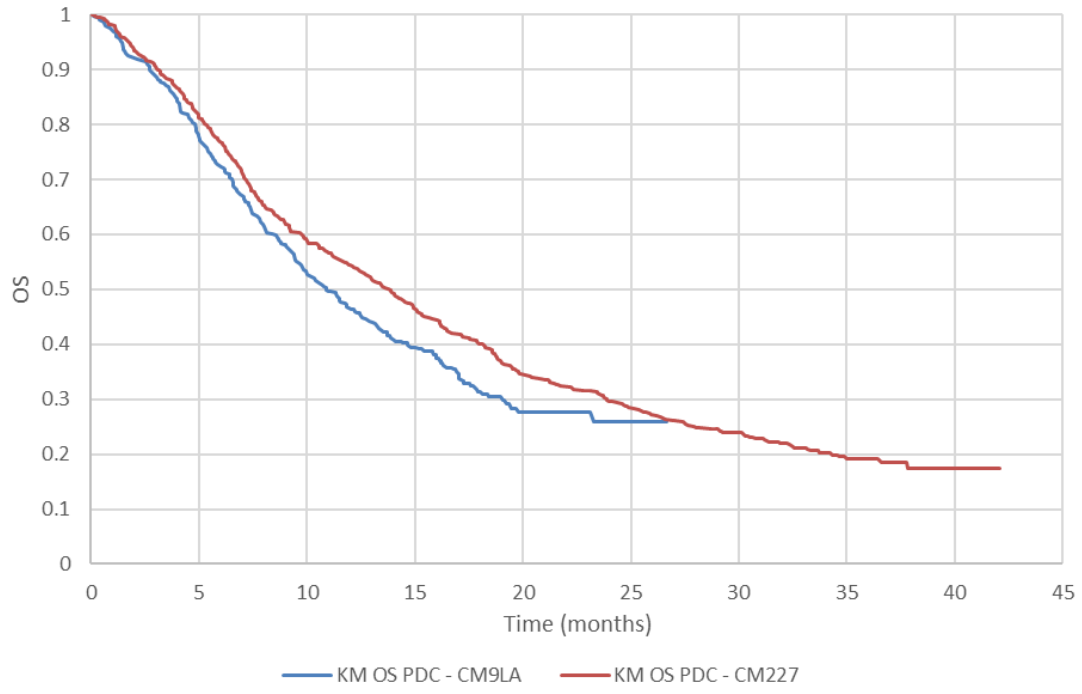
A3. The survival curves in figure 18 (company submission) report a longer median overall survival (OS) for the platinum doublet chemotherapy (PDC) arm in the CM-227 trial (OS: 13.9, 95% confidence interval [CI]: 12.2-15.1) than the PDC arm in the CM-9LA trial (Figure 11, OS: 10.7; 95% CI, 9.5-12.4). This is also seen in figure 48. Please comment on this and provide a rationale which may explain the difference and clarify which estimate is most appropriate.

Both CheckMate-9LA (CM-9LA) and CheckMate-227 (CM-227) Part 1 were conducted in similar first-line NSCLC populations with histology-based PDC as a control and OS as the primary endpoint. BMS acknowledges that there was variability in performance across studies, including the PDC arms (median OS in the chemotherapy arm was 10.74 months in CM-9LA, 13.9 months in CM-227. While median OS in the chemotherapy arm was lower in CM-9LA than in CM-227, in CM-9LA it was within the range that has recently been reported in other phase 3 first-line NSCLC studies, which had similar patient populations (e.g., median OS, 10.7-11.3 months in KeyNote-189 and 11.3-11.6 months in KeyNote-407), and we therefore consider this the most appropriate OS estimate to use.

The proportion of subjects receiving subsequent immunotherapy in the chemotherapy arm was numerically lower in CM-9LA than CM-227 with 27.9% vs. 40.8%, respectively. However, these differences may be a function of shorter

minimum follow-up in CM-9LA (8.1 months) versus CM-227 (29.3 months). It appears unlikely that subsequent immunotherapy would be the sole driver for the differences in performance in the PDC arms, given the initial shape of the chemotherapy OS Kaplan-Meier curves—as shown in Figure 48, the chemotherapy curve in CM-9LA is lower than the chemotherapy curves in CM-227 soon after randomisation).

Figure 48 in the Company Submission. Comparison of overall survival for the PDC control group in CheckMate-227 part 1 versus CheckMate-9LA



Abbreviations: CM = CheckMate; IO = immuno-oncology; KM = Kaplan-Meier; PDC = platinum doublet chemotherapy; OS = overall survival.

A4. Section B.2.7.2 states that the proportional hazard assumption was not met. Please analyse CheckMate-9LA and CheckMate-227 trial data to provide estimates of OS and progression free survival (PFS) using an alternative model, which does not require the proportional hazards assumption to be met.

Section B.2.7.2 of the dossier relates to CheckMate-227 only. In CheckMate-227, the stratified log-rank test, not the Cox model, was the primary statistical test used to determine statistical significance of the survival curves. The stratified log-rank test is not dependent upon the assumption of proportional hazards; so, it is valid to determine that the nivolumab + ipilimumab and chemotherapy groups are statistically different in Figure 26 of Document B.

In addition, the hazard ratio (HR) represents the hazard reduction over the entire course of the study, and thus can be viewed as an overall estimate of the benefit. However, while the overall HR represents the entire curve and represents a conventional and useful summary average of the overall benefit of treatment, BMS agrees that it may not provide all of the information needed to inform clinical decisions. Kaplan-Meier curves, and additional non-parametric data points (e.g., medians and landmark OS rates) are necessary to capture the comparison appropriately since they are not dependent upon proportionality assumption.

In their totality, the OS data show not just a statistically significant, but also clinically meaningful, durable benefit.

A5. Figure 3 in Section B.1.2 illustrated patients' varying pattern of response to immune-oncology therapies. From the 9 March 2020 database lock, please provide data on the proportion of patients who had:

a) a conventional response,

b) a slow steady decline in tumour burden,

c) a late response after initial progression,

d) new lesions appear and then decline along with target lesion.

Figure 3 in the company submission was included as a graphical representation of types of response seen in patients treated with immunotherapy drugs and does not provide full definitions or classification. Therefore, CM-9LA was not designed to answer this question and there are several issues with providing such an analysis:

- Responders with a late response or new lesions at 12 weeks followed by a response were not traced in 9LA, as IO treatment would be terminated at the time of initial progression per protocol.
- Although some patients might have received treatment beyond progression, additional response data was not systematically collected in either CM-9LA or CM-227.
- These subgroups of response are at concept level, without predefined classification in protocol.

Therefore any ad hoc analysis would be subjective and inappropriate.

Histology and PD-L1 sub-populations

A6. PRIORITY The ERG considers there to be four sub-populations based on tumour histology and PD-L1 expression, resulting in different treatment options available in the treatment pathway and listed in the scope. Please provide results for each of the four sub-populations in Table 1 for both the CheckMate-9LA and CheckMate-227 trials, including:

a) ***median estimates for OS, PFS, overall response rate (ORR) and treatment duration for each treatment arm.***

b) ***hazard ratios (HRs) for OS, PFS, ORR and treatment duration.***

c) ***Kaplan-Meier data and plots for OS, PFS and duration of response including the events, number at risk and number censored at each time-point.***

Table 1 – Treatment options for first line NSCLC (adapted from Figure 6, CS, pg. 22)

Decision/population	**1**	**2**	**3**	**4**
Histology	Non-squamous		Squamous	
PD-L1 expression	1.a) < 1, 1.b) 1%-49%	≥ 50%	3.a) < 1, 3.b) 1%-49%	≥ 50%
Interventions in decision	Nivolumab + Ipilimumab + limited PDC	Nivolumab + Ipilimumab + limited PDC	Nivolumab + Ipilimumab + limited PDC	Nivolumab + Ipilimumab + limited PDC
	Pemetrexed in combination with cisplatin*	Pemetrexed in combination with cisplatin*	Platinum combination chemotherapy (i.e., cisplatin or carboplatin, and either gemcitabine or vinorelbine)	Platinum combination chemotherapy (i.e., cisplatin or carboplatin, and either gemcitabine or vinorelbine)
	Atezolizumab + bevacizumab + carboplatin + paclitaxel	Pembrolizumab monotherapy		Pembrolizumab monotherapy

*Note, for non-squamous NSCLC that has not progressed immediately after initial therapy with a NICE-recommended platinum-based chemotherapy regimen, maintenance treatment with pemetrexed is recommended as an option

The efficacy results described in parts a and b (OS, PFS, treatment duration and ORR) for the requested subgroups for CheckMate-9LA are presented in Table 2 and

for CheckMate-227 in Table 3. In addition, data for populations relevant to current approved NICE treatment options have been provided: the mixed histology subgroups and PD-L1 < 50% subgroups (including mixed histology PD-L1 ≥ 50% to allow comparison with pembrolizumab monotherapy and squamous < 50% PD-L1 to allow comparison with atezolizumab). The Kaplan-Meier plots (part c of the request) for the same subgroups are provided below in Figure 1 to Figure 24 for CheckMate-9LA and in Figure 25 to Figure 48 for CheckMate-227.

It is important to note that subgroup analyses may be impacted by the non-stratified nature of the comparison, and small patient numbers leading to loss of statistical power and higher uncertainty in point estimates (larger confidence intervals). In addition, performing multiple exploratory subgroup analyses (including using PD-L1 levels which are not established for PD-1 + CTLA-4 inhibition) there is an increased risk of inconsistent and potentially accidental findings. Therefore, the outcome for the predefined endpoint, in a large, randomised and stratified studies, constitutes the most accurate, robust and reliable estimate of benefit for the overall population.

A number of clinical trials in lung cancer (such as: CheckMate-9LA, CheckMate-227, and MYSTIC) investigating the PD-(L)1 + CTLA-4 combination support the lack of utility of PD-L1 expression for predicting survival benefit. A key driver is the mechanism of action of CTLA-4 inhibition, which is independent of PD-L1 expression. As can be observed by the results presented below, CheckMate-9LA shows a consistent OS benefit regardless of PD-L1 expression with nivolumab + ipilimumab + limited PDC (2 cycles) over chemotherapy (4 cycles) ± pemetrexed in first-line metastatic or recurrent NSCLC.

The CheckMate-227 data suggest no consistent correlation of PD-L1 expression levels and the benefit of nivolumab + ipilimumab relative to PDC, as shown in Table 3. The performance of the nivolumab + ipilimumab arm was similar between part 1a and 1b.

In pre-specified descriptive analyses in CheckMate-227, patients with no PD-L1 expression had a median OS of 17.2 months, 1-year OS rate of 60% and a 2-year OS rate of 40%. Those with PD-L1 expression (≥ 1%) had a median OS of 17.1 months, 1-year OS rate of 63% and a 2-year OS rate of 40%. Of note, subgrouping

of patients within PD-L1 ≥ 1% (part 1a) is discouraged as it is caveated by lack of stratification and potential imbalances in unknown factors may have influenced the results. Similarly, previous reports in melanoma and renal cell carcinoma also showed that the benefit of NIVO + IPI was irrespective of PD-L1 level (Larkin et al., 2019; Motzer et al., 2018).

Using these subgroup data as part of unadjusted cross-study comparisons is not appropriate, since all results are influenced by the demographic and baseline characteristics maturity of follow-up, and performance of comparator arms.

Given the uncertainty in relation to exploratory results in non-stratified subgroups, small patient numbers and the overall lack of a consistent trend across the entire spectrum of PD-L1 expression (with similar magnitude of OS benefit in the PD-L1 < 1% and PD-L1 ≥ 50% subgroups), these data should be interpreted with caution. The robust results for the primary endpoint OS, obtained from a large, randomised study and supported by results across all efficacy endpoints, are likely the best estimate for benefit in the ITT population.

Table 2. CheckMate-9LA subgroup data

Histology	Non-squamous				Squamous				All			
PD-L1	**< 1%**	**1%-49%**	**< 50%**	**≥ 50%**	**< 1%**	**1%-49%**	**< 50%**	**≥ 50%**	**< 1%**	**1%-49%**	**< 50%**	**≥ 50%**
N												
N+I+PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS												
Median N+I+PDC (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median PDC (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS												
Median N+I+PDC (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median PDC (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ORR												
N+I+PDC Best ORR n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PDC Best ORR n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment duration												

Histology	Non-squamous				Squamous				All			
PD-L1	**< 1%**	**1%-49%**	**< 50%**	**≥ 50%**	**< 1%**	**1%-49%**	**< 50%**	**≥ 50%**	**< 1%**	**1%-49%**	**< 50%**	**≥ 50%**
N+I+PDC (n)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PDC (n)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median N+I+PDC (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median PDC (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 3. CheckMate-227 subgroup data

Histology	**Non-squamous**				**Squamous**				**All**			
PD-L1	**< 1%**	**1%-49%**	**< 50%**	**≥ 50%**	**< 1%**	**1%-49%**	**< 50%**	**≥ 50%**	**< 1%**	**1%-49%**	**< 50%**	**≥ 50%**
N												
N+I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS												
Median N+I (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median PDC (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS												
Median N+I (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median PDC (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ORR												
N+I Best ORR n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PDC Best ORR n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment duration												
N+I (n)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Histology	Non-squamous				Squamous				All			
PD-L1	**< 1%**	**1%-49%**	**< 50%**	**≥ 50%**	**< 1%**	**1%-49%**	**< 50%**	**≥ 50%**	**< 1%**	**1%-49%**	**< 50%**	**≥ 50%**
PDC (n)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median N+I (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median PDC (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 1. CheckMate-9LA, overall survival Kaplan-Meier plot, non-squamous and PD-L1 < 1%

Figure 2. CheckMate-9LA, overall survival Kaplan-Meier plot, non-squamous and PD-L1 1%-49%

Figure 3. CheckMate-9LA, overall survival Kaplan-Meier plot, non-squamous and PD-L1 < 50%

Figure 4. CheckMate-9LA, overall survival Kaplan-Meier plot, non-squamous and PD-L1 ≥ 50%

Figure 5. CheckMate-9LA, overall survival Kaplan-Meier plot, squamous and PD-L1 < 1%

Figure 6. CheckMate-9LA, overall survival Kaplan-Meier plot, squamous and PD-L1 1%-49%

Figure 7. CheckMate-9LA, overall survival Kaplan-Meier plot, squamous and PD-L1 < 50%

Figure 8. CheckMate-9LA, overall survival Kaplan-Meier plot, squamous and PD-L1 ≥ 50%

Figure 9. CheckMate-9LA, PFS Kaplan-Meier plot, non-squamous and PD-L1 < 1%

Figure 10. CheckMate-9LA, PFS Kaplan-Meier Plot, non-squamous and PD-L1 1%-49%

Figure 11. CheckMate-9LA, PFS Kaplan-Meier plot, non-squamous and PD-L1 < 50%

Figure 12. CheckMate-9LA, PFS Kaplan-Meier plot, non-squamous and PD-L1 ≥ 50%

Figure 13. CheckMate-9LA, PFS Kaplan-Meier plot, squamous and PD-L1 < 1%

Figure 14. CheckMate-9LA, PFS Kaplan-Meier plot, squamous and PD-L1 1%-49%

Figure 15. CheckMate-9LA, PFS Kaplan-Meier plot, squamous and PD-L1 < 50%

Figure 16. CheckMate-9LA, PFS Kaplan-Meier plot, squamous and PD-L1 ≥ 50%

Figure 17. CheckMate-9LA, DoR Kaplan-Meier plot, non-squamous and PD-L1 < 1%

Figure 18. CheckMate-9LA, DoR Kaplan-Meier plot, non-squamous and PD-L1 1%-49%

Figure 19. CheckMate-9LA, DoR Kaplan-Meier plot, non-squamous and PD-L1 < 50%

Figure 20. CheckMate-9LA, DoR Kaplan-Meier plot, non-squamous and PD-L1 ≥ 50%

Figure 21. CheckMate-9LA, DoR Kaplan-Meier plot, squamous and PD-L1 < 1%

Figure 22. CheckMate-9LA, DoR Kaplan-Meier plot, squamous and PD-L1 1%-49%

Figure 23. CheckMate-9LA, DoR Kaplan-Meier plot, squamous and PD-L1 < 50%

Figure 24. CheckMate-9LA, DoR Kaplan-Meier plot, squamous and PD-L1 ≥ 50%

Figure 25. CheckMate-227, overall survival Kaplan-Meier plot, non-squamous and PD-L1 < 1%

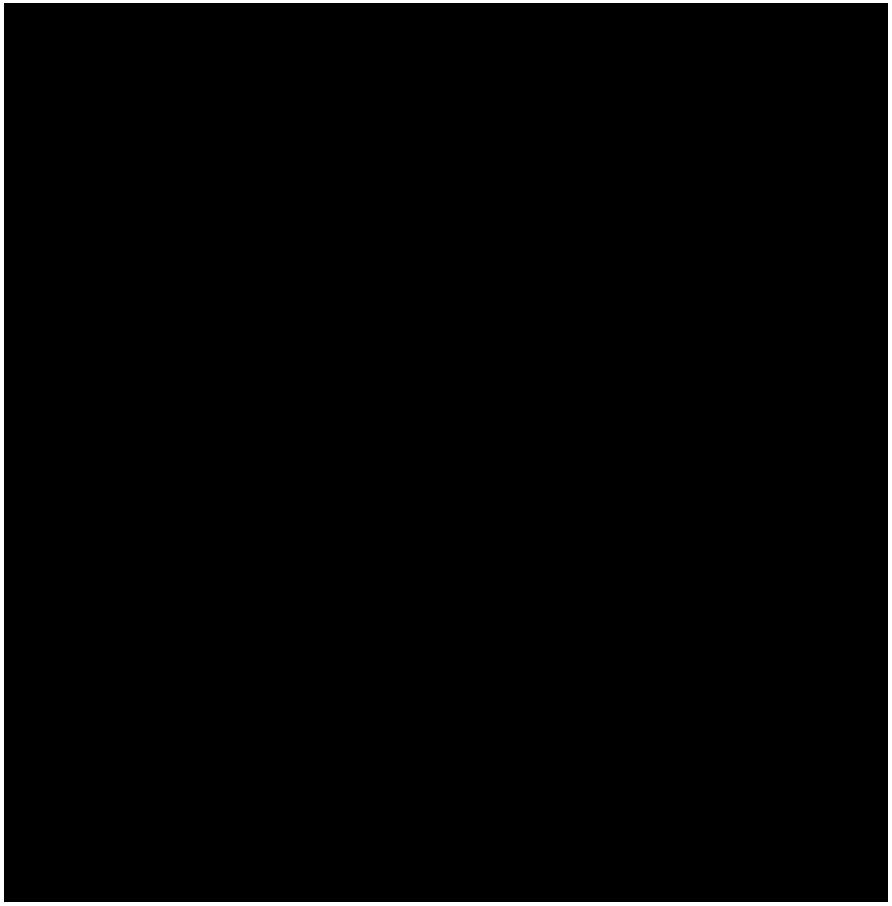


Figure 26. CheckMate-227, overall survival Kaplan-Meier plot, non-squamous and PD-L1 1%-49%

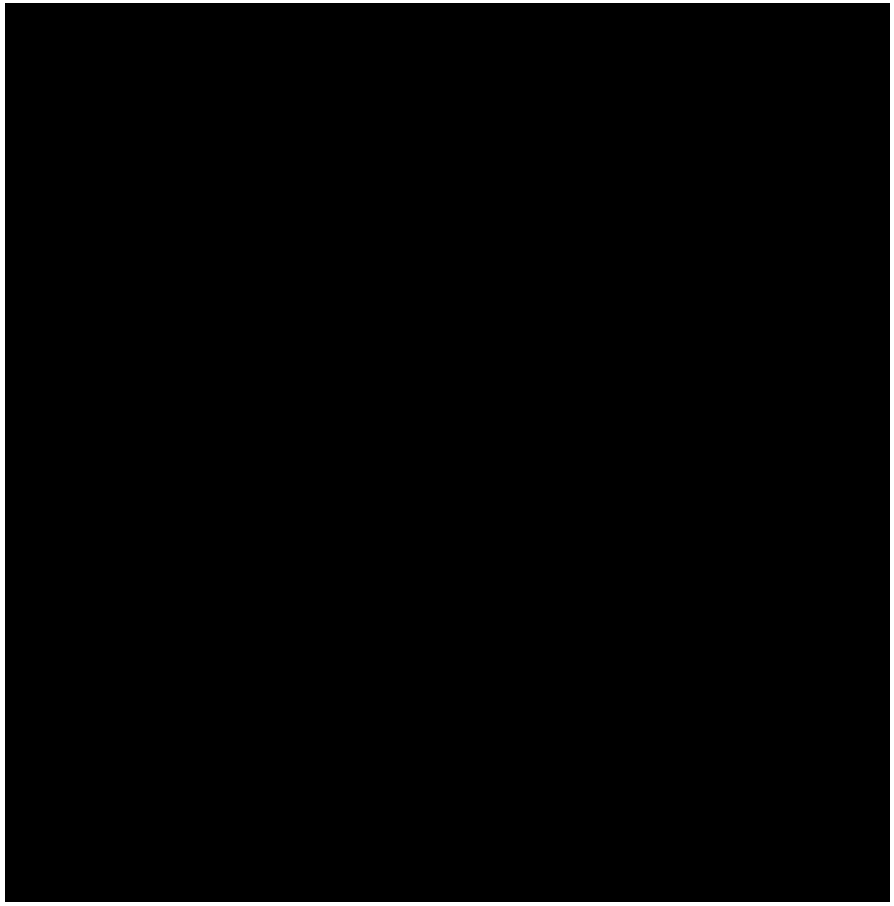


Figure 27. CheckMate-227, overall survival Kaplan-Meier plot, non-squamous and PD-L1 < 50%

Figure 28. CheckMate-227, overall survival Kaplan-Meier plot, non-squamous and PD-L1 ≥ 50%

Figure 29. CheckMate-227, overall survival Kaplan-Meier plot, squamous and PD-L1 < 1%

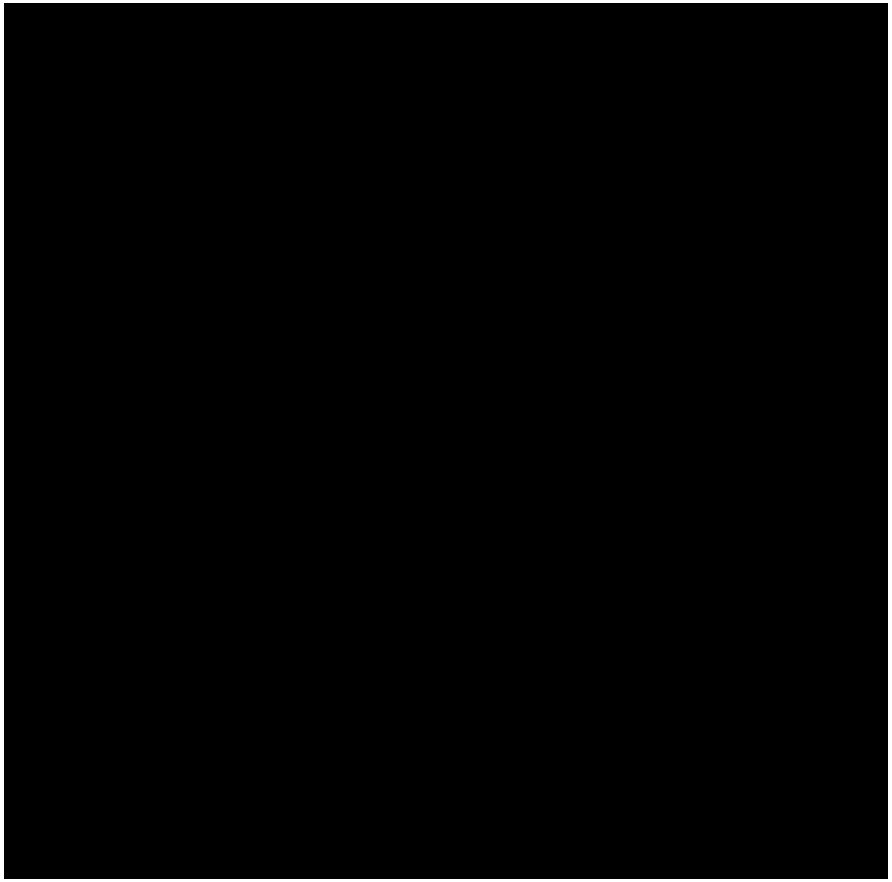


Figure 30. CheckMate-227, overall survival Kaplan-Meier plot, squamous and PD-L1 1%-49%

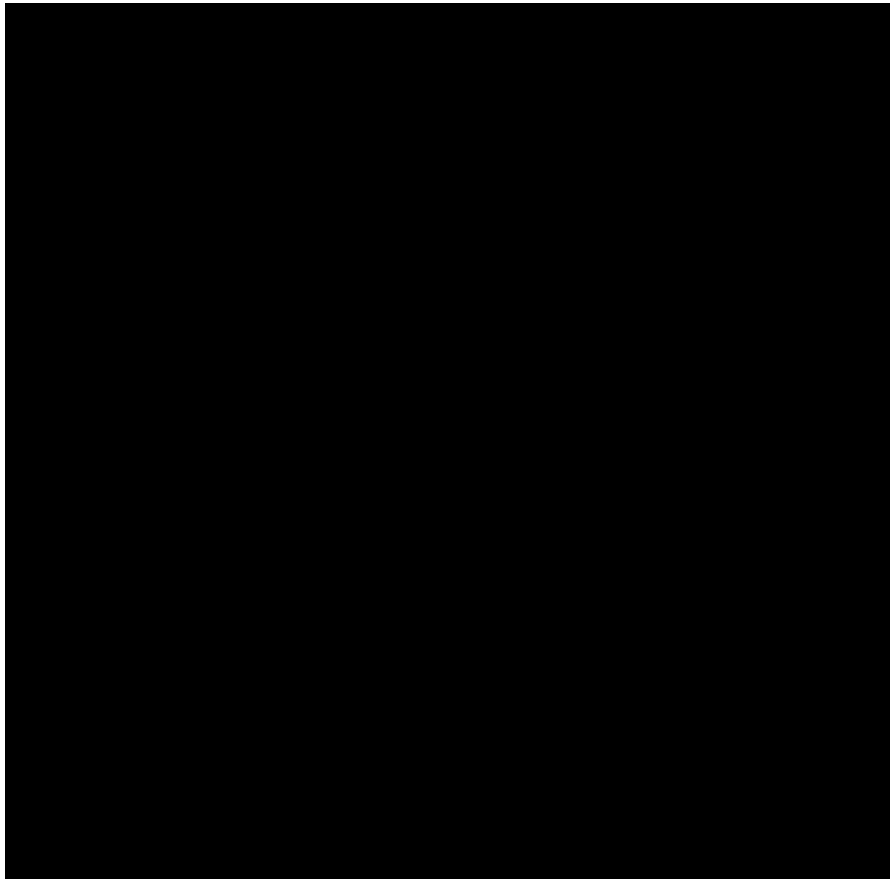


Figure 31. CheckMate-227, overall survival Kaplan-Meier plot, squamous and PD-L1 < 50%

Figure 32. CheckMate-227, overall survival Kaplan-Meier plot, squamous and PD-L1 ≥ 50%

Figure 33. CheckMate-227, PFS Kaplan-Meier plot, non-squamous and PD-L1 < 1%

Figure 34. CheckMate-227, PFS Kaplan-Meier plot, non-squamous and PD-L1 1%-49%

Figure 35. CheckMate-227, PFS Kaplan-Meier plot, non-squamous and PD-L1 < 50%

Figure 36. CheckMate-227, PFS Kaplan-Meier plot, non-squamous and PD-L1 ≥ 50%

Figure 37. CheckMate-227, PFS Kaplan-Meier plot, squamous and PD-L1 < 1%

Figure 38. CheckMate-227, PFS Kaplan-Meier plot, squamous and PD-L1 1%-49%

Figure 39. CheckMate-227, PFS Kaplan-Meier plot, squamous and PD-L1 < 50%

Figure 40. CheckMate-227, PFS Kaplan-Meier plot, squamous and PD-L1 ≥ 50%

Figure 41. CheckMate-227, DoR Kaplan-Meier plot, non-squamous and PD-L1 < 1%

Figure 42. CheckMate-227, DoR Kaplan-Meier plot, non-squamous and PD-L1 1%-49%

Figure 43. CheckMate-227, DoR Kaplan-Meier plot, non-squamous and PD-L1 < 50%

Figure 44. CheckMate-227, DoR Kaplan-Meier plot, non-squamous and PD-L1 ≥ 50%

Figure 45. CheckMate-227, DoR Kaplan-Meier plot, squamous and PD-L1 < 1%

Figure 46. CheckMate-227, DoR Kaplan-Meier plot, squamous and PD-L1 1%-49%

Figure 47. CheckMate-227, DoR Kaplan-Meier plot, squamous and PD-L1 < 50%

Figure 48. CheckMate-227, DoR Kaplan-Meier plot, squamous and PD-L1 ≥ 50%

A7. Please also provide the HR for the subgroup of patients in the CM-227 trial with PD-L1 ≥ 50%.

As presented in Table 3, in the CM-227 PD-L1 ≥ 50% subgroup, the OS HR (95% CI): [redacted] and PFS HR (95% CI): [redacted].

A8. Section B.2.3.1 states patients whose PD-L1 status was "not quantifiable" were stratified as "PD-L1 < 1%". Please provide reasons why some patients' PD-L1 status could not be quantified.

In the protocol of CM-9LA, the total number of PD-L1 "not quantifiable" subjects was capped to not exceed 10% of the total randomised population. In CM-9LA, 47 patients (6.5%) had not quantifiable PD-L1 results. Not quantifiable includes either "Not evaluable" or "Indeterminate" PD-L1 results. Not evaluable includes samples with insufficient tumour content (< 100 viable tumour cells) in the specimen meaning analysis could not be completed. Indeterminate, includes samples from which the pathologist was not able to confidently report a result despite having sufficient tumour content.

A9. Figure 6.2.1-1 in the BMS CheckMate-9LA CSR addendum 2020 shows overall survival by subgroups and a HR of [redacted] for patients whose PD-L1 status was "not quantifiable". Please explain why these patients may be responding less well than to those with a quantifiable PD-L1 status.

This is variability due to sample size. There were only 22 subjects in the experimental arm and 25 subjects in the control arm. Therefore, the confidence internals are wide, there is considerable uncertainty around the result and no conclusive interpretation can be made.

A10. Figure 30 shows greater OS (%) for patients with PD-L1 ≥ 1% who have complete or partial response at 6 months compared those with stable disease or progressive disease. Can the company comment on whether patients who initially had a late response after progression or the appearance of new lesions, have the same likelihood as conventional responders to achieve a complete or partial response at 6 months?

Figure 30 in the company submission presents a landmark analysis by Ramalingham et al. (2020) in which OS in CheckMate-227 was plotted based on response at 6-

months. This question links with Question A5. As described there, data are not available based on type of response as no further tumour assessments were made one a patient had progressed.

Indirect treatment comparisons

A11. PRIORITY Providing as much detail as possible for all studies included in the ITC networks, please provide additional baseline characteristics separately for squamous and non-squamous patients with the following PD-L1 expression-levels:

a) <1

b) 1-49

c) <50 (i.e., a and b together)

d) >50

Baseline characteristics according to histology and PD-L1 expression levels as described above are provided for CheckMate-9LA in Table 4 and for CheckMate-227 in Table 5. Corresponding data for the other studies included in the indirect treatment comparison (ITC) networks (ERACLE, PRONOUNCE, KN-024, KN-042 and IMpower-150) were not identified in the publicly-available literature.

Table 4. Baseline Characteristics: CheckMate-9LA

Histology	**Non-squamous**								**Squamous**							
PD-L1	**< 1%**		**1%-49%**		**< 50%**		**≥ 50%**		**< 1%**		**1%-49%**		**< 50%**		**≥ 50%**	
	N+I+C	**C**	**N+I+C**	**C**	**N+I+C**	**C**	**N+I+C**	**C**	**N+I+C**	**C**	**N+I+C**	**C**	**N+I+C**	**C**	**N+I+C**	**C**
N	[redacted]															
Age, years																
< 65	[redacted]															
≥ 65	[redacted]															
ECOG PS, %																
0	[redacted]															
1	[redacted]															
Not reported	[redacted]															
Smoking status, %																
Never smoker	[redacted]															
Current/former smoker	[redacted]															
Metastases, %																
Bone	[redacted]															
Liver	[redacted]															
Central nervous system	[redacted]															

Table 5. Baseline Characteristics: CheckMate-227

Histology	Non-squamous								Squamous							
PD-L1	< 1%		1%-49%		< 50%		≥ 50%		< 1%		1%-49%		< 50%		≥ 50%	
	N+I+C	C	N+I+C	C	N+I+C	C	N+I+C	C	N+I+C	C	N+I+C	C	N+I+C	C	N+I+C	C
N	[redacted]															
Age, years																
< 65	[redacted]															
≥ 65	[redacted]															
ECOG PS, %																
0	[redacted]															
1	[redacted]															
≥ 2	[redacted]															
Not reported	[redacted]															
Smoking status, %																
Never smoker	[redacted]															
Current/former smoker	[redacted]															
Unknown	[redacted]															
Metastases, %																
Bone	[redacted]															
Liver	[redacted]															

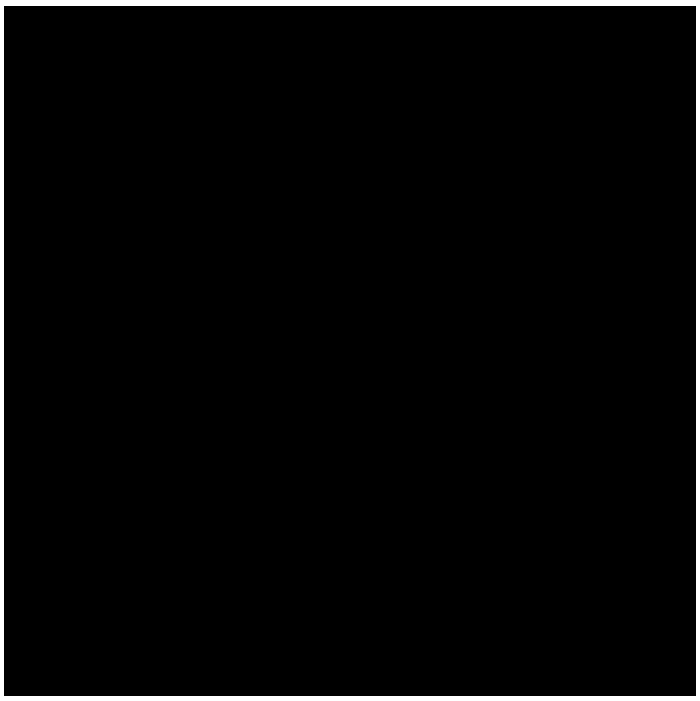
Histology	Non-squamous								Squamous							
PD-L1	< 1%		1%-49%		< 50%		≥ 50%		< 1%		1%-49%		< 50%		≥ 50%	
	N+I+C	C	N+I+C	C	N+I+C	C	N+I+C	C	N+I+C	C	N+I+C	C	N+I+C	C	N+I+C	C
N	[redacted]															
Central nervous system	[redacted]															

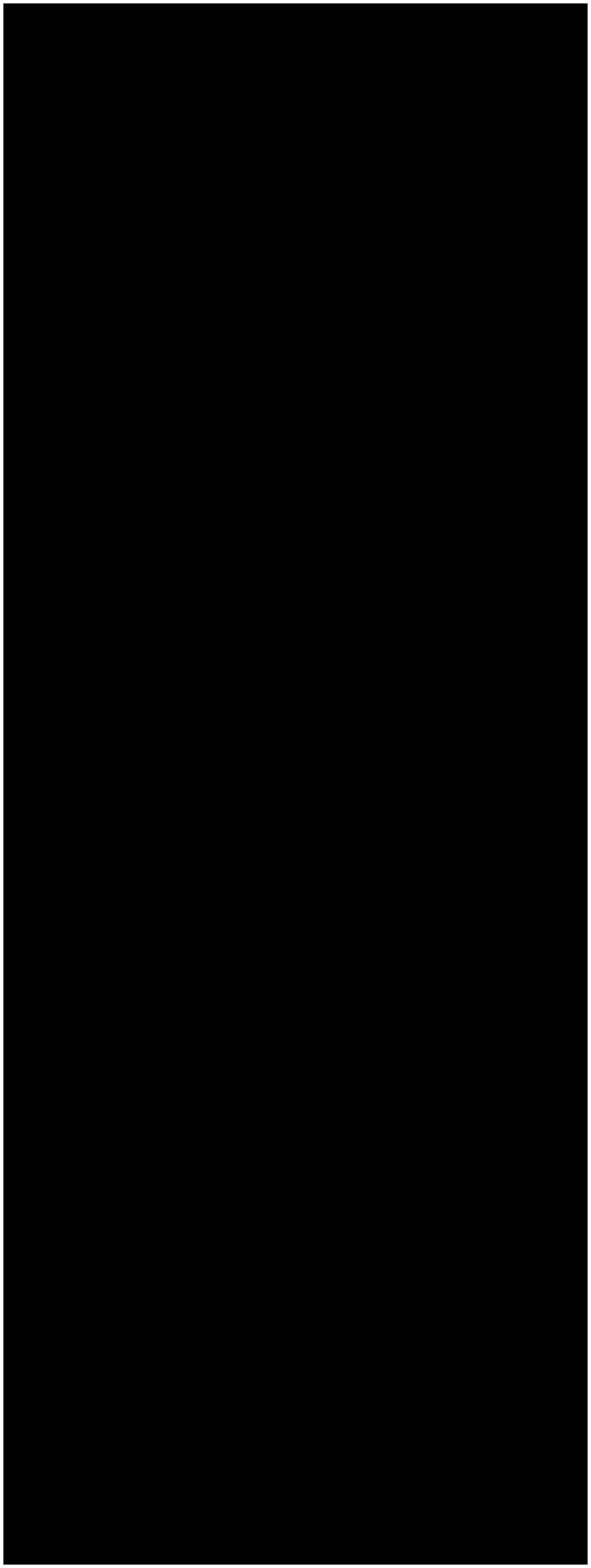
A12. PRIORITY Fractional polynomial models were used to perform network meta-analyses (NMAs) of the relevant trials.

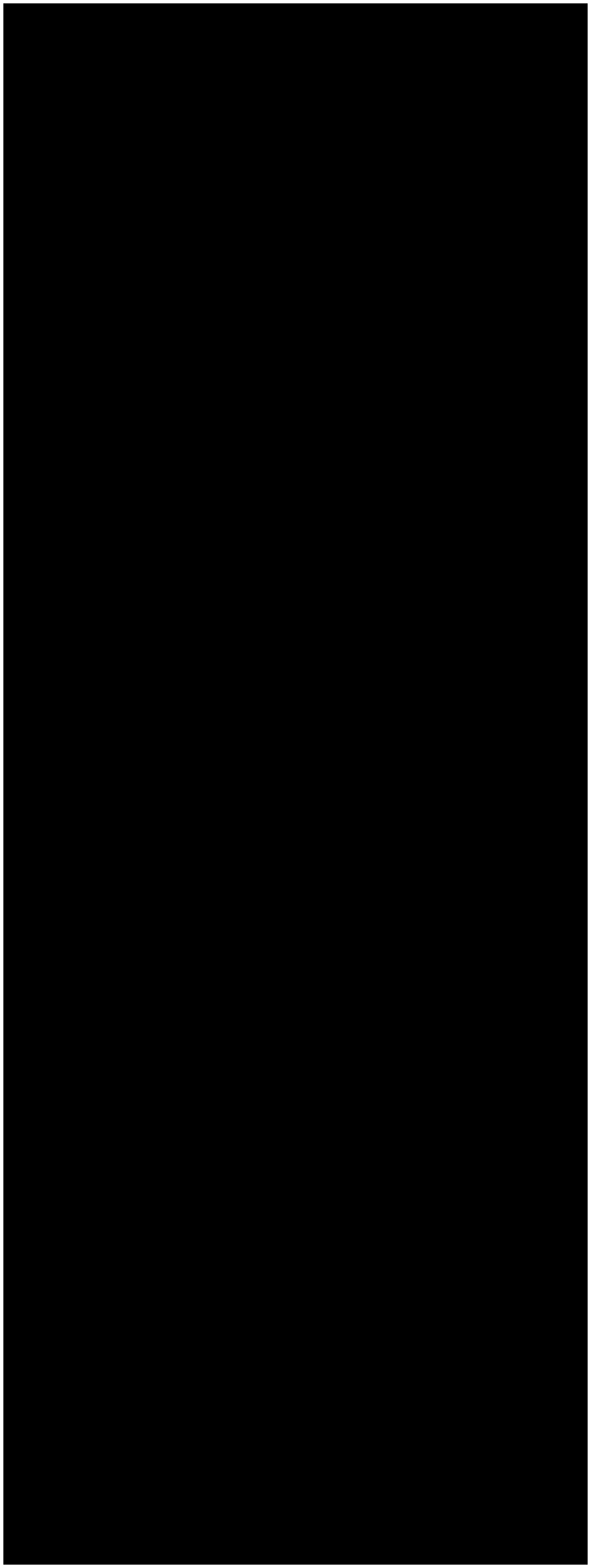
a) ***Please provide full details of software used, including code, data and initial values so that analyses can be checked and reproduced. If full data cannot be provided for commercial reasons, please provide an equivalent data structure to allow code to be checked.***

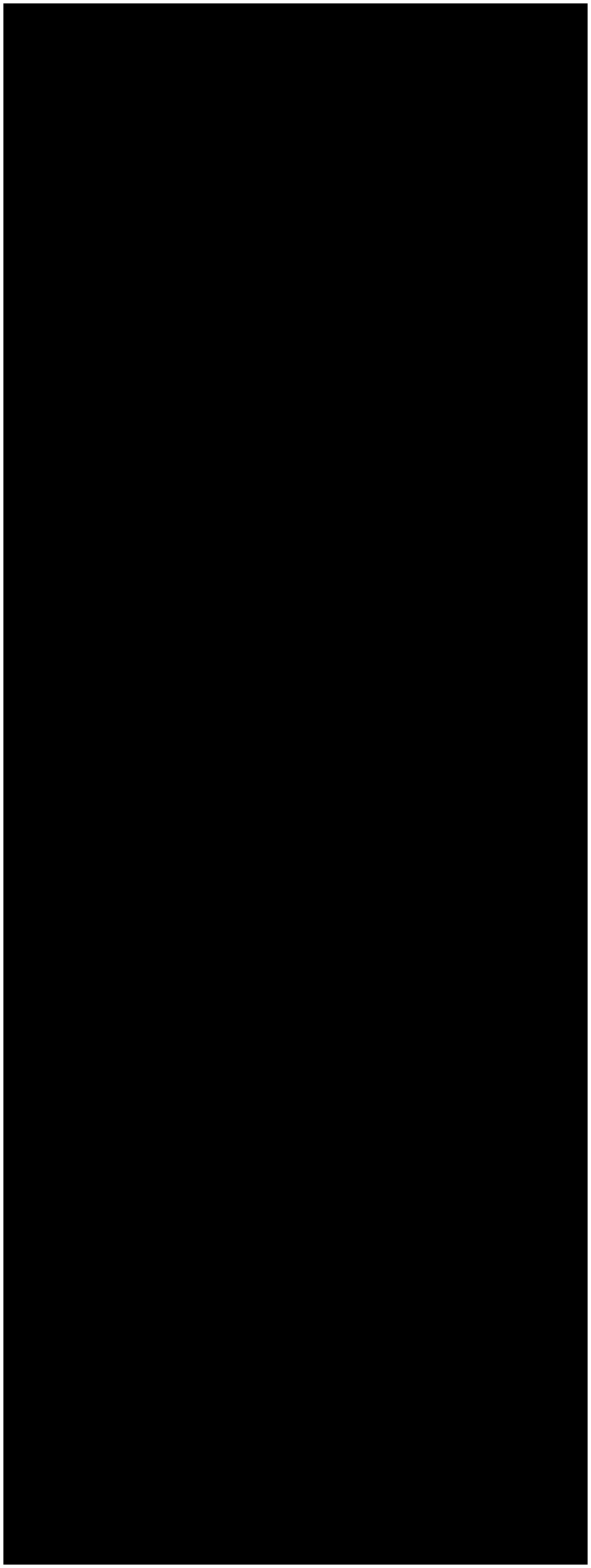
Analyses were conducted using JAGS (V4.3.0) and run through R (V3.6.1) using the package rjags (V4-8).

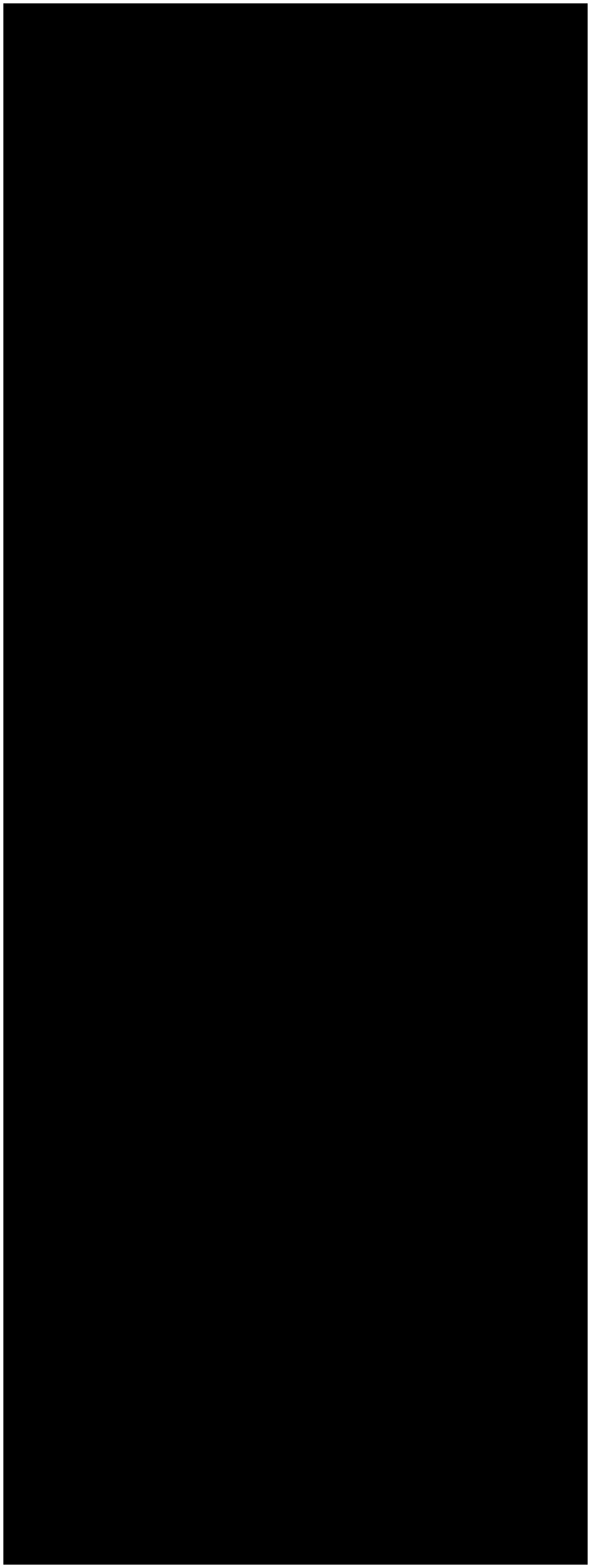
[redacted]











b) ***Please provide details of the number of burn-in iterations and size of the Markov chain Monte Carlo (MC) posterior samples used.***

40,000 burn-in iterations were used, and 60,000 additional iterations were used for the posterior sample. Every other iteration was kept to avoid correlation in the chains (i.e., thin = 2).

c) ***Please provide details of convergence checks made to ensure meaningful posterior summaries have been obtained.***

Convergence checks were conducted on the treatment effect parameters (d's) using the following methods: trace plots, density plots, Gelman plots, and autocorrelation plots [redacted]

d) ***Please check that MC error is less than 5% of the standard deviation for the posterior estimates.***

These criteria were fulfilled for the d parameters in each model run. In addition, the convergence checks described in A12 c) were performed and satisfied for each model.

A13. PRIORITY The company submission (Section B.2.9.2.1) and Appendix N, state the values for the powers P1 and P2 of the fractional polynomial models to be in the set {−1, −0.5, 0, 0.5, 1}. However, Jansen (2011) recommends also considering powers −2 and 2.

a) ***Please explain why −2 and 2 were not considered.***

Jansen (2011) describes the fractional polynomial model, and indeed provides examples of models fit using powers that include −2, 2, as well as 3. [redacted]

[redacted]

The most recent publications co-authored by Jansen have involved a subset of candidate powers, limited to having the first power drawn from the set of {0.1} (i.e., Weibull- and Gompertz-based) and the second power from the set {−1, −0.5, 0, 0.5, 1}.(Cope et al., 2019; Goring et al., 2019; Lorenzi et al., 2019) In our experience, this subset of candidate models continues to provide a flexible framework that provides good fit to time-to-event data in oncology, and eliminates combinations and powers that tend to have greater fluctuation in the tails and clinically implausible extrapolations. For example, incorporating terms with t2 (i.e., power of 2) with positive coefficients can produce hazard functions that increase rapidly and unbounded in long-term extrapolation periods, which are clinically implausible in the current setting. Hence, we aligned our candidate set of models based on the most recent work by Jansen: less computationally expensive for model run, less likely to provide clinically implausible extrapolations, yet continuing to provide a flexible set of clinically plausible hazard models for OS and PFS and showing good model fit.

b) In addition, the model results presented in Appendix N only show models where P1=0 or 1, other values in the set are not considered for this parameter. Please explain this decision and comment on the possibility of a better model fit if other values of P1 were considered.

Please see response to A.13 a)

A14. PRIORITY Bucher indirect comparisons were also carried out using the HR of relevant trials. Please provide details of all data and code used to carry out these calculations.

The HR data used in the Bucher ITCs can be found below (Table 6) and in Section N.4.3 of the submission appendices.

Table 6. Input data used in Bucher ITCs of overall and progression-free survival

Trial	Histology	PD-L1	Overall Survival HR (95% CI)	Progression-Free Survival HR (95% CI)
CheckMate-9LA	Mixed	All-comers	0.66 (0.55-0.80)	0.68 (0.57-0.82)
CheckMate-9LA	Mixed	PD-L1 ≥ 50%	0.66 (0.44-0.99)	[redacted]
CheckMate-9LA	Non-squamous	PD-L1 < 50%	[redacted]	[redacted]
KeyNote-024 + -042	Mixed	PD-L1 ≥ 50%	0.69 (0.58-0.81)	0.72 (0.62-0.85)
IMpower-150	Non-squamous	PD-L1 < 50%	0.81 (0.65-1.02)	0.68 (0.56-0.82)

Abbreviations: CI = confidence interval; HR = hazard ratio; ITC PD-L1 = programmed death-ligand 1

The main formula to perform the Bucher ITCs using HR (95% CI) from two trials is as follows:

[redacted]

A15. PRIORITY For Figure 37 please clarify that these show results for the chosen model '[redacted].

These are overlays showing the overlays of the chosen model, [redacted], and the observed Kaplan-Meier curves. Note that for the modelled data displayed in the figures for KeyNote-024 and KeyNote-042, these show the meta-analysed differences (i.e., meta-analysed treatment effects for pembrolizumab relative to the chemotherapy curve based on KeyNote-024 and KeyNote-042), added to the study-specific baseline.

In reviewing the Appendix, it appears that some footnotes in other figures/tables refer to the incorrect model; as such please refer to Table 7 regarding the models selected for each network/appendix subsection in the original submission:

Table 7. Fractional polynomial models used in original submission

Target population/ network	Endpoint	Model selected	Corresponding section
PD-L1 ≥ 50%; mixed histology	OS	[redacted]	N.4.2.1
PD-L1 ≥ 50%; mixed histology	PFS	[redacted]	N.4.2.2
PD-L1 < 50%; NSQ	OS	[redacted]	N.4.2.3
PD-L1 < 50%; NSQ	PFS	[redacted]	N.4.2.4

Abbreviations: HR = hazard ratio; NSQ = non-squamous; OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = progression-free survival.

A16. Appendix Section N.2.3 lists studies in the evidence base for the indirect treatment comparison (ITC). However, studies KeyNote-189, KeyNote-407 and IMpower-130 do not appear to have been included in any network. Please give reasons for inclusion/exclusion of each study in the ITC.

This is an error in the Appendix Section N.2.3. The studies above were excluded as they are not relevant to the NICE scope; this has now been amended.

A17. PRIORITY Appendix Section N.2.8 states that [redacted]

[redacted] **However, Figure 58, Appendix N shows** [redacted]**.**

a) ***Please confirm whether a*** [redacted] ***ITC/NMA was used for the network of non-squamous and PD-L1 < 50% patients and provide details of code, data and model fit.***

In the Bucher ITC, a simple 3-node network was used (as described in Section N.2.8; results provided in Section N.4.3).

In the fractional polynomial models, no such assumption was required, hence a 4-node network was used (as presented in Figure 58).

Code and data are provided in response to question A12. Model fit statistics provided in Table 132 and Table 137 of submission.

b) ***The ERG prefers the*** [redacted] ***. If this was not the network used, please provide results for the fractional polynomial models using the*** [redacted] ***in Figure 58, Appendix N.***

The four-node network was indeed used in the fractional polynomial NMA.

A18. PRIORITY Please provide separate NMA/ITC analyses for each of the 4 sub-populations in table 1 (see question A6) using only the relevant CM-9LA data, and provide details of code, data and model fit (see question A12). Where there are only two treatment options please present sub-population results from the trial.

We have provided Bucher ITCs and fractional polynomial estimates for the following populations, based on the request in question A6. We have prepared estimate for population 1 (non-squamous, PD-L1 < 50%) and we have prepared estimates for the consolidated populations 2 and 4 (squamous and non-squamous, PD-L1 ≥ 50%) based on sample size limitations. For population 3 (squamous, PD-L1 < 50%), neither ATEZO-BEV-PD, nor pembrolizumab are relevant comparators, hence indirect comparisons with these regimens were not conducted.

Bucher ITCs are provided in the tables below:

Table 8. Bucher hazard ratio estimates for NIVO-IPI-Chemo relative to Pembrolizumab; target population of PD-L1 ≥ 50% and mixed histology (populations 2 + 4 in question A6). Inputs from each RCT are based on subgroups that match the target population.

Endpoint	Hazard ratio (95% CI)	Input data**
Overall survival	[redacted]	CM-9LA: PD-L1 ≥ 50% subgroup KN-024: ITT population (PD-L1 ≥ 50%) KN-042: PD-L1 ≥ 50% subgroup
Progression-free survival	[redacted]	

Notes: For A vs. B comparisons, an HR < 1 favours A.

[redacted]

** See response to A14 for input data

Table 9. Bucher hazard ratio estimates for NIVO-IPI-Chemo relative to ATEZO-BEV-PD; target population of PD-L1 < 50% and non-squamous histology (population 1 in question A6). Inputs from each RCT are based on subgroups that match the target population.

Endpoint	Hazard ratio (95% CI)*	Input data
Overall survival	[redacted]	CM-9LA: PD-L1 < 50% NSQ subgroup Imp-150: PD-L1 < 50% ITT-WT subgroup (NSQ)
Progression-free survival	[redacted]	

Notes: For A vs. B comparisons, an HR < 1 favours A.

[redacted]

** See response A14 for input data

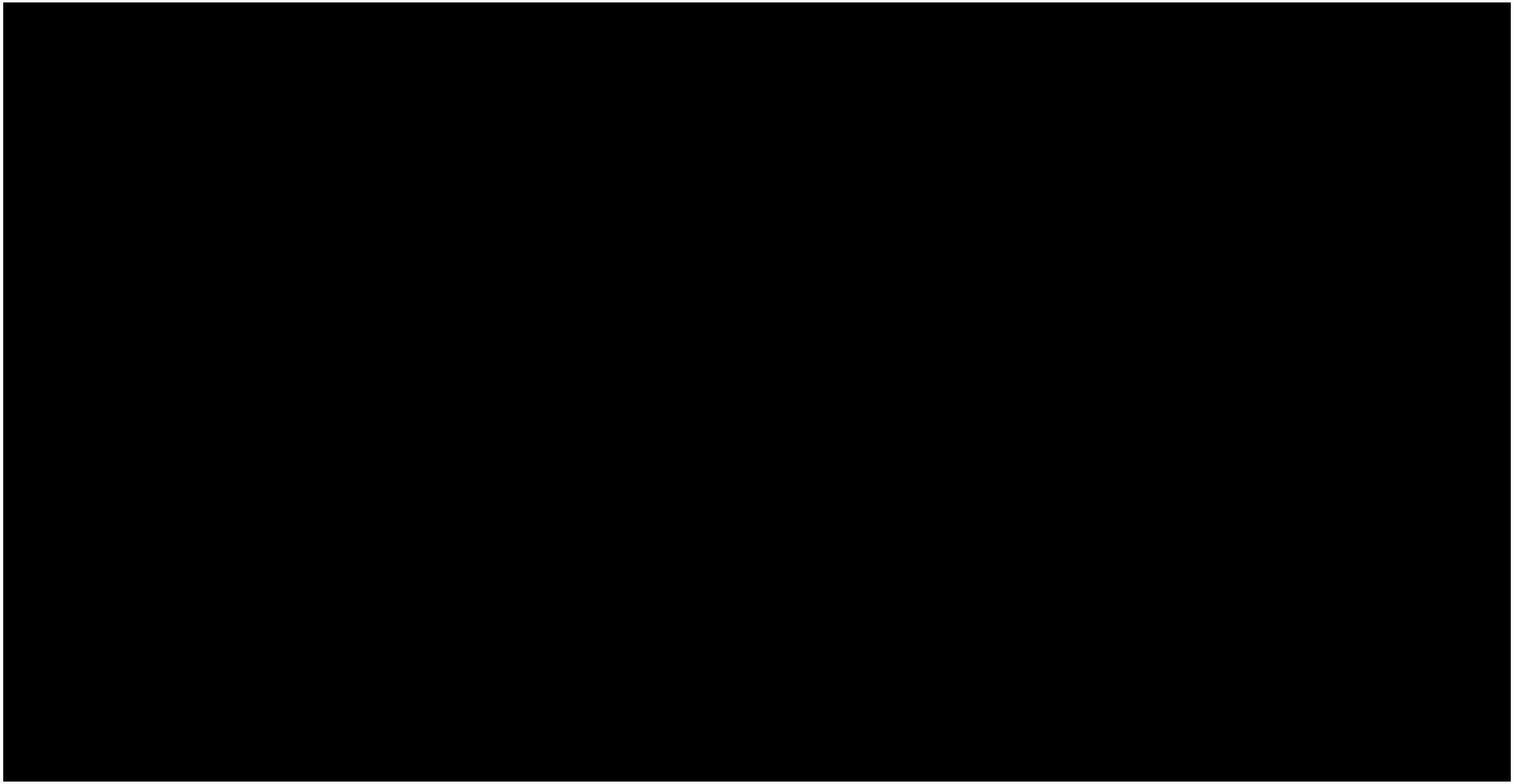
We re-fit fractional polynomial models using subgroup data from CheckMate-9LA that aligns with the requested populations (population 1 (NSQ; PD-L1 <50%); population 2+4 (mixed histology; PD-L1 ≥ 50%).

For the re-fit models involving pembrolizumab monotherapy, the updated models (in which PD-L1 ≥ 50% subgroup data from CheckMate-9LA were used) were deemed clinically implausible based on a priori assumptions. Specifically, for overall survival, among all top-fitting models, the NIVO-IPI-Chemo and chemo survival curves crossed in the long-term projection, which is neither aligned with the observed data in CheckMate-227, nor with the expected duration of response associated with immunotherapies. The unexpected model projections may have been due to over-fitting to the smaller sample size that has greater fluctuations (and uncertainty) in the month-to-month discrete hazards.

In the Bucher ITC (Table 8) and the KM curve overlays (Figure 49) it is evident that during the observed period, the ITT input from 9LA provides similar yet slightly more

conservative estimates of relative effect for NIVO-IPI-Chemo relative to Chemo. Hence, the fractional polynomial model involving ITT-based inputs from CheckMate-9LA were used, which were thought to provide more conservative HR estimates during the observed period, and more clinically plausible extrapolations.

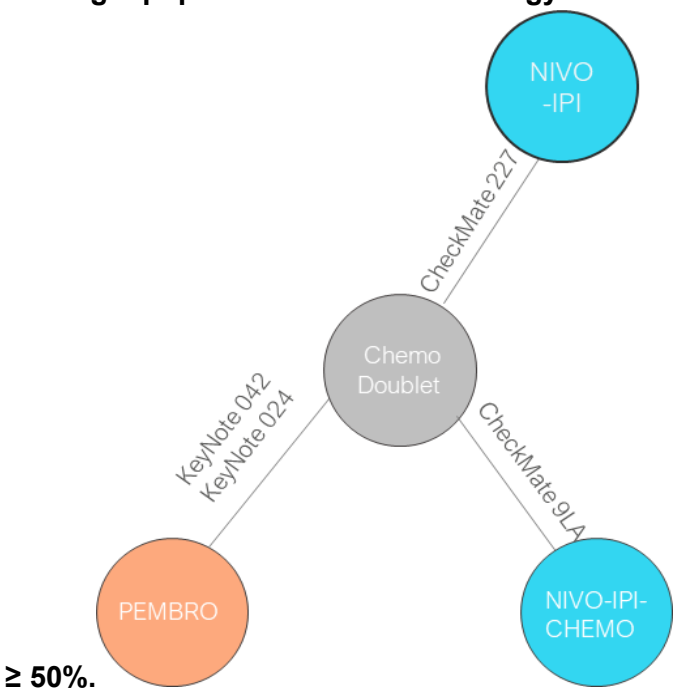
Figure 49. Kaplan-Meier curves for overall survival (left) and progression-free survival (right) from CheckMate-9LA: comparison of overall ITT population and PD-L1 ≥ 50% subgroup.



ITT: intention to treat; 9LA: CheckMate-9LA

To better reflect the clinical expectation that longer-term trends from CheckMate-9LA will follow longer-term trends from CheckMate-227, we have updated this analysis to include CheckMate-227 into the network of evidence. This choice reflected clinical and methodological input received after the original submission to NICE.

Figure 50. Network diagram for overall survival, and for progression-free survival for target population of mixed histology and PD-L1 expression level ≥ 50%.



The updated models produced relative effect estimates (Table 14; Table 15) that were similar to those in the original submission, with minor differences reflecting the addition of CheckMate-227 into the network of evidence, leading to a different choice of model.

Table 10. Hazard ratios of nivolumab + ipilimumab + limited PDC versus comparators over time for overall survival (target population: mixed histology and PD-L1 ≥ 50%)

NIVO + IPI + limited PDC vs.	Time point (months)	[redacted]
PDC	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
Pembrolizumab	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]

CrI = credible interval; HR = hazard ratio; IPI = ipilimumab; NIVO = nivolumab; PD-L1 = programmed death-ligand 1; PDC = platinum doublet chemotherapy.

Note: Estimates obtained from the following model: p0p1; treatment effect on scale, 1st shape.

Note: Estimates in original submission (which did not incorporate CM-227) were based on the following models: p1p1; treatment effect on scale, 1st shape (see Table 125 in original submission for estimates)

Table 11. Hazard ratios of nivolumab + ipilimumab + limited PDC versus comparators over time for progression-free survival (target population: mixed histology and PD-L1 ≥ 50%)

NIVO + IPI + limited PDC vs.	Time point (months)	[redacted]
PDC	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
Pembrolizumab	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	

CrI = credible interval; HR = hazard ratio; IPI = ipilimumab; NIVO = nivolumab; PD-L1 = programmed death-ligand 1; PDC = platinum doublet chemotherapy.

Note: Estimates obtained from the following model: p0p-1; treatment effect on scale, 1st shape

Note: Estimates in original submission (which did not incorporate CM-227) were based on the same model: p0p-1; treatment effect on scale, 1st shape (see Table 130 in original submission for estimates)

Additional details of the fractional polynomial models, including the parameter estimates and goodness of fit, are provided below. Data inputs and code are as provided in response to question A12.

For comparisons of overall survival between NIVO-IPI-Chemo and PEMBRO, in the mixed histology PD-L1 ≥ 50% population, the selected model was the model, p0 p1, with treatment effects on scale and the first shape parameter. As in the original submission, this was selected according to deviance information criterion alongside a predefined heuristic that additionally incorporated additional penalisation for model complexity, visual inspections of observed versus modelled outputs, and clinical plausibility of model extrapolation periods. A full listing of model DICs is provided in the excel spreadsheet provided (Sheet 1).

Model estimates, provided in Table 12 and Table 13, can be incorporated into a fractional polynomial model of the functional form:

$$\log \text{hazard} = (\mu1 + d1) + \ln(t)*(\mu2 + d2) + \mu3*t$$

Study-specific estimates for μ1, μ2, and μ3, which define the reference curve, are provided, and can be replaced with updated estimates, against which differences can be applied. Hazard ratios for treatment X versus treatment Y can be calculated using the formula below:

$$EXP((d1[X]-d1[Y]) + (d2[X]-d2[Y])*\ln(t))$$

Table 12. Mu_mean parameters for overall survival for the target population of mixed histology and PD-L1 ≥ 50% in first-line advanced NSCLC (data inputs: ITT for CheckMate-9LA, CheckMate-227; PD-L1 ≥ 50% for KeyNote-024 and KeyNote-042)

Parameter	Estimate	Variance	Correlation (12)	Correlation (13)	Correlation (23)
Mu_mean1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mu_mean2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mu_mean3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Please note that the following estimates for mu are *not* outputs of the NMA - these have been provided as a baseline onto which treatment effects can be added; however, the choice of reference curve should be updated as appropriate. Currently, these are estimated using the average mus of the reference treatment (Chemo).
Estimates obtained from the following model: p0p1; treatment effect on scale, 1st shape

Table 13. d parameters for overall survival for the target population of mixed histology and PD-L1 ≥ 50% in first-line advanced NSCLC (data inputs: ITT for CheckMate-9LA, CheckMate-227; PD-L1 ≥ 50% for KeyNote-024 and KeyNote-042)

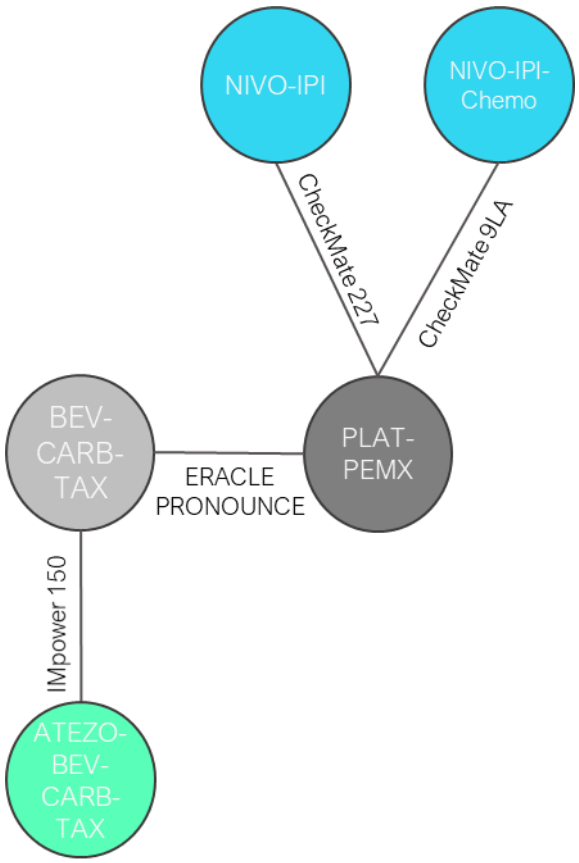
Treatment	d1 Estimate	d1 Variance	d2 Estimate	d2 Variance	d12 Correlation
Chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NIVO-IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NIVO-IPI-Chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

For comparisons of progression-free survival between NIVO-IPI-Chemo and PEMBRO, in the mixed histology PD-L1 ≥ 50% population, the selected model was a repeated powers model, p0 p-1, with treatment effects on scale and the first shape parameter. This was selected according to deviance information criterion alongside a predefined heuristic that additionally incorporated additional penalisation for model complexity, visual inspections of observed versus modelled outputs, and clinical plausibility of model extrapolation periods. A full listing of model DICs is provided in the excel spreadsheet provided (Sheet 2).

Using subgroup data from CheckMate-9LA that matches population 1 (question A6; PD-L1 < 50% & NSQ), we re-ran the fractional polynomial models comparing NIVO-IPI-Chemo with ATEZO-BEV-PD. In the updated fractional polynomial models, we incorporated CheckMate-227 into the network of evidence, based on input received between the time of the original submission to NICE and current (i.e., to better incorporate the long-term trends from CheckMate-227 into the CheckMate-9LA extrapolations). Hence the updated network diagram is as below (Figure 51):

Figure 51. Network diagram for overall survival, and for progression-free survival for target population of non-squamous histology and PD-L1 expression level < 50%.



Model fit statistics from the updated models are provided in the embedded spreadsheets below. As in the original submission, the model selection process followed a predefined heuristic that incorporated DIC as well as additional penalisation for model complexity, visual inspections of observed versus modelled outputs, and clinical plausibility of model extrapolation periods. Fit statistics are available in the excel spreadsheets provided (Sheets 3 and 4).

The updated models produced relative effect estimates similar to in the original submission (Table 14, Table 15), with minor differences reflecting the updated input data from CheckMate-9LA, the addition of CheckMate-227 into the network of evidence, and a difference choice of model for PFS (note that the updated model choice had more conservative estimates for the HRs between BEV-PLAT-TAX and PLAT-PEMX).

Table 14. Hazard ratios of nivolumab + ipilimumab + limited PDC versus comparators over time for overall survival

NIVO + IPI + limited PDC vs.	Time point (months)	HR (95% CrI)
PDC	[redacted]	[redacted]
BEV + PLAT + TAX	[redacted]	[redacted]
ATEZO + BEV + PLAT + TAX	[redacted]	[redacted]

ATEZO = atezolizumab; BEV = bevacizumab; CrI = credible interval; HR = hazard ratio; IPI = ipilimumab; NIVO = nivolumab; PDC = platinum doublet chemotherapy; PLAT = platinum; TAX = paclitaxel.

[redacted]

Note: Updated estimates were obtained from the following model: p1 p1, treatment effect on scale

Table 15. Hazard ratios of nivolumab + ipilimumab + limited PDC versus comparators over time for progression-free survival

NIVO + IPI + limited PDC vs.	Time point (months)	HR (95% CrI)
PDC	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
BEV + PLAT + TAX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
ATEZO + BEV + PLAT + TAX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]

ATEZO = atezolizumab; BEV = bevacizumab; CrI = credible interval; HR = hazard ratio; IPI = ipilimumab; NIVO = nivolumab; PDC = platinum doublet chemotherapy; PLAT = platinum; TAX = paclitaxel.

Note: Estimates in original submission (based in ITT inputs from CM-9LA) were based on the following models: p0 p0, treatment effect on scale, and 1st shape (see Table 140 in original submission for estimates)

Note: Updated estimates were obtained from the following model: p0 p-1, treatment effect on scale, 2nd shape

Additional details of the fractional polynomial models, including the parameter estimates and goodness of fit, are provided below. Data inputs and code are as provided in response to question A12.

For comparisons of overall survival between NIVO-IPI-Chemo and ATEZO-BEV-PD, in the non-squamous PD-L1 < 50% population, the selected model was a repeated powers model, p1 p1, with treatment effects on scale (i.e., constant HR).

This model was the second-best ranked model according to DIC, with a DIC only 0.37 units different from the top-ranked model. It was selected over the top-ranked

model based on a predefined heuristic involving systematic assessment of visual inspection of model fits, and clinical plausibility of model extrapolations.

Model estimates, provided in Table 16 and Table 17, can be incorporated into a fractional polynomial model of the functional form:

$$\log \text{hazard} = (\mu1 + d1) + t*\mu2 + \mu3*t*\ln(t)$$

Study-specific estimates for μ1, μ2, and μ3, which define the reference curve, are provided, and can be replaced with updated estimates, against which differences can be applied. Hazard ratios for treatment X versus treatment Y can be calculated using the formula below:

$$EXP(d1[X]-d1[Y])$$

Table 16. Mu_mean parameters for overall survival for the population of non-squamous histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for CheckMate-9LA, CheckMate-227, and IMpower-150; PD-L1 all-comers for ERACLE and PRONOUNCE)

Parameter	Estimate	Variance	Correlation (12)	Correlation (13)	Correlation (23)
Mu_mean1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mu_mean2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mu_mean3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Please note that the following estimates for mu are *not* outputs of the NMA - these have been provided as a baseline onto which treatment effects can be added; however, the choice of reference curve should be updated as appropriate. Currently, these are estimated using the average mus of the reference treatment (Chemo).

[redacted]

Table 17. d parameters for overall survival for the target population of non-squamous histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for CheckMate-9LA, CheckMate-227, and IMpower-150; PD-L1 all-comers for ERACLE and PRONOUNCE)

Treatment	d1 Estimate	d1 Variance
Chemo	[redacted]	[redacted]
BEV-PLAT-TAX	[redacted]	[redacted]
ATEZO-BEV-PLAT-TAX	[redacted]	[redacted]
NIVO-IPI	[redacted]	[redacted]
NIVO-IPI-Chemo	[redacted]	[redacted]

[redacted]

For comparisons of progression-free survival between NIVO-IPI-Chemo and ATEZO-BEV-PD, in the non-squamous PD-L1 < 50% population, the selected model was a

repeated powers model, p0 p-1, with treatment effects on scale and the second shape parameter. Model estimates, provided in Table 18 and Table 19, can be incorporated into a fractional polynomial model of the functional form:

$$\log \text{hazard} = (\mu 1 + d1) + \ln(t)*\mu 2 + (\mu 3 + d3)*t^{-1}$$

Study-specific estimates for μ1, μ2, and μ3, which define the reference curve, are provided, and can be replaced with updated estimates, against which differences can be applied. Hazard ratios for treatment X versus treatment Y can be calculated using the formula below:

$$EXP((d1[X]-d1[Y]) + (d3[X]-d3[Y])*t^{-1})$$

Table 18. Mu_mean parameters for progression-free survival for the target population of non-squamous histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for CheckMate-9LA, CheckMate-227, and IMpower-150; PD-L1 all-comers for ERACLE and PRONOUNCE)

Parameter	Estimate	Variance	Correlation (12)	Correlation (13)	Correlation (23)
Mu_mean1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mu_mean2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mu_mean3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Please note that the following estimates for mu are *not* outputs of the NMA - these have been provided as a baseline onto which treatment effects can be added; however, the choice of reference curve should be updated as appropriate. Currently, these are estimated using the average mus of the reference treatment (Chemo).

[redacted]

Table 19. d parameters for progression-free survival for the target population of non-squamous histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for CheckMate-9LA, CheckMate-227, and IMpower-150; PD-L1 all-comers for ERACLE and PRONOUNCE)

Treatment	d1 Estimate	d1 Variance	d3 Estimate	d3 Variance	d13 Correlation
Chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BEV-PLAT-TAX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ATEZO-BEV-PLAT-TAX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NIVO-IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NIVO-IPI-Chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

A19. Appendix Section 3.3.4 (page 277) gives details of analyses for duration of response using the HR and thus assuming proportional hazards. Was the

proportional hazards assumption assessed for this outcome? If so, please provide brief details of the main findings.

The proportional hazards assumption was tested and there were no violations in ITT or for PD-L1 ≥ 50% for CheckMate- 9LA, KeyNote-024 or KeyNote-042 (which are the studies in the figures referred to in the question). It is important to note that data from CheckMate-9LA are immature, so there will be changes with longer follow-up.

Section B: Clarification on cost-effectiveness data

Results

B1. PRIORITY The results for pembrolizumab monotherapy in the executable model do not correspond with the results presented in the company submission. Please investigate this discrepancy, and provide an updated economic model and cost-effectiveness results as required.

Upon opening the model, the comparison against the atezolizumab combination is set up and is shown in the 'Results' sheet. To show results for the comparison against pembrolizumab monotherapy using the results of the fractional polynomial NMA, the user should select 'Pembrolizumab monotherapy' in the 'FPNMA' sheet by altering the drop-down list in cell 'FPNMA_comp_USER.' Results for the comparison against pembrolizumab monotherapy will then be available in the Results sheet.

As discussed in the responses to questions in Section A, since the original submission additional work has been completed on the FP NMA and these updates have also been incorporated into the model. On the FPNMA sheet, additional models including CheckMate 227 data have been incorporated and can now be selected using the updated dropdown in the 'FPNMA_comp_USER' cell.

Table 20 shows the FPNMA networks that can now be selected.

Table 20. FPNMA Networks and Models Available in Updated Model

Network	CM 9LA & CM 227 data input in network	Population_user setting in Model settings sheet	Recommended model OS	Recommended model PFS
PD-L1 >=50% & mixed histology; CM 9LA ITT	All comers	All comers	p1 p1 - scale, 1st shape	p0 p-1 - scale, 1st shape
PD-L1 < 50% & NSQ; CM 9LA ITT	All comers	All comers	p1 p1 - no shape effects	p0 p0 - scale, 1st shape
PD-L1 >=50% & mixed histology; CM 9LA & CM 227 ITT	All comers	All comers	p0 p1 - scale, 1st shape	p0 p-1 - scale, 1st shape
PD-L1 < 50% & NSQ; CM 9LA & CM 227 PD-L1 < 50% & NSQ	PD-L1 < 50% and NSQ	PD-L1 < 50% and NSQ	p1 p1 - scale	p0 p-1 - scale, 2nd shape

CM = checkmate; FPNMA = fractional polynomial network meta-analysis; OS = overall survival; PFS = progression-free survival

When updating the network selection in the FPNMA sheet, the user must also manually update the selected models for both OS and PFS in the 'FPNMA_model_OS' and 'FPNMA_model_PFS' cells, respectively.

Results presented in this document are run using the originally submitted networks, but the updated networks are built into the model for the ERG to select.

B2. PRIORITY Please present the results of the company's base case economic analyses as fully-incremental results.

a) Please make sure to include all relevant interventions, including those deemed to be dominated in the company's base case analyses as the inclusion of confidential patient access schemes for comparators may change the base case results.

Table 21 presents the fully incremental results for the comparison with pembrolizumab monotherapy.

Table 21. Base-case results: fully incremental vs. pembrolizumab monotherapy

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Nivolumab + Ipilimumab with PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29,133
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality-adjusted life-year.

Table 22 presents the fully incremental results for the comparison with atezolizumab + bevacizumab + carboplatin + paclitaxel.

Table 22. Base-case results: fully incremental vs. atezolizumab + bevacizumab + carboplatin + paclitaxel

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Nivolumab + Ipilimumab with PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29,133

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab + bevacizumab + carboplatin + paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality-adjusted life-year.

b) Please include the functionality in the economic model for results of the fully incremental analyses to be replicated.

This functionality is included in the updated economic model.

B3. PRIORITY Please present fully incremental economic results for the four separate sub-populations in table 1 (see question A6), under the assumptions in the company's base case analysis. Please follow steps a) and b) described in question B2.

The model has now been programmed to include results for comparisons based on the subgroups presented in response to question A6. Due to the level of work required to complete all analyses and incorporate into the model, sufficient time has not been available to consider the most appropriate distributions to model survival for nivolumab + ipilimumab + limited PDC or PDC.

The model contains the functionality to allow exploration of the cost-effectiveness analysis for subgroups. Due to time constrains following the large amount of new analyses requested, validation of predicted survival for each distribution has not been feasible. Thus, selection of the most appropriate distributions to be used for each subgroup has not been feasible in time for submitting the response. We will continue to work on selecting the most appropriate curves for the subgroup analyses and plan to submit our base case analyses before the technical engagement stage.

B4. PRIORITY Using the population-specific event rates from CheckMate-227 produced in response to the ERG's clarification question A6, please fit independent parametric models (as presented in the company submission in Section B.3.3.1.4) to the Kaplan-Meier data for nivolumab + ipilimumab + limited PDC and for PDC. Please include plots of the KM data with the

extrapolated models, statistical goodness of fit indicators and landmark survival.

Figure 52 to Figure 75 presents KM data with the extrapolated models for each treatment arm and subgroup and **Error! Reference source not found.** to Table 40 presents statistical goodness of fit and landmark survival for extrapolated independent parametric models fitted to CheckMate-227 subgroup data as requested.

Figure 52. Independent parametric models overlaying the overall survival Kaplan-Meier data for Nivo + Ipi PD-L1 < 50 NSQ for CheckMate-227 part 1

Figure 53. Independent spline models overlaying the overall survival Kaplan-Meier data for Nivo + Ipi PD-L1 < 50 NSQ for CheckMate-227 part 1

Figure 54. Independent parametric models overlaying the overall survival Kaplan-Meier data for PDC PD-L1 < 50 NSQ for CheckMate-227 part 1

Figure 55. Independent spline models overlaying the overall survival Kaplan-Meier data for PDC PD-L1 < 50 NSQ for CheckMate-227 part 1

Table 23. Statistical goodness-of-fit indicators (AIC/BIC) values for independent parametric models fitted to overall survival data Nivo + Ipi PD-L1 < 50 NSQ for CheckMate-227 part 1

Distribution	AIC	BIC
Log-logistic	1646.5	1653.7
Spline on odds 1 knot	1646.7	1657.5
Spline on probit link of survival 2 knots	1647.7	1662.1
Spline on hazards 1 knot	1648.0	1658.8
Lognormal	1646.5	1653.7
Spline on odds 2 knots	1648.0	1662.5
Spline on hazards 2 knots	1648.4	1662.8
Spline on probit link of survival 1 knot	1648.4	1659.2
Gompertz	1648.4	1655.6
Generalised gamma	1648.5	1659.3
Spline on probit link of survival 3 knots	1649.2	1667.2
Weibull	1660.8	1668.0
Spline on odds 3 knots	1649.6	1667.7
Spline on hazards 3 knots	1649.8	1667.9
Gamma	1663.3	1670.5
Exponential	1664.5	1668.1

Table 24. Statistical goodness-of-fit indicators (AIC/BIC) values for independent parametric models fitted to overall survival data PDC PD-L1 < 50 NSQ for CheckMate-227 part 1

Distribution	AIC	BIC
Log-logistic	1835.2	1842.5
Generalised gamma	1841.3	1852.3
Lognormal	1841.7	1849.0
Spline on odds 1 knot	1837.2	1848.2
Spline on odds 2 knots	1839.0	1853.6
Gamma	1850.5	1857.8
Spline on hazards 3 knots	1839.4	1857.6
Spline on odds 3 knots	1839.7	1857.9
Spline on probit link of survival 2 knots	1840.0	1854.6
Exponential	1851.9	1855.6
Gompertz	1852.4	1859.7
Spline on probit link of survival 3 knots	1840.1	1858.3
Weibull	1852.5	1859.8
Spline on hazards 2 knots	1840.3	1854.9
Spline on probit link of survival 1 knot	1840.4	1851.3
Spline on hazards 1 knot	1841.7	1852.6

Table 25. Overall survival at different landmark points for distributions fitted to Nivo + Ipi PD-L1 < 50 NSQ

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 26. Overall survival at different landmark points for distributions fitted to PDC PD-L1 < 50 NSQ

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 56. Independent parametric models overlaying the progression-free survival Kaplan-Meier data for Nivo + Ipi PD-L1 < 50 NSQ for CheckMate-227 part 1

[redacted]

Figure 57. Independent spline models overlaying the progression-free survival Kaplan-Meier data for Nivo + Ipi PD-L1 < 50 NSQ for CheckMate-227 part 1

Figure 58. Independent parametric models overlaying the progression-free survival Kaplan-Meier data for PDC PD-L1 < 50 NSQ for CheckMate-227 part 1

Figure 59. Independent spline models overlaying the progression free survival Kaplan-Meier data for PDC PD-L1 < 50 NSQ for CheckMate-227 part 1

Table 27. Statistical goodness-of-fit indicators (AIC/BIC) values for independent parametric models fitted to progression free survival data Nivo + Ipi PD-L1 < 50 NSQ for CheckMate-227 part 1

Distribution	AIC	BIC
Generalised gamma	1307.9	1318.8
Spline on odds 1 knot	1301.0	1311.9
Spline on odds 2 knots	1301.3	1315.7
Spline on hazards 2 knots	1302.0	1316.5
Lognormal	1312.0	1319.3
Spline on hazards 1 knot	1302.3	1313.1
Spline on odds 3 knots	1302.6	1320.6
Log-logistic	1314.2	1321.4
Spline on probit link of survival 3 knots	1303.9	1322.0
Gompertz	1319.9	1327.1
Weibull	1359.7	1366.9
Spline on hazards 3 knots	1304.4	1322.4
Gamma	1373.5	1380.7
Spline on probit link of survival 1 knot	1305.5	1316.3
Spline on probit link of survival 2 knots	1306.3	1320.7
Exponential	1389.5	1393.1

Table 28. Statistical goodness-of-fit indicators (AIC/BIC) values for independent parametric models fitted to progression free survival data PDC PD-L1 < 50 NSQ for CheckMate-227 part 1

Distribution	AIC	BIC
Log-logistic	1300.4	1307.7
Lognormal	1306.3	1313.6
Generalised gamma	1307.0	1317.9
Spline on odds 3 knots	1300.9	1319.1
Spline on probit link of survival 3 knots	1301.3	1319.5
Gamma	1323.6	1330.9
Spline on hazards 3 knots	1302.3	1320.5
Spline on odds 1 knot	1302.3	1313.3
Spline on hazards 2 knots	1302.9	1317.5
Weibull	1328.5	1335.8
Gompertz	1329.2	1336.5
Spline on probit link of survival 2 knots	1303.9	1318.4
Exponential	1329.5	1333.1
Spline on odds 2 knots	1304.0	1318.5
Spline on hazards 1 knot	1305.9	1316.8
Spline on probit link of survival 1 knot	1306.3	1317.2

Figure 60. Independent parametric models overlaying the overall survival Kaplan-Meier data for Nivo + Ipi PD-L1 < 50 SQ for CheckMate-227 part 1

Figure 61. Independent spline models overlaying the overall survival Kaplan-Meier data for Nivo + Ipi PD-L1 < 50 SQ for CheckMate-227 part 1

Figure 62. Independent parametric models overlaying the overall survival Kaplan-Meier data for PDC PD-L1 < 50 SQ for CheckMate-227 part 1

Figure 63. Independent spline models overlaying the overall survival Kaplan-Meier data for PDC PD-L1 < 50 SQ for CheckMate-227 part 1

Table 29. Statistical goodness-of-fit indicators (AIC/BIC) values for independent parametric models fitted to overall survival data Nivo + Ipi PD-L1 < 50 SQ for CheckMate-227 part 1

Distribution	AIC	BIC
Log-logistic	712.4	717.7
Spline on probit link of survival 1 knot	713.8	721.8
Spline on hazards 1 knot	714.3	722.3
Spline on odds 1 knot	714.4	722.4
Lognormal	712.4	717.7
Spline on probit link of survival 2 knots	715.8	726.4
Spline on hazards 2 knots	716.2	726.8
Generalised gamma	714.0	722.0
Spline on odds 2 knots	716.3	727.0
Exponential	714.2	716.9
Gompertz	715.3	720.6
Spline on probit link of survival 3 knots	717.3	730.6
Spline on hazards 3 knots	717.5	730.8
Spline on odds 3 knots	717.9	731.2
Gamma	716.1	721.4
Weibull	716.2	721.5

Table 30. Statistical goodness-of-fit indicators (AIC/BIC) values for independent parametric models fitted to overall survival data PDC PD-L1 < 50 SQ for CheckMate-227 part 1

Distribution	AIC	BIC
Log-logistic	724.2	729.5
Lognormal	724.3	729.6
Generalised gamma	725.8	733.9
Spline on probit link of survival 1 knot	725.7	733.8
Spline on odds 1 knot	726.1	734.2
Gamma	729.5	734.9
Spline on hazards 1 knot	726.3	734.4
Spline on probit link of survival 2 knots	727.6	738.4
Spline on odds 2 knots	727.7	738.4
Weibull	731.5	736.9
Exponential	732.3	735.0
Spline on hazards 2 knots	728.3	739.1
Gompertz	734.3	739.7
Spline on probit link of survival 3 knots	729.6	743.0
Spline on odds 3 knots	729.6	743.1
Spline on hazards 3 knots	730.2	743.7

Table 31. Overall survival at different landmark points for distributions fitted to Nivo + Ipi PD-L1 < 50 SQ

Distribution	1 Year	2 Years	5 years	10 Years
[redacted]				

Table 32. Overall survival at different landmark points for distributions fitted to PDC PD-L1 < 51 SQ

Distribution	1 Year	2 Years	5 years	10 Years
[redacted]				

Figure 64. Independent parametric models overlaying the progression-free survival Kaplan-Meier data for Nivo + Ipi PD-L1 < 50 SQ for CheckMate-227 part 1

Figure 65. Independent spline models overlaying the progression-free survival Kaplan-Meier data for Nivo + Ipi PD-L1 < 50 SQ for CheckMate-227 part 1

Figure 66. Independent parametric models overlaying the progression-free survival Kaplan-Meier data for PDC PD-L1 < 50 SQ for CheckMate-227 part 1

Figure 67. Independent spline models overlaying the progression free survival Kaplan-Meier data for PDC PD-L1 < 50 SQ for CheckMate-227 part 1

Table 33. Statistical goodness-of-fit indicators (AIC/BIC) values for independent parametric models fitted to progression-free survival data Nivo + Ipi PD-L1 < 50 SQ for CheckMate-227 part 1

Distribution	AIC	BIC
Generalised gamma	516.1	524.1
Spline on odds 3 knots	514.0	527.3
Spline on probit link of survival 3 knots	514.2	527.5
Spline on hazards 3 knots	515.2	528.5
Spline on probit link of survival 2 knots	517.9	528.6
Spline on odds 2 knots	519.7	530.4
Lognormal	529.5	534.8
Spline on probit link of survival 1 knot	519.9	527.9
Log-logistic	532.4	537.7
Gompertz	537.8	543.2
Spline on hazards 2 knots	521.0	531.6
Weibull	553.4	558.8
Spline on odds 1 knot	524.0	532.0
Spline on hazards 1 knot	525.5	533.5
Gamma	558.0	563.3
Exponential	559.5	562.2

Generalised Gamma	516.1	524.1

Table 34. Statistical goodness-of-fit indicators (AIC/BIC) values for independent parametric models fitted to progression-free survival data PDC PD-L1 < 50 SQ for CheckMate-227 part 1

Distribution	AIC	BIC
Log-logistic	439.2	444.6
Lognormal	448.5	453.9
Generalised gamma	449.9	458.0
Spline on probit link of survival 3 knots	435.0	448.4
Spline on odds 3 knots	435.2	448.7
Gamma	468.0	473.4
Spline on hazards 2 knots	435.2	446.0
Spline on hazards 3 knots	436.1	449.6
Spline on odds 2 knots	438.3	449.0
Weibull	478.5	483.9
Exponential	484.0	486.7
Spline on probit link of survival 2 knots	439.3	450.1
Gompertz	484.8	490.2
Spline on odds 1 knot	441.2	449.2
Spline on hazards 1 knot	443.3	451.4
Spline on probit link of survival 1 knot	450.4	458.5

Figure 68. Independent parametric models overlaying the overall survival Kaplan-Meier data for Nivo + Ipi PD-L1 > 50 for CheckMate-227 part 1

Figure 69. Independent spline models overlaying the overall survival Kaplan-Meier data for Nivo + IpiPD-L1 > 50 for CheckMate-227 part 1

Figure 70. Independent parametric models overlaying the overall survival Kaplan-Meier data for PDC PD-L1 > 50 for CheckMate-227 part 1

Figure 71. Independent spline models overlaying the overall survival Kaplan-Meier data for PDC PD-L1 > 50 for CheckMate-227 part 1

Table 35. Statistical goodness-of-fit indicators (AIC/BIC) values for independent parametric models fitted to overall survival data Nivo + Ipi PD-L1 > 50 for CheckMate-227 part 1

Distribution	AIC	BIC
Generalised gamma	1108.9	1118.9
Spline on probit link of survival 3 knots	1104.9	1121.5
Spline on hazards 3 knots	1105.4	1121.9
Spline on odds 3 knots	1105.5	1122.1
Lognormal	1109.9	1116.6
Spline on probit link of survival 1 knot	1110.4	1120.4
Spline on probit link of survival 2 knots	1111.5	1124.8
Spline on odds 1 knot	1113.1	1123.1
Gompertz	1112.1	1118.8
Log-logistic	1115.3	1121.9
Spline on odds 2 knots	1113.6	1126.8
Weibull	1122.9	1129.5
Spline on hazards 1 knot	1113.7	1123.6
Spline on hazards 2 knots	1114.5	1127.8
Gamma	1126.7	1133.4
Exponential	1144.2	1147.5

Table 36. Statistical goodness-of-fit indicators (AIC/BIC) values for independent parametric models fitted to overall survival data PDC PD-L1 > 50 for CheckMate-227 part 1

Distribution	AIC	BIC
Lognormal	1201.9	1208.4
Log-logistic	1202.8	1209.3
Generalised gamma	1203.8	1213.6
Spline on odds 1 knot	1201.4	1211.2
Spline on hazards 1 knot	1201.5	1211.3
Gompertz	1207.5	1213.9
Spline on hazards 3 knots	1202.3	1218.6
Spline on odds 3 knots	1202.4	1218.7
Spline on probit link of survival 3 knots	1202.4	1218.7
Weibull	1215.9	1222.5
Exponential	1216.3	1219.5
Spline on probit link of survival 2 knots	1203	1216.1
Gamma	1217.4	1223.9
Spline on odds 2 knots	1203.1	1216.1

Spline on hazards 2 knots	1203.2	1216.3
Spline on probit link of survival 1 knot	1203.8	1213.5

Table 37. Overall survival at different landmark points for distributions fitted to Nivo + Ipi PD-L1 > 50

Distribution	1 Year	2 Years	5 years	10 Years
[redacted]				

Table 38. Overall survival at different landmark points for distributions fitted to PDC PD-L1 > 50

Distribution	1 Year	2 Years	5 years	10 Years
[redacted]				

Figure 72. Independent parametric models overlaying the progression-free survival Kaplan-Meier data for Nivo + Ipi PD-L1 > 50 for CheckMate-227 part 1

Figure 73. Independent spline models overlaying the progression-free survival Kaplan-Meier data for Nivo + Ipi PD-L1 > 50 for CheckMate-227 part 1

Figure 74. Independent parametric models overlaying the progression-free survival Kaplan-Meier data for PDC PD-L1 > 50 for CheckMate-227 part 1

Figure 75. Independent spline models overlaying the progression-free survival Kaplan-Meier data for PDC PD-L1 > 50 for CheckMate-227 part 1

Table 39. Statistical goodness-of-fit indicators (AIC/BIC) values for independent parametric models fitted to progression-free survival data Nivo + Ipi PD-L1 > 50 for CheckMate-227 part 1

Distribution	AIC	BIC
Spline on hazards 2 knots	1040.7	1054.0
Spline on odds 2 knots	1042.0	1055.3
Spline on hazards 3 knots	1042.7	1059.3
Generalised gamma	1048.1	1058.1
Spline on odds 3 knots	1044.1	1060.7
Spline on probit link of survival 2 knots	1046.0	1059.3
Lognormal	1057.3	1063.9
Spline on probit link of survival 1 knot	1046.3	1056.2
Log-logistic	1065.7	1072.3
Gompertz	1074.8	1081.4
Spline on probit link of survival 3 knots	1046.3	1062.9
Weibull	1084.7	1091.4
Spline on odds 1 knot	1049.5	1059.5
Spline on hazards 1 knot	1050.3	1060.3
Gamma	1095.2	1101.8
Exponential	1136.0	1139.3

Table 40. Statistical goodness-of-fit indicators (AIC/BIC) values for independent parametric models fitted to progression-free survival data PDC PD-L1 > 50 for CheckMate-227 part 1

Distribution	AIC	BIC
Log-logistic	869.1	875.6
Lognormal	871.7	878.2
Generalised gamma	872.7	882.5
Spline on odds 3 knots	863.3	879.5
Spline on probit link of survival 3 knots	864.7	881.0
Gamma	881.8	888.3
Spline on hazards 3 knots	866.0	882.3
Spline on odds 1 knot	870.6	880.4
Spline on hazards 2 knots	870.6	883.7
Weibull	887.8	894.3
Exponential	893.3	896.6
Spline on probit link of survival 2 knots	871.8	884.8
Gompertz	895.3	901.8
Spline on probit link of survival 1 knot	872.2	881.9
Spline on odds 2 knots	872.6	885.6
Spline on hazards 1 knot	872.6	882.4

B5. PRIORITY Using the results from clarification questions A6 and B4 and the population-specific relative treatment effects produced in response to the ERG's clarification question A18, please produce the results of fully incremental economic analyses for each of the four defined sub-populations (see table 1). Please follow steps a) and b) described in question B2.

Please see response to question B3.

Treatment effectiveness

B6. PRIORITY Please provide details of how the results of the network meta-analysis at each time point are included in the economic model to estimate outcomes for pembrolizumab monotherapy and for atezolizumab combination therapy. Please include details of the exact results of the NMA used in the company's base case including standard errors. Please include the functionality in the economic model to allow the ERG to select between all the different NMA fractional polynomial models assessed, including those requested in Question B3.

The flow of the FPNMA data through various sheets of the model is as follows: FPNMA_datastore → FPNMA → Model parameters → ReSurv_FPNMA → ReSurv_Initial (→ Rest of model up to results).

The FPNMA_datastore sheet contains the model inputs obtained from the FPNMA. The Model parameters sheet contains the list of model parameters that feed into the model engines, including where probabilistic inputs are generated. The ReSurv_FPNMA sheet contains the FPNMA engine where the time-varying HRs between comparators are constructed and then applied to the selected reference curve's survival function. ReSurv_Initial contains the OS general population mortality rates (threshold) and PFS < OS restriction.

Because of time constraints, not all of the FPNMA models assessed were able to be incorporated into the model. Only plausible FPNMA models were incorporated into the model. Many of the FPNMA models were not plausible; as such, incorporation of these FPNMA outputs into the model would not be of value.

Time on treatment

B7. Figure 71 in the company submission presents the Kaplan-Meier plot for duration of treatment for nivolumab + ipilimumab + limited PDC. The CSR for CheckMate-9LA describes how patients may experience partial discontinuation, that is, they discontinue ipilimumab while continuing treatment with nivolumab.

a) ***Please describe how this is captured within the economic analysis. If it is not reflected in the analysis, please incorporate individual time on treatment for nivolumab and for ipilimumab.***

Separate discontinuation of nivolumab + ipilimumab is not captured within the economic model. A combined time-to-treatment discontinuation curve is used to calculate the cost of nivolumab + ipilimumab treatment. It should be noted that this is a conservative assumption, as it is correctly indicated that patients may experience partial discontinuation. Therefore, the cost of nivolumab + ipilimumab + limited PDC in the model is likely to be overestimated.

b) ***Please present the Kaplan-Meier plots for duration of treatment for nivolumab and for ipilimumab.***

Kaplan-Meier plots showing separate discontinuation for nivolumab and ipilimumab in CheckMate 9LA are shown in Figure 76 and Figure 77, respectively. The overall ITT population is represented by the solid line in each plot.

Figure 76. Kaplan-Meier Plot of Time to Treatment Discontinuation of Nivolumab – All Treated Subjects for Overall (ITT) and PD-L1 <1% NSQ Population of CheckMate 9LA

Figure 77. Kaplan-Meier Plot of Time to Treatment Discontinuation of Ipilimumab - All Treated Subjects for Overall (ITT) and PD-L1 <1% NSQ Population of CheckMate 9LA

B8. The number of doses of PDC predicted by the economic model in the PDC arm (, estimated in the "Cost_calcs" tab) appears to differ to the mean number of doses in CheckMate-9LA (estimated by the ERG as from data presented in table 17 of the submission).

a) Please explain this discrepancy.

We are unable to replicate the estimated number of doses that the ERG has presented. However, the maximum number of doses of PDC per protocol is 4. The model-predicted mean number of PDC doses received of 3.27 is well aligned with the trial-reported mean number of 3.3 to 3.4 .

b) Please provide an explanation as to why the Kaplan-Meier plot for PDC represents approximately 25% of patients on treatment at 5 months and 10% of patients on treatment at two years, when according to the

protocol, only four cycles of PDC are given and should be completed by week 10.

After treatment with PDC, patients can receive pemetrexed maintenance therapy. This is reflected in the time-to-treatment discontinuation Kaplan-Meier plot.

B9. Despite acknowledging that PFS is not a good proxy for duration on treatment (DOT), for other comparators, PFS curves were used in the model as a proxy for DOT. While the company may not have access to the relevant trial data to estimate DOT, there are a number of publications available that present evidence for time on treatment for the comparator treatments.[1,2]

Please include a scenario in which the DOT of atezolizumab + bevacizumab + carboplatin + paclitaxel and the DOT of pembrolizumab monotherapy is based on published DOT for the respective comparators. Please include the functionality in the economic model for results to be replicated.

The option of using the DOT of atezolizumab + bevacizumab + carboplatin + paclitaxel has been included based on digitised survival curves reported in the NICE appraisal for atezolizumab (TA584). This can be selected using the dropdown selection in the Survival sheet cell H249 and selecting 'Parametric extrapolation'.

Similar data that would allow for a parametric function of DOT to be adequately applied for pembrolizumab have not been identified. Thus, PFS has been maintained in the model to represent DOT for pembrolizumab.

Second-line treatment

B10. The analysis currently assumes that 100% of patients who discontinue treatment will receive second-line therapy. However, this was found to be

[1] Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med. 2016 Nov 10;375(19):1823-33.

[2] NICE. Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer (TA584). National Institute for Health and Care Excellence; 2019.

unrealistic in previous appraisals and is also far higher than patients who received second-line treatment in CheckMate-9LA.

a) ***Please provide a scenario in the economic model and present the results for the following:***

Scenario 1: The proportion receiving subsequent therapy after the immunotherapy regimens is 30% and the proportion receiving subsequent therapy after PDC is 40% (based on the proportion having subsequent systemic therapy in the CheckMate-9LA trial).

Scenario 2: The proportion receiving subsequent therapy is 60%.

We believe that the statement in this question that 100% of patients receive subsequent therapy is a misunderstanding. The base-case setting in the model is consistent with the proportion of patients receiving subsequent systemic therapy in CheckMate-9LA (31%), as shown in 'Costs!H639:S639.' Requested Scenario 2 has been run in the model, and the results are shown below.

Table 41 presents this scenario for the comparison with pembrolizumab monotherapy.

Table 41. Subsequent therapy (60%) scenario vs. pembrolizumab monotherapy

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Nivolumab + Ipilimumab with PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25,072
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality-adjusted life-year.

Table 42 presents this scenario for the comparison with atezolizumab + bevacizumab + carboplatin + paclitaxel.

Table 42. Subsequent therapy (60%) scenario vs. atezolizumab + bevacizumab + carboplatin + paclitaxel

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Nivolumab + Ipilimumab with PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25,072
Atezolizumab + bevacizumab + carboplatin + paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality-adjusted life-year.

b) Please comment on the difference between the proportions receiving subsequent therapy after discontinuation of their primary therapy in the CheckMate-9LA trial. Does the lower proportion of patients receiving second-line therapy after nivolumab + ipilimumab + limited PDC suggest that these patients are less fit at the point of discontinuation and therefore less likely to receive a second systemic treatment?

Based on clinical input (see question B11), we do not believe that the proportion of patients receiving subsequent treatment is low.

c) Nivolumab is currently an option for second-line therapy through the cancer drugs fund (CDF) so please conduct scenario 1 and scenario 2 without this option.

Results for this scenario are presented below. PDC patients receiving subsequent nivolumab in the base-case analysis are distributed proportionally across the other subsequent treatment options (51.5% of patients receive pembrolizumab, 25.8% of patients receive atezolizumab, and 22.7% of patients receive docetaxel).

Table 43 presents this scenario for the comparison with pembrolizumab monotherapy, without nivolumab as a second-line treatment option and the base case setting for the proportion of patients receiving subsequent therapy.

Table 43. Subsequent therapy (without nivolumab) scenario vs. pembrolizumab monotherapy

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Nivolumab + Ipilimumab with PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	28,195
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality-adjusted life-year.

Table 44 presents this scenario for the comparison with atezolizumab + bevacizumab + carboplatin + paclitaxel, without nivolumab as a second-line treatment option and the base case setting for the proportion of patients receiving subsequent therapy..

Table 44. Subsequent therapy (without nivolumab) scenario vs. atezolizumab + bevacizumab + carboplatin + paclitaxel

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Nivolumab + Ipilimumab with PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	28,195
Atezolizumab + bevacizumab + carboplatin + paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality-adjusted life-year.

Table 45 presents this scenario for the comparison with pembrolizumab monotherapy, without nivolumab as a second-line treatment option and 60% of patients receiving subsequent therapy.

Table 45. Subsequent therapy (without nivolumab) scenario vs. pembrolizumab monotherapy

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Nivolumab + Ipilimumab with PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	23,672

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality-adjusted life-year.

Table 46 presents this scenario for the comparison with atezolizumab + bevacizumab + carboplatin + paclitaxel, without nivolumab as a second-line treatment option and 60% of patients receiving subsequent therapy.

Table 46. Subsequent therapy (without nivolumab) scenario vs. atezolizumab + bevacizumab + carboplatin + paclitaxel

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Nivolumab + Ipilimumab with PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	23,672
Atezolizumab + bevacizumab + carboplatin + paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality-adjusted life-year.

B11. One of the benefits of providing limited PDC in combination with nivolumab and ipilimumab is that it preserves additional PDC as a future treatment option.

a) What proportion might take PDC after nivolumab + ipilimumab + limited PDC?

At a recent UK advisory board, clinicians were asked what proportion of patients might be expected to receive second-line therapy after IO + limited chemotherapy. Clinicians felt that 10%-20% would receive second-line therapy – either docetaxel +/- nintedanib or PDC. This compares with 31% of patients in the Nivolumab + ipilimumab + PDC arm in CheckMate-9LA receiving subsequent therapy as captured in the model.

b) Please include a plausible scenario in the economic model and present the results of this scenario.

Results for this scenario are presented below. It is assumed that 50% of patients receiving subsequent therapy receive PDC (25% receive Cisplatin and 25% receive Carboplatin) and 50% receive docetaxel.

Table 47 presents this scenario for the comparison with pembrolizumab monotherapy.

Table 47. Subsequent therapy (PDC) scenario vs. pembrolizumab monotherapy

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Nivolumab + Ipilimumab with PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29,135
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality-adjusted life-year.

Table 48 presents this scenario for the comparison with atezolizumab + bevacizumab + carboplatin + paclitaxel.

Table 48. Subsequent therapy (PDC) scenario vs. atezolizumab + bevacizumab + carboplatin + paclitaxel

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Nivolumab + Ipilimumab with PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29,135
Atezolizumab + bevacizumab + carboplatin + paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality-adjusted life-year.

Quality of life

B12. In the executable economic model, it appears that incorrect utility values are applied for all arms except nivolumab + ipilimumab + limited PDC, when the option to apply time to death (TTD) utilities (with no treatment effect) is

selected. It appears that treatment-specific rather than pooled utilities are applied. Please investigate this potential error and provide a corrected model, if required.

Thank you for pointing out this error in the model programming. This has been updated and is reflected in all new results presented.

B13. Please provide the mean (and 95% CI) baseline utility, as measured by EQ-5D, in each treatment arm in CheckMate-9LA.

At baseline, the mean and 95% CI of each treatment is as follows:

- Nivolumab + ipilimumab + PDC (n = 330): 0.726 (95% CI, 0.699-0.753)
- Chemo (n = 320): 0.695 (95% CI, 0.665-0.726)

B14. Please estimate the mean utility value at baseline in each treatment arm in the model, when the TTD utility method (with no treatment effect and with treatment effect) is applied, and compare this to the mean baseline utility values in CheckMate-9LA.

All available utility values, including those at baseline, were classified into the appropriate time-to-death category. Therefore, no estimates specifically for baseline values would be produced. The estimated utility values per time category from the TTD model can be found in Table 56 of the company submission.

B15. Please clarify whether the EQ-5D questionnaire was administered in CheckMate-9LA after patients discontinued their primary treatment or after disease progression.

After patients discontinued primary treatment or after disease progression, the EQ-5D was administered at follow-up visits that occurred 35 days (follow-up visit 1) and 115 days (follow-up visit 2) after the last dose and then at survival follow-up visits, which occurred every 3 months after follow-up visit 2 until death.

There were 705 patients in the CheckMate-9LA study with at least one observed utility index value available. There were 1,004 postprogression observations available in 353 of these patients.

B16. For each time point that the EQ-5D questionnaire was administered in CheckMate-9LA, please provide the total patients available and the number of completed questionnaires, for

a) all patients in each treatment arm,

See completion rate tables below. No assessment was scheduled at week 24; thus, data at week 24 represent a delay of an earlier scheduled assessment.

Table 49. Completion Rate of the EQ-5D index (UK), all randomised subjects (N = 719)

Assessment time point	Nivolumab + ipilimumab + chemotherapy (n = 361)			Platinum doublet chemotherapy (n = 358)		
	N.Comp.[a]	Out of enrolled	Out of expected[b]	N.Comp.[a]	Out of enrolled	Out of expected[b]
Baseline	348	348/361 (96.4%)	348/361 (96.4%)	340	340/358 (95.0%)	340/358 (95.0%)
Week 3	303	303/361 (83.9%)	303/338 (89.6%)	304	304/358 (84.9%)	304/323 (94.1%)
Week 6	288	288/361 (79.8%)	288/324 (88.9%)	250	250/358 (69.8%)	250/283 (88.3%)
Week 9	285	285/361 (78.9%)	285/304 (93.8%)	246	246/358 (68.7%)	246/265 (92.8%)
Week 12	256	256/361 (70.9%)	256/274 (93.4%)	155	155/358 (43.3%)	155/175 (88.6%)
Week 15	238	238/361 (65.9%)	238/255 (93.3%)	139	139/358 (38.8%)	139/152 (91.4%)
Week 18	215	215/361 (59.6%)	215/239 (90.0%)	116	116/358 (32.4%)	116/129 (89.9%)
Week 21	198	198/361 (54.8%)	198/214 (92.5%)	101	101/358 (28.2%)	101/109 (92.7%)
Week 24	97	97/361 (26.9%)	97/191 (50.8%)	42	42/358 (11.7%)	42/90 (46.7%)
Week 30	149	149/361 (41.3%)	149/170 (87.6%)	61	61/358 (17.0%)	61/71 (85.9%)
Week 36	132	132/361 (36.6%)	132/144 (91.7%)	51	51/358 (14.2%)	51/58 (87.9%)
Week 42	107	107/361 (29.6%)	107/128 (83.6%)	41	41/358 (11.5%)	41/45 (91.1%)
Week 48	100	100/361 (27.7%)	100/113 (88.5%)	39	39/358 (10.9%)	39/43 (90.7%)
Week 54	80	80/361 (22.2%)	80/100 (80.0%)	36	36/358 (10.1%)	36/41 (87.8%)
Week 60	72	72/361 (19.9%)	72/90 (80.0%)	33	33/358 (9.2%)	33/39 (84.6%)
Week 66	71	71/361 (19.7%)	71/76 (93.4%)	29	29/358 (8.1%)	29/32 (90.6%)
Week 72	50	50/361 (13.9%)	50/54 (92.6%)	15	15/358 (4.2%)	15/22 (68.2%)
Week 78	28	28/361 (7.8%)	28/33 (84.8%)	16	16/358 (4.5%)	16/17 (94.1%)
Week 84	16	16/361 (4.4%)	16/18 (88.9%)	7	7/358 (2.0%)	7/8 (87.5%)
Week 90	9	9/361 (2.5%)	9/11 (81.8%)	7	7/358 (2.0%)	7/7 (100.0%)
Week 96	3	3/361 (0.8%)	3/6 (50.0%)	2	2/358 (0.6%)	2/4 (50.0%)
Week 102	4	4/361 (1.1%)	4/4 (100.0%)	2	2/358 (0.6%)	2/3 (66.7%)
Follow-up 1	162	162/361 (44.9%)	162/240 (67.5%)	204	204/358 (57.0%)	204/276 (73.9%)
Follow-up 2	102	102/361 (28.3%)	102/160 (63.8%)	128	128/358 (35.8%)	128/197 (65.0%)

Assessment time point	Nivolumab + ipilimumab + chemotherapy (n = 361)			Platinum doublet chemotherapy (n = 358)		
	N.Comp.[a]	Out of enrolled	Out of expected[b]	N.Comp.[a]	Out of enrolled	Out of expected[b]
Survival follow-up 1	74	74/361 (20.5%)	74/120 (61.7%)	79	79/358 (22.1%)	79/143 (55.2%)
Survival follow-up 2	48	48/361 (13.3%)	48/75 (64.0%)	63	63/358 (17.6%)	63/103 (61.2%)
Survival follow-up 3	37	37/361 (10.2%)	37/46 (80.4%)	41	41/358 (11.5%)	41/66 (62.1%)
Survival follow-up 4	16	16/361 (4.4%)	16/25 (64.0%)	21	21/358 (5.9%)	21/40 (52.5%)
Survival follow-up 5	10	10/361 (2.8%)	10/10 (100.0%)	7	7/358 (2.0%)	7/11 (63.6%)
Survival follow-up 6	3	3/361 (0.8%)	3/3 (100.0%)	0	0/358 (0.0%)	0/0 (0.0%)
Survival follow-up 7	0	0/361 (0.0%)	0/0 (0.0%)	1	1/358 (0.3%)	1/1 (100.0%)

[a] Completed PROs consist of those having a non-missing EQ-5D Index (UK) value.

[b] Expected population includes those alive and, given the date of randomisation and date of treatment discontinuation, were expected to have reached the on-treatment or follow-up week according to the study protocol schedule.

b) all patients in each treatment arm, for each progression status (pre-progression and post-progression),

Table 50. Completion rate of the EQ-5D index (UK) by progression status all randomised subjects (N = 719)

Assessment time point	Nivolumab + ipilimumab + chemotherapy (n = 361)					Platinum doublet chemotherapy (n = 358)				
	Preprogression		Postprogression		Total	Preprogression		Postprogression		Total
	Comp.[a]	Exp.[b]	Comp.[a]	Exp.[b]	Exp.[b]	Comp.[a]	Exp.[b]	Comp.[a]	Exp.[b]	Exp.[b]
Baseline	347	360	1	1	361	340	358	0	0	358
Week 3	302	337	1	1	338	304	323	0	0	323
Week 6	279	315	9	9	324	243	276	7	7	283
Week 9	276	295	9	9	304	244	263	2	2	265
Week 12	234	252	22	22	274	150	170	5	5	175
Week 15	214	231	24	24	255	138	151	1	1	152
Week 18	184	208	31	31	239	109	122	7	7	129
Week 21	174	190	24	24	214	101	109	0	0	109
Week 24	86	180	11	11	191	40	88	2	2	90

Assessment time point	Nivolumab + ipilimumab + chemotherapy (n = 361)					Platinum doublet chemotherapy (n = 358)				
	Preprogression		Postprogression		Total	Preprogression		Postprogression		Total
	Comp.[a]	Exp.[b]	Comp.[a]	Exp.[b]	Exp.[b]	Comp.[a]	Exp.[b]	Comp.[a]	Exp.[b]	Exp.[b]
Week 30	129	150	20	20	170	58	68	3	3	71
Week 36	116	128	16	16	144	50	57	1	1	58
Week 42	91	112	16	16	128	41	45	0	0	45
Week 48	87	100	13	13	113	37	41	2	2	43
Week 54	72	92	8	8	100	35	40	1	1	41
Week 60	62	79	10	11	90	30	36	3	3	39
Week 66	58	63	13	13	76	28	31	1	1	32
Week 72	41	45	9	9	54	15	22	0	0	22
Week 78	21	26	7	7	33	16	17	0	0	17
Week 84	13	15	3	3	18	7	8	0	0	8
Week 90	7	9	2	2	11	7	7	0	0	7
Week 96	2	5	1	1	6	2	4	0	0	4
Week 102	3	3	1	1	4	2	3	0	0	3
Follow-up 1	47	124	115	116	240	89	161	115	115	276
Follow-up 2	31	89	71	71	160	27	96	101	101	197
Survival follow-up 1	19	64	55	56	120	7	70	72	73	143
Survival follow-up 2	14	41	34	34	75	8	48	55	55	103
Survival follow-up 3	11	20	26	26	46	4	29	37	37	66
Survival follow-up 4	6	15	10	10	25	4	23	17	17	40
Survival follow-up 5	6	6	4	4	10	1	5	6	6	11
Survival follow-up 6	3	3	0	0	3	0	0	0	0	0
Survival follow-up 7	0	0	0	0	0	1	1	0	0	1

[a] Completed PROs consist of those having a non-missing EQ-5D Index (UK) value.

[b] Expected population includes those alive and, given date of randomisation and date of treatment discontinuation, were expected to have reached the on-treatment or follow-up week according to the study protocol schedule

c) all patients in each treatment arm, in each TTD category.

Table 51. Completion Rate of the EQ-5D index (UK) By TTD All Randomised Subjects (N = 719)

	Nivolumab + ipilimumab + chemotherapy (n = 361)					Platinum doublet chemotherapy (n = 358)				
	TTD N Completed[a]				N Exp.[b]	TTD N Completed[a]				N Exp.[b]
Assessment time point	> 52 weeks	27-52 weeks	5-26 weeks	≤ 4 weeks	Total	> 52 weeks	27-52 weeks	5-26 weeks	≤ 4 weeks	Total
Baseline	223	60	56	8	361	157	90	84	8	358
Week 3	196	52	53	2	338	140	78	71	11	323
Week 6	182	51	48	4	324	126	54	64	3	283
Week 9	166	53	48	7	304	121	54	59	4	265
Week 12	140	43	45	3	274	73	31	38	1	175
Week 15	113	46	36	2	255	68	24	30	3	152
Week 18	96	43	27	2	239	52	16	26	1	129
Week 21	74	37	27	1	214	38	16	15	3	109
Week 24	33	15	10	0	191	16	6	5	0	90
Week 30	37	22	14	0	170	15	10	6	1	71
Week 36	22	11	12	1	144	12	5	4	0	58
Week 42	12	3	13	1	128	5	4	1	0	45
Week 48	9	2	10	1	113	6	2	2	0	43
Week 54	3	1	4	0	100	2	0	4	0	41
Week 60	1	0	2	0	90	0	0	4	0	39
Week 66	0	0	1	1	76	0	0	2	1	32
Week 72	0	0	0	0	54	0	0	0	0	22
Week 78	0	0	0	0	33	0	0	0	0	17
Week 84	0	0	0	0	18	0	0	0	0	8
Week 90	0	0	0	0	11	0	0	0	0	7
Week 96	0	0	0	0	6	0	0	0	0	4

Assessment time point	Nivolumab + ipilimumab + chemotherapy (n = 361)					Platinum doublet chemotherapy (n = 358)				
	TTD N Completed[a]				N Exp.[b]	TTD N Completed[a]				N Exp.[b]
	> 52 weeks	27-52 weeks	5-26 weeks	≤ 4 weeks	Total	> 52 weeks	27-52 weeks	5-26 weeks	≤ 4 weeks	Total
Week 102	0	0	0	0	4	0	0	0	0	3
Follow-up 1	32	25	46	10	240	49	38	75	7	276
Follow-up 2	19	4	25	2	160	26	25	33	5	197
Survival follow-up 1	10	3	14	3	120	4	11	20	7	143
Survival follow-up 2	2	1	1	3	75	3	4	16	3	103
Survival follow-up 3	1	0	2	0	46	0	1	6	4	66
Survival follow-up 4	0	0	1	0	25	0	0	2	1	40
Survival follow-up 5	0	0	0	0	10	0	0	1	0	11
Survival follow-up 6	0	0	0	0	3	0	0	0	0	0
Survival follow-up 7	0	0	0	0	0	0	0	0	0	1

[a] Completed PROs consist of those having a non-missing EQ-5D Index (UK) value.

[b] Expected population includes those alive and, given, date of randomisation and date of treatment discontinuation, were expected to have reached the on-treatment or follow-up week according to the study protocol schedule.

B17. In order to estimate the quality adjusted life years (QALYs) lost from adverse events (AEs), please provide details of the duration of each AE that a disutility was applied for in the model.

The cost and disutility of AEs are applied as a one-off in the first model cycle. That is, the total treatment cost and disutility per episode of each AE is multiplied by the proportion of each AE and included in week 1. It is assumed that both the treatment cost per episode and disutility per episode accounts for the duration of the AE. The application of AE costs and disutility in week 1 is potentially a conservative assumption for two reasons:

- AEs that are incurred after 1 year on treatment would be discounted in terms of costs and QALYs; therefore, applying these costs in week 1 will overestimate the impact of AEs.
- Week 1 has the maximum number of patients on treatment (patients in PFS at risk of experiencing AEs); therefore, applying the cost and disutility of AEs in week 1 will overestimate the impact of AEs.

Resource use and costs

B18. The submission describes how the relative dose intensity was applied for each treatment option. Please describe how vial wastage and sharing was accounted for in the analysis.

Vial sharing is not considered in the base-case analysis, but it can be switched on in the model by using drop-down selections in the Costs sheet (Cells G207:G289).

B19. The dose of a number of treatment options is based on patient body surface area. Please state the assumptions regarding the body surface area used in these calculations, and the method used to estimate the mean dose required.

The model uses information from the CheckMate-9LA trial to estimate body surface area. In CheckMate-9LA, the average weight of patients was 72.33 kg, and the average height of patients was 171.5 cm. The Du Bois formula is used to calculate the body surface area in the Datastore sheet (cell E21).

Other

B20. Please provide details of the surveillance, epidemiology, and end results (SEER) data and the Swedish and Norwegian registry data used to validate the survival extrapolations. Please include the baseline characteristics of patients included in the study groups as well as the OS results.

The profile of age and stage at diagnosis is shown in Table 52 for the 5,666 patients with advanced NSCLC in the SEER registry diagnosed in 1994 who met the sample criteria for this analysis. Approximately 60% of patients were male, and approximately two thirds (3,762 of 5,666) were diagnosed with stage IV disease.

Table 52. Patients with advanced NSCLC diagnosed in 1994 by stage and sex: SEER registry

	Stage IIIB		Stage IV		Stage IIIB/IV	
Sex	**N**	**%**	**N**	**%**	**N**	**%**
Male	1,172	61.6	2,265	60.2	3,3437	60.7
Female	732	38.4	1,497	39.8	2,229	39.3
Total	1,904	100.0	3,762	100.0	5,666	100

Table 53 shows the cumulative age distribution of the patient cohort. Note that the median age is approximately 68 years, with a wide range of ages at diagnosis. More than 15% of patients were 55 years or younger at diagnosis while approximately 25% were older than 75 years.

Table 53. Patients with advanced NSCLC diagnosed in 1994 by age: SEER registry

Age, years	Cumulative (%)
≤ 45	3.9
≤ 50	8.4
≤ 55	15.5
≤ 60	25.4
≤ 65	39.6
≤ 68	50.0
≤ 70	58.2
≤ 80	88.4
≤ 85	95.9

Overall survival results for the SEER cohort of patients with stage IIIB and IV NSCLC diagnosed in 1994 are shown in Table 54, along with the 5-year conditional survival at each milestone.

Table 54. Patients diagnosed in 1994 by overall survival and conditional survival: SEER registry

Year	Survival from diagnosis at annual milestone	5-Year conditional survival at each milestone
0	100.00%	1.82%
1	15.55%	9.52%
2	5.60%	22.14%
3	3.32%	33.43%
4	2.30%	40.43%
5	1.82%	47.25%
6	1.48%	53.38%
7	1.24%	58.87%
8	1.11%	63.06%
9	0.93%	68.82%
10	0.86%	61.63%
11	0.79%	59.96%
12	0.73%	56.16%
13	0.70%	NA
14	0.64%	NA
15	0.53%	NA
16	0.45%	NA
17	0.41%	NA

Overall survival results for the Norwegian registry are shown in Table 55, along with the conditional survival at each year.

Table 55. Patients' overall survival and conditional survival: Norwegian registry

Year	Survival from diagnosis at annual milestone	Conditional survival at each milestone
0	100.00%	
1	17.24%	17.24%
2	6.25%	36.24%
3	3.38%	54.14%
4	2.44%	72.22%
5	1.90%	77.88%
6	1.48%	77.78%
7	1.48%	100.00%
8	1.48%	100.00%

Year	Survival from diagnosis at annual milestone	Conditional survival at each milestone
9	1.06%	71.43%
10	0.96%	91.11%
11	0.75%	78.05%

Section C: Textual clarification and additional points

Clinical Systematic Literature Review (SLR)

C1. The search strategies used for the 9 previous searches listed in table 3, p.7 (initial search and search updates #1- #8) appear to be missing from appendix D. Please could they be provided?

The same search strategies were used in all of the core searches but with different date limits.

C2. Please clarify what the search strategies in tables 5, 6 and 7, (appendix D), were used for. They appear to be identical to the search strategy in table 4, (appendix D), however do not contain a date limit, nor do they have the search results per line.

We have removed Tables 5-7 from the appendix, as we agree they present the same search strategies as Table 4.

C3. Table 9 in appendix D lists 68 studies identified in the SLR and states that 'a summary of all the included and excluded studies as well as reasons for exclusion are incorporated in this report', however we cannot see this. Please provide the reasons for inclusion/exclusion for each study.

A summary of included and excluded studies is provided in Section D.3.1.1 of the Appendix, with a narrative description of the includes and excludes by update in the subsections. Table 9 presents a list of the included studies.

Cost-effectiveness Systematic Literature Review (SLR)

C4. In Section G.1 (page 68, appendix G) it states that conference abstracts (published from 16 March 2018 to 20 April 2020) were included in the SLR. As conference abstracts were removed from the Embase results (see tables 30,

37, 34, 41), please provide full details of the search methods and sources used to identify conference abstracts.

Conference abstracts from electronic literature databases were not included to limit identification of older conference material that had been superseded by peer-reviewed publication. However, hand-searching of conferences was conducted to include the latest evidence that had not been published in journals. For the years 2018-2020, the following conferences were hand-searched:

- American Society of Clinical Oncology (ASCO)
- ASCO Quality Care Symposium (ASCO-QoC)
- American Association for Cancer Research (AACR)
- European Cancer Congress (ECC)/European Society for Medical Oncology (ESMO)
- European Lung Cancer Conference (ELCC)
- Chicago Multidisciplinary Symposium in Thoracic Oncology
- IASLC World Lung Conference
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) (Europe and international)
- International Society for Quality of Life Research (ISOQoL)

C5. Please provide the search interface/provider used to search NHS EED and the HTA database (page 68, appendix G). Neither database has been available via the Cochrane Library (Wiley) since 7th August 2018

The National Health Service Economic Evaluation Database (NHS EED) and the Cochrane Health Technology Assessment Database (HTAD) were searched using the CRD (University of York Centre for Reviews and Dissemination) platform for the period available.

C6. There appear to be some gaps in the date coverage of the search strategies presented in appendix G:

a) ***Table 37 – date limits shown at lines 15 and 16 indicate that articles added to EMBASE during the period 01/01/2018 to 15/03/2018 were not searched for. Please explain why this time period is missing. Also, provide the number of hits retrieved by line 16, which is missing, and***

indicate which results (at line 15, 16, or both) were downloaded for screening?

Tables in the original appendix were collated numbers. We have now provided separate data tables for each update in document “ID1566 ERG responses C6 supplement eSLR search strategies”.

b) ***Table 39 – the date limit shown at line 15 indicates that this search only covered articles from the Cochrane Library published between 2012-2017. Please explain why the search did not cover articles with a publication year of 2018.***

Tables in the original appendix were collated numbers. We have now provided separate data tables for each update in document “ID1566 ERG responses C6 supplement eSLR search strategies”.

c) ***Table 41 – the date limit shown at line 15 indicates that this search only covered articles from Embase published between 2012-2017. Please explain why the search did not cover articles with a publication year of 2018.***

Tables in the original appendix were collated numbers. We have now provided separate data tables for each update in document “ID1566 ERG responses C6 supplement eSLR search strategies”.

c) ***Table 43 - the date limit shown at line 38 indicates that this search only covered articles from the Cochrane Library published from 2012-2017. Please explain why the search did not cover articles with a publication year of 2018.***

Tables in the original appendix were collated numbers. We have now provided separate data tables for each update in document “ID1566 ERG responses C6 supplement eSLR search strategies”.

C7. Table 38 (appendix G) contains errors at line numbers 18 and 19. Line numbers 34 and 35 do not exist therefore cannot be combined, and the search

would not run in PubMed. Please could the correct strategy for Table 38 be provided.

This has been updated in the appendix document. EndNote wrongly detected a reference because of {} in the string.

C8. Table 42 (appendix G) contains errors at line numbers 10, 11, 12. Line numbers 34, 35, 36 do not exist therefore cannot be combined, and the search would not run in PubMed. Please could the correct strategy for table 42 be provided.

This has been updated in the appendix document. EndNote wrongly detected a reference because of {} in the string.

Cancer Drugs Fund

C9. It is stated in the company submission that a period in the CDF would be beneficial because additional maturity OS data would reduce uncertainty. However, a CDF data collection proposal has not been submitted.

a) ***If applicable, please provide the details of your CDF data collection proposal.***

This has been submitted separately.

b) ***Please comment on how the collection of these data within the CDF period would address key uncertainties in evidence.***

The currently available data from CheckMate-9LA include a minimum follow-up of 12.7 months and thus are immature. Additional analyses will be undertaken [redacted] as more follow-up data accrue. These analyses will provide further evidence of the long-term benefit associated with nivolumab + ipilimumab + PDC over current standard of care and reduce uncertainty in the longer-term outcomes. Therefore, BMS consider nivolumab + ipilimumab + PDC to be a candidate for entry into the CDF.

Textual clarifications

C10. The number of patients at risk at months 3 and 6 differ between figures 11 and 12 (company submission). Please provide a reason for these differences,

given that all patients should have reached at least 6 months follow-up when both the initial and updated analysis took place.

At the original database lock (in October 2019), the death date was unknown for 3 patients (1 in the nivolumab + ipilimumab + limited PDC arm and 2 in the PDC arm), due to loss of follow-up or withdraw of consent. Therefore, the death dates were imputed following conventions used for imputing partial or missing dates. The actual death dates were subsequently obtained prior to the database lock in March 2020, all of which were later than the imputed death date used in the analysis based on the October 2019 database lock, increasing the number of patients at risk at months 3 and 6 very slightly.

C11. In figure 23 (company submission), median OS in months for patients with CNS metastasis is reported as not reported (NR). However, a HR is still calculated and displayed. Please provide the missing data or give a reason why these data are missing.

In the forest plots, NR means “not reached.” Therefore, although data are available, the median OS is not yet available (i.e., > 50% of patients remained alive at database lock). The HR represents the hazard reduction over the entire course of follow-up and thus can be calculated based on available data and viewed as an overall estimate of the benefit, but it is subject to minor changes at later analyses.

C12. Table 24 (company submission) lists the studies included in the ITC. The reference column for the IMpower-150 trials lists two studies with the same reference (Socinski et al., 2018). Please clarify if this should be two different study references or is it is a typo.

The OS and PFS data in Document B are taken from the Socinski et al. (2018) NEJM article. These have now been updated in Document B.

C13. Table 25 (company submission) has missing rows for the PD-L1 status column. Please add PD-L1 status in Table 25 for the following trials: OS in KN-024, OS in KN-042 and PFS in IMpower-150.

The PD-L1 status for each trial was the same for the OS and PFS analysis. This has now been added to Table 25 in Document B.

C14. Please clarify what the * refers to in the last row of the 'Treatment 2' column in table 28 (company submission).

The note that was under Table 28 was the footnote that the * should have referred to (* This is the NSQ regimen in the CheckMate-9LA trial). This has now been corrected in Document B.

C15. The table 63 title mentions the proportion of patients treated with each PDC, however, this does not appear to correspond to the values presented. Please clarify.

The Title of Table 63 in Document B has been corrected to read "Relative dose intensity of all treatments applied in the model."

C16. PRIORITY Appendix N is all highlighted as AIC. However, identical text and graphs in the company submission are not highlighted with AIC, for e.g., Figure 32 in the main submission is not highlighted with AIC, whereas Figure 49 in Appendix N is AIC. Please confirm which version of confidentiality marking should be used.

The mark-up in Document B and the Appendix has been amended to match.

C17. PRIORITY Appendix N, figures 43 and 44 have the same heading.

a) ***Please confirm which figure is for overall survival and which is for PFS.***

Figure 44 is for PFS and has been renamed to reflect this.

b) ***Please also provide these both figures with a labelled axis and clarify the meaning of the vertical lines.***

.

C18. In the equation defining the log-hazards (appendix N, page 257, after table 127), please confirm whether the last term should read $\mu_3 * t^{-1}$ (i.e., confirm that −1 is the power of t).

Yes, the text in the Appendix has been corrected to read "log hazard = (μ1 + d1) + ln(t)*(μ2 + d2) + $\mu 3 * t^{-1}$".

C19. Table 145 (appendix N) – the text states this table summarises the KeyNote studies, when in fact it appears to summarise the IMpower study. Please clarify which study is being summarised.

The wording in the title of Section 4.3.4 and below it has been corrected to state that this section describes the comparison with atezolizumab using IMpower-150, the table and title is correct.

References

Bristol Myers Squibb. Clinical study report for Part 1 of study CA209227. An open-label randomized phase 3 trial of nivolumab, or nivolumab plus ipilimumab, or nivolumab plus platinum doublet chemotherapy versus platinum doublet chemotherapy in subjects with chemotherapy-naïve stage IV or recurrent non-small cell lung cancer (NSCLC); 2019.

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Cope S, Ayers D, Zhang J, Batt K, Jansen JP. Integrating expert opinion with clinical trial data to extrapolate long-term survival: a case study of CAR-T therapy for children and young adults with relapsed or refractory acute lymphoblastic leukemia. BMC Med Res Methodol. 2019 Sep 2;19(1):182.

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Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med. 2019 Oct 17;381(16):1535-46.

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Motzer RJ, Tannir NM, McDermott DF, Aren Frontera O, Melichar B, Choueiri TK, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med. 2018 Apr 5;378(14):1277-90.

NICE National Institute for Health and Care Excellence

Patient organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Roy Castle Lung Cancer Foundation
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Roy Castle Lung Cancer Foundation is a UK wide lung cancer charity. We fund lung cancer research, tobacco control initiatives and work in lung cancer patient care (information, support and advocacy activity). Our funding base is a broad mixture including community, retail, corporate, legacies and charitable trusts. Clearly, our patient group members and contacts are a self-selected group, who have taken the step to seek out information or have accessed specialist support services. As most lung cancer sufferers tend to be older, from lower social class groups and with the five year survival being around 15%, less physically well, we acknowledge that our patients are perhaps not representative of the vast majority of lung cancer patients, who are not so well informed. It is, however, important that the opinions expressed to us, be passed on to NICE, as it considers the place of this product in the management of lung cancer
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and	As a result of the COVID pandemic, our contact with patients and carers has become virtual. The Foundation has contact with patients/carers through its UK wide network of Lung Cancer Patient Support Groups, patient/carer panel, online forums, Keep in Touch' service and its nurse-led Lung Cancer Information Helpline.

carers to include in your submission?	
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	According to the National Lung Cancer Audit, the one year survival for lung cancer overall is 37% and for those diagnosed at Stage IV, it is only 17%. Thus, this group of lung cancer patients have a particularly poor outlook. with an obvious impact on family and carers. Symptoms such as breathlessness, cough and weight loss are difficult to treat, without active anti-cancer therapy. Furthermore, these are symptoms which can be distressing for loved ones to observe.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	In recent years, we have seen new therapy options for some patients with Non Small Cell Lung Cancer – Target Therapies and Immunotherapies. There is, however, a need to identify further new targets and therapies. Current systemic treatment, for those patients with good Performance Status Stage IV disease, which does not have treatable targets, is a combination of platinum-based chemotherapy and immunotherapy. Side effects of the current standard treatment may be considerable.
8. Is there an unmet need for patients with this condition?	Yes

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	1. We are aware of the CheckMate-9LA study. This study compared Ipilimumab + Nivolumab+ 2 cycles of chemotherapy, with 4 cycles of chemotherapy, in patients with untreated metastatic NSCLC. The study reported a median survival of 15.6 months in the Ipilimumab + Nivolumab+ chemotherapy arm, compared with 10.9 months in the chemotherapy alone arm. Studies which show improvements in survival are of obvious importance to patients. It should be noted, however, that at this time, most patients in this indication will currently receive a single agent Immunotherapy, as first systemic treatment. 2. The side effect profile of this combination appears to be similar to the known side effects, we see with immunotherapy and chemotherapy agents in first line NSCLC treatment. 3. This combination represents the first dual immunotherapy regimen in NSCLC. In other cancers (melanoma and renal cell carcinoma), long term survival has been demonstrated with this combination. Offers hope to patients. 4. Two cycles of chemotherapy, as compared with four would be preferable to patients.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	As with other combinations, the side effects of chemotherapy and immunotherapy. The immunotherapy agents are administered, intravenously, for up to 2 years.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Despite recent advances, NSCLC remains a disease of unmet need, especially in the patient group, which do not have treatable targets.
- We are pleased to see new treatment options, which may benefit patients with metastatic NSCLC.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Evidence Review Group's Report
Nivolumab with ipilimumab and chemotherapy for untreated advanced non-small-cell lung cancer

Produced by CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Sahar Sharif and Ruth Walker wrote the clinical effectiveness sections of the report. Lindsay Claxton and Peter Murphy wrote the cost effectiveness sections and conducted the ERG economic analyses. Melissa Harden wrote the search strategy sections. Sofia Dias checked the indirect treatment comparisons and took overall responsibility for the report.

Note on the text

All commercial-in-confidence (CIC) data have been [redacted], all academic-in-confidence (AIC) data are [redacted].

Copyright statement

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List of abbreviations

AE	Adverse event
ALK	Anaplastic lymphoma kinase
ASBI	Average Symptom Burden Index
AUC	Area under the concentration-time curve
CASP	Critical Appraisal Skills Programme
CDF	Cancer Drugs Fund
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence/credible interval
CS	Company submission
CSR	Clinical study report
CTLA-4	T-lymphocyte antigen-4
DIC	Deviance information criterion
DOR	Duration of response
ECOG	Eastern cooperative oncology group
EGFR	Epidermal growth factor receptor
EQ-5D	EuroQol five dimension scale
EQ-5D-3L	EQ-5D 3-Level
ERG	Evidence review group
HRQOL	health-related quality of life
HRT	Hormone replacement therapy
ICER	Incremental cost-effectiveness ratios
IgG4	Human immunoglobulin G4
IMAEs	Immune mediated adverse events
IO	Immuno-oncology
IPI	Ipilimumab
ITC	Indirect treatment comparisons
ITT	Intention to treat
LCSS	Lung Cancer Symptom Scale
MID	Minimally important difference
NIVO	Nivolumab
NMA	Network meta-analysis
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PDC	Platinum doublet chemotherapy
PD-L1	Programmed death-ligand 1
PFC	Points for clarification
PFS	Progression free survival
PS	Performance status
RCT	Randomised controlled trial
SAE	Serious adverse event
STA	Single technology appraisal
VAS	Visual analogue scale

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report: Evidence Review Group Report.

All issues identified represent the ERG's view, not the opinion of NICE.

1.1 Overview of the ERG's key issues

Table 1 Summary of key issues

ID1566	Summary of issue	Report sections
1. Sub-populations for decision-making	• The ERG considers there is heterogeneity across histology and PD-L1 expression, which is not captured by considering a single decision for the whole (all-comer) population. • This includes potential heterogeneity in effects and different in-scope comparators included in the economic model. • The ERG considers there to be four distinct sub-populations based on tumour histology and PD-L1 expression. • There is evidence to suggest that absolute and relative treatment effects may be different in each of the four sub-populations. • In scope comparators, atezolizumab and pembrolizumab have marketing authorisations which cover different sub-populations. • The ERG considers the approach to implementing the clinical effectiveness data from the all-comer population from CheckMate-9LA and CheckMate-227 to be appropriate, however decision modelling should consider distinct sub-populations based on tumour histology and PD-L1 expression.	2.3 3.2.4.2 3.3 4.2.3
2. Representativeness of trial populations	• There are potential differences between the trial populations and the NHS population that would be eligible for this indication.	3.2.2

	• There were only a small number of patients from the UK in both CheckMate trials. • Patients in both trials may be healthier and younger than patients eligible for treatment in the NHS population. • The differences described suggest that the trial populations may not be fully representative of the NHS population for this indication.	
3. Heterogeneity across studies in the ITCs	• Studies included in the ITC differed by both PD-L1 expression and histology. There were also notable differences in patient characteristics and trial design, including definition of PDC, crossover and second-line treatment across trials. • In both NMAs the PDC comparator arms have been combined into a common node to allow indirect comparisons to be made. The company submission (CS) and clinical advice to the ERG state evidence showing potentially better efficacy associated with certain types of PDC regimens.	3.3
4. Validation of fractional polynomial NMA results after inclusion of CheckMate-227	• The fractional polynomial NMA was updated at the clarification stage to include CheckMate-227 to better inform the long-term extrapolation of the curves. However, the company were not able to clinically validate the new models. • Therefore, the ERG is uncertain about the reliability of the results	3.4.1.1 3.4.2.1
5. Treatment efficacy in subgroups	• The OS efficacy benefit of nivolumab treatment was not seen for patients ≥ 75 years old, patients who had never smoked and patients with liver and bone metastases in both CheckMate trials. • There may be a significant proportion of the population who may not benefit from treatment with nivolumab + ipilimumab + limited PDC compared with PDC.	3.2.4.2
6. Treatment costs of PDC	• PDC is composed of different agents in each trial, and CheckMate-9LA excludes some chemotherapy agents listed in the NICE scope for squamous patients. • The most commonly used chemotherapy for NSCLC in clinical practice, gemcitabine, was not used in the model. • Treatment costs of PDC may not be representative of clinical practice. • In clinical practice PDC regimens differ according to histology. • The company's approach fails to allow for heterogeneity in the cost of PDC regimens, which differ according to histology. • Treatment duration will also vary between the histology-based subgroups, as maintenance	4.2.4.1

	pemetrexed therapy is only licensed for non-squamous patients.	
7. Survival in patient subgroups	• Survival in the nivolumab and PDC arms was estimated from the all-comer populations of CheckMate-9LA and CheckMate-227. • However, subgroup-specific survival curves may be more appropriate in comparisons to pembrolizumab and atezolizumab + bevacizumab + PDC, which have histology-based and PD-L1-based marketing authorisations.	3.2.4.2 4.2.6.1 4.2.6.2
8. Survival predictions for PDC	• Survival for PDC uses data from CheckMate-9LA for the first 13 months of treatment. CheckMate-227 provides more optimistic estimates of survival for PDC, which may be due to higher rates of subsequent immunotherapy. • The rate of subsequent therapy in CheckMate-227 is more consistent with the expected rate in clinical practice, and so this study may be more appropriate to use to model PDC.	4.2.6.1
9. Duration of treatment benefit with immunotherapies	• The company assumed a lifelong survival benefit for nivolumab + ipilimumab + limited PDC. A five-year duration of treatment benefit may be more realistic.	4.2.6.3
10. Duration of treatment administration	• The modelled duration of treatment (DOT) of nivolumab + ipilimumab + limited PDC and PDC follows the observed DOT from Checkmate-9LA. • However, the follow-up duration of Checkmate-9LA is immature and the time on treatment may be underestimated. • PFS was used as a proxy for DOT for pembrolizumab and atezolizumab + bevacizumab + PDC. • Discontinuation prior to progression may occur. For atezolizumab + bevacizumab + PDC, PFS as a proxy for DOT will underestimate the treatment duration and associated treatment costs.	4.2.6.3
11. Health state utilities	• The approach taken by the company was to predict HRQoL by proximity to death. This approach could not be fully validated and further details are required on the statistical models fit to the EQ-5D data. Progression-based utilities may be more conceptually valid than TTD-based utilities.	4.2.7
12. Drug costs	• Drug acquisition costs may be underestimated, because the relative dose intensity was applied to the estimated cost rather than the number of required vials.	4.2.8
13. Subsequent therapy	• The rate used for modelling subsequent therapies is based on immature trial data from CheckMate-9LA and may be underestimated. It is also lower than expected rates in clinical practice.	4.2.8

	• Docetaxel was not considered to be an appropriate subsequent therapy after PDC.	
14. Other issues	• End of Life criteria apply to the squamous, PD-L1< 50% population due to the absence of available immunotherapies listed in the scope, however the criteria do not apply to any other patient populations. • The company propose access through the Cancer Drugs Fund.	7

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are:

- The ERG prefers to divide the decision problem into three distinct decisions to align with the differing in-scope comparators, whereas the company base case assumes a single decision problem to address the population covered by the marketing authorisation;
- The ERG considers there to be the potential for heterogeneity across sub-populations defined by histology and PD-L1 expression (i.e. aligning with the three decision problems). This includes heterogeneity in treatment effects and in-scope chemotherapy;
- The addition of PDC regimens listed in the scope and frequently used in clinical practice was the ERG's preference, whereas the company preferred those included in CheckMate-9LA. In addition, the ERG preferred the PDC distribution to differ according to sub-population, rather than the company-preferred single distribution used to represent all histology and PD-L1 sub-populations;
- The updated fractional polynomial network meta-analysis (FPNMA) in which CheckMate-227 is included is preferred by the ERG, whereas the company's preference is to use the original FPNMA based on CheckMate-9LA alone;
- A lifetime treatment benefit is assumed by the company, whereas the ERG prefers the assumption of a 5-year treatment benefit to align with previous appraisals;
- Time-to-death utilities are preferred by the company, yet the ERG considers there to be more conceptual validity to using progression-based utilities;
- Rates and distribution of subsequent therapy based on CheckMate-9LA and the inclusion of docetaxel are preferred by the company, the ERG prefers the more mature CheckMate-227 and excludes docetaxel.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing overall survival;
- Increasing progression-free survival:
- Having a more favourable safety profile compared to some of the other treatments.

Overall, the technology is modelled to affect costs due to:

- Its higher unit price than some current treatments:
- Greater disease management costs accrued due to longer survival.

The modelling assumptions that have the greatest effect on the ICER are:

- The distribution of treatments in PDC and duration of PDC;
- The generalisability of the PDC OS data from CheckMate-9LA;
- The modelling of relative treatment effects from the fractional polynomial network including CheckMate-227;
- The duration of nivolumab + ipilimumab + limited PDC survival benefit;
- The use of time-to-death utilities;
- The source of subsequent therapy data.

1.3 The decision problem: summary of the ERG's key issues

Issue 1 Sub-populations for decision making

Report section	2.3, 3.2.4.2, 3.3 and 4.2.3
Description of issue and why the ERG has identified it as important	Treatments for metastatic NSCLC are recommended based on histology and PD-L1 expression. In scope comparators, atezolizumab and pembrolizumab have marketing authorisations which cover different sub-populations. The ERG considers there to be four distinct sub-populations based on tumour histology and PD-L1 expression These are:

	• Non-squamous patients with PD-L1 < 50%, • Non-squamous patients with PD-L1 ≥ 50%, • Squamous patients with PD-L1 < 50%, • Squamous patients with PD-L1 ≥ 50%. There is heterogeneity across histology and PD-L1 expression, which is not captured by considering a single decision for the whole (all-comer) population and there is evidence to suggest that absolute and relative treatment effects may be different in each of the four sub-populations.
What alternative approach has the ERG suggested?	Decision modelling should consider distinct sub-populations based on tumour histology and PD-L1 expression, with three separate sub-decisions including, • Non-squamous, PD-L1 < 50% (sub-population 1) • Squamous, PD-L1 < 50% (sub-population 3) • Any histology, PD-L1 ≥ 50% (sub-populations 2 and 4) using a fully incremental analysis within each problem.
What is the expected effect on the cost-effectiveness estimates?	This approach allows for more accurate estimates of cost-effectiveness across sub-populations.
What additional evidence or analyses might help to resolve this key issue?	Further clinical input on assumptions and analyses that may be subpopulation-specific (see Issues 3, 7, 8) would allow more accurate estimates of cost-effectiveness in each decision problem.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

Issue 2 Representativeness of trial populations

Report section	3.2.2
Description of issue and why the ERG has identified it as important	There are potential differences between the trial populations and the NHS population that would be eligible for this indication. There were a small number of patients from the UK, only [redacted] patients ([redacted]%) in the CheckMate-9LA trial and [redacted] patients ([redacted]%) in the CheckMate-227 trial. Patients in both trials may be healthier than patients eligible for treatment in the NHS population as only patients with ECOG PS of 0 or 1 were included. Patients in CheckMate-9LA and CheckMate-227 had median ages of 65 years and 64 years, respectively, which is

	substantially younger than the median age of patients with NSCLC in England and Wales, which is 73 years old. The differences described suggest that the trial populations may not be fully representative of the NHS population for this indication.
What alternative approach has the ERG suggested?	N/A
What is the expected effect on the cost-effectiveness estimates?	Impacts on the uncertainty in the generalisability of the results but impact on ICERs is expected to be limited
What additional evidence or analyses might help to resolve this key issue?	Further clinical advice should be obtained on whether the differences are clinically important and whether they reduce the generalisability of the trial population to the NHS population eligible for nivolumab + ipilimumab + limited PDC.

Issue 3 Population-specific relative survival effects

Report section	3.3, 4.2.4
Description of issue and why the ERG has identified it as important	Evidence suggests that there may be differences in relative survival effects between nivolumab + ipilimumab + limited PDC and PDC in each histology- and PD-L1-based subgroup. Studies included in the ITC differed by both PD-L1 expression and histology. There were also notable differences in patient characteristics and trial design, including types of PDC, crossover and second-line treatment across trials. The NMA of patients with all-comer histology and PD-L1 ≥ 50% used the PD-L1 all comer population from the CheckMate-9LA and CheckMate-227 trials. The proportion of non-squamous patients varied between trials. The NMA of non-squamous patients with PD-L1 expression < 50% used the any PD-L1 expression populations of the ERACLE and PRONOUNCE trials. In both NMAs the PDC comparator arms have been combined into a common node to allow indirect comparisons to be made. It is unclear whether different PDC regimens can be assumed to have similar efficacy. The PDC regimens in each of the studies also varied by dose and number of cycles.

	The ERG considers the PDC comparator arms of the studies included in the ITC to be heterogenous and thus combining them may reduce the reliability of the results. The mixed populations and treatments in the ITCs could lead to an underlying bias.
What alternative approach has the ERG suggested?	The ERG suggested considering only the relevant patients from each study. However, not all studies presented relevant subgroups and the company stated that PD-L1 ≥ 50% subgroup data from CheckMate-9LA were deemed clinically implausible. Hence, the full ITT population of CheckMate-9LA was used for the ITC of patients with mixed histology and PD-L1 ≥ 50%. In the CheckMate trials, patients with PD-L1 ≥ 50% could not be split into squamous and non-squamous due to sample size limitations. Additionally, the relevant subgroups of ERACLE and PRONOUNCE were not publicly available.
What is the expected effect on the cost-effectiveness estimates?	Reduction in uncertainty of the relative effects used in the economic analysis and subsequent reduction in uncertainty of cost-effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	Further clinical advice should be obtained on whether the studies included in the ITC can be assumed sufficiently similar considering the differences described above.

Issue 4 The inclusion of CheckMate-227 in the fractional polynomial NMA

Report section	3.4.1.1, 3.4.2.1, 4.2.6.1
Description of issue and why the ERG has identified it as important	The fractional polynomial NMA was updated at the clarification stage to include CheckMate-227 to better inform the long-term extrapolation of the curves. However, the company were not able to clinically validate the new models. Therefore, the ERG is uncertain about the reliability of the results. The trend in HR over time for pembrolizumab estimated from the NMA including CheckMate-227 contradict those estimated from the NMA without CheckMate-227.

	Therefore, there is remaining uncertainty regarding the relative treatment effect of pembrolizumab and atezolizumab + bevacizumab + PDC, and their cost-effectiveness compared with nivolumab + ipilimumab + limited PDC.
What alternative approach has the ERG suggested?	The ERG prefers the NMA including CheckMate-227, as there is more data to inform the long-term extrapolations, giving more precise estimates. The most clinically plausible fractional polynomial model is not yet known.
What is the expected effect on the cost-effectiveness estimates?	Compared to the company base case including ERG corrections, there is no change in the ICER for nivolumab + ipilimumab + limited PDC versus PDC since this analysis does not use results from any NMA. Atezolizumab + bevacizumab + PDC remains dominated, when costed at list price. Pembrolizumab has an ICER of £936,367 in the fully incremental analysis in the PD-L1 ≥ 50% subgroup.
What additional evidence or analyses might help to resolve this key issue?	Clinical validation of the new models including CheckMate-227 would give credibility to the results produced, and provide greater certainty and reliability of longer-term extrapolations.

Issue 5 Treatment efficacy in subgroups

Report section	3.2.4.2
Description of issue and why the ERG has identified it as important	In CheckMate-9LA there was no evidence of OS benefit of nivolumab + ipilimumab + limited PDC and in CheckMate-227 there was no evidence of benefit of nivolumab + ipilimumab compared to PDC alone, for patients ≥ 75 years old, patients who had never smoked and patients with liver and bone metastases. Clinical advice to the ERG is that a substantial proportion of the NHS population eligible for nivolumab + ipilimumab + limited PDC are patients over 75 years old and around 20-30% have bone or liver metastases. Therefore, there may be a significant proportion of the population who may not benefit from treatment with nivolumab + ipilimumab + limited PDC compared with PDC.

What alternative approach has the ERG suggested?	N/A
What is the expected effect on the cost-effectiveness estimates?	No impact on cost-effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	Further clinical advice on whether the subgroup analyses are clinically meaningful and plausible would help to validate the results. Additionally, clinical advice on whether patients over 75 years old, patients who have never smoked and patients with liver/bone metastases would receive this treatment in practice would help to understand the importance of the lack of effect in these patients.

1.5 The cost-effectiveness evidence: summary of the ERG's key issues

Issue 6 Representativeness of PDC

Report section	2.2 and 4.2.4
Description of issue and why the ERG has identified it as important	The distribution of agents in PDC in the model were based on those used in CheckMate-9LA. The chemotherapy agent used in CheckMate-9LA, paclitaxel, is rarely used in the NHS for this indication. Gemcitabine is considered more representative of NHS clinical practice. The efficacy of each PDC regimen can be considered equivalent, and so the survival predictions in CheckMate-9LA are not limited by the exclusion of gemcitabine as a PDC element. However, each PDC regimen has different associated acquisition and administration costs, and so the treatment costs for PDC predicted by the model may not be accurate.

What alternative approach has the ERG suggested?	The cost of PDC should be estimated using a distribution of PDC agents that is aligned with UK practice. Patients receiving chemotherapy can be assumed to receive gemcitabine.
What is the expected effect on the cost-effectiveness estimates?	In a scenario where the distribution and duration of PDC are subgroup specific and aligned with UK practice, compared to the company base case including ERG corrections, the ICER for nivolumab + ipilimumab + limited PDC versus PDC: • Increases from £29,133 to £34,621 in the squamous, PD-L1 < 50% subgroup, • Increases from £29,133 to £34,916 in the non-squamous, PD-L1 < 50% subgroup, • Increases from £29,133 to £34,824 in the PD-L1 ≥ 50% subgroup Atezolizumab + bevacizumab + PDC and pembrolizumab remain dominated, when costed at list price.
What additional evidence or analyses might help to resolve this key issue?	Confirmation from clinical or regulatory bodies, such as NHS England, on the chemotherapy agent(s) most used in NHS practice for untreated, advanced NSCLC, could resolve this issue.

Issue 7 Population-specific composition and duration of PDC

Report section	4.2.4
Description of issue and why the ERG has identified it as important	The company's approach attributes an average cost of PDC treatment across all sub-populations, based on the distribution of regimens in the all-comer population of CheckMate-9LA. This approach fails to allow for heterogeneity in the cost of PDC regimens, which differ according to histology. Treatment duration will also vary between the histology-based subgroups, as maintenance pemetrexed therapy is only licensed for non-squamous patients.
What alternative approach has the ERG suggested?	The ERG considers a more appropriate assumption is to apply the population-specific distribution and duration of PDC within each of the three decision problems, when estimating the cost of treatment.
What is the expected effect on the cost-effectiveness estimates?	In a scenario where the distribution and duration of PDC are subgroup specific and aligned with UK practice, compared to the company base case including ERG corrections, the ICER for nivolumab + ipilimumab + limited PDC versus PDC: • Increases from £29,133 to £34,621 in the squamous, PD-L1 < 50% subgroup, • Increases from £29,133 to £34,916 in the non-squamous, PD-L1 < 50% subgroup, • Increases from £29,133 to £34,824 in the PD-L1 ≥ 50% subgroup Atezolizumab + bevacizumab + PDC and pembrolizumab remain dominated, when costed at list price.
What additional evidence or analyses might help to resolve this key issue?	N/A

Issue 8 Population-specific absolute survival effects

Report section	3.2.4.2 and 4.2.4
Description of issue and why the ERG has identified it as important	There may be differences in absolute survival effects between each histology- and PD-L1-based subgroup. This means that the

	total life time costs and QALYs for nivolumab + ipilimumab + limited PDC and for PDC, which are based on observed (absolute) survival, may differ between subgroups. Since relative treatment effects for pembrolizumab and atezolizumab + bevacizumab + PDC are applied to these survival projections, this will also influence the magnitude of the relative costs and QALYs for these comparators as well.
What alternative approach has the ERG suggested?	Subgroup-specific survival curves for nivolumab + ipilimumab + limited PDC and for PDC may be more appropriate than survival curves estimated from the all-comer population of the trial. However, considering that these analyses would be based on reduced sample sizes, they may not be as robust as if the all-comers population were used, and any differences (between treatments and between subgroup-specific and all-comer populations) may not be significant. Subgroup-specific survival curves provided at the clarification stage are in the process of being clinically validated by the company. At present, it is not possible to comment on whether it is appropriate to use subgroup-specific survival data or which are the most appropriate survival models, and so the ERG suggests that these are used in an exploratory analysis only until they are validated.
What is the expected effect on the cost-effectiveness estimates?	Compared to the company base case including ERG corrections, the ICER for nivolumab + ipilimumab + limited PDC versus PDC: • Increases from £29,133 to £52,528 in the squamous, PD-L1 < 50% subgroup, • Increases from £29,133 to £33,684 in the non-squamous, PD-L1 < 50% subgroup, • Decreases from £29,133 to £27,460in the PD-L1 ≥ 50% subgroup Atezolizumab + bevacizumab + PDC and pembrolizumab remain dominated, when costed at list price.

What additional evidence or analyses might help to resolve this key issue?	Validation of the predictions of the subgroup-specific survival curves and comparison to all-comer based survival projections are required to inform the selection of the model for use in the economic analysis. Clinical input to the predictive impact of PD-L1 expression and histology would help to validate the approach.

Issue 9 Survival of patients on PDC

Report section	4.2.6.1
Description of issue and why the ERG has identified it as important	Modelling the outcomes of PDC was based on the first 13 months of data from CheckMate-9LA, followed by data from CheckMate-227. Compared with CheckMate-227, survival is more pessimistic in CheckMate-9LA, and the use of CheckMate-9LA may underestimate survival projections. The survival difference may be due to the extent to which subsequent immunotherapy is used after PDC, which is lower in CheckMate-9LA. It is generally considered that 50% would receive subsequent immunotherapy in UK practice which is more aligned with the rate in CheckMate-227.
What alternative approach has the ERG suggested?	An alternative approach is to use data from CheckMate-227 to model survival for PDC over the whole patient lifetime. This approach also avoids the need to switch between sources of data, and the need to consider whether any adjustments for differences in populations are required. However, the same approach cannot be taken for nivolumab + ipilimumab + limited PDC as the initial part of the survival curve will not capture the impact of limited PDC. Therefore, in this scenario, survival should be estimated using the relative effect estimated from the NMA (including CheckMate-227), with the fractional polynomial form capturing the varying hazard rate compared to PDC.
What is the expected effect on the cost-effectiveness estimates?	Compared to the company base case including ERG corrections, the ICER for nivolumab + ipilimumab + limited PDC versus

	PDC increases from £29,133 to £31,442 in all three sub-populations. Atezolizumab + bevacizumab + PDC and pembrolizumab remain dominated, when costed at list price.
What additional evidence or analyses might help to resolve this key issue?	Further validation of the projected survival would help to determine whether using this approach is a more appropriate alternative than that used in the base case analysis.

Issue 10 Duration of treatment benefit

Report section	4.2.6.1
Description of issue and why the ERG has identified it as important	The company assumed a lifelong survival benefit for patients receiving first-line immunotherapy. Evidence provided by the company to support their assumption is of limited relevance, as it is based on four years of follow-up data and is for a previously treated population. As a result, survival projections may be too optimistic for nivolumab + ipilimumab + limited PDC – the projected survival rate reaches that of the general population after approximately 18 years and 10% of patients alive, implying a cure for these patients.
What alternative approach has the ERG suggested?	A benefit of treatment limited to five years after discontinuation was preferred by the ERG. The more conservation assumption of a three-year benefit was also explored.
What is the expected effect on the cost-effectiveness estimates?	When the duration of survival benefit is limited to three years, the ICER for nivolumab + ipilimumab + limited PDC versus PDC increases from £29,133 to £36,251 in all three subgroups. When the duration of survival benefit is limited to five years, the ICER for nivolumab + ipilimumab + limited PDC versus PDC increases from £29,133 to £32,879 in all three subgroups. Atezolizumab + bevacizumab + PDC and pembrolizumab remain dominated, when costed at list price.
What additional evidence or analyses might help to resolve this key issue?	Uncertainties regarding long-term survival of patients receiving nivolumab + ipilimumab + limited PDC may be resolved through

	additional follow-up in CheckMate-9LA. However, it is unlikely that data would be sufficiently mature at the end of the CDF assessment period to support a five-year survival benefit duration. Analyses of long-term data from Phase III trials of other immunotherapies, such as five-year survival recently reported for KeyNote-024, may provide supporting evidence for a durable treatment benefit.

Issue 11 Duration of treatment

Report section	4.2.6.3
Description of issue and why the ERG has identified it as important	a) The modelled duration of treatment (DOT) of nivolumab + ipilimumab + limited PDC and PDC follows the observed DOT from Checkmate-9LA. However, 21% of patients in the nivolumab arm remained on treatment at the time of analysis and so the time on treatment may be underestimated. b) Modelled PFS for pembrolizumab and for atezolizumab + bevacizumab + PDC was used as a proxy for DOT. However, this may underestimate the treatment duration and associated treatment costs, since discontinuation can occur prior to progression, e.g. due to treatment-related adverse events.
What alternative approach has the ERG suggested?	Observed data from IMPower150 were preferred to model DOT for atezolizumab and bevacizumab individually. Observed DOT curves were not available for pembrolizumab; however, as this is a monotherapy with a good tolerability, PFS is a relatively good proxy for DOT.
What is the expected effect on the cost-effectiveness estimates?	Atezolizumab + bevacizumab + PDC remains dominated, when costed at list price.
What additional evidence or analyses might help to resolve this key issue?	Uncertainties regarding the duration of treatment for patients receiving nivolumab + ipilimumab + limited PDC may be resolved through additional follow-up in CheckMate-9LA. Censoring marks and numbers at risk on the nivolumab + ipilimumab + limited PDC and PDC Kaplan-Meier plots of DOT used in the model would indicate how complete these data are, and the extent of the uncertainty that needs to be resolved.

Issue 12 Utility values estimated from proximity to death

Report section	4.2.7
Description of issue and why the ERG has identified it as important	The approach taken by the company was to predict HRQoL by proximity to death. This approach could not be fully validated and further details are required on the statistical models fit to the EQ-5D data to estimate health state utilities.
What alternative approach has the ERG suggested?	The ERG prefers the use of progression-based health state utilities estimated from CheckMate-9LA data. Progression-based utilities are more conceptually valid than TTD-based utilities, as time to death is not a causal determinant of HRQoL and can only be measured retrospectively. Progression-based utilities may also support a more robust analysis. There are a large number of available EQ-5D observations for the progressed health state, as data continued to be collected from patients after progression until death. In contrast, there are only a small number of observations for the health state representing the period closest to death.
What is the expected effect on the cost-effectiveness estimates?	Compared to the company base case including ERG corrections, the ICER for nivolumab + ipilimumab + limited PDC versus PDC increases from £29,133 to £32,052 in all three subgroups. Atezolizumab + bevacizumab + PDC and pembrolizumab remain dominated, when costed at list price.
What additional evidence or analyses might help to resolve this key issue?	For validation purposes, further details of the models fit to the EQ-5D data (e.g. repeated measures) are required, and details of whether any other time category cut offs were tested, or whether time as a continuous variable was considered. A comparison of the fit of the progression-based and proximity to death-based models would aid in determining which is statistically the most appropriate. Explanation so to why there were fewer observations available for the TTD health states than the progression-based health states would be useful.

	The company may also wish to amend their model structure to allow the mean utility for the cohort to be estimated on a per-cycle basis, to allow for the validation of predicted utility values over time.

Issue 13 Estimation of drug costs using relative dose intensity

Report section	4.2.8.1
Description of issue and why the ERG has identified it as important	Drug acquisition costs may be underestimated, because the relative dose intensity was applied to the estimated cost rather than the number of required vials.
What alternative approach has the ERG suggested?	The ERG considers it most appropriate where relative dose intensity is applied to the expected dose rather than the expected cost.
What is the expected effect on the cost-effectiveness estimates?	When the relative dose intensity adjustment is applied to the number of vials, the ICER for nivolumab + ipilimumab + limited PDC versus PDC increases from £29,133 to £29,507 in all three subgroups.
What additional evidence or analyses might help to resolve this key issue?	The company should provide a rationale for why dose adjustments were made for each comparator, and whether these would result in fewer vials being used. If there are some comparators where a change in dose would lead to a change in vial requirements, the relative dose adjustment for that comparator should be applied to the expected dose rather than the expected cost.

Issue 14 The proportion of patients receiving subsequent therapy

Report section	4.2.8.3
Description of issue and why the ERG has identified it as important	The proportion of patients on subsequent anticancer therapy was based on relatively immature trial data from CheckMate-9LA. The rates are likely an underestimation since approximately a fifth of nivolumab + ipilimumab + limited PDC arm patients remained on their first-line treatment at the latest follow up visit.

	The use of CheckMate-9LA to model rates of subsequent therapy is also internally inconsistent with the approach to modelling survival. Data from CheckMate-227 was used to model survival after 13 months, which is when the expected survival benefits associated with subsequent therapy would most likely to manifest. The proportion receiving subsequent therapy in the model and in CheckMate-9LA than is lower than expected usage in UK clinical practice, where approximately 50% of patients would receive an immunotherapy after discontinuing first-line chemotherapy. This has implications for both the costs of treatment and the survival benefit after discontinuation, which may be underestimated in the PDC arm of CheckMate-9LA.
What alternative approach has the ERG suggested?	The ERG's preferred assumption uses data from the CheckMate-227 trial, in which 40% of the nivolumab + ipilimumab + limited PDC arm and 60% of the PDC arm receive a subsequent anticancer therapy. This trial has longer follow-up than CheckMate-9LA.
What is the expected effect on the cost-effectiveness estimates?	In all three subgroups, the ICER for nivolumab + ipilimumab + limited PDC versus PDC decreases from £29,133 to £24,890. Atezolizumab + bevacizumab + PDC and pembrolizumab remain dominated, when costed at list price.
What additional evidence or analyses might help to resolve this key issue?	Uncertainties regarding the rates of subsequent therapy may be resolved through additional follow-up in CheckMate-9LA. However, if rates in CheckMate-9LA are lower than those expected in clinical practice, the benefits of these treatments would not appropriately captured in the economic model.

Issue 15 The distribution of subsequent therapy

Report section	4.2.8.3
Description of issue and why the ERG has identified it as important	Docetaxel was not considered to be an appropriate subsequent therapy after PDC. Clinical experts confirmed that, after

	chemotherapy, patients would have an immunotherapy monotherapy if they are well enough for subsequent treatment. Since nivolumab has only recently become part of routine commissioning for previously treated NSCLC, after transitioning out of the Cancer Drugs Fund, there is uncertainty regarding the distribution between immunotherapy agents after PDC.
What alternative approach has the ERG suggested?	Docetaxel has been removed as a second-line therapy option after PDC.
What is the expected effect on the cost-effectiveness estimates?	In all three subgroups, the ICER for nivolumab + ipilimumab + limited PDC versus PDC decreases from £29,133 to £27,774. Atezolizumab + bevacizumab + PDC and pembrolizumab remain dominated, when costed at list price.
What additional evidence or analyses might help to resolve this key issue?	Input from clinical or regulatory bodies, such as NHS England, on the expected usage of immunotherapies after chemotherapy in NHS practice could resolve this issue.

1.6 Other key issues: summary of the ERG's view

Issue 16 End of life criteria

Report section	7
Description of issue and why the ERG has identified it as important	The company considered the End of Life criteria for the licensed (all-comer) population for nivolumab + ipilimumab + limited PDC. The ERG considers there to be a number of distinct decision problems based on histology and PD-L1 expression, and that survival may differ between each subgroup. End of Life criteria may apply to the squamous, PD-L1 < 50% population due to the absence of available immunotherapies listed in the scope. The expected life expectancy of PDC in this population is [redacted], and nivolumab + ipilimumab + limited PDC is associated with a survival benefit of greater than 3 months.
What alternative approach has the ERG suggested?	End of Life criteria should be considered in each individual decision problem. The company should also present undiscounted life years in their analysis when considering if End of Life are met.
What is the expected effect on the cost-effectiveness estimates?	If End of Life are met for any of the populations, then the ICER may be compared against a higher threshold.

What additional evidence or analyses might help to resolve this key issue?	Further validation of the projected survival for each comparator is required to determine whether End of Life criteria are met (described in Issue 8 in Section 1.5)

Issue 17 Access to Cancer Drugs Fund (CDF)

Report section	n/a
Description of issue and why the ERG has identified it as important	The company have indicated that they wish for nivolumab + ipilimumab + limited PDC to be considered for entry into the CDF.
What alternative approach has the ERG suggested?	Key uncertainties in the clinical and economic analysis should be resolved before entry into the CDF can be approved. The minimum follow-up of CM-9LA is currently 12.7 months. A key driver of the analysis is the duration of survival benefit for nivolumab + ipilimumab + limited PDC after discontinuation of treatment. A 3-year benefit duration has previously been considered to be a conservative estimate; therefore, at the end of the data collection period, the data may not yet be sufficiently mature to determine the duration of benefit.
What is the expected effect on the cost-effectiveness estimates?	No impact.
What additional evidence or analyses might help to resolve this key issue?	Key uncertainties regarding the clinical evidence are discussed in Section 1.3 and uncertainties regarding the economic evidence are discussed in Section 1.5.

1.7 Summary of ERG's preferred assumptions and resulting ICER

Modelling errors identified and corrected by the ERG are described in Section 5.3. For further details of the exploratory and sensitivity analyses done by the ERG, see Section 6. The results of the ERG's exploratory analyses including the ERG's preferred base case are presented in Table 2, Table 3 and Table 4.

Table 2 ERG exploratory scenarios: Squamous, PD-L1 < 50%

Scenario	Interventions	Costs	QALYs	ICER	Change from company base case
Company base-case	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,133	-
Correction of errors	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,279	+£146
1) Composition of PDC	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£34,621	£5,487
2) Subgroup-specific survival modelling	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£52,528	+£23,394
3) FPNMA – include CM-227	PDC	n/a	n/a	-	-
	NIVO + IPI + limited PDC	n/a	n/a	n/a	n/a
2 + 3) Sub groups specific + include CM-227 in the network	PDC	n/a	n/a	-	-
	NIVO + IPI + limited PDC	n/a	n/a	n/a	n/a
4) Outcomes for PDC based on CM-227, outcomes for other interventions are relative effects from FPNMA	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£31,442	+£2,308
5a) PFS model selection – NIVO + IPI + limited PDC	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,879	+£745
5b) PFS model selection - PDC	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,355	+£221
6a) Duration of survival benefit: 3 years	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£36,251	+£7,117
6b) Duration of survival benefit: 5 years	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£32,879	+£3,746
7) Duration of ATEZO+BEV+PDC based on DOT	PDC	n/a	n/a	-	-
	NIVO + IPI + limited PDC	n/a	n/a	n/a	n/a
8) Progression-based utilities	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£32,052	+£2,919
9) Subsequent therapy: no docetaxel as a second line therapy after PDC	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£27,774	-£1,360
	PDC	[redacted]	[redacted]	-	-

10) CheckMate-227 to inform rates of subsequent therapy	NIVO + IPI + limited PDC	[redacted]	[redacted]	£24,890	-£4,244
11) Second-line PAS for nivolumab	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,734	+£601
12a) Dose intensity adjustment	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,507	+£374
12b) Remove dose intensity	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£31,223	+£2,090
ERG base case: Error correction, 1, 5a, 5b, 6b, 8, 9, 10 & 11	**PDC**	[redacted]	[redacted]	**-**	**-**
	NIVO + IPI + limited PDC	[redacted]	[redacted]	**£36,915**	**+£7,782**

Table 3 ERG exploratory scenarios: Non-squamous, PD-L1 < 50%

Scenario	Interventions	Costs	QALYs	ICER	Change from company base case
Company base-case	PDC	[redacted]	[redacted]	-	
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,133	-
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	-
Correction of errors	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,279	+£146
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	-
1) Composition of PDC	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£34,916	£5,783
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	-
2) Subgroup-specific survival modelling	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£33,684	+£4,551
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	-
3) FPNMA – include CM-227	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,279	+£146
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	-
2 + 3) Sub groups specific + include CM-227 in the network	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£33,684	+£4,551
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	-

4) Outcomes for PDC based on CM-227, outcomes for other interventions are relative effects from FPNMA	PDC	[redacted]	[redacted]	-	
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£32,127	+£2,993
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	
5a) PFS model selection – NIVO + IPI + limited PDC	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,879	+£745
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	-
5b) PFS model selection - PDC	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,355	+£221
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	-
6a) Duration of survival benefit: 3 years	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£36,251	+£7,117
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	-
6b) Duration of survival benefit: 5 years	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£32,879	+£3,746
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	-
7) Duration of ATEZO+BEV+PDC based on DOT	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,279	+£146
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	-
8) Progression-based utilities	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£32,052	+£2,919
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	-
9) Subsequent therapy: no docetaxel as a second line therapy after PDC	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£27,774	-£1,360
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	-
10) CheckMate-227 to inform rates of subsequent therapy	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£24,890	-£4,244
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	-
11) Second-line PAS for nivolumab	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,734	+£601
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	-
	PDC	[redacted]	[redacted]	-	-

12a) Dose intensity adjustment	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,507	£374
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	-
12b) Remove dose intensity	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£31,223	£2,090
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	-
ERG base case: Error correction, 1, 3, 5a, 5b, 6b, 7, 8, 9, 10 & 11	**PDC**	[redacted]	[redacted]	**-**	**-**
	NIVO + IPI + limited PDC	[redacted]	[redacted]	**£37,420**	**+£8,286**
	ATEZO + BEV + PDC	[redacted]	[redacted]	**Dominated**	**-**

Table 4 ERG exploratory scenarios: Mixed histology, PD-L1 ≥ 50%

Scenario	Interventions	Costs	QALYs	ICER	Change from company ICER
Company base-case	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,133	-
	PEMBRO	[redacted]	[redacted]	Dominated	-
Correction of errors	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,279	+£146
	PEMBRO	[redacted]	[redacted]	Dominated	-
1) Composition of PDC	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£34,824	£5,691
	PEMBRO	[redacted]	[redacted]	Dominated	-
2) Subgroup-specific survival modelling	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£27,460	-£1,674
	PEMBRO	[redacted]	[redacted]	Dominated	-
3) FPNMA – include CM-227	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,279	+£146
	PEMBRO	[redacted]	[redacted]	£937,419	-
2 & 3) Sub groups specific + CM-227 in the network	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£27,460	-£1,674
	PEMBRO	[redacted]	[redacted]	£936,367	-
4) Outcomes for PDC based on CM-227, outcomes for other interventions are	PDC	[redacted]	[redacted]	-	
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£31,442	+£2,308
	PEMBRO	[redacted]	[redacted]	£494,309	-

relative effects from FPNMA					
5a) PFS model selection – NIVO + IPI + limited PDC	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,879	+£745
	PEMBRO	[redacted]	[redacted]	Dominated	-
5b) PFS model selection - PDC	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,355	+£221
	PEMBRO	[redacted]	[redacted]	Dominated	-
6a) Duration of survival benefit: 3 years	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£36,251	+£7,117
	PEMBRO	[redacted]	[redacted]	Dominated	-
6b) Duration of survival benefit: 5 years	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£32,879	+£3,746
	PEMBRO	[redacted]	[redacted]	Dominated	-
7) Duration of ATEZO+BEV+PDC based on DOT	PDC	n/a	n/a	n/a	n/a
	NIVO + IPI + limited PDC	n/a	n/a	n/a	n/a
	PEMBRO	n/a	n/a	n/a	n/a
8) Progression-based utilities	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£32,052	+£2,919
	PEMBRO	[redacted]	[redacted]	Dominated	-
9) Subsequent therapy: no docetaxel as a second line therapy after PDC	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£27,774	-£1,360
	PEMBRO	[redacted]	[redacted]	Dominated	-
10) CheckMate-227 to inform rates of subsequent therapy	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£24,890	-£4,244
	PEMBRO	[redacted]	[redacted]	Dominated	-
11) Second-line PAS for nivolumab	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,734	+£601
	PEMBRO	[redacted]	[redacted]	Dominated	-
12a) Dose intensity adjustment	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,507	+£374
	PEMBRO	[redacted]	[redacted]	Dominated	-
12b) Remove dose intensity	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£31,223	+£2,090
	PEMBRO	[redacted]	[redacted]	Dominated	-

ERG base case: Error correction, 1, 3, 5a, 5b, 6b, 8, 9, 10 & 11	**PDC**	[redacted]	[redacted]	**-**	**-**
	NIVO + IPI + limited PDC	[redacted]	[redacted]	**£37,262**	**+£8,129**
	PEMBRO	[redacted]	[redacted]	**£287,171**	**-**

EVIDENCE REVIEW GROUP REPORT

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This appraisal concerns the treatment of untreated stage IV or recurrent non-small cell lung cancer (NSCLC) without sensitising epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) fusions. NSCLC can be divided into three main histological subtypes, squamous cell carcinoma, adenocarcinoma, and large-cell carcinoma, accounting for ~25-30%, ~40% and ~10-15% of cases, respectively. Together adenocarcinoma, and large-cell carcinoma (along with other minority subtypes) are known as non-squamous NSCLC. During 2018, ~35,239 people in England and Wales were diagnosed with NSCLC which accounts for 80-85% of all lung cancers. Approximately 49% of patients are diagnosed with stage IV disease.[1]

Disease- related symptoms include cough, dyspnoea, pain, anorexia and fatigue. An estimated 90% of patients with advanced NSCLC will experience two or more of these disease-related symptoms, which can cause psychological distress and negatively affect patient's health-related quality of life (HRQOL). For most patients with advanced NSCLC, the aim of treatment is to prolong overall and progression free survival (PFS) and improve quality of life.

2.2 Background

2.2.1 Critique of company's description of underlying health problem

The ERG considers the company's description of the underlying health problem to be appropriate and relevant to the decision problem under consideration. The CS explains that long-term survival for patients with advanced or metastatic NSCLC remains poor, with 1-year survival rates for patients with stage IV NSCLC estimated at 15.5% and 5-year survival for all stage IV lung cancer patients estimated at 2.9%.[2]

The CS describes that better understanding of lung disease has led to the identification of subgroups of patients who can benefit most from new treatments. This includes the identification of patients with the protein biomarker programmed death-ligand 1 (PD-L1). This biomarker is expressed on a continuum that can be classified into ≥ 50%, 1% - 49% and < 1%. A pooled analysis of seven clinical trials of nivolumab (N=4,972) showed that the proportion of patients with NSCLC exhibiting PD-L1 expression levels ≥ 50%, 1% - 49% and < 1%, were 29.8%, 34.8%, and 35.4%, respectively.[3] The ERG were unable to verify these figures as they differed slightly from those reported in the citation provided in the CS (Krigsfeld et al., 2017[3]).

The CS explains that patients whose tumours have higher PD-L1 expression may have a greater likelihood of benefit when treated with anti-PD1-L1 immuno-oncology (IO) therapies. Clinical advice to the ERG agrees that this would be expected in practice. The ERG notes that a recent systematic review looking at treatment effect modification of immunotherapy-based regimens in first-line advanced NSCLC, showed that higher PD-L1 expression levels may yield larger relative treatment effects for IO monotherapy (for PFS and OS) and IO therapy plus chemotherapy (for PFS only). There was no evidence suggesting PD-L1 expression levels influence relative effect sizes for OS in IO therapy plus chemo, and for IO dual therapy (two immuno-oncology therapies used in combination) for PFS or OS.[4] Although these results demonstrate potential differences in the effect of PD-L1 expression on clinical outcomes, they are not directly relevant to the decision problem which is for IO dual therapy plus chemotherapy.

The CS states that PD-L1 is not an exclusionary biomarker and considers patients regardless of PD-L1 expression levels, including those with low or no PD-L1 expression. As PD-L1 expression can influence the interventions given in clinical practice (Table 5) and given the contradictory evidence regarding the effect of PD-L1 expression on clinical outcomes,[4] PD-L1 subgroups are explored in further detail in section 3.2.4.2.

2.2.2 Critique of company's overview of current service provision

The CS explains that treatment choices are influenced by the presence of biological markers (including EGFR mutation, ALK translocation and PD-L1 expression status), histology (non-squamous and squamous), clinical factors and previous treatment experience.

This appraisal concerns patients with advanced stage NSCLC who are previously untreated and are without sensitising EGFR mutations or ALK translocations. Table 5 shows the first-line treatment options available for patients with a good performance status in the NHS in England. These are histology-based platinum doublet chemotherapy (PDC), pembrolizumab for squamous or non-squamous patients with a PD-L1 expression level ≥ 50% and atezolizumab + bevacizumab + PDC for non-squamous patients with PD-L1 expression level < 50%.

Clinical advice to the ERG was that the suitability of newer treatment options for patients with an ECOG PS > 1 is largely unknown, as clinical trials have tended to focus on those with a good performance status.

Table 5 First-line treatment options for patients with previously untreated advanced NSCLC without EGFR or ALK mutations and good performance status (Adapted from figure 6 in the CS).

Histology	Non-squamous			Squamous		
PD-L1 expression level	**<1%**	**1%-49%**	**≥50%**	**<1%**	**1%-49%**	**≥50%**
First-line treatment options			PEMBRO			PEMBRO
	ATEZO + BEV +PDC					
	PDC (Cisplatin or carboplatin + docetaxel, gemcitabine, paclitaxel or vinorelbine) **For patients with adenocarcinoma or large cell carcinoma:** PDC (Pemetrexed + cisplatin with or without pemetrexed maintenance therapy).			PDC (Cisplatin or carboplatin + docetaxel, gemcitabine, paclitaxel or vinorelbine) [5]*		

Abbreviations: ATEZO = atezolizumab; BEV = bevacizumab; NSCLC = non-small cell lung cancer; NSQ = non-squamous; PDC = platinum doublet chemotherapy; PD-L1 = programmed death-ligand 1; PEMBRO = pembrolizumab; SQ = squamous.
*CS states only PDC (Cisplatin or carboplatin + gemcitabine or vinorelbine).

A number of PDC regimens are recommended by NICE as first line treatment options for squamous patients (Table 5). The most commonly used regimen in England is carboplatin plus gemcitabine.[5] Clinical advice to the ERG was that gemcitabine is preferred as it has a better side effect profile. Carboplatin plus vinorelbine is used in a minority of cases. Carboplatin in combination with paclitaxel or docetaxel are used very rarely due to their association with hair loss.[5] For non-squamous patients, clinical advice to the ERG was that carboplatin in combination with pemetrexed is the preferred PDC regimen and that the option of atezolizumab + bevacizumab + PDC is used in some centres for non-squamous patients PD-L1 expression level <50% and who have liver metastasis.

The CS explains that pembrolizumab with carboplatin and paclitaxel is also recommended as an option for metastatic untreated squamous NSCLC via the Cancer Drugs Fund (CDF). As this combination is not in routine commissioning, it cannot be considered as a comparator. However, clinical advice to the ERG was that that this treatment option is currently being used in clinical practice and would be considered before any other treatment options for both squamous and non-squamous patients, with PD-L1 expression level < 50%, whilst pembrolizumab alone is used for those with a PD-L1 ≥ 50%.

2.2.3 Critique of the company's description of the technology

This appraisal is for nivolumab + ipilimumab + limited PDC. The company define limited PDC as that used in clinical trials: two cycles of chemotherapy every 3 weeks, which differs by histology (non-squamous: pemetrexed + cisplatin or carboplatin; squamous: paclitaxel + carboplatin).

The CS explains that the action of nivolumab and ipilimumab are distinct and complementary. Nivolumab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody that targets and blocks the programmed death-1 (PD-1) receptor, whilst ipilimumab is a recombinant human anti–cytotoxic T-lymphocyte antigen-4 (CTLA-4) monoclonal antibody that blocks the effects of CTLA-4 to enhance T-cell–mediated immune responses to tumour cells. Clinical advice to the ERG suggests it is plausible that the therapies are complimentary to each other with nivolumab modifying the tumour environment and ipilimumab mediating the immune response.

The CS explains that there are key differences between IO therapies and standard anti-cancer therapies and that varying patterns of response to IO therapies can be observed. These include:

- a 'conventional' response
- a slow steady decline in tumour burden
- a late response after initial progression
- new lesions appear and then decline along with target lesion

Clinical advice to the ERG suggests that response to IO therapies may be slower than the response to chemotherapies, and that the addition of limited PDC may help to prevent early disease progression. It was also noted that a late response after initial progression has been reported in melanoma patients treated with immunotherapy, but may not be the case in NSCLC patients. On the 17th September 2020, nivolumab received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) which recommended an extension to the existing indication for NSCLC to include nivolumab in combination with ipilimumab and 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.

2.3 Critique of company's definition of decision problem

Table 6 Summary of decision problem (adapted from Table 1 in the CS)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale*	ERG comment
Population	Adults with untreated metastatic NSCLC without sensitising EGFR mutations or ALK fusions.	Adults with untreated stage IV or recurrent NSCLC without sensitising EGFR mutations or ALK fusions.	NR	The clinical evidence submitted by the company matches the patient population described in the final scope, with the addition of patients with recurrent NSCLC without sensitising EGFR mutations or ALK fusions. Clinical advice to the ERG suggests that patients presenting with recurrent disease would have undergone surgery +/- adjuvant chemotherapy or radiotherapy, but would not be expected to respond differently to treatment compared to those with untreated stage IV disease. Also considered in this appraisal are patients with stage IIIB disease and malignant pleural or pericardial effusion ("wet" stage IIIB). The CS explain that guidelines recommended that they be treated as though they have stage IV disease and in updated staging criteria, such patients are now considered stage IV. Clinical advice to the ERG confirmed that they are treated as stage IV. Therefore, ERG agrees that these patients should be included.
Intervention	Nivolumab with ipilimumab and standard chemotherapy	Nivolumab (Opdivo®) with ipilimumab (Yervoy®) and standard chemotherapy	NA	The intervention described in the company's submission matches the intervention described in the final scope. The key supporting phase 3 trial, CheckMate-9LA includes nivolumab (360 mg every three weeks) administered intravenously with ipilimumab (1 mg/kg every six weeks), plus 2 cycles of histology-based chemotherapy (every 3 weeks). Further details of the method of administration and dosing, include that of the supporting CheckMate-227 trial are reported in section 3.2.1.
Comparator(s)	For adults with non-squamous histology:	For adults with non-squamous histology:	NA	The comparators included in the decision problem addressed by the company match the NICE scope for adults with non-squamous and squamous histology.

	Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) (for people with adenocarcinoma or large cell carcinoma only) With (following cisplatin-containing regimens only) or without pemetrexed maintenance treatment Chemotherapy (docetaxel, gemcitabine, paclitaxel, or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) With or without pemetrexed maintenance treatment Atezolizumab with bevacizumab, carboplatin, and paclitaxel (for people whose tumours express PD-L1 with < 50% TPS) Pembrolizumab (for people whose tumours express PD-L1 with ≥ 50% TPS) For adults with squamous histology: Chemotherapy (docetaxel, gemcitabine, paclitaxel, or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) Pembrolizumab (for people whose tumours express PD-L1 with ≥ 50% TPS)	Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) (for people with adenocarcinoma or large cell carcinoma only) With (following cisplatin-containing regimens only) or without pemetrexed maintenance treatment Chemotherapy (docetaxel, gemcitabine, paclitaxel, or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) With or without pemetrexed maintenance treatment Atezolizumab with bevacizumab, carboplatin, and paclitaxel (for people whose tumours express PD-L1 with < 50% TPS) Pembrolizumab (for people whose tumours express PD-L1 with ≥ 50% TPS) For adults with squamous histology: Chemotherapy (docetaxel, gemcitabine, paclitaxel, or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) Pembrolizumab (for people whose tumours express PD-L1 with ≥ 50% TPS)		The network meta-analysis with a target population of non-squamous patients with PD-L1 < 50%, includes clinical trials comparing bevacizumab in combination with PDC to facilitate indirect comparison between PDC alone and atezolizumab in combination with bevacizumab and PDC. This is discussed further in section 3.4. Clinical advice to the ERG was that pembrolizumab with carboplatin and paclitaxel is also being used in clinical practice for metastatic untreated squamous NSCLC, via the Cancer Drugs Fund, so does not form part of the comparators of interest in this submission.
Outcomes	• Overall survival (OS)	• Overall survival (OS)	NA	The outcomes in the company's submission match those described in the final scope. For the clinical trial CheckMate-9LA

	• Progression-free survival (PFS) • Response rate • Adverse effects of treatment • Health-related quality of life	• Progression-free survival (PFS) • Response rate • Adverse effects of treatment • Health-related quality of life		the CS reports, OS, PFS, overall response rate (ORR), duration of response (DOR), adverse effects of treatment and health related quality of life measured using the Lung Cancer Symptom Scale (LCSS) Average Symptom Burden Index (ASBI), EQ-5D visual analogue scale (VAS), and EQ-5D 3-Level (EQ-5D-3L) Utility Index. A summary of these outcomes and those of the supporting trials CheckMate-227 and CheckMate-568, are reported in section 3.4.2
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life-year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be conducted. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be considered. If appropriate, the economic modelling should include the costs associated with diagnostic testing for biological markers (e.g., PD-L1) in people with	As per scope.	NA	The only departure from the scope was the company's presentation of the cost-effectiveness results. The company presented pairwise ICERs for nivolumab + ipilimumab + limited PDC versus each of the comparators, including PDC, pembrolizumab monotherapy, and atezolizumab + bevacizumab + PDC. The ERG considers it more appropriate to include all options within a fully incremental analysis.

	NSCLC who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.			
Subgroups	If evidence allows, subgroup analysis by level of PD-L1 expression will be considered. Guidance will only be issued according to the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator	We present the CheckMate-9LA trial ITT population as the base case. The overall survival benefit of nivolumab + ipilimumab + limited PDC was consistent across subgroups in CheckMate-9LA; therefore, histological and PD-L1 subgroups will only be considered to align with positioning of the in-scope comparators.	NA	The CS includes the subgroup analyses specified in the NICE scope (PD-L1 expression level). For the clinical trial CheckMate-9LA, OS is presented by PD-L1 expression level (< 1%, ≥ 1%, 1-49%, ≥ 50%) and by histology (squamous and non-squamous). As PD-L1 expression and tumour histology are potential effect modifiers and define the comparator treatments, four sub-populations were identified by the ERG (Table 12). Baseline characteristic and efficacy data for the four sub-populations were provided by the company in response to clarification and are discussed in sections 3.2.4 and 3.3.1. Other subgroups considered are age, sex, ECOG status, smoking status, tumour histologic type, liver metastasis, bone metastasis and CNS metastasis. These are discussed in section 3.2.4.2.
Special considerations including issues related to equity or equality	None	NA	NA	There are no equality issues identified. The company does not claim end-of-life criteria apply and the ERG agree that they do not apply.

*If different from the NICE scope NA-not applicable, NR-not reported. ALK= Anaplastic lymphoma kinase; ASBI =Average Symptom Burden Index; CNS = central nervous system; CS= company submission; DOR = duration of response; ECOG= Eastern cooperative oncology group; EGFR= Epidermal growth factor receptor; EQ-5D-3L = EQ-5D 3-Level; LCSS= Lung Cancer Symptom Scale; ICER = Incremental cost-effectiveness ratio; NSCLC = non-small cell lung cancer; PDC = platinum doublet chemotherapy; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; ORR = overall response rate; OS = overall survival; VAS = visual analogue scale.

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3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The CS describes a systematic literature review (SLR) of all RCTs comparing relevant therapies in the first line treatment of advanced NSCLC. Details of the SLR methods are presented in Appendix D of the CS and in a separate SLR report provided by the company.[6]

3.1.1 Searches

Appendix D of the company submission contained a description of 9 sets of updated searching of the databases MEDLINE, EMBASE and CENTRAL, carried out over the period June 2016 to March 2020. However, only the March 2020 search strategies were provided in full, showing the search results per line. A further systematic review report was provided by the company; however, the update search strategies were not reported here either.[6] The company clarified in their response to the PFCs that the March 2020 search strategies reported in Appendix D were used for all previous update searches but with different date limits applied. No major errors were found with the March 2020 search strategies, however, without seeing all of the previous update search strategies, including the method used for limiting by date, the ERG could not fully appraise the search strategies for the clinical effectiveness review.

Table 7 ERG appraisal of evidence identification for the clinical effectiveness review

Topic	ERG response	Note
Is the report of the search clear and comprehensive?	PARTLY	The reporting of the March 2020 update search for MEDLINE, EMBASE and CENTRAL, the conference abstracts search and the clinical trials registers search was clear and comprehensive. However, as noted above, previous database search strategies were not provided in the submission, additional SR report[6] or in the response to the PFCs.
Were appropriate sources searched?	YES	- Sources of both published and unpublished studies were included in the search. - Reference checking of previous reviews or included studies was not reported as a search method.
Was the timespan of the searches appropriate?	PARTLY	The description of the searches indicated that the database searches took place between 2nd June 2016 and 14th March

		2020. However, this could not be fully checked by the ERG as previous update search strategies were not provided.
Were appropriate parts of the PICOS included in the search strategies?	YES	NSCLC (P) AND (nivolumab, ipilimumab (I) OR relevant comparators (C)) AND RCTs (S)
Were appropriate search terms used?	YES	
Were any search restrictions applied appropriate?	UNCLEAR	- This could not be fully checked by the ERG as previous update search strategies were not provided. - The March 2020 database searches were restricted to articles published during the year 2020. This approach runs the risk of missing any relevant studies published in previous years but only added to the databases in 2020.
Were any search filters used validated and referenced?	PARTLY	RCT study design search filters by the Scottish Intercollegiate Guidelines Network (SIGN) were used in the search strategies for MEDLINE and EMBASE. It is unclear if these search filters have been validated.[7]

ERG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

Inclusion criteria

Full eligibility criteria for the clinical SLR are presented in Table 2, Appendix D of the CS. RCTs involving nivolumab (with or without ipilimumab and PDC) and relevant comparators including, targeted therapies, PDC, non-platinum-based chemotherapy, monotherapies and BSC for the first line treatment of advanced and recurrent NSCLC were included in the review. There were no language limits applied and there is no detail on whether there were date limits applied.

The study selection methods described by the CS are appropriate. Two independent reviewers screened titles and abstracts using the inclusion criteria stated above. The full texts were then screened for inclusion, before decisions were compared. Any disagreements or queries were referred to a third independent reviewer.

A PRISMA flow diagram is presented in Figure 7 of the CS. However, the CS does not present a list of the 166 studies excluded. The SLR included 68 unique trials, which are detailed in Table 6 of Appendix D.3.1.1, although reasons for inclusion or exclusion of each study were not provided even after being requested by the ERG. Two RCTs of relevance were identified in the SLR: CheckMate-9LA[8, 9] which evaluates nivolumab + ipilimumab + limited PDC and CheckMate-227[10] which

investigates nivolumab + ipilimumab. One additional phase II, single arm trial of nivolumab + ipilimumab + limited PDC, CheckMate-568,[11] was not identified in the SLR but is presented in the submission as it is considered relevant to this appraisal.

Critique of data extraction

The methods of data extraction are described on page 23 of Appendix D. Information for each included study was extracted by a single individual, in the first instance and was independently verified and validated by a second extractor. The ERG considers the methods to be appropriate and sound. Data from the two-phase III trials: CheckMate-9LA and CheckMate-227 and the phase II trial CheckMate-568 are presented in the submission.

Quality assessment

The quality of the trials was assessed based on the recommendations in the NICE "Guide to the methods of technology appraisal". The checklist covered randomisation, concealment of treatment allocation, similarity of baseline characteristics, blinding, imbalances in dropouts, completeness of outcome reporting, intention-to-treat analysis and representation of routine clinical practice. Results of the quality assessment of the CheckMate-9LA and CheckMate-227 trials are presented in Table 14 and 15 of the CS, which were updated at the PFC stage, see Section 3.2.3 for more details. CheckMate-568 is a non-randomised study, therefore it was assessed using the Critical Appraisal Skills Programme (CASP) quality assessment tool. The results are presented in Table 16 of the CS and an updated table was provided at the clarification stage.

Evidence synthesis

CheckMate-9LA is the key trial in this indication as it evaluates nivolumab + ipilimumab + limited PDC, which is in line with the NICE scope and decision problem. Results of the full ITT population of CheckMate-9LA are presented in section B.2.6.1, which informs the base-case economic model. CheckMate-227 provides supporting evidence for the efficacy of nivolumab + ipilimumab. Results of the modified intention-to-treat population of CheckMate-227 are presented in section B.2.6.2.1, which are used to inform the revised fractional polynomial NMA and the long-term survival analyses in the economic model.

Safety data are presented for CheckMate-9LA, which are most relevant to the decision problem, with the phase II study CheckMate-568 providing supporting information. This is discussed in Section 3.2.5 of this report. An ITC was conducted to assess the clinical effectiveness of nivolumab + ipilimumab + limited PDC relative to other comparators identified in the NICE scope. This is described in Section 3.3 of this report.

Ongoing studies

The CheckMate-9LA and CheckMate-227 trials are currently ongoing. Additional data cuts are anticipated over the next 12 to 18 months.

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

The company submission included two international, multicentre, phase III RCTs: CheckMate-9LA as the key trial in support of the indication and CheckMate-227 as supporting evidence, used for the revised fractional polynomial network meta-analysis (NMA) and the long-term survival analyses in the economic model. An additional multicentre, single-arm, phase II RCT: CheckMate-568 was included for evidence on the safety of nivolumab + ipilimumab but was not used to inform the economic model as it does not include a comparator arm. CheckMate-9LA and CheckMate-568 evaluated nivolumab + ipilimumab + limited PDC in patients with stage IV or recurrent NSCLC, which is in line with the NICE scope and decision problem (Section 2.3). CheckMate-227 evaluated nivolumab + ipilimumab in patients with stage IV or recurrent NSCLC.

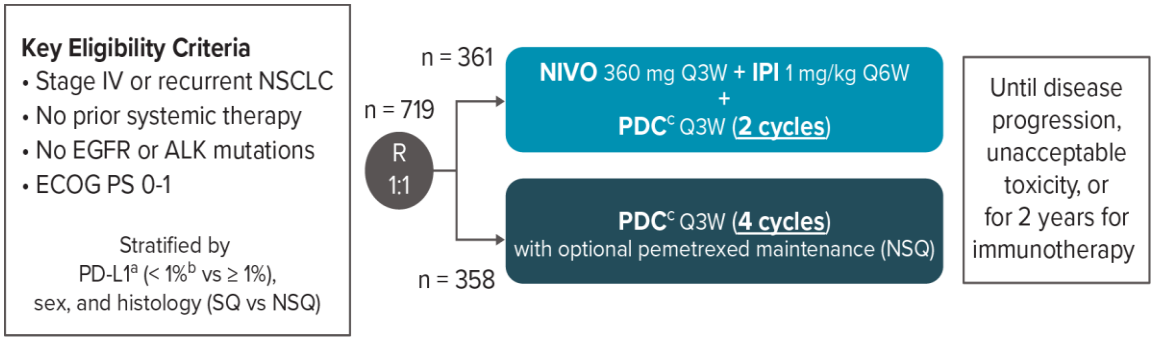
3.2.1 Trial Designs and Methods

Details of the design and methodology of all trials are reported in Section B.2.3 and Appendix D of the CS.

3.2.1.1 CheckMate-9LA

This trial was conducted at 103 sites in 19 countries across Europe, the Americas and Japan. Patients were randomised 1:1 to treatment with nivolumab + ipilimumab + limited PDC or PDC. PDC consisted of carboplatin area under the curve (AUC) 6 + paclitaxel 200 mg/m^2 or 175 mg/m^2 for squamous patients and carboplatin AUC 5 or 6 + pemetrexed 500 mg/m^2 or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2 for non-squamous patients. Randomisation was stratified by PD-L1 level (≥ 1% and < 1%), histology (squamous vs non-squamous) and gender. The study design is shown in Figure 1. The primary endpoint was OS and secondary endpoints include PFS and ORR.

Figure 1 Study design for CheckMate-9LA (from CS, Figure 8)



Abbreviations: ALK = anaplastic lymphoma kinase; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; IPI = ipilimumab; NIVO = nivolumab; NSCLC = non-small cell lung cancer; NSQ = non-squamous; PD-L1 = programmed death-ligand 1; PDC = platinum doublet chemotherapy; Q3W = every 3 weeks; Q6W = every 6 weeks; R = randomised; SQ = squamous.

Notes: Interim database lock: October 3, 2019; minimum follow-up: 8.1 months for OS and 6.5 months for all other endpoints.

Updated database lock: March 9, 2020; minimum follow-up: 12.7 months for OS and 12.2 months for all other endpoints.

[a] Determined by the PD-L1 immunohistochemistry 28-8 pharmDx assay (Dako).

[b] Patients unevaluable for PD-L1 were stratified to PD-L1 < 1% and capped to 10% of all randomised patients.

[c] NSQ: pemetrexed + cisplatin or carboplatin; SQ: paclitaxel + carboplatin.

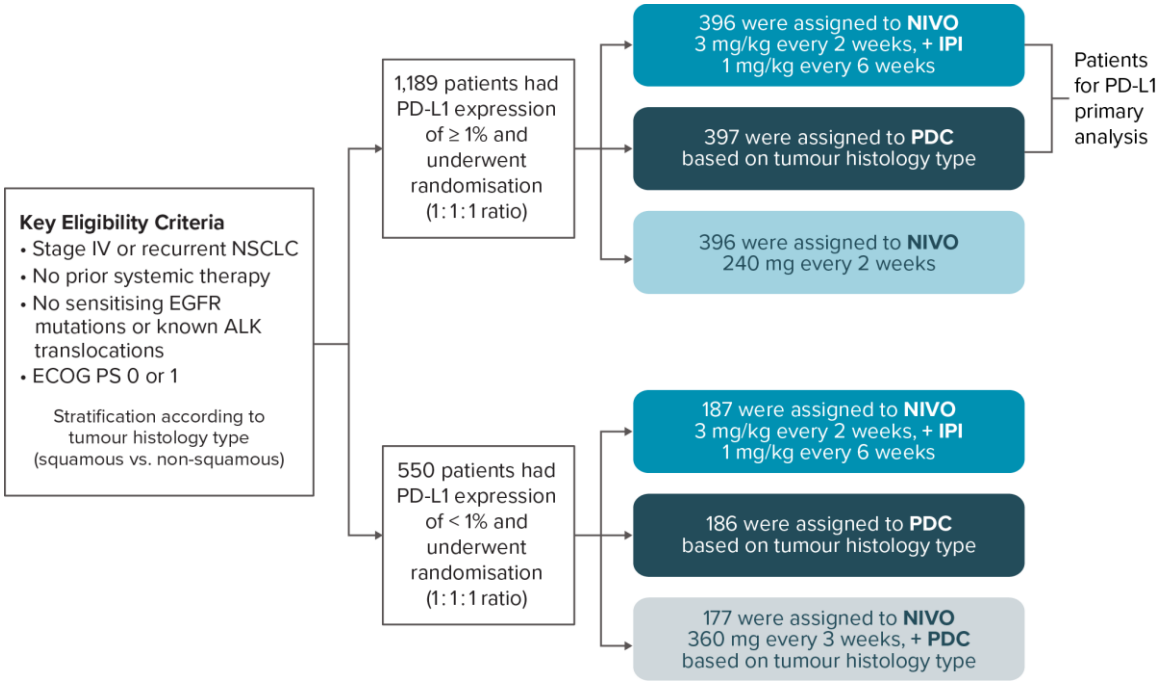
Source: Reck, Ciuleanu [8]

The CS explains that varying patterns of response to IO therapies can be observed (see Section 2.2.3). In the clarification response, the company explain that in the clinical trial CheckMate-9LA, IO therapy was terminated for patients with a late response or new lesions at 12 weeks followed by a response, at the time of initial progression. Additional response data was not systematically collected for these patients.

3.2.1.2 CheckMate-227

CheckMate-227 consists of three parts (1a, 1b and 2), of which part 1a and 1b are relevant to this submission. Part 2 evaluated nivolumab + PDC versus PDC, which is not the relevant intervention and thus is not discussed further. The trial was conducted in 239 sites in 32 countries across Europe, the Americas and East Asia. Patients in part 1a were randomised in a 1:1:1 ratio to nivolumab monotherapy, nivolumab + ipilimumab and PDC. Patients in part 1b were randomised in a 1:1:1 ratio to nivolumab + ipilimumab, nivolumab + PDC and PDC. Randomisation was stratified by PD-L1 level (≥ 1% and < 1%), histology (squamous vs non-squamous) and gender. The primary outcome was OS in patients with PD-L1 ≥ 1% and PFS in patients with TMB ≥ 10.

Figure 2 Study design for CheckMate-227 (from CS, Figure 9)



Abbreviations: ALK = anaplastic lymphoma kinase; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancerPD-L1 = programmed death-ligand 1.

Source: Hellmann (2019)[10]

3.2.1.3 Phase II study: CheckMate-568

CheckMate-586 consists of two parts, with part two being relevant to the decision problem as part one only evaluated nivolumab + ipilimumab. Therefore, only part two is discussed. The trial was conducted at 12 sites in the US and evaluated a single arm of nivolumab + ipilimumab + 2 cycles of chemotherapy. The primary endpoint was ORR in patients with PD-L1 ≥ 1% and < 1%

3.2.2 Trial populations

The population of interest in the CS is adults with untreated stage IV or recurrent NSCLC of squamous or non-squamous histology. Patients must have had Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1 and no prior systemic anticancer therapies given as primary therapy for advanced or metastatic disease. Both the patient populations in CheckMate-9LA and CheckMate-227 are in line with the NICE scope and decision problem. However, there were only [redacted] patients ([redacted]) in the nivolumab + ipilimumab + limited PDC arm and [redacted] patients ([redacted] in the PDC arm in the CheckMate-9LA trial from the UK. There were [redacted] patients from the UK in the CheckMate-227 trial, [redacted] ([redacted]) in the nivolumab + ipilimumab arm and [redacted] ([redacted]) in the PDC arm. Furthermore, patients in both trials may be fitter and healthier than patients eligible for treatment in the NHS population as only patients with ECOG PS of 0 or 1 were included. Therefore, although the ERG

considers the base-case trial population to be in line with the population that could be given nivolumab + ipilimumab + PDC in practice, the population in the trials may not fully represent the NHS population.

Exclusion criteria in CheckMate-9LA and CheckMate-227 included patients with known EGFR mutations or ALK translocations sensitive to targeted inhibitor therapy. CheckMate-9LA also excluded patients with untreated central nervous system metastases. The full inclusion and exclusion criteria were not presented in the CS but were accessible from the clinical study reports (CSR).

The baseline characteristics of the CheckMate-9LA trial and the CheckMate-227 trial are reported in Tables 8 and 10 of the CS, respectively. Patients included in both trials are mostly comparable. Patients had a median age of 65 years old and 64 years old in the CheckMate-9LA and CheckMate-227 trials, respectively. The median age for patients with NSCLC in England and Wales is 73, suggesting that the age of the trial populations is substantially younger than patients in the NHS population.[2] Across both trials, 30%-34% of patients were female. Most patients in CheckMate-9LA were white (88.7%), with a small proportion being Japanese (7%). Ethnicity was not reported for CheckMate-227. The majority of patients had an ECOG PS of 1 (64.7% to 68%), were current or former smokers (85.2% to 87%) and had a non-squamous histology (69% to 72.2%) across both trials.

A larger proportion of patients had a PD-L1 expression ≥ 1% (67.9% in the nivolumab + ipilimumab arm and 68.1% in the PDC arm) in the CheckMate-227 trial than in the CheckMate-9LA trial (60% in the nivolumab + ipilimumab + limited PDC arm and 61% in the PDC arm). In the CheckMate-9LA trial, the PDC arm had more patients with 4 metastatic sites (10.3%) than the nivolumab + ipilimumab + limited PDC arm (5.8%). Clinical advice to the ERG is that patients with multiple metastatic sites are expected to have a poorer prognosis than patients with fewer metastatic sites. Overall, the baseline characteristics of both the CheckMate-9LA and CheckMate-227 trials do not show any concerning imbalances across the treatment arms (Table 8).

Patients included in the CheckMate-568 trial were comparable to the other two CheckMate trials. Median age was slightly higher at 70 years old and there was a larger proportion of patients with PD-L1 expression < 1% (60%) than with PD-L1 ≥ 1% (40%). An overview of the baseline characteristics in CheckMate-568 are presented in Table 11 of the CS.

Table 8 Baseline characteristics of the CheckMate-9LA and CheckMate-227 trials (adapted from Tables 8 and 10 of the CS)

Characteristics	CM-9LA		CM-227	
	NIVO + IPI + limited PDC (n = 361)	PDC (n = 358)	NIVO + IPI (n=583)	PDC (n=583)
Age, median (range), years	65 (35-81)	65 (26-86)	64 (26-87)	64 (29-87)
Female, %	30	30	32.6	34.0
ECOG PS,[a] %				
0	31	31	35.0	32.8
1	68	68	64.7	66.2
Smoking status, %				
Never smoker	13	14	13.6	13.4
Current/former smoker	87	86	85.2	85.6
Histology, %				
Squamous	31	31	28.0	27.8
Non-squamous	69	69	71.9	72.2
Metastases, %				
Bone	27	31	27.9	26.2
Liver	19	24	20.9	22.3
Central nervous system	18	16	11.0	8.7
Tumour PD-L1 expression[b, c] %				
< 1%	40	39	32.1	31.9
≥ 1%	60	61	67.9	68.1
1%-49%	38	32	32.8	35.2
≥ 50%	22	29	35.2	32.9

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; IPI = ipilimumab; NIVO = nivolumab; PDC = platinum doublet chemotherapy; PD-L1 = programmed death-ligand 1.

[a] ECOG PS was not reported for 1 patient (0.3%) in each of the Nivolumab + ipilimumab + limited PDC and PDC arms in the CheckMate-9LA trial. In CheckMate-227 study treatment only in PD-L1 ≥ 1% population

[b] Six percent and 7% of patients in the Nivolumab + ipilimumab + limited PDC and PDC arms, respectively, were unevaluable for PD-L1 in the CheckMate-9LA trial. Calculated as a percentage of quantifiable patients.

[c] In the CheckMate-227 trial PD-L1 immunohistochemistry 28-8 pharmDx assay (Dako) was used.

3.2.3 Quality Assessment

A summary of the quality assessment of the CheckMate-9LA, CheckMate-227 and CheckMate-568 trials is presented in Tables 14, 15 and 16 of the CS. These tables were updated at the clarification stage (Tables 14, 15 and 16 of the clarification response document). Both CheckMate-9LA and CheckMate-227 were RCTs and randomisation was appropriately conducted by an interactive web response system. The trials were open label, therefore there was no blinding to treatment or concealment of treatment allocation, which increases the risk of selection bias and also increases the risk of performance bias for patient reported outcomes, including EQ-5D and Lung cancer symptom scale (LCSS)

The CS reported that there was evidence to suggest that authors measured more outcomes than they reported in the CheckMate-9LA trial, suggesting there is a high risk of outcome reporting bias. In the CheckMate-227 trial it was not clear whether an intention to treat population was used, therefore there may be a risk of attrition bias. In both trials baseline characteristics were mostly balanced between groups. However, it was not clear how closely the RCTs reflected routine clinical practice as different PDC regimens may be used in practice compared with those used in the trials. Furthermore, pembrolizumab combination therapy, which clinical advice states is the preferred treatment in practice, particularly for patients with PD-L1 < 50%, could not be included as a comparator due to it being through the CDF. Overall, both CheckMate RCTs seem to be of low quality with a high risk of bias in several domains.

3.2.4 Summary of the results of the included trials

3.2.4.1 Efficacy outcomes

Results for primary and secondary outcomes assessing efficacy and quality of life for the CheckMate-9LA and CheckMate-227 trials are presented in Section B.2.6 of the CS, including OS, PFS, ORR, DOR, LCSS score, EQ-5D-3LVAS and utility index score.

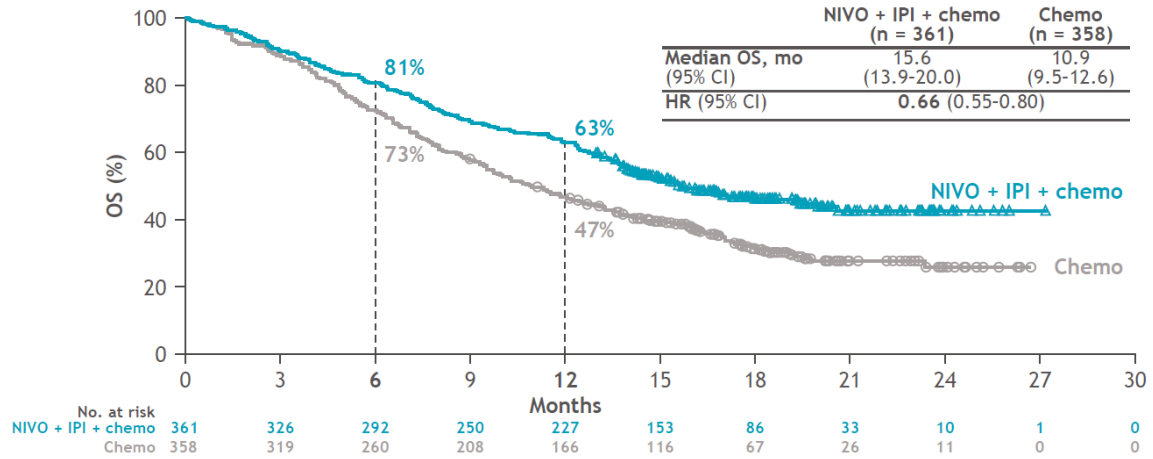
CheckMate-9LA

The OS, PFS and ORR results presented are from the updated analysis based on the March 2020 database lock, with a minimum follow up of 12.7 months. Progression-free survival and ORR was assessed by blinded independent committee review (BICR).

OS

Overall survival was the primary endpoint for the CheckMate-9LA trial. There was a statistically significant difference in overall survival favouring nivolumab + ipilimumab + limited PDC compared with PDC (15.64 months vs 10.91 months; HR: 0.66, 95% CI: 0.55 to 0.80). Overall survival rates were higher in the nivolumab + ipilimumab + limited PDC arm compared with the PDC arm: 80.9% versus 72.6% at 6 months and 62.9% versus 46.9% at 12 months.

Figure 3 Kaplan-Meier of overall survival in all randomised patients in CheckMate-9LA (from CS, Figure 12)



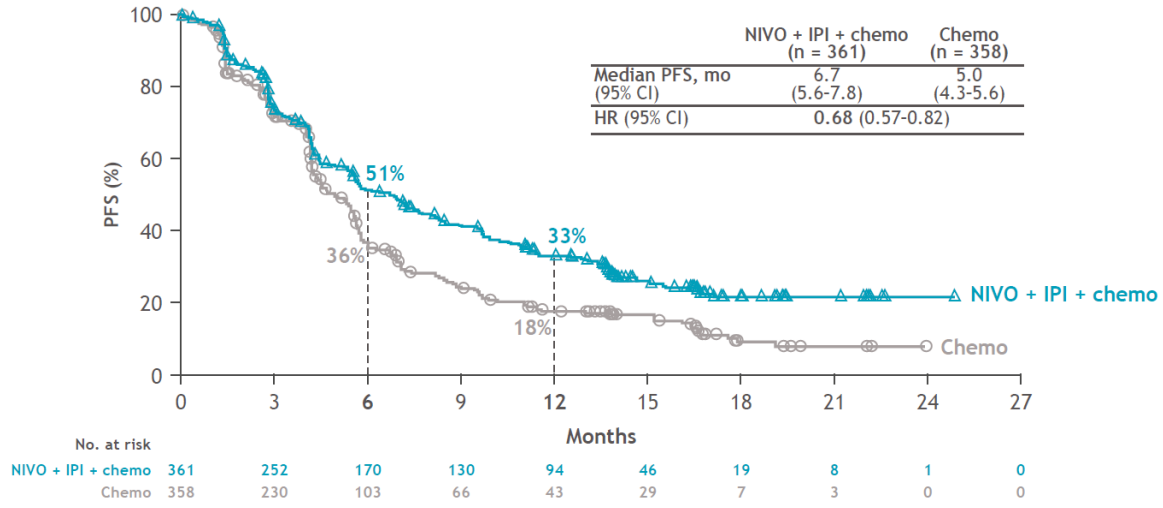
Abbreviations: CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; NIVO = nivolumab; OS = overall survival.

Note: *Chemo* refers to platinum doublet chemotherapy. Source: Reck, Ciuleanu [8]

PFS

Median PFS was longer in the nivolumab + ipilimumab + limited PDC arm compared with the PDC arm (6.74 months versus 4.96 months, respectively), with a statistically significant HR of 0.68, 95% CI: 0.57-0.82. Progression-free survival rates were higher with nivolumab + ipilimumab + limited PDC compared with PDC: 51.3% versus 35.7% at 6 months and 32.9% versus 17.6% at 12 months

Figure 4 Kaplan-Meier of PFS in all randomised patients in CheckMate-9LA (from CS, Figure 13)



Abbreviations: CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; NIVO = nivolumab; PFS = progression-free survival.
Note: *Chemo* refers to platinum doublet chemotherapy. Source: Reck et al. (2020)[8]

ORR

BICR-assessed ORR was higher with nivolumab + ipilimumab + limited PDC than with PDC: 38.2% (95% CI, 33.2%-43.5%) versus 24.9% (95% CI, 20.5%-29.7%). A higher proportion of patients had a best overall response of complete response (CR; 2.2% vs. 1.1%) or partial response (PR; 36.0% vs. 23.7%), however a lower proportion of patients had a best overall response of stable disease (SD; 45% vs. 52%). The median DOR was more than double for all confirmed responders treated with nivolumab + ipilimumab + limited PDC than with PDC, with non-overlapping CIs (DOR, 11.30 vs. 5.59 months).

Table 9 Trial results of CheckMate-9LA (adapted from CS, Tables 18, 19 and 20)

Trial results	NIVO + IPI + limited PDC (n = 361)	PDC (n = 358)
Median OS survival, months	15.6 (13.9-20.0)	10.9 (9.5-12.6)
	HR: 0.66 (95% CI: 0.55-0.80)	
OS rate at 6 months (95% CI)	80.9 (76.4-84.6)	72.6 (67.7-76.9)
OS rate at 12 months (95% CI)	62.9 (57.7-67.6)	46.9 (41.6-51.9)
Median PFS (months)	6.7 (5.6-7.8)	5.0 (4.3-5.6)
	HR: 0.68 (95% CI: 0.57-0.82)	
PFS rate at 6 months (95% CI)	51.3 (45.9-56.5)	35.7 (30.3-41.1)
PFS rate at 12 months (95% CI)	32.9 (27.8-38.0)	17.6 (13.4-22.2)
Objective response rate, n (%)	138 (38)	89 (25)
	OR: 1.9 (95% CI: 1.4-2.6)	
Complete response* n (%)	8 (2)	4 (1)
Partial response* n (%)	130 (36)	85 (24)
Stable disease* n (%)	164 (45)	185 (52)
Progressive disease* n (%)	32 (9)	45 (13)
Median duration of response, months	11.3	5.6

*Best overall response. NIVO = nivolumab; IPI = ipilimumab; PDC = platinum doublet chemotherapy; HR = hazard ratio; OS = overall survival; PFS = progression free survival; OR = odds ratio.

Health-related quality of life

The company presented health related quality of life outcomes including the LCSS, Average Symptom Burden Index (ASBI), EQ-5D visual analogue scale (VAS) and EQ-5D 3-level Utility Index. The ERG notes that the number of patients with a measurement at week 24 for LCSS and EQ-5D was substantially lower than at week 30. The CSR states that the compliance rate for week 24 does not reflect compliance with the LCSS or EQ-5D instruments since many subjects were not eligible for an assessment and were not included in the denominator. However, the ERG are unclear why participants were not eligible for an assessment.

The outcomes were generally similar between the nivolumab + ipilimumab + limited PDC and PDC arms. The mean change from baseline in LCSS ASBI score in both arms did not meet the minimally important difference (MID) of 10 at any time.

The EQ-5D-3L VAS score generally improved in both arms, with the PDC arm reaching a MID of 7 at week 72 and reaching the UK general population norm (82.8) at weeks 72 and 78. The nivolumab + ipilimumab + limited PDC arm reached the MID of 7 at week 72 and 84. However, mean scores did not reach the UK general population norm (82.8) at any point.

Similarly, the EQ-5D utility index scores did not reach the UK general population norm (0.86) at any time. The mean change from baseline exceeded the MID of 0.08 in the nivolumab + ipilimumab + limited PDC arm at week 84 only, whereas the PDC arm did not meet the MID at any time point.

CheckMate-227

Results for CheckMate-227 part 1 are presented in Section B.2.6.2.1. They are based on the database lock of February 2020, [redacted].

OS

[redacted]

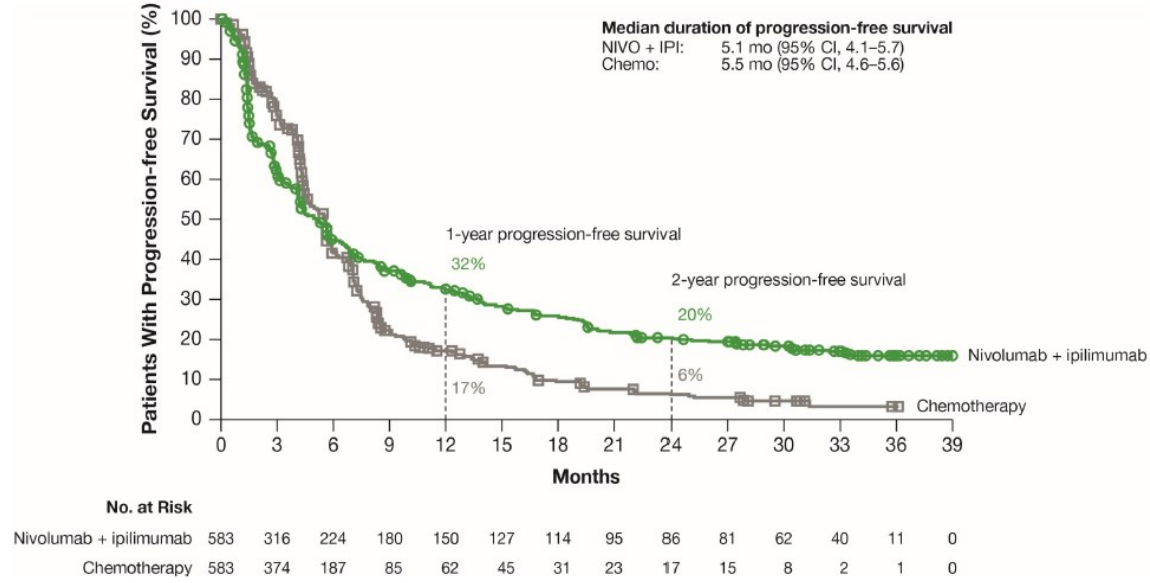
Figure 5 Kaplan-Meier of OS in CheckMate-227 part 1 (from CS, Figure 19)

Abbreviations: CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; NIVO = nivolumab; PDC = platinum doublet chemotherapy.
Source: Bristol Myers Squibb data on file (2020)[12]

PFS

Median duration of progression-free survival was similar but slightly shorter in the nivolumab + ipilimumab arm (5.1 months, 95% CI: 4.1 to 5.7) compared with the PDC arm (5.5 months, 95% CI: 4.6-5.6), with a reported HR of 0.79 (95% CI: 0.69 to 0.91). However, the progression-free survival rates at 2 years were 20% in the nivolumab + ipilimumab arm and 6% in the PDC arm.

Figure 6 Kaplan-Meier of PFS in all patients in Checkmate-227 (from CS, Figure 20)



Abbreviations: CI = confidence interval; IPI = ipilimumab; NIVO = nivolumab.
Note: *Chemotherapy* refers to platinum doublet chemotherapy. Source: Hellmann et al. (2019)[10]

ORR

The objective response rates between the nivolumab + ipilimumab and PDC arms were similar, 33.1% vs 27.8%, respectively. The best overall response for patients achieving a complete response and partial response were slightly higher in the nivolumab + ipilimumab arm (4.6% and 28.5%, respectively) compared with the PDC arm (1.5% and 26.2%, respectively). However, the best overall response for patients with stable disease was lower in the nivolumab + ipilimumab arm versus the PDC arm.

Table 10 Trial results of CheckMate-227 (adapted from CS, Figure 19, 20 and Table 21)

Trial results	NIVO + IPI (n = 583)	PDC (n = 583)
Median OS survival, months[a]	[redacted]	[redacted]
	[redacted]	
OS rate at 12 months %	62	54
OS rate at 24 months %	40	30
Median PFS (months)	5.1 (4.1-5.7)	5.5 (4.6-5.6)
	HR: 0.79 (95% CI: 0.69 to 0.91)	
PFS rate at 12 months %	32	17
PFS rate at 24 months %	20	6
Objective response rate, n (%)	193 (33.1)	162 (27.8)
Complete response [b] n (%)	27 (4.6)	9 (1.5)
Partial response [b] n (%)	166 (28.5)	153 (26.2)
Stable disease [b] n (%)	189 (32.4)	287 (49.2)
Progressive disease* n (%)	135 (23.2)	74 (12.7)
Median duration of response, months (95% CI)	19.6 (16.1-28.6)	5.8 (5.4-6.9)

[a] Based on 3-year update analysis, with minimum follow up of 37.7 months. [b] Best overall response. NIVO = nivolumab; IPI = ipilimumab; PDC = platinum doublet chemotherapy; HR = hazard ratio; OS = overall survival; PFS = progression free survival; OR = odds ratio.

CheckMate-568

Results for CheckMate-568 part 2 are presented in Section B.2.6.2.2. Median OS was 19.4 months (95% CI: 6.5 to Not Estimable) and median PFS was 10.8 months (95% CI: 5.3 to 16.1) for nivolumab + ipilimumab + limited PDC. The ORR was 47%, with 42% achieving partial response and 42% achieving stable disease. The median DOR was 12.7 months.

3.2.4.2 Subgroup Analysis

The CS reported a range of subgroup analyses in CheckMate-9LA (CS Figure 23) and in CheckMate-227 (CS Figure 27) for OS. The subgroup analyses for PFS and ORR were reported in the CSRs. In the CheckMate-9LA trial the efficacy benefit of nivolumab + ipilimumab + limited PDC was not seen for patients ≥ 75 years old (HR: 1.21, 95% CI: 0.69 to 2.12), patients who had never smoked (HR: 1.14, 95% CI: 0.66 to 1.97) and patients with liver (HR: 0.83, 95% CI: 0.57 to 1.20) and bone metastases (HR: 0.74, 95% CI: 0.53 to 1.01). Clinical advice to the ERG is that a substantial proportion of the NHS population eligible for nivolumab + ipilimumab + limited PDC are patients over 75 years old and around 20-30% have bone or liver metastases. Therefore, there may be a significant proportion of the population who may not benefit from treatment with nivolumab + ipilimumab + limited PDC compared with PDC. However, it is important to note that the non-stratified nature of subgroup analyses and smaller sample sizes reduces the reliability of these results.

The never smoked subgroup and over 75 years old subgroup had relatively small patient numbers, which can lead to higher uncertainty in point estimates.

Similarly, in the CheckMate-227 trial, the efficacy benefit of nivolumab + ipilimumab was not seen for patients [redacted]. CheckMate-227 also reported further subgroup analyses, which did not show benefit of nivolumab + ipilimumab compared with PDC, including [redacted] (Table 11). A systematic review[4] found that factors such as liver metastases and sex may modify IO treatment effect, though they may be correlated with other factors. The ERG notes that similarly to the CheckMate-9LA trial, the subgroups of patients over 75 years old and CNS metastases had relatively small sample sizes, which may reduce the reliability of these results.

Table 11 Subgroup analyses with significant interactions for OS, PD-L1 expression and histology (adapted from CS, Figure 27 and CheckMate-9LA CSR, Figure 6.2.1-1 and 6.3.1-1)

Subgroup	Median OS, months		HR (95% CI)
	NIVO + IPI + PDC	PDC	
CM-9LA			
≥ 75 years old (n=70)	8.5	11.5	1.21 (0.69-2.12)
Never smoked (n=98)	14.1	17.7	1.14 (0.66-1.97)
Liver metastases (n=154)	10.2	8.1	0.83 (0.57-1.20)
Bone metastases (n=207)	11.9	8.3	0.74 (0.53-1.01)
PD-L1 < 1% (n=264)	16.8	9.9	0.62 (0.45-0.85)
PD-L1 ≥ 1% (n=407)	15.8	10.9	0.64 (0.50-0.82)
PD-L1 1-49% (n=233)	15.4	10.4	0.61 (0.44-0.84)
PD-L1 ≥ 50% (n=174)	18.0	12.5	0.66 (0.44-0.99)
Squamous histology (n=227)	14.46	9.12	0.62 (0.45-0.86)
Non-squamous histology (n=492)	16.99	11.86	0.69 (0.55-0.87)
CM-227			
65 to <75 years old (n=442)	[redacted]	[redacted]	[redacted]
≥ 75 years old (n=113)	[redacted]	[redacted]	[redacted]
Female (n=388)	[redacted]	[redacted]	[redacted]
Never smoked (n=157)	[redacted]	[redacted]	[redacted]
Liver metastases (n=252)	[redacted]	[redacted]	[redacted]
Bone metastases (n=316)	[redacted]	[redacted]	[redacted]
CNS metastases (n=115)	[redacted]	[redacted]	[redacted]
PD-L1 < 1% (n=373)	[redacted]	[redacted]	[redacted]
PD-L1 ≥ 1% (n=793)	[redacted]	[redacted]	[redacted]
PD-L1 1-49% (n=396)	[redacted]	[redacted]	[redacted]

PD-L1 ≥ 50% (n=397)	[redacted]	[redacted]	[redacted]
Squamous histology (n=328)	[redacted]	[redacted]	[redacted]
Non-squamous histology (n=838)	[redacted]	[redacted]	[redacted]

NIVO = nivolumab; IPI = ipilimumab; PDC = platinum doublet chemotherapy; HR = hazard ratio; CI= confidence interval; OS = overall survival; PD-L1= Programmed death-ligand 1; CNS= central nervous system

PD-L1 expression

PD-L1 expression has been shown to be associated with increased tumour proliferation and aggressiveness as well as shorter patient survival. Several studies have shown that non-squamous patients with high expression (≥ 50%) of PD-L1 had shorter survival times, suggesting that prognosis differs in patients depending on PD-L1 expression.[13, 14]

The CS reported subgroup analyses based on PD-L1 expression of < 1%, ≥ 1%, 1-49% and ≥ 50%. For the CheckMate-9LA trial, the CS states that the efficacy benefit of nivolumab + ipilimumab + limited PDC versus PDC was observed regardless of PD-L1 status for OS. The ERG agrees this is true for the subgroups of patients with PD-L1 < 1%, ≥ 1% and 1-49% (Table 11). However, in patients with PD-L1 ≥ 50%, the confidence interval is wider and very close to 1 (HR:0.66, 95% CI: 0.44 to 0.99). This suggests that the effectiveness of nivolumab + ipilimumab + limited PDC in these patients compared with PDC is more uncertain.

In the CheckMate-227 trial, the CS states that the OS benefit with nivolumab + ipilimumab as compared with PDC was observed regardless of PD-L1 expression. However, the company reported that the proportional hazards assumption was not met for OS in patients with PD-L1 ≥ 1%. Therefore, this estimate may not be reliable.

Histology

The identification and characterization of histology, particularly squamous and non-squamous seem to be very important in determining patients with a good response to immunotherapy. Several studies have shown different treatment effects for non-squamous and squamous patients, suggesting that histology has an effect on patient survival.[13, 14]

In the CheckMate-9LA trial the efficacy benefit of nivolumab + ipilimumab + limited PDC was observed in both squamous (HR: 0.62, 95% CI: 0.45 to 0.86) and non-squamous (HR: 0.69, 95% CI: 0.55 to 0.87) subgroups for OS. Similar results were seen in CheckMate 227 (squamous: [redacted]) (Table 11).

Sub-populations

The ERG considers there to be four sub-populations based on tumour histology and PD-L1 expression, as described in Table 12.

Table 12 Sub-populations of patients with NSCLC (adapted from CS, Figure 6)

Decision/population	1	2	3	4
Histology	Non-squamous		Squamous	
PD-L1 expression	1.a) < 1, 1.b) 1-49%	≥ 50%	3.a) < 1, 3.b) 1-49%	≥ 50%
Interventions in decision	Nivolumab + Ipilimumab + limited PDC	Nivolumab + Ipilimumab + limited PDC	Nivolumab + Ipilimumab + limited PDC	Nivolumab + Ipilimumab + limited PDC
	Pemetrexed in combination with cisplatin*	Pemetrexed in combination with cisplatin*	Platinum combination chemotherapy (i.e., cisplatin or carboplatin, and either gemcitabine or vinorelbine)	Platinum combination chemotherapy (i.e., cisplatin or carboplatin, and either gemcitabine or vinorelbine)
	Atezolizumab + bevacizumab + carboplatin + paclitaxel	Pembrolizumab monotherapy		Pembrolizumab monotherapy

*Note, for non-squamous NSCLC that has not progressed immediately after initial therapy with a NICE-recommended platinum-based chemotherapy regimen, maintenance treatment with pemetrexed is recommended as an option. PD-L1= Programmed death-ligand 1. PDC = platinum doublet chemotherapy.

The ERG has identified these four sub populations for a number of reasons. First, there is evidence to suggest that relative treatment effects may be different in each of the four sub-populations. PD-L1 expression may be a potential effect modifier in CheckMate-9LA, as discussed in Section 3.2.4.2. A systematic review[4] found that higher PD-L1 expression levels may yield larger relative treatment effects for mono-IO (for PFS and OS) and IO-chemo (for PFS only) (see Section 2.2.1). Additionally, the final appraisal determination for pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, NSCLC noted that that 5-year overall survival for people with only non-squamous tumours may be lower than for squamous patients because they are not as fit as those with squamous tumours.[5] However, clinical advice to the ERG suggests that squamous NSCLC may represent a more aggressive form of NSCLC. Several other studies suggest prognosis differs in patients depending on PD-L1 expression and histology,[13] however there are contradictory results in the literature.[15] Therefore, evaluating these four subgroups separately will allow exploration of potential sources of heterogeneity and inform sound decision making, which otherwise may fail to identify treatment benefits in the appropriate patient populations.

Second, the interventions for untreated metastatic NSCLC are recommended based on PD-L1 expression and histology (Table 5). Pembrolizumab is recommended for patients with mixed histology (both squamous and non-squamous) and PD-L1 ≥ 50% and atezolizumab + bevacizumab + PDC is recommended for non-squamous patients with PD-L1 < 50%. Clinical advice to the ERG is that PD-L1 expression determines which treatments are offered as there is evidence that anti-PD-L1 immunotherapies such as nivolumab may have a greater effect in patients with high PD-L1 expression. Similarly, the histology of patients with NSCLC determines which chemotherapy is provided. Patients with non-squamous histology have more options, including pemetrexed in combination with a platinum drug with or without pemetrexed maintenance treatment. Whereas, patients with squamous histology are generally treated with chemotherapy in combination with a platinum drug. The different interventions used in each sub-population consequently impact on the cost-effectiveness analysis that needs to be conducted.

The company state that the overall survival benefit of nivolumab + ipilimumab + limited PDC was consistent across subgroups. Therefore, histological and PD-L1 subgroups were only considered to align with the positioning of the in-scope comparators. The company provided baseline characteristics (see Table 13 and Table 14) alongside subgroup analyses for each of the four sub-populations as requested by the ERG at the clarification stage. Kaplan-Meier plots of OS, PFS and DOR for each subgroup were also provided (Figures 1 to 40 of the clarification response document). The company state that subgroup analyses may be impacted by the non-stratified nature of the comparison and small patient numbers, leading to loss of statistical power and higher uncertainty in point estimates. In addition, performing multiple exploratory subgroup analyses increases the risk of inconsistent and potentially accidental findings. The ERG agrees that there are limitations due to the non-stratified nature and small patient numbers of the subgroups and these should be considered when interpreting the results.

The subgroup analyses show that in CheckMate-9LA, the treatment benefit of nivolumab + ipilimumab + limited PDC is not statistically significant in population 2, non-squamous patients with PD-L1 ≥ 50% for both OS or PFS (Table 15). [redacted]

[redacted]. Therefore, the results suggest that there are differences in both the absolute and relative treatment effects for OS and PFS across these sub-populations. However, the ERG cautions that sub-populations 3 and 4 have very small sample sizes and therefore may not provide reliable conclusions.

[redacted] Again, results show that there are differences in absolute and relative treatment effects in OS and PFS across some of the sub-populations. Although sample sizes of the subgroups are larger in CheckMate-227 than CheckMate-9LA, they are still small for population 3 and 4 (squamous patients), which increases uncertainty in the results.

Table 13 Baseline characteristics of the four sub-populations in CheckMate-9LA (from clarification response document, Table 4)

Histology	**Non-squamous**								**Squamous**							
PD-L1	**< 1%**		**1-49%**		**< 50%**		**≥ 50%**		**< 1%**		**1-49%**		**< 50%**		**≥ 50%**	
	N+I+C	**C**	**N+I+C**	**C**	**N+I+C**	**C**	**N+I+C**	**C**	**N+I+C**	**C**	**N+I+C**	**C**	**N+I+C**	**C**	**N+I+C**	**C**
N																
Age, years																
<65																
≥65																
ECOG PS,%																
0																
1																
Not reported																
Smoking status, %																
Never smoker																
Current/former smoker																
Metastases, %																
Bone																
Liver																
Central nervous system																

PD-L1= Programmed death-ligand 1

Table 14 Baseline characteristics of the four sub-populations in the CheckMate-227 trial (from clarification response document, Table 5)

Histology	**Non-squamous**								**Squamous**							
PD-L1	**< 1%**		**1-49%**		**< 50%**		**≥ 50%**		**< 1%**		**1-49%**		**< 50%**		**≥ 50%**	
	N+I+C	**C**	**N+I+C**	**C**	**N+I+C**	**C**	**N+I+C**	**C**	**N+I+C**	**C**	**N+I+C**	**C**	**N+I+C**	**C**	**N+I+C**	**C**
N																
Age, years																
<65																
≥65																
ECOG PS,%																
0																
1																
≥2																
Not reported																
Smoking status, %																
Never smoker																
Current/former smoker																
Unknown																
Metastases, %																
Bone																
Liver																
Central nervous system																

Table 15 Subgroup analyses for CheckMate-9LA (from clarification response document, Table 2)

Histology	**Non-squamous**				**Squamous**			
PD-L1	**< 1%**	**1-49%**	**< 50%**	**≥ 50%**	**< 1%**	**1-49%**	**< 50%**	**≥ 50%**
NIVO+IPI+PDC (N)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PDC (N)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS HR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median OS NIVO+IPI+PDC (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median OS PDC (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS HR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NIVO+IPI+PDC Best ORR n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PDC Best ORR n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment duration HR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NIVO = nivolumab; IPI = ipilimumab; PDC = platinum doublet chemotherapy; HR = hazard ratio; OS = overall survival; ORR= overall response rate; PFS = progression free survival; PD-L1= Programmed death-ligand 1

Table 16 Subgroup analyses for CheckMate-227 (from clarification response document, Table 3)

Histology	**Non-squamous**				**Squamous**			
PD-L1	**< 1%**	**1-49%**	**< 50%**	**≥ 50%**	**< 1%**	**1-49%**	**< 50%**	**≥ 50%**
NIVO+IPI (N)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PDC (N)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS HR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median OS NIVO+IPI (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median OS PDC (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS HR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NIVO+IPI Best ORR n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PDC Best ORR n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR Treatment duration (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NIVO = nivolumab; IPI = ipilimumab; PDC = platinum doublet chemotherapy; HR = hazard ratio; OS = overall survival; ORR = overall response rate; PFS = progression free survival; PD-L1= Programmed death-ligand 1

3.2.5 Safety

The company investigated the safety of nivolumab + ipilimumab + limited PDC using primarily data from CheckMate-9LA with supporting information from the phase II trial, CheckMate-568. Safety data from CheckMate-9LA were reported in Section B.2.10.1 and from CheckMate-568 in Section B.2.10.2 of the CS.

Table 17 summarises the safety results from randomised patients in the CheckMate-9LA trial. In CheckMate-9LA, the proportion of any grade, all-cause and treatment-related adverse events (AEs) were similar between the two arms. For grade 3-4 all-cause and treatment-related AEs were higher in the nivolumab + ipilimumab + limited PDC arm compared to the PDC arm. The most common treatment related adverse events are detailed in Table 17.

The proportion of all-cause and treatment-related AEs leading to discontinuation was higher in the nivolumab + ipilimumab + limited PDC arm compared to the PDC arm, the most common of which were diarrhoea ([redacted]%), pneumonitis ([redacted]%), and colitis ([redacted]%) for those treated with nivolumab + ipilimumab + limited PDC and anaemia ([redacted]%) for those treated with PDC alone.[12]

Table 17. Summary of safety results from randomised patients from the clinical trial CheckMate-9LA (adapted from table 34 in the CS).

CheckMate-9LA **Adverse events, % of patients**	**NIVO + IPI + limited PDC (n = 358)**		**PDC (n = 349)**	
	Any grade	**Grade 3-4**	**Any grade**	**Grade 3-4**
Any	99.4	68.4	98.0	53.9
Any treatment related	91.6	46.9	87.7	37.8
Serious	60.1	47.2	42.7	32.1
Serious treatment related	29.6	25.4	17.8	14.6
Treatment related leading to discontinuation	19.3	16.2	7.4	4.6
Treatment-related deaths	2.0		1.7	
Common treatment related adverse events (affecting >15% of subjects in either arm)				
Nausea	26.8	1.4	35.8	0.9
Anaemia	23.2	5.9	37.8	14.3
Asthenia	20.9	0.8	17.8	2.3
Diarrhoea	20.9	3.9	11.7	0.6
Pruritus	20.9	0.8	1.7	0
Rash	18.7	1.7	3.2	0

CheckMate-9LA Adverse events, % of patients	NIVO + IPI + limited PDC (n = 358)		PDC (n = 349)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Fatigue	17.0	2.2	10.9	0.6
Decreased appetite	16.5	1.1	15.8	1.1
Neutropenia	9.8	6.7	16.9	9.2

NIVO = nivolumab; IPI = ipilimumab; PDC = platinum doublet chemotherapy

Serious adverse events

The proportions of all-case and treatment related SAEs were higher in the nivolumab + ipilimumab + limited PDC arm compared to the PDC arm. Grade 3-4 all-cause and treatment-related SAEs were also higher in the nivolumab + ipilimumab + limited PDC arm compared to the PDC arm (Table 17). The most frequently reported treatment-related SAEs were febrile neutropenia (3.1%), anaemia (2.2%), acute kidney injury and adrenal insufficiency (1.7%, each), and colitis (1.4%), for patients treated with nivolumab + ipilimumab + limited PDC and anaemia (3.4%), febrile neutropenia (2.6%), thrombocytopenia (1.7%), and pancytopenia (1.4%) for patients treated with PDC alone.[12]

Immune mediated adverse events

Immune mediated adverse events (IMAEs) are caused by the inflammatory mechanism of the immune system and are directly due to the immunologic mode of action of IO therapies. Treatment is with steroids or other immunosuppressants. Hormone replacement therapy may be used for endocrine disorders.

The CheckMate-9LA CSR presents the proportion of patients experiencing IMAEs within 100 days of the last dose of nivolumab + ipilimumab + limited PDC and PDC alone (

Table 18). There were some differences in the proportion of IMAEs in the checkmate-9LA trial and the supporting CheckMate-568 trial, for example, any grade Diarrhoea/colitis, [redacted] (

Table 18 and Table 19). However, the number of patients in the CheckMate-569 trial is small (n=36). Advice to the ERG was that in CheckMate-9LA, grade 3 and 4 toxicities may be lower than expected, particularly diarrhoea/colitis, which is lower than anticipated from of studies of nivolumab + ipilimumab. Broadly, the proportion of IMAEs in the CheckMate-9LA trial is comparable to that in the previous technology appraisals of nivolumab + ipilimumab for untreated advanced renal cell carcinoma (TA581).[16]

The CheckMate-9LA CSR states that [redacted]

For non-endocrine IMAEs, [redacted] Some endocrine IMAEs [redacted].[12] Clinical advice to the ERG was that these conditions may require long-term treatment with HRT.

Table 18 Summary of immune mediated adverse events for all randomised patients in the CheckMate-9LA trial (adapted table 5 from the CheckMate-9LA clinical study report.[12])

CheckMate-9LA Adverse events, % of patients	NIVO + IPI + limited PDC (n = 358)		PDC (n = 349)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Diarrhoea/colitis	[redacted]	[redacted]	[redacted]	[redacted]
Hepatitis	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]	[redacted]	[redacted]
Nephritis/Renal dysfunction	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Hypersensitivity/infusion reaction	[redacted]	[redacted]	[redacted]	[redacted]
Adrenal insufficiency	[redacted]	[redacted]	[redacted]	[redacted]
Hypophysitis	[redacted]	[redacted]	[redacted]	[redacted]
Hypothyroidism/Thyroiditis	[redacted]	[redacted]	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Diabetes Mellitus	[redacted]	[redacted]	[redacted]	[redacted]

NIVO = nivolumab; IPI = ipilimumab; PDC = platinum doublet chemotherapy

Other events of special interest, included encephalitis [redacted], pancreatitis [redacted] and uveitis [redacted] in patients treated with nivolumab + ipilimumab + limited PDC and myositis [redacted] in patients treated with PDC alone.

Supporting safety results

Supporting safety results from the single-arm trial CheckMate-568 are reported in Table 19. There are some differences between the values reported in the CS and the CheckMate-568 CSR. These are detailed in the footnote of Table 19. The ERG note that in the CheckMate-568 trial, hypothyroidism is reported as a common treatment related adverse event (occurring in 17% of patients). However, in the

CheckMate-9LA trial, hypothyroidism is reported only as an immune mediated adverse event only (occurring in [redacted] of patients).[12]

Table 19 Summary of supporting safety results from the single arm study CheckMate-568 (adapted from table 8.1-1 in the CheckMate-568 clinical study report)[17]

CheckMate-568	NIVO + IPI + limited PDC (n = 36) PDC (n = 349)		
Adverse events, % of patients	**Any grade**	**Grade 3-4**	**Grade 5**
Any	100	[redacted][1]	[redacted][2]
Any treatment related	92	58	
Serious	72	[redacted][5]	[redacted][5]
Serious treatment related	36	33	
Treatment related leading to discontinuation	22	19	
Treatment related deaths	0		
Common treatment related adverse events (affecting >15% of subjects in either arm)			
Pruritus	[redacted][3]	0	0
Fatigue	28	0	0
Rash	[redacted][4]	3	0
Diarrhoea	19	0	0
Nausea	19	0	0
Anaemia	19	6	0
Hypothyroidism	17	3	0
Maculo-papular rash	17	3	0
Lipase increased	17	17	0
Immune mediated adverse events' (Treated with immune modulating medication)			
Diarrhoea/colitis	[redacted]	[redacted]	[redacted]
Hepatitis	[redacted]	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]	[redacted]
Nephritis/Renal dysfunction	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]
Hypersensitivity/infusion reaction	[redacted]	[redacted]	[redacted]
Adrenal insufficiency	[redacted]	[redacted]	[redacted]
Hypophysitis	[redacted]	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]	[redacted]
Thyroiditis	[redacted]	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]	[redacted]
Diabetes Mellitus	[redacted]	[redacted]	[redacted]

Immune mediated adverse events‘ (Treated with or without immune modulating medication)			
Adrenal insufficiency	[redacted]	[redacted]	[redacted]
Hypophysitis	[redacted]	[redacted]	[redacted]
Hypothyroidism*	[redacted]	[redacted]	[redacted]
Thyroiditis	[redacted]	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]	[redacted]
Diabetes Mellitus	[redacted]	[redacted]	[redacted]

Reported in the CS as: [1] 27 events (75%), [2] 4 events (11%), [3] 12 events (33%), [4] 9 events (25%), [5] NR.
*Also reported in the common treatment related adverse events category in the CheckMate-568 CSR. ‘ Occurring within 100 days of last dose. NIVO = nivolumab; IPI = ipilimumab; PDC = platinum doublet chemotherapy

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

There was only one RCT identified in the SLR, which investigated the efficacy of nivolumab + ipilimumab + limited PDC (CheckMate-9LA) and there was no head to head trial evidence of nivolumab + ipilimumab + limited PDC versus the relevant comparators including histology based PDC, pembrolizumab and atezolizumab + bevacizumab + PDC. Therefore, an ITC was considered appropriate.

Details of study selection for the ITC are reported in Appendix N. The studies included in the ITC evidence synthesis were restricted to key IO-based RCTs identified in the SLR to inform direct comparisons between the intervention and comparators of interest. Of the 67 unique studies identified, six were selected for inclusion in the ITC, listed in Table 24 of the CS. The ERG requested reasons for excluding each of the 61 studies, however this was not provided. The studies included in the ITC consisted of one study of nivolumab + ipilimumab + limited PDC (CheckMate-9LA), two studies of pembrolizumab (KeyNote-024 and KeyNote-042) and one of atezolizumab + bevacizumab + PDC (Impower-150). Two further studies (ERACLE and PRONOUNCE) were included to make a connected network of comparisons, as there was no common node between the IMpower-150 RCT and the CheckMate-9LA RCT. At the PFC stage, the company also added the CheckMate-227 study to the ITC, which compares nivolumab + ipilimumab with PDC to better reflect the clinical expectation that longer-term trends from CheckMate-9LA will follow longer-term trends from CheckMate-227, see Section 3.4.1.

The methods of data extraction and quality assessment are specified in Appendix D.2.4. The quality assessment of the included studies is reported in Table 26 of Appendix D.12. Studies poorly reported the method of randomisation and concealment; thus, randomisation and concealment of treatment allocation were assessed as unclear for all studies except the two KeyNote studies, for which full

protocols were available. Baseline characteristics were balanced and analysis was conducted according to the ITT population in all studies except for CheckMate-227, where this was stated as not clear. All trials except KeyNote-024 were not blinded, therefore there was a greater risk of selection bias and performance bias for patient reported outcomes. All studies reported all outcomes measured except for the CheckMate-9LA and CheckMate-227 trials in which there is a high risk of reporting bias and in ERACLE this was not clear. The ERG did not undertake independent searches to check that all relevant studies were included in the ITC, due to time constraints. However, a comparison of studies included in this STA, with the earlier STAs of pembrolizumab, atezolizumab + bevacizumab + PDC and PDC was undertaken and no relevant trials appear to have been excluded from the ITC.

The company conducted two separate ITC analyses: one of treatment-naïve individuals with advanced or recurrent NSCLC with mixed histology and PD-L1 expression ≥ 50% and one of treatment naïve patients with advanced or recurrent NSCLC with non-squamous histology and PD-L1 < 50%.

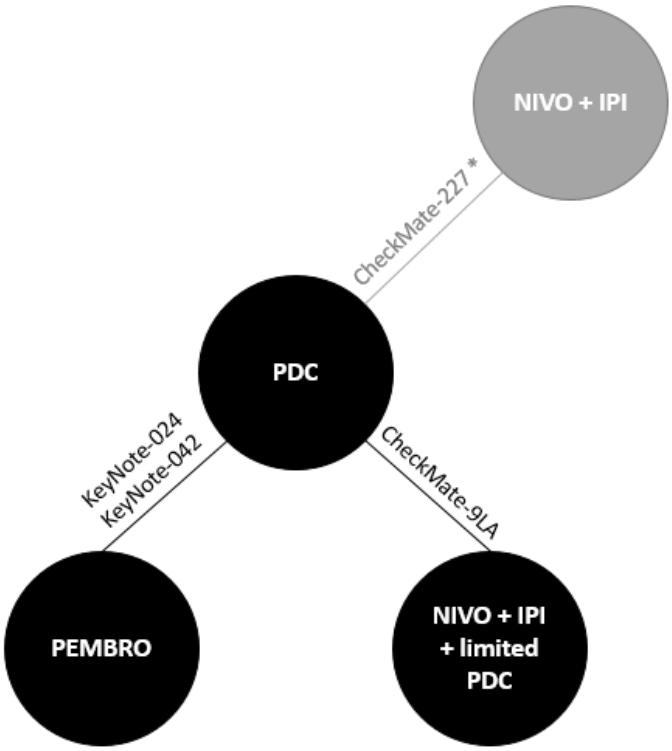
The full ITT population of CheckMate-9LA was used in both initial ITC analyses. At the clarification stage, the ERG requested that the company conduct the ITC using only relevant sub-population data from CheckMate-9LA. In response, the company presented revised ITC analyses using subgroup data from CheckMate-9LA and CheckMate-227 that aligns with the requested population 1 (non-squamous and PD-L1 < 50%). However, it only provided an ITC for consolidated populations 2 + 4 (any histology and PD-L1 ≥ 50%) due to sample size limitations. The company stated that the updated models, in which PD-L1 ≥ 50% subgroup data from CheckMate-9LA were used were deemed clinically implausible based on a priori assumptions (see company's response to clarification question A18). Hence, the full ITT population of CheckMate-9LA was used for the ITC in population 2 + 4 (patients with mixed histology and PD-L1 ≥ 50%). The full ITT population of CheckMate-227 was also used for this ITC. The ERG accepts the reasoning to consolidate population 2 and 4.

For population 3 (squamous, PD-L1 < 50%), the only relevant comparator is PDC and there is already direct evidence comparing nivolumab + ipilimumab + limited PDC and PDC from CheckMate-9LA, hence an indirect comparison in this sub-population was not required.

3.3.1 Network of patients with mixed histology and PD-L1 ≥ 50%

The relevant comparators for patients with PD-L1 ≥ 50% are PDC and pembrolizumab. The network for indirect comparisons is presented in Figure 7 and includes four studies: KeyNote-024, KeyNote-042, CheckMate-9LA and CheckMate-227. The latter was added in an updated analysis at the PFC stage. Efficacy endpoints of OS over four years and PFS over three years were used to conduct the analyses.

Figure 7 Network diagram for the target population of mixed histology and PD-L1 ≥ 50% (adapted from CS, Figure 36)



Abbreviations: IPI = ipilimumab; NIVO = nivolumab; PDC=platinum-doublet chemotherapy; PEMBRO = pembrolizumab.
PDC regimens were as follows: **CheckMate-9LA**: paclitaxel + carboplatin or pemetrexed + cisplatin or carboplatin; **CheckMate-227**: gemcitabine + cisplatin or carboplatin or pemetrexed + cisplatin or carboplatin; **KeyNote- 024**: gemcitabine + cisplatin or carboplatin, paclitaxel + carboplatin or pemetrexed + cisplatin or carboplatin; **KeyNote- 042**: paclitaxel + carboplatin or pemetrexed + carboplatin.
* CheckMate-227 was included as an additional analysis at the points for clarification stage.

In each trial, different types of PDC were used depending on histology. Details are provided in Table 20. In this report we will refer to all of these as PDC.

Table 20 Treatment and comparator details of studies included in the network of patients with PD-L1 ≥ 50% (adapted from CS, Table 26)

Trial name	Population		Intervention	Comparator
	PD-L1	Histology		
CM-9LA	All-comer	Squamous	NIVO-IPI + Paclitaxel + carboplatin	Paclitaxel 200mg/m^2 + carboplatin AUC 6
	All-comer	Non-squamous	NIVO-IPI + Pemetrexed + cisplatin or carboplatin	Pemetrexed 500mg/m^2 + cisplatin 75mg/m^2 or carboplatin AUC 5/6
CM-227	All-comer	Squamous	NIVO-IPI 3mg/kg -IPI 1mg/kg	Gemcitabine 1250mg/m^2 + Cisplatin 75mg/m^2 or carboplatin AUC
	All-comer	Non-squamous	NIVO-IPI 3mg/kg -IPI 1mg/kg	Pemetrexed 500mg/m^2 + cisplatin 75mg/m^2 or carboplatin AUC

Trial name	Population		Intervention	Comparator
KN-024	≥50%	Squamous	PEMBRO 200mg	Gemcitabine 1250mg/m^2 + cisplatin 75mg/m^2 or carboplatin AUC 5/6 or paclitaxel 200mg/m^2 + carboplatin AUC 5/6
	≥50%	Non-squamous	PEMBRO 200mg	Pemetrexed 500mg/m^2 + cisplatin 75mg/m^2 or carboplatin AUC 5/6
KN-042	≥1%	Squamous	PEMBRO 200mg	Paclitaxel + carboplatin
	≥1%	Non-squamous	PEMBRO 200mg	Pemetrexed or carboplatin

IPI = ipilimumab; NIVO = nivolumab; PDC=platinum-doublet chemotherapy; PEMBRO = pembrolizumab. AUC = area under the curve.

The CS presents the baseline characteristics of the studies included in this network in Appendix D.6, Table 9. The baseline characteristics reported were similar across arms in most of the trials. However, in KeyNote-024 there was a higher proportion of patients who had never smoked in the PDC arm (12.6%) compared with the Pembrolizumab arm (3.2%). In the network of patients with mixed histology and PD-L1 ≥ 50%, the proportion of male patients was substantially lower in the KeyNote-024 trial (60% in the Pembrolizumab arm and 63% in the PDC arm) than in CheckMate-9LA (70%), CheckMate-227 (66.7%) and KeyNote-042 (71%) trials (Table 21). In CheckMate-227, sex was shown to be a potential effect modifier (Section 3.2.4.2). The proportion of patients who had never smoked also varied between trials, with the highest proportion in the KeyNote-042 trial (22%) and lower proportions in the CheckMate-9LA and CheckMate-227 trials (13.5%) and the lowest in the KeyNote-024 trial (3.2% in the Pembrolizumab arm and 12.6% in the PDC arm) (Table 21). As discussed in 3.2.4.2, in the CheckMate trials, patients who had never smoked did not benefit from treatment with an IO therapy. This may be one reason why there is a smaller effect size reported in KeyNote-042 compared with KeyNote-024. The company also provided baseline characteristics for patients with PDL1 ≥ 50% from the CheckMate-9LA trial at the clarification stage (Table 13).

[redacted] (Table 20). [redacted]. Although, clinical advice to the ERG is that the type of PDC treatment used does have a significant effect on efficacy, for the purposes of analysis it was reasonable to combine PDC comparator arms. Furthermore, the clinical advisor stated that there is some evidence to suggest cisplatin is more effective than carboplatin and KeyNote-042 is the only study that does not use cisplatin. The PDC regimens in each of the studies also varied by dose and number of cycles.

Therefore, the ERG considers the PDC comparator arms of the studies included in the ITC to be heterogenous and thus combining them may reduce the reliability of the results.

Histology and PD-L1 defined populations

Both KeyNote trials included only patients with PD-L1 expression ≥ 50%, whereas the PD-L1 all comer population was used for the CheckMate-9LA and CheckMate-227 trials, in which only 24.2% and 34% of patients had PD-L1 ≥ 50%, respectively (Table 21). The CS states that the PD-L1 all comer population of CheckMate-9LA was used to preserve the RCT design and maximise sample size due to the subgroup analyses showing similar relative effect sizes across PD-L1 defined categories. However, as discussed in Section 3.2.4.2, in patients with PD-L1 ≥ 50%, the confidence interval is wider and very close to 1 (HR:0.66, 95% CI: 0.44 to 0.99). This suggests that nivolumab + ipilimumab + limited PDC may not be as effective in these patients compared with PDC.

Additionally, the histology all-comer population, that is patients with both squamous and non-squamous NCSLC, was used for CheckMate-9LA, CheckMate-227 and for both KeyNote studies. However, KeyNote-024 included a substantially higher proportion of patients with non-squamous histology, 81.2% in the pembrolizumab arm and 82.1% in the PDC arm. Whereas CheckMate-9LA, CheckMate-227 and KeyNote-042 had similar but lower proportions of patients with non-squamous histology (69% in CheckMate-9LA, 68% in CheckMate-227 and 61.4% in KeyNote-042) (Table 21). The CS states that the histology all-comer population was used to preserve study design and power given that the effect size for nivolumab + ipilimumab + limited PDC relative to PDC was similar across squamous and non-squamous histology. However, in the CheckMate-227 trial, subgroup analyses showed that the OS benefit of nivolumab + ipilimumab vs PDC was not seen in patients with non-squamous NSCLC. Furthermore, previous studies have reported contradictory results when assessing the relationship between PD-L1 expression, histology and clinical outcomes. The mixed populations presented could lead to an underlying bias.

Other issues

There were some additional differences in trial design between the three included trials. The KeyNote-024 trial permitted patients to crossover treatment from the control arm to the experimental Pembrolizumab arm. However, the KeyNote-042, CheckMate-9LA or CheckMate-227 studies did not. This may be why the KeyNote-024 study reports a greater effect with Pembrolizumab than the KeyNote-042 trial. The presence of second line treatment was reported in all trials, except KeyNote-024, which did not have a second-line treatment.

Table 21 Baseline characteristics of studies included in the network of patients with mixed histology and PD-L1 ≥ 50% (adapted from Appendix D.6, Tables 9 and 10)

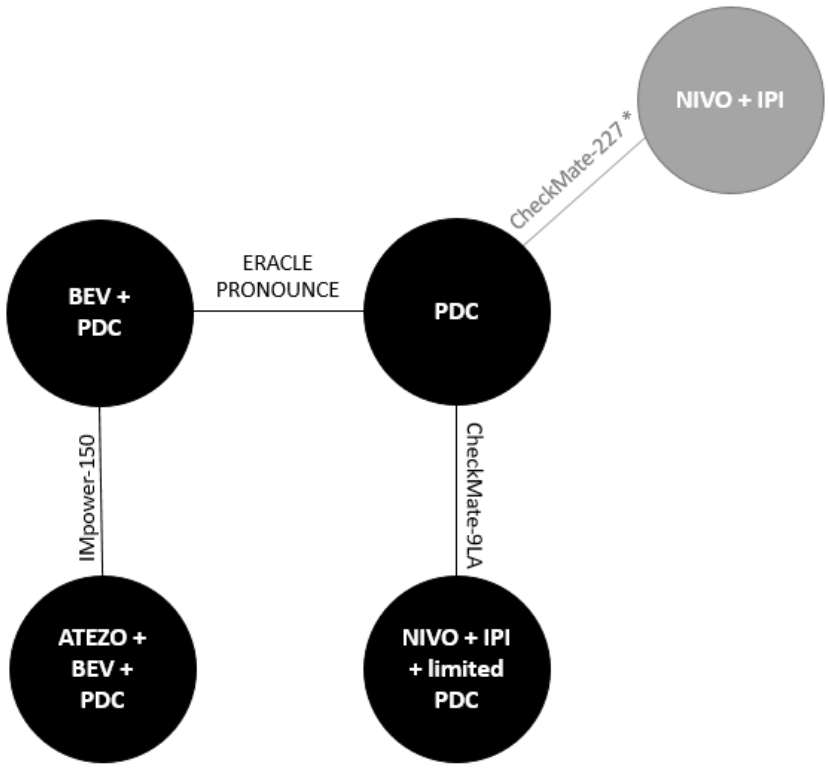
Intervention	CM-9LA (All-comer)		CM-227 (All-comer)		KN-024 (PD-L1 ≥ 50%)		KN-042 (PD-L1 ≥ 50%)	
	NIVO + IPI + limited PDC	PDC	NIVO + IPI	PDC	PEMBRO	PDC	PEMBRO	PDC
N	361	358	583	583	154	151	637	637
Male, %	252 (70)	250 (70)	393 (67.4)	385 (66)	92 (60)	95 (63)	452 (71)	452 (71)
Age (years), median (range)	65 (35-81)	65 (26-86)	64 (26-87)	64 (29-87)	64.5 (33-90)	66 (38-85)	63 (25-89)	63 (31-90)
ECOG PS (%)								
0	31 (8.6)	31 (8.6)	204 (35)	191 (32.8)	54 (35.1)	53 (35.1)	198 (31.1)	192 (30.1)
1	68 (18.8)	68 (19.0)	377 (64.7)	386 (66.2)	99 (64.3)	98 (64.9)	439 (68.9)	445 (69.9)
2	-	-	2 (0.3)	4 (0.7)	1 (0.6)	0	-	-
Never smoked (%)	47 (13)	50 (14)	79 (13.5)	78 (13.4)	5 (3.2)	19 (12.6)	140 (22.0)	140 (22.0)
Histology (%)								
Squamous	112 (31)	111 (31)	163 (28)	162 (27.8)	29 (18.8)	27 (17.9)	243 (38.1)	249 (39.1)
Non-squamous	249 (69)	247 (69)	419 (71.9)	421 (72.2)	125 (81.2)	124 (82.1)	394 (61.9)	388 (60.9)
PD-L1 expression (%)								
<1%	135 (37.4)	129 (36.0)	187 (32.1)	186 (31.9)	0	-	-	-
<50%	262 (72.6)	235 (70.7)	378 (64.8)	391 (67.1)	0	-	-	-
≥ 50%	76 (21.1)	98 (27.4)	205 (35.2)	192 (32.9)	154 (100)	151 (100)	637 (100)	637 (100)

IPI = ipilimumab; NIVO = nivolumab; PDC=platinum-doublet chemotherapy; PEMBRO = pembrolizumab. ECOG = Eastern cooperative oncology group; PD-L1 = Programmed death-ligand 1.

3.3.2 Network of non-squamous patients with PD-L1 < 50%

The relevant comparators for treatment-naïve patients with advanced or recurrent NSCLC with non-squamous histology and PD-L1 < 50% are atezolizumab + bevacizumab + PDC and PDC alone. Bevacizumab + PDC was also included to allow indirect comparisons between the relevant comparators. The company conducted an ITC including five studies: ERACLE, PRONOUNCE, Impower-150, CheckMate-9LA and CheckMate-227 (added in an updated analysis at the PFC stage). Figure 8 shows the network diagram. Efficacy endpoints of OS (constant HR) and PFS over two years were reported.

Figure 8 Network diagram for the target population of patients with non-squamous histology and PD-L1 < 50% (adapted from CS, Figure 38)



Abbreviations: ATEZO = atezolizumab; BEV = bevacizumab; IPI = ipilimumab; NIVO = nivolumab; NSQ = non-squamous; PDC=platinum-doublet chemotherapy.
PDC regimens were as follows: **CheckMate-9LA**: paclitaxel + carboplatin or pemetrexed + cisplatin or carboplatin; **CheckMate-227**: gemcitabine + cisplatin or carboplatin or pemetrexed + cisplatin or carboplatin; IMpower-150: paclitaxel + carboplatin; **ERACLE**: paclitaxel + carboplatin or pemetrexed + cisplatin; **PRONOUNCE**: paclitaxel + carboplatin or pemetrexed + carboplatin.
* CheckMate-227 was included as an additional analysis at the points for clarification stage.

In each trial, different types of PDC were used depending on histology. In Impower-150, paclitaxel + carboplatin was used, whereas in ERACLE and PRONOUNCE, pemetrexed + cisplatin and pemetrexed + carboplatin were used, respectively (Table 22).

Table 22 Treatment and comparator details of studies included in the network of non-squamous patients with PD-L1 < 50% (adapted from CS, Table 28)

Trial name	Population		Intervention	Comparator
	PD-L1	Histology		
CM-9LA	<50%	Non-squamous	NIVO-IPI + Pemetrexed + cisplatin or carboplatin	Pemetrexed 500mg/m^2 + cisplatin 75mg/m^2 or carboplatin AUC 5/6
CM-227	<50%	Non-squamous	NIVO-IPI 3mg/kg -IPI 1mg/kg	Pemetrexed 500mg/m^2 + cisplatin 75mg/m^2 or carboplatin AUC
IMpower-150	<50%	Non-squamous	Atezolizumab + bevacizumab 15mg + carboplatin + paclitaxel 200mg	Bevacizumab 15mg + carboplatin + paclitaxel 200mg
ERACLE	All-comer	Non-squamous	Bevacizumab 15 mg + paclitaxel 200mg + carboplatin	Pemetrexed 500mg + cisplatin 75mg
PRONOUNCE	All-comer	Non-squamous	Bevacizumab 15mg + paclitaxel 200mg + carboplatin	Pemetrexed 500mg + carboplatin

IPI = ipilimumab; NIVO = nivolumab; PD-L1 = Programmed death-ligand 1; AUC = Area under the curve

The CS presents the baseline characteristics of the IMpower-150, ERACLE and PRONOUNCE studies included in this ITC in Appendix D.6, Table 9. In response to the PFC, the company also provided baseline characteristics for the sub-population of non-squamous patients with PD-L1 < 50% in CheckMate-9LA and CheckMate-227 (Table 23). The baseline characteristics reported were similar across arms in most of the trials. However, in ERACLE there was a higher proportion of male patients in the bevacizumab + PDC arm (78%) compared with the PDC arm (70%) and there was also a higher proportion of patients who had never smoked in the bevacizumab + PDC arm (28%) than in the PDC arm (22%).

There were also notable differences in baseline characteristics across trials. The proportion of male patients was substantially higher in the ERACLE (78% in the bevacizumab + PDC arm and 70% in the PDC arm) trial, whereas it was lower in the PRONOUNCE (58%) and the Impower-150 (60%) trials. ECOG PS also varied between trials, ERACLE had a much higher proportion of patients with ECOG PS of 0 (78.5%) compared to Impower-150 (42.6%), CheckMate-9LA (31%) and CheckMate-227 (33.9%). Similarly, the proportion of patients who had never smoked varied substantially from 7% in PRONOUNCE to 25% in ERACLE (Table 23). Furthermore, no baseline characteristics for metastases were provided, which were shown in the subgroup analyses to be potential effect modifiers (Section 3.2.4.2). The differences described increase the risk of between study, across-comparison heterogeneity, which reduces the reliability of the ITC results.

Histology and PD-L1 defined populations

The PD-L1 all comer population was originally used for the CheckMate-9LA trial. However, as requested by the ERG, after PFC the company included only the non-squamous patients with PD-L1 < 50% from the CheckMate-9LA and CheckMate-227 trials. The all-comer PD-L1 populations of

ERACLE and PRONOUNCE trials were included and the ERG could not access any details regarding the different proportions of PD-L1 expression in each study.

[redacted]. Furthermore, clinical advice is that there is some evidence to suggest differences in efficacy between cisplatin and carboplatin. Therefore, the heterogeneity in PDC treatments across the trials may increase uncertainty in the results.

Other issues

None of the studies permitted crossover, with the exception of PRONOUNCE, which did not report any details regarding crossover treatment. Therefore, it is uncertain whether patients in PRONOUNCE received cross over treatment during the follow up period. Furthermore, all trials reported second-line treatment, except for Impower-150, which did not report any details of this.

Table 23 Baseline characteristics of studies included in the network of non-squamous patients with PD-L1 < 50% (adapted from Appendix D.6, Tables 9 and 10 and clarification response, Tables 4 and 5)

Intervention	CM-9LA		CM-227		Impower-150		ERACLE		PRONOUNCE	
	NIVO + IPI + limited PDC	PDC	NIVO + IPI	PDC	ATEZO + BEV + PDC	PDC	BEV + PDC	PDC	BEV + PDC	PDC
N	[redacted]	[redacted]	[redacted]	[redacted]	400	400	58	60	179	182
Male, %	-	-	-	-	240 (60)	240 (60)	45 (78)	42 (70)	104 (58)	105 (58)
Age (years), median (range)	-	-	-	-	63 (31-89)	63 (31-90)	62 (41-71)	60 (35-72)	65 (41-86)	66 (38-84)
ECOG performance status (%)										
0	[redacted]	[redacted]	[redacted]	[redacted]	160 (40.1)	180 (45.1)	46 (79)	47 (78)	84 (47)	85 (47)
1	[redacted]	[redacted]	[redacted]	[redacted]	240 (60)	220 (55)	12 (21)	13 (22)	95 (53)	96 (53)
2	[redacted]	[redacted]	[redacted]	[redacted]	-	-	0	-	0	0
Never smoked (%)	[redacted]	[redacted]	[redacted]	[redacted]	82 (20.5)	77 (19.2)	16 (28)	12 (22)	7 (4)	18 (10)
Histology (%)										
Squamous	0	0	0	0	19 (4.8)	17 (4.2)	0	0	33 (18.4)	28 (15.4)
Non-squamous	100	100	100	100	378 (94.5)	377 (94.2)	100	100	146 (81.5)	153 (84)
PD-L1 expression (%)										
<1%	-	-	-	-	-	-	-	-	-	-
1-49%	-	-	-	-	-	-	-	-	-	-
<50%	100	100	100	100	100	100	-	-	-	-
≥ 50%	0	0	0	0	0	0	-	-	-	-

*These values are reported in the clarification response document; however, they seem to be incorrect and are more likely to be the values for patients who are current/former smokers ATEZO = atezolizumab; BEV = bevacizumab; IPI = ipilimumab; NIVO = nivolumab; PDC=platinum-doublet chemotherapy; ECOG = Eastern cooperative oncology group; PD-L1 = Programmed death-ligand 1

3.4 Critique of the indirect comparison and/or multiple treatment comparison

3.4.1 Critique of the indirect comparison methods

Indirect treatment comparisons were carried out using a fractional polynomial network meta-analysis model as the CS reported that the proportional hazards assumption was not met. The company also presented ITCs assuming proportional hazards using the Bucher method for time-to-event outcomes (OS, PFS) for completeness, which is reported in Appendix N.4.3. The ERG will comment mainly on the fractional polynomial results for conclusions on clinical effectiveness as these are the most relevant analyses and are used in the economic model.

3.4.1.1 Fractional polynomial NMA

The company conducted three tests to assess proportional hazards, which are in line with recommendations in the literature.[18] The KM curves of each included study were visually inspected and the Schoenfeld residual plots for OS and PFS were assessed. The residual plots are presented in Appendix N.4.1 (Figures 45-48) and the Schoenfeld residual global test results across included trials are presented in Table 25 of the CS. The log-cumulative hazard plots for each pair of curves were also examined (Figures 32-35 of the CS).

Results showed that PFS from KeyNote-024 and PFS and OS from KeyNote-042 were significantly different from proportional hazards based on the Schoenfeld residuals global test. However, from inspection of the log-cumulative hazards plots, all plots except OS from KeyNote-024 cross at one or more times. Therefore, the CS reports that there is a clear indication of non-proportional hazards across all comparators. Furthermore, the appraisal of atezolizumab (which also included the IMpower-150 study)[19] confirmed that the assumption of non-proportionality was reasonable and clinically justified. Non-proportionality has also been demonstrated in several earlier IO appraisals in NSCLC (TA531, TA428, TA484 and TA584),[19-22] as well as for the supporting CheckMate-227 trial. Therefore, the company implemented a fractional polynomial NMA. The ERG agrees that an ITC assuming proportional hazards was not appropriate, however it notes that fractional polynomial models can be complex to implement and difficult to interpret.

Unlike using a method in which the treatment effect is represented by a single parameter, i.e. the hazard ratio, fractional polynomials model the hazard functions of the interventions compared in a randomized controlled trial which are allowed to vary over time, and the difference between the parameters of these fractional polynomials within a trial are synthesized across studies. With this approach a network meta-analysis of survival can be performed with models that can be fitted more closely to the data. The company followed the approach outlined by Jansen et al. (2011)[23] and used code detailed by Jansen et al. (2015) and Dias et al. (2018).[24, 25] IPD were reconstructed based on

digitised Kaplan-Meier curves.[26] The log hazards of OS and PFS were then fit as a function of time using the following parametric equations:

$$\log \text{hazard} = \mu_1 + \mu_2 t^{P1} + \mu_3 t^{P2}$$

where μ_1 represents the scale parameter, μ_2 and μ_3 represent shape parameters, t represents time and $P1$ and $P2$ are powers from the set {-1, -0.5, 0, 0.5, 1} with $t^0 = ln(t)$. If $P1$=$P2$=P then the model becomes a "repeated powers" model:

$$\log \text{hazard} = \mu_1 + \mu_2 t^{P} + \mu_3 t^{P} ln(t)$$

Differences, d_1, d_2 and/or d_3 are then added to the μ's within each term to capture treatment effects;

$$\log \text{hazard} = (\mu_1 + d_1) + (\mu_2 + d_2) t^{P1} + (\mu_3 + d_3) t^{P2}$$

these ds are then meta-analysed.

The company did not provide details of the number of burn-in iterations, the size of the Markov chain Monte Carlo (MC) posterior samples used or convergence checks carried out, these were requested by the ERG at the clarification stage. The company stated that 40,000 burn-in iterations were used and 60,000 additional iterations were used for the posterior sample. Convergence checks included assessing trace plots, density plots, Gelman plots and autocorrelation plots, although these were not provided to the ERG.

For both networks, 44 fixed effect models were fitted, including first and second order models, that is models with only $P1$ or with both $P1$ and $P2$, and different combinations of powers for $P1$ and $P2$. Appendix N, states that the values for the powers $P1$ and $P2$ are in the set {-1, -0.5, 0, 0.5, 1}. However, Jansen (2011)[23] recommends also considering additional powers and only powers 0 and 1 were considered for $P1$. In response to the PFC the company stated that they aligned their candidate set of models based on the most recent work by Jansen, which involves a subset of values between -1 and 1.[27-29] These are less computationally expensive for model run, less likely to provide clinically implausible extrapolations, yet continuing to provide a flexible set of clinically plausible hazard models for OS and PFS and showing good model fit, which seems appropriate to the ERG. The models were ranked according to fit, based on deviance information criterion (DIC). The company selected the best fitting model by choosing the model with the lowest DIC. A model with a higher DIC was chosen if the modelled versus fitted data captured the relative effects better. The modelled versus fitted data was also inspected to assess the clinical plausibility of relative effects captured in the tails and beyond-trial projections. However, in some cases the best fitting models were clinically implausible and therefore, were not selected as the most appropriate models.

Random effects models were not fit due to the small number of studies in each network. The ERG agrees that there were too few studies included to produce reliable estimates of between-study variation for random-effects models. However, heterogeneity may still be present among the included studies even though it cannot be quantified.

The assumption of consistency could not be tested because no closed evidence loops are present in the networks [redacted] The ERG agrees that statistical homogeneity can be validated clinically by comparison of study conditions, patient characteristics, and outcome measures. The trials included in the ITC comparisons vary by sex, PD-L1 expression, histology, PDC regimen, smoker status and ECOG PS as discussed in Section 3.3. These variations contribute to differences in placebo response rates which can be an indicator of potential differences in the relative efficacy of the interventions compared with placebo. Therefore, the ERG considers the analyses based on FE meta-analysis models acceptable but they need to be interpreted with caution due to the possibility of imbalance in effect modifying covariates across studies.

The ITC originally only included CheckMate-9LA as evidence for nivolumab + ipilimumab + limited PDC. However, at the PFC stage, the company included CheckMate-227 in the fractional polynomial ITCs, to better inform the long-term extrapolation of the curves. The ERG agrees that the NMA including CheckMate-227 is preferred as there are more data to inform the long-term extrapolations of the fractional polynomial model, giving more precise estimates. However, due to time restrictions the company were not able to clinically validate the new models. The best fitting models were selected according to DIC alongside a pre-defined heuristic that additionally incorporated additional penalization for model complexity, visual inspections of observed versus modelled outputs, and clinical plausibility of model extrapolation periods. However, these inspections were not provided. The ERG produced Kaplan-Meier curve overlays of observed versus modelled outputs for OS for each RCT included in the updated NMAs, which include CheckMate-227 (see Section 3.5 and Appendix 1). These allow additional critique of the model fit. However, Kaplan-Meier curve overlays were not produced for PFS, due to time constraints. However, the ERG is cautious about relying solely on the updated results without further validation by the company. Therefore, the results of the updated NMA including CheckMate-227 will be reported alongside the original NMA results excluding CheckMate-227.

Analyses were conducted within a Bayesian framework in R (V3.6.1) using JAGS (V4.3.0) software. The ERG requested the full code, data and initial values so that the analyses could be checked and reproduced. The company provided data in the form of discrete hazards and the JAGS code adapted from the literature to run the fractional polynomial ITC. The ERG confirms that the code correctly implements the models and were able to reproduce some results for OS (due to time constraints only a few results were checked but all these could be reproduced).

3.4.1.2 Bucher ITC

Bucher indirect comparisons were also conducted for completeness. The Bucher ITC method is described in Appendix N.3.4 and the characteristics of each included study are described in Table 138 and 142 of Appendix N. [redacted] The ERG requested the full code and data used to conduct the analyses, which were provided at the clarification stage. The ERG is satisfied that the method is correctly implemented.

Study CheckMate-227 would not have added relevant information to comparisons using the Bucher approach and was therefore not included in any of the ITCs.

Network of patients with mixed histology and PD-L1 ≥ 50%

Three studies were included in this network: CheckMate-9LA, KeyNote-024 and KeyNote-042 (Table 24). [redacted] The subgroup of patients with mixed histology and PD-L1 ≥ 50% was used from all three studies.

Network of non-squamous patients with PD-L1 < 50%

Two studies were included in the network of non-squamous patients with PD-L1 < 50%: CheckMate-9LA and Impower-150 (Table 24). The subgroup of non-squamous patients with PD-L1 < 50% was used from both studies. There was no common node between the IMpower-150 RCT (which had a control arm of bevacizumab + PDC) and the CheckMate-9LA RCT (which has a comparator of PDC). The company states that a meta-analysis of head-to-head evidence from two RCTs: ERACLE and PRONOUNCE suggests that the two control arms bevacizumab + PDC and PDC have similar efficacy in terms of OS and PFS. Therefore, the company lumped the two nodes together and performed a three-node ITC. However, the ERG doesn't agree that combining the two nodes is appropriate as this increases the number of assumptions and is likely to underestimate the uncertainty. Therefore, the ERG conducted the ITC using the full network structure (Figure 8, excluding CheckMate-227).

Table 24 Studies included in Bucher ITC (adapted from clarification response document, Table 6)

Trial	Histology	PD-L1	Overall Survival HR (95% CI)	Progression-Free Survival HR (95% CI)
Network of patients with mixed histology and PD-L1 ≥ 50%				
CheckMate-9LA	Mixed	PD-L1 ≥ 50%	0.66 (0.44-0.99)	[redacted]
KeyNote-024 + -042	Mixed	PD-L1 ≥ 50%	0.69 (0.58-0.81)	0.72 (0.62-0.85)
Network of non-squamous patients with PD-L1 < 50%				
CheckMate-9LA	Non-squamous	PD-L1 < 50%	[redacted]	[redacted]
ERACLE/PRONOUNCE	Non-squamous	All-comer	[redacted]*	[redacted]*
IMpower-150	Non-squamous	PD-L1 < 50%	0.81 (0.65-1.02)	0.68 (0.56-0.82)

*Estimates from a meta-analysis of ERACLE and PRONOUNCE, reported in Appendix N.2.8 PD-L1 = Programmed death-ligand 1, HR = hazard ratio; CI = confidence interval.

3.4.2 Indirect comparison results

3.4.2.1 Fractional polynomial NMA

Network of patients with mixed histology and PD-L1 ≥ 50%

Three RCTs were originally included in the NMA of mixed histology and PD-L1 ≥ 50%, with CheckMate-227 being added in an updated analysis. Table 25 presents the studies and the data used in the updated NMA.

Table 25 Included RCTs in network of patients with mixed histology and PD-L1 ≥ 50% (adapted from CS, Table 26)

Study	PD-L1	Histology	Treatment 1	Treatment 2	OS HR (95% CI)	PFS HR (95% CI)
KN-024	≥ 50%	Mixed	PEMBRO	PDC	0.65 (0.50-0.86)	0.50 (0.37-0.68)
KN-042	≥ 50%	Mixed	PEMBRO	PDC	0.70 (0.58-0.86)	0.83 (0.69-1.00)
CM-9LA	All-comers	Mixed	NIVO + IPI + limited PDC	PDC	0.66 (0.55-0.80)	0.68 (0.57-0.82)
CM-227	All-comers	Mixed	NIVO + IPI	PDC	0.73 (0.64-0.84)	0.79 (0.69-0.91)

NIVO= nivolumab; IPI= ipilimumab; PDC = platinum doublet chemotherapy; PEMBRO = pembrolizumab; HR = hazard ratio; CI = confidence interval; OS = overall survival; PFS = progression free survival.

OS in patients with mixed histology and PD-L1 ≥ 50%

For the original NMA without CM-227, the model fit statistics for OS are presented in Table 122 of Appendix N. The fractional polynomial model with $P1=P2=1$ with treatment effect on the two shape parameters fits the data best. However, the model with $P1=P2=1$ and treatment effect on the scale and 1st shape parameters was chosen as it resolved clinical implausibilities in the tail of the fitted curves. Although, this model does not capture the early crossing of curves in KeyNote-042, the ERG is

satisfied with this selection. The modelled versus raw Kaplan-Meier data for OS for each included study is presented in Figure 37 of the CS. For the updated NMA including the CheckMate-227 study, the fractional polynomial model with *P*1=0, *P*2=1 and treatment effects on the scale and first shape parameters was selected. The modelled versus raw Kaplan-Meier data for the updated model for each included study is presented in the Appendix (Figure 30). The fit of the updated model is similar to the model without CheckMate-227 for all included trials. It does not capture the early crossing of curves in KeyNote-042, however the model seems to fit well to the data from CheckMate-227.

The results for the updated NMA including CheckMate-227 were slightly different to the original NMA (

Table 26). [redacted]

[redacted] (

Table 26). [redacted]

[redacted]

[redacted] (Table 26) [redacted]

Table 26 Hazard ratios of Nivolumab + ipilimumab + limited PDC versus comparators for OS in patients with PD-L1 ≥ 50% (adapted from CS, Table 27 and clarification response, Table 10)

		Including CheckMate-227 [a]	Excluding CheckMate-227 [b]
NIVO + IPI + limited PDC vs.	**Time point (months)**	**HR (95% CrI)**	**HR (95% CrI)**
PDC	1	[redacted]	[redacted]
	6	[redacted]	[redacted]
	12	[redacted]	[redacted]
	24	[redacted]	[redacted]
	36	[redacted]	[redacted]
	48	[redacted]	[redacted]
PEMBRO	1	[redacted]	[redacted]
	6	[redacted]	[redacted]
	12	[redacted]	[redacted]
	24	[redacted]	[redacted]

		Including CheckMate-227 [a]	Excluding CheckMate-227 [b]
NIVO + IPI + limited PDC vs.	**Time point (months)**	**HR (95% CrI)**	**HR (95% CrI)**
	36	[redacted]	[redacted]
	48	[redacted]	[redacted]

[a] model with *P*1=0, *P*2=1 and treatment effects on scale and 1st shape; [b] model with P1=P2=1 and treatment effects on scale and 1st shape parameter. NIVO= nivolumab; IPI= ipilimumab; PDC = platinum doublet chemotherapy; PEMBRO = pembrolizumab; HR = hazard ratio; CrI = credible interval.

PFS in patients with mixed histology and PD-L1 ≥ 50%

For the NMA without CheckMate-227, the model fit statistics for PFS are presented in Table 127 of Appendix N. The fractional polynomial model with *P*1=0, *P*2=-1 and treatment effects on the scale and 1st shape parameters had the lowest DIC. The company reported that there was no evidence of clinical implausibility of the estimated treatment effects after inspecting the modelled versus fitted data of each study. However, in the KeyNote-024 trial, the modelled curves seem to overestimate the effect in the PDC arm and underestimate the effect in the pembrolizumab arm. The KeyNote-024 trial has a very short follow up, therefore it is difficult to check the fit of the long term modelled data. The company stated that they conducted sensitivity analyses without KeyNote-024 due to the short follow up, however these were not provided to the ERG. However, overall the ERG is satisfied that this model is appropriate. The modelled versus raw Kaplan-Meier data for PFS for each included study is presented in Figure 40 of the CS. The same model was used for the updated NMA including CheckMate-227.

[redacted]

(

Table **27**). [redacted]

Table 27 Hazard ratios of Nivolumab + ipilimumab + limited PDC versus comparators over 18 months for PFS for patients with mixed histology and PD-L1 ≥ 50% (adapted from CS, Table 31 and clarification response, Table 11

		Including CheckMate-227 [a]	Excluding CheckMate-227 [a]
Nivolumab + ipilimumab + limited PDC versus	**Time point (months)**	**HR (95% CrI)**	**HR (95% CrI)**
PDC	1	[redacted]	[redacted]
	6	[redacted]	[redacted]
	12	[redacted]	[redacted]
	24	[redacted]	[redacted]
	36	[redacted]	[redacted]
PEMBRO	1	[redacted]	[redacted]
	6	[redacted]	[redacted]
	12	[redacted]	[redacted]
	24	[redacted]	[redacted]
	36	[redacted]	[redacted]

[a] model with *P*1=0, *P*2=-1 and treatment effects on scale and first shape parameter. NIVO= nivolumab; IPI= ipilimumab; PDC = platinum doublet chemotherapy; PEMBRO = pembrolizumab; HR = hazard ratio; CrI = credible interval

Network of non-squamous patients with PD-L1 < 50%

Four RCTs were included in the NMA of non-squamous patients with PD-L1 < 50%, with CheckMate-227 being added in an updated analysis. Table 28 presents the studies and the data used in the NMA.

Table 28 Studies included in the NMA of non-squamous patients with PD-L1 < 50% (adapted from CS, Table 28 and Table 32)

Study	PD-L1	Histology	Treatment 1	Treatment 2	OS HR (95% CI)	PFS HR (95% CI)
ERACLE [30]	All-comers	NSQ	PDC	BEV+PDC	0.93 (0.60-1.43)	0.79 (0.53-1.17)
PRONOUNCE [31]	All-comers	NSQ	PDC	BEV+PDC	1.07 (0.84-1.37)	1.06 (0.84-1.34)
IMpower-150[32]	< 50%	NSQ	ATEZO+BEV+ PDC	BEV+PDC	0.81 (0.65-1.02)	0.68 (0.56-0.82)
CM-9LA	< 50%	NSQ	NIVO+IPI+ limited PDC	PDC	0.62 (0.47-0.82)[a]	0.69 (0.53-0.88)[a]
CM-227	< 50%	NSQ	NIVO + IPI	PDC	[redacted]	[redacted]

[a] In the NMA without CM-227, the all-comer population of CM-9LA was used, with an OS estimate of HR: 0.66, 95% CI: 0.55-0.80 and PFS estimate of HR: 0.68, 95% CI: 0.57-0.82. NIVO= nivolumab; IPI= ipilimumab; PDC = platinum doublet chemotherapy; PEMBRO = pembrolizumab; ATEZO = atezolizumab; BEV = bevacizumab; HR = hazard ratio; CI = confidence interval; OS = overall survival; PFS = progression free survival.

OS in non-squamous patients with PD-L1 < 50%

For the NMA without CheckMate-227, the model fit statistics for OS are presented in Table 132 of Appendix N. The fractional polynomial model with $P1=P2=1$ and no shape effects (i.e. constant HR) was chosen. The company states that there was no evidence of clinical implausibility and when compared with the best-fitting time-varying models, HRs showed little change over time. The ERG notes that the modelled data fits quite well to the raw Kaplan-Meier data. However, in IMpower-150, the modelled tails are wider than the raw Kaplan-Meier data, which may slightly overestimate the long-term treatment effect. Overall, the ERG considers the chosen model to be appropriate. The modelled versus observed OS Kaplan-Meier data for each included study is presented in Figure 39 of the CS. However, the ERACLE and PRONOUNCE Kaplan-Meier comparisons of model fit seem to be incorrect. The published Kaplan Meier plot from the PRONOUNCE trial resembles the ERACLE plot in the CS. Therefore, it seems that the plot titles have been mistakenly switched and the plots have the wrong trial names.

The selected model for the updated NMA including CheckMate-227 was a repeated powers model with $P1=P2=1$, with treatment effects on scale (i.e. constant HR). This model was the second-best ranked model according to DIC, with a DIC 0.37 units different from the top-ranked model (a difference that is considered small in DIC units). The modelled versus raw Kaplan-Meier data for the updated model for each included study is presented in Figure 2 of the Appendix. The model fit for each study is very similar to the original model, however it does not capture the early crossing of curves in CheckMate-227 and seems to reverse the early treatment effect of nivolumab + ipilimumab versus PDC.

The results of the updated NMA were very similar to the results of the NMA excluding CheckMate-227 (Table 29). [redacted]

Table 29 Hazard ratios of Nivolumab + ipilimumab + limited PDC versus comparators for OS for non-squamous patients with PD-L1 < 50% (adapted from CS, Table 29 and clarification response, Table 14)

		Including CheckMate-227 [a]	Excluding CheckMate-227 [b]
NIVO + IPI + limited PDC vs.	**Time point (months)**	**HR (95% CrI)**	**HR (95% CrI)**
PDC	Constant HR	[redacted]	[redacted]
BEV+PDC	Constant HR	[redacted]	[redacted]
ATEZO+BEV+PDC	Constant HR	[redacted]	[redacted]

[a] Repeated powers model with *P*1=*P*2=1 and treatment effects on scale [b] model with *P*1=*P*2=1 and no shape effects. NIVO= nivolumab; IPI = ipilimumab; PDC = platinum doublet chemotherapy; ATEZO = atezolizumab; BEV = bevacizumab; HR = hazard ratio; CrI = credible interval.

PFS in non-squamous patients with PD-L1< 50%

The model fit statistics for the NMA model including CM-227 are presented in Table 137 of Appendix N. The fractional polynomial model with *P*1=*P*2=0 and treatment effects on the scale and 1st shape parameters was chosen, as it achieved the lowest DIC. The ERG notes that the modelled data fits the raw data well in all trials, except PRONOUNCE, where it misses the early and late separation of curves. Overall the ERG is satisfied with the selection of model. The model selected for the updated NMA including CheckMate-227 had *P*1=0, *P*2=-1 and treatment effects on the scale and second shape parameters, with a DIC 6.21 units greater than the model with the lowest DIC. This can be considered a moderate DIC difference, however no reasoning was given for why this model was chosen.

The results of the updated NMA including CheckMate-227 were similar to the results of the NMA excluding CheckMate-227 (Table 30). [redacted]

Table 30 Hazard ratios of Nivolumab + ipilimumab + limited PDC versus comparators for PFS in non-squamous patients with PD-L1 < 50% (from CS, Table 33 and clarification response, Table 15)

		Including CheckMate-227 [a]	Excluding CheckMate-227 [b]
NIVO + IPI + limited PDC vs.	**Time point (months)**	**HR (95% CrI)**	**HR (95% CrI)**
PDC	**1**	[redacted]	[redacted]
	6	[redacted]	[redacted]
	12	[redacted]	[redacted]
	24	[redacted]	[redacted]
BEV + PDC	**1**	[redacted]	[redacted]
	6	[redacted]	[redacted]
	12	[redacted]	[redacted]
	24	[redacted]	[redacted]
ATEZO + BEV + PDC	**1**	[redacted]	[redacted]
	6	[redacted]	[redacted]
	12	[redacted]	[redacted]
	24	[redacted]	[redacted]

[a] model with *P*1=0, *P*2=-1, treatment effects on scale and 2nd shape parameter [b] model with *P*1=*P*2=0, treatment effects on scale and 1st shape parameter. NIVO= nivolumab; IPI= ipilimumab; PDC = platinum doublet chemotherapy; PEMBRO = pembrolizumab; ATEZO = atezolizumab; BEV = bevacizumab; HR = hazard ratio; CrI = credible interval;

Limitations of the fractional polynomial ITC/NMA

The follow up time period differed across trials, with 37.7 months for CheckMate-227 but only 12.7 months for CheckMate-9LA. The model fit is informed by data within the trial follow-up, therefore, any extrapolations beyond this are uncertain. Although, CheckMate-227 was added to the fractional polynomial NMA to better inform the long-term extrapolation of the curves, the company were not able to clinically validate the new models including CheckMate-227. Therefore, the ERG considers the extrapolations provided by the NMA beyond the follow-up of CheckMate-9LA to be uncertain. Clinical validation of the new models including CheckMate-227 would provide greater certainty and reliability of longer-term extrapolations.

Studies included in the ITC differed by both PD-L1 expression and histology. The NMA of patients with all-comer histology and PD-L1 ≥ 50% used the PD-L1 all comer population from the CheckMate-9LA and CheckMate-227 trials and the proportion of non-squamous patients varied between trials. The NMA of non-squamous patients with PD-L1 expression < 50% used the any PD-L1 expression populations of the ERACLE and PRONOUNCE trials. There were also notable differences in patient characteristics and trial design, including definition of PDC, crossover and

second-line treatment across trials. The mixed populations in the ITCs could lead to an underlying bias.

In both NMAs the PDC comparator arms were combined into a common node to allow indirect comparisons to be made. The CS and clinical advice to the ERG state evidence showing potentially better efficacy associated with certain types of PDC regimens. The ERG considers the PDC comparator arms of the studies included in the ITC to be heterogenous and thus combining them may reduce the reliability of the results.

3.4.2.2 Bucher ITC results

Network of patients with mixed histology and PD-L1 ≥ 50%

The OS estimate for nivolumab + ipilimumab + limited PDC relative to pembrolizumab in patients with PD-L1 ≥ 50% was similar to the estimates obtained using the fractional polynomial model (HR: [redacted]

Network of non-squamous patients with PD-L1 < 50%

The OS Bucher estimate for nivolumab + ipilimumab + limited PDC versus atezolizumab + bevacizumab + PDC is similar to the estimate obtained using the fractional polynomial model (HR: [redacted] (HR: [redacted]).

Table 31 Hazard ratio estimates using Bucher ITC (adapted from clarification response, Tables 8 and 9)

Treatments	Endpoint	HR (95% CI)
NMA of mixed histology patients with PD-L1 ≥ 50%		
NIV + IPI + limited PDC vs PEMBRO	Overall survival	[redacted]
	Progression-free survival	[redacted]
NMA of non-squamous patients with PD-L1 < 50%		
NIV + IPI + limited PDC vs ATEZO + BEV + PDC	Overall survival	[redacted] *
	Progression-free survival	[redacted] *

*These estimates were produced by the ERG from the 4-node network (Figure 8, excluding CheckMate-227), the estimates provided by the company's 3-node network are OS: [redacted] and PFS: [redacted] NIVO= nivolumab; IPI= ipilimumab; PDC = platinum doublet chemotherapy; PEMBRO = pembrolizumab; ATEZO = atezolizumab; BEV = bevacizumab; HR = hazard ratio; CI = confidence interval; PD-L1 = Programmed death-ligand 1.

Limitations of the Bucher ITC

Studies included in the ITC differed by both PD-L1 expression and histology. The proportion of squamous and non-squamous patients varied between trials in the NMA of patients with all-comer histology and PD-L1 ≥ 50%. The ITC of non-squamous patients with PD-L1 expression < 50% used the any PD-L1 expression populations of the ERACLE and PRONOUNCE trials. There were also notable differences in patient characteristics and trial design, including definition of PDC, crossover and second-line treatment across trials. These heterogenous populations could lead to an underlying bias and therefore, reduce certainty in the treatment efficacy estimates in certain patient populations.

Similarly, to the fractional polynomial model, in both ITCs the PDC comparator arms were combined into a common node to allow indirect comparisons to be made. The CS and clinical advice to the ERG state evidence showing potentially better efficacy associated with certain types of PDC regimens. The ERG considers the PDC comparator arms of the studies included in the ITC to be heterogenous and thus combining them may reduce the reliability of the results.

Both networks assumed proportional hazards although the company state that there is a clear indication of non-proportional hazards across all comparators. Therefore, these results may be unreliable. However, the chosen OS fractional polynomial model for the network of non-squamous patients with PD-L1 < 50% assumed a constant hazard, therefore, the hazard ratio for nivolumab + ipilimumab + limited PDC versus atezolizumab + bevacizumab + PDC is very similar between the fractional polynomial model (HR: [redacted]) and the Bucher model (HR: [redacted]

3.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG validated the company's code for fractional polynomial NMA and Bucher ITC and revised the Bucher ITC for the non-squamous, PD-L1 < 50% population to use the full network presented in Figure 8 (excluding study CheckMate-227 which does not add information in this simple approach). Results are presented in Table 31.

The ERG produced Kaplan-Meier curve overlays of observed versus modelled data for OS for each RCT included in the updated NMA models including Checkmate-227. The plots are presented in the Appendix (Figure 30 and Figure 31) and show a similar fit to the models without CheckMate-227. The model fits well to the CheckMate-227 data for the network of mixed histology and PD-L1 ≥ 50%, however, it does not capture the early crossing of curves in CheckMate-227 for the network of non-squamous patients with PD-L1 < 50% and seems to reverse the early treatment effect of nivolumab + ipilimumab versus PDC.

3.6 Conclusions of the clinical effectiveness section

The clinical evidence presented in the submission is based on two RCTs (CheckMate-9LA and CheckMate-227). CheckMate-9LA is the most relevant trial as it compares nivolumab + ipilimumab + limited PDC with PDC, which is in line with the final scope. Whereas, CheckMate-227 compares nivolumab + ipilimumab with PDC. An ITC was conducted to compare nivolumab + ipilimumab + limited PDC with pembrolizumab and atezolizumab as there was no head to head evidence directly comparing these treatments. Clinical advice to the ERG was that pembrolizumab with carboplatin and paclitaxel is also being used in clinical practice for metastatic untreated squamous NSCLC. However, this is via the Cancer Drugs Fund, therefore it does not form part of the comparators of interest in this submission.

The population considered in the submission was adults with untreated stage IV or recurrent NSCLC without sensitising EGFR mutations or ALK fusions, which is in line with the scope. Trial inclusion criteria appear to have been appropriate. However, there were only [redacted] patients ([redacted]%) in the CheckMate-9LA trial and [redacted] patients ([redacted]%) in the CheckMate-227 trial from the UK. Furthermore, patients in both trials may be healthier than patients eligible for treatment in the NHS population as only patients with ECOG PS of 0 or 1 were included. Patients in CheckMate-9LA and CheckMate-227 had median ages of 65 years and 64 years, respectively, which is substantially younger than the median age of patients with NSCLC in England and Wales, which is 73 years old. Additionally, the majority of patients in the trials had non-squamous histology (69% to 72.2% across both trials). However, clinical advice to the ERG is that slightly more patients with squamous NSCLC are observed in practice than patients with non-squamous NSCLC. The differences described suggest that the trial populations may not be fully representative of the NHS population for this indication.

In CheckMate-9LA, there was a statistically significant difference in overall survival favouring nivolumab + ipilimumab + limited PDC compared with PDC (15.64 months vs 10.91 months; HR: 0.66, 95% CI: 0.55 to 0.80). Median PFS was also longer in the nivolumab + ipilimumab + limited PDC arm compared with the PDC arm (6.7 months versus 5.0 months, respectively), with a statistically significant HR of 0.68, 95% CI: 0.57-0.82. The HRQoL outcomes were generally similar between the nivolumab + ipilimumab + limited PDC and PDC arms. The EQ-5D-3L VAS score reached a MID of 7 at week 72 in both arms at week 84 in the nivolumab + ipilimumab + limited PDC arm. The UK general population norm (82.8) was met at weeks 72 and 78 in the PDC arm only. The mean change from baseline in EQ-5D utility index scores exceeded the MID of 0.08 in the nivolumab + ipilimumab + limited PDC arm at week 84 only, whereas the PDC arm did not meet the MID at any time point. In CheckMate-227, [redacted]

[redacted]. Median duration of progression-free survival was similar but slightly shorter in the nivolumab + ipilimumab arm (5.1 months, 95% CI: 4.1 to 5.7) compared with the PDC arm (5.5 months, 95% CI: 4.6-5.6), with a reported HR of 0.79 (95% CI: 0.69 to 0.91).

In CheckMate-9LA the efficacy benefit of nivolumab + ipilimumab + limited PDC and in CheckMate-227 the efficacy benefit of nivolumab + ipilimumab was not seen for patients ≥ 75 years old, patients who had never smoked and patients with liver and bone metastases (Section 3.2.4.2). Clinical advice to the ERG is that a substantial proportion of the NHS population eligible for nivolumab + ipilimumab + limited PDC are patients over 75 years old and around 20-30% have bone or liver metastases. Therefore, there may be a significant proportion of the population who may not benefit from treatment with nivolumab + ipilimumab + limited PDC compared with PDC. However, it is important to note that the non-stratified nature of subgroup analyses and smaller sample sizes may reduce the reliability of these results.

The ERG considers there to be four sub-populations based on tumour histology and PD-L1 expression, as described in Table 12. There is evidence to suggest that relative treatment effects may be different in each of the four sub-populations due to differences in potential effect modifiers PD-L1 expression and histology, as discussed in Section 3.2.4.2. Therefore, evaluating these four subgroups separately will allow exploration of potential sources of heterogeneity and inform sound decision making, which otherwise may fail to identify treatment benefits in the appropriate patient populations. Additionally, the interventions for untreated metastatic NSCLC are recommended based on PD-L1 expression and histology (Table 5). The different interventions used in each sub-population consequently impact on the cost-effectiveness analysis that needs to be conducted. The company provided subgroup analyses for each of the four sub-populations at the clarification stage. However, the ERG notes that there are limitations due to the non-stratified nature and small patient numbers of the subgroups and these should be considered when interpreting the results.

The subgroup analyses show that in CheckMate-9LA, [redacted]. The results suggest that there are differences in both the absolute and relative treatment effects for OS and PFS across these sub-populations. However, the ERG cautions that sub-populations 3 and 4 have very small sample sizes and therefore may not provide reliable conclusions.

The ITC appears to have included all relevant trials of nivolumab + ipilimumab + limited PDC and the relevant comparators. Studies were assessed for quality, which suggested that the risk of bias for studies was varied, with each study scoring high risk of bias for at least one domain. The company conducted two separate ITC analyses: one of treatment-naïve individuals with advanced or recurrent NSCLC with mixed histology and PD-L1 expression ≥ 50% and one of treatment naïve patients with advanced or recurrent NSCLC with non-squamous histology and PD-L1 < 50%.

Inevitably the trials included in the ITCs vary by design and patient characteristics. In both networks, the proportion of male patients and the proportion of patients who had never smoked differed between trials (Table 21). Subgroup analyses showed, sex and smoker status may be potential effect modifiers (Section 3.2.4.2). The NMA of patients with all-comer histology and PD-L1 ≥ 50% used the PD-L1 all comer population from the CheckMate-9LA and CheckMate-227 trials and the histology all-comer population, that is patients with both squamous and non-squamous NCSLC, was used for CheckMate-9LA, CheckMate-227 and both KeyNote studies (Table 21). Consequently, the proportion of patients with non-squamous histology varied substantially between trials. Furthermore, the NMA of non-squamous patients with PD-L1 expression < 50% used the all-comer PD-L1 expression populations of the ERACLE and PRONOUNCE trials. The mixed populations included in the ITCs could lead to an underlying bias. There were also notable differences in trial design, including the definition of PDC, crossover and second-line treatment across trials. The differences described increase the risk of between study, across-comparison heterogeneity, which reduces the reliability of the ITC results.

[redacted]. Although, clinical advice to the ERG is that the type of PDC treatment used does not have a significant effect on efficacy, the clinical advisor stated that there is some evidence to suggest cisplatin is more effective than carboplatin. The PDC regimens in each of the studies also varied by dose and number of cycles. Therefore, the ERG considers the PDC comparator arms of the studies included in the ITC to be heterogenous and thus combining them may reduce the reliability of the results.

Indirect treatment comparisons were carried out using a fractional polynomial network meta-analysis model as the proportional hazards assumption was not met. The company also presented ITCs assuming proportional hazards using the Bucher method for completeness. The ITC originally only included CheckMate-9LA as evidence for nivolumab + ipilimumab + limited PDC. However, at the

PFC stage, the company included CheckMate-227 in the fractional polynomial ITCs, to better inform the long-term extrapolation of the curves as the follow up time period was 37.7 months for CheckMate-227 but only 12.7 months for CheckMate-9LA.The ERG agrees that the NMA including CheckMate-227 is preferred as there is more data to inform the long-term extrapolations, giving more precise estimates. However, due to time restrictions, the company were not able to clinically validate the new models. Therefore, the ERG considers the extrapolations provided by the NMA beyond the follow-up of CheckMate-9LA to be uncertain. The ERG produced Kaplan-Meier curve overlays of observed versus modelled data for OS for each RCT included in the updated NMA models including Checkmate-227, which showed a similar fit to the models without CheckMate-227. However, these were not drawn for PFS due to time constraints. Clinical and visual validation of the new models including CheckMate-227 for both OS and PFS are desirable as they would provide greater certainty and reliability of longer-term extrapolations.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4 COST EFFECTIVENESS

4.1 ERG comment on company's review of cost-effectiveness evidence

The company presented summary results from a systematic search for literature on economic evaluation of adults on first-line treatment for advanced or metastatic NSCLC (CS section B.3.1 and Appendix G). The ERG regards the company's search strategy to be comprehensive, although there were some elements that were unclear (see Appendix 2 ERG critique of the company's economics searches).

The review identified 38 studies reporting economic evidence, of which 19 conducted cost-utility analysis and 13 conducted cost-effectiveness analysis. Five studies reported an economic evaluation for the UK,[33-37] and two further studies reported economic findings for a range of countries that included the UK,[38, 39] summarised in Table 32.

One UK-based study included nivolumab as a comparator,[33] but not in combination with ipilimumab and limited PDC. None of the UK-based studies included atezolizumab as a comparator. Two studies evaluated erlotinib compared with best supportive care or placebo, and one study compared various first-line PDC regimens. The remainder included pembrolizumab monotherapy compared with either chemotherapy, nivolumab monotherapy or pembrolizumab combination therapy.

While none of the studies provided evidence for nivolumab within the present decision problem, they provide a potential source for cross-validation of results from the submitted model for pembrolizumab.

Table 32 Included economic evaluation for first-line treatment of advanced/metastatic NSCLC in the UK

Study author	Study year	Study type	Publication type	Country	Comparators
Verma[33]	2020	Cost-utility analysis	Abstract	UK	Pembrolizumab vs nivolumab
Harding[34]	2019	Cost-utility analysis	Abstract	UK	Pembrolizumab + carboplatin+ paclitaxel vs Carboplatin + paclitaxel vs pembrolizumab monotherapy
Khan[36]	2015	Cost-utility analysis	JA	UK	Erlotinib vs placebo
Brown[37]	2013	Cost-utility analysis	HTA submission	UK	Various first-line PDC regimens
Hu[35]	2018	Cost-effectiveness analysis	JA	UK	Pembrolizumab vs chemotherapy
Georgieva[38]	2018	Cost-effectiveness analysis	JA	US and UK	Pembrolizumab vs chemotherapy
Walleser[39]	2012	Cost-effectiveness analysis	JA	UK, Germany, France, Spain, and Italy	Erlotinib vs best supportive care

Abbreviations: JA = journal article; HTA = health technology assessment

The company (Table 39, CS) also summarised key modelling elements from previous NICE technology appraisals for the first-line treatments for advanced NSCLC that are within scope, and how they were used to inform the present appraisal. These included:

- Pemetrexed first line (TA181)[40]
- Pemetrexed maintenance (TA402)[41]
- Pembrolizumab (TA531)[20]
- Atezolizumab (TA584)[19]

Although not in scope, the technology appraisal of pembrolizumab with pemetrexed and platinum chemotherapy for untreated metastatic non-squamous NSCLC (TA557)[5] and pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous NSCLC (TA600)[42] also include comparators relevant to this decision problem.

4.2 Summary and critique of the company's submitted economic evaluation by the ERG

Sections B.3.2 to B.3.11 of the CS report on the methods and results of a new economic model developed by the company for this appraisal.

4.2.1 NICE reference case checklist

The ERG assessment of whether the submitted economic evaluation complies with NICE reference case requirements is shown in Table 33. We consider that the company's analysis broadly conforms to the reference case, except that the modelled decision problem differs from the NICE scope. We discuss these differences in the following sections.

Table 33 NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Decision problem	The scope developed by NICE	The CS is appropriate
Comparator(s)	As listed in the scope developed by NICE	The company economic analysis omits comparators in the scope
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The CS is appropriate
Perspective on costs	NHS and PSS	The CS is appropriate
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The CS does not include a full incremental analysis, but this was provided in response to clarification question B2.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The CS is appropriate. Patients enter at the age of 63.7 years old and a maximum age of 88.7 is assumed.
Synthesis of evidence on health effects	Based on systematic review	The CS is appropriate
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	The CS is appropriate
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	The CS is appropriate
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The CS is appropriate
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The CS is appropriate.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	The CS is appropriate

Discounting	The same annual rate for both costs and health effects (currently 3.5%)	The CS is appropriate.

PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.

4.2.2 Model structure

The company submitted a cohort-based partitioned survival model that simulates the long-term outcomes of patients with untreated stage IV or recurrent NSCLC with no known EGFR mutation or ALK translocation over their lifetime. Patients receive nivolumab + ipilimumab + limited PDC or alternative therapy options, which depend on tumour histology (i.e. squamous or non-squamous) and PD-L1 expression (i.e. ≥ 50% or < 50%). For a description of the comparators available for each of the patient sub-populations, see Table 12, Section 3.2.4.2.

The company justified their model structure based on the health states of a partitioned survival model matching the primary and secondary outcomes of Checkmate-9LA (OS, PFS) and consistency with approaches adopted in previous NSCLC appraisals.[22, 43-45]

The model has three mutually exclusive health states: pre-progression, post-progression, and death. In partitioned survival models, the proportion of patients in each health state is determined directly from the survival curves. All patients enter the model in the pre-progression health state. The PFS curve directly informs the proportion of patients remaining in the pre-progression state. The proportion of patients who are in the post-progression state corresponds to the difference between the proportion of patients alive (given by the OS curve) and the proportion of patients in the pre-progression state (given by the PFS curve). A graphical depiction of this can be seen in Figure 9. This is done for each modelled intervention.

Figure 9 Partitioned survival model diagram

A 1-week model cycle length is used for the first 28 weeks, this increases to a 4-week model cycle from week 28 onwards. A half-cycle correction is applied to outcomes and costs, except in the first cycle.

For the modelled outcomes in the company's base case, rather than assuming individual nivolumab + ipilimumab + limited PDC and comparator health state utilities according to state occupancy (i.e. pre-progression and post-progression utilities), the model applies disutilities in each arm according to the time to death, and additional disutilities for adverse events (see Section 4.2.7 for more information).

Health state costs and intervention costs are applied in the model according to health state occupancy and the treatment received. The model used Kaplan-Meier data for the time on treatment measured for both nivolumab + ipilimumab + limited PDC and PDC in Checkmate-9LA. However, modelled PFS curves were used as a proxy for time on treatment for pembrolizumab and atezolizumab + bevacizumab + PDC in the company's base case (see Section 4.2.6.3 for further details).

ERG Comment

The ERG considers that the company's model is appropriate for decision making and in line with previous cancer STAs. The ERG notes that partitioned survival models are easy to implement and generally predict trial endpoints well for the within-trial period. However, one of the drawbacks of this approach is the difficulty in estimating robust extrapolations over a long period of time into the future (25 years in the company base case) based on the immature Checkmate-9LA trial data (see

Section 4.2.6 for more information). An additional drawback is that partitioned survival models assume structural independence between OS and PFS, which implies that the extrapolation of an endpoint reflects the within-trial trend of that endpoint alone, and it may lead to logical inconsistencies between PFS and OS. This is observed in the modelled base-case survival results for pembrolizumab, which show the same landmark OS and PFS proportions at 10, 15, 20 and 25 years (see Section 4.2.6.1 and Section 4.2.6.2 for the company base case OS and PFS results). The results, albeit not impossible, are implausible as it implies individuals die immediately upon progression. These results may be mitigated by the inclusion of CheckMate-227 in the network, which results in plausible OS and PFS estimates, although these results are yet to be validated.

The lack of a half-cycle correction in the first model cycle is a small error and one that is very unlikely to impact the ICER. The ERG has, however, corrected this as the omission of the half-cycle correction assumes patients cannot die within the first cycle. The impact of this alteration on the ICER is small and can be seen in Section 6.

4.2.3 Population

The population in the decision problem is adults with untreated stage IV or recurrent NSCLC without sensitising EGFR mutations or ALK fusions, in accordance with the licensed indication. In the company's model, the population corresponds to the patient population in Checkmate-9LA. Their characteristics at model entry are summarised in Table 34.

Table 34 Population characteristics at model entry

Model parameter	Value	Source
Age (years)	[redacted]	CheckMate-9LA, ITT population
Male (%)	[redacted]	CheckMate-9LA, ITT population
Average BSA (m^2)	[redacted]	CheckMate-9LA, ITT population, estimated with the Du Bois formula[46]
Average bodyweight (kg)	[redacted]	CheckMate-9LA, ITT population

BSA = body surface area; ITT = intention to treat

ERG Comment

The modelled population characteristics included in the economic model (Table 34) are reflective of the CheckMate-9LA and CheckMate-227 populations, and in turn are considered to be generalisable to the population expected to receive nivolumab + ipilimumab + limited PDC in practice. Note the ICERs are insensitive to changes in the modelled population characteristics.

Despite the modelled population parameters being generalisable, the ERG considers there to be a number of areas of uncertainty in the generalisability of the CheckMate-9LA and CheckMate-227 to the population of interest. For example, the trials show a greater proportion of non-squamous patients than would be expected in practice according to clinical advice received by the ERG (see Section 3.2.2 for further detail). If it is believed that squamous histology is a treatment effect modifier, then using the all-comer population from the trial means there may be considerable uncertainty in the ICER. The use of the histology-specific results from CheckMate-9LA and CheckMate-227 will mitigate this issue of generalisability of effect (see Section 4.2.3.1 for further details). The ERG considers the impact of using histology-specific results in Section 6.

An additional area of uncertainty resides in the enrolled trial population in CheckMate-9LA: only [redacted] of patients in the nivolumab + ipilimumab + limited PDC arm and [redacted] in the PDC arm in the CheckMate-9LA trial are from the UK. This remains an area of uncertainty, although the ERG considers the impact on the ICER to be minimal.

4.2.3.1 Sub-populations

As detailed in Section 3.2.4.2, the ERG considers the stratification of the all-comer population into distinct sub-populations based on tumour histology and PD-L1 expression to be an appropriate alternative approach to the decision problem.

This distinction is important for a number of reasons. First, clinically there are reasons to consider that patients may respond differently to nivolumab + ipilimumab + limited PDC and PDC based on histology and PD-L1 expression. Clinical advice provided to the ERG reiterated the potential for treatment effect to differ across sub-populations (for full details, see Section 3.2.4.2). Following response to clarification questions, the company presented results of CheckMate-9LA and CheckMate-227 stratified by sub-population, which shows differences in absolute treatment effects (Section 3.2.4.2).

The failure to acknowledge this potential heterogeneity across subgroups has implications for the cost-effectiveness estimates: if benefits differ by patient characteristics then estimates of treatment benefit should match the patient population that is expected to receive the treatment in routine clinical practice. Making a 'one size fits all' recommendation may result in a potentially cost-effective treatment being withheld from a subset of patients for whom the treatment would represent an appropriate use of NHS resources. Conversely, a treatment which appears cost-effective for the total population may not be cost-effective in particular subgroups. The exploration of sources of heterogeneity and the use of subgroup analysis is recommended within the NICE reference case analysis.[47]

Second, the in-scope comparators considered differ according to sub-population (Table 12). The nature of these differing clinical interventions based on the sub-populations is an important distinction when it comes to the results of the cost-effectiveness analysis. If two or more comparator treatments are being included in a cost-effectiveness analysis, a fully incremental cost-effectiveness analysis must consider all of the available alternatives, but only the relevant alternatives.[48] As Table 12 shows, the comparators available in the NHS differ depending on PD-L1 expression and histology, meaning four separate fully incremental analyses for each of the sub-populations should be conducted.

Following clarification questions, the company presented clinical and cost-effectiveness results for three sub-populations:

- Non-squamous, PD-L1 < 50% (sub-population 1)
- Squamous, PD-L1 < 50% (sub-population 3)
- Mixed histology, PD-L1 ≥ 50% (sub-populations 2 and 4)

The company did not consider squamous and non-squamous histologies separately in the PD-L1 > 50% population to allow comparison with pembrolizumab monotherapy in the NMA (see Section 3.3 and Section 3.4). The results, as presented by the company, can be seen in Section 6.

Although the consolidation of the mixed histology, PD-L1 ≥ 50% population into a single population does not allow for heterogeneity in treatment effects according to histology, the ERG considers this population to be appropriate for decision making for a number of reasons. Limited patient numbers with PD-L1 ≥ 50% in CheckMate-9LA means retaining a single mixed histology population avoids decision making on limited numbers. The CheckMate-9LA ITT analysis included [redacted] and [redacted] mixed histology, PD-L1 ≥ 50% patients in the Nivolumab + ipilimumab + limited PDC and PDC arms, respectively (see Section 3.2.4.2). In addition, clinical advice to the ERG is that anti-PD-L1 immunotherapies such as nivolumab may have a greater effect in patients with high PD-L1 expression; therefore, the single consolidated population does not violate this. Finally, the in-scope comparators for population 2 and 4 are the same (see Table 12). It should be noted there are, however, differences in the use of pemetrexed maintenance therapy according to histology, which is permitted only in population 2 (see Section 4.2.4). The ERG will refer to the three sub-populations throughout the remainder of the cost-effectiveness sections. The cost-effectiveness results of the three sub-populations, along with a number of scenarios will be considered in Section 6.

4.2.4 Interventions and comparators

4.2.4.1 Modelled interventions and comparators

The intervention is nivolumab + ipilimumab + limited PDC, as per the decision problem. Nivolumab is modelled as a flat 360 mg dose administered via IV every 3 weeks. Ipilimumab is modelled as a weight-based dose of 1 mg/kg administered via IV every 6 weeks.

The PDC in the intervention arm is modelled as various doublet combinations of cisplatin, paclitaxel, carboplatin and pemetrexed. This is based on the Checkmate-9LA protocol in which patients with squamous histology were given carboplatin + paclitaxel, and those with non-squamous histology were given carboplatin + pemetrexed or cisplatin + pemetrexed. Choice of carboplatin or cisplatin for non-squamous patients was based on investigator assessment of cisplatin eligibility. The modelled distribution of the PDC combinations can be seen in Table 35.

Table 35 Distribution of PDC

PDC regimen	NIVO + IPI + limited PDC	PDC
Carboplatin + paclitaxel	[redacted]	[redacted]
Carboplatin + pemetrexed	[redacted]	[redacted]
Cisplatin + pemetrexed	[redacted]	[redacted]
Pemetrexed maintenance therapy	[redacted]	[redacted]

IPI = ipilimumab; NIVO = nivolumab; PCD = platinum doublet chemotherapy

Carboplatin is modelled as a flat dose of 685 mg via IV infusion. Paclitaxel, pemetrexed and cisplatin are modelled as body surface area-based doses of 200, 500 and 75 mg/m^2, respectively. All PDC regimens are assumed to be delivered every 3 weeks.

PDC is limited to 2 cycles in the nivolumab + ipilimumab + limited PDC arm and 4 cycles in the PDC arm. Maintenance therapy is included in the model as per the Checkmate-9LA protocol in which optional pemetrexed maintenance is permitted for patients with non-squamous histology following 4 cycles of PDC. The model assumes 45% of patients in the PDC arm received pemetrexed to represent the 66.4% of patients with non-squamous histology who received maintenance therapy (note, 69% of Checkmate-9LA patients had non-squamous histology).

The additional comparators assessed in the economic evaluation are dependent on the population under consideration. In the non-squamous, ≥ 50% PD-L1 expression population and the squamous, ≥ 50% PD-L1 expression population, the modelled comparators are PDC and pembrolizumab. In the non-squamous, < 50% PD-L1 expression population, the modelled comparators are PDC and atezolizumab + bevacizumab + PDC. Finally, in the squamous, < 50% PD-L1 expression population,

PDC is the only modelled comparator (Table 12). The modelled proportions of the PDC regimen can be seen in Table 35.

Pembrolizumab is modelled as a 200 mg IV infusion administered every 3 weeks. Atezolizumab is modelled as a flat dose of 1200 mg and bevacizumab is modelled as a weight-based dose of 15 mg/kg. The PDC in the atezolizumab + bevacizumab + PDC arm is modelled as carboplatin and paclitaxel with a dose of 692 mg and 200 mg/m^2, respectively. All comparators are assumed to be administered via IV every 3 weeks.

ERG comment

The ERG considers the interventions and comparators included in the economic model to be broadly appropriate and consistent with the decision problem. The modelled doses match those used in Checkmate-9LA. In addition, the distribution of PDC regimens included in the model matches the proportions used in Checkmate-9LA. However, the ERG's clinical advisor suggests the distribution of squamous and non-squamous patients in CheckMate-9LA is not representative of the population likely to be seen in the NHS. As PDC agents are determined by histology, the modelled distribution of PDC may not be representative either. This issue remains in the results in which the all-comer population is modelled, and is mitigated by considering separate decision problems based on PD-L1 expression and histology (see Section 4.2.3.1).

This lack of heterogeneity included within the model is also seen in the in-scope comparators, which differ according to patient PD-L1 expression and histology (see Section 4.2.3.1). The company's approach to modelling the various PDC regimens by averaging the proportions from the trial (i.e. the all-comer population) and applying this average to all populations in the model fails to address this heterogeneity. The heterogeneity in PDC regimens has implications for the modelled effectiveness (see Section 3.3 and 4.2.6) and the attributable PDC costs (see Section 4.2.8).

A similar problem arises in the company's modelling of maintenance pemetrexed therapy, which is only available for non-squamous patients according to the scope. The CheckMate-9LA CSR states that [redacted] of the patients in the PDC arm had non-squamous histology and of these, [redacted] received pemetrexed maintenance therapy. The company model therefore assumes 45% of all patients in the PDC arm receive maintenance therapy (calculated as [redacted]) rather than applying the relevant pemetrexed costs to [redacted] of non-squamous patients only. This again fails to allow for heterogeneity in the chemotherapy regimens used and results in costs being attributed to squamous patients despite not receiving this intervention in practice.

As described in the Section 4.2.3, an alternative approach to modelling the entire population covered by the decision problem is to model separate sub-populations based on histology and PD-L1

expression. This will allow for heterogeneity in PDC costs and for the inclusion of pemetrexed maintenance therapy costs to be properly apportioned to the relevant population.

Following response to clarification questions, the company presented the results of the economic model in which three sub-populations were considered (see Section 4.2.3); the results of this scenario can be seen in Section 6. However, the ERG notes the company's approach is to retain the distribution of PDC regimens estimated for the all-comer population and to include the 45% of pemetrexed maintenance therapy for all three sub populations. The ERG considers this to incorrectly apportion cost to sub-populations, therefore a scenario is conducted in which the PDC regimens and maintenance therapy for each specific sub-population are correctly attributed. The impact of this on the company's ICER will be explored in Section 6.

Missing chemotherapy agents included in the scope

In modelling the chemotherapy regimens used in CheckMate-9LA, the model may be omitting some chemotherapy regimens that are used in clinical practice on the NHS. Gemcitabine, vinorelbine and docetaxel were also listed in the NICE scope, and gemcitabine was used in PDC regimens in the CheckMate-227, KeyNote-024 and KeyNote-042 trials. In NHS clinical practice, carboplatin plus gemcitabine is the most commonly used chemotherapy regimen for squamous NSCLC.[42] Carboplatin in combination with vinorelbine is used in a minority of cases, and carboplatin in combination with a taxane (paclitaxel, docetaxel) is very rarely used as 1st line therapy.

As discussed in Section 3.2.4.2 there is heterogeneity between the various PDC regimens that are available in clinical practice. Clinical advice to the ERG is that the type of PDC treatment used does not have a significant impact on efficacy, and that all standard chemotherapy treatments can be considered to be of equal efficacy. However, there may be implications on the cost of treatment if only the regimens in CheckMate-9LA are included. There is a small cost difference between the chemotherapy agents, and each have different associated administration costs (see Section 4.2.8). There may also be implications to HRQoL if the safety profiles between the different chemotherapy regimens differ. For example, paclitaxel is associated with a higher degree of hair loss than gemcitabine.[49]

To address this, the ERG implements a scenario in which alternative distribution of PDC regimens are included in the economic model. The distributions are based on reported UK market shares for non-squamous and squamous patients, as described in TA600 and TA557 (see Section 6.2).

Pembrolizumab combination

Clinical advice to the ERG suggests the preferred treatment in practice is pembrolizumab combination therapy for PD-L1 expression < 50%, in both non-squamous and squamous populations. However,

due to its inclusion in the CDF, it was not listed as an in-scope comparator or included in the economic model. The ERG, however, emphasises the importance of considering the relative cost-effectiveness of all comparators used in the population to ensure continued efficient use of scarce NHS resources.

4.2.5 Perspective, time horizon and discounting

The model adopts the NHS and Personal Social Services perspective. In the company's base-case, the model discounts costs and outcomes at 3.5%, in line with the NICE reference case. Sensitivity analyses use discount rates of 1.5% and 6% for both costs and outcomes. A lifetime time horizon of 25 years was used in the company's base case.

ERG comment

The ERG considers the company's approach to the perspective and discount rate to be appropriate. The use of a lifetime time horizon is also appropriate to ensure all costs and outcomes are captured and the ERG notes the 25-year time horizon exceeds the time horizon used in previous recent NSCLC appraisals.[19, 44]

4.2.6 Treatment effectiveness and extrapolation

The primary data sources for the economic model were derived from the CheckMate-9LA and CheckMate-227 trials. Table 36 provides a summary of the survival distributions and data sources used in the company's base case analysis for OS and PFS. For nivolumab + ipilimumab + limited PDC and PDC, the base-case uses a piecewise approach to modelling OS and PFS using individual patient data from CheckMate-9LA and parametric extrapolation of CheckMate-227. The data cut-off dates for these respective trials are 9th March 2020 and 28th February 2020.

For the two comparators not included in the CheckMate-9LA or CheckMate-227 trials, the OS and PFS used in the company's base case are based on extrapolations from the fractional polynomial network meta-analyses which were applied to the nivolumab + ipilimumab + limited PDC survival predictions (see Section 3.4).

Table 36 Summary of survival distributions and sources applied in the company's base-case

Intervention	Overall survival	Progression-free survival
NIVO + IPI + limited PDC	KM data from CM-9LA up to 13 months, then 2 knot spline model (on normal) using the CM-227 data	KM data from CM-9LA up to 13 months, then 2 knot spline model (on odds) using the CM-227 data
PDC	KM data from CM-9LA up to 13 months, then loglogistic model using the CM-227 data	KM data from CM-9LA up to 13 months, then 2 knot spline model (on normal) using the CM-227 data

PEMBRO	Relative risks from FPNMA as a function of NIVO + IPI + limited PDC arm using data from KN-024, KN-042, CM-9LA and CM-227.	Relative risks from FPNMA as a function of NIVO + IPI + limited PDC arm using data from KN-024, KN-042, CM-9LA and CM-227.
ATEZO + BEV + PDC	Relative risks from FPNMA as a function of NIVO + IPI + limited PDC arm. Using ERACLE, PRONOUNCE, Impower-150, CM-9LA and CM-227	Relative risks from FPNMA as a function of NIVO + IPI + limited PDC arm. Using ERACLE, PRONOUNCE, Impower-150, CM-9LA and CM-227

ATEZO = atezolizumab; BEV = bevacizumab; CM = CheckMate; FPNMA = fractional polynomial network meta-analysis; KM = Kaplan-Meier; KN = KeyNote; PDC = platinum doublet chemotherapy; PEMBRO = pembrolizumab

4.2.6.1 Overall survival

Nivolumab + Ipilimumab + limited PDC and PDC

The company's base case model adopts a hybrid approach to modelling OS. Observed OS data were used from each arm of the CheckMate-9LA study up to 13 months, followed by use of parametric survival models fit to data from CheckMate-227 thereafter. This approach was adopted to inform the long-term extrapolations of the data as a considerable proportion of trial participants were still alive in the CheckMate-9LA database lock used for this appraisal (see Section 3.2). The company added that long-term extrapolation of the CheckMate-9LA data alone *"would not fully capture short-term treatment response and long-term survival that are unique for the dual IO being investigated"* (CS, pg. 104). The company do present scenario analyses using parametric curves fit to the CheckMate-9LA data alone. The approach to using external data to inform long-term extrapolation has been described by the NICE DSU.[50] The company justify the use of CheckMate-227 data based on the similar interventions being compared and the comparable OS curves (see Figure 10 and Figure 11).

Figure 10 Comparison of OS for nivolumab + ipilimumab + limited PDC (CM-9LA) with nivolumab + ipilimumab (CM-227 part 1) (taken from Figure 47, CS, pg. 105)

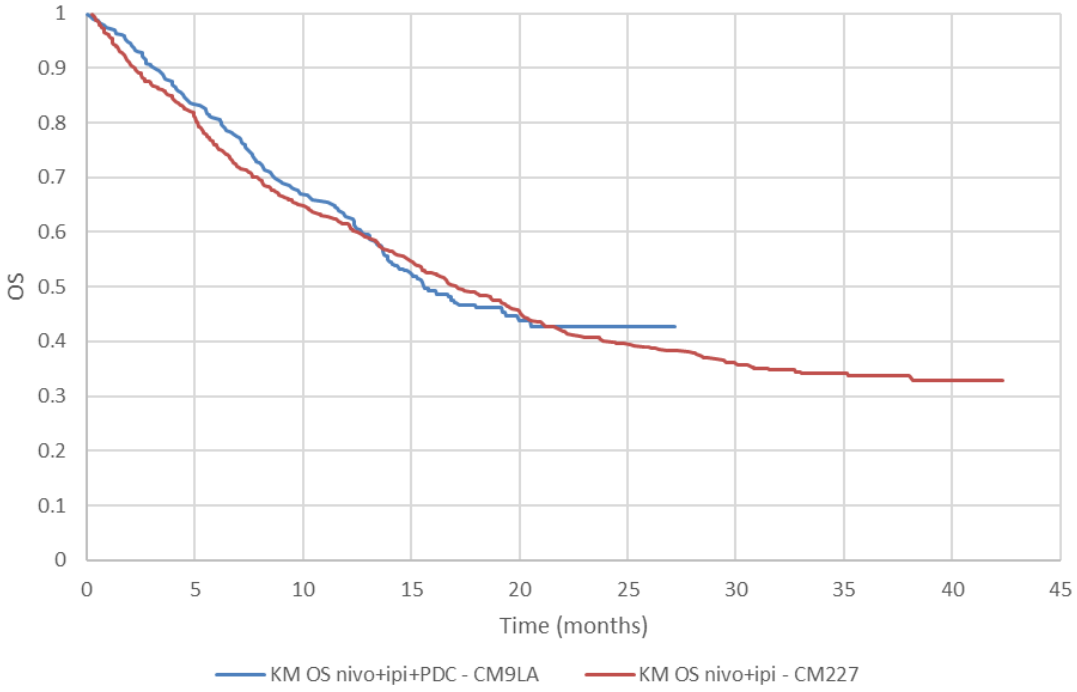
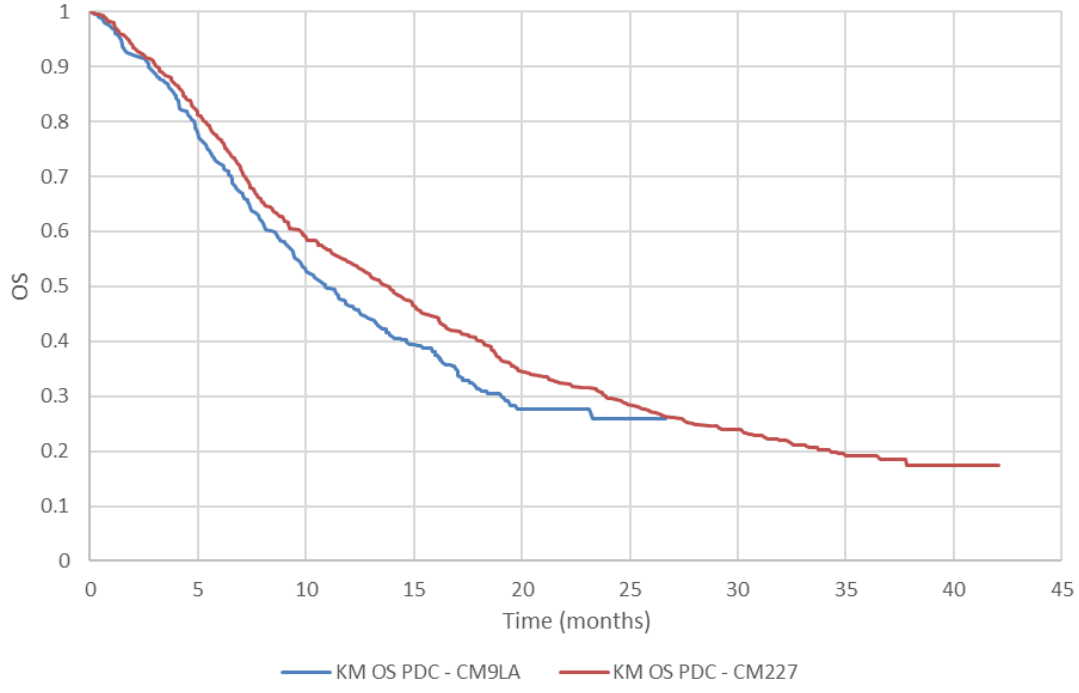


Figure 11 Comparison of OS for PDC in CM-9LA with PDC in CM-227 part 1 (taken from Figure 48, CS, pg. 105)



The company's process for fitting survival models was by testing the proportional hazards assumptions (using log-cumulative hazards plots and Grambsch-Therneau correlation tests between Schoenfield residuals) then fitting dependent or independent models to each treatment arm based on the results of the proportional hazards test. Model selection was based on Akaike information criterion (AIC) and Bayesian information criterion (BIC); visual fit; the desire for common functional form of models to both arms; and clinical plausibility of the survival predictions.

The company fitted independent parametric models (following the result of the violation of the proportional hazards assumption) to both arms of the CheckMate-9LA and the CheckMate-227 data. The company's process for model selection (as described above) was followed. The AIC and BIC for the models fitted to both arms of the CheckMate-9LA and CheckMate-227 data can be seen in Table 41-44 of the CS; visual inspection of the models overlying the Kaplan-Meier data can be seen in Figure 54, 55, 58 and 59 of the CS. Despite the company's hybrid approach to modelling OS, parametric models used beyond the switching point were fit to the complete CheckMate-227 Kaplan-Meier data from baseline to 3 years. The company stated *"the first 13 months was included to prevent loss of information and avoids the problem of fitting models to low numbers of patients at risk."*

The company presented two OS extrapolations: the hybrid approach and the approach using CheckMate-9LA data only. The switching time point of 13 months was selected due to the large degree of censoring in the CheckMate-9LA OS data after this time point (see Section 3.2.4). The company did not statistically test for the switching point but did explore alternative switching points in scenario analysis.

In the hybrid approach, the company's model transitions from the CheckMate-9LA data to the parametric data by adjusting the survival proportion in CheckMate-9LA at the fixed switching point using conditional OS probabilities calculated from the parametric model. The conditional probabilities estimate the probability of surviving to the end of a model cycle given an individual was alive at the start of that cycle. These probabilities are calculated using the OS rates per model cycle from the CheckMate-227 parametric model. Survival is adjusted according to the ONS general population mortality life tables[51] to ensure it is never better than the general population.

The OS for the two approaches to modelling (hybrid and CheckMate-9LA) along with the best fitting parametric model distributions can be seen in Table 37 and Table 38. For the base-case, the company selected the hybrid approach, selecting the spline on normal link 2 knots model for the nivolumab + ipilimumab + limited PDC arm, and the log-logistic model for the PDC arm. Note that these models were based on the entire 3-year CheckMate-227 data. The company considered all long-term survival predictions based on the CheckMate-9LA alone to be too pessimistic in both arms. Therefore, the landmark survival of the company base case predicts that in the nivolumab + ipilimumab + limited

PDC arm, [redacted] of patients are alive at 1 year and [redacted] are alive at 10 years. In the PDC arm, it is estimated that [redacted] are alive at 1 year and [redacted] are alive at 10 years.

Table 37 Landmark OS for the best fitting parametric models – nivolumab + ipilimumab + limited PDC (adapted from Table 45, CS and the economic model)

	Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 5 (%)	Year 10 (%)
NIVO + IPI + limited PDC							
CM-9LA KM data	KM	-	62.8	42.6	-	-	-
CM-9LA–only approach	Log-logistic	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline on odds 1 knot	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gamma	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Exponential	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hybrid approach	Lognormal	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline on probit link 1 knot	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline on probit link 2 knots **Company base-case*	**4**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline on odds 1 knot	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline on hazards 1 knot	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Validation data	CM-227 part 1 KM data		[redacted]	[redacted]	[redacted]		
	Constructed KM OS curve (1-year CM-9LA data)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Constructed KM OS curve (2-year CM-9LA data)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AIC; Akaike information criterion; CM-227, CheckMate-227; CM-9LA, CheckMate-9LA; IPI, ipilimumab; KM, Kaplan-Meier; NIVO, Nivolumab.

Table 38 Landmark OS for the best fitting parametric models – PDC (adapted from Table 46, pg. 123, CS and the economic model)

	Distribution	Rank (AIC)	Year 1, %	Year 2, %	Year 3, %	Year 5, %	Year 10, %
PDC							
CM-9LA KM data	KM	-	46.9	25.9	-	-	-
CM-9LA only	Log-logistic	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline on odds 1 knot	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline on odds 2 knots	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline on hazards 2 knots	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline on probit link of survival 2 knots	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline on probit link of survival 1 knot	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hybrid approach	**Log-logistic** **Company base-case*	**1**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline on odds 1 knot	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline on odds 2 knots	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline on probit link 1 knot	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline on hazards 2 knots	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline on hazards 1 knot	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Validation data	CM-227 part 1 KM data		[redacted]	[redacted]	[redacted]		
	ERG-preferred estimate for SOC from NICE TA 447					[redacted]	[redacted]
	NICE committee estimated range of 5-year survival for SOC in TA557					[redacted]	
	Insinga et al. (2018) [ref]					[redacted]	[redacted]

AIC; Akaike information criterion; CM-227, CheckMate-227; CM-9LA, CheckMate-9LA; IPI, ipilimumab; KM, Kaplan-Meier; NIVO, Nivolumab; TA, technology appraisal.

Pembrolizumab and atezolizumab + bevacizumab + PDC

The generated OS predictions for the comparators not included in CheckMate-9LA and CheckMate-227 were based on the results of the fractional polynomial network meta-analysis. For a description of the chosen models and the results, see Section 0. OS predictions required for pembrolizumab and atezolizumab + bevacizumab + PDC were modelled as a function of the nivolumab + ipilimumab + limited PDC arm. Note that the original CS included CheckMate-9LA only as evidence for nivolumab + ipilimumab + limited PDC. However, at the PFC stage, the company included CheckMate-227 in the fractional polynomial ITCs, to better inform the long-term extrapolation of the curves (see Section 3.4).

Separate network meta-analyses were conducted for the mixed histology, PD-L1 ≥ 50% and non-squamous, PD-L1 < 50% expression populations. In the mixed histology, PD-L1 ≥ 50% network, the fractional polynomial model with [redacted] was selected by the company. For the updated NMA including the CheckMate-227 study, the fractional polynomial model with [redacted] was selected (see Section 0). [redacted] The time varying hazard ratios for nivolumab + ipilimumab + limited PDC compared to pembrolizumab can be seen in Section 0.

In the non-squamous, PD-L1 < 50% network, the fractional polynomial model with [redacted] was chosen for the company base case. Following the update of the NMA including CheckMate-227, the preferred fractional polynomial model was [redacted]. The results of the updated NMA were very similar to the results of the NMA excluding CheckMate-227 (see Section 0). The constant hazard ratios for nivolumab + ipilimumab + limited PDC and atezolizumab + bevacizumab + PDC can be seen in Section 0. Alternative models were implemented in the economic model by the company. The modelled curves for atezolizumab + bevacizumab + PDC and pembrolizumab compared to the observed atezolizumab and pembrolizumab KM data can be seen in Figure 12 and Figure 13. The resulting OS curves used in the economic model, and forming the company base case for the intervention and all comparators, can be seen in Figure 14.

Bucher ITC were also conducted for both networks; however, the ERG does not consider the impact of these results on the ICER as the FPNMA is deemed a more appropriate model.

Figure 12 Observed atezolizumab OS and the modelled survival curve

Figure 13 Observed pembrolizumab OS and the modelled survival curve

Figure 14 Company base case survival curves for all treatment options

Company base case landmark survival predictions

The company's base case landmark survival predictions up to 25 years for the intervention and all three comparators can be seen in Table 39.

Table 39 Landmark overall survival for modelled interventions

	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 5 (%)	Year 10 (%)	Year 15 (%)	Year 20 (%)	Year 25 (%)
NIVO + IPI + limited PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ATEZO + BEV + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Sub-populations

As described in Section 4.2.3, the ERG considers there to be a number of decision problems based on tumour histology and PD-L1 expression. This is in part driven by the in-scope comparators, which differ according to the sub-populations, but is also based on clinical plausibility that treatment effectiveness may differ in different sub-populations. Following response to clarification questions, the company presented OS Kaplan-Meier curves from CheckMate-9LA for three sub-populations:

- Non-squamous, PD-L1 < 50%

- Squamous, PD-L1 < 50%
- Any histology, PD-L1 ≥ 50%

In response to clarification question, the company fit independent parametric models to the respective sub-populations Kaplan-Meier data from CheckMate-227.

The parametric models along with AIC and BIC can be seen for each arm and in each sub-population in the company's response to clarification question B4. Likewise, with the all-comer population (any histology and any PD-L1 expression) described above, the ERG considers model selection should be based on validation of survival predictions rather than overreliance on fit criteria. Due to time constraints, the company did not validate the OS predictions. In clarification response (Question B3), the company detailed their validation will be presented prior to technical engagement.

ERG Comment

Hybrid approach

As there are no long-term data from CheckMate-9LA from which to extrapolate the observed hazards, the uncertainty in the long-term modelling assumptions is substantial. The minimum time of follow-up of patients in CheckMate-9LA was 12.7 months and the modelled time horizon in the company's base case is 25 years, meaning the observed data accounts for approximately 4% of the total modelled time horizon. The use of external data facilitates long-term modelling but the long-term mortality of the population in the external data should match that of the disease population receiving the intervention.[50]

The ERG is satisfied that the long-term mortality of the populations in the two trials match. First, as detailed in Section 3.2.2, the ERG considers the external data, CheckMate-227, to be in line with the NICE scope. In addition, the baseline characteristics of the patients in both trials are comparable. This indicates that based on the prognostic baseline characteristic, the long-term survival of patients in CheckMate-227 should match that of patients in CheckMate-9LA. Second, the main difference between the two trials is the lack of 'limited PDC' in the treatment arm in CheckMate-227 (this trial was evaluating nivolumab + ipilimumab vs PDC in the first-line NSCLC setting). However, the company suggest the 'limited PDC' regimen is there to mitigate the risks of early disease progression, the ERG notes delayed response patterns seen in immunotherapies are well documented.[52] Clinical advice to the ERG reiterated this message stating that PDC would be expected to provide short benefit for the first couple of months but that any long-term benefit is due to the immunotherapies. In addition, the observed OS from both trials appears to be largely comparable in the nivolumab arms up to the 13-month switching point (see Figure 10). Therefore, the ERG considers that after 13 months,

the hazards in the nivolumab + ipilimumab arm of CheckMate-227 can be considered equivalent to that in CheckMate-9LA.

The company based the 13-month switching point on the high number of censored patients in CheckMate-9LA beyond 13 months. The ERG agrees with the company that switching prior to the large degree of censoring maintains a suitable sample size, however a statistical test, e.g. a Chow test, which identifies any potential structural change in the cumulative hazard at any specific time point, could have been used in addition to strengthen the evidence for the switching point. The ERG notes scenario analysis conducted by the company shows changing the switching point to 18-months does not have a substantive impact on the ICER.

Overall, the ERG considers the hybrid approach of combining OS data from CheckMate-9LA and CheckMate-227 to be appropriate for the nivolumab + ipilimumab + limited PDC arm. The increased uncertainty based on the lack of limited PDC in the treatment arm of CheckMate-227 is more than mitigated by the reduced uncertainty in the survival extrapolations based on the additional 2-years of OS data. The ERG notes that there remains a large degree of uncertainty in the long-term results, given 3 years' worth of OS data are extrapolated to the 25-year time horizon of the model.

PDC overall survival

The ERG does have some concerns regarding the comparison of the OS curves of the PDC arms in the two trials (Figure 11). Median OS in the chemotherapy arm was 10.74 months in CheckMate-9LA and 13.9 months in CheckMate-227. Following response to clarification questions, the company stated that although median OS in the chemotherapy arm was lower in CheckMate-9LA, it was within the range that has recently been reported in other phase 3 first-line NSCLC studies, which had similar patient populations (e.g., median OS, 10.7-11.3 months in KeyNote-189 [53] and 11.3-11.6 months in KeyNote-407. [54] The ERG disagrees with the company's assertion that the OS curves for PDC are similar as the ERG considers there to be a divergence in the curves at approximately 10-13 months (see Figure 11).

The company states any difference in the median OS between the two curves could be a result of subsequent therapy, which was numerically lower in CheckMate-9LA than in CheckMate-227 with 27.9% vs. 40.8%, respectively. This could explain the divergence given median PFS in CheckMate-9LA was approximately 5 months (see Section 4.2.6.2), meaning 10-13 months corresponds to when patients would be on second line therapy. Note, these subsequent therapies include immunotherapies, which can display a delayed response. Although this is not an issue for the ITC (which is based on relative effects), the modelled benefit for the PDC arm is based on the absolute effects from the CheckMate-9LA trial. More patients receiving subsequent therapy after PDC will mean that their OS will be improved. If the OS in the PDC arm is underestimated in the model, this will underestimate

the ICER. The ERG considers the proportion of patients with subsequent therapy in CheckMate-9LA to be lower than would be expected in practice; in CheckMate-227, this is closer to the anticipated proportion in NHS practice (see Section 4.2.8.3). The PDC arm in CheckMate-227 therefore appears to be better for the purpose of decision making in the NHS, however this trial is not evaluating the in-scope intervention and so for the nivolumab + ipilimumab + limited PDC intervention, using CheckMate-9LA is preferable.

Using CheckMate-227 alone for the PDC arm and the company's hybrid approach to nivolumab + ipilimumab + limited PDC arm would result in inconsistency between approaches and the comparison of different trial populations in the first 13 months. Alternatively, using the CheckMate-227 alone for the PDC arm and hazard ratios for nivolumab + ipilimumab + limited PDC from the ITC could be an approach, however this fails to use the CheckMate-9LA IPD. The ERG does not consider the benefits of these alternative approaches to be sufficient to replace the company's base case but does consider the potential underestimation of OS for PDC to have the potential to impact the ICER. Scenario analysis is presented in Section 6 in which PDC is based on CheckMate-227 alone, and relative effects for nivolumab + ipilimumab + limited PDC are used from the ITC with CheckMate-227.

Model selection

The company's approach to model selection is reasonable, however the ERG notes that in the hybrid approach, the AIC and BIC for each of the parametric models are based solely on the CheckMate-227 data. As the first 13 months of these data are not being used, rather the CheckMate-9LA data are used up to the switching point, the use of the model fit criteria within the model selection process is of limited relevance. This is particularly important in the case of CheckMate-227 as the model is likely overfitting to the first portion of the curve, i.e. the portion without the benefit of limited PDC. There should not be an overreliance on the statistical fit, rather validation of the predicted survival is of more importance. The company did outline this stating that OS model selection was on the basis of "plausible" projections.

Part of the company's validation was the use of a 'constructed' OS curve. This approach uses data from a number of sources and calculated conditional survival for various time intervals, i.e. calculated as the proportion alive at the start of the interval who survive to the end of the interval. The sources and the survival estimates can be seen in Table 40.

Table 40 Data source for constructed OS curve and survival % (adapted from Figure 52, pg. 113, CS)

Year	Source	Description	Conditional survival	Survival of constructed curve

1	CM-9LA	RCT evaluating NIVO + IPI + limited PDC in untreated NSCLC	[redacted]	[redacted]
2	CM-227	RCT evaluating NIVO + IPI in untreated NSCLC	[redacted]	[redacted]
3	CM-227	RCT evaluating NIVO + IPI in untreated NSCLC	[redacted]	[redacted]
5	Pooled CM-017 & CM-057	RCTs evaluating NIVO in second line NSCLC	[redacted]	[redacted]
10	Norwegian registry data	Observational data Norway	[redacted]	[redacted]
15	SEER data	Observational data of advanced NSCLC patients diagnosed in 1994	[redacted]	[redacted]

The ERG considers data used to validate the predictions to be reasonable, although with some drawbacks. The use of CheckMate-227 provides a good estimate of the 1 to 3 year survival of patients in CheckMate-9LA. CheckMate-017 and CheckMate-057 are evaluating a different intervention (nivolumab monotherapy) and the patient population are previously treated NSCLC, nevertheless the survival predictions can be used to help guide survival plausibility. The Norwegian registry data and the SEER data, however cannot be relied on too heavily as the interventions used by the participants in these observational studies are not applicable to the current healthcare system.

Clinical advice to the ERG suggests that the company base case survival predictions for nivolumab + ipilimumab + limited PDC are all on the optimistic side. In the appraisal of pembrolizumab combination therapy for untreated NSCLC,[42] the committee concluded that the company's OS estimates (5-year OS probability = 20%; 10-year OS probability = 11%) were too optimistic and preferred the ERG's 'pessimistic analysis'. The exact 5- and 10-year survival predictions are, however redacted. There remains uncertainty around plausible survival predictions and the ERG notes this is an important issue and one which has a considerable impact on the ICER.

The OS predictions for PDC were validated using ERG and NICE committee-preferred survival estimates from previous NICE submissions[5, 55] and predictions of chemotherapy from a cost-effectiveness analysis of pembrolizumab (Table 38). The ERG notes that in TA557 the committee determined 5-year survival of between 8% and 11% to be reasonable.[5] The ERG therefore considers the company's 5- and 10-year survival predictions to be appropriate.

Fractional polynomial network meta-analysis

The ERG agrees that the use of the FPNMA (i.e. time varying hazard ratios) is appropriate for the economic model. The company's model selection for the FPNMA including CheckMate-9LA data only, were deemed appropriate.

Addressing clarification questions, the company included CheckMate-227 data in the networks. The ERG agrees that including CheckMate-227 is preferred as there is more data to inform the long-term extrapolations, giving more precise estimates. The modelled hazard ratios in the updated NMA are considered to be more realistic. For example, in the PD-L1, ≥ 50% NMA, a hazard ratio of [redacted] (including CheckMate-227) rather than [redacted] (excluding CheckMate-227) at month 1 makes intuitive sense given pembrolizumab is a monotherapy and there is expected to be short term benefit of limited PDC in the nivolumab + ipilimumab + limited PDC arm.

However, due to time restrictions the company were not able to clinically validate the new selected models. Validation of the models is expected prior to technical engagement. Given the ERG's preference for the FPNMA to include the CheckMate-227 data, the economic results presented in Section 6 will include CheckMate-227.

Sub-populations

As described in Section 3.2.2, the ERG considers there to be clinical plausibility of heterogeneity in treatment effects based on tumour histology and PD-L1 expression, and as such, there is a trade-off between using the all-comer and the sub-population specific OS results from CheckMate-9LA and CheckMate-227.

This heterogeneity should be captured in the OS estimates as if benefits differ by patient characteristics then estimates of treatment benefit should match the patient population that is expected to receive the treatment in routine clinical practice. This in turn has implications for the cost-effectiveness estimates, particularly given the model is driven by survival benefit. However, the reduced uncertainty through addressing heterogeneity brings with it a number of issues for the CheckMate-9LA and CheckMate-227 data.

The stratification of the trial data means reduced patient numbers and fewer numbers of events on which to fit the parametric models. However, the ERG considers the number of patients in each of the three subpopulations in CheckMate-9LA and CheckMate-227 to be sufficient (see Table 13 and Table 14, Section 3.2.4.2.). In addition, the trial was not stratified for histology or PD-L1 expression therefore separating the all-comer population may break randomisation.

Given this potential heterogeneity, the ERG considers the exploration of OS based on histology and PD-L1 expression to be an important one. Scenario analyses are conducted in Section 6 in which the impact on the ICER of trial population stratified by histology and PD-L1 expression are estimated. The ERG notes, the result of the all-comer population from CheckMate-9LA and CheckMate-227 (as in the company's base case) are appropriate for decision-making and will be retained in the ERG's base case.

Duration of treatment benefit

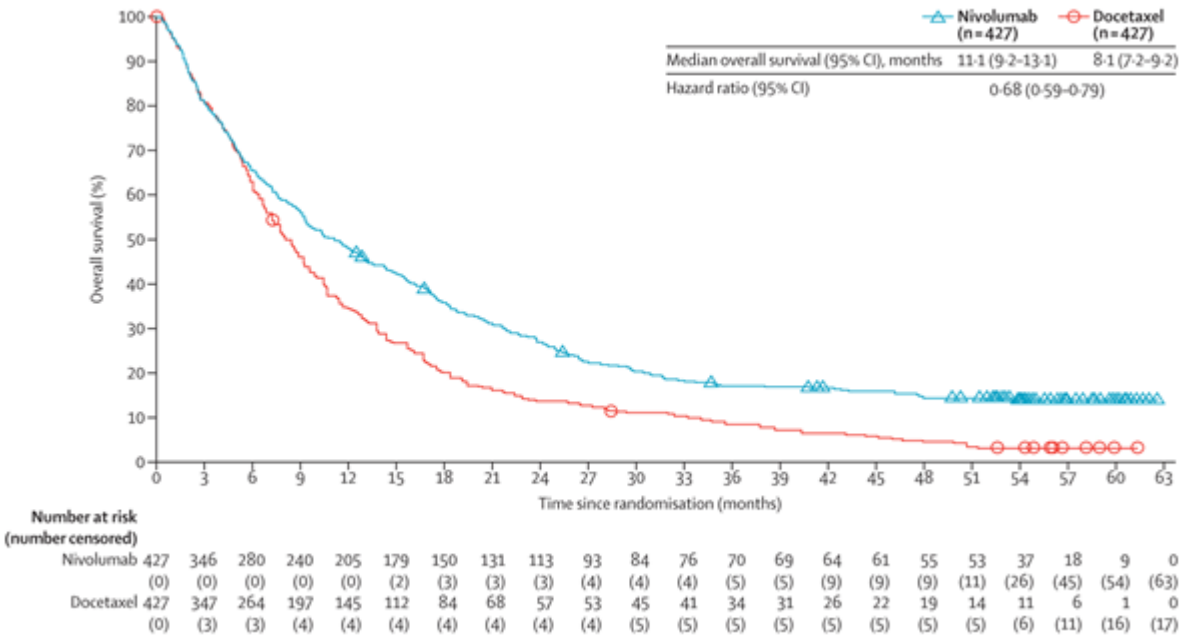
The company assumed a lifetime treatment effect of nivolumab + ipilimumab + limited PDC. A scenario explored the impact of a loss of treatment effect at 3 years after end of immunotherapy. In this scenario, the mortality rate for nivolumab was set equal to that of PDC after three years, and as such it assumes a complete loss of treatment effect after 3 years, rather than a gradual waning of effect over time. The duration of treatment benefit has been demonstrated in previous appraisals to be an influential assumption, where analyses have shown that removing the treatment effect at earlier timepoints increases the ICER considerably.

A lifetime treatment benefit is inconsistent with previous appraisals of first-line NSCLC (TA600, TA531, TA584). The committees for these appraisals concluded that a lifetime treatment effect was implausible and that scenarios based on 3- and 5-year benefit durations from when treatment was stopped were plausible and appropriate for decision making.

According to the company's Kaplan-Meier plot of time on treatment (Figure 71 and Figure 72, pg. 144, CS), the probability of remaining on treatment at 1 year is approximately 30%, and all patients within the trial will discontinue treatment with nivolumab by 2 years. Therefore, the company's model assumes that the effect of nivolumab on OS persists long after patients have stopped receiving treatment (i.e. a patient who is alive 10 years after discontinuing nivolumab has a lower mortality rate and will have a better survival prognosis compared with an identical surviving patient who did not receive nivolumab).

The company referenced the results of a study to support their assumption of a lifelong benefit of treatment effect lasting beyond discontinuation for immunotherapies.[56] The ERG considers that the study is of limited relevance to the present decision problem as it considers a second-line indication of nivolumab, and patients received nivolumab monotherapy. Further, since the study only presented survival outcomes up until 4 years, it cannot support the assumption of a treatment effect that is lifelong. In a comparison presented between nivolumab and docetaxel (Figure 15), there does appear to be a widening gap between the survival curve between 36 months and 48 months, but it cannot be assumed to continue as the difference between the two curves is not uniform throughout the observation period. There is a large degree of censoring in the nivolumab arm after 4 years, so it is uncertain what the relative difference would be after this time.

Figure 15 Overall survival in previously treated NSCLC (Source: Antonia et al.[56])



In the CDF reappraisal of nivolumab for previously-treated NSCLC (TA655), the committee considered that a lifetime treatment effect was not supported by the evidence, and that a scenario based on 3 years of continued benefit after treatment had stopped was more appropriate, although likely to be conservative. Treatment effect was unlikely to stop immediately after 5 years, and the company presented a range of scenarios for different durations of benefit and the proportions of patients who would continue to benefit. These were all considered arbitrary and none were selected as a preferred scenario, but the ICER remained under the threshold under all assumptions.

Although it is biologically plausible for the treatment effect to continue after stopping nivolumab, its duration was uncertain. Given the short follow-up from CheckMate-9LA, the ERG believes that it is unknown whether, or for how long, the effects of nivolumab on OS are maintained after treatment discontinuation. This is a key area of uncertainty which may be resolved through additional follow-up in CheckMate-9LA.

4.2.6.2 Progression-free survival

Nivolumab + Ipilimumab + limited PDC and PDC

For consistency with the modelling of OS, the company adopted a hybrid approach to constructing PFS curves, again using a 13-month switching point to join the CheckMate-9LA Kaplan-Meier data with the parametric curve fit to CheckMate-227. Note that CheckMate-9LA had a minimum follow-

up of 12.2 months. The company also presented a scenario in the economic model in which the results are based solely on parametric extrapolation of the CheckMate-9LA data. The comparison of the Kaplan-Meier curves from CheckMate-9LA and CheckMate-227 in the nivolumab + ipilimumab + limited PDC and PDC arms can be seen in Figure 16 and Figure 17.

Figure 16 Comparison of PFS for nivolumab + ipilimumab + limited PDC (CM-9LA) with nivolumab + ipilimumab (CM-227 part 1) (Fig 49, CS, pg. 106)

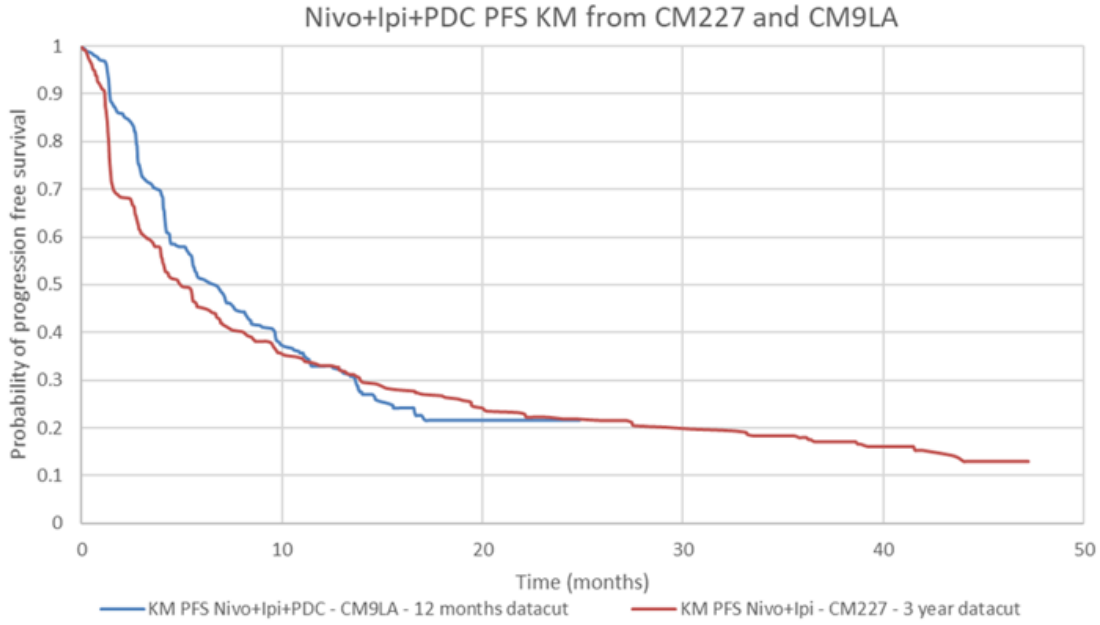
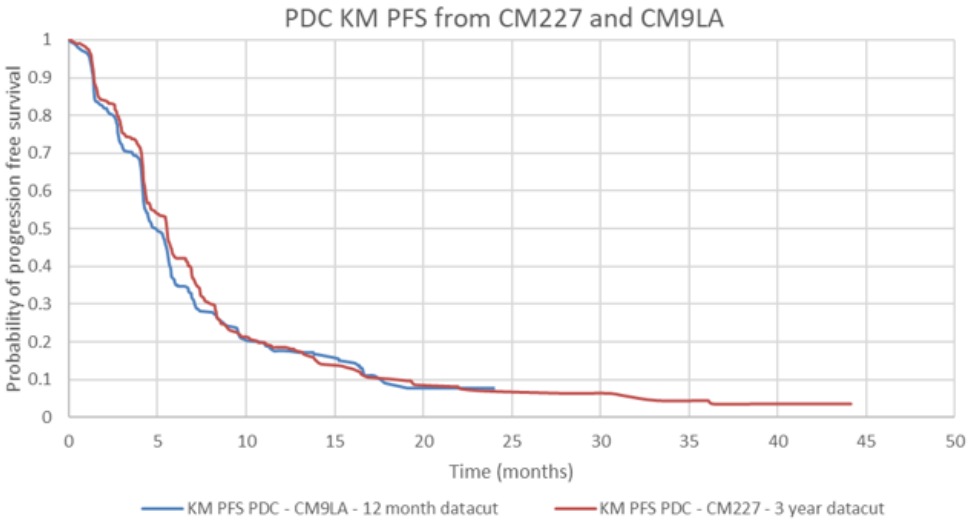


Figure 17 Comparison of PFS for PDC in CM-9LA with PDC in CM-227 part 1 (Fig 50, CS, pg. 106)



The company adopted the same approach to fitting parametric models to the PFS data as was applied to the OS data. The results of the Schoenfeld residuals plot and the Grambsch-Therneau test showed a violation of the proportional hazards assumption, therefore independent parametric models were fitted to the nivolumab + ipilimumab + limited PDC and PDC arms of CheckMate-227. The best fitting five distributions along with the progression-free survival landmark predictions for nivolumab + ipilimumab + limited PDC and PDC can be seen in Table 41 and Table 42, respectively.

The company based their model selection in the nivolumab + ipilimumab + limited PDC arm largely on validation of the predicted landmark PFS. Validation of the nivolumab + ipilimumab + limited PDC PFS predictions was based on pooled data from CheckMate-017 and CheckMate-057. In this pooled analysis, conditional survival from year 2 to 5 was calculated to be 59.7%. This was applied to the 2-year survival from CheckMate-227, which was 20.2%, producing an estimated survival of 12.9%. The company therefore selected the spline on odds 2 knots model.

For the PDC arm, the company determined the PFS data was sufficiently mature to base the model selection on model fit criteria. The company's selected model was spline on normal, 2 knots.

Table 41 Landmark PFS for the best fitting parametric models – Nivolumab + ipilimumab + limited PDC (adapted from Table 48, pg. 130, CS)

	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 5 (%)	Year 10 (%)
CM-9LA KM	-	32.9	21.5	-	-	-
Hybrid approach						
Spline on hazards 2 knots	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline on odds 2 knots **Company base-case*	**2**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline on odds 1 knot	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline on probit link 1 knot	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline on hazards 1 knot	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Validation						
CM-227 part 1 KM data (3-year database lock)		[redacted]	[redacted]	[redacted]		
Estimated 5-year PFS based on CM-227 3-year estimate and conditional PFS from 3-5 years pooled from CM-057 and CM-017					[redacted]	

AIC; Akaike information criterion; CM-017, CheckMate-017; CM-057, CheckMate-057; CM-227, CheckMate-227; CM-9LA, CheckMate-9LA; IPI, ipilimumab; KM, Kaplan-Meier; NIVO, Nivolumab.

Table 42 Landmark PFS for the best fitting parametric models –PDC (adapted from Table 50, pg. 132, CS)

	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 5 (%)	Year 10 (%)
CM-9LA KM	-	17.6	-	-	-	-
Hybrid approach						
Spline on hazards 2 knots	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline on normal link 2 knots **Company base-case*	**2**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline on odds 2 knots	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline on odds 1 knot	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Validation						
CM-227 part 1 KM data (3-year database lock)		[redacted]	[redacted]	[redacted]		
Estimated 5-year PFS based on CM-227 3-year estimate and conditional PFS from 3-5 years pooled from CM-057 and CM-017					[redacted]	[redacted]

AIC; Akaike information criterion; CM-017, CheckMate-017; CM-057, CheckMate-057; CM-227, CheckMate-227; CM-9LA, CheckMate-9LA; IPI, ipilimumab; KM, Kaplan-Meier; NIVO, Nivolumab.

Pembrolizumab and atezolizumab + bevacizumab + PDC

As in the case for OS, the company generated the PFS results for pembrolizumab and atezolizumab + bevacizumab + PDC through the fractional polynomial ITC. Separate networks were conducted for the mixed histology, PD-L1 ≥ 50% and non-squamous, PD-L1 < 50% expression populations. Note that the original CS included CheckMate-9LA only as evidence for nivolumab + ipilimumab + limited PDC. However, at the PFC stage, the company included CheckMate-227 to better inform the long-term extrapolation of the curves (see Section 3.4).

The fractional polynomial model with [redacted] was selected for the mixed histology, PD-L1 ≥ 50% network. This was selected for [redacted]. The time varying hazard ratios can be seen in Section 0. For the non-squamous, PD-L1 < 50% network, the preferred fractional polynomial model was a [redacted]. In the updated NMA, the model with [redacted] was selected. [redacted] An alternative model in which Keynote-024 was excluded from the PD-L1

≥ 50%, Mixed Histology (CheckMate-9LA only) network was included in the executable economic model.

Bucher ITC were conducted for both networks; however, the ERG does not consider the impact of these results on the ICER as the FPNMA is deemed to be appropriate.

Company base case landmark survival predictions

The company's base case landmark PFS predictions up to 25 years for the intervention and all three comparators can be seen in Table 43.

Table 43 Landmark progression-free survival for the intervention and comparators

	Year 1	Year 2	Year 3	Year 5	Year 10	Year 15	Year 20	Year 25
NIVO + IPI + limited PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ATEZO + BEV + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Sub-populations

Following clarification questions, the company presented sub-population specific Kaplan-Meier data from CheckMate-9LA and CheckMate-227 based on histology and PD-L1 expression. The company fitted independent parametric models to the latter. The parametric models along with AIC and BIC can be seen for each arm and in each sub-population in the company's response to clarification question B4.

ERG Comment

Model Selection

As with OS (see Section 4.2.6.1) the ERG considers the company's approach to model selection to be reasonable. In the case of PDC, the relatively mature CheckMate-227 data (approximately 95% of participants had progressed at the 3-year time point) are used meaning model selection based on fit criteria is a reasonable approach. This is strengthened by the similarity of the PFS curves (Figure 17) given the first 13 months of Kaplan-Meier data used in the model are not from CheckMate-227.

In the case of the nivolumab + ipilimumab + limited PDC arm, the caution regarding selection based on model fit and an emphasis on 'plausible' projection of PFS at landmark points is appropriate. The CheckMate-227 PFS Kaplan-Meier curves show heavy censoring throughout (see Figure 20, CS),

lending support to the approach of not over relying on model fit. However, basing model selection on plausible PFS predictions is not without its issues. This is a result of there being limited data with which to validate survival predictions and no clinical experience with the intervention for the modelled time horizon (25 years) with which to based decisions on. The company's constructed curve used to validate PFS predicted 12.9% PFS at 5 years. This is generated using data from CheckMate-017 and CheckMate-057 (nivolumab in second-line NSCLC). The ERG agrees with the company that this could be considered a conservative estimate, however there is uncertainty given the different patient populations.

The company state the second-best fitting distribution (spline on odds 2 knots) was selected in order *"to be conservative"* when comparing the landmark PFS for the fitted models to the constructed curves. The ERG considers this choice to be less conservative than the best fitting distribution (spline on hazards 2 knots), which predicts a PFS of 13.2%, rather than 13.8% in the company's base case.

For the model selection for the PDC arm, the company stated data was sufficiently mature to base on fit alone, yet the company did not select the best fitting model (spline on hazards 2 knots). The ERG presents scenarios in Section 6.2 in which spline on hazards 2 knots is fit to both nivolumab + ipilimumab + limited PDC and PDC arms. Note, the selection of both of these models has the benefit of satisfying another of the company's model selection criteria in that a common functional form of models is applied to both arms.

The company's base-case predicts PFS to be 3.5% at 25 years in the nivolumab + ipilimumab + limited PDC arm, implying a cure in this proportion of the population. In TA600, the committee considered the company's modelling approach in which it was assumed that about 10% of people having pembrolizumab combination therapy for untreated NSCLC would be cured after 18 years to be too high. It was stated that such a cure rate would be optimistic given the increased risk of secondary cancers and the other comorbidities in this population. The ERG considers this an area of unresolved uncertainty and one which will impact on the ICER.

Fractional polynomial network meta-analysis

The ERG considers the use of the FPNMA to be appropriate. The company's model selection for the FPNMA including CheckMate-9LA data only, were deemed appropriate. However, the ERG prefers the network, which includes CheckMate-227 owing to increased precision in the results (see Section 0). As with the updated FPNMA results for OS, the company have not clinically validated the new selected PFS models. Validation of the models is expected prior to technical engagement. Given the ERG's preference for the FPNMA to include the CheckMate-227 data, the economic results presented in Section 6 will include CheckMate-227.

Sub-population

Due to time constraints, the company did not validate their PFS predictions based on sub-population data. In clarification response (Question B3), the company detailed their validation will be presented prior to technical engagement. The ERG explores the impact of sub-population specific results on the ICER in Section 6. However, the best choice of parametric model for each of the sub-populations remains an area of unresolved uncertainty.

4.2.6.3 Duration of treatment and stopping rules

Nivolumab + ipilimumab + limited PDC

Duration of treatment (DOT) in the model was based on the Kaplan-Meier plot for nivolumab + ipilimumab + limited PDC to reflect treatment use in CheckMate-9LA, where 7% patients received one cycle and 93% received two cycles of limited PDC. A stopping rule of 24 months for nivolumab + ipilimumab was applied in the model, consistent with the trial and in alignment with the recent NICE appraisals of untreated NSCLC.[19, 42, 44, 57] After 2 cycles of PDC, treatment with nivolumab and ipilimumab could continue until progression or unacceptable toxicity.

A single Kaplan-Meier plot was used to model DoT for nivolumab + ipilimumab and limited PDC. However, at least [redacted] of patients discontinued ipilimumab earlier than nivolumab (page 181 CSR). For those who discontinued ipilimumab first, the mean time on treatment for nivolumab was [redacted] days. Therefore, the cost of nivolumab + ipilimumab + limited PDC in the model is likely to be overestimated.

PDC

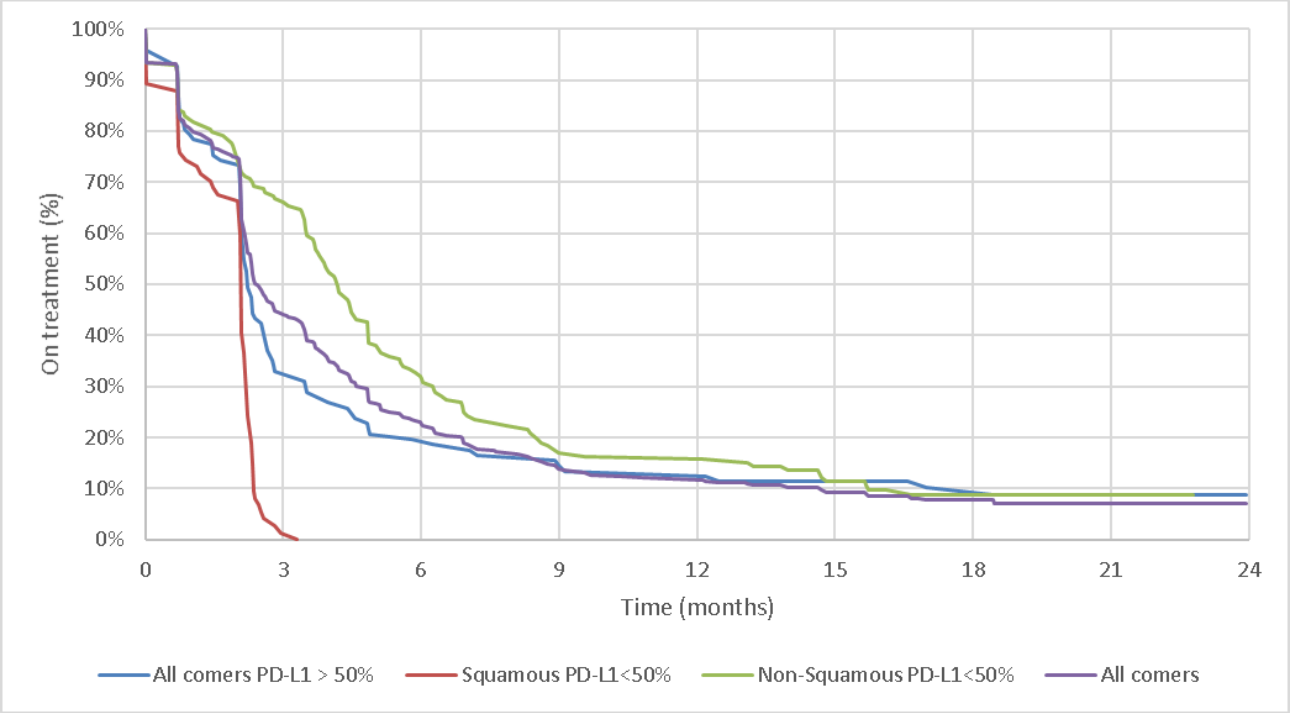
Treatment costs of PDC were modelled according to the DOT Kaplan-Meier plot from CheckMate-9LA. PDC is discontinued after 4 cycles of treatment after which non-squamous patients who have not progressed can continue on pemetrexed maintenance therapy. Table 44 presents the number of patients receiving each number of doses in CheckMate-9LA and in the economic model.

Table 44 Patients receiving PDC

Proportion receiving chemotherapy cycles	CheckMate-9LA	Economic model
1 dose	100.00%	100.00%
2 doses	93.40%	86.25%
3 doses	79.40%	77.94%
4 doses	74.8%	63.04%
Mean number of doses	3.46	3.27
Pemetrexed maintenance therapy	66.4%	45.1%

Following clarification questions, the company provided observed DOT Kaplan-Meier curves for PDC and maintenance therapy, stratified by sub-population (i.e. according to the histology and PD-L1 expression sub-populations described in Section 4.2.3). These can be seen in Figure 18. Pemetrexed maintenance therapy is not licensed for patients with squamous histology, and so none of these patients remain on treatment after around three months. DOT in the all-comers population, used in the company base case analysis, was similar to that in the PD-L1≥50% group. The impact of subgroup-specific DOT on cost-effectiveness are explored by the ERG (see Section 6).

Figure 18 Observed DOT for PDC for histology and PD-L1 sub-populations



Pembrolizumab

Time on treatment for pembrolizumab was modelled using the PFS curve as a proxy for DOT. A maximum treatment duration of 2 years (35 cycles) was assumed for pembrolizumab, in line with the KeyNote-024 protocol and the current recommendations for the use of pembrolizumab for the treatment of patients with advanced NSCLC.

As per the licence, patients treated with pembrolizumab are treated until disease progression is confirmed or unacceptable toxicity. Pembrolizumab is well tolerated as a monotherapy and discontinuation due to TRAEs occurred in 7.1% of patients. [58] Limited data is available in the public domain regarding the proportion of patients on treatment over time. Analyses of KeyNote-024 reported that the median duration of treatment in the pembrolizumab arm was 7.9 months, and that

25.3% of patients completed 35 cycles of pembrolizumab. The company's model predicted that [redacted] would be in the PFS state at two years and will have received 35 cycles of pembrolizumab, which is quite similar to the reported values.

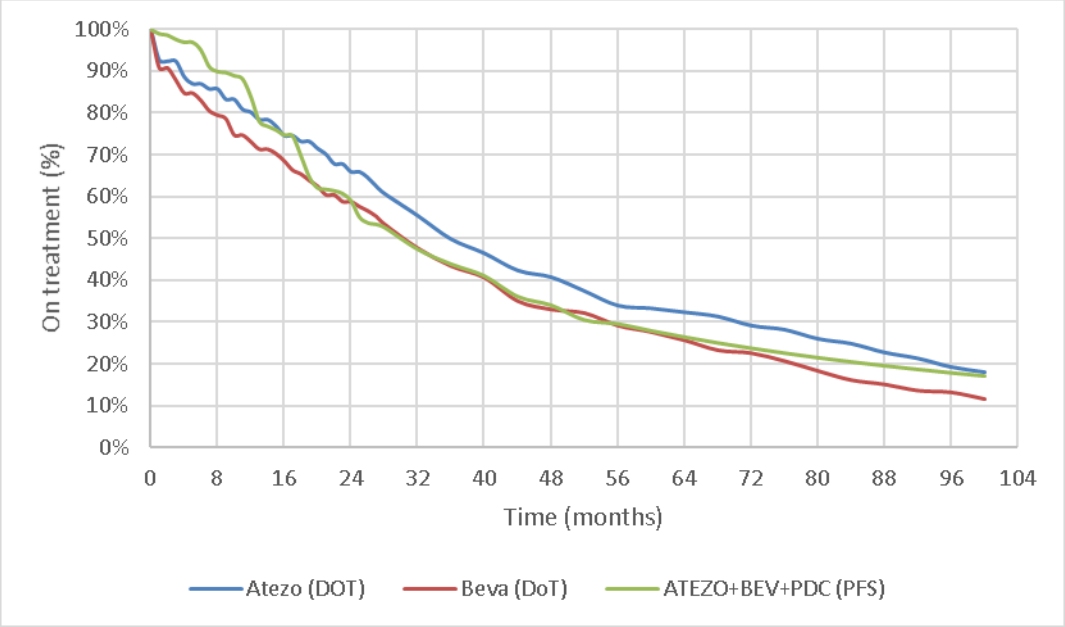
Atezolizumab + bevacizumab + PDC

Time on treatment for atezolizumab and bevacizumab was modelled in the company analysis using the PFS curve as a proxy for DOT. A stopping rule at 2 years was applied to treatment with atezolizumab + bevacizumab + PDC, consistent with previous NICE committee decisions for atezolizumab.

Atezolizumab is administered until loss of clinical benefit or unacceptable toxicity. There is evidence to suggest that some patients continue to receive treatment with atezolizumab beyond disease progression, while some patients will discontinue treatment before progression. Comparison of the Kaplan-Meier plots from IMpower150, in TA583, showed that patients tended to stop treatment before progression in the early part of the trial, with similar rates of treatment and progression free survival after about 9 months. Therefore, PFS as a proxy for DOT will provide a small overestimation of atezolizumab treatment costs.

Bevacizumab is administered until progressive disease or unacceptable toxicity. PFS exceeded bevacizumab treatment duration throughout the trial, and comparison of the Kaplan-Meier plots shows that patients tended to stop treatment before progression in the early part of the trial, with similar rates of treatment and progression free survival after about 9 months (TA584). As such, PFS is not a good surrogate for the treatment duration of bevacizumab as it is likely to underestimate the true treatment duration expected in clinical practice, and subsequently, treatment cost.

Figure 19 Observed vs modelled DoT for atezolizumab and bevacizumab



ERG comment

Nivolumab time on treatment

The short duration of follow-up of the CheckMate-9LA study makes the estimated mean duration of treatment with nivolumab + ipilimumab uncertain. At the time of analysis, around 21% of patients in the nivolumab arm remained on treatment. Since the company did not provide censoring marks or the number at risk, it is not clear how complete the DOT KM plots are.

Use of PFS as proxy for DOT

The ERG considers the company's approach with respect to using observed DOT for nivolumab and PDC to be appropriate as it more accurately reflects treatment use in the clinical trial. However, the use of PFS as proxy for DOT may overestimate treatment costs for pembrolizumab and atezolizumab.

As can be seen in Figure 17, and to a lesser extent Figure 16, the DOT curves lie below the PFS curves, meaning patients discontinued treatment before progression. The modelled costs of treatment when using the DOT curve will be less compared to the modelled cost of treatment for the same intervention when using the PFS curve. This inconsistent approach results in the nivolumab + ipilimumab + limited PDC and PDC arms having potentially unfairly reduced costs compared to pembrolizumab and atezolizumab + bevacizumab + PDC. Thus, potentially biasing the ICERs in favour of nivolumab + ipilimumab + limited PDC or PDC compared to pembrolizumab or atezolizumab + bevacizumab + PDC.

To address this, the ERG requested the company model pembrolizumab and atezolizumab + bevacizumab + PDC using observed DOT from the literature. In the company's response to clarification question, the DOT Kaplan-Meier curves were digitised for atezolizumab and bevacizumab as reported in the NICE appraisal for atezolizumab in combination for first-line non-squamous NSCLC (TA584).[19] TA548 shows DOT curves lying below the PFS curve, indicating again that patients discontinue prior to progression. The Kaplan Meier curves can be seen in Figure 19 compared to the PFS curve used in the company's base case.

However, in contrast to TA548, the observed DOT curves for atezolizumab and bevacizumab lie above or on the company's base case PFS curve (see Figure 19). This inconsistency is due to a disconnect between the NMA and the observed DOT curves but is no longer a problem in the ERG base case as the DOT curve lies below PFS curve. The impact of the use of the observed DOT data from TA548 on the company's ICER can be seen in Section 6.

Similarly, observed DOT data were not available for pembrolizumab and so the PFS curve was retained. The ERG considers this a reasonable approximation for pembrolizumab as monotherapies are generally well tolerated. Nevertheless, this assumption is still likely to overestimate the cost of pembrolizumab.

Combined DOT for combination therapy

The economic model applies a single observed DOT curve to represent the nivolumab + ipilimumab + limited PDC patients. This is despite the CSR for CheckMate-9LA permitting separate discontinuation, that is, patients can discontinue ipilimumab while continuing treatment with nivolumab (note, discontinuation of nivolumab alone is not permitted).

In the company's response to clarification questions, the company acknowledged the lack of modelling of separate discontinuation of ipilimumab in the economic model due to the use of the combined nivolumab + ipilimumab + limited PDC DOT curve. According to the CheckMate-9LA CSR, [redacted] of patients in the nivolumab + ipilimumab + limited PDC arm discontinued ipilimumab. The ERG agrees with the company that this omission from the model results in the likely overestimation of the costs of nivolumab + ipilimumab + limited PDC. Following discontinuation, the median number of nivolumab doses received was [redacted]. The impact on the ICER is expected to be limited and therefore this is not considered further.

Similarly, it is not accurate to use the pooled DOT curve for atezolizumab + bevacizumab as each individual immunotherapy has different decision rules for stopping treatment. Comparing the Kaplan-Meier plots for DOT from IMpower150 to the PFS predicted in this model (Figure 19) shows that DOT may be initially overestimated, and then underestimated from approximately 16 weeks onwards.

4.2.6.4 Adverse events

AEs included in the economic model were Grade 3+ and with ≥ 5% incidence in either treatment arm. The incidence of AEs were taken from CheckMate-9LA and relevant comparator studies. [19, 59, 60] Modelled AEs for the intervention and each comparator can be seen in Table 47.

ERG comment

As the follow-up of CheckMate-9LA is short and a number of patients remain on treatment, the ERG is concerned that the rates predicted by the trial may be underestimated, and that the serious, longer term toxicities of nivolumab + ipilimumab (colitis, pneumonitis, hepatitis etc) may not have been fully captured in the economic model.

Immunotherapies have been shown to have a different toxicity profile than chemotherapy. For example, nivolumab has been shown to be associated with immune-mediated endocrinopathies (see Table 15, Section 3.2.5). While the incidence of these Grade 3-4 events is relatively low, some endocrine IMAEs may require long-term treatment with HRT, and so may contribute to costs and disutilities more so than other adverse events. Grade 1-2 immune-mediated events may require resources above that which are required to usually manage events of this grade.

There were some discrepancies between the values reported in the CS, in the company model and in the CSR for CheckMate-9LA. The ERG considers that the CSR is the most reliable source of data and has corrected the model to reflect these values.

The criteria for inclusion of Grade 3-4 TRAEs in the economic analysis was stated as being an incidence of at least 5% in subjects in any treatment arm. However, there are some events which do not occur in more than 5% in any treatment arm, such as fatigue, white blood cell decrease and thrombocytopenia. Therefore, other events could have been included if a lower incidence threshold was considered, which would also be consistent with previous appraisals, such as diarrhoea (3.9% for nivolumab) or asthenia (2.3% for PDC).

The analysis only considers the impact of one TRAE per patient. However, data in the CSR implies that patients may experience more than one of each event. Therefore, the total impact of TRAEs may not be captured in the economic analysis.

AEs may manifest in patients on second-line therapy; however, these events are not considered within the company's model.

4.2.7 Health related quality of life

4.2.7.1 Health state utilities

Health state utilities in the economic analysis were estimated from health-related quality of life (HRQoL) data collected in CheckMate-9LA. Data were collected using the EQ-5D-3L questionnaire, and utility scores were estimated using a UK value set. In the trial, EQ-5D assessments were taken every three weeks (on the first day of each treatment cycle in the nivolumab arm) for the first 6 months of the study, and then every 6 weeks (every 2 treatment cycles in the nivolumab arm) up to 2 years thereafter. After patients discontinued primary treatment or after disease progression, assessments were administered at follow-up visits that occurred 35 days and 115 days after the last dose, and then every 3 months until death.

The company considered two approaches for deriving health state utilities, either based on progression status or on time to death (TTD) (Table 45). The TTD utilities were derived based on the following time before death categories:

- Group 1: less than 4 weeks before death,
- Group 2: more than 5 and less than 26 weeks,
- Group 3: more than 27 and less than 52 weeks,
- Group 4: more than 52 weeks before death.

Table 45 Summary of health state utilities

Health state	Overall utilities, mean (SE)	NIVO + IPI + limited PDC, mean (SE)	PDC, mean (SE)
Time to death			
> 52 weeks	[redacted]	[redacted]	[redacted]
27-52 weeks	[redacted]	[redacted]	[redacted]
5-26 weeks	[redacted]	[redacted]	[redacted]
≤ 4 weeks	[redacted]	[redacted]	[redacted]
Progression status			
Progression free	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]

SE, standard error; NIVO, nivolumab; IPI, ipilimumab; PDC, platinum doublet chemotherapy

There were 705 patients in the CheckMate-9LA study with at least one observed EQ-5D assessment. At clarification, the company provided completion rates for the questionnaire over time, and for each of the health state categories used in their utility modelling. There were 6,007 observations in total,

6,007 available observations for the progression-based health states and 4,402 observations for the TTD health states (Table 46).

Table 46 Total number of EQ-5D observations for each health state

Health state	Nivolumab	PDC	Total
Time to death			
> 52 weeks	1371	913	2284
27-52 weeks	472	469	941
5-26 weeks	495	568	1063
≤ 4 weeks	51	63	114
Progression status			
Progression free	2935	2138	5073
Progressed disease	566	438	1004

Little information was provided in the CS on the specific statistical models that were fit to the data. The CS seemed to suggest that the analysis was based on the first year of data from CheckMate-9LA (page 136, CS), although it was not clear on why data from later time points were not used. For example, it was not clear how repeated measures were accounted for, whether the analysis adjusted for baseline utility, or the number of observations that were included in the statistical model.

In the base case analysis, utilities were based on the TTD model with no treatment effect, justified by the company on the basis that TTD utilities have been used and accepted in recent appraisals by NICE on first-line NSCLC (citing TA531, but also TA584). The company provided a scenario analysis using utility values based on progression status, and treatment-specific TTD. Health utilities were not adjusted by age.

ERG comment

Without more details on the statistical approach used by the company to estimate utilities, it was difficult to verify their approach. Utility was estimated as a function of arbitrary categories of time to death, and it does not appear that the fit of such a model or any other time category cut offs were tested, or whether time as a continuous variable was considered. It was not clear why there were fewer observations available for the TTD health states than the progression-based health states. One potential approach to validation would be to compare the utility values to those estimated from similar models in previous appraisals in NSCLC. However, it is difficult to do so as these are mostly redacted, and those that are not, used different time cut-off points. The utility value estimated for the

time category closest to death (≤ 4 weeks before death) was considerably lower than that estimated for the time category closest to death (≤ 5 weeks before death) in a previous appraisal.

The TTD approach was selected by the company on the basis that it had been accepted in previous appraisals of treatments for first-line NSCLC. In previous appraisals, a common rationale was that the TTD approach offers a better statistical fit than other progression-based approaches, and there were criticisms of the more typically used progression-based approach. In many of the appraisals, there was no statistically significant difference between the utilities of patients pre- and post-progression. In these cases, utility data were collected up to drug discontinuation or at the 30-day-post-study safety follow-up visit, but no further, resulting in utility values for the post-progression state being based on values taken shortly after progression when the full effects of health deterioration would not yet be evident, potentially causing an overestimate of the utility in this health state.

However, this is not the case in this appraisal, where utilities of patients in CheckMate-9LA were captured until death, and there are a large number of data points contributing to the progressed disease health state. There were 1,004 post-progression observations available from 353 patients, of which around a third were observed after 6 months after progression. In contrast, there were 114 observations in the category of < 4 weeks to death.

The ERG also has concerns regarding the conceptual issues linking the prediction of HRQoL to time to death. Time to death is not a causal determinant of HRQoL, as it can only be measured retrospectively and an event that occurs in the future cannot determine something that occurred in the past. Therefore, the observed correlation between HRQoL and time to death is most likely due to confounding, and time to death is a proxy for severity of disease, which is likely to be highly correlated with both OS and HRQoL. The relationship observed between HRQoL and time to death is therefore essentially stating nothing more complicated than sicker patients will feel worse.

Consideration of two scenarios illustrates how this interpretation of time to death as causal determinant of HRQoL produces logically inconsistent predictions. Considering HRQoL at baseline, the time point at which patients enter the model and start treatment, the statistical model used by the company would predict that HRQoL for patients in cycle one to be different in the treatment and comparator arms, which should theoretically be equivalent. This is because patients in one of the treatment arms would be associated with a higher mean OS, i.e. a longer time until death at baseline, resulting in a higher HRQoL at this time. However, patients' HRQoL at baseline should be the same in both the treatment and comparator arms, since patients should be at the same point in the treatment pathway and have only just initiated treatment, and it is not known how long their survival would be at this time point.

The method by which the company use to apply TTD utilities also means that it is difficult to validate the predicted utility values over time. Time to death at any point in the time horizon is known for the cohort as a whole based upon the overall survival curve, and the model uses this to calculate the proportion of patients who die each cycle. For each TTD category, a per-cycle QALY loss relative to the health state furthest from death (> 52 weeks) was estimated. In the model, the utility value for the TTD health state furthest from death (> 52 weeks) was applied throughout the patients' lifetime, and then, upon death, a QALY loss was applied that accounts for all TTD-related decrements incurred over the lifetime. As such, the model did not directly estimate the mean utility of the cohort on a per-cycle basis.

Therefore, the ERG considers that the conceptual issues mean that using time to death to calculate utility is inappropriate and leads the model to make inconsistent predictions about the HRQoL of patients in the model.

4.2.7.2 Impact of AEs

To account for the impact of AEs on quality of life, utility decrements from published literature were applied in the model. QALY losses were applied in the model as a one-off decrement during the first model cycle, based on the incidence of AEs for each treatment and corresponding utility decrement (Table 47).

Table 47 Impact of AEs on HRQoL

Adverse event	NIVO + IPI + limited PDC	Pembrolizumab	Atezolizumab + bevacizumab + PDC	PDC	Disutility	Reference
Anaemia	5.87%	0.89%	6.40%	14.3%	−0.125	Lloyd, van Hanswijck de Jonge [61]
Lipase increased	6.15%	0.00%	0.00%	9.2%[1]	0	Assumption
Febrile neutropenia	0.00%[2]	0.00%	8.40%	0.0%[3]	−0.5	Nafees, Stafford [62]
Neutrophil count decreased	0.00%[4]	0.00%	8.70%	0.0%[5]	−0.46	Nafees, Stafford [62]
Thrombocytopenia	2.79%	0.13%	4.30%	2.58%	−0.184	Attard, Brown [63]
Platelet count decreased	0.00%[6]	0.00%	5.10%	0.0%[7]	0	Assumption
White blood cell count decreased	0.00%[8]	0.00%	3.30%	0.0%[9]	−0.46	Nafees, Stafford [62]
Neutropenia	6.7%	0.13%	14.00%	0.0%[10]	−0.46	Nafees, Stafford [62]
Fatigue	2.23%	0.63%	3.30%	0.57%	−0.41	Nafees, Stafford [62]

Total AE-related disutility	-0.052	-0.005	-0.191	-0.067		

[1]Value in the model and the CSR (page 285) is 0.86%. [2] Value in the CSR is 3.9%. [3] Value in the CSR is 2.9%. [4] Value in the CSR is 3.4%. [5] Value in the CSR is 2.6%. [6] Value in the CSR is 0.6%. [7] Value in the CSR is 1.4%. [8] Value in the CSR is 1.4%. [9] Value in the CSR is 0.6%. [10] Value in the model and the CSR is 9.2%.

ERG comment

The ERG considers that it was appropriate to capture the HRQoL impact of AEs. Given the EQ-5D assessment was completed on the first day of a treatment cycle in the CheckMate-9LA trial, it is unlikely that it captures impact any treatment-related adverse effects, and trial-derived utilities will underestimate disutilities associated with adverse events, and therefore an additional disutility must be applied.

As discussed in Section 4.2.6.4, there are some concerns that the full AE impact on HRQoL is not captured, due to the exclusion of immune-related adverse events and adverse events relating to second-line therapy.

The adverse events for the PDC arm were based on those in the CheckMate-9LA trial. The regimen used for patients of squamous histology was paclitaxel plus carboplatin, however gemcitabine is more commonly used in NHS practice. There also may be implications to HRQoL if the safety profiles between the different chemotherapy regimens differ. For example, paclitaxel is associated with a higher degree of hair loss than gemcitabine.[49]

4.2.8 Resources and costs

The types of costs considered in the economic model included:

- Drug acquisition costs of the intervention and comparators,
- Administration costs of the intervention and comparators,
- Management of the disease,
- Terminal care,
- Management of AEs.

Testing costs to identify patients' level of PD-L1 expression were excluded from the analysis. PD-L1 testing is routine in the NHS for all new diagnoses of NSCLC and since every patient considered by the model should receive the test, its cost does not differ between strategies.

4.2.8.1 Drug acquisition

Drug costs were taken from British National Formulary and eMIT (Table 47). Nivolumab and ipilimumab currently have an agreed confidential patient access scheme (PAS) discount, [redacted]

[redacted]. For the indication being appraised with the current submission, [redacted]. There are also confidential discounts to the NHS for atezolizumab, bevacizumab, pembrolizumab and pemetrexed; the ERG provides results including all existing confidential discounts in a separate confidential appendix to this report.

Dosing schedules for nivolumab and ipilimumab were taken from the CheckMate-9LA trial and the drug's anticipated license.

Where the dose per administration was based on patient weight or body surface area, baseline characteristics of patients in CheckMate-9LA were used to estimate the expected dose. The mean patient weight was estimated as 72.33 kg (based on a cohort of 29.9% female, and a mean weight of 75.43kg for males and 65.06kg for females). The body surface area was estimated as 1.847 m^2, based on the mean patient weight and mean patient height (171.50 cm), calculated with the Du Bois formula.[46]

Table 48 Drug acquisition costs and dosing schedules

Treatment	Dose per vial / pack (mg)	Cost per vial / pack	Dose per administration	Frequency of administration (days)
Nivolumab	40	£439.00	360 mg	21
	100	£1,097.00		
Ipilimumab	50	£3,750.00	1 mg/kg	42
	200	£15,000.00		
Pembrolizumab	100	£2,630.00	200 mg	21
	50	£1,315.00		
Cisplatin	10	£2.64	75 mg/m^2	21
	50	£4.12		
	100	£6.66		
Carboplatin	50	£3.75	400 mg/m^2	21
	150	£11.14		
	450	£27.90		
	600	£28.22		
Pemetrexed	100	£150.00	500 mg/m^2	21
	500	£450.00		
Docetaxel	20	£4.61	75 mg/m^2	21
	80	£12.50		
Paclitaxel	30	£4.69	200 mg/m^2	21
	100	£23.06		

Treatment	Dose per vial / pack (mg)	Cost per vial / pack	Dose per administration	Frequency of administration (days)
	300	£39.32		
Bevacizumab	100	£242.66	15 mg/m^2	21
	400	£924.40		
Atezolizumab	1,200	£3,807.69	1,200 mg	21

The number of vials required for each dose administration was estimated from the licensed dose presented in Table 48. It was assumed that vial sharing between patients would not occur when estimating the number of vials required for each administration. The mean relative dose intensity was incorporated in the model to reflect the extent of exposure to study treatment observed in the clinical trials of each treatment, and was applied to the number of vials required per dose, as described above. Relative dose intensities for comparator treatments were taken from previous NICE submissions. [19, 44] They were not applied to paclitaxel or carboplatin in the atezolizumab arm. Relative dose intensities were not applied to second-line therapies.

Table 49 Relative dose intensity

Treatment	Relative dose intensity
Nivolumab	[redacted]
Ipilimumab	[redacted]
Cisplatin (nivolumab + ipilimumab + limited PDC arm)	[redacted]
Carboplatin cisplatin (nivolumab + ipilimumab + limited PDC arm)	[redacted]
Paclitaxel cisplatin (nivolumab + ipilimumab + limited PDC arm)	[redacted]
Pemetrexed cisplatin (nivolumab + ipilimumab + limited PDC arm)	[redacted]
Cisplatin (PDC arm)	[redacted]
Carboplatin (PDC arm)	[redacted]
Paclitaxel (PDC arm)	[redacted]
Pemetrexed (PDC arm)	[redacted]
Pembrolizumab	99.21%
Atezolizumab	94.00%
Bevacizumab	93.80%

ERG comment

Relative dose intensity was applied to the drug acquisition costs, after this had been estimated from the required number of vials that was based on the licensed treatment dose. However, it is more appropriate to apply the relative dose intensity to the expected required treatment dose, and then

estimate the associated number of vial units and treatment costs from the adjusted expected dose. In some cases, the licensed treatment dose adjusted by relative dose intensity would not result in a reduced number of required vials and a reduction in dose will not result in a reduction in costs: in this case, the model will underestimate drug acquisition costs.

The model applies drug acquisition costs according to their associated treatment schedule (i.e. so these costs only occur in Week 0, Week 3, Week 6 of the model etc). However, the majority of patients have at least one dose that is delayed (57.8%, CSR page 173), so in combination with the DOT curve, this may underestimate drug costs. Furthermore, drug costs were estimated from the half-cycle corrected DOT curve, while they should be estimated from the proportion of patients on treatment at the start of the cycle.

4.2.8.2 Administration

Combination administrations were costed as a complex parenteral chemotherapy administration (£259.08), applied within the nivolumab + ipilimumab + limited PDC, PDC, and atezolizumab + bevacizumab + PDC arms. Monotherapy administrations were costed as a simple parenteral chemotherapy administration (£183.54), applied within the pembrolizumab monotherapy arm and for pemetrexed maintenance therapy within the PDC arm. Unit costs were obtained from NHS Reference Costs. [64]

All second-line therapies were assumed be administered as a simple parenteral chemotherapy administration.

ERG comment

The model appeared to be incorrectly estimating the administration cost within the PDC arm, whereby only a third of the unit cost was applied.

By using the complex parenteral chemotherapy administration cost for all treatment procedures in the nivolumab + ipilimumab + limited PDC arm, the model may be slightly overestimating the administration costs in this arm. Since nivolumab and ipilimumab have different treatment schedules, there are some cycles where only nivolumab would be administered, and it may be more appropriate to apply the simple parenteral chemotherapy administration unit cost.

Unit costs of administration in previous appraisals of first-line treatments for NSCLC were somewhat higher than those used in this appraisal. In the technology appraisal of atezolizumab (TA584), the administration cost of atezolizumab + bevacizumab + PDC was assumed to be that of a day case rather than an outpatient. The higher cost of "Deliver Complex Chemotherapy, including Prolonged

Infusional Treatment" is considered more appropriate for doses including paclitaxel as it requires a pre-medication to be given in advance of treatment and is administered as a 3-hour infusion time.

4.2.8.3 Subsequent therapy

The company's economic model included a subsequent line of therapy for patients who discontinued their first-line therapy. The proportion of patients receiving subsequent systemic therapy in the model was 31% for nivolumab + ipilimumab + limited PDC, and 40% for PDC, as reported in CheckMate-9LA.The proportion of patients receiving subsequent treatment after first-line treatment with pembrolizumab and atezolizumab + bevacizumab + PDC was assumed to be the same as nivolumab + ipilimumab + limited PDC.

The CheckMate-9LA trial collected data on subsequent therapies for patients initially receiving nivolumab + ipilimumab + PDC; however, these data were not used in the company base case. The ERG considers this appropriate as they were not in line with current UK practice, with 17% of the trial participants on nivolumab receiving subsequent therapy received an immunotherapy and 16% received a targeted therapy (CSR page 67).

As assumed in previous technology appraisals, patients receiving immunotherapy first line who receive subsequent therapy were assumed to receive docetaxel. This is reflective of UK clinical practice and in line with the second-line marketing authorisation of cancer immunotherapies. The company assumed that patients initially treated with PDC are subsequently treated with an immunotherapy monotherapy or docetaxel. The distribution of therapies after discontinuation of PDC was based on those accepted in previous NICE appraisals (TA584, TA600). The duration of subsequent therapies was those used in the previous appraisal of atezolizumab that took the duration of each subsequent immunotherapy from the appraisal in its second-line indication.

Table 50 Subsequent therapies after discontinuation

Drug	NIVO + IPI + limited PDC	PDC	Pembro	Atezo + bev + PDC	Average treatment duration (weeks)	Total treatment cost
Receiving subsequent therapy						
Proportion	31%	40%	31%	31%	-	-
Distribution of subsequent therapies						
Nivolumab [2]	-	34%	-	-	26.52	£20,807
Pembrolizumab	-	34%	-	-	21.59	£37,856
Atezolizumab	-	17%	-	-	35.80	£45,441
Docetaxel	100%	15%	100%	100%	18 [1]	£114.98

[1] Applied as 13.1 weeks in the model. [2] Posology in the company analysis was 3 mg/kg every two weeks.

Second-line treatment costs were applied as one-off costs at the point of disease progression of first-line therapy, rather than after discontinuation.

ERG comment

The proportion on subsequent treatment may be underestimated

The ERG notes that the 31% used for modelling subsequent therapies in the nivolumab + ipilimumab + limited PDC arm is likely an underestimation. At the most recent database lock of CheckMate-9LA, the CSR states approximately [redacted] of nivolumab patients and [redacted] of PDC patients remained on their first-line treatment (page 6 CSR). Therefore, once the data mature it is likely that the proportion of subsequent therapy after nivolumab will increase. The proportion receiving subsequent therapy after nivolumab and after PDC is higher in CheckMate-227 ([redacted] and [redacted], respectively). Therefore, the proportion of subsequent therapy is inconsistent with the data used to predict survival in the long-term.

[redacted] Further database locks are planned for CheckMate-227 which provides supporting evidence in this population and currently has up to 3-years follow-up. In lieu of this information, the ERG implements a scenario in which 40% of the nivolumab + ipilimumab + limited PDC arm receive a subsequent anticancer therapy to align with the proportion in the PDC arm. The impact on the company's base case ICER can be seen in Section 6.2.

The economic models do not capture the benefits of subsequent treatments appropriately

The ERG noted that the rates at which patients receive subsequent therapy in CheckMate-9LA and in CheckMate-227 is somewhat lower than those used in previous appraisals. In the appraisal of atezolizumab (TA584) and pembrolizumab in combination with chemotherapy (TA600), clinical experts advised that 50% of people would have immunotherapy after disease progression on PDC.

A scenario increasing the proportion of second-line treatments in the PDC arm of the model to reflect NHS clinical practice will result in increased costs but will not capture the associated benefits on survival, with the use of CheckMate-9LA and CheckMate-227 to estimate survival.

The distribution of subsequent treatments in the economic model does not reflect current NHS clinical practice.

Docetaxel was not considered to be an appropriate second-line therapy after PDC to be included in the analysis. Clinical experts for previous appraisals confirmed that, after chemotherapy, patients would have an immunotherapy monotherapy if they are well enough for subsequent treatment.

During the time that the ERG prepared their report, nivolumab for previously treated NSCLC transitioned from the Cancer Drugs Fund and was recommended by NICE for routine commissioning.[65] Given the recency of this development, the distribution between the three immunotherapies in clinical practice is unclear. The recommended posology of nivolumab after the CDF re-appraisal was updated to be 240 mg every two weeks. The PAS that was applied in the model to second-line nivolumab was agreed as part of the appraisal process for previously treated NSCLC ([redacted]).[65]

Further, the relative split between each immunotherapy may differ according to patient subgroup. The Cancer Drugs Fund clinical lead for the appraisal of pembrolizumab in combination with chemotherapy (TA600) stated that for people whose tumours express PD-L1 with a tumour proportion score lower than 50% and who are fit enough for second-line treatment with an immunotherapy, atezolizumab is given more often than pembrolizumab in current NHS practice (about 75% and 25% respectively).

Subsequent PDC

The CS states that one of the benefits of providing limited PDC in combination with nivolumab and ipilimumab is that it may preserve additional PDC as a future treatment option (page 14, CS). In CheckMate-9LA, of those who received subsequent systemic therapy after nivolumab, 58% received carboplatin or cisplatin (64/111). The company presented a scenario assuming that 50% of patients receiving subsequent therapy receive PDC and 50% receive docetaxel, and it made little difference to the ICER. Still, it remains unclear on whether patients would take PDC following discontinuation of nivolumab, since it is not given after other immunotherapies that do not include a PDC element, such as pembrolizumab monotherapy.

4.2.8.4 Health state costs

The health state costs in the model include monitoring and disease management costs. The total cost per 4-week cycle in the PFS health state is £139.86 and for the PD state is £392.78. The main source of resource utilisation per health state used in this submission is a published NIHR HTA study by Brown (2013), which were also used in previous NICE appraisals[19, 22, 42, 44, 45] of treatments for NSCLC. Unit costs were obtained from a previous nice appraisal (TA531).[44] The mean costs associated with being progression-free or having progressed disease are assumed to be the same across all treatment options.

Table 51 Summary of health state costs

Items	Frequency (per annum)	Unit cost
Progression free		
Outpatient visit	9.61	£142.58

Items	Frequency (per annum)	Unit cost
Chest radiography	6.79	£28.36
CT scan (chest)	0.62	£103.61
CT scan (other)	0.36	£115.19
Electrocardiogram	1.04	£143.86
4-week cost in progression-free health state		**£139.86**
Progressed		
Outpatient visit	7.91	£142.58
Chest radiography	6.5	£28.36
CT scan (chest)	0.24	£103.61
CT scan (other)	0.42	£115.19
Electrocardiogram	0.88	£143.86
General practitioner home visit	26.09	£89.76
Therapist visit	26.09	£48.00
4-week cost in progressed health state		**£392.78**

ERG comment

The costs applied by the company were generally consistent with previous appraisals, however community nurse visit, clinical nurse specialist and GP surgery visit costs, which were used in TA531, TA584 and TA600, and in Brown (2013),[37] were excluded in this appraisal for unknown reasons.

4.2.8.5 Terminal care costs

A one-off cost relating to terminal care was applied to patients at the moment of dying, and was reported as being estimated as £5,377.51 per patient. The total cost for end-of-life care reflected treatment received in various care settings, and included community nurse visits, GP home visits, Macmillan nurses, drugs and equipment, terminal care in hospital and terminal care in hospice. Unit costs and resource consumption were consistent with those used in previous NICE appraisals of treatments for NSCLC[16, 19, 22, 42, 44, 45, 66] and a published NIHR HTA study by Brown (2013).[37]

Table 52 Unit costs of terminal care patients (adapted from Table 67, CS)

Item	Unit cost	Proportion of patients	Consumption	Reference
Community nurse visit	£131	27%	28.00 hours	Curtis [67]
GP home visit	£89.76	27%	7.00 visits	Curtis [67]

Item	Unit cost	Proportion of patients	Consumption	Reference
Macmillan nurse	£87.38	27%	50.00 hours	National Institute for Health and Care Excellence [20]
Drugs and equipment	£283.16	27%	Average drug and equipment usage	Brown, Pilkington [37]
Terminal care in hospital	£3,833.61	56%	1 episode (9.66 days)	National Institute for Health and Care Excellence [20]
Terminal care in hospice	£4,792.01	17%	1 episode (9.66 days)	National Institute for Health and Care Excellence [20]
Weighted total cost for end-of-life care	**£5,377.51**			

ERG comment

There was a minor discrepancy with the value reported in the CS, and the value applied in the model (£4946.46), where it appears that the cost in Table 52 was assumed to apply for a month and was converted to 28 days. It was unclear why the company made this adjustment and it would seem that is not necessary. As stated by Brown (2013), the resource use for terminal care pertained to a 14-day period. [ref]

It was not clear how costs were inflated to present values, as the inflation index used was not reported.

4.2.8.6 AE management costs

Costs of the management of AEs were taken from previous NICE technology appraisals [21, 37, 44, 64] and inflated to the current price year. Total costs of treating AEs were estimated by multiplying the event rate (Table 47) with the associated unit cost, and applied in the first cycle of the model.

The total cost of treating each AE in each arm was £287 for nivolumab combination therapy, £492 for PDC, £43 for pembrolizumab monotherapy, and £1,045 for atezolizumab combination therapy.

ERG comment

The approach taken by the company for estimating health care resources and costs is in line with previous NICE technology appraisals for NSCLC, although the resource use estimates used in the model are from outdated sources and need updating. It was not clear on how costs were inflated to present values, as the inflation index used was not reported.

As discussed in Section 4.2.6.4, there are some concerns that the full AE impact on costs is not captured, due to the exclusion of immune-related adverse events, and adverse events relating to second-line therapy.

The adverse events for the PDC arm were based on those in the CheckMate-9LA trial. The regimen used for patients of squamous histology was paclitaxel plus carboplatin, however gemcitabine is more commonly used in NHS practice. There also may be implications to AE costs if the safety profiles between the different chemotherapy regimens differ.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

This section summarises the results presented in the CS. It should be noted that the model contains several errors; the model results incorporating the corrections of these errors are presented as part of the ERG's exploratory analyses in Section 6. The impact of these errors on the results is small. The results include the confidential PAS discounts for nivolumab and bevacizumab: results with the PAS discounts for pembrolizumab, atezolizumab, bevacizumab and pemetrexed are provided in a confidential appendix separate to this report.

Deterministic results

The company presented pairwise ICERs for nivolumab + ipilimumab + limited PDC versus each of the comparators, including PDC, pembrolizumab monotherapy, and atezolizumab + bevacizumab + PDC (Tables 71-73, pg. 153, CS). The ERG considers it more appropriate to include all options within a fully incremental analysis, and requested that the company present these results at the clarification stage.

The comparison with pembrolizumab monotherapy is presented in Table 53 and the comparison with atezolizumab + bevacizumab + PDC is presented in Table 54. However, there are inconsistencies between the pairwise results presented in the CS and the fully incremental analysis provided by the company at the clarification stage as a result of an error introduced to the model when it was updated by the company. The results presented in this section reflect those provided by the company at the clarification stage.

LYG presented by the company were discounted at a rate of 3.5%.

Compared with PDC, nivolumab + ipilimumab generated [redacted] incremental QALYs, and had higher total lifetime costs. The ICER was £29,139 per QALY gained.

Compared with pembrolizumab monotherapy and with atezolizumab + bevacizumab + PDC, nivolumab + ipilimumab + limited PDC was dominant, as it generated higher QALYs and had lower total lifetime costs.

Table 53 Company base-case results: fully incremental vs. pembrolizumab

Technologies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER incremental (£/QALY)
PDC	[redacted]	[redacted]	[redacted]	-	-	-	-

Technologies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER incremental (£/QALY)
NIVO + IPI + limited PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29,133
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality-adjusted life-year
[1] Discounted LYG are presented by the company

Table 54 Company base-case results: fully incremental vs. atezolizumab + bevacizumab + carboplatin + paclitaxel

Technologies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER incremental (£/QALY)
PDC	[redacted]	[redacted]	[redacted]	-	-	-	-
NIVO + IPI + limited PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29,133
ATEZO + BEV + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality-adjusted life-year.
[1] Discounted LYG are presented by the company
[3] Correct incremental cost presented in the table. Value presented by the company was an error.

Probabilistic results

Probabilistic results were similar to deterministic results for nivolumab + ipilimumab + limited PDC and for PDC. However, the number of QALYs produced by the probabilistic analysis for pembrolizumab monotherapy and for atezolizumab + bevacizumab + PDC were higher than those estimated by the deterministic analysis. The company stated that the uncertainty in the ICER appeared to be driven by the variation in treatment efficacy, resource utilisation, body weight, and utility weights, as these had a high impact on the results of the model.

Figure 20 and Figure 21 present the CEACs for the fully incremental analyses of nivolumab + ipilimumab + limited PDC, PDC and pembrolizumab monotherapy, and nivolumab + ipilimumab + limited PDC, PDC and atezolizumab + bevacizumab + PDC. In the comparison with pembrolizumab, nivolumab + ipilimumab + limited PDC had a probability of being cost-effective greater than 50% from willingness-to-pay thresholds above £31,000 per QALY. In the comparison with atezolizumab + bevacizumab + PDC, nivolumab + ipilimumab + limited PDC had the greatest probability of being cost-effective from willingness-to-pay thresholds above £29,000 per QALY.

Figure 20. Cost-effectiveness acceptability curve for nivolumab + ipilimumab + limited PDC, PDC and pembrolizumab (generated from company model)

Figure 21. Cost-effectiveness acceptability curve for nivolumab + ipilimumab + limited PDC, PDC and atezolizumab + bevacizumab + PDC (generated from company model)

5.2 Company's additional analyses

Sensitivity analysis

In the deterministic sensitivity analysis, important parameters were changed with ± 20% to study the impact on the ICER. As the company did not vary each parameter within the limits of its confidence interval, the sensitivity analyses do not present the range of plausible ICERs for each parameter.

Figure 22, Figure 23 and Figure 24 present the results of the company's DSAs in the form of a tornado diagram for the pairwise comparisons of nivolumab + ipilimumab + limited PDC versus PDC, pembrolizumab monotherapy, and atezolizumab + bevacizumab + PDC.

Based on these analyses, the ICER is estimated to range from £28,070 to £30,294 per QALY gained. Across all the parameter ranges tested by the company, nivolumab + ipilimumab + limited PDC remained dominant compared with pembrolizumab, and with atezolizumab + bevacizumab + PDC.

These analyses suggest that the most influential model parameters are the average body weight, the utility value applied for patients who are ≥ 360 days from death and the discount rate for health outcomes.

Figure 22 Tornado diagram for the deterministic sensitivity analysis of nivolumab + ipilimumab versus PDC (replicated from CS, Figure 79, pg. 164)

Figure 23 Tornado diagram for the deterministic sensitivity analysis of nivolumab + ipilimumab versus pembrolizumab (replicated from CS, Figure 80, pg. 165)

Figure 24 Tornado diagram for the deterministic sensitivity analysis of nivolumab + ipilimumab versus atezolizumab + bevacizumab + PDC (replicated from CS, Figure 81, pg. 165)

Scenario analyses

Table 55 summarises the results of the company's scenario analyses for nivolumab + ipilimumab + limited PDC versus PDC. The use of CheckMate-9LA data only to extrapolate OS led to a substantial increase in the ICERs for all comparisons. In addition, the inclusion of a loss of treatment effect at 5 years leads to a moderate increase in the ICER. The table also shows that alternative scenarios regarding the modelling PFS and treatment-specific utility values have little impact on the model results.

Nivolumab + ipilimumab + limited PDC remains a dominant treatment option versus pembrolizumab and atezolizumab + bevacizumab + PDC across all scenarios. The results of these scenario analyses are provided in Tables 81 and 82 of the CS.

Table 55 Scenario analyses: nivolumab + ipilimumab + limited PDC versus PDC

Scenario		Base case assumption	Assumption in scenario	Incremental costs	Incremental QALYs	ICER
1	Base case	-	-	[redacted]	[redacted]	**29,139**
3	Switch to using CM-227 data for OS	13 months	18 months	[redacted]	[redacted]	31,903
4	Use CM-9LA data only for OS	CM-9LA and CM-227	CM-9LA: Log-logistic distribution for NIVO + IPI + limited PDC and PDC	[redacted]	[redacted]	47,643
5	Use CM-9LA data only for OS	CM-9LA and CM-227	CM-9LA: Spline on odds 1 knot distribution for NIVO + IPI + limited PDC and PDC	[redacted]	[redacted]	53,280
6	Use CM-9LA data only for PFS	CM-9LA and CM-227	CM-9LA: Spline on odds 2 knots distribution for NIVO + IPI + limited PDC and PDC	[redacted]	[redacted]	30,587
7	Utilities	Time-to-death approach, pooled	Progression-based utilities	[redacted]	[redacted]	32,150
8	Utilities	Time-to-death approach, pooled	Time-to-death approach, treatment-specific	[redacted]	[redacted]	30,133
9	DOT	TTD KM for CM-9LA comparators, PFS as proxy for others	PFS as proxy for all comparators: Spline on odds 2 knots distribution for NIVO + IPI + limited PDC and PDC PFS	[redacted]	[redacted]	33,344
10	Duration of treatment effect	Lifetime	3 years after end of IO therapy	[redacted]	[redacted]	35,149

Subgroup analyses

The company did not present any subgroup analyses.

5.3 Model validation and face validity check

Company validation of the economic analysis

The CS stated that the predictions from the model were compared against relevant external data sources to ensure that they are clinically plausible (B.3.10.1). The company's validation of survival predictions was discussed in Section 4.2.6.

The CS also states that the model approach and inputs were validated at an advisory workshop attended by two UK health economists and one UK clinician. According to the CS, the discussions focused on the model structure, the comparator and subsequent treatments for NSCLC in the second-line setting, resource use and costs. Additionally, clinical experts reviewed the survival curves for the best-fitting models for OS for nivolumab + ipilimumab + limited PDC, and identified those that they considered to be clinically plausible as well as those that they considered were too optimistic or pessimistic.

ERG validation of the company model

The ERG adopted a number of approaches to critically appraise the company's submitted economic analyses and the underlying health economic model upon which this was based. These included:

- Consideration of key items contained within published economic evaluation and health economic modelling checklists.
- Scrutiny of the company's model by health economic modellers and discussion of issues identified amongst the members of the ERG.
- Double-programming of the deterministic version of the company's model to fully assess the logic of the company's model structure, to draw out any unwritten assumptions and to identify any apparent errors in the implementation of the model.
- Examination of the correspondence between the description of the model reported in the CS and the company's executable model.
- Replication of the base case results, PSA, DSAs and scenario analyses presented within the CS.
- Checking of parameter values used in the company's model against their original data sources.
- The use of expert clinical input to judge the credibility of the company's economic evaluation and the assumptions underpinning the model.

During the process of validating the model, the ERG identified the following errors in the company's submitted model:

(a) **Correction of health state utility values**: The model was amended so that the utility value for the 5-26 weeks to death health state was [redacted] rather than zero.
(b) **PDC administration cost:** The company's cost calculations were amended so that they did not erroneously divide the unit cost by three.
(c) **Amendment of AE rates:** The rates of AEs in the model were updated to reflect the rates presented in the CSR (Table 11, pg. 26).

(d) **Consistency of application of half-cycle correction:** The model was amended so that this is now also applied in the first cycle of the model.

These errors were corrected by the ERG, and a revised model supplied to the company with altered cells highlighted to aid verification. These corrections did not impact substantively on the model's predictions. Revised results are presented in Section 6.

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 ERG approach to the decision problem

As has been previously described, the ERG considers there to be three distinct decision problems based on histology and PD-L1 expression. This is driven by the in-scope comparators, which differ according to histology and PD-L1 expression (see Table 12, Section 3.2.4.2). The three decision problems are:

1. Squamous, PD-L1 < 50%
2. Non-squamous, PD-L1 <50%
3. Mixed histology, PD-L1 ≥50%

These decision problems seem to be a deviation from the company's approach to the decision problem but they do align with the company's fully-incremental results. The company base case results for decision problem 2 are identical to the results for nivolumab + ipilimumab + limited PDC vs. atezolizumab + bevacizumab + PDC. Likewise, the company's base case results for decision problem 3 are identical to the nivolumab + ipilimumab + limited PDC vs. pembrolizumab results. However, the ERG considers the distinction of the three decisions outlined above to be appropriate due to the differing in-scope comparators. In addition, heterogeneity in treatment effects according to histology and PD-L1 expression can be explored using the ERG-defined decisions.

The company base case results for each of the three decision problems can be seen below. The ERG presents the deterministic and probabilistic results, in addition to the CEACs for each decision problem. All exploratory ERG analyses conducted in Section 6.2 are based on the three ERG-defined decision problems.

6.1.1 Squamous, PD-L1 < 50%

Table 56 Company base case results - Squamous, PD-L1 < 50%

	Total costs	Total QALYs	ICER
Deterministic results			
Platinum doublet chemo	[redacted]	[redacted]	-
Nivolumab + ipilimumab combined with PDC	[redacted]	[redacted]	£29,279
Probabilistic results			
Platinum doublet chemo	[redacted]	[redacted]	-
Nivolumab + ipilimumab combined with PDC	[redacted]	[redacted]	£29,130

ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality adjusted life years; PDC, platinum doublet chemotherapy

Figure 25 CEAC - Squamous, PD-L1 < 50%

6.1.2 Non-squamous, PD-L1 < 50%

Table 57 Company base case results – Non-squamous, PD-L1 < 50%

	Total costs	Total QALYs	ICER
Deterministic results			
Platinum doublet chemo	[redacted]	[redacted]	-
Nivolumab + ipilimumab combined with PDC	[redacted]	[redacted]	£29,279
Atezolizumab + bevacizumab + carboplatin + paclitaxel	[redacted]	[redacted]	Dominated
Probabilistic results			
Platinum doublet chemo	[redacted]	[redacted]	-
Nivolumab + ipilimumab combined with PDC	[redacted]	[redacted]	£29,130
Atezolizumab + bevacizumab + carboplatin + paclitaxel	[redacted]	[redacted]	Dominated

ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality adjusted life years; PDC, platinum doublet chemotherapy

Figure 26 CEAC - Squamous, PD-L1 < 50%

6.1.3 Mixed histology, PD-L1 ≥ 50%

Table 58 Company base case results – Mixed histology, PD-L1 ≥ 50%

	Total costs	Total QALYs	ICER
Deterministic results			
Platinum doublet chemo	[redacted]	[redacted]	-
Nivolumab + ipilimumab combined with PDC	[redacted]	[redacted]	£29,133
Pembrolizumab monotherapy	[redacted]	[redacted]	Dominated
Probabilistic results			
Platinum doublet chemo	[redacted]	[redacted]	-
Nivolumab + ipilimumab combined with PDC	[redacted]	[redacted]	£28,326
Pembrolizumab monotherapy	[redacted]	[redacted]	Dominated

ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality adjusted life years; PDC, platinum doublet chemotherapy

Figure 27 CEAC - Mixed histology, PD-L1 ≥50%

6.2 Exploratory analyses undertaken by the ERG

The ERG conducted the following exploratory analyses for patients with untreated NSCLC.

1) Composition of PDC

This exploratory analysis considers two issues with the modelling of treatment costs of PDC. Firstly, the company's approach to modelling treatment costs in the PDC arm is to use the proportions on each chemotherapy in CheckMate-9LA (i.e. the all-comer population) and applying this average to all populations. There are different recommended PDC regimens according to histology: those with squamous tumours receive chemotherapy and a platinum compound, and those with non-squamous tumours receive either chemotherapy or pemetrexed, and a platinum compound, with a proportion of those receiving pemetrexed eligible for pemetrexed maintenance therapy.

Secondly, the modelled PDC regimens failed to include agents routinely used in NHS clinical practice and listed in the scope (see Section 4.2.4). One of these, gemcitabine, is the most commonly used in clinical practice; paclitaxel, the treatment costed in the company's analysis, is rarely used in the NHS.

In an exploratory analysis, a subgroup-specific distribution of PDC agents and proportion receiving maintenance therapy was applied in the model. Patients receiving chemotherapy were assumed to receive gemcitabine, and the distribution of agents was based on estimates of market share for each

population previously reported in appraisals of first-line NSCLC.[5, 42] The values applied in the model are summarised in Table 62.

Table 59. Distribution of PDC

PDC regimen	Squamous histology	Non-squamous histology	Mixed histology
Gemcitabine + carboplatin	69%	3.3%	[redacted]
Gemcitabine + cisplatin	31%	19%	[redacted]
Pemetrexed + carboplatin	0%	33.90%	[redacted]
Pemetrexed + cisplatin	0%	43.90%	[redacted]
Pemetrexed maintenance therapy	0%	[redacted]	[redacted]

Note, for squamous histology these interventions are compared to PDC; for non-squamous histology these interventions are compared to PDC and atezolizumab + ipilimumab + PDC; and for mixed-histology these interventions are compared to pembrolizumab.

2) Sub-population specific OS and PFS

As detailed in Section 3.2.2, it is assumed that histology and PD-L1 expression are not treatment effect modifiers. Survival curves for nivolumab + ipilimumab + limited PDC and for PDC were estimated from data for the all-comer (ITT) population in CheckMate-9LA and CheckMate-227. The company's base case economic analysis relied on this assumption and used the all-comer population from the two trials. However, subgroup-specific survival curves for nivolumab + ipilimumab + limited PDC and PDC may be more appropriate in comparisons to pembrolizumab and atezolizumab, which have histology-based and PD-L1-based marketing authorisations. Following clinical advice, the ERG considered there may be differences in absolute survival effects between each histology- and PD-L1-based subgroup (Section 3.2.4.2).

At the clarification stage, the ERG requested that the company stratify the CheckMate-9LA data based on the three populations of interest: *i)* squamous histology and PD-L1 < 50%; *ii)* non-squamous histology and PD-L1 < 50; *iii)* mixed histology, PD-L1 ≥ 50%. The company also fit survival curves for both treatment arms in CheckMate-227 data based on the three populations. These are currently in the process of being clinically validated by the company, and further analysis may be undertaken at the technical engagement stage, if required.

Despite the lack of validation, the ERG presents the trial results stratified by histology and PD-L1 expression to match the three decision problems defined above. The approach uses the company's base case hybrid approach, i.e. switching from the CheckMate-9LA Kaplan-Meier data to the parametric model fit to CheckMate-227 at 13 months. The company presented the AIC and BIC for the parametric models as part of their PFC response. However, the ERG cautions against an over reliance on model fit based on the fact that the first 13 months are from a different trial (i.e. CheckMate-9LA). For this reason, along with the fact that results are yet to be clinically validated by

the company, the ERG presents the results of this scenario using the company base case preferred models as fit to the all-comer population. These are:

- OS, nivolumab + ipilimumab + limited PDC: ***spline on normal, 2 knots***
- OS, PDC: ***log logistic***
- PFS, nivolumab + ipilimumab + limited PDC: ***spline on odds, 2 knots***
- PFS, PDC: ***spline on normal, 2 knots***

The sub-population specific landmark OS and PFS, compared to the company's base case results in the all-comer population, can be seen in Table 60 and Table 61, respectively.

Table 60 Histology and PD-L1 expression sub-population landmark OS

	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 5 (%)	Year 10 (%)
NIVO + IPI + limited PDC					
All comer (company preferred)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SQ, PD-L1 >50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NSQ, PD-L1 >50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MH, PD-L1 ≥50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PDC					
All comer (company preferred)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SQ, PD-L1 >50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NSQ, PD-L1 >50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MH, PD-L1 ≥50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

MH, mixed histology; NIVO + IPI + limited PDC, nivolumab + ipilimumab + limited PDC; NSQ, non-squamous; SQ, squamous

Table 61 Histology and PD-L1 expression sub-population landmark PFS

	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 5 (%)	Year 10 (%)
NIVO + IPI + limited PDC					
All comer (company preferred)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SQ, PD-L1 >50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NSQ, PD-L1 >50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MH, PD-L1 ≥50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PDC					
All comer (company preferred)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SQ, PD-L1 >50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NSQ, PD-L1 >50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MH, PD-L1 ≥50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

MH, mixed histology; NIVO + IPI + limited PDC, nivolumab + ipilimumab + limited PDC; NSQ, non-squamous; SQ, squamous

Note, this scenario also utilises subgroup specific observed DOT curves to model the DOT for nivolumab + ipilimumab + limited PDC and PDC.

3) Inclusion of CheckMate-227 in the FPNMA

The company's base case FPNMA used the all-comer data from CheckMate-9LA. The ERG wished to explore whether histology and PD-L1 expression were predictors of relative effect and requested the company provide an updated FPNMA using subgroup-specific data from CheckMate-9LA to inform the network. In their response, the company provided two updated networks that also included data from CheckMate-227: i) Based on PD-L1 ≥ 50 and mixed histology for pembrolizumab-containing trials and all-comers for nivolumab trials; ii) Based on PD-L1 < 50 and non-squamous histology.

As such, it is not possible to disentangle the two issues of whether CheckMate-227 should be included in the network and whether subgroup-specific data should be included in the network. Further, it is only possible to explore the impact of subgroup-specific data for the network including atezolizumab. The company provide only one form of FPNMA for the new network, and all forms are in the process of being validated by the company. Despite this, the ERG considers the inclusion of CheckMate-227 in the NMA to be preferred and presents a scenario demonstrating the impact on the ICER.

The impact on the ICER of the alternative models from the CheckMate-9LA only networks are not considered. This is both due to the ERG's preference for the networks including CheckMate-227, and the fact that the only alternative model available for selection in the mixed histology, PD-L1 ≥ 50% network, produces *'clinically implausible results*.'

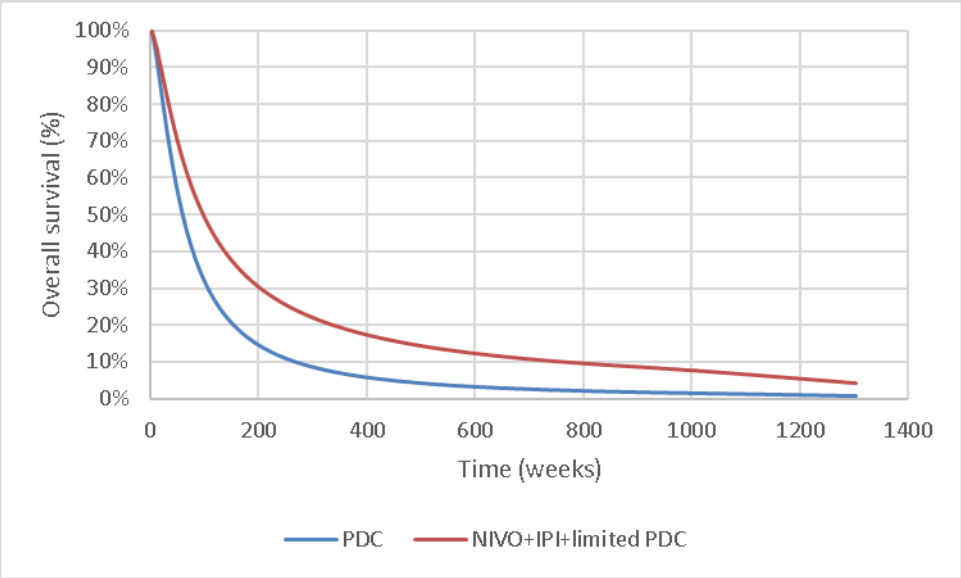
As the updated networks have yet to be validated, no alternative network results have been implemented as scenario analyses. The ERG welcomes the validation of the model results and the inclusion of alternative models in the economic model to explore the impact on the company's and ERG's base case ICERs.

4) Appropriate baseline survival curve for PDC

As described in Section 4.2.6.1, the ERG considers the PDC arm in CheckMate-227 to better reflect the expected OS for patients in the NHS. The use of subsequent therapy in CheckMate-227 is more representative of NHS practice, meaning CheckMate-9LA may underestimate survival in the PDC arm. This approach also avoids the need to switch between data sets, as in the hybrid approach. However, CheckMate-227 cannot be used to represent nivolumab + ipilimumab + limited PDC as the initial part of the curve won't capture the impact of limited PDC. In addition, it is preferable not to compare PDC from CheckMate-227 with nivolumab + ipilimumab + limited PDC from CheckMate-9LA/CheckMate-227 as this then compares two different populations naively at the beginning.

This scenario is implemented by using the CheckMate-227 data only for the PDC arm and relative effects from the FPNMA (which captures changing hazard over time) including CheckMate-227. Overall survival over time in this scenario is presented in Figure 28.

Figure 28. Overall survival for PDC (using CheckMate-227 data) and NIVO+IPI+limited PDC (using relative treatment effects from FPNMA)



5) PFS model selection

In Section 4.2.6.2, the ERG discussed inconsistency in the company's approach to PFS model selection (i.e. model fit and plausible survival prediction) and the subsequently chosen model.

For nivolumab + ipilimumab + limited PDC, the company chose the second-best fitting model (2 knots spline on odds) despite the best fitting model (2 knots spline on hazards) having a 5-year PFS prediction closer to the company's own 5-year survival prediction using their own constructed curve. In addition, the company detailed their approach to be 'conservative', whereas the best fitting model is more conservative.

For the PDC arm, the company again outlined the maturity of the PFS data used for the PDC arm and therefore based model selection on model fit alone. The ERG notes the company actually selected the second-best fitting model (2 knots spline on normal) rather than the best fitting (2 knots spline on hazards).

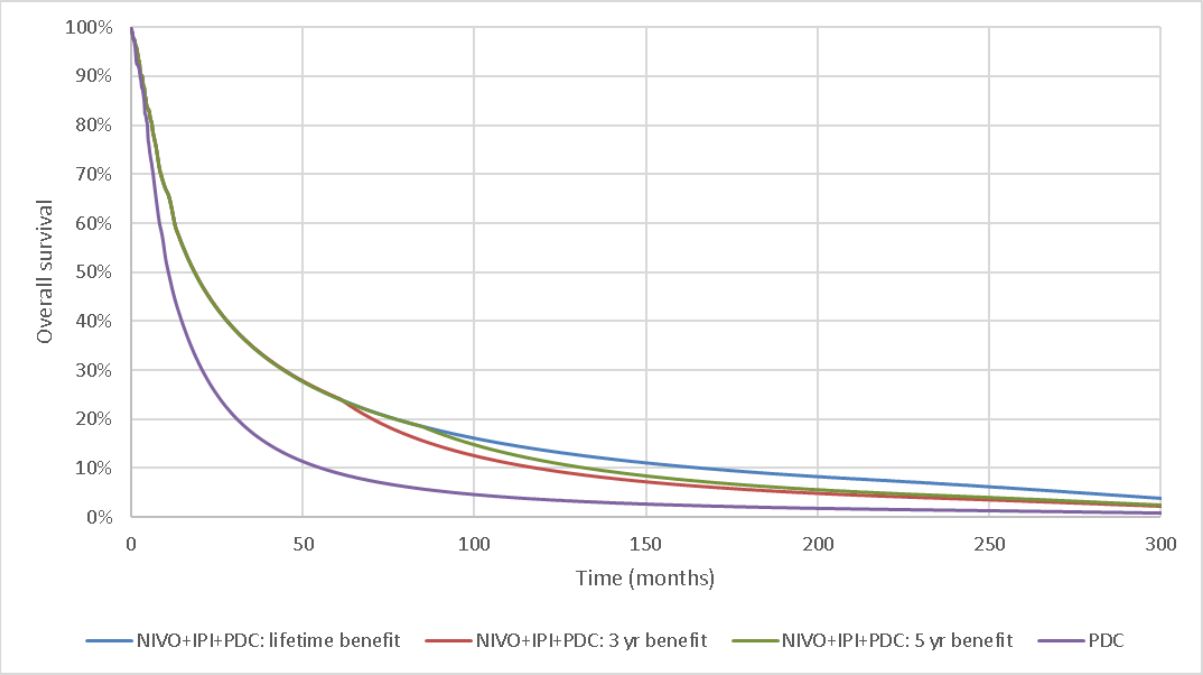
The ERG does caution against over reliance on model fit, however the ERG deems it reasonable to use the best fitting models for the PFS data based on the company's justification described above. The scenario analyses presented in this section use a) spline on hazards, 2 knot model for nivolumab + ipilimumab + limited PDC, and b) spline on hazards, 2 knot model for PDC.

6) Duration of survival benefit

The company's survival analysis of nivolumab assumed a lifetime benefit of treatment that extended beyond discontinuation. As detailed in Section 4.2.6.1, there is not currently the evidence to support such a strong assumption, and previous appraisals of first-line treatments of NSCLC have preferred to model a shorter duration of benefit. The scenario analyses presented in this section assume *a)* a three-year benefit, and *b)* a five-year benefit after discontinuation.

After the treatment effect of nivolumab is assumed to cease, the model reverts to using the per-cycle hazard rate in the PDC arm. Figure 29 presents the survival of nivolumab + ipilimumab + limited PDC, assuming different durations of treatment benefit, compared with the survival of PDC.

Figure 29 Overall survival with different durations of treatment benefit for nivolumab



As detailed in Section 4.2.6.3, the ERG considers the company's approach to modelling DOT for each intervention by using observed DOT curves for nivolumab + ipilimumab + limited PDC and PDC, and PFS curves for atezolizumab + bevacizumab + PDC and pembrolizumab to be inconsistent. Following PFCs, the company extracted observed DOT curves for atezolizumab and bevacizumab from TA548 and used these to represent modelled DOT for these respective comparators. Observed DOT curves for pembrolizumab were not available therefore the PFS is retained in the model to represent DOT for pembrolizumab.

7) Progression-based utilities

As described in Section 4.2.7, in the base case analysis, utilities were based on the TTD model with no treatment effect, justified by the company on the basis that TTD utilities have been used and accepted in recent appraisals by NICE on first-line NSCLC (citing TA531, but also TA584). The company provided a scenario analysis using utility values based on progression status, and treatment-specific TTD.

8) Subsequent therapy: no docetaxel as a second line therapy after PDC

A described in Section 4.2.8.3, the ERG does not consider docetaxel to be a relevant subsequent therapy following PDC, as patients will receive an immunotherapy after discontinuation of first-line chemotherapy regimens. This scenario removes docetaxel from the subsequent therapies in the PDC arm.

9) CheckMate-227 to inform rates of subsequent therapy

Section 4.2.8.3 details the ERG preference for using CheckMate-227 as an alternative source of data to inform the rates at which patients receive subsequent therapy: 45.3% receive subsequent therapy after nivolumab + ipilimumab + limited PDC and the other immunotherapies, 60.7% receive subsequent therapy after PDC. The ERG considers these rates to be more aligned with those expected to receive subsequent therapy in UK clinical practice, and creates a consistency between the data source used to model OS after one year in the model. Therefore, this scenario explores the use of the CheckMate-227 subsequent therapy data.

10) Dose intensity

Relative dose intensity was inappropriately applied in the company model, as it was applied to the drug cost estimated from the required number of vials that was based on the licensed treatment dose. It is more appropriate to apply the relative dose intensity to the expected required treatment dose, and then estimate the associated number of vial units and treatment costs from the adjusted expected dose.

6.3 Impact on the ICER

In the analyses presented in this section, the PAS was applied for nivolumab and ipilimumab and the remainder of interventions were included at list price. Results with confidential PAS discounts for atezolizumab, bevacizumab, pembrolizumab and pemetrexed are provided in a confidential appendix to this report.

6.3.1 Squamous, PD-L1 < 50%

Table 62 ERG exploratory scenarios: Squamous, PD-L1 < 50%

Scenario	Interventions	Costs	QALYs	ICER	Change from company base case
Company base-case	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,133	-
Correction of errors	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,279	+£146
1) Composition of PDC	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£34,621	£5,487
2) Subgroup-specific survival modelling	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£52,528	+£23,394
3) FPNMA – include CM-227 *Note, not applicable as the FPNMA is used to generate results for comparators not included in CheckMate-9LA*	PDC	n/a	n/a	-	-
	NIVO + IPI + limited PDC	n/a	n/a	n/a	n/a
2 + 3) Sub groups specific + include CM-227 in the network *Note, not applicable as the FPNMA is used to generate results for comparators not included in CheckMate-9LA*	PDC	n/a	n/a	-	-
	NIVO + IPI + limited PDC	n/a	n/a	n/a	n/a
	PDC	[redacted]	[redacted]	-	

4) Outcomes for PDC based on CM-227, outcomes for other interventions are relative effects from FPNMA	NIVO + IPI + limited PDC	[redacted]	[redacted]	£31,442	+£2,308
5a) PFS model selection – NIVO + IPI + limited PDC	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,879	+£745
5b) PFS model selection - PDC	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,355	+£221
6a) Duration of survival benefit: 3 years	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£36,251	+£7,117
6b) Duration of survival benefit: 5 years	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£32,879	+£3,746
7) Duration of ATEZO+BEV+PDC based on DOT	PDC	n/a	n/a	-	-
	NIVO + IPI + limited PDC	n/a	n/a	n/a	n/a
8) Progression-based utilities	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£32,052	+£2,919
9) Subsequent therapy: no docetaxel as a second line therapy after PDC	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£27,774	-£1,360
10) CheckMate-227 to inform rates of subsequent therapy	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£24,890	-£4,244
11) Dose intensity adjustment	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,507	+£374
ERG base case: Error correction, 1, 5a, 5b, 6b, 8, 9, 10 & 11	**PDC**	[redacted]	[redacted]	**-**	**-**
	NIVO + IPI + limited PDC	[redacted]	[redacted]	**£36,915**	**+£7,782**

6.3.2 Non-squamous, PD-L1 < 50%

Table 63 ERG exploratory scenarios: Non-squamous, PD-L1 < 50%

Scenario	Interventions	Costs	QALYs	ICER	Change from company base case
Company base-case	PDC	[redacted]	[redacted]	-	
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,133	-
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	-
Correction of errors	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,279	+£146
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	-
1) Composition of PDC	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£34,916	£5,783
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	-
2) Subgroup-specific survival modelling	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£33,684	+£4,551
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	-
3) FPNMA – include CM-227	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,279	+£146
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	-
2 + 3) Sub groups specific + include CM-227 in the network	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£33,684	+£4,551
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	-
4) Outcomes for PDC based on CM-227, outcomes for other interventions are relative effects from FPNMA	PDC	[redacted]	[redacted]	-	
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£31,442	+£2,308
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	

5a) PFS model selection – NIVO + IPI + limited PDC	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,879	+£745
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	-
5b) PFS model selection - PDC	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,355	+£221
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	-
6a) Duration of survival benefit: 3 years	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£36,251	+£7,117
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	-
6b) Duration of survival benefit: 5 years	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£32,879	+£3,746
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	-
7) Duration of ATEZO+BEV+PDC based on DOT	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,279	+£146
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	-
8) Progression-based utilities	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£32,052	+£2,919
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	-
9) Subsequent therapy: no docetaxel as a second line therapy after PDC	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£27,774	-£1,360
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	-
10) CheckMate-227 to inform rates of subsequent therapy	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£24,890	-£4,244
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	-
11) Dose intensity adjustment	PDC	[redacted]	[redacted]	-	-

	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,507	£374
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	-
ERG base case: Error correction, 1, 3, 5a, 5b, 6b, 7, 8, 9, 10 & 11	**PDC**	[redacted]	[redacted]	**-**	**-**
	NIVO + IPI + limited PDC	[redacted]	[redacted]	**£37,420**	**+£8,286**
	ATEZO + BEV + PDC	[redacted]	[redacted]	**Dominated**	**-**

6.3.3 Mixed histology, PD-L1 ≥ 50%

Table 64 ERG exploratory scenarios: Mixed histology, PD-L1 ≥ 50%

Scenario	Interventions	Costs	QALYs	ICER	Change from company ICER
Company base-case	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,133	-
	PEMBRO	[redacted]	[redacted]	Dominated	-
Correction of errors	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,279	+£146
	PEMBRO	[redacted]	[redacted]	Dominated	-
1) Composition of PDC	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£34,824	£5,691
	PEMBRO	[redacted]	[redacted]	Dominated	-
2) Subgroup-specific survival modelling	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£27,460	-£1,674
	PEMBRO	[redacted]	[redacted]	Dominated	-
3) FPNMA – include CM-227	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,279	+£146

	PEMBRO	[redacted]	[redacted]	£937,419	-
2 & 3) Sub groups specific + CM-227 in the network	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£27,460	-£1,674
	PEMBRO	[redacted]	[redacted]	£936,367	-
4) Outcomes for PDC based on CM-227, outcomes for other interventions are relative effects from FPNMA	PDC	[redacted]	[redacted]	-	
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£31,442	+£2,308
	PEMBRO	[redacted]	[redacted]	£494,309	-
5a) PFS model selection – NIVO + IPI + limited PDC	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,879	+£745
	PEMBRO	[redacted]	[redacted]	Dominated	-
5b) PFS model selection - PDC	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,355	+£221
	PEMBRO	[redacted]	[redacted]	Dominated	-
6a) Duration of survival benefit: 3 years	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£36,251	+£7,117
	PEMBRO	[redacted]	[redacted]	Dominated	-
6b) Duration of survival benefit: 5 years	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£32,879	+£3,746
	PEMBRO	[redacted]	[redacted]	Dominated	-
7) Duration of ATEZO+BEV+PDC based on DOT	PDC	n/a	n/a	n/a	n/a
	NIVO + IPI + limited PDC	n/a	n/a	n/a	n/a
	PEMBRO	n/a	n/a	n/a	n/a
8) Progression-based utilities	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£32,052	+£2,919
	PEMBRO	[redacted]	[redacted]	Dominated	-

9) Subsequent therapy: no docetaxel as a second line therapy after PDC	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£27,774	-£1,360
	PEMBRO	[redacted]	[redacted]	Dominated	-
10) CheckMate-227 to inform rates of subsequent therapy	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£24,890	-£4,244
	PEMBRO	[redacted]	[redacted]	Dominated	-
11) Dose intensity adjustment	PDC	[redacted]	[redacted]	-	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£29,507	+£374
	PEMBRO	[redacted]	[redacted]	Dominated	-
ERG base case: Error correction, 1, 3, 5a, 5b, 6b, 8, 9, 10 & 11	**PDC**	[redacted]	[redacted]	**-**	**-**
	NIVO + IPI + limited PDC	[redacted]	[redacted]	**£37,262**	**+£8,129**
	PEMBRO	[redacted]	[redacted]	**£287,171**	**-**

Table 65 ERG base case, probabilistic results

Population	Intervention	Costs	QALYs	ICER	Probability of being cost-effective at £30,000 per QALY
Squamous, PD-L1 <50%	PDC	[redacted]	[redacted]	-	88.9%
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£36,455	11.1%
Non-squamous, PD-L1 <50%	PDC	[redacted]	[redacted]	-	91.8%
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£37,536	8.2%
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	0.0%
Mixed histology, PD-L1 ≥50%	PDC	[redacted]	[redacted]	-	88.9%
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£37,206	6.4%
	PEMBRO	[redacted]	[redacted]	£287,171	4.7%

6.4 Conclusions of the cost effectiveness section

The company performed a targeted literature review to identify cost-effectiveness evaluations of adults on first-line treatment for advanced or metastatic NSCLC. No prior economic evaluations of nivolumab + ipilimumab + limited PDC were identified in the review, but several relevant UK-based studies were identified for other treatments including other immunotherapies. The company also summarised key modelling elements from previous NICE technology appraisals for the first-line treatments of advanced NSCLC.

The company developed a *de novo* economic analysis to appraise the cost and benefits of nivolumab + ipilimumab + limited PDC in patients with untreated stage IV or recurrent NSCLC. Nivolumab + ipilimumab + limited PDC was compared to BSC, which comprised histology-guided platinum-based chemotherapy. Nivolumab + ipilimumab + limited PDC was also compared to pembrolizumab, licensed for those with PD-L1 expression ≥ 50%, and atezolizumab + bevacizumab + PDC, licensed for those with non-squamous histology and PD-L1 expression < 50%.

The model took a cohort-based partitioned survival approach, with health states based on pre-progression, post-progression, and death. Kaplan-Meier data from CheckMate-9LA were used to model survival outcomes for nivolumab + ipilimumab + limited PDC and for PDC up to 13 months. Thereafter, survival was modelled by parametric survival curves fit to data from CheckMate-227. Relative risks from a FPNMA using data from the KeyNote-024, KeyNote-042 and CheckMate-9LA trials were used to model the treatment effect of pembrolizumab, and relative risks from a FPNMA using data from the ERACLE, PRONOUNCE, IMpower150, CheckMate-9LA trials were used to model the treatment effect of atezolizumab + bevacizumab + PDC.

In the company's base case fully incremental analyses, pembrolizumab and atezolizumab + bevacizumab + PDC were both dominated, and the ICER for nivolumab + ipilimumab + limited PDC compared to BSC was £29,133. PSAs suggested the probability of nivolumab + ipilimumab + limited PDC being the most cost-effective option was approximately 20% and 50% at thresholds of £20,000 and £30,000, respectively.

The ERG's critique identified substantive structural uncertainties associated with the company's approach that potentially limit the reliability of company's analysis.

Two comparators in the analysis, pembrolizumab and atezolizumab + bevacizumab + PDC, have histology-based and PD-L1-based marketing authorisations. As such, the ERG considers there to be three decision problems based on histology and PD-L1 expression. There may be heterogeneity in effects and different in-scope comparators included in the economic model between each decision problem. There may be differences in absolute and relative survival effects between each histology-

and PD-L1-based subgroup. Therefore, subgroup-specific survival curves for nivolumab and PDC may be more appropriate than survival curves estimated from the all-comer population. The company's approach also fails to allow for heterogeneity in chemotherapy regimens, which are given according to histology and should vary in composition between each of the three decision problems. Although efficacy might be similar between agents, acquisition and administration costs may be slightly different.

Modelling the outcomes of PDC based on CheckMate-9LA may underestimate survival projections. Compared with CheckMate-227, survival is more pessimistic in CheckMate-9LA. The survival difference may be due to the extent to which subsequent immunotherapy is used after PDC, which is lower in CheckMate-9LA. It is generally considered that 50% would receive subsequent immunotherapy in UK practice which is more aligned with the rate in CheckMate-227.

The economic analysis also makes strong assumptions about the durability of the treatment effect, assuming that the benefits to mortality gained while on treatment are maintained beyond treatment discontinuation. Although it is biologically plausible for the treatment effect to continue after stopping nivolumab + ipilimumab + limited PDC, its duration was uncertain. Given the short follow-up from CheckMate-9LA, the ERG believes that it is unknown whether, or for how long, the effects of nivolumab on OS are maintained after treatment discontinuation. As a result, survival projections for nivolumab are likely overoptimistic.

The fractional polynomial NMA was updated at the clarification stage to include CheckMate-227 to better inform the long-term prediction of the hazard ratios. However, the company were not able to clinically validate the new models. Therefore, there is remaining uncertainty regarding the relative treatment effect of pembrolizumab and atezolizumab + bevacizumab + PDC, and their cost-effectiveness compared with nivolumab + ipilimumab + limited PDC.

In addition, the ERG also identified a number of issues relating to the inputs and assumptions used in the model. These related to:

- Immaturity of data from CheckMate-9LA, meaning that a number of outcomes, such as duration of treatment and rates of subsequent therapy, may be underestimated for nivolumab + ipilimumab + limited PDC,
- The distribution of agents in PDC, which is not reflective of UK clinical practice,
- PFS used as a proxy for time on treatment for atezolizumab + bevacizumab + PDC,
- The prediction of HRQoL by proximity to death;
- The use of relative dose intensity to estimate drug costs,
- The rate of subsequent therapy and the distribution of therapies.

To address these concerns the ERG implemented extensive further scenario analyses and proposed an alternative base-case analysis to address several of the key uncertainties identified. The main changes implemented by the ERG included:

- Using a distribution of PDC elements that is aligned with UK practice and reflects the population in the sub-analysis;
- Inclusion of CheckMate-227 in the FPNMAs,
- A duration of treatment benefit limited to *a)* three-years, and *b)* five-years after discontinuation;
- The incorporation of progression-based utilities,
- Revision of assumptions regarding subsequent therapy, so that patients do not receive docetaxel after discontinuation of PDC, and CheckMate-227 is used as an alternative source of data to inform the rates at which patients receive subsequent therapy.

All of these scenarios were found to have an impact on the ICER. The scenarios that had a considerable impact on the ICER (i.e. > £2,000) were changing the composition of PDC according to the sub-population; using the PDC OS curve from CheckMate-227; using a 3- or 5-year duration of survival benefit; progression-based utilities; using the CheckMate-227 as a source of subsequent therapies; and removing the dose intensity.

With PAS applied for nivolumab and ipilimumab and the remainder of interventions at list price, the results of the ERG's revised base-case imply deterministic ICERs for nivolumab + ipilimumab + limited PDC compared to PDC of £36,915 in the squamous, PD-L1 < 50% population (Table 62). In the non-squamous, PD-L1 < 50% population (Table 63), the ICER of nivolumab + ipilimumab + limited PDC compared to PDC was £37,420, and atezolizumab + bevacizumab + PDC was dominated by nivolumab + ipilimumab + limited PDC. In the mixed histology, PD-L1 ≥ 50% population (Table 64), the fully incremental analysis estimated that the ICER of nivolumab + ipilimumab + limited PDC compared to PDC was £37,262 and the ICER of pembrolizumab was £287,171.

The probabilistic results show the probability of nivolumab + ipilimumab + limited PDC being cost effective at a threshold of £30,000 per QALY is 11.1%, 8.2% and 6.4% for the squamous, PD-L1 < 50% population, the non-squamous, PD-L1 < 50% population and the mixed histology, PD-L1 ≥ 50% population, respectively (Table 65).

7 END OF LIFE

In order for end-of-life criteria to be considered, both criteria need to be satisfied, that is 1) the treatment is indicated for patients with a short life expectancy, normally less than 24 months; and 2) there is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.

The CS (Table 38, pg.99) suggests NICE's end-of-life criteria are not met for the patient population in CheckMate-9LA. Specifically, the company state '*patients with advanced or metastatic NSCLC are expected to have a life expectancy of more than 24 months if treated with IO therapies*.'

The ERG acknowledges that the company's approach was to consider the all-comer population from CheckMate-9LA, yet the ERG considers there to be a number of distinct decision problems based on histology and PD-L1 expression.

In the squamous, PD-L1 < 50% population, the company's base case results predict mean survival of [redacted] for those treated with PDC. According to the scope, there are no alternative comparators, indicating the life expectancy criterion (i.e. less than 24 months) would be met in this sub-population. The ERG's base case also predicts mean survival to be [redacted] for PDC patients.

In the non-squamous, PD-L1 < 50% and the mixed histology, PD-L1 ≥ 50% populations, immunotherapies are available in practice. The company's base case predicts mean survival of [redacted] for those treated with atezolizumab + bevacizumab + PDC (i.e. non-squamous, PD-L1 < 50%) and [redacted] for those treated with pembrolizumab (i.e. mixed histology, PD-L1 ≥ 50%). Whereas the ERG's base case predicts survival of [redacted] for atezolizumab + bevacizumab + PDC and [redacted] for pembrolizumab. Note, the ERG's base case survival predictions for the immunotherapy arms are based on the results of the updated FPNMA (i.e. including CheckMate-227) which have yet to be validated. The results clearly demonstrate in the sub-populations in which immunotherapies are available, life expectancy is estimated to be greater than 24 months.

Both the company's and the ERG's base case results indicate the criterion of an addition to life of 3 months (as a result of nivolumab + ipilimumab + limited PDC) is satisfied for all three sub-populations: both predict survival to be [redacted].

For these reasons, notwithstanding the uncertainty in the estimates yet to be validated, the ERG disagrees with the company that end-of-life criteria are not met, and considers the criteria met for the squamous, PD-L1 < 50% population. However, the criteria are not met for the non-squamous, PD-L1 < 50% and the mixed histology, PD-L1 ≥ 50% populations.

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APPENDICES

Appendix 1 Updated model fit including CheckMate-227

Appendix Figure 30 presents the Kaplan Meier curve overlays of the observed versus updated modelled data of OS for each included study in the network of patients with mixed histology and PD-L1 ≥ 50%

Figure 30 Comparison of model fit to Kaplan Meier curves of contributing RCTs for OS for the network of patients with mixed histology and PD-L1 ≥ 50%

Appendix Figure 31 presents the Kaplan Meier curve overlays of the observed versus updated modelled data of OS for each included study in the network of non-squamous with PD-L1 < 50%. The selected model was a repeated powers model with $P1=P2=1$, with treatment effects on scale, which assumes proportional hazards. However, at later time points the curves in the Impower150 and PRONOUNCE graphs cross, which violates the proportional hazards assumption. This may be due to the low number of observations in these trials.

Figure 31 Comparison of model fit to Kaplan Meier curves of contributing RCTs for OS for the network of non-squamous patients with PD-L1 < 50%

Appendix 2 ERG critique of the company's economics searches

Search strategy

The company submission included the searches to identify economic evaluations, health-related quality of life studies, and cost and resource use studies in adults with advanced or metastatic NSCLC. A detailed description of the searches and most of the search strategies were included in Appendix G (p. 68-81). A further document was provided by the company in response to the ERG PFCs, including additional search strategies and corrections to errors identified by the ERG.

Table 66 ERG appraisal of evidence identification

Topic	ERG response	Note
Is the report of the search clear and comprehensive?	PARTLY	In the original submission, some search strategies were missing and errors were found. Most errors were corrected and the missing search strategies were provided with the company response to the PFCs.
Were appropriate sources searched?	YES	MEDLINE, Embase, EconLit, NHS EED, HTA database, manual searches of conference abstracts, HTA agency websites, CEA Registry, reference checking of relevant reviews.
Was the timespan of the searches appropriate?	YES	The original search strategies were updated 3 times and covered the period 2012 to 20th April 2020.
Were appropriate parts of the PICOS included in the search strategies?	YES	NSCLC (P) AND Economic evaluations (S) OR costs (O) OR health-state utility values (O)
Were appropriate search terms used?	YES	
Were any search restrictions applied appropriate?	YES	Date limits were applied appropriately in the corrected set of searches strategies provided with the PFCs.
Were any search filters used validated and referenced?	UNCLEAR	Retrieval was restricted to economic evaluations, cost or health related quality of life studies. No references were provided for any study design search filters, therefore it is unclear if validated search filters were used.

ERG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

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

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5:00pm on Tuesday 24 November 2020** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Error in Naming of CheckMate 568

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
CheckMate 568 trial described as CheckMate 586 on pages 3, 52 and 53	Correct to CheckMate 568 on 4 occasions	To ensure the trial is correctly identified, no impact on decision making	Amended

Issue 2 Error in Reporting of CheckMate 227 PFS

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG Response</th></tr>
<tr>
<td>Error in Table 10 on page 60 – PFS rates presented as 6 and 12 months should read 12 and 24 months and the comparators/ timings have been reversed,</td>
<td>Current table rows:
<table>
<tr><th>Trial results</th><th>NIVO + IPI (n = 583)</th><th>PDC (n = 583)</th></tr>
<tr><td>…</td><td></td><td></td></tr>
<tr><td>PFS rate at 6 months %</td><td>32</td><td>20</td></tr>
<tr><td>PFS rate at 12 months %</td><td>17</td><td>6</td></tr>
</table>
Should read:
<table>
<tr><th>Trial results</th><th>NIVO + IPI (n = 583)</th><th>PDC (n = 583)</th></tr>
<tr><td>…</td><td></td><td></td></tr>
<tr><td>PFS rate at 12 months %</td><td>32</td><td>17</td></tr>
<tr><td>PFS rate at 24 months %</td><td>20</td><td>6</td></tr>
</table>
</td>
<td>To ensure correct reporting, no impact on decision making</td>
<td>Amended</td>
</tr>
</table>

Issue 3 Error in narrative regarding ORR in CkeckMate 568

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 60 – paragraph under Table 10, refers to “partial disease” when it should be “partial response”	Reword sentence to read: The ORR was 47%, with 42% achieving partial response and 42% achieving stable disease.	To ensure correct reporting, no impact on decision making	Amended

Issue 4 Error in narrative on page 61 regarding age subgroups in CheckMate 9LA and 227

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
2 lines at top of page 61 read “The never smoked subgroup and under 75 years old subgroup had relatively small patient numbers, which can lead to higher uncertainty in point estimates” and should refer to the over 75 subgroup. The same mistake is made at the bottom of the paragraph above Table 11.	The never smoked subgroup and over 75 years old subgroup had relatively small patient numbers, which can lead to higher uncertainty in point estimates” The ERG notes that similarly to the CheckMate-9LA trial, the subgroups of patients over 75 years old and CNS metastases had relatively small sample sizes, which may reduce the reliability of these results.	To ensure correct reporting, no impact on decision making	Amended

Issue 5 Error in reporting of CheckMate 227 AEs on page 61-63

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The subgroup data presented in Table 11 for CheckMate 227, and described in narrative above, relate to the PD-L1 ≥ 1%	Update CM-227 rows of Table 11 and narrative relating to this on pages 61-63 to reflect the subgroup analysis based on all patients in CM-227. Similarly, in the CheckMate-227 trial, the efficacy	Some of the subgroups in CM-227 that the report currently highlights as nivolumab + ipilimumab not showing a significant OS benefit,	The ERG acknowledges the company’s error at submission and clarification. Values and text have been

<table>
<tr>
<td>subgroup of the trial, and not the full all-comer population which is available in Table 7.4.1.1-1 of the CSR and is more appropriate for use. This was an error in the CS and additional data included by the ERG repeat this error.</td>
<td>benefit of nivolumab + ipilimumab was not seen for patients [redacted] CheckMate-227 also reported further subgroup analyses, which did not show benefit of nivolumab + ipilimumab compared with PDC, including ~~patients aged 65 to 75 years old~~, [redacted] ~~patients with non-squamous NSCLC and patients with CNS metastases~~ (Error! Reference source not found.).
<table>
<tr><th rowspan="2">Subgroup</th><th colspan="2">Median OS, months</th><th rowspan="2">HR (95% CI)</th></tr>
<tr><th>NIVO + IPI</th><th>PDC</th></tr>
<tr><td colspan="4">CM-227</td></tr>
<tr><td>65 to <75 years old (n=442)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>≥ 75 years old (n=113)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Female (n=388)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Never smoked (n=157)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Liver metastases (n=252)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Bone metastases (n=316)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>CNS</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td>
<td>are significant with the correct data.</td>
<td>updated to agree with the CSR, as requested.

Text on page 63 of the report was also amended: ‘PD-L1 expression may be a potential effect modifier in CheckMate-9LA, as discussed in Section 3.2.4.2.’</td>
</tr>
</table>

metastases (n=115)			
PD-L1 < 1% (n=373)	[redacted]	[redacted]	[redacted]
PD-L1 ≥ 1% (n=793)	[redacted]	[redacted]	[redacted]
PD-L1 1-49% (n=396)	[redacted]	[redacted]	[redacted]
PD-L1 ≥ 50% (n=397)	[redacted]	[redacted]	[redacted]
Squamous histology (n=328)	[redacted]	[redacted]	[redacted]
Non-squamous histology (n=838)	[redacted]	[redacted]	[redacted]

In the CheckMate-9LA trial the efficacy benefit of nivolumab + ipilimumab + limited PDC was observed in both squamous (HR: 0.62, 95% CI: 0.45 to 0.86) and non-squamous (HR: 0.69, 95% CI: 0.55 to 0.87) subgroups for OS. Similar results were seen in CheckMate 227 (squamous: [redacted]; non-squamous: [redacted])

~~However, in CheckMate-227, the subgroup of patients with non-squamous NSCLC did not see an OS benefit with nivolumab + ipilimumab (**Error! Reference source not found.**), suggesting that histology may be an effect modifier for treatment with nivolumab + ipilimumab.~~

Issue 6 Error in an AE on page 72

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Under Table 18 the narrative refers to uvulitis, when it should state uveitis.	Other events of special interest, included encephalitis [redacted], pancreatitis [redacted] and uveitis ~~uvulitis~~ [redacted] in patients treated with nivolumab + ipilimumab + limited PDC and myositis [redacted] in patients treated with PDC alone.	To ensure correct reporting, no impact on decision making	Amended

Issue 7 Errors in Table 19

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Table 19, page 73: Patient number in PDC arm given in table header row, when CheckMate 568 was single arm. Some of the data included under IMAEs are "all-causality IMAEs within 100 day of last dose, by category, treated with immune-modulating medication" and some are "all-causality endocrine IMAEs within 100 day of last dose, by category, treated with or without immune-modulating medication", where table 8.1-1 in the CSR reports results for an AE in both categories, it is not clear how the ERG have decided which to report – or that results differ.	Delete PDC (n=349) Suggest that the all IMAE data are presented consistently for all, as shown below. **All-causality Immune mediated adverse events** within 100 day of last dose, by category, treated with immune-modulating medication Diarrhoea/colitis [redacted] Hepatitis [redacted] Pneumonitis [redacted] Nephritis/Renal dysfunction [redacted] Rash [redacted] Hypersensitivity/infusion reaction [redacted] Adrenal insufficiency [redacted] Hypophysitis [redacted] Hypothyroidism* [redacted]	To ensure correct reporting, no impact on decision-making	Amended Table updated to differentiate between IMAEs treated with immune modulating medications and those treated with *or* without.

	Thyroiditis	[redacted]			
	Hyperthyroidism	[redacted]			
	Diabetes Mellitus	[redacted]			

Issue 8 Error in Figure 12

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Figure 12, page 120: Label states 'Modelled pembro'	Should state 'Modelled atezo'	To ensure correct reporting, no impact on decision-making	Amended

Issue 9 Error in Scenario 11

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Scenario 11, Page 171: Updated PAS discount for second-line nivolumab and subsequently in ERG exploratory scenarios tables	Retain second-line PAS discount for second-line nivolumab from original submission	The current submission is under consideration for the CDF. Therefore, it is our understanding that an additional PAS discount arrangement can be agreed without impacting the current PAS discount for nivolumab in other indications (including second-line NSCLC). The impact on decision making will be that the small adjustment to the ICER resulting from this scenario will not be considered.	This scenario has been removed from the ERG report and the assumption removed from the ERG base case.

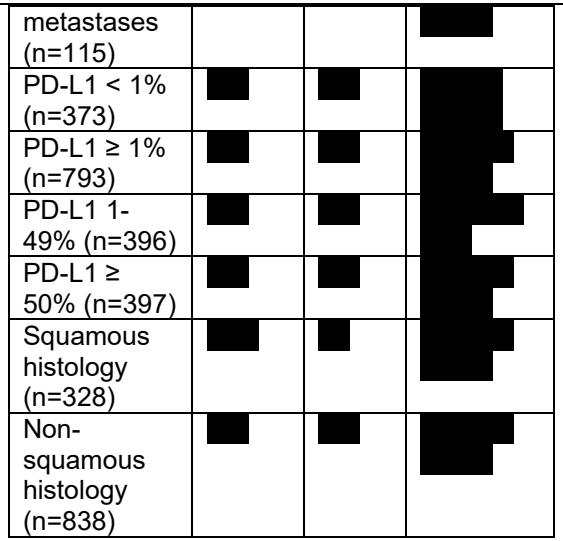
Issue 10 Error in Scenario 11

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
ERG's interpretation of relative dose intensity. Page 146-147 as well as instance where this argument has been used; Page 14, 15, 16, 29, 171-172, 174, 177, 182-183 Table, 2-4, 62-64	Retain dose intensity as incorporated by company.	The ERG has interpreted the relative dose intensity as a reduction of dose given per instance of treatment. However, as pointed out by the ERG no dose reduction were allowed for nivolumab or ipilimumab. Thus, each dose received where the prescribed 360mg of nivolumab and the 1mg/kg of ipilimumab. The relative dose intensity accounts for number of doses received compared to planned number of doses (eg. missed dose due to dose delays lasting longer than the frequency of dose delivery). Thus, the relative dose intensity reflects a reduction of the cost of treatment due to fewer doses being administrated during the 24 months of treatment than reflected by duration of therapy.	Thank you for the additional detail regarding the relative dose intensity of nivolumab and ipilimumab. This scenario has been removed from the ERG report and the ERG base case now uses the assumption explored in Scenario 12a (now labelled Scenario 11).

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG Response
Table 11, subgroup OS data from CSR for CheckMate 227	In line with other marking, mark all the medians, HRs and 95% CIs from the	Similarly, in the CheckMate-227 trial, the efficacy benefit of nivolumab + ipilimumab	CIC added

	CSR as CIC, as presented in issue 5, above.	was not seen for patients [redacted]. CheckMate-227 also reported further subgroup analyses, which did not show benefit of nivolumab + ipilimumab compared with PDC, including, [redacted] (**Error! Reference source not found.**).	

Subgroup	**Median OS, months**		**HR (95% CI)**
	NIVO + IPI	**PDC**	
CM-227			
65 to <75 years old (n=442)	[redacted]	[redacted]	[redacted]
≥ 75 years old (n=113)	[redacted]	[redacted]	[redacted]
Female (n=388)	[redacted]	[redacted]	[redacted]
Never smoked (n=157)	[redacted]	[redacted]	[redacted]
Liver metastases (n=252)	[redacted]	[redacted]	[redacted]
Bone metastases (n=316)	[redacted]	[redacted]	[redacted]
CNS	[redacted]	[redacted]	[redacted]

		 In the CheckMate-9LA trial the efficacy benefit of nivolumab + ipilimumab + limited PDC was observed in both squamous (HR: 0.62, 95% CI: 0.45 to 0.86) and non-squamous (HR: 0.69, 95% CI: 0.55 to 0.87) subgroups for OS. Similar results were seen in CheckMate 227 (squamous: [redacted] non-squamous: [redacted]	

(Please add further lines to the table as necessary)

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

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **15 January 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.

Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

- Do not include medical information about yourself or another person that could identify you or the other person.

Do not use abbreviations.

Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Bristol-Myers Squibb**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Sub-populations for decision-making	**NO**	Although current clinical practice is dependent on histology and PD-L1 expression, the evidence from CheckMate-9LA suggests that histology and PD-L1 expression are not effect modifiers for the combination of nivolumab +ipilimumab + limited PDC. Given the combination of 3 different mechanisms of action, the nivolumab + ipilimumab + limited PDC combination is not expected to have the same efficacy differences by histology/PD-L1 as is seen for some PD-L1 inhibitors as monotherapy or in combination with PDC. • Therefore, we feel that it is more appropriate to use the totality of data from CheckMate-9LA. • Where subgroup data are available for comparators and data suggest that histology and PD-L1 are effect modifiers, the relevant comparator subgroup data for decision making are preferred. • Nonetheless, survival analyses for the CheckMate-9LA subgroups are presented in response to issues below.
Key issue 2: Representativeness of trial populations	**YES**	We acknowledge that the trial population may have slightly different demographic characteristics than the population expected to receive treatment in the UK setting. However, we do not anticipate that this would have a significant impact on clinical outcomes. The CheckMate-9LA and CheckMate-227 trials provide the best available evidence for nivolumab + ipilimumab + PDC in this indication. Clinical opinion sought during technical engagement confirmed that there are differences between the CheckMate-9LA trial population and the population that would be treated in UK clinical practice. However, the clinician advised that this is the case across all clinical trials in this therapeutic area and that 1 advantage of the CheckMate-9LA trial is that it included UK sites, which has not always been the case in previous trials in lung cancer. Overall, the clinician considered the differences in demographic and clinical characteristics to be relatively minor and

Key issue	Does this response contain new evidence, data or analyses?	Response
		would not expect any major differences in efficacy in the clinical practice setting compared with the trial.
Key issue 3: Population-specific relative survival effects	**NO**	As noted in Key Issue 1, BMS consider that the intention-to-treat data from CheckMate-9LA are more appropriate than the subgroups that were not prespecified and contain very low patient numbers. Input was sought during development of the indirect treatment comparison at 2 advisory boards that included both clinical and HTA experts. The experts suggested that it was appropriate to combine the different PDC regimens together as summarised in the submission appendix. All experts consulted agreed with the methodological approaches presented, specifically with the approaches to: (1) combining and splitting chemotherapy nodes, (2) matching input data to the target population in the presence of effect modification, and (3) investigating assumptions for both constant hazard ratios (HRs) and time-varying HRs.
Key issue 4: The inclusion of CheckMate-227 in the fractional polynomial NMA	**NO**	We agree the fractional polynomial (FP) analysis including CheckMate-227 is appropriate for use in the base case. The following a priori assumptions were used to assess clinical plausibility of the FP models: • Long-term OS (or PFS) hazards in immuno-oncology therapy–based arms should not substantially exceed the OS (or PFS) hazard in chemotherapy arms (durable response). • Absolute hazards should not have a steep and monotonically increasing upward trend over the long-term. • HRs should not have a steep and monotonically increasing upward trend over the long-term. • Long-term HRs for CheckMate-9LA should align with those for CheckMate-227. • Additional consideration 1: PFS should not cross OS, based on an assumed reference treatment curve. • Additional consideration 2: Account for background mortality of the target population. Appendix A provides more detail about the heuristics used for selection of FP models.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 5: Treatment efficacy in subgroups	**NO**	Although there is some uncertainty around OS benefit in some specific subgroups, these were not prespecified and patient numbers are extremely low, resulting in wide confidence intervals (CIs) around treatment effect (as can be seen in the ERG report): • Overall trial population: CheckMate-9LA = 719; CheckMate-227 = 1,166 • Patients aged ≥ 75 years (overall): CheckMate-9LA = 70; CheckMate-227 = 113 • Patients who had never smoked (overall): CheckMate-9LA = 98; CheckMate-227 = 157 • Patients with liver metastases (overall): CheckMate-9LA = 154; CheckMate-227 = 252 • Patients with bone metastases (overall): CheckMate-9LA = 207; CheckMate-227 = 316 – In CheckMate-9LA, the HR in this subgroup was 0.74 (95% CI, 0.53-1.01) – In CheckMate-227, the HR in this subgroup was [redacted] Therefore, it is not appropriate to base decision making on these analyses; further limiting treatment by age and smoking status would introduce ethical challenges.
Key issue 6: Representativeness of PDC	**YES**	The approach suggested by the ERG here is reasonable in terms of calculating the costs of PDC based on the regimen used in England. Feedback from clinical input sought on this area of uncertainty is presented below. Further clinical opinion suggested that the CheckMate-9LA regimen does not fully reflect the current PDC regimens most likely to be used in the UK setting, especially for the squamous population. Squamous patients would receive the following regimens (proportion): • Carboplatin + gemcitabine (~60%) • Carboplatin + paclitaxel (~20%) • Carboplatin + vinorelbine (~20%) Non-squamous patients would receive the following regimens (proportion): • Carboplatin + pemetrexed (~80%) • Cisplatin + pemetrexed (~20%) The model is updated to include an option to model the PDC regimen as above, although additional clinical input and discussion would help identify which breakdown of PDC regimens is most appropriate.

<table>
<tr><th>Key issue</th><th>Does this response contain new evidence, data or analyses?</th><th>Response</th></tr>
<tr><td>Key issue 7: Population-specific composition and duration of PDC</td><td>NO</td><td>The approach suggested by the ERG here is reasonable for subgroup-specific analyses. However, we believe that using the totality of the CheckMate-9LA data would be scientifically most robust and that the all-comers population should be retained as the base case. Therefore, we have added an option to the PDC regimens in the model to include gemcitabine and vinorelbine and continue to weight the PDC costs for all comers in the base case.</td></tr>
<tr><td>Key issue 8: Population-specific absolute survival effects</td><td>YES</td><td>As discussed in responses to Key Issues 1, 3, 6, and 7, the all-comers population data are the most robust and should be used in the base case. However, as requested by the ERG, subgroup-specific survival analyses are also presented.
The most plausible survival distributions for the subgroups have been selected; Table 3 presents the updated base-case ICERs. As noted by the ERG, lower patient numbers within the subgroups may mean that the estimation of absolute survival effects within these populations is less robust than the all-comers population. Furthermore, there are fewer external clinical data available to guide selection of the most appropriate distribution, which necessitates a reliance on clinical opinion. This means that the curve selections are likely to be associated with greater uncertainty than in the all-comers population.
Curve selection for subgroups was conducted following the same principles as for the all-comers population in the original submission and is detailed in full for each subgroup in Appendix B. Table 1 and Table 2 present the base-case selections for each subgroup for OS and PFS, respectively.
Table 1. Summary of OS curve selection
<table>
<tr><th></th><th>Nivolumab + ipilimumab + PDC</th><th>PDC</th></tr>
<tr><td>PD-L1 > 50% mixed histology</td><td>Generalised gamma</td><td>Spline odds 1 knot</td></tr>
<tr><td>PD-L1 < 50% non-squamous</td><td>Log-logistic</td><td>Spline odds 2 knot</td></tr>
<tr><td>PD-L1 < 50% squamous</td><td>Log-logistic</td><td>Log-logistic</td></tr>
</table>
</td></tr>
</table>

Key issue	Does this response contain new evidence, data or analyses?	Response

Table 2. Summary of PFS curve selection

	Nivolumab + ipilimumab + PDC	PDC
PD-L1 > 50% mixed histology	Generalised gamma	Log-logistic
PD-L1 < 50% non-squamous	Spline odds 1 knot	Spline odds 2 knot
PD-L1 < 50% squamous	Spline normal 1 knot	Spline hazards 2 knot

Table 3 presents the impact on the ICER when subgroup-specific survival curves are applied to the updated company base case.

Table 3. Impact of updated curve selections on the ICER

	Interventions	Costs	QALYs	ICER
Company base case (all comers)	PDC	[redacted]	[redacted]	
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£38,406
Squamous PD-L1 < 50%				
	PDC	[redacted]	[redacted]	
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£57,767
Non-squamous PD-L1 < 50%				
	PDC	[redacted]	[redacted]	
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£53,999
Mixed histology PD-L1 > 50%				
	PDC	[redacted]	[redacted]	
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£31,987

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 9: Survival of patients on PDC	**NO**	For consistency of approach across treatment arms in the model and in the interest of using the most relevant evidence from the pivotal trial, the approach used to model survival in the PDC arm in the original submission is the most appropriate. Furthermore, as stated in the response to Key Issue 2, clinical experts feel that the CheckMate-9LA clinical trial is sufficiently representative of the UK clinical population.
Key issue 10: Duration of treatment benefit	**NO**	The ERG correctly notes that this is a key area of uncertainty and it would be of value to further explore as part of a CDF data collection agreement. We do not fully agree with the ERG's assessment of the evidence on this point. Although the reference cited in support of a lifetime treatment effect of nivolumab + ipilimumab + limited PDC is in a previously treated population,[1] it remains the most robust and relevant available evidence with which to inform this assumption because it draws on data from patients with NSCLC treated with nivolumab. Therefore, it is important that this evidence is not completely disregarded as irrelevant but is treated with appropriate scrutiny. This evidence suggests a robust and durable treatment effect lasting beyond discontinuation for nivolumab in patients with NSCLC.
Key issue 11: Duration of treatment	**NO**	The approach suggested by the ERG here is reasonable.
Key issue 12: Utility values estimated from proximity to death	**NO**	The ERG noted that not enough information on the utility data used in the model was presented. Additional information on utility data and model fit is presented here. There were 705 subjects in the CheckMate-9LA study with at least 1 observed utility index value available. There were 6,077 observations available, with 5,073 preprogression in 703 subjects and 1,004 postprogression in 353 subjects. There were 703 subjects with 4,402 observations in the time-to-death (TTD) analysis (Table 4). The reason for slightly fewer subjects and observations in the TTD than the progression-based approach is due to the exclusion of observations within 364 days of death.

Table 4. Numbers of subjects and observations by study populations

	Total	Nivolumab + ipilimumab + PDC	PDC
Overall	705/6,077	358/3,501	347/2,576
Progression status			
Preprogression	703/5,073	356/2,935	347/2,138
Postprogression	353/1,004	170/566	183/438
TTD category			
Overall	703/4,402	357/2,389	346/2,013
> 52 weeks	390/2,284	227/1,371	163/913
27-52 weeks	251/941	114/472	137/469
5-26 weeks	357/1,063	157/495	200/568
≤ 4 weeks	111/114	49/51	62/63

In terms of model fit statistics, 0 provides −2*log-likelihood, AIC, and BIC for model fit. The statistical significance (95% CI not covering “0”) of decrement due to progression in combined scenario 1 and decrement due to “died” within 1 year in combined scenario 2 demonstrates the independent contributions of progression-based and TTD-based health states. In the TTD analyses, EQ-5D observations within 1 year before study end of alive subjects were excluded because we are not be able to determine when subjects will die. Therefore, the fit statistics (i.e., −2*log-likelihood, AIC, and BIC) for progression-based and TTD-based models are not directly comparable.

Key issue	Does this response contain new evidence, data or analyses?	Response

Table 5. Model fit statistics

Model without treatment							
	N Param	**AIC**	**BIC**	**−2*logL**	**Chi-square**	**DF**	***P* value**
Progression	2	−2,329	−2,311	−2,337			
TTD	4	−1,296	−1,269	−1,308			
Model with treatment[a]							
	N Param	**AIC**	**BIC**	**−2*logL**	**Chi-Square**	**DF**	***P* value**
Progression	4	−2,335	−2,307	−2,347	9.5	2	0.009
TTD	8	−1,306	−1,261	−1,326	18.26	4	0.001

Note: For AIC/BIC, a smaller value means better model fit.

[a] In models with treatment, the interaction terms between treatment and all other variables in the model without treatment were included.

The ERG ask whether the time category cutoffs used in the TTD approach were arbitrary. We can confirm that this was not the case. Other time category cutoffs (1, 2, or 3 months) for the closest to death were tested using trial data from CheckMate-227 and assumed to also be applicable to CheckMate-9LA. After reviewing statistical results, “within 4 weeks” was selected for practical reasons: namely, the estimated utility can be comparable with estimates from other trials, and the number of EQ-5D observations was acceptable.

The ERG also ask whether time as a continuous variable was considered. This was not considered in the current utility analysis. In cases in which 1 trial arm has a shorter assessment period and steeper slope vs. another trial arm, which has a longer assessment period and flatter slope, least squares estimates with mean time will cause an underestimate for one and an

Key issue	Does this response contain new evidence, data or analyses?	Response
		overestimate for the other. Therefore, time as a continuous variable needs to be considered on a case-by-case basis; in this case, it was not deemed appropriate. Furthermore, the ERG assert that progression-based utilities are more conceptually valid than TTD-based utilities and therefore should be used for decision making. We maintain that TTD-based utilities should be used because this approach enables the model to better capture the variation in health-related quality of life of a patient between the time of progression and death. Progression-based utilities provide only snapshots of health-related quality of life, which are assessed shortly after progression has occurred. Therefore, progression-based utilities are expected to be biased upwards owing to a lack of observations collected in more severe patients who are closer to death. The ERG correctly state that more observations are captured for progression-based health states than TTD-based health states, especially in the TTD health state with the closest proximity to death. This is because a significant number of patients remained alive postprogression at the latest database lock. Further, the assessment schedule for CheckMate-9LA included only 3 scheduled follow-up visits after treatment discontinuation. Although it is important to recognise that there are drawbacks associated with both approaches, we do not share the view that progression-based utilities are more conceptually valid. On balance, the TTD-based approach is more clinically plausible and has been previously used in similar oncology indications.[2,3]
Key issue 13: Estimation of drug costs using relative dose intensity	**NO**	As presented in the factual accuracy of the ERG report, the relative dose intensity accounts for number of doses (cycles of treatment) received compared with planned number of doses (e.g., missed dose due to dose delays lasting longer than the frequency of dose delivery). Thus, the relative dose intensity reflects a reduction in the cost of treatment due to fewer doses being administrated during the 24 months of treatment than reflected by duration of treatment (DOT). The dose intensity does not reflect a reduced dose per se, as interpreted by the ERG. Each dose delivered will still be based on prescribed dose and number of vials. Thus, adjusting for the dose intensity as incorporated in the model by the ERG with reduced dose is not reflective of the impact this will have on costs. Therefore, we argue that the company approach should be maintained with regards to estimation of drug costs using relative dose intensity.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 14: The proportion of patients receiving subsequent therapy	**NO**	The clinical input provided during technical engagement suggests that the proportion of patients receiving subsequent therapy in the CheckMate-9LA trial may be lower than would be expected in a trial setting. However, in terms of UK clinical practice, the proportions of patients receiving subsequent therapy in the CheckMate-9LA trial were considered accurate. Furthermore, the ERG suggest that docetaxel would not be considered as a second-line treatment option for patients who had received PDC. We agree that, in an ideal world, this is correct. However, clinical input sought after technical engagement suggested that there could be a subset of patients who may not be clinically eligible for immuno-oncology therapy and who may instead receive PDC rechallenge, docetaxel, or docetaxel + nintedanib. We acknowledge this uncertainty but also that this has a minor impact on the ICER. We are happy to include the ERG's approach in the base case. Further clinical input during committee discussion could be valuable.
Key issue 15: The distribution of subsequent therapy	**NO**	The approach suggested by the ERG here is reasonable.
Key issue 16: End of life criteria	**NO**	We agree that end of life (EoL) criteria are not met in the entire population under consideration. For the squamous population with PD-L1 < 50%, mean OS predicted in the updated model is [redacted] for those treated with PDC and nivolumab + ipilimumab + limited PDC. Furthermore, nivolumab + ipilimumab + limited PDC results in a predicted survival of [redacted], suggesting that EoL criteria are met in this population. In the non-squamous PD-L1 < 50% and mixed histology PD-L1 ≥ 50% populations, in which other immuno-oncology products are standard of care, predicted survival is greater than 24 months; therefore, EoL criteria are not met.
Key issue 17: Access to Cancer Drugs Fund (CDF)	**NO**	There are existing areas of uncertainty given that the minimum follow-up of CheckMate-9LA is currently 12.7 months. Entry to the CDF would allow the uncertainty to be reduced. During the data collection period, additional follow-up from CheckMate-9LA would reduce uncertainty in terms of the long-term benefit in OS that nivolumab + ipilimumab + limited PDC provides. The benefit of longer follow-up was already seen when comparing the interim analysis

Key issue	Does this response contain new evidence, data or analyses?	Response
		at 8.1 months of minimum follow-up with the interim analysis at a minimum of 12.7 months of follow-up (Section B2.6.1.1 of company submission). Experience with nivolumab + ipilimumab in other indications, including renal cell carcinoma and melanoma, supports our expectation that the survival curve for nivolumab + ipilimumab + limited PDC will flatten, with long-term survival predicted in some patients, providing substantial benefit over comparators. A period in the CDF would also allow the collection of real-world data on the efficacy of nivolumab + ipilimumab + limited PDC via the Systemic Anti-Cancer Therapy (SACT) database. As long as treatment with nivolumab + ipilimumab + limited PDC was not limited by PD-L1 status, this would provide a large data set and allow further analysis of the impact of PD-L1 subgroups to aid future decision making.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g., at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	YES/NO	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	YES/NO	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making

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Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Errors identified by the ERG	Programming of TTD utility, PDC administrative cost, adverse event rate, discounting of LYGs, and half-cycle correction	Corrections made	+£335 vs. PDC
Key Issue 4: Validation of fractional polynomial NMA results after inclusion of CheckMate-227	Fractional polynomial analysis not including CheckMate-227 data	Fractional polynomial analysis including CheckMate-227 data	Pembrolizumab is no longer dominated Atezolizumab + bevacizumab + carboplatin + paclitaxel remains dominated
Key Issue 6: Representativeness of PDC	PDC regimens from CheckMate-9LA clinical trial	PDC regimens from clinical input following technical engagement	+£146 vs. PDC
Key Issue 11: Duration of treatment (DOT)	PFS used as a proxy for DOT for atezolizumab + bevacizumab + PDC	DOT used directly to model DOT for atezolizumab + bevacizumab + PDC	Atezolizumab + bevacizumab + carboplatin + paclitaxel remains dominated
Key Issue 14: The proportion of patients receiving subsequent therapy	Docetaxel considered to be an appropriate subsequent therapy after PDC.	Docetaxel not considered to be an appropriate subsequent therapy after PDC.	−£1,476 vs. PDC Pembrolizumab and atezolizumab + bevacizumab +

<table>
<tr><th>Key issue(s) in the ERG report that the change relates to</th><th>Company's base case before technical engagement</th><th>Change(s) made in response to technical engagement</th><th>Impact on the company's base-case ICER</th></tr>
<tr><td></td><td></td><td></td><td>carboplatin + paclitaxel remain dominated</td></tr>
<tr><td>Company's preferred base case following technical engagement</td><td>Incremental QALYs vs. PDC: 1.33</td><td>Incremental costs vs. PDC: £51,074</td><td>£38,406</td></tr>
<tr><td>Fully incremental analysis 1</td><td colspan="3"><table>
<tr><th></th><th>Total costs</th><th>Total LYs</th><th>Total QALYs</th><th>ICER</th></tr>
<tr><td>PDC</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>—</td></tr>
<tr><td>Nivolumab + ipilimumab + PDC</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£38,406</td></tr>
<tr><td>Atezolizumab + bevacizumab + carboplatin + paclitaxel</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>Dominated</td></tr>
</table></td></tr>
<tr><td>Fully incremental analysis 2</td><td colspan="3"><table>
<tr><th></th><th>Total costs</th><th>Total LYs</th><th>Total QALYs</th><th>ICER</th></tr>
<tr><td>PDC</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>—</td></tr>
<tr><td>Nivolumab + ipilimumab + PDC</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£38,406</td></tr>
<tr><td>Pembrolizumab monotherapy</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£167,011</td></tr>
</table></td></tr>
</table>

References

1. Antonia SJ, Borghaei H, Ramalingam SS, Horn L, De Castro Carpeno J, Pluzanski A, et al. Four-year survival with nivolumab in patients with previously treated advanced non-small-cell lung cancer: a pooled analysis. Lancet Oncol. 2019 Oct;20(10):1395-408.
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Appendix I: Updated Cost-Effectiveness Tables

The tables below show the cost-effectiveness results presented in the main document using [redacted].

Table 6. Impact of updated curve selections on the ICER (Updated Discount)

	Interventions	Costs	QALYs	ICER
Company base case (all comers)	PDC	[redacted]	[redacted]	
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£36,380
Squamous PD-L1 < 50%				
	PDC	[redacted]	[redacted]	
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£54,877
Non-squamous PD-L1 < 50%				
	PDC	[redacted]	[redacted]	
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£51,337
Mixed histology PD-L1 > 50%				
	PDC	[redacted]	[redacted]	
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£30,534

Table 7. Company Base Case following Technical Engagement (Updated Discount)

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Errors identified by the ERG	Programming of TTD utility, PDC administrative cost, adverse event rate, discounting of LYGs, and half-cycle correction	Corrections made	+£298 vs. PDC
Key Issue 4: Validation of fractional polynomial NMA results after inclusion of CheckMate-227	Fractional polynomial analysis not including CheckMate-227 data	Fractional polynomial analysis including CheckMate-227 data	Pembrolizumab is no longer dominated Atezolizumab + bevacizumab + carboplatin + paclitaxel remains dominated
Key Issue 6: Representativeness of PDC	PDC regimens from CheckMate-9LA clinical trial	PDC regimens from clinical input following technical engagement	+£146 vs. PDC
Key Issue 11: Duration of treatment (DOT)	PFS used as a proxy for DOT for atezolizumab + bevacizumab + PDC	DOT used directly to model DOT for atezolizumab + bevacizumab + PDC	Atezolizumab + bevacizumab + carboplatin + paclitaxel remains dominated
Key Issue 14: The proportion of patients receiving subsequent therapy	Docetaxel considered to be an appropriate subsequent therapy after PDC.	Docetaxel not considered to be an appropriate subsequent therapy after PDC.	−£1,476 vs. PDC Pembrolizumab and atezolizumab + bevacizumab + carboplatin + paclitaxel remain dominated

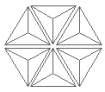
Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Company's preferred base case following technical engagement	Incremental QALYs vs. PDC: 1.33	Incremental costs vs. PDC: £48,381	£36,380

Fully incremental analysis 1

	Total costs	Total LYs	Total QALYs	ICER
PDC	[redacted]	[redacted]	[redacted]	—
Nivolumab + ipilimumab + PDC	[redacted]	[redacted]	[redacted]	£36,380
Atezolizumab + bevacizumab + carboplatin + paclitaxel	[redacted]	[redacted]	[redacted]	Dominated

Fully incremental analysis 2

	Total costs	Total LYs	Total QALYs	ICER
PDC	[redacted]	[redacted]	[redacted]	—
Nivolumab + ipilimumab + PDC	[redacted]	[redacted]	[redacted]	£36,380
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	£315,308



Appendix A: Fractional Polynomial Heuristic Description

1 METHODS: FRACTIONAL POLYNOMIAL MODELING

1.1 Overview of fractional polynomial approach

The methodology used to fit the fractional polynomials followed the approach outlined by Jansen *et al*.[1] Specifically, after reconstruction of individual patient-level data (IPD) based on digitized Kaplan-Meier (KM) curves were completed, using the methodology described by Guyot *et al*.[2] the log hazard of overall survival (OS) and progression-free survival (PFS) from eligible randomized controlled trials (RCTs) were fit as a function of time using parametric models of the form:

$$\log \text{hazard} = \mu_0 + \mu_1 t^{P1} + \mu_2 t^{P2}$$

where μ_0 represents the scale parameter, μ_1 and μ_2 represent shape parameters, t represents time, and $P1$ and $P2$ are powers from the set {-1,-0.5, 0, 0.5, 1}, where $t^0 = \ln(t)$; when P1=P2 the model is structured as a repeated powers model (see Jansen 2011). Whereas Jansen *et al*. initially described a wider set of powers, including -3, -2, and 2, more recent publications by Jansen and others have focused on the subset of candidate powers described above.[3-5] Furthermore, the models have been limited to having the first power drawn from the set of {0.1} (i.e. Weibull- and Gompertz-based) and the second power from the set {-1,-0.5, 0, 0.5, 1}.[3-5]

Models involving only the first two terms are called first-order models; those with all three terms are called second order models. Differences, d_0, d_1, and/or d_2, were then added to μs within each term to capture treatment effects; these ds were then meta-analysed.

$$\log \text{hazard} = (\mu_{0+} d_0) + (\mu_1 + d_1) t^{P1} + (\mu_2 + d_2) t^{P2}$$

For each network, 44 fixed effect models were fit, capturing a range of different functional forms, spanning first- and second-order models; the different combinations of powers P1 and P2; and inclusion of d_0 alone, d_0 and d_1 *without* d_2, d_0 and d_2 *without* d_1, or d_0 and d_1 and d_2. As such, resulting models varied in complexity, depending on the number of terms in the model and how many treatment effects were included (Figure 1):

- **Complexity 1**: A first-order fractional polynomial in which treatment effects were placed on the scale parameter (d_0), but no shape parameters, resulting in a proportional hazards model;
- **Complexity 2**: A first-order fractional polynomial in which treatment effects were placed on the scale parameter (d_0), and the shape (i.e., time-related) parameter (d_1); in this model, hazard ratios could vary over time;
- **Complexity 3**: A second-order fractional polynomial in which treatment effects were placed on the scale parameter (d_0) but no shape parameters, resulting in a proportional hazards model;
- **Complexity 4a and 4b**: A second-order fractional polynomial in which treatment effects were placed on the scale parameter (d_0) and one shape parameter (either d_1 or d_2); in this model, hazard ratios could vary over time;

- **Complexity 5**: A second-order fractional polynomial in which treatment effects were placed on the scale parameter (d_0) and both shape parameters, d_1 and d_2; in this model, hazard ratios could vary over time.

Figure 1. Fractional polynomial model development and candidate models

Complexity	Scale	Shape 1 (P1)	Shape 2 (P2)	Number of combinations[a]
1	$(\mu_0 + d_0)$	$\mu_1 \ln(t)$	None	1
	$(\mu_0 + d_0)$	$\mu_1 t$	None	1
2	$(\mu_0 + d_0)$	$(\mu_1 + d_1) \ln(t)$	None	1
	$(\mu_0 + d_0)$	$(\mu_1 + d_1) t$	None	1
3	$(\mu_0 + d_0)$	$\mu_1 \ln(t)$	$\mu_2 t^{P2a}$	5
	$(\mu_0 + d_0)$	$\mu_1 t$	$\mu_2 t^{P2a}$	5
4a	$(\mu_0 + d_0)$	$(\mu_1 + d_1) \ln(t)$	$\mu_2 t^{P2a}$	5
	$(\mu_0 + d_0)$	$(\mu_1 + d_1) t$	$\mu_2 t^{P2a}$	5
4b	$(\mu_0 + d_0)$	$\mu_1 \ln(t)$	$(\mu_2 + d_2) t^{P2a}$	5
	$(\mu_0 + d_0)$	$\mu_1 t$	$(\mu_2 + d_2) t^{P2a}$	5
5	$(\mu_0 + d_0)$	$(\mu_1 + d_1) \ln(t)$	$(\mu_2 + d_2) t^{P2a}$	5
	$(\mu_0 + d_0)$	$(\mu_1 + d_1) t$	$(\mu_2 + d_2) t^{P2a}$	5

[a]The number of combinations is based on setting P2 to each value within the set {−1,−0.5,0,0.5,1}.

Source: Goring et al. ISPOR 2019[5]

All models were fit as fixed effect models; random effects models were not fit due to the small number of studies (at most two) on each link within the networks.

1.2 Model selection heuristic

Once all models were fit, the best-suited model was selected using a pre-defined heuristic that incorporated both statistical goodness of fit and clinical plausibility.[5]

For clarity, the process is described using the model selection process used for the fractional polynomial (FP) network meta-analysis (NMA) of OS for the programmed death-ligand 1 (PD-L1) >=50% & mixed histology target population.

1. **Deviance information criterion (DIC):** The DIC for each model was standardized by subtracting the smallest DIC among all models. Models in the top-ranked cluster according to DIC were retained as candidate models (Figure 2). In this example, the top ranked cluster was identified by models that fell within 2 points from the top model (i.e.,

models with data points to the left of the heavy dotted line in Figure 2). In this example, this resulted in having four candidate models based on DIC:

- P1=1 (Gompertz-based), P2=0.5;
- P1=1 (Gompertz-based), P2=0;
- P1=0 (Weibull-based), P2=1;
- P1=0 (Weibull -based), P2=0.5.

Figure 2. Standardized DICs across evaluated models and identification of candidate models based on DIC

Note: "Weibull" refers to models with P1=0; "Gompertz" refers to models having P1 = 1. Complexity levels correspond to those described in Figure 1.
Abbreviations: DIC = deviance information criterion

2. **Additional model complexity penalties:** As the DIC may insufficiently penalize for complexity, less-complex models from the same families in the identified cluster of best-fitting models were also retained for consideration. To limit the number of candidate models, and to focus on relatively good-fitting models, only those with a standardized DIC < 20 were retained. This resulted in considering all models with datapoints falling within the red rectangles in Figure 2).

3. **Visual inspection of observed versus modeled output:** Study-specific FP model survival curves were overlaid upon observed KM survival curves to visualize the goodness of fit between observed and parameterized curves within the observed study period.

4. **Clinical plausibility of extrapolation periods:** For extrapolations beyond the observed period of each study, the clinical plausibility was evaluated. Plausibility was guided by

several *a priori* assumptions, which have been reviewed by and updated according to input from clinical and methodological experts:

- Long term OS (or PFS) hazards in immunotherapy (IO)-based arms should not substantially exceed OS (or PFS) hazard in chemo arms
    - This is based on pan-tumor evidence that IOs are associated with more durable response than chemotherapies;
    - This may be confounded by durable responses from second and later lines of IO in the first-line chemotherapy arm, hence the focus is on *substantial* deviations from this trend;
- Absolute hazards should not have a steep & monotonically increasing upward trend over the long-term;
- Hazard ratios should not have a steep & monotonically increasing upward trend over the long-term;
- Long-term hazard ratios for CheckMate 9LA should align with those for CheckMate 227;
- Long term hazards should generally trend toward the background mortality hazards for the target population.

To illustrate components 3 and 4 of the heuristic, KM overlays from the top candidate model based on DIC alone is presented in

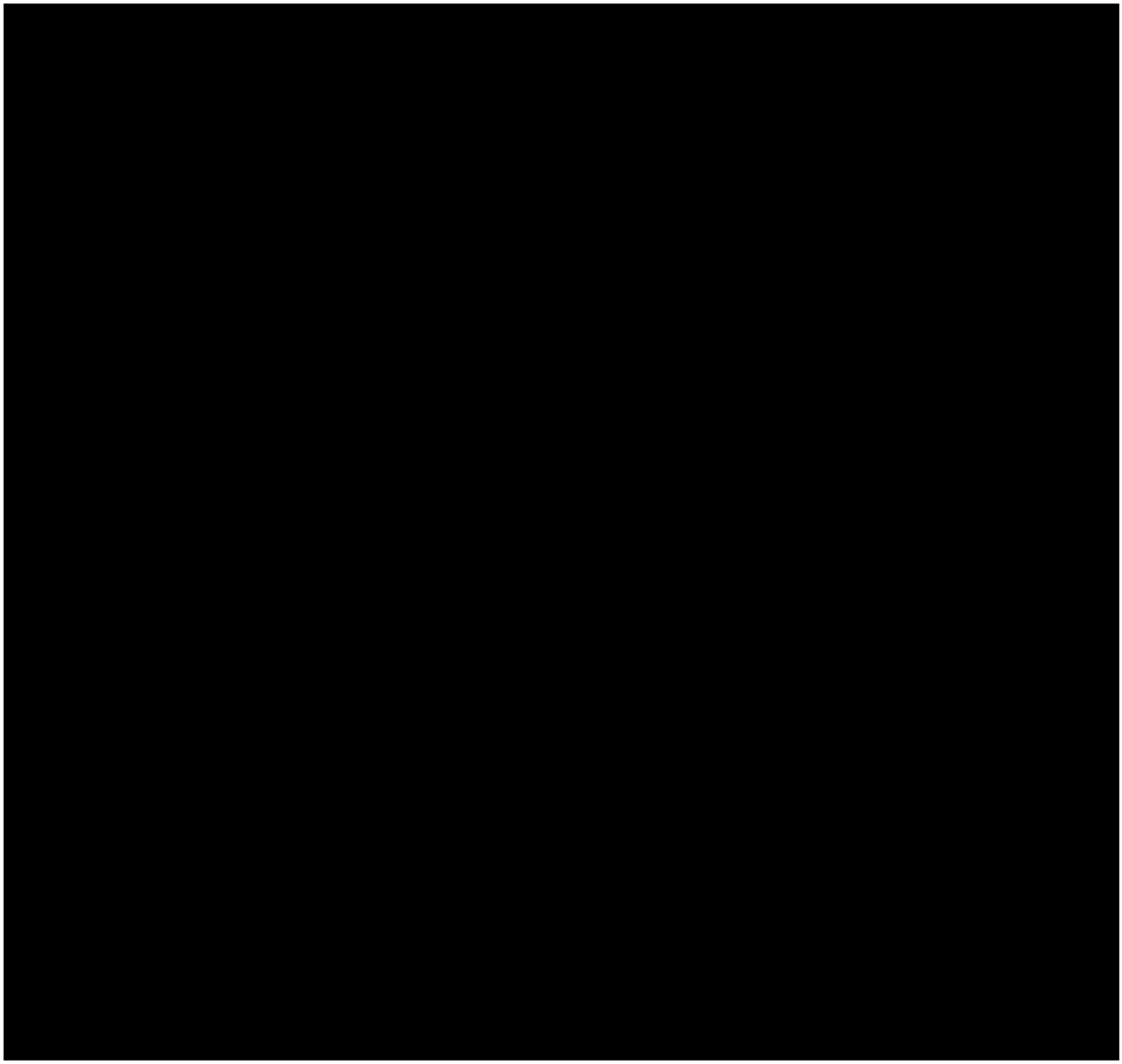
Figure 3. [redacted]

These same plots were reviewed for all seven candidate models identified in Figure 2. The plots were reviewed in order of increasing standardized DIC. The final selected model was the best-ranked model based on DIC that also addressed all the three other components of the heuristic: reasonable model complexity, good alignment with the modeled vs. observed survival curves based on visual inspection, and clinically plausible projections beyond the observed period. The curves associated with the selected model in this example are provided in

Figure 4.

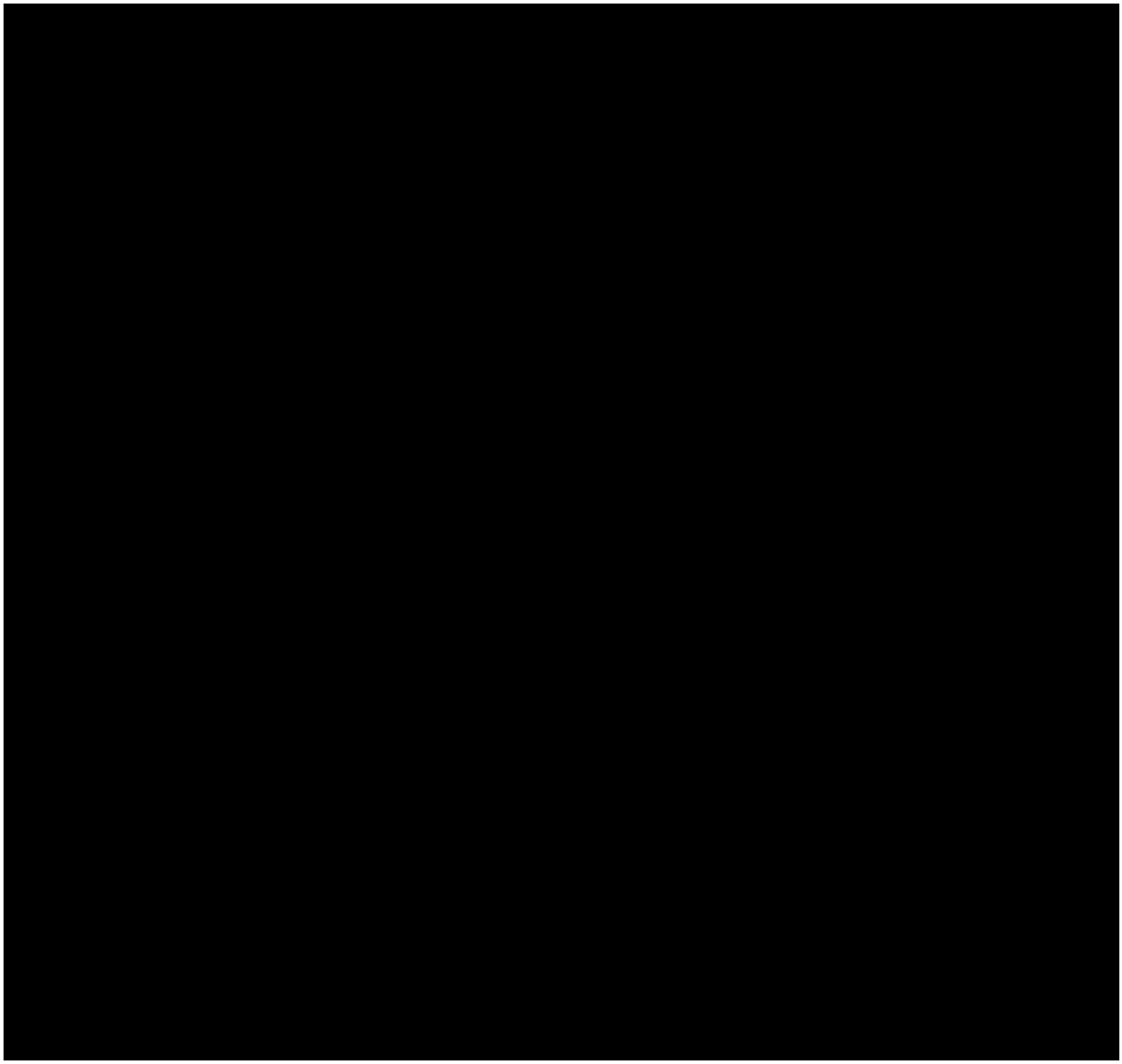
In all model output, hazard ratios that were based on time points beyond the observed period were clearly annotated as such, to ensure a transparent distinction between observed and projected hazard ratios.

Figure 3. KM overlays from top OS model based on DIC alone (P1=1 P2=0; treatment effects on scale and both shape parameters)



Note: Curves fit to KeyNote 024 and KeyNote 042 capture the meta-analyzed differences from both RCTs for PEMBRO vs. chemo, rather than the study-specific differences
Abbreviations: Chemo = chemotherapy; IPI = ipilimumab; KM = Kaplan-Meier; NIVO = nivolumab; PEMBRO = pembrolizumab

Figure 4. KM overlays from selected OS model (P1=0 P2=1; treatment effects on scale, and 1st shape parameter)



Note: Curves fit to KeyNote 024 and KeyNote 042 capture the meta-analyzed differences from both RCTs for PEMBRO vs. chemo, rather than the study-specific differences
Abbreviations: Chemo = chemotherapy; IPI = ipilimumab; KM = Kaplan-Meier; NIVO = nivolumab; PEMBRO = pembrolizumab

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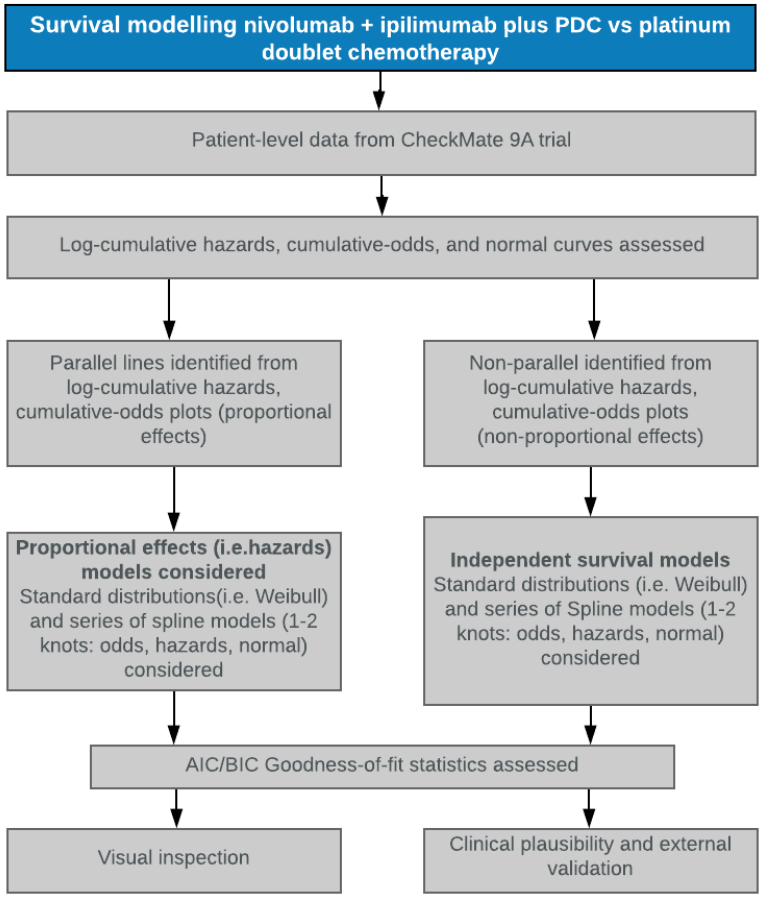
Appendix B. Curve selection for subgroups

The same process for fitting and selecting survival models (outlined below) was used for the subgroups as for the ITT population in the original submission. However, as noted by the ERG, lower patient numbers within the subgroups may mean that the estimation of absolute survival effects within these populations is less robust than the all-comers population. Furthermore, there is a paucity of external histology and PD-L1 specific clinical data available to guide selection of the most appropriate distribution and this necessitates higher reliance on clinical opinion. This means that the curve selections are likely to be associated with greater uncertainty for the subgroups than in the all-comers population.

The process for fitting survival models to patient-level data was based on methods guidance from the DSU at NICE.[1] Figure 1 presents the process for identifying the survival model for both PFS and OS. The steps required to determine the most appropriate curve fits in the model included the following:

- Testing the proportional effects assumption: The log-cumulative hazards, log-cumulative odds, and standardised normal curve plots were assessed to determine if the data indicate proportional effects. This assessment was done both by testing the significance of the Grambsch-Therneau correlation test between Schoenfeld residuals and log of time as well as visual inspection to determine if the survival curves of each arm were parallel.
- Based on the assessment of proportional hazards, survival models fitted to the data from the clinical trial either as dependent models with a treatment effect or independently to each treatment arm were explored and assessed.
- Within the various survival models, the Akaike information criterion (AIC) and Bayesian information criterion (BIC) goodness-of-fit statistics were assessed to identify differences in statistical fit among the survival models.
- The choice of survival model used for the base-case economic model was based on the following:
  - The AIC and BIC statistics of the survival models, which provide goodness of fit to the Kaplan-Meier data
  - Visual fit compared with the Kaplan-Meier data
  - Clinical plausibility and external validation of the extrapolated survival compared with real-world survival data (following same conditional survival approach as used in the original curve selection for ITT) and input from UK clinicians

Figure 1. Identifying the parametric survival curves for the economic model



Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; PDC = platinum doublet chemotherapy.

Overall survival

PD-L1 > 50% mixed histology

Table 1 shows that the proportional hazards assumption is violated, with the Grambsch-Therneau test showing that the hazards were significantly different from proportional (*P* = 0.0062504). Furthermore, Figure 2 shows the log-cumulative hazard plots are crossing, which indicates that the hazards are not constant over time. Therefore, only independent models were investigated.

Table 1. PD-L1 > 50% mixed histology Grambsch-Therneau test

	Chi-squared	df	*P* value
Treatment	7.476654	1	0.0062504
Global	7.476654	1	0.0062504

Figure 2. PD-L1 > 50% mixed histology log-cumulative hazard plot

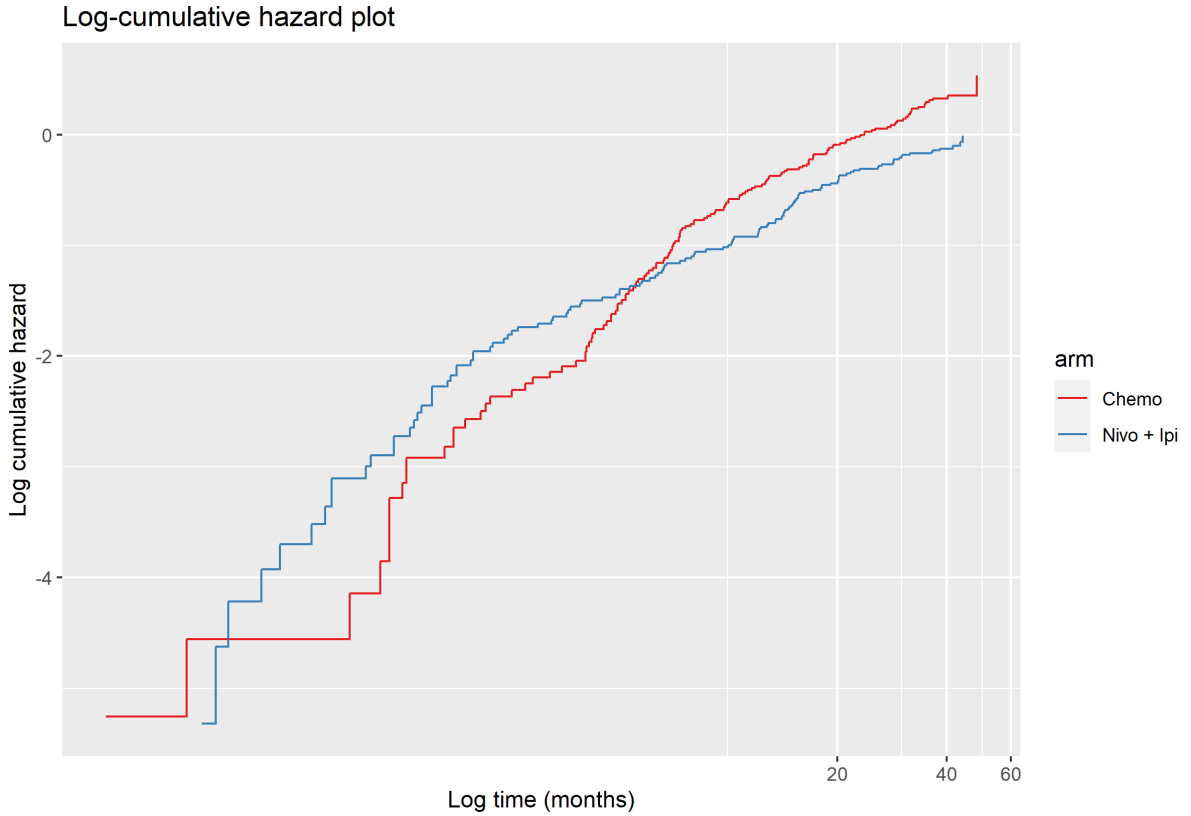


Table 2 presents goodness-of-fit statistics for the parametric curves based on data from the nivolumab + ipilimumab arm of CheckMate-227 part 1. The generalised gamma and lognormal are statistically the best-fitting distributions, followed by spline models. For AIC, distributions with a difference of less than 4 to the distribution with the lowest AIC were considered appropriate based on the Burnham and Anderson rule of thumb.[2] This suggests that not all models would provide a reasonable fit to the data because the range of values observed is much larger.

Table 2. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to overall survival data for nivolumab + ipilimumab

Independent model	AIC	BIC
Generalised gamma	1,108.94	1,118.91
Lognormal	1,109.91	1,116.56
Spline on probit link of survival 1 knot	1,110.40	1,120.37
Spline on probit link of survival 2 knots	1,111.48	1,124.77
Gompertz	1,112.12	1,118.77
Spline on odds 1 knot	1,113.12	1,123.09
Spline on odds 2 knots	1,113.56	1,126.85
Spline on hazards 1 knot	1,113.65	1,123.62
Spline on hazards 2 knots	1,114.53	1,127.82
Log-logistic	1,115.28	1,121.93
Weibull	1,122.89	1,129.53
Gamma	1,126.72	1,133.36
Exponential	1,144.16	1,147.49

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; PDC = platinum doublet chemotherapy.

Table 3 presents goodness-of-fit statistics for the parametric curves based on data from the PDC arm of CheckMate-227 part 1. The odds 1 knot, hazard 1 knot, and lognormal are statistically the best-fitting distributions, followed by log-logistic and other spline models.

Table 3. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to overall survival data for PDC

Independent model	AIC	BIC
Spline on odds 1 knot	1,201.44	1,211.21
Spline on hazards 1 knot	1,201.49	1,211.26
Lognormal	1,201.86	1,208.38
Log-logistic	1,202.76	1,209.27
Spline on probit link of survival 2 knots	1,203.03	1,216.06
Spline on odds 2 knots	1,203.10	1,216.13
Spline on hazards 2 knots	1,203.24	1,216.27
Spline on probit link of survival 1 knot	1,203.77	1,213.54
Generalised gamma	1,203.82	1,213.59
Gompertz	1,207.46	1,213.97
Weibull	1,215.96	1,222.48
Exponential	1,216.27	1,219.52
Gamma	1,217.45	1,223.96

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; PDC = platinum doublet chemotherapy.

Figure 3 shows the independent parametric models for nivolumab + ipilimumab with the best statistical fit based on AIC. All curves fit the KM data reasonably well within the trial period.

Figure 3. Independent parametric models overlaying the overall survival Kaplan-Meier data for nivolumab + ipilimumab

Table 4 presents the predicted landmark survival for patients treated with nivolumab + ipilimumab from the analyses performed on the CheckMate-227 data, and Table 5 presents the predicted landmark survival for the hybrid approach using the combined CheckMate-9LA and CheckMate-227 data.

Clinical opinion confirmed that the range of landmark survival of 20% at 10 years was plausible. All the distributions in Table 4 fall around this range; as such, the distribution with the lowest AIC value (generalised gamma) is selected.

Table 4. Overall survival at different landmark points with the best-fitting distributions using CheckMate-227 trial approach in the nivolumab + ipilimumab

Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
Generalised gamma	1	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Lognormal	2	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Normal 1 knot	3	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Normal 2 knots	4	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Odds 1 knot	6	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Validation data							
CheckMate-227		[redacted]%	[redacted]%	[redacted]%	[redacted]%		
Constructed curve		[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%

Table 5. Overall survival at different landmark points with the best-fitting distributions using CheckMate-227 + CheckMate-9LA trial approach in the nivolumab + ipilimumab + limited PDC arm

Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
Generalised gamma	1	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Lognormal	2	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Normal 1 knot	3	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Normal 2 knots	4	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Odds 1 knot	6	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Validation data							
CheckMate-9LA		[redacted]%					
CheckMate-227		[redacted]%	[redacted]%	[redacted]%	[redacted]%		
Constructed curve		[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%

Figure 4 shows the independent parametric models for PDC with the best statistical fit based on AIC. All curves fit the KM data reasonably well within the trial period.

Figure 4. Independent parametric models overlaying the overall survival Kaplan-Meier data PDC

Table 6 presents the predicted landmark survival for patients treated with PDC from the analyses performed on the CheckMate-227 data. Table 7 presents the predicted landmark survival for the hybrid approach using the combined CheckMate-9LA and CheckMate-227 data.

Clinical opinion confirmed that the range of landmark survival of 7% to 10% at 10 years was plausible. All the distributions in Table 7 fall around this range; as such, the distribution with the lowest AIC value (spline on odds 1-knot) is selected.

Table 6. Overall survival at different landmark points with the best-fitting distributions using CheckMate-227 trial approach in the PDC arm

Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
Odds 1 knot	1	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
hazard 1 knot	2	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Lognormal	3	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Log-logistic	4	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
normal 2 knots	5	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Validation data							
CheckMate-227		[redacted]%	[redacted]%	[redacted]%	[redacted]%		
ERG-preferred estimate for SOC from NICE TA 447						9.6%	1.5%
NICE committee estimated range of 5-year survival for SOC in TA557						5%-11%	
Insinga et al. (2018)						7.6%	2.9%

Table 7. Overall survival at different landmark points with the best-fitting distributions using CheckMate-9LA + CheckMate-227 trial approach in the PDC arm

Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
Odds 1 knot	1	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Hazard 1 knot	2	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Lognormal	3	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Log-logistic	4	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
normal 2 knots	5	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Validation data							
CheckMate-9LA		[redacted]%					
CheckMate-227		[redacted]%	[redacted]%	[redacted]%	[redacted]%		
ERG-preferred estimate for SOC from NICE TA 447						9.6%	1.5%
NICE committee estimated range of 5-year survival for SOC in TA557						5%-11%	
Insinga et al. (2018)						7.6%	2.9%

PD-L1 < 50% non-squamous

The proportional hazards assumption was violated with the Grambsch-Therneau test showing that the hazards were significantly different from proportional (P = 0.0061963) (Table 8).

Furthermore, Figure 5 shows the log-cumulative hazard plots are crossing, which indicates that the hazards were not constant over time. Therefore, only independent models were investigated.

Table 8. PD-L1 < 50% non-squamous Grambsch-Therneau test

	Chi-squared	df	*P* value
Treatment	7.49232	1	0.0061963
Global	7.49232	1	0.0061963

Figure 5. PD-L1 < 50% non-squamous log-cumulative hazard plot

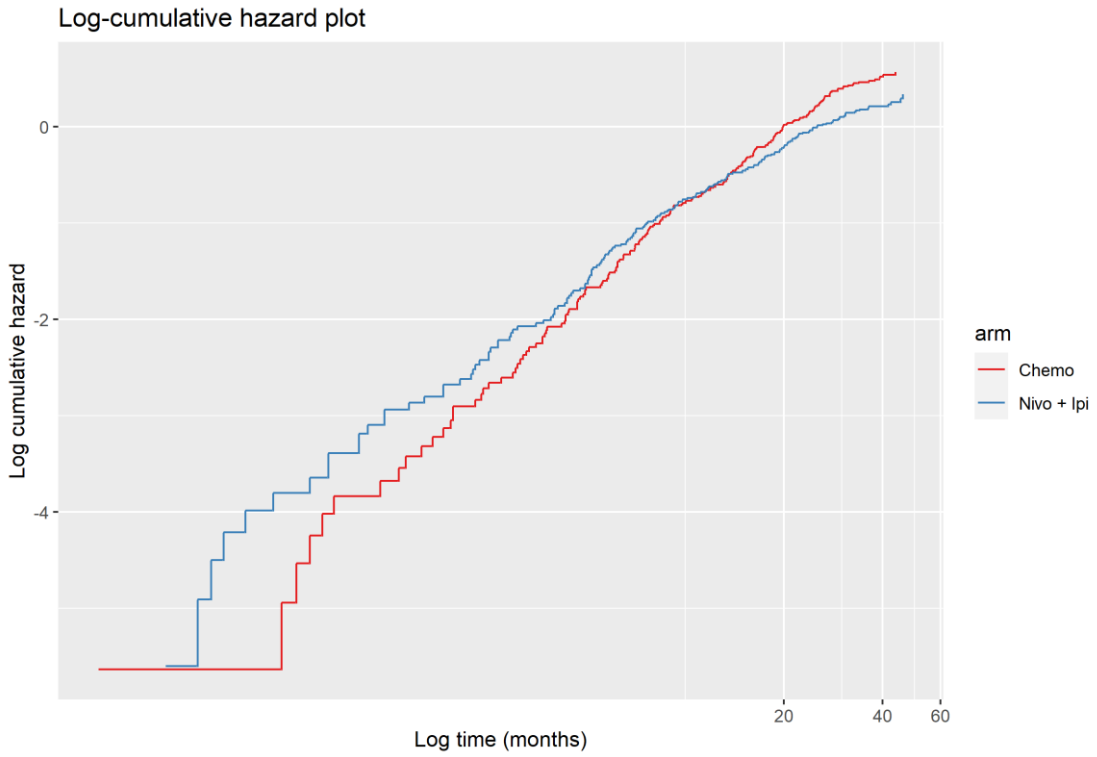


Table 9 presents goodness-of-fit statistics for the parametric curves based on data from the nivolumab + ipilimumab arm of CheckMate-227 part 1. The log-logistic, lognormal and odds 1 knot are statistically the best-fitting distributions, followed by other spline models.

Table 9. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to overall survival data for nivolumab + ipilimumab

Independent model	AIC	BIC
Log-logistic	1,646.53	1,653.74
Lognormal	1,646.53	1,653.74
Spline on odds 1 knot	1,646.72	1,657.54
Spline on probit link of survival 2 knots	1,647.69	1,662.11
Spline on hazards 1 knot	1,648.03	1,658.85
Spline on odds 2 knots	1,648.03	1,662.46

Independent model	AIC	BIC
Gompertz	1,648.36	1,655.57
Spline on hazards 2 knots	1,648.37	1,662.80
Spline on probit link of survival 1 knot	1,648.40	1,659.22
Generalised gamma	1,648.49	1,659.31
Spline on probit link of survival 3 knots	1,649.21	1,667.24
Spline on odds 3 knots	1,649.64	1,667.67
Spline on hazards 3 knots	1,649.82	1,667.85
Weibull	1,660.80	1,668.01
Gamma	1,663.33	1,670.54
Exponential	1,664.49	1,668.10

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; PDC = platinum doublet chemotherapy.

Table 10 presents goodness-of-fit statistics for the parametric curves based on data from the PDC arm of CheckMate-227 part 1. The log-logistic is statistically the best-fitting distribution, followed by spline models.

Table 10. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to overall survival data for PDC

Independent model	AIC	BIC
Log-logistic	1,835.24	1,842.53
Spline on odds 1 knot	1,837.24	1,848.16
Spline on odds 2 knots	1,839.04	1,853.60
Spline on probit link of survival 2 knots	1,839.99	1,854.56
Spline on hazards 2 knots	1,840.34	1,854.90
Spline on probit link of survival 1 knot	1,840.39	1,851.32
Generalised gamma	1,841.33	1,852.26
Spline on hazards 1 knot	1,841.65	1,852.58
Lognormal	1,841.68	1,848.96
Gamma	1,850.49	1,857.78
Exponential	1,851.92	1,855.56
Gompertz	1,852.40	1,859.68
Weibull	1,852.54	1,859.82

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; PDC = platinum doublet chemotherapy.

Figure 6 shows the independent parametric models for nivolumab + ipilimumab with the best statistical fit based on AIC. All curves fit the KM data reasonably well within the trial period.

Figure 6. Independent parametric models overlaying the overall survival Kaplan-Meier data for nivolumab + ipilimumab

Table 11 presents the predicted landmark survival for patients treated with nivolumab + ipilimumab from the analyses performed on the CheckMate-227 data. Table 12 presents the predicted landmark survival for the hybrid approach using the combined CheckMate-9LA and CheckMate-227 data.

Clinical opinion confirmed that the range of landmark survival of 8% to 11% at 10 years was plausible and most likely towards the lower end of this range. The distribution with the lowest AIC value (log-logistic) has a landmark survival of 8.7% at year 10 and therefore is selected.

Table 11. Overall survival at different landmark points with the best-fitting distributions using CheckMate-227 trial approach in the nivolumab + ipilimumab

Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
Log-logistic	1	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Lognormal	2	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Odds 1 knot	3	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Normal 2 knots	4	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Hazard 1 knot	5	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Validation data							
CheckMate-227		[redacted]%	[redacted]%	[redacted]%			
Constructed curve		[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%

Table 12. Overall survival at different landmark points with the best-fitting distributions using CheckMate-227 + CheckMate-9LA trial approach in the nivolumab + ipilimumab + limited PDC arm

Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
Log-logistic	1	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Lognormal	2	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Odds 1 knot	3	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Normal 2 knots	4	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Hazard 1 knot	5	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Validation data							
CheckMate-9LA		[redacted]%					
CheckMate-227		[redacted]%	[redacted]%	[redacted]%			
Constructed curve		[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%

Figure 7 shows the independent parametric models for PDC with the best statistical fit based on AIC. All curves fit the KM data reasonably well up to 24 months of trial period. A relatively poor fit can be seen after 24 months, with extrapolations overpredicting survival up until approximately 40 months and slightly underpredicting the tail of the KM data.

Figure 7. Independent parametric models overlaying the overall survival Kaplan-Meier data for PDC

Table 13 presents the predicted landmark survival for patients treated with PDC arm from the analyses performed on the CheckMate-227 data. Table 14 presents the predicted landmark survival for the hybrid approach using the combined CheckMate-9LA and CheckMate-227 data.

Clinical opinion noted that the range of survival estimates is perhaps slightly low, as it might not fully capture the impact of IO therapy in the second line. Therefore, the most optimistic distribution that falls within the Burnham rule of thumb for candidate distributions based on AIC is selected, which is the spline on odds 2-knot distribution.

Table 13. Overall survival at different landmark points with the best-fitting distributions using CheckMate-227 trial approach in the PDC arm

Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
Log-logistic	1	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Odd 1 knot	2	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Odds 2 knots	3	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Normal 2 knots	4	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Hazards 2 knots	5	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Validation data							
CheckMate-227		[redacted]%	[redacted]%	[redacted]%			
ERG-preferred estimate for SOC from NICE TA 447						9.6%	1.5%
NICE committee estimated range of 5-year survival for SOC in TA557						5%-11%	
Insinga et al. (2018)						7.6%	2.9%

Table 14. Overall survival at different landmark points with the best-fitting distributions using CheckMate-227 + CheckMate-9LA trial approach in the PDC arm

Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
Log-logistic	1	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Odd 1 knot	2	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Odds 2 knots	3	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Normal 2 knots	4	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Hazards 2 knots	5	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Validation data							
CheckMate-9LA		[redacted]%					
CheckMate-227		[redacted]%	[redacted]%	[redacted]%			
ERG-preferred estimate for SOC from NICE TA 447						9.6%	1.5%

Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
NICE committee estimated range of 5-year survival for SOC in TA557						5%-11%	
Insinga et al. (2018)						7.6%	2.9%

PD-L1 < 50% squamous

The Grambsch-Therneau test did not show that hazards were significantly different from proportional (*P* = 0.3789592) (Table 15). However, Figure 8 shows the log-cumulative hazard plots are crossing, which indicates that the hazards were not constant over time. Therefore, and in line with argument presented in the original submission around different mechanisms of action and long-term proportionality, only independent models were investigated.

Table 15. PD-L1 < 50% non-squamous Grambsch-Therneau test

	Chi-squared	df	*P* value
Treatment	0.7740755	1	0.3789592
Global	0.7740755	1	0.3789592

Figure 8. PD-L1 < 50% Squamous log-cumulative hazard plot

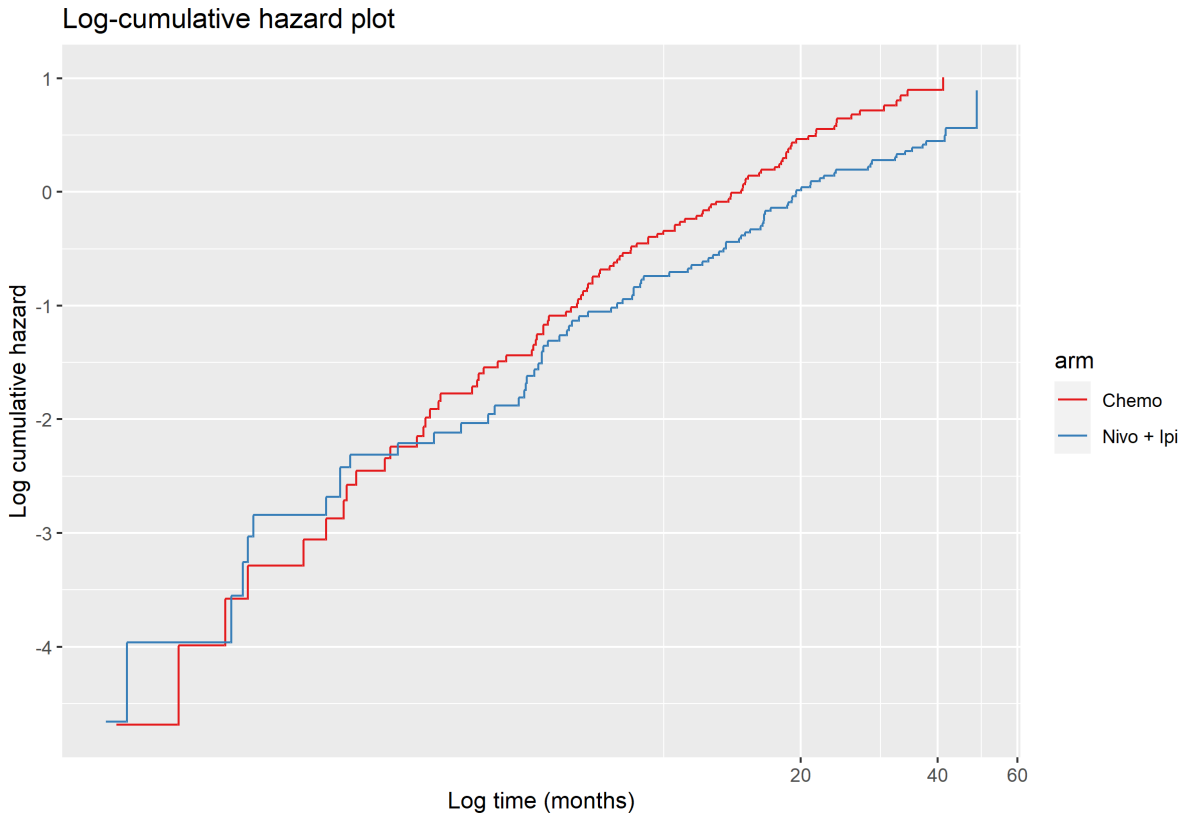


Table 16 presents goodness-of-fit statistics for the parametric curves based on data from the nivolumab + ipilimumab arm of CheckMate-227 part 1. The log-logistic and lognormal are

statistically the best-fitting distributions, followed by spline model, generalised gamma, and exponential.

Table 16. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to overall survival data for nivolumab + ipilimumab

Independent model	AIC	BIC
Log-logistic	712.42	717.74
Lognormal	712.42	717.75
Spline on probit link of survival 1 knot	713.79	721.78
Generalised gamma	713.97	721.96
Exponential	714.19	716.85
Spline on hazards 1 knot	714.33	722.32
Spline on odds 1 knot	714.42	722.41
Gompertz	715.28	720.61
Spline on probit link of survival 2 knots	715.78	726.43
Gamma	716.07	721.40
Spline on hazards 2 knots	716.18	726.84
Weibull	716.19	721.52
Spline on odds 2 knots	716.32	726.97
Spline on probit link of survival 3 knots	717.28	730.60
Spline on hazards 3 knots	717.47	730.79
Spline on odds 3 knots	717.93	731.24

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; PDC = platinum doublet chemotherapy.

Table 17 presents goodness-of-fit statistics for the parametric curves based on data from the PDC arm of CheckMate-227 part 1. The log-logistic and lognormal are statistically the best-fitting distributions, followed by survival 1 knot, generalised gamma, and spline models.

Table 17. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to overall survival data for PDC

Independent model	AIC	BIC
Log-logistic	724.15	729.53
Lognormal	724.25	729.64
Spline on probit link of survival 1 knot	725.68	733.75
Generalised gamma	725.85	733.92
Spline on odds 1 knot	726.13	734.20
Spline on hazards 1 knot	726.34	734.42
Spline on probit link of survival 2 knots	727.62	738.39
Spline on odds 2 knots	727.65	738.42
Spline on hazards 2 knots	728.30	739.06
Gamma	729.50	734.88

Independent model	AIC	BIC
Weibull	731.53	736.91
Exponential	732.33	735.03
Gompertz	734.33	739.71

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; PDC = platinum doublet chemotherapy.

Figure 9 shows the independent parametric models for nivolumab + ipilimumab with the best statistical fit based on AIC. All curves fit the KM data reasonably well except the exponential distribution, within the trial period.

Figure 9. Independent parametric models overlaying the overall survival Kaplan-Meier data for nivolumab + ipilimumab

Table 18 presents the predicted landmark survival for patients treated with nivolumab + ipilimumab arm from the analyses performed on the CheckMate-227 data. Table 19 presents the predicted landmark survival for the hybrid approach using the combined CheckMate-9LA and CheckMate-227 data.

Clinical opinion confirmed that the range of landmark survival of 3% to 5% at 10 years was plausible but that it could be higher than this. Therefore, based on clinical opinion, the most optimistic distribution in Table 19, which is also the distribution with the lowest AIC value, is selected (log-logistic).

Table 18. Overall survival at different landmark points with the best-fitting distributions using CheckMate-227 trial approach in the nivolumab + ipilimumab arm

Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
Log-logistic	1	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Lognormal	2	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Normal 1 knot	3	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Generalised gamma	4	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Exponential	5	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Validation data							
CheckMate-227		[redacted]%	[redacted]%	[redacted]%	[redacted]%		
Constructed curve		[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%

Table 19. Overall survival at different landmark points with the best-fitting distributions using CheckMate-227 + CheckMate-9LA trial approach in the nivolumab + ipilimumab + limited PDC arm

Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
Log-logistic	1	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Lognormal	2	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Normal 1 knot	3	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Generalised gamma	4	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Exponential	5	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Validation data							
CheckMate-9LA		[redacted]%					
CheckMate-227		[redacted]%	[redacted]%	[redacted]%	[redacted]%		
Constructed curve		[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%

Figure 10 shows the independent parametric models for PDC with the best statistical fit based on AIC. All curves fit the KM data reasonably well within the trial period.

Figure 10. Independent parametric models overlaying the overall survival Kaplan-Meier data for PDC

Table 20 presents the predicted landmark survival for patients treated with PDC arm from the analyses performed on the CheckMate-227 data. Table 21 presents the predicted landmark survival for the hybrid approach using the combined CheckMate-9LA and CheckMate-227 data.

Clinical opinion noted that the range of survival estimates is perhaps slightly low, as it might not fully capture the impact of IO therapy in the second line. Therefore, the most optimistic distribution, the log-logistic, is selected.

Table 20. Overall survival at different landmark points with the best-fitting distributions using CheckMate-227 trial approach in the PDC arm

Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
Log-logistic	1	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Lognormal	2	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Normal knot 1	3	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Generalised gamma	4	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Odds knot 1	5	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Validation data							
CheckMate-227		[redacted]%	[redacted]%	[redacted]%	[redacted]%		
ERG-preferred estimate for SOC from NICE TA 447		-	-			9.6%	1.5%

Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
NICE committee estimated range of 5-year survival for SOC in TA557		-	-			5%-11%	
Insinga et al. (2018)						7.6%	2.9%

Table 21. Overall survival at different landmark points with the best-fitting distributions using CheckMate-227 + CheckMate-9LA trial approach in the PDC arm

Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
Log-logistic	1	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Lognormal	2	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Normal knot 1	3	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Generalised gamma	4	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Odds knot 1	5	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Validation data							
CheckMate-9LA		[redacted]%					
CheckMate-227		[redacted]%	[redacted]%	[redacted]%	[redacted]%		
ERG-preferred estimate for SOC from NICE TA 447						9.6%	1.5%
NICE committee estimated range of 5-year survival for SOC in TA557						5%-11%	

Progression-free survival

PD-L1 > 50% mixed histology

Table 22 presents goodness-of-fit statistics for the parametric curves based on data from the nivolumab + ipilimumab arm of CheckMate-227 part 1.

Table 22. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to progression-free survival data for nivolumab + ipilimumab

Independent model	AIC	BIC
Spline on hazards 2 knots	1,040.7	1,054.0
Spline on odds 2 knots	1,042.0	1,055.3
Spline on probit link of survival 2 knots	1,046.0	1,059.3
Spline on probit link of survival 1 knot	1,046.3	1,056.2
Generalised gamma	1,048.1	1,058.1
Spline on odds 1 knot	1,049.5	1,059.5
Spline on hazards 1 knot	1,050.3	1,060.3

Independent model	AIC	BIC
Lognormal	1,057.3	1,063.9
Log-logistic	1,065.7	1,072.3
Gompertz	1,074.8	1,081.4
Weibull	1,084.7	1,091.4
Gamma	1,095.2	1,101.8
Exponential	1,136.0	1,139.3

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; PDC = platinum doublet chemotherapy.

Table 23 presents goodness-of-fit statistics for the parametric curves based on data from the nivolumab + ipilimumab arm of CheckMate-227 part 1. The log-logistic shows statistically the best-fitting distribution, followed by spline models, and lognormal.

Table 23. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to progression-free survival data for PDC

Independent model	AIC	BIC
Log-logistic	869.1	875.6
Spline on odds 1 knot	870.6	880.4
Spline on hazards 2 knots	870.6	883.7
Lognormal	871.7	878.2
Spline on probit link of survival 2 knots	871.8	884.8
Spline on probit link of survival 1 knot	872.2	881.9
Spline on odds 2 knots	872.6	885.6
Spline on hazards 1 knot	872.6	882.4
Generalised gamma	872.7	882.5
Gamma	881.8	888.3
Weibull	887.8	894.3
Exponential	893.3	896.6
Gompertz	895.3	901.8

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; PDC = platinum doublet chemotherapy.

Figure 11 shows the independent parametric models for nivolumab + ipilimumab + PDC with the best statistical fit based on AIC. All distributions are a relatively good fit to the KM data up to 12 months, and a poor visual fit to the KM data can be seen after that until the end of trial period.

Figure 11. Independent parametric models overlaying the progression-free survival Kaplan-Meier data for nivolumab + ipilimumab

Table 24 presents the predicted landmark survival for patients treated with nivolumab + ipilimumab arm from the analyses performed on the CheckMate-227 data. Table 25 presents the predicted landmark survival for the hybrid approach using the combined CheckMate-9LA and CheckMate-227 data.

Clinical opinion suggested that the range of landmark progression-free survival of 8% to 12% at 10 years is pessimistic, as most surviving patients long-term would likely be progression-free. Therefore, based on clinical opinion, the generalised gamma distribution is selected.

Table 24. Progression-free survival at different landmark points with the best-fitting distributions using CheckMate-227 trial approach in the nivolumab + ipilimumab

Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
Hazard 2 knots	1	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Odds 2 knots	2	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Normal 2 knots	3	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Normal 1 knot	4	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Generalised gamma	5	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Validation data							
CheckMate-227		[redacted]%	[redacted]%	[redacted]%	[redacted]%		

Table 25. Progression-free survival at different landmark points with the best-fitting distributions using CheckMate-227 + CheckMate-9LA trial approach in the nivolumab + ipilimumab + limited PDC arm

Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
Hazard 2 knots	1	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Odds 2 knots	2	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Normal 2 knots	3	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Normal 1 knot	4	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Generalised gamma	5	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Validation data							
CheckMate-9LA		[redacted]%					
CheckMate-227		[redacted]%	[redacted]%	[redacted]%			
Constructed curve		[redacted]%	[redacted]%	[redacted]%		[redacted]%	

Figure 12 shows the independent parametric models for PDC with the best statistical fit based on AIC. All curves fit the KM data reasonably well within the trial period.

Figure 12. Independent parametric models overlaying the progression-free survival Kaplan-Meier data for PDC

Table 26 presents the predicted landmark survival for patients treated with PDC arm from the analyses performed on the CheckMate-227 data. Table 27 presents the predicted landmark survival for the hybrid approach using the combined CheckMate-9LA and CheckMate-227 data.

Clinical opinion suggested that the range of landmark progression-free survival at 10 years is pessimistic, as the subset of patients receiving second-line IO therapy would perform well. Therefore, based on clinical opinion, the most optimistic distribution (log-logistic) is selected.

Table 26. Progression-free survival at different landmark points with the best-fitting distributions using CheckMate-227 trial approach in the PDC arm

Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
Log-logistic	1	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Odds 1 knot	2	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Hazard 2 knots	3	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Chemo-Lognormal	4	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Normal 2 knots	5	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Validation data							
CheckMate-227		[redacted]%	[redacted]%	[redacted]%			
Constructed curve		[redacted]%	[redacted]%	[redacted]%			

Table 27. Progression-free survival at different landmark points with the best-fitting distributions using CheckMate-227 + CheckMate-9LA trial approach in the PDC arm

Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
Log-logistic	1	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Odds 1 knot	2	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Hazard 2 knots	3	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Lognormal	4	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Normal 2 knots	5	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Validation data							
CheckMate-9LA		[redacted]%					
CheckMate-227		[redacted]%	[redacted]%	[redacted]%			
Constructed Curve		[redacted]%	[redacted]%	[redacted]%		[redacted]%	

PD-L1 < 50% non-squamous

Table 28 presents goodness-of-fit statistics for the parametric curves based on data from the nivolumab + ipilimumab arm of CheckMate-227 part 1. The splines on odds 1 knot and odds 2 knot are statistically the best-fitting distributions, followed by other spline models.

Table 28. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to progression-free survival data for nivolumab + ipilimumab

Independent model	AIC	BIC
Spline on odds 1 knot	1,301.0487	1,311.8661

Independent model	AIC	BIC
Spline on odds 2 knots	1,301.2815	1,315.7047
Spline on hazards 2 knots	1,302.0485	1,316.4717
Spline on hazards 1 knot	1,302.3141	1,313.1,315
Spline on probit link of survival 1 knot	1,305.4995	1,316.3169
Spline on probit link of survival 2 knots	1,306.2649	1,320.6881
Generalised gamma	1,307.9485	1,318.7659
Lognormal	1,312.0493	1,319.2609
Log-logistic	1,314.1519	1,321.3635
Gompertz	1,319.8768	1,327.0884
Weibull	1,359.7075	1,366.9191
Gamma	1,373.4994	1,380.711
Exponential	1,389.4825	1,393.0883

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; PDC = platinum doublet chemotherapy.

Table 29 presents goodness-of-fit statistics for the parametric curves based on data from the PDC arm of CheckMate-227 part 1. The log-logistic is statistically the best-fitting distribution, followed by other spline models.

Table 29. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to progression-free survival data for PDC

Independent model	AIC	BIC
Log-logistic	1,300.4176	1,307.7014
Spline on odds 1 knot	1,302.3446	1,313.2704
Spline on hazards 2 knots	1,302.8978	1,317.4654
Spline on probit link of survival 2 knots	1,303.8804	1,318.4481
Spline on odds 2 knots	1,303.9763	1,318.5439
Spline on hazards 1 knot	1,305.8792	1,316.805
Lognormal	1,306.2748	1,313.5586
Spline on probit link of survival 1 knot	1,306.2991	1,317.2249
Generalised gamma	1,306.9533	1,317.8791
Gamma	1,323.6267	1,330.9105
Weibull	1,328.5461	1,335.8299
Gompertz	1,329.1961	1,336.4799
Exponential	1,329.4817	1,333.1236

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; PDC = platinum doublet chemotherapy.

Figure 13 shows the independent parametric models for nivolumab + ipilimumab with the best statistical fit based on AIC. All distributions fit the KM data reasonably well up to month 20 of the trial period.

Figure 13. Independent parametric models overlaying the progression-free survival Kaplan-Meier data for nivolumab + ipilimumab

Table 30 presents the predicted landmark survival for patients treated with nivolumab + ipilimumab arm from the analyses performed on the CheckMate-227 data. Table 31 presents the predicted landmark survival for the hybrid approach using the combined CheckMate-9LA and CheckMate-227 data.

Clinical opinion suggested that the range of landmark progression-free survival at 10 years is fairly accurate and would most likely be closer to the higher end of the range. Therefore, based on clinical opinion, the most optimistic distribution (spline on odds 1 knot) is selected.

Table 30. Progression-free survival at different landmark points with the best-fitting distributions using CheckMate-227 trial approach in the nivolumab + ipilimumab

Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
Odds 1 knot	1	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Odds 2 knots	2	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Hazard 2 knots	3	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Hazard 1 knot	4	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Normal 1 knot	5	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Validation data							
CheckMate-227		[redacted]%	[redacted]%	[redacted]%			

Table 31. Progression-free survival at different landmark points with the best-fitting distributions using CheckMate-227 + CheckMate-9LA trial approach in the nivolumab + ipilimumab + limited PDC arm

Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
Odds 1 knot	1	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Odds 2 knots	2	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Hazard 2 knots	3	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Hazard 1 knot	4	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Normal 1 knot	5	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Validation data							
CheckMate-9LA		[redacted]%					
CheckMate-227		[redacted]%	[redacted]%	[redacted]%			
Constructed curve		[redacted]%	[redacted]%	[redacted]%		[redacted]%	

Figure 14 shows the independent parametric models for PDC with the best statistical fit based on AIC. All curves fit the KM data reasonably well during the trial period.

Figure 14. Independent parametric models overlaying the progression-free survival Kaplan-Meier data for PDC

Table 32 presents the predicted landmark survival for patients treated with PDC arm from the analyses performed on the CheckMate-227 data. Table 33 presents the predicted landmark survival for the hybrid approach using the combined CheckMate-9LA and CheckMate-227 data.

Clinical opinion suggested that the range of landmark progression-free survival at 10 years is pessimistic, as the subset of patients receiving second-line IO therapy would perform well. Therefore, based on clinical opinion, the most optimistic distribution (spline on odds 2 knot) is selected.

Table 32. Progression-free survival at different landmark points with the best-fitting distributions using CheckMate-227 trial approach in the PDC arm

Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
Log-logistic	1	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Odds 1 knot	2	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Hazard 2 knots	3	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Normal 2 knots	4	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Odds 2 knots	5	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Validation data							
CheckMate-227		[redacted]%	[redacted]%	[redacted]%	[redacted]%		

Table 33. Progression-free survival at different landmark points with the best-fitting distributions using CheckMate-227 + CheckMate-9LA trial approach in the PDC arm

Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
Log-logistic	1	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Odds 1 knot	2	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Hazard 2 knots	3	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Normal 2 knots	4	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Odds 2 knots	5	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Validation data							
CheckMate-9LA		[redacted]%					
CheckMate-227		[redacted]%	[redacted]%	[redacted]%	[redacted]%		
Constructed curve		[redacted]%	[redacted]%	[redacted]%	[redacted]%		

PD-L1 < 50% squamous

Table 34 presents goodness-of-fit statistics for the parametric curves based on data from the nivolumab + ipilimumab arm of CheckMate-227 part 1. The generalised gamma is statistically the best-fitting distribution, followed by other spline models.

Table 34. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to progression-free survival data for nivolumab + ipilimumab

Independent model	AIC	BIC
Generalised gamma	516.1	524.1

Independent model	AIC	BIC
Spline on probit link of survival 2 knots	517.9	528.6
Spline on odds 2 knots	519.7	530.4
Spline on probit link of survival 1 knot	519.9	527.9
Spline on hazards 2 knots	521.0	531.6
Spline on odds 1 knot	524.0	532.0
Spline on hazards 1 knot	525.5	533.5
Lognormal	529.5	534.8
Log-logistic	532.4	537.7
Gompertz	537.8	543.2
Weibull	553.4	558.8
Gamma	558.0	563.3
Exponential	559.5	562.2

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; PDC = platinum doublet chemotherapy.

Table 35 presents goodness-of-fit statistics for the parametric curves based on data from the PDC arm of CheckMate-227 part 1. The hazard knot 2 is statistically the best-fitting distribution, followed by odds knot 2, log-logistic, and other spline models.

Table 35. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to progression-free survival data for PDC

Independent model	AIC	BIC
Spline on hazards 2 knots	435.2	446.0
Spline on odds 2 knots	438.3	449.0
Log-logistic	439.2	444.6
Spline on probit link of survival 2 knots	439.3	450.1
Spline on odds 1 knot	441.2	449.2
Spline on hazards 1 knot	443.3	451.4
Lognormal	448.5	453.9
Generalised gamma	449.9	458.0
Spline on probit link of survival 1 knot	450.4	458.5
Gamma	468.0	473.4
Weibull	478.5	483.9
Exponential	484.0	486.7
Gompertz	484.8	490.2

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; PDC = platinum doublet chemotherapy.

Figure 15 shows the independent parametric models for nivolumab + ipilimumab with the best statistical fit based on AIC. All curves have a reasonable fit the KM data during the trial period, apart from the exponential distribution, which overpredicts survival within trial and appears to be pessimistic long-term.

Figure 15. Independent parametric models overlaying the Progression-free survival Kaplan-Meier data for nivolumab + ipilimumab

Table 36 presents the predicted landmark survival for patients treated with nivolumab + ipilimumab arm from the analyses performed on the CheckMate-227 data. Table 37 presents the predicted landmark survival for the hybrid approach using the combined CheckMate-9LA and CheckMate-227 data.

Clinical opinion suggested that the range of landmark progression-free survival at 10 years is plausibly between 3% and 5% and could even be higher. Therefore, based on clinical opinion, the spline on normal 1 knot distribution is selected.

Table 36. Progression-free survival at different landmark points with the best-fitting distributions using CheckMate-227 trial approach in the nivolumab + ipilimumab

Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
Generalised gamma	1	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Normal knot 2	2	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Odds knot 2	3	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Lognormal	4	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Normal knot 1	5	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Validation data							
CheckMate-227		[redacted]%	[redacted]%	[redacted]%			

Table 37. Progression-free survival at different landmark points with the best-fitting distributions using CheckMate-227 + CheckMate-9LA trial approach in the nivolumab + ipilimumab + limited PDC arm

Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
Generalised gamma	1	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Normal knot 2	2	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Odds knot 2	3	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Lognormal	4	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Normal knot 1	5	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Validation data							
CheckMate-9LA		[redacted]%					
CheckMate-227		[redacted]%	[redacted]%	[redacted]%			
Constructed curve		[redacted]%	[redacted]%	[redacted]%		[redacted]%	

Figure 16 shows the independent parametric models for PDC with the best statistical fit based on AIC. None of the curves provide a good visual fit to the KM data during the 6-12 months trial period. However, several of the spline models provide a good fit to the tail of the KM data.

Figure 16. Independent parametric models overlaying the progression-free survival Kaplan-Meier data for PDC

Table 38 presents the predicted landmark survival for patients treated with PDC arm from the analyses performed on the CheckMate-227 data. Table 39 presents the predicted landmark survival for the hybrid approach using the combined CheckMate-9LA and CheckMate-227 data.

Clinical opinion suggested that the range of landmark progression-free survival at 10 years is pessimistic, as a subset of patients receiving second-line IO therapy would perform well. Therefore, based on clinical opinion, the most optimistic distribution (spline on hazard 2 knots) is selected.

Table 38. Progression-free survival at different landmark points with the best-fitting distributions using CheckMate-227 trial approach in the PDC arm

Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
Hazard knot 2	1	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Odds knot 2	2	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Log-logistic	3	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Normal knot 2	4	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Odds knot 1	5	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Validation data							
CheckMate-227		[redacted]%	[redacted]%	[redacted]%			

Table 39. Progression-free survival at different landmark points with the best-fitting distributions using CheckMate-227 + CheckMate-9LA trial approach in the PDC arm

Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
Hazard knot 2	1	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Odds knot 2	2	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Log-logistic	3	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Normal knot 2	4	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Odds knot 1	5	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Validation data							
CheckMate-9LA		[redacted]%					
CheckMate-227		[redacted]%	[redacted]%	[redacted]%			
Constructed curve		[redacted]%	[redacted]%	[redacted]%		[redacted]%	

Summary of curve selection results

Table 40 and Table 41 summarise the base-case curve selections for OS and PFS in each subgroup.

Table 40. Summary of OS curve selection

	Nivolumab + ipilimumab + PDC	PDC
PD-L1 > 50% mixed histology	Generalised gamma	Spline odds 1 knot
PD-L1 < 50% non-squamous	Log-logistic	Spline odds 2 knot

	Nivolumab + ipilimumab + PDC	PDC
PD-L1 < 50% squamous	Log-logistic	Log-logistic

Table 41. Summary of PFS curve selection

	Nivolumab + ipilimumab + PDC	PDC
PD-L1 > 50% mixed histology	Generalised gamma	Log-logistic
PD-L1 < 50% non-squamous	Spline odds 1 knot	Spline odds 2 knot
PD-L1 < 50% squamous	Spline normal 1 knot	Spline hazards 2 knot

References

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2. Burnham K, Anderson D. Model selection and multimodel inference. A Practical Information-theoretic Approach. 2004 01 Jan.

3. Insinga RP, Vanness DJ, Feliciano JL, Vandormael K, Traore S, Burke T. Cost-effectiveness of pembrolizumab in combination with chemotherapy in the 1st line treatment of non-squamous NSCLC in the US. J Med Econ. 2018 Dec;21(12):1191-205.

NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

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

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **15th January 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted]. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with untreated advanced non-small-cell lung cancer and current treatment options	
About you	
1. Your name	**Alastair Greystoke**
2. Name of organisation	**Newcastle University/ Newcastle upon Tyne Hospitals NHS trust**
3. Job title or position	**Senior Lecturer and Honorary Consultant in Medical Oncology**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
The aim of treatment for this condition	
8. What is the main aim of treatment with nivolumab with ipilimumab? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Maintain quality of life and prevent disability, improve survival, improve or prevent cancer related symptom. Long term disease control in a proportion of the population.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	An improvement in survival by 2 months. A response rate of over 30% maintained for over 2 months. Any increase in 5 year survival.

or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes 1) The number of long term survivors treated with immunotherapy (either as single agent or in combination with chemotherapy) whilst significant is still only a small minority of the population. This needs to be increased and more effective treatments are required for patients whose cancers progress on immunotherapy. 2) Toxicity with chemotherapy and immunotherapy combinations can be problematic, restricting treatment to the very fittest populations. Attribution and appropriate treatment of toxicity can be challenging when giving these combinations. 3) The longer length of treatment associated with immunotherapy (either as single agent or in combination with chemotherapy) has put additional strain on stretched chemotherapy delivery services. It also means that patients may be on continuous treatment with a potential detriment to their quality of life.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Fit patients with performance status 0-1 will normally receive either chemotherapy and immunotherapy in combination or single agent immunotherapy if the cancer tumour proportion score for PDL1 is >50% (this has been temporarily changed to PDL1 >1% as a COVID-19 pandemic temporary measure). These regimens include Non-squamous lung cancer Regardless of PDL1: carboplatin-pemetrexed-pembrolizumab PDL1<50%: carboplatin-paclitaxel-atezolizumab-bevacizumab Squamous lung cancer PDL1 <50% carboplatin-paclitaxel-pembrolizumab

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Treatment is based around the technology appraisals above including TA 557, TA584, TA600. The NICE guideline NG122 (https://www.nice.org.uk/guidance/ng122/resources) also outlines these treatment options as does The European Society of Medical Oncology guideline (https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer: however this includes regimens that are not licensed or funded in the NHS).
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathways of care are well defined. Clinicians may vary in their use of chemo-immunotherapy combinations (over single agent immunotherapy) in the patients with cancer with PDL1 >50%; and in their preferred chemotherapy regimen for non-squamous cancers with PDL1< 50% (with both carboplatin-pemetrexed-pembrolizumab and carboplatin-paclitaxel-atezolizumab-bevacizumab approved for use).
• What impact would the technology have on the current pathway of care?	It would provide another 1st line treatment option, and one that allowed the use of relatively small amounts of chemotherapy in the 1st line setting
12. Will the nivolumab with ipilimumab be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes. This combination is already used in other conditions, and toxicity management algorithms for immunotherapy are well embedded in standard NHS clinical practice.
• How does healthcare resource use differ between the technology and current care?	This regimen would have similar healthcare resource use to other chemotherapy and immunotherapy combinations in routine use in the NHS. All require frequent visits for systemic therapy administration, and all come with the risk of toxicity that may require hospital admission and expert management by a multi-disciplinary team.

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist cancer centres or units.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None. Doctors and nurses already well versed in similar treatment administration and management of toxicity.
13. Do you expect the nivolumab with ipilimumab to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	Yes compared to platinum doublet chemotherapy (as in scope of appraisal); No compared to chemotherapy-immunotherapy combinations as routinely used in the NHS with Cancer Drugs Fund funding.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes compared to platinum doublet chemotherapy (as in scope of appraisal); Possibly compared to other chemotherapy-immunotherapy combinations as amount of chemotherapy given is significantly less particularly when compared to the platinum-pemetrexed-pembrolizumab combination where patients continue maintenance pemetrexed until disease progression or excess toxicity. This commonly leads to chronic fatigue, anaemia and renal impairment which should be less likely with this regimen.

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	None
The use of the nivolumab with ipilimumab	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Yes compared to platinum doublet chemotherapy (as in scope of appraisal) as need to be able to manage the sometimes complicated toxicity that can arise in patients on combinations of chemotherapy and immunotherapy; No compared to chemotherapy-immunotherapy combinations as routinely used in the NHS.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology?	It is presumed that this combination will be used in patients first presenting with metastatic disease. Treatment will normally be continued until disease progression (normally demonstrated by a CT scan) but sometimes continued

Do these include any additional testing?	beyond progression on CT scans until there is a lack of clinical benefit. Treatment may also stopped due to excess toxicity, and once two years has passed from the start of therapy.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	No
• Is the technology a 'step-change' in the management of the condition?	Not in my opinion.
• Does the use of the technology address any particular unmet need of the patient population?	It provides a chemotherapy light option, but in my opinion it does not definitively meet any of the major areas of unmet need that I outlined above in question 10.

19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side-effects of chemotherapy and immunotherapy combinations can be split into those from the chemotherapy and the immunotherapy. Some of these will overlap in nature. Chemotherapy will result in some toxicity in most patients including nausea and fatigue with the risk of neutropenic sepsis, which can lead to significant inpatient stays and loss of independence in frail/ pre-frail individuals. In general apart from neuropathy chemotherapy toxicity is short-lived on cessation of therapy. Immunotherapy is well tolerated in many patients but if immune related side-effects occur they can be severe, long-lasting and difficult to manage with prolonged courses of steroids and other disease modifying agents. With this combination you might expect to less chemotherapy induced toxicity but the addition of iplimumab to the regimen will add to the risk of immunotherapy toxicity (in particular diarrhoea).
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	No. The control arm was platinum doublet chemotherapy; whilst standard of care in fit patients is now chemotherapy-immunotherapy combinations as in Question 11.
• If not, how could the results be extrapolated to the UK setting?	A network meta-analysis may help answer this question

• What, in your view, are the most important outcomes, and were they measured in the trials?	Overall survival, Patient reported outcomes including health related quality of life, response rate, toxicity and progression free survival. All are captured within the clinical trial
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance [TA584, TA181, TA190, TA402, TA531, TA557, TA600]?	No

23. How do data on real-world experience compare with the trial data?	In general outcomes with immunotherapy (including combinations with chemotherapy) have been similar to clinical trials in terms of response and survival, but toxicity rates tend to be higher in the real world.
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
24b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
Representativeness of the trial population 25a. People were only included in CheckMate-9LA trial and 47 CheckMate-227 trial if they had a ECOG performance status of 0 or 1. Is a ECOG performance status	It is presumed that if this regimen is approved it would be restricted by NHSE to the PS0-1 population that were enrolled in the clinical trials, although this does not represent the global lung cancer population. This has certainly been the case with previous chemotherapy -immunotherapy approvals. In addition given the potential toxicity of any chemotherapy immunotherapy regimen I would be reluctant to use the Checkmate-9LA regimen in the PS2 population without supporting data.

of 0 or 1 reflective of the population with advanced NSCLC expected to be treated with nivolumab + ipilimumab + limited PDC in clinical practice? 25b. Patients in CheckMate-9LA and CheckMate-227 had median ages of 65 years and 64 years, respectively, which is substantially younger than the median age of patients with NSCLC in England and Wales, which is 73 years old. Do you expect this to affect the estimates of treatment benefits? If so, how?	This is very similar to the median age in other clinical trials and is unlikely to have a major impact on outcomes. In addition whilst the median age of patients diagnosed with lung cancer in the UK is 73; the median age receiving systemic therapy is 67.
Platinum doublet chemotherapy (PDC) use 26. Please complete the following table informing us of:	

Platinum doublet chemotherapy regimen	Proportion used (distribution of PDC regimens)
Example: Carboplatin + paclitaxel	Example: 25%
Carboplatin and pemetrexed	45%
Cisplatin and pemetrexed	10%
Carboplatin and paclitaxel	5%
Carboplatin and gemcitabine	30%
Carboplatin and vinorelbine	10%

a) which PDC regimens are used in clinical practice, and

b) proportionally how much each regimen is used?

Subsequent therapy

27a. Please fill in the following table informing us about subsequent therapy usage following first-line treatment for NSCLC.

Drug	Nivolumab + ipilimumab + limited PDC	PDC	Pembrolizumab monotherapy	Atezolizumab + bevacizumab + PDC
Receiving subsequent therapy				
Proportion	35	45	45	35
Distribution of subsequent treatments				
Nivolumab	0	3	0	0
Pembrolizumab	0	7	0	0
Atezolizumab	0	22	0	0
Docetaxel	5	3	0	10
Other, please specify.				
PDC (rechallenge)	20	5	45	5
Nintedanib and docetaxel	10	5	0	20

Numbers shown are 2nd line therapy; some patients will transit onto 3rd line +

Sub-populations

28. Treatments for metastatic non-small-cell lung cancer (NSCLC) are recommended based on histology and PD-L1

It is anticipated that patients with PDL1 >50% will get additional benefit from immunotherapy use regardless of histology, compared to tumours with PDL1 <50%. Whilst this cut-off is commonly used in clinical practice and within trials in actuality it is probably a spectrum with those tumours with PDL1 90-100% deriving most benefit.
Patients in this sub-group of tumours with PDL1 >50% are more likely to respond, have longer PFS and a higher incidence of long term disease control with immunotherapy (both when given as single agent and in combination with chemotherapy) compared to tumours with PDL1 <50%.

expression. From this comes 4 distinct sub-populations: • Non-squamous patients with PD-L1 < 50%, • Non-squamous patients with PD-L1 ≥ 50%, • Squamous patients with PD-L1 < 50%, • Squamous patients with PD-L1 ≥ 50%. Do you expect the absolute and relative (compared with current clinical management) treatment benefits of nivolumab with ipilimumab to vary across these sub-populations? If so, how?	
Survival benefits	Yes compared to platinum doublet chemotherapy (as in scope of appraisal); No compared to chemotherapy-immunotherapy combinations as routinely used in the NHS with Cancer Drugs Fund funding.

29. In CheckMate-9LA there was no evidence of overall survival benefit of nivolumab + ipilimumab + limited platinum doublet chemotherapy (PDC) and in CheckMate-227 there was no evidence of benefit of nivolumab + ipilimumab compared to PDC alone, for patients ≥ 75 years old, patients who had never smoked and patients with liver and bone metastases. Do you expect nivolumab with ipilimumab to improve survival compared with current clinical management?	There may be sub-groups who derive less benefit such as > 75 (but low recruitment to studies); never smokers and those with liver and bone metastases (however there is limited detail in clinical trials as to these cohorts; i.e. how many metastases, what size they were and any impact on the patient).
Indirect treatment comparison 30. Studies included in the ITC (CheckMate-9LA and -227, ERACLE and PRONOUNCE) differed by both PD-L1 expression and histology. There were also	**In general it is thought that platinum doublets are approximately similar in efficacy, although with small improvements using pemetrexed in non-squamous and small detriments using pemetrexed in squamous patients (see meta-analysis Treat et al Lung Cancer, 2012; 76 (2), 222–227).** **Cross-over rates and the use of subsequent immunotherapy will have a significant impact on overall survival rates and will need to be considered in any ITC. As discussed above PDL1 status will impact on efficacy of any immunotherapy received; some studies have suggested that patients with high PDL1 cancers derive less benefit from chemotherapy but that is not consistent.**

notable differences in patient characteristics and trial design, including types of PDC, crossover and second-line treatment across trials. Noting these differences, is it reasonable to assume the studies included in the ITC are similar?

Duration of treatment benefits

31. After treatment is stopped, what is the expected duration of treatment benefit for the following treatments?

Drug	Duration of treatment benefit after treatment is stopped
Nivolumab + ipilimumab + limited PDC	This will depend on the reason that treatment is stopped. If treatment stopped due to toxicity or a 2 year stopping rule then benefit may be prolonged and long-lasting. We have assumed that on average patients get 3 months benefit beyond PD with IO as can be single site progression and/ or some ongoing biological impact on survival and subsequent therapy
PDC	If stopped due to progression, ongoing benefit thought to be minimal. If stopped due to completion of therapy may be on average 3 to 6 months benefit
Pembrolizumab monotherapy	As for Nivolumab + ipilimumab + limited PDC
Atezolizumab + bevacizumab + PDC	As for Nivolumab + ipilimumab + limited PDC

End of life criteria

Subgroup	Treatment	Survival (years)	Comments

31. Estimates of overall survival are based on extrapolations of short term survival data taken from CheckMate-9LA and CheckMate-227. These estimates differ depending on histology (squamous, non-squamous, mixed) and PD-L1 expression (< 50%, ≥ 50%). Please can you comment on the plausibility of the following estimates in the table.	Squamous, PD-L1 < 50%	PDC	[redacted]	[redacted]
	Non-squamous, PD-L1 <50%	Atezolizumab + bevacizumab + PDC	[redacted] (company estimate) [redacted] (ERG estimate)	[redacted]
	Mixed histology, PD-L1 ≥ 50%	Pembrolizumab	[redacted] (company estimate) [redacted] (ERG estimate)	[redacted]
	Full population	Nivolumab + ipilimumab + limited PDC	[redacted]	[redacted]
	Please comment on the plausibility of the survival estimates in the table			

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: Sub-populations for decision-making	The key sub-population should be decided according to both histology (non-squamous vs squamous) and by PD-L1 status (negative; 1-49% and >50%) as these are the factors that impact on prognosis and treatment decisions with the present NICE algorithms
Key issue 2: Representativeness of trial populations	This is a reasonable trial population see response to question 25 (a and b). There are no other factors of concern that would mean not representable to UK population
Key issue 3: Population-specific relative survival effects	
Key issue 4: The inclusion of CheckMate-227 in the fractional polynomial NMA	The set-up of the study is different. Checkmate-227 looked at the addition of nivolumab to chemotherapy and the potential use of nivolumab-ipilimumab in a chemo-free regimen rather than the limited chemotherapy used in this immunotherapy chemotherapy combination. Randmomisation varied according to PDL1 level unlike in this study It can give useful data as to long term outcomes and give some confidence in long term outcomes with therapies.

Key issue 5: Treatment efficacy in subgroups	Patients with PDL1 tumours >50% will derive greater benefit from immunotherapy based treatment
Key issue 6: Representativeness of PDC	Carboplatin and pemetrexed is the most common regimen used in the UK for non-squamous population. Carboplatin and gemcitabine is probably still the most common regimen that is used in the uk in chemotherapy alone for the squamous cancer; whilst carboplatin and paclitaxel is used in chemotherapy-immunotherapy combinations in this population as pre previous NICE appraisals. However there is not thought to be major differences between PDC combinations except the use of pemetrexed in non squamous populations (see previous meta-analyses)
Key issue 7: Population-specific composition and duration of PDC	
Key issue 8: Population-specific absolute survival effects	
Key issue 9: Survival of patients on PDC	
Key issue 10: Duration of treatment benefit	Discussed in question 31
Key issue 11: Duration of treatment (DOT)	

Key issue 12: Utility values estimated from proximity to death	
Key issue 13: Estimation of drug costs using relative dose intensity	
Key issues 14: The proportion of patients receiving subsequent therapy	This is very important as default treatment option on progression for patients on PDC will be immunotherapy; although a large proportion will not be fit for this. Subsequent therapy using this new combination will depend on the point of progression but could be PDC given the limited chemotherapy given up front. Discussed in 27a
Key issue 15: The distribution of subsequent therapy	Opinion given in 27a
Key issue 16: End of life criteria	Patients with PDL1 >50% in my opinion do not meet end of life criteria given the likely prognosis in this population (if PS0-1). I believe patients with PDL1<1% do still meet end of life criteria given the present outcomes. In PDL1 1-49% it is less clear, and there may be a discrepancy between patients with squamous and non-squamous histology (with squamous having worse outcomes).
Key issue 17: Access to Cancer Drugs Fund (CDF)	Would be appropriate if additional data-cuts as to survival will lead to increased confidence in the costs / benefits of the regimen. Unlikely to derive significant UK data in this time as to outcomes; only time on therapy, and subsequent treatments
Are there any important issues that have been missed in ERG report?	

PART 3 - Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Would provide another 1st line option with limited chemotherapy which may be attractive to some patients
- Survival likely to be similar to other 1st line chemotherapy-immunotherapy combinations which are standard of care in the NHS at present (rather than Platinum doublet chemotherapy).
- Toxicity profiles may be different from other 1st line chemotherapy-immunotherapy combinations due to the limited chemotherapy and the use of ipilimumab.
- There should be no major barriers to use within the NHS in terms of resources and training
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

.....

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The information that you provide on this form will be used to contact you about the topic above.

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

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

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **15th January 2021**

NICE National Institute for Health and Care Excellence

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted]. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with untreated advanced non-small-cell lung cancer and current treatment options	
About you	
1. Your name	**Professor Mary O'Brien**
2. Name of organisation	**Royal Marsden Hospital as employer. Subchair of NCRI lung CSG, member of BTOG.**
3. Job title or position	**Consultant in Medical Oncology** Professor of practice (medical oncology) Imperial college London.
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
The aim of treatment for this condition	
8. What is the main aim of treatment with nivolumab with ipilimumab? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	For advanced lung cancer, the aim is to decrease rate of progression, improve overall survival with manageable toxicity.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	An improvement in progression free survival of at least 2 mths although this has not been a reliable endpoint in immunotherapy studies given the inflammatory response and 'pseudoprogression'. However if there is significant crossover it is the endpoint that must be met. An improvement in overall survival of at least 6 months as these treatment are long and expensive. This level of survival gain has been

or a reduction in disease activity by a certain amount.)	demonstrate in Keynote 024. Response rate like PFS has been more difficult in immunotherapy studies but a response rate of at least 30% should be achieved.
10. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes There is an unmet need for better treatments that give longer survival, but there are treatments available which have activity. Within Keynote 024 – the most mature dataset to date with median followup of 3 years, only 25% of patients completed the full 2 years of treatment.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	In the NHS the treatment currently given is on the basis of the KEYNOTE 189 (TA 557), 407 (TA 600) and 024 (TA531) trials already reviewed and approved by NICE. TA 557 and 600 available on CDF. Keynote 189 uses 4 courses of chemotherapy + immunotherapy (carboplatin, pemetrexed and pembrolizumab) – same and then maintenance treatment with up to 14 cycles of 2 drugs pemetrexed and pembrolizumab (2 years of treatment) in the non squamous subgroup. For the squamous subgroup, Keynote 407 described 4 courses of chemotherapy and maintenance pembrolizumab alone for 14 cycles. This technology CM- 9LA uses 4 drugs for 2 cycles in all patients and then 16 cycles of nivolumab and ipilumab to give 2 years of treatment. The chemotherapy core for both squamous and non squamous is the same as in keynote 189 and keynote 407. Currently, high PDL1 >50% in either pathology subgroup has the option of single agent pembrolizumab for 2 years but if there is a significant burden of symptoms and disease, then the combination of immunotherapy with PDC is used as above.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The NICE guideline NG122 (https://www.nice.org.uk/guidance/ng122/resources The European Society of Medical Oncology guideline (https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer: There are similar US guidelines.

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The biggest question we face now is in a patient with PDL1 >50% if we should use combination chemo immunotherapy or single agent immunotherapy. All other groups who are fit enough and have no contraindications for immunotherapy should receive combinations of PDC and immunotherapy.
• What impact would the technology have on the current pathway of care?	It is another option with a smaller quantity of chemotherapy, therefore easier on the kidneys and bone marrow and less alopecia. Alopecia is very common with paclitaxel containing PDC.
12. Will the nivolumab with ipilimumab be used (or is it already used) in the same way as current care in NHS clinical practice?	Nivo ipi is a frequently used regimen in melanoma and renal cancer. It is not used with chemotherapy outside lung cancer.
• How does healthcare resource use differ between the technology and current care?	I think there will be very little difference as the skill set on handling the toxicities is already in place.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Should be prescribed by a consultant oncologist with experience in immunotherapy, and confidence in the setting that they can deliver safely and monitor toxicity appropriately.

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nothing new needed. They group of patients is the same – there will be no new groups of patients needing new careplans for this technology.
13. Do you expect the nivolumab with ipilimumab to provide clinically meaningful benefits compared with current care?	No
• Do you expect the technology to increase length of life more than current care?	No, the best and most mature figures are with Keynote 024 for PDL1>50%. The current CDF regimens will remain unchallenged but some patients with particular needs e.g. not wanting alopecia, increased risk of myelosuppression and renal dysfunction will have more options with this technology.
• Do you expect the technology to increase health-related quality of life more than current care?	No, toxicity can be managed. This data needs to be updated with crossover figures which will need to be monitored over 2 years.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
The use of the nivolumab with ipilimumab	

15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	No, nothing different from TA 557 and 600. More toxicity than TA 531. More toxicity than chemotherapy alone as the immunotherapy toxicity risk will go on for up to 2 years. This is never obvious in the reported trial toxicity figures (all trials) as chemotherapy toxicity is acute early and largely reversible. Immunotherapy toxicity can occur over 2 yrs of treatment (and indeed in the year after while not on treatment) and can be irreversible e.g irresversible colitis seen at year 4, despite being of immunotherapy 2 years before.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The same rules that are applied to current standard of care will apply.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in	No

the quality-adjusted life year (QALY) calculation?	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	No
• Is the technology a 'step-change' in the management of the condition?	No – the step has already been taken. Nivolumab alone was disappointing and seems less active than pembrolizumab alone.
• Does the use of the technology address any particular unmet need of the patient population?	Alopecia happens with paclitaxel, so less gives less chance, the same for kidney and marrow toxicity.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Toxicity does affect management and QOL. This new regimen will not be toxicity free. In fact it has taken may trials of the nivo ipi combination to get the schedules to a manageable level of toxicity.

Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	No. Unfortunately things move face and the control arm in this study is not the control arm in current practice – this trial was designed and cared out late in the development of immunotherapy for lung cancer. It is a small variation on the other practice changing studies TA 557, 584 and 600.
• If not, how could the results be extrapolated to the UK setting?	Further follow up and crossover data should be requested for alignment with e.g. Keynote 189 and 024 – with 60% crossover to immunotherapy in the chemotherapy alone arm.
• What, in your view, are the most important outcomes, and were they measured in the trials?	The trial reports appropriate outcomes in a standard way. The results are good but would have needed to be even better, with HR of the order of 0.4 to really make us feel this was a different regimen. Interestingly, and unexplained the PFS curve did not separate until after 3 months.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No – but adverse events occur during the whole 2 years and the year after. This does not happen with chemotherapy. This would not have been captured with a median followup of 12 mths.
21. Are you aware of any relevant evidence that might not be found	No

by a systematic review of the trial evidence?	
22. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance [TA584, TA181, TA190, TA402, TA531, TA557, TA600]?	No
23. How do data on real-world experience compare with the trial data?	They appear comparable.
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
24b. Consider whether these issues are different from issues with current care and why.	N/A

Topic-specific questions	
Representativeness of the trial population 25a. People were only included in CheckMate-9LA trial and 47 CheckMate-227 trial if they had a ECOG performance status of 0 or 1. Is a ECOG performance status of 0 or 1 reflective of the population with advanced NSCLC expected to be treated with nivolumab + ipilimumab + limited PDC in clinical practice? 25b. Patients in CheckMate-9LA and CheckMate-227 had median ages of 65 years and 64 years, respectively, which is substantially younger than the median age of patients with NSCLC in England and Wales, which is 73 years old. Do you	25a. This is the same as all immunotherapy studies to date – only patients with PS 0 and 1 have been included. This would be an ideal regimen to explore in patients with PS 2 who represent a significant number of patients and have a large burden of symptoms and might benefit from a limited quantity of PDC. 25b. Patients in clinical trials are selected for many things in addition to performance status – good renal function, all indices normal etc. In general age is not a prognostic or predictive factor for treatment outcomes in NSCLC, so this would not be a concern.

expect this to affect the estimates of treatment benefits? If so, how?

Platinum doublet chemotherapy (PDC) use

26. Please complete the following table informing us of:

a) which PDC regimens are used in clinical practice, and

b) proportionally how much each regimen is used?

Platinum doublet chemotherapy regimen	Proportion used (distribution of PDC regimens)
Example: Carboplatin + paclitaxel	Example: 25%
Carboplatin and pemetrexed	55%
Cisplatin and pemetrexed	1%
Carboplatin and paclitaxel	35%
Carboplatin and gemcitabine	4%
Carboplatin and vinorelbine	5%

I have replied, given that non squamous carcinomas are either equal or more common than squamous, and this is PS 0,1 with stage IV disease and in combination with immunotherapy.

PDL1 <50%

Subsequent therapy

27a. Please fill in the following table informing us about subsequent therapy usage following first-line treatment for NSCLC.

Drug	Nivolumab + ipilimumab + limited PDC	PDC	Pembrolizumab monotherapy	Atezolizumab + bevacizumab + PDC
Receiving subsequent therapy				
Proportion	20%	65%	40%	10%
Distribution of subsequent treatments				
Nivolumab	0	1%	0	0
Pembrolizumab	0	40%	0	0
Atezolizumab	0	20%	0	0
Docetaxel	2%	1%	2%	2%%
Other, please specify.			PDC 35%	
PDC (rechallenge)	14%	2%	NA	5%

	Nintedanib and docetaxel: 4% | 1% | 3% | 3% Numbers shown are 2nd line therapy; some patients will transit onto 3rd line +
Sub-populations 28. Treatments for metastatic non-small-cell lung cancer (NSCLC) are recommended based on histology and PD-L1 expression. From this comes 4 distinct sub-populations: • Non-squamous patients with PD-L1 < 50%, • Non-squamous patients with PD-L1 ≥ 50%, • Squamous patients with PD-L1 < 50%, • Squamous patients with PD-L1 ≥ 50%.	**I think with a follow up of 12 mths, this data is not mature and subgroups are quite dangerous. In general a significant benefit is expected and is reported across all subgroups.** **Long term survivors have been seen in all subgroups right from the very first phase I studies.** **Tumours can be heterogeneous in their expression of PDL1.** **The only significance currently of a PDL1 zero, is that these patients should not in general be treated with single agent immunotherapy as there change of responding to it is lower than in other subgroups.** **And on the other hand with the long term keynote 024 data, we know the median survival of patients with a high PDL1 is 36mths – which is the best ever figure in lung cancer.** **We believe that the combination of chemotherapy and immunotherapy will not be PDL1 dependent in general.**

Do you expect the absolute and relative (compared with current clinical management) treatment benefits of nivolumab with ipilimumab to vary across these sub-populations? If so, how?	
Survival benefits 29. In CheckMate-9LA there was no evidence of overall survival benefit of nivolumab + ipilimumab + limited platinum doublet chemotherapy (PDC) and in CheckMate-227 there was no evidence of benefit of nivolumab + ipilimumab compared to PDC alone, for patients ≥ 75 years old, patients who had never smoked and patients with liver and bone metastases. Do you expect nivolumab with ipilimumab to	Patients with lung cancer who have never smoked are a unique population and probably have a driver mutation – in these studies patients did not have an EGFR or ALK – but we do now know that the harder we look – with repeat biopsies and now NGS – that we can find a driver in up to 60% of these cases. Patients with driver mutations do get less benefit from immunotherapy than patients without driver mutations – the only study to explore this was IMPOWER 150 (TA 584) and this regimen contained bevacuzimab as well as chemotherapy and immunotherapy. Age has reported mixed results across the studies. We don't really believe that any one site will not respond to these treatment – so this data does not overly concern me. In particular bone metastases are very difficult to assess for response.

<table>
<tr><td>improve survival compared with current clinical management?</td><td></td></tr>
<tr><td>Indirect treatment comparison

30. Studies included in the ITC (CheckMate-9LA and -227, ERACLE and PRONOUNCE) differed by both PD-L1 expression and histology. There were also notable differences in patient characteristics and trial design, including types of PDC, crossover and second-line treatment across trials. Noting these differences, is it reasonable to assume the studies included in the ITC are similar?</td><td>The studies are not similar but have similarities, these are indirect comparisons as you state.
It is reasonable to look at this data. We are looking for big signals but we are not finding it.</td></tr>
<tr><td>Duration of treatment benefits

31. After treatment is stopped, what is the expected duration</td><td><table><tr><th>Drug</th><th>Duration of treatment benefit after treatment is stopped</th></tr><tr><td>Nivolumab + ipilimumab + limited PDC</td><td>IN keynote 024, 25% of patients completed 2 years of treatment. In the first year after stopping treatment about 30% relapsed. I expect the results with CM-9LA to be similar.</td></tr></table></td></tr>
</table>

of treatment benefit for the following treatments?

PDC	This will be the same data as generated with the use of secondline immunotherapy. At least 60% of patients should receive this and have a median duration of PFS of 7mths with about 20% being alive and well at 2 years.
Pembrolizumab monotherapy	As for Nivolumab + ipilimumab + limited PDC
Atezolizumab + bevacizumab + PDC	As for Keynote 024 I think but Impower data is still maturing.

End of life criteria

31. Estimates of overall survival are based on extrapolations of short term survival data taken from CheckMate-9LA and CheckMate-227. These estimates differ depending on histology (squamous, non-squamous, mixed) and PD-L1 expression (< 50%, ≥ 50%). Please can you comment on the plausibility of the following estimates in the table.

Please comment on the plausibility of the survival estimates in the table

Subgroup	Treatment	Survival (years)	Comments
Squamous, PD-L1 < 50%	PDC	[redacted]	[redacted]
Non-squamous, PD-L1 <50%	Atezolizumab + bevacizumab + PDC	[redacted] (company estimate) [redacted] (ERG estimate)	[redacted]
Mixed histology, PD-L1 ≥ 50%	Pembrolizumab	[redacted] (company estimate) [redacted] (ERG estimate)	[redacted]
Full population	Nivolumab + ipilimumab + limited PDC	[redacted]	[redacted]

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: Sub-populations for decision-making	This is new evidence about the additive effect of chemotherapy and immune therapy. Benefit in all subgroups irrespective of PDL1 expression and histology is not a new finding.
Key issue 2: Representativeness of trial populations	The trial is representative of lung cancer patients with stage IV disease who are fit for this treatment and have a performance status of 0 or 1.
Key issue 3: Population-specific relative survival effects	The survival effects are the usual candidates in this type of study which have been also used in similar studies e.g. Keynote189 and Keynote 407.
Key issue 4: The inclusion of CheckMate-227 in the fractional polynomial NMA	I don't think this is useful – if anything the deep analysis of Checkmate 227 showed the lack of activity of nivolumab alone when PDL1 is <1% and the small additive effect of nivolumab alone to chemotherapy. Other drugs in this situation e.g. pembrolizumab were more effective. This ipiluimab is a very important component of this immunotherapy. Checkmate 227 was a complicated trial that had its therapy arms changed along the way to give us a trial that had some statistical power. The initial tumour mutation burden (TMB), which was the original biomarker in this study was not proven as useful in the end as standard PDL1 on immunohistochemistry.

Key issue 5: Treatment efficacy in subgroups	Yes the treatment is active in all the subgroups.
Key issue 6: Representativeness of PDC	The PDC, platinum doublet chemotherapy is representative – cis gem and carbo/pem are all used in the UK – there is variation but none of it we believe to be relevant – as outcome from all regimens about the same.
Key issue 7: Population-specific composition and duration of PDC	Representative groups and duration of PDC was 2 cycles.
Key issue 8: Population-specific absolute survival effects	The outcome overall in the control arm – PDC alone, is reasonable and expected. However at a FU of 12.7 mths, the effects of crossover would not be seen yet – patients who cross over to immunotherapy and respond well to it – could be on treatment for another 2 years. We need crossover data and would expect a crossover rate of at least 60% as described in the Keynote 024 study. If this is not seen then the control arm would not be consider a standard of care.
Key issue 9: Survival of patients on PDC	The PFS curve is interesting – it does not show any separation until at least 4 mths. One benefit of the early PDC and immunotherapy should be to prevent early progression – this is seen in some other studies of chemotherapy and immunotherapy e.g. Keynote 189 and Keynote 407.
Key issue 10: Duration of treatment benefit	Duration of response is good in favour of combined regimen.
Key issue 11: Duration of treatment (DOT)	The combined treatment is a longer treatment. We would need crossover date on the use of IO in the PDC arm for this to have meaning.
Key issue 12: Utility values estimated from proximity to death	

Key issue 13: Estimation of drug costs using relative dose intensity	
Key issues 14: The proportion of patients receiving subsequent therapy	
Key issue 15: The distribution of subsequent therapy	
Key issue 16: End of life criteria	
Key issue 17: Access to Cancer Drugs Fund (CDF)	
Are there any important issues that have been missed in ERG report?	

PART 3 - Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Would provide another 1st line option with limited chemotherapy which may be attractive to some patients
- Survival likely to be similar to other 1st line chemotherapy-immunotherapy combinations which are standard of care in the NHS at present (rather than Platinum doublet chemotherapy).

- Toxicity profiles may be different from other 1st line chemotherapy-immunotherapy combinations due to the limited chemotherapy and the use of ipilimumab.
- There should be no major barriers to use within the NHS in terms of resources and training
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

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

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form

In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please return this form by **5pm** on **15th January 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with untreated advanced non-small-cell lung cancer and current treatment options	
About you	
1.Your name	**Peter Barton**
2. Are you (please tick all that apply):	☐ a patient with untreated advanced non-small-cell lung cancer? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with untreated advanced non-small-cell lung cancer? ☒ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	Manchester University NHS Foundation Trust
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☒ No, (please review all the questions below and provide answers where possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience. ☐ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with untreated advanced non-small-cell lung cancer ? If you are a carer (for someone with untreated advanced non-small-cell lung cancer) please share your experience of caring for them.	My role is to support patients with a lung cancer diagnosis. This can be symptomatically, emotionally and socially but a holistic approach is needed. We support through treatments also.
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for untreated advanced non-small-cell lung cancer on the NHS?	There are options that are guided by molecular results and if not available then standard treatment is. When supporting patients at this stage their performance status can be a factor. Current treatments are of benefit and services are available to support however improvement is always necessary.

7b. How do your views on these current treatments compare to those of other people that you may be aware of? -	
8. If there are disadvantages for patients of **current NHS treatments** for untreated advanced non-small-cell lung cancer (for example how nivolumab with ipilimumab is given or taken, side effects of treatment etc) please describe these	Disadvantages of current treatments are not too dissimilar to the proposed treatment. Side effects of associated with treatment and treatment regimes.
Advantages of this treatment	
9a. If there are advantages of nivolumab with ipilimumab over current treatments on the NHS please describe these. For example, the impact on your Quality of Life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?	Feel the effects on QOL would be similar to current treatments with a focus on the support available.

9c. Does nivolumab with ipilimumab help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	Similar to current regimes
Disadvantages of this treatment	
10. If there are disadvantages of nivolumab with ipilimumab over current treatments on the NHS please describe these? For example, are there any risks with nivolumab with ipilimumab? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	From my experience at present the disadvantages are similar to current treatments.
Patient population	
11. Are there any groups of patients who might benefit more from nivolumab with ipilimumab or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with	There are established patient groups who are not suitable for either treatment.

mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
Equality	
12. Are there any potential equality issues that should be taken into account when considering untreated advanced non-small-cell lung cancer and nivolumab with ipilimumab? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found	**To my knowledge there are no equality issues around this treatment.**

at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	None

PART 2 – Technical engagement questions for patient experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
14. What are the main benefits of this treatment for patients?	More options for patients who are diagnosed at an advanced stage

If there are several benefits please list them in order of importance. Are there any benefits of this treatment that have not been captured?	
15. Are there any important issues that have been missed in ERG report?	

PART 3 - Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Feel treatment is of overall benefit to patients at an advanced stage
- Symptom profile feel would be manageable for healthcare professionals
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Single Technology Appraisal (STA)

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

ERG addendum: review of company's response to technical engagement

Produced by CRD and CHE Technology Assessment Group, University of York, Heslington, York YO10 5DD

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None

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in [redacted], all academic-in-confidence (AIC) data are highlighted in [redacted].

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1 Overview

This addendum to the Evidence Review Group (ERG) report presents the ERG's critique of the additional evidence provided by the company in their responses to the technical engagement issues which emerged from the ERG report.

The technical engagement covered 17 key issues for consideration. The company's responses to the technical engagement indicated that they accepted the ERG's judgement on some aspects of Issues 2, 3, 4, 6, 8, 11, 15, 16 and 17. The company's responses to all the other issues are discussed in Section 2.

Issue	**Resolved?**
Key issue 1: Sub-populations for decision-making	Unresolved
Key issue 2: Representativeness of trial populations	Resolved (some uncertainty remaining)
Key issue 3: Population-specific relative survival effects	Partially resolved (some uncertainty remaining)
Key issue 4: The inclusion of CheckMate-227 in the fractional polynomial NMA	Partially resolved
Key issue 5: Treatment efficacy in subgroups	Unresolved
Key issue 6: Representativeness of PDC	Partially resolved (some uncertainty remaining)
Key issue 7: Population-specific composition and duration of PDC	Unresolved
Key issue 8: Population-specific absolute survival	Resolved (some uncertainty remaining)
Key issue 9: Survival of patients on PDC	Unresolved
Key issue 10: Duration of treatment benefit	Unresolved
Key issue 11: Duration of treatment	Partially resolved (some uncertainty remaining)
Key issue 12: Utility values estimated from proximity to death	Unresolved
Key issue 13: Estimation of drug costs using relative dose intensity	Unresolved
Key issue 14: The proportion of patients receiving subsequent therapy	Unresolved
Key issue 15: The distribution of subsequent therapy	Partially resolved
Key issue 16: End of life criteria	Resolved
Key issue 17: Access to Cancer Drugs Fund (CDF)	Partially resolved

2 Description and critique of additional evidence

2.1 Issue 1: Sub-populations for decision-making

The ERG considers there are a number of decision problems based on the in-scope comparators, defined by tumour histology and PD-L1 expression. These are listed below and are detailed in Section 4.2.3 of the ERG report.

- Squamous, PD-L1 < 50%,
- Non-squamous, PD-L1 < 50%,
- Mixed histology, PD-L1 > 50%.

The company's response to technical engagement outlined that the evidence from CheckMate-9LA suggests that histology and PD-L1 expression are not effect modifiers, as a result of the 3 different mechanisms of action of the nivolumab + ipilimumab + limited PDC combination. However, the ERG considers there are two separate questions to consider:

1. Should there be individual decisions based on histology and PD-L1 expression?
2. What is the most appropriate source of clinical effectiveness evidence for the decisions (see Issues 3 and 5)?

The answer to question 2 is discussed in Issues 3 and 5. Here we are concerned with the definition of the populations for decision-making, which is separate from the type of evidence that will be used to inform those decisions.

As described above, the ERG considers the answer to question 1 to be yes, individual decisions should be considered. Additionally, there is precedent for histology-specific decisions made by NICE for a single intervention within an advanced, NSCLC population (i.e. untreated metastatic squamous and non-squamous NSCLC), in which pembrolizumab combination therapy was appraised across two separate TAs, TA600[1] for the squamous population and TA557[2] for the non-squamous population.

There are a number of elements of the analysis that may differ between individual decision problems. These include:

- In-scope comparators differing across decisions (Issue 7);
- End-of-life criteria being different across decisions (Issue 16);
- The potential for histology and PD-L1 expression to be effect modifiers (Issue 3);
- The potential for histology and PD-L1 expression to be prognostic indicators (Issue 8).

As described in the ERG report (Section 4.2.3.1), this is an issue of heterogeneity. Making a 'one size fits all' recommendation for nivolumab across all patients regardless of histology and PD-L1 expression may result in a potentially cost-effective treatment being withheld from a subset of patients for whom the treatment would represent an appropriate use of NHS resources. Conversely, a treatment which appears cost-effective for the total population may not be cost-effective in a particular sub-population. Making individual decisions avoids the potential scenario of a one size fits all decision for nivolumab + ipilimumab + limited PDC.

It is unclear what the company favour regarding the issue of individual decisions as the company's response to this issue only referred to the question of whether to use sub-groups in the clinical effectiveness evidence which is covered by Issues 3 and 5. The company do agree with the ERG on the End of Life criteria, in which it was stated that the criteria are met for the squamous, PD-L1 < 50% population but not for the non-squamous, PD-L1 < 50% and the mixed histology, PD-L1 > 50% (see Issue 16). Accepting that the criteria are met for one population and not for others implicitly assumes there are a number of individuals decisions based on the populations, and not a one size fits all decision. However, it should be noted in response to Issue 17 the company state '*As long as treatment with nivolumab + ipilimumab + limited PDC was not limited by PD-L1 status, this would provide a large data set and allow further analysis of the impact of PD-L1 subgroups to aid future decision making*.' This suggests a single decision, at least not stratifying by PD-L1 expression, is preferred.

Heterogeneity plays an important role in this appraisal given the differing in-scope comparators, potential treatment effect modifiers and End of Life criteria, and as a result the ERG considers separate decisions have to be made. A number of issues would be resolved by considering separate decisions (e.g. Issues 7 and 16). This issue does, however, remain unresolved and therefore input during committee discussion is required.

2.2 Issue 2: Representativeness of trial populations

The company sought clinical opinion during technical engagement regarding differences between the CheckMate-9LA trial population and the population that would be treated in the UK and the impact this may have on the efficacy of the nivolumab + ipilimumab + limited PDC when used in clinical practice. Clinical opinion to the company was that differences between the CheckMate-9LA trial population and the population that would be treated in UK clinical practice are minor and differences in efficacy in the UK setting would not be expected.

The ERG believes there are still some discrepancies between the trial populations in CheckMate-9LA and CheckMate-277 and the NHS population, particularly with regards to the patient age (see also Issue 5). Section 3.2.2 of the ERG report explains that *"Patients had a median age of 65 years old*

and 64 years old in the CheckMate-9LA and CheckMate-227 trials, respectively. The median age for patients with NSCLC in England and Wales is 73, suggesting that the age of the trial populations is substantially younger than patients in the NHS population." As such the ERG considers the issue only partially resolved as it is possible that the treatment effect observed in the trials does not reflect what would be expected in an older population. Further clinical input during committee discussion could be valuable.

2.3 Issue 3: Population-specific relative survival effects

Although the ERG prefers to assume that there are three distinct populations for decision-making (see Issue 1), there is uncertainty about what is the best source of evidence on the relative effects of survival of nivolumab + ipilimumab + limited PDC against PDC to inform each decision.

The company consider that the intention-to-treat data from CheckMate-9LA are more appropriate than the PD-L1 and histology-based subgroups that were not pre-specified and, the company argues, contain very low patient numbers. The ERG agrees that the intention-to-treat data provide a more robust analysis, although there is still uncertainty regarding differences in efficacy in these subgroups which could lead to bias in the relative treatment effects used in the model.

There were notable differences in patient characteristics and trial design, including types of PDC, crossover and second-line treatment across trials comparing different interventions. In both NMAs, the different PDC comparator arms were combined into a common node to allow indirect comparisons to be made. The company's response states that input was sought during development of the indirect treatment comparison at two advisory boards that included both clinical and HTA experts. The experts suggested that it was appropriate to combine the different PDC regimens together as summarised in the submission appendix.

Although the company have not presented any new data here, the ERG welcomes the clinical advice sought by the company. The ERG suggests that further clinical input at the committee meeting on whether the studies included in the NMA can be assumed to be sufficiently similar, and whether histology and PD-L1 are potential effect modifiers, would be beneficial and would reduce uncertainty in the results.

2.4 Issue 4: The inclusion of CheckMate-227 in the fractional polynomial NMA

The fractional polynomial NMA was updated at the clarification stage to include CheckMate-227 to better inform the long-term extrapolation of the survival curves. The company agrees that the fractional polynomial (FP) analysis including CheckMate-227 is appropriate for use in the base case and lists the a priori assumptions that were used to assess clinical plausibility.

Appendix A of the company's technical engagement response provides more detail about the heuristics used for selecting fractional polynomial models and, in particular, the selection of models for the NMA of patients with PD-L1 ≥ 50% with mixed histology. The ERG is satisfied with the statistical and clinical validation described. However, the company did not provide full details of each step for all of the eight models identified in Figure 2 of Appendix A. This was only presented for the best model based on DIC alone and the final selected model. Furthermore, there was no description of the validation steps for the models selected for the NMA of non-squamous patients with PD-L1 < 50%. Although, in principle, the ERG assumes the same methodology will have been used, it would have been useful to see the model selection for both NMAs.

The ERG also considers that further clinical validation of the survival projections presented in Tables 37 and 38 of the ERG report by the committee would give credibility to the results produced and provide greater certainty and reliability of longer-term extrapolations.

2.5 Issue 5: Treatment efficacy in subgroups

The company agree that there is uncertainty around the OS benefit in some subgroups, such as patients aged ≥ 75 years, patients who had never smoked, patients with liver metastases and patients with bone metastases, where confidence intervals span one (i.e. no effect). However, the company state that these subgroups were not pre-specified and patient numbers are extremely low, resulting in wide confidence intervals. The company have provided the number of patients within each subgroup of the CheckMate-9LA and CheckMate-227 trials, where there is uncertainty around the OS benefit (Table 1). The ERG does not agree that patient numbers are extremely low and believes that there remains uncertainty around the OS benefit for patients ≥ 75 years old, patients who had never smoked and patients with liver and bone metastases in both CheckMate trials. Given that the proportion of these patients in the trial populations (Table 1 below and Table 8 of the ERG report) may not be representative of the UK population in clinical practice (see also Issue 2), the true effect size of nivolumab may differ from that estimated in the trials, the extent to which is uncertain. As such, the ERG considers the issue unresolved and believes that further clinical input during committee discussion would be valuable.

Table 1 Number of patients within each subgroup of the CheckMate-9LA and CheckMate-227 trials, where there is uncertainty around the OS benefit.

Subgroup	CheckMate-9LA (N=719)	CheckMate-227 (N=1,166)
Patients aged ≥ 75 years, N (%)	70 (9.73)	113 (9.69)
Patients who had never smoked, N (%)	98 (13.63)	157 (13.46)
Patients with liver metastases, N (%)	154 (21.41)	252 (21.61)
Patients with bone metastases, N (%)	207 (28.78)	316 (27.10)

2.6 Issue 6: Representativeness of PDC regimens

The company and ERG agree that the PDC regimens in CheckMate-9LA and applied in the company's original economic model are not representative of those used in the UK setting. In response to technical engagement, the company presented updated PDC regimens informed by clinical advice, which were used to inform their new base-case analysis. These are relatively similar to the ERG-preferred PDC costs, which were based on reported UK market shares for non-squamous and squamous patients, as described in TA600[1] and TA557[2] (see ERG report, Section 4.2.4.1, pg. 111).

The company estimated the weighted average of PDC regimens based on the proportion of patients with non-squamous histology ([redacted]), which was applied to the PDC arm in all analyses (i.e. regardless of whether it was being compared to an intervention used in a histology-specific population, such as atezolizumab for patients with non-squamous histology). The ERG-preferred and the company-preferred PDC regimens and proportions can be seen in Table 2. Clinical input and discussion would help identify which distribution of PDC regimens is most reflective of UK clinical practice. However, given the small difference in costs between the two approaches, the impact on the ICER is minimal.

Table 2 ERG preferred and updated company preferred PDC regimens

	ERG preferred PDC regimens			**Updated company preferred PDC regimens**		
	Squamous, PD-L1 < 50%	**Non-squamous, PD-L1 < 50%**	**Mixed histology, PD-L1 > 50%**	**Squamous**	**Non-squamous**	**Average**
Carboplatin + gemcitabine	69%	3.3%	[redacted]	60%	0%	[redacted]
Cisplatin + gemcitabine	31%	19%	[redacted]	0%	0%	[redacted]
Carboplatin + paclitaxel	0%	0%	[redacted]	20%	0%	[redacted]
Carboplatin + vinorelbine	0%	0%	[redacted]	20%	0%	[redacted]
Carboplatin + pemetrexed	0%	33.9%	[redacted]	0%	80%	[redacted]
Cisplatin + pemetrexed	0%	0%	[redacted]	0%	20%	[redacted]
Cost per dose	-	-	[redacted]	-	-	[redacted]

PDC: platinum double chemotherapy

2.7 Issue 7: Population-specific composition and duration of PDC

The ERG and company have different preferred approaches to modelling PDC. Using the distributions presented in Issue 6, the company's preferred approach is to generate an average PDC regimen from both distributions, weighted according to the proportion of squamous and non-squamous patients in the trial. This average regimen is then applied to both squamous and non-squamous patients in the model. In response to technical engagement, the company asserted their approach to using the totality of the CheckMate-9LA data, stating it would be scientifically most robust and that the all-comers population should be retained as the base case.

The ERG preferred approach is to use the population-specific distributions for each individual population. This allows for heterogeneity in PDC regimens across the sub-populations.

Using the average (the company-preferred approach) across all populations and applying that to each individual decision results in the inclusion of regimens that are not available in practice. For example, carboplatin + gemcitabine is not available for non-squamous populations, yet using the average cost across all populations for a non-squamous decision inherently includes a proportion of the cost of carboplatin + gemcitabine in the comparator arm for this specific decision. A further example is in the inclusion of pemetrexed maintenance therapy, which is not licensed for use in squamous populations. Using the average cost of PDC will be implicitly apportion the cost of pemetrexed therapy to squamous populations and incorrectly inflate the cost of PDC. This can potentially over or under estimate comparator costs and therefore increase uncaptured uncertainty in the decision.

In addition, the ERG considers the company's description of scientific robustness being the reason to ignore evident heterogeneity in the in-scope comparators to be misleading. The distribution of the PDC regimens for each population, both in the ERG and company preferred base case, rely on previous TAs and clinical guidance, respectively (see Issue 6).

The issue of whether to use a single, average distribution of PDC or whether to use the individual distributions in the economic model remains unresolved.

2.8 Issue 8: Population-specific absolute survival

The company provided clinically validated parametric model selection as fitted to the PFS and OS Kaplan-Meier data from CheckMate-9LA for the subgroups corresponding to the three decision problems. The company presented landmark survival for both CheckMate-9LA and the hybrid approach (i.e. CheckMate-9LA switching to CheckMate-227 data at 13 months).

The company used the same approach to model selection as in the original CS. That is, violation of the proportional hazards assumption was tested, independent parametric models were fitted to both

trial arms and ranked according to model fit based on AIC and BIC. Finally, model selection was based on clinical validation of the landmark survival.

A summary of the landmark OS and PFS of the company-preferred model for each of the populations being considered can be seen in Table 3. For a more detailed comparison of the various models and the subsequent landmark survival projections for each population, see Section 2.8.1 and Section 2.8.2.

Table 3 Summary of the landmark overall survival and progression-free survival for the three populations based on the company's preferred distributions

	Distribution	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
Overall survival							
Squamous, PD-L1 < 50%							
Nivo + IPI + limited PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-squamous, PD-L1 < 50%							
Nivo + IPI + limited PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mixed-histology, PD-L1 > 50%							
Nivo + IPI + limited PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free survival							
Squamous, PD-L1 < 50%							
Nivo + IPI + limited PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-squamous, PD-L1 < 50%							
Nivo + IPI + limited PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mixed-histology, PD-L1 > 50%							
Nivo + IPI + limited PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PDC, platinum doublet chemotherapy

Clinical input and discussion would help identify the most appropriate distribution based on model fit criteria and landmark survival prediction.

It should be noted that it remains unclear whether histology and PD-L1 expression are effect modifiers and whether treatment effectiveness should be obtained from the sub-populations or all-comer population (see Issue 5). The ERG's base case retains effectiveness from the all-comer population, however the impact of the company validated survival models on the ERG base case is shown in Section 3.

2.8.1 Overall survival

The best fitting models selected by the company and the landmark survival predictions can be seen in Table 4 - Table 9. The distribution outlined in the box within each table represents the company-preference.

Table 4 - Overall survival at different landmark points for nivolumab + ipilimumab + limited PDC, squamous PD-L1 < 50% (adapted from Table 18 & 19, Technical Engagement response)

	Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
NIVO + IPI + limited PDC, Squamous PD-L1<50%								
CM-9LA–only approach	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hybrid approach	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Validation data	[redacted]		[redacted]					
	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]		
	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AIC; Akaike information criterion; CM-227, CheckMate-227; CM-9LA, CheckMate-9LA; IPI, ipilimumab; KM, Kaplan-Meier; NIVO, Nivolumab.

Table 5 - Overall survival at different landmark points for PDC, squamous PD-L1 < 50% (adapted from Table 20 & 21, Technical Engagement response)

	Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
PDC, Squamous PD-L1<50%								
CM-9LA–only approach	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hybrid approach	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Validation data	[redacted]		[redacted]					
	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	

	Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
PDC, Squamous PD-L1<50%								
	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]

AIC; Akaike information criterion; CM-227, CheckMate-227; CM-9LA, CheckMate-9LA; IPI, ipilimumab; KM, Kaplan-Meier; NIVO, Nivolumab.

Table 6 - Overall survival at different landmark points for nivolumab + ipilimumab + limited PDC, non-squamous PD-L1 < 50% (adapted from Table 11 & 12, Technical Engagement response)

	Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
NIVO + IPI + limited PDC, Non-squamous PD-L1<50%								
CM-9LA–only approach	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hybrid approach	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Validation data	[redacted]		[redacted]					
	[redacted]		[redacted]	[redacted]	[redacted]			
	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AIC; Akaike information criterion; CM-227, CheckMate-227; CM-9LA, CheckMate-9LA; IPI, ipilimumab; KM, Kaplan-Meier; NIVO, Nivolumab.

Table 7 - Overall survival at different landmark points for PDC, non-squamous PD-L1 < 50% (adapted from Table 13 & 14, Technical Engagement response)

	Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
PDC, Non-squamous PD-L1<50%								
CM-9LA–only approach	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
PDC, Non-squamous PD-L1<50%								
Hybrid approach	[redacted]							
Validation data	[redacted]							

AIC; Akaike information criterion; CM-227, CheckMate-227; CM-9LA, CheckMate-9LA; IPI, ipilimumab; KM, Kaplan-Meier; NIVO, Nivolumab.

Table 8 - Overall survival at different landmark points for nivolumab + ipilimumab + limited PDC, mixed histology PD-L1 > 50% (adapted from Table 4 & 5, Technical Engagement response)

	Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
NIVO + IPI + limited PDC, Mixed histology, PD-L1>50%								
CM-9LA–only approach	[redacted]							
Hybrid approach	[redacted]							
Validation data	[redacted]							

AIC; Akaike information criterion; CM-227, CheckMate-227; CM-9LA, CheckMate-9LA; IPI, ipilimumab; KM, Kaplan-Meier; NIVO, Nivolumab.

Table 9 - Overall survival at different landmark points for PDC, mixed histology PD-L1 > 50% (adapted from Table 6 & 7, Technical Engagement response)

	Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
PDC, Mixed histology, PD-L1>50%								
CM-9LA–only approach								
Hybrid approach								
Validation data								

AIC; Akaike information criterion; CM-227, CheckMate-227; CM-9LA, CheckMate-9LA; IPI, ipilimumab; KM, Kaplan-Meier; NIVO, Nivolumab.

2.8.2 Progression-free survival

The best fitting models selected by the company and the landmark survival predictions can be seen in Table 10 - Table 15. The distribution outlined in the box within each table represents the company-preference.

Table 10 – Progression-free survival at different landmark points for nivolumab + ipilimumab + limited PDC, squamous PD-L1 < 50% (adapted from Table 36 & 37, Technical Engagement response)

	Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
NIVO + IPI + limited PDC, Squamous PD-L1<50%								
CM-9LA–only approach	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hybrid approach	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Validation data	[redacted]		[redacted]					
	[redacted]		[redacted]	[redacted]	[redacted]			
	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	

AIC; Akaike information criterion; CM-227, CheckMate-227; CM-9LA, CheckMate-9LA; IPI, ipilimumab; KM, Kaplan-Meier; NIVO, Nivolumab.

Table 11 - Progression-free survival at different landmark points for PDC, squamous PD-L1 < 50% (adapted from Table 38 & 39, Technical Engagement response)

	Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
PDC, Squamous PD-L1<50%								
CM-9LA–only approach	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hybrid approach	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Validation data	[redacted]		[redacted]					
	[redacted]		[redacted]	[redacted]	[redacted]			
	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	

AIC; Akaike information criterion; CM-227, CheckMate-227; CM-9LA, CheckMate-9LA; IPI, ipilimumab; KM, Kaplan-Meier; NIVO, Nivolumab.

Table 12 - Progression-free survival at different landmark points for nivolumab + ipilimumab + limited PDC, non-squamous PD-L1 < 50% (adapted from Table 30 & 31, Technical Engagement response)

	Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
NIVO + IPI + limited PDC, Non-squamous PD-L1<50%								
CM-9LA–only approach	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hybrid approach	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Validation data	[redacted]		[redacted]					
	[redacted]		[redacted]	[redacted]	[redacted]			
	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	

AIC; Akaike information criterion; CM-227, CheckMate-227; CM-9LA, CheckMate-9LA; IPI, ipilimumab; KM, Kaplan-Meier; NIVO, Nivolumab.

Table 13 - Progression-free survival at different landmark points for PDC, non-squamous PD-L1 < 50% (adapted from Table 32 & 33, Technical Engagement response)

	Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
PDC, Non-squamous PD-L1<50%								
CM-9LA–only approach	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hybrid approach	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Validation data	[redacted]		[redacted]					
	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]		
	[redacted]		[redacted]	[redacted]	[redacted]			

AIC; Akaike information criterion; CM-227, CheckMate-227; CM-9LA, CheckMate-9LA; IPI, ipilimumab; KM, Kaplan-Meier; NIVO, Nivolumab.

Table 14 - Progression-free survival at different landmark points for nivolumab + ipilimumab + limited PDC, mixed histology PD-L1 > 50% (adapted from Table 24 & 25, Technical Engagement response)

	Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
NIVO + IPI + limited PDC, Mixed histology, PD-L1>50%								
CM-9LA–only approach	[redacted]							
	[redacted]							
	[redacted]							
	[redacted]							
	[redacted]							
Hybrid approach	[redacted]							
	[redacted]							
	[redacted]							
	[redacted]							
	[redacted]							
Validation data	[redacted]							
	[redacted]							
	[redacted]							

AIC; Akaike information criterion; CM-227, CheckMate-227; CM-9LA, CheckMate-9LA; IPI, ipilimumab; KM, Kaplan-Meier; NIVO, Nivolumab.

Table 15 - Progression-free survival at different landmark points for PDC, mixed histology PD-L1 > 50% (adapted from Table 26 & 27, Technical Engagement response)

	Distribution	Rank (AIC)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)	Year 10 (%)
PDC, Mixed histology, PD-L1>50%								
CM-9LA–only approach	[redacted]							
	[redacted]							
	[redacted]							
	[redacted]							
	[redacted]							
Hybrid approach	[redacted]							
	[redacted]							
	[redacted]							
	[redacted]							
	[redacted]							
Validation data	[redacted]							
	[redacted]							
	[redacted]							

AIC; Akaike information criterion; CM-227, CheckMate-227; CM-9LA, CheckMate-9LA; IPI, ipilimumab; KM, Kaplan-Meier; NIVO, Nivolumab.

2.9 Issue 9: Survival of patients on PDC

The survival of patients in the PDC arm of CheckMate-9LA appears to be more pessimistic than the PDC arm in CheckMate-227, and the ERG considered that the use of CheckMate-9LA may underestimate survival projections for these patients. The survival difference may be due to the extent to which subsequent immunotherapy is used after PDC, which is lower in CheckMate-9LA than in CheckMate-227. The ERG also considers that the rate of subsequent therapy after PDC in CheckMate-9LA is lower than what would be expected in UK clinical practice, where it is generally considered that 50% would receive subsequent immunotherapy, which is more aligned with the rate in CheckMate-227 (see Issue 14).

The company stated that for consistency of approach across treatment arms in the model and in the interest of using the most relevant evidence from the pivotal trial, the approach used to model survival in the PDC arm in the original submission is the most appropriate (i.e. CheckMate-9LA data used for the first 12 months for PDC and for nivolumab, followed by data from CheckMate-227). In addition, it was highlighted that in response to Issue 2, the company's clinical experts feel that the CheckMate-9LA clinical trial is representative of the UK clinical population. However, the company's response to Issue 2 commented only on the demographics of the trial and made no reference to the representativeness of subsequent therapies (detailed in Issue 14).

The issue remains unresolved as the company have provided little compelling evidence for why survival is different between the two trials, and why CheckMate-9LA is preferred to CheckMate-227 for representing the survival of patients on PDC. Since the PDC regimen and population in CheckMate-227 are both aligned with the decision problem for this appraisal, the ERG considers that the use of this data to model survival for PDC should not be disregarded by the committee, and that it is a more appropriate source of data for PDC given the concerns about the use of subsequent immunotherapy.

The impact of this alternative approach on the ICER for the ERG base case can be seen in Section 3.2. In this scenario, data from CheckMate-227 is used to model survival for the PDC arm, and the survival in the nivolumab + ipilimumab + limited PDC arm is modelled using the results of the fractional polynomial NMA.

2.10 Issue 10: Duration of treatment benefit

The company assumed a lifelong survival benefit for patients receiving first-line immunotherapy in their base-case analysis, which was considered by the ERG to be too optimistic. The ERG preferred to limit the benefit of treatment to five years after discontinuation.

The ERG considered that the evidence provided by the company to support their assumption is of limited relevance, as it is based on four years of follow-up data and is for a population receiving nivolumab as a second-line immunotherapy. The company did not provide any new analyses or evidence to support their initial assumption, and responded that it is important that the study originally presented is not completely disregarded as irrelevant but is treated with appropriate scrutiny, and that it suggests *"a robust and durable treatment effect lasting beyond discontinuation for nivolumab in patients with NSCLC"*.

As such, there is remaining uncertainty regarding the long-term survival benefit of patients receiving nivolumab + ipilimumab + limited PDC, which may be resolved to some extent through additional follow-up of CheckMate-9LA. As described in the ERG report (Section 4.2.6), the assumption of a five-year benefit post-continuation for immunotherapies is preferred by the ERG.

2.11 Issue 11: Duration of treatment

The company accepted the approach suggested by the ERG to model duration of treatment (DOT) with atezolizumab + bevacizumab + PDC, in which observed data from IMPower150 were preferred to model DOT for atezolizumab and bevacizumab individually rather than using PFS as a proxy for DOT.

The ERG also raised concerns regarding the DOT with nivolumab + ipilimumab + limited PDC, which follows the observed DOT from Checkmate-9LA and may be underestimated, given that 21% of patients remained on treatment at the time of analysis. Censoring marks and numbers at risk on the nivolumab + ipilimumab + limited PDC Kaplan-Meier plots of DOT would indicate how complete these data are, and the extent of the uncertainty that needs to be resolved. However, these were not provided by the company in their technical engagement response and the ERG maintains that there remains unresolved uncertainty in this matter.

2.12 Issue 12: Utility values estimated from proximity to death

The company used the patients' proximity to death to predict HRQoL, while the ERG prefers the use of progression-based health state utilities.

Firstly, the ERG considered that progression-based utilities may support a more robust analysis. There are a large number of available EQ-5D observations for the progressed health state, while there are only a small number of observations for the health state representing the period closest to death. The company explains that the reason for fewer subjects and observations in the TTD than the progression-based approach is due to the exclusion of subjects who were alive at last follow-up with follow-up time less than a year, as it is not possible to determine which TTD category the observations from these patients fall into.

The company provided further details of how the TTD utility models were selected. Other cut-off points were tested by the company for the closest to death time category, and "4 weeks" was selected for practical reasons: the estimated utility can be comparable with estimates from other trials, and the number of EQ-5D observations was acceptable. The company also provided model fit statistics (−2*log-likelihood, AIC, and BIC) for the progression-based and proximity to death-based utility models (Table 5 in company's response to TE). For the model without treatment as a covariate, the progression-based model had a lower AIC and BIC value than the TTD-based model, suggesting a better fit, although the company argues that the fit statistics for progression-based and TTD-based models are not directly comparable due to the large number of observations that were excluded from the TTD analyses.

Time as a continuous variable was not deemed appropriate and was consequently not explored by the company, explaining that because one trial arm has a shorter assessment period (i.e. patients living longer in one arm) and a "steeper slope" than the other trial arm, least squares estimates with mean time will cause an underestimate for one and an overestimate for the other. The ERG does not consider this a valid reason for not exploring time as a continuous variable, since utility data from both arms of the trial were pooled for the analysis.

Additionally, the ERG considered that progression-based utilities are more conceptually valid than TTD-based utilities, as time to death is not a causal determinant of HRQoL and can only be measured retrospectively. The company did not comment on this specifically but asserted that TTD-based utilities better captures the variation in HRQoL of a patient between the time of progression and death. Progression-based utilities are assessed shortly after progression has occurred, and therefore are expected to be biased upwards owing to a lack of observations collected in more severe patients who are closer to death.

While it is common for trials to record utility only once shortly after progression, this is not the case in the CheckMate-9LA trial, where assessments were administered at follow-up visits that occurred 35 days and 115 days after the last dose, and then every 3 months until death. There are a large number of data points contributing to the progressed disease health state: 1,004 post-progression observations were available from 353 patients, of which around a third were observed 6 months after progression (Section 4.2.7.1 of the ERG report). The ERG considers that the difference between the progression-free and the post-progression utility are large enough ([redacted] for progression-free and [redacted] for post-progression) to suggest that impact of progression is adequately captured.

The ERG also suggested that the company amends their model structure to allow the mean utility for the cohort to be estimated on a per-cycle basis, to allow for the validation of predicted utility values over time; however, this was not undertaken.

Consequently, the ERG does not consider that the company has provided compelling evidence to support a TTD-based approach, and that progression remains a statistically and conceptually superior approach to estimating utility values.

2.13 Issue 13: Estimation of drug costs using relative dose intensity

The ERG was concerned that drug acquisition costs may have been underestimated by the company, because the relative dose intensity was applied to the estimated cost rather than the number of required vials (the expected dose).

In their technical engagement response, the company clarified that the relative dose intensity accounts for number of doses received compared with the planned number of doses, as some doses may be missed due to dose delays lasting longer than the frequency of dose delivery. As such, the company maintains that the relative dose intensity reflects a reduction in the cost of treatment due to fewer doses being administrated during treatment which is not reflected by DOT.

The ERG acknowledges that dose reductions of nivolumab or ipilimumab were not permitted in CheckMate-9LA, and so agrees with the company that the relative dose intensity for these patients represents the reduction in total required doses. However, dose reductions of chemotherapy were permitted in CheckMate-9LA, which were mostly due to adverse events: the proportion of subjects with at least one dose reduction of chemotherapy was between 9% and 24.5% in the nivolumab arm, and between 12% and 27.9% in the PDC arm. Therefore, the relative dose intensity for chemotherapy will represent the reduction in total doses but also a reduction in the size of doses, which may not be associated with a reduction in required vials.

The impact of relative dose intensity for chemotherapy most likely lies between the company and the ERG assumptions, although this uncertainty does not have a substantial impact on the cost-effectiveness results: the ERG's scenario of dose intensity results in a small change to the ICER (an increase of less than £500 per QALY).

2.14 Issue 14: The proportion of patients receiving subsequent therapy

The ERG highlighted a number of concerns regarding the proportion of patients on subsequent therapy, firstly that it is likely to have been underestimated in the company analysis due to the immaturity of the trial data on which it was calculated, and secondly that the use of subsequent therapy in CheckMate-9LA was lower than what is expected in UK practice.

Approximately 50% of patients would receive an immunotherapy after discontinuing first-line chemotherapy in UK clinical practice.[1, 4] In CheckMate-9LA, the rates of subsequent therapy were 31% for nivolumab + ipilimumab + limited PDC, and 40% for PDC. This has implications for both

the costs of treatment and the survival benefit after discontinuation, which may be particularly underestimated in the PDC arm of CheckMate-9LA (see Issue 9).

In their response, the company described clinical input provided during technical engagement that suggested that the proportion of patients receiving subsequent therapy in the CheckMate-9LA trial may be lower than would be expected in a trial setting but that it could be considered reflective of UK clinical practice.

The ERG maintains their original position on the proportion receiving subsequent therapy, using rates from CheckMate-227 in their alternative base-case analysis (45.3% and 60.7%, for nivolumab + ipilimumab + limited PDC and PDC, respectively) which are more aligned with clinical practice. The use of these rates is also more internally consistent with the approach to modelling survival in the company's model, where data from CheckMate-227 was used to model survival after 13 months, which is when the expected survival benefits associated with subsequent therapy would most likely to manifest. Further clinical input would be of value to help resolve this issue.

2.15 Issue 15: The distribution of subsequent therapy

Docetaxel was not considered to be an appropriate subsequent therapy after PDC, and was removed as a second-line therapy option after PDC in the ERG's base-case analysis. Clinical input sought by the company after technical engagement suggested that there could be some patients who may not be clinically eligible for immunotherapy and may instead receive PDC re-challenge, docetaxel, or docetaxel + nintedanib. The ERG also notes that the use of docetaxel as a third-line therapy after first-line chemotherapy and second-line immunotherapy was highlighted in the committee papers for pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous NSCLC (TA600[1]). The company concluded that this has a minor impact on the ICER and accepted the approach suggested by the ERG.

Further clinical input during committee discussion could be valuable to address this issue. Additionally, the ERG notes that nivolumab has recently become part of routine commissioning for previously treated NSCLC, after transitioning out of the Cancer Drugs Fund, and that input from clinical or regulatory bodies on the expected usage of immunotherapies after chemotherapy could help resolve uncertainty in this issue.

2.16 Issue 16: End of life criteria

The company agree with the ERG that the end of life (EoL) criteria are met for the squamous, PD-L1 < 50% population and that the criteria are not met for the non-squamous PD-L1 < 50% and mixed histology PD-L1 ≥ 50% populations. This is driven by the absence of a comparator immunotherapy in the squamous, PD-L1 < 50% population, making PDC the only available comparator.

2.17 Issue 17: Access to Cancer Drugs Fund (CDF)

Given that the minimum follow-up of CheckMate-9LA is currently 12.7 months, the company agreed that entry to the CDF would allow some of the uncertainties in the analysis to be reduced, such as around the long-term benefit in OS. The ERG notes that uncertainties around the long-term safety profile and the mean time spent on treatment with nivolumab + ipilimumab + limited PDC could also be reduced.

The company also noted that a period in the CDF would also allow for the collection of real-world data on the efficacy of nivolumab + ipilimumab + limited PDC via the Systemic Anti-Cancer Therapy (SACT) database. This could allow further analysis of the impact in different PD-L1 subgroups to aid future decision making.

However, the ERG remains concerned that the data collection period of the CDF will not provide sufficiently long-term data on overall survival to provide evidence for one of the key assumptions of the company analysis, that the duration of survival benefit for nivolumab + ipilimumab + limited PDC continues over the remainder of the patient's lifetime (Issue 10).

3 Results

3.1 Company analysis

Modelling assumptions

In response to the issues noted by the ERG and following the technical engagement teleconference, the company updated their base case cost-effectiveness analyses.

The following ERG-preferred assumptions are incorporated within the company's revised model:

- Correction of errors identified by the ERG,
- Issue 4: Fractional polynomial network meta-analysis including CheckMate-227 data;
- Issue 11: Observed DOT used to model DOT for atezolizumab + bevacizumab + PDC;
- Issue 15: Docetaxel not considered to be an appropriate subsequent therapy after PDC.

In addition, the following assumptions have been altered in the company's revised model:

- Issue 6: PDC regimens from clinical input (distribution of chemotherapy regimens from clinical advice to the company during TE).

The company maintain their original position on the following assumptions, which differ from the ERG's preferred assumptions:

- Issue 1: Consideration of distinct decision problems for each subpopulation.
- Issue 7: Population-specific composition and duration of PDC,
- Issue 9: Survival of patients on PDC,
- Issue 10: Duration of treatment benefit,
- Issue 12: Utilities estimated by proximity to death,
- Issue 13: Estimation of drug costs using relative dose intensity,
- Issue 14: The proportion of patients receiving subsequent therapy based on rates in CheckMate-9LA.

Deterministic results

These results include the confidential PAS discounts [redacted]. Results with the PAS discounts for pembrolizumab, atezolizumab, bevacizumab and pemetrexed are provided in a confidential appendix separate to this report.

As described in Section 2.1, it is unclear whether the company agree with the ERG that it is appropriate for nivolumab + ipilimumab + limited PDC to be evaluated under three distinct sub-decision problems that each correspond to a subset of the indicated population (based on histology and PD-L1 expression). The company has provided results for their analysis that do not appear to correspond to specific subpopulations, and the two sets of results reflect the fact that these comparators will not ever be compared to each other as they are licensed for two different populations that do not overlap.

The results of the company's updated base-case analysis for nivolumab + ipilimumab + limited PDC versus PDC and atezolizumab + bevacizumab + PDC are shown in Table 16, and the results for nivolumab + ipilimumab + limited PDC versus PDC and pembrolizumab are shown in Table 17.

Compared with PDC, nivolumab + ipilimumab generated [redacted] incremental QALYs, and had higher total lifetime costs. The ICER was £27,920 per QALY gained.

Compared with atezolizumab + bevacizumab + PDC, nivolumab + ipilimumab + limited PDC was dominant, as it generated higher QALYs and had lower total lifetime costs. Compared with pembrolizumab, nivolumab + ipilimumab + limited PDC generated fewer QALYs but had lower lifetime costs, and the ICER of pembrolizumab versus nivolumab + ipilimumab + limited PDC was £934,713 per QALY gained.

Table 16 Company base-case results: fully incremental vs. atezolizumab + bevacizumab + carboplatin + paclitaxel (with PAS for nivolumab and ipilimumab)

	Total costs	Total LYs	Total QALYs	ICER
PDC	[redacted]	[redacted]	[redacted]	—
Nivolumab + ipilimumab + PDC	[redacted]	[redacted]	[redacted]	£36,380
Atezolizumab + bevacizumab + carboplatin + paclitaxel	[redacted]	[redacted]	[redacted]	Dominated

ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality-adjusted life-year

[1] Discounted LYG are presented by the company

Table 17 Company base-case results: fully incremental vs. pembrolizumab (with PAS for nivolumab and ipilimumab)

	Total costs	Total LYs	Total QALYs	ICER
PDC	[redacted]	[redacted]	[redacted]	—
Nivolumab + ipilimumab + PDC	[redacted]	[redacted]	[redacted]	£36,380
Pembrolizumab	[redacted]	[redacted]	[redacted]	£315,308

ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality-adjusted life-year

[1] Discounted LYG are presented by the company

Probabilistic results

The results of the PSA for nivolumab + ipilimumab + limited PDC versus PDC and atezolizumab + bevacizumab + PDC are shown in Table 18 and Figure 1, and the results of the PSA for nivolumab + ipilimumab + limited PDC versus PDC and pembrolizumab are shown in Table 19 and Figure 2.

Under the company's preferred assumptions, the probability of nivolumab + ipilimumab + limited PDC being the most cost-effective treatment compared with PDC and atezolizumab + bevacizumab + PDC is [redacted], [redacted] and [redacted] at thresholds of £20,000, £30,000 and £50,000 per QALY respectively.

The probability of nivolumab + ipilimumab + limited PDC being the most cost-effective treatment compared with PDC and pembrolizumab is 0.0%, 10.1% and 53.4% at thresholds of £20,000, £30,000 and £50,000 per QALY respectively.

Table 18 Results of the company's PSA: fully incremental vs. atezolizumab + bevacizumab + carboplatin + paclitaxel (with PAS for nivolumab and ipilimumab)

	Total costs	Total QALYs	ICER
PDC	[redacted]	[redacted]	-
Nivolumab + ipilimumab + limited PDC	[redacted]	[redacted]	£35,325
Atezolizumab + bevacizumab + carboplatin + paclitaxel	[redacted]	[redacted]	Dominated

Figure 1 Cost-effectiveness acceptability curve for the company's base-case analysis: nivolumab + ipilimumab + limited PDC, PDC and atezolizumab + bevacizumab + PDC (generated from company model, with PAS for nivolumab and ipilimumab)

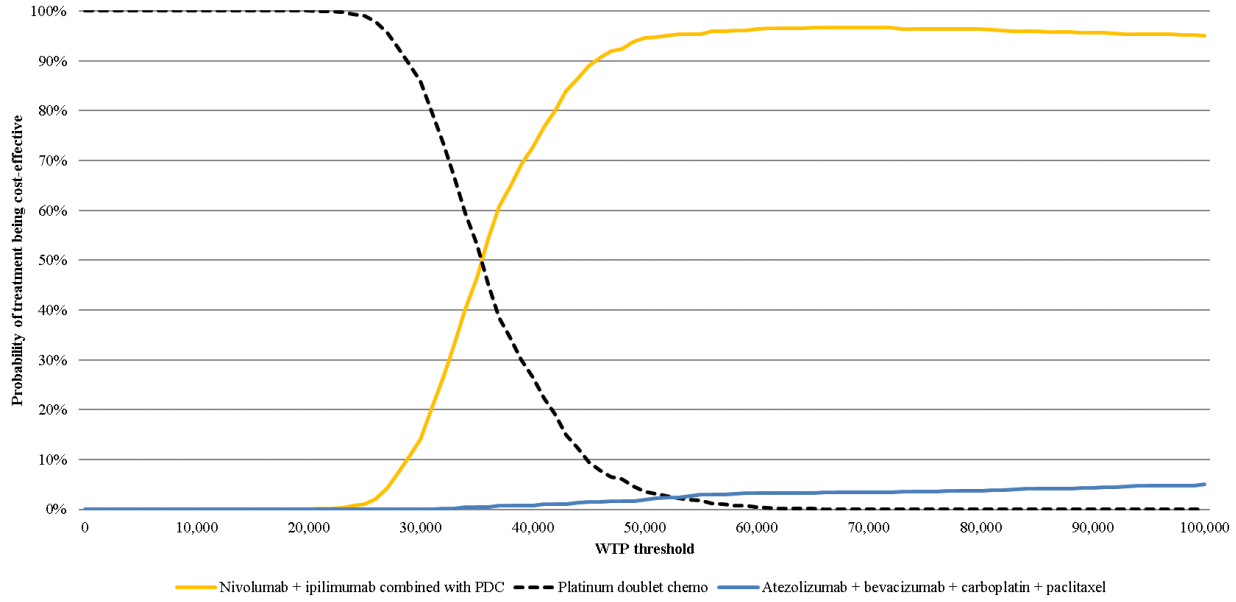
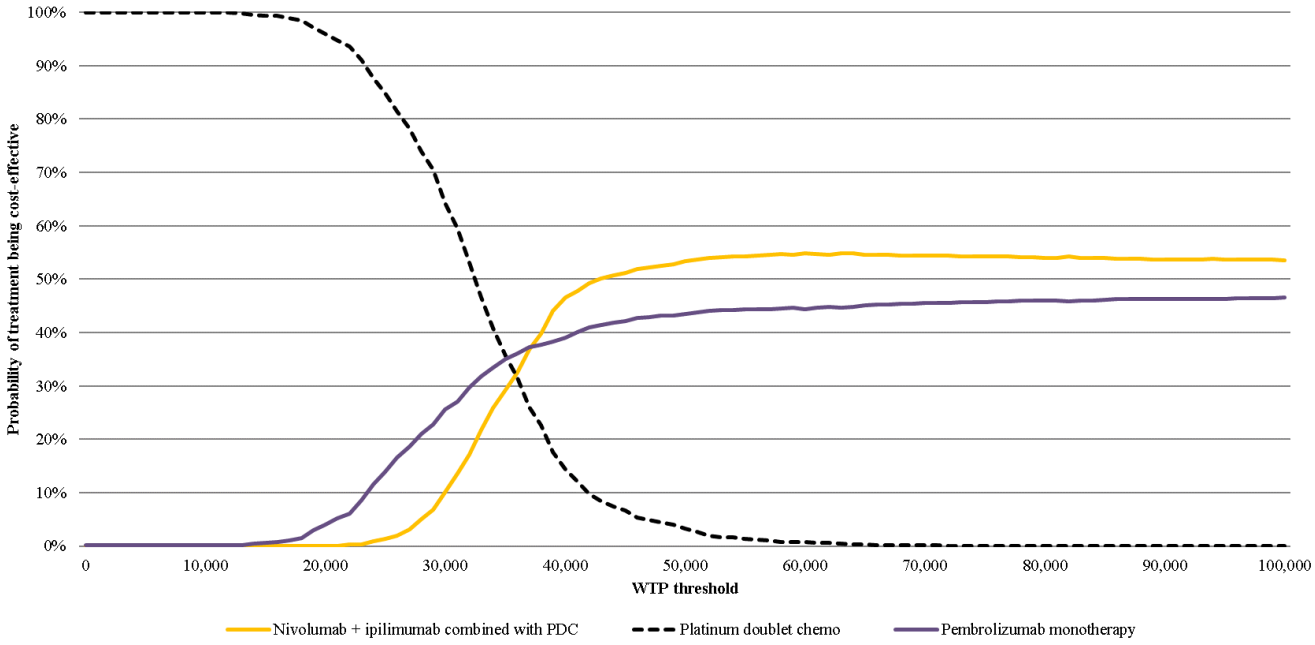


Table 19 Results of the company's PSA: fully incremental vs pembrolizumab (with PAS for nivolumab and ipilimumab)

	Total costs	Total QALYs	ICER
PDC	[redacted]	[redacted]	-
Nivolumab + ipilimumab + limited PDC	[redacted]	[redacted]	£35,296
Pembrolizumab	[redacted]	[redacted]	£315,308

Figure 2 Cost-effectiveness acceptability curve for the company's base-case analysis: nivolumab + ipilimumab + limited PDC, PDC and pembrolizumab (generated from company model, with PAS for nivolumab and ipilimumab)



3.2 ERG analysis

Deterministic results

The results of the ERG alternative base case analyses are presented in Table 20. These results include the PAS discounts for nivolumab and ipilimumab. Results with the confidential PAS discounts for the remaining comparators are presented in a confidential appendix separate to this report.

The ERG considers there are three distinct decision problems based on the in-scope comparators, defined by tumour histology and PD-L1 expression.

In the squamous, PD-L1 < 50% population, nivolumab + ipilimumab + limited PDC generated [redacted] incremental QALYs, and had higher total lifetime costs than PDC. The ICER was £47,872 per QALY gained. In the squamous, PD-L1 subgroup, there are only two comparators of interest and the EoL criteria are met. This ICER for nivolumab + ipilimumab + limited PDC versus PDC in the non-squamous, PD-L1 < 50% subgroup was £38,451per QALY gained, and in the PD-L1 ≥ 50% subgroup the ICER was £41,160 per QALY gained. However, the relevant comparators in these subgroups include an immunotherapy, and so the EOL criteria for nivolumab are not met.

In the non-squamous, PD-L1 < 50% population, nivolumab + ipilimumab + limited PDC dominated atezolizumab + bevacizumab + PDC, as it generated higher QALYs and had lower total lifetime costs.

In the PD-L1 ≥ 50% subgroup, nivolumab + ipilimumab + limited PDC generated fewer QALYs but had lower lifetime costs compared with pembrolizumab. The ICER of pembrolizumab versus nivolumab + ipilimumab + limited PDC was £85,350 per QALY gained.

Table 20 ERG base-case results (with PAS for nivolumab and ipilimumab)

Population	Intervention	Costs	QALYs	ICER
Squamous, PD-L1 < 50%	PDC	[redacted]	[redacted]	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£47,872
Non-squamous, PD-L1 < 50%	PDC	[redacted]	[redacted]	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£38,451
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated
Mixed histology, PD-L1 ≥ 50%	PDC	[redacted]	[redacted]	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£41,160
	PEMBRO	[redacted]	[redacted]	£85,350

ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality-adjusted life-year

Survival in the PDC arm estimated from CheckMate-227

The ERG conducted an additional scenario on their base case analysis, where survival in the PDC arm is estimated from CheckMate-227 data (see Issue 9). The results are presented in Table 21.

In the squamous, PD-L1 < 50% population, the ICER for nivolumab + ipilimumab + limited PDC compared to PDC was £54,486 per QALY gained. This is higher than the ICER in the non-squamous, PD-L1 < 50% subgroup (£44,000 per QALY gained) and the PD-L1 ≥ 50% subgroup (£45,189 per QALY gained, although nivolumab + ipilimumab + limited PDC was extendedly dominated by pembrolizumab). The ICER increased relative to the ERG base-case scenario in Table 20 due to the more favourable survival outcomes in the PDC arm, reducing the QALY gains for nivolumab + ipilimumab + limited PDC.

In the non-squamous, PD-L1 < 50% population, nivolumab + ipilimumab + limited PDC remained dominant compared with atezolizumab + bevacizumab + PDC. In the PD-L1 ≥ 50% subgroup, nivolumab + ipilimumab + limited PDC was extendedly dominated by pembrolizumab, and the ICER of pembrolizumab compared with nivolumab + ipilimumab + limited PDC decreased to £28,336 per QALY gained.

Table 21 Scenario analyses on the ERG base case analysis (with PAS for nivolumab and ipilimumab)

Population	Intervention	Costs	QALYs	ICER
Scenario: PDC survival using CheckMate-227 data and relative effects from nivo from FPNMA				
Squamous, PD-L1 <50%	PDC	[redacted]	[redacted]	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£54,486
Non-squamous, PD-L1 <50%	PDC	[redacted]	[redacted]	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£44,000
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated
Mixed histology, PD-L1 ≥50%	PDC	[redacted]	[redacted]	-
	NIVO + IPI + limited PDC	[redacted]	[redacted]	Extendedly dominated
	PEMBRO	[redacted]	[redacted]	£44,158

Probabilistic results

PSA was conducted on the ERG's alternative base case analysis, using 1,000 iterations (Table 22, Figure 3 to Figure 5).

The likelihood of nivolumab + ipilimumab + limited PDC being the most cost-effective treatment in the squamous, PD-L1 < 50% population is 0.1% and 60.1% at thresholds of £30,000 and £50,000 per QALY, respectively. In the non-squamous, PD-L1 < 50% population, nivolumab + ipilimumab + limited PDC has a likelihood of 6.3% and 95.0% at thresholds of £30,000 and £50,000 per QALY, respectively. In the PD-L1 ≥ 50% subgroup, the likelihood is 3.4% and 50.8%, at thresholds of £30,000 and £50,000 per QALY, respectively.

Table 22 ERG probabilistic base-case results (with PAS for nivolumab and ipilimumab)

Population	Intervention	Costs	QALYs	ICER	Probability cost-effective at £20,000 per QALY	Probability cost-effective at £30,000 per QALY	Probability cost-effective at £50,000 per QALY
Squamous, PD-L1 < 50%	PDC	[redacted]	[redacted]	-	100.0%	99.9%	39.9%
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£47,936	0.0%	0.1%	60.1%
Non-squamous, PD-L1 < 50%	PDC	[redacted]	[redacted]	-	99.9%	93.7%	4.9%
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£38,065	0.1%	6.3%	95.0%
	ATEZO + BEV + PDC	[redacted]	[redacted]	Dominated	0.0%	0.0%	0.1%
Mixed histology, PD-L1 ≥ 50%	PDC	[redacted]	[redacted]	-	98.1%	82.0%	5.0%
	NIVO + IPI + limited PDC	[redacted]	[redacted]	£39,861	0.1%	3.4%	50.8%
	PEMBRO	[redacted]	[redacted]	£85,350	1.8%	14.6%	44.2%

Figure 3 Cost-effectiveness acceptability curve for the ERG's base-case analysis: Squamous, PD-L1 < 50 subgroup (generated from company model, with PAS for nivolumab and ipilimumab)

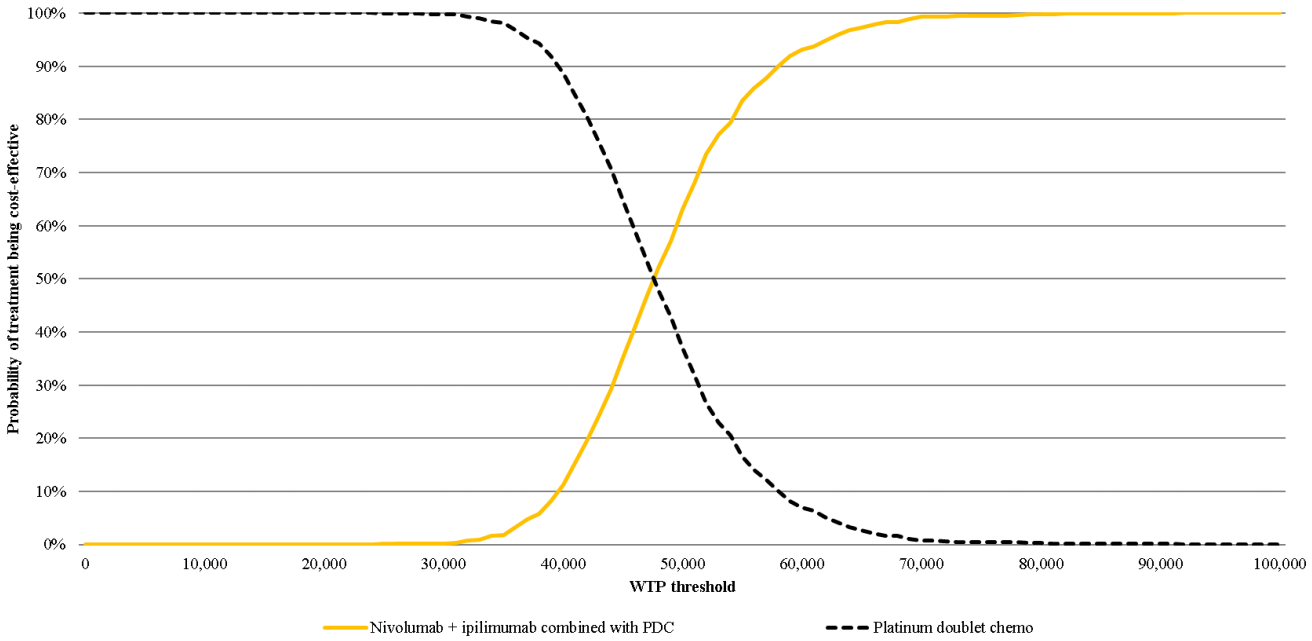


Figure 4 Cost-effectiveness acceptability curve for the ERG's base-case analysis: Non-squamous, PD-L1 < 50% subgroup (generated from company model, with PAS for nivolumab and ipilimumab)

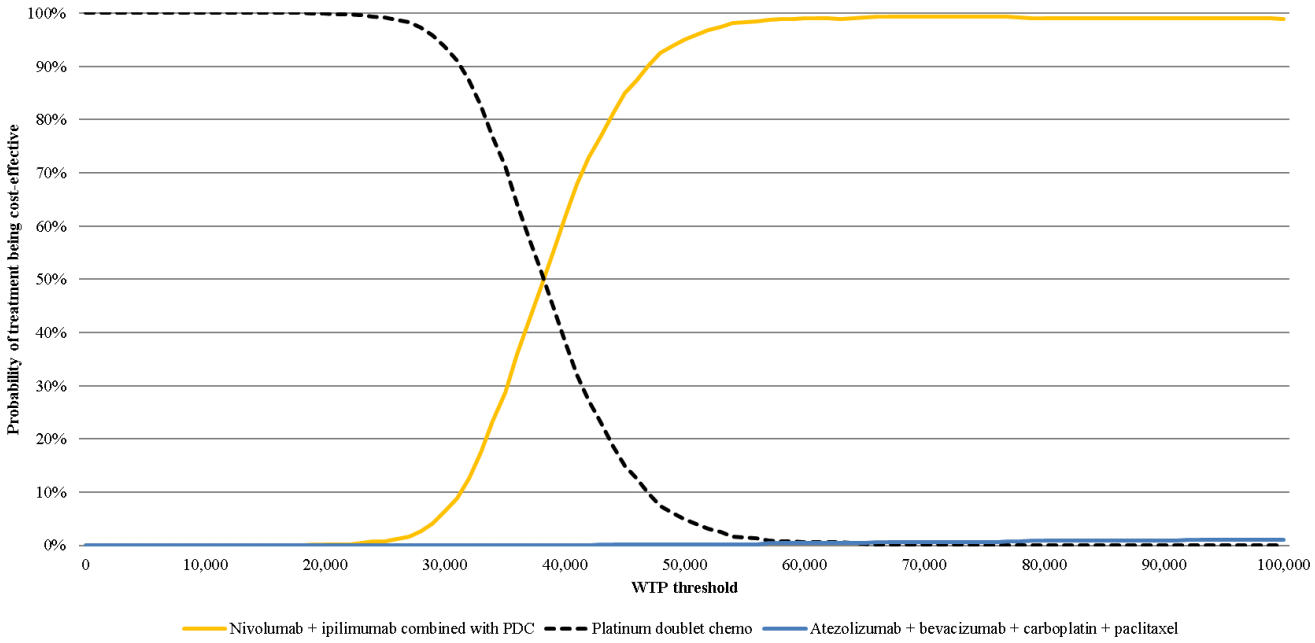
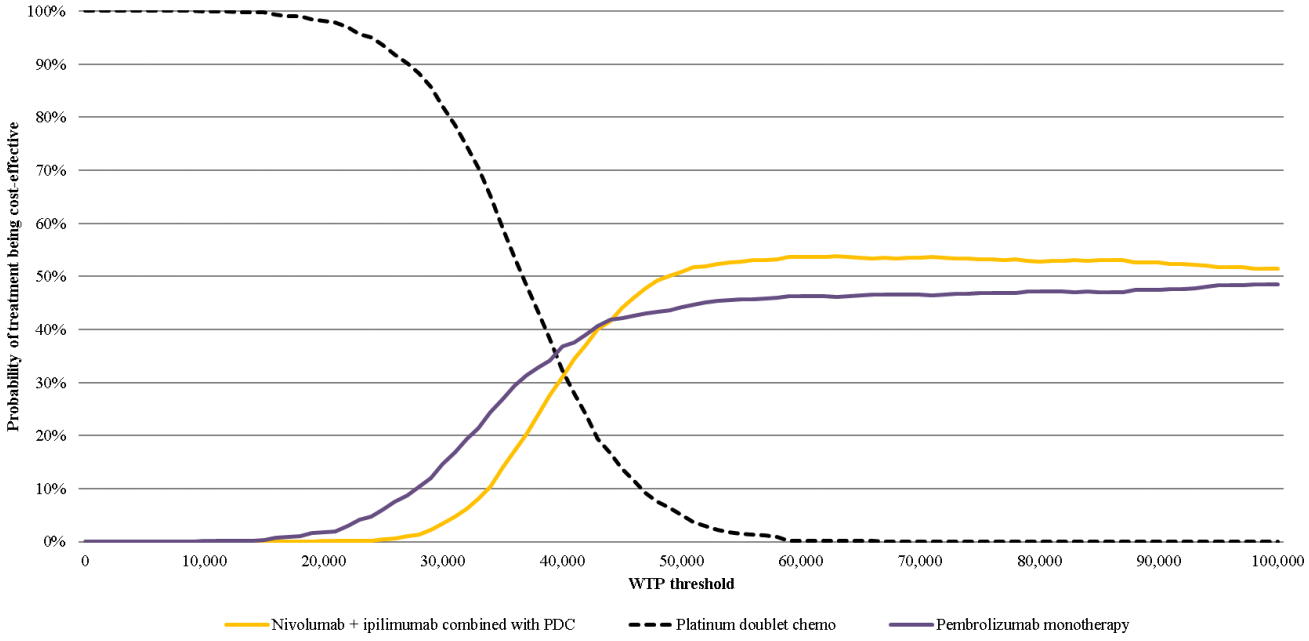


Figure 5 Cost-effectiveness acceptability curve for the ERG's base-case analysis: Mixed histology, PD-L1 ≥ 50% subgroup (generated from company model, with PAS for nivolumab and ipilimumab)



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