NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nivolumab with chemotherapy for neoadjuvant treatment of resectable non-small-cell lung cancer [ID3757]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Nivolumab with chemotherapy for neoadjuvant treatment of resectable non-small-cell lung cancer [ID3757]

Contents:

The following documents are made available to stakeholders:

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

1. **Company submission** from Bristol Myer Squibb

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. Roy Castle Lung Cancer Foundation
   b. Royal College of Pathologists

4. **External Assessment Report** prepared by Newcastle TAR
   a. EAG report
   b. EAG report addendum

5. **External Assessment Report – factual accuracy check**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Nivolumab with chemotherapy for neoadjuvant treatment of resectable non-small cell lung cancer [ID3757]

Document B

Company evidence submission

Submitted by Bristol Myers Squibb Pharmaceuticals, Ltd.

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Contents

B.1 DECISION PROBLEM, DESCRIPTION OF THE TECHNOLOGY, AND CLINICAL CARE PATHWAY 14

B.1.1 Decision problem 14
B.1.2 Description of the technology being evaluated 17
B.1.3 Health condition and position of the technology in the treatment pathway 19
B.1.3.1 Disease background 19
B.1.3.2 Diagnosis 20
B.1.3.3 Prevalence and incidence 21
B.1.3.4 Mortality and survival 21
B.1.3.5 Morbidity 24
B.1.3.6 Clinical pathway of care 24
B.1.4 Equality considerations 31

B.2 CLINICAL EFFECTIVENESS 32

B.2.1 Identification and selection of relevant studies 32
B.2.2 List of relevant clinical effectiveness evidence 32
B.2.3 Summary of methodology of the relevant clinical effectiveness evidence 34
B.2.3.1 CheckMate-816: methodology 34
B.2.3.2 CheckMate-816: baseline characteristics 38
B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence 39
B.2.4.1 CheckMate-816 39
B.2.5 Critical appraisal of the relevant clinical effectiveness evidence 43
B.2.6 Clinical effectiveness results of the relevant studies 44
B.2.6.1 CheckMate-816 44
B.2.7 Subgroup analysis 57
B.2.8 Meta-analysis 60
B.2.9 Indirect and mixed treatment comparisons 60
B.2.9.1 Evidence base 60
B.2.9.2 Network meta-analysis method assessment 61
B.2.9.3 Summary of results 61
B.2.9.4 Uncertainties in the indirect and mixed treatment comparisons 67
B.2.10 Adverse reactions 68
B.2.11 Supporting studies 70
B.2.11.1 Study CA209-159 70
B.2.11.2 NEOSTAR 71
B.2.11.3 NADIM 71
B.2.11.4 NADIM II 72
B.2.11.5 NCT03366766 72
B.2.12 Ongoing Bristol Myers Squibb nivolumab randomised controlled trials 73

B.2.13 Interpretation of clinical effectiveness and safety evidence for nivolumab + PDC in CheckMate-816 73
B.3 COST-EFFECTIVENESS 75
B.3.1 Published cost-effectiveness studies in non-metastatic NSCLC 75
B.3.2 Economic analysis 77
B.3.2.1 Patient population 77
B.3.2.2 Model structure 78
B.3.2.3 Perspective 84
B.3.2.4 Time horizon 84
B.3.2.5 Cycle length and half-cycle correction 84
B.3.2.6 Discounting 85
B.3.2.7 Intervention technology and comparators 85
B.3.3 Clinical parameters and variables 86
B.3.3.1 Parametric survival modelling for Event-Free and Locoregional Recurrence transition probabilities 86
B.3.3.2 Distant Metastasis health state 125
B.3.3.3 Cure assumption 130
B.3.3.4 Adverse reactions 133
B.3.4 Measurement and valuation of health effects 134
B.3.4.1 Health-related quality of life data from clinical trials 134
B.3.4.2 Mapping 135
B.3.4.3 Health-related quality of life studies 136
B.3.4.4 Health-related quality of life data used in the cost-effectiveness analysis 136
B.3.5 Cost and healthcare resource use identification, measurement, and valuation 138
B.3.5.1 Intervention and comparators' costs and resource use 140
B.3.5.2 Health-state unit costs and resource use 144
B.3.5.3 Adverse reaction unit costs and resource use 147
B.3.6 Uncertainty 148
B.3.7 Summary of base-case analysis inputs and assumptions 148
B.3.7.1 Summary of base-case analysis inputs 148
B.3.7.2 Assumptions 150
B.3.8 Base-case results 153
B.3.8.1 Base-case incremental cost-effectiveness analysis results 153
B.3.9 Exploring uncertainty 156
B.3.9.1 Probabilistic sensitivity analysis 156
B.3.9.2 Deterministic sensitivity analysis 161
B.3.9.3 Scenario analysis 163
B.3.10 Subgroup analysis 168
B.3.11 Validation 169
B.3.11.1 Validation of cost-effectiveness analysis 169
B.3.11.2 Internal validation 169
B.3.12 External validation 169

B.3.12.1 Validation Methods 169
B.3.12.2 Predictive Validation Against External Data 173
B.3.12.3 AUC Comparison Against Conditional Survival 173
B.3.12.4 Naive external validation 176
B.3.13 Predictive Validation Against Trial Data 178
B.3.13.1 Neoadjuvant Nivolumab + PDC 178
B.3.14 Interpretation and conclusions of economic evidence 180
B.4 REFERENCES 181
B.5 APPENDICES 191
APPENDIX C. SUMMARY OF PRODUCT CHARACTERISTICS (SMPC) AND UK PUBLIC ASSESSMENT REPORT 192
APPENDIX D. IDENTIFICATION, SELECTION, AND SYNTHESIS OF CLINICAL EVIDENCE 192
APPENDIX E. SUBGROUP ANALYSIS 192
APPENDIX F. ADVERSE REACTIONS 192
APPENDIX G. PUBLISHED COST-EFFECTIVENESS STUDIES 192
APPENDIX H. HEALTH-RELATED QUALITY OF LIFE STUDIES 192
APPENDIX I. COST AND HEALTHCARE RESOURCE IDENTIFICATION, MEASUREMENT, AND VALUATION 192
APPENDIX J. CLINICAL OUTCOMES AND DISAGGREGATED RESULTS FROM THE MODEL 192
APPENDIX K. PRICE DETAILS OF TREATMENTS INCLUDED IN THE SUBMISSION 192
APPENDIX L. CHECKLIST OF CONFIDENTIAL INFORMATION 192
APPENDIX M. INDIRECT TREATMENT COMPARISONS 192
APPENDIX N. EXPERT INPUT INTO THE SUBMISSION 192
APPENDIX O. SURVIVAL ANALYSES OF EFS 192
APPENDIX P. SOURCES FOR VALIDATION OF SURVIVAL EXTRAPOLATION 192

Tables

Table 1. The decision problem 15
Table 2. Technology being evaluated 17
Table 3. Summary of revisions from the seventh edition of the AJCC/UICC staging system to the eighth edition 20
Table 4. Patients with stage IB-IIIA (AJCC/UICC eighth edition), PS 0-1 NSCLC who were treated with systemic anticancer therapy or targeted treatment in England in 2019 29
Table 5. Analyses assessing association between pathologic complete response, event-free survival, and overall survival 30
Table 6. CheckMate-816: clinical effectiveness evidence 32
Table 7. CheckMate-816: summary of trial methodology 36
Table 8. CheckMate-816: baseline characteristics of patients 38
Table 9. CheckMate-816: summary of the statistical analyses 41
Table 10. CheckMate-816: quality assessment 44
Table 11. CheckMate-816: treatment summary 45
Table 12. CheckMate-816: subsequent therapies 46
Table 13. CheckMate-816: summary of event-free survival 48
Table 14. CheckMate-816: objective response rate and best overall response 51
Table 15. CheckMate-816: radiographic downstaging before and after treatment by stage of disease 51
Table 16. CheckMate-816: surgical outcomes summary 55
Table 17. EQ-5D-3L in the neoadjuvant period 57
Table 18. Comparators included in the network meta-analysis 61
Table 19. CheckMate-816: adverse events 68
Table 20. CheckMate-816: most frequent treatment-related adverse events (≥ 15% of patients in any treatment group) and surgery-related adverse events (≥ 5% of patients in any treatment group) 69
Table 21. CheckMate-816: adverse events leading to surgery delay and/or cancellation 70
Table 22. Summary list of published cost-effectiveness studies 76
Table 23. CheckMate-816: population characteristics 77
Table 24. HTA submissions for adjuvant/neoadjuvant treatments in non-metastatic solid tumours 79
Table 25. Appraisal committee meeting feedback on atezolizumab in adjuvant resected NSCLC 81
Table 26. Comparators in the economic analysis 85
Table 27. Summary of clinical inputs 86
Table 28. CheckMate-816: time to locoregional recurrence—summary of observed data 90

Table 29. Time to locoregional recurrence: goodness-of-fit statistics 93
Table 30. Time to locoregional recurrence: predicted median, mean, and landmarks (nivolumab + PDC) 95
Table 31. Time to locoregional recurrence: predicted median, mean, and landmarks (PDC)..... 95
Table 32. CheckMate-816: time to distant metastasis—summary of observed data 98
Table 33. CheckMate-816: time to any progression—summary of observed data..... 99
Table 34. Time to any progression: goodness-of-fit statistics..... 102
Table 35. Time to any progression: predicted median, mean, and landmarks (nivolumab + PDC)..... 105
Table 36. Time to any progression: median, mean, and landmarks (PDC) 105
Table 37. Event-free survival: landmark comparison versus external data..... 107
Table 38. Key trial outputs from LuCaBIS used to derive transition probability from Locoregional Recurrence to Distant Metastasis 110
Table 39. Estimates of annual transition probability from Locoregional Recurrence to Distant Metastasis per key opinion leader input 111
Table 40. Mortality in event-free patients: goodness-of-fit statistics (pooled data)..... 113
Table 41. Mortality in event-free patients: predicted median, mean, and landmarks (pooled data)..... 115
Table 42. Mortality after locoregional recurrence: goodness-of-fit statistics (pooled data) 118
Table 43. Mortality after locoregional recurrence: goodness-of-fit statistics for spline fitting (pooled data) 121
Table 44. Inputs for Distant Metastasis health state..... 128
Table 45. Distribution of treatment in Distant Metastasis health state 129
Table 46. Base-case cure parameters 133
Table 47. Percentage of patients experiencing grade 3 or 4 adverse events 133
Table 48. EQ-5D-3L utility index (UK weights): number of patients, observations, and least squares mean estimates..... 135
Table 49. Summary of utility values for cost-effectiveness analysis 136
Table 50. Alternative utility estimates used in the base case and scenario analysis .. 137
Table 51. Adverse event–related disutilities..... 138
Table 52. Summary of costs in the economic model..... 139
Table 53. Distribution of PDC received in the neoadjuvant setting..... 140
Table 54. Patients on neoadjuvant treatments who continue with adjuvant treatments 141
Table 55. Treatments received in the adjuvant setting..... 141
Table 56. Dosing regimen for each treatment..... 142
Table 57. Patient characteristics: weight and estimation of body surface area..... 142
Table 58. Unit drug acquisition costs 142

Table 59. Drug administration costs 143
Table 60. Radiotherapy costs 143
Table 61. Rate of surgery and distribution of surgical approach by treatment 144
Table 62. Unit costs for surgery 144
Table 63. Estimated costs of surgery by treatment arm 144
Table 64. Distribution of patients in Locoregional Recurrence health state by treatment modality 145
Table 65. Routine medical resource use annual frequency by health state 146
Table 66. Unit costs for routine medical resource use 146
Table 67. Treatment monitoring costs 147
Table 68. Distribution of patients by type of end-of-life care and costs of terminal care 147
Table 69. Adverse event unit costs 148
Table 70. Summary of variables applied in the economic model 148
Table 71. Key model assumptions 151
Table 72. Base-case results: nivolumab + PDC versus surgery 154
Table 73. Base-case results: nivolumab + PDC versus neoadjuvant chemoradiation 154
Table 74. Base-case results: nivolumab + PDC versus adjuvant PDC 154
Table 75. Net health benefit 155
Table 76. Model parameters varied in PSA and distributions 156
Table 77. Base-case probabilistic results: nivolumab + PDC versus surgery 157
Table 78. Base-case probabilistic results: nivolumab + PDC versus neoadjuvant chemoradiation 157
Table 79. Base-case probabilistic results: nivolumab + PDC versus adjuvant PDC ... 158
Table 80. Scenario analyses overview 163
Table 81. Results of scenario analyses nivolumab + PDC versus surgery 165
Table 82. Results of scenario analyses nivolumab + PDC versus neoadjuvant chemoradiation 166
Table 83. Results of scenario analyses nivolumab + PDC versus adjuvant PDC 167
Table 84. Model settings for external validation 170
Table 85. Conditional survival curve construction 171
Table 86. Model outputs versus conditional survival life-year estimates 174
Table 87. Neoadjuvant PDC OS Validation (Naïve): Landmark Comparison 177
Table 88. Neoadjuvant Nivolumab + PDC OS Validation: Model Outcomes vs. Trial Data; Survival by Six Month Interval 178
Table 89. Neoadjuvant PDC OS Validation: Model Outcomes vs. Trial Data; Survival by Six Month Interval 180

Figures

Figure 1. Stage distribution of lung cancer for 2017 in England and Wales 21
Figure 2. Causes of cancer deaths in the United Kingdom in 2020 22
Figure 3. Overall survival according to AJCC/UICC seventh edition staging system ... 23
Figure 4. Treatments used for resectable NSCLC in clinical practice in England 25
Figure 5. Potential position of nivolumab + PDC in the treatment pathway for resectable NSCLC in clinical practice in England and Wales 26
Figure 6. CheckMate-816: study design 34
Figure 7. CheckMate-816: planned analyses 40
Figure 8. CheckMate-816: pathologic complete response according to BIPR 47
Figure 9. CheckMate-816: event-free survival according to BICR 48
Figure 10. CheckMate-816: overall survival 49
Figure 11. CheckMate-816: time to death or distant metastases 50
Figure 12. CheckMate-816: event-free survival 2 52
Figure 13. CheckMate-816: event-free survival by pathologic complete response 53
Figure 14. CheckMate-816: pathologic complete response according to BIPR by subgroup 58
Figure 15. CheckMate-816: event-free survival according to BICR by subgroup 59
Figure 16. Network of evidence for event-free survival and overall survival 62
Figure 17. Event-free survival hazard ratio estimates of all relevant comparators vs. neoadjuvant chemotherapy (fixed effect estimates) 63
Figure 18. Overall survival hazard ratio estimates for all relevant comparators vs. neoadjuvant chemotherapy (fixed effect estimates) 63
Figure 19. Pathologic complete response odds ratio estimates for all relevant comparators vs. neoadjuvant chemotherapy (fixed effect estimates) 63
Figure 20. Time to locoregional recurrence hazard ratio estimates for all relevant comparators vs. neoadjuvant chemotherapy (fixed effect estimates) 64
Figure 21. Time to distant metastases hazard ratio estimates for all relevant comparators vs. neoadjuvant chemotherapy (fixed effect estimates) 64
Figure 22. Network diagram for TTLR for Scenario Analysis: Potentially resectable & completely resected, 3rd generation chemotherapies 65
Figure 23. Network meta-analysis output: vs. reference treatment (CT) for TTLR for Scenario Analysis: Potentially resectable & completely resected, 3rd generation chemotherapies (fixed effect model) 65
Figure 24. Network diagram for TTDM for Scenario Analysis: Potentially resectable & completely resected, 3rd generation chemotherapies 66
Figure 25. Network meta-analysis output: vs. reference treatment (neoCT) for TTDM for Scenario Analysis: Potentially resectable & completely resected, 3rd generation chemotherapies (fixed effect model) 66
Figure 26. Four-state semi-Markov model diagram 82

Figure 27. Survival model selection process algorithm presented by NICE Decision Support Unit and referenced by other HTA agencies 87
Figure 28. CheckMate-816: time to locoregional recurrence: observed data 90
Figure 29. Time to locoregional recurrence in the intention-to-treat population: log-log plot, Schoenfeld residuals plot and QQ-plot 91
Figure 30. Time to locoregional recurrence: within-trial fittings (nivolumab + PDC) 92
Figure 31. Time to locoregional recurrence: within-trial fittings (PDC) 92
Figure 32. Time to locoregional recurrence: long-term extrapolations (nivolumab + PDC) 93
Figure 33. Time to locoregional recurrence: long-term extrapolations (PDC arm) 94
Figure 34. Time to locoregional recurrence: comparison versus external data - PDC ... 96
Figure 35. CheckMate-816: time to distant metastasis—observed data 98
Figure 36. CheckMate-816: time to any progression—observed data 99
Figure 37. Time to progression in the intention-to-treat population: log-log plot, Schoenfeld residuals plot, and QQ-plot 100
Figure 38. Time to any progression: within-trial fittings (nivolumab + PDC) 101
Figure 39. Time to any progression: within-trial fittings (PDC) 102
Figure 40. Time to any progression: long-term extrapolations (nivolumab + PDC) 103
Figure 41. Time to any progression: long-term extrapolations (PDC) 104
Figure 42. Event-free survival: visual comparison versus external data for PDC 107
Figure 43. Time to Death or Distant Metastasis: long-term extrapolations (nivolumab + PDC) 109
Figure 44. Time to Death or Distant Metastasis: long-term extrapolations (PDC) 109
Figure 45. CheckMate-816: mortality in event-free patients—observed data 112
Figure 46. CheckMate-816: mortality in event-free patients—observed data (pooled) 112
Figure 47. Mortality in event-free patients: within-trial fittings (pooled data) 114
Figure 48. Mortality in event-free patients: long-term extrapolations (pooled data) 114
Figure 49. Patient-level meta-analysis versus long-term event-free mortality extrapolations from CheckMate-816 116
Figure 50. CheckMate-816: mortality after locoregional recurrence—observed data .. 117
Figure 51. CheckMate-816: mortality after locoregional recurrence—observed data (pooled) 118
Figure 52. Mortality after locoregional recurrence: within-trial fittings (pooled data) 119
Figure 53. Mortality after locoregional recurrence: long-term extrapolations (pooled data) 120
Figure 54. Mortality after locoregional recurrence: observed and predicted survival from 2-4 degrees of freedom on hazard, odds, and normal scales for short-term (top), long-term (bottom), and pooled data 122
Figure 55. Comparison of mortality in Locoregional Recurrence health state versus PACIFIC[132] and Goldstraw et al. (2016)[31] 124
Figure 56. Long-term splines and parametric extrapolations 125

Figure 57. One-off approach for Distant Metastasis health state 126
Figure 58. Hazard of progression in early-stage resected NSCLC 131
Figure 59. Long-term event-free survival from neoadjuvant PDC studies 132
Figure 60. Costs by health state 139
Figure 61. PSA Results—Cost-effectiveness plane nivolumab + PDC vs. surgery 158
Figure 62. PSA Results—Cost-effectiveness plane nivolumab + PDC vs. neoadjuvant chemoradiation 159
Figure 63. PSA Results—Cost-effectiveness plane nivolumab + PDC vs. adjuvant PDC 159
Figure 64. Cost-effectiveness acceptability curve: Nivolumab + PDC vs. surgery 160
Figure 65. Cost-effectiveness acceptability curve: Nivolumab + PDC vs. neoadjuvant chemoradiation 160
Figure 66. Cost-effectiveness acceptability curve: Nivolumab + PDC vs. adjuvant PDC 161
Figure 67. Deterministic sensitivity analysis—nivolumab + PDC vs. surgery 162
Figure 68. Deterministic sensitivity analysis—Nivolumab + PDC vs. PDC (adjuvant) .. 162
Figure 69. Deterministic sensitivity analysis—Nivolumab + PDC vs. Neoadjuvant CRT .. 163
Figure 70. Conditional survival for neoadjuvant nivolumab + PDC 172
Figure 71. Conditional survival for neoadjuvant PDC 172
Figure 72. Plotted Conditional Survival Curve: Nivolumab+ PDC 173
Figure 73. Plotted conditional survival curve: neoadjuvant PDC 173
Figure 74. Model-generated overall survival versus conditional survival: neoadjuvant nivolumab + PDC 175
Figure 75. Model-generated overall survival versus conditional survival: neoadjuvant PDC 175
Figure 76. Comparison of modelled overall survival versus external data 177
Figure 77. Neoadjuvant Nivolumab + PDC OS Validation: Model Outcomes vs. Trial Data .. 178
Figure 78. Neoadjuvant PDC OS Validation: Model Outcomes vs. Trial Data 179

Abbreviations

Abbreviation	Definition
adjCT	adjuvant chemotherapy
AE	adverse event
AFT	accelerated failure time
AIC	Akaike information criteria
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
AUC	area under the curve
BIC	Bayesian information criteria
BICR	blinded independent central review
BIPR	blinded independent pathologic review
BMS	Bristol Myers Squibb
BSA	body surface area
CAD	Canadian dollar
CADTH	Canadian Agency for Drugs and Technologies in Health
CEM	cost-effectiveness model
CI	confidence interval
CM-816	CheckMate-816
CNS	central nervous system
cRR	clinical response rate
CRT	chemoradiation
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumour DNA
DF	degree of freedom
DFS	disease-free survival
DM	Distant Metastasis
DMC	data monitoring committee
DSU	Decision Support Unit
EAG	evidence assessment group
ECOG	Eastern Cooperative Oncology Group
EEPRU	Economic Methods of Evaluation in Health and Social Care Policy Research Unit
EF	Event-Free
EFS	event-free survival
EFS2	event-free survival on second-line therapy/event-free survival 2
EGFR	epidermal growth factor receptor
FA	final analysis
HAS	French National Authority for Health
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
HRQOL	health-related quality of life
HSE	Health Survey for England
HTA	health technology assessment

Abbreviation	Definition
ICER	incremental cost-effectiveness ratio
ICUR	incremental cost-utility ratio
I-O	immuno-oncology
IQR	interquartile range
IRT	Interactive Response Technology
ITC	indirect treatment comparison
ITT	intention to treat
IV	intravenous
KM	Kaplan-Meier
KOL	key opinion leader
LR	Locoregional Recurrence
LSM	least squares mean
LY	life-year
LYG	life-year gained
MA	meta-analysis
mut/MB	mutations per megabase
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
MID	minimally important difference
MPR	major pathologic response
MRI	magnetic resonance imaging
MRU	medical resource use
MST	median survival time
NA	not available
NCI	National Cancer Institute
NE	not estimable
neoCRT	neoadjuvant chemoradiotherapy
neoCT	neoadjuvant chemotherapy
neoNIVO-CT	neoadjuvant nivolumab-chemotherapy
NHB	net health benefit
NHS	National Health Service
NHS EED	National Health Service's Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NIVO	nivolumab
NLCA	National Lung Cancer Audit
NMA	network meta-analysis
NR	not reached/not reported
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PAS	patient access scheme
PBAC	Pharmaceutical Benefits Advisory Committee
pCR	pathologic complete response
PD-1	programmed cell death protein 1
PDC	platinum doublet chemotherapy

Abbreviation	Definition
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PET	positron emission tomography
PFS	progression-free survival
PFS2	progression-free survival 2
PH	proportional hazard
PICOS	patients, intervention, comparator, outcomes, and study design
PK	pharmacokinetics
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	performance status
PSA	probabilistic sensitivity analysis
Q3W	every 3 weeks
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RT	radiotherapy
SACT	systemic anticancer therapy
SAE	serious adverse event
SD	standard deviation
SE	standard error
SEER	Surveillance, Epidemiology, and End Results
SG	standard gamble
SLR	systematic literature review
SMC	Scottish Medicines Consortium
SOC	standard of care
TA	technology appraisal
TMB	tumour mutational burden
TPS	Tumour Proportion Score
TTDM	time to death or distant metastases (in CheckMate-816) / time to distant metastases (in NMA and CEM)
TTLR	time to locoregional recurrence
TTO	time–trade-off
UI	utility index
UICC	Union for International Cancer Control
UK	United Kingdom
US	United States
VAS	visual analogue scale
WHO	World Health Organization
WTP	willingness to pay

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

B.1.1Decision problem

This submission covers the full marketing authorisation for nivolumab in combination with platinum doublet chemotherapy (nivolumab + PDC) for the neoadjuvant treatment of resectable (tumours ≥ 4 cm or node positive) non-small cell lung cancer (NSCLC) in adults.[1] 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	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with resectable NSCLC[a]	As per the scope	N/A
Intervention	Nivolumab with platinum-doublet chemotherapy	As per the scope	N/A
Comparator(s)	Established clinical management without nivolumab with chemotherapy, which may include: ▪ Neoadjuvant chemoradiotherapy ▪ Adjuvant chemotherapy ▪ Active monitoring For people whose tumours express PD-L1 with at least a 50% tumour proportion score ▪ Atezolizumab after adjuvant cisplatin-based chemotherapy (subject to NICE appraisal) [b]	As per the scope (note: surgical resection alone equates to active monitoring) [b]	N/A
Outcomes	The outcome measures to be considered include: ▪ disease-free survival ▪ overall survival ▪ response rates ▪ adverse effects of treatment ▪ health-related quality of life.	▪ EFS rather than DFS is presented because it is the primary endpoint in CheckMate-816. ▪ Rather than response rate, we include the more specific outcome of pCR, which is a primary outcome in the trial.	▪ DFS does not capture progression of disease preventing surgical resection; therefore, EFS is more appropriate.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Subgroups to be considered	If evidence allows, results by disease stage and level of PD-L1 expression will be considered	CheckMate-816 was not powered to detect differences in subgroups, and insufficient events have occurred to make meaningful conclusions regarding subgroups. In line with the trial population and licence, we present the concurrently randomly assigned population[c] as the population base case. A significant patient benefit was observed in the primary analysis population, with a statistically significant and clinically relevant improvement in EFS and pCR vs. PDC alone (pCR, 24% vs. 2%; median EFS, 31.6 months vs. 20.8 months, respectively).	
Special considerations, including issues related to equity or equality	Guidance will only be issued in accordance with 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.	There are no equity or equality issues associated with this appraisal.	

EFS = event-free survival; DFS = disease-free survival; N/A = not applicable; NSCLC = non-small cell lung cancer; pCR = pathologic complete response; PD-1 = programmed cell death protein 1; PDC = platinum doublet chemotherapy; PD-L1 = programmed death-ligand 1.

[a] Tumour resectability is assessed at diagnosis and again after the administration of a neoadjuvant treatment but before surgery. Therefore, some patients may be deemed potentially eligible for resection at diagnosis, but their resectability status may change before surgery. In the remainder of the document, *potentially resectable* is referred to as *resectable* when relating to neoadjuvant treatment.

[b] Although in the NICE scope, NICE confirmed at the checkpoint meeting that atezolizumab is no longer a relevant comparator because it is only recommended for use within the Cancer Drugs Fund, not in routine commissioning and it is not therefore included in this submission.[2]

[c] The original study design also included a study arm with nivolumab + ipilimumab, which was stopped in a protocol revision and is not relevant to this appraisal. This decision was based on evidence from the metastatic setting and external data from the NADIM trial, which demonstrated a more promising pCR benefit for nivolumab + PDC than seen for nivolumab + ipilimumab in the NEOSTAR trial. Therefore, the clinical development of nivolumab + PDC was prioritised in CheckMate 816. The population presented in this submission is the concurrently randomly assigned population, described as the “intention-to-treat” population in the remainder of this document.

B.1.2Description of the technology being evaluated

As summarised in Section B.1.1, this appraisal is for nivolumab + PDC for adults with resectable (tumours ≥ 4 cm or node positive) NSCLC in the neoadjuvant setting.

Nivolumab + PDC (cisplatin with either gemcitabine or pemetrexed, or carboplatin with paclitaxel) for the neoadjuvant treatment of adults with resectable NSCLC received marketing authorisation in the United Kingdom (UK) on 16 August 2022.1 It has been compared with PDC (cisplatin with either gemcitabine, pemetrexed, vinorelbine, or docetaxel, or carboplatin with paclitaxel) in the CheckMate-816 clinical trial in adults with resectable IB-IIIA (American Joint Committee on Cancer [AJCC]/Union for International Cancer Control [UICC] seventh edition) NSCLC (Table 2).[3]

Table 2. Technology being evaluated

UK approved name and brand name	Nivolumab (Opdivo®) with PDC
Mechanism of action	Nivolumab is a fully human, immunoglobulin type 4, PD-1 receptor-blocking monoclonal antibody that prevents inactivation or reactivates the ability of T cells to attack the tumour.[4,5] Nivolumab binds to PD-1 receptors on T cells with high affinity[4] and selectively disrupts inhibitory signalling triggered by PD-L1 and PD-L2, thereby restoring normal T-cell antitumour function. Expression of PD-1 is increased on immune cells in patients with several types of cancer.[6,7]
Marketing authorisation/cost-effectiveness mark status	The application for marketing authorisation with the MHRA was submitted via Project ORBIS in February 2022 and was approved on 16 August 2022.[1]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Neoadjuvant treatment of resectable (tumours ≥ 4 cm or node positive) NSCLC in adults.[1]
Method of administration and dosage	Nivolumab is administered as an intravenous infusion at a dosage of 360 mg every 3 weeks + PDC every 3 weeks for up to 3 cycles.
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: £3,951. ▪ PDC price per dose: dependent on combination ▪ 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 approved by the regional Department of Health that is applicable to this appraisal.

MHRA = Medicines and Healthcare Products Regulatory Agency; NSCLC = non-small cell lung cancer; PAS = patient access scheme; PD-1 = programmed cell death protein 1; PDC = platinum doublet chemotherapy; PD-L1 = programmed death-ligand 1; PD-L2 = programmed death-ligand 2; UK = United Kingdom.

[a] Cost of a course of nivolumab + PDC at list price based on 3 cycles of therapy as received in the CheckMate-816 trial per protocol for all event-free patients.

Nivolumab is an immuno-oncology agent that acts to restore the body's natural antitumour response by inhibiting the suppression that the tumour exerts on antitumour immune responses. Programmed cell death protein 1 (PD-1) is an immune checkpoint involved in T-cell differentiation and function. PD-1 is specifically involved in inhibiting T-cell destruction of healthy "self-cells" at the effector (later) stage of the immune response. Tumour cells can exploit this pathway by upregulating proteins (i.e., programmed death-ligand 1 [PD-L1], programmed death-ligand 2 [PD-L2]) that engage PD-1 to limit the activity of T cells at the tumour site.8 Used before surgery, nivolumab-based regimens are expected to help prime the body's immune response not only to target primary tumour cell activity before surgery and promote responses against micro-metastases already present but to kill tumour cells released during surgery, limiting recurrence.[9]

Evidence from animal models, supported by clinical evidence in some tumours, suggests that surgery and the body's response to the associated trauma can be a trigger for the development of metastases.[9] First, although cells from the primary tumour are present in the blood stream in most patients and are generally rapidly destroyed, the disruption of the primary tumour that occurs during surgery may result in increasing levels of circulating tumour cells by as much as 10-fold.[9]

Second, surgery has been found to reduce natural killer cell cytotoxic activity and impair macrophage functioning, both of which can promote the development of metastases.[9] Other perioperative factors such as the use of opioids for pain management, blood transfusions, hypothermia during surgery, and the effects of anaesthetics may also have immunosuppressive effects that reduce the body's antitumour activity.[9]

Third, the acute inflammatory response to surgery has been found to provide conditions which increase the capture of tumour cells in locations which favour their growth. For example, in response to tissue injury, neutrophils form neutrophil extracellular traps which capture the tumour cells, thus promoting their growth.[9] Taken together, priming the antitumour activity of the immune system before surgery could decrease the presence of tumour cells in the blood stream and encourage an antitumour immune response to help reduce the risk of both local and distant recurrence after surgery.[9]

A further theoretical rationale for use of immuno-oncology agents in the neoadjuvant setting is that they may be more effective in the presence of a macroscopic tumour burden due to higher levels of endogenous tumour antigen present in the primary tumour that enhance T-cell priming.[10] Thus, the effects of immuno-oncology agents to promote the antitumour immune response are expected to be optimal when initiated before surgery because they would help overcome the adverse effects of surgery related to micro-metastatic spread and immunity impairment, thereby overcoming important limitations of current treatment approaches. On this note, preclinical models support better outcomes with neoadjuvant immuno-oncology therapy than adjuvant immuno-oncology therapy.[11]

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

B.1.3.1 Disease background

Lung cancer is the second most common cancer worldwide, and is the most frequent cause of cancer deaths both worldwide and in the UK.[12,13]

There are 2 major groups of lung cancer that differ based on histology: NSCLC (80%-85% of lung cancers) and small cell lung cancer (15%-20% of lung cancers).[14] NSCLC is divided into 2 main histological subtypes: squamous cell carcinoma (25%-30%) and nonsquamous NSCLC (75%, primarily composed of adenocarcinoma [~40%] and large cell carcinoma [~5%-10%]).[14-16] A few other subtypes of NSCLC, such as adenosquamous carcinoma and sarcomatoid carcinoma, are much less common.[15]

NSCLC can also be categorised according to the presence of molecular markers; the patients with these mutations can be treated with targeted therapy and are generally not considered for immuno-oncology therapy in resectable disease.[17] These biomarkers include epidermal growth factor receptor (EGFR), BRAF, Kirsten rat sarcoma virus (KRAS), anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1 (ROS1), and neurotrophic tyrosine receptor kinase (NTRK).[18-29]

The AJCC/UICC staging system for NSCLC classifies patients at diagnosis into stages of disease that predict survival outcomes. It is based on 3 features of the tumour:

- Size and extent of the main tumour (T)
- Spread to nearby lymph nodes (N)
- Spread (metastasis) to distant sites (M)

Numbers or letters after T, N, and M provide more details about each of these factors, describing the size of the tumour and how far it has spread. Within the T, N and M stages, higher numbers mean the cancer is more advanced. Letters are used as modifiers or to provide further parameters, such as the grade of the tumour, any invasion present, completeness of the operation, timing or method used to determine the tumour stage.

The seventh edition of the AJCC/UICC TNM staging system defines 9 stages of disease, from occult carcinoma to metastatic disease. In this classification, stages I-II are considered to correspond to early disease, whereas locally advanced disease corresponds to stage III. A broader category, non-metastatic disease, is considered to include stages I-III and includes all stages in which distant metastases are not present (i.e., M category is M0).

The eighth edition of the AJCC/UICC TNM staging system includes revised definitions for some of the stages and the addition of stage IIIC; broadly, tumour size in the eighth edition is generally smaller than that in the same stages of the seventh edition. Table 3 compares these editions of the AJCC/UICC.

In the CheckMate-816 trial, the patient inclusion criteria are based on the AJCC/UICC seventh edition criteria with included patients being required to have stage IB (with tumour size ≥ 4 cm) to IIIA disease. This largely corresponds to stages IB (with tumour size 4 cm) to

IIIB (non-N3 and non–N2-T4) in the eighth edition. The changes that are relevant to the nivolumab indication are as follows: some patients within IB are reclassified as IIA depending on tumour size, all IIA patients are reclassified as IIB, some patients within IIB are reclassified as IIIA depending on tumour size, and some patients within the IIIA category are reclassified as IIIB. Note that the seventh edition is used when referring to CheckMate-816 patients throughout this appraisal; patients have not been reclassified into the eighth edition.

Table 3. Summary of revisions from the seventh edition of the AJCC/UICC staging system to the eighth edition

	TNM categorisation	
Stage	**Seventh edition**	**Eighth edition**
IA	N0, T1 (≤ 3 cm)	N0, T1 (≤ 3 cm)
IB	N0, T2a **(> 3-5 cm)**	N0, T2a **(> 3-4 cm)**
IIA	N0, T2b **(> 5-7 cm)** N1, T1-T2a (≤ 5 cm)	N0, T2b **(> 4-5 cm)**
IIB	N0, T3 **(> 7 cm)** N1, T2b (5-7 cm)	N0, T3 **(> 5-7 cm)** N1, **T1-T2 (≤ 5 cm)**
IIIA	N0, T4 (invasive) N1, T3-T4 (> 7 cm or invasive) N2, T1-T3 (any size, non-invasive)	N0, T4 **(> 7 cm)** N1, T3-T4 **(> 5 cm)** N2, T1-**T2 (≤ 5 cm)**
IIIB	N2, T4 (invasive) N3, T1-T4 (any size)	N2, **T3**-T4 **(> 5 cm)** N3, T1-**T2 (≤ 5 cm)**
IIIC	Not included	**N3, T3-T4 (> 5 cm)**

AJCC = American Joint Committee on Cancer; UICC = Union for International Cancer Control.

Notes: Properties of the tumour are indicated as T = size and extent of the main tumour; N = spread to nearby lymph nodes; M = metastasis to distant sites.

0-4 denotes increasing severity of T, N, or M. Bold text indicates differences between the seventh and eighth editions of the AJCC/UICC TNM staging system.

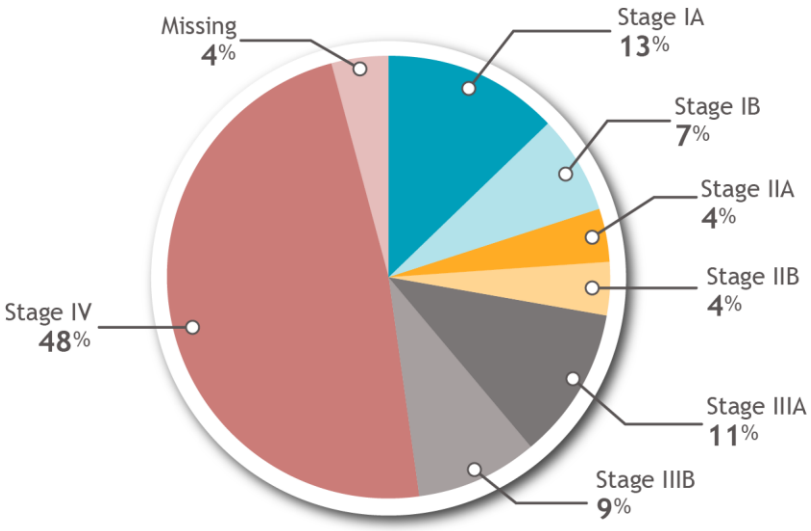
Sources: Detterbeck et al. (2009)[30]; Goldstraw et al. (2016)[31]

B.1.3.2 Diagnosis

Most lung cancers are diagnosed at an advanced stage when the cancer has spread to the lymph nodes and other organs in the chest (locoregional disease; stage III) or to other parts of the body (metastatic disease; stage IV).[32] Of all lung cancer cases, 26% were diagnosed at stages IB-IIIA in England in 2019.[i,33,34]

[i] Note, although 2020 data are available from the NLCA, given the impact of COVID-19 on diagnosis and treatment in 2020, the 2019 data are presented and used in this submission. 2017 data are also used in certain cases where it is necessary to ensure alignment with the seventh edition of the AJCC/UICC TNM staging system used in the CheckMate-816 trial.

Figure 1. Stage distribution of lung cancer for 2017 in England and Wales



AJCC = American Joint Committee on Cancer; UICC = Union for International Cancer Control.

Note: Data are from the 2018 audit (2017 data) to ensure alignment with the seventh edition of the AJCC/UICC TNM staging system used in the CheckMate-816 trial.

Source: Royal College of Physicians (2018)[34]

B.1.3.3 Prevalence and incidence

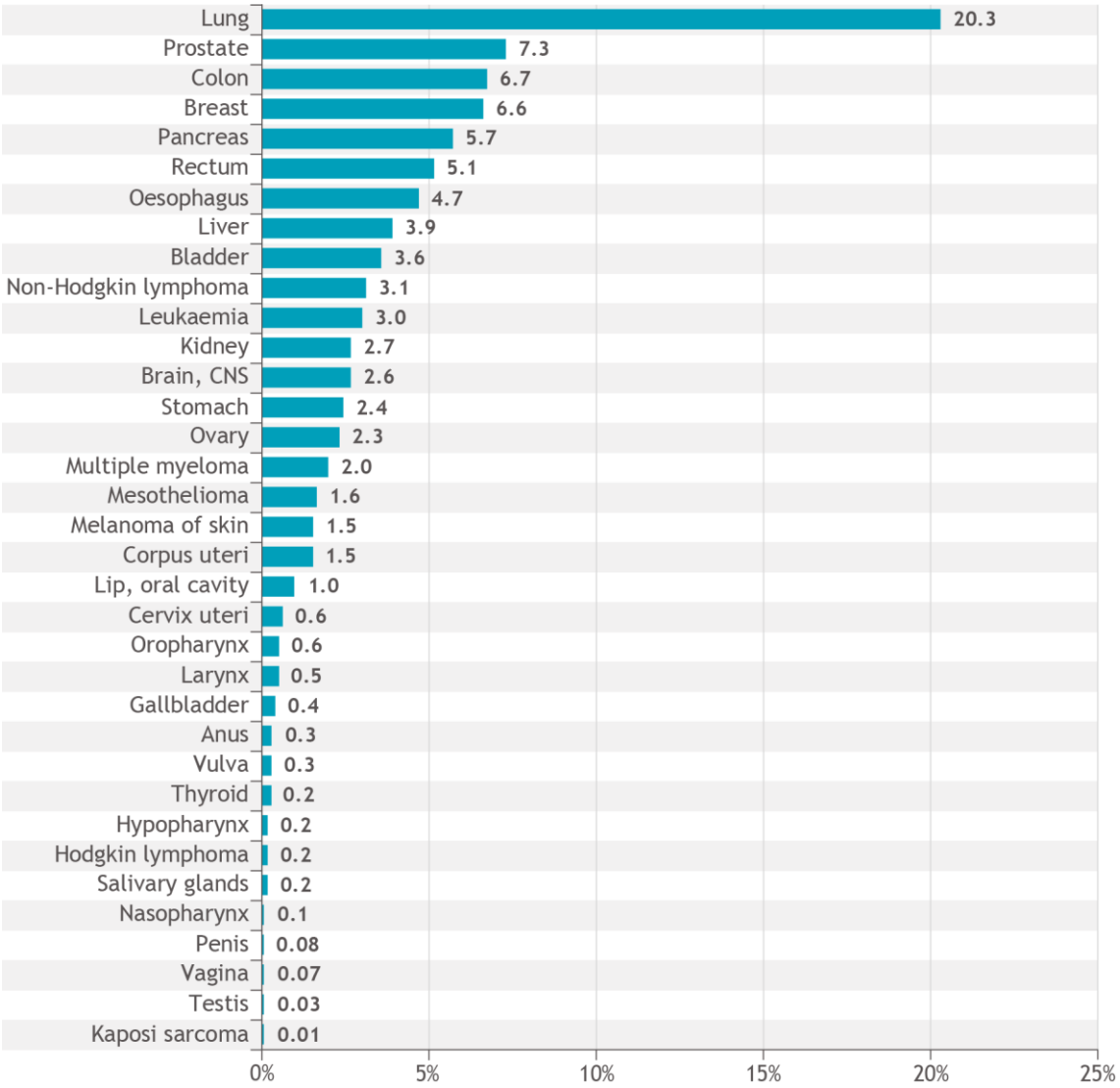
Approximately 35,000 people were diagnosed with lung cancer in England and Wales in 2019; of these, 29,481 had NSCLC in England and 7,665 were diagnosed at stages IB-IIIA and, therefore, were potentially eligible for curative resection.[33,34ii]

B.1.3.4 Mortality and survival

Lung cancer is the most common cause of cancer death worldwide and in the UK (Figure 2); the percentage of patients who die from lung cancer is similar to that of patients who die from prostate cancer, colon cancer, and breast cancers combined (20.6%).[12,13]

[ii] Note: number of patients eligible for curative resection were calculated using proportions of patients diagnosed by stage from the 2018 audit (2017 data), which were applied to 2019 data. This is to ensure alignment with the seventh TNM staging edition used in the CheckMate-816 trial.

Figure 2. Causes of cancer deaths in the United Kingdom in 2020



CNS = central nervous system.

Source: GLOBOCAN (2020)[35]

According to National Lung Cancer Audit (NLCA) data from England and Wales, median survival (by stage, AJCC/UICC eighth edition) in 2019 was not reached (and therefore was greater than 1 year) for all patients with stage I and II disease, whereas median survival for all patients with stage III and IV disease was 362 and 100 days, respectively.[33] The overall 1-year relative survival rate for NSCLC in 2019 was 46% in England and 42% in Wales.[33,36] The 1-year survival rates for lung cancer in England decreased with increasing stage: 87.7%, 73.0%, 48.7%, and 19.3% for stages I, II, III, and IV, respectively (2013-2017 data, TNM staging edition not listed).[37]

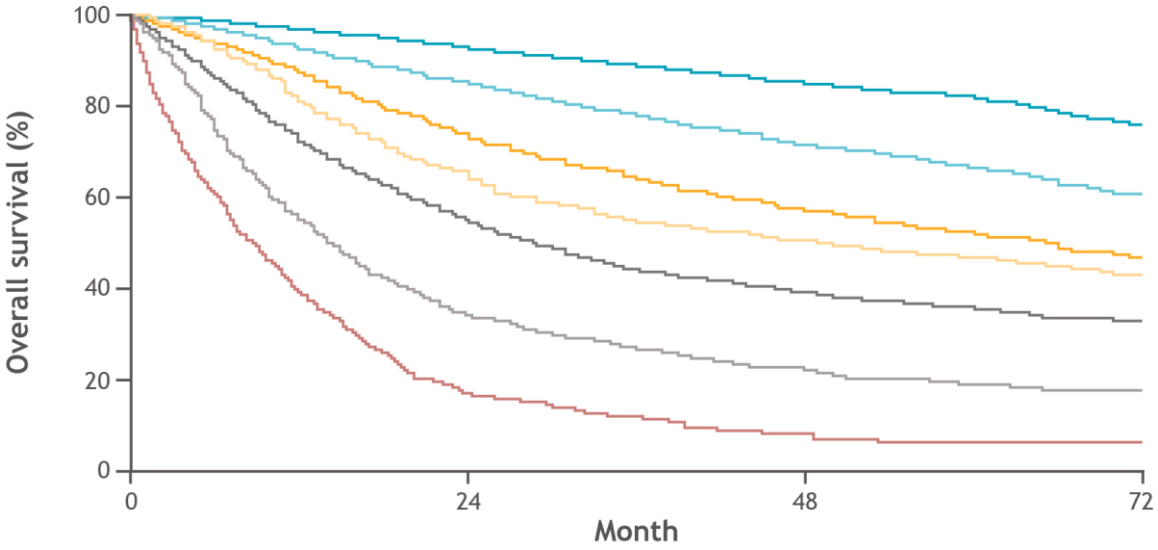
In England only, 21.1% of patients with lung cancer were alive at 2 years, and 11.3% at 3 years (2018 data, AJCC/UICC eighth edition).[iii,38] The 5-year survival rates for lung cancer

[iii] This is a different cohort of patients, including those in the 2014-2017 annual reports.

in England decreased with increasing stage: 56.6%, 34.1%, 12.6%, and 2.9% for stages I, II, III, and IV, respectively (2013-2017 data, TNM staging edition not listed).[37]

Variation in overall survival (OS) is determined by the extent of disease at diagnosis. Figure 3 presents the range in 5-year OS according to the AJCC/UICC seventh edition. For patients potentially eligible for nivolumab + PDC neoadjuvant therapy, 5-year (60-month) OS ranged from 36% to 66% according to the seventh edition (i.e., stages IB to IIIA).[31]

Figure 3. Overall survival according to AJCC/UICC seventh edition staging system



7th edition	IA	IB	IIA	IIB	IIIA	IIIB	IV
Events/N	1,119/6,303	768/2,492	424/1,008	382/824	2,139/3,334	2,101/2,624	664/882
MST (months)	NR	NR	66.0	49.0	29.0	14.1	8.8
Overall survival							
24-month	93%	85%	74%	64%	55%	34%	17%
60-month	82%	66%	52%	47%	36%	19%	6%

AJCC = American Joint Committee on Cancer; MST = median survival time; N = patient number; NR = not reached; UICC = Union for International Cancer Control.

Source: Goldstraw et al. (2016)[31]

B.1.3.4.1 Disease progression and survival

The current prognosis of resectable NSCLC remains poor despite the curative intent of surgery. Risk of disease progression increases by tumour stage, while OS decreases by stage (and severity of metastases in advanced disease).[33,39] This has been demonstrated in a retrospective study performed in France, Germany and the UK that included 831 patients diagnosed with stage IB-IIIA NSCLC (AJCC/UICC seventh edition).[39] Over a median follow-up of 26 months, 33% of patients developed recurrence, and 24% progressed to metastatic disease.[39] Median disease-free survival (DFS), a measure of the risk of relapse, decreased with increasing disease stage (DFS in stage IB disease: not reached; DFS in stage IIA: 42.3 months; DFS stage III disease: 28.5 months). Therefore, optimising systemic treatment in the resectable setting is important to prevent and/or delay disease progression to metastatic disease, which is associated with worse survival outcomes, reduced health-related quality of life (HRQOL), and increased healthcare costs.[31,33,39-41]

Cure

Patients with resectable disease may be considered cured if there is no disease relapse at a defined timepoint; at this stage, patients are no longer followed up regularly, and risk of disease recurrence and risk of death are similar to people in the age-matched general population (this was confirmed by clinical experts; Appendix N).[42,43]

Several cancers may be considered cured if diagnosed and treated in the early stage of disease; for example, 75% of breast cancers can be cured if found at an early stage. Other cancers, such as colon cancer, prostate cancer, and pancreatic cancer, may be cured if they are detected and treated in stages I-II.[44-46] This is also the case in resectable NSCLC; long-term evidence suggests that some patients who are treated for resectable non-metastatic NSCLC may remain recurrence-free at 5 years and thus be considered cured (see Section B.3.3.3 for further detail on cure).

B.1.3.5 Morbidity

Fatigue, dyspnoea, pain, and cough are the most troublesome symptoms associated with non-metastatic disease and impact HRQOL.[47-49]

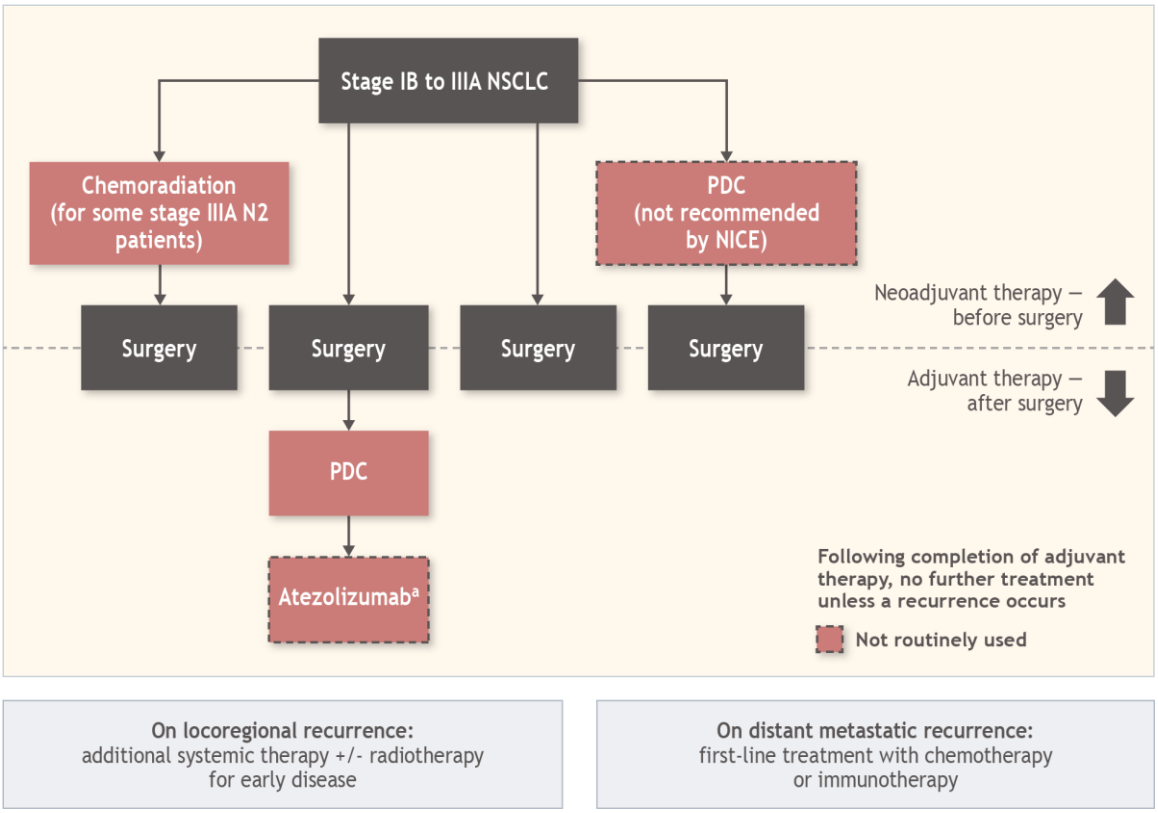
Disease recurrence, and progression to locoregional or distant metastatic disease, are associated with worsening symptoms, including those associated with specific sites of metastases. Bone metastases (occurring in 30%-40% of patients with lung cancer[50]) and brain metastases (occurring in 30%-40% of patients with NSCLC[50]) are associated with specific debilitating symptoms such as bone pain, risk of fracture, headache, seizures, and other neurological complications, all of which substantially impact HRQOL.[51-55] Therefore, optimising systemic treatment in the non-metastatic setting is important to prevent the worsening of symptoms and deterioration of HRQOL that occur during disease progression.

Resectable NSCLC does not only affect the patient; caregivers for patients with NSCLC also experience a considerable burden associated with care.[40,41] Improved treatment options may therefore also help reduce the burden on caregivers.

B.1.3.6 Clinical pathway of care

Treatment options for patients with newly diagnosed, potentially resectable NSCLC are determined based on both the stage of disease and operability of the patients. NICE (2019)[17] recommends surgery, radiotherapy, chemotherapy, or a combination of these for resectable disease (Figure 4).

Figure 4. Treatments used for resectable NSCLC in clinical practice in England



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

[a] Atezolizumab was recommended for use within the Cancer Drugs Fund in August 2022. It is an option for adjuvant treatment after complete tumour resection in adults with stage II-IIIa NSCLC with PD-L1 ≥ 50% whose disease has not progressed after adjuvant PDC, but is not considered a comparator in this submission.[2]

Source: NICE (2019)[17]

Surgical resection is the standard of care (SOC) for most eligible patients with resectable NSCLC.[17] In addition to surgery, the patient may also receive neoadjuvant or adjuvant treatment with the aim of improving long-term patient outcomes, although options are limited.[17] Current neoadjuvant and adjuvant chemotherapy regimens offer only modest benefits to patients[56-60] and many patients choose not to have adjuvant chemotherapy because of these modest improvements (i.e., an absolute improvement in 5-year OS of approximately 5%[56,61]), while wanting to avoid any toxicities, or are simply not fit enough to tolerate chemotherapy following surgery (Appendix N). Notably, chemotherapy is only recommended by NICE in the adjuvant setting.

Chemoradiotherapy (chemotherapy in combination with radiotherapy) followed by surgery may be considered for use in patients with stage IIIA-N2 disease, although such patients only comprise approximately 7% of all patients with NSCLC[62] and a smaller proportion of these are resectable; clinical experts have also confirmed that this subpopulation is small, and that only 7%-8% patients eligible for resection are treated with chemoradiotherapy (Appendix N).

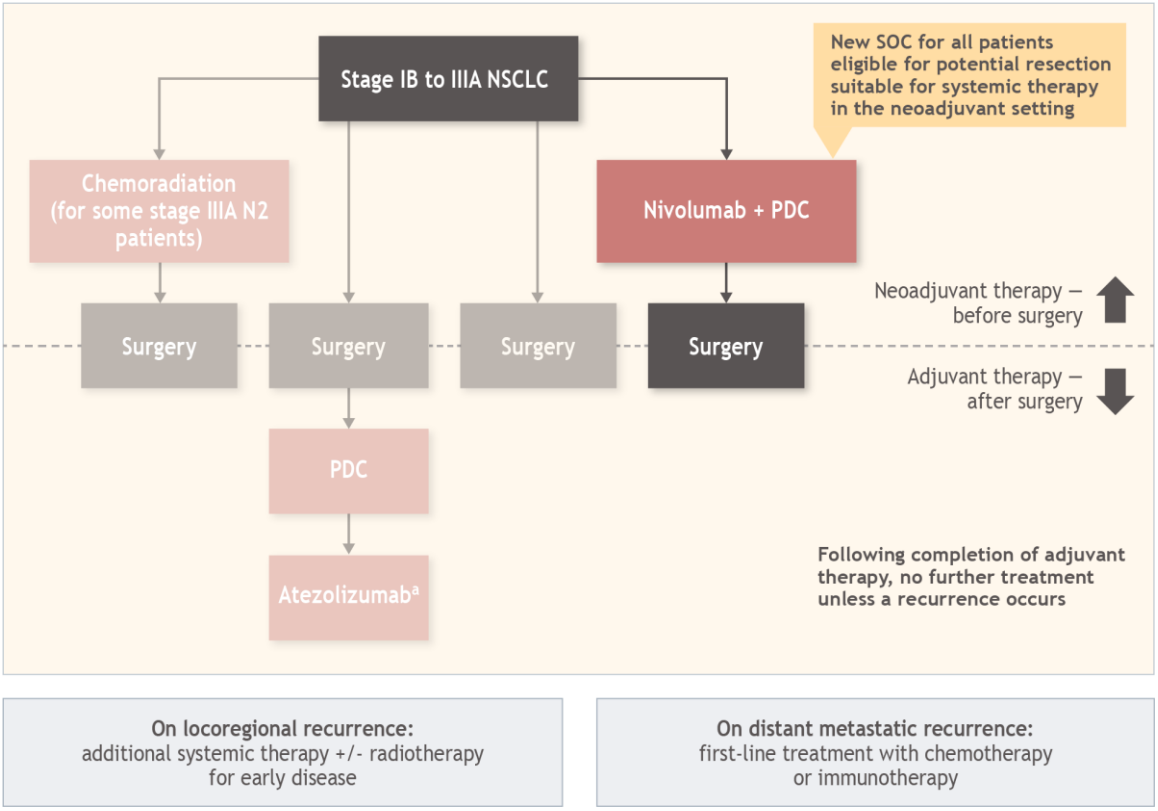
Immuno-oncology therapies are being evaluated for the treatment of resectable NSCLC in the adjuvant or neoadjuvant settings, and have shown strong promise in other early-stage disease settings, and long-term effectiveness in metastatic NSCLC.[63] Atezolizumab after

adjuvant PDC has recently been reviewed by NICE for NSCLC and is now recommended for use in the Cancer Drugs Fund while additional data are collected.[2]

When immuno-oncology treatments (such as nivolumab) are initiated before surgery, they are designed to help prime the body's immune response not only to target primary tumour cell activity before surgery and promote responses against micro-metastases already present but to kill tumour cells released during surgery, limiting recurrence.[9]

Based on the above, there is a clear unmet need for an active treatment that can effectively prevent disease recurrence and progression to metastatic disease. Importantly, metastatic disease is associated with worse survival outcomes, reduced HRQOL, and increased healthcare costs compared with non-metastatic disease.[31,33,39-41] An effective immuno-oncology therapy that can be used for all patients with stage IB-IIIA disease and that provides a clear treatment pathway with a short duration of treatment is expected to result in better adherence to the published NICE guidelines across English and Welsh National Health Service (NHS) trusts, and improved outcomes for patients with resectable NSCLC. The introduction of neoadjuvant nivolumab + PDC into the treatment pathway would provide a clear, evidence-based SOC therapy for patients with resectable, stage IB-IIIA NSCLC, with the potential to improve adherence to guidelines and clinical outcomes in England and Wales (Figure 5).

Figure 5. Potential position of nivolumab + PDC in the treatment pathway for resectable NSCLC in clinical practice in England and Wales



NSCLC = non-small cell lung cancer; PDC = platinum doublet chemotherapy; PD-L1 = programmed death-ligand 1; SOC = standard of care.

[a] Atezolizumab was recommended for use within the Cancer Drugs Fund in August 2022. It is an option for adjuvant treatment after complete tumour resection in adults with stage II-IIIa NSCLC with PD-L1 ≥ 50% whose disease has not progressed after adjuvant PDC but is not considered a comparator in this submission.[2]

B.1.3.6.1 Surgical treatment

Surgical resection is the SOC for most eligible patients with stage IB-IIIA NSCLC if the tumour is clinically assessed as being resectable and the patient is eligible for surgery.[17] Tumour resectability is assessed at diagnosis and again after the administration of a neoadjuvant treatment but before surgery.[17] Therefore, some patients may be deemed eligible for potential resection at diagnosis, but their resectability status may change before surgery.

Surgery may involve:

- Removal of a whole lung (pneumonectomy),
- Removal of a whole lobe (lobectomy), or
- Removal of part of a lobe—segmentectomy or wedge resection.

Surgery is associated with an immediate postoperative mortality of approximately 3% after lobectomy and 7% after pneumonectomy.[64,65,66] Lobectomy (a surgery to remove one of the lobes of the lungs, either via open surgery or thoracoscopy [a type of video-assisted surgery that is considered less invasive]) is offered to eligible patients.[67] Hilar and mediastinal lymph-node sampling (for staging purposes) or 'en bloc' resection (to remove any local invasion) are performed in parallel with lobectomy for all patients undergoing surgery with curative intent. More extensive surgery (pneumonectomy [removal of an entire lung], broncho-angioplasty, bilobectomy) is performed only when needed to obtain clear margins; these surgeries are associated with worse HRQOL and mortality.[17,64,68] For patients with T3 NSCLC with chest wall involvement who are undergoing surgery, the aim is complete resection of the tumour using either extrapleural or en bloc chest wall resection.[17]

Given the risk of recurrence after surgery, neoadjuvant or adjuvant treatment may be considered. Neoadjuvant immuno-oncology treatment may optimise surgical outcomes and facilitates minimally invasive surgery (and shorten the duration of surgery), which, in turn, is associated with improved patient HRQOL.[3,69] For example, minimally invasive surgery rates are higher in patients treated with neoadjuvant immuno-oncology therapies such as nivolumab + PDC, versus patients treated with PDC alone (29.5% vs. 21.5%, respectively). Further, a higher proportion of patients treated with PDC alone have been shown to undergo pneumonectomy rather than lobectomy versus those treated with nivolumab + PDC (lobectomy, 60.7% vs. 77.2% %; pneumonectomy, 25.2% vs. 16.8%, respectively). Therefore, nivolumab + PDC treatment in the neoadjuvant setting may confer substantial surgical outcome benefits to patients with resectable NSCLC.

B.1.3.6.2 Neoadjuvant treatment

As discussed in Section B.1.3.6, neoadjuvant chemotherapy is not currently recommended by NICE outside a clinical trial,[17] although neoadjuvant and adjuvant chemotherapy regimens offer similar and only modest improvements in 5-year OS.[56-59]

Based on the NICE guidelines, chemoradiotherapy with surgery should be considered (with surgery scheduled 3-5 weeks after chemoradiotherapy) for patients with operable stage IIIA–N2 NSCLC who can have surgery and are healthy enough for multimodality therapy. For eligible patients with stage IIIA-N2 NSCLC who cannot tolerate or who decline

chemoradiotherapy (with or without surgery), radical radiotherapy (either conventional or hyperfractionated) should be considered.[17] However, patients with stage IIIA-N2 NSCLC account for only approximately 7% of patients with NSCLC,[62] which is confirmed by clinical experts (Appendix N). Further, stage IIIA-N2 NSCLC comprises a heterogeneous group of patients with both resectable and unresectable NSCLC; therefore, the number of patients with *resectable* stage IIIA-N2 NSCLC is likely to be limited further.

Patients are actively monitored for cancer recurrence. If the cancer comes back, treatment options and prognosis depend on the site of the recurrence (see Section B.1.3.4.1).

B.1.3.6.3 Adjuvant treatment

Based on the NICE guidelines, postoperative cisplatin-based combination chemotherapy should be:

- Offered to patients with good performance status (World Health Organization [WHO] 0 or 1) with T1a-4, N1-2, M0 NSCLC.
- Considered for patients with good performance status (WHO 0 or 1) and T2b-4, N0, M0 NSCLC with tumours greater than 4 cm in diameter.[17]

B.1.3.6.4 Real-world evidence on treatment of resectable lung cancer

Although the NICE guidelines provide guidance on the appropriate treatments for resectable lung cancer, data from the NLCA provide real-world evidence on the current treatment pathway in England. Based on data from 2019 (to ensure the impact of COVID-19 on treatments is not considered), only 3,881 of 6,716 patients (58%) with stage IA-IIB and Performance Status (PS) 0-2 NSCLC (AJCC/UICC eighth edition) in England underwent surgical resection with curative intent in 2019.[33] Furthermore, according to clinical experts (Appendix N), approximately half of patients who undergo surgery go on to have adjuvant chemotherapy in the UK for a variety of reasons as described in Section B.1.3.6 above. Similarly, Felip et al. (2010)[70] assessed the treatment of patients with resectable NSCLC in Spain, Germany, Portugal, Sweden, and Switzerland and found that 34% of patients with NSCLC stages IB-IIIA who were allocated to receive adjuvant chemotherapy did not begin treatment.[70]

NLCA data from January 2017 to June 2018 showed that 15% of patients with stage IA to IIB NSCLC (TNM staging edition not listed) who did not have surgery declined surgery due to patient wishes, and 11% of patients did not have surgery due to their comorbidities. However, the reason for not having surgery was not documented in 75% of patients, and is thus unclear in most patients.[71]

According to the NLCA, in patients with stage IIIA disease and PS 0-2 (AJCC/UICC edition not listed), 11% underwent surgery alone and 12% underwent surgery followed by chemotherapy.[71] Of the remaining patients, 12% underwent concurrent chemoradiotherapy and 7% underwent sequential chemoradiotherapy (note, in addition, some patients only received best-supportive care or palliative therapies).[71] Although chemoradiotherapy and adjuvant chemotherapy are recommended for patients with stage IIIA NSCLC, there is currently no clear treatment pathway for these patients in NHS trusts across England.

Overall, only half of patients with stage IB-IIIA NSCLC are treated with any form of systemic anticancer therapy and it is unclear if these patients also have surgery (Table 4).

From the audit data, it is clear that there is no preferred treatment for patients with resectable NSCLC in England. For the basis of this appraisal, surgery alone, with some patients also receiving adjuvant platinum-based chemotherapy, most closely reflects clinical practice and is considered the most relevant comparator for this appraisal.

Table 4. Patients with stage IB-IIIA (AJCC/UICC eighth edition), PS 0-1 NSCLC who were treated with systemic anticancer therapy or targeted treatment in England in 2019

Stage	Number of NSCLC cases	Number with SACT or targeted treatment	% with SACT or targeted treatment
IB	1,181	96	8.13%
IIA	349	74	21.20%
IIB	1,234	479	38.82%
IIIA	2,157	1,319	61.15%

AJCC = American Joint Committee on Cancer; NSCLC = non-small cell lung cancer; PS = performance status; SACT = systemic anticancer therapy; UICC = Union for International Cancer Control.

Source: Royal College of Physicians (2022)[33]

B.1.3.6.5 Goals of treatment

As with all cancers, improvement in OS is a key final endpoint of interest. However, because of the early nature of the disease and associated improved prognosis versus metastatic disease, OS data can be immature at the time of regulatory and health technology assessments for neoadjuvant therapies. At the time of this submission, CheckMate-816 does not have mature Kaplan-Meier OS data (see Section B.2.6.1.3). However, in resectable NSCLC, potential surrogate endpoints that are indicative of the survival benefit include pathologic complete response (pCR) and event-free survival (EFS).

An association between pCR and EFS, pCR and OS, and EFS and OS has been consistently demonstrated[72-75] as shown by the following studies conducted in patients with resectable NSCLC treated with neoadjuvant chemotherapy:

- CA2098Y9: a systematic literature review (SLR) and meta-analysis with the key objective of identifying studies that examined the association between pCR and EFS/OS and between EFS and OS and meta-analysing the magnitude of the association from the available literature.[72]
- CA2097 C4: a retrospective, observational real-world study that uses electronic health record data supplemented with chart review with the key objective of characterising the relationship between pCR and EFS/OS and between EFS and OS.[74]
- CA2097L8: a pooled meta-analysis of individual patient-level data from completed randomised controlled trials (RCTs) with the key objective of determining the magnitude of the association between pCR and EFS/OS and between EFS and OS.[73]
- An SLR and meta-analysis with the key objective of identifying studies that examined the association between EFS and OS following neoadjuvant therapy for NSCLC.[75]

An association between pCR and EFS/OS and between EFS and OS for patients with resectable NSCLC treated with neoadjuvant chemotherapy was demonstrated (Table 5). Further, it has been found in several studies that patients who have a pCR have improved EFS and OS outcomes versus patients who do not achieve a pCR.[72,76-81]

Table 5. Analyses assessing association between pathologic complete response, event-free survival, and overall survival

Study/sample size	Data source	Patient-level EFS and OS by pCR HR (95% CI)	EFS to OS HR (95% CI)
CA2098Y9 (SLR/literature-based meta-analysis)[72,82] N = 8,542	Based on literature[a] including RCTs and real-world studies	OS: ▪ Frequentist: 0.49 (0.42-0.57) [redacted] EFS: ▪ Frequentist: 0.49 (0.41-0.60) ▪ [redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Study/sample size	Data source	Patient-level EFS and OS by pCR HR (95% CI)	EFS to OS HR (95% CI)
[redacted]	[redacted]	[redacted]	[redacted]
SLR/literature-based meta-analysis[75] N = NR	74 sources (18 = RCTs; 26 = single-arm studies; 30 = observational studies) Of the 74 sources, 39 reported both median EFS and median OS, and 8 reported HRs from RCTs.		Positive linear correlation found between median EFS and median OS, weighted Pearson's correlation coefficient r = 0.819; 95% CI, 0.728-0.922; *P* < 0.05). Analysis of treatment effects from RCTs found a positive linear correlation between EFS and OS log HRs (weighted r = 0.864; 95% CI, 0.809-0.992; *P* < 0.05), and a strong association between log treatment effects (random effects meta-regression, R 2 = 0.777).

CI = confidence interval; EFS = event-free survival; HR = hazard ratio; NR = not reached; OS = overall survival; pCR = pathologic complete response; RCT = randomised controlled trial; SLR = systematic literature review; US = United States.

Note: A trial-level analysis was conducted for studies CA2098Y9 and CA2097L8, and no association between treatment effect on pCR and improvement in OS or EFS was found. However, the number of trials included in the analysis was small.

[a] Patient-level survival data were reconstructed from Kaplan-Meier curves to calculate an HR when authors did not report one.

[b] OS HR by EFS status before landmark

B.1.4Equality considerations

No equality issues are foreseen.

B.2 Clinical effectiveness

- CheckMate-816 is the first phase 3 study to demonstrate significantly improved EFS and pCR for an immuno-oncology–based combination in the neoadjuvant setting of resectable stage IB-IIIA NSCLC.[3]
- With only 3 cycles of treatment, nivolumab + PDC reduced the risk of disease recurrence, progression, or death by 37% versus PDC alone.[3]
- Nivolumab + PDC demonstrated a significant improvement in pCR versus PDC alone (24% for nivolumab + PDC vs. 2% for PDC alone).[3]
- Nivolumab + PDC demonstrated a significantly longer EFS versus PDC alone (HR, 0.63; 97.38% confidence interval [CI], 0.43-0.91).[3]
- Longer EFS was observed in patients who achieved pCR versus those who did not across both arms of CheckMate-816 (HR, 0.13 [95% CI, 0.05-0.37] for nivolumab + PDC; HR was not computed for the PDC arm).[3]
- Median time to death or distant metastases (TTDM) was not reached for nivolumab + PDC and was 26.7 months for PDC alone.[3]
- 31% of patients treated with nivolumab + PDC had a radiographic downstaging of their disease versus 24% of those treated with neoadjuvant PDC alone.[3]
- A prespecified interim analysis for OS showed a promising early trend in OS with an HR of 0.57 (not statistically significant); OS will continue to be followed in upcoming analyses.[3]
- Feasibility of surgery was maintained with nivolumab + PDC versus neoadjuvant PDC alone: numerically more patients underwent surgery, had a less invasive surgery and had a shorter duration of surgery with similar length of hospital stay. Furthermore, nivolumab + PDC did not increase postsurgical complications.[3]
- In terms of safety, nivolumab + PDC showed no statistically significant detriment versus PDC alone (all-cause grade 3/4 adverse event [AE] rates were 41% vs. 44% for nivolumab + PDC and PDC alone, respectively). Finally, most immune-mediated AEs reported were of low grade.[3]

B.2.1Identification and selection of relevant studies

B.2.2List of relevant clinical effectiveness evidence

An SLR was conducted to identify RCTs relevant to the decision problem. One RCT that evaluated nivolumab + PDC as neoadjuvant therapy for the treatment of patients with resectable NSCLC was identified: CheckMate-816 (Table 6). This is the key study relevant to the decision problem described in Section B.1.1. See Appendix D for full details of the process and methods used to identify and select the clinical evidence.

Table 6. CheckMate-816: clinical effectiveness evidence

Study	**NCT02998528; Forde et al. (2022)[3]**
Study design	Phase 3, randomised, open-label trial
Population	Patients with newly diagnosed, resectable, stage IB-IIIA (AJCC/UICC seventh edition) NSCLC

Study	NCT02998528; Forde et al. (2022)[3]
Intervention(s)	Nivolumab administered as an intravenous infusion at a dosage of 360 mg every 3 weeks + PDC every 3 weeks for up to 3 cycles. Investigator choice of PDC administered as an intravenous infusion.[a]
Comparator(s)	Neoadjuvant PDC alone[b]
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	As the key study that is relevant to the decision problem, CheckMate-816 is the basis of the economic model.
Reported outcomes specified in the decision problem	▪ **DFS (EFS)** ▪ OS ▪ pCR and MPR ▪ **AEs of treatment** ▪ **HRQOL**
All other reported outcomes	▪ **TTDM** ▪ pCR, MPR, cRR, EFS, TTDM, and OS by PD-L1 status ▪ cRR ▪ Feasibility of surgery, peri- and postoperative complications ▪ PK ▪ EFS2 ▪ Biomarkers (TMB; tumour inflammatory gene expression signatures; and potential predictive biomarkers in peripheral blood and tumour specimens, e.g., proteins and/or genes involved in regulating immune responses, such as PD-L1)

AE = adverse event; AJCC = American Joint Committee on Cancer; AUC = area under the curve; cRR = clinical response rate; DFS = disease-free survival; EFS = event-free survival; EFS2 = event-free survival on second-line therapy; HRQOL = health-related quality of life; MPR = major pathologic response; NSCLC = non-small cell lung cancer; OS = overall survival; pCR = pathologic complete response; PDC = platinum doublet chemotherapy; PD-L1 = programmed death-ligand 1; PK = pharmacokinetics; TMB = tumour mutational burden; TTDM = time to death or distant metastases; TTLR = time to locoregional recurrence; UICC = Union for International Cancer Control.

Note: Outcomes marked in bold are incorporated into the cost-effectiveness model.

[a] In the intervention arm, PDC may include cisplatin (75 mg/m^2 on day 1 of a 3-week cycle for up to 3 cycles) and either gemcitabine (1,000 mg/m^2 or 1,250 mg/m^2 [per local prescribing information] on days 1 and 8 of a 3-week cycle for up to 3 cycles, squamous histology) or pemetrexed (500 mg/m^2 on day 1 of a 3-week cycle for up to 3 cycles, nonsquamous histology); or carboplatin (AUC 5 or 6 on day 1 of a 3-week cycle for up to 3 cycles) and paclitaxel (175 or 200 mg/m^2 on day 1 of a 3-week cycle for up to 3 cycles, any histology).

[b] In the comparator arm, PDC may include cisplatin (75 mg/m^2 on day 1 of a 3-week cycle for up to 3 cycles) and either gemcitabine (1,000 mg/m^2 or 1,250 mg/m^2 [per local prescribing information] on days 1 and 8 of a 3-week cycle for up to 3 cycles, squamous histology), pemetrexed (500 mg/m^2 on day 1 of a 3-week cycle for up to 3 cycles, nonsquamous histology), vinorelbine (25 mg/m^2 or 30 mg/m^2 [per local prescribing information] on days 1 and 8 of a 3-week cycle for up to 3 cycles), or docetaxel (60 mg/m^2 or 75 mg/m^2 [per local prescribing information] on day 1 of a 3-week cycle for up to 3 cycles); or carboplatin (AUC 5 or 6 on day 1 of a 3-week cycle for up to 3 cycles) and paclitaxel (175 or 200 mg/m^2 on day 1 of a 3-week cycle for up to 3 cycles, any histology).

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

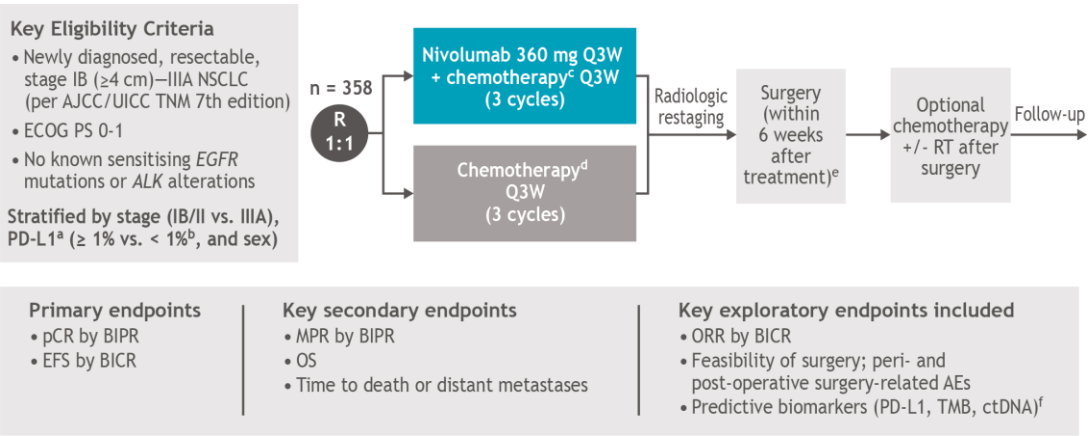
B.2.3.1 CheckMate-816: methodology

CheckMate-816 was a randomised, open-label trial comparing nivolumab + PDC with PDC as neoadjuvant treatment of newly diagnosed resectable (stage IB [≥ 4 cm], stage II, or stage IIIA (N2), AJCC/UICC seventh edition) NSCLC.[3] See Section B.1.3.4 for a description of the AJCC/UICC staging system.

Nivolumab was evaluated in a 360 mg flat dose + PDC every 3 weeks up to 3 cycles versus PDC alone (Figure 6). Table 7 outlines the trial methodology.[3] Additional details of the statistical analyses and endpoints are provided in Section B.2.4.

The original study design also included a study arm with nivolumab + ipilimumab, which was stopped in a protocol revision and is not relevant to this appraisal. This decision was based on evidence from the metastatic setting and external data from the NADIM trial, which demonstrated a more promising pCR benefit for nivolumab + PDC than seen for nivolumab + ipilimumab in the NEOSTAR trial. Therefore, the clinical development of nivolumab + PDC was prioritised in CheckMate-816.[83]

Figure 6. CheckMate-816: study design



AE = adverse event; *ALK* = anaplastic lymphoma kinase; BICR = blinded independent central review; BIPR = blinded independent pathologic review; CT = computed tomography; ctDNA = circulating tumour DNA; ECOG PS = Eastern Cooperative Oncology Group performance status; EFS = event-free survival; *EGFR* = epidermal growth factor receptor; MPR = major pathologic response; MRI = magnetic resonance imaging; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; pCR = pathologic complete response; PD-L1 = programmed death-ligand 1; Q3W = every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumours; RT = radiotherapy; TMB = tumour mutational burden.

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

[b] Included patients with PD-L1 expression status not evaluable and indeterminate.

[c] Nonsquamous: pemetrexed + cisplatin or paclitaxel + carboplatin; squamous: gemcitabine + cisplatin or paclitaxel + carboplatin.

[d] Vinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (squamous only), pemetrexed + cisplatin (nonsquamous only), or paclitaxel + carboplatin.

[e] Postoperative assessments with CT with contrast of the chest including the adrenal glands and CT or MRI of other additional suspected/known sites of disease. The first tumour assessment should occur 12 weeks (± 7 days) after definitive surgery per RECIST 1.1 and then should occur every 12 weeks (± 7 days) for 2 years (104 weeks), then every 6 months (24 weeks ± 7 days) for 3 years, and then every year (52 weeks ± 7 days) for 5 years or until disease recurrence or progression confirmed by BICR.

[f] Performed using tumour-guided personalised ctDNA panel.

Source: Forde et al. (2022)[3]

CheckMate-816 included adults aged ≥ 18 years with stage IB (≥ 4 cm), stage II, or stage IIIA NSCLC and an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 who had not been previously treated with prior chemotherapy or any other cancer therapy for resectable NSCLC, and who had no active brain metastases, autoimmune disease, or known *EGFR* mutations or ALK translocations.[83]

Patients who had a resectable tumour at diagnosis were enrolled; at the time of study design, the study investigators considered the appropriate comparator to be neoadjuvant PDC.[iv] Therefore, 358 patients were concurrently randomly assigned 1:1 to treatment with nivolumab + PDC (n = 179) or PDC alone (n = 179). The stratification factors for randomisation were PD-L1 expression (≥ 1% vs. < 1%/not evaluable/indeterminate), disease stage (IB/II vs. IIIA), and gender/sex (male vs. female).[3,83]

Treatments administered in the study arms are presented in Table 7; 3 cycles of treatment were provided in both arms. In the nivolumab + PDC arm, PDC was investigator's choice and consisted of either cisplatin (with either gemcitabine or pemetrexed depending on histology), or carboplatin and paclitaxel. In the PDC arm, PDC consisted of either cisplatin (and gemcitabine or pemetrexed depending on histology) combined with either gemcitabine, pemetrexed, vinorelbine, or docetaxel; or carboplatin and paclitaxel.[3]

Surgery was required within 6 weeks post-neoadjuvant treatment and adjuvant treatment with chemotherapy and/or radiotherapy was permitted at the discretion of the healthcare provider. No immuno-oncology therapy was allowed in the adjuvant setting.[83]

The independent primary endpoints were blinded independent central review (BICR)–assessed pCR, and EFS. Secondary endpoints were blinded independent pathologic review (BIPR)–assessed major pathologic response (MPR), OS and BICR-assessed TTDM. It is important to note that in CheckMate-816, the outcome TTDM is time to death or distant metastases, whereas in the economic model described in Section B.3 and the network meta-analysis that informs it described in Section B.2.9, TTDM refers to time to distant metastases only. Exploratory endpoints included EFS on the next line of therapy (EFS2) and safety.[3,83] Safety assessments were based on the frequency of deaths, serious adverse events, adverse events (AEs) leading to discontinuation or dose modification, overall AEs, clinical laboratory assessments (haematology, serum chemistry, liver, and thyroid function tests), and vital sign measurements.[83] The feasibility of surgery and rate of perioperative and postoperative complications (within 90 days of surgery) were additional exploratory objectives.[3,83]

[iv] Because neoadjuvant chemoradiotherapy is often used for borderline resectable or Pancoast tumours, this was not deemed an appropriate comparator for nivolumab + PDC in this indication.

Table 7. CheckMate-816: summary of trial methodology

Location	111 sites in 14 countries (Argentina, Brazil, Canada, China, France, Greece, Italy, Japan, South Korea, Romania, Spain, Taiwan, Turkey, and US)	
Trial design	International, multicentre, open-label, randomised, active-controlled phase 3 trial	
Eligibility criteria for participants	Inclusion criteria: ▪ Males and females aged ≥ 18 years ▪ Histologically confirmed, resectable, stage IB (≥ 4 cm), stage II, or stage IIIA NSCLC (according to AJCC/UICC seventh edition) confirmed by PET/CT with contrast ▪ If the CT component of the PET/CT is of insufficient diagnostic quality for RECIST 1.1 measurements, an additional CT with contrast of the chest, abdomen, and other suspected areas of disease will be performed ▪ Lung function capacity capable of tolerating the proposed lung surgery ▪ ECOG performance status of 0-1 ▪ Tissue from the primary lung tumour to be available for PD-L1 immunohistochemistry testing	Exclusion criteria: ▪ Patients who have received prior chemotherapy or any other cancer therapy for resectable NSCLC ▪ Patients with distant active brain metastases ▪ Patients with an active, known or suspected autoimmune disease ▪ Known EGFR mutations or ALK translocations
Settings and locations where the data were collected	See location	
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Permitted and disallowed concomitant medication**	▪ Nivolumab + PDC (n = 176) – Nivolumab at a flat dose of 360 mg as 30-minute IV infusion every 3 weeks for up to 3 cycles – Investigator's choice of PDC (IV): • Cisplatin (75 mg/m^2 every 3 weeks for up to 3 cycles) and 1 of the following: • Gemcitabine (1,000 mg/m^2 or 1,250 mg/m^2 on days 1 and 8 of a 3-week cycle for up to 3 cycles) (squamous histology) • Pemetrexed (500 mg/m^2 on day 1 of a 3-week cycle for up to 3 cycles) (nonsquamous histology) • Carboplatin (AUC 5 or 6 on day 1 of a 3-week cycle for up to 3 cycles) and paclitaxel (175 or 200 mg/m^2 on day 1 of a 3-week cycle for up to 3 cycles) (any histology) ▪ PDC (n = 176) – Investigator's choice of PDC (IV): • Cisplatin (75 mg/m^2 on day 1 of a 3-week cycle for up to 3 cycles) and 1 of the following:	

	• Gemcitabine (1,000 mg/m^2 or 1,250 mg/m^2 on days 1 and 8 of a 3-week cycle for up to 3 cycles) (squamous histology) • Pemetrexed (500 mg/m^2 on day 1 of a 3-week cycle for up to 3 cycles) (nonsquamous histology) • Vinorelbine (25 mg/m^2 or 30 mg/m^2 on days 1 and 8 of a 3-week cycle for up to 3 cycles) • Docetaxel (60 mg/m^2 or 75 mg/m^2 on day 1 of a 3-week cycle for up to 3 cycles) • Carboplatin (AUC 5 or 6 on day 1 of a 3-week cycle for up to 3 cycles) and paclitaxel (175 or 200 mg/m^2 on day 1 of a 3-week cycle for up to 3 cycles)
Primary outcomes (including scoring methods and timings of assessments)	▪ EFS: time from randomisation to any progression of disease precluding surgery, progression or recurrence of disease (per BICR using RECIST 1.1) after surgery, or death due to any cause. Patients who did not undergo surgery for reasons other than progression were considered to have an event at RECIST 1.1 progression or death. ▪ pCR rate: number of randomly assigned patients with absence of residual viable tumour cells in both lung and lymph nodes as evaluated by BIPR, divided by the number of randomly assigned patients for each treatment group.
Other outcomes used in the economic model/ specified in the scope	▪ TTLR: time between the date of randomisation and the first date of locoregional recurrence ▪ TTDM: time between the date of randomisation and the first date of distant metastasis or the date of death in the absence of distant metastasis. Patients who had not developed distant metastasis or died at the time of the analysis were censored on the date of their last evaluable tumour assessment. ▪ OS: time between the date of randomisation and the date of death. Censored on the last date a patient was known to be alive. ▪ HRQOL: Mean scores and mean change from baseline in total scores through follow-up in EQ-5D-3L in both the VAS and the utility index. Proportion of patients reporting problems for the 5 EQ-5D-3L dimensions at each assessment. ▪ Adverse events: Frequency of deaths, AEs, SAEs, AEs leading to discontinuation of study drug, select AEs, IMAEs, OESIs, and laboratory abnormalities. Analyses were conducted using the 30-day and/or 100-day safety window from day of last dose received.
Preplanned subgroups	Age, sex, race, region, baseline ECOG performance status, tobacco use, disease stage at study entry, cell type at study entry, PD-L1 status, tumour tissue TMB, and type of platinum therapy

AJCC = American Joint Committee on Cancer; ALK = anaplastic lymphoma kinase; AUC = area under the curve; BICR = blinded independent central review; BIPR = blinded independent pathological review; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EFS = event-free survival; EGFR = epidermal growth factor receptor; IV = intravenous; MPR = major pathologic response; NSCLC = non-small cell lung cancer; pCR = pathologic complete response; PDC = platinum doublet chemotherapy; PD-L1 = programmed death-ligand 1; PET = positron emission tomography; RECIST = Response Evaluation Criteria in Solid Tumours; TMB = tumour mutational burden; TTDM = time to death or distant metastases; UICC = Union for International Cancer Control; US = United States.

Source: BMS data on file (2021)[83]

B.2.3.2 CheckMate-816: baseline characteristics

Demographics and baseline disease characteristics in the 2 treatment arms in CheckMate-816 were balanced and generally representative of a resectable NSCLC population (Table 8); UK clinical experts confirmed that the study population is similar to that in the UK, other than expected differences between trial and real-world evidence. These included minor differences in median age and proportion of patients with squamous histology (see Appendix N).

Patients had a median age of 64 to 65 years, and 71% were male. Twenty-three percent of patients were from Europe in the nivolumab + PDC group and 14% in the PDC group. There were 65% to 69% of patients with an ECOG performance status of 0, and the remainder (31%-35%) had a performance status of 1. Overall, 49% to 53% of patients had squamous cell carcinoma, 43% to 44% of patients had PD-L1 < 1%, and 88% to 89% of patients were current or former smokers.[3]

Table 8. CheckMate-816: baseline characteristics of patients

Characteristic	Nivolumab + chemotherapy (n = 176)	Chemotherapy (n = 176)
Age (years), median (range)	64 (41-82)	65 (34-84)
Female, n (%)	51 (28.5)	52 (29.1)
Geographic region, n (%)		
North America	41 (22.9)	50 (27.9)
Europe	41 (22.9)	25 (14.0)
Asia	85 (47.5)	92 (51.4)
Rest of the world[a]	12 (6.7)	12 (6.7)
ECOG PS, n (%)[b]		
0	124 (69.3)	117 (65.4)
1	55 (30.7)	62 (34.6)
Disease stage, n (%)[c]		
IB or II	65 (36.3)	62 (34.6)
IIIA	113 (63.1)	115 (64.2)
Baseline weight, median (range) [kg]	68.1 (40.4-147.9)	67.2 (35.7-114.6)
Smoking status, %[d]		
Never smoker	19 (10.6)	20 (11.2)
Current/former smoker	160 (89.4)	158 (88.3)
Histology, n (%)		
Squamous	87 (48.6)	95 (53.1)
Nonsquamous	92 (51.4)	84 (46.9)
Tumour PD-L1 expression, %[e]		
< 1%	78 (43.6)	77 (43.0)
≥ 1%	89 (49.7)	89 (49.7)
1%-49%	51 (28.5)	47 (26.3)

Characteristic	Nivolumab + chemotherapy (n = 176)	Chemotherapy (n = 176)
≥ 50%	38 (21.2)	42 (23.5)
Not evaluable	12 (6.7)	13 (7.3)
TMB, n (%)[f]		
≥ 12.3 mut/MB	39 (21.8)	37 (20.7)
< 12.3 mut/MB	49 (27.4)	53 (29.6)
Not evaluable or reported[g]	91 (50.8)	89 (49.7)
Type of platinum therapy, n (%)[g]		
Cisplatin	124 (69.3)	134 (74.9)
Carboplatin	39 (21.8)	33 (18.4)

ECOG PS = Eastern Cooperative Oncology Group performance status; mut/MB = mutations per megabase; PD-L1 = programmed death-ligand 1; TMB = tumour mutational burden.

[a] This category includes Argentina and Turkey only.

[b] ECOG PS scores range from 0-5, with higher scores indicating greater disability.

[c] Data for disease stage are from case report forms, with the TNM Classification of Malignant Tumours, seventh edition, used for classification.

[d] 1 patient in the chemotherapy-alone group had stage IA disease, and 1 patient in each group had stage IV disease.

[e] 1 patient in the chemotherapy-alone group had unknown smoking status.

[f] Percentages are based on the primary analysis population. The status of PD-L1 expression was determined with the use of the PD-L1 immunohistochemistry 28-8 pharmDx assay (Dako); patients with tumour tissue that could not be assessed for PD-L1 expression (≤ 10% of all the patients who underwent randomisation) were stratified to the subgroup with a PD-L1 expression level of less than 1% at randomisation.

[g] TMB was not analysed from patients in China, and these patients are included in the Not Reported category.

Source: Forde et al. (2022)[3]; BMS data on file (2021)[83]

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

B.2.4.1 CheckMate-816

An analysis of pCR was planned when all patients were available for assessment of pCR, followed by 2 prespecified interim analyses for EFS after 148 EFS events (80% of events required for final analysis) and 167 EFS events (90% of events required for final analysis), respectively.[83] The 2 EFS interim analyses were planned in 358 randomly assigned patients to ensure an 82% power, assuming a hazard ratio (HR) of 0.65 between the 2 arms. [83] The first database lock for EFS, triggered after 148 EFS events occurred on 20 October 2021, and results from this analysis are presented in this submission, alongside the final analysis of pCR (database lock, 16 September 2020). Results from [redacted] are expected to be available within the timelines of this appraisal and the [redacted] will be provided once available. However, the timeframe of the appraisal will not allow [redacted]. Figure 7 presents a summary of all planned analyses, the analysis that is the basis of this submission is highlighted in red.

Figure 7. CheckMate-816: planned analyses

EFS = event-free survival; FA = final analysis; IA = interim analysis; OS = overall survival; pCR = pathologic complete response.

Note: EFS and OS tested using each their own O'Brien-Fleming alpha-spending function.

[a] Analysis occurred based on 16 September 2020 database lock.

[b] Analysis occurred based on 20 October 2021 database lock.

Source: BMS data on file (2018)[84]; BMS data on file (2021)[83]

Table 9 summarises the statistical analyses in CheckMate-816. The sample size of the study was calculated based on the primary endpoint of EFS and accounted for the 2 primary endpoints comparisons: pCR rate (per BIPR) and EFS (per BICR).

A total of [redacted] EFS events ensured that an overall 2-sided 5% significance level sequential test procedure with 2 interim analyses after 148 events ([redacted]% of events required for final analysis) and 167 events ([redacted]% of events required for final analysis) in 358 randomised subjects would have 82% power, assuming a HR of 0.65 between the 2 arms.[83]

For the pCR outcome, it was estimated that a sample of approximately 350 randomly assigned patients would provide more than 90% power to detect an odds ratio of 3.857 with a 2-sided type I error of 1%.[83]

A total of [redacted] OS events ensures that an overall 2-sided [redacted]% significance level sequential test procedure with 3 interim analyses after approximately [redacted], [redacted], and [redacted] events ([redacted]%, [redacted]%, and [redacted]% of events required for final analysis) in 358 randomly assigned patients would have [redacted]% power, assuming an exponential distribution with the median OS time in the chemo arm being 54 months and in the nivolumab + PDC arm being [redacted] months (corresponding to a target HR of 0.65).[83]

Table 9. CheckMate-816: summary of the statistical analyses

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management and patient withdrawals	Missing data
To compare the efficacy and safety of NIVO+PDC vs. PDC in participants with operable stage IB-IIIA (AJCC/UICC seventh edition) NSCLC	EFS (primary analysis) was compared between the treatment arms via a stratified log-rank test. The stratification factors per IRT were PD-L1 level (≥ 1% vs. < 1% or not evaluable/indeterminate) disease stage [IB/II vs. IIIA], and gender/sex) with a 2-sided *P* value. The HR and the corresponding (1-adjusted alpha) CI were estimated for the treatment comparison using a stratified Cox proportional hazards model with the randomly assigned arm as a single covariate. EFS was estimated using the KM product-limit method. The median and 2-sided 95% CI for median EFS in each treatment arm was computed via the log-log transformation method. EFS rates at different timepoints were estimated using KM estimates on the EFS curve for each randomly assigned arm. Associated 2-sided 95% CIs were calculated using the Greenwood formula for variance derivation (using log-log transformation). TTDM and EFS2 were analysed descriptively without hypothesis testing and compared between the treatment groups using the same methods as those described above for EFS. EFS (based on BICR assessments, primary definition) KM curves were generated by pCR status and by MPR status from randomisation for all concurrently randomly assigned patients in the treatment arms. Median and 95% CI were provided. HR and 95% CIs were provided by pCR and by MPR status, as well as HR of pCR/MPR vs. no pCR/MPR by treatment arm. In addition, these analyses were repeated, landmarked at the time of surgery (i.e., time from surgery to progression or	For pCR, it was estimated that a sample of approximately 350 randomly assigned patients would provide more than 90% power to detect an odds ratio of 3.857 with a 2-sided type I error of 1%, under the assumption that 10% of the patients in the PDC alone group would have a pCR. If the between-group difference in pCR was significant, a comparison of EFS between the 2 groups was to be performed with a 2-sided alpha level of 5%. It was estimated that approximately [redacted] events of disease progression, disease recurrence, or death would provide the trial with 82% power assuming an HR of 0.65 and a 2-sided type I error of 5%, with interim analyses performed when 80% and 90% of the total planned events had occurred. If the between-group difference EFS was significant, OS was to be tested hierarchically.	EFS was censored at the last evaluable tumour assessment on or before the date of subsequent therapy (protocol-specified adjuvant therapy was permitted). OS was censored on the last date a patient was known to be alive. For TTDM, patients who had not developed distant metastasis or died at the time of the analysis were censored on the date of their last evaluable tumour assessment. For EFS2, patients who were alive and without progression after the next line of therapy were censored at last known alive date. Safety assessments were based on the frequency of deaths, SAEs, AEs leading to discontinuation or dose modification, overall AEs, AEs of special clinical	EFS sensitivity analysis: accounting for missing tumour assessments before the EFS event; for patients with 2 or more missed visits before the EFS event, EFS was censored at the last tumour assessment before the EFS event.

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management and patient withdrawals	Missing data
	death) and limited to patients with pCR or MPR status available who underwent surgery. Median and 95% CIs were provided. HRs and 95% CIs for concurrently randomly assigned patients were provided by pCR and by MPR status, as well as HR of pCR/MPR vs. no pCR/MPR by treatment arm. Descriptive analyses were conducted to report the distribution of tumour cell PD-L1 and TMB using continuous values or categories. Association of PD-L1 and TMB with efficacy endpoints (EFS) was explored by running separate analyses for each category of the biomarker. A Cox proportional hazards regression model was fitted for EFS with PD-L1 (or TMB), treatment arm, and PD-L1 (or TMB) by treatment arm interaction, among all biomarker evaluable patients and reported a plot of estimated log HR with 95% CI vs. PD-L1 expression (or TMB). Descriptive analyses were conducted to report the distribution of ctDNA, ctDNA clearance, and ctDNA reduction, using continuous values or categories. Descriptive statistics of safety were presented using NCI CTCAE version 4.0 by treatment group. The analysis of EQ-5D-3L was restricted to all concurrently randomly assigned patients who had an assessment at baseline and at least 1 postbaseline assessment.	The significance boundaries (0.0262 for EFS and 0.0033 for OS at the first interim analysis) were adjusted with the use of a Lan–DeMets alpha-spending function with an O'Brien-Fleming type of boundary that accounted for the actual number of events.	interest that are potentially associated with the use of nivolumab and ipilimumab (i.e., select AEs, immune-mediated AEs), clinical laboratory assessments (haematology, serum chemistry, liver, and thyroid function tests), and vital sign measurements.	

AE = adverse event; AJCC = American Joint Committee on Cancer; BICR = blinded independent central review; CI = confidence interval; CTCAE = Common Terminology Criteria for Adverse Events; ctDNA = circulating tumour DNA; EFS = event-free survival; EFS2 = event-free survival on second-line therapy; HR = hazard ratio; IRT = Interactive Response Technology; KM = Kaplan-Meier; MPR = major pathologic response; NCI = National Cancer Institute; NIVO = nivolumab; NSCLC = non-small cell lung cancer; OS = overall survival; pCR = pathologic complete response; PDC = platinum doublet chemotherapy; PD-L1 = programmed death-ligand 1; SAE = serious adverse event; TMB = tumour mutational burden; TTDM = time to death or distant metastases; UICC = Union for International Cancer Control.

Sources: BMS data on file (2018)[84]; BMS data on file (2021)[83]; Forde et al. (2022)[3]

B.2.5Critical appraisal of the relevant clinical effectiveness evidence

Table 10 presents the quality assessment for CheckMate-816. CheckMate-816 was an open-label study because of the differences in chemotherapy-related and immuno-oncology therapy–related toxicities; histology-dependent chemotherapy options; dose modification rules for safety management, including different dose-delay rules per treatment arm; and premedication requirements according to chemotherapy made blinding impractical. An open-label design also helped ensure that immune-related toxicities in patients receiving immuno-oncology therapy were promptly identified and managed. Bristol Myers Squibb (BMS) was blinded to the aggregated safety and efficacy data by treatment assignments.

Patients meeting eligibility criteria were randomly assigned to one of the treatment arms through Interactive Response Technology. Demographics and baseline disease characteristics were balanced between treatment arms (see Section B.2.3.2) and generally representative of the population with resectable NSCLC. A BIPR was used to review pathological data and tumour assessment for all randomly assigned patients. During the review, the BMS personnel remained blinded to treatment group assignment. Personnel who conducted the PD-L1 testing, scoring for tumour cell PD-L1, and assessed tumour mutational burden data, were blinded to patient treatment group assignment. Unblinded data reviewed by the data monitoring committee (DMC) at regular safety review meetings were not shared with BMS until formal pCR and EFS analysis achieved the prespecified significance level and unblinding thresholds as specified in the statistical analysis plan/DMC charter. No unexpected imbalances in dropouts between groups were reported.

Although neoadjuvant PDC was the comparator used in CheckMate-816, the current SOC in England is surgery alone or adjuvant platinum-based chemotherapy (see Section B.1.3.6). Nonetheless, evidence suggests that neoadjuvant and adjuvant chemotherapy regimens offer similar improvements in 5-year OS.[56-59]

Table 10. CheckMate-816: quality assessment

Was randomisation carried out appropriately?	Yes
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?	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?**	Yes
How closely does the RCT(s) reflect routine clinical practice?	Unclear – current SOC in England is surgery alone or adjuvant platinum-based chemotherapy rather than neoadjuvant chemotherapy.

RCT = randomised controlled trial; SLR = systematic literature review; SOC = standard of care.

Note: this has been updated from the SLR report, and is now based on the full publication by Forde et al. (2022).

Sources: Forde et al. (2022)[3]; BMS data on file (2021)[83]

B.2.6Clinical effectiveness results of the relevant studies

B.2.6.1 CheckMate-816

Results presented here are based on the first prespecified interim analysis of EFS and OS (database lock, 20 October 2021; minimum follow-up, 21 months; median follow-up, 29.5 months) and the final analysis of pCR (database lock, 16 September 2020).[3]

Because the comparison between nivolumab + PDC versus PDC in concurrently randomly assigned patients was statistically significant for EFS (as per the 20 October 2021 database lock), formal testing for the secondary objective, OS, was subsequently performed by the DMC. Although readouts were favourable for nivolumab + PDC, with a clear visual separation in the Kaplan-Meier survival curves, the *P* value for OS did not cross the significance boundary at the first interim analysis. Overall survival will be formally tested again at the second interim OS analysis.[3]

Results presented in this section represent all patients relevant to NICE's decision problem.

B.2.6.1.1 Summary of treatment

Table 11 presents a summary of treatments in CheckMate-816. All patients were no longer receiving treatment at the time of the database locks; 93.8% in the nivolumab + PDC group and 84.7% in the PDC group had fully completed the prespecified neoadjuvant treatment, while 6.2% and 15.3%, respectively, had stopped treatment due to toxicity, disease progression or other reasons. Adjuvant chemotherapy was received by 11.9% of patients treated with nivolumab + PDC and 22.2% of those treated with PDC alone.[3]

Table 11. CheckMate-816: treatment summary

Treatment and exposure	NIVO+PDC (n = 179)	PDC (n = 179)
Patients receiving neoadjuvant treatment, n (%)	176 (98.3)	176 (98.3)
Reason off neoadjuvant treatment, n (%)[a]		
Completed (3 cycles)	165 (93.8)	149 (84.7)
Study drug toxicity	10 (5.7)	12 (6.8)
Disease progression	1 (0.6)	2 (1.1)
Other[b]	0	13 (7.4)
Patients receiving adjuvant treatment, n (%)[a]	35 (19.9)	56 (31.8)
Chemotherapy (≤ 4 cycles) alone	21 (11.9)	39 (22.2)
Radiotherapy alone	9 (5.1)	12 (6.8)
Chemotherapy and radiotherapy	5 (2.8)	5 (2.8)

NIVO = nivolumab; PDC = platinum doublet chemotherapy.

[a] Denominator based on patients receiving neoadjuvant treatment.

[b] Reasons were adverse event unrelated to study drug in 3 patients, patient request to discontinue study treatment in 5 patients, patient withdrew consent in 4 patients, and patient no longer met study criteria in 1 patient.

Source: Forde et al. (2022)[3]

Any subsequent cancer therapy (excluding adjuvant treatment) was received by 21.2% of the patients in the nivolumab + PDC group and 43.6% of those in the PDC group; subsequent systemic therapy was received by 17.3% and 36.3% of patients, respectively (Table 12).[3] Chemotherapy is the most commonly prescribed subsequent treatment for both nivolumab + PDC and PDC alone, representing 15.1% and 22.3% received, respectively; clinical experts confirmed that this would reflect clinical practice after treatment with nivolumab + PDC (Appendix N). These data reinforce the long-term benefit of nivolumab + PDC in delaying recurrence; a lower proportion of patients require subsequent treatment following nivolumab + PDC and a greater proportion of patients who have responded remain event-free (see Event-free survival in Section B.2.6.1.2).

Table 12. CheckMate-816: subsequent therapies

	NIVO+PDC (n = 179)	PDC (n = 179)
Any	38 (21.2)	78 (43.6)
Radiotherapy	20 (11.2)	38 (21.2)
Surgery[a]	3 (1.7)	6 (3.4)
Systemic therapy	31 (17.3)	65 (36.3)
Chemotherapy	27 (15.1)	40 (22.3)
Targeted therapy	13 (7.3)	21 (11.7)
Immuno-oncology therapy	10 (5.6)	42 (23.5)
Pembrolizumab	4 (2.2)	22 (12.3)
Nivolumab	2 (1.1)	8 (4.5)
Atezolizumab	2 (1.1)	8 (4.5)
Durvalumab	2 (1.1)	6 (3.4)
Toripalimab	0	1 (0.6)
Sintilimab	0	1 (0.6)

NIVO = nivolumab; PDC = platinum doublet chemotherapy.

Note: Subsequent therapy was defined as therapy started on or after first dosing date (randomisation date if patient never treated) outside the protocol-specified adjuvant therapy. Patients may have received more than 1 type of subsequent therapy.

[a] Any subsequent anticancer (non-small cell lung cancer) surgery. Most were for palliative reasons or in patients with oligo-metastatic disease; some patients underwent subsequent surgery for the primary tumour.

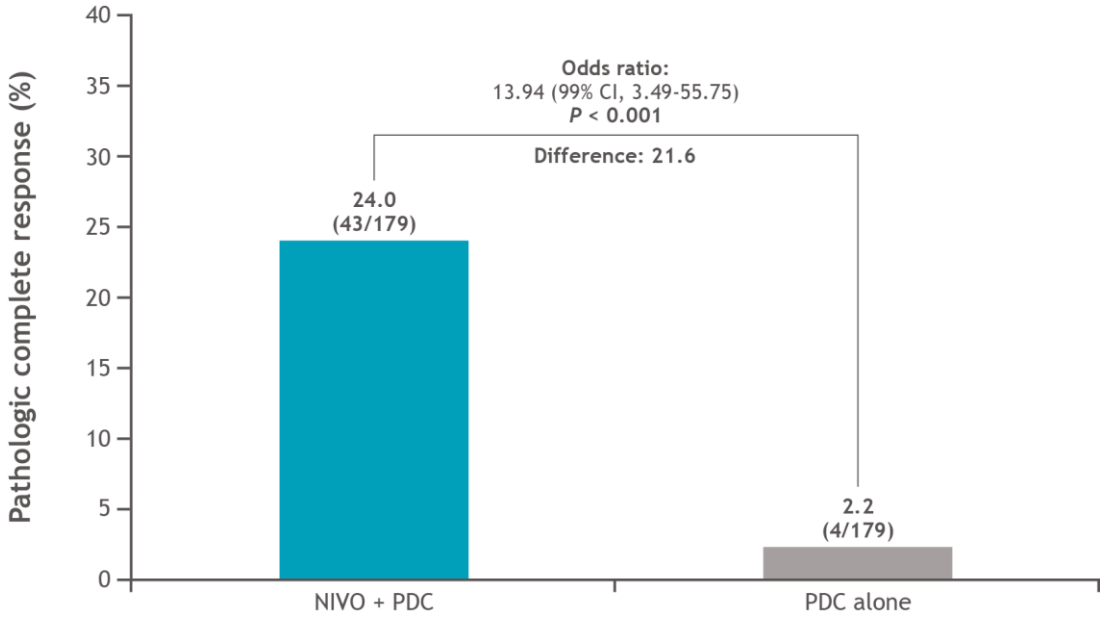
Source: Forde et al. (2022)[3]

B.2.6.1.2 Primary outcomes

Pathologic complete response

Among all patients in the primary analysis population (database lock, 15 September 2020), 24.0% (95% confidence interval [CI], 18.0%-31.0%) treated with nivolumab + PDC had a pCR versus 2.2% (95% CI, 0.6%-5.6%) treated with PDC alone (odds ratio, 13.94; 99% CI, 3.49-55.75; $P < 0.001$) (Figure 8).[3]

Figure 8. CheckMate-816: pathologic complete response according to BIPR



BIPR = blinded independent pathologic review; CI = confidence interval; NIVO = nivolumab; PDC = platinum doublet chemotherapy.

Source: Forde et al. (2022)[3]

Achieving a pCR (i.e., an absence of residual tumour in lung resected tissue and lymph nodes) is clinically meaningful because this has been shown to be associated with improved EFS and OS; early evidence of a benefit in these outcomes indicates a stronger EFS and OS benefit in the longer term than patients who did not achieve a pCR (see Section B.1.3.6.5 for further detail).[72-75] Thus, the statistically significant increases in pCR observed with nivolumab + PDC versus PDC alone suggest that nivolumab + PDC may improve survival outcomes versus PDC alone.[3]

Event-free survival

With a minimum follow-up of 21 months, the median EFS was 31.6 months with nivolumab + PDC and 20.8 months with PDC alone, a 37% reduction in the risk of recurrence or death (HR, 0.63; 97.38% CI, 0.43-0.91; *P* = 0.005) (Table 13 and Figure 9).[3] Early separation of the Kaplan-Meier curves favours patients treated with nivolumab + PDC (Figure 9). After this timepoint, nivolumab + PDC is associated with consistently longer EFS versus patients treated with PDC alone, with an increasing incremental gain versus PDC alone in landmark observed EFS rates (Table 13). The EFS benefit with nivolumab + PDC was maintained after adjusting for optional adjuvant therapy (HR for disease progression, disease recurrence, or death, 0.65; 95% CI, 0.47-0.90).[3] A total of 64.2% patients in the nivolumab + PDC arm and 51.4% patients in the PDC arm were censored at their last tumour assessment.[83]

Table 13. CheckMate-816: summary of event-free survival

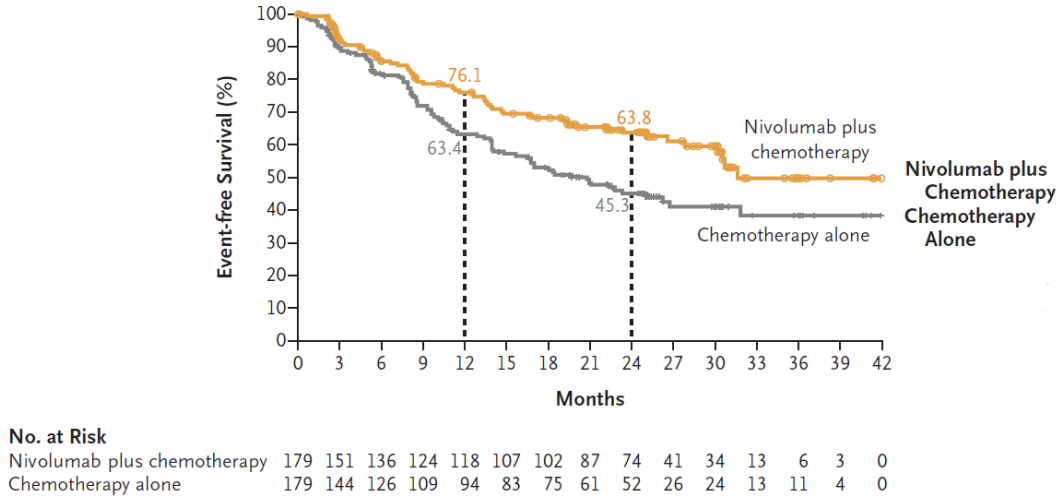
	NIVO+PDC (n = 179)	PDC (n = 179)
Median EFS (95% CI)	31.6 (30.2-NR)	20.8 (14.0-26.7)
HR for disease progression, disease recurrence, or death	0.63	
97.38% CI	0.43-0.91	
P value	*P* = 0.005	
1-year EFS	76.1%	63.4%
2-year EFS	63.8%	45.3%

CI = confidence interval; EFS = event-free survival; HR = hazard ratio; NIVO = nivolumab; NR = not reached; PDC = platinum doublet chemotherapy.

Note: 115 of 179 patients (64.2%) in the nivolumab + PDC arm and 92 of 179 (51.4%) in the PDC arm were censored for EFS per blinded independent central review at database lock.

Source: Forde et al. (2022)[3]

Figure 9. CheckMate-816: event-free survival according to BICR



BICR = blinded independent central review.

Note: *Chemotherapy* refers to platinum doublet chemotherapy.

Source: Forde et al. (2022)[3]

These data further support a durable benefit with nivolumab + PDC. It is clear from the Kaplan-Meier curves and favourable HR that nivolumab + PDC offers a substantial, clinically relevant benefit for patients in terms of EFS versus PDC alone, a benefit that is expected to be sustained with longer term follow-up and ultimately is expected to translate into OS benefit, as suggested in other studies.[75] Although longer follow-up is required, the existing evidence on attaining a cure at 5 years in resectable NSCLC suggests this is likely to occur in patients treated with nivolumab + PDC with additional follow-up.

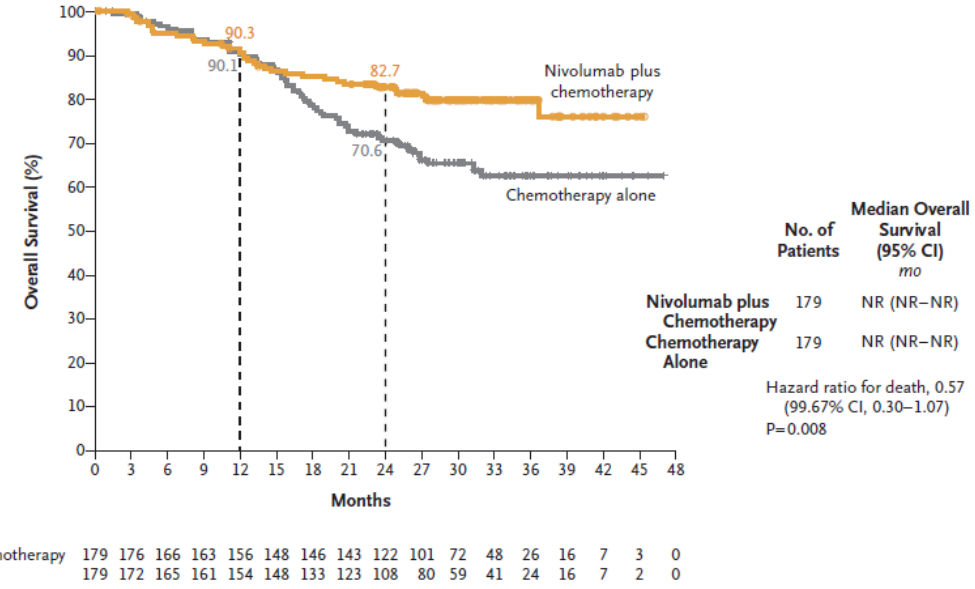
B.2.6.1.3 Secondary outcomes

Overall survival

In the interim analysis, median OS was not reached in either the nivolumab + PDC group or the PDC alone group at the time of the interim database lock due to immaturity of the data (minimum follow-up of 21 months; HR for death, 0.57; 99.67% CI, 0.30-1.07; *P* = 0.008) (Figure 10). The first prespecified interim analysis was conducted in line with the statistical plan because of the number of EFS events that had occurred; however, few OS events had occurred and the *P* value for OS did not cross the boundary for statistical significance (0.0033).[3] However, the trend in data indicates the hazard of death is lower for patients treated with nivolumab + PDC versus patients treated with PDC alone.

The Kaplan-Meier curves show similar OS at start of treatment in both the nivolumab + PDC and PDC alone arms; they overlap until a clear and consistent separation is seen after approximately 15 months, which suggests improved survival with nivolumab + PDC.[3] Although these data are not yet mature, they suggest, alongside the statistically significant comparative difference in pCR and EFS for nivolumab + PDC versus PDC alone, that a continued relative benefit for nivolumab + PDC and a statistically significant difference in OS may be observed once more events have accrued.

Figure 10. CheckMate-816: overall survival



CI = confidence interval; NR = not reached.

Note: *Chemotherapy* refers to platinum doublet chemotherapy.

Source: Forde et al. (2022)[3]

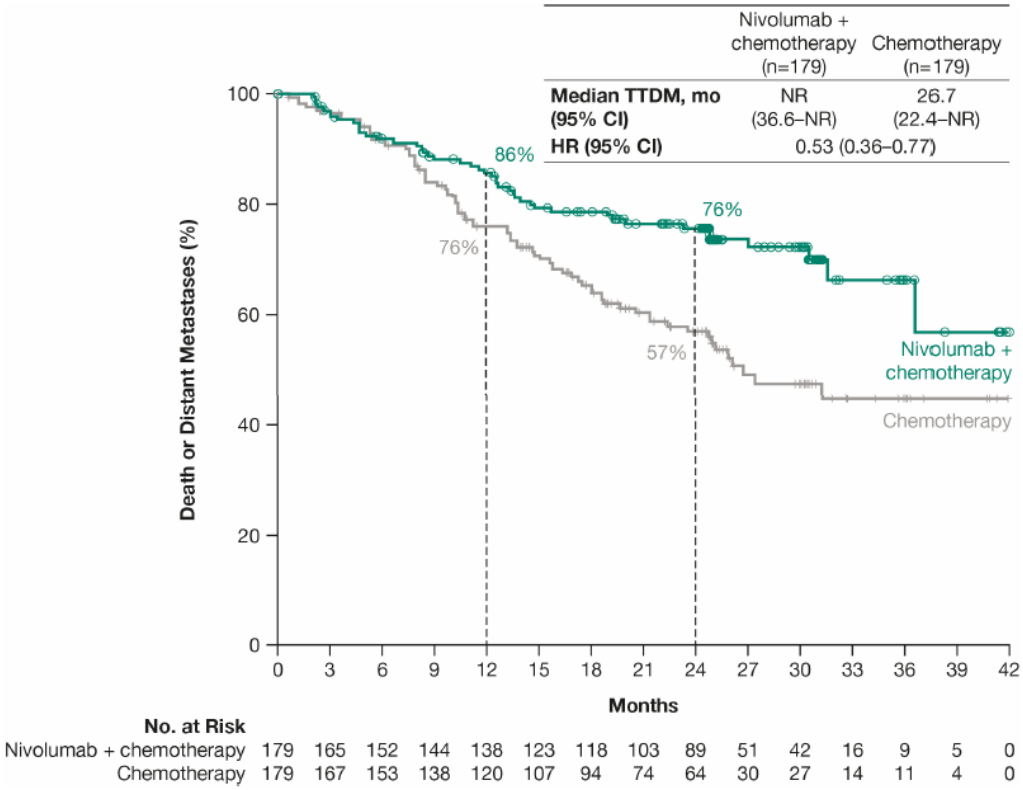
Major pathologic response rate by BIPR

The percentage of patients with an MPR was substantially higher with nivolumab + PDC than with PDC alone in the primary analysis population (36.9% vs. 8.9%; odds ratio, 5.70; 95% CI, 3.16-10.26).[3]

Time to death or distant metastases according to BICR

Time to death or distant metastases was defined as the time between the date of randomisation and the first date of distant metastasis or the date of death in the absence of distant metastasis.[3] Results favoured nivolumab + PDC over PDC alone (HR, 0.53; 95% CI, 0.36-0.77) (Figure 11).[3] The Kaplan-Meier curves are similar between treatment arms as the curves overlap; after approximately 6 months, the curves separate where nivolumab + PDC begins to improve TTDM.

Figure 11. CheckMate-816: time to death or distant metastases



CI = confidence interval; HR = hazard ratio; NR = not reached; TTDM = time to death or distant metastases.

Note: *Chemotherapy* refers to platinum doublet chemotherapy.

Source: Forde et al. (2022)[3]

B.2.6.1.4 Exploratory outcomes

Clinical response rate by BICR

Rates of response according to BICR were higher with nivolumab + PDC than with PDC alone (Table 14).[3]

Table 14. CheckMate-816: objective response rate and best overall response

	No. of patients (%)	
	NIVO+PDC (n = 179)	PDC (n = 179)
Objective response rate[a]	96 (53.6)	67 (37.4)
95% CI	46.0-61.1	30.3-45.0
Best overall response		
Complete response	1 (0.6)	3 (1.7)
Partial response	95 (53.1)	64 (35.8)
Stable disease	70 (39.1)	88 (49.2)
Progressive disease	8 (4.5)	11 (6.1)
Not evaluable	1 (0.6)	1 (0.6)
Not reported	4 (2.2)	12 (6.7)

CI = confidence interval; NIVO = nivolumab; PDC = platinum doublet chemotherapy.

[a] Objective response rate per blinded independent central review was defined as a complete or partial response from baseline to the presurgery scan per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1.

Source: Forde et al. (2022)[3]

Incidence of radiographic downstaging

The incidence of radiographic downstaging (reduction of disease stage from baseline) was 30.7% and 23.5% with nivolumab + PDC versus PDC, respectively (Table 15).[3]

Table 15. CheckMate-816: radiographic downstaging before and after treatment by stage of disease

	No. of patients (%)			
	NIVO+PDC (n = 179)		PDC (n = 179)	
Stage	Disease stage at study entry	Disease stage after neoadjuvant treatment	Disease stage at study entry	Disease stage after neoadjuvant treatment
0	0	2 (1.1)	0	2 (1.1)
IA	0	23 (12.8)	1 (0.6)	13 (7.3)
IB	10 (5.6)	14 (7.8)	8 (4.5)	23 (12.8)
IIA	30 (16.8)	29 (16.2)	32 (17.9)	20 (11.2)
IIB	25 (14.0)	15 (8.4)	22 (12.3)	12 (6.7)
IIIA	113 (63.1)	81 (45.3)	115 (64.2)	87 (48.6)
IIIB	0	3 (1.7)	0	6 (3.4)
IV	1 (0.6)	7 (3.9)	1 (0.6)	5 (2.8)
Not reported	0	5 (2.8)	0	11 (6.1)

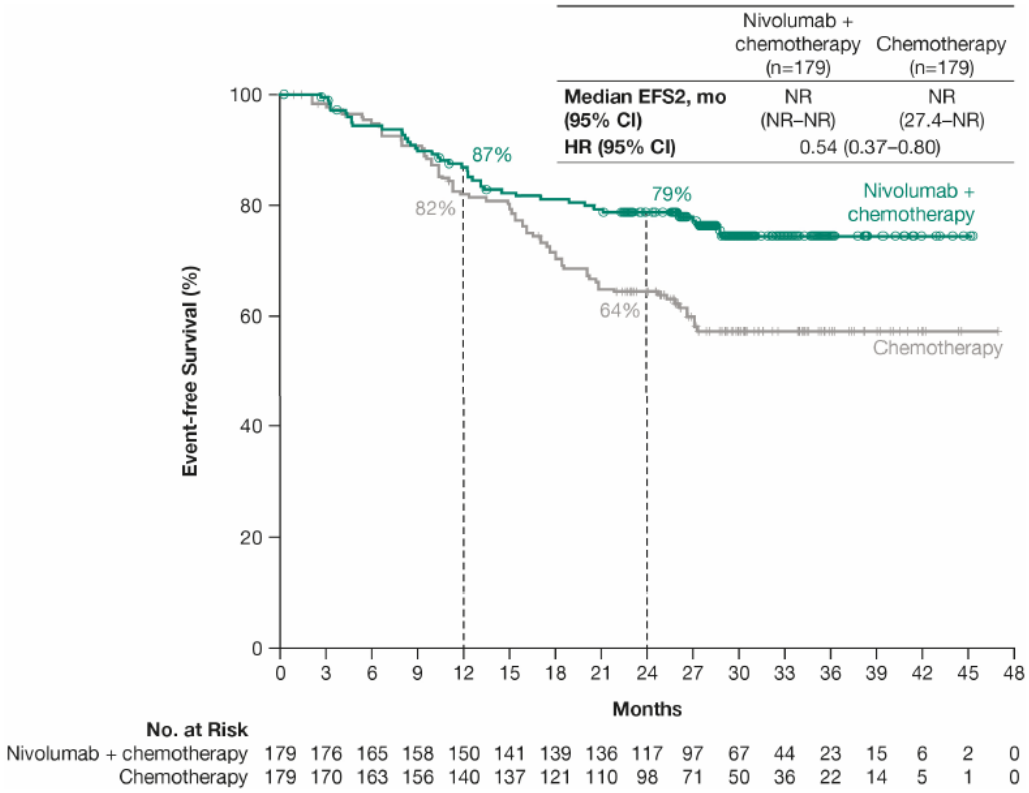
NIVO = nivolumab; PDC = platinum doublet chemotherapy.

Source: Forde et al. (2022)[3]

Event-free survival 2

Event-free survival 2 (EFS2) was defined as time from randomisation to objectively documented progression, per investigator assessment, after the next line of therapy or to death from any cause, whichever occurs first; patients without documented progression on the next line who started a second next line of subsequent therapy were considered to have had an event at the start of second next line of therapy. This definition aligns with the standard progression-free survival 2 (PFS2) definition used in the metastatic setting.[83] Nivolumab + PDC demonstrated a 46% statistically significant reduction in risk of EFS2 (HR, 0.54; 95% CI, 0.37-0.80) (Figure 12).[3] The Kaplan-Meier curve displays overlapping curves representative of similar EFS2 rates between treatment arms until a separation is seen after approximately 9 months, where nivolumab + PDC begins to show improved EFS2. This is sustained after the separation, which supports the durability of the benefit seen with nivolumab + PDC.

Figure 12. CheckMate-816: event-free survival 2



CI = confidence interval; EFS2 = event-free survival 2; HR = hazard ratio; NR = not reached.

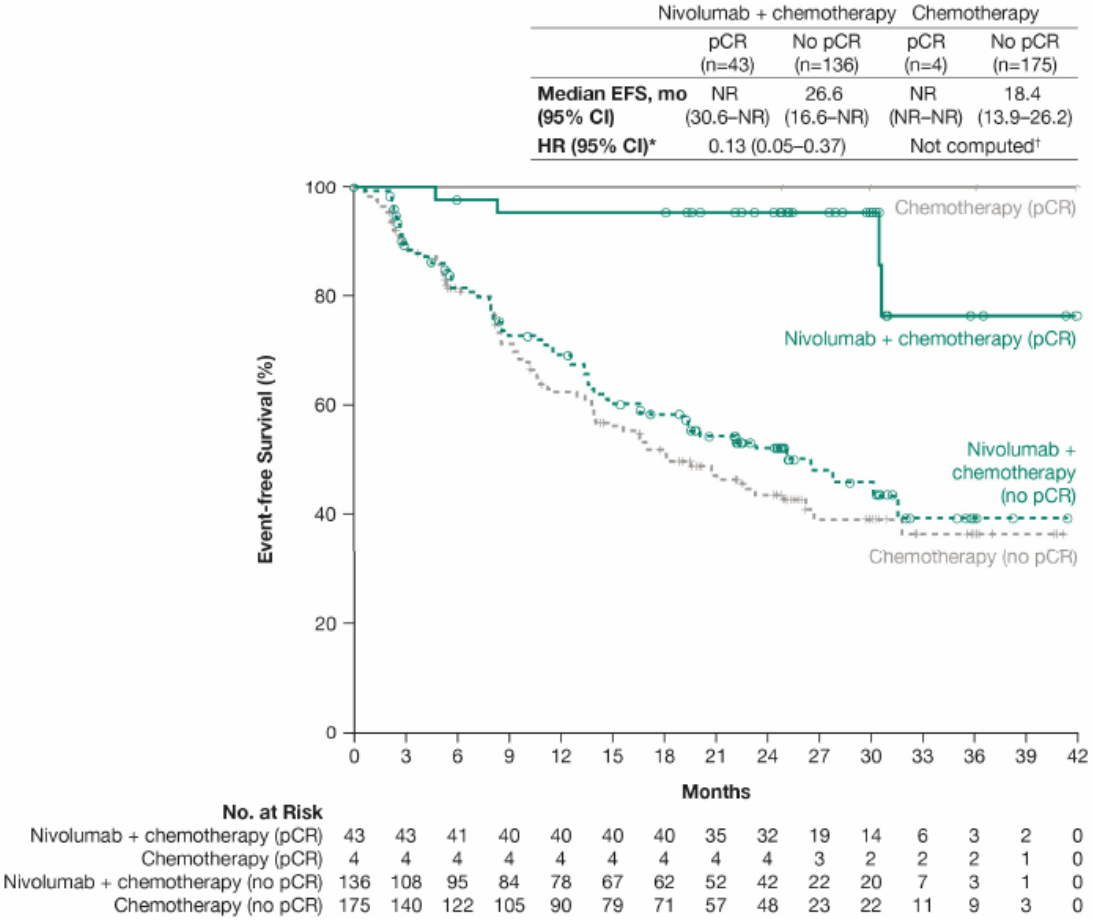
Note: *Chemotherapy* refers to platinum doublet chemotherapy.

Source: Forde et al. (2022)[3]

Event-free survival according to pathologic complete response status

As shown in Figure 13, EFS was longer in patients with a pCR than in those without a pCR. Among patients with a pCR, median EFS was not reached in either treatment group.3 In patients without a pCR, the median EFS was 26.6 months with nivolumab + PDC and 18.4 months with PDC alone (HR for disease progression, disease recurrence, or death, 0.84; 95% CI, 0.61-1.17).[3] As a higher proportion of patients treated with nivolumab + PDC achieve pCR, we anticipate that EFS will continue to show an improved benefit versus chemotherapy with longer follow-up.

Figure 13. CheckMate-816: event-free survival by pathologic complete response



CI = confidence interval; EFS = event-free survival; HR = hazard ratio; NR = not reached; pCR = pathologic complete response.

Note: *Chemotherapy* refers to platinum doublet chemotherapy.

* HR (95% CI) for nivolumab + PDC versus PDC in patients without a pCR was 0.84 (0.61-1.17).

† HR was not computed for the chemotherapy arm because only 4 patients had a pCR.

Source: Forde et al. (2022)[3]

Feasibility of surgery and rates of perioperative and postoperative complications

Feasibility of surgery was maintained with nivolumab + PDC versus neoadjuvant PDC alone: numerically more patients underwent surgery with nivolumab + PDC, had a less invasive and less extensive surgery, had a shorter duration of surgery and had a similar length of hospital stay.

Among all the patients who underwent concurrent randomisation, 149 (83.2%) in the nivolumab + PDC group and 135 (75.4%) in the PDC group underwent definitive surgery (Table 16). Surgery was cancelled for 28 (15.6%) and 37 (20.7%) of the patients, respectively; reasons for cancellation included disease progression (12 [6.7%] and 17 [9.5%], respectively), AEs (2 [1.1%] and 1 [0.6%]), and other (14 [7.8%] and 19 [10.6%] [including patient refusal, unresectability, and poor lung function]). The percentage of patients with delayed surgery was similar in the 2 treatment groups.[3]

The median duration of surgery was numerically shorter and the use of minimally invasive approaches was more common in the nivolumab + PDC group than in the PDC alone group. Notably, minimally invasive surgery rates were 29.5% and 21.5% in the nivolumab + PDC and PDC alone groups, respectively, and rates of conversion from minimally invasive to open surgery were higher in the PDC group (11.4% vs. 15.6%). Further, a higher proportion of patients underwent lobectomy rather than pneumonectomy in the nivolumab + PDC group than in the PDC group (lobectomy, 77.2% vs. 60.7%; pneumonectomy, 16.8% vs. 25.2%, respectively). Thus, in CheckMate-816, patients treated with nivolumab + PDC were more likely to undergo surgery and surgery was more likely to be minimally invasive, which is associated with reduced mortality and improved HRQOL as discussed in Section B.1.3.6.1, than patients treated with neoadjuvant PDC alone.[3]

For those patients who underwent definitive surgery, a higher proportion of those treated with nivolumab + PDC (83.2%) than PDC alone (77.8%) had a complete resection with no residual tumour (R0).

The median length of hospital stay for surgery was 10 days in both treatment arms.3 This is longer than the expected length of hospital stay in the UK (according to clinical expert opinion; Appendix N) and is driven by the SOC in some of the Asian countries included in the study, where longer hospital stays are the norm. Nonetheless, use of nivolumab + PDC did not increase length of stay versus neoadjuvant PDC alone.[3]

Table 16. CheckMate-816: surgical outcomes summary

	NIVO+PDC (n = 179)	PDC (n = 179)
Patients with definitive surgery,[a] n (%)	149 (83.2)	135 (75.4)
Time from last neoadjuvant dose to definitive surgery, median weeks (IQR)	5.3 (4.6-6.0)	5.0 (4.6-5.9)
Patients with cancelled definitive surgery, n (%)	28 (15.6)	37 (20.7)
Disease progression	12 (6.7)	17 (9.5)
Adverse event	2 (1.1)	1 (0.6)
Other[b]	14 (7.8)	19 (10.6)
Patients with delayed surgery,[c,d] n (%)	31 (20.8)	24 (17.8)
Administrative reason	17 (11.4)	8 (5.9)
Adverse event	6 (4.0)	9 (6.7)
Other	8 (5.4)	7 (5.2)
Median length of delay in surgery, weeks (IQR)	2.0 (0.6-3.0)	2.4 (1.0-3.7)
Of patients with delayed surgery, proportion with delay of,[e] n (%)		
≤ 2 weeks	17 (54.8)	11 (45.8)
> 2 and ≤ 4 weeks	8 (25.8)	8 (33.3)
> 4 and ≤ 6 weeks	3 (9.7)	2 (8.3)
> 6 weeks	3 (9.7)	3 (12.5)
Median duration of surgery,[f] minutes (IQR)	185.0 (133.0-260.0)	213.5 (150.0-283.0)
Surgical approach,[d] n (%)		
Thoracotomy	88 (59.1)	85 (63.0)
Minimally invasive[g]	44 (29.5)	29 (21.5)
Minimally invasive to thoracotomy	17 (11.4)	21 (15.6)
Type of surgery,[d,h] n (%)		
Lobectomy	115 (77.2)	82 (60.7)
Sleeve lobectomy	2 (1.3)	10 (7.4)
Bilobectomy	3 (2.0)	4 (3.0)
Pneumonectomy	25 (16.8)	34 (25.2)
Other	24 (16.1)	21 (15.6)
Completeness of resection,[d] n (%)		
R0 (no residual tumour)	124 (83.2)	105 (77.8)
R1 (microscopic residual tumour)	16 (10.7)	21 (15.6)
R2 (macroscopic residual tumour)	5 (3.4)	4 (3.0)
Rx (unknown)	4 (2.7)	5 (3.7)
Median no. of sampled lymph nodes (IQR)	19 (12-25)	18.5 (10-26)
Median length of hospital stay, days (IQR)	10.0 (7.0-14.0)	10.0 (7.0-15.0)
Median length of hospital stay by surgery type, days (IQR)		
Lobectomy	10.0 (7.0-15.0)	9.0 (6.0-14.0)
Pneumonectomy	10.0 (8.0-13.0)	11.0 (9.0-16.0)
Other[i]	8.5 (4.0-13.0)	9.0 (7.0-14.0)

	NIVO+PDC (n = 179)	PDC (n = 179)
Median length of hospital stay by region, days (IQR)		
North America	4.0 (4.0-7.0)	6.0 (4.0-8.0)
Europe	9.5 (8.0-14.0)	13.0 (7.0-18.0)
Asia	11.0 (9.0-16.0)	13.0 (10.0-16.0)

IQR = interquartile range; NIVO = nivolumab; PDC = platinum doublet chemotherapy.

[a] Definitive surgery was not reported in 2 patients in the NIVO+PDC group and 7 in the PDC group.

[b] Other reasons were patient refusal in 9 patients in the NIVO+PDC arm and 8 patients in the PDC arm; consent withdrawal in 3 patients in the PDC arm; COVID-19 in 1 patient in the PDC arm; unfit for surgery due to poor lung function in 2 patients in the NIVO+PDC arm and 4 patients in the PDC arm; and unresectability in 2 patients in each arm.

[c] Time from last dose to neoadjuvant surgery > 6 weeks.

[d] Denominator based on patients with definitive surgery (n = 149 in the NIVO+PDC group; n = 135 in the PDC group).

[e] Denominator based on patients with delayed surgery.

[f] Patients with reported duration of surgery: NIVO+PDC, 122; PDC, 121.

[g] Thoracoscopic/robotic.

[h] Patients may have had more than 1 surgery type.

[I] Includes bilobectomy, sleeve lobectomy, and other.

Source: Forde et al. (2022)[3]

Patient-reported outcomes

The addition of nivolumab to PDC had no detrimental impact on HRQOL during the neoadjuvant period.[85] Health-related quality of life was assessed using the EQ-5D-3L. A mixed-effects model repeated measures analysis evaluated longitudinal changes from baseline in EQ-5D visual analogue scale (range 0 to 100) and utility index (UI; range −0.594 to 1) scores during the neoadjuvant period (week 4, week 7, and post-neoadjuvant visit 1); higher scores reflect better HRQOL.

EQ-5D-3L completion rates were > 80% in both treatment arms at baseline and during the neoadjuvant period. Baseline EQ-5D-3L visual analogue scale and UI scores were consistent with UK population norms. Scores during the neoadjuvant period were generally similar to baseline for both treatment arms; there were no clinically meaningful differences between nivolumab + PDC versus PDC (Table 17). In both treatment arms, most patients reported “no problems” for individual EQ-5D-3L dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) at baseline and during treatment.[85]

Table 17. EQ-5D-3L in the neoadjuvant period

	LSM change from baseline-95% CI		LSM difference-95% CI
VAS; MID = 7	**Nivolumab + PDC**	**PDC**	**Nivolumab + PDC vs. PDC**
Overall	−0.9 to 2.4, 0.7	−1.5 to 3.1, 0.1	0.6 to 1.5, 2.7
Wk 4	−0.4 to 2.1, 1.4	−1.7 to 3.5, 0.1	1.3 to 1.0, 3.7
Wk 7	−1.3 to 3.2, 0.6	−0.8 to 2.7, 1.2	−0.6 to 3.2, 2.0
Post-neoadjuvant visit 1	−0.8 to 2.9, 1.2	−2.0 to 4.1, 0.2	1.1 to 1.7, 3.9
UI; MID = 0.08			
Overall	−0.003 to 0.024, 0.019	−0.011 to 0.033, 0.011	0.008 to 0.020, 0.036
Wk 4	0.012 to 0.011, 0.036	0.001 to 0.023, 0.025	0.011 to 0.021, 0.043
Wk 7	−0.006 to 0.033, 0.021	−0.004 to 0.031, 0.023	−0.002 to 0.038, 0.034
Post-neoadjuvant visit 1	−0.014 to 0.043, 0.015	−0.029 to 0.059, 0.001	0.015 to 0.025, 0.056

CI = confidence interval; LSM = least squares mean; MID = minimally important difference; PDC = platinum doublet chemotherapy; UI = utility index; VAS = visual analogue scale.

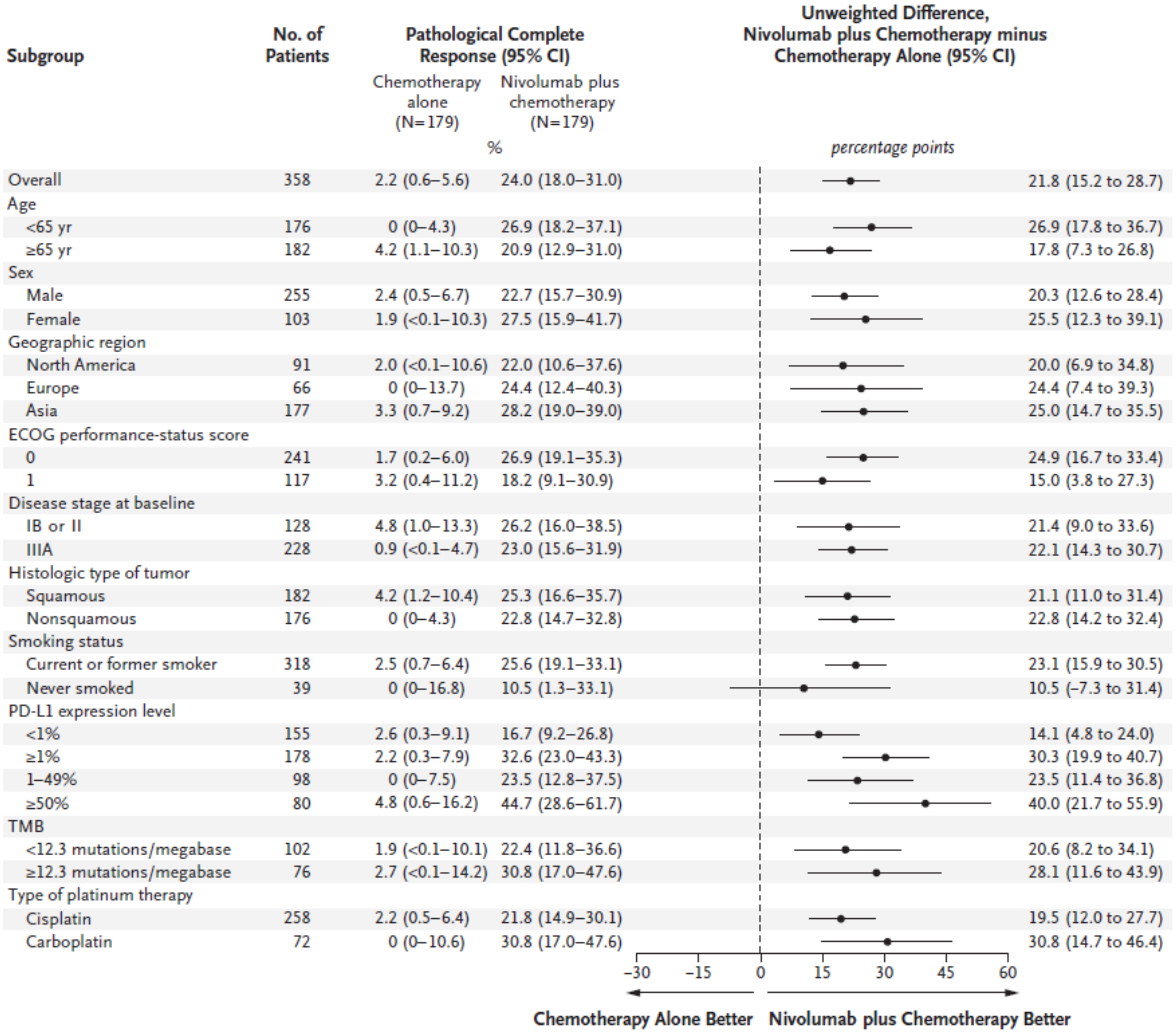
Source: Felip (2022)[85]

B.2.7Subgroup analysis

Prespecified subgroup analyses were conducted in line with the study protocol. However, patient numbers in some subgroups are low and very few events had occurred by the time of the database lock. Therefore, these analyses are not appropriate for decision-making, and the decision problem population included in CheckMate-816 is more appropriate; this was also highlighted by clinical experts (Appendix N).

A benefit with nivolumab + PDC with respect to pCR was observed across all subgroups excluding patients who never smoked (Figure 14).[3] Of note, a pCR benefit was seen regardless of stage and PD-L1 status. Analyses have consistently demonstrated an association between pCR and EFS/OS as well as EFS and OS[72-75]; therefore, early evidence of a benefit in these outcomes indicates an OS benefit in the longer term (see Section B.1.3.6.5 for further detail).

Figure 14. CheckMate-816: pathologic complete response according to BIPR by subgroup



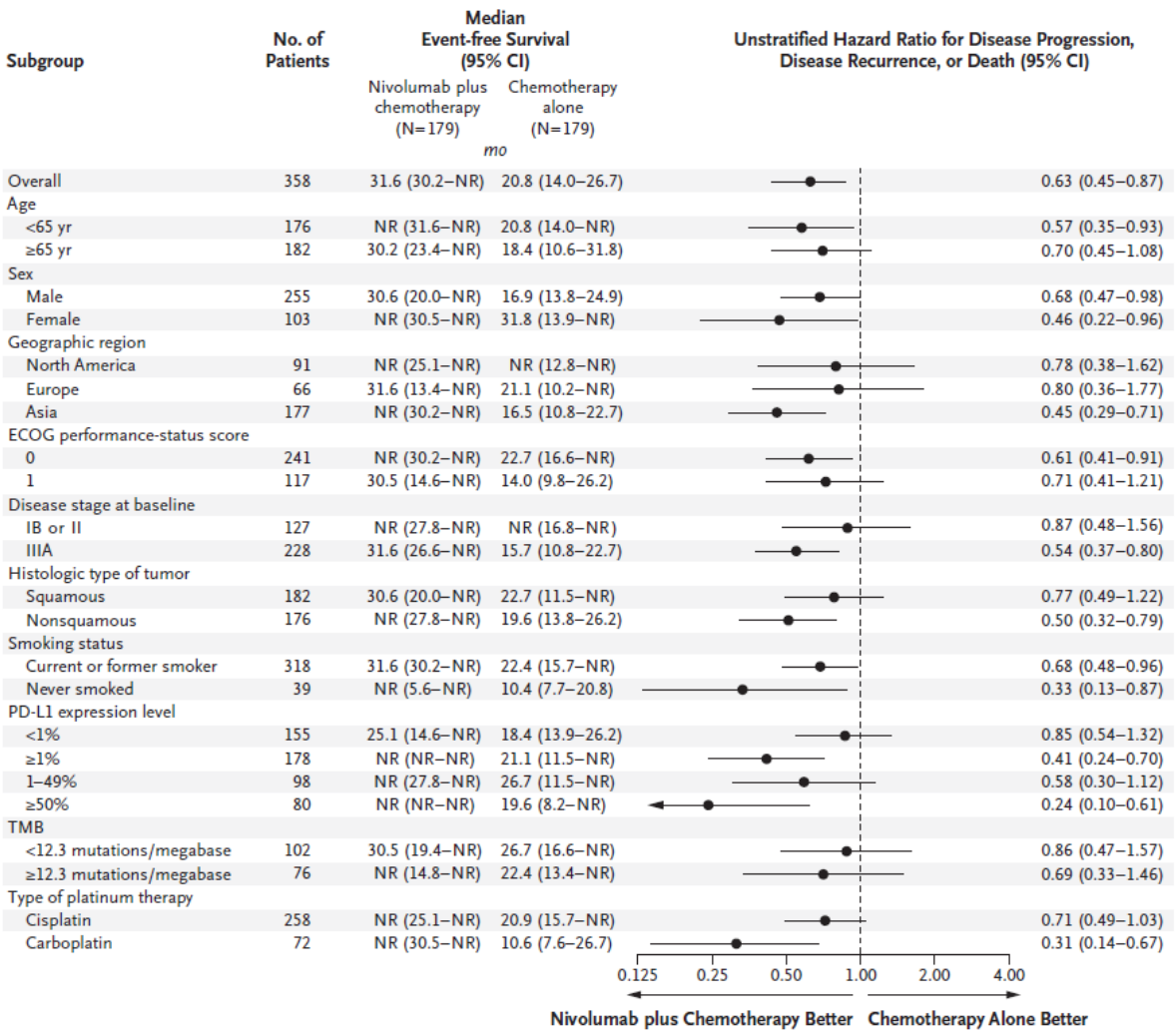
BIPR = blinded independent pathologic review; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; PD-L1 = programmed death-ligand 1; TMB = tumour mutational burden.

Note: *Chemotherapy* refers to platinum doublet chemotherapy.

Source: Forde et al. (2022)[3]

Event-free survival across most subgroups in the subgroup analyses favoured nivolumab + PDC (Figure 15).[3] However, subgroups were underpowered and an insufficient number of events have occurred to demonstrate statistical significance across all subgroups. The pCR benefit seen across all subgroups, as described above, is anticipated to result in longer term EFS benefit once more events have occurred with longer follow-up.

Figure 15. CheckMate-816: event-free survival according to BICR by subgroup



BICR = blinded independent central review; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; NR = not reached; PD-L1 = programmed death-ligand 1; TMB = tumour mutational burden.

Note: *Chemotherapy* refers to platinum doublet chemotherapy.

Source: Forde et al. (2022)[3]

Although CheckMate 816 was not powered for subgroup analyses, nivolumab + PDC was favoured versus PDC in a descriptive, exploratory subgroup analysis of EFS and pCR across disease stages. While a greater EFS and pCR benefit was observed in patients with stage IIIA disease, a numerical benefit was observed in patients with stage IB-II (AJCC/UICC seventh TNM edition). Clinical experts highlighted the considerable benefit seen in all stages (including IB-II), which they noted is as substantial as that of other treatments (Appendix N). Further, they considered that from a patient perspective, nivolumab + PDC would be beneficial, particularly with only 3 cycles of treatment.

Nivolumab + PDC was also favoured versus PDC regardless of PD-L1 expression in the descriptive, exploratory subgroup analysis. While a greater EFS and pCR benefit was observed in PD-L1 ≥ 1%, a numerical benefit was also observed in PD-L1< 1%; clinical experts confirmed this and reiterated the fact that the CheckMate-816 trial is not powered to make conclusions based on these subgroup data (Appendix N).

B.2.8Meta-analysis

Only 1 phase 3 RCT (CheckMate-816) was identified via the SLR that has investigated the efficacy and safety of nivolumab + PDC for the neoadjuvant treatment of resectable NSCLC. As such, a meta-analysis could not be conducted, as this would require 2 or more studies that contained the intervention of interest.

B.2.9Indirect and mixed treatment comparisons

In the absence of head-to-head trial evidence of nivolumab + PDC versus all UK relevant comparators of interest, an indirect treatment comparison was necessary to enable a comparison for this submission. A summary of the performed analysis is presented in this section with more details presented in Appendix M.

B.2.9.1 Evidence base

Treatment comparisons were informed by a network meta-analysis (NMA) based on data extracted from a previously conducted SLR of RCTs. The evidence base identified included both RCTs where potentially resectable patients were randomised before surgery (mainly neoadjuvant RCTs) and RCTs where completely resected patients were randomised after surgery (mainly adjuvant RCTs). It is also worth noting that completely resected patients are a subset of all potentially resectable patients, as not all surgeries are successful in achieving negative margins. Performing robust indirect treatment comparisons when time of randomisation and patient populations between different RCTs differ substantially is challenging and may lead to biased results. For this reason, the base-case NMA focused on evidence from RCTs conducted among potentially resectable patients, to be aligned with patients eligible for nivolumab + PDC. In addition, in order to reduce heterogeneity in the chemotherapy regimens considered in RCTs, only 3rd generation chemotherapy regimens were included in the base-case analysis, as they were deemed the most relevant to the decision problem. These inclusion criteria were relaxed in sensitivity analysis, where RCTs enrolling completely resectable patients and evaluating 2nd generation chemotherapies were admitted into the NMA network of evidence. Extending the analysis to RCTs enrolling completely resected patients after surgery enabled the comparison between nivolumab + PDC and adjuvant PDC for all endpoints of interest, which is part of the scope of this appraisal.

The comparators of interest included in this analysis reflect the comparators considered in the decision problem addressed in this submission and presented in Table 18. Please note the terminology used for the different treatment options in the NMA. It should be noted that the analysis was conducted from a broader perspective than required for this appraisal and thus also included neoadjuvant chemotherapy (3rd generation PDC).

Table 18. Comparators included in the network meta-analysis

Comparator	Abbreviation
Neoadjuvant nivolumab in combination with a 3rd generation platinum doublet chemotherapy	neoNIVO-CT
Neoadjuvant chemoradiotherapy (3rd generation platinum doublet chemotherapy)	neoCRT
Adjuvant chemotherapy (3rd generation platinum doublet chemotherapy)	adjCT
Surgery alone	S

Note: comparator abbreviations used in this section correspond to full terms in the remainder of the submission; abbreviations are used here to align with data figures.

The primary outcomes of interest were EFS and OS. Secondary outcomes of interest were time to locoregional recurrence (TTLR), TTDM, pCR and safety endpoints. Within the NMA section, TTDM refers to time to distant metastases only, as opposed to the CM816 trial definition of time to death or distant metastases. This is because deaths have been censored to allow for accurate transition probabilities to be calculated for the economic model. For EFS, the following author-reported endpoints were included: DFS, relapse-free survival, and progression-free survival (PFS).

B.2.9.2 Network meta-analysis method assessment

Event-free survival, OS, TTLR and TTDM were analysed as time-to-event data, using HRs while pCR was reported as odds ratios. Where relevant, Kaplan-Meier curves were digitised and individual patient-level data were generated. Proportional hazards (PHs) assumptions were evaluated by reconstructing Kaplan-Meier curves and examining log-cumulative hazard plots, Schoenfeld residual plots, and Grambsch-Therneau tests. The NMA conduct and reporting were in alignment with good practice guidelines published by NICE Decision Support Unit (DSU) Technical Support Documentation and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance. Random and fixed effect models were implemented for both time-to-event and binary endpoints. All analyses were performed using R version 4.0.2 and WinBUGS version 1.4.3.

Both random- and fixed- effects models were developed. However, the sparse evidence base available to inform the network did not provide sufficient evidence to calculate the between-study standard deviation; therefore, the fixed effect results were preferred.

B.2.9.3 Summary of results

Of the 58 RCTs identified for inclusion in the SLR (see Appendix D), [redacted] were eligible for inclusion in the NMA. Among these, [redacted] were included in the base case as they were conducted among patients deemed candidates for surgery and evaluated 3rd generation chemotherapies.[3,70,86-91] In addition, [redacted] were included in the sensitivity analyses expanding to [redacted],[92-96] [redacted] were included in the sensitivity analyses expanding to [redacted].[97-100] A total of [redacted] met the NMA PICOS (patients, intervention, comparator, outcomes, and study design) criteria but were not included in any analyses; these RCTs included completely resected patients and

investigated a 2nd generation chemotherapy or tegafur and uracil (UFT, a therapy relevant only in Japan).[101-104]

B.2.9.3.1 Disposition and baseline/demographic characteristics

Among the [redacted] included in the base-case NMA, median age ranged from [redacted]. There was some heterogeneity in terms of: [redacted]).

B.2.9.3.2 Primary endpoint results

The network of evidence describing the totality of the evidence included in the base-case analysis for EFS and OS is presented in Figure 16; results for EFS and OS are presented in Figure 17 and Figure 18, respectively. Given that the treatment effect in the model was applied via the common node in the network (neoCT), the tables present results versus neoCT to be consistent with values used in the economic model. The NMA results suggest that neoNIVO-CT is associated with improved EFS and OS relative to neoCT, neoCRT, S, and adjCT. Results of the sensitivity analyses were generally in line with the base-case results.

Figure 16. Network of evidence for event-free survival and overall survival

adjCT = adjuvant chemotherapy; neoCRT = neoadjuvant chemoradiotherapy; neoCT = neoadjuvant chemotherapy; neoNIVO-CT = neoadjuvant nivolumab-chemotherapy; S = surgery.

Sources: Forde et al. (2022)[3], Felip et al. (2010)[70], Girard et al. (2010)[86], Katakami et al. (2012)[87], Pless et al. (2015)[88], Li et al. (2009)[89], Pisters et al. (2010)[90], Scagliotti et al. (2012)[91]

Figure 17. Event-free survival hazard ratio estimates of all relevant comparators vs. neoadjuvant chemotherapy (fixed effect estimates)

CrI = credible interval; HR = hazard ratio; neoNIVO-CT = neoadjuvant nivolumab-chemotherapy.

Figure 18. Overall survival hazard ratio estimates for all relevant comparators vs. neoadjuvant chemotherapy (fixed effect estimates)

CrI = credible interval; HR = hazard ratio; neoNIVO-CT = neoadjuvant nivolumab-chemotherapy.

B.2.9.3.3 Secondary endpoint results

(Figure 19). The network of evidence for pCR does not include S and adjCT, given that pCR is an endpoint specific to neoadjuvant treatments. Evidence with respect to TTLR (Figure 20) Evidence with respect to TTDM (Figure 21) shows a

Figure 19. Pathologic complete response odds ratio estimates for all relevant comparators vs. neoadjuvant chemotherapy (fixed effect estimates)

CrI = credible interval; neoNIVO-CT = neoadjuvant nivolumab-chemotherapy; OR = odds ratio.

Figure 20. Time to locoregional recurrence hazard ratio estimates for all relevant comparators vs. neoadjuvant chemotherapy (fixed effect estimates)

CrI = credible interval; neoNIVO-CT = neoadjuvant nivolumab-chemotherapy; OR = odds ratio.

Figure 21. Time to distant metastases hazard ratio estimates for all relevant comparators vs. neoadjuvant chemotherapy (fixed effect estimates)

CrI = credible interval; HR = hazard ratio; neoNIVO-CT = neoadjuvant nivolumab-chemotherapy.

Scenario analysis results

As shown in the results above, the Figure 22 shows the evidence network for TTLR and Figure 23 shows the results of the analysis, while Figure 24 and Figure 25 show the evidence network and results for TTDM.

Figure 22. Network diagram for TTLR for Scenario Analysis: Potentially resectable & completely resected, 3rd generation chemotherapies

adjCT = adjuvant chemotherapy; neoCRT = neoadjuvant chemoradiotherapy; neoCT = neoadjuvant chemotherapy; neoNIVO-CT = neoadjuvant nivolumab-chemotherapy; S = surgery; TTLR = time to locoregional recurrence.

Note: The reference treatment is neoadjuvant chemotherapy.

Sources: Forde et al. (2022)[3], Girard et al. (2010)[86], Katakami et al. (2012)[87], Pless et al. (2015)[88] Pisters et al. (2010)[90], Douillard et al. (2006)[98], Ou et al. (2010)[99]

Figure 23. Network meta-analysis output: vs. reference treatment (CT) for TTLR for Scenario Analysis: Potentially resectable & completely resected, 3rd generation chemotherapies (fixed effect model)

adjCT = adjuvant chemotherapy; CrI = credible interval; HR = hazard ratio; neoCRT = neoadjuvant chemoradiotherapy; neoCT = neoadjuvant chemotherapy; neoNIVO-CT = neoadjuvant nivolumab-chemotherapy; S = surgery; TTLR = time to locoregional recurrence.

Figure 24. Network diagram for TTDM for Scenario Analysis: Potentially resectable & completely resected, 3rd generation chemotherapies

adjCT = adjuvant chemotherapy; neoCRT = neoadjuvant chemoradiotherapy; neoCT = neoadjuvant chemotherapy; neoNIVO-CT = neoadjuvant nivolumab-chemotherapy; S = surgery; TTDM = time to death or distant metastases.

Note: The reference treatment is neoCT.

Sources: Forde et al. (2022)[3], Girard et al. (2010)[86], Katakami et al. (2012)[87], Pisters et al. (2010)[90], Douillard et al. (2006)[98], Ou et al. (2010)[99]

Figure 25. Network meta-analysis output: vs. reference treatment (neoCT) for TTDM for Scenario Analysis: Potentially resectable & completely resected, 3rd generation chemotherapies (fixed effect model)

adjCT = adjuvant chemotherapy; CrI = credible interval; HR = hazard ratio; neoCRT = neoadjuvant chemoradiotherapy; neoCT = neoadjuvant chemotherapy; neoNIVO-CT = neoadjuvant nivolumab-chemotherapy; S = surgery; TTDM = time to death or distant metastases.

Adverse events

Quantitative synthesis of safety data was not conducted, as it was considered inappropriate given the sparseness of the data and the differences in treatment regimens across the base-case studies. Only 3 studies reported grade 3 and 4 AEs; the proportion

of patients experiencing AEs ranged from 11% (S, Scagliotti et al. (2012)[91]) to 60% (neoCT, Pless et al. (2015)[88]).

B.2.9.4 Uncertainties in the indirect and mixed treatment comparisons

This quantitative analysis produced estimates of comparative efficacy of neoNIVO-CT relative to a broad range of therapies used for individuals with potentially resectable NSCLC.

Key strengths of the NMA included the use of an evidence base informed by a comprehensive SLR, a homogeneous base-case analysis (restricted to 3rd generation chemotherapies and potentially resectable patients) that was validated with extensive sensitivity analyses, and alignment with best practice guidance for the conduct of systematic reviews and network meta-analyses. Several limitations were apparent, however, mainly due to the limited body of evidence in resectable NSCLC. In the base-case network, connections were informed by at most 3 studies. Of the studies included, some were dated, were stopped early and were underpowered to detect a statistically significant benefit, had relatively short follow-up, and were somewhat heterogeneous in terms of stage (including the staging version) and outcome definitions. Across all analyses, the sparseness of the evidence also led to insufficient data to estimate the between-study standard deviation with enough precision, precluding the consideration of the random effects model.

Despite these limitations, the available evidence suggests that neoNIVO-CT confers a strong added benefit in terms of survival-based endpoints and pathological complete response versus neoadjuvant therapies and surgery alone. Analyses conducted in this NMA suggest that neoNIVO-CT lowers patients' risk of experiencing disease recurrence/progression (as per CM816 EFS definition) and death relative to neoCT +/- radiotherapy, surgery alone, or adjCT. However, due to the sparseness and limited sample size within the evidence base, some comparisons were associated with considerable uncertainty, leading to non-statistically significant estimates of relative effect in some cases. NeoNIVO-CT was also associated with statistically significant higher odds of achieving pCR relative to neoCT +/- radiotherapy.

There is also evidence of benefit in terms of progression-based endpoints, such as time to locoregional recurrence and distant metastases. For TTDM, the findings consistently demonstrated a trend suggesting that neoNIVO-CT may be associated with approximately half the risk of distant metastasis relative to all comparators in the base case (neoCT, neoCRT, surgery alone; with HRs ranging from [redacted] to [redacted]), although estimates of relative effect were not statistically significant for the comparison with neoCRT. This finding is consistent with the hypothesis that utilising immunotherapy in the neoadjuvant setting is the earliest opportunity to treat micro-metastases. Similar trends were observed relating to TTLR, except for a change in the direction of association for TTLR between neoNIVO-CT and neoCRT (in favour of neoCRT), although it did not reach statistical significance.

The results from the TTDM and TTLR analyses for neoCRT align with the expectations that adding radiotherapy to neoCT may reduce the risk of locoregional recurrence relative to neoCT alone, via its localized delivery, but does not reduce the risk of distant metastases, as has been seen in other indications. Conversely, neoNIVO-CT conferred a similar magnitude of effect over neoCT for both TTDM and TTLRR. By extension, the magnitude of effect between neoNIVO-CT relative to neoCRT is stronger for TTDM than for TTLRR, although in the current analysis, none of the estimates were statistically significant due to small sample sizes and studies that were not powered to detect differences in these endpoints.

In terms of AEs, no quantitative synthesis was conducted due to the paucity of data, however, the addition of NIVO to neoCT backbone in Forde 2022 did not lead to an increase in grade 3-4 treatment-related AEs.

B.2.10 Adverse reactions

Overall, nivolumab + PDC as neoadjuvant therapy was well tolerated, having a similar incidence of treatment-related AEs, surgery-related AEs, AEs leading to discontinuation, and serious AEs versus PDC. No new safety signals were observed.[3]

Adverse events of any cause occurred in 92.6% of the patients in the nivolumab + PDC group and in 97.2% of those in the PDC group.[3] The incidence of grade 3 or 4 treatment-related AEs was 33.5% and 36.9% in the respective groups (Table 19).[3]

Treatment-related AEs of any grade leading to discontinuation of treatment occurred in 10.2% of the patients in the nivolumab + PDC group and in 9.7% of those in the PDC alone group.[3]

Table 19. CheckMate-816: adverse events

	NIVO+PDC (n = 176)		PDC (n = 176)	
	Any grade	**Grade 3 or 4**	**Any grade**	**Grade 3 or 4**
AEs of any cause, n (%)[a]				
All	163 (92.6)	72 (40.9)	171 (97.2)	77 (43.8)
Leading to discontinuation of treatment	18 (10.2)	10 (5.7)	20 (11.4)	7 (4.0)
Serious	30 (17.0)	19 (10.8)	24 (13.6)	17 (9.7)
Treatment-related AEs, n (%)[a]				
All	145 (82.4)	59 (33.5)	156 (88.6)	65 (36.9)
Leading to discontinuation of treatment	18 (10.2)	10 (5.7)	17 (9.7)	6 (3.4)
Serious	21 (11.9)	15 (8.5)	18 (10.2)	14 (8.0)
Death[b]	0		3 (1.7)	
Surgery-related AEs, n/total n (%)[c]	62/149 (41.6)	17/149 (11.4)	63/135 (46.7)	20/135 (14.8)

AE = adverse event; NIVO = nivolumab; PDC = platinum doublet chemotherapy.

[a] Included are events reported between the first neoadjuvant dose and 30 days after the last neoadjuvant dose.

[b] Treatment-related deaths in the PDC-alone group were due to pancytopenia, diarrhoea, and acute kidney injury (all in 1 patient); enterocolitis; and pneumonia.

[c] The denominators are based on patients who underwent definitive surgery. Included are events reported up to 90 days after definitive surgery. Grade 5 surgery-related AEs (defined as events that led to death ≤ 24 hours after the onset of an AE) were reported in 2 patients in the nivolumab + PDC group and were deemed by the investigator to be unrelated to the trial drugs (1 each due to pulmonary embolism and aortic rupture).

Source: Forde et al. (2022)[3]

The most common grade 3 or 4 treatment-related AEs across both treatment arms were neutropenia (8.5% with nivolumab + PDC and 11.9% with PDC alone) and decreased neutrophil count (7.4% and 10.8%, respectively) (Table 20).[3]

Table 20. CheckMate-816: most frequent treatment-related adverse events (≥ 15% of patients in any treatment group) and surgery-related adverse events (≥ 5% of patients in any treatment group)

	No. of patients (%)			
	NIVO+PDC (n = 176)		PDC (n = 176)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Treatment-related AEs[a]				
All	145 (82.4)	59 (33.5)	156 (88.6)	65 (36.9)
Nausea	58 (33.0)	1 (0.6)	73 (41.5)	1 (0.6)
Anaemia	42 (23.9)	5 (2.8)	40 (22.7)	6 (3.4)
Constipation	37 (21.0)	0	36 (20.5)	2 (1.1)
Decreased appetite	29 (16.5)	2 (1.1)	38 (21.6)	4 (2.3)
Neutropenia	28 (15.9)	15 (8.5)	29 (16.5)	21 (11.9)
Decreased neutrophil count	26 (14.8)	13 (7.4)	37 (21.0)	19 (10.8)
Surgery-related AEs[b,c]				
All	62 (41.6)	17 (11.4)	63 (46.7)	20 (14.8)
Anaemia	18 (12.1)	3 (2.0)	17 (12.6)	3 (2.2)
Pain	11 (7.4)	1 (0.7)	21 (15.6)	0
Wound complication	11 (7.4)	1 (0.7)	8 (5.9)	0
Procedural pain	9 (6.0)	0	6 (4.4)	0
Pneumonia	8 (5.4)	3 (2.0)	8 (5.9)	4 (3.0)

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; NIVO = nivolumab; PDC = platinum doublet chemotherapy.

[a] Included events reported between the first neoadjuvant dose and 30 days after the last neoadjuvant dose as per CTCAE Version 4.0; Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0.

[b] Includes events reported up to 90 days after definitive surgery. CTCAE Version 4.0; MedDRA Version 23.0.

[c] Denominator based on patients with definitive surgery (n = 149 in the nivolumab + PDC group; n = 135 in the PDC group).

Source: Forde et al. (2022)[3]

Overall, the incidence of immune-mediated AEs was low, and events were mainly of grade 1 or 2. The most common immune-mediated AE of any grade with nivolumab + PDC was rash (in 8.5% of the patients); 2 patients (1.1%) had grade 1 or 2 pneumonitis. Three treatment-related deaths were noted, all in the PDC alone group.[3]

Adverse events of any grade led to delayed surgery in 3.4% of the patients receiving nivolumab + PDC and in 5.1% of those receiving PDC alone and led to cancellations in 1.1% and 0.6%, respectively. Adverse events of any grade that were identified as surgical complications occurred in 41.6% of the patients in the nivolumab + PDC group and in 46.7% of those in the PDC alone group; grade 3 or 4 surgery-related AEs occurred in 11.4% and 14.8% of the patients in the respective groups. Grade 5 surgery-related AEs were reported in 2 patients treated with nivolumab + PDC and were deemed to be unrelated to the trial drugs by the investigator (1 each due to pulmonary embolism and aortic rupture).[3]

Table 21. CheckMate-816: adverse events leading to surgery delay and/or cancellation

	No. of patients (%)			
	NIVO+PDC (n = 176)		PDC (n = 176)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
All AEs leading to surgery delay	6 (3.4)	2 (1.1)	9 (5.1)	4 (2.3)
Bronchitis	1 (0.6)	0	0	0
Pneumonia	1 (0.6)	1 (0.6)	0	0
Herpes zoster	0	0	1 (0.6)	0
Increased lipase	1 (0.6)	0	0	0
Lung diffusion test	0	0	1 (0.6)	0
Decreased neutrophil count	0	0	1 (0.6)	0
Decreased white blood cell count	0	0	1 (0.6)	0
Pneumonitis	1 (0.6)	0	0	0
Pulmonary embolism	0	0	2 (1.1)	1 (0.6)
Maculopapular rash	1 (0.6)	0	0	0
Embolism	1 (0.6)	1 (0.6)	0	0
Deep vein thrombosis	0	0	1 (0.6)	0
Ventricular thrombosis	0	0	1 (0.6)	1 (0.6)
Myocardial infarction	0	0	1 (0.6)	1 (0.6)
Stress cardiomyopathy	0	0	1 (0.6)	1 (0.6)
Colitis	0	0	1 (0.6)	1 (0.6)
Ataxia	0	0	1 (0.6)	0
All AEs leading to surgery cancellation	2 (1.1)	0	1 (0.6)	0
Ischaemic stroke	1 (0.6)	0	0	0
Tuberculosis	1 (0.6)	0	0	0
Increased blood creatinine	0	0	1 (0.6)	0

AE = adverse event; NIVO = nivolumab; PDC = platinum doublet chemotherapy.

Source: Forde et al. (2022)[3]

B.2.11 Supporting studies

The following studies provide evidence for the efficacy of nivolumab in the neoadjuvant setting and support the CheckMate-816 trial.

B.2.11.1 Study CA209-159

The phase 1 study, CA209-159 (NCT02259621), investigated nivolumab monotherapy and nivolumab + ipilimumab as neoadjuvant therapy in patients with resectable NSCLC.[105] Early results indicated that nivolumab as neoadjuvant therapy is generally well tolerated in patients with newly diagnosed resectable stage I–IIIA disease and does not impede feasibility of surgery. Nivolumab neoadjuvant therapy induced MPR in 45% of patients.

Updated 5-year outcomes have recently been published.[106] At a median follow-up of 63 months, 3-, 4- and 5-year survival rates were 85%, 80%, and 80% respectively and recurrence-free survival rates at 3-, 4- and 5-years were 65%, 60%, and 60% respectively. Furthermore, at 5-year follow-up, 8 of 9 (89%) patients with a MPR were alive and no cancer deaths had occurred. Amongst patients with a MPR (n = 9), 1 had a cancer recurrence in the mediastinum treated successfully with definitive chemoradiotherapy. Both patients with a pCR were alive and without recurrence.

B.2.11.2 NEOSTAR

NEOSTAR (NCT03158129) was a phase 2 randomised trial comparing neoadjuvant therapy consisting of nivolumab, nivolumab + ipilimumab, or nivolumab + PDC, followed by surgery in patients with operable NSCLC (stage IA–IIIA, AJCC/UICC seventh edition).[78] The arms investigating nivolumab alone and nivolumab + ipilimumab are not relevant to this submission and are not described here. In the nivolumab + PDC arm, nivolumab was given at a dosage of 3 mg/kg on days 1, 15, and 29 or 360 mg intravenously + PDC (cisplatin on days 1, 22, and 43 with docetaxel or pemetrexed on days 1, 22, and 43, all intravenously).[107]

The results of the NEOSTAR study support the results from CheckMate-816. In the nivolumab + PDC group (n = 22), 86% of patients completed the planned neoadjuvant therapy; all of these patients underwent curative surgery, with 91% achieving complete resection. In the overall population, 32% of patients achieved an MPR, 4 patients (18%) had a pCR, and the objective response rate was 41%, including 9 partial responses. No new safety concerns were noted.[78]

B.2.11.3 NADIM

The phase 2 NADIM trial (CA209-547, NCT03081689) provides supporting evidence relating to the feasibility and safety profile of neoadjuvant nivolumab + PDC, and the pCR rates achieved with the treatment in patients with newly diagnosed resectable stage IIIA disease.[76]

All 46 patients completed the planned course of neoadjuvant therapy and 41 (89%) proceeded to undergo surgery, all of whom achieved complete resection, while pathological downstaging was observed in 37 (90%) of patients.[108] There was no operative mortality at either 30 or 90 days. Of patients who underwent surgery, 37 (90%) received adjuvant nivolumab for a median of 10.8 months,[76] and 12 (29%) experienced postoperative complications.

A total of 34 (83%) patients of those who underwent surgery achieved at least an MPR, including 26 (63%) who had a pCR. 88.4% of patients with an MPR were progression-free at 2 years, versus 77.1% of the total modified intention-to-treat (ITT) population. Similarly, of the 26 patients (63%) who achieved a pCR, 96.2% were progression free at 2 years, a difference that was statistically significant versus patients with a MPR (P = 0.041) or an incomplete pathological response (P = 0.0023).[76] These data thus support the expected survival benefit of achieving pCR.

An updated analysis with a median follow-up time of 37.9 months demonstrated that PFS at 36 and 42 months in the ITT population were 69.6% (95% CI, 54.1-80.7) in both cases. Similarly, PFS at 36 and 42 months in the per-protocol population were 81.1% (95% CI, 64.4-90.5) in both cases. The percentage of patients who were alive at 36 and 42 months in the modified ITT population were 81.86% (95% CI, 66.8-90.6) and 78.94% (95% CI, 63.1-88.6), respectively.[109]

Neoadjuvant therapy was generally well tolerated. Approximately a third (30%) of patients experienced ≥ grade 3 AEs, with the most frequently reported being increased lipase (7%) and febrile neutropenia (7%). None of the AEs experienced during neoadjuvant treatment led to treatment discontinuation, dose reduction, surgery delay or death. The most frequently reported AEs of any grade (> 30% of patients) were asthenia or fatigue (24 patients), alopecia (17 patients) and neurotoxicity (15 patients).[76]

B.2.11.4 NADIM II

NADIM II (NCT03838159) is an open-label, randomised, two-arm, phase II, multicentre clinical trial conducted in 87 patients with resectable locally advanced disease, and supports the superiority of neoadjuvant nivolumab + PDC versus PDC in terms of pCR, as well as the feasibility of surgery, with a moderate increase in grade 3-4 toxicity.[110] Nivolumab + PDC in the neoadjuvant setting significantly increased the pCR rate versus PDC (36.2% vs. 6.8%; relative risk 5.25 [99% CI, 1.32-20.87]; *P* = 0.0071). Nivolumab + PDC also improved MPR rates versus PDC (52 % vs. 14 %), as well as objective response rate (74 % vs. 48%). Definitive surgery occurred for 91% of patients treated with nivolumab + PDC and 69% with PDC; surgery was cancelled rarely due to AEs (1 patient/experimental arm) and due to disease progression in 1 and 4 patients in the experimental and control arm respectively. Grade 3-4-related AEs were reported in 24 % vs. 10% in the nivolumab + PDC versus PDC arms, respectively. In the ITT experimental arm, patients with pCR had higher PD-L1 Tumour Proportion Score (TPS) (median 70%, interquartile range 5%-90%) versus non-responders (median 0%, interquartile range 0%-37.5%, *P* = 0.0035). Area under the curve to predict pCR was 0.734 (95% CI, 0.59-0.88; *P* = 0.005). The pCR rate rose across increasing categories of PD-L1 TPS (< 1% 14.3%; 1%-49% 41.7%; ≥ 50% 61.1%; *P* = 0.008).[110]

A further analysis with a median follow-up time was 21.9 months (95% CI, 18.7-23.3). showed that PFS at 24 months was 67.3% (95% CI, 55.5-81.6) for patients treated with nivolumab + PDC versus 52.6% (95% CI, 36.8- 75.2) for patients treated with PDC (HR, 0.56; 95% CI, 0.28-1.15; *P* = 0.117). Overall survival at 24 months was 85.3% (95% CI, 75.7-96.1) with nivolumab + PDC versus 64.8% (95% CI, 47.4-86.4) with PDC (HR, 0.37; 95% CI, 0.14-0.93; *P* = 0.003). In the experimental arm, PD-L1 expression (≥ 1%) significantly identified patients with improve PFS (HR, 0.26; 95% CI, 0.08-0.77; *P* = 0.015). Pathological complete response rate was 36.2% in the experimental arm versus 6.8% in the control arm (*P* = 0.007). None of the patients showing a pCR has progressed or deceased (*P* log-rank < 0.001 and *P* log-rank = 0.013 for PFS and OS, respectively).[111]

B.2.11.5 NCT03366766

NCT03366766 was an investigator-initiated trial including 13 patients with newly diagnosed locally advanced NSCLC with a potentially resectable tumour.[112] Pre-surgical grade 3 toxicity occurred in 2 of 13 patients treated with nivolumab + PDC, 1 of whom was changed to carboplatin for courses 2 and 3. Grade 3 toxicities were neutropenia (2/13), anaemia (1/13), and renal (1/13). One patient developed hypothyroidism 4 months after surgery. One patient died 6 weeks after surgery from complications unrelated to study drugs. The primary endpoint was met: 11/13 (85%) patients had at least an MPR with 6/13 (46%) patients and 5/13 (38%) patients having an MPR and pCR respectively. Radiologic response rate was 46% (partial response 5, complete response 1). Patients with either PD-L1-positive or PD-L1-negative status had MPRs. No recurrences were seen within the median follow-up of 10 months.[112]

B.2.12 Ongoing Bristol Myers Squibb nivolumab randomised controlled trials

CheckMate-816 is ongoing. Results from [redacted] are expected to be available within the timelines of this appraisal and the [redacted] will be provided once available. However, the timeframe of the appraisal will not allow [redacted]

Further support for nivolumab + PDC as neoadjuvant therapy for resectable NSCLC is likely to come from the ongoing phase 3 trial CheckMate-77T, which is being performed in sites in North America, South America, Europe, Asia, and Australia.[113] This trial is a randomised and double-blinded, whereby patients are randomly assigned to receive either:

- Neoadjuvant nivolumab + PDC followed by surgery followed by adjuvant nivolumab
- Placebo + PDC followed by surgery followed by placebo

The trial involves newly diagnosed patients with resectable stage IIA–IIIB (T3N2 only, eighth edition of AJCC/UICC) NSCLC and having an ECOG PS of 0-1. Patients with EGFR/ALK mutations, brain metastasis, previous systemic anticancer treatment or radiotherapy, and autoimmune disease are excluded. The trial aims to enrol approximately 452 patients. The primary endpoint is EFS, assessed by BICR. Secondary endpoints include OS, pCR, and MPR assessed by BIPR, as well as safety and tolerability.

Nivolumab is also being investigated in the ANVIL trial, a randomised, open-label, phase 3 study of nivolumab after surgical resection in patients with stage IB-IIIA NSCLC being conducted by the National Cancer Institute.[114,115] ANVIL is being performed in over 600 sites in the United States (US), and patients are randomly assigned to either nivolumab or SOC observation and stratified by stage, histology, prior adjuvant treatment, and PD-L1 status (≥ 1% or < 1%). Adjuvant chemotherapy and/or radiotherapy is allowed but not required. The trial involves patients who have undergone complete surgical resection of their tumour (stage IB [≥ 4 cm], II, or IIIA NSCLC [AJCC/UICC seventh edition]) and have had negative surgical margins. The trial aims to enrol approximately 900 patients; DFS and OS are primary endpoints, and the incidence of AEs is a secondary endpoint.[114,115]

B.2.13 Interpretation of clinical effectiveness and safety evidence for nivolumab + PDC in CheckMate-816

Nivolumab is an immuno-oncology agent that acts to restore the body's natural antitumour response by inhibiting the suppression that the tumour exerts on antitumour immune responses. Used before surgery, nivolumab-based regimens are expected to help prime the body's immune response not only to target primary tumour cell activity before surgery and promote responses against micro-metastases already present but to kill tumour cells released during surgery, limiting recurrence.[9]

CheckMate-816 is the first phase 3 study to demonstrate significantly improved EFS and pCR for an immuno-oncology–based combination in the neoadjuvant setting of resectable stage IB-IIIA NSCLC.[3] Further, the efficacy of the regimen is achieved with only 3 cycles of treatment, which is expected to reduce burden on patients, limit the occurrence of treatment-

related AEs, improve adherence, and reduce costs versus other immuno-oncology regimens which often require up to 2 years of therapy in later lines.

Feasibility of surgery was maintained with nivolumab + PDC versus neoadjuvant PDC alone: numerically more patients underwent surgery, had a less invasive surgery and had a shorter duration of surgery with similar length of hospital stay.[3]

Nivolumab + PDC demonstrated a significantly longer EFS versus PDC alone (HR, 0.63; 97.38% CI, 0.43-0.91).[3] Significantly more patients treated with nivolumab + PDC had a pCR versus those treated with PDC alone; longer EFS was observed in patients who achieved pCR versus those who did not across both arms of CheckMate-816. Therefore, the higher rates of pCR for patients treated with nivolumab + PDC may result in increased EFS benefit with longer follow-up.[3] Of note, as described in Section B.1.3.6.5, analyses using data from clinical trials of neoadjuvant treatment in patients with stage IB-IIIA NSCLC have demonstrated an association between pCR and both improved EFS and improved OS, which is consistent across subgroups.[72-75]

Further, a prespecified interim analysis for OS in CheckMate-816 showed a promising early trend in OS. Although these OS data are not yet mature, they suggest, alongside the significant comparative difference in pCR and EFS for nivolumab + PDC versus PDC alone and the demonstrated association between pCR and OS and between EFS and OS, that a significant difference in OS may be observed once more events have occurred.

The safety profile of 3 cycles of nivolumab + PDC was consistent with safety profiles in other disease settings and tumours. Furthermore, nivolumab + PDC did not increase postsurgical complications.[3]

B.3 Cost-effectiveness

- A de novo four-state semi-Markov model was developed to assess the cost-effectiveness of nivolumab with chemotherapy for the neoadjuvant treatment of resectable NSCLC compared with current SOC in the UK. The modelled health states were Event-Free (EF), Locoregional Recurrence (LR), Distant Metastasis (DM), and Dead.
- The modelled population and key clinical inputs were based on the CheckMate-816 trial. Comparators considered were, neoadjuvant chemoradiation (CRT), surgery alone, and adjuvant PDC. As CheckMate-816 did not include individual treatment arms for neoadjuvant CRT, adjuvant PDC, or surgery alone, efficacy estimates for these treatments are based on an indirect treatment comparison conducted using data available in the published literature.
- The model considered costs related to treatment acquisition and administration, surgery, AEs, terminal care, ongoing medical resource use (MPR) (e.g., tests, scheduled medical specialist visits).
- Health-state utility values were based on CheckMate-816. The model also considers the disutility of grade 3 and 4 AEs.
- The results of the cost-effectiveness analysis showed improved survival for patients treated with nivolumab + PDC, versus all comparators. This resulted in an increase of [redacted], [redacted] and [redacted] quality-adjusted life-years (QALYs) versus surgery alone, neoadjuvant CRT, and adjuvant PDC respectively. Based on the current simple patient access schemes for nivolumab, approved by the Department of Health, this resulted in an incremental cost-effectiveness ratio (ICER) of £2,685 per QALY versus surgery alone and being dominant versus both neoadjuvant CRT and adjuvant PDC. The results were robust for all scenario analyses conducted with only one extreme scenario resulting in an ICER above £20,000 per QALY.
- In conclusion, nivolumab + PDC offers an innovative, clinically effective treatment and cost-effective option in resectable non-metastatic NSCLC.

B.3.1 Published cost-effectiveness studies in non-metastatic NSCLC

In the targeted review for health economic models in resectable non-metastatic NSCLC, only 2 studies were identified to potentially inform the model design (see Appendix G). One study sought to investigate the cost-effectiveness of adjuvant vinorelbine plus cisplatin versus observation only,[116] and the other sought to investigate the relative cost-effectiveness of PDC options in the neoadjuvant setting.[117] Both studies were based directly on their respective trials, and neither study presented an explicit description of their model structure. As such, they were not found to be useful for aiding in the development of a cost-effectiveness analysis for nivolumab + PDC in non-metastatic NSCLC. In addition, 2 other sources were identified through a review of the health authority bodies of Canada and the UK; both studies focused on adjuvant osimertinib versus active monitoring in EGFR mutation-positive NSCLC after complete tumour resection (Table 22).

Table 22. Summary list of published cost-effectiveness studies

Author, year, country	Treatments evaluated	Methodology	Cost year and currency discounting	ICER and ICUR
Ng, 2007[118] Canada JBR.10 Trial	Adjuvant chemotherapy vs. observation	Retrospective economic analysis of a subset (stage IB and stage II NSCLC) of patients in the NCIC CTG JBR.10 study. Treatment benefit was based on mean survival in the trial. Resource use including surgery and chemotherapy (including preparation and administration), pharmacy technician and pharmacist salaries, nursing care, physicians' fees, emergency department visits, hospitalisation and outpatient visits) was derived from trial data and patient records and local costs applied.	2005 CAD 5% discounting	$10,096/LYG (95% CI, −$819, $55,651) (undiscounted) $7,175/LYG (95% CI, −$3,463, $41,565) (discounted)
Wong, 2017[119] Canada JBR.10 Trial	Clinical stage-directed approach, adjuvant chemotherapy vs. observation	CEA based on Ng et al. (2007)[118], retrospective review of a subset (stage IB and stage II NSCLC) of patients in the NCIC CTG JBR.10 study with treatment approach directed by 1) clinical stage[a] 2) gene signature[b] and 3) a combined approach[c]	2015 CAD 5% discounting	$7081/LYG (95% CI, −$2,370, $14,721) (discounted) $9194/QALY (95% CI, −$4,104, $23,952) (discounted)
	Gene signature-directed approach, adjuvant chemotherapy vs. observation		2015 CAD 5% discounting	$10,421/LYG (95% CI, $466-$19,568) (discounted) $13,452/QALY (95% CI, $373-$31,949) (discounted)
	Combined approach, adjuvant chemotherapy vs. observation		2015 CAD 5% discounting	$8037/LYG (95% CI:-$1,925, $16,502) (discounted) $10,194/QALY (95% CI:-$3,130, $25,957) (discounted)
CADTH STA, March 2022[120] Canada	Adjuvant osimertinib vs. active surveillance in patients with Stage IB to IIIA, EGFR+ NSCLC following full resection.	Economic evaluation used a state transition, semi-Markov model with 5 health states: (1) disease-free, (2) locoregional recurrence, (3) first-line treatment for distant metastases, (4) second-line treatment for distant metastases, and (5) dead	NR, CAD Discounting NR	$328,026/QALY

Author, year, country	Treatments evaluated	Methodology	Cost year and currency discounting	ICER and ICUR
NICE STA January 2022[121] UK	Adjuvant osimertinib vs. active monitoring in patients with Stage IB to IIIA, EGFR+ NSCLC following full resection.	Economic evaluation used a state transition, semi-Markov model with 5 health states as for Canada	NR, £ Discounting NR	ERG preferred analysis, with no cure: £17,219/QALY

CAD = Canadian dollar; CEA = cost-effectiveness analysis; CI = confidence interval; EGFR = epidermal growth factor receptor; ERG = evidence review group; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; LYG = life-year gained; NR = not reported; NSCLC = non-small cell lung cancer; QALY = quality-adjusted life-year; UK = United Kingdom.

[a] Patients with stage IB disease and a tumour size of at least 4 cm were treated with adjuvant chemotherapy, while those with stage IB disease and a smaller tumour size were observed.

[b] All patients have their genes profiled, and those that were deemed high risk were given adjuvant treatment, while those with low-risk disease were observed.

[c] Patients with stage IB disease had gene profiling performed and high-risk patients received adjuvant treatment along with patients who had stage II disease.

Source: BMS data on file (2022)[122]

B.3.2Economic analysis

A de novo model was developed for this analysis because no appropriate model was identified through the targeted literature review (see Section B.3.1). This section describes the de novo economic model constructed for the submission, and the rationale for the model development.

B.3.2.1 Patient population

The population evaluated in the analysis is aligned with the indication for nivolumab in the neoadjuvant treatment of resectable (tumours ≥ 4 cm or node positive) NSCLC in adults.[1] Patient characteristics for the model were based on those in CheckMate-816 and have been validated by clinical expert feedback to be relevant for England (Appendix N). Table 23 presents specific baseline characteristics, such as age, sex, and disease stage.

Table 23. CheckMate-816: population characteristics

Characteristic	NIVO+PDC	PDC alone
N	179	179
Median age (years)	64	65
Age ≥ 65 years	48.0%	53.6%
Male	71.5%	70.9%
Region		
North America	22.9%	27.9%
Europe	22.9%	14.0%
Asia	47.5%	51.4%

Characteristic	NIVO+PDC	PDC alone
Rest of the world	6.7%	6.7%
ECOG status		
0	69.3%	65.4%
1	30.7%	34.6%
Disease stage at study entry		
IB or II	36.3%	34.6%
IIIA	63.1%	64.2%
Histology		
Squamous	48.6%	53.1%
Nonsquamous	51.4%	46.9%
PD-L1 TPS		
< 1%	43.6%	43.0%
≥ 1%	49.7%	49.7%
1%-49%	28.5%	26.3%
≥ 50%	21.2%	23.5%
NE/indeterminate	6.7%	7.3%
Smoking status		
Current/former	89.4%	88.3%
Never	10.6%	11.2%
N	179	179

NIVO = nivolumab; PDC = platinum doublet chemotherapy; ECOG = Eastern Cooperative Oncology Group; NE = not estimable; PD-L1 = programmed death-ligand 1; TPS = Tumour Proportion Score.

Source: BMS data on file (2021)[83]

B.3.2.2 Model structure

Given that no published models identified through the literature review were deemed suitable for the current submission (see Section B.3.1) a de novo model was developed. To inform the model development a supplementary review of recent health technology assessment (HTA) submissions for adjuvant/neoadjuvant treatments in non-metastatic solid tumours was conducted in 2021 to help inform the model structure. In addition to the review, input from experts in clinical and health economics and outcomes research was sought through several advisory boards and expert meetings to inform the model development. A summary of each meeting is provided in Appendix N.

1. UK HE expert meeting, February 2022
2. UK HTA clinical expert meeting, March 2022
3. Global HTA advisory board meeting, May 2022 (included 1 UK clinical expert and 1 UK HE expert)
4. UK clinical advisory board, May 2022
5. UK HTA clinical validation meeting, August 2022

For the supplementary review of HTA submissions, no submissions in the neoadjuvant or adjuvant treatment setting were available for NSCLC;[v] therefore, the search examined other solid-tumour cancers, where surgery combined with neoadjuvant or adjuvant treatment were part of the treatment pathway. The NICE website was searched first, as a baseline, and the same agents and indications were subsequently sought out in other HTA websites. The specific HTAs included were NICE (UK), Canadian Agency for Drugs and Technologies in Health (CADTH), Pharmaceutical Benefits Advisory Committee (PBAC; Australia), Scottish Medicines Consortium (SMC), and French National Authority for Health (HAS).Table 24 summarises the submissions identified.

Table 24. HTA submissions for adjuvant/neoadjuvant treatments in non-metastatic solid tumours

Disease area[a]	Drug	Indication	Neoadjuvant/ adjuvant?	Model structure
Prostate cancer	Darolutamide	High-risk, non-metastatic, castration-resistant	Adjuvant	3-state partitioned survival (PBAC, CADTH, SMC, NICE)
	Enzalutamide	High-risk, non-metastatic, castration-resistant	Adjuvant	5-state Markov (SMC, PBAC, CADTH), semi-Markov (HAS, NICE)
Breast cancer	Neratinib	Early-stage hormone-positive, HER2-overexpressed or amplified	Extended adjuvant (i.e., after other adjuvant therapy)	5-state Markov (PBAC, CADTH, NICE)
	Trastuzumab emtansine	HER2-positive, early stage	Adjuvant	6-state Markov (PBAC, CADTH, HAS), 7-state Markov (NICE, SMC)
	Pertuzumab	HER2-positive, early stage	Neoadjuvant and adjuvant	4-state Markov (SMC, PBAC), 5-state Markov (NICE, adjuvant), 7-state Markov (NICE, neoadjuvant)
Lung cancer	Osimertinib	Non-metastatic, EGFR mutation-positive NSCLC	Adjuvant	5-state Markov Model (NICE)

CADTH = Canadian Agency for Drugs and Technologies in Health; EGFR = epidermal growth factor receptor; HAS = French National Authority for Health; HER2 = human epidermal growth factor receptor 2; HTA = health technology assessment; NSCLC = non-small cell lung cancer; PBAC = Pharmaceutical Benefits Advisory Committee; SMC = Scottish Medicines Consortium.

[a] The only submission for pancreatic cancer was in advanced/metastatic disease. There were no HTA submissions for kidney cancer, and the only relevant HTA submission for colorectal cancer was older than 5 years and thus excluded.

[v] Note, since the original review was conducted, the NICE appraisal of atezolizumab after adjuvant PDC has been published,[2] but it was not considered during the early stages of model development.

Among the 21 submissions reviewed, Markov models were the most frequent model structure, accounting for 17 of the reviewed models. The remaining 4 models took a partitioned survival analysis (PartSA) approach, and all were related to submissions in support of darolutamide as a treatment of patients who are at high risk of non-metastatic, castration-resistant prostate cancer. NICE feedback regarding the darolutamide submission also suggested that the treatment pathway would have been better accommodated by a Markov model.[123]

Given the early stage of disease and associated immature time-to-event data from CheckMate-816, a key limitation of PartSA framework is that the extrapolations of frequently used outcomes such as EFS and OS could generate unrealistic estimated hazards (i.e., the risk of an event in the OS curve being higher than the risk of an event in the EFS curve). Moreover, incomplete OS data from CheckMate-816 presents challenges in generating a robust surrogate relationship with EFS which would be required for a traditional PartSA. In early-stage NSCLC, subsequent treatments are expected to have a considerable impact on long-term outcomes given the likelihood of different recurrence events (conditional on locoregional or distant metastasis) and multiple lines of therapy. For this reason, a model framework with more than 3 health states is required to accurately map the prognostic nature of intermediate health states in the extrapolation period, and for differential treatment effects, resource use and costs to be applied to different states of the disease process.[124]

Since the targeted literature review was performed, there have been 2 NICE appraisals submissions within the non-metastatic NSCLC treatment pathway. The first NICE submission was for osimertinib as an adjuvant treatment in non-metastatic NSCLC. Although it was released after the search, it was considered to be highly relevant because it focused on resectable NSCLC and was published during the development stages of the model. For this submission, a 5-state Markov model was developed. Although the evidence assessment group (EAG) objected to specific aspects of the approach (e.g., how different types of treatment costs were applied), it found that the model structure and approach were generally appropriate to the disease area and decision problem. The second appraisal was in support of the use of atezolizumab as adjuvant treatment of patients with resected NSCLC. This appraisal was published very close to the submission of the current submission, but NICE feedback on the atezolizumab appraisal was carefully considered to ensure that the cost-effectiveness model (CEM) for nivolumab + PDC in neoadjuvant non-metastatic NSCLC would be appropriate for NICE decision-making. Table 25 presents key feedback and how it is addressed in the neoadjuvant nivolumab + PDC model.

Table 25. Appraisal committee meeting feedback on atezolizumab in adjuvant resected NSCLC

Critique	How BMS will address this issue
Modelling in the metastatic setting was overly-complex	A simplifying assumption is made regarding the consequences of DM; a one-off cost, QALY, and LY total is applied to patients entering this state, reducing the overall burden of data needed to characterise metastatic NSCLC in the model.
Metastatic outcomes did not align with previous metastatic NICE appraisals	The implementation of a one-off approach to model DM in the neoadjuvant nivolumab + PDC CEM allows to leverage outcomes from previous metastatic NICE appraisals and therefore ensure consistency.
Questions regarding clinical data identification and justification of sources	Outcomes for neoadjuvant nivolumab + PDC and neoadjuvant PDC are primarily informed by data from the pivotal trial (CheckMate-816). Data sources used to inform the ITC were identified via a systematic literature review.
Modelling guidelines were not followed for proportional hazards assessment and choice of extrapolation distribution	Selection of extrapolations followed the NICE DSU algorithm described in Figure 27. Assessment of proportional hazards and accelerated failure time was conducted.
The EAG and NICE critiqued the “ramp-up” period for cure, which began before the cure timepoint (i.e., ”ramp-up” begins at year 3, and the full proportion of cure is reached at year 6). Further, most appropriate assumptions for cure were discussed.	A more conservative approach to cure is taken, whereby cure begins at year 5 and is achieved by 95% of patients at year 7. The length of time between the start and the end of the cure effect is tested in sensitivity analysis. This is a noted data gap. The model has the flexibility to test different values for the following parameters: ▪ Time at which cure begins ▪ Time at which cure is “complete” (i.e., when the full cure proportion is reached) ▪ Maximum cure proportion (i.e., the percentage of patients in EFS with cure by the time at which cure is complete)
The assumption that no patients would receive immuno-oncology therapy in the metastatic setting after receiving I-O in the adjuvant setting was challenged and NHS England representative present during committee meeting argued that retreatment with I-O would be likely.	The expected treatment rules around I-O are anticipated to allow retreatment with I-O agents after 6 months to 1 year after initial I-O treatment, if patients did not relapse while receiving initial I-O treatment. The neoadjuvant nivolumab + PDC CEM inputs consider these rules and applies a proportion of patients who would not be eligible for I-O retreatment, based on progression data from CheckMate-816.

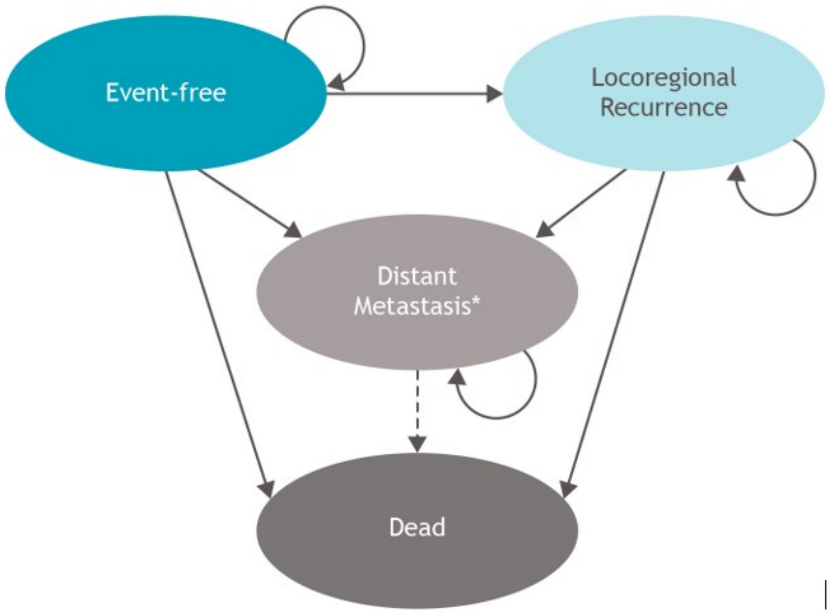
BMS = Bristol Myers Squibb; CEM = cost-effectiveness model; DM = distant metastasis; DSU = Decision Support Unit; EFS = event-free survival; EAG = evidence assessment group; I-O = immuno-oncology; ITC = indirect treatment comparison; LY = life-year; NHS = National Health Service; NSCLC = non-small cell lung cancer; PDC = platinum doublet chemotherapy; QALY = quality-adjusted life-year.

In summary, the results of the HTA review suggested that a Markov approach with 4 or more health states has a strong precedent in early disease modelling and is particularly useful when later lines of treatment could be important to the decision question.

Based on the findings from the HTA review, both clinical and health economics and outcomes research experts were consulted in the Global HTA advisory board meeting, May 2022, to inform the development of the economic model (see Appendix N). The health economics and outcomes research experts surveyed noted that current data limitations could impact the feasibility of PartSA and thus a Markov model were seen to be preferable. Further, the experts expressed that a 4-state model is well aligned with the natural history of the disease versus a 3-health-state model. Patients who progress may experience significantly different outcomes on the basis of the type of progression experienced. For example, patients with local or regional recurrence will, on average, live longer than patients with distant metastasis, and experience a higher quality of life. Conversely, patients with distant metastasis would be anticipated to require more intensive care (both in terms of healthcare resource utilisation and treatment received), and also experience a greater reduction in quality of life than patients with local recurrence. Additionally, the duration of treatments in the 2 states varies significantly: advisory board feedback indicated that patients with LR would be anticipated to receive limited care, whereas patients with distant metastasis would need lifelong treatment.

In concordance with the natural history of the disease, previous neoadjuvant and adjuvant HTA submissions, and feedback from clinical and economic experts, a 4-state semi-Markov cohort model was developed and implemented in Excel (Figure 26).

Figure 26. Four-state semi-Markov model diagram



DM = Distant Metastasis; LY = life-year; QALY = quality-adjusted life-year.

* A one-off cost, life-year and quality-adjusted life-year consequence is applied to patients entering distant metastasis. The subsequent transition from DM to Dead is implicitly captured by the one-off cost, LY and QALY amount applied to patients entering that state but is not explicitly tracked in the model.

This model includes 4 health states: Event-Free (EF), Locoregional Recurrence (LR), Distant Metastasis (DM), and Dead. All patients enter the model in the EF health state, where patients may experience 1 of 2 types of progression: LR or DM. Additionally, patients in the EF health state may also die, moving to the Dead health state. Patients in the LR health state may experience further progression, moving to the DM or Dead health states.

When patients experience distant metastasis, a one-off cost, QALY, and life-year (LY) total representing subsequent treatment mix is applied; further outcomes are no longer explicitly tracked, and the patient does not make any further state transitions. Patients in all health states except DM are subject to a probability of death each cycle (for patients in DM, this probability is implicitly considered in the LY and QALY total applied). The rationale for providing "one-off" outcomes for the distant metastasis health state it outlined in Section B.3.3.2.

Health states were selected based on the CheckMate-816 trial endpoints and the current understanding of the disease area (see Section B.2.3.1). The EF health state was designed to align with the definition of EFS used in CheckMate-816, where EFS was a primary endpoint (see Section B.2.2). Event-free survival begins from the time of randomisation, rather than from the time of surgery. This allows the model to indicate the possibility that some patients who are unresponsive to neoadjuvant therapy could see their disease progress prior to surgical resection and the prognoses of these patients will be captured in the time-to-event data.

The definitions of LR and DM also follow their given definitions from the CheckMate-816 trial. Specifically, patients with LR had disease progression per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 criteria but did not have any identified lesions outside the thorax; conversely, patients with DM were those who had developed 1 or more new lesions outside the thorax. Separation of the composite trial endpoint of EFS from CheckMate-816 into time to LR and DM also lends credibility to any modelled survival benefit. This is because separate health states for LR and DM allow the model to accurately capture real-life patterns of progression, by considering distinct survival and progression trajectories, quality of life, and costs associated with each type of progression.

In general, the transition probabilities used by the model are computed based on results from CheckMate-816. One exception is for transitions out of the LR state, which are informed by publicly available data in the literature; this transitional probability was not possible to inform from the trial because further study imaging was not required for patients who experienced documented locoregional recurrence without a distant lesion. Greater detail on the analyses used to derive transition probabilities is provided in Section B.3.3.1.

Once patients experience an event, appropriate treatment is initiated based on the type of event. Costs were assigned to each health state, and utilities were applied according to patients' disease progression status, treatment received, and any AEs experienced.

Following NICE (2019)[17], patients in the LR state can receive treatment in up to 3 modalities: PDC, radiotherapy, and surgery. Because patients may receive more than one type of treatment (e.g., patients could concurrently receive both PDC and radiotherapy), the

distribution is not mutually exclusive and can total a value greater than 100%. Additional detail on the costs of care considered in the LR is provided in Section B.3.5.2.1. The care received in LR is not explicitly considered in terms of how it may affect the mortality and likelihood of experiencing subsequent DM, which is assumed to be the same for all patients in the model, regardless of the treatment received or time spent in the EF state. Additional detail on the inputs used to describe the likelihood of DM for patients with LR is provided in Section B.3.3.1.4, and the mortality for patients with LR in Section B.3.3.1.6.

As discussed during the decision problem meeting with NICE, the model applies one-off cost, QALY, and LY values to patients entering the DM state to capture the outcomes for this population; no further explicit modelling of outcomes was implemented to inform the costs and consequences of transitions into this state (e.g., treatment received, duration of therapy, PFS, and OS). The specific cost, QALY, and LY totals accrued are based on discounted values from existing NICE appraisals of first-line metastatic NSCLC treatments provided by NICE. The treatments are weighted such that the shares of patients who are receiving immuno-oncology and chemotherapy treatment are reflective of UK clinical practice.

B.3.2.3 Perspective

In accordance with NICE guidelines,[125] the model takes an NHS perspective, considering direct costs incurred by the NHS, i.e., drug acquisition and administration costs, surgery costs, routine medical resource use (MRU) costs, terminal costs, and treatment-related AE costs.

B.3.2.4 Time horizon

The model takes a lifetime horizon in the base case, although it has the flexibility to consider shorter time horizons (e.g., 1 year, 5 years, 15 years, or 20 years). There are 2 key reasons why a lifetime horizon is employed in the base case. First, nivolumab + PDC is anticipated to extend patient lifespans based on the strong EFS performance we have observed in the IA2 data. Second, resected patients will require continued check-ins and other care over time; many will require subsequent treatment if their disease progresses. Thus, a lifetime horizon can fully capture the costs and benefits of nivolumab + PDC as neoadjuvant treatment of patients with resectable non-metastatic NSCLC.

Lifetime is implemented as the point in time when fewer than 1% of patients are alive in the model engine. Based the modelled survival, we found that this threshold was crossed at approximately 34.5 years. Rounding up to the nearest integer, the lifetime time horizon used in the base-case analysis was 35 years.

B.3.2.5 Cycle length and half-cycle correction

The model adopts a 21-day (i.e., 3-week) cycle length. This aligns with the treatment schedule for nivolumab and PDC in the CheckMate-816 trial; treatments are administered once every 3 weeks (see Section B.2.3.1). The 3-week cycle length also aligns with the dosage schedule for many current treatment options in the adjuvant and post-progression settings (e.g., docetaxel, pemetrexed, cisplatin, carboplatin, paclitaxel, atezolizumab, and pembrolizumab; see Table 7).

Most results are adjusted using a half-cycle correction, distributing the costs, LYs, and QALYs accrued across the cycle duration. Half-cycle correction is not applied to drug acquisition and administration costs because all patients received pharmacological treatment at the start of each cycle.

B.3.2.6 Discounting

Both cost and health outcomes are discounted based on the time at which they are accrued in the model to capture the opportunity cost of money and to properly evaluate the present value of future outcomes. This is set to 3.5% per annum for both cost and health outcomes in the base case, per NICE recommendations.[125] The model includes the flexibility to adjust both discounting rates to allow for adaptation to settings that may recommend different rates other than the 3.5% per annum recommended by NICE, and for the purposes of sensitivity analysis.[125]

B.3.2.7 Intervention technology and comparators

As described in Section B.1.3.6 and the decision problem (see Table 1), surgical resection is the SOC for early-stage disease if the tumour is resectable and the patient is suitable for surgery. In addition to surgery alone, the patient may also receive neoadjuvant chemoradiotherapy or adjuvant PDC treatment. As a result, the current analysis investigates the cost-effectiveness of neoadjuvant nivolumab + PDC versus surgery, neoadjuvant CRT, and adjuvant PDC, as outlined in Table 26 and as set out by the final NICE scope. Note that analyses comparing nivolumab + PDC to adjuvant atezolizumab (TA10751]) have not been generated as adjuvant atezolizumab has entered the Cancer Drugs Fund as is not a relevant comparator for this appraisal.

Table 26. Comparators in the economic analysis

Strategy	Description of treatment strategy
Surgery only	Patients proceed immediately to surgery. No neoadjuvant or adjuvant treatment is received, although these patients are monitored after surgery.
Neoadjuvant CRT	Patients receive neoadjuvant PDC + radiotherapy, followed by surgery. Some patients may also receive adjuvant treatment.
Adjuvant PDC	Patients proceed immediately to surgery, and subsequently receive a course of adjuvant PDC.

CRT = chemoradiation; PDC = platinum doublet chemotherapy.

B.3.3Clinical parameters and variables

Table 27 presents a high-level summary of transition probabilities considered by the model, and sources to inform the base-case analysis.

Table 27. Summary of clinical inputs

Transition captured		
From	**To**	**Base-case source**
EF	LR	Analysis of CheckMate-816 data (time to LR)
	DM	Analysis of CheckMate-816 data (time to any progression minus time to LR)
	Dead	Analysis of CheckMate-816 data (time to death); mortality risk for all patients who are EF, pooled across treatment arms
LR	DM	Estimate based on data from Chouaid et al. (2018)[39] and KOL feedback
	Dead	Analysis of mortality risk from CheckMate-816 for patients who had LR, pooled across treatment arms
DM	Dead	One-off LY and QALY impact calculated based on previous HTA submissions in metastatic NSCLC

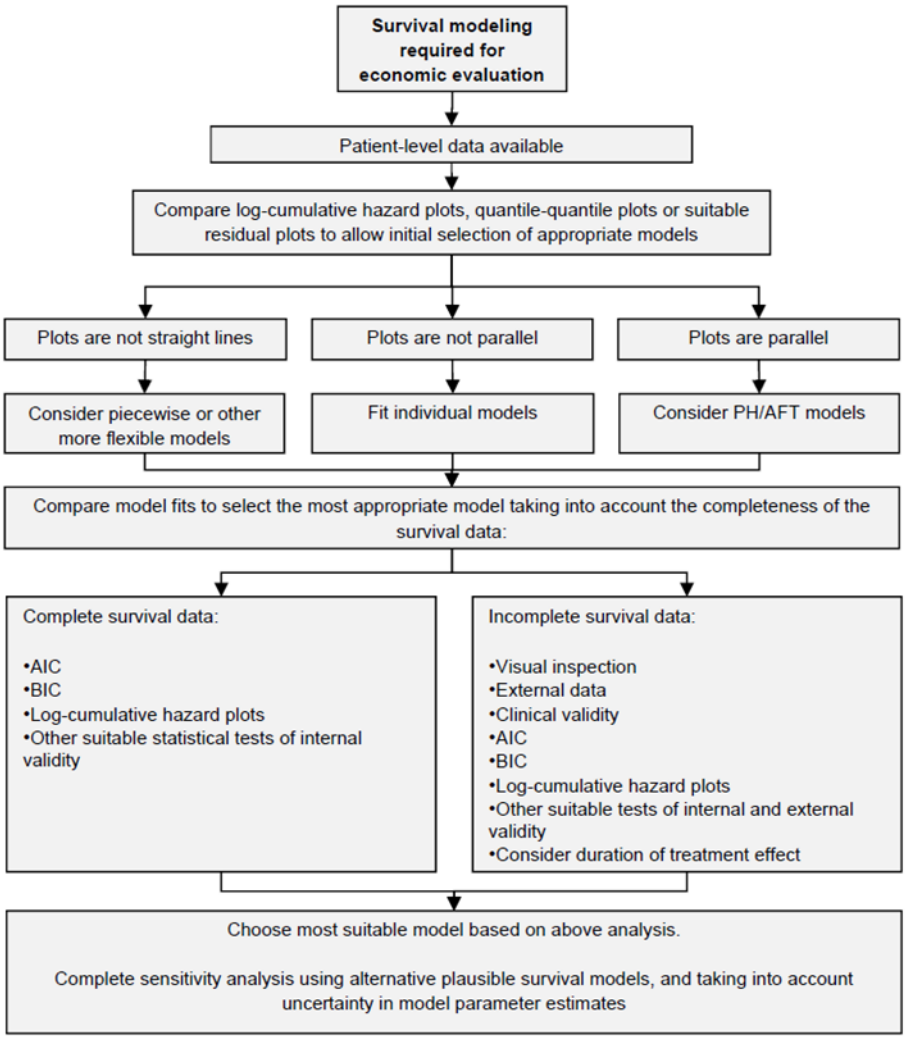
DM = Distant Metastasis; EF = Event-Free; HTA = health technology assessment; KOL = key opinion leader; LR = Locoregional Recurrence; LY = life-year; NSCLC = non-small cell lung cancer; QALY = quality-adjusted life-year.

B.3.3.1 Parametric survival modelling for Event-Free and Locoregional Recurrence transition probabilities

B.3.3.1.1 Approach to parametric fitting and assessment

To allow the model to accurately reflect clinical data from CheckMate-816, parametric survival modelling was conducted. This allows for estimation of time-dependent transition probabilities beyond the end of the existing Kaplan-Meier trial data. Parametric survival modelling is the common approach for extrapolation of time-to-event outcomes and is recommended by the UK's NICE DSU for the analysis of survival outcomes for economic evaluations, alongside clinical trials for projection.[126] Figure 27 presents the approach to parametric survival modelling.

Figure 27. Survival model selection process algorithm presented by NICE Decision Support Unit and referenced by other HTA agencies



AFT = accelerated failure time; AIC = Akaike information criteria; BIC = Bayesian information criteria; HTA = health technology assessment; PH = proportional hazard.

Parametric survival modelling assumes that the time-to-event outcome follows a parametric distribution. The following distributions were investigated: exponential, Weibull, Gompertz, log-logistic, log-normal, gamma, and the generalised gamma distribution. If none of these distributions produced a reasonable fit, more sophisticated fittings, specifically, spline models, were explored. The properties of these distributions have been described by Ishak et al. (2013)[127] and can be found in standard textbooks on survival analysis, such as in the book by Collett (2003)[128]. They cover a broad range of possible shapes of hazards. The analytical process involves testing various potential statistical distributions and assessing fit over the observed data period and beyond to ensure reliable projection. The approach to fitting the curves is outlined in Ishak et al. (2013)[127], which provides the technical details behind the steps of the analyses described below. The process of selecting a best-fitting distribution involves both statistical and clinical considerations, as well as considerations based on the observed data in assessing goodness-of-fit and plausibility of results. Thus, although the process involves distinct steps, it is not necessarily algorithmic. The comparator arm in CheckMate-816, neoadjuvant PDC, is not considered SOC in the UK and thus not a comparator within scope in the current appraisal. Nevertheless, extrapolations were conducted for both arms of the trial. The rationale for extrapolation of both arms was that the neoadjuvant PDC arm is the common comparator in the evidence network and thus can be used for extrapolation of other comparators within scope through the indirect treatment comparison–derived HRs.

Fitting of models

Equations based on distributions were fitted to the data. This was done using the flexsurv package in R. Spline fittings were conducted using the STPM2 package in STATA. This procedure produces estimates of the scale and shape parameters of the distributions and allows the scale parameter to be regressed on explanatory variables. The Akaike information criteria (AIC) and Bayesian information criteria (BIC) were compared among fitted models to determine best statistical fit (with lower values indicating better fit). Regression models were fitted both by including treatment (nivolumab + PDC vs. PDC alone) as a categorical explanatory variable and by conducting fully stratified analyses where separate models are fitted for each treatment.

Graphical assessment of fits

For all parametric distributions, graphical assessment of model fit will be made by comparing the Kaplan-Meier survival curves with the fitted survival curves. Furthermore, for the exponential, Weibull, log-logistic, and log-normal distributions, assessment of fit will also be made based on diagnostic plots associated with each of these distributions. For example, a plot of log-survival probabilities against time can be used to assess fit for an exponential model; log-negative log-survival versus log of time can be used for Weibull, etc. A linear pattern in these graphs indicates that the distribution may be adequate and, conversely, deviation from linearity indicates poor fit. Because of the parametric formulation of the generalised gamma distribution, assessment of fit based on diagnostic plots is not possible. Similarly, graphical tests for the Gompertz distribution are problematic because they do not rely purely on the observed data but also on unverifiable assumptions.

The statistical and graphical fit to the Kaplan-Meier data is meant to provide a preliminary assessment of suitability of each distribution for consideration in further assessments; some distributions may be cut from further consideration, but it is possible that all are carried forward despite poor fit for comparison purposes.

Assessment of clinical plausibility

Fitted parametric models must provide good fit over the observed period and plausible extrapolations beyond. The former is assessed in the previous step with the AIC and BIC statistics and diagnostic plots. The latter must rely on clinical judgement of plausibility of extrapolations and may be assessed by examining the shape of the long-term projection of the curve, and based on measures derived from the predicted curve. For example, the estimate of the median and/or mean event time, or 3-year survival can be a way of judging validity; estimates that contradict common perceptions would be indicative of inadequate fit. To assess long-term plausibility, extrapolations were compared against relevant Kaplan-Meier curves from the literature for individual endpoints. Clinician input was also sought to check whether extrapolated curves were concordant with expert opinion. Finally, the OS predicted by the model (including all extrapolations) was compared with a constructed conditional survival built using available evidence (e.g., meta-analyses of neoadjuvant and adjuvant trials, and registry data).

This information was used to determine the best-fitting parametric model. However, best fitting does not necessarily imply good fit; the best-fitting distribution may still deviate from the observed data or produce clinically implausible long-term projections. If this is the case, alternate methods may need to be considered.

Output of standard parametric survival models

The output from the standard parametric survival models includes:

- Diagnostic graphs for each of the commonly used distributions, including probability plots
- A table summarising estimated values of the parameters for the fitted distributions, including variance covariance matrix, fit statistics, and projected median and life-expectancy estimates
- Observed versus predicted plots for each fitted model
- Long-term projection plots for each fitted model

B.3.3.1.2 Time to Locoregional Recurrence health state

Observed data

Estimates for transition probabilities characterising TTLR were based on data collected from the CheckMate-816 trial. In total, [redacted] LR events were observed in the nivolumab + PDC arm ([redacted]), and [redacted] LR events were observed in the PDC arm ([redacted]). The median time to LR could not be estimated for either arm, although a lower 95% CI could be estimated for the PDC arm. The data translated to an overall HR of 0.65 for nivolumab + PDC versus PDC alone. A

summary of the observations, and the Kaplan-Meier curves, are depicted in Table 28 and Figure 28, respectively.

Table 28. CheckMate-816: time to locoregional recurrence—summary of observed data

	NIVO+PDC	PDC
N	[redacted]	[redacted]
Events (%)	[redacted]	[redacted]
Median in months (95% CI)	[redacted]	[redacted]

CI = confidence interval; NE = not estimable; NIVO = nivolumab; PDC = platinum doublet chemotherapy.

Figure 28. CheckMate-816: time to locoregional recurrence: observed data

chemo = chemotherapy; CI = confidence interval; HR = hazard ratio; KM = Kaplan-Meier; NE = not estimable; NIVO = nivolumab.

Diagnostic plots assessing whether PH or accelerated failure time (AFT) assumptions hold between the 2 treatment arms are presented in Figure 29. The log-log plot (top left panel in Figure 29), where points representing observations in the nivolumab + PDC and PDC treatment arms were relatively parallel during the entire follow-up suggested that the PH assumption holds. This finding was further supported by Schoenfeld residuals test (*P* value 0.46) (bottom left panel in Figure 29). Additionally, the points forming a relatively straight line in the QQ-plot (top right panel in Figure 29) suggested that both sets of observed quantiles in the nivolumab + PDC and PDC treatment arms came from the same AFT distribution and

that the AFT assumption holds. Therefore, the use of jointly fitted distributions with treatment arm as predictor was recommended for the ITT population.

Figure 29. Time to locoregional recurrence in the intention-to-treat population: log-log plot, Schoenfeld residuals plot and QQ-plot

The statistical tests suggested that both AFT and PH assumptions hold. Therefore, the use of jointly fitted distributions with the treatment arm as a predictor was selected to extrapolate TTLR.

Extrapolations

Because the PH assumption was found to hold, it was determined that jointly fitted curves would provide the best fit to the data. Figure 30 and Figure 31 present the short-term projections of the standard parametric functions for the nivolumab + PDC and PDC alone arms, respectively. Table 29 summarises goodness-of-fit statistics.

Figure 30. Time to locoregional recurrence: within-trial fittings (nivolumab + PDC)

PDC = platinum doublet chemotherapy.

Figure 31. Time to locoregional recurrence: within-trial fittings (PDC)

PDC = platinum doublet chemotherapy.

Table 29. Time to locoregional recurrence: goodness-of-fit statistics

Distribution	AIC	BIC
Log-normal	814.4	826.1
Generalised gamma	816.1	831.6
Exponential	816.8	824.6
Log-logistic	817.3	829
Gompertz	817.9	829.6
Weibull	818.8	830.4
Gamma	818.8	830.5

AIC = Akaike information criteria; BIC = Bayesian information criteria.

All of the curves were considered to fit the Kaplan-Meier data reasonably well during the within-trial period. The log-normal and exponential distributions were considered to provide the best statistical fit of the data based on AIC and BIC.

Long-term extrapolated outcomes and context

Figure 32 and Figure 33 present long-term extrapolations versus Kaplan-Meier data for the nivolumab + PDC and PDC alone arms, respectively. Table 30 and Table 31 detail the median and mean TTLR months for all the distributions, along with the percentage of patients who were LR free at 1, 3, 5, 10, 20, and 30 years for the nivolumab + PDC and PDC alone arms.

Figure 32. Time to locoregional recurrence: long-term extrapolations (nivolumab + PDC)

PDC = platinum doublet chemotherapy.

Figure 33. Time to locoregional recurrence: long-term extrapolations (PDC arm)

PDC = platinum doublet chemotherapy.

Table 30. Time to locoregional recurrence: predicted median, mean, and landmarks (nivolumab + PDC)

Distribution	Median (months)	Mean (months)	1 year	3 years	5 years	10 years	20 years	30 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PDC = platinum doublet chemotherapy.

Table 31. Time to locoregional recurrence: predicted median, mean, and landmarks (PDC)

Distribution	Median (months)	Mean (months)	1 year	3 years	5 years	10 years	20 years	30 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NE = not estimable; PDC = platinum doublet chemotherapy.

As noted previously, all extrapolations tested were found to fit the data well during the within-trial period. However, in the long-term, significant divergence was observed in the curve tails for various extrapolations. For example, at 20 years in the PDC arm, the predicted survival based on the exponential extrapolation was found to be [redacted]% versus [redacted]% in the log-normal extrapolation.

Therefore, to ensure that the long-term projections for PDC were realistic, the estimates were firstly compared against external sources (Figure 34). Published evidence on TTLR in this population is limited, and only 2 external sources were identified (see Table 27):

- Estimates of TTLR collected as part of the 2014 NSCLC Collaborative Group meta-analysis[129]
- The base-case extrapolation used in NICE TA761[121] (osimertinib for adjuvant treatment of EGFR mutation-positive NSCLC after complete tumour resection)

The comparison with TA761 was conducted due to the lack of available data from sources more closely approximating the CheckMate-816 population, despite the difference in patient population (TA761 considered all patients with EGFR mutation-positive NSCLC, whereas patients with known EGFR mutation-positive NSCLC were excluded from CheckMate-816). For the comparison (Figure 34) exponential and log-normal distributions were selected for comparison given that they provide the best statistical fit to the observed data based on BIC and AIC, respectively.

Figure 34. Time to locoregional recurrence: comparison versus external data - PDC

CM-816 = CheckMate-816; KM = Kaplan-Meier; NSCLC = non-small cell lung cancer; PDC = platinum doublet chemotherapy; SOC = standard of care; TA = technology appraisal.

The extrapolations of TTLR based on CheckMate-816 data were generally more pessimistic than those observed in the NSCLC Collaborative Group meta-analysis. This discrepancy is likely primarily due to the difference in disease stage in CheckMate-816 (which included more patients with stage IIIA) versus the NSCLC Collaborative Group meta-analysis (which included more patients with stage I/II). In the long-term, the log-normal distribution was similar to the log-normal distribution for TTLR from TA761.

Summary: base-case input selection

The standard parametric distributions (exponential, Weibull, log-normal, log-logistic, Gompertz, generalised gamma, and gamma) were fit to the TTLR data from CheckMate-816. Visual inspection of the within-trial data suggested all tested extrapolations generally fit well. Assessment of AIC and BIC suggested the exponential and log-normal distributions were the best fitting based on BIC and AIC, respectively. Comparison of the curve tails against external data suggested (Figure 34) the log-normal distribution would provide the best fit in the long-term. This was also confirmed from the feedback received where the clinical experts consulted suggested the log-normal distribution was plausible for TTLR in the long-term. Therefore, the log-normal distribution was used in the base case to describe TTLR for EF patients for both the neoadjuvant nivolumab + PDC and neoadjuvant PDC arms of the model.

B.3.3.1.3 Time to any progression and derivation of time to distant metastasis health state

Observed data for TTDM from the CheckMate-816 trial were immature with a relatively low event count. In total, only [redacted] DM events were observed in the nivolumab + PDC arm ([redacted] and [redacted] DM events were observed in the PDC arm ([redacted] Median was not reached in either arm. Figure 35 presents the Kaplan-Meier curves, and Table 32 summarises the observed data.

Figure 35. CheckMate-816: time to distant metastasis—observed data

chemo = chemotherapy; CI = confidence interval; HR = hazard ratio; KM = Kaplan-Meier; NE = not estimable; NIVO = nivolumab.

Table 32. CheckMate-816: time to distant metastasis—summary of observed data

	NIVO+PDC	PDC
N	[redacted]	[redacted]
Events (%)	[redacted]	[redacted]
Median in months (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	[redacted]

CI = confidence interval; HR = hazard ratio; NE = not estimable; NIVO = nivolumab; PDC = platinum doublet chemotherapy.

The immature TTDM data from the CheckMate-816 trial prevented the development of reliable parametric fittings and long-term extrapolations. Instead, a constructed TTDM curve was calculated as the difference between the long-term estimates from time to any progression and TTLR. The consensus opinion of the experts consulted as part of the during the Global HTA advisory board meeting, May 2022 (Appendix N) was that this would be an appropriate approach. The estimates of time to any progression and the derivation of TTDM extrapolations are presented in the following sections.

Time to any progression

Observed data

Estimates for time to any progression were based on data collected from the CheckMate-816 trial. The observed time to any progression curves were derived from the EFS data but with death events censored. In total, [redacted] progression events were observed in the nivolumab + PDC arm ([redacted] and [redacted] progression events were observed in the PDC arm ([redacted] The median time to progression for the PDC arm was [redacted] months and the median [redacted] for the nivolumab + PDC arm. The data translated to an overall HR of 0.60 for nivolumab + PDC versus PDC alone. The Kaplan-Meier curves and a summary of the observations are depicted in Figure 36 and Table 33, respectively.

Figure 36. CheckMate-816: time to any progression—observed data

chemo = chemotherapy; CI = confidence interval; HR = hazard ratio; KM = Kaplan-Meier; NE = not estimable; NIVO = nivolumab.

Table 33. CheckMate-816: time to any progression—summary of observed data

	NIVO+PDC	PDC
N	[redacted]	[redacted]
Events (%)	[redacted]	[redacted]
Median in months (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	[redacted]

CI = confidence interval; HR = hazard ratio; NE = not estimable; NIVO = nivolumab; PDC = platinum doublet chemotherapy.

Diagnostic plots assessing whether PH or AFT assumptions hold between the 2 treatment arms are presented in Figure 37. The log-log plot (top left panel in Figure 37), where points representing observations in the NIVO+PDC and PDC treatment arms were relatively parallel during the entire follow-up suggested that the PH assumption holds. This finding was further supported by Schoenfeld residuals test (*P* value of 0.44; bottom left panel in Figure 37). Additionally, the points forming a relatively straight line in the QQ-plot (top right panel in Figure 37), except some deviation between months 10 and 13 (for PDC), suggested that both sets of observed quantiles in the NIVO+PDC and PDC treatment arms came from the same AFT distribution and that the AFT assumption holds. Therefore, the use of jointly fitted distributions with treatment arm as predictor was recommended for the ITT population.

Figure 37. Time to progression in the intention-to-treat population: log-log plot, Schoenfeld residuals plot, and QQ-plot

chemo = platinum doublet chemotherapy; NIVO = nivolumab.

Extrapolations

Figure 38 and 0 present the short-term projections of the standard parametric functions for the nivolumab + PDC and PDC alone arms, respectively. Table 34 summarises goodness-of-fit statistics. Because the curves are jointly fitted, the same goodness-of-fit statistics apply to both arms.

Figure 38. Time to any progression: within-trial fittings (nivolumab + PDC)

PDC = platinum doublet chemotherapy.

Figure 39. Time to any progression: within-trial fittings (PDC)

PDC = platinum doublet chemotherapy.

Table 34. Time to any progression: goodness-of-fit statistics

Distribution	AIC	BIC
Log-normal	1,228.8	1,240.4
Generalised gamma	1,230.4	1,245.9
Log-logistic	1,233.00	1,244.60
Gompertz	1,235.40	1,247.10
Exponential	1,237.10	1,244.80
Weibull	1,238.90	1,250.60
Gamma	1,239.1	1,250.7

AIC = Akaike information criteria; BIC = Bayesian information criteria.

All of the curves were considered to fit the Kaplan-Meier data reasonably well during the within-trial period. The log-normal distribution was considered to be the best fitting, based on AIC and BIC.

Long-term extrapolated outcomes and context

Long-term extrapolations are shown versus Kaplan-Meier data for the nivolumab + PDC and PDC arms in Figure 40 and Figure 41, respectively. Table 35 and Table 36 detail the predicted median and mean months of time to any progression for all the distributions, along

with the percentage of patients who were EF at 1, 3, 5, 10, 20, and 30 years for the nivolumab + PDC and PDC alone arms.

Figure 40. Time to any progression: long-term extrapolations (nivolumab + PDC)

PDC = platinum doublet chemotherapy.

Figure 41. Time to any progression: long-term extrapolations (PDC)

PDC = platinum doublet chemotherapy.

Table 35. Time to any progression: predicted median, mean, and landmarks (nivolumab + PDC)

Distribution	Median (months)	Mean (months)	1 year	3 years	5 years	10 years	20 years	30 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NE = not estimable; PDC = platinum doublet chemotherapy.

Table 36. Time to any progression: median, mean, and landmarks (PDC)

Distribution	Median (months)	Mean (months)	1 year	3 years	5 years	10 years	20 years	30 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NE = not estimable; PDC = platinum doublet chemotherapy.

Based on statistical assessment, the jointly fitted log-normal distribution provided the best fit to the observed time to any progression data. However, in the long-term, substantial differences were observed in the trials for various extrapolations similarly to long-term projections of TTLR.

Given the lack of literature specifically reporting time to progression, and that time to any progression represents a subset of EFS outcomes (i.e., all progression events, excluding death), a comparison of EFS extrapolations against available external sources was conducted to aid in the selection of clinically plausible distributions for time to progression. Only a small proportion of CheckMate-816 EFS events were deaths ([redacted] across nivolumab + PDC and PDC arms); therefore, it was assumed that the same shape selected for EFS would be equally applicable to the projection of time to any progression outcomes. The EFS long-term projections (details of EFS estimation are presented in Appendix O) were compared with several external sources, including:

- The NSCLC Collaborative Group meta-analysis conducted in 2014[130]
- A patient-level meta-analysis conducted by BMS (CA2097L8)[73]
- A US oncology real-world study[131]

An additional constructed curve was created from 2 selected studies in the meta-analysis with up to 5 years of follow-up and weighted to reflect patients' stage distribution in CheckMate-816. One study—Pless et al. (2015)[88]—was a phase 3 randomised clinical trial that enrolled 232 patients with stage IIIA NSCLC, randomly assigned to chemoradiotherapy (3 cycles of neoadjuvant chemotherapy [100 mg/m^2 cisplatin and 85 mg/m^2 docetaxel]) or neoadjuvant chemotherapy alone. The other study—Felip et al. (2010)[70]—was a phase 3 trial including 624 patients with stage IA, IB, or II NSCLC, randomly assigned to surgery alone (212 patients), 3 cycles of preoperative paclitaxel-carboplatin followed by surgery (201 patients), or surgery followed by 3 cycles of adjuvant paclitaxel/carboplatin (211 patients). The constructed EFS curve is generated by weighting EFS curves from Felip (stage I-II) and Pless (stage III based on the stage distribution from CheckMate-816 baseline (35.7% stage I-II and 64.3% stage III). Table 37 presents a comparison of landmarks, while Figure 42 presents a selection of curves Appendix P presents additional details on the sources used for the validation.

NSCLC Collaborative meta-analysis and BMS patient-level meta-analysis (CA2097L8) data suggest almost 40% of patients remain in EFS at 5 years, and approximately 35% at 7 years, while the EFS derived from US oncology data is significantly lower: 25% of patients were in EFS at 5 years and 22% at 7 years. Based on the constructed Felip/Pless curve, 28% of patients are in EFS at 5 years, an estimate similar to that from the US oncology study.

Based on this comparison, the exponential, Weibull and gamma distributions appear to be overly pessimistic in the long run (EFS of approximately 7% at 7 years). Therefore, they lack clinical plausibility and are not suitable for EFS extrapolation. Event-free survival at 5 years based on Gompertz, log-normal and generalised gamma projections (25%-28% at year 5) is within 5% of the estimated Felip/Pless EFS (27.4% at year 5), and close to the BMS US Oncology study, while log-logistic is more pessimistic (22.9%). Based on this assessment,

Gompertz, log-normal and generalised gamma could be considered to be the best candidates, but there was no single obvious best candidate.

Input from 6 clinicians consulted during the Global HTA advisory board meeting, May 2022 (Appendix N) all agreed that the log-normal extrapolation provided is clinically plausible long-term estimates of EFS.

Table 37. Event-free survival: landmark comparison versus external data

	Absolute EFS (%)				
Source	**1 year**	**2 years**	**3 years**	**5 years**	**7 years**
CM-816 EFS – exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CM-816 EFS – Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CM-816 EFS – Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CM-816 EFS – log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CM-816 EFS – log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CM-816 EFS – gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CM-816 EFS – generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMS patient-level meta-analysis (CA2097L8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NSCLC meta-analysis 2014[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMS US oncology study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Felip/Pless EFS constructed[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EFS = event-free survival; NSCLC = non-small cell lung cancer; US = United States.

[a] Constructed by weighting EFS from Felip (stage I-II) and Pless (stage III); weights are based on stage distribution from CM-816 baseline (35.7% stage I-II and 64.3 stage III).

Figure 42. Event-free survival: visual comparison versus external data for PDC

BMS = Bristol Myers Squibb; CM-816 = CheckMate-816; EFS = event-free survival; MA = meta-analysis; NSCLC = non-small cell lung cancer; PDC = platinum doublet chemotherapy; US = United States.

Note: Weibull and gamma are not presented in the figure given their close similarity with exponential. Similarly, log-logistic is not presented, given it closely resembles log-normal.

Summary: base-case input selection

The log-normal distribution is used in the base case to describe time to any progression for EF patients for both the neoadjuvant nivolumab + PDC and neoadjuvant PDC arms of the model.

The standard parametric distributions (exponential, Weibull, log-normal, log-logistic, Gompertz, generalised gamma, and gamma) were fit to the time to any progression data both jointly and independently to each arm of CheckMate-816.

Jointly fit parametric extrapolations were selected based on diagnostic testing.

Visual inspection of the within-trial data suggested all extrapolations tested generally fit well. Assessment of AIC and BIC suggested the log-normal distribution was the best fitting.

Comparison of the EFS curve against external data suggested the log-normal, generalised gamma or Gompertz distribution would provide plausible fit in the long-term.

Expert feedback from the Global HTA advisory board meeting held May 2022 suggested that the log-normal distribution was plausible for EFS, which is understood to be representative of time to any progression, given that progressions represent a large proportion of all EFS events (approximately 85%).

Derivation of time to Death or Distant Metastases health states

Instead of directly projecting the TTDM curve based on the immature data from CheckMate-816, TTDM was derived as the difference of time to any progression and TTLR at any model cycle, such that:

$$Hazard_{Distant\ Metastasis} = Hazard_{Any\ Progression} - Hazard_{Locoregional\ Recurrence}$$

The hazards of time to any progression and TTLR were based on the best-fitting extrapolation curves for the corresponding transitions. In the base case, the log-normal distribution was selected for both transitions. Figure 43 and Figure 44 illustrate the resulting long-term TTDM estimates for the nivolumab + PDC and PDC alone arms, respectively.

This modelling approach was considered appropriate by several health economics and outcomes research experts consulted as part of the Global HTA advisory board meeting, May 2022 (see Appendix N).

Note that in the ITC and CEM sections, TTDM refers to time to distant metastases only, as opposed to the CM816 trial definition of time to death or distant metastases. This is because deaths have been censored to allow for accurate transition probabilities to be calculated for the economic model.

Figure 43. Time to Death or Distant Metastasis: long-term extrapolations (nivolumab + PDC)

DM = Distant Metastasis; KM = Kaplan-Meier; LR = Locoregional Recurrence; PDC = platinum doublet chemotherapy.

Figure 44. Time to Death or Distant Metastasis: long-term extrapolations (PDC)

DM = Distant Metastasis; KM = Kaplan-Meier; LR = Locoregional Recurrence; PDC = platinum doublet chemotherapy.

B.3.3.1.4 Locoregional Recurrence to Distant Metastasis health states

In CheckMate-816, patient monitoring for progression events after the first progression was not required in the trial protocol; hence, estimates of the probability of transition between the LR and DM health states were not available for all patients at risk. Therefore, the model had to rely on external sources to inform this estimate.

Published data captured in the SLR conducted for MRU and utilities (see Appendix H) were used to address this gap. Specifically, data from LuCaBIS (Lung Cancer Burden of Illness Study),[39] a retrospective study of NSCLC conducted in the UK, France, and Germany, were found to be suitable to estimate the rate at which patients with LR experience DM because it included patients with resectable NSCLC and provided sufficient follow-up to track them to the time of LR and through to DM. Table 38 presents key outputs used to derive the rate of transition from LR to DM.

Table 38. Key trial outputs from LuCaBIS used to derive transition probability from Locoregional Recurrence to Distant Metastasis

Variable	N (%)
Total patient population	**831**
Patients with recurrence	272 (32.7%)
Patients with LR only	86 (31.6% of total cohort)
Patients with LR progressing to DM	14 (16.3% of patients with LR)
Mean follow-up period	26 months

DM = Distant Metastasis; LR = Locoregional Recurrence.

Based on these parameters, 16.3% of patients with LR were estimated to experience progression in 26 months. This was converted to an annual transition probability of 7.7% (0.46% per model cycle). In the model, this probability was applied as a constant hazard, and does not change over time.

This input was subsequently reviewed by clinicians (in the Global HTA advisory board meeting, May 2022 and in the UK validation meeting, August 2022) to evaluate its appropriateness. The unanimous consensus among the clinicians consulted was that the calculated probability estimate of LR to DM from LuCaBIS was too low, and that these patients were likely to experience DM at a faster rate than suggested by the LuCaBIS data. Six clinicians provided estimated annual transition probabilities. The suggested probabilities are summarised in Table 39. The estimates were used to estimate an overall transition probability (the mid-point of any range provided was used to calculate the average). The average estimate of 20% (which is the same as the average from the 2 UK key opinion leaders [KOLs]) was used in the base-case analysis with the values from LuCaBIS tested in a scenario analysis.

Table 39. Estimates of annual transition probability from Locoregional Recurrence to Distant Metastasis per key opinion leader input

KOL geography	Estimated annual probability
United Kingdom	10%-20% (15% used in average) and 25% from 2 KOLs
United States	20%
France	15%
Canada	20%-30% (25% used in calculation of average)
Italy	20%
Average	**20%**

KOL = key opinion leader.

B.3.3.1.5 Mortality for event-free patients

Observed data

Data characterising mortality risks for patients who had not yet experienced a progression event were available from CheckMate-816. In general, due to relatively immature follow-up data available for OS due to the early stage of disease and positive treatment impact, the number of pre-progression deaths were low; there were [redacted] pre-progression deaths out of 179 patients in the nivolumab + PDC arm and [redacted] pre-progression deaths out of 179 patients in the PDC arm. Kaplan-Meier curves for both treatment arms were overlapping (Figure 45), which suggested no difference in mortality, at the current trial follow-up, among EF patients between treatment arms. Therefore, data from both the treatment arms were pooled for conducting the parametric survival analyses of EF mortality with a larger sample size and therefore less uncertainty. It should be acknowledged however that assuming pooled OS for EFS patients is a conservative assumption; nivolumab + PDC may be prognostic on survival compared with chemotherapy alone in areas additional to delayed disease progression alone. The pooled Kaplan-Meier curve is illustrated in Figure 46. These data were still immature despite a larger sample size; [redacted]% of patients were event-free at the end of the trial follow-up.

Figure 45. CheckMate-816: mortality in event-free patients—observed data

chemo = chemotherapy; CI = confidence interval; HR = hazard ratio; KM = Kaplan-Meier; NE = not estimable; NIVO = nivolumab.

Figure 46. CheckMate-816: mortality in event-free patients—observed data (pooled)

CI = confidence interval; KM = Kaplan-Meier; NE = not estimable

Extrapolations

The goodness-of-fit statistics (AIC and BIC) of all distributions fitted are presented in Table 40. Based on the goodness-of-fit statistics, the generalised gamma (AIC = 301.2 and BIC = 312.9) and exponential (AIC = 304.1 and BIC = 308) distributions provided the best fit to the observed data. However, the difference in the AIC and BIC between all distributions was minimal (< 6 points). Therefore, external data were considered for selecting the best clinically plausible distribution.

Table 40. Mortality in event-free patients: goodness-of-fit statistics (pooled data)

Distribution	AIC	BIC
Generalised gamma	301.2	312.9
Log-normal	303.5	311.3
Exponential	304.1	308
Gompertz	304.5	312.3
Log-logistic	305.7	313.5
Weibull	306	313.8
Gamma	306	313.8

AIC = Akaike information criteria; BIC = Bayesian information criteria

Visual inspection of observed vs. predicted pre-progression survival curves in Figure 47 showed good fit during the observed follow-up for all distributions. The long-term projections (Figure 48) for the distributions differed substantially, as expected. Long-term survival estimates from the log-normal and log-logistic distributions were similar. Long-term projections from Gompertz and generalised gamma suggested a plateau after 100 months (approximately 8 years). Long-term survival estimates from exponential, Weibull and gamma distributions were relatively shorter. Table 41 details the predicted median and mean alive months from EF for all the distributions, along with the percentage of those who were EF at 1, 3, 5, 10, 20 and 30 years for the pooled population.

Figure 47. Mortality in event-free patients: within-trial fittings (pooled data)

KM = Kaplan-Meier.

Figure 48. Mortality in event-free patients: long-term extrapolations (pooled data)

KM = Kaplan-Meier.

Table 41. Mortality in event-free patients: predicted median, mean, and landmarks (pooled data)

Distribution	Median (months)	Mean (months)	1 year	3 years	5 years	10 years	20 years	30 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NE = not estimable.

Context and selection of base-case input

Given that most EF mortality extrapolations fit reasonably well in the short-term while diverging over the long-term, the predicted outcomes based on the extrapolations from CheckMate-816 were compared against observed outcomes from a separate patient-level meta-analysis conducted by BMS.[73] The meta-analysis pooled results observed in published neoadjuvant chemotherapy trials, and was sufficiently granular to allow for an analysis of EF mortality among those patients. Expert feedback collected from the Global HTA advisory board meeting, May 2022, confirmed that the meta-analysis is a reasonable source that can be used to better understand long-term mortality outcomes for EF patients To ensure the long-term CheckMate-816 extrapolations were plausible, estimates were capped to UK general population mortality (i.e., adjusted such that the minimum hazard of death is never lower than what would be expected among the general population for that age), with a sex distribution based on CheckMate-816 (Figure 49).

Figure 49. Patient-level meta-analysis versus long-term event-free mortality extrapolations from CheckMate-816

BMS = Bristol Myers Squibb; CM816 = CheckMate-816; KM = Kaplan-Meier.

When a general population mortality cap is applied, most of the projections estimated that patients would die more slowly versus what would have been expected based on the patient-level meta-analysis. Considering both good statistical fit (in terms of AIC/BIC) and the external data, the exponential distribution is selected in the model base case. The

exponential is also the predicting the most severe long-term event-free mortality which would be a conservative assumption given higher proportion of EFS in the nivolumab arm.

B.3.3.1.6 Mortality for patients with locoregional recurrence

Observed data

As in the estimates for EF mortality, estimates of mortality for patients who have experienced LR are pooled and assumed to be the same across treatment arms due to a relatively small number of events in the treatment (n = [redacted]) and control arms (n = [redacted]) respectively. Additionally, the Kaplan-Meier curves, developed using data collected from CheckMate-816, overlapped for the first 12 months following progression, after which nivolumab + PDC showed a benefit. However, the 95% CI of the estimated HR for the 2 curves crossed 1 (range, [redacted]), meaning that this difference was not statistically significant. Figure 50 presents the treatment-specific Kaplan-Meier curves, and Figure 51 presents the pooled Kaplan-Meier curve.

Figure 50. CheckMate-816: mortality after locoregional recurrence—observed data

chemo = chemotherapy; CI = confidence interval; HR = hazard ratio; KM = Kaplan-Meier; NE = not estimable; NIVO = nivolumab.

Figure 51. CheckMate-816: mortality after locoregional recurrence—observed data (pooled)

CI = confidence interval; KM = Kaplan-Meier; NE = not estimable

Extrapolations

Table 42 presents the goodness-of-fit statistics (AIC and BIC) of all fitted distributions. Based on the goodness-of-fit statistics, the log-logistic (AIC = 278.3 and BIC = 283) and exponential (AIC = 279.7 and BIC = 282.1) distributions provided the best fit to the observed data. However, the difference in the AIC and BIC between all distributions was minimal (< 6 points). Therefore, similar to all other extrapolations discussed, long-term projections and clinical expert opinion should be considered when selecting the most plausible distribution.

Table 42. Mortality after locoregional recurrence: goodness-of-fit statistics (pooled data)

Distribution	AIC	BIC
Log-logistic	278.3	283
Log-normal	278.6	283.2
Exponential	279.7	282.1
Gamma	280.5	285.1
Generalised gamma	280.5	287.5
Weibull	281	285.6
Gompertz	281.6	286.2

AIC = Akaike information criteria; BIC = Bayesian information criteria.

Visual inspection of observed versus predicted post-LR survival curves in Figure 52 shows that none of the distributions provided a good fit during the observed follow-up period. The long-term projections (Figure 53) for the distributions differed substantially. Long-term projections from generalised gamma, Gompertz, log-normal, and log-logistic were similar. Long-term survival estimates from exponential, Weibull, and gamma distributions were relatively shorter.

Figure 52. Mortality after locoregional recurrence: within-trial fittings (pooled data)

KM = Kaplan-Meier; LR = Locoregional Recurrence.

Figure 53. Mortality after locoregional recurrence: long-term extrapolations (pooled data)

KM = Kaplan-Meier; LR = Locoregional Recurrence.

Because none of the distributions provided a good fit to the observed post-LR mortality data, splines analyses of post-LR mortality data were performed. Up to 3 knots (i.e., up to 4 degrees of freedom [DFs]) and 3 scales (cumulative hazards, cumulative odds, or normal equivalent deviate [probit] scale) were used to fit post-LR mortality data in the pooled data from the nivolumab + PDC and PDC alone treatment arms. Table 43 presents goodness-of-fit of each fitted spline model.

Table 43. Mortality after locoregional recurrence: goodness-of-fit statistics for spline fitting (pooled data)

		Spline in pooled NIVO+PDC and PDC treatment arms	
Degree of freedom	**Scale**	**AIC**	**BIC**
2	Hazard	155.92	162.91
2	Odds	154.85	161.84
2	Normal	155.03	162.02
3	Hazard	151.59	160.91
3	Odds	151.67	161.00
3	Normal	152.06	161.38
4	Hazard	153.49	165.14
4	Odds	153.58	165.24
4	Normal	153.84	165.50

AIC = Akaike information criteria; BIC = Bayesian information criteria; NIVO = nivolumab; PDC = platinum doublet chemotherapy.

For post-LR survival, the models with 3 DFs on the hazard, odds and normal scale provided similar outcomes and the best fit to the observed data based on AIC and BIC. The predicted vs. observed plots and long-term extrapolations from these models with 2-4 DFs are shown in Figure 54. The models with 3 DFs provided a much better fit to the observed post-LR survival versus standard parametric models and models with 2 DFs by visual inspection. The models with 4 DFs produced similar fit to that with 3 DFs. Based on AIC and BIC and visual inspection, and a preference for simplicity (i.e., favouring fewer knots when the fit is similar), models with 3 DFs (2 knots) were selected to be the best-fitting spline.

The estimated median and mean post-LR survival were [redacted] and [redacted] months for the 3-DF model on the hazard scale, 27.1 and not estimable for the 3-DF model on the odds scale and [redacted] and [redacted] months for the 3-DF model on the normal scale, respectively. The plausibility of the estimated mean survival time confirmed that the 3-DF spline with hazard scale was the most appropriate fitting to be included in the model.

Figure 54. Mortality after locoregional recurrence: observed and predicted survival from 2-4 degrees of freedom on hazard, odds, and normal scales for short-term (top), long-term (bottom), and pooled data

DF = 2

DF = 3

DF = 4

DF = degree of freedom.

Context and selection of base-case input

The extrapolated estimates were compared against estimates from external data to assess the plausibility of the generated extrapolations. A source that precisely replicated the post-LR progression patients from CheckMate-816 was not available. Therefore, 2 sources were explored relating 3 populations that were different from the post-LR progression patients from CheckMate-816 but similar enough to serve as benchmarks. Specifically, this included the placebo arm from PACIFIC[132] (a trial of durvalumab in patients with stage III, unresectable NSCLC) and Goldstraw et al. (2016)[31], which reported long-term survival estimates for patients by stage (specifically, patients with stage IIIA disease and patients with stage IIIB were most relevant for this purpose). Figure 55 presents these curves, along with the best-fitting parametric and spline models for mortality in LR.

Figure 55. Comparison of mortality in Locoregional Recurrence health state versus PACIFIC[132] and Goldstraw et al. (2016)[31]

CM816 = CheckMate-816; DF = degree of freedom; LR = Locoregional Recurrence

The post-LR survival projected by log-logistic distribution was the most pessimistic estimation. The estimation by log-normal distribution and spline fitting with 2 DFs were similar. The 4 curves align well with the data from PACIFIC placebo arm. Spline fittings with 3 DFs and 4 DFs provided more optimistic and almost identical projection and align better with the curves from Goldstraw et al. (2016)[31] in the longer term.

In the Global HTA advisory board meeting, May 2022, the consensus among the consulted clinicians (see Appendix N) was that the stage IIIA population as reported in Goldstraw et al. (2016)[31] was the most appropriate population; therefore, the spline (DF = 3, hazard) should be favoured because it appears to adhere more closely to the Goldstraw stage IIIA Kaplan-Meier curve than the log-logistic extrapolation in the long run. Thus, the spline (DF = 3, hazard) is used in the base-case setting, and the log-logistic distribution is explored in sensitivity analysis.

The selection of the spline with 3 DF's and hazard scale is further justified by comparing it against other spline fittings in the long-term (Figure 56). The best-fitting spline with 2 DFs (odds scale) produces outcomes that align with parametric fittings in the long-term, and these did not fit well to the data (see Section B.3.3.1.6). The best-fitting spline with 4 DFs (hazard scale) produces outcomes similar to those obtained with the 3 DF (hazard scale) spline. Due to the similar outcomes between the 4 DF and 3 DF outcomes, the spline with fewer knots is preferred to prevent overfitting.

Figure 56. Long-term splines and parametric extrapolations

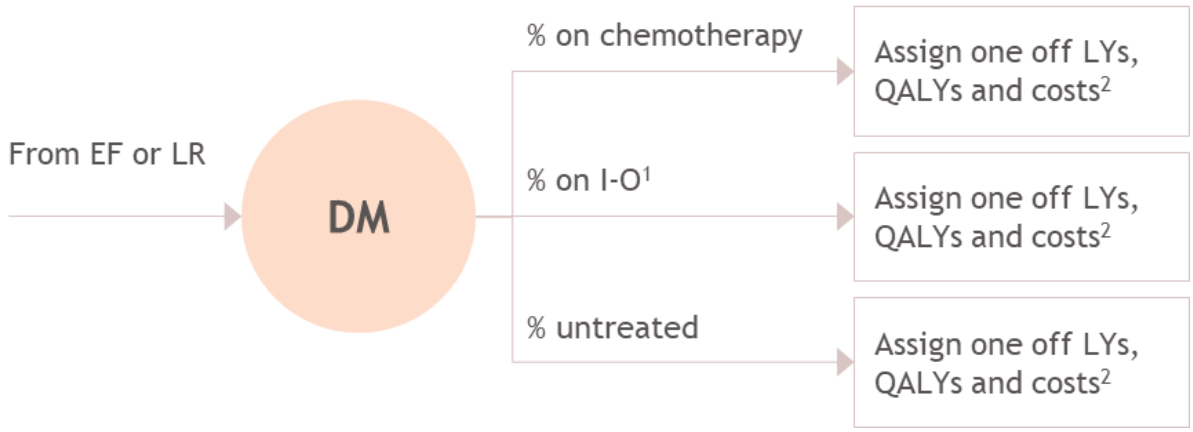
DF = degree of freedom; KM = Kaplan-Meier.

B.3.3.2 Distant Metastasis health state

Patients entered the DM health state upon experiencing a progression to distant metastasis from the EF or LR state and remained in the DM state until death. In the DM state, patients were expected to receive a mix of therapies for first-line metastatic disease, in line with UK clinical practice. Instead of explicitly modelling the outcomes for post-DM treatments, one-off LYs, QALYs, and costs were applied upon entry into the DM state (Figure 57). The one-off approach was selected to avoid developing a series of metastatic models that track progression and survival time in the DM state for various first-line metastatic therapies, which substantially increases the computational complexity and data burden of this neoadjuvant NSCLC CEM and is outside the scope of the current decision problem, which pertains to resectable non-metastatic NSCLC. The same approach was considered pragmatic and reasonable by the NICE Appraisal Committees in the 2018 submission of dabrafenib + trametinib in the adjuvant treatment of patients with melanoma.[133] In addition, the one-off modelling approach in the DM state was validated by clinical experts and health economists during the Global HTA advisory board meeting in May 2022, see Appendix N. Finally, in the recent adjuvant atezolizumab NSCLC NICE appraisal,[2] the company submission was criticised for having produced an adjuvant NSCLC CEM which was overly complex and produced metastatic NSCLC outcomes that were inconsistent with previous

NICE appraisals in first-line metastatic NSCLC; the one-off approach addresses this issue by allowing the outcomes from previous appraisals to be used directly as model inputs.

Figure 57. One-off approach for Distant Metastasis health state



DM = Distant Metastasis; EF = Event-Free; I-O = immuno-oncology; LR = Locoregional Recurrence; LY = life-year; QALY = quality-adjusted life-year.

[1] Multiple I-O therapies approved in England captured, with their respective LYs, QALYs and costs.

[2] This one-off cost captures all costs associated with the DM state, including costs for subsequent treatment (e.g., second line), associated resource use, and terminal care.

To populate the cost, life-year and QALY inputs associated with each of the first-line metastatic appraisals we scraped the published committee papers from the NICE website associated with each of the following STAs:

- TA770: Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer
- TA531: Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer
- TA683: Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, nonsquamous non-small-cell lung cancer
- TA584: Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer

Due to being consistently redacted it was not possible to extract the costs, life-years and QALY inputs from the respective committee papers. Therefore, to ensure the outcomes in our DM health state were reflective of the published costs, QALYs and life-years associated with the above approved first-line metastatic NSCLC NICE TAs, BMS proposed a collaboration with NICE so that NICE could directly incorporate the confidential outcomes into our economic model. By facilitating this approach, we could reduce uncertainty in the subsequent treatments section of our economic model.

NICE has agreed to this approach and is preparing the inputs for consideration during this submission's upcoming committee meeting. However, given the confidential nature of these values, NICE will not provide the inputs to BMS and the results of the economic model that incorporates these inputs will only be available as a confidential appendix that will be shared solely with the EAG and appraisal committee.

Because we cannot be provided the confidential inputs by NICE, BMS has sourced alternative input values for the cost, life-year and QALY input values, which can be used as placeholder values within the BMS base case cost effectiveness analysis for the purpose of this submission. These values were sourced from a previous NICE STA for nivolumab + ipilimumab in untreated advanced non-small cell lung cancer (TA724), specifically using the ERG-preferred values from the ACD document (Table 44)[134]. However, 2 relevant subsequent treatments were not included in this submission (pembrolizumab + carboplatin + paclitaxel in squamous NSCLC; atezolizumab monotherapy). Inputs for pembrolizumab + carboplatin + paclitaxel in squamous NSCLC were instead sourced from the nivolumab + ipilimumab submission for untreated advanced NSCLC submission to SMC.[135] Atezolizumab monotherapy was not included in either the NICE or SMC submission for nivolumab + ipilimumab in untreated advanced NSCLC and no publicly available information about costs, life-years and QALYs for this treatment could be identified. In the absence of data, input values for atezolizumab monotherapy were set equal to the other monotherapy immuno-oncology agent available in the UK, pembrolizumab (Table 44). Given that pembrolizumab has an approval in PD-L1> 50% only and atezolizumab is approved for any PD-L1, this assumption is likely to be biased. However, given the very limited uptake of atezolizumab in the UK at the time of submission (estimated to be [redacted]), the impact of this limitation on the model results is expected to be negligible. Finally, following clinical expert elicitation, it was advised that 25% of patients that are eligible for first-line metastatic NSCLC treatment may only receive best supportive care (BSC; palliative care only). Due to the paucity of data for the life-years and QALYs associated with BSC, we elicited expert opinion on the hazard ratio associated with BSC compared to patients receiving PDC. We then applied this hazard ratio (0.9) to the PDC life-years and QALYs to generate the input values for BSC.

Changes to the DM inputs are explored in sensitivity and scenario analyses, shown in Sections B.3.9.2 and 0.

Table 44. Inputs for Distant Metastasis health state

Outcome	Pembrolizumab	Pembrolizumab + carboplatin + paclitaxel (squamous)	Pembrolizumab + carboplatin + paclitaxel (nonsquamous)	Atezolizumab + carboplatin + paclitaxel (nonsquamous)	PDC	BSC
LYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Source	Table 14 of ID1566 nivolumab ERG comments on company response to ACD	Table 3 of unredacted SMC DAD	Table 12 of ID1566 nivolumab ERG comments on company response to ACD	Table 12 of ID1566 nivolumab ERG comments on company response to ACD	Calculated weighted average based on PDC subgroup values from ID1566 company submission and proportion of patients in CheckMate-9LA in squamous/non-squamous and PD-L1 > 50% subgroups from ID1566 company submission	LY and QALYs 0.9 times that of PDC based on UK clinical input

ACD = appraisal consultation document; DAD = detailed advice document; DM = Distant Metastasis; LY = life year; NSCLC = non-small cell lung cancer; PDC = platinum doublet chemotherapy; PD-L1 = programmed death-ligand 1; QALY = quality-adjusted life-year; SMC = Scottish Medicines Consortium.

Source: NICE (2021)[134],SMC (2021)[135]

In the model, immuno-oncology therapy retreatment restrictions are considered. In the base-case analysis, patients who progress on or within 6 months after treatment completion with nivolumab + PDC in the neoadjuvant setting are not eligible for further treatment with immuno-oncology therapies; for those patients, immuno-oncology therapy weights are set to zero and redistributed across remaining treatment options. A retreatment restriction of 6 months was selected following input from Peter Clark during the first appraisal committee meeting for adjuvant atezolizumab (TA10751), who notified the committee that the NHS were considering retreatment within 6-12 months. Six months is the most conservative of the two time points for our economic model results.

Based on data from CheckMate-816, [redacted] of patients treated with nivolumab + PDC experienced an event while on treatment or within 6 months of treatment completion and were not eligible for further treatment with immuno-oncology therapy. A scenario analysis was performed in which the retreatment restriction was extended to 12 months: [redacted] of patients treated with nivolumab + PDC experienced an event while on treatment or within 12 months.

Table 45 presents the distribution of treatments received in the DM health state based on market data collected by BMS. The distribution of treatments in the DM state are equally adjusted for nivolumab + PDC to reflect retreatment criteria, that is, [redacted] of patients treated with neoadjuvant nivolumab + PDC were not eligible for further immune-oncology treatment because they experienced an event while on treatment or within 6 months of treatment completion with nivolumab + PDC (Table 45).

Table 45. Distribution of treatment in Distant Metastasis health state

Treatment	Pembrolizumab	Pembrolizumab + carboplatin + paclitaxel (squamous)	Pembrolizumab + carboplatin + paclitaxel (nonsquamous)	Atezolizumab	PDC	BSC
Nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25.0%
PDC (neoadjuvant)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25.0%
Neoadjuvant CRT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25.0%
PDC (adjuvant)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25.0%
Surgery only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25.0%

CRT = chemoradiation; PDC = platinum doublet chemotherapy; BSC = best supportive care.

Source: BMS market share data on file

B.3.3.3 Cure assumption

As presented in Section B.1.3.4, long-term evidence exists that suggests patients who are treated for resectable non-metastatic NSCLC may be able to achieve cure, defined as (1) no risk of progression and (2) no excess cancer-related mortality versus an age- and sex-matched population. In general, inclusion of cure in the model rested on 3 key pillars:

- Engagement with clinical experts, among whom there was consensus that the cure assumption was reasonable in this indication
- Precedent from previous NICE appraisals, namely, inclusion of the cure assumption in NICE TA761[121] and NICE TA10751[2], and NICE's finding that this inclusion was indeed appropriate
- Empirical evidence, that is, trial data showing reduction in hazard of progression at 5 years, and EFS data among patients treated with neoadjuvant PDC from beyond 5 years showing "plateau"

B.3.3.3.1 Clinical expert feedback for cure assumption

The key rational for implementation of cure within the model relies on to the clinical plausibility and relevance. Therefore in terms of expert engagement, clinical experts with experience treating non-metastatic NSCLC were asked both as part of the UK HTA clinical expert meeting, March 2022 and the Global HTA advisory board meeting, May 2022 (Appendix N) about the plausibility of cure in this setting, as well as their assessment of the likely timepoint and proportion of patients achieving cure. There was broad consensus that cure is a plausible outcome that the model should consider, and that 5 years is an appropriate timepoint to consider cure as having occurred. However, there was no clear consensus on the percentage of patients achieving cure.

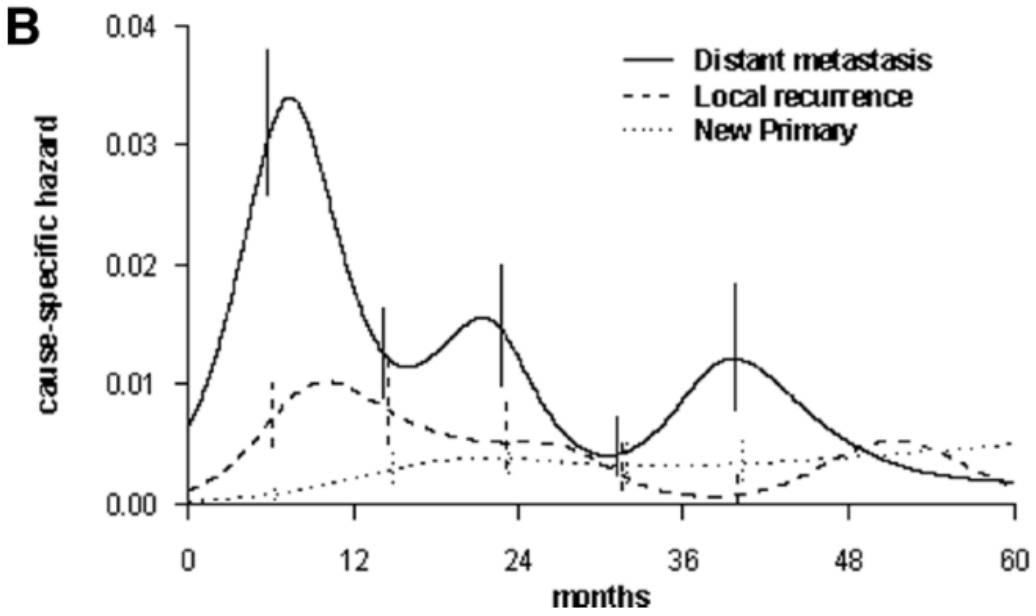
B.3.3.3.2 Precedent for cure assumption

In terms of precedent, 2 recent NICE appraisals in early-stage NSCLC included a cure assumption in the model based on clinical input and published evidence. The first of these was NICE TA761, which assessed adjuvant osimertinib with or without PDC in patients who had undergone surgical resection and had EGFR mutation-positive, early-stage NSCLC.[121] Specifically, in that submission, it was assumed that 95% of patients who were progression-free at 5 years would be cured (i.e., experience no further risk of progression) and return to mortality expected for an age- and sex-matched population without cancer.[121] While the EAG did note that the 5-year timepoint used in the submission might be "too generous," it did not criticise the use of the cure assumption itself, instead opting to use an 8-year timepoint in its recommended analysis.[121] The second recent appraisal is the appraisal of atezolizumab or adjuvant treatment of resected NSCLC.[2] In that appraisal a cure proportion of t 91.5% was assumed based on published literature and a cure timepoint of 5 year was applied in the company base case. The committee agreed that there were uncertainty around both cure timepoint and proportion but agreed that a cure timepoint of 6 or 7 years would be plausible for atezolizumab and 5 years for active monitoring in relation to the preferred survival extrapolations in that submission.

B.3.3.3.3 Empirical evidence

In terms of empirical data, 2 bodies of evidence were assessed that suggest cure. The first of these was a paper published by Demicheli et al. (2012)[42]. In this study, the authors sought to investigate how the hazard of different types of progression changes over time among patients with resected, early-stage NSCLC. As depicted in Figure 58, results of the study appear to suggest that the risk of LR or DM fluctuates over the first 5 years after resection, approaching zero at approximately 5 years.

Figure 58. Hazard of progression in early-stage resected NSCLC



NSCLC = non-small cell lung cancer.

Source: Demicheli et al. (2012)[42]; figure reprinted here without permission

Long-term EFS outcomes were also assessed across studies evaluating neoadjuvant PDC. Additional detail on the sources cited are provided in Appendix P. In general, the trend across all of the included studies showed that the EFS curves flatten out after approximately 5 years (Figure 59).

Figure 59. Long-term event-free survival from neoadjuvant PDC studies

NSCLC = non-small cell lung cancer; PDC = platinum doublet chemotherapy; US = United States.

Sources: Pless et al. (2015)[88]; Felip et al. (2010)[70]; Scagliotti et al. (2012)[91]; Pisters et al. (2010)[90]; NSCLC Meta-analyses Collaborative Group (2010)[56]; BMS data on file (2021)[73]; BMS data on file (2021)[131]

B.3.3.3.4 Implementation of cure in model

There are 2 potential methods that may be used to account for cure in survival extrapolations.[136] These are an "uninformed" approach, wherein the cure fraction is a model output based on observations from the relevant trial data, and an "informed" approach, wherein the cure fraction is a model input applied on the basis of known long-term survival estimates. Because no plateau suggesting cure was yet observed in the Kaplan-Meier data from CheckMate-816, the uninformed approach was ruled out as a method to consider cure in this model. Instead, based on the long-term observations and clinical expert input discussed in Section B.3.3.1.1, the informed approach was deemed to be feasible and was used in the model.

The implementation of cure in the model uses 3 key inputs:

- The proportion of patients achieving cure
- The timepoint at which cure is applied
- The period over which cure occurs

The pool of patients eligible for cure consists of those who have not yet experienced progression at the cure timepoint. Once the cure starting timepoint is reached, cure is applied using a constant rate over a period (with the specific rate calculated as a function of the period and cure proportion) until the full cure proportion is reached. The same cure parameters are applied to every treatment considered in the model; but the cured proportion

will differ across the treatment and comparator arm because transition probabilities from EF differs between treatments, so state membership in EF is different between arms over time. Table 46 presents the base-case cure parameters. As presented above and as discussed in the appraisals of osimertinib and atezolizumab there seems to be a clinical consensus that patients would be considered cured in a 5-8-year timeframe. However, there are still uncertainties around the exact cure timepoint as well as the proportion of patients being cured. Therefore, these assumptions were extensively tested in scenario analyses to investigate the impact of these assumptions on the results.

Table 46. Base-case cure parameters

Parameter	Input
Time at which patients in EFS begin to be considered cured	5 years
Time from beginning to end of cure process	2 years (year 5 to year 7)
Percentage of patients cured at completion of cure process	95%

EFS = event-free survival.

B.3.3.4 Adverse reactions

Adverse events may impact the costs associated with taking a given drug, as well as the quality of life of patients receiving treatment. Therefore, the safety profile of a given drug may be an important differentiating factor in a cost-effectiveness or cost-utility model. Grade 3 and 4 AEs were collected from CheckMate-816 trial data for neoadjuvant nivolumab + PDC and neoadjuvant PDC. Neoadjuvant CRT was assumed to have the same AE profile as neoadjuvant PDC. Adverse events for adjuvant PDC were collected from an SLR previously conducted by BMS.[137] Adverse events were considered not to be applicable to the surgery only arm, as these patients do not receive systemic therapy.

Lower-grade AEs (i.e., grade 1 to 2) were not considered, as they are generally not understood to have significant cost or quality of life implications (typically, grade 1 to 2 AEs are manageable by the patient, e.g., via over-the-counter medication, whereas grade 3 or 4 AEs require inpatient management).

Specific events included were those experienced by at least 5% or more of patients in at least 1 of the comparators included in the model. Rates were generally similar between nivolumab + PDC and PDC alone. The consequences of AE captured by the model were expressed in terms of their management cost (see Section B.3.5.3.1 for more detail) and utility (see Section B.3.4.4.2 for more detail). In addition, only AEs associated with initial (i.e., current line) treatment were considered, and AEs associated with subsequent lines were not considered. Table 47 presents the percentage of patients experiencing a grade 3 or 4 AE by treatment arm.

Table 47. Percentage of patients experiencing grade 3 or 4 adverse events

Event	NIVO+PDC	Neoadjuvant PDC	Neoadjuvant CRT	Adjuvant PDC	Surgery only
Anaemia	4.0%	5.1%	5.1%	8.2%	0.0%
Neutropenia	16.5%	22.7%	22.7%	51.1%	0.0%

Event	NIVO+PDC	Neoadjuvant PDC	Neoadjuvant CRT	Adjuvant PDC	Surgery only
Leukopenia	1.7%	3.4%	3.4%	16.3%	0.0%
Thrombocytopenia	2.3%	0.6%	0.6%	5.2%	0.0%
Fatigue or asthenia	0.6%	1.7%	1.7%	10.9%	0.0%
Nausea and/or vomiting	2.2%	1.2%	1.2%	13.7%	0.0%
Sources	CheckMate-816[83]		Assumed same as neoadjuvant PDC	BMS SLR (Appendix D)	Not applicable

CRT = chemoradiation; NIVO = nivolumab; PDC = platinum doublet chemotherapy; SLR = systematic literature review.

B.3.4Measurement and valuation of health effects

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

B.3.4.1.1 Methods

EQ-5D-3L utility data were collected in the CheckMate-816 clinical study in line with the clinical study protocol. The utility analysis used the EQ-5D-3L index score (utility index) at all timepoints in the study.

As per protocol, patients completed the EQ-5D-3L on the first day of each 3-week treatment cycle at baseline (day 1 of the first 3-week cycle) and on day 1 of every cycle during the neoadjuvant period (baseline and 2 on-treatment assessments), then post-neoadjuvant visits 1 (30 days from last dose and before surgery) and 2 (70 days from post-neoadjuvant visit 1). EQ-5D-3L was also completed in the adjuvant period (3 months after post-neoadjuvant visit 2 or after surgery) every 3 weeks for up to 4 cycles. The timing and number of EQ-5D-3L assessments were the same during the neoadjuvant period (baseline, week 4, week 7, and post-neoadjuvant visit 1) but after that could vary within patients and between treatment arms depending on whether patients underwent surgery or received adjuvant treatment. The dates of the EQ-5D-3L assessments were used to assign EQ-5D-3L assessments to health states (days were calculated relative to the date of randomisation + 1 day).

B.3.4.1.2 Estimating utility values for health states

For patients with progression or recurrence, EQ-5D-3L assessments were grouped by the date of the EQ-5D-3L assessment relative to the date of progression or recurrence and by the type of recurrence (locoregional or distant metastases) and classified as pre-progression, locoregional recurrence, or distant metastases. Patients with progression type recorded as “not reported” were classified as locoregional recurrence and those with “both locoregional and distant metastases” were classified as distant metastases.

To estimate mean values of EQ-5D-3L for each health state, a mixed-model approach was used to account for repeated EQ-5D-3L measurements per patient within a health state (mixed model for repeated measures). The initial model (intercept only) did not include any health states in order to estimate the mean utility overall and by treatment group. For each

health-state model, 2 statistical models were fit: one with and one without treatment. The variables defining health states, treatment, and their interaction, if any, were included in the model as fixed effects. The model without treatment included the health states only. The model with treatment included treatment, health state, and the interaction of treatment and health state in the model. A random intercept was used to account for repeated measurements within each patient. An unstructured covariance structure was used. The baseline EQ-5D-3L was considered a pre-progression value (not included as a covariate), and there was no imputation of missing data.

B.3.4.1.3 Utility results

Among the 353 patients eligible for analysis, there were [redacted] utility index observations available, with [redacted] observations before progression or recurrence in [redacted] patients and [redacted] observations after progression or recurrence in [redacted] patients. Of the [redacted] post-progression observations, [redacted] ([redacted] patients) were after locoregional recurrence, and [redacted] ([redacted] patients) were after distant metastases.

Table 48 presents the mean utility estimates for type of recurrence by health-state utility (pre-progression or recurrence, locoregional recurrence, and distant metastases). The comparison of models with and without treatment did not show any statistically significant difference in model fit (P = 0.355), indicating no significant difference between treatments.

Table 48. EQ-5D-3L utility index (UK weights): number of patients, observations, and least squares mean estimates

	Model without treatment	Model with treatment		
Health state	**Overall**	**Overall**	**NIVO+PDC**	**PDC**
No. of patients/no. of observations				
Pre-progression or recurrence	[redacted]	[redacted]	[redacted]	[redacted]
LR	[redacted]	[redacted]	[redacted]	[redacted]
DM	[redacted]	[redacted]	[redacted]	[redacted]
Least squares means (95% CI)				
Pre-progression or recurrence	[redacted]	[redacted]	[redacted]	[redacted]
LR	[redacted]	[redacted]	[redacted]	[redacted]
DM	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; DM = Distant Metastasis; LR = Locoregional Recurrence; NIVO = nivolumab; PDC = platinum doublet chemotherapy; UK = United Kingdom.

B.3.4.2 Mapping

EQ-5D data were collected in CheckMate-816 in line with the NICE reference case. Utility values for AEs for which CheckMate-816 data could not be used were obtained from the literature. Therefore, there was no need to use mapping techniques.

B.3.4.3 Health-related quality of life studies

An SLR was undertaken to identify HRQOL studies relevant to the decision problem from the published literature. In particular, costs and utility data related to neoadjuvant, peri-adjuvant, and adjuvant treatment of early-stage NSCLC in Australia, Canada, France, Germany, Italy, Spain, the UK, and the US were sought. The SLR followed established best practices used in systematic review research[138,139] and was conducted according to the PRISMA guidelines.

Searches were performed in the MEDLINE and MEDLINE in-process (via PubMed) database, the National Health Service's Economic Evaluation Database (NHS EED), and the Embase database to identify articles on human subjects published from the start of database indexing to May 2022. The SLR also captured a review of the grey literature, which included data from sources that were not indexed in the literature databases but were available from various scientific conferences or website.

The SLR was performed using the inclusion and exclusion criteria and the search strategy. In summary, it included observational studies, RCTs, and primary data from economic analyses reporting cost and utility data for adults with early-stage NSCLC. Appendix H presents full details of the search and a summary of the studies identified.

A total of 23 studies, reporting data on 20 unique study populations, were identified that met the eligibility criteria for the review.[23,63-81] However, none of the studies evaluated reported on EQ-5D in an appropriate population. Because no studies using the EQ-5D or mapping utilities were identified, detailed data extraction of the identified studies is not presented in this submission. Utilities from the CheckMate-816 study are used in the CEM in line with the reference case.

B.3.4.4 Health-related quality of life data used in the cost-effectiveness analysis

Table 49 summarises the utilities used in the model base case. Overall, non–treatment-specific utilities by health state were used and were applicable for all comparators equally.

Table 49. Summary of utility values for cost-effectiveness analysis

Health state	Utility value: mean (standard error)	95% CI
Event-Free	[redacted]	[redacted]
Locoregional Recurrence	[redacted]	[redacted]

CI = confidence interval.

As noted above, the model applies a one-off QALY consequence in the DM health state; therefore, no utility value was associated with this health state.

The utility values from the CheckMate-816 trial are higher than might be expected for patients with NSCLC in the UK given that the age-adjusted utility value for the general population has been reported at 0.833.[140]

Clinical input received as part of the UK HTA clinical validation meeting, August 2022 indicated that they thought that the absolute values for both EF and LR seemed a higher than expected and that specifically the decrement from EF to LR was smaller than expected.

To at account for the higher absolute values for utilities in both health states the EF value was therefore capped at general population mortality in the base case and LR based on the EF to LR decrement observed in CheckMate-816. Given the clinical input received on the decrement likely being smaller than clinically expected this could be seen as a conservative assumption with regards to treatment effect. The trial values without adjustment were tested in a scenario analysis. Table 50 presents the alternative health-state utilities included in the base case and scenario analysis.

Table 50. Alternative utility estimates used in the base case and scenario analysis

	Description	EF	LR	LR to EF decrement
Base case	CM-816 EF capped with general population, with LR decrement from CM-816	0.833	[redacted]	[redacted]
Scenario	Unadjusted values from CM-816	[redacted]	[redacted]	[redacted]

CM-816 = CheckMate-816; EF = Event-Free; LR = Locoregional Recurrence.

B.3.4.4.1 Impact of adverse events on utility

Utility decrements were included in the model to capture the effect of grade 3/4 AEs on HRQOL, reflecting the safety profile of each treatment.

The model estimated the average QALY loss due to AEs for each treatment by considering the treatment-specific AE rates, the mean utility decrements associated with these AEs, and the mean duration of each AE episode.

Only grade 3/4 AEs occurring in ≥ 3% of patients in the study were included. The total mean QALY loss associated with AEs for each treatment was determined by calculating the sum of individual QALY loss associated with each AE. The total QALY loss due to AEs was applied once at the start of the model, assuming that AEs occurred within the early period of treatment. Utility decrements associated with AEs were not explicitly collected in the CheckMate-816 utility study; these values were sourced from the published study by Nafees et al. (2008)[141]. The study by Nafees et al. (2008)[141] considered HRQOL, as measured by the EQ-5D, in patients with metastatic NSCLC. However, there is a more recent study from Nafees et al. (2017)[142]. Of note, the 2008 study used the standard gamble (SG) valuation method to determine utility scores, whereas the 2017 study used the time–trade-off (TTO) method. Evidence suggests that TTO and SG methods do not produce the same estimates, and differences between these 2 approaches may be greater in more severe health states[143]. In addition, the TTO method tends to produce lower utilities than the SG method[143]. The application of higher disutilities from the Nafees et al. (2008)[141] publication should be seen as a conservative assumption for this analysis. If there were no data for certain AEs, utility decrements were based on assumptions (Table 51).

Table 51. Adverse event–related disutilities

Adverse event	Disutility	Reference/note
Anaemia	−0.08973	Assumed the same as neutropenia
Neutropenia	−0.08973	Nafees et al. (2008)[141]
Leukopenia	−0.08973	Assumed the same as neutropenia
Thrombocytopenia	−0.08973	Assumed the same as neutropenia
Fatigue or asthenia	−0.07346	Nafees et al. (2008)[141]
Nausea and/or vomiting	−0.04802	Nafees et al. (2008)[141]

B.3.4.4.2 Age adjustment

An age adjustment was applied to the utility values in the model based on the latest NICE DSU report on estimating EQ-5D-3L by age and sex for the UK.[140] Different sources used to adjust health-state utility values can produce varying estimates, and there is currently no guidance from NICE on the preferred source for age adjustment of utility in economic models. The DSU report provides EQ-5D-3L estimates by age and sex from 2 sets of more recent sources: the 2014 wave of the Health Survey for England (HSE) and a large-scale UK survey conducted by the Economic Methods of Evaluation in Health and Social Care Policy Research Unit (EEPRU). The DSU recommended to use the estimates obtained by HSE, which indicated that the EQ-5D-3L decreases as age increases; these estimates were consistent with published studies.

In the model, the set of expected EQ-5D-3L estimates by age and sex using HSE 2014 data was applied as the norms for the general UK population. First, the baseline mean utility was assigned to the model starting age (63.9 years), and the EQ-5D-5L norms at 63.9 years were considered as the reference (female = 0.8124, male = 0.8412, weighted = 0.8329). An age-adjustment multiplier was assigned to each age by comparing its EQ-5D-5L estimate with the reference utility. For example, the multiplier for age 75 years was calculated as follows: the utility norm 0.7866 at age 75 is (female = 0.7561, male = 0.7990, weighted = 0.7866) divided by reference 0.8329 = 94.4%. The age-adjusted utility values used in the model were derived by applying this multiplier to the mean utility for each health state. Therefore, for patients at 75 years of age in the EF state, the age-adjusted utility is 0.824 (0.872 × 94.4%).

B.3.5Cost and healthcare resource use identification, measurement, and valuation

Modelled costs are linked to disease states and treatments received; therefore, costs are closely linked to clinical outcomes. Key cost categories and what they include are summarised in Table 52 and below. Figure 60 presents costs by health state.

Costs included costs of treatment (drug acquisition and administration) for patients receiving neoadjuvant and adjuvant treatment. Treatment costs were also modelled for patients in the LR and DM health states. Costs of surgery were applied for patients undergoing surgical resection in the EF state. In addition, the model incorporated costs of routine MRU and treatment monitoring, AE management, and terminal care costs.

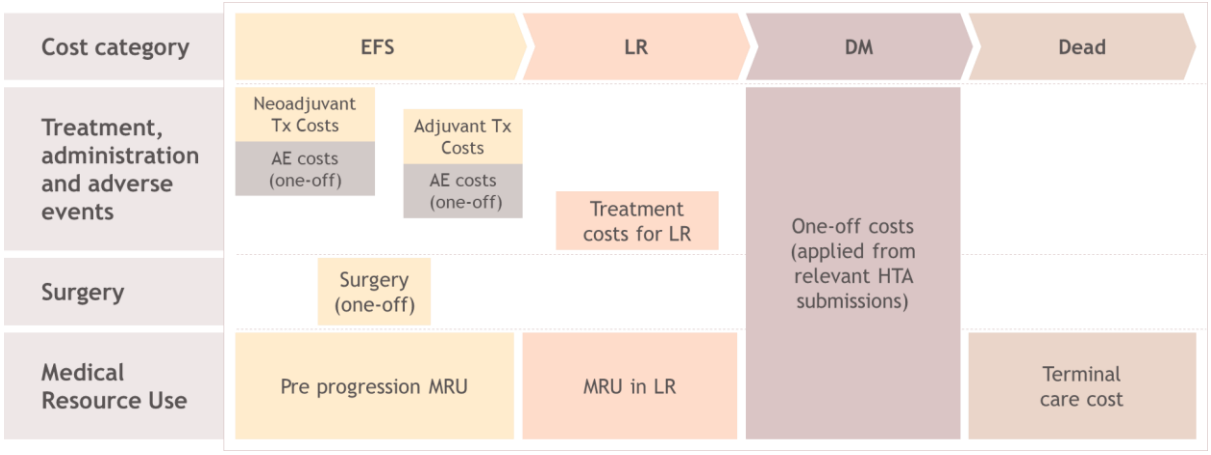
Unit costs of drug acquisition, administration, surgery, AEs, and MRU for routine care and treatment monitoring were abstracted from standard costing databases in the UK.

Table 52. Summary of costs in the economic model

Cost category	What is included?
Drug acquisition costs	Costs for intervention and comparator medications. Drug acquisition costs considered depend on the treatment regimens included in the neoadjuvant and adjuvant setting (e.g., for neoadjuvant strategies, this reflects neoadjuvant drugs; for adjuvant strategies, this reflects adjuvant drugs).
Drug administration costs	Patients who receive intravenous drugs will incur an intravenous administration cost per each visit.
Surgery costs	One-time cost of surgical resection for patients in the EF health state. Surgery costs are adjusted for the proportion of patients receiving each surgical approach (i.e., thoracotomy vs. minimally invasive operation).
Routine MRU and treatment monitoring	Considers costs of routine MRU and monitoring associated with the disease state and treatment received. Costs include general practitioner, nurse, and oncologist visits; laboratory tests; and scans.
AE management costs	Only grade 3+ AEs by CTCAE are included because events less severe than grade 3 are expected to not impose significant costs. AE costs are estimated as an average of costs for each AE considered, weighted by the incidence of each event.
Terminal costs	Cost of end-of-life care for patients who enter the Dead health state (estimated as a weighted average of patients receiving end-of-life care in hospice, hospital, or at home).

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; EF = Event-Free; MRU = medical resource use.

Figure 60. Costs by health state



AE = adverse event; DM = Distant Metastasis; EFS = event-free survival; HTA = health technology assessment; LR = Locoregional Recurrence; MRU = medical resource use; Tx = treatment.

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Drug acquisition cost of neoadjuvant treatment

The cost of neoadjuvant treatment reflects nivolumab and the basket of PDC received in CheckMate-816. Table 53 presents the composition of PDC in the nivolumab + PDC and PDC alone treatment arms. For patients in the nivolumab + PDC arm, all patients received nivolumab in addition to the listed distribution of PDC. The distribution of PDC for the neoadjuvant CRT comparator was assumed to be the same as the distribution from neoadjuvant PDC. However, during the UK HTA clinical validation meeting, August 2022, clinical experts advised that gemcitabine is not given concurrently with CRT because it is radio-sensitising and that vinorelbine is most widely used in the UK. To reflect this, cisplatin + gemcitabine and carboplatin + gemcitabine shares were set to [redacted]% and added to cisplatin + vinorelbine and carboplatin + vinorelbine, respectively.

Table 53. Distribution of PDC received in the neoadjuvant setting

PDC types		NIVO+PDC[a]	Neoadjuvant PDC	Neoadjuvant chemoradiation[b]
Cisplatin +	Pemetrexed	[redacted]	[redacted]	[redacted]
	Gemcitabine	[redacted]	[redacted]	[redacted]
	Vinorelbine	[redacted]	[redacted]	[redacted]
	Docetaxel	[redacted]	[redacted]	[redacted]
Carboplatin +	Paclitaxel	[redacted]	[redacted]	[redacted]
	Pemetrexed	[redacted]	[redacted]	[redacted]
	Gemcitabine	[redacted]	[redacted]	[redacted]
	Vinorelbine	[redacted]	[redacted]	[redacted]
	Docetaxel	[redacted]	[redacted]	[redacted]

NIVO = nivolumab; PDC = platinum doublet chemotherapy.

[a] In addition to the specified PDC, all patients in this treatment arm also received nivolumab.

[b] In addition to the specified PDC, all patients in this treatment arm also received radiation therapy.

Patients incurred costs for 3 full cycles of neoadjuvant treatment. For patients who progressed before completing 3 cycles of treatment, costs of neoadjuvant treatment were applied until the time of progression.

For patients who continued to receive adjuvant treatment after surgery, costs were adjusted for the proportion of patients receiving adjuvant treatment and the type of treatment received informed by the CheckMate-816 trial (Table 54). Treatment costs were applied for the mean number of treatment cycles received among patients in the adjuvant setting in the CheckMate-816 trial.

Table 54. Patients on neoadjuvant treatments who continue with adjuvant treatments

Treatment	% receiving adjuvant systemic therapy (PDC)	% receiving adjuvant radiotherapy
NIVO+PDC	[redacted]	[redacted]
Neoadjuvant chemoradiation	[redacted]	[redacted]

NIVO = nivolumab; PDC = platinum doublet chemotherapy.

B.3.5.1.2 Drug acquisition cost of adjuvant treatment

The distribution of treatment regimens for adjuvant PDC (Table 55) was assumed to be the same as the regimen distribution for neoadjuvant PDC (see Table 53). Adjuvant PDC was administered for 3 cycles.

Table 55. Treatments received in the adjuvant setting

Therapy received		Adjuvant PDC
Cisplatin +	Pemetrexed	[redacted]
	Gemcitabine	[redacted]
	Vinorelbine	[redacted]
	Docetaxel	[redacted]
Carboplatin +	Paclitaxel	[redacted]
	Pemetrexed	[redacted]
	Gemcitabine	[redacted]
	Vinorelbine	[redacted]
	Docetaxel	[redacted]

PDC = platinum doublet chemotherapy.

B.3.5.1.3 Drug dose and unit costs

The dosing regimen for each treatment option included in the neoadjuvant and adjuvant settings was based on the dosing used in the CheckMate-816 trial (Table 56). The dosing of some intravenous treatments depends on a patient's body surface area (BSA). A mean BSA of 1.84 m^2 was derived based on patient characteristics in CheckMate-816 (Table 57) and the average height of the UK population.

Table 58 presents unit costs and package information for each treatment option. For treatments that depend on BSA, there is potential for drug wastage if perfect vial sharing is not implemented. For the base case, the model included drug wastage (no vial sharing).

Table 56. Dosing regimen for each treatment

Treatment	Dose dependency	Dose per administration	Administration route	Treatment cycle length (weeks)	Number of administrations per treatment cycle
Nivolumab	Fixed dose	360 mg	IV	3	1
PDC (neoadjuvant and adjuvant)					
Carboplatin	AUC	900 mg	IV	3	1
Cisplatin	BSA	75 mg/m^2	IV	3	1
Paclitaxel	BSA	175 mg/m^2	IV	3	1
Gemcitabine	BSA	1,250 mg/m^2	IV	3	2
Pemetrexed	BSA	500 mg/m^2	IV	3	1
Docetaxel	BSA	75 mg/m^2	IV	3	1
Vinorelbine	BSA	25 mg/m^2	IV	3	2
Radiotherapy	1.5 gy twice daily (45 gy in 3 weeks)			3	30

AUC = area under the curve; BSA = body surface area; IV = intravenous; PDC = platinum doublet chemotherapy.

Table 57. Patient characteristics: weight and estimation of body surface area

Patient characteristics	Mean (SD)	Source
Starting age (years)	[redacted]	CheckMate-816[83]
Weight (kg)	[redacted]	CheckMate-816[83]
Height (cm)	Male: 178.21 Female: 163.94	World Population Review (2022)[144]
BSA (m^2)[a]	1.84 (0.184)	Gehan and George (1970)[145]

BSA = body surface area; SD = standard deviation.

[a] BSA estimated using the Gehan and George formula: 0.01545 × (height^0.54468) × (weight^0.46336).

Table 58. Unit drug acquisition costs

	Treatment	Cost per pack/vial	Dose/vial concentration	Pack size/vial volume	Source
PDC	Carboplatin	£13.51	450 mg	1	Drugs and pharmaceutical electronic market information tool[146]
	Cisplatin	£8.97	100 mg	1	
	Paclitaxel	£15.97	300 mg	1	
	Gemcitabine	£9.37	38 mg/mL	26.3 mL	
	Docetaxel	£8.90	80 mg	1	
	Vinorelbine	£57.88	10 mg	10	
	Pemetrexed	£800.00	500 mg	1	Monthly Index of Medical Specialities – UK Drug Database[147]
Other drugs	Nivolumab	£439.00	10 mg/mL	4 mL	

PDC = platinum doublet chemotherapy; UK = United Kingdom.

B.3.5.1.4 Drug administration costs

Drug administration cost was applied per administration for drugs administered intravenously. Unit costs for drug administration were based on values reported in the UK National Schedule of NHS Costs (Table 59). A cost of £363.09 was applied in the first treatment cycle, and a cost of £261.58 was applied for subsequent cycles.

Table 59. Drug administration costs

Administration type	Cost per administration	Source
Deliver complex chemotherapy, including prolonged infusional treatment, at first attendance (SB14Z, outpatient)	£363.09	National Schedule of NHS Costs for 2019-2020[148] (inflated to 2020/2021 values)
Deliver subsequent elements of a chemotherapy cycle (SB15Z, outpatient)	£261.58	

NHS = National Health Service.

B.3.5.1.5 Cost of radiotherapy

Unit costs for radiotherapy were based on values reported in the UK National Schedule of NHS Costs (Table 60). A cost of £2,200.73 was applied for radiotherapy given as part of neoadjuvant CRT, and a cost of £153.86 was applied for postoperative radiotherapy.

Table 60. Radiotherapy costs

Administration type	Cost per administration	Source
Deliver a fraction of complex treatment on a megavoltage machine (SC23Z, outpatient)	£153.86	National Schedule of NHS Costs for 2019-2020[148] (inflated to 2020/2021 values)
Deliver a fraction of intraluminal brachytherapy (SC30Z, outpatient)	£2,200.73	

NHS = National Health Service.

B.3.5.1.6 Cost of surgery

The proportion of patients undergoing surgery after nivolumab + PDC was informed by the CheckMate-816 trial. The proportion of patients undergoing surgery after neoadjuvant CRT was assumed to be the same as the proportion of patients in the neoadjuvant PDC arm. For adjuvant comparators, the proportion undergoing surgery was informed by the literature.[70] For patients only undergoing surgery without any systemic therapy, the proportion of potentially resectable patients who received surgery was assumed to be the same as that observed for adjuvant treatment, given that, in both cases, patients would not receive any treatment between model entry and surgery.

The costs of surgery were estimated as a weighted average of costs by surgery approach (minimally invasive surgery vs. thoracotomy). In the model, the proportion of patients undergoing each type of surgery was based on observed patterns for patients enrolled in CheckMate-816[149] (Table 61).

Table 61. Rate of surgery and distribution of surgical approach by treatment

Treatment	% of patients undergoing surgery	% of patients undergoing thoracotomy[a]	% of patients undergoing minimally invasive surgery[a]
NIVO+PDC	83.2%	70.5%	29.5%
Neoadjuvant CRT	75.4%	78.5%	21.5%
PDC (adjuvant)	95.7%	78.5%	21.5%
Surgery only	95.2%	78.5%	21.5%

CRT = chemoradiation; NIVO = nivolumab; PDC = platinum doublet chemotherapy.

[a] As a proportion of patients undergoing surgery.

The distribution of surgical approach for other comparators (neoadjuvant CRT, adjuvant PDC, and surgery only) was assumed to be the same as the distribution for neoadjuvant PDC. Unit costs of surgery for each surgical approach were obtained from the UK National Schedule of NHS Costs (Table 62). Table 63 presents the estimated surgery costs for each treatment in the model.

Table 62. Unit costs for surgery

Surgery approach	Unit cost	Source
Thoracotomy (DZ02H-M weighted average, elective inpatient)	£9,873.41	National Schedule of NHS Costs for 2019-2020[148] (inflated to 2020/2021 values)
Minimally invasive (DZ67Z, elective inpatient)	£3,242.25	

NHS = National Health Service.

Table 63. Estimated costs of surgery by treatment arm

Treatment	Cost of surgery[a]
NIVO+PDC	£6,587.13
PDC (neoadjuvant)	£6,369.57
Neoadjuvant CRT	£6,369.57
PDC (adjuvant)	£8,084.46
Surgery only	£8,042.22

CRT = chemoradiation; NIVO = nivolumab; PDC = platinum doublet chemotherapy.

[a] Calculated by weighting unit costs for surgery (Table 62) based on rate of surgery and distribution by surgical approach (Table 61).

B.3.5.2 Health-state unit costs and resource use

B.3.5.2.1 Treatment for patients in Locoregional Recurrence health state

Treatment costs for patients in the LR health state were estimated using a basket approach. Treatment costs for LR were applied as a one-time cost, calculated as a weighted average of costs of PDC, single-modality radiotherapy, and surgery. The distribution of treatment modalities for patients in the LR health state is informed by

interviews with KOLs and reflects current clinical practice in the UK (Table 64). Data relating to treatment patterns among progressed patients in the CheckMate-816 trial were considered immature and therefore were not used.

Table 64. Distribution of patients in Locoregional Recurrence health state by treatment modality

Treatment modality	Distribution of patients	Source
PDC	58%	Key opinion leader validation interview
Radiotherapy	30%	
Salvage surgery	17.5%	
No treatment	22.5%	

PDC = platinum doublet chemotherapy.

Unit costs for each treatment modality were extracted from standard costing databases in the UK. Four cycles of cisplatin + pemetrexed were considered for the costing of PDC during the LR health state aligned with PDC regimen used for costing in the osimertinib NICE appraisal in adjuvant non-metastatic NSCLC.[121] The total weighted cost of treatment for patients in the LR state was estimated to be £6,913 per patient.

B.3.5.2.2 Routine medical resource use and treatment monitoring costs

The costs of routine MRU were applied for patients in the EF and LR health states. Costs were not estimated for the DM health state because a one-off costing approach was applied for DM in the model (see Section B.3.3.2).

A micro-costing approach was applied to estimate costs for routine MRU for patients in the EF and LR states. The monthly cost of MRU was calculated as the sum of costs across MRU categories, where costs for each MRU category were estimated as a product of frequency of MRU and respective unit cost. The model includes the flexibility to apply an aggregated cost of routine care for the EF and LR states.

Routine MRU frequency for patients in the EF and LR states was informed by the LuCaBIS study by Andreas et al. (2018)[150]. The LuCaBIS study[150] was used to inform MRU for routine care in a previous HTA submission for NSCLC.[151]

Unit costs for clinic visits, hospitalisation, and diagnostics were extracted from the UK National Schedule of NHS Costs. The overall annual cost of MRU was estimated to be £3,019 per year for patients in the EF health state and £9,305 per year for patients in the LR state. Table 65 and Table 66 describe the frequency of MRU and unit costs for routine medical care for patients in the EF and LR states in the model.

Table 65. Routine medical resource use annual frequency by health state

MRU category	Health state	
	EF	LR
Nurse visit	0	12
Oncologist visit	2.24	8.28
Surgeon visit	1.69	2.4
Other specialist visit	4	4
Hospitalisation	0.2	1
Emergency department visit	0.76	1.56
Computed tomography scan	2	3
Magnetic resonance imaging	0	1
Positron emission tomography scan	0.2	2
Electrocardiogram	1	1

EF = Event-Free; LR = Locoregional Recurrence; MRU = medical resource use; UK = United Kingdom.

Source: Resources from [150] and adjusted based on UK clinical input (Appendix N)

Table 66. Unit costs for routine medical resource use

MRU category	Service code, currency code	Unit costs for routine MRU	Source
Nurse visit	NURS, N02AF	£44.78	National Schedule of NHS Costs – Year 2019-20[148] (inflated to 2020/2021 values)
Oncologist visit	370, WF01A	£206.36	
Surgeon visit	173, WF01A	£189.59	
Other specialist visit	370, WF01A	£206.36	
Hospitalisation	EL, DZ17L-V[a]	£2,931.05	
Emergency department visit	AE, VB01Z-09Z[a]	£208.55	
Computed tomography scan	IMAGOP, RD22Z	£190.86	
Magnetic resonance imaging	IMAGOP, RD03Z	£315.99	
Positron emission tomography scan	IMAGOP, RN07A	£749.69	
Electrocardiogram	320, EY51Z	£134.27	

MRU = medical resource use; NHS = National Health Service.

[a] Elective inpatient; calculated as a weighted average.

Treatment monitoring costs were applied when patients were on treatment and receiving monitoring tests such as full blood count or liver function test. Table 67 presents the frequency of patients receiving monitoring tests during the EF and LR health states, along with the unit costs of the tests.

Table 67. Treatment monitoring costs

	Full blood count	Metabolic panel	Liver function test	Renal function test	Sources
Treatment monitoring frequency per cycle during EF health state (for all comparators)	1	1	1	1	Key opinion leader validation interview
Total treatment monitoring frequency during LR health state (for all comparators)	4	4	4	4	
Unit cost of tests	£2.63	£9.89	£8.65	£12.36	National Schedule of NHS Costs – Year 2019-20[148] (inflated to 2020/2021 values)

EF = Event-Free; LR = Locoregional Recurrence; NHS = National Health Service.

B.3.5.2.3 Terminal care costs

A one-off cost of terminal care was applied to patients who entered the Dead health state. The cost of terminal care was estimated as a weighted average of costs of end-of-life care received in 3 different settings: hospice, hospital, and at home. The proportion of patients receiving each type of end-of-life care was informed by sources used in the recent osimertinib submission for adjuvant treatment of EGFR-positive NSCLC after complete resection.[151] Unit costs for terminal care were extracted from standard costing databases and previous HTA submissions. The one-time cost of terminal care was estimated to be £2,338.74 (Table 68).

Table 68. Distribution of patients by type of end-of-life care and costs of terminal care

Resource	% of patients	Cost	Sources
Hospital	55.8%	£2,386.88	Distribution of patients: Brown et al. (2015)[152]
Hospice	16.9%	£2,983.59	Costs: NICE TA761[151]; National Schedule of NHS Costs for 2018-2019[153] (inflated to 2020/2021 values)
Home	27.3%	£1,841.15	

NHS = National Health Service.

B.3.5.3 Adverse reaction unit costs and resource use

B.3.5.3.1 Adverse event management costs

Costs of grade 3 or 4 AEs occurring in ≥ 5% of patients in CheckMate-816 were considered in the model. Adverse event costs were applied as a one-time cost in the first model cycle when patients were receiving active treatments. Adverse event costs were

estimated as a weighted average of treatment costs for each AE considered, with weights being the AE rates (see Section B.3.3.2). Table 69 presents the unit costs for each AE considered in the model.

Table 69. Adverse event unit costs

Treatment	Unit cost	Source
Anaemia	£1,276.17	National Schedule of NHS Costs for 2019-2020[153] (inflated to 2020/2021 values)
Neutropenia	£1,840.6	
Leukopenia	£1,580.6	
Thrombocytopenia	£1,974.07	
Fatigue or Asthenia	£1 379,66	
Nausea and/or Vomiting	£1 537,62	

NHS = National Health Service.

B.3.6Uncertainty

An uncertainty with the current appraisal is the fact that OS data is still not mature from CheckMate-816 and data from next data cut will not be available until Q1 2023. However, the strong pCR data, the association between pCR and OS and the fact that a higher proportion of patients treated with nivolumab + PDC achieved pCR suggest that a continued relative benefit for nivolumab + PDC and a statistically significant difference in OS may be observed once more events have accrued. Further, validation of the model presented in Section B.3.11 shows that the modelled OS are well aligned with expected survival from these patients.

B.3.7Summary of base-case analysis inputs and assumptions

B.3.7.1 Summary of base-case analysis inputs

The settings of the base-case analysis are presented in Table 70. A complete list of model parameters is provided in Appendix J.

Table 70. Summary of variables applied in the economic model

Area	Variable	Value	Justification	Reference to section in submission
Model settings	Time horizon	Lifetime (35 years)	NICE reference case	Section B.3.2.4
	Discount rate	3.5% for both health benefit and cost	NICE reference case	Section B.3.2.6
	Perspective	Payer	NICE Reference case	Section B.3.2.3

Area	Variable	Value	Justification	Reference to section in submission
Clinical inputs	Time to any progression	Log-normal	Found as the best-fitting distribution for EFS, given lack of TTP external data to validate, assumption that the same distribution would also be best fitting for TTP given that 85% of EFS events were progressions.	Section B.3.3.1.3
	Time to LR	Log-normal	Judged to be most plausible fitting on basis of statistical fit, clinician feedback, comparison against external sources	Section B.3.3.1.2
	Hazard rate of EF to DM	Calculated, hazard rate of EF to DM = hazard rate of EF to any progression – hazard rate of EF to LR	While progression from EF to DM could be informed by EF to DM progressions captured in CheckMate-816, this approach was considered more reliable as it allows the extrapolations to be informed by a larger number of events.	Section B.3.3.1
	Transition from LR to DM	20% per year	UK clinical input	Section B.3.3.1.4
	Mortality in EFS	Exponential	Judged to be most plausible fitting on basis of statistical fit, clinician feedback, comparison against external sources	Section B.3.3.1.5
	Mortality in LR	Spline	Judged to be most plausible fitting on basis of statistical fit, clinician feedback, comparison against external sources	Section B.3.3.1.6
	Cure assumption	Yes	Evidence from the literature, KOL feedback, and NICE precedent (specifically TA761 and TA10751) all supported use of cure assumption	Section B.3.3.3
	Onset of cure	5 years	Estimate based on literature and KOL feedback	Section B.3.3.3.4
	Time from onset of cure to cure completion	2 years	Assumption	Section B.3.3.3.4
	% patients cured	95%	Assumption	Section B.3.3.3.4
	DM LY estimate	Based on previous HTA submissions and expected treatment patterns in first-line metastatic NSCLC.	This approach allows the model to use previously -reported first-line metastatic NSCLC appraisal results directly without undue complexity to maintain consistency with current standard of care in the UK regarding expected cost and treatment effect of all treatments	Section B.3.3.2
Cost inputs	Duration of neoadjuvant treatment	3 cycles	In CheckMate-816, most patients received the full course of neoadjuvant treatment. Given the relatively higher cost of nivolumab, assuming all patients who do not progress or die receive the full 3 cycles is a conservative assumption	Section B.3.5.1.1

Area	Variable	Value	Justification	Reference to section in submission
	Duration of adjuvant treatment	3 cycles	Based on treatment duration for adjuvant trials included in the ITC. Based on treatment duration reported in ITC.	Section B.3.5.1.2
	MRU frequency	Based on LuCaBIS study	Recent study identified as part of SLR, aligns well with the patient population	Section B.3.5.2.2
	Cost of DM	Based on previous DM HTA submissions and expected treatment patterns in first-line metastatic NSCLC.	This approach has been discussed with NICE and allows the model to use previously reported first-line metastatic NSCLC results directly without undue complexity	Section B.3.3.2
Utility Inputs	Baseline utility in EFS adjusted for general population utility	0.833	Based on data collected in the CheckMate-816 study (UK weights) with adjustments for general population utility	Section B.3.4.4
	Based on utility decrement observed in LR vs. EFS	[redacted]	Based on data collected in the CheckMate-816 study (UK weights)	Section B.3.4.4
	DM QALY estimate	Based on previous HTA submissions and expected treatment patterns in first-line metastatic NSCLC.	This approach allows the model to use previously reported first-line metastatic NSCLC results directly without undue complexity	Section B.3.3.2

DM = Distant Metastasis; EF = Event-Free; EFS = event-free survival; HTA = health technology assessment; ITC = indirect treatment comparison; KM = Kaplan-Meier; KOL = key opinion leader; LR = Locoregional Recurrence; LY = life-year; MRU = medical resource use; NSCLC = non-small cell lung cancer; QALY = quality-adjusted life-year; SLR = systematic literature review; TTDM = time to distant metastasis; TTLR = time to locoregional recurrence; TTP = time to progression; UK = United Kingdom.

B.3.7.2 Assumptions

Table 71 presents the key assumptions used in the models.

Table 71. Key model assumptions

Category	Assumption	Rationale
Patient population	The CheckMate-816 population is assumed to be representative of patients receiving treatment for resectable non-metastatic NSCLC.	This is a necessary limitation of a cohort-level approach.
Treatment efficacy	All PDC regimens administered as neoadjuvant treatment have the same efficacy.	It is known to be the case that across different practices, the use of specific combinations in PDC differ from CheckMate-816[83] (even in CheckMate-816, choice of PDC was based on physician discretion). Expert feedback suggested that no significant difference in efficacy would be expected between PDC combinations. Furthermore, data are not available to account for efficacy differences between specific PDC regimens, given the CheckMate-816 trial design with PDC regimen was based on the investigator's choice. Therefore, adjusting the distribution of PDC in the model can impact costs, but will not impact estimated survival.
Treatment efficacy	The CEM compares multiple treatment strategies for resectable non-metastatic NSCLC. Each of these involves a sequence of treatments (e.g., neoadjuvant PDC, followed by surgery, followed by optional adjuvant PDC). Efficacy data in the CEM are based on an indirect treatment comparison of treatments. When comparing treatment strategies in the CEM, changes in the proportion of patients receiving a specific treatment within 1 strategy (e.g., % receiving surgery in the strategy outlined above) will only affect cost and utility, but not survival.	Data to explicitly consider the clinical impact of changes within a treatment strategy, such as percentage of patients undergoing surgery or percentage receiving adjuvant treatment, are not available. These figures are implicitly considered in the existing data.
Comparators	In the adjuvant PDC arm, all patients are assumed to receive adjuvant treatment.	This assumption is made for logical consistency. Patients who do not receive adjuvant treatment should not be considered in the adjuvant comparator arms.
Disease progression	The probability of experiencing distant metastasis remains constant over time among patients with locoregional recurrence.	This is an assumption made to cover a lack of data necessary to characterise the time-dependency of this risk.
Occurrence of distant metastasis	Rather than extrapolating the likelihood of distant metastasis from EFS directly, it is computed as the difference between the hazard of any progression and the hazard of locoregional recurrence.	There were not enough distant metastasis events in CheckMate-816 to develop reliable extrapolations. This approach leverages the number of total and locoregional progression events, which are sufficient to develop extrapolations.

Category	Assumption	Rationale
Mortality	Prior to progression to metastatic disease, patients' mortality is dependent only on the health state they occupy (EF or LR), and not on the non-metastatic NSCLC treatment strategy received.	This assumption is justified on the basis of data from CheckMate-816 that show no difference in expected mortality across treatment arms among patients in the same health state. Furthermore, pooling the data across treatment arms increases the overall number of events upon which extrapolations may be based, increasing their predictive power. Clinical and economic experts noted that this assumption may overestimate mortality in the nivolumab + PDC arm, making this a conservative assumption.
Long-term mortality risk	Patients will not be able to achieve better mortality outcomes than would be expected among the general population. Accordingly, if the risk of mortality based on survival projections ever decreases below what would be expected based on published life tables, the estimate from the life table will be applied instead.	This is a common assumption in cost-effectiveness analysis and is based on the reasoning that the best possible outcome in terms of mortality impact for a given treatment would be a *lack* of any disease-specific or excess mortality.
Functional cure	95% of patients who remain event-free for at least 5 years achieve functional cure, with no risk of progression and mortality equal to that expected for the general population.	This assumption follows available evidence in the literature suggesting a strong plateau in EFS starting at 5 years. It was validated by clinical experts who suggested that cure is a possibility after successful resection.
Distant metastasis cost and outcomes	It is assumed that weighted results from previous HTA appraisals of in first-line metastatic NSCLC treatments applied as a one-off impact to patients with distant metastasis can reasonably approximate the cost, survival, and utility expectations for these patients.	This is a simplifying assumption made to reduce the complexity required in the model to capture treatments in metastatic NSCLC, especially in consideration of the understanding that these treatments fall outside the scope of the decision problem of treatment in resectable non-metastatic NSCLC. This approach has been previously used and deemed acceptable by NICE, specifically, in the evaluation for dabrafenib with trametinib for adjuvant treatment of resected BRAF V600 mutation-positive melanoma (TA544).
Treatment discontinuation	Discontinuation from neoadjuvant treatment is not explicitly considered. Therefore, all patients receiving neoadjuvant treatment and remaining in EFS are assumed to incur the cost of a full course of treatment.	Most patients in CheckMate-816 (93.8% in the nivolumab + PDC arm and 84.7% in the neoadjuvant PDC arm) completed the 3 cycles of neoadjuvant treatment. Given the relatively limited cost of any missed treatment cycles this is likely to not have a major impact on the model result. Further, this is a conservative assumption, given the relatively higher cost of nivolumab.
Treatment costs	Half-cycle correction is never applied to drug acquisition and administration costs in the neoadjuvant and adjuvant settings.	The objective of half-cycle correction is to distribute costs and benefits across a model cycle, rather than counting them all at the beginning of the cycle. However, it is known that patients will receive treatment at the beginning of each model cycle; therefore, these costs should not be redistributed across the cycle.

CEM = cost-effectiveness model; EF = Event-Free; EFS = event-free survival; HTA = health technology assessment; LR = Locoregional Recurrence; NSCLC = non-small cell lung cancer; PDC = platinum doublet chemotherapy.

B.3.8Base-case results

B.3.8.1 Base-case incremental cost-effectiveness analysis results

This section presents total costs, life-years gained (LYGs), QALYs, and incremental cost per QALY with nivolumab (including the confidential patient access scheme discount of [redacted]) + PDC versus surgery, neoadjuvant CRT, and adjuvant PDC. Per NICE guidelines the results are presented as pairwise comparisons given that nivolumab + PDC is expected to replace the individual comparators.

- Compared with surgery, nivolumab + PDC generated [redacted] incremental QALYs and [redacted] incremental LYs, and the nivolumab + PDC–treated cohort had higher total lifetime costs as shown in Table 72. The ICER was £2,685 per QALY gained.
- Compared with neoadjuvant CRT, nivolumab + PDC was dominant, as it generated [redacted] incremental QALYs and [redacted] incremental LYs and had slightly lower total lifetime costs as presented in Table 73.
- Compared with adjuvant PDC, nivolumab + PDC was dominant as it generated [redacted] incremental QALYs and [redacted] incremental LYs and had higher total lifetime costs as presented in Table 74.

Table 72. Base-case results: nivolumab + PDC versus surgery

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
NIVO+PDC	[redacted]	[redacted]	[redacted]	–	–	–	–
Surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2,685

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

Table 73. Base-case results: nivolumab + PDC versus neoadjuvant chemoradiation

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
NIVO+PDC	[redacted]	[redacted]	[redacted]	–	–	–	–
Neoadjuvant CRT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

CRT = chemoradiation; ICER = incremental cost-effectiveness ratio; LYG = life-year gained; NIVO = nivolumab; PDC = platinum doublet chemotherapy; QALY = quality-adjusted life-year.

Table 74. Base-case results: nivolumab + PDC versus adjuvant PDC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
NIVO+PDC	[redacted]	[redacted]	[redacted]				
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

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

0 presents the net health benefit per treatment. As can be seen, nivolumab + PDC results in the highest net health benefit of all the treatments.

Table 75. Net health benefit

Technologies	Total costs (£)	Total QALYs	NHB at £20,000	NHB at £30,000
NIVO+PDC	[redacted]	[redacted]	2.56	3.63
Surgery	[redacted]	[redacted]	1.54	2.56
Neoadjuvant CRT	[redacted]	[redacted]	2.22	3.31
Adjuvant PDC	[redacted]	[redacted]	1.85	2.92

CRT = chemoradiation; NIVO = nivolumab; PDC = platinum doublet chemotherapy; NHB = net health benefit; QALY = quality-adjusted life-year.

B.3.9Exploring uncertainty

To explore the uncertainty of parameter precision, choice of data sources and modelling assumptions probabilistic and deterministic sensitivity analyses as well as scenario analyses have been conducted and results of these are presented in this section.

B.3.9.1 Probabilistic sensitivity analysis

For the probabilistic sensitivity analysis (PSA), uncertainties in parameter precision were estimated, including the parametric values of long-term extrapolations, disease management costs, treatment costs, and utilities. For each parametric function in the model, a Cholesky decomposition of the covariance matrix was used to correlate the function parameters. Distributions used in the PSA are presented in Table 76. Measurement of uncertainties was captured by 95% CI or standard errors (SEs) of each parameter. In the absence of CIs or SEs from published ranges, the SE of the parameter was assumed to be 20% of the mean value.

Upon processing all iterations, the model generates a scatterplot illustrating the distribution of incremental costs and QALYs emerging from the PSA, as well as a cost-effectiveness acceptability curve depicting the likelihood nivolumab + PDC is cost-effective relative to a comparator given maximum willingness to pay (WTP) for a QALY.

Table 76. Model parameters varied in PSA and distributions

Category	Parameter	Distribution for PSA
Patient characteristics	Starting age	Normal
	Weight	Normal
	BSA	Normal
Clinical inputs	EF to LR - Nivolumab + PDC, survival parameters	Normal/ Cholesky
	EF to LR - PDC, survival parameters	Normal/ Cholesky
	EF to LR constant HRs	Log-normal
	EF to progression - Nivolumab + PDC, survival parameters	Normal/ Cholesky
	EF to progression - PDC, survival parameters	Normal/ Cholesky
	EF to DM constant HR	Log-normal
	Death during event free, survival parameters	Normal/ Cholesky
	Death during LR, survival parameters	Normal/ Cholesky
	LR to DM transition, per cycle	Beta
	Life-years during DM (by DM treatment)	Gamma
Treatment costs	Drug acquisition cost, per cycle	Gamma
	Drug administration cost, per cycle (initial, subsequent)	Gamma
	Adjuvant costs after neoadjuvant care	Gamma
	Surgery cost	Gamma

Category	Parameter	Distribution for PSA
	Cost during LR	Gamma
	Cost during DM (by DM treatment)	Gamma
Disease management	MRU per cycle (EF, LR, DM)	Gamma
	Monitoring per cycle (EF, LR)	Gamma
	Terminal care cost	Gamma
	AE cost	Gamma
	Income loss per cycle (EF, LR)	Gamma
Utility values	Utility values - EF, LR	Beta
	Utility value of DM (by DM treatment)	Gamma
	Aggregated AE disutility	Beta

AE = adverse event; BSA = body surface area; DM = Distant Metastasis; EF = Event-Free; HR = hazard ratio; LR = Locoregional Recurrence; MRU = medical resource use; PSA = probabilistic sensitivity analysis.

B.3.9.1.1 Probabilistic sensitivity analysis results

The PSA results are based on 1,000 repeated simulations, that drew from the distributions of parametric functions, costs, and utility values. The number of replications was considered sufficient, because the expected values of incremental QALYs and costs by the number of replications demonstrated stability well before 1,000 replications (around 300-600 dependent on comparator). The mean incremental cost, LY, and QALY of nivolumab + PDC vs. each comparator in the model over the PSA iterations are summarised from Table 77 to Table 79.

Table 77. Base-case probabilistic results: nivolumab + PDC versus surgery

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
NIVO+PDC	[redacted]	[redacted]	[redacted]		–	–	–
Surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2,655

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

Table 78. Base-case probabilistic results: nivolumab + PDC versus neoadjuvant chemoradiation

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
NIVO+PDC	[redacted]	[redacted]	[redacted]	–	–	–	–
Neoadjuvant CRT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

CRT = chemoradiation; ICER = incremental cost-effectiveness ratio; LYG = life-year gained; NIVO = nivolumab; PDC = platinum doublet chemotherapy; QALY = quality-adjusted life-year.

Table 79. Base-case probabilistic results: nivolumab + PDC versus adjuvant PDC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
NIVO+PDC	[redacted]	[redacted]	[redacted]	–	–	–	–
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

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

The incremental cost and QALY result for each iteration is plotted in Figure 61 through Figure 63 for each comparator. In general, the shape of the clouds plotted on the cost-effectiveness plane were wider on the x-axis compared with the -y axis, reflective of uncertainty in the survival estimates obtained from the indirect treatment comparison. As discussed in section B.2.9.4, the limited body of evidence in resectable NSCLC, and the methodological challenges incurred when comparing different trial designs and patient populations, led to estimated hazard ratios within the ITC that were associated with high uncertainty for some of the endpoints of interest (particularly TTLR).

The majority of the incremental cost and QALY coordinates relating to the comparison between neoadjuvant nivolumab + PDC and surgery fell within the northeast quadrant. This indicates that nivolumab + PDC was likely to deliver higher costs and gains in QALYs versus surgery alone (see Figure 61). Results versus neoadjuvant CRT and adjuvant PDC, as show in Figure 62 and Figure 63 respectively, were distributed more evenly across the 4 quadrants, although the majority of the iterations were in the southeast quadrant indicating that nivolumab + PDC would be more effective and less costly.

Figure 61. PSA Results—Cost-effectiveness plane nivolumab + PDC vs. surgery

CE = cost-effectiveness; PDC = platinum doublet chemotherapy; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year.

Figure 62. PSA Results—Cost-effectiveness plane nivolumab + PDC vs. neoadjuvant chemoradiation

CE = cost-effectiveness; PDC = platinum doublet chemotherapy; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year.

Figure 63. PSA Results—Cost-effectiveness plane nivolumab + PDC vs. adjuvant PDC

CE = cost-effectiveness; PDC = platinum doublet chemotherapy; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year.

The cost-effectiveness acceptability curves are presented in Figure 64 through Figure 66 for each comparator in the model.

Figure 64. Cost-effectiveness acceptability curve: Nivolumab + PDC vs. surgery

CEAC = cost effectiveness acceptability curve; PDC = platinum doublet chemotherapy.

This figure shows that at a willingness to pay threshold of £10,000, £20,000 or £30,000 per QALY gained, there is a [redacted]%, [redacted]% and [redacted]% probability, respectively, that nivolumab + PDC is cost-effective compared to surgery alone.

Figure 65. Cost-effectiveness acceptability curve: Nivolumab + PDC vs. neoadjuvant chemoradiation

CRT = chemoradiation; PDC = platinum doublet chemotherapy.

This figure shows that at a willingness to pay threshold of £10,000, £20,000 or £30,000 per QALY gained, there is a [redacted]%, [redacted] and [redacted]probability, respectively, that nivolumab + PDC is cost-effective compared to neoadjuvant chemoradiation.

Figure 66. Cost-effectiveness acceptability curve: Nivolumab + PDC vs. adjuvant PDC

CEAC = cost-effectiveness acceptability curve; PDC = platinum doublet chemotherapy.

This figure shows that at a willingness to pay threshold of £10,000, £20,000 or £30,000 per QALY gained, there is a [redacted]%, [redacted]% and [redacted]% probability, respectively, that nivolumab + PDC is cost-effective compared to adjuvant PDC.

B.3.9.2 Deterministic sensitivity analysis

Deterministic sensitivity analysis was conducted comparing nivolumab + PDC to each comparator in the model. The analyses varied the key model settings, efficacy inputs, costs and utility values. Results are presented in the form of tornado diagrams in Figure 41 through Figure 44. Specific drivers of each result differ by comparator. Given that nivolumab + PDC dominated both neoadjuvant chemoradiation and adjuvant PDC the tornado diagrams for the deterministic sensitivity analyses are constructed based on incremental net health benefits based on a willingness to pay threshold of £20,000 to facilitate interpretation of the results.

Figure 67. Deterministic sensitivity analysis—nivolumab + PDC vs. surgery

CI = confidence interval; DM = Distant Metastasis; DSA = deterministic sensitivity analysis; EF = Event-Free; HR = hazard ratio; INHB = incremental net health benefit; LR = Locoregional Recurrence; PDC = platinum doublet chemotherapy

Figure 68. Deterministic sensitivity analysis—Nivolumab + PDC vs. PDC (adjuvant)

CI = confidence interval; DM = Distant Metastasis; DSA = deterministic sensitivity analysis; EF = Event-Free; HR = hazard ratio; INHB = incremental net health benefit; LR = Locoregional Recurrence; PDC = platinum doublet chemotherapy

Figure 69. Deterministic sensitivity analysis—Nivolumab + PDC vs. Neoadjuvant CRT

CI = confidence interval; CRT = chemoradiation DM = Distant Metastasis; DSA = deterministic sensitivity analysis; EF = Event-Free; HR = hazard ratio; INHB = incremental net health benefit; LR = Locoregional Recurrence; PDC = platinum doublet chemotherapy

Overall, the following parameters were identified to have the greatest impact to the incremental NHB:

- TTLR and TTDM HRs
- The drug acquisition cost of nivolumab + PDC (for all comparisons)
- TTLR and TTDM distribution parameters (for all comparators)
- Discount rate for health benefits
- Surgery costs (for all comparators)

As can be seen in Figure 41 through Figure 44, variations in only 2 parameters for the comparison with neoadjuvant chemoradiation resulted in nivolumab + PDC not providing higher incremental net health benefits. For all other variations in parameters, treatment with nivolumab + PDC resulted in higher net health benefits than the comparator.

B.3.9.3 Scenario analysis

Scenario analyses were undertaken to investigate the effect of certain model inputs on costs and outcomes. The following scenarios conducted and the rational for each scenario is presented in Table 80 and the results of the scenario analyses are presented in Table 81 to Table 83.

Table 80. Scenario analyses overview

Scenario	Parameter tested	Parameter value in base case	Parameter value in scenario	Rational for scenario
1	Base case			

Scenario	Parameter tested	Parameter value in base case	Parameter value in scenario	Rational for scenario
2	Utility	Trial EFS utility caped to general population utility values	Unadjusted trial values	Using the utility values observed during CheckMate-816 without any adjustments for general population utility values
3	Cure	95% of patients assumed to be cured from year 5 to year 7	No patients are cured	Testing the impact of cure assumption with the assumption that no patients would be cured. This should be seen as an extreme scenario given previous precedence in NICE appraisals for this disease area [2,151] and clinical input received as part developing the current submission
4	Cure onset	5 years	8 years	Testing the impact of when cure can first be achieved by patients. 8 years was considered appropriate in NICE TA761[151]
5	Time from beginning to end of cure process	2 years	Immediate	Testing the assumption of cure being applied gradually or immediately as discussed in NICE TA10751[2]
6	DM QALY outcome	Based on one-off outcomes for 1st line metastatic treatments.	QALY of subsequent treatments = 5 QALYs	Setting the QALY per patient in DM to an extreme value to show the robustness of the results to the DM outcomes given that current values are not based on NICE preferred values. 5 QALYs is higher than QALYs gained in the EF health state in the base case and would therefore not be clinically plausible given the severity of DM
7	DM cost outcome	Based on one-off outcomes for 1st line metastatic treatments.	No cost of subsequent treatment	Similar to the QALY scenario this is to show the robustness of the results even if no costs are assumed for the DM health state.
8	PDC regimen		Vinorelbine used instead of docetaxel and paclitaxel in PDC regimen	UK clinical input received highlighted that vinorelbine and gemcitabine are preferred instead of docetaxel and paclitaxel in PDC regimen. It was therefore assumed that proportions treated with docetaxel and paclitaxel would get vinorelbine instead in this scenario to test the impact on costs.
9	IO retreatment	IO retreatment restriction 6 month	IO retreatment restriction extended to 12 months	This scenario was conducted to test the impact of when patients would be considered for retreatment with IO in the nivolumab arm.
10	IO retreatment	IO retreatment restriction 6 month	IO retreatment restriction not included	This scenario was conducted to test the impact of the assumption that all patients would be considered for retreatment with IO in the nivolumab arm
11	Patients on neoadjuvant treatments who continue with adjuvant treatments	NIVO+PDC 8.0% Neoadjuvant chemoradiation 9.7%	5% radiotherapy for both treatments based on UK clinical input	UK clinical input provided indicated that proportion who would receive radiotherapy in the UK could be slightly lower than that observed in CheckMate-816

Scenario	Parameter tested	Parameter value in base case	Parameter value in scenario	Rational for scenario
12	LR to DR transition probability	20% annual transition probability	7.7% from the LuCaBIS study[150]	An alternative value for transitioning from LR to DR was identified in the literature. Clinical input received considered this to be too low so clinical input was used in the base case. However, the published value was tested in this scenario
13	Distribution for TTLR extrapolation	Log-normal	Exponential	Best-fitting distribution based on BIC
14	Distribution for any progression extrapolation	Log-normal	Generalised Gamma	Second best AIC and plausible long-term extrapolations
15	Distribution for event-free mortality	Exponential	Generalised Gamma	Best statistical fit and converge towards general population mortality which would be in alignment with the assumption of cure
16	Distribution for locoregional recurrence mortality	Spline	Log-logistic	Based on best-fitting standard parametric and more pessimistic than spline models
17	Treatment effect for local and distant recurrence	ITC results based on TTLR and TTDM outcomes	EFS ITC treatment effect for both TTLR and TTDR	Given that the criteria of potentially resectable patients had to be relaxed for all comparators to be included in ITC of TTLR and TTDR a common effect across both outcomes based on the EFS ITC were tested. This allowed for the original inclusion criteria to be used with regards to potentially resectable.

AIC = Akaike information criteria; BIC = Bayesian information criteria; DM = Distant Metastasis; DR = Distant Recurrence; EF = Event-Free; EFS = event-free survival; I-O = immuno-oncology; ITC = indirect treatment comparison; NIVO = nivolumab; QALY = quality-adjusted life-year; TTDM = time to distant metastases; TTLR = time to locoregional recurrence.

Table 81. Results of scenario analyses nivolumab + PDC versus surgery

Scenario	Parameter	Parameter value in scenario	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
1	Base case		[redacted]	[redacted]	£2,685
2	Utility	Unadjusted trial values	[redacted]	[redacted]	£2,536
3	Cure	No patients are cured	[redacted]	[redacted]	£3,492
4	Cure onset	8 years	[redacted]	[redacted]	£2,857
5	Time from beginning to end of cure process	Immediate	[redacted]	[redacted]	£2,665
6	DM QALY outcome	QALY of subsequent treatments = 5 QALYs	[redacted]	[redacted]	£4,356
7	DM cost outcome	No cost of subsequent treatment	[redacted]	[redacted]	£12,706

Scenario	Parameter	Parameter value in scenario	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
8	PDC regimen	Vinorelbine used instead of docetaxel and paclitaxel in PDC regimen	[redacted]	[redacted]	£2,823
9	I-O retreatment	I-O retreatment restriction extended to 12 months	[redacted]	[redacted]	£1,537
10	IO retreatment	IO retreatment restriction not included	[redacted]	[redacted]	£4,638
11	Patients on neoadjuvant treatments who continue with adjuvant treatments	5% radiotherapy based on UK clinical input	[redacted]	[redacted]	£2,629
12	LR to DR transition probability	7.7% from the LuCaBIS study	[redacted]	[redacted]	£3,045
13	Distribution for TTLR extrapolation	Exponential	[redacted]	[redacted]	£3,306
14	Distribution for any progression extrapolation	Generalised gamma	[redacted]	[redacted]	£3,374
15	Distribution for event-free mortality	Generalised Gamma	[redacted]	[redacted]	£2,864
16	Distribution for locoregional recurrence mortality	Log-logistic	[redacted]	[redacted]	£2,908
17	Treatment effect for local and distant recurrence	EFS ITC treatment effect for both TTLR and TTDM	[redacted]	[redacted]	£2,483

EFS = event-free survival; I-O = immuno-oncology; ITC = indirect treatment comparison; LR = Locoregional Recurrence; QALY = quality-adjusted life-year; TTDM = time to distant metastases; TTLR = time to locoregional recurrence; UK = United Kingdom.

Table 82. Results of scenario analyses nivolumab + PDC versus neoadjuvant chemoradiation

Scenario	Parameter	Parameter value in scenario	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
1	Base case		[redacted]	[redacted]	Dominant
2	Utility	Unadjusted trial values	[redacted]	[redacted]	Dominant
3	Cure	No patients are cured	[redacted]	[redacted]	Dominant
4	Cure onset	8 years	[redacted]	[redacted]	Dominant
5	Time from beginning to end of cure process	immediate	[redacted]	[redacted]	Dominant
6	DM QALY outcome	QALY of subsequent treatments = 5 QALYs	[redacted]	[redacted]	Dominant
7	DM cost outcome	No cost of subsequent treatment	[redacted]	[redacted]	£21,496

Scenario	Parameter	Parameter value in scenario	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
8	PDC regimen	Vinorelbine used instead of docetaxel and paclitaxel in PDC regimen	[redacted]	[redacted]	Dominant
9	I-O retreatment	I-O retreatment restriction extended to 12 month	[redacted]	[redacted]	Dominant
10	IO retreatment	IO retreatment restriction not included	[redacted]	[redacted]	£2,719
11	Patients on neoadjuvant treatments who continue with adjuvant treatments	5% radiotherapy based on UK clinical input	[redacted]	[redacted]	Dominant
12	LR to DR transition probability	7.7% from the LuCaBIS study	[redacted]	[redacted]	Dominant
13	Distribution for TTLR extrapolation	Exponential (	[redacted]	[redacted]	Dominant
14	Distribution for any progression extrapolation	Generalised Gamma	[redacted]	[redacted]	Dominant
15	Distribution for event-free mortality	Generalised Gamma	[redacted]	[redacted]	Dominant
16	Distribution for locoregional recurrence mortality	Log-logistic	[redacted]	[redacted]	Dominant
17	Treatment effect for local and distant recurrence	EFS ITC treatment effect for both TTLR and TTDM	[redacted]	[redacted]	Dominant

DM = Distant Metastasis; I-O = immuno-oncology; LR = Locoregional Recurrence; QALY = quality-adjusted life-year; TTDM = time to distant metastases; TTLR = time to locoregional recurrence; UK = United Kingdom.

Table 83. Results of scenario analyses nivolumab + PDC versus adjuvant PDC

Scenario	Parameter	Parameter value in scenario	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
1	Base case		[redacted]	[redacted]	Dominant
2	Utility	Unadjusted trial values	[redacted]	[redacted]	Dominant
3	Cure	No patients are cured	[redacted]	[redacted]	Dominant
4	Cure onset	8 years	[redacted]	[redacted]	Dominant
5	Time from beginning to end of cure process	immediate	[redacted]	[redacted]	Dominant
6	DM QALY outcome	QALY of subsequent treatments = 5 QALYs	[redacted]	[redacted]	Dominant
7	DM cost outcome	No cost of subsequent treatment	[redacted]	[redacted]	£12,737
8	PDC regimen	Vinorelbine used instead of docetaxel and paclitaxel in PDC regimen	[redacted]	[redacted]	Dominant

Scenario	Parameter	Parameter value in scenario	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
9	I-O retreatment	I-O retreatment restriction extended to 12 months	[redacted]	[redacted]	Dominant
10	IO retreatment	IO retreatment restriction not included	[redacted]	[redacted]	£3,022
11	Patients on neoadjuvant treatments who continue with adjuvant treatments	5% radiotherapy based on UK clinical input	[redacted]	[redacted]	Dominant
12	LR to DR transition probability	7.7% from the LuCaBIS study	[redacted]	[redacted]	£284
13	Distribution for TTLR extrapolation	Exponential	[redacted]	[redacted]	£602
14	Distribution for any progression extrapolation	Generalised gamma	[redacted]	[redacted]	£502
15	Distribution for event-free mortality	Generalised Gamma	[redacted]	[redacted]	£143
16	Distribution for locoregional recurrence mortality	Log-logistic based on best-fitting standard parametric and more pessimistic than spline models	[redacted]	[redacted]	Dominant
17	Treatment effect for local and distant recurrence	EFS ITC treatment effect for both TTLR and TTDM	[redacted]	[redacted]	Dominant

DM = Distant Metastasis; EFS = event-free survival; I-O = immuno-oncology; ITC = indirect treatment comparison; LR = Locoregional Recurrence; QALY = quality-adjusted life-year; TTDM = time to distant metastases; TTLR = time to locoregional recurrence; UK = United Kingdom.

As shown by the results of the scenario analyses the results are robust to all changes tested. For the majority of the changes the alternative assumptions have a very small impact on the results. For all scenarios except one, the ICER also stays below £20,000 for all comparators. The only scenario where the ICER is above £20,000 is the extreme scenario whereby the cost of subsequent treatment is set to £0, resulting in the ICER of £21,496 for nivolumab + PDC versus CRT. This scenario is unrealistic but represents an extreme lower bound for DM costs. The scenarios investigating the impact of the cure assumption are also important. The cure assumption has been subject to discussions in several previous appraisals; however these scenario analyses show that nivolumab + PDC remains cost-effective in all the scenarios in which the cure assumption is varied – including when no cure is assumed.

B.3.10 Subgroup analysis

No subgroup analyses were performed as CheckMate-816 was not powered to detect differences in subgroups. Patient numbers in some subgroups are low and very few events had occurred by the time of the database lock. Therefore, these analyses are not appropriate for decision-making, and the decision problem population included in CheckMate-816 is more appropriate. This was also highlighted by clinical experts (Appendix N).

B.3.11 Validation

B.3.11.1 Validation of cost-effectiveness analysis

B.3.11.2 Internal validation

B.3.11.2.1 Technical validation by model developer

In addition to the comparisons against external data conducted, the model was assessed by an expert modeller not otherwise involved in the programming of the model. The logical structure of the model, mathematical formulae, sequences of calculations, and values of numbers supplied as model inputs were all verified. An extreme value test was run to check for unexpected model behaviour. The appropriateness of distributions used in the probabilistic analysis of the model were checked. A standard operating procedure was followed, with detailed checklists, to ensure validation was complete and thorough. Following the validation, correction of identified errors or bugs was incorporated into the revised model.

B.3.11.2.2 Third-party validation

Following the internal validation by the model developer, the model underwent a second round of validation conducted by another vendor. This validation was undertaken by experienced health economics outcomes research modelling staff in June and July of 2022 and primarily focused on assessing the model's conceptual validity (i.e., an assessment of the model structure, logic, mathematical, and causal relationships at the conceptual level) and the internal technical validity of the model (i.e., ensuring that the programming and physical implementation of the conceptual model has been completed correctly). This validation also included technical pressure testing via extreme value analysis, and directional input testing, where input parameters are modified individually and their directional relationship with cost and QALY outcomes are evaluated. This approach is in line with established Good Model Validation Practice guidance as presented by ISPOR,[154] NICE,[125] AdviSHE,[155] and TECH-VER.[156]

Overall, the results of this additional round of validation lends further confidence to the technical and conceptual validity of the model. Only 1 error was identified (and subsequently corrected) that could impact model results.

B.3.12 External validation

B.3.12.1 Validation Methods

Model outcomes were compared against a conditional survival curve constructed using available data from the literature. The process of building this curve is described in the section below. Additionally, estimated survival curves were compared directly to external survival data (without the conditional approach).

As a result of the one-off approach to capturing DM outcomes adopted in the model, it was not possible to generate an OS curve that would be suitable for direct comparison against

curves built from external data. Therefore, the external validation attempted to address this issue in 2 ways:

- Aggregate LYs (calculated as the area under the curve) based on the conditional survival curve were compared with the LYs output by the model, over the same timeframe.
- Multiple approaches were explored to generate an OS curve corresponding to the aggregate LYs accrued in DM used in the model. This allowed for generation of a combined OS curve from the model that could be directly compared with the conditional survival curve for validation.
  - **Approach 1:** An exponential distribution of survival time in DM was estimated so that its area under the curve produced the model base-case LYs in DM
    - [redacted] LY in DM for patients treated with neoadjuvant nivolumab + PDC
    - [redacted] LY in DM for patients treated with neoadjuvant PDC
  - **Approach 2:** An exponential distribution of survival time in DM was estimated based on an estimated [redacted] LY accrued in DM, which assumes 75% of first-line patients with metastatic NSCLC were treated with PDC and 25% receive best supportive care (BSC)
  - **Approach 3:** The OS Kaplan-Meier curve for PDC from the CheckMate-9LA clinical study in first-line metastatic NSCLC was assumed as representative of DM survival time

Model settings used to run the comparisons are described in Sections B.3.12.2 and B.3.12.3.1 and are summarised in Table 84.

Table 84. Model settings for external validation

Parameter	Input
Time horizon	20 years (selected to match follow-up data available from literature)
Cure timing	Year 5 to year 7
Fitting for EF to LR	Joint log-normal
Fitting for EF to any progression	Joint log-normal
Transition probability from LR to DM	20% per year
Fitting for EF to Dead	Exponential
Fitting for LR to Dead	Spline (DF = 3, hazard)

DF = degree of freedom; DM = Distant Metastasis; EF = Event-Free; LR = Locoregional Recurrence.

B.3.12.1.1 Construction of conditional survival curve

As no single source is available that can supply survival data to inform timespans approaching the model time horizon, survival estimates from multiple sources were connected using a conditional survival approach. The first source used provides an absolute

value, and absolute numbers of patients still surviving to subsequent intervals are computed using conditional survival from additional sources for each subsequent timespan. This approach allows known long-term estimates of survival to be adjusted to account for new, short-term survival data. Specifically, 3 sources were used to construct the conditional survival curves:

- Data from CheckMate-816 (Up to year 3)
- Data from the BMS patient-level meta-analysis (CA2097L8; from years 3 to 15)
- Data from the Surveillance, Epidemiology, and End Results registry (SEER; from years 15 to 20)

Two conditional survival curves were constructed: one for neoadjuvant nivolumab + PDC and one for neoadjuvant PDC. The key difference between the 2 curves is in the first 3 years, for which data from the CheckMate-816 trial are used directly. Subsequent years use the same data sources for both treatment arms. Table 85 presents the absolute and conditional survival estimates for the 2 curves.

Table 85. Conditional survival curve construction

Source	Time (years)	Absolute survival	Conditional survival
CheckMate-816	[redacted]	[redacted]	[redacted]
BMS patient-level meta-analysis (CA2097L8)	[redacted]	[redacted]	[redacted]
SEER[a]	[redacted]	[redacted]	[redacted]

PDC = platinum doublet chemotherapy; SEER = Surveillance, Epidemiology, and End Results.

[a] Reflective of patients diagnosed in 1997.

Figure 70 and Figure 71 present the calculation steps for the neoadjuvant nivolumab + PDC and neoadjuvant PDC conditional survival curves, respectively, and Figure 72 and Figure 73 present the conditional survival curves.

Figure 70. Conditional survival for neoadjuvant nivolumab + PDC

Figure 71. Conditional survival for neoadjuvant PDC

Figure 72. Plotted Conditional Survival Curve: Nivolumab+ PDC

Figure 73. Plotted conditional survival curve: neoadjuvant PDC

B.3.12.2 Predictive Validation Against External Data

B.3.12.3 AUC Comparison Against Conditional Survival

First, the model outcomes in terms of total undiscounted LY generated (using the settings summarised in Table 84) were compared against the total LY that would be generated from the conditional survival curves plotted in Figure 72 and Figure 73 (i.e., the area under the curve). For the purposes of this analysis, 75% of patients in the DM state were assigned to PDC and the other 25% were assigned to BSC, receiving an estimated total of [redacted] life years upon progression to the DM state (see Section B.3.3.2 for more detail). Table 86 presents the results for each treatment.

Table 86. Model outputs versus conditional survival life-year estimates

Treatment	Model output	Conditional survival LY	% Deviation in model output from conditional survival
Neoadjuvant Nivolumab + PDC	[redacted]	[redacted]	[redacted]
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]

LY = life-year; PDC = platinum doublet chemotherapy.

The estimated model outputs were found to align with the conditional survival curve closely, albeit resulting in lower long-term LYs across both treatment arms, producing [redacted]% fewer LYs for the neoadjuvant nivolumab + PDC arm and [redacted]% fewer LYs for the neoadjuvant PDC arm. Additionally, the deviation was similar across arms and thus not likely to bias the incremental result, although the slight underprediction for nivolumab + PDC versus the neoadjuvant PDC arm could lead to results from the model being conservative.

B.3.12.3.1 Visual comparison

For the visual comparison, patient survival in DM over time was considered via the use of survival curves (as opposed to the one-off LY consequence applied in the model base case), which allowed an OS curve to be generated by the semi-Markov model. The same 3 curves were explored:

- Exponential distributions of survival time in DM estimate such that the area under the curve produces the model base-case LYs in DM (2.68 LY in DM for neoadjuvant nivolumab + PDC; [redacted] LY in DM for neoadjuvant PDC; approach 1 in Section B.3.12)
- Exponential curve was generated that resulted in patients accruing [redacted] LY in the DM state, based on the [redacted] LY estimate for survival among patients treated with neoadjuvant PDC used in the DM state assuming 75% of patients receive PDC and 25% receive BSC (approach 2 in Section B.3.12)
- OS survival data from the CheckMate-9LA trial among patients with first-line metastatic NSCLC (approach 3 in Section B.3.12)

The resulting OS curves are compared against the conditional survival curves in Figure 74 for nivolumab + PDC and Figure 75 for neoadjuvant PDC.

Figure 74. Model-generated overall survival versus conditional survival: neoadjuvant nivolumab + PDC

Figure 75. Model-generated overall survival versus conditional survival: neoadjuvant PDC

Overall, the survival estimated by the model fit closely to the estimates generated by the conditional survival curve, particularly for the first 3 years, and after 16 years. Selection of the approach to estimating survival for patients in DM had only a small impact on the overall shape of the curve. To assess whether the divergence observed between years 4 and 14 was due to the linear conditional survival approach failing to capture the overall shape of the curve, supplementary curves were generated based on annual conditional survival; the more granular curves showed approximately the same amount of divergence.

Therefore, it is hypothesised that the divergence between the conditional survival curves and model estimated results between year 4 and 14 is due to some key differences between the patient population upon which segments of the conditional survival curve are based, and the CheckMate-816 trial population. Specifically, the BMS patient-level meta-analysis (CA2097L8[73]) is different in 2 ways:

- The majority of the CheckMate-816 population had stage IIIA disease at baseline (63.3% in the nivolumab + PDC arm; 64.2% in the neoadjuvant PDC arm), while [redacted]% of patients in the BMS patient-level meta-analysis (CA2097L8) had stage IA-II disease.
- Patients in the BMS patient-level meta-analysis (CA2097L8) were on average approximately 10 years younger than patients in the CheckMate-816 trial.

The first difference could be controlled for by splitting the OS curve from the patient-level meta-analysis into OS curves by stage, and re-weighting them to match the staging distribution in CheckMate-816. The second difference (i.e., divergence in age) could not be controlled for, but it would be expected that a younger patient population would face lower risk of mortality versus an older patient population. Therefore, the relatively shorter predicted survival for the modelled (relatively older) population is sensible versus the conditional survival (relatively younger) population.

B.3.12.4 Naive external validation

As a first step to validate the model the OS projections from the model were compared directly to survival outcomes from external sources that have comparable patient population to that enrolled in CheckMate-816. Since neoadjuvant nivolumab + PDC is a novel intervention for the target population and its survival outcomes were not discussed in any previous studies, it was not feasible to validate the long-term OS of nivolumab + PDC against the external data. Therefore, the long-term validation was conducted for the neoadjuvant PDC arm only.

Data from the patient-level meta-analysis conducted by BMS[73] were identified as the most appropriate source for survival outcomes from patients with stage I-III NSCLC receiving neoadjuvant therapy. It has sufficiently long follow-up (15 years), enabling survival comparisons in the long-term. The survival data by stage were also available from the patient-level meta-analysis to allow the construction of a weighted OS to reflect patients' stage distributions in CheckMate-816. Survival outcomes were also compared with data published in Goldstraw et al. (2016)[31], which considered a database of 94,708 cases of NSCLC from 35 sources across 16 countries around the globe, with survival data for approximately 20,000 patients with stage IB-IIIA NSCLC.

The model OS curve, generated using the same settings as in Table 84, was compared against the external sources in Figure 76; Table 87 presents a landmark comparison. The exponential OS curve for patients in first-line metastatic NSCLC based on the estimated [redacted] LY was used for this comparison, as the age of the data for comparison suggested that these patients would have been most likely to receive PDC upon progression to metastatic NSCLC. Specifically, the BMS patient-level meta-analysis (CA2097L8) included trials with study periods prior to 2012; [redacted]% of the studies in the analysis were conducted before 2007, and immuno-oncology therapies have only come into widespread use in the last decade.

Overall, the modelled OS for neoadjuvant PDC aligns well with the external data, especially in the long-term. The modelled OS starts with higher probability of survival during the within-trial period, converges with the Goldstraw data between 4 and 5 years, and approaches the BMS patient-level meta-analysis (CA2097L8) data gradually from year 5 to year 7. From years 7 onward, the modelled OS matches very closely to the survival from the meta-analysis.

Figure 76. Comparison of modelled overall survival versus external data

[redacted]

Table 87. Neoadjuvant PDC OS Validation (Naïve): Landmark Comparison

Source	Year 1	Year 3	Year 5	Year 10	Year 15
Modelled OS for neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Goldstraw et al., 2016	85.1%	60.4%	48.5%	NA	NA
BMS patient-level meta-analysis (CA2097L8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NA = not available; OS = overall survival; PDC = platinum doublet chemotherapy.
Sources: Forde et al. (2022)[3], Goldstraw et al. (2016)[31], BMS data on file (2021)[73]

B.3.13 Predictive Validation Against Trial Data

Finally, the model OS was compared against OS data from CheckMate-816 for both the nivolumab + PDC and neoadjuvant PDC comparators to assess the degree to which the model-predicted OS aligns with observed survival outcomes during the within-trial period.

B.3.13.1 Neoadjuvant Nivolumab + PDC

The graphical comparison of the CheckMate-816 OS for nivolumab + PDC versus the model extrapolations for nivolumab + PDC is shown in Figure 77, and the percentage of patients alive at each six month interval is shown in Table 88.

Figure 77. Neoadjuvant Nivolumab + PDC OS Validation: Model Outcomes vs. Trial Data

[redacted]

Table 88. Neoadjuvant Nivolumab + PDC OS Validation: Model Outcomes vs. Trial Data; Survival by Six Month Interval

Source	Month 6	Month 12	Month 18	Month 24	Month 30	Month 36
Modelled OS for neoadjuvant nivolumab + PDC, Approach 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Modelled OS for neoadjuvant nivolumab + PDC, Approach 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source	Month 6	Month 12	Month 18	Month 24	Month 30	Month 36
CheckMate-816 OS K-M; Nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

In general, the modelled OS fit well to the K-M data from CheckMate-816. Consideration of approach 1 ([redacted]LY in DM following UK treatment patterns) and approach 2 ([redacted]LY, assuming 75% of patients receive PDC and 25% receive BSC in DM) showed that the two approaches are quite close during the within trial period. The greatest deviation from the trial data was observed at month 36, with the projected OS falling [redacted]% below the trial data (approach 1) and [redacted]% below the trial data (approach 2). However, it should be noted that there were only [redacted] patients at risk at month 36 (out of 179 randomized to nivolumab + PDC, or [redacted]%). Before month 36, both approaches and the trial data are quite close, with the largest observed deviation occurring in month 12 (difference of [redacted]% vs. approach 1, and [redacted]% vs approach 2).

Overall, comparison of the trial data vs. predicted model OS outcomes suggest that the model replicates the outcomes of CheckMate-816 quite well.

B.3.13.2 Neoadjuvant PDC

The graphical comparison of the CheckMate-816 OS for neoadjuvant PDC versus the model extrapolations for neoadjuvant PDC is shown in Figure 78, and the percentage of patients alive at each six month interval is shown in Table 89.

Figure 78. Neoadjuvant PDC OS Validation: Model Outcomes vs. Trial Data

[redacted]

Table 89. Neoadjuvant PDC OS Validation: Model Outcomes vs. Trial Data; Survival by Six Month Interval

Source	Month 6	Month 12	Month 18	Month 24	Month 30	Month 36
Modelled OS for neoadjuvant PDC, Approach 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Modelled OS for neoadjuvant PDC, Approach 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CheckMate-816 OS KM - PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

In general, the modelled OS fit well to the K-M data from CheckMate-816, although slightly greater variation was observed relative to the nivolumab + PDC arm comparison. Consideration of approach 1 ([redacted] LY in DM following UK treatment patterns) and approach 2 ([redacted] LY, assuming 75% of patients receive PDC and 25% receive BSC in DM) showed that the two approaches generate similar outcomes during the within trial period. The greatest deviation from the trial data was observed at month 24, with the projected OS [redacted]% higher than the trial data (approach 1) and [redacted]% higher than the trial data (approach 2). Notably, the greatest deviation from the trial data predicted higher survival for neoadjuvant PDC than reported in the trial, so this deviation is not likely to bias model results in favour of nivolumab.

B.3.14 Interpretation and conclusions of economic evidence

In CheckMate-816, nivolumab + PDC showed improved EFS versus PDC in the neoadjuvant treatment of resectable NSCLC in adults. In the CEM, the improved EFS for patients treated with nivolumab + PDC resulted in an increase of [redacted], [redacted] and [redacted] QALYs versus surgery alone, neoadjuvant CRT, and adjuvant PDC, respectively. Based on the current simple patient access schemes for nivolumab, approved by the Department of Health, this resulted in an incremental cost-effectiveness ratio (ICER) of £2,685 per QALY versus surgery alone and being dominant versus both neoadjuvant CRT and adjuvant PDC. The results were robust for all scenario analyses conducted with only one extreme scenario resulting in an ICER above £20,000 per QALY. The scenario analyses showed that even when relaxing the assumption of cure which has previously been discussed and critiqued in recent similar appraisals, the ICER is still below £20,000.

The results of the internal and external validation of the model show that although the OS data from CheckMate-816 is still immature, the modelled survival is well aligned with external data and conditional survival curves constructed based on a combination of CheckMate-816 trial data and external evidence.

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B.5 Appendices

The following appendices are provided in a separate document:

Appendix C. Summary of product characteristics (SmPC) and UK public assessment report 192

Appendix D. Identification, selection, and synthesis of clinical evidence 192

Appendix E. Subgroup analysis 192

Appendix F. Adverse reactions 192

Appendix G. Published cost-effectiveness studies 192

Appendix H. Health-related quality of life studies 192

Appendix I. Cost and healthcare resource identification, measurement, and valuation . 192

Appendix J. Clinical outcomes and disaggregated results from the model 192

Appendix K. Price details of treatments included in the submission 192

Appendix L. Checklist of confidential information 192

Appendix M. Indirect treatment comparisons 192

Appendix N. Expert input into the submission 192

Appendix O. Survival analyses of EFS 192

Appendix P. Sources for validation of survival extrapolation 192

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Nivolumab with chemotherapy for neoadjuvant treatment of resectable non-small-cell lung cancer [ID3757]

Clarification questions and responses

20 October 2022

File name	Version	Contains confidential information	Date
ID3757 nivolumab clarification letter BMS responses [redacted]	0.1	Yes	20/10/2022

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Decision Problem-subgroup analyses by disease status

A1. The NICE scope states that "If evidence allows, results by disease stage and level of PD-L1 expression will be considered." Figure 4 in the company submission CS suggests that neoadjuvant chemoradiation is only relevant for the Stage IIIA subgroup. Additionally, Kaplan-Meier curves for the Stage IB-II and stage IIIA subgroups reported in Appendix E suggest the effectiveness of nivolumab may differ across subgroups, notwithstanding the smaller sample sizes informing the analyses. There appear to be sufficient studies in the network meta-analysis (NMA) to inform the relative effectiveness of comparators for event free survival (EFS) in each subgroup.

a) **State the relevant comparators for the Stage IB-II subgroup and for the Stage IIIA subgroup (are they different, or are all comparators relevant to both subgroups as well as the Stages IB-IIIA altogether)**

The main comparators for neoadjuvant nivolumab + PDC do not differ by stage or PD-L1 expression; surgery alone or surgery followed by adjuvant chemotherapy are the standard of care treatments for all patients with resectable Stage IB-IIIA NSCLC. As per the NICE clinical guidelines, neoadjuvant CRT is only recommended for a small subset of stage IIIA patient (stage IIIA-N2 patients), and according to clinical expert opinion, very few stage IIIA-N2 patients in England receive neoadjuvant CRT, at the discretion of the treating clinician. CRT is typically reserved for patients who are considered surgically unresectable

and, as such CRT was not a treatment option in CheckMate-816. Therefore, information on CRT is included for completeness in line with the NICE scope and clinical guidelines, but CRT should not be considered as a key comparator for this submission.

b) Reproduce the survival analyses for these two subgroups (the EAG acknowledges the number of locoregional events will be low, especially for nivolumab + PDC, but still considers the subgroup analysis to be useful)

It is not possible to provide results by disease stage or level of PD-L1 expression at this stage. We have provided the number of events for each of the requested subgroups in Table 1 based on interim analysis 1 results. These event numbers are far too low for credible extrapolations of time to event outcomes and resulting analyses would not be useful for decision making. However, clinical outputs from the interim analysis 2 data will be available in [redacted] BMS will prepare an updated clinical section of the company submission document in relation to the interim analysis 2 data, and the possibility of undertaking the requested analyses within the economic model will be revisited at this time.

Table 1. Number of events by subgroup (interim analysis 1 from CheckMate-816)

Subgroup	EF to LR		EF:DM	
	Nivolumab + PDC	Neoadjuvant PDC	Nivolumab + PDC	Neoadjuvant PDC
Stage IB-II	[redacted]	[redacted]	[redacted]	[redacted]
Stage IIIA	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 <1%	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 ≥ 1%	[redacted]	[redacted]	[redacted]	[redacted]

EF = Event-free; LR = local recurrence; DM = distant metastases

c) Undertake an NMA for EFS for these two subgroups, or fit survival curves to the constructed Kaplan-Meier curves if there is only one study per comparison

Please see answers to questions A1. a) and b).

d) Produce probabilistic and deterministic full-incremental cost-effectiveness results for these two subgroups.

Please see answers to questions A1. a) and b).

Systematic Review and Data Inputs to Network Meta-Analysis

A3. Appendix D: The NICE health technology evaluations manual (2022) recommends the systematic review relating to effectiveness evidence should be completed using a pre-defined protocol. Could the company please provide the protocol, give details of whether it was registered in the public domain (e.g., PROSPERO), and list any deviations?

The SLR was conducted according to a predefined protocol[1] provided with this response, and from which there were no deviations. The protocol was not registered with PROSPERO or another register.

A4. Appendix D, Table D-5 (p.21): Please can the company provide the following clarifications regarding Table D-5.

a) The table states that studies in the “elderly” were excluded but the mean age of participants in the CheckMate-816 trial was around 65 years. Please define what is meant by “elderly” and explain the rationale behind excluding this population.

Studies conducted where all patients were (for example) >65 years were to be excluded because these patients are not representative of the adult population as a whole. This additional exclusion criteria was added to help manage the scope of the review but no RCTs where the population was "elderly" were identified, and therefore no studies were excluded for this reason. The mean age in CheckMate-816 is reflective of the total population of patients with non-metastatic NSCLC, and the aim was to identify similar comparator RCTs.

b) Please further define “poor PS” in the population exclusion criteria.

Any study conducted with patients with high PS (>2) were to be excluded because again those patients are frail and not representative of the target population (CheckMate-816 included patients with PS 0-1 only). However, we did not identify any RCTs conducted in a PS>2 population and therefore no studies were excluded for this reason.

c) Please clarify the definition of “targeted therapy”.

Targeted therapies include all therapies for actionable mutations in NSCLC (e.g. EGFR, KRAS).

d) Please explain the rationale behind excluding studies using only one type of surgery for resectable NSCLC.

Studies where only one type of surgery (e.g. just pneumectomy) was performed would not be representative of the target population and were therefore to be excluded. However, no RCTs where only one type of surgery was used were identified and therefore no studies were excluded for this reason.

A5. Appendix D, Section D.2:

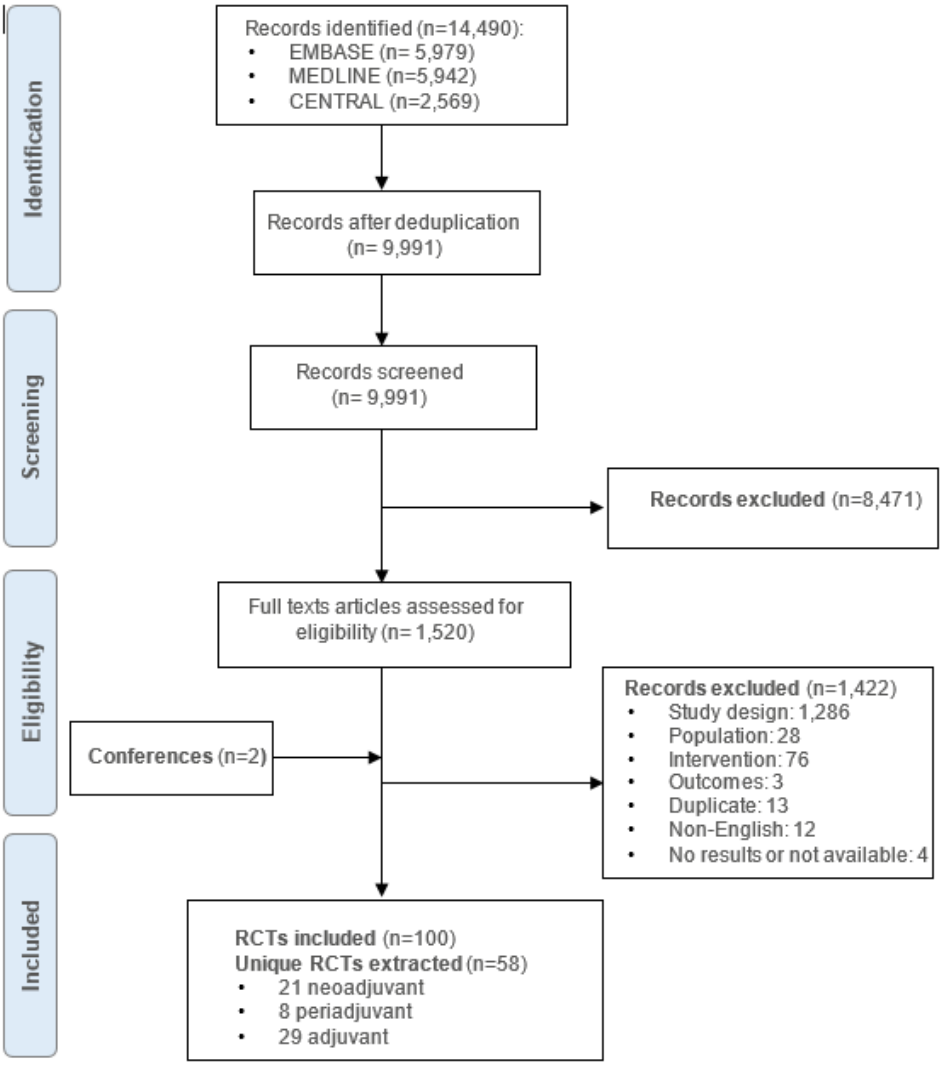
a) No list of excluded studies from the SLR or reasons for exclusion appear to have been provided. Please provide a full list of all studies excluded at full text and reasons for their exclusion.

See the Excel file “List of Excluded Records_FINAL” provided with this response, which includes the list of excluded studies with reasons.

b) Figure D-1 (p.24): 113 studies were excluded for an unspecified reason (‘other’). Please provide specific reasons why these studies were excluded in relation to the review eligibility criteria.

Please see revised PRISMA chart below (Figure D-1). This has also been updated in the revised Appendix document. We have eliminated the category "other" and provided specific reason for each record. 9 records in the category "other" were secondary publications of included RCT. These 9 records should be counted as "include" and we have moved them to the "Included RCTs" box.

Figure D-1. PRISMA: comparative efficacy and safety



A6. Appendix D, Section D.2.1.1. (p.24): "1 RCT of camrelizumab + chemotherapy versus chemotherapy presented at a conference was identified but not presented here due to limited data available". Please clarify what is meant by "limited data", as this abstract could still provide useful information.

We identified the conference abstract but were unable to obtain the poster/oral presentation. Limited data was presented in the abstract for inclusion in the review.

A7. Appendix D, Section D.2.1.4. (p.29): Please explain the rationale behind only reporting on the eight largest RCTs in the neoadjuvant setting within this table.

We limited this calculation to the largest RCTs to avoid "outliers" from small trials.

A8. Appendix D, Section D.1.3.5.6, Table D-19 (p. 38-9) and Section M.3.2 (p.188): Please clarify the following regarding adverse events.

a) Please explain the rationale behind only presenting AEs that are reported by at least two RCTs.

This table is intended to give an overview of the most common Grade 3&4 AEs in this setting. The intent was not to give an exhaustive list of all AEs.

b) 22 non-haematological AEs are reported by at least two RCTs in Table D-19 but only five of these are reported in full for each RCT on page 41. Please provide information on all non-haematological AEs for all RCTs included in the SLR.

We had provided the 5 most common AEs across RCTs. Table D-23 has now been expanded to show all AEs in the revised appendices.

c) What was the rationale behind extending the analysis in the NMA to include grade 5 treatment-related AEs but not within the SLR?

In the NMA, no analysis of safety data was conducted. Treatment-related grade 3/4 AEs were not meta-analysed given the challenges of pooling across different chemotherapies, but rather summarised in tabular form. Three studies reported the proportion of patients experiencing any AEs of grades 3 to 4.[2] No Grade 5 (fatal) treatment-related adverse events were identified in these three studies.

A9. Appendix D, Section D.1.2.5.7. (p.42) and Section D.2.2.1.6. (p.63): Only short narrative descriptions of the HRQOL results of the RCTs have been reported in these sections. Please provide all HRQOL data reported in these RCTs.

There were very limited HRQoL data and reported with different instruments. Westeel et al. (2013)[3] and Barlesi et al. (2015)[4] present data for EORTC-QLQ-C30 and LC13; Detterbeck et al. (2008)[5] and Gralla et al. (2009)[6] for the LCSS-lung cancer symptom scale; Gilligan et al. (2007)[7] for the SF-36; Butts et al. (2010)[8], Bezjak et al. (2008)[9] and Winton et al. (2005)[10] for the EORTC-QLQ-C30. None of the studies reported the EQ-5D-3L which was the HRQOL outcome included in CheckMate-816 and therefore no comparisons are possible.

A10. Appendix M, Section M.4.1.3 (p.120):

“[redacted]

[redacted]". Please clarify how it was determined whether a regimen was considered to be relevant for the NMA.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Table 2. Reasons for inclusion or exclusion in the network meta-analysis of studies identified in the systematic literature review

Author Year	Trial Name	Treatment comparison as described in NMA	Treatment comparison (detailed)	Reason for exclusion
Included, base case				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Included, sensitivity analyses				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Included, exploratory analyses				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]		[redacted]
Included, but combined two features of sensitivity analyses (not included in any analyses)				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Excluded				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]				

Abbreviations: adj, adjuvant; CARB, carboplatin; CIS, cisplatin; CRT, chemoradiotherapy; CT, chemotherapy; CYCLO, cyclophosphamide; DA, danvatirsen; DURVA, durvalumab; ETO, etoposide; GEF, gefitinib; GEM, gemcitabine; IFO, ifosfamide; IPI, ipilimumab; MIT, mitomycine; MONA, monalizumab; neo, neoadjuvant; OLEC, oleclumab; PEMX, pemetrexed; RT, radiotherapy; S, surgery; TARGET, Targeted agent; TAX, paclitaxel; TXT, docetaxel; UFT, uracul-tegafur; VBA, vinblastine; VDE, vindesine; VNB, vinorelbine.
Notes: The symbol => indicates treatment sequence (*e.g.* S=>CARB-TAX represents adjuvant carboplatin plus paclitaxel).

Network meta-analyses

A11. Appendix M provides helpful data regarding inputs into the NMA. However, please provide all data sets required to reproduce the company analyses, including log hazard ratios and their standard errors for all comparisons, variance of baseline arms where relevant (and formula used to estimate these), etc.

The data sets have been provided in supplementary document [redacted].

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

A12. Please provide Kaplan Meier curves, in a similar format to Figure M-40 in Appendix M, for studies included in NMAs of time to locoregional recurrence so that the EAG can assess the validity of the proportional hazards assumption for these analyses.

The proportional hazard assessment for time to locoregional recurrence was [redacted] (see **Table M-16** of main submission document).

The Kaplan Meier curves for time to locoregional recurrence from CheckMate-816 are provided in **Figure 1.** In addition, the log cumulative hazard plot along with Schoenfeld residuals are provided in **Figure 2.** The Grambsch-Therneau test was applied to obtain a p-value regarding the null hypothesis that hazards are proportional. In this case, the assumption of a proportional hazard violation was [redacted]

Figure 1. Time to locoregional recurrence in CheckMate-816

[redacted]

Figure 2. Proportional hazard assessment for time to locoregional recurrence in CM816

A13. In the EAG's view, Figure M-40 in Appendix M

.

a) Please run additional NMAs using a Weibull distribution (which can estimate survivor functions consistent with proportional hazards), and any other distribution of the company's choosing that does not require the PH assumption, for EFS outcome (see Ouwens *et al*, NMA of parametric survival curves)

To explore the impact of the proportional hazards violation in xxxxxxxxxxxxxxxxxxxxxxx NMAs for EFS that permit time-varying hazard ratios were run, including NMAs using Weibull and Gompertz distributions, as well as more complex second-order fractional polynomial models, based on the methodology proposed by Jansen (2011)[13]. Full details of the approach are provided in along with detailed results from the two best fitting models.

In summary, the best fitting model according to the deviance information criterion (DIC) involved ; however, the next most suitable model (which had a DIC that was within of the aforementioned involved indicates that the and that the

Results from both the time-varying and constant-hazard ratio fractional polynomial NMA models were presented in **Appendix M** (**Figure M-7**) of the main submission (Table 3). The original NMA estimates were than the updated constant hazard-ratio fractional polynomial model estimates, and were

[redacted] the time-varying hazard ratio fractional polynomial models, [redacted]

Table 3. EFS hazard ratios for neoNIVO-CT vs. comparators based on a time-varying fractional polynomial model

Comparator	Timepoint (months)	EFS Hazard Ratio (95% CrI) for NeoNIVO-CT vs Comparator		
		Time-varying model from FP NMA	PH model from FP NMA	Results from submitted PH NMA*
neoCT	6	[redacted]	[redacted]	[redacted]
	12			
	24			
	36			
	48			
	60			
adjCT	6		[redacted]	[redacted]
	12			
	24			
	36			
	48			
	60			
S	6		[redacted]	[redacted]
	12			
	24			
	36			
	48			
	60			
neoCRT	6		[redacted]	[redacted]
	12			
	24			
	36			
	48			
	60			

*See **Figure M-7** of main submission
Note: Estimates obtained from the following model: p0p-1; treatment effect on scale and second shape parameter; gray shading indicates the timepoints at which neoNIVO-CT estimates are based on projections and not on observed findings (following 42 months of follow-up).

b) Please provide model fit statistics (such as deviance information criterion (DIC), total residual deviance) and between-study standard deviations (where applicable) that compare goodness of fit for the base case model, Weibull model, and any other alternative model(s) proposed by the company

A figure of standardized DICs [redacted] along with an embedded excel file describing absolute DICs are available in [redacted] All FP models were fit as [redacted] Hence, between-studies standard deviations [redacted]

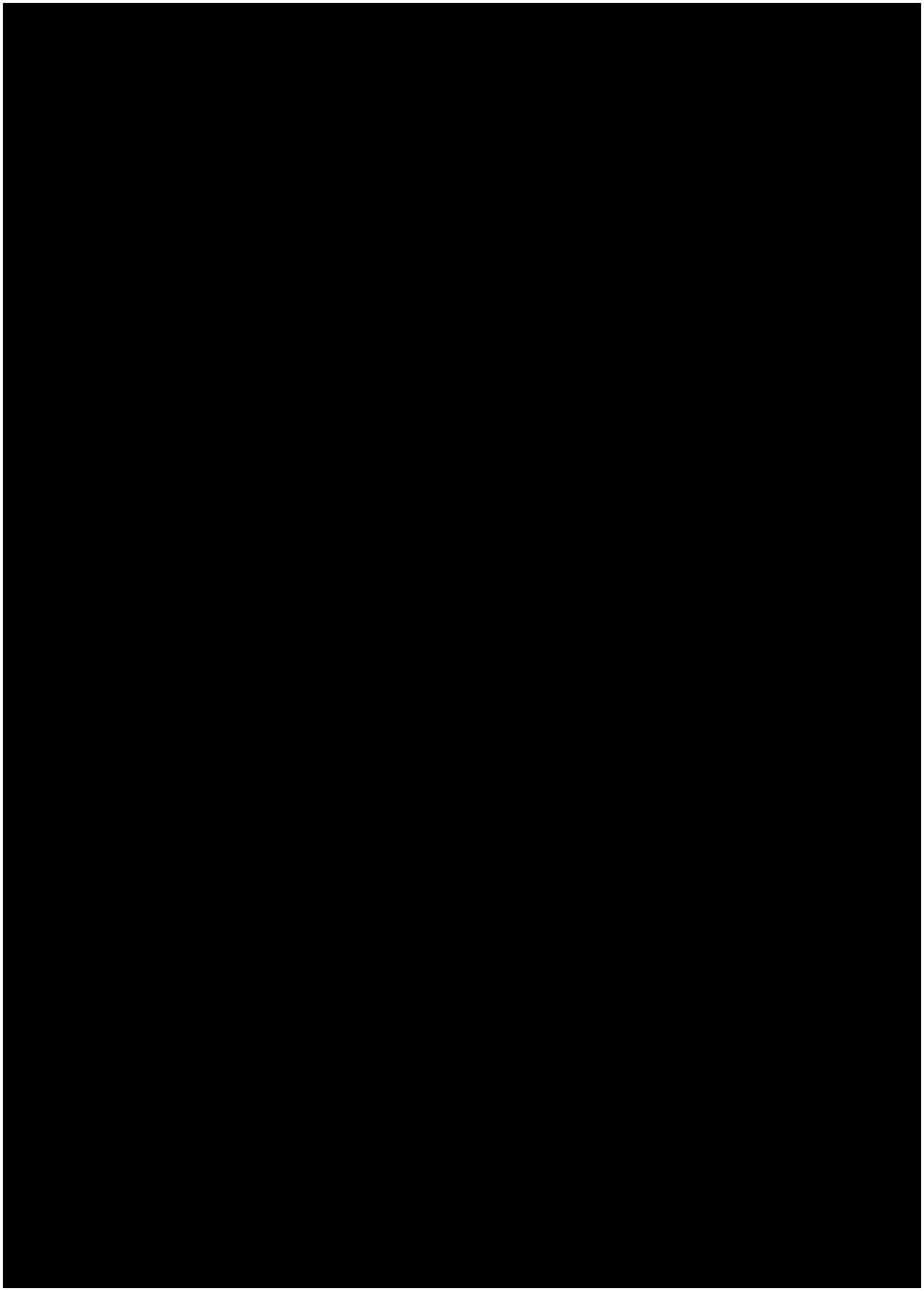
c) Please provide all WinBUGS code and data inputs to the NMA required to reproduce the results for these additional analyses

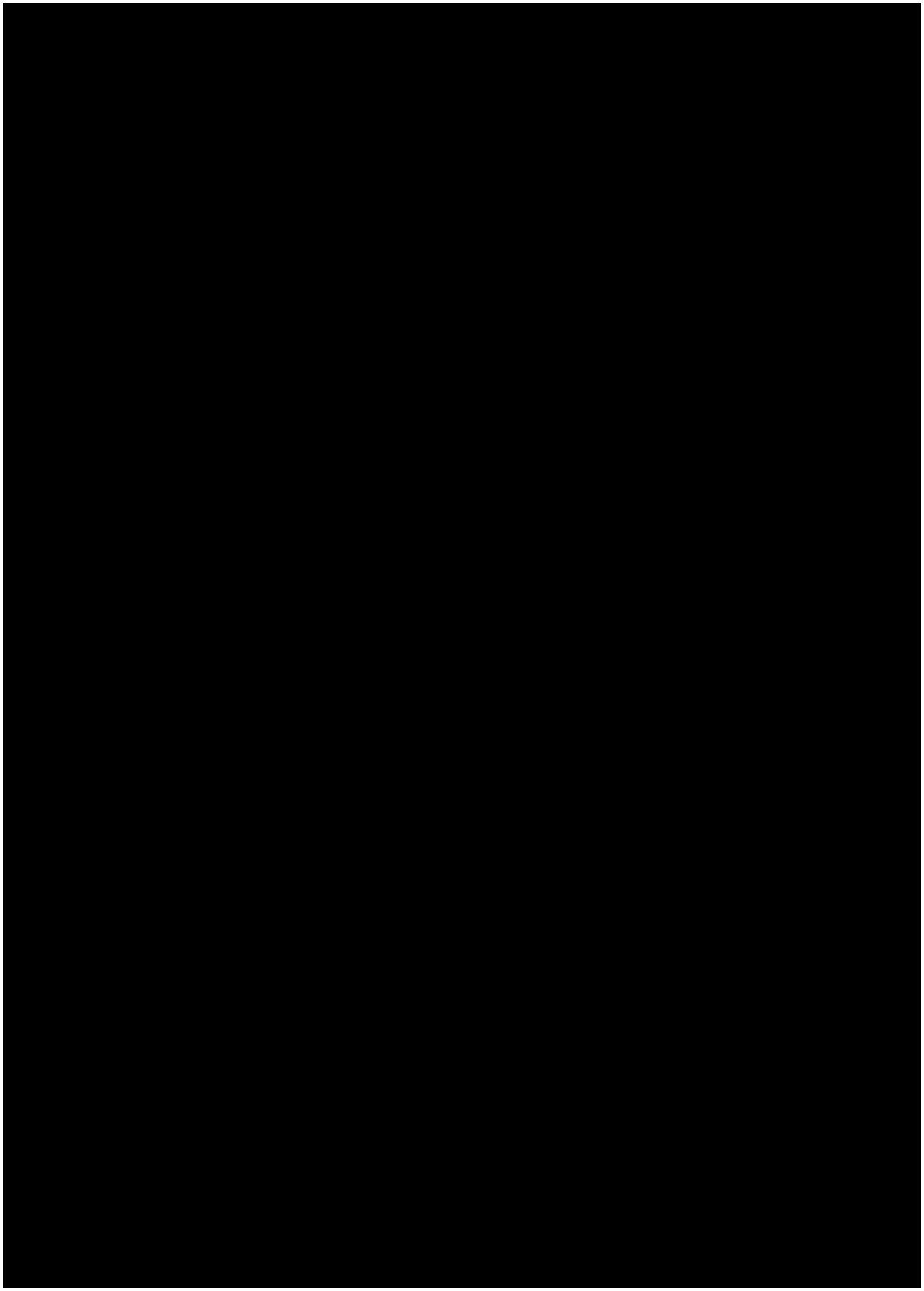
Analyses were conducted using [redacted] and run through [redacted] using the package [redacted]

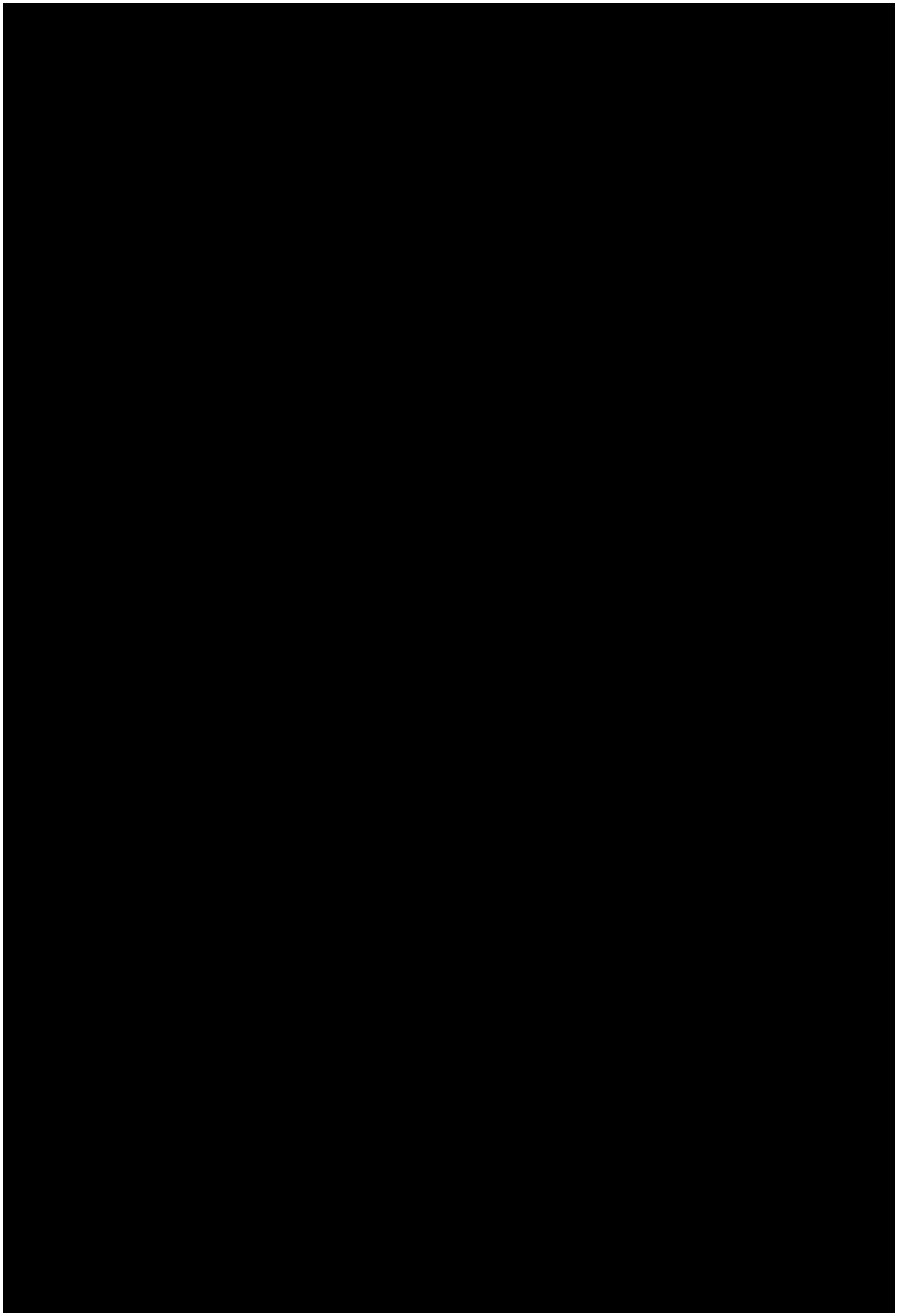
- JAGS code for the 1st and 2nd order fixed-effects models can be found below [redacted]
- Data in the form of discrete hazards are provided in embedded excel workbooks below [redacted]

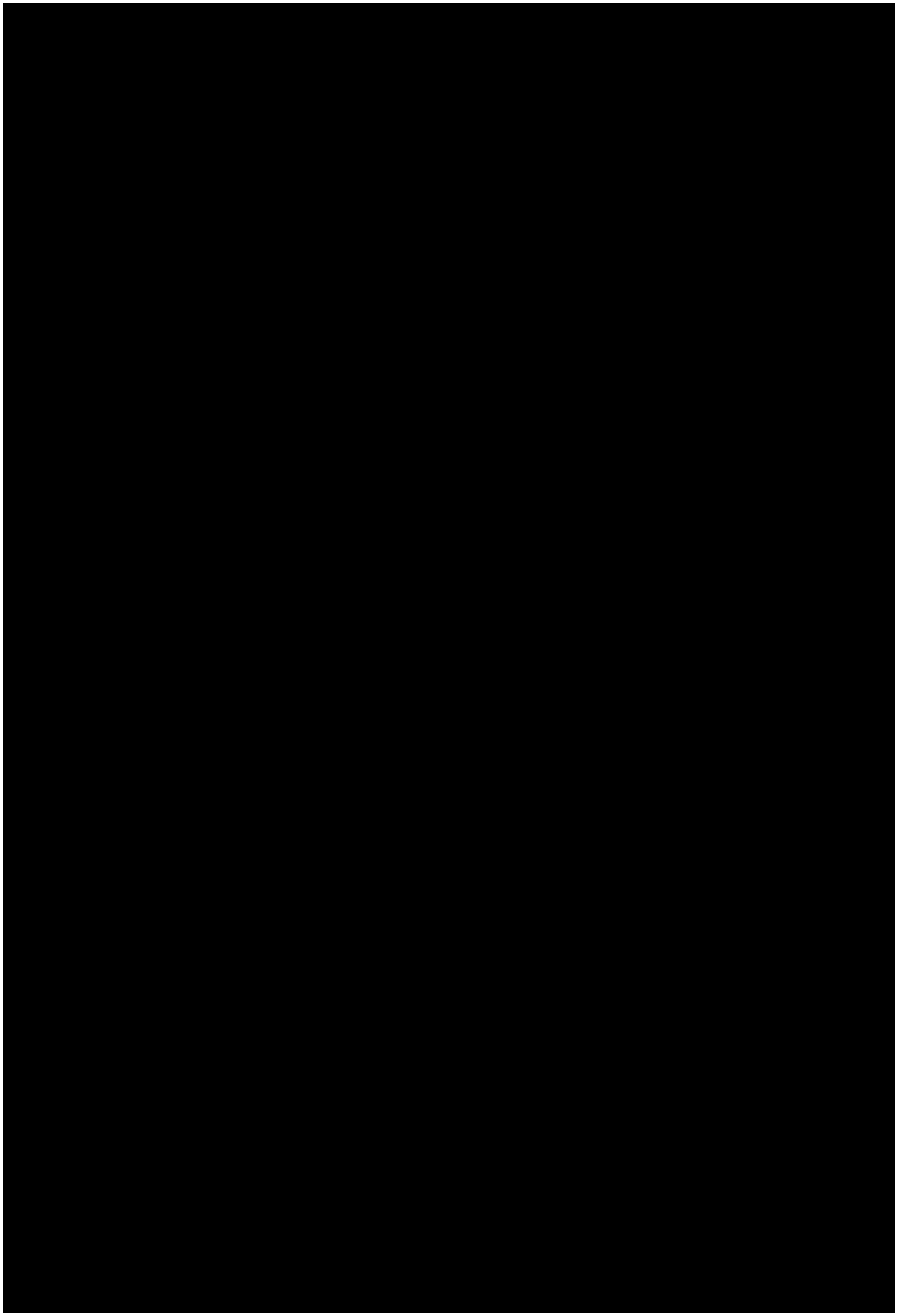
[redacted]

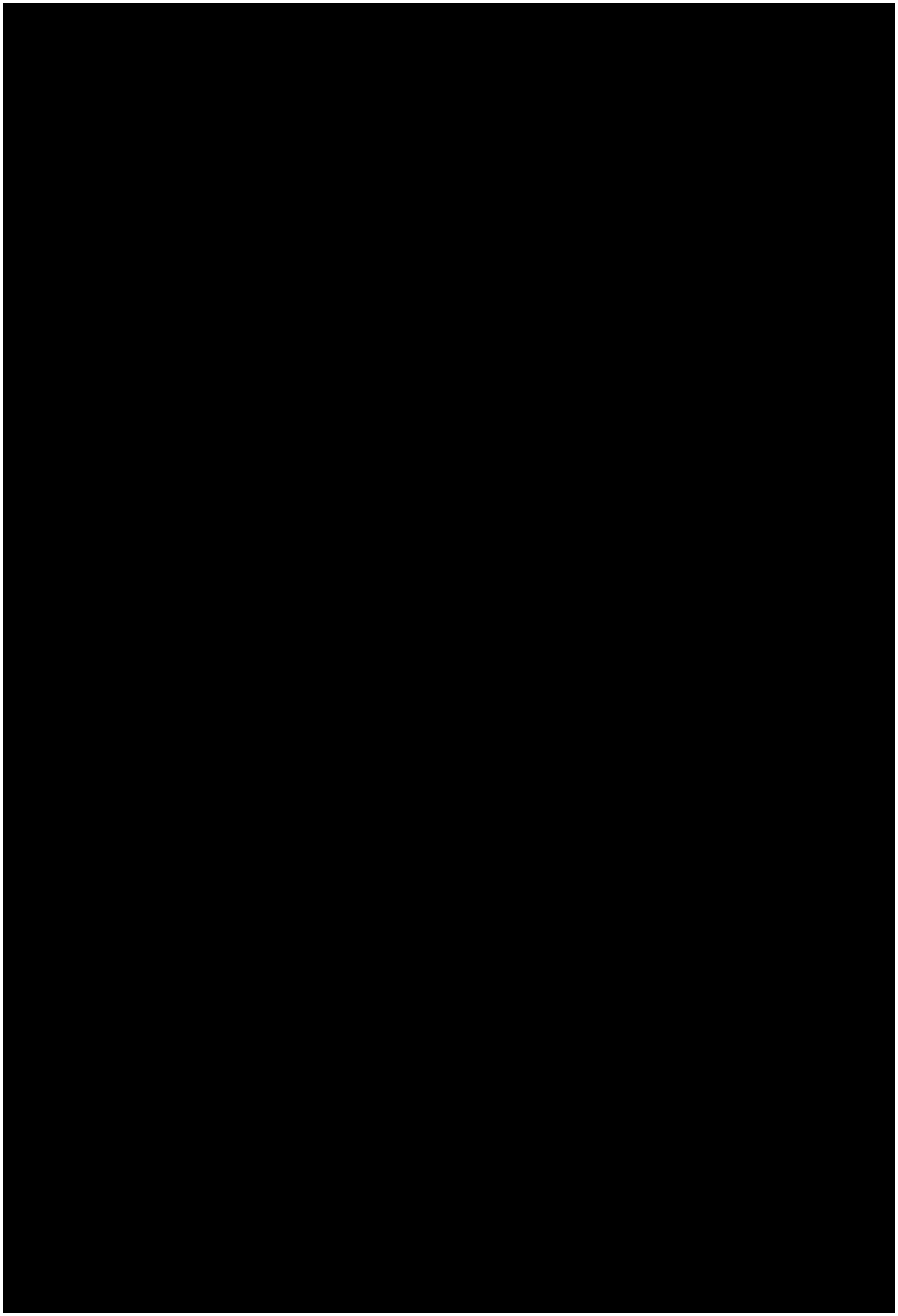
[redacted]











[redacted]

[redacted] burn-in iterations were used, and [redacted] additional iterations were used for the posterior sample [redacted]

Convergence checks were conducted on the treatment effect parameters (d's) using the following methods: trace plots, density plots, Gelman plots, and autocorrelation plots. Trace plots showed [redacted] while density plots showed [redacted] Autocorrelation plots were [redacted] Finally, the Gelman and Rubin convergence diagnostic showed [redacted]

Clinical Trial: CheckMate-816

A14. The clinical study report for CheckMate-816 states that nivolumab + PDC was added to the trial later than other trial arms. Please comment on whether this may have introduced bias with respect to the randomisation procedure or any other of the trial methods.

In the original protocol for CheckMate-816, an exploratory nivolumab + ipilimumab arm was included but enrolment closed early based on evolving external data highlighting promising results with IO + PDC (from KEYNOTE-021 in patients with metastatic NSCLC and NADIM in patients with resectable NSCLC) which became available during conduct of the trial and BMS remained blinded to the CheckMate 816 study results while taking this decision. Therefore, a nivolumab + PDC arm was added to CheckMate 816 in Revised Protocol 02.2017.[14] When enrolment to nivolumab + ipilimumab closed, the primary analysis became nivolumab + PDC vs. PDC (contemporaneously randomised population) and the nivolumab + ipilimumab arm became exploratory only.

The analysis presented in the submission and cited publications focused on the patient population randomised at the same time in the nivolumab + PDC and PDC arms, which are the primary endpoint populations for pCR and EFS.[15-17] The patients randomised to the PDC arm (n = 34 patients) before the opening of the nivolumab + PDC arm (i.e. during the

nivolumab + ipilimumab vs PDC initial randomisation period) were not included in that analysis. This was prespecified to ensure the primary analysis was not impacted by the late addition of the nivolumab + chemotherapy arm to the trial.

A15. Section B.2.2., Table 6 (p.33): Time to locoregional recurrence (TTLR) is listed as an additional outcome in CheckMate-816. Please clarify whether TTLR was a secondary outcome measure within CheckMate-816 and, if so, can the company please provide this effectiveness data.

TTLR was not a pre-specified outcome in the analysis plan for CheckMate-816 and is therefore not included in Section B2. However, a post-hoc analysis was conducted to support development of HTA submissions and the cost-effectiveness model. We have removed TTLR from Table 6 where it was included as a secondary outcome for the analysis by PD-L1 status in error. TTLR has been added to Table 7 since it is used in the model.

A16. Section B.2.3.1, Table 7 (p.36): CheckMate-816 does not contain any participants in the UK and most of the participants are from Asia (47.5% in the intervention arm and 51.4% in the control arm). Please comment on the extent to which these data are generalisable to the UK in terms of:

a) Population demographics and characteristics

CheckMate-816 is a global trial and therefore it is common to enrol more patients in one country or region over another. Region was not a stratification factor in the trial and therefore no conclusions can be drawn from post-hoc analyses by region which may be impacted by imbalances disease or patient characteristics between study arms.

As mentioned in section B.2.3.2 of Document B, UK clinical experts confirmed that the study population of CheckMate-816 is similar to that of the UK population, other than expected differences between trial and real-world evidence.

b) The healthcare system in relation to care of resectable NSCLC

A Pan-Asian Guidelines Adaptation (PAGA) is not yet available for resectable NSCLC (similar to those developed for metastatic or unresectable NSCLC); however, national guidelines generally align with ESMO and NCCN for lung cancer treatment.[18]

NCCN, ESMO and NICE guidelines highlight that systemic treatment approaches for patients with resectable NSCLC disease are similar pre- and post-surgery (see section B.1.3.6 of Document B).[19-21] Of note, EGFR testing of resectable NSCLC was required for patients in Asian countries included in CheckMate-816 and this has now been adopted in the UK, meaning the patient population will be similar in that respect. Note that NCCN guidelines have now included neoadjuvant nivolumab + PDC as a new treatment option for patients.[21]

A17. Section B.2.3.1, Table 7 (p.36-7): Please clarify the following points regarding Table 7.

a) Please clarify the difference between EFS and EFS2 as reported in Section B.2.6.1.4 (p.52).

EFS is defined as the time from randomization to any progression of disease precluding surgery, progression or recurrence of disease (per BICR using RECIST 1.1) after surgery, or death due to any cause, whereas EFS2 is the time from randomization to progression **after the next line of therapy** or to death from any cause, whichever occurred first.

b) HRQOL and adverse events are not mentioned in Table 7. Please clarify whether HRQOL and adverse events are CheckMate-816 outcomes relevant to the cost-effectiveness analysis, and therefore should be included in Table 7. If these are relevant, please provide similar details to the other outcomes reported in Table 7.

HRQOL and adverse events are CheckMate-816 outcomes relevant to the cost-effectiveness analysis, and we have therefore added these to Table 7 in the revised Document B.

c) Section B.2.3.1, Table 8 (p.38-9): Race/ethnicity is noted to be a subgroup consideration in the CheckMate-816 methods (Section B.2.2., Table 6) but is not reported within the participant characteristics. Please provide information on the participants' race and ethnicity.

Data on participants' race and ethnicity is provided in Table 4.

Table 4. CheckMate-816: patient ethnicity in the nivolumab + PDC and PDC arms

Race, n (%)	Nivolumab + PDC (n = 179)	PDC (n = 179)
White	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Asian Indian	[redacted]	[redacted]
Chinese	[redacted]	[redacted]
Japanese	[redacted]	[redacted]
Asian Other	[redacted]	[redacted]
Other	[redacted]	[redacted]

Source: BMS data on file (2021)[17]

A18. Please provide the median and range of length of follow-up times in each of the CheckMate-816 arms.

These data are not currently available by treatment arm, we have requested them and will provide once available.

A19. Section B.2.6.1.4, Table 16 (p.55): Please clarify the following points about the surgical outcomes for CheckMate-816.

a) The patient representative submission received by NICE has noted that there is a concern that people might have their surgical resection cancelled or delayed due to receiving neoadjuvant treatment. In Table 16, the company have not specified what 'other' reasons there were for delaying surgery. Please clarify these 'other' reasons for resection delay.

The footnote to Table 16 states "Other reasons were patient refusal in 9 patients in the NIVO+PDC arm and 8 patients in the PDC arm; consent withdrawal in 3 patients in the PDC arm; COVID-19 in 1 patient in the PDC arm; unfit for surgery due to poor lung function in 2 patients in the NIVO+PDC arm and 4 patients in the PDC arm; and unresectability in 2 patients in each arm".

b) The footnotes of Table 16 note that participants may have undergone more than one surgery type. Please clarify how many participants in each arm underwent more than one type of surgery and what this consisted of.

These data are not currently available; we have requested them and will provide once available.

A20. Section B.2.6.1.4, p.56: "EQ-5D-3L completion rates were > 80% in both treatment arms at baseline and during the neoadjuvant period." Please provide the exact rates for both arms of the study.

The EQ-5D completion rates for nivolumab + PDC and PDC, respectively, are presented in Table 5.

Table 5. CheckMate-816: EQ-5D completion rates in the nivolumab + PDC and PDC arms

Visit	EQ-5D completion rate by treatment arm	
	Nivolumab + PDC	PDC
Baseline (Cycle 1 Day 1)	94%	96%
Week 4 (Cycle 2 Day 1)	97%	96%
Week 7 (Cycle 3 Day 1)	91%	94%
Post-neoadjuvant Visit 1 (~30 days after last dose)	89%	84%
Post-neoadjuvant Visit 2 (~70 days after post-neoadjuvant Visit 1)	84%	84%

Source: Felip (2022)[22]

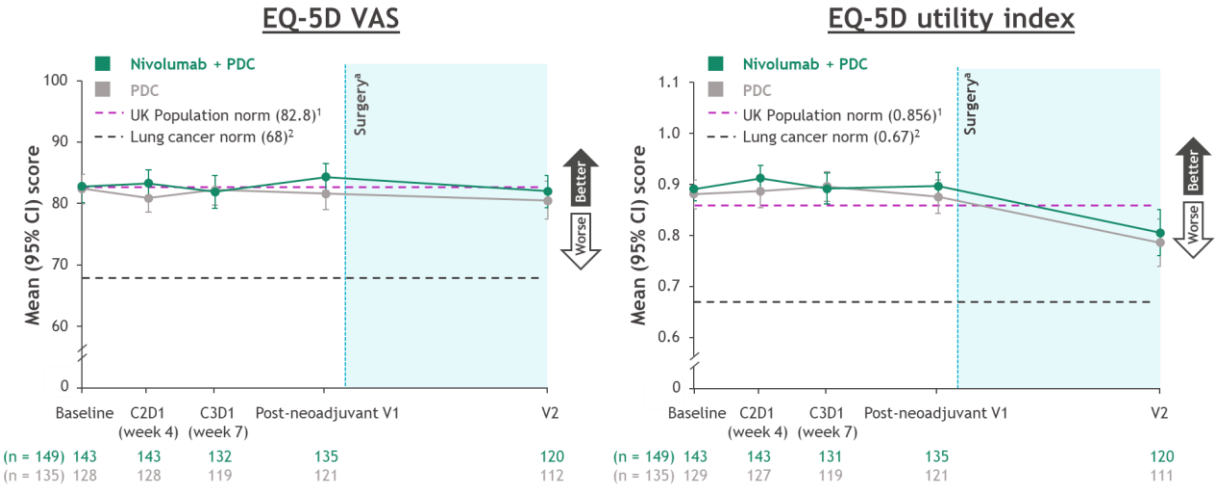
A21. Section B.2.6.1.4, p.56-7: What was the rationale behind measuring and reporting EQ-5D-3L scores only for the neoadjuvant period and post-neoadjuvant visit and not post-resection?

EQ-5D-3L scores were measured during the post-neoadjuvant and post-surgery periods, but were not available at the time of submission as were only presented at ESMO in September 2022.

Post-resection rates for EQ-5D are now available and are included in Figure 3.[22] This analysis focuses on the neoadjuvant period, post-neoadjuvant visit 1 (mostly pre-surgery) and post-neoadjuvant visit 2 (mostly after surgery). Further analysis and reporting of all remaining time points after surgery will be conducted at a later time.

However, utilities incorporated in the economic model leverage data on the whole duration of follow-up and are estimated by health state, as relevant for the economic model.

Figure 3. EQ-5D VAS and utility index scores during the neoadjuvant period and post-surgery: patients who received surgery



A22. Section B.2.7. (p.57): Subgroup analyses for race/ethnicity have not been presented, though it is listed as a key subgroup for the trial in Section B.2.2.1, Table 7 (p.36). Please provide subgroup analyses by race/ethnicity.

In CheckMate-816, race/ethnicity and region were not stratification factors, and as a result, the data are limited by potential imbalances in known or unknown prognostic factors and should be interpreted with caution. In exploratory subgroup analyses, no conclusion should be made as these analyses are not statistically powered. Furthermore, a review of the literature on immuno-oncology agents shows that immuno-oncology regimens globally improved outcomes as compared with chemotherapy in metastatic NSCLC across several trials in both Asian and non-Asian populations.[23] Therefore, there is no statistical or clinical rationale to assess efficacy by race/ethnicity.

Nonetheless, if we consider the pCR data from CheckMate-816 by race, the unweighted differences in pCR rate (between nivolumab + PDC and PDC) [redacted] As data mature, the difference in pCR seen between the treatment arms in all subgroups by race should translate into benefits in terms of EFS and subsequently OS.

In terms of EFS, [redacted] Since race was not a stratification factor, imbalances in baseline disease or patient characteristics (such as PD-L1 status, EGFR mutation status and ECOG Performance Status) may contribute to the different results observed. To facilitate a better understanding [redacted] demographics, baseline characteristics, and post-baseline surgical parameters for these 2 subgroups were reviewed (Table 6). In the [redacted] subgroup compared to the [redacted] subgroup (both arms), there was a [redacted] proportion of subjects with [redacted], and a [redacted] proportion of subjects with [redacted] Within the [redacted] subgroup, there were also [redacted] between the nivolumab + PDC vs PDC arms. Among [redacted] subjects, there was a [redacted] proportion of subject with [redacted] treated with nivolumab + PDC [redacted] and a [redacted] proportion of subjects with [redacted] who have been shown to have a [redacted] Other [redacted] subgroups include a [redacted] proportion of subjects who were [redacted] and a [redacted] proportion of subjects with [redacted].

Table 6. CheckMate-816: Demographics, baseline characteristics and post-baseline surgical parameters with clinically relevant imbalances by race (white and Asian) – all concurrently randomised subjects in the nivolumab + PDC and PDC arms.

	Number (%) of subjects			
	White		Asian	
	Nivolumab + PDC (N = 89)	PDC (N = 80)	Nivolumab + PDC (N = 86)	PDC (N = 93)
Female	[redacted]	[redacted]	[redacted]	[redacted]
Age < 65 years	[redacted]	[redacted]	[redacted]	[redacted]
Cell type at study entry				
Squamous	[redacted]	[redacted]	[redacted]	[redacted]
Non-squamous	[redacted]	[redacted]	[redacted]	[redacted]
Baseline ECOG PS				
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1				
<1%	[redacted]	[redacted]	[redacted]	[redacted]
≥ 1%	[redacted]	[redacted]	[redacted]	[redacted]
1-49%	[redacted]	[redacted]	[redacted]	[redacted]

≥ 50%	[redacted]	[redacted]	[redacted]	[redacted]
Not available	[redacted]	[redacted]	[redacted]	[redacted]
Definitive surgery	[redacted]	[redacted]	[redacted]	[redacted]
Surgery outcome of negative margin[a]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Denominator based on number of subjects with surgery.

Therefore, it is inappropriate to conduct analyses by these subgroups. Furthermore, event rates remain low in CheckMate-816 and the event rates in the subgroups are even lower, therefore too few events have occurred for a valid analysis, particularly of the time-to-event outcomes.

A23. Section B.2.10, Table 21 (p.70): Increased lipase, embolism, ischaemic stroke and tuberculosis are all listed as adverse events in the nivolumab + PDC arm of CheckMate-816 that do not appear to be present in the BNF's list of side-effects for nivolumab. Can the company please state whether these adverse events were related to the treatment?

Ischaemic stroke and tuberculosis occurrence in CheckMate-816 are not treatment-related (ie, not deemed related to nivolumab + PDC treatment). Increased lipase and embolism are considered treatment-related; however, because these are not immune-mediated AEs (IMAEs), it is suggestive that they are associated with the PDC component of the nivolumab + PDC regimen, rather than with nivolumab.

A24. Section B.2.6.1.2, CheckMate-816: Primary outcomes, Figure 9, Page 48: There is a step-change in event-free survival close to month 30. Part of this will have a statistical explanation- a combination of lower patients at risk and random clustering of events. Is the company aware of any potential clinical reason for this?

The minimum follow-up for EFS at this time is 21 months, with a median follow-up of 29.5 months; therefore censoring (due to patients not yet having an event) after 24 months is observed, and no conclusions can be drawn beyond this timepoint. Longer follow-up is needed to characterise EFS for both nivolumab + PDC and PDC beyond 24 months.

A25. Section B.2.7 Subgroup analysis, Figure 15, Page 59: There seems to be a noticeable difference in event-free survival in the North America and Europe subgroup compared to the Asian countries subgroup.

a) **Please provide time-to-event analysis results for the outcomes relevant to the cost-effectiveness analysis nivolumab + PDC for the North America and Europe subgroup for the base-case population (stages IB-IIIA).**

As discussed in response to question A22, region was not a stratification factor in CheckMate-816, and as a result, the data are limited by potential imbalances in known or unknown prognostic factors and should be interpreted with caution. Moreover, in exploratory subgroup analyses, no conclusion should be made as these analyses are not statistically powered.

Nonetheless, if we consider the pCR data from CheckMate-816 by region, results are similar. The unweighted pCR rate difference between nivolumab + PDC and PDC for North America was 20.0% (95% CI: 6.9-34.8), for Europe was 24.4% (95% CI: 7.4-39.3), and for Asia was 25.0% (95% CI: 14.7-35.5). For EFS, unstratified HR between the 2 treatment arms for North America was 0.78 (95% CI: 0.38-1.62), for Europe was 0.80 (95% CI: 0.36-1.77), and for Asia was 0.45 (95% CI: 0.29-0.71).[16]

Since region was not a stratification factor, imbalances in baseline disease or patient characteristics (such as PD-L1 status, EGFR mutation status and ECOG Performance Status) may contribute to the different results observed. To facilitate a better understanding of the different treatment effect for nivolumab + PDC vs PDC in the European subgroup (EFS HR = 0.80; 95% CI: 0.36, 1.77) compared with the Asian subgroup (EFS HR = 0.45; 95% CI: 0.29, 0.71), demographics, baseline characteristics, and post-baseline surgical parameters for these subgroups were reviewed.

[redacted] are summarized in Table 7. Some of these [redacted] may contribute to the [redacted] In the [redacted] subgroup compared to the [redacted] subgroup (both arms), there was a [redacted] proportion of subjects who had [redacted] and [redacted] and a [redacted] proportion of subjects with [redacted] % (particularly in the [redacted] (Table 7). Within the [redacted] subgroup, there was a [redacted] proportion of subjects with [redacted] in the [redacted] Other [redacted] in [redacted] as compared to [redacted] include a [redacted] proportion in [redacted] of subjects who were [redacted] Within the [redacted] subgroup, there was a [redacted] proportion of subjects who were [redacted] in the [redacted]

Table 7. **CheckMate-816: Demographics, baseline characteristics and post-baseline surgical parameters with clinically relevant imbalances by region (North America, Europe, Asia, Rest of the World) – all concurrently randomised subjects in the nivolumab + PDC and PDC arms.**

	Number (%) of subjects							
	North America		Europe		Asia		Rest of World	
	Nivolumab + PDC (N = 41)	PDC (N =50)	Nivolumab + PDC (N = 41)	PDC (N = 25)	Nivolumab + PDC (N = 85)	PDC (N = 92)	Nivolumab + PDC (N = 12)	PDC (N = 12)
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age < 65 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race								
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cell type at study entry								
Squamous	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-squamous	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline ECOG PS								
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1								
<1%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 1%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1-49%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Definitive surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery outcome of negative margin[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Denominator based on number of subjects with surgery.

Therefore, it is inappropriate to conduct analyses by these subgroups. Furthermore, event rates remain low in CheckMate-816 and the event rates in the subgroups are even lower, therefore too few events have occurred for a valid analysis, particularly of the time-to-event outcomes.

b) Please provide NMA results specifically using North America and Europe evidence where feasible for the base-case population.

See A25 a).

c) Please provide cost-effectiveness results for a scenario using evidence for North America and Europe for the base-case population. Please use base case NMA results in this analysis if it is not feasible to conduct a NMA using North America and Europe evidence.

See A25 a).

Literature searching

A26. Appendix G, Section G.1.1. (p. 70-71): Search strategy does not include term(s) for surgery, which is included as a comparator in the economic model. Please confirm that papers will be picked up with the strategy used.

We can confirm that the search strategy did not include terms for surgery. However, we argue that this is not problematic.

In the context of the resource use and utility searches, surgery has been a treatment option for many years, and it is therefore unlikely that a review would capture new evidence in 2022. New trials and studies would instead be expected to focus on better understanding neoadjuvant / adjuvant treatment.

In the context of economic evaluations, surgery was also not included as a search term. In this case, we argue it is not a problem because it is unclear what the comparators would be in an economic evaluation focused on surgery only as the main intervention (by analogy, economic evaluations are not routinely conducted on BSC / palliative care in other indications). Furthermore, we would expect that neoadjuvant / adjuvant search terms would pick up the data needed for surgery only, given that surgery is necessarily included as a component of either.

Section B: Clarification on cost-effectiveness data

B1. Please present the cost-effectiveness results in the report and economic model as a full incremental analysis, including all the relevant comparators.

Given that nivolumab is expected to specifically replace the individual comparators, pairwise comparisons instead of fully incremental analyses have been provided in accordance with the technology appraisal manual.

Health-related quality of life

B2. Section B.3.4.4.1, please answer the following questions in relation to utility values for Adverse Events (AEs).

a) What information was used to support the assumption that the following AEs, thrombocytopenia, leukopenia and anaemia, could be assigned the same utility value as neutropenia? Is there evidence to support alternative values to be used in scenario analysis, and, if so, what are these values?

Data on utility decrements for these AEs was not identified during model development. Given the lack of evidence, it was assumed that these haematological AEs have similar impact on utility. During the preparation of this response, further values for anaemia and thrombocytopenia were however identified (Table 6) and could be used for scenario analyses should the EAG wish.

Table 8. Disutility of grade 3/4 adverse events

Adverse event	Disutility	Reference
Anaemia	−0.125	Lloyd et al. (2008)[24]
Thrombocytopenia	−0.184	Attard et al. (2014)[25]

b) Why were the higher utility values for AEs derived using time-trade off by Nafees et al (2017) not used in a scenario analysis, given it is a more recent paper than Nafees et al (2008)?

AEs have a minimal effect on the results overall and therefore alternative data assumptions were not explored for these utilities; scenarios were focused on what we considered key aspects of uncertainty in the submission.

c) The duration of AEs of one week is not provided in the report, only in the model. How was the duration determined?

The duration of 1 week for AEs was based on an assumption. Given the short duration of neoadjuvant treatments, a one-week duration was considered reasonable.

B3. Section B.3.4.4.2, please answer the following questions in relation to the age adjustment applied to utility values.

a) Would those with resectable NSCLC be expected to experience the same utility value as the general population just based on age and sex especially those with more advanced disease (i.e. Stage IIIA). Was clinical advice provided?

Yes, patients in the EF health state experience the same utility value as the general population based on age and sex in the base case analysis. Clinical advice was provided regarding the utility values but although the clinical experts thought that the utility value from CheckMate-816 (not capped to general population) for EF was marginally higher than expected, they did not provide an alternative value that they thought would be more clinically plausible.

b) Given that clinical advice suggested the utility value for the event free (EF) health state was too high, did they provide an alternative utility value or range of values to be incorporated in a scenario analysis? If yes, please provide these values.

As stated above, no alternative value was provided.

c) To which other health states was the sex-age adjustment applied, as the example provided on p138 is only applicable to the scenario analysis?

The age adjustment is applied to both the EF and LR health states. The description provided on p138 is not only applicable to the scenario analysis. The adjustment in utility for the EF health state in the base case (capping utility to general population) is applied so that the mean utility for EF is equal that of the age and sex matched population in the model at treatment initiation. In the subsequent modelling over time, the utility value is adjusted for both EF and LR to account for decline in utility with age.

B4. Section B.3.4.4: Please answer the following questions in relation to the derivation of the utility value for the locoregional (LR) health state

a) Given that the clinical advice suggested the utility decrement from the EF to LR health state was lower than expected, did the clinical experts provide an alternative utility value or a range of values to be

incorporated in a scenario analysis? If yes, please provide these values.

The clinical advisors didn't provide an estimate of the utility decrement when consulted. However, one of the clinical advisors stated that he thought the utility value would be around 0.75 for patients in LR. The indicated lower utility value for LR, and thereby higher decrement compared to EF, would have been a non-conservative assumption and thus it was decided to keep the utility values based on data collected in CheckMate 816 to not overestimate the benefit of nivolumab.

b) How were the 95% confidence intervals (CIs) surrounding the LR health state utility estimated for the base-case if the average utility value was assumed to be 0.062 utilities fewer than the EF state? Please provide the 95% CIs.

The CI interval surrounding the LR health state in the base case was based on the assumption that the standard error for the calculated mean was equal to the standard error of the mean LR utility value from CheckMate 816. This resulted in a CI of [redacted].

c) The utility values for the LR state are different in Tables 49 and 50. Please confirm which value is correct.

Values in table 49 for the unadjusted LR utilities are correct and table 50 should have been as presented below; these have been corrected in Document B.

Table 9. Alternative utility estimates used in the base case and scenario analysis

	Description	EF	LR	LR to EF decrement
Base case	CM-816 EF capped with general population, with LR decrement from CM-816	0.833	[redacted]	[redacted]
Scenario	Unadjusted values from CM-816	[redacted]	[redacted]	[redacted]

CM-816 = CheckMate-816; EF = Event-Free; LR = Locoregional Recurrence.

B5. Section B.3.9.1, Table 76: Why does the utility value of the DM state have a gamma distribution?

To clarify, the parameter in question is not a utility value. Rather, it is a QALY total - the one-off amount accrued by patients moving into the DM state. Therefore, the typical use of a beta distribution is not appropriate (and is furthermore mathematically impossible given that beta distributions will only generate values between 0 and 1; the total QALYs in DM per base case estimates are >1.) Gamma was selected instead as it has a lower-bound of zero, ensuring that valid values would be drawn during the PSA.

Estimation of costs

B6. Please elaborate on the following queries on how treatment costs were derived.

a) **Section B.1.2, Table 2 on p.17 states that the average cost of a course of treatment is based on the mean number of doses in the CheckMate-816 trial. However, this data is not provided in the report. Please provide this information.**

Apologies, the footnote for this calculation should have stated "Cost of a course of nivolumab + PDC at list price based on 3 cycles of therapy as received in the CheckMate-816 trial per protocol for all patients event free", and has now been corrected in Documents A and B. As pointed out in the company submission, although most patients received the full course of neoadjuvant treatment in CheckMate 816, given the relatively higher cost of nivolumab, assuming all patients who do not progress or die receive the full 3 cycles is a conservative assumption.

b) **Section B.3.5.1.1: Please clarify how the information in Tables 53-55 is used to derive the treatment cost estimates.**

Table 53 is used to calculate the overall cost of neoadjuvant PDC in consideration of the different possible regimens for each comparator. Specifically, each regimen has a separate cost, and the overall comparator cost is the weighted average of the % of patients receiving each regimen and the cost of each regimen. It's the same as the other basket / weighted average costs in the model.

Table 54 relates the % of patients in neoadjuvant treatment comparators who go on to receive adjuvant treatment (can be either PDC or radiotherapy) after surgery. The percentage of patients specified in the table for each comparator arm incur these costs. For example, if the overall cost of the adjuvant PDC basket is £1,000, and 15% of patients receiving neoadjuvant nivolumab + PDC go on to receive adjuvant systemic therapy, a cost of £150 (£1,000 * 15%) is applied.

Table 55 is similar to Table 53, but applies to adjuvant chemotherapies. It is also used to compute the adjuvant chemotherapy cost for neoadjuvant comparators applied per Table 54.

c) **Section B.3.5.1.1: Please clarify how the percentages in Table 54 were derived based on the data provided in Table 11.**

The data in Table 54 of the company submission is taken from Table S.4.1.9 of the CSR for CheckMate-816. This is the same underlying data as presented in Table 11 of the submission but for Chemotherapy (≤ 4 cycles) alone + Chemotherapy and radiotherapy has been pooled together to estimate % receiving adjuvant systemic therapy, and Chemotherapy

and radiotherapy + Radiotherapy alone has been pooled to estimate % receiving adjuvant radiotherapy.

B7. Section B.3.5.1.1, in Table 53, in the first column NIVO+PDC, the sum of the distribution of PDC received exceeds 100%. Please explain why this is the case.

The [redacted] in Table 53 of the submission is due to rounding. In the model the treatments sums to 100%.

B8. Please answer the following on assumptions made regarding treatment regimens, AEs and surgery.

a) **Section B.3.5.1.2: It was assumed that the distribution of treatment regimens for adjuvant PDC was the same as the regimen distribution for neoadjuvant PDC. How was this assumption verified?**

KOLs were asked about the distribution of treatment regimens for neoadjuvant PDC and the model was updated based on the input received from the clinicians. As part of this discussion, it was not explicitly asked if they agreed with the assumption of adjuvant PDC being equal to neoadjuvant PDC. However, the clinical experts referred to the PDCs used in the adjuvant setting when validating data observed in CheckMate 816 and from the discussion clearly considered PDCs to be similar in the adjuvant and neoadjuvant settings.

b) **Section B.3.3.4: It was assumed that neoadjuvant CRT had the same AE profile has neoadjuvant PDC. How was this assumption verified?**

In the SLR of neoadjuvant treatments, only one paper was found reporting AEs for radiotherapy (Pless 2015; Table 10).

Table 10. Radiotherapy-related toxic effects (Pless 2015)

	Chemoradiotherapy group (n=98)	
	Grade 1–2	Grade 3
Non-haematological		
Dysphagia	70 (71%)	7 (7%)
Alopecia	40 (41%)	0
Fatigue	36 (37%)	1 (1%)
Cough	24 (25%)	0
Skin toxic effects	24 (25%)	0
Nausea/vomiting	20 (20%)	0
Neurotoxic effects	18 (18%)	1 (1%)
Dyspnoea	14 (14%)	0
Anorexia	12 (12%)	0
Fluid retention	9 (9%)	0
Infection	5 (5%)	0

Haematological		
Anaemia	98 (100%)	0
Leucopenia	98 (100%)	0
Neutropenia	98 (100%)	0
Thrombocytopenia	98 (100%)	0

In that paper, most AEs associated with RT were not Grade 3 or 4, and thus not included in the model. However, an additional 1% of patients experienced fatigue; the model could be updated to consider this. Additionally, the 7% of patients experiencing dysphagia mean that this event could be included given the 5% cut-off; a cost and disutility for dysphagia would need to be retrieved. However, the current inputs are fundamentally conservative: higher AE rates for CRT will make results more favourable for neoadjuvant nivolumab + PDC (Table 11).

Table 11. Sensitivity analysis: 1% increase in fatigue for neoadjuvant CRT

Outcomes: Nivolumab + PDC vs.	**Base case**			**1% increase in fatigue AE for Neoadjuvant CRT**		
	Incr. Costs	*Incr. QALY*	*ICER / QALY*	*Incr. Costs*	*Incr. QALY*	*ICER*
Neoadjuvant CRT	[redacted]	[redacted]	Nivolumab dominant	[redacted]	[redacted]	Nivolumab dominant
PDC (adjuvant)	[redacted]	[redacted]	Nivolumab dominant	[redacted]	[redacted]	£ 381.00
Surgery only	[redacted]	[redacted]	£ 2,685.00	[redacted]	[redacted]	£ 1,538.00

c) Section B.3.5.1.6: It was assumed that neoadjuvant CRT, adjuvant PDC and surgery only have the same distribution of surgical approaches as neoadjuvant CRT. What was the rationale for this assumption? Was there no published evidence on the surgery distributions? Was this assumption verified by KoLs?

As a point of clarification, the reviewer's assertion that the distribution of surgical approaches for adjuvant PDC and surgery only is assumed the same as neoadjuvant CRT is not quite correct; rather, all three are assumed to have the same distribution of surgical approaches as neoadjuvant PDC per CheckMate-816 data. KOLs were asked about the distribution of surgical approaches, but the information gained from this was vague / not suitable for use as model inputs. In light of this gap, we elected to proceed with the assumption that the distribution of surgery for neoadjuvant CRT, adjuvant PDC, and surgery only was the same as for neoadjuvant PDC in CheckMate-816.

We tested the impact of the assumptions with some supplementary scenario analyses (see Table 12). In one scenario, we applied the nivolumab + PDC distribution to all comparators;

in the other, we applied the neoadjuvant PDC distribution to nivolumab + PDC. Both scenarios represent a more conservative approach to surgery costing than the base case, as they imply neoadjuvant nivolumab + PDC only decreases the overall surgery rate but does not cause a change in the distribution of surgical approaches (whereas the base case implies both occur). In both analyses, incremental costs of nivolumab + PDC increased, although neither scenario led to a numerical ICER versus neoadjuvant CRT (dominated by nivolumab + PDC in both cases). Adjuvant PDC incremental costs changed from negative to positive in both scenarios, although the resulting ICER remains low. For surgery only, the ICER decreases when all treatments use the nivolumab + PDC distribution, and increases when all treatments use the neoadjuvant CRT distribution; however, in both cases, the ICER remains below the commonly-used CE threshold of £20,000.

Table 12. Scenario analysis: surgery distribution

Outcomes: Nivolumab + PDC vs.	Base case			Assume nivo + PDC surgery distribution for all comparators			Assume neoadjuvant PDC surgery distribution for nivo + PDC		
	Incr. Costs	*Incr. QALY*	*ICER / QALY*	*Incr. Costs*	*Incr. QALY*	*ICER*	*Incr. Costs*	*Incr. QALY*	*ICER*
Neoadjuvant CRT	[redacted]	[redacted]	Nivo dominant	[redacted]	[redacted]	Nivo dominant	[redacted]	[redacted]	Nivo dominant
PDC (adjuvant)	[redacted]	[redacted]	Nivo dominant	[redacted]	[redacted]	£381.00	[redacted]	[redacted]	£287.00
Surgery only	[redacted]	[redacted]	£2,685.00	[redacted]	[redacted]	£1,538.00	[redacted]	[redacted]	£3,058.00

d) Section B.3.5.1.6: Please comment on the reasons for the lower rate of surgery in the nivolumab+PDC arm compared to the PDC arm of the CheckMate-816 trial.

In the CheckMate-816 trial, the rate of patients receiving surgery was higher, not lower, for those who were treated with neoadjuvant nivolumab + PDC (83.2%) than those who were treated with neoadjuvant PDC alone (75.4%).

e) Section B.3.5.3.1: The CS states that AEs were estimated as weighted averages of the treatment costs for each AE, referencing Section B.3.3.2. However, there were no details of how this weighting was undertaken in Section B.3.3.2. What were the data and methods used to weight AE costs?

AE unit costs were based on standard UK sources (specifically the national schedule of NHS costs for 2019 - 2020.[26] The "weighting" refers to the calculation of the overall cost of AE for each treatment, which is as follows:

(%Anaemia * CostAnaemia) + (%Neutropenia * CostNeutropenia) + (%Febrile neutropenia * CostFebrileNeutropenia) + (%Thrombocytopenia * CostThrombocytopenia) + (%Leukopenia * CostLeukopenia)

To be clear, the %AE used in the above are treatment-specific.

Upon review of the dossier during the development of this response, we noted that there was a disconnect between costs reported in the dossier and those used in the model. This has been amended in the updated dossier.

B9. Section B.3.5.2.1, Table 64 provides the distribution of patients by treatment modality, but further details are required to explain how this data were used to estimate the total weighted cost of treatment for patients.

The total cost of LR = (%PDC * costPDC) + (%Radiotherapy * costRadiotherapy) + (%surgery * costSurgery). The calculations are also clearly shown in the model cost calculations sheet, rows 60 – 70.

As noted in the model citations:

- the cost of PDC is based on the cost of 4 cycles of Cisplatin + Pemetrexed (calculated using micro-cost approach as for other drugs);
- the cost of radiotherapy is based on the cost of intraluminal brachytherapy [National Schedule of NHS Costs SC30Z];
- the cost of salvage surgery is based on the cost of thoracotomy [National Schedule of NHS Costs DZ02H-M].

B10. Sections B.3.5.1 – B.3.5.3: Please clarify how were costs inflated to 2021/2022 values?

We apologize as it seems there is an error in the text of the report; where it says “costs are inflated to 2021/2022 values” it should say “costs are inflated to 2020/2021 values”. Costs for 2021/2022 wouldn’t be available until the end of 2022, so the most recent costs available are 2020/2021.

In terms of the calculation, inflation is applied as base cost * inflation factor, where the inflation factor is contingent on the base year for the cost. We also shared this information in the model; see the ‘Inflation Table’ sheet. For example, a cost with the base year of 2019/2020 would be multiplied by 1.0308 to arrive at that same cost in year 2020/2021.

B.11 Sections B.3.3.1.4: Please clarify why were data used to inform MRU only taken from the LuCaBIS study when 10 studies with resource use data were found in the SLR?

Of the 10 studies identified, it was the only one inclusive of UK-specific data (of the remainder, 6 were in the US, 2 in Italy, and 1 in Canada). Additionally, the LuCaBIS study reported data by health state needed to populate the model. Therefore, the LuCaBIS study was deemed most suitable among what was found to populate the economic model.

Economic model

B12. The following issues were based on the Engine – nivolumab + PDC sheet but will also apply to the other Engine sheets in the Excel model.

a) **Column T: Please explain why a rate-to-probability formula has been used when the arguments to the function appear to be probabilities**

b) **Column X: Please explain why a rate-to-probability formula has been used when the arguments to the function appear to be probabilities**

c) **Column U: Please explain why cells U12:U660 use a rate-to-probability formula when the arguments to the function appear to be probabilities, and cell U11 does not use a rate-to-probability formula**

d) **Is the use of the rate-to-probability formula the reason that the values in columns U, V and W are different to columns K, M and O? If all the values are probabilities, then a weight derived from those probabilities multiplied a probability which is the sum of the probabilities in denominator of the weight should result in the same probability.**

If there are errors here, please correct and reproduce the cost-effectiveness results.

The economic model employs the approach to consideration of competing risk that is described in Williams 2017.[27] However, whereas Williams et al used R to calculate transition probabilities (which can handle time continuously), the submitted model is programmed in MS Excel, where time must be considered discretely (i.e. in cycles). Therefore, the approach described in Williams et al was modified to be compatible with an Excel-based economic model.

Specifically, three time to event analyses were conducted to estimate the hazard for moving from the EF state to the LR, DM and the Death state (see Figure 4):

1. **EF-->LR:** Parametric survival analysis for time to LR was conducted by censoring deaths and DM. The log-normal was identified as the best fitting distribution. We denote the hazard of this log-normal distribution at time t as $h_1(t)$, and the corresponding survival function $S_1(t)$

2. **EF-->DM:** Parametric survival analysis for time to DM was conducted by censoring deaths and LR. The log-normal was identified as the best fitting distribution. We denote the hazard of this log-normal distribution at time t as $h_2(t)$, and the corresponding survival function $S_2(t)$

3. **EF-->Death:** Parametric survival analysis for time to death was conducted by censoring LR and DM. The exponential was identified as the best fitting distribution based on clinical opinion from an ad-board meeting. We denote the hazard of this exponential distribution at time t as $h_3(t) = \lambda_3$ as the hazard of the exponential distribution does not vary with time.

The engine of the CEM uses a piecewise-constant approximation for the hazards of the fitted log-normal distributions. Therefore, during each model cycle i:

- h_1 is approximated by $\lambda_1(i) = \frac{(S_{1(i)} - S_{1(i+1)})}{S_1(i)}$, assuming that it remains constant within that cycle (but changes in the next cycle). $\lambda_1(i)$ is saved in column K

- h_2 is approximated by $\lambda_2(i) = \frac{(S_{2(i)} - S_{2(i+1)})}{S_2(i)}$ assuming that it remains constant within that cycle (but changes in the next cycle). $\lambda_2(i)$ is saved in column M

- h_3 is approximated by $\lambda_3(i) = \frac{(S_{3(i)} - S_{3(i+1)})}{S_3(i)}$, but because of the exponential distribution we have constant λ_3 over time. λ_3 is stored in column O.

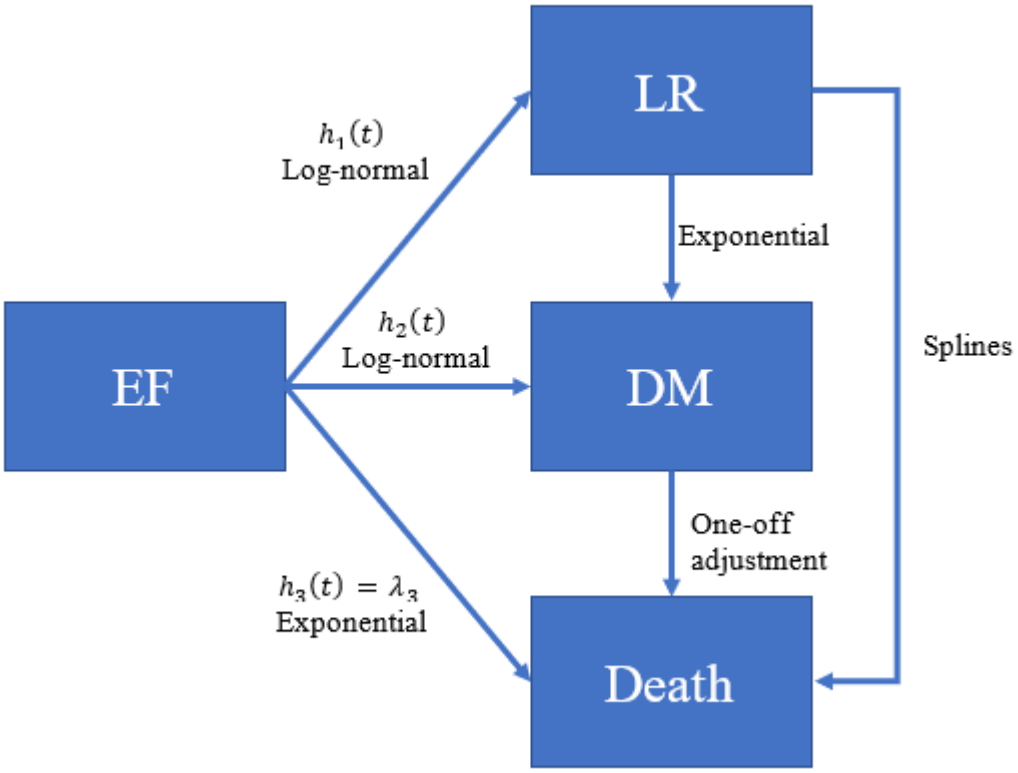
Once $\lambda_1(\mathrm{i})$, $\lambda_2(i)$, and λ_3 are calculated, the probability of remaining in the EF state during model cycle i is estimated by $S(i) = e^{-(l_1(i) + l_2(i) + l_3) * 1}$ (where 1 represents the time of 1 cycle) and therefore the probability of leaving the EF state during cycle i is $1 - S(i)$.

- **Proportion of patients in EF:** Estimated by the product of probabilities of remaining in the EF state during consecutive model cycles (e.g. in cycle 3, the proportion is $1 * S(1) * S(2)$
- **Proportion of new (incident) patients transitioning from EF to LR:** Estimated by the proportion of patients in EF in the previous cycle $i - 1$, multiplied by $\frac{\lambda_1(i)}{\lambda_1(i) + \lambda_2(i) + \lambda_3} S(i)$ [which represents the probability of starting in the EF state at the beginning of cycle i and moving to the LR state at the end of cycle i (assuming instant transition at the end of the cycle)].
- **Proportion of new (incident) patients transitioning from EF directly to DM:** Estimated by the proportion of patients in EF in the previous cycle $i - 1$, multiplied by $\frac{\lambda_2(i)}{\lambda_1(i) + \lambda_2(i) + \lambda_3} S(i)$ [which represents the probability of starting in the EF state at the

beginning of cycle i and moving to the DM state at the end of cycle i (assuming instant transition at the end of the cycle)].

- **Proportion of patients transitioning from EF directly to the death state:** Estimated by the proportion of patients in EF in the previous cycle $i-1$, multiplied by $\frac{\lambda_3}{\lambda_1(i)+\lambda_2(i)+\lambda_3} S(i)$ [which represents the probability of starting in the EF state at the beginning of cycle i and dying at the end of cycle i (assuming instant transition to the death state at the end of the cycle)].

Figure 4. Overview of model transitions



In general, this mirrors the approach used in TA761 for osimertinib,[28] which was not criticized by the ERG.

The formulae in cells U12:U660 (use U12 to illustrate) [=IFERROR(K12/SUM(K12,M12,O12)*(1-EXP(-SUM(K12,M12,O12))),0] are equivalent to U11 [=IFERROR(K11/SUM(K11,M11,O11)*T11,0)], as T12 = 1-EXP(-SUM(K12,M12,O12). We should have auto-filled U12:U660 to make them consistent with the formula in U11, but the calculated values would be exactly the same and therefore there is no impact on the results.

B13. The company appropriately fit a selection of dependent parametric models to the Kaplan-Meier data for the CheckMate-816 trial. These models estimate survivor functions that are consistent with a time-varying hazard ratio. Please present the hazard rate curves for the intervention and comparator and the hazard ratio curve for time to locoregional recurrence, time to any progression, and time to death from event-free survival derived from the estimated survivor functions.

Hazard rate plots of all distributions fitted to each outcome have been provided as requested, below (Figure 5 to Figure 25). Although models with time-varying hazards have been fitted, the dependent models fitted for TTP and TTLR rely on the proportional hazards assumption (fixed hazard ratio with time). Therefore, figures representing the hazard ratio with time have not been provided; they would simply be a flat line.

Additionally, as one point of clarification, a hazard ratio is not considered in the time to death from EFS estimates at all – the same curve is used for all treatments in the model.

Hazard curves for TTLR

Figure 5. Hazard Plot: Time to LR from EF (Exponential)

Figure 6. Hazard Plot: Time to LR from EF (Weibull)

Figure 7. Hazard Plot: Time to LR from EF (Gompertz)

Figure 8. Hazard Plot: Time to LR from EF (Log-logistic)

Figure 9. Hazard Plot: Time to LR from EF (Log-normal)

Figure 10. Hazard Plot: Time to LR from EF (Gamma)

Figure 11. Hazard Plot: Time to LR from EF (Generalized gamma)

Hazard curves for TTP

Figure 12. Hazard Plot: Time to any progression from EF (Exponential)

Figure 13. Hazard Plot: Time to any progression from EF (Weibull)

Figure 14. Hazard Plot: Time to any progression from EF (Gompertz)

Figure 15. Hazard Plot: Time to any progression from EF (Log-logistic)

Figure 16. Hazard Plot: Time to any progression from EF (Log-normal)

Figure 17. Hazard Plot: Time to any progression from EF (Gamma)

Figure 18. Hazard Plot: Time to any progression from EF (Generalized gamma)

Hazard curves for TTDM

Figure 19. Hazard Plot: Time to death from EF (Exponential)

Figure 20. Hazard Plot: Time to death from EF (Weibull)

Figure 21. Hazard Plot: Time to any progression from EF (Gompertz)

Figure 22. Hazard Plot: Time to any progression from EF (Log-logistic)

Figure 23. Hazard Plot: Time to any progression from EF (Log-normal)

Figure 24. Hazard Plot: Time to any progression from EF (Gamma)

Figure 25. Hazard Plot: Time to any progression from EF (Generalized gamma)

B14. Please clarify whether

a) **DM cases as well as deaths were included as censored cases in the EFS to LR time-to-event analysis**

Yes, this is correct. All events that were not locoregional recurrence were censored in the analysis of EFS to LR.

b) **Any progression cases were included as censored cases in the EFS to death time-to-event analysis**

Yes, this is correct. All events that were not deaths were censored in the analysis of EFS to death.

B15. Section B.3.3.1: Please present each plot in Figure 29 and Figure 37 individually as they are currently too small.

Each plot from Figure 29 of the submission is presented in Figure 26 to Figure 28 below.

Figure 26. Time to locoregional recurrence in the intention-to-treat population: log-log plot

Figure 27. Time to locoregional recurrence in the intention-to-treat population: QQ-plot

Figure 28. Time to locoregional recurrence in the intention-to-treat population: Schoenfeld residuals plot

Each plot from Figure 37 of the submission is presented in Figure 29 to Figure 31 below.

Figure 29. Time to progression in the intention-to-treat population: log-log plot

Figure 30. Time to progression in the intention-to-treat population: QQ-plot

Figure 31. Time to progression in the intention-to-treat population: Schoenfeld residuals plot

B16. Section B.3.3.1: To properly assess the predictive accuracy of the modelled time to locoregional recurrence (TTLR) and any progression, event predictions for each comparator intervention is useful. Please report the base-case predictions of TTLR and of time to any progression for each of the comparator interventions in the decision problem and comment on how realistic these predictions are in clinical practice.

The base case predicted TTLR per treatment are provided in Figure 32 and time to distant metastases per treatment in Figure 33. Time to distant metastases has been provided instead of the time to any progression as treatment effect in the model for distant metastases is applied to the hazard rate of event free to DM (calculated based on hazard rate of event free to any progression - hazard rate of event free to LR) thus analyses has not been conducted to predict treatment dependent time to any progression.

As presented within the company submission both the fitted distributions for TTLR and time to any progression was presented to clinical experts. For both outcomes the selected distributions were deemed to be clinically plausible.

Figure 32. Predicted time to local recurrence per comparator

Figure 33. Predicted time to distant recurrence per comparator

B17. Please provide a detailed description of the methods used to derive the transition probabilities from event free survival to locoregional recurrence, to DM and to death for each comparator intervention in the decision problem, including the role of the ITC analysis estimates.

The same approach as described in the answer to Question B12 was used for outside trial comparators. The only difference is the survival functions for TTLR and TTDM were derived

by applying the constant HRs obtained from the ITC to the survival function of the neo PDC reference curve, before going through the process as described in Question B12.

B18. Section B.3.3.1.3: Please provide a specific definition of "any progression".

As stated in the company submission time to any progression curves were derived from the EFS data but with death events censored. EFS was defined as (see Table 7 of the company submission): time from randomisation to any progression of disease precluding surgery, progression or recurrence of disease (per BICR using RECIST 1.1) after surgery, or death due to any cause. As such time to any progression is defined as: time from randomisation to any progression of disease precluding surgery, progression or recurrence of disease (per BICR using RECIST 1.1) after surgery.

B19. Section B.3.3.2: Please answer the following in relation to the distribution of treatment in the distant metastasis health state:

a) **Where does the data for treatment proportions come from and how it was obtained?**

The data is based on quantitative Market Research whereby data on treatment prescriptions are pulled from a rolling sample of 50 UK-based physicians. In a questionnaire provided to theses clinicians they are asked to provide details of current treatments used. The market shares used for estimating the proportion of subsequent treatment are based on these inputs.

b) **It was assumed that all comparison interventions follow the same treatment distribution as PDC (neoadjuvant). How was this assumption verified?**

Clinical input received regarding treatment in the distant metastasis health state confirmed that this would not differ by prior treatment except for no retreatment with immunotherapy for patients having a recurrence within 6-12 months after the first immunotherapy.

B20. The cost-effectiveness model applies the cure assumption (where a percentage of patients are no longer at risk of recurrence or death due to cancer). Please comment on the following:

a) **If a patient is assumed to be cured at 5 years (increasing to 7), when are they in fact cured? Were they always cured after surgery or after adjuvant therapy, but that they could not be confirmed cured until 5 years later? How does existing evidence suggest that a percentage of patients are cured after 5 years?**

In clinical reality patients are considered cured when no reoccurrence has occurred from the same disease. A posteriori these patients have then been cured since surgery, but clinicians can't determine who will be cured a priori (at surgery). As presented in the company submission current clinical practice is to consider patients cured if they haven't had a recurrence at 5 years. However, even at that point the clinicians cannot ascertain that none of these patients will have a recurrence event at a later point in time, only that the probability of recurrence is low. This is the rational for assuming that 5% of the population will remain at risk of recurrence after 5 years.

As presented in the dossier similar methods and assumptions regarding cure have been applied in two recent appraisals of early-stage NSCLC treatments.[28] [29] However, as noted in the company submission we acknowledge that there are uncertainties around the exact cure timepoint as well as the proportion of patients being cured. Therefore, this was extensively tested in scenario analyses to investigate the impact of these assumptions on the results. As presented in the company submission even assuming no patients being cured resulted in ICER's well below £20,000.

b) **If patients considered cured at 5 years are in fact effectively cured immediately after surgery or adjuvant therapy then would not the progression rates and mortality rates observed in the follow-up period of the relevant clinical trials be the rates associated with those who are not cured, i.e. the rates in this group are higher? Therefore, would not the actual rates that apply when 95% of patients are assumed cured in fact be higher than those included in the model?**

Please see response to a) regarding patients not being identified as cured after surgery. Based on that all patients are being followed up and included in the survival data.

c) **If patients considered cured at 5 years are in fact effectively cured immediately after surgery or adjuvant therapy then, taking the time period from the end of adjuvant therapy, the percentage assumed to be cured could be removed and the time-to-event curves fitted, and that either (a) the weighted average of progression and of death would be applied to the post adjuvant therapy time period, or (b) the higher rates of progression and of death for those not cured could be applied from 5 years onwards in the weighted average calculations. It would be assumed that general mortality rates would be relatively small. Pease comment on the validity of these alternative modelling approaches.**

As presented in Company submission section 3.3.3.4 alternative methods to implement cure could have been taken. One approach would have been to explicitly model cure as proposed

in this question (referred to as “uninformed” approach in the company submission). However, as presented in our response to a), the patients who would be cured or not is not know until long term data become available from CheckMate 816. Fitting explicit cure models when limited follow up data is available has previously been reported to be prone to biases.[30] Therefore, modelling cure explicitly based on the current data from CheckMate 816 was not seen as a valid approach and the modelling of cure in the company submission was, in alignment with recent appraisals[28] [29], incorporated based on what is referred to as an “informed” approach in the company submission.

B21. Section B.3.9.3: Please provide the scenario parameter values for Scenarios 2 and 17 in Table 80 that were inputted in the model to generate the scenario results and their base-case counterpart.

For Scenario 2 utility values in cell E12:E16 on the utility sheet was set to [redacted] and utility values in cell E22:E18 on the utility sheet was set to [redacted]

For scenario 17 HR’s in cell E32:E34 and E63:E65 was substituted with the EFS HR’s presented in Figure 17 of the submission. However, in preparation of this response we see that the wrong results have been provided the scenario results table. This has been amended in the updated dossier.

B22. There is no mention of disease severity in the CS. This is a consideration in the 2022 NICE methods guidance. Does the company consider the QALY shortfall for this disease to be far less than the minimum required for a QALY multiplier and therefore this is not considered relevant for this evidence submission?

We can confirm that the shortfall was calculated prior to submission and found to be less than the minimum required for a QALY multiplier and therefore this is not considered relevant for this evidence submission.

B23. Section B.3.5.1.3: the company used mean patient characteristics from the CheckMate-816 trial to calculate a mean BSA to estimate drug acquisition costs in the base-case analysis. If there are different dose/vial sizes, please provide alternative cost acquisition estimates based on minimising cost and accounting for variation in population body surface area (BSA) or weight, and the different dose/vial sizes and cost.

Nivolumab is administered based on a fixed dose and thus would not be affected by adjustments to BSA or weight. The model has not been set up with alternative vials, but impact is likely to be marginal. However, running analyses assuming no drug wastage results in very small differences compared with the base case analyses and can be seen in the table below (then include table)

B24. Please comment on the feasibility of a cost-effectiveness analysis for the PD-L1>50% tumour proportion score.

Please see answer to question A1. Based on this these analyses have not been provided.

Section C: Textual clarification and additional points

C1. In Table 34 the last 3 rows are a repetition of the previous 3 rows. It is believed that this is an error, please confirm that this is the case.

We can confirm that this is an error and should be presented as Table 13 below; this has been updated in Document B (Table 34).

Table 13. Time to any progression: goodness-of-fit statistics

Distribution	AIC	BIC
Log-normal	1,228.8	1,240.4
Generalised gamma	1,230.4	1,245.9
Log-logistic	1,233.00	1,244.60
Gompertz	1,235.40	1,247.10
Exponential	1,237.10	1,244.80
Weibull	1,238.90	1,250.60
Gamma	1,239.1	1,250.7

AIC = Akaike information criteria; BIC = Bayesian information criteria.

C2. Macros not working: Sheet "Clinical Inputs", Cells G13, G42, G73, and G81. The macros connecting the "Clinical Inputs" sheet to the "Markov Details" sheet are not working correctly.

Clarification: These are links, not macros. The links have been updated in the model.

C3. Please clarify the meaning of the statement on p.136, "There are 2 key reasons why utility values might be expected for patients with NSCLC in the UK."

This is an error and has been removed in Document B.

C4. The term "nmNSCLC" is frequently used within the Appendices to refer to non-metastatic NSCLC but is not used within the main submission (Document B). For clarity, is there any difference between the company's definitions of resectable NSCLC and resectable nmNSCLC?

The terms 'resectable NSCLC' and 'resectable nmNSCLC' are interchangeable in this submission.

C5. Appendix D, Section D.2.1.3 (p.28The reported percentage of males in the 21 neoadjuvant RCTs ranged from 41.7% to 94% but go on to state that the lowest percentage of males was in the GINEST study, with 53% male participants. Please clarify this discrepancy.

This has been amended in the appendices and reference to the GINEST study removed.

C6. Section B.2.2., and Table 7 (p.37): TTLR is listed as an additional outcome in CheckMate816 but is not marked as being used in the economic model Table 6 (p.33). TTLR is not mentioned in Table 7 (p.37) as used in the model. However, TTLR is subsequently used in the economic model (Section B3.3.1.2). Please clarify this discrepancy.

As discussed in response to question A15, TTLR was not a pre-specified outcome in CheckMate-816. However, a post-hoc analysis was conducted for use in the model, this has now been included in Table 7.

Section D: Technical team queries

D.1 In Section B.3.3.2 of the CS, information for life years (LYs), quality-adjusted life years (QALYs), and costs accrued from development of distant metastasis (DM) until death from TA531, TA683, TA770, and TA705 were requested to reduce the uncertainty in the subsequent treatments of the economic model. LYs, QALYs and costs have been extracted from TA531, TA683, TA770, and TA705 and permission to use the information in the current appraisal (ID3757) has been requested from the respective companies. Should permission be granted this information will be provided as confidential information to the EAG to run a scenario for which the results will be published in the confidential appendix.

a) **In the spreadsheet provided to the technical team following the decision problem meeting (DPM), "dummy values" were provided to inform the distribution of treatments during DM (Cells C21 to G21). This proportion appears to reflect "retreatment with IO allowed" in appraisals (TA531, TA770, TA683 and TA705). However, the technical team notes that in TA531 retreatment was discussed in technical engagement, but not included in any analysis and in TA683, TA770, and TA705 retreatment is unclear and no data were identified to extract. The technical team**

understood from the DPM that these values would be informed by clinical opinion or market share data, please clarify expectation in respect of the requested input. The technical team would suggest that these assumptions could be based on input provided by stakeholders during the appraisal process, for example.

The term “retreatment with IO allowed” used in the spreadsheet provided is not referring to if whether IO was allowed subsequent to the 1st line therapy provided (and thereby included in TA531, TA770, TA683 and TA705) but whether IO would be allowed subsequent to neoadjuvant nivolumab. Clinical input received for the preparation of the company submission and the recent appraisal of adjuvant atezolizumab[29] indicate that retreatment with IO within 6-12 months after initial treatment would be considered appropriate. To allow for this assumption to be tested, we therefore need a distant metastasis treatment mix estimated for both a situation with and with without retreatment with IO included (post-neoadjuvant nivolumab).

With regards to the distribution of subsequent treatments, Table 45 of the company submission includes our estimates of market shares for each treatment. Please also see response to B19 for clarification on source of this information.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nivolumab with chemotherapy for neoadjuvant treatment of resectable non-small-cell lung cancer [ID3757]

Patient Organisation Submission

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

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- 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	Medical Director
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 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 largely 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?	In patents with early stage lung cancer, who have a surgical resection of the tumour, with curative intent, the 5 year survival rates are reported to be up to 50%, with relapses in distant sites accounting for most failures. Symptoms of recurrent disease, such as breathlessness, cough and weight loss are often 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?	Neoadjuvant therapy is a promising approach for prolonging survival and increasing the chance of cure, for patients with potentially resectable disease. It is well established in other cancers, such as breast cancer. Neoadjuvant therapy provides several theoretical benefits in managing patients with non small cell lung cancer (nsclc). - downstaging of the cancer by reducing the tumour bulk, making it more operable and so, improving resection rates - treating subclinical micro-metastases - compliance with neoadjuvant treatment is generally thought to be better than in the adjuvant (after surgery) setting. However, it is important that, in administering neoadjuvant therapy, the window for successful surgery is not missed.

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?	Nivolumab is available in other indications in the treatment of non small cell lung cancer. It is generally well tolerated and clinicians are used to managing side effects etc.. We note the Forde et al publication, in the NEJM of May 2022, - It concludes that, in patients with resectable nsclc , neoadjuvant nivolumab plus chemotherapy resulted in significantly longer event-free survival and a higher percentage of patients with a pathological complete response than chemotherapy alone. The addition of nivolumab to neoadjuvant chemotherapy did not increase the incidence of adverse events or impede the feasibility of surgery.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The side effects associated with the therapy. Delays, whilst undergoing neoadjuvant treatment and the potential for disease progression, making surgery not feasible. In this situation, patients could have been treated with up-front surgery (+/- adjuvant treatment) and potentially curative therapy, had neoadjuvant therapy not been undertaken.

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:

- Neoadjuvant treatment has potential benefits in the management of patients with early stage non small cell lung cancer
- There is a need to develop treatments to reduce cancer recurrence, after lung cancer resection surgery
-
-
-
-
-

Thank you for your time.

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Single Technology Appraisal

Nivolumab with chemotherapy for neoadjuvant treatment of resectable non-small-cell lung cancer [ID3757]

Professional organisation submission

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 the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

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About you

1. Your name	[redacted]
2. Name of organisation	Royal College of Pathologist
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The Royal College of Pathologists is a professional membership organisation with charitable status, concerned with all matters relating to the science and practice of pathology. It is a body of its Fellows, Affiliates and trainees, supported by the staff who are based at the College's London offices.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To reduce the likelihood of recurrence of non-small cell lung cancer following surgery
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	As a pathologist, I do not have the expertise to answer this
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Non-small cell lung cancer has an abysmal prognosis, particularly in the UK. The only prospect of cure is in the small proportion of patients who present at an early stage. However, even amongst these patients a significant proportion will experience disease recurrence. It is therefore important that all measures are taken to ensure that this small proportion of potentially curative patients are given the best chance possible of having their disease cured.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	These patients generally undergo surgery without neoadjuvant treatment, but may receive adjuvant treatment based on the post-operative pathological findings.
9a. Are any clinical guidelines used in the	As a pathologist, I do not have the expertise to answer this

treatment of the condition, and if so, which?	
9b. 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.)	As a pathologist, I do not have the expertise to answer this
9c. What impact would the technology have on the current pathway of care?	It would mean, for a subset of patients, administering nivolumab prior to surgery. The patient would then have surgery as at present. From a pathology point of view: ▪ Assuming there is no need for PD-L1 testing to determine eligibility for neoadjuvant nivolumab, there will be no need for additional testing as a result of this technology. ▪ It is likely that examination of resected lung cancers which have undergone neoadjuvant treatment will be more challenging and require additional resources.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	As a pathologist, I do not have the expertise to answer this
10a. How does healthcare resource use differ between the technology and current care?	Examination of resected lung cancers following neoadjuvant treatment will require additional resource compared to those not treated with neoadjuvant therapy. We have experience of this already with breast cancers, which are often treated with neoadjuvant therapy. ▪ Pathologists will need to spend more time examining the tissue to identify the tumour. ▪ Pathologists will need to assess the degree of response to neoadjuvant therapy, which will take time. ▪ It is likely that pathologists will need to sample more tissue to accurately identify the tumour, which will require additional pathologist and laboratory staff time, and increase the use of laboratory reagents and consumables. ▪ It is likely that pathologists will need to request more immunohistochemistry, which will require additional pathologist and laboratory staff time, and increase the use of laboratory reagents and consumables.

	All this will likely lead to small delays in returning the final histology report. It will also require additional pathologist and laboratory staffing.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	As a pathologist, I do not have the expertise to answer this
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	See above. From a pathology point of view, the following will be needed: ▪ Pathologist time ▪ Laboratory staff time ▪ Consumables and reagents in the laboratory Per case, it is likely that these extra resources will be small. However, if there is substantial uptake of this technology the resource implications could be significant.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	As a pathologist, I do not have the expertise to answer this
11a. Do you expect the technology to increase length of life more than current care?	As a pathologist, I do not have the expertise to answer this
11b. Do you expect the technology to increase health-related quality of life more than current care?	As a pathologist, I do not have the expertise to answer this
12. Are there any groups of people for whom the technology would be more or less effective (or	As a pathologist, I do not have the expertise to answer this

appropriate) than the general population?	

The use of the technology

13. 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.)	See above. The use of this technology will introduce added complexity for pathology departments both in terms of handling resected lung cancers and assessing the degree of response to neoadjuvant treatment.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	As a pathologist, I do not have the expertise to answer this
15. Do you consider that the use of the technology will result in any	As a pathologist, I do not have the expertise to answer this

substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. 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?	As a pathologist, I do not have the expertise to answer this
16a. Is the technology a 'step-change' in the management of the condition?	As a pathologist, I do not have the expertise to answer this
16b. Does the use of the technology address any particular unmet need of the patient population?	As a pathologist, I do not have the expertise to answer this
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	As a pathologist, I do not have the expertise to answer this

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	As a pathologist, I do not have the expertise to answer this
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	As a pathologist, I do not have the expertise to answer this
20. How do data on real-world experience compare with the trial data?	As a pathologist, I do not have the expertise to answer this

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	None
21b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• This technology is important in that it maximises the good outcomes from the small proportion of NSCLC who are potentially curable • However, it will require additional resourcing for pathology departments to fund the extra work required to handle resected lung cancers and to assess the response to treatment • • •

Thank you for your time.

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Nivolumab with chemotherapy for neoadjuvant treatment of resectable non-small cell lung cancer [ID3757]

Post Factual Accuracy Check

Produced by Newcastle University

Authors Tara Homer, Senior Research Associate, Newcastle University
Eugenie Johnson, Research Assistant, Newcastle University
Louise Tanner, Research Associate, Newcastle University
Giovany Orozco-Leal, Research Assistant, Newcastle University
Tomos Robinson, Senior Research Associate, Newcastle University
Sedighe Hosseinijebeli, Research Associate, Newcastle University
Nick Meader, Principal Research Associate, Newcastle University
Ryan Kenny, Research Associate, Newcastle University
Sheila Wallace, Research Fellow, Newcastle University
Catherine Richmond, Research Assistant, Newcastle University
Claire Eastaugh, Research Assistant, Newcastle University
Alistair Greystoke, Clinical Senior Lecturer, Newcastle University
Stephen Rice, Senior Lecturer, Newcastle University

Correspondence to Stephen Rice, Newcastle University
Baddiley Clark Building,
Newcastle University,
Newcastle upon Tyne
NE2 4BN

Date completed 16/12/2022

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Declared competing interests of the authors

Ryan Kenny contributed to the following Newcastle University NIHR Innovation Observatory technology briefing:

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Prof Luke Vale proofread the report.

Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Confidential comparator prices are highlighted in green throughout the report.

Any de-personalised data are highlighted in pink throughout the report.

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

Stephen Rice acted as project lead. Louise Tanner acted as lead effectiveness reviewer. Tara Homer acted as lead health economist. Nick Meader and Ryan Kenny reviewed the network meta-analyses. Catherine Richmond acted as lead reviewer of the literature search methods. Eugenie Johnson acted as assistant effectiveness reviewer. Tomos Robinson, Giovany Orozco-Leal and Sedighe Hosseinijebeli acted as assistant health economics reviewers. Claire Eastaugh assisted in reviewing the literature search methods. Sheila Wallace assisted in reviewing the literature search methods and reviewing the effectiveness section. Alastair Greystoke provided clinical expert opinion.

Abbreviations

AACR	American Association for Cancer Research
Adj-CT	Adjuvant chemotherapy
AE	Adverse event
AFT	Accelerated Failure Time
AIC	Akaike Information Criteria
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
ASCO	American Society of Clinical Oncology
BI	Budget impact
BIC	Bayesian information criterion
BICR	Blinded independent pathologic review
BIPR	Blinded independent pathologic review
BNF	British National Formulary
BSC	Best supportive care
CAS	Chemical Abstracts Service
CE	Cost-effectiveness
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CEM	Company Economic Model
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence Interval
CRD	Centre for Reviews and Dissemination
CR	Complete response
CrI	Credible interval
cRR	Clinical response rate
CRT	Chemoradiotherapy
CS	Company submission
CSR	Clinical study report
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events
CUA	Cost-utility analysis
DFS	Disease-free survival
DM	Distant metastasis
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	Evidence Assessment Group
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EF	Event free
EFS	Event free survival
EGFR	Epidermal growth factor receptor
ELCC	European Lung Cancer Congress
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
eMIT	Electronic market information tool
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European Public Assessment Report
ESMO	European Society for Medical Oncology
FACT-L	Functional Assessment of Cancer Therapy–Lung
FAD	Final appraisal document
FU	Follow up
HR	Hazard ratio

HRQOL	Health-related quality of life
HSUV	Health state utility value
HTA	Health technology assessment
IA	Interim analysis
IASLC	International Association for the Study of Lung Cancer
IC	Indirect comparison
ICER	Incremental cost-effectiveness ratio
INHB	Incremental net health benefit
I-O	Immuno-oncology
IQR	Interquartile range
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
KM	Kaplan Meier
LCSS	Lung Cancer Symptom Scale
LR	Locoregional recurrence
LYs	Life years
LYG	Life years gained
LSM	Least squares mean
LYG	Life years gained
MedDRA	Medical Dictionary for Regulatory Activities
MeSH	Medical subject headings
MID	Minimally important difference
MIMS	Monthly Index of Medical Specialities
MPR	Major pathologic response
MRU	Medical Resource Use
mut/MB	Mutations per megabase
NA	Not applicable
neoCRT	Neoadjuvant chemoradiotherapy
neoCT	Neoadjuvant chemotherapy
NIVO	Nivolumab
NHB	Net health benefit
NHS	National Health Service
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Network meta-analysis
NR	Not reported, or not reached
NSC	Non-squamous cell
NSCLC	Non-small-cell lung cancer
OR	Odds ratio
OS	Overall survival
PAS	Patient access scheme
pCR	Pathologic complete response
PD	Progressive disease
PDC	Platinum doublet chemotherapy
PD-L1	Programmed death-ligand 1
PET	Positron emission tomography
PfC	Points of clarification
PFS	Progression-free survival
PH	Proportional hazards
PICOS	Patient, Intervention, Comparator, Outcome, and Study design
PK	Pharmacokinetics
PR	Partial response
PRESS	Peer Review of Electronic Search Strategies

PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRISMA-S	Preferred Reporting Items for Systematic reviews and Meta-Analyses literature search extension
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PS	Performance status
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life year
QLQ-C30	Quality of Life Questionnaire
QoL	Quality of life
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RFS	Recurrence-free survival
RID	Residual invasive disease
RR	Relative risk; Risk ratio
RT	Radiotherapy
S	Surgery
SAE	Serious Adverse Events
SC	Squamous cell
SD	Standard deviation
SE	Standard error
SEER	Surveillance, Epidemiology, and End Results
SIGN	Scottish Intercollegiate Guidelines Network
SITC	Society for Immunotherapy of Cancer
SLR	Systematic literature review
SOC	Standard of care
STA	Single technology appraisal
TA	Technology assessment
TLR	Targeted literature review
TKI	Tyrosine kinase inhibitor
TMB	Tumour mutational burden
TTaP	Time to any progression
TTDM	Time to distant metastasis
TTLR	Time to locoregional recurrence
TTO	Time trade-off
TTOT	Time-to-off treatment
UI	Utility index
UICC	Union for International Cancer Control
UK	United Kingdom
USA	United States of America
VAS	Visual analogue scale
WCLC	World Conference on Lung Cancer
WHO	World Health Organization

Table of Contents

1 EXECUTIVE SUMMARY 14

1.1 Overview of the EAG's key issues 14
1.2 Overview of key model outcomes 14
1.3 The decision problem: summary of the EAG's key issues 15
1.4 The clinical effectiveness evidence: summary of the EAG's key issues 16
1.5 The cost-effectiveness evidence: summary of the EAG's key issues 19
1.6 Other key issues: summary of the EAG's view 23
1.7 Summary of the EAG's view 23

2 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM 26

2.1 Population 30
2.2 Intervention 30
2.3 Comparators 30
2.4 Outcomes 31
2.5 Other relevant factors 32

3 CLINICAL EFFECTIVENESS 34

3.1 Critique of the methods of review(s) 34
3.1.1 Searches 34
3.1.2 Inclusion criteria 37
3.1.3 Data extraction 39
3.1.4 Quality assessment 40
3.1.5 Evidence synthesis 40
3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these) 41
3.2.1 CheckMate-816 design and quality assessment 41
3.2.2 Statistical approach adopted for the analysis of CheckMate-816 study data 45
3.2.3 CheckMate-816 eligibility criteria and baseline characteristics including treatments received 45
3.2.4 CheckMate-816 treatment summary, subsequent therapies and surgical data 49
3.2.5 CheckMate-816 efficacy 53
3.2.6 Participant-reported outcomes in CheckMate-816 56
3.2.7 Adverse events in CheckMate-816 58
3.2.8 Subgroup analyses in CheckMate-816 62
3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison 66
3.3.1 Baseline characteristics for included studies in the NMA 66
3.3.2 Results of the NMA 69
3.4 Critique of the indirect comparison and/or multiple treatment comparison 70
3.5 Additional work on clinical effectiveness undertaken by the EAG 71
3.6 Conclusions of the clinical effectiveness section 72

4 COST-EFFECTIVENESS 74

4.1 EAG comment on company's review of cost-effectiveness evidence 74
4.1.1 Searches performed for cost-effectiveness section 74
[redacted] Inclusion/exclusion criteria 80

4.1.3 Conclusions of the cost-effectiveness review 82
4.2 Summary and critique of company's submitted economic evaluation by the EAG 82
4.2.1 NICE reference case checklist 82
4.2.2 Model structure 85
4.2.3 Population 86
4.2.4 Interventions and comparators 87
4.2.5 Perspective, time horizon and discounting 88
4.2.6 Treatment effectiveness and extrapolation 88
4.2.7 Adverse events 106
4.2.8 Health-related quality of life 108
4.2.9 Resources and costs 112
4.2.10 Summary of company assumptions applied in base-case analysis 118
5 COST-EFFECTIVENESS RESULTS 122
5.1 Company's cost-effectiveness results 122
5.2 Company's sensitivity analyses 125
5.2.1 Probabilistic sensitivity analysis 125
5.2.2 Scenario analysis 130
5.2.3 Deterministic sensitivity analysis 134
5.3 Severity of the condition 136
5.4 Model validation and face validity check 136
5.4.1 Face validity assessment and technical verification 136
5.4.2 Comparison with external data 136
6 EVIDENCE ASSESSMENT GROUP'S ADDITIONAL ANALYSES 139
6.1 Exploratory and sensitivity analyses undertaken by the EAG 139
6.1.1 EAG base-case 139
6.1.2 EAG exploratory scenario analyses 151
6.1.3 EAG subgroup analyses 152
6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG 154
6.2.1 The EAG base-case, scenario and subgroup analyses 154
[redacted] Severity of the condition 171
6.3 EAG's preferred assumptions 171
6.4 Conclusions of the cost-effectiveness section 174
REFERENCES 178
7 Appendix 1: Nivolumab and PDC time-to-event and hazard rate curves 183

Table of Tables

Table 1.1: Summary of key issues 14

Table 1.2: Key issue [1] – Effectiveness of nivolumab + PDC more uncertain for patients with Stage IB or II NSCLC 15

Table 1.3: Key issue [2] - Applicability of the CheckMate-816 population to England 16

Table 1.4: Key issue [3] – Uncertainty in the effectiveness of different nivolumab + PDC regimens 17

Table 1.5: Key issue [4] – Applicability of surgical approach and resection type used in CheckMate-816 to the English clinical setting 18

Table 1.6: Key issue [5] – Uncertainty in extrapolation models used to estimate time to any progression (TTaP) and time to locoregional recurrence (TTLR) 19

Table 1.7: Key issue [6] – Uncertainty in the cure assumption 20

Table 1.8: Key issue [7] – Uncertainty in the event-free and locoregional recurrence utility estimates 21

Table 1.9: Key issue [8] – Uncertainty in the immuno-oncology (I-O) retreatment restrictions and distribution of chemotherapies in the DM state 21

Table 1.10: Key issue [9] – Uncertainty in the effectiveness of the comparators 22

Table 1.11: Summary of EAG's preferred assumptions and ICER – nivolumab + PDC versus neoadjuvant CRT 24

Table 1.12: Summary of EAG's preferred assumptions and ICER – nivolumab + PDC versus adjuvant PDC 25

Table 1.13: Summary of EAG's preferred assumptions and ICER – nivolumab + PDC versus surgery alone 25

Table 2.1: Statement of the decision problem (as presented by the company) 26

Table 3.1: Summary of searches conducted by the company for clinical effectiveness studies on 1 April 2022 35

Table 3.2: Eligibility criteria used in search strategy for RCT and non-RCT evidence 37

Table 3.3: CheckMate-816 study design 41

Table 3.4: Quality assessment of CheckMate-816 according to CS 43

Table 3.5: Key population eligibility criteria for CheckMate-816 46

Table 3.6: Baseline characteristics of participants in CheckMate-816 46

Table 3.7: Treatment summary for CheckMate-816 50

Table 3.8: Subsequent therapies received by participants in CheckMate-816 50

Table 3.9: Surgical outcomes for participants in CheckMate-816 51

Table 3.10: Summary of efficacy results for CheckMate-816 53

Table 3.11: Incidence of radiographic downstaging before and after treatment by stage of disease in CheckMate-816 55

Table 3.12: EQ-5D-3L in the neoadjuvant period of CheckMate-816 56

Table 3.14: Summary of AEs in CheckMate-816 59

Table 3.15: Most frequent treatment-related AEs in CheckMate-816 60

Table 3.16: Most frequent surgery-related AEs in CheckMate-816 60

Table 3.17: Adverse events leading to surgery delay and/or cancellation in CheckMate-816 61

Table 3.20: Subgroup analyses by ethnicity (white versus Asian) as provided by the company 64

Table 3.21: Demographic and prognostic information of in base case studies of NMA 66

Table 3.22: EFS definitions for studies included in the NMA 67

Table 3.23: Neoadjuvant chemotherapy regimens reported in the studies included in the NMA 69

Table 3.24: Summary of network meta-analyses results in base-case studies (compared with neo-adjuvant chemotherapy (neoCT)) 70

Table 3.25: Comparing company base case with sensitivity analyses (versus neo-CT) for event free survival 71

Table 4.1: Summary of the searches undertaken for the TLR of economic evaluations 75

Table 4.2: Eligibility criteria for Targeted Literature Review 77

Table 4.3: Resources searched for HRQOL and cost and resource use evidence 78

Table 4.4: Eligibility criteria for the systematic literature reviews 80

Table 4.5: NICE reference case checklist 82

Table 4.6: HRs for time to LR 97

Table 4.7: HRs for time to DM 97

Table 4.8: Inputs for Distant Metastasis health state 99

Table 4.9: Distribution of treatment in Distant Metastasis health state in CS 100

Table 4.10: Distribution of treatment in Distant Metastasis health state in CEM 101

Table 4.11: Base-case cure parameters 103

Table 4.12: Percentage of patients experiencing grade 3 or 4 adverse events 106

Table 4.13: Adverse event-related disutilities 107

Table 4.14: Summary of utility values for cost-effectiveness analysis 109

Table 4.15: Alternative utility estimates used in the base case and scenario analysis 109

Table 4.16: Utility values in model and patient numbers 110

Table 4.17: Drug dosing regimens 113

Table 4.18: Drug acquisition cost per treatment arm and model cycle 114

Table 4.19: Adverse event unit costs 116

Table 4.20: Company model assumptions 118

Table 5.1: Base-case deterministic economic analysis results (with PAS) – nivolumab + PDC versus surgery 123

Table 5.2: Base-case deterministic economic analysis results (with PAS) – nivolumab + PDC versus neoadjuvant CRT 123

Table 5.3: Base-case deterministic economic analysis results (with PAS) – nivolumab + PDC versus adjuvant PDC 123

Table 5.4: Mean PSA results (with PAS) – nivolumab + PDC versus surgery 125

Table 5.5: Mean PSA results (with PAS) – nivolumab + PDC versus neoadjuvant CRT 127

Table 5.6: Mean PSA results (with PAS) – nivolumab + PDC versus adjuvant PDC 129

Table 5.7: Scenario analysis results of nivolumab + PDC versus surgery 130

Table 5.8: Scenario analysis results of nivolumab + PDC versus neoadjuvant CRT 132

Table 5.9: Scenario analysis results of nivolumab + PDC versus adjuvant PDC 133

Table 6.1: Overview of key issues related to the cost-effectiveness (conditional on fixing errors highlighted in Section 5.1) 141

Table 6.2: Predictive values of EFS and never recurrence for PDC by scenario 150

Table 6.3: Predictive values of EFS and never recurrence for nivolumab + PDC by scenario 150

Table 6.4: Deterministic EAG base-case results (unless otherwise stated) – nivolumab + PDC versus neoadjuvant CRT 154

Table 6.5: Deterministic EAG base-case results (unless otherwise stated) – nivolumab + PDC versus adjuvant PDC 155

Table 6.6: Deterministic EAG base-case results (unless otherwise stated) – nivolumab + PDC versus surgery alone 156

Table 6.7: List of EAG scenario analyses 158

Table 6.8: Deterministic results of EAG scenario analyses (nivolumab + PDC versus neoadjuvant CRT) 159

Table 6.9: Deterministic Results of EAG Scenario Analyses (nivolumab + PDC versus adjuvant PDC) 161

Table 6.10: Deterministic results of EAG scenario analyses (nivolumab + PDC versus surgery alone) 163

Table 6.11: Deterministic results of EAG subgroup analyses (nivolumab + PDC versus neoadjuvant CRT) 165

Table 6.12: Deterministic results of EAG subgroup analyses (nivolumab + PDC versus adjuvant PDC) 165

Table 6.13: Deterministic results of EAG subgroup analyses (nivolumab + PDC versus surgery alone) 165

Table 6.14: Probabilistic results of EAG subgroup analyses (nivolumab + PDC versus neoadjuvant CRT) 166

Table 6.15: Probabilistic results of EAG subgroup analyses (nivolumab + PDC versus adjuvant PDC) 166

Table 6.16: Probabilistic results of EAG subgroup analyses (nivolumab + PDC versus surgery alone) 167

Table 6.17: Deterministic results of EAG subgroup analyses (nivolumab + PDC versus neoadjuvant CRT) with the HR of LR and DM for comparators adjusted to have a similar ratio as for nivolumab + PDC 168

Table 6.18: Deterministic results of EAG subgroup analyses (nivolumab + PDC versus adjuvant PDC) with the HR of LR and DM for comparators adjusted to have a similar ratio as for nivolumab + PDC 168

Table 6.19: Deterministic results of EAG subgroup analyses (nivolumab + PDC versus surgery alone) with the HR of LR and DM for comparators adjusted to have a similar ratio as for nivolumab + PDC 169

Table 6.20: Probabilistic results of EAG subgroup analyses (nivolumab + PDC versus neoadjuvant CRT) with the HR of LR and DM for comparators adjusted to have a similar ratio as for nivolumab + PDC 170

Table 6.21: Probabilistic results of EAG subgroup analyses (nivolumab + PDC versus adjuvant PDC) with the HR of LR and DM for comparators adjusted to have a similar ratio as for nivolumab + PDC 170

Table 6.22: Probabilistic results of EAG subgroup analyses (nivolumab + PDC versus surgery alone) with the HR of LR and DM for comparators adjusted to have a similar ratio as for nivolumab + PDC 171

Table of Figures

Figure 3.1: EQ-5D VAS and utility index scores during the neoadjuvant period and post-surgery: participants who received surgery 57

Figure 3.2: CheckMate-816 subgroup analyses for pCR by BIPR as presented in CS 63

Figure 3.3: CheckMate-816 subgroup analyses for EFS by BICR as presented in CS 64

Figure 4.1: Model structure 86

Figure 4.2: Time to Locoregional Recurrence: comparison versus external data – nivolumab + PDC arm 89

Figure 4.3: Time to locoregional recurrence: long-term extrapolations (nivolumab + PDC) 90

Figure 4.4: Models of TTLR for PDC alone with and without the cure assumption 91

Figure 4.5: Event-free survival: comparison versus external data – PDC alone arm 92

Figure 4.6: Time to any progression: long-term extrapolations (nivolumab + PDC) 93

Figure 4.7: Nivolumab + PDC company base-case model 94

Figure 4.8: PDC alone company base-case model 94

Figure 4.9: Patient-level meta-analysis versus long-term event-free mortality extrapolations from CheckMate-816 95

Figure 4.10: Hazard ratios for TTLR 98

Figure 4.11: Hazard ratios for TTDM 98

Figure 4.12: Hazard of progression in early-stage resected NSCLC 104

Figure 4.13: Long-term EFS from neoadjuvant PDC studies 105

Figure 5.1: Cost-effectiveness plane for nivolumab versus surgery 126

Figure 5.2: Cost-effectiveness acceptability curve for nivolumab + PDC versus surgery 127

Figure 5.3: Cost-effectiveness plane for nivolumab + PDC versus neoadjuvant CRT 128

Figure 5.4: Cost-effectiveness acceptability curve for nivolumab + PDC versus neoadjuvant CRT 128

Figure 5.5: Cost-effectiveness plane for nivolumab + PDC versus adjuvant PDC 129

Figure 5.6: Cost-effectiveness acceptability curve for nivolumab + PDC versus adjuvant PDC 130

Figure 5.7: DSA tornado plot for nivolumab + PDC versus surgery 135

Figure 5.8: DSA tornado plot for nivolumab + PDC versus neoadjuvant CRT 135

Figure 5.9: DSA tornado plot for nivolumab + PDC versus adjuvant PDC 136

Figure 6.1: Time to locoregional recurrence: long-term extrapolations (nivolumab + PDC arm) 143

Figure 6.2: Time to locoregional recurrence: long-term extrapolations (PDC arm) 144

Figure 6.3: Time to Locoregional Recurrence: comparison versus external data – nivolumab + PDC arm 145

Figure 6.4: Patient-level meta-analysis versus long-term event-free mortality extrapolations from CheckMate-816 146

Figure 6.5: TTLR curves for PDC for different models 148

Figure 6.6: LR hazard rate curves for PDC for different models 148

Figure 6.7: TTDM curves for PDC for different models 149

Figure 6.8: DM hazard rate curves for PDC for different models 149

Figure 6.9: Cost-effectiveness acceptability curve for nivolumab + PDC versus neoadjuvant CRT . 172

Figure 6.10: Cost-effectiveness acceptability curve for nivolumab + PDC versus adjuvant PDC 172

Figure 6.11: Cost-effectiveness acceptability curve for nivolumab + PDC versus surgery alone 173

Figure 7.1: TTLR curves for nivolumab + PDC for different models 183

Figure 7.2: LR hazard rate curves for nivolumab + PDC for different models 184

Figure 7.3: TTDM curves for nivolumab + PDC for different models 184

Figure 7.4: DM hazard rate curves for nivolumab + PDC for different models 185

1 EXECUTIVE SUMMARY

1.1 Overview of the EAG's key issues

Table 1.1: Summary of key issues

ID3757	Summary of issue	Report sections
Key issue [1]	Effectiveness of nivolumab + PDC more uncertain for patients with Stage IB or II NSCLC	3.2.8, 3.5, 4.2.3, 6.1.3, 6.2.1
Key issue [2]	Applicability of the CheckMate-816 population to England	3.2.3, 3.2.8, 4.2.3, 6.1.3, 6.2.1
Key issue [3]	Uncertainty in the effectiveness of different nivolumab + PDC regimens	3.2.3, 3.2.8, 3.5, 4.2.4, 6.1.3, 6.2.1
Key issue [4]	Applicability of resection type and surgical approach used in CheckMate-816 to the English clinical setting	3.2.4, 4.2.9, 6.1.2, 6.2.1
Key issue [5]	Uncertainty in extrapolation models used to estimate time to any progression (TTaP) and time to locoregional recurrence (TTLR)	4.2.6, 6.1.1, 6.1.2, 6.2.1
Key issue [6]	Uncertainty in the cure assumption	4.2.6, 6.1.2, 6.2.1
Key issue [7]	Uncertainty in the event-free utility estimate	4.2.6, 6.1.1, 6.1.2, 6.2.1
Key issue [8]	Uncertainty in the immuno-oncology (I-O) retreatment restrictions and distribution of chemotherapies in the DM state	4.2.8, 6.1.2, 6.2.1
Key issue [9]	Uncertainty in the effectiveness of the comparators	3.3.1.3, 3.5, 4.2.6, 6.1.3, 6.2.1
Abbreviations: NSCLC = non-small cell lung cancer; PDC = platinum doublet chemotherapy; TTaP = time to any progression; TTLR = time to locoregional recurrence; I-O = immune-oncology.		

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are a matter of judgement relating to the generalisability of the data available and the absence of evidence. This is with respect to the data that was available from the CheckMate-816 trial, the survival models chosen and the cure assumption.

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 incremental cost-effectiveness ratio (ICER) is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing the time to locoregional recurrence
- Increasing the time to distant metastasis.

Overall, the technology is modelled to affect costs by:

- Increasing the time to locoregional recurrence
- Increasing the time to distant metastasis
- Difference in cost of the interventions

- Difference in proportion of patients receiving surgery and the type of surgery across interventions
- Difference in adjuvant chemotherapy treatments across interventions including neoadjuvant treatments
- Proportion of patients ineligible for retreatment with immuno-oncology (IO) treatments
- Difference in rates of adverse events across interventions.

The modelling assumptions that have the greatest effect on the ICER are:

- Extrapolation of locoregional recurrence time-to-event curve
- Extrapolation of any progression time-to-event curve
- Extrapolation of survival curve for patients who are event-free
- The probability of distant metastasis in the locoregional recurrence state
- The proportion of patients receiving surgery across interventions
- Differences in the rates of adverse events across interventions
- Proportion of patients ineligible for retreatment with IO treatments

1.3 The decision problem: summary of the EAG's key issues

Table 1.2: Key issue [1] – Effectiveness of nivolumab + PDC more uncertain for patients with Stage IB or II NSCLC

Report section	**3.2.8, 3.5, 4.2.3, 6.1.3, 6.2.1**
Description of issue and why the EAG has identified it as important	According to the subgroup analyses of CheckMate-816, in terms of EFS, nivolumab + PDC [redacted] in patients with Stage IB or II NSCLC ([redacted]) compared with patients with Stage IIIA disease ([redacted]), albeit that the result is less precise for Stage IB-II disease indicating that this analysis was underpowered. [redacted]
What alternative approach has the EAG suggested?	The EAG considers that conducting the NMA for Stage IB-II patients and Stage IIIA patients separately can provide data to inform whether nivolumab + PDC differs in effectiveness (and hence cost-effectiveness) by disease stage.
What is the expected effect on the cost-effectiveness estimates?	The EAG conducted subgroup analyses for the EFS NMA analyses. These data suggest there may be a difference in the estimates of effectiveness of nivolumab between the different stages of disease. However, data were sparse compared with base-case NMA analyses. In the EAG scenario analysis, there were changes in the ICER for those with earlier stages of disease (Stage IB-II). In this scenario analysis, adjuvant PDC dominated nivolumab and the ICER for nivolumab compared with surgery alone increased to £16,143. The ICER for neoadjuvant CRT compared with nivolumab was not estimable for this subgroup due to lack of data available. Furthermore, in the UK clinical context neoadjuvant CRT is generally reserved to patients at stages of disease more severe than captured by this subgroup.

Report section	3.2.8, 3.5, 4.2.3, 6.1.3, 6.2.1
What additional evidence or analyses might help to resolve this key issue?	The EAG has conducted subgroup analyses for the NMA with Stage IB-II and Stage IIIA participants presented in separate analyses. The EAG used the data from the NMA to undertake a scenario analysis to estimate cost-effectiveness, however these data were subject to uncertainty. Further CheckMate-816 evidence from a later data cut, which is not currently available, would help reduce uncertainty.
Abbreviations: CI = confidence interval; CRT = chemoradiotherapy; EAG = Evidence Assessment Group; EFS = event-free survival; HR = hazard ratio; ICER = incremental cost effectiveness ratio; NMA = network meta-analysis; NSCLC = non-small cell lung cancer; PDC = platinum doublet chemotherapy	

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Table 1.3: Key issue [2] - Applicability of the CheckMate-816 population to England

Report section	3.2.3, 3.2.8, 3.5, 4.2.3, 6.1.3, 6.2.1
Description of issue and why the EAG has identified it as important	Characteristics of the patients enrolled in CheckMate-816 may not be reflective of patients seen in clinical practice in England. There were no patients from the UK enrolled in CheckMate-816 and the majority of participants (47.5% in the intervention arm and 51.4% in the control arm) were enrolled from Asia. This could potentially affect the external validity of the RCT's findings as subgroup analyses by geographic region for EFS are subject to imprecision consistent with nivolumab + PDC potentially being more or less effective than in the Asian population.
What alternative approach has the EAG suggested?	The EAG considers that the characteristics of the North American and European subgroups presented in CheckMate-816 may be more applicable to the English clinical setting.
What is the expected effect on the cost-effectiveness estimates?	The EAG argued that the data from North American and European subgroups would be more applicable to England. These data were included in the EAG scenario analysis and because the effectiveness of nivolumab was reduced in these analyses, nivolumab was dominated by neoadjuvant CRT and the ICER for nivolumab versus surgery alone increased to only £4,890. The difference between nivolumab and adjuvant PDC could not be estimated for this subgroup due to the lack of available data.
What additional evidence or analyses might help to resolve this key issue?	The EAG has conducted subgroup analyses for the NMA by the participants enrolled from Europe and North America. These data were used to conduct an EAG CE scenario analysis. However, these data are subject to uncertainty and further CheckMate-816 evidence from a later data cut, which is not currently available, would help reduce uncertainty.
Abbreviations: CE = cost effectiveness; CRT = chemoradiotherapy; EAG = Evidence assessment group; EFS = event-free survival; ICER = incremental cost effectiveness ratio; NMA = network meta-analysis; PDC = platinum doublet chemotherapy; RCT = randomised controlled trial	

Table 1.4: Key issue [3] – Uncertainty in the effectiveness of different nivolumab + PDC regimens

Report section	**3.2.3, 3.2.8, 4.2.4, 6.1.3, 6.2.1, 6.2.1**
Description of issue and why the EAG has identified it as important	Subgroup analyses for pCR and EFS suggest that nivolumab + cisplatin-based PDC may be less effective than nivolumab + carboplatin-based PDC, although this is uncertain. In CheckMate-816, 21.8% of participants in the nivolumab + PDC arm and 18.4% in the PDC alone arm received carboplatin-based PDC. Clinical advice to the EAG suggested that carboplatin-based PDC would rarely be used within the UK clinical setting; however, it could potentially be paired with nivolumab, should nivolumab be recommended. Additionally, clinical advice to the EAG identified that cisplatin + vinorelbine would be the most commonly used PDC regimen in the UK clinical context of the PDC regimens used within CheckMate-816. PDC was not further disaggregated by type of cisplatin-based PDC in the study. Additionally, cisplatin + vinorelbine was only used in the comparator arm of the study and not the nivolumab + PDC arm.
What alternative approach has the EAG suggested?	The EAG suggests further subgroup analysis within the NMA containing only the patients undertaking cisplatin-based PDC from CheckMate-816 in order to produce evidence depending on the likely nivolumab combination used in the UK clinical setting. With regards to cisplatin + vinorelbine, PDC was not further disaggregated by type of cisplatin-based PDC in the study. Therefore, the EAG cannot suggest an alternative approach to analysis by specific PDC regimen.
What is the expected effect on the cost-effectiveness estimates?	The EAG explored a subgroup analysis using data for patients receiving treatment with cisplatin-based PDC alone. The impact this has on intervention costs was small; however, the effectiveness of nivolumab potentially decreases relative to neoadjuvant CRT (becoming cheaper but less effective with an ICER for neoadjuvant CRT of £3,420 per QALY gained), while the effectiveness relative to surgery alone increases (decreasing the ICER to £2,627). Data were not available for adjuvant PDC.
What additional evidence or analyses might help to resolve this key issue?	The EAG has conducted subgroup analyses for the NMA only including participants from CheckMate-816 who received cisplatin-based PDC. The EAG has conducted a CE scenario analysis using the available evidence for nivolumab + cisplatin and for nivolumab + carboplatin. However, these data are subject to significant uncertainty. Additional data from CheckMate-816 from a subsequent data-cut point would help reduce this uncertainty.

Report section	3.2.3, 3.2.8, 4.2.4, 6.1.3, 6.2.1, 6.2.1
	Further evidence on the LR and DM HRs for each of the comparators would also help reduce the uncertainty. However, the EAG does not know of any additional evidence.
Abbreviations: CE = cost-effectiveness; CRT = chemoradiotherapy; DM = distant metastasis; EAG = Evidence Assessment Group; EFS = event-free survival; HR = hazard ratios; ICER = incremental cost-effectiveness ratio; LR = locoregional recurrence; NMA = network meta-analysis; pCR = pathologic complete response; PDC = platinum doublet chemotherapy; QALY = quality-adjusted life year	

Table 1.5: Key issue [4] – Applicability of surgical approach and resection type used in CheckMate-816 to the English clinical setting

Report section	3.2.4, 4.2.9. 6.1.3, 6.2.1
Description of issue and why the EAG has identified it as important	Surgical approach: In CheckMate-816, 59.1% of participants in the nivolumab + PDC arm and 63% of participants in the PDC alone arm underwent thoracotomy. Clinical advice to the EAG highlighted that minimally-invasive surgery is more common in UK clinical practice, but in CheckMate-816 only 29.5% of participants in the nivolumab + PDC arm and 21.5% in the PDC alone arm underwent minimally-invasive surgery. As such, the approach to surgery mainly undertaken in CheckMate-816 may not reflect English clinical practice and this may also have an impact on health-related quality of life (HRQOL) and costs compared with what might be expected in English clinical practice. Resection type: Additionally, 16.8% of participants in the nivolumab + PDC arm and 25.2% in the PDC-alone arm underwent pneumonectomy within CheckMate-816. Clinical advice to the EAG highlighted that pneumonectomy is now very uncommon for NSCLC resection within UK clinical practice. It is unclear to the EAG if resection type is associated with different recurrence rates and HRQOL.
What alternative approach has the EAG suggested?	Surgical approach: Following clinical expert advice, the EAG considered the surgical rates presented by the company to not be generalisable to the UK. The EAG undertook the following two scenario analyses: 1) minimally invasive surgery makes up 50% of surgery; and 2) minimally invasive surgery as assumed for all treatment arms and there was no difference in surgery rates. Resection type: No alternative approach is suggested. The CEM assumed that patients only had minimally invasive surgery or thoracotomy, which affects the cost estimate.
What is the expected effect on the cost-effectiveness estimates?	Surgical approach: The ICER slightly increased when both scenario analyses were applied to the EAG base-case but nivolumab was still the most cost-effective treatment option assuming a £20,000 value for an additional QALY. 1) Nivolumab dominated neoadjuvant CRT. Nivolumab had an ICER of £1,881 compared with adjuvant PDC, and nivolumab had an ICER of £4,037 compared to surgery alone.

Report section	3.2.4, 4.2.9. 6.1.3, 6.2.1
	2) Nivolumab dominated neoadjuvant CRT. Nivolumab had an ICER of £3,094 compared with adjuvant PDC, and nivolumab had an ICER of £4,696 compared to surgery alone.
What additional evidence or analyses might help to resolve this key issue?	Effectiveness: Evidence on the association between surgical approach and outcomes and between resection type and outcomes. Effectiveness evidence by surgical approach and resection type in the trials included in the NMA and then incorporated into the CEA.
Abbreviations: CEA = cost-effectiveness analysis; CEM = company economic model; CRT = chemoradiotherapy; EAG = Evidence Assessment Group; HRQOL = health-related quality of life; ICER = incremental cost-effectiveness ratio; NMA = network meta-analysis; NSCLC = non-small cell lung cancer; PDC = platinum doublet chemotherapy; QALY = quality-adjusted life year	

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Table 1.6: Key issue [5] – Uncertainty in extrapolation models used to estimate time to any progression (TTaP) and time to locoregional recurrence (TTLR)

Report section	4.2.6, 6.1.1, 6.1.2, 6.2.1
Description of issue and why the EAG has identified it as important	The parametric models used to extrapolate time to any progression (TTaP) and time to locoregional recurrence (TTLR) beyond the trial follow-up plays an important role in determining the efficacy of the intervention. There is considerable uncertainty around the extrapolation of the TTaP and TTLR curves. The company performed limited scenario analyses. The CS suggested two main candidate extrapolation models (exponential and log-normal) as they had a good fit to the CheckMate-816 data but generated different predictions over the long-term. Four other parametric models were fitted to the data in the CS. The company scenario selecting the exponential model for the locoregional recurrence curve produced an implausible distant metastasis curve.
What alternative approach has the EAG suggested?	Additional scenario analyses could be conducted by the company using different extrapolation models. The EAG considered the log-logistic distribution to be a feasible alternative for TTaP and TTLR. This distribution was chosen as it generated an in-between prediction relative to the other models (log-normal and exponential), which is also perhaps potentially more consistent with external evidence. The EAG also verified this choice with clinical opinion.
What is the expected effect on the cost-effectiveness estimates?	The EAG applied a log-logistic distribution to both TTLR and time to any progression (TTaP). In this scenario analysis, the ICER for nivolumab compared with adjuvant PDC decreased to £185 and the ICER for nivolumab compared with surgery alone decreased to £2,899. Nivolumab still dominated adjuvant CRT and would be considered cost-effective in all three pairwise comparisons.

Report section	4.2.6, 6.1.1, 6.1.2, 6.2.1
What additional evidence or analyses might help to resolve this key issue?	Data from a later data cut in the CheckMate-816 trial would provide more evidence on the shape of the TTLR curve.
Abbreviations: CEM = cost-effectiveness model; CRT = chemoradiotherapy; CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; PDC = platinum doublet chemotherapy; TTaP = time to any progression; TTLR = time to locoregional recurrence	

Table 1.7: Key issue [6] – Uncertainty in the cure assumption

Report section	4.2.6, 6.1.1, 6.1.2, 6.2.1
Description of issue and why the EAG has identified it as important	The company use a "cure assumption" in the economic model with little empirical evidence to support this assumption. The "cure assumption", based mainly on clinical advice, predicts that 95% of patients who are event-free at 5 years would be 'cured' and their risk of recurrence and mortality would be the same as predicted from an age- and sex-matched general population. There was variation in clinical expert estimates for this cure assumption.
What alternative approach has the EAG suggested?	The EAG suggest using the Gompertz distribution for the TTLR and TTaP transitions from: 1) month 60 (EAG base-case); and 2) month 46 (EAG scenario analysis) instead of the log-normal distribution selected for the company base-case analysis. No additional methods were required to adjust outcomes for the cure assumption.
What is the expected effect on the cost-effectiveness estimates?	In the EAG sensitivity analyses with the cure assumption removed but the Gompertz distribution applied, there was little change in the overall conclusions. 1) In the EAG base-case nivolumab dominated neoadjuvant CRT. The ICER for nivolumab compared with adjuvant PDC was £879 and the ICER for nivolumab compared with surgery was £3,478. 2) Nivolumab dominated neoadjuvant CRT. The ICER for nivolumab compared with adjuvant PDC decreased to £697 and the ICER for nivolumab compared with surgery decreased to £3,224.
What additional evidence or analyses might help to resolve this key issue?	There is consensus among clinical experts that the cure assumption occurs between years five and eight but there is not consensus on the rates of cure. There is no empirical evidence to support this assumption. As such, longer-term follow-up of NSCLC patients is needed.
Abbreviations: CRT = chemoradiotherapy; EAG = Evidence assessment group; ICER = incremental cost-effectiveness ratio; NSCLC = non-small cell lung cancer; PDC = platinum doublet chemotherapy; TTaP = Time to any progression; TTLR = time to locoregional recurrence	

Table 1.8: Key issue [7] – Uncertainty in the event-free and locoregional recurrence utility estimates

Report section	4.2, 6.1.2, 6.2.1
Description of issue and why the EAG has identified it as important	The utility value for the event-free (EF) state in CheckMate-816 is higher than the age-adjusted utility value at the same age in the UK. Therefore, the company cap this utility at the general population value (0.833) and retain the decrement from CheckMate-816 for the locoregional recurrence (LR) health state. The EAG consider both these utility values to be uncertain.
What alternative approach has the EAG suggested?	The EAG suggests the use of alternative utility values based on expert opinion and related studies in the literature.
What is the expected effect on the cost-effectiveness estimates?	The EAG undertook a number of scenario analyses applying different utility values to the EF health states based on the literature and clinical advice. The conclusions did not change in that nivolumab was cost-effective but there were slight changes in the ICER. Nivolumab dominated neoadjuvant CRT in all scenario analyses. The ICER for nivolumab compared with adjuvant PDC ranged from £887 to £1,233. The ICER for nivolumab compared with surgery alone ranged from £3,462 to £4,706.
What additional evidence or analyses might help to resolve this key issue?	The EAG considers this issue to be unresolvable due to the lack of available evidence.
Abbreviations: CRT = chemoradiotherapy; EAG = Evidence assessment group; EF = Event free; ICER = incremental cost-effectiveness ratio; LR = Locoregional Recurrence; PDC = platinum doublet chemotherapy	

Table 1.9: Key issue [8] – Uncertainty in the immuno-oncology (I-O) retreatment restrictions and distribution of chemotherapies in the DM state

Report section	4.2.6, 6.1.2, 6.2.1
Description of issue and why the EAG has identified it as important	The company assumed that patients who were initially treated with immuno-oncology (I-O) agents (i.e. nivolumab) and experienced progression at or within six-months could not be retreated with I-O treatments. There is uncertainty in the proportion of patients ineligible for retreatment with I-O and the timelines of these restrictions. The company explored this assumption as a scenario analysis, which had a significant effect on the ICER. The company also assumed that the distribution of chemotherapies in the DM health state would be different for I-O and non-I-O treatments. There is uncertainty regarding this assumption.
What alternative approach has the EAG suggested?	Additional scenario analysis could be conducted by the company assuming the distribution of chemotherapies in the DM state is the same for I-O and non-I-O treatments.
What is the expected effect on the cost-effectiveness estimates?	In the EAG sensitivity analysis, the EAG conducted one sensitivity analysis which assumed the I-O retreatment restrictions were not included. The conclusions did not change in that nivolumab was cost-effective, but there were changes in the ICER. The ICER for nivolumab compared to neoadjuvant CRT increased to £6,429. The ICER for nivolumab compared to

Report section	4.2.6, 6.1.2, 6.2.1
	adjuvant PDC increased to £3,535. The ICER for nivolumab compared to surgery increased to £4,949. The EAG also conducted a sensitivity analysis which assumed the distribution of chemotherapies in the DM state was the same for I-O and non-I-O treatments. Once more, the conclusions did not change in that nivolumab was cost-effective, but there were changes in the ICER. The ICER for nivolumab compared to neoadjuvant CRT increased to £8,046. The ICER for nivolumab compared to adjuvant PDC increased to £4,212. The ICER for nivolumab compared to surgery alone increased to £5,508.
What additional evidence or analyses might help to resolve this key issue?	Further evidence regarding the distribution of chemotherapies used for I-O and non-I-O treatments in the DM state would help resolve this issue.
Abbreviations: CRT = chemoradiotherapy; DM = distant metastasis; EAG = Evidence assessment group; ICER = incremental cost-effectiveness ratio; I-O = immuno-oncology; PDC = platinum doublet chemotherapy;	

Table 1.10: Key issue [9] – Uncertainty in the effectiveness of the comparators

Report section	3.3.1.3, 3.5, 4.2.6, 6.1.2, 6.2.1
Description of issue and why the EAG has identified it as important	The company estimated the HR of LR and DM using available evidence for use in the CEM. The company have stated that there was limited evidence available to estimate the HRs of LR and DM for the comparators (neoadjuvant CRT, adjuvant PDC and surgery alone). The company applied a proportional hazards assumption to estimate LR and DM probabilities for each of the comparators. This was the only possible approach for these outcomes given that some data were proportions of people experiencing an event and these were used to estimate hazard rates. There was considerable uncertainty in effect estimates likely due to the low number of recurrence events (LR/DM) and/or small sample sizes. The difference in the mean estimates of the HRs of LR and DM were significantly greater for the comparators than for the nivolumab + PDC, although there was considerable uncertainty in estimates. This could be due to the nature of the interventions; the company argue that neoCRT is more likely to reduce LR than DM. But part of it could also be due to definitions of outcomes, the nature of the data collection and data reported.
What alternative approach has the EAG suggested?	The EAG cannot recommend the use of known additional data or a more robust statistical method for estimating the HR of LR and DM because of lack of quality evidence. In addition to the probabilistic sensitivity analysis run by the company, the EAG conducted additional scenario analyses to explore the sensitivity of the results to very different HRs of LR and DM.

Report section	3.3.1.3, 3.5, 4.2.6, 6.1.2, 6.2.1
What is the expected effect on the cost-effectiveness estimates?	In the company base-case and EAG base-case, nivolumab + PDC had an ICER ranging from absolute dominance (versus neoadjuvant CRT) to absolute dominance and £879 (versus adjuvant PDC), and to £2,685-£3,478 (versus surgery alone). There is very high uncertainty in the results considering the low ICERs (probability of being cost-effective of [redacted] compared to neoadjuvant CRT, and [redacted] compared to adjuvant PDC in the EAG base-case). In subgroup analyses where the nivolumab + PDC HR is closer to 1 but also with greater uncertainty, the ICER is much higher in a couple of analyses and very uncertain. When HRs of LR and DM similar to the relative values of these outcomes for nivolumab + PDC are assumed, then the ICER increases or nivolumab + PDC becomes dominated. If the HRs of LR and DM are both set to the values of the HR of EFS then nivolumab + PDC dominates the comparators. The EAG does not disagree with the approach to estimating the HRs of LR and DM by the company. This Key Issue is here to emphasise the uncertainty in cost-effectiveness estimates, especially in the subgroup analyses. The cost-effectiveness of nivolumab + PDC at a threshold of £20,000/QALY in the base-case is robust to changes in the HRs of LR and DM in deterministic analysis, despite the uncertainty revealed in the probabilistic analysis results. Nivolumab + PDC could be more or less cost-effective in the subgroup analyses.
What additional evidence or analyses might help to resolve this key issue?	HR estimates or Kaplan-Meier curves for LR and DM with competing risks treated as censored would be required from the authors of the studies included in the NMA. This is an unlikely prospect. The EAG does not know if there are other ongoing trials that could be included in the NMA. There is no immediate prospect of further evidence.
Abbreviations: CEM = company economic model; CIs = confidence intervals; CRT = chemoradiotherapy; CS = company submission; DM = distant metastasis; EAG = Evidence assessment group; EFS = event free survival; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; LR = locoregional recurrence; neoCRT = neoadjuvant chemoradiotherapy; NMA = network meta-analysis; PDC = platinum doublet chemotherapy; QALY = quality-adjusted life year	

1.6 Other key issues: summary of the EAG's view

None.

1.7 Summary of the EAG's view

The EAG base-case includes the EAG preferred assumptions and was undertaken for all three pairwise comparisons. Based on the deterministic results, nivolumab + PDC dominated neoadjuvant CRT: the ICER was £879 for nivolumab plus PDC compared with adjuvant PDC, and the ICER was £3,478 for nivolumab plus PDC compared with surgery alone. The probabilistic EAG base-case analyses indicated cost-effectiveness probabilities of [redacted], [redacted], and [redacted] compared with neoadjuvant CRT, adjuvant PDC and surgery respectively alone at a willingness to pay threshold of £20,000 per QALY gained.

The most influential scenario analyses for all three pairwise comparisons were: 1) assuming the cost of subsequent treatments was £0 (company scenario analysis #7), 2) assuming the same distribution of chemotherapy for I-O and non-I-O therapies and 3) assuming no I-O restrictions (company scenario #10). The only scenario in the base-case where nivolumab + PDC was not cost-effective at a £20,000/QALY threshold was the first of these influential scenarios. In the company scenario analysis, the ICER was £21,496 for an additional QALY, when nivolumab + PDC was compared to neoadjuvant CRT and in the EAG scenario analysis the ICER was £32,718. But the EAG considers this to be an extreme scenario.

Nivolumab + PDC was not cost-effective at a threshold of £20,000/QALY in one subgroup analysis when compared to adjuvant PDC. This was in the stage IB-II subgroup: nivolumab + PDC was dominated. When compared to surgery alone, the ICER for this subgroup was £16,143 (deterministic estimate) and £23,607 (probabilistic estimate). The ICER was sensitive to alternative hazard ratios for LR and DM. There was no ICER for neoadjuvant CRT for this subgroup due to it being used in stage IIIA patients. There was uncertainty in the cost-effectiveness of nivolumab + PDC compared with neoadjuvant CRT in two subgroup analyses (using data from North America and Europe only and assuming cisplatin was the only PDC regimen).

The cost-effectiveness results were robust across scenario analyses, despite the considerable decision uncertainty due to significant uncertainty in the effectiveness of the comparators. Nivolumab + PDC was cost-effective at a threshold of £20,000/QALY across subgroup analyses apart from the stage IB-II subgroup analyses, when compared to adjuvant PDC and surgery alone. There was further uncertainty in the geographical and PDC regimens when nivolumab + PDC was compared with neoadjuvant CRT. The decision uncertainty in the subgroup analyses was related to even greater uncertainty in the comparator effectiveness and greater uncertainty in the nivolumab + PDC effectiveness in these subgroups. Further data from later data-cut points in CheckMate-816 would reduce the uncertainty surrounding the effectiveness of nivolumab + PDC in these subgroups. Better and more evidence to inform the effectiveness of the comparators is harder to obtain.

Table 1.11: Summary of EAG's preferred assumptions and ICER – nivolumab + PDC versus neoadjuvant CRT

Scenario	Incremental cost	Incremental QALYs	ICER
Company's base-case after clarification	[redacted]	[redacted]	Dominant
Company's base-case after clarifications and including EAG corrections and updating the PAS for nivolumab	[redacted]	[redacted]	Dominant
Matters of judgement 3: mortality with log-normal extrapolation (Key issue 6)	[redacted]	[redacted]	Dominant
Matters of judgement 4: Gompertz distribution applied to TTLR (key issue 7)	[redacted]	[redacted]	Dominant
Matters of judgement 5: Gompertz distribution applied to TTaP (Key issue 7)	[redacted]	[redacted]	Dominant
EAG's preferred base-case	[redacted]	[redacted]	Dominant
EAG base-case probabilistic*	[redacted]	[redacted]	Dominant

Scenario	Incremental cost	Incremental QALYs	ICER
EAG = Evidence Assessment Group; PDC = platinum doublet chemotherapy; CRT = chemoradiotherapy; ICER = incremental cost effectiveness ratio; QALYs = quality-adjusted life years; TTLR = time to locoregional recurrence; TTaP = time to any progression			

Table 1.12: Summary of EAG's preferred assumptions and ICER – nivolumab + PDC versus adjuvant PDC

Scenario	Incremental cost	Incremental QALYs	ICER
Company's base-case after clarification	[redacted]	[redacted]	Dominant
Company's base-case after clarifications and including EAG corrections and updating the PAS for nivolumab	[redacted]	[redacted]	£207
Matters of judgement 3: mortality with log-normal extrapolation (Key issue 6)	[redacted]	[redacted]	£401
Matters of judgement 4: Gompertz distribution applied to TTLR (key issue 7)	[redacted]	[redacted]	£248
Matters of judgement 5: Gompertz distribution applied to TTaP (Key issue 7)	[redacted]	[redacted]	Dominant
EAG's preferred base-case	[redacted]	[redacted]	£879
EAG base-case probabilistic*	[redacted]	[redacted]	£1,197
EAG = Evidence Assessment Group; PDC = platinum doublet chemotherapy; ICER = incremental cost effectiveness ratio; QALYs = quality-adjusted life years; TTLR = time to locoregional recurrence; TTaP = time to any progression			

Table 1.13: Summary of EAG's preferred assumptions and ICER – nivolumab + PDC versus surgery alone

Scenario	Incremental cost	Incremental QALYs	ICER
Company's base-case after clarification	[redacted]	[redacted]	£2,685
Company's base-case after clarifications and including EAG corrections and updating the PAS for nivolumab	[redacted]	[redacted]	£2,991
Matters of judgement 3: mortality with log-normal extrapolation (Key issue 6)	[redacted]	[redacted]	£3,054
Matters of judgement 4: Gompertz distribution applied to TTLR (key issue 7)	[redacted]	[redacted]	£3,181
Matters of judgement 5: Gompertz distribution applied to TTaP (Key issue 7)	[redacted]	[redacted]	£2,398
EAG's preferred base-case	[redacted]	[redacted]	£3,478
EAG base-case probabilistic*	[redacted]	[redacted]	£4,559
EAG = Evidence Assessment Group; PDC = platinum doublet chemotherapy; ICER = incremental cost effectiveness ratio; QALYs = quality-adjusted life years; TTLR = time to locoregional recurrence; TTaP = time to any progression			

2 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG Comment
Population	Adults with resectable NSCLC	As per the scope	NA.	The population is in line with the NICE scope. The company note in footnotes to Table 1 in the company submission that tumour resectability is assessed at diagnosis and again after administration of neoadjuvant therapy but before surgery. It is therefore possible that some patients may be deemed to be eligible for resection when diagnosed but their status may change before surgery. As such, the company use the term "resectable" to mean "potentially resectable" in relation to neoadjuvant treatment.[1]
Intervention	Nivolumab with platinum-doublet chemotherapy	As per the scope	NA.	The intervention is in line with the NICE scope.
Comparator(s)	Established clinical management without nivolumab with chemotherapy, which may include: • Neoadjuvant chemoradiotherapy • Adjuvant chemotherapy • Active monitoring	As per the scope (note: surgical resection alone equates to active monitoring)	NA.	The comparators included in the economic evaluation matched those in the NICE scope. The comparators were not included in CheckMate-816 so a network meta-analysis (NMA) was conducted.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG Comment
	For people whose tumours express programmed death-ligand 1 (PD-L1) with at least a 50% proportion score Atezolizumab after adjuvant cispatin-based chemotherapy (subject to NICE appraisal)			
Outcomes	The outcome measures to be considered include: • Disease-free survival • Overall survival • Response rates • Adverse effects of treatment • Health-related quality of life	Overall survival, adverse effects of treatments and health-related quality of life were assessed by the company, as per the NICE scope • EFS rather than DFS is presented because it is the primary endpoint in CheckMate-816 • Rather than the response rate, the more specific outcome of pCR was assessed and this is a primary outcome in the trial • Major pathologic response (MPR) is also assessed as a measure of response rate as a secondary outcome	The company rationalise the change from DFS to EFS within CheckMate-816 by saying that DFS does not capture disease preventing surgical resection. The type of response rate was not specified in NICE's decision problem. The company used pCR and MPR to assess response rate. They validated this measure by providing references to studies supporting the association between pCR and survival outcomes.	The EAG's clinical advisor confirmed that pCR is an acceptable measure of response rate, whereas MPR is less relevant.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed	The company made no statement on this component in the dcision problem table.	NA.	The EAG assesses that the CS adhered to the NICE reference case.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG Comment
	in terms of incremental cost per quality-adjusted life year. 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 commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account.			
Special considerations	Guidance will only be issued in accordance with the	The company made no statement on this component	NA.	NA.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG Comment
including issues related to equity or equality	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.	in the decision problem table.		

Based on Table 1 and pages 15 to 16 of the CS.[1]

CS = company submission; DFS = disease-free survival; EFS = event-free survival; MPR = major pathological response; N/A = not applicable; NHS = National Health Service; NICE = National Institute of Health and Care Excellence; NSCLC = non-small-cell lung cancer; PAS = patient access scheme; pCR = pathological complete response; PDC = platinum doublet chemotherapy; PD-L1 = programmed death-ligand 1; QALY = quality-adjusted life year; RID = residual invasive disease

2.1 Population

The population as defined in the NICE scope is: adults with resectable NSCLC.[2] The definition of "resectable" within the CS is tumours that are ≥ 4 cm or node positive (Section B.1.1).[1] The company state in footnotes to CS Section B.1.1 Table 1 that tumour resectability is assessed at diagnosis and again after administration of neoadjuvant therapy but before surgery; they stated it was therefore possible that some patients may be deemed to be eligible for resection when diagnosed but their status may change before surgery. As such, the company use the term "resectable" to mean "potentially resectable" in relation to neoadjuvant treatment.[1]

CheckMate-816 is the clinical trial providing evidence for Nivolumab in the CS. Within CheckMate-816, participants with Stages IB-IIIA NSCLC were recruited, based on the definitions used in the seventh edition of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC).[3,4] The company state that people with NSCLC Stage IB (tumour size B ≥ 4 cm) to Stage IIIA disease in the AJCC/UICC seventh edition mainly corresponds to Stages IB (with tumour size 4 cm) to IIIB (non-N3 and non-N2-T4) in the eighth edition (CS Section B.1.3.1, p.19-20).[1] Furthermore, the company summarise the differences between the seventh and eighth editions of the AJCC/UICC classification systems (CS Section B.1.3.1, Table 3, p.20), while noting the following impacts on the nivolumab indication: some patients may be reclassified as IIA dependent on tumour size; all IIA patients are reclassified as IIB; some patients within IIB may be reclassified as IIIA dependent on tumour size; and some patients within the IIIA category may be reclassified as IIIB.[1] Participants in CheckMate-816 were assessed using the seventh edition of the AJCC/UICC and were not reclassified into the eighth edition criteria.[1]

EAG Comment: Overall, the population of CheckMate-816 fits with the NICE scope.

2.2 Intervention

The intervention as described by the NICE scope is: Nivolumab with platinum-doublet chemotherapy (PDC).[2] The CheckMate-816 trial used neoadjuvant nivolumab administered as an intravenous infusion at a dosage of 360 mg every 3 weeks plus PDC every three weeks for up to three cycles (CS Section B.1.2, Table 2, p.17).[1]

In CheckMate-816, the PDC administered alongside nivolumab in the intervention arm was decided upon investigator choice and consisted of one of the following combinations (CS Section B.2.2, Table 6 footnotes, p.32-33).[1]

- Cisplatin (75 mg/m^2 on day 1 of a 3week cycle for up to 3 cycles) plus gemcitabine (1,000 mg/m^2 or 1,250 mg/m^2 [per local prescribing information] on days 1 and 8 of a 3-week cycle for up to 3 cycles, squamous histology)
- Cisplatin (75 mg/m^2 on day 1 of a 3week cycle for up to 3 cycles) plus pemetrexed (500 mg/m^2 on day 1 of a 3-week cycle for up to 3 cycles, nonsquamous histology)
- Carboplatin (AUC 5 or 6 on day 1 of a 3-week cycle for up to 3 cycles) and paclitaxel (175 or 200 mg/m^2 on day 1 of a 3-week cycle for up to 3 cycles, any histology).

EAG Comment: The use of neoadjuvant nivolumab + PDC is within the NICE scope.

2.3 Comparators

The comparators according to the NICE scope were established clinical management without nivolumab with chemotherapy, including neoadjuvant chemoradiotherapy, adjuvant chemotherapy and

active monitoring.[2] These were all included in the economic evaluation. In CheckMate-816, the comparator was neoadjuvant PDC alone, so a NMA was conducted.[1] Little evidence was provided in the CS regarding the comparability of the comparator treatments across trials. In the comparator arm, PDC could include one of the following (CS Section B.2.2, Table 6 footnotes, p.32-33).[1]

- Cisplatin (75 mg/m^2 on day 1 of a 3-week cycle for up to 3 cycles) plus gemcitabine (1,000 mg/m^2 or 1,250 mg/m^2 [per local prescribing information] on days 1 and 8 of a 3-week cycle for up to 3 cycles, squamous histology)
- Cisplatin (75 mg/m^2 on day 1 of a 3-week cycle for up to 3 cycles) plus pemetrexed (500 mg/m^2 on day 1 of a 3-week cycle for up to 3 cycles, nonsquamous histology)
- Cisplatin (75 mg/m^2 on day 1 of a 3-week cycle for up to 3 cycles) plus vinorelbine (25 mg/m^2 or 30 mg/m^2 [per local prescribing information] on days 1 and 8 of a 3-week cycle for up to 3 cycles)
- Cisplatin (75 mg/m^2 on day 1 of a 3-week cycle for up to 3 cycles) plus docetaxel (60 mg/m^2 or 75 mg/m^2 [per local prescribing information] on day 1 of a 3-week cycle for up to 3 cycles);
- Carboplatin (AUC 5 or 6 on day 1 of a 3-week cycle for up to 3 cycles) and paclitaxel (175 or 200 mg/m^2 on day 1 of a 3-week cycle for up to 3 cycles, any histology).

Section 3.5 below explores the impact of including cisplatin or carboplatin in sensitivity analyses for NMA analyses.

For people whose tumours expressed PD-L1 with at least 50% tumour proportion score, atezolizumab after adjuvant cisplatin-based chemotherapy would also have been an eligible comparator, subject to NICE appraisal.[2] The company state that atezolizumab was not included in the submission because at a NICE checkpoint meeting it was noted that atezolizumab was no longer relevant as a comparator because it is only available through the Cancer Drugs Fund and not in routine commissioning (CS Section B.1.1, Table 1, p.16).[1] Published technology appraisal guidance from NICE [TA823] confirms that atezolizumab is recommended for use within the Cancer Drugs Fund as more data is required to address uncertainties surrounding its effectiveness and cost-effectiveness.[5]

EAG comment: The comparators included in the economic evaluation were consistent with NICE scope. As the comparators were not included in CheckMate-816 study, the effectiveness of nivolumab + PDC relative to the comparators depends on the assumption of comparability of the control treatment in each study in the NMA in terms of effectiveness. The NMA is reported in Section B.2.9 of the CS (pp.60-68),[1] and in Appendix M of the CS (pp. 116-221).[6] The EAG comments on and critiques the NMA in Section 3.3 of the EAG Report.

2.4 Outcomes

The outcomes as defined by the NICE scope were: disease-free survival (DFS); overall survival (OS); response rates; adverse effects of treatment; and health-related quality of life.[2]

In line with the NICE scope, the company reported adverse effects of treatment, OS and health-related quality of life. The company assessed EFS instead of DFS in CheckMate-816, as it was the primary endpoint of the trial but also because they believed EFS to be more appropriate as DFS does not capture progression of disease preventing surgical resection (CS Section B.1.1, Table 1, p.15).[1]

Instead of response rate, the company included pCR, a primary outcome of the CheckMate-816 study (CS Section B.1.1, Table 1, p.15).[1]

Other outcomes measured by CheckMate-816 that were not listed in the NICE scope are described below (CS Section B.2.2, Table 6, p.33).[1]

- MPR
- Time to distant metastasis (TTDM);
- pCR, MPR, clinical response rate (cRR), EFS, TTDM and OS by PD-L1 status
- cRR
- Feasibility of surgery, peri- and postoperative complications
- Pharmacokinetics (PK)
- EFS2
- Biomarkers (tumour mutational burden (TMB); tumour inflammatory gene expression signatures; and potential predictive biomarkers in peripheral blood and tumour specimens, e.g., proteins and/or genes involved in regulating immune responses, such as PD-L1)

EAG Comment: OS, adverse events and HRQOL were all assessed by CheckMate-816, in line with the NICE scope.[2]

However, the company measured EFS instead of DFS because EFS was the primary endpoint in CheckMate-816. This decision was further rationalised by the company, who stated that DFS does not capture progression of disease preventing surgical resection, and that EFS was a more appropriate outcome measure as a result (CS Table 1).[1] Clinical advice to the EAG suggested that measuring of EFS instead of DFS was clinically appropriate.

Instead of response rate as specified in the NICE scope, CheckMate-816 measured pathologic complete response (pCR), which was also a primary endpoint in the study.[1] Clinical advice to the EAG stated that pCR was an acceptable primary outcome for CheckMate-816.

2.5 Other relevant factors

The NICE scope notes that, if evidence allows, results should be presented by disease stage and level of PD-L1 expression.[2] CheckMate-816 presented subgroup analyses by disease stage (IB and II versus IIIA) and PD-L1 expression (<1% versus ≥ 1% versus 1-49% versus ≥ 50%) for pCR by blinded independent pathological review (BIPR) and EFS by blinded independent central review (BICR) in CS Section B.2.7.[1] In CheckMate-816, several other subgroup analyses were planned, as described in CS Section B.2.3.1 (Table 7, p.37). The company stated that there were no further special considerations in CheckMate-816, including those related to equity or equality.

EAG Comment: Nivolumab is currently licensed in the UK for use in a range of advanced cancers, including melanoma, renal cell carcinoma, NSCLC, malignant pleural mesothelioma, colorectal cancer, urothelial carcinoma, squamous cell cancer of the head and neck, classical Hodgkin lymphoma and oesophageal carcinoma.[7]

NICE recommends nivolumab as an option for treating locally-advanced of metastatic squamous or non-squamous NSCLC in adults following chemotherapy under specific clinical conditions.[8,9] Currently, neoadjuvant therapy for NSCLC is not recommended in the NICE clinical pathway, except in a small proportion of Stage IIIA-N2 participants, where chemoradiotherapy may be considered.[10] The company estimate that around 7-8% of NSCLC patients are treated with neoadjuvant chemoradiotherapy (CS Appendix N, p.231).[6] Surgical resection alone is the current standard of care for most eligible patients with resectable NSCLC.[10] The company are positioning nivolumab + PDC as being the new standard of care for all patients eligible for potential resection and suitable for systemic therapy in the neoadjuvant setting within the NICE pathway (CS Figure 5, p.26).

The company have presented subgroup analyses for pCR by BIPR and EFS by BICR in CS Section B.2.7, as per the NICE scope.[1]

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The CS includes a systematic literature review (SLR) of the effectiveness, safety and impacts on HRQOL of nivolumab with PDC as neoadjuvant therapy for the treatment of patients with resectable non-metastatic (stage I-III) non-small cell lung cancer (NSCLC) compared with surgery + chemotherapy with or without radiotherapy (RT), surgery + immunotherapy with or without RT, surgery + targeted therapy with or without RT, surgery + RT and surgery + best supportive care (BSC) or no treatment. The SLR methods are reported in Appendix D of the CS.[6]

The company undertook a single SLR with a wider scope than required by the NICE decision problem,[2] The relevant results informed both the SLR (EAG Report Section 3.1) and the NMA (EAG Report Section 3.3). The company reported that they identified only one RCT of nivolumab that was directly relevant to the NICE decision problem, CheckMate-816 (CS Section B.2.2). Therefore, indirect comparisons were undertaken "based on data extracted from a previously conducted SLR of RCTs" (CS Section B.2.9.1), with no reference given.[1] However, CS Appendix D describes a "previously conducted SLR", which is likely the SLR in question.[1]

3.1.1 Searches

The summary, table and EAG comments below relate to the one SLR conducted by the company, The scope of the SLR was wider than that of the NICE decision problem and so the company report only the relevant parts of their SLR.[1,6]

The company undertook a search for RCTs and observational studies with a wider scope than that required by the NICE decision problem,[2] the methods for which are described in CS Appendix D, Section D.1.1.[6] The company reference their 'in-house' draft report of the wider SLR.[11] This may have been the SLR reported within the Appendix but it was not 100% clear. The company conducted the original search on 10 March 2019 and updated this search three times on: 6 May 2020; 1 November 2021; and 1 April 2022. A range of electronic bibliographic databases were searched and the company report the use of pre-tested study design filters (CS Appendix D Section D.1.1.1).[6] Abstracts from specific conferences were sought on Embase (on Ovid SP) covering 2018 to 2020 inclusive. The company stated that no time limitations were imposed on the searches (other restrictions were applied at other stages of the review process, for example, at the data extraction stage a restriction to 'English language only' was applied (CS Table D-6, Appendix D).[6] A summary of the search-related information provided by the company in the CS is provided in Table 3.1.

The search strategy encompassed concepts from the 'population', combined (using 'AND') with an amalgamation (using 'OR') of the 'intervention', 'comparator' and 'timing' concepts of the NICE decision problem.

The EAG were able to only partially critically appraise the searches performed for the SLR using the PRESS checklist and the latest NICE methods manual (NICE 2022, PMG36).[12,13] This was because only the search strategies for the most recent of the main electronic database searches (1 April 2022) are presented. The number of records retrieved per search line was not shown and the methods and terms used to search the conference abstracts on Embase were not presented as might be expected when using the 'Preferred reporting items for systematic reviews and meta-analyses' extension for reporting literature searches (PRISMA-S) reporting guidance.14

Table 3.1: Summary of searches conducted by the company for clinical effectiveness studies on 1 April 2022

Resource - category	Resource	Host source	Date Range	Date of search	Search strategy/string/ terms reported	N hits per line	Reported in PRISMA flowchart
Electronic bibliographic databases	MEDLINE, MEDLINE Epub Ahead of Print, MEDLINE In-Process and Other Non-Indexed Citations and MEDLINE Daily	Ovid SP	NR	01.04.22[a]	Yes	NR	Yes
	Embase						
	CENTRAL[b]						
Conference proceedings[d]	IASLC/ESMO/ELCC	Ovid SP	2018-2020	NR	NR	NR	Yes[c]
	AACR						
	ASCO						
	SITC						
	ESMO Congress						
	IASLC WCLC						
	IASLC WCLC-Europe						
	ESMO Asia Congress						

Source: Based on information presented in CS Appendix D.[6]

[a] The company reports the original search was run on 10 March 2019 then subsequently updated on: 6 May 2020, 1 November 2021 and 1 April 2022 (CS Appendices, Section D.2, Appendix D).[6]

[b] Reported as EBM Reviews - Cochrane Central Register of Controlled Trials (CENTRAL).

[c] Eligible conferences reported only.

[d] The company report that they had removed five conferences which were included in the protocol "due to complete lack of any relevant studies coming from these smaller conferences" (footnote to CS Appendices, Section D.1.1.1.1, p. 20).[6] The conferences removed included, 'ACCR IASL International Joint Conference, AACR Tumor Immunology and Immunotherapy, ASCO-SITC clinical immune-oncology symposium, ESMO immuno-oncology Congress, and AACR-NCI-EORTC International Conference on Molecular targets and cancer therapeutics'.[6]

Abbreviations: AACR = American Association for Cancer Research; ASCO = American Society of Clinical Oncology; CENTRAL = Cochrane Central Register of Controlled Trials; EBM = Evidence-based medicine; ELCC = European Lung Cancer Congress; ESMO = European Society for Medical Oncology; IASLC =

International Association for the Study of Lung Cancer; N = number; NA = not applicable; NR = not reported; PRISMA = Preferred reporting items for systematic reviews and meta-analyses; SITC = Society for Immunotherapy of Cancer; WCLC = World Conference on Lung Cancer

EAG comment:

- The EAG is uncertain if all potentially relevant studies have been retrieved as the search did not include any clinical trials registries or platforms and no mention is made of searches of reference lists of included studies or other relevant articles. It may have been helpful to include a multidisciplinary electronic database as a source (e.g. Scopus, Web of Science) although, with the wide scope of the searches, the EAG recognises this could have produced an exceedingly large set of search records.
- The combination of search elements means that only surgery combined with other treatments was sought; surgery alone, as a comparator, would not be retrieved.
- The years covered by the MEDLINE and Embase searches on Ovid SP are not reported (availability across institutions can vary) and so it is not possible to comment on this aspect of the search.
- The pre-tested study design filters used are reported as being those developed by the Scottish Intercollegiate Guidelines Network (SIGN), although no reference(s) was provided to help verify exactly which of a number of filters was/were used, as would be considered good practice.
- No mention is made of a search for adverse effects.
- The search is wider than that necessary to cover the NICE decision problem.[2] The search relies very heavily on a relatively small set of search terms for each of the concepts covered. Retrieval could have been enhanced through the following.
    - The set of 'population' textword terms could have potentially been expanded slightly beyond 'lung' to cover 'pulmonary' or 'bronchus' (suitably truncated). 'Adenocarcinoma*' could also have been added to the second half of the search string.
    - The set of 'surgery-related' textword terms could have been expanded by allowing for, 'lobectom*', 'presurger*', 'presurgical*', 'postsurger*', 'postsurgical*', 'pneumectom*', 'pneumoresect*', 'pulmonectom*'(key: * used as a truncation symbol in Ovid).
    - The set of textword terms for the other comparators could have been expanded by allowing for 'radiation' or 'systemic' within the first part of the first half of the search string and the addition of the term 'chemoradiation' in the second half of the search string (after 'immunotherap*') (subject to suitable truncation).
    - For the main intervention 'nivolumab' and for the 'other comparators', no general, generic or specific drug-related terms are used (controlled vocabulary terms, textword terms, Chemical Abstracts Service (CAS) registry numbers). The EAG was not in a position to verify if the use of any or all of these terms would have led to the retrieval of additional relevant records.
- Conference abstracts were removed from the searches of Embase and Cochrane Central Register of Controlled Trials (CENTRAL) (using specific general 'conference abstract-related' terms combined with the final search using 'NOT'). However specific conferences were searched on Embase (details in Table 3.1 above), although the search terms used and how this was done was not described in the CS.
- Although the search date of 1 April 2022 is reported to be an update of three previous searches, it is presented as a 'standalone' search with no details of the previous searches and how they relate to this updated search. For example, was the most recent search imported into an existing database and deduplicated against it and only those new records screened?

3.1.2 Inclusion criteria

The company presented the eligibility criteria in Table D-5 of the CS appendices (Sections D.1.2., p.20-21).[6] Summaries of these eligibility criteria are presented in Table 3.2. Two reviewers independently screened studies at the title and abstract and full text stage, with a third reviewer adjudicating unresolved discrepancies regarding screening decisions.

Table 3.2: Eligibility criteria used in search strategy for RCT and non-RCT evidence

	Description	Justification
Inclusion criteria		
Population	Adult patients with resectable non-metastatic (stages I-III) NSCLC	As per the NICE scope
Interventions/ comparators	Surgery + chemotherapy with or without RT Surgery + immunotherapy with or without RT Surgery + targeted therapy[a] with or without RT Surgery + RT Surgery + BSC or no treatment	In the absence of head-to-head trial evidence of nivolumab + PDC versus all UK relevant comparators, an indirect treatment comparison was undertaken
Outcomes	Efficacy: Response Radiographic/clinical response (complete response (CR), partial response (PR), stable disease and progressive disease (PD)) pCR, MPR, and other pathologic responses with viable tumour cells cut-offs other than 0% and 10%) Survival outcomes OS, EFS (including PFS, RFS and DFS) Surrogacy associations between endpoints pCR/MPR ↔ OS/EFS; EFS ↔ OS[b] Patient-reported outcomes (PROs) Health-related quality of life (HRQOL) Safety: Adverse events	The outcomes in the NICE scope are included.
Study design	Interventional clinical trials (RCT and other trials)	RCTs represent the gold standard for assessing intervention effectiveness
Language restrictions	None	N/A

	Description	Justification
Exclusion criteria		
Population	Studies in superior sulcus, pleural effusion, elderly, and poor performance status (PS)	The company informed the EAG that these studies would not be representative of the target population. This was confirmed by the EAG's clinical advisor.
Interventions	Old immunotherapies (e.g., interferon) and cell therapies; studies focusing on one type of surgery	The company informed the EAG that studies focusing on one type of surgery would not be representative of the target population. However, the EAG was informed by their clinical advisor that in the UK it is usual for patients to only have one type of surgery (minimally invasive).
Outcomes	N/A	N/A
Study design	Case reports and case series	These studies do not include a comparison group therefore it is not possible to compare the effects of the intervention with alternative treatments or best supportive care.
Language restrictions	No language restrictions were placed	-

Source: CS Appendix D, Tables D-7 and D-8[6]

[a] Footnotes to Table D-5 state that targeted therapies included oncogene-targeted therapies such as TKIs and agents such as bevacizumab.

[b] The meaning of the arrows utilised in the CS is not clearly defined but the EAG assumes that these represent a potential relationship between outcomes

Abbreviations: BSC = best supportive care; CR = complete response; DFS = disease-free survival; EFS = event-free survival; HRQOL = health-related quality of life; MPR = major pathological response; N/A = not applicable; NICE = National Institute for Health and Care Excellence; NSCLC = non-small cell lung cancer; OS = overall survival; pCR = pathologic complete response; PD = progressive disease; PFS = progression-free survival; PR = partial response; PRO = patient-reported outcome; PS = performance status; RCT = randomised controlled trial; RFS = recurrence-free survival; RT = radiotherapy; TKI = tyrosine kinase inhibitor

EAG Comment: The population of interest in the SLR were adult patients with resectable non-metastatic (stages I-III) NSCLC, as per the NICE scope. CS Appendix D states: "studies in superior sulcus, pleural effusion, elderly, and poor PS" and "studies focusing on one type of surgery" were excluded from the review (Section D.1.2, Table D5, p.21). The EAG asked in points for clarification to define what was meant by "elderly" and "poor PS", as well as to justify the exclusion of the elderly population from the SLR (Questions A4a and A4b).

The company response to Question A4a. was that the term "elderly" referred to patients aged ≥ 65 years and these studies were to be excluded "because these patients are not representative of the adult population as a whole" and "to help manage the scope of the review".[15] Data show that lung cancer (of which NSCLC comprises approximately 80 to 85% of cases) is strongly related to age, with the highest rates being in older people aged 75 and over (UK, data from 2016-18).[16] Based on these data, it is the opinion of the EAG that a subgroup or sensitivity analysis of data from older patients may provide useful information regarding the effectiveness of nivolumab + PDC in the age group most affected by

the condition in the England. However, the company confirmed that no RCTs where the population was "elderly" were identified and therefore no studies were excluded for this reason.[15] Consequently, the EAG does not consider this as an issue that would have impacted the results.

The company response to Question A4b was that "any study conducted with patients with high PS (> 2) were to be excluded because again those patients are frail and not representative of the target population (CheckMate-816 included patients with PS 0-1 only)".[15] The EAG's clinical advisor agreed with the company's rationale for excluding these studies. Additionally, the company confirmed that no studies were excluded from the review for this reason. Consequently, the EAG does not consider this as an issue that would have impacted the results.

The interventions excluded from the review were old immunotherapies (e.g. interferon) and cell therapies, as well as studies focusing on one type of surgery. The EAG asked the company to clarify why studies focusing on one type of surgery were excluded (points for clarification Question A4d). The company responded by saying that "studies where only one type of surgery (e.g. just pneumectomy) was performed would not be representative of the target population and were therefore to be excluded".[15] The EAG was informed by their clinical advisor that it is usual practice in England for patients to only have one type of (minimally invasive) surgery, therefore these studies would have been representative of England practice and therefore should not have been excluded from the review. However, the company also confirmed that "no RCTs where only one type of surgery was used were identified, therefore no studies were excluded for this reason".[15] Therefore, due to no evidence being identified for these populations, the EAG is satisfied that the results of the systematic review will not have been affected by this issue.

The comparators included in the SLR were relevant to the NICE scope. The outcomes included in the SLR included all of those in the NICE scope.

Interventional clinical trials (RCT and other trials) were included in the review. When appropriately designed, conducted and reported, RCTs represent the gold standard in evaluating the effectiveness of healthcare interventions.[17] The approach taken by the company to screening studies represents a gold standard approach.[18]

3.1.3 Data extraction

The company describe their methods for data extraction in CS Appendix D, Section D.1.2.1 (pp.21-22).[6] In the CS Appendix D it is stated that "one researcher extracted the data and an independent reviewer verified and validated key fields using a clean copy of the publication" (CS Section D.1.2.1, p. 21).[6]

EAG comment: The company's method represents a pragmatic approach to data extraction where staff resources are limited. However, it does not represent best practice, where two people independently extract data that is critical for interpretation of results (e.g. outcome data).[18] It is unclear whether the company approached individual study authors for missing data or to clarify information. Additionally, the company do not state which "key fields" were checked by a second reviewer. The criteria used for data extraction were also narrower compared to the study selection criteria. The company explained this was to align more with the NICE scope and to provide relevant comparators for the NMA.

In the CS, there were discrepancies between Table D-5 (Eligibility criteria for study selection) and Table D-6 (Eligibility criteria for extraction of comparative efficacy studies).[6] Firstly, it was not clear why the company restricted to English language only at the data extraction stage, when no language restrictions were placed at study screening. The EAG is unable to assess the possible effects of

excluding non-English studies on the SLR results. Additionally, observational studies were eligible for data extraction but these studies would have been excluded from the review at the study selection stage where they do not appear to have been eligible for inclusion. The company also indicate in Table D-6 that observational studies are eligible for inclusion only if published between 2008 and 2019, but no justification is provided for the date range.[6] Although RCTs represent the gold standard in evaluating the effectiveness of healthcare interventions,[17] relevant observational studies may have provided further real-world evidence that could have impacted on the results.

3.1.4 Quality assessment

The company describe their process for assessing risk of bias in CS Appendix D, Section D.1.2.2 (p. 23).[6] Quality assessment was undertaken based on recommendations by NICE in 'Single technology appraisal: User guide for company evidence submission template'.[19]

EAG Comment: The risk of bias results for each domain and overall were presented for each study in CS Sections D.1.2.5.8. (Figure D-3, p.42) and CS Section D.2.2.1.7 (Figure D-4, p.63-64).[6] The process for undertaking this assessment (e.g. how many reviewers were involved and how discrepancies were resolved) was not reported. Best practice involves two reviewers independently undertaking risk of bias assessment for each included study,[20] but the EAG cannot comment on the appropriateness of the methods used to appraise study quality in the SLR. Additionally, studies were not excluded from the SLR based on study quality therefore the lack of second reviewer is unlikely to affect the findings of the SLR.

3.1.5 Evidence synthesis

Overall, 58 RCTs were included in the SLR. Of these 8 were excluded for being in the periadjuvant setting. 50 RCTs were set in either the neoadjuvant or adjuvant setting (CS, Section D.2, p.23-24).[6] Twenty-one RCTs were identified in the neoadjuvant setting and 29 were identified in the adjuvant setting. Eight RCTs set in the periadjuvant setting were identified but not considered further by the company as they were deemed irrelevant to the NICE scope.

EAG Comment: Only one study investigating nivolumab identified in the SLR of clinical trials was directly relevant to the NICE decision problem (CheckMate-816, reported as Forde 2022 in the SLR and NMA).[21]

[redacted]

The EAG asked the company to clarify the 'other' reasons for exclusions at full-text in the SLR as presented in the PRISMA Diagram (CS Figure D-1, points for clarification question A5b).[15] The company provided reasons for these 'other' exclusions but also noted that nine records originally classified as 'other' were secondary publications of already-included studies.[15] However, no information was provided as to which included RCTs these additional reports related to. Additionally, an abstract of an RCT comparing camrelizumab + chemotherapy versus chemotherapy alone was excluded due to there being "limited data". The EAG asked the company to clarify what was meant by "limited data" (points for clarification Question A6); the company responded: "We identified the conference abstract but were unable to obtain the poster/oral presentation. Limited data was presented in the abstract for inclusion in the review." It is unclear whether the company contacted the study authors for additional information; the impact of this exclusion on the results is unknown.

The EAG also asked the company to clarify why the SLR only reported on Grade 3 and 4 AEs (CS Section D.1.2.5.6) while the NMA (CS Section M.5.8.1) reported on Grade 3, 4 and 5 AEs (points for clarification Question A8c).[6] The company responded to clarify that no Grade 5 (fatal) treatment-related AEs were identified in the three studies that reported on Grade 3 and 4 AEs.[15,21-23] However, it is unclear whether any other studies in the SLR reported on Grade 5 AEs.

In CS Section D.1.2.5.6 (Table D-19, p. 38-9), only AEs reported by at least two RCTs were reported by the company. We asked the company to clarify the rationale behind this (points for clarification, Question A8a); they responded to say that the table is intended to give an overview of common Grade 3 and 4 AEs, not to be an exhaustive list.[15] While this is a pragmatic approach, this means it is likely that not all Grade 3 and 4 AEs reported in the included studies are reported in the SLR. If an AE reported by only one RCT was particularly common, and the RCT had a large sample size, this may represent selective reporting bias within the SLR. However, the impact of this reporting on the results is unknown.

The company reported only short narrative descriptions of the HRQOL results in CS Appendix D, Section D.1.2.5.7. (p.42) and Section D.2.2.1.6. (p.63).[6] The EAG asked the company to provide all HRQOL data reported in these RCTs (points for clarification, Question A9). The company responded by saying that "there were very limited HRQOL data and reported with different instruments" and "none of the studies reported the EQ-5D-3L which was the HRQOL outcome included in CheckMate-816 and therefore no comparisons are possible".[15] As HRQOL is included within the NICE scope, it would have been informative if the company had contacted the authors of primary to request unreported HRQOL data. These data could have been synthesised narratively with a graphical illustration of the effect direction if meta-analysis was not feasible.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The company identified a single RCT comparing neoadjuvant nivolumab plus PDC with PDC alone for which published data were available, CheckMate-816.[1,21] The phase III trial compared the efficacy and safety of neoadjuvant nivolumab with PDC against PDC alone in adult patients with newly diagnosed, resectable NSCLC of AJCC/UICC seventh edition stages IB-IIIA.

3.2.1 CheckMate-816 design and quality assessment

The evidence for the effectiveness of neoadjuvant nivolumab plus PDC against neoadjuvant PDC alone came from the CheckMate-816 study (NCT02998528).[21,24] This is a phase III, ongoing, parallel-arm, open-label study in 358 adults with resectable, stage IB-IIIA NSCLC according to AJCC/UICC seventh edition criteria. The study was conducted in 111 sites across 14 countries internationally; none of the participants were recruited from the UK. A summary of the trial methodology is shown in Table 3.3.

Table 3.3: CheckMate-816 study design

Category of design	Details
Trial design	Phase 3, randomised, open-label trial
Population	Patients with newly diagnosed, resectable, stage IB-IIIA (AJCC/UICC seventh edition) NSCLC
Intervention(s)	Nivolumab administered as an intravenous infusion at a dosage of 360 mg every 3 weeks + PDC every 3 weeks for up to 3 cycles. Investigator choice of PDC administered as an intravenous infusion. PDC could include: Cisplatin (75 mg/m^2 on day 1 of a 3week cycle for up to 3 cycles) plus gemcitabine (1,000 mg/m^2 or 1,250 mg/m^2 [per local prescribing

	information] on days 1 and 8 of a 3-week cycle for up to 3 cycles, squamous histology) Cisplatin (75 mg/m^2 on day 1 of a 3week cycle for up to 3 cycles) plus pemetrexed (500 mg/m^2 on day 1 of a 3-week cycle for up to 3 cycles, nonsquamous histology) Carboplatin (AUC 5 or 6 on day 1 of a 3-week cycle for up to 3 cycles) and paclitaxel (175 or 200 mg/m^2 on day 1 of a 3-week cycle for up to 3 cycles, any histology).
Comparator(s)	Neoadjuvant PDC alone. PDC could include: Cisplatin (75 mg/m^2 on day 1 of a 3-week cycle for up to 3 cycles) plus gemcitabine (1,000 mg/m^2 or 1,250 mg/m^2 [per local prescribing information] on days 1 and 8 of a 3-week cycle for up to 3 cycles, squamous histology) Cisplatin (75 mg/m^2 on day 1 of a 3-week cycle for up to 3 cycles) plus pemetrexed (500 mg/m^2 on day 1 of a 3-week cycle for up to 3 cycles, nonsquamous histology) Cisplatin (75 mg/m^2 on day 1 of a 3-week cycle for up to 3 cycles) plus vinorelbine (25 mg/m^2 or 30 mg/m^2 [per local prescribing information] on days 1 and 8 of a 3-week cycle for up to 3 cycles) Cisplatin (75 mg/m^2 on day 1 of a 3-week cycle for up to 3 cycles) plus docetaxel (60 mg/m^2 or 75 mg/m^2 [per local prescribing information] on day 1 of a 3-week cycle for up to 3 cycles); Carboplatin (AUC 5 or 6 on day 1 of a 3-week cycle for up to 3 cycles) and paclitaxel (175 or 200 mg/m^2 on day 1 of a 3-week cycle for up to 3 cycles, any histology).
Location	111 sites in 14 countries (Argentina, Brazil, Canada, China, France, Greece, Italy, Japan, South Korea, Romania, Spain, Taiwan, Turkey, and USA)
Duration of study	[redacted]
Method of randomisation	Randomised 1:1 using Interactive Response Technology. Stratification factors: PD-L1 expression (≥ 1% vs. < 1%/not evaluable/indeterminate), disease stage (IB/II vs. IIIA), and gender/sex (male vs. female)
Methods of blinding	Open label study for participants and physicians. Bristol Myers Squibb was blinded to the aggregated safety and efficacy data by treatment assignment.
Primary endpoints (including scoring methods and timings of assessments)	EFS: time from randomisation to any progression of disease precluding surgery, progression or recurrence of disease (per BICR using Response Evaluation Criteria in Solid Tumours (RECIST) 1.1) after surgery, or death due to any cause. Participants who did not undergo surgery for reasons other than progression were considered to have an event at RECIST 1.1 progression or death. pCR rate: number of randomly assigned participants with absence of residual viable tumour cells in both lung and lymph nodes as evaluated by BIPR, divided by the number of randomly assigned participants for each treatment group.
Secondary endpoints (including scoring methods and timings of assessments)*	Time to locoregional recurrence (TTLR): time between the date of randomisation and the first date of locoregional recurrence TTDM: time between the date of randomisation and the first date of distant metastasis or the date of death in the absence of distant

	metastasis. Participants who had not developed distant metastasis or died at the time of the analysis were censored on the date of their last evaluable tumour assessment. OS: time between the date of randomisation and the date of death. Censored on the last date a participant was known to be alive. HRQOL: Mean scores and mean change from baseline in total scores through follow-up in EQ-5D-3L in both the VAS and the utility index. Proportion of participants reporting problems for the EQ-5D-3L dimensions at each assessment.[a] Adverse events: Frequency of deaths, AEs, SAEs, AEs leading to discontinuation of study drug, select AEs, IMAEs, OESIs, and laboratory abnormalities. Analyses were conducted using the 30-day and/or 100-day safety window from day of last dose received.
Source: CS Table 6 (Section B.2.2, p.32-33), Table 7 (CS Section B.2.3.1, p.36-27), Section B.2.3.1 (CS Figure 6, p. 34), CS Section B.2.4.1 (p.39-40), CS Section B.2.5 (p.43-44),[1] updated CS provided by company[25] and the company response to the clarification letter *TTLR, HRQOL and Adverse events were added post-clarification letter [a] It is unclear from the CS what "problems" were reported on the EQ-5D-3L. Abbreviations: AJCC = American Joint Committee on Cancer; BICR = blinded independent central review; CS = company submission; EFS = event-free survival; IA = interim analysis; NSCLC = non-small cell lung cancer; OS = overall survival; pCR = pathologic complete response; PDC = platinum doublet chemotherapy; RECIST = Response Evaluation Criteria in Solid Tumours; TTDM = time to distant metastasis; UICC = Union for International Cancer Control; USA = United States of America	

The company submission notes that the original trial design also included an arm with nivolumab + ipilimumab, which was stopped in a protocol revision (CS Section B.2.3.1, p.34).[1] This decision was reached based on evidence from the metastatic setting, a more promising benefit from external data from the NADIM trial,[26] as well as less favourable results for nivolumab and ipilimumab in the NEOSTAR trial.[27] The nivolumab plus ipilimumab arm is therefore not considered within the company submission.[1]

Quality assessment of the CheckMate-816 trial as reported by the CS is presented in Table 3.4 (Section B.2.5, Table 10, p.44). The company noted that the quality assessment had been updated from the SLR and was based on the full Forde *et al.,* 2022 publication.[21]

Table 3.4: Quality assessment of CheckMate-816 according to CS

Question	Assessment
Was randomisation carried out appropriately?	Yes
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 participants 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?	No

Question	Assessment
Was randomisation carried out appropriately?	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?	Unclear – current SOC in England is surgery alone or adjuvant platinum-based chemotherapy rather than neoadjuvant chemotherapy.
Source: CS Section B.2.5 (Table 10, p.44)[1] Abbreviations: CS = company submission; RCT = Randomised controlled trial; SOC = standard of care	

EAG Comment: The nivolumab + PDC arm of CheckMate-816 was added to the trial later than the nivolumab + ipilimumab and the PDC alone arm. The EAG asked the company to comment on whether the addition of the nivolumab + PDC arm in their revised protocol added bias with the respect to the randomisation procedure or any other trial methods used (points for clarification, question A14).[15] The company stated that the decision to add the nivolumab + PDC arm came in light of promising results from the KEYNOTE-021 trial (in metastatic NSCLC) and in the NADIM study (in resectable NSCLC); Bristol Myers Squibb were blinded to the results and allocation of CheckMate-816 during this process.[26] The company stated in the points for clarification that the analyses presented in the submission and associated publications focused on the participant population randomised at the same time in the nivolumab + PDC and PDC alone arms.[15] The 34 participants randomised to the PDC alone arm before the opening of the nivolumab + PDC arm are not included in these analyses to ensure the analyses were not impacted by the late addition of the nivolumab + PDC arm to CheckMate-816.[15] In the EAG's opinion, this is an acceptable approach to adding the nivolumab + PDC arm that minimises bias.

CheckMate-816 did not recruit any participants from the UK. This poses an issue for the applicability of the participants and, therefore, the results of the trial. In their quality assessment, the company note that the study may not reflect routine clinical practice in the UK, as the current standard of care in the UK is surgery alone or adjuvant PDC, as opposed to neoadjuvant chemotherapy (see Table 3.4 above). Issues surrounding generalisability of the participants to the UK population is explored in further depth in EAG Report Section 3.2.3.

The company explain what they consider to be "resectable" in the context of CheckMate-816 as tumours that are ≥ 4 cm or node positive (CS Section B.1.1).[1] The company also acknowledge that resectability status can change over time. CheckMate-816 used the seventh edition of the AJCC/UICC staging system instead of the more recent eighth edition, though this is likely due to when the study commenced.[3,4] Participants were not reclassified into the AJCC/UICC eighth edition; the company note that there may be some differences in how the participants may have been classified had they been reassessed using the eighth edition.[1] However, the impact that this restaging may have had on the overall results of CheckMate-816 is unknown, as it is not possible to know how many of the participants would have been restaged.

In CS Appendix N (p.231) it was noted by a consultant in medical oncology and a lead respiratory clinician, both from large centres in England, in discussion with the company, that there is limited taxane use in UK clinical practice because it "makes patients sick".[6] According to CS Appendix N, this includes the use of cisplatin-docetaxel and carboplatin-paclitaxel, two of the PDC regimens used within

the CheckMate-816 study. By contrast, the clinicians noted in CS Appendix N that platinum + either vinorelbine or gemcitabine would be more common, with vinorelbine more often used in conjunction with platinum.[6] Clinical advice provided to the EAG confirmed that cisplatin + vinorelbine is likely the most common PDC in use within the UK. However, this PDC regimen was only given as part of the PDC alone arm of CheckMate-816 and not as part of the nivolumab + PDC arm. Additionally, clinical advice provided to the EAG suggested that cisplatin + docetaxel, another of the combinations used only in the PDC alone arm of CheckMate-816, would rarely be used within UK clinical practice. The combinations of cisplatin-based PDC given in both arms of CheckMate-816 (cisplatin + gemcitabine and cisplatin + pemetrexed) were confirmed by clinical advice to the EAG to be in use within the UK but as minor regimens or only used in some centres. It is therefore difficult to judge whether the PDC regimens used within either arm of CheckMate-816 were applicable to UK clinical practice. Clinical advice to the EAG suggested there were not known large differences in effectiveness across cisplatin-based regimens.

As reported in Section 2.4 above, the outcome measures presented within CheckMate-816 do not completely match with the NICE scope; a full critique of these differences can be found in EAG Report Section 2.4. The EAG asked the company to clarify the outcome measures used within CheckMate-816 as presented within the Table 7 of the CS (Section B.2.3.1, pp.36-27).[1] The company stated in the points for clarification (questions A15 and A17b) that TTLR, HRQOL (assessed using EQ-3D-5L) and adverse events were other outcomes used in the economic model.[15] These were subsequently added to Table 7 in the updated CS.[25]

In terms of the quality assessment of CheckMate-816, the method of randomisation to the study seems reasonable and appropriate stratification factors were considered. CheckMate-816 was an open-label study, which leaves the study open to potential bias due to lack of blinding of participants and personnel.[18] However, Bristol Myers Squibb were blinded to aggregated safety and efficacy data by treatment assignment, potentially limiting bias due to company involvement (CS Section B.2.5, p.43).[1]

3.2.2 Statistical approach adopted for the analysis of CheckMate-816 study data

A summary of the statistical approach taken by the company for analyses within CheckMate-816 are presented in Table 9 within the CS (Section B.2.4.1, p. 41-42).[1] To adjust for sequential analyses the company used the O'Brien-Fleming alpha-spending function. This involves using more stringent p-values for interim analyses (for OS) and more lenient ones for later analyses. Initial analyses were planned to be conducted at approximately 30 months for the pathological complete response (pCR) outcome, followed by further interim analyses at approximately 48 months (after 148 EFS events and/or 101 OS events). Results reported in the CS are from the ~48-month interim analyses (first interim analysis of EFS).[1]. [redacted]. The company refers to the second interim analysis of EFS a maximum of 1 year after the 48-month analysis as 'EFS interim analysis 2'.

EAG Comment: The company analyses use standard methods and were consistent with pre-specified statistical analysis plans. However, fewer OS events than expected had occurred and therefore the OS data is relatively immature and did not cross the boundary of statistical significance.

3.2.3 CheckMate-816 eligibility criteria and baseline characteristics including treatments received

A summary of the CheckMate-816 baseline characteristics and eligibility criteria are detailed in Table 3.5 and Table 3.6.

Table 3.5: Key population eligibility criteria for CheckMate-816

Inclusion	Exclusion
Males and females aged ≥ 18 years	Participants who have received prior chemotherapy or any other cancer therapy for resectable NSCLC
Histologically confirmed, resectable, stage IB (≥ 4 cm), stage II, or stage IIIA NSCLC (according to AJCC/UICC seventh edition) confirmed by PET/CT with contrast	Participants with distant active brain metastases
If the CT component of the PET/CT is of insufficient diagnostic quality for RECIST 1.1 measurements, an additional CT with contrast of the chest, abdomen, and other suspected areas of disease will be performed	Patients with an active, known or suspected autoimmune disease
Lung function capacity capable of tolerating the proposed lung surgery	Known EGFR mutations or ALK translocations
ECOG performance status of 0-1	
Tissue from the primary lung tumour to be available for PD-L1 immunohistochemistry testing	

Source: CS Table 7 (Section B.2.3.1, p.36)[1]

Abbreviations: AJCC = American Joint Committee on Cancer; ALK = anaplastic lymphoma kinase; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; NSCLC = non-small-cell lung cancer; PD-L1 = programmed death-ligand 1; PET = positron emission tomography; RECIST = Response Evaluation Criteria in Solid Tumours; UICC = Union for International Cancer Control

Table 3.6: Baseline characteristics of participants in CheckMate-816

Characteristic	Population	
	Nivolumab + PDC (n = 176)*	PDC alone (n = 176)*
Age (years), median (range)	64 (41-82)	65 (34-84)
Female, %	51 (28.5)	52 (29.1)
Region, n (%)		
North America	41 (22.9)	50 (27.9)
Europe	41 (22.9)	25 (14.0)
Asia	85 (47.5)	92 (51.4)
Rest of the world[a]	12 (6.7)	12 (6.7)
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
ECOG PS, n (%)[b]		
0	124 (69.3)	117 (65.4)
1	55 (30.7)	62 (34.6)
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Baseline weight, median (range) [kg]	68.1 (40.4-147.9)	67.2 (35.7-114.6)
Smoking status, n (%)[d]		
Never smoker	19 (10.6)	20 (11.2)
Current/former smoker	160 (89.4)	158 (88.3)
Histology, n (%)		
Squamous	87 (48.6)	95 (53.1)
Nonsquamous	92 (51.4)	84 (46.9)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Tumour PD-L1 expression, %[e]		
< 1 %	78 (43.6)	77 (43.0)
≥ 1 %	89 (49.7)	89 (49.7)
1% to 49%	51 (28.5)	47 (26.3)
≥ 50%	38 (21.2)	42 (23.5)
Not evaluable	12 (6.7)	13 (7.3)
TMB, n (%)[f]		
≥ 12.3 mut/MB	39 (21.8)	37 (20.7)
< 12.3 mut/MB	49 (27.4)	53 (29.6)

Not evaluable or reported[f]	91 (50.8)	89 (49.7)
Type of platinum therapy, n (%)[g]		
Cisplatin	124 (69.3)	134 (74.9)
Carboplatin	39 (21.8)	33 (18.4)

Source: CS Table 8 (Section B.2.3.2, p.38-39)[1] and [redacted] updated CS supplied by the company[25]

[a] CS states that this category contains only Argentina and Turkey

[b] CS states ECOG PS scores range from 0-5, higher scores indicate greater disability

[c] CS states that data for disease stage are from case report forms, with TNM Classification of Malignant Tumours, seventh edition, used for classification. The CS footnotes to Table 8 also note that 1 participant in the PDC alone group had stage IA disease and 1 participant in each group had stage IV disease.

[d] CS notes that 1 participant in the PDC alone group had an unknown smoking status

e CS notes that the percentages are based on primary analysis population. States that the status of PD-L1 expression was determined with the use of the PD-L1 immunohistochemistry 28-8 pharmDx assay (Dako); participants with tumour tissue that could not be assessed for PD-L1 expression (≤ 10% of all the participants who underwent randomisation) were stratified to the subgroup with a PD-L1 expression level of less than 1% at randomisation.

[f] CS states that TMB was not analysed in participants from China; as such, these participants are included in the 'not reported' category

[g] The numbers of participants receiving carboplatin-based or cisplatin-based PDC within the characteristics table of the CS do not total 176. It is unclear why there is a discrepancy in the numbers presented.

*In the company response to the clarification letter, the company state 179 in each arm, rather than 176. The results tables are based on 179 patients.

Abbreviations: CS = company submission; ECOG PS = Eastern Cooperative Oncology Group performance status; mut/MB = mutations per megabase; PDC = platinum doublet chemotherapy; PD-L1 = programmed death-ligand 1; TMB = tumour mutational burden

EAG Comment: Overall, the distribution of characteristics between the nivolumab + PDC and PDC alone arms was generally balanced. However, there are questions surrounding the generalisability of the participants within CheckMate-816 to English clinical practice.

According to the CheckMate-816 Clinical Study Report,[28] 63.1% of participants in the nivolumab + PDC arm and 64.2% of participants in the PDC alone arm had newly-diagnosed Stage IIIA NSCLC. However, data presented by Cancer Research UK regarding the proportion of cancer cases by stage at diagnosis in 2019 in England suggest that only 18.5% of lung cancer incidences are diagnosed at Stage III.[29] The data presented by Cancer Research UK also suggests that 19.3% of lung cancer diagnoses occur at Stage I, with the majority (42.4%) diagnosed at Stage IV.[29] This suggests that the number of people newly-diagnosed with Stage IIIA resectable NSCLC in CheckMate-816 may not be representative of diagnoses of lung cancer within England.

We asked the company to provide data surrounding the ethnicity of the participants included within CheckMate-816, as this was not presented within the original CS (points for clarification question A17c). The company provided this data in the PfC, which [redacted]. This potentially poses an issue for generalisability of the CheckMate-816 results. Analysis from data from Public Health England between 2013-2017 has shown that 92% of people who develop lung cancer in England are white.[30] Though the data presented in Delon *et al*., 2022 does not discriminate between small cell lung cancer and NSCLC,[30] it does suggest the balance between ethnic groups in CheckMate-816 may not be representative of lung

cancer incidence in England. The potential impact of this on the overall results is further explored in Section 3.2.8 (Subgroup analyses).

Additionally, more participants in CheckMate-816 received cisplatin-based chemotherapy compared with carboplatin-based PDC (69.3% in the nivolumab + PDC arm compared with 74.9% in the PDC alone arm). As reported in Section 3.2.1 of the EAG report, Appendix N of the CS (p.231) notes that PDC with a taxane is currently limited, included the use of carboplatin + paclitaxel.[6] However, clinical advice to the EAG noted that cisplatin-based PDC, particularly cisplatin + vinorelbine, would be the most commonly used PDC regimen in the UK. It is unclear what cisplatin-based PDC regimen was utilised most in each arm of CheckMate-816 so how comparable the regimens used within CheckMate-816 are to English clinical practice is unknown.

3.2.4 CheckMate-816 treatment summary, subsequent therapies and surgical data

Section B.2.6.1.1 (p.45-46) of the CS summarises the treatment received by participants in CheckMate-816 and subsequent therapies, which is summarised here in Table 3.6.[1] The CS states that 98.3% of participants in each arm of the study received neoadjuvant treatment, with 165 (93.8%) in the nivolumab + PDC arm and 149 (84.7%) in the PDC arm completing 3 cycles of treatment.[1]

Subsequent therapies were defined by the CS as therapy started on or after the first dosing date outside the protocol-specified adjuvant therapy; participants could receive more than 1 subsequent therapy (Section B.2.6.1.1, footnotes to Table 12).[1] Subsequent treatments were received by 38 (21.2%) of participants in the nivolumab + PDC arm and 78 (43.6%) in the PDC alone arm.[1]

Section B.2.6.1.4 (p.54-56) details the surgical outcomes for CheckMate-816; in total, 149 (83.2%) of participants in the nivolumab + PDC arm and 135 (75.4%) of participants in the PDC alone arm underwent definitive surgery.[1] In the nivolumab + PDC arm, 28 (15.6%) of participants had definitive surgery cancelled, compared with 37 (20.7%) in the PDC alone arm.[1]

Table 3.7 summarises the treatments received by participants in CheckMate-816, Table 3.8 summarises subsequent therapies and Table 3.9 summarises surgical data according to the CS.[1]

Table 3.7: Treatment summary for CheckMate-816

Treatment and exposure	Nivolumab +PDC (n = 179)	PDC (n = 179)
Participants receiving neoadjuvant treatment, n (%)	176 (98.3)	176 (98.3)
Reason off neoadjuvant treatment, n (%)[a]		
Completed (3 cycles)	165 (93.8)	149 (84.7)
Study drug toxicity	10 (5.7)	12 (6.8)
Disease progression	1 (0.6)	2 (1.1)
Other[b]	0	13 (7.4)
Participants receiving adjuvant treatment, n (%)[a]	35 (19.9)	56 (31.8)
Chemotherapy (≤ 4 cycles) alone	21 (11.9)	39 (22.2)
Radiotherapy alone	9 (5.1)	12 (6.8)
Chemotherapy and radiotherapy	5 (2.8)	5 (2.8)

Source: CS Table 11 (Section B.2.6.11, p.45)[1]

[a] CS states denominator based on participants receiving neoadjuvant treatment.

[b] CS states reasons were adverse event unrelated to study drug in 3 participants, participant request to discontinue study treatment in 5 participants, participant withdrew consent in 4 participants, and participant no longer met study criteria in 1 participant.

Abbreviations: PDC = platinum doublet chemotherapy

Table 3.8: Subsequent therapies received by participants in CheckMate-816

	Nivolumab + PDC (n = 179)	PDC (n = 179)
Any	38 (21.2)	78 (43.6)
Radiotherapy	20 (11.2)	38 (21.2)
Surgery[a]	3 (1.7)	6 (3.4)
Systemic therapy	31 (17.3)	65 (36.3)
Chemotherapy	27 (15.1)	40 (22.3)
Targeted therapy	13 (7.3)	21 (11.7)
Immuno-oncology therapy	10 (5.6)	42 (23.5)
Pembrolizumab	4 (2.2)	22 (12.3)
Nivolumab	2 (1.1)	8 (4.5)
Atezolizumab	2 (1.1)	8 (4.5)
Durvalumab	2 (1.1)	6 (3.4)
Toripalimab	0	1 (0.6)
Sintilimab	0	1 (0.6)

Source: CS Table 12 (Section B.2.6.1.1, p.46)[1]

[a] CS states this was any subsequent anticancer (non-small cell lung cancer) surgery. Most were for palliative reasons or in participants with oligo-metastatic disease; some participants underwent subsequent surgery for the primary tumour.

Abbreviations: PDC = platinum doublet chemotherapy

Table 3.9: Surgical outcomes for participants in CheckMate-816

	NIVO+PDC (n = 179)	PDC (n = 179)
Participants with definitive surgery,[a] n (%)	149 (83.2)	135 (75.4)
Time from last neoadjuvant dose to definitive surgery, median weeks (IQR)	5.3 (4.6-6.0)	5.0 (4.6-5.9)
Participants with cancelled definitive surgery, n (%)	28 (15.6)	37 (20.7)
Disease progression	12 (6.7)	17 (9.5)
Adverse event	2 (1.1)	1 (0.6)
Other[b]	14 (7.8)	19 (10.6)
Participants with delayed surgery,[c,d] n (%)	31 (20.8)	24 (17.8)
Administrative reason	17 (11.4)	8 (5.9)
Adverse event	6 (4.0)	9 (6.7)
Other	8 (5.4)	7 (5.2)
Median length of delay in surgery, weeks (IQR)	2.0 (0.6-3.0)	2.4 (1.0-3.7)
Of participants with delayed surgery, proportion with delay of,[e] n (%)		
≤ 2 weeks	17 (54.8)	11 (45.8)
> 2 and ≤ 4 weeks	8 (25.8)	8 (33.3)
> 4 and ≤ 6 weeks	3 (9.7)	2 (8.3)
> 6 weeks	3 (9.7)	3 (12.5)
Median duration of surgery,[f] minutes (IQR)	185.0 (133.0-260.0)	213.5 (150.0-283.0)
Surgical approach,[d] n (%)		
Thoracotomy	88 (59.1)	85 (63.0)
Minimally invasive[g]	44 (29.5)	29 (21.5)
Minimally invasive to thoracotomy	17 (11.4)	21 (15.6)
Type of surgery,[d,h] n (%)		
Lobectomy	115 (77.2)	82 (60.7)
Sleeve lobectomy	2 (1.3)	10 (7.4)
Bilobectomy	3 (2.0)	4 (3.0)
Pneumonectomy	25 (16.8)	34 (25.2)
Other	24 (16.1)	21 (15.6)
Completeness of resection,[d] n (%)		
R0 (no residual tumour)	124 (83.2)	105 (77.8)
R1 (microscopic residual tumour)	16 (10.7)	21 (15.6)
R2 (macroscopic residual tumour)	5 (3.4)	4 (3.0)
Rx (unknown)	4 (2.7)	5 (3.7)
Median no. of sampled lymph nodes (IQR)	19 (12-25)	18.5 (10-26)
Median length of hospital stay, days (IQR)	10.0 (7.0-14.0)	10.0 (7.0-15.0)
Median length of hospital stay by surgery type, days (IQR)		
Lobectomy	10.0 (7.0-15.0)	9.0 (6.0-14.0)
Pneumonectomy	10.0 (8.0-13.0)	11.0 (9.0-16.0)

	NIVO+PDC (n = 179)	PDC (n = 179)
Other[i]	8.5 (4.0-13.0)	9.0 (7.0-14.0)
Median length of hospital stay by region, days (IQR)		
North America	4.0 (4.0-7.0)	6.0 (4.0-8.0)
Europe	9.5 (8.0-14.0)	13.0 (7.0-18.0)
Asia	11.0 (9.0-16.0)	13.0 (10.0-16.0)

Source: CS Table 16 (Section B.2.6.1.4, p.55-56)[1]

[a] CS states definitive surgery was not reported in 2 participants in the nivolumab +PDC group and 7 in the PDC group.

[b] In CS, PDC states other reasons were participant refusal in 9 participants in the nivolumab +PDC arm and 8 participants in the PDC arm; consent withdrawal in 3 participants in the PDC arm; COVID-19 in 1 participant in the PDC arm; unfit for surgery due to poor lung function in 2 participants in the nivolumab +PDC arm and 4 participants in the PDC arm; and unresectability in 2 participants in each arm.

[c] CS states time from last dose to neoadjuvant surgery > 6 weeks.

[d] CS states denominator based on participants with definitive surgery (n = 149 in the nivolumab +PDC group; n = 135 in the PDC group).

[e] CS states denominator based on participants with delayed surgery.

[f] CS states with reported duration of surgery: nivolumab +PDC, 122; PDC, 121.

[g] CS states thoracoscopic/robotic.

[h] CS states participants may have had more than 1 surgery type.

[i] CS states this includes bilobectomy, sleeve lobectomy, and other.

Abbreviations: NIVO+PDC = nivolumab + platinum doublet chemotherapy; PDC = platinum doublet chemotherapy

EAG Comment: Most participants in CheckMate-816 (59.1% in the nivolumab + PDC arm and 63% in the PDC alone arm) underwent thoracotomy, with only 29.5% of participants in the nivolumab + PDC arm and 21.5% in the PDC alone arm undergoing minimally invasive procedures. As already noted, clinical advice to the EAG suggested that minimally invasive approaches now accounted for over 50% of cases within the UK. This is corroborated by a 2017 audit of lung cancer clinical outcomes in the UK stated that lung cancer surgeries using minimal-access approaches were the most common procedures, particularly video-assisted thoracic surgeries, which accounted for 55.8% of resections.[31]

The clinical advisor to the EAG also stated that pneumonectomy is now very uncommon. The 2017 audit of lung cancer clinical outcomes in the UK noted that pneumonectomy comprised only 3.5% of all resections, with 77% of resections being lobectomies or bilobectomies.[31] The lobectomy rate in the nivolumab + PDC arm of CheckMate-816 (77.2%) seems consistent with the rate of lobectomies in the UK, though in the PDC alone arm the rate of lobectomy is much lower than the UK average (60.7%). Additionally, the rates of pneumonectomy in CheckMate-816 are far higher than what is currently performed in the UK (16.8% in the nivolumab + PDC arm and 25.2% in the PDC alone arm). While the higher rate of lobectomy in the nivolumab + PDC arm may be due to increased response rates allowing for less intensive surgery, as highlighted by the clinical advice to the EAG, the rate of pneumonectomy in CheckMate-816 does not appear representative of UK practice.

In the nivolumab + PDC arm, 19.9% of participants received adjuvant treatment, compared with 31.8% of participants in the PDC alone arm. However, as stated by clinical advisors to the company in Appendix N of the CS (p. 225), it is unlikely that participants in England would receive both neoadjuvant and adjuvant chemotherapy for NSCLC. This was confirmed by clinical advice to the EAG. It is therefore unclear whether the results for the participants who received both neoadjuvant and

adjuvant chemotherapy are representative of resectable NSCLC participants in the UK, as data for these participants are included within the CheckMate-816 analyses.

In the nivolumab + PDC arm, 21.2% of participants had some form of subsequent therapy that did not include adjuvant therapy, compared with 43.6% in the PDC alone arm. In addition, the footnotes of CS Table 16 noted that participants may have undergone more than one surgery type. We asked the company to clarify how many participants underwent more than one type of surgery and what this consisted of; in the points for clarification, they responded to say that these data were currently unavailable but has been requested (question A19b).[15] It is difficult for the EAG to comment on the potential impact of participants receiving more than one surgery or on the rate of non-adjuvant therapies on the overall results of CheckMate-816.

In the participant representative submission received by NICE, there were concerns that undergoing neoadjuvant therapy may lead to participants having surgical resection cancelled or delayed.[32] In CheckMate-816, 15.6% of participants in the nivolumab + PDC arm and 20.7% of participants in the PDC alone arm had their definitive surgery cancelled; reasons were mostly due to disease progression and, in a small minority of participants, adverse events. In light of the concerns of the participant submission, it is possible that a number of people with lung cancer will have their surgery cancelled, though the risk of this seems slightly lower for those undergoing nivolumab + PDC. In the nivolumab + PDC arm, 20.8% of participants had their resection delayed, compared with 17.8% of participants in the PDC alone arm. 5.4% in the nivolumab + PDC arm and 5.2% in the PDC alone arm had their surgery delayed for "Other" reasons that were not explained in the CS (points for clarification question A19a). The EAG asked the company to clarify these "Other" reasons but the company did not provide this information, instead repeating the "Other" reasons for cancelled surgery.[15]

In Appendix N of the CS (p.229), attendees at a virtual meeting with UK clinical experts suggested that the length of stay in CheckMate-816 was "about 3-times the length they would expect in the UK". However, this difference may be due to differences in health systems and practice across the international setting of CheckMate-816.[6] Clinical advice provided to the EAG stated that participants could expect a length of stay of 2 to 4 days in the UK if their surgery was minimally-invasive, while median length of stay in the UK in 2017 was estimated to be 6 days.[31]

Clinical advice to the EAG suggested that the subsequent therapies received by the participants in CheckMate-816 seemed similar to what would be expected in English clinical practice.

3.2.5 CheckMate-816 efficacy

The evidence presented by the company is derived from the CheckMate-816 trial using the results from the first database lock for EFS on 20 October 2021 (minimum follow-up 21 months, median follow-up 29.5 months), when 148 EFS had occurred, alongside results from the final analysis of pCR (database lock 16 September 2020) (CS Section B2.4.1, p. 39; Section B.2.6.1, p.44).[1,21]

[redacted]. Table 3.10 presents the efficacy results in CheckMate-816 as presented by the CS.[1]

Table 3.10: Summary of efficacy results for CheckMate-816

Outcome and measure	Nivolumab + PDC (n = 179)	PDC alone (n = 179)

pCR (by BIPR)				
Subjects with events, n (%) 95% CI	43 (24) 18.0%-31.0%		4 (2.2) 0.6%-5.6%	
OR 99% CI P value	13.94 3.49-55.75 < 0.001			
EFS (by BICR)				
Median EFS (95% CI)	31.6 (30.2-NR)		20.8 (14.0-26.7)	
HR for disease progression 97.38% CI P value	0.63 0.43-0.91 0.0052			
Censored at database lock (Interim analysis 1- 20 October 2021), n (%)	115 (64.2)		92 (51.4)	
1-year EFS (%)	76.1		63.4	
2-year EFS (%)	63.8		45.3	
EFS2				
Events, n (%)				
Median EFS2, mo 95% CI	NR NR-NR		NR NR-NR	
HR 95% CI P value	0.54 0.37-0.80 NR			
EFS according to pathologic complete response status				
	pCR (n = 43)	No pCR (n = 136)	pCR (n = 4)	No pCR (n = 175)
Median EFS, months 95% CI	NR 30.6-NR	26.6 16.6-NR	NR NR-NR	18.4 13.9-26.2
HR 95% CI	0.13 0.05-0.37		Not computeda	
OS (Interim analysis 1- 20 October 2021)				
HR for death 99.67% CI P value	0.57 0.30-1.07 0.008			
[redacted]				
[redacted]	[redacted]		[redacted]	
[redacted]	[redacted]			
MPR (by BIPR)				
Participants with MPR, (%)	36.9		8.9	
OR 95% CI P value	5.70 3.16-10.26 NR			
Time to death or distant metastases (by BICR)				
Median TTDM (months)	NR		NR	

95% CI	36.6-NR	22.4-NR
HR 95% CI P value	0.53 0.36-0.77 NR	
Clinical response rates (by BICR)		
Objective response rate [d], n (%) 95% CI	96 (53.6) 46.0-61.1	67 (37.4) 30.3-45.0
Best overall response		
Complete response, n (%)	1 (0.6)	3 (1.7)
Partial response, n (%)	95 (53.1)	64 (35.8)
Stable disease, n (%)	70 (39.1)	88 (49.2)
Progressive disease, n (%)	8 (4.5)	11 (6.1)
Not evaluable, n (%)	1 (0.6)	1 (0.6)
Not reported, n (%)	4 (2.2)	12 (6.7)

Source: CS;[1] [redacted]

[a] Footnotes to CS Figure 13 note that HR was not computed for the chemotherapy arm because only four participants had a pCR

[redacted]

[d] Objective response rate per blinded independent central review was defined as a complete or partial response from baseline to the presurgery scan per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1

Abbreviations: BICR = blinded independent central review; BIPR = blinded independent pathologic review; CI = confidence interval; EFS = event free survival; HR = hazard ratio; MPR = major pathologic response; NR = not reached; OR = odds ratio; pCR = pathologic complete response; PDC = platinum doublet chemotherapy

Incidence of radiographic downstaging (defined as reduction of disease stage from baseline) is reported in CS Section B.2.6.1.4 (Table 15, p.51) and presented in Table 3.11.[1] The company reported that incidence of radiographic downstaging occurred in 30.7% of participants in the nivolumab + PDC group compared with 23.5% in the PDC alone group.[1]

Table 3.11: Incidence of radiographic downstaging before and after treatment by stage of disease in CheckMate-816

	No. of participants (%)			
	Nivolumab + PDC (n = 179)		PDC (n = 179)	
Stage	Disease stage at study entry	Disease stage after neoadjuvant treatment	Disease stage at study entry	Disease stage after neoadjuvant treatment
0	0	2 (1.1)	0	2 (1.1)
IA	0	23 (12.8)	1 (0.6)	13 (7.3)
IB	10 (5.6)	14 (7.8)	8 (4.5)	23 (12.8)
IIA	30 (16.8)	29 (16.2)	32 (17.9)	20 (11.2)
IIB	25 (14.0)	15 (8.4)	22 (12.3)	12 (6.7)
IIIA	113 (63.1)	81 (45.3)	115 (64.2)	87 (48.6)

Stage	No. of participants (%)			
	Nivolumab + PDC (n = 179)		PDC (n = 179)	
	Disease stage at study entry	Disease stage after neoadjuvant treatment	Disease stage at study entry	Disease stage after neoadjuvant treatment
IIIB	0	3 (1.7)	0	6 (3.4)
IV	1 (0.6)	7 (3.9)	1 (0.6)	5 (2.8)
Not reported	0	5 (2.8)	0	11 (6.1)

Source: CS (Section B.2.6.1.4, Table 15, p.51)[1]
Abbreviations: PDC = platinum doublet chemotherapy

EAG Comment: In general, when assessed as a whole cohort, nivolumab + PDC seems effective in people with Stage IB-IIIA resectable NSCLC. Those undertaking nivolumab + PDC are more likely to demonstrate higher odds of pCR (OR 13.94, 99% CI 3.49-55.75, P < 0.001), longer EFS (HR 0.63, 97.38% CI 0.43-0.91, P = 0.0052), and have better chance of OS (HR for death 0.57, 99.67% CI 0.30-1.07, P = 0.008).

We asked the company to provide follow-up time for each arm within the PfCs (question A18); the company stated that these data were not yet available by treatment arm but can be shared once available.[15] If there is an imbalance between the length of follow-up between the two arms, this may potentially present a bias in the results, as the arm with reduced average follow-up had less time to experience events. However, it is not possible to comment without the information provided.

The EAG has further concerns surrounding the efficacy of nivolumab + PDC in subgroups that may be of more relevance to the UK population; this is explored in more depth in EAG Report Section 3.2.8 below (Subgroup analyses).

3.2.6 Participant-reported outcomes in CheckMate-816

HRQOL in the CheckMate-816 study was measured using the EQ-5D-3L during the neoadjuvant period (weeks 3 and 7, and post-neoadjuvant visit 1).[1] The assessment measured an EQ-5D VAS (range 0 to 100) and utility index (UI, range -0.594 to 1), with higher scores reflecting better HRQOL. Completion rates were > 80% in both the nivolumab + PDC arm and the PDC alone arm. Table 3.12 presents the ED-5D VAS and utility scores for HRQOL in CheckMate-816 as presented by the CS.[1]

Table 3.12: EQ-5D-3L in the neoadjuvant period of CheckMate-816

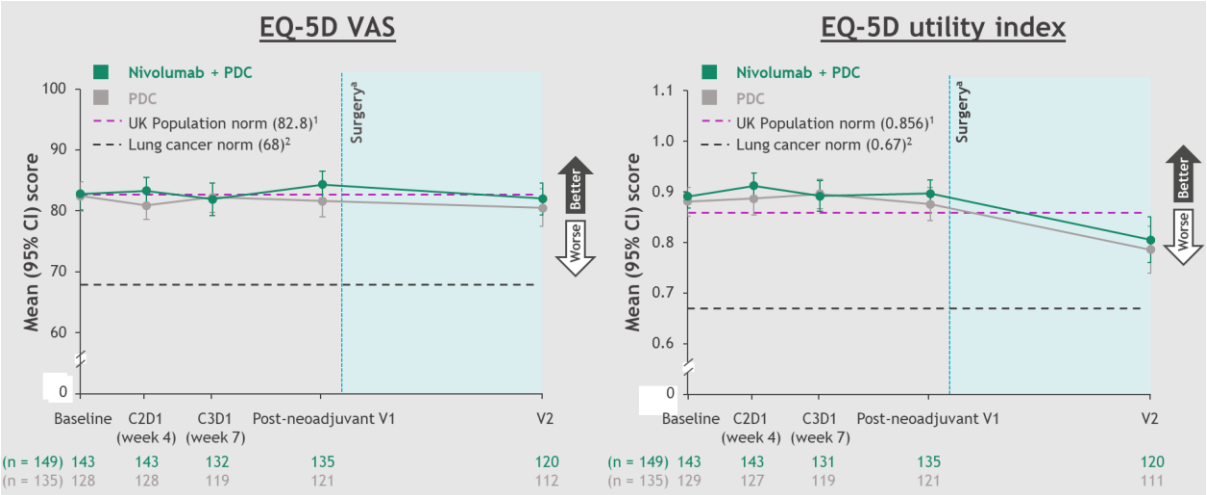
VAS; MID = 7	**LSM change from baseline-(95% CI)**		**LSM difference-(95% CI)**
	Nivolumab + PDC	**PDC**	**Nivolumab + PDC vs. PDC**
Overall	−0.9 (-2.4, 0.7)*	−1.5 (-3.1, 0.1)	0.6 (-1.5, 2.7)
Week 4	−0.4 (-2.1, 1.4)	−1.7 (-3.5, 0.1)	1.3 (-1.0, 3.7)
Week 7	−1.3 (-3.2, 0.6)	−0.8 (-2.7, 1.2)	−0.6 (-3.2, 2.0)
Post-neoadjuvant visit 1	−0.8 (-2.9, 1.2)	−2.0 (-4.1, 0.2)	1.1 (-1.7, 3.9)
UI; MID = 0.08			
Overall	−0.003 (-0.024, 0.019)	−0.011 (-0.033, 0.011)	0.008 (-0.020, 0.036)

VAS; MID = 7	LSM change from baseline-(95% CI)		LSM difference-(95% CI)
	Nivolumab + PDC	PDC	Nivolumab + PDC vs. PDC
Week 4	0.012 (-0.011, 0.036)	0.001 (-0.023, 0.025)	0.011 (-0.021, 0.043)
Week 7	−0.006 (-0.033, 0.021)	−0.004 (-0.031, 0.023)	−0.002 (-0.038, 0.034)
Post-neoadjuvant visit 1	−0.014 (-0.043, 0.015)	−0.029 (-0.059, 0.001)	0.015 (-0.025, 0.056)

Source: CS (Section B.2.6.1.4, Table 17, p.56-57)[1]
*The company reported this as '−0.9 to 2.4, 0.7'. The EAG believes this was an error.
Abbreviations: CI = confidence interval; CS = company submission; LSM = least squares mean; MID = minimally important difference; PDC = platinum doublet chemotherapy; UI = utility index; VAS = visual analogue scale

We asked the company why only data for the post-neoadjuvant visit was presented in the CS and not data for post-resection (points for clarification question A21).[15] They confirmed that post-surgical HRQOL scores were measured but were not available at the time of submission. However, the company provided the post-resection data in the points for clarification; this is presented in Figure 3.1. The analysis provided by the company in the points for clarification focused on the neoadjuvant period, post-neoadjuvant visit 1 (mainly pre-surgery) and post-neoadjuvant visit 2 (mainly post-surgery). The company confirmed that further analysis and reporting of all remaining time-points will be reported at a later time.[15]

Figure 3.1: EQ-5D VAS and utility index scores during the neoadjuvant period and post-surgery: participants who received surgery



Source: PfC Figure 3 (p.24)[15]
Abbreviations: CI = confidence interval; PDC = platinum doublet chemotherapy; VAS = visual analogue scale

EAG Comment: Although not explicitly stated in the report, the EAG assumes that the utilities of the EQ-5D were generated using the algorithm from Dolan (1997; see also EAG Report Table 4.5).[33] The completion rate of the EQ-5D-3L was > 80% in both arms of the study. We asked the company to provide the completion rates by arm (points for clarification question A20).[15] In the PfC, the company

confirmed that, at the second post-neoadjuvant visit, the completion rate was 84% in both the nivolumab + PDC and PDC alone arms. The non-completion rate seems balanced and generally low between arms.[15] As such, the EAG has no concerns surrounding completion rates of the EQ-5D-3L.

There was no clinically significant difference between nivolumab + PDC versus PDC alone for either the VAS or the utility index at the time-points presented in the original CS. At post-neoadjuvant visit 2, as provided by the company in the points for clarification (question A21), both arms of the study appear to report a decrease in both the VAS and utility index but the mean scores appear similar.[15] The decrease in HRQOL seems unsurprising given the nature of resection for NSCLC. It is therefore not possible to say that nivolumab + PDC infers any meaningful benefit to HRQOL compared with PDC alone.

3.2.7 Adverse events in CheckMate-816

Adverse events (AEs) recorded in CheckMate-816 were reported in CS Section B.2.10.[1] Table 3.13 summarises the number of AEs that occurred in each arm of the study, as reported by the CS.[1] The company state that no new safety signals were observed during CheckMate-816 (Section B.2.10, p.68).[1]

In general, 145 (82.4%) of participants in the nivolumab + PDC group and 156 (88.6%) of participants in the PDC alone group experienced treatment-related AEs. The number of participants experiencing Grade 3 or 4 treatment-related AEs was 59 (33.5%) in the nivolumab + PDC group and 65 (36.9%) in the PDC alone group. Treatment-related AEs leading to discontinuation of treatment was experienced by 18 participants (10.2%) in the nivolumab + PDC group and 17 (9.7%) in the PDC alone group. Serious treatment-related AEs were experienced by 21 participants (11.9%) in the nivolumab + PDC group and 18 participants (10.2%) in the PDC alone group. Treatment-related death occurred in 3 participants (1.7%) in the PDC alone group; no treatment-related deaths were recorded in the nivolumab + PDC group.

Footnotes to CS Section B.2.10, Table 19 (p.68) note that Grade 5 surgery-related AEs (defined as events leading to death ≤ 24 hours after the onset of an AE) were reported in 2 participants in the nivolumab + PDC group (1 each due to pulmonary embolism and aortic rupture) but these were deemed by the investigator to be unrelated to the trial medications.[1]

Table 3.13: Summary of AEs in CheckMate-816

	Nivolumab + PDC (n = 176)		PDC (n = 176)	
	Any grade	**Grade 3 or 4**	**Any grade**	**Grade 3 or 4**
AEs of any cause, n (%)[a]				
All	163 (92.6)	72 (40.9)	171 (97.2)	77 (43.8)
Leading to discontinuation of treatment	18 (10.2)	10 (5.7)	20 (11.4)	7 (4.0)
Serious	30 (17.0)	19 (10.8)	24 (13.6)	17 (9.7)
Treatment-related AEs, n (%)[a]				
All	145 (82.4)	59 (33.5)	156 (88.6)	65 (36.9)
Leading to discontinuation of treatment	18 (10.2)	10 (5.7)	17 (9.7)	6 (3.4)
Serious	21 (11.9)	15 (8.5)	18 (10.2)	14 (8.0)
Death[b]	0		3 (1.7)	
Surgery-related AEs, n/total n (%)[c]	62/149 (41.6)	17/149 (11.4)	63/135 (46.7)	20/135 (14.8)

Source: CS (Section B.2.10, Table 19, p.68)[1]

[a] Events reported between first neoadjuvant dose and 30 days after final neoadjuvant dose

[b] CS footnotes to Table 19 state that the treatment-related death in the PDC alone group were due to pancytopenia, diarrhoea and kidney injury (all in a single participant); enterocolitis; and pneumonia.

[c] CS states denominators for surgery-related AEs is based on participants who underwent definitive surgery. Surgery-related AEs include events reported up to 90 days after definitive surgery.

Abbreviations: AE = adverse event; CS = company submission; PDC = platinum doublet chemotherapy

Table 3.14 summarises the most frequently experienced treatment-related AEs in CheckMate-816 (defined as being experienced by ≥ 15% of participants in any treatment group) according to the CS (Section B.2.10, Table 20, p.68-69).[1] The company reported treatment-related AEs reported between the first neoadjuvant dose and 30 days after the last neoadjuvant dose as per Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0; Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 (Section B.2.10, footnotes to Table 20, p.69).[1]

Treatment-related AEs of any grade were experienced by 145 participants (82.4%) in the nivolumab + PDC group and 156 participants (88.6%) in the PDC alone group. Grade 3 or 4 treatment-related AEs were reported by 59 participants (33.5%) in the nivolumab + PDC group and 65 participants (36.9%) in the PDC alone group. Nausea was the most reported treatment-related AE, reported by 58 participants (33%) in the nivolumab + PDC group and 73 (41.5%) in the PDC alone group. Neutropenia was the most common Grade 3 or 4 event, reported by 15 participants (8.5%) in the nivolumab + PDC group and 21 participants (11.9%) in the PDC alone group.

The company state that the incidence of immune-mediated AEs in CheckMate-816 was low and mainly of Grade 1 or 2 (CS Section B.2.10, p.69).[1] The company state that the most common immune-mediated AE of any grade in the nivolumab + PDC group was rash (in 8.5% of participants), while 2 participants (1.1%) had Grade 1 or 2 pneumonitis. Immune-mediated AEs were not reported for the PDC alone group.

Table 3.14: Most frequent treatment-related AEs in CheckMate-816

	No. of participants (%)			
	Nivolumab + PDC (n = 176)		PDC (n = 176)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
All	145 (82.4)	59 (33.5)	156 (88.6)	65 (36.9)
Nausea	58 (33.0)	1 (0.6)	73 (41.5)	1 (0.6)
Anaemia	42 (23.9)	5 (2.8)	40 (22.7)	6 (3.4)
Constipation	37 (21.0)	0	36 (20.5)	2 (1.1)
Decreased appetite	29 (16.5)	2 (1.1)	38 (21.6)	4 (2.3)
Neutropenia	28 (15.9)	15 (8.5)	29 (16.5)	21 (11.9)
Decreased neutrophil count	26 (14.8)	13 (7.4)	37 (21.0)	19 (10.8)

Source: CS (Section B.2.10, Table 20, p.69)[1]
Abbreviations: AE = adverse event; PDC = platinum doublet chemotherapy

Table 3.15 summarises the most frequently experienced surgery-related AEs in CheckMate-816 (defined as being experienced by ≥ 5% of participants in any treatment group) according to the CS (Section B.2.10, Table 20, p.68-69).[1] According to the footnotes of Table 20 in the CS, surgery-related AEs included events reported up to 90 days after definitive surgery (CTCAE Version 4.0; MedDRA Version 23.0); the denominator for these events was based on participants who underwent definitive surgery (149 in the nivolumab + PDC group and 135 in the PDC alone group).

The most reported surgery-related AE was anaemia, reported in 18 participants (12.1%) in the nivolumab + PDC group and 17 participants (12.6%) in the PDC alone group.

Table 3.15: Most frequent surgery-related AEs in CheckMate-816

	No. of participants (%)			
	Nivolumab + PDC (n = 149)		PDC (n = 135)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
All	62 (41.6)	17 (11.4)	63 (46.7)	20 (14.8)
Anaemia	18 (12.1)	3 (2.0)	17 (12.6)	3 (2.2)
Pain	11 (7.4)	1 (0.7)	21 (15.6)	0
Wound complication	11 (7.4)	1 (0.7)	8 (5.9)	0
Procedural pain	9 (6.0)	0	6 (4.4)	0
Pneumonia	8 (5.4)	3 (2.0)	8 (5.9)	4 (3.0)

Source: CS (Section B.2.10, and amended from Table 20, p.69)[1]
Abbreviations: AE = adverse event; PDC = platinum doublet chemotherapy

AEs leading to delay or cancellation of surgery is reported in CS Section B.2.10 (Table 21, p.69-70).[1] These are summarised in Table 3.16. In general, AEs leading to surgery were rare in both arms, with 6 (3.4%) in the nivolumab + PDC arm and 9 (5.1%) in the PDC alone arm. AEs leading to surgery cancellation were also rare, with two cases (1.1%) in the nivolumab + PDC arm and 1 case (0.6%) in the PDC alone arm.

Table 3.16: Adverse events leading to surgery delay and/or cancellation in CheckMate-816

	No. of participants (%)			
	Nivolumab + PDC (n = 176)		PDC (n = 176)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
All AEs leading to surgery delay	6 (3.4)	2 (1.1)	9 (5.1)	4 (2.3)
Bronchitis	1 (0.6)	0	0	0
Pneumonia	1 (0.6)	1 (0.6)	0	0
Herpes zoster	0	0	1 (0.6)	0
Increased lipase	1 (0.6)	0	0	0
Lung diffusion test	0	0	1 (0.6)	0
Decreased neutrophil count	0	0	1 (0.6)	0
Decreased white blood cell count	0	0	1 (0.6)	0
Pneumonitis	1 (0.6)	0	0	0
Pulmonary embolism	0	0	2 (1.1)	1 (0.6)
Maculopapular rash	1 (0.6)	0	0	0
Embolism	1 (0.6)	1 (0.6)	0	0
Deep vein thrombosis	0	0	1 (0.6)	0
Ventricular thrombosis	0	0	1 (0.6)	1 (0.6)
Myocardial infarction	0	0	1 (0.6)	1 (0.6)
Stress cardiomyopathy	0	0	1 (0.6)	1 (0.6)
Colitis	0	0	1 (0.6)	1 (0.6)
Ataxia	0	0	1 (0.6)	0
All AEs leading to surgery cancellation	2 (1.1)	0	1 (0.6)	0
Ischaemic stroke	1 (0.6)	0	0	0
Tuberculosis	1 (0.6)	0	0	0
Increased blood creatinine	0	0	1 (0.6)	0

Source: CS Section B.2.10 (Table 21, p.69-70).[1]
Abbreviations: AE = adverse event; PDC = platinum doublet chemotherapy

EAG Comment: The EAG identified that increased lipase, embolism, ischaemic stroke and tuberculosis were all listed as adverse events in the nivolumab + PDC arm of CheckMate-816 that do not appear to be present in the British National Formulary's (BNF) list of known adverse events for nivolumab.[7] We asked the company to clarify whether these AEs were related to the treatment with nivolumab + PDC within the points for clarification (question A23).[15] In response, the company stated that the occurrence of ischaemic stroke and tuberculosis were not treatment-related. Furthermore, the company stated that the increased lipase and embolism were considered treatment-related but as these were not immune-related AEs it is likely that they were due to the PDC and not nivolumab.[15] Embolism or pulmonary embolism are listed as AEs with unknown frequency for cisplatin and carboplatin in the BNF.[34,35] Increased lipase is not a listed side-effect in the BNF for any of the PDC drugs used within CheckMate-816. However, as only one participant in the nivolumab + PDC arm experienced this AE,

this may not represent cause for concern. Increased lipase is not a listed side-effect in the BNF for any of the PDC drugs used within CheckMate-816. However, as only one participant in the nivolumab + PDC arm experienced this AE, this may not represent cause for concern.

In general, AEs across the groups seem relatively balanced, which may be suggestive that adding nivolumab to PDC does not lead to more AEs than with PDC alone.

As reported previously in Section 3.2.4, the patient representative submission noted concerns that undergoing neoadjuvant therapy may lead to participants having surgical resection cancelled or delayed.[32] In general, AEs leading to surgery cancellation or delay were very few in both arms.

3.2.8 Subgroup analyses in CheckMate-816

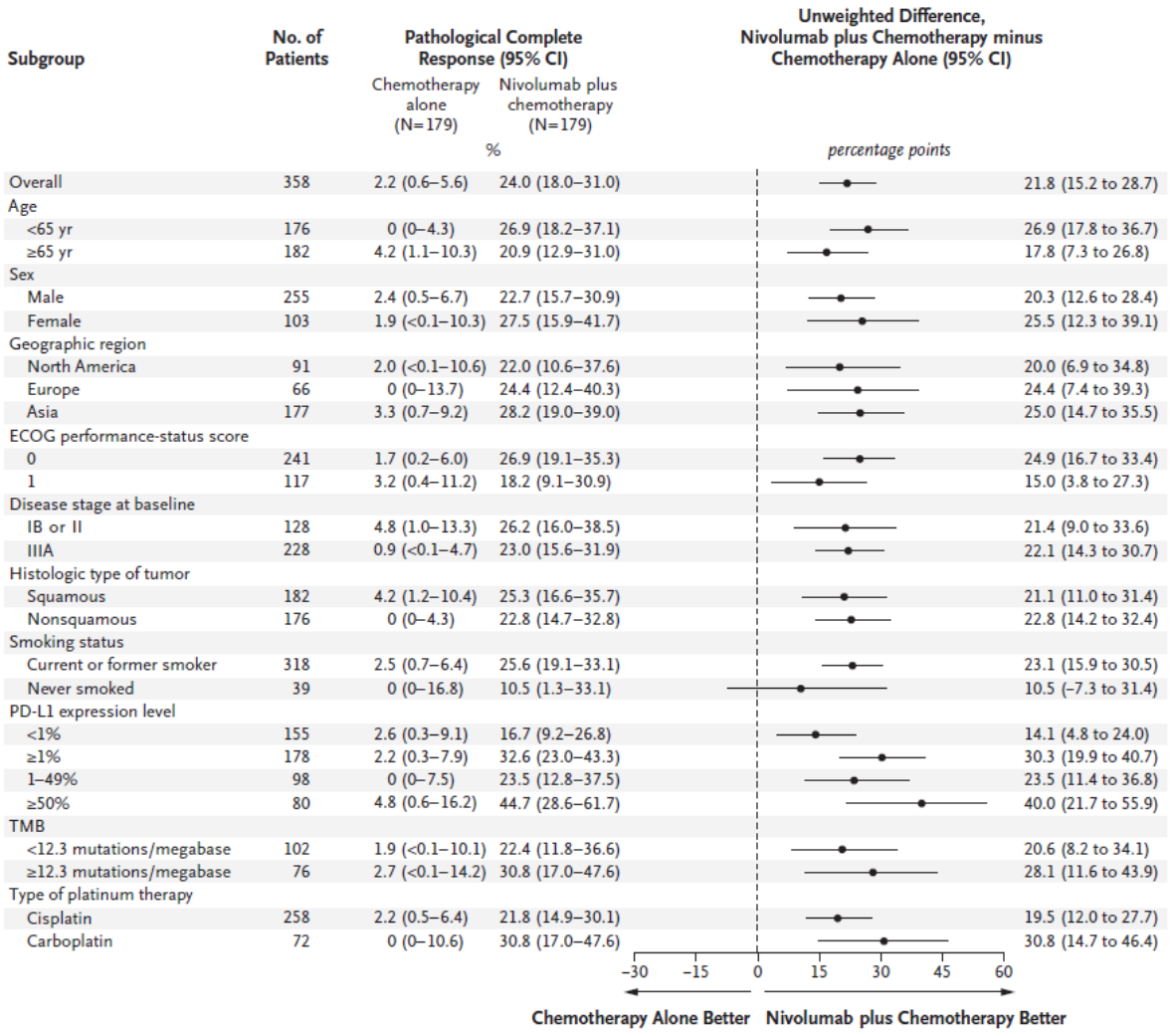
Subgroup analyses by disease stage and PD-L1 status were specified in the NICE scope.[2] The company reports that the following subgroup analyses were planned for CheckMate-816 (CS Section B.2.3.1, Table 7, p.37).[1]

- Age (< 65 versus ≥ 65)
- Sex (male versus female)
- Race
- Geographic region (North America versus Europe versus Asia)
- Baseline ECOG performance status (0 versus 1)
- Tobacco use (Current or former smoker versus never smoked)
- Disease stage at study entry (IB or II versus IIIA)
- Cell type at study entry (squamous versus non-squamous)
- PD-L1 status (< 1% versus ≥ 1% versus 1-49% versus ≥ 50%)
- Tumour tissue TMB (< 12.3 mutations/megabase versus ≥ 12.3 mutations/megabase)
- Type of platinum therapy (cisplatin versus carboplatin)

However, although listed as a planned analysis, the company submission did not provide subgroup analyses by race. We asked the company to provide subgroup analyses by ethnicity in the points for clarification (question A22).[15] The company responded by providing data segregated by white and Asian participants for pCR rate and EFS.[15] The company also responded to a request to provide clinical effectiveness data where data for North America and Europe were pooled versus Asia alone (points for clarification question A25).[15] The company did not provide this information and reiterated the subgroups by individual region already presented in the CS.[15]

Subgroup analyses for pCR according to BIPR and EFS according to BICR are reported in CS Section B.2.7.[1] The subgroup analyses for pCR by BIPR from the CS is presented in Figure 3.2. In general, a benefit in favour of nivolumab + PDC was observed across all subgroups. There was greater uncertainty surrounding the benefit of nivolumab + PDC for those who had never smoked, as the 95% CI was wide and crossed the line of no effect.

Figure 3.2: CheckMate-816 subgroup analyses for pCR by BIPR as presented in CS

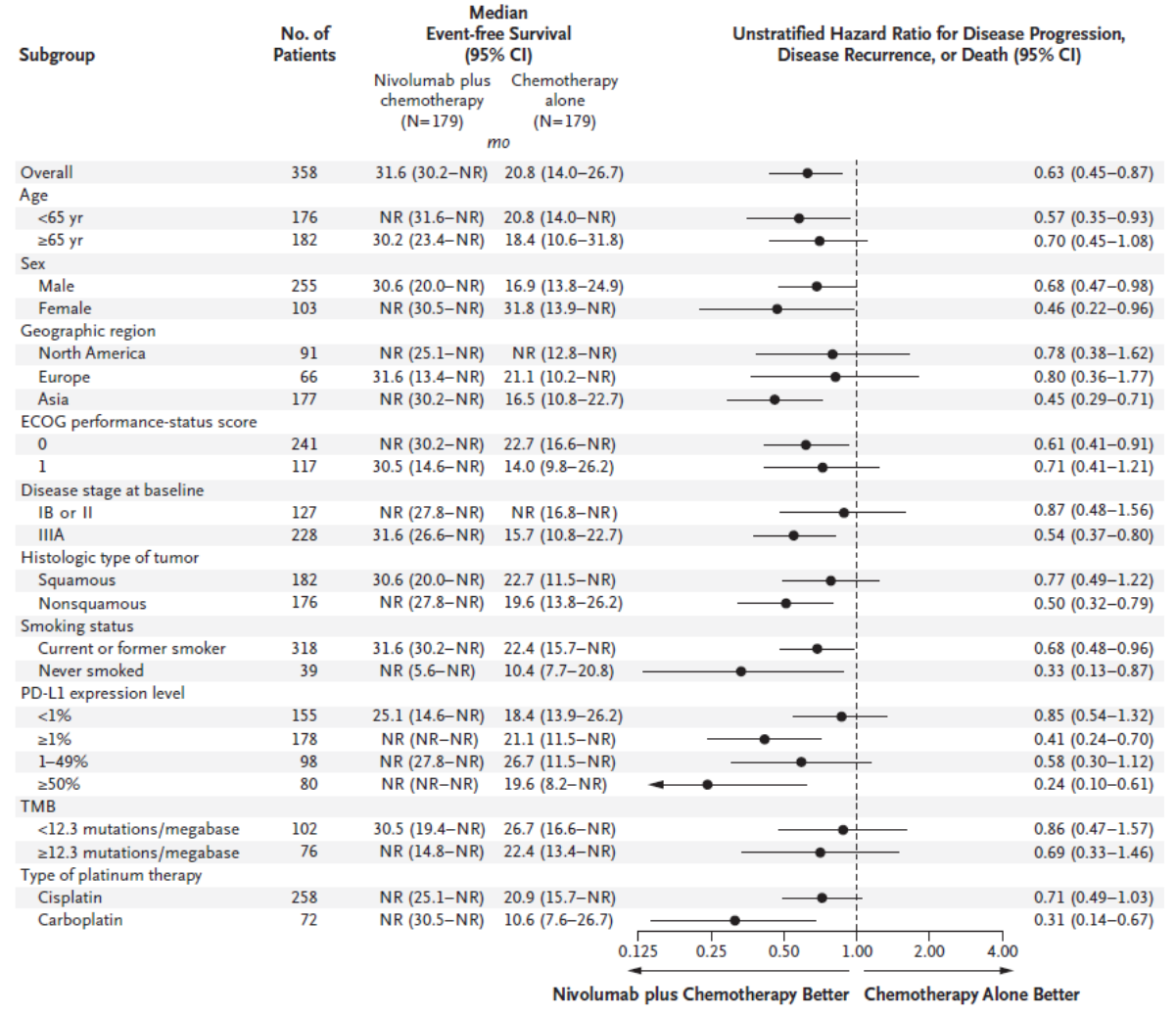


Subgroup	No. of Patients	Pathological Complete Response (95% CI)	
		Chemotherapy alone (N=179)	Nivolumab plus chemotherapy (N=179)
		%	
Overall	358	2.2 (0.6–5.6)	24.0 (18.0–31.0)
Age			
<65 yr	176	0 (0–4.3)	26.9 (18.2–37.1)
≥65 yr	182	4.2 (1.1–10.3)	20.9 (12.9–31.0)
Sex			
Male	255	2.4 (0.5–6.7)	22.7 (15.7–30.9)
Female	103	1.9 (<0.1–10.3)	27.5 (15.9–41.7)
Geographic region			
North America	91	2.0 (<0.1–10.6)	22.0 (10.6–37.6)
Europe	66	0 (0–13.7)	24.4 (12.4–40.3)
Asia	177	3.3 (0.7–9.2)	28.2 (19.0–39.0)
ECOG performance-status score			
0	241	1.7 (0.2–6.0)	26.9 (19.1–35.3)
1	117	3.2 (0.4–11.2)	18.2 (9.1–30.9)
Disease stage at baseline			
IB or II	128	4.8 (1.0–13.3)	26.2 (16.0–38.5)
IIIA	228	0.9 (<0.1–4.7)	23.0 (15.6–31.9)
Histologic type of tumor			
Squamous	182	4.2 (1.2–10.4)	25.3 (16.6–35.7)
Nonsquamous	176	0 (0–4.3)	22.8 (14.7–32.8)
Smoking status			
Current or former smoker	318	2.5 (0.7–6.4)	25.6 (19.1–33.1)
Never smoked	39	0 (0–16.8)	10.5 (1.3–33.1)
PD-L1 expression level			
<1%	155	2.6 (0.3–9.1)	16.7 (9.2–26.8)
≥1%	178	2.2 (0.3–7.9)	32.6 (23.0–43.3)
1–49%	98	0 (0–7.5)	23.5 (12.8–37.5)
≥50%	80	4.8 (0.6–16.2)	44.7 (28.6–61.7)
TMB			
<12.3 mutations/megabase	102	1.9 (<0.1–10.1)	22.4 (11.8–36.6)
≥12.3 mutations/megabase	76	2.7 (<0.1–14.2)	30.8 (17.0–47.6)
Type of platinum therapy			
Cisplatin	258	2.2 (0.5–6.4)	21.8 (14.9–30.1)
Carboplatin	72	0 (0–10.6)	30.8 (17.0–47.6)

(Source: CS Section B.2.7, Figure 14 (p.58))[1]
(CS notes that "chemotherapy" in the figure refers to platinum doublet chemotherapy)
(Abbreviations: BIPR = blinded independent pathologic review; CI = confidence interval; CS = company submission; ECOG = Eastern Cooperative Oncology Group; PD-L1 = programmed death-ligand 1; TMB = tumour mutational burden)

Subgroup analyses for EFS by BICR as reported in the CS is shown in Figure 3.3 (Section B.2.7, Figure 15, p.59).[1] Most subgroups suggest that outcomes are similar or favour nivolumab + PDC but with greater imprecision surrounding subgroups by geographical region, smoking status, PD-L1 status and type of platinum therapy used. The company have stated that they anticipate that the benefit shown in the subgroup results will be reflected in the EFS results once more events have occurred and there is longer follow-up.[1]

Figure 3.3: CheckMate-816 subgroup analyses for EFS by BICR as presented in CS



(Source: CS Section B.2.7, Figure 15 (p.59))[1]
(CS notes that "chemotherapy" in the figure refers to platinum doublet chemotherapy)
(Abbreviations: BICR = blinded independent central review; CI = confidence interval; CS = company submission; ECOG = Eastern Cooperative Oncology Group; PD-L1 = programmed death-ligand 1; TMB = tumour mutational burden)

In the PfC (question A22), the company reported on pCR rate and EFS for the white and Asian subgroups.[15] However, the company did not stratify the data for pCR rate by arm (nivolumab + PDC or PDC alone). A summary of this information provided by the company is presented within Table 3.17.

Table 3.17: Subgroup analyses by ethnicity (white versus Asian) as provided by the company

	Number (%) subjects			
	White		**Asian**	
Outcome	**Nivolumab + PDC (** [redacted]	**PDC** [redacted]	**Nivolumab + PDC (** [redacted]	**PDC** [redacted]
pCR rate				
%	[redacted]		[redacted]	
95% CI	[redacted]		[redacted]	

EFS		
HR	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Source: [redacted] Abbreviations: CI = confidence interval; EFS = event-free survival; HR = hazard ratio; pCR = pathologic complete response; PDC = platinum doublet chemotherapy; PfC = points for clarification		

EAG Comment: In the subgroup analyses for pCR by BIPR as presented in the CS, most subgroups show a benefit for nivolumab + PDC and 95% CIs for individual subgroups generally overlap. The only outlier is the subgroup for people who have never smoked, which has a wide CI that crosses the line of no effect (10.5%, 95% CI -7.3 to 31.4). However, the imprecision in this result is likely due to there being very sparse data (only 39 participants were in the never smoked group).

Results for subgroup analyses for EFS as presented in the CS vary more widely. Notably, EFS by disease stage varies between participants with IB or II disease (HR 0.87, 95% CI 0.48-1.56) and those with stage IIIA disease (HR 0.54, 95% CI 0.37-0.80), suggesting that nivolumab + PDC may be less effective in those with lower stage disease. There was also a difference in effectiveness between the cisplatin-based PDC subgroup (HR 0.71, 95% CI 0.49-1.03) and the carboplatin-based PDC subgroup (HR 0.31, 95% CI 0.14-0.67). While it may be possible to suggest that nivolumab + carboplatin-based PDC may result in better EFS than nivolumab + cisplatin-based PDC, the imprecision in the result and 95% CI for the carboplatin subgroup may be due to fewer participants in this subgroup (n = 72) compared with the cisplatin subgroup (n = 258).

The mean EFS HR estimates were higher in the North America and Europe subgroups than in the Asia subgroup. The EFS HR estimates were HR 0.78, 95% CI 0.38-1.62 in the North America subgroup, HR 0.80, 95% CI 0.36-1.77 in the Europe subgroup, and HR 0.45, 95% CI 0.29-0.71 in the Asia subgroup. However, the confidence intervals are wide, reflecting the smaller sample sizes: North America (n = 91), Europe (n = 66) and Asia (n = 177), and there is no strong evidence for a difference in effectiveness between specific regions. As previously mentioned, the EAG asked the company to combine data for the North American and European subgroups versus the Asia subgroup in the points for clarification (question A25).[15] The company did not provide this information and reiterated the subgroups by individual region already presented in the CS.

The company provided outcome data for pCR rate and EFS subgrouped by ethnicity (white versus Asian) at the request of the EAG (PfC question A22).[15] Results are presented in Table 3.20 above. It is difficult to draw conclusions on the effectiveness of nivolumab + PDC by white ethnicity versus Asian ethnicity for pCR rate presented by the company, as the percentages are not broken down by arm (nivolumab + PDC versus PDC alone for both white and Asian subgroups). [redacted] As previously discussed, analysis from data from Public Health England between 2013-2017 has shown that 92% of people who develop lung cancer in England are white.[30] [redacted]

[redacted] It is not possible to draw definitive conclusions on the effectiveness of neoadjuvant treatment in a white population.

[redacted]

3 18 [redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

3.3 Conclusions of the clinical effectiveness section

A systematic literature review (SLR) was undertaken to identify evidence addressing the NICE decision problem.[2] Data were extracted from 58 RCTs. Only one clinical trial of nivolumab identified in the SLR of was directly relevant to the NICE decision problem (CheckMate-816, reported as Forde 2022 in the SLR and NMA).[21] Patients in this study were randomised to receive either nivolumab with PDC or PDC

alone as neo-adjuvant therapy. Eight RCTs were included in the network meta-analyses, which provided indirect evidence of neo-adjuvant nivolumab with PDC versus all the comparators in the NICE scope.

CheckMate-816 is a randomised, parallel assignment, open-label phase III trial conducted in 111 sites across 14 countries. The trial compared neoadjuvant nivolumab + PDC with neoadjuvant PDC alone in adults with newly diagnosed, resectable Stage IB-IIIA NSCLC according to the seventh edition of the AJCC/UICC.[1] No UK centres were included within CheckMate-816 and most participants were recruited from Asia (47.5% in the nivolumab arm and 51.4% in the PDC alone arm). There were also potential differences in the administration of PDC, with 21.8% in the nivolumab arm and 18.4% in the PDC alone arm receiving carboplatin-based PDC. Clinical advice to the EAG suggested that carboplatin-based PDC would rarely be used within English clinical practice. Pneumonectomy was also considered by clinical advice to the EAG and a 2017 audit of clinical outcomes of lung cancer to be very uncommon in the UK,[31] but was conducted in 16.8% of participants in the nivolumab arm and 25.2% of participants in the PDC alone arm. These factors mean the applicability of the CheckMate-816 results to the English clinical setting is uncertain.

[redacted]

[redacted]

[redacted]

4 COST-EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

This section is concerned with the review of Cost-Effectiveness Analysis (CEA) studies which is provided by the company in Appendix G.[6] It also covers the search for additional parameters important to CEA, such as the measurement and valuation of health effects, healthcare resources and costs.

4.1.1 Searches performed for cost-effectiveness section

The following paragraphs contain summaries and critiques of all searches related to the CEA presented in the CS.[1] The company conducted two literature searches: one Targeted Literature Review (TLR) to review modelling approaches in CEA studies, and one Systematic Literature Review (SLR) on HRQOL, healthcare resources and costs.

4.1.1.1 Searches for cost-effectiveness analysis review

A TLR was conducted to identify modelling approaches and structures previously used in economic evaluations of treatments for early-stage NSCLC to inform the development of the Cost-Effectiveness Model (CEM).

Searches for the TLR were conducted across a range of electronic bibliographic databases to identify articles on economic analyses reporting CE results in early-stage (Stage I – IIIA) NSCLC, published from 1 January 2013 to April 2022 (although no explanation for this date restriction was given) and the CEA Registry (for which no date restriction is given).[6] As part of the TLR, additional CEA studies were identified through: 1) hand-searching of included study reference lists; 2) searching the reference lists of recent SLRs (restricted to 'published in the past 5 years'); and 3) searching relevant online sources and websites, such as the health technology agency websites for England, France, Germany and Canada, and two other international bodies, WHO and "the Cochrane Collaboration." The date on which the searches were conducted was not provided. A summary of the searches undertaken is provided in Table 4.1.

The company state that "case reports, editorials, comments/commentary, guidelines, news, or narrative reviews were excluded from the searches" (CS Appendix G).[6] Conference abstracts were removed from the Embase search, although this was not reported in the text. Other restrictions were applied at later stages of the review process. For example, at the screening or later stage, a restriction to only English language articles was applied (CS Table G-3, Appendix G).[6]

The search strategy encompassed the concepts of 'population,' 'stage of disease' and 'timing of treatment'. Both controlled vocabulary (Medical Subject Headings (MeSH) in MEDLINE and Emtree terms in Embase) and free-text terms were used.

The EAG were able to only partially critically appraise the searches performed for the TLR using the PRESS checklist and the latest NICE methods manual (NICE 2022, PMG36).[12,13] This was because search strategies for only two of the sources searched were presented. The methods and terms used to search the other databases and websites were not presented, as might be expected when using the PRISMA-S reporting guidance.[14]

The company reported that a single reviewer screened the abstracts and eligible full-text papers and to ensure that the highest-quality evidence is included in the TLR, additional inclusion criteria were employed. These additional criteria include publications in higher-tier journals, reporting data for larger sample sizes (> 100 patients), rigorous study designs and most generalisable findings.

A summary of the eligible papers can be found in the CS Appendix G.[6]

Table 4.1: Summary of the searches undertaken for the TLR of economic evaluations

Resource - category	Resource	Host source or platform	Date Range	Date of search	Search strategy/ string/terms reported	N hits per line	Reported in PRISMA flowchart[a]
Electronic bibliographic databases	MEDLINE	PubMed	January 2013 – April 2022	NR	Yes	Yes	NA
	Embase	Ovid					
	Centre for Reviews and Dissemination (CRD)[b]	NR		NR	NR	NR	
	CEA Registry	NR	NR	NR	NR	NR	NA
Other sources	Canadian Agency for Drugs and Technologies in Health (CADTH)	NR	NR	NR	NR	NR	NA
	NICE						
	Haute Autorité de Santé (HAS; National Authority for Health)						
	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)						
	World Health Organization (WHO)						
	'Cochrane collaboration'[c]						
References lists of relevant studies and 'recent'[d] systematic reviews	NA	NA	Any relevant CEA found	NR	NA	NA	NA

Source: Based on information presented in Appendix D.[6]

[a] A PRISMA diagram was not presented for this TLR

[b] The company did not supply a strategy for the CRD databases and did not specify which of the three databases available were searched

[c] No other details were given

[d] 'published in the past 5 years' - no date of search was given

Abbreviations: CEA = Cost-Effectiveness Analysis; CRD = Centre for Reviews and Dissemination; N = number; NA = not applicable; NR = not reported; PRISMA = Preferred reporting items for systematic reviews and meta-analyses; TLR = targeted literature review

EAG comment: The company did not explicitly explain why they used a TLR approach to identify relevant CEAs in the CS.[1] The EAG critically appraised the searches performed for the SLR using the PRESS checklist and the latest NICE methods manual (NICE 2022, PMG36).[12,13] The company reviewed a good range of databases (both electronic bibliographic databases and a manual search of references) and used predefined inclusion and exclusion criteria. However, although the company report that they searched the 'CRD databases' they did not provide details of which of the CRD databases were searched. It is therefore unclear if the National Health Service Economic Evaluation Database (NHS EED) was included in the search. Although this database has not been updated since end of March 2015, there would be potentially relevant CEA studies identified in this database. The EAG are therefore unable to comment as to whether all relevant databases were searched.

The EAG is uncertain if all potentially relevant studies the company aimed to capture (detailed in CS Appendix Table G-3) have been captured as the search did not directly include elements for 'chemotherapy', 'chemoradiotherapy' or 'radiotherapy'; 'immunotherapy' was only directly covered in relation to adjuvant use.[6] For the main intervention, nivolumab, and for the other comparators, no general, generic or specific drug-related terms are used (controlled vocabulary terms, text word terms, CAS registry numbers). The EAG was not in a position to verify whether the use of any or all these terms would have led to the retrieval of additional relevant records.

Surgery-related studies were not sought, and no terms related to surgery were included in the two strategies presented, despite surgery being included as a comparator in the economic model. The EAG asked about the absence of surgery-related terms in the points for clarification letter (Question A26).[15] The company responded that all studies, including surgery, would be captured, as they would expect these studies to be picked up as "surgery is necessarily included as a component of" studies looking at neoadjuvant or adjuvant treatments.[15] The EAG was not in a position to be able to test that the company's assumption was correct.

The company used a specific period for the database search coverage (January 2013 to April 2022) and a five-year period for the published SLRs they checked the reference lists of. However, they did not provide any reasons for these date restrictions.

The company do not report the use of (or provide references for) any validated search filters related to study design or age groups. However, both the strategies presented a set of terms that may be related to both these concepts. The 'age group' terms appear to be aimed at removing younger age groups from the search results and the 'study design' terms appear to be aimed at capturing particular types of economic study. If the use of a search filter is considered necessary, then the use of (and referencing of) validated search filters, when available, is considered advisable to help maximise retrieval of relevant studies.

The abstracts and full text studies were screened by one reviewer and were not checked by another reviewer, as recommended by the 'Cochrane Handbook for Systematic Reviews of Interventions' and so, potentially, the company may have missed some eligible papers.[18]

It is noteworthy that the company employed additional criteria to include high quality evidence. They applied these criteria at the full-text screening stage. However, they did not clarify what these criteria precisely were. For example, they mentioned consideration of higher tier publications but did not explain which journals they targeted nor their relevance to the topic of the review. In addition, they mentioned inclusion of rigorous and generalisable study designs but did not provide information about how rigour and generalisability of study design was assessed.

4.1.1.2 Eligibility criteria for inclusion of studies

Table 4.2 provides the criteria used to screen CEA studies retrieved in the TLR. The criteria provided are based on patients, intervention, comparator, outcomes, and study design (PICOS).

Table 4.2: Eligibility criteria for Targeted Literature Review

Domain	Inclusion criteria	Exclusion criteria
Patient population	Adults (aged 18 years or older) with early-stage NSCLC	Patients < 18 years old Patients with later-stage NSCLC
Intervention/ Comparator	The following treatments used in the neoadjuvant, periadjuvant, or adjuvant settings: • Radiotherapy • Chemotherapy, including but not limited to: • Cisplatin • Carboplatin • Vinorelbine • Etoposide • Gemcitabine • Docetaxel • Pemetrexed • Paclitaxel • Immunotherapy, including but not limited to: Durvalumab	Treatments other than those listed in the inclusion criteria
Outcomes(s) (Published economic evaluations)	Cost-effectiveness measures, including: • LY/QALYs • CERs/ICERs • Cost-utility	Studies reporting outcomes not related to cost-effectiveness measures
Study design	Economic analyses (CEAs, CUAs, cost-benefit analyses, cost-minimisation analyses) Health technology assessments	Case reports, editorials, comments/commentary, guidelines, news, or narrative reviews Animal studies, in vitro studies, gene/protein expression studies
Others	Published in English	Studies published in languages other than English

Source: CS Appendix G. Table G-3[6]
Abbreviations: NSCLC = non-small cell lung cancer; LY= Life years; QALYs = Quality-adjusted life years; CERs = cost-effectiveness ratios; ICERs = incremental cost-effectiveness ratios; CEAs = cost-effectiveness analyses; CUAs = cost-utility analyses

EAG comment: The eligibility criteria presented by the company are acceptable and cover all PICOS parameters.

4.1.1.3 Searches for model inputs

An SLR was undertaken to identify the following model inputs: 1) costs and healthcare resource use; and 2) HRQOL. The SLR covered neoadjuvant, periadjuvant, and adjuvant treatment of early-stage NSCLC in the US, Canada, UK, France, Germany, Italy, Spain and Australia. A description of the searches undertaken was given in the CS Appendices (Appendix H.1.1).[6]

The company undertook a search across three electronic bibliographic databases for the period 'from the start of database indexing to April 2022'. This was supplemented by a search of the proceedings of three conferences, each covering a two-year time period, as well as through searching reference lists of relevant SLRs 'published in the past 5-years'. No dates on which any of the searches were conducted were reported by the company. A summary of the searches undertaken by the company for the SLR are presented in Table 4.3 below.

The company report that "case reports, editorials, comments/commentary, guidelines, news, or narrative reviews were excluded from the searches" (CS Appendix H, Section H.1.1).[6] Conference abstracts were removed from the Embase search, although this was not reported in the text. Although no geographical or language limitations were imposed directly on the searches, these limits were applied during the screening or later stage of the SLR process (Appendices Table H-4).[6]

The search strategy encompassed the concepts of 'population', 'stage of disease' and 'timing of treatment'.

The EAG were able to only partially critically appraise the searches performed for the SLR using the PRESS checklist and the latest NICE methods manual (NICE 2022, PMG36).[12,13] This was because the methods and terms used to search the conference abstracts were not presented, as might be expected when using the PRISMA-S reporting guidance.[14]

Table 4.3: Resources searched for HRQOL and cost and resource use evidence

Resource – category	Resource	Host/ platform	Date range	Date of search	Search strategy/ string/ terms reported	N hits per line reported	Itemised report in PRISMA flowchart
Electronic bibliographic databases	MEDLINE and MEDLINE In-Process	PubMed	From 'the start of database indexing' [a] until to April 2022	NR	Yes	Yes	No
	EMBASE	Ovid		NR	Yes	Yes	No
	NHS Economic Evaluation Database (NHS EED)	NR		NR	Yes	Yes	No
	American Society of	NR		NR	NR	NR	No

Conference proceedings	Clinical Oncology		2018-2019				
	ESMO[b]	NR					No
	International Society for Pharmaco-economics and Outcomes Research[b]	NR	2017-2018				No
Reference lists of relevant 'recent'[c] systematic reviews	NA	NA	'Published in the last 5 years'[c]	NR	NA	NA	No

Source: Based on information presented in Appendix H.[6]

[a] No precise dates given for the start of the search date range – the company state 'from the start of database indexing'

[b] The company reports the available conference abstracts and poster presentations from the past two meetings were searched.

[c] 'published in the past 5 years' - no date of search was given

Abbreviations: ESMO = European Society for Medical Oncology; HRQOL = health related quality of life; N = number; NA = not applicable; NHS EED = NHS Economic Evaluation Database; NR = not reported; PRISMA = Preferred reporting items for systematic reviews and meta-analyses

EAG comment: The company used a wide range of databases to identify relevant literature on HRQOL, costs and healthcare resource use. However, the company did not explicitly state the exact date when the searches were conducted.

Due to the similarities in the structure of the searches for this SLR and that of the TLR (reported in CS Appendix G), many of the comments related to the search for economic evaluations above also apply to those for HRQOL, costs and resource use, including those related to the comprehensiveness of the searches for the intervention of interest, the comparators (including surgery), the staging of disease and the use of validated search filters.

The EAG asked about the absence of surgery-related terms in the clarification letter (Question A26).[15] The company responded that "In the context of the resource use and utility searches, surgery has been a treatment option for many years, and it is therefore unlikely that a review would capture new evidence in 2022". However, the EAG is not certain that all useful information about the differences in resource use and utilities/disutilities relating to surgical approach (minimally invasive or thoracotomy) or resection type (pneumonectomy or lumpectomy/lobectomy/other) would have been captured. As highlighted in Key issue 4 this issue may be particularly important in the English clinical setting. The EAG considers that additional search terms, such as 'end of life care' or 'terminal care costs,' could have been used.

The company only looked at the reference lists of relevant SLRs "published in the past 5-years" to identify additional relevant studies but did not provide any justification for this.

There was no rationale provided by the company as to why the countries included in the SLR were key markets and how HRQOL, costs and healthcare resource use reported in these countries could be comparable to England.

The EAG consider this SLR to be very large and think that two SLRs, one on HRQOL and one on costs and healthcare resource use, should have been undertaken.

4.1.2 Inclusion/exclusion criteria

The eligibility criteria employed to screen the search results of SLR of cost and HRQOL studies are provided in Table 4.4 below, subdivided by study PICOS as presented by company in Appendix H[6].

All titles and abstracts identified in the SLR were manually reviewed against the inclusion and exclusion criteria by a single reviewer. A second reviewer checked 30% of the rejected abstracts to confirm accuracy. Full-text screening was conducted by a single reviewer and all excluded studies were checked by a second reviewer. Any discrepancies were resolved by an independent third reviewer as described in appendix H.[6]

After identifying the articles eligible for inclusion, a reviewer compiled a list of included studies, as well as a list of full-text articles that were excluded, organised by reason for exclusion. The PRISMA flow diagram was populated based on the results of the search and screening process.[6]

Table 4.4: Eligibility criteria for the systematic literature reviews

Domain	Inclusion criteria	Exclusion criteria
Patient population	Adults (aged 18 years or older) with early-stage NSCLC (stage I-IIIa)	Patients < 18 years old Patients with later-stage NSCLC (stage IIIB and IV) or diseases other than NSCLC
Intervention/ Comparator	Neoadjuvant, periadjuvant, or adjuvant treatment with one or more of the following: Radiotherapy Chemotherapy Chemoradiation Immunotherapy	Non-pharmacological or radiological treatments

Domain	Inclusion criteria	Exclusion criteria
Outcomes	Costs (as reported, overall and itemised) Direct costs (e.g., costs related to hospitalisations, medication, physician visits) Indirect costs (e.g., work loss, productivity loss) Caregiver costs (direct and indirect) Resource use including but not limited to: Hospitalisations Length of stay Readmissions Emergency department visits Physician visits Utilities EQ-5D 15D SF-6D SF-36 HUI3 EORTC-8D QLU-C10D Others available as reported	Cost, resource use, or utilities outcomes NR
Study design	Economic analyses with primary data (excluding CEAs) Observational studies, including prospective and retrospective cohort studies as well as cross-sectional analyses RCTs	Case reports, editorials, comments/commentary, guidelines, news, or narrative review Animal studies, in vitro/ex vivo studies, gene expression/protein expression studies
Time period	Studies published through May 2022	Studies published after May 2022

Domain	Inclusion criteria	Exclusion criteria
Others	Countries Limited to studies conducted in the US, Canada, UK, France, Germany, Italy, Spain, and Australia Language Published in English	Studies conducted outside the countries listed in the inclusion criteria or with mixed locations in which data are not separable for countries of interest. Studies published in languages other than English
Source: CS, Appendix H[6] Abbreviations: NSCLC = non-small cell lung cancer; SF-36 = 36-Item Short Form Survey; HUI3 = health utility index; EORTC-8D = European Organisation for Research and Treatment of Cancer 8 Dimension questionnaire; QLU-C10D = Quality of Life Utility Measure-Core 10 dimensions; CEAs = Cost-effectiveness analysis; RCTs = Randomised Control trial.		

EAG comment: The EAG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify utility, healthcare resource use and costs associated with managing adults with early-stage NSCLC.

4.1.3 Conclusions of the cost-effectiveness review

The CS provided an overview of the different search strategies used to identify eligible studies that could be used to inform the development of and populate the CEM.[6] The company conducted two independent literature reviews for this purpose: a TLR to retrieve the studies on CEAs; and an SLR to identify relevant studies on costs, healthcare resource use and HRQOL.

EAG comment: Further justification could have been provided by the company as to why an SLR was not undertaken to identify key CEA studies, it is not clear to the EAG if the NHS EED was used for the TLR, and regarding some of the eligibility criteria, particularly for the SLR (e.g. key markets of interest). Despite this, the EAG considers to the reviews to be adequately conducted.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 4.5: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Defining the decision problem	As listed in the scope developed by NICE.	Complied with the reference case.
Comparators	Established clinical management without nivolumab with chemotherapy, which may include: • Neoadjuvant chemoradiotherapy • Adjuvant chemotherapy • Active monitoring	As per scope.

Element of health technology assessment	Reference case	EAG comment on company's submission
	• For people whose tumours express PD-L1 with at least a 50% tumour proportion score • Atezolizumab after adjuvant cisplatin-based chemotherapy (subject to NICE appraisal).	
Perspective on outcomes	The outcome measures to be considered include: • Disease-free survival • Overall survival • Response rates • Adverse effects of treatment • Health-related quality of life	EFS is presented rather than DFS because it is the primary endpoint in the pivotal CheckMate-816. pCR is presented rather than response rate as this is a primary endpoint in the CheckMate-816 trial.
Perspective on costs	NHS and PSS	The company used an NHS perspective
Type of economic evaluation	Cost-utility analysis with fully incremental analysis.	The company has provided a cost-utility analysis, in line with NICE reference case. This is based on a de novo semi-Markov state transition model. Given that nivolumab is expected to specifically replace individual comparators, pairwise comparisons instead of a full incremental analysis have been provided in accordance with the technology appraisal manual.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared.	Yes. The model takes a lifetime horizon.
Synthesis of evidence on health effects	Based on systematic review.	A targeted review for health economic models in resectable non-metastatic NSCLC was undertaken, however none were deemed suitable for the submission. A SLR was undertaken to identify utilities, but no eligible studies were identified so health effects were gathered from CheckMate-816 study.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D-3L is the preferred measure of health-related quality of life in adults.	QALYs were based on EQ-5D-3L data from the pivotal CheckMate-816 trial. Although not explicitly stated in the report, it is assumed the utilities were generated using the algorithm from Dolan (1997),[33]

Element of health technology assessment	Reference case	EAG comment on company's submission
		in line with the NICE reference case. The disutilities from AEs partially from published sources and partially assumptions. The duration of the utilities was assumed to be one week in length.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers.	Yes, for the EF and LR health states, obtained from the CheckMate-816 study, and the literature. For the AE disutilities, the source of measurement was from published sources and company assumptions.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population.	Not stated in the CS, but the EQ-5D-3L utility weights are assumed to be taken from Dolan (1997)[33] in line with NICE reference case.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	Yes
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.	Yes. Costs have been sourced using NHS reference costs, PSSRU Unit Costs of Health and Social Care and published literature.
Discounting	The same annual rate for both costs and health effects (currently 3.5%).	Yes, the discount rate chosen in the base case analysis was in line with NICE reference case.

Source: CS, Appendix H[6]
Abbreviations: NICE = National Institute for Health and Care Excellence; EAG = external assessment group; PD-L1 = Programmed death-ligand 1; EFS = event-free survival; DFS = disease-free survival; NHS = national health service; PSS = personal social services; pCR = Pathologic complete response; NSCLC = non-small cell lung cancer; QALYs = quality-adjusted life years; EF = event-free; LR = locoregional recurrence; AE = adverse event; UK = United Kingdom; CS = company submission.

4.2.2 Model structure

4.2.2.1 Health states/events and transitions

The company's economic model adopted a *de novo* state-transition semi-Markov approach, with adjustment for competing risks. The model comprised four health states: 1) Event-Free (EF), 2) Locoregional Recurrence (LR), 3) Distant Metastasis (DM), and 4) Dead (See Figure 4.1Error! Reference source not found.).

All patients were assumed to enter the model in the EF health state and receive either nivolumab + PDC treatment, neoadjuvant CRT, surgery alone, or adjuvant PDC. Not all patients in the EF health state received surgery and the proportion of patients receiving surgery varied across comparators. The distribution of type of surgery also varied across comparators. Model cycles had a three-week duration matching the dosing schedule of the treatment regimens used, and a half-cycle correction was applied to costs and outcomes (except drug acquisition and administration).[1]

Patients in EF incurred the costs of surgery (and chemotherapy treatments, if applicable) in the first cycle, except for adjuvant PDC patients, who received the costs of chemotherapy after the first cycle. For each three-week model cycle, the model included the following transitions across health states.

- Patients in EF can remain event-free in EF, transition to LR, transition to DM, or die.
- Patients in LR can remain metastasis-free in LR, transition to DM or die.

For nivolumab + PDC), the transition from EF to LR was modelled using a parametric survival model fitted to data on time to LR (TTLR) from the CheckMate-816 trial.[1] A parametric survival model was also fitted to data on time to any progression (TTaP). The hazard rate of DM at EF was derived from the hazard rate difference between any progression and LR in CheckMate-816.[1]

PDC alone, the control arm in CheckMate-816, was not a comparator in the economic evaluation but a parametric survival model was fitted to the PDC data. For the comparators in the CS base-case model, the transitions from EF to LR and from EF to DM were derived by multiplying the PDC hazard rates for LR and for DM at EF by the hazard ratios for each comparator versus PDC, estimated by the NMA (see Sections 3.3, 3.4).

For nivolumab and the comparators, the transitions EF to dead, and LR to dead were modelled using parametric survival models fitted to pooled nivolumab and PDC data on time to event from the CheckMate-816 trial.[1] The transition between LR and DM was derived from clinical expert opinion sought by the company.[6] The transitions from all alive states to the dead state included a constraint where the risk of death was at least as high as that for the age- and sex-adjusted general population risk.[43] The transition probabilities applied in each health state were adjusted to account for competing risks.

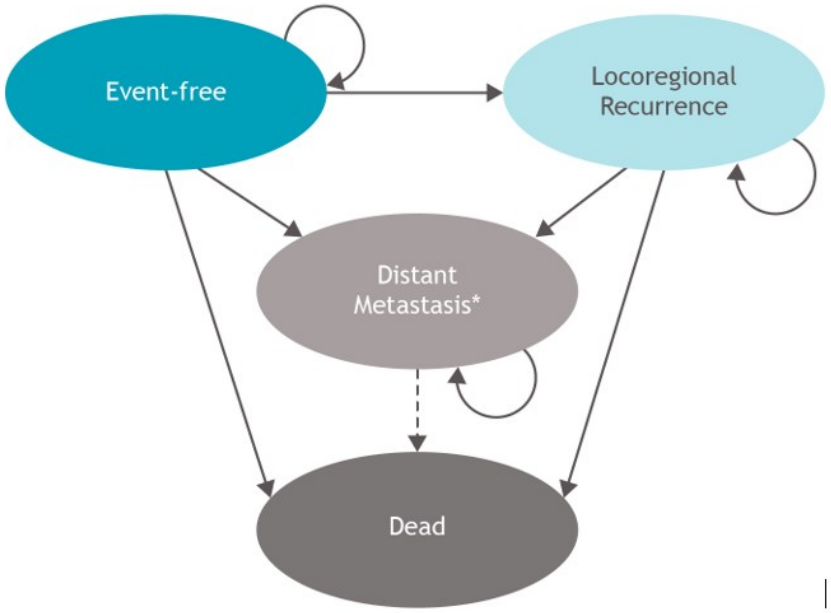
The CS base-case model included a "cure assumption" between years five to seven, where the probabilities of recurrence (either to LR or DM) from EF, and the probability of death in EF, were reduced linearly to 5% of their estimated values for all treatment groups at each time point across the two years (albeit mortality risk was still capped by the general population mortality risk).

DM was an absorbing state. When patients experienced DM, a one-off cost, life-year (LY) and QALY pay-off was applied, representing the total costs, LYs and QALYs accrued in this state following the subsequent treatment mix.

HRQOL was adjusted by sex and age based on estimates from Hernández Alava *et al.,* 2022,[44] which varied across health states. HRQOL was assumed to be lower in the LR state than in the EF state and lower still in the DM state. The same utilities were applied across treatment groups. The model also included a short-term QALY loss to reflect AEs (Grades 3 and 4) associated with adjuvant treatment, which was applied during the first cycle of the model only. The model does not explicitly include further QALY losses associated with AEs arising due to further treatment for recurrence.

The model included costs associated with: 1) drug acquisition and administration for neoadjuvant therapy, 2) surgery 3) drug acquisition and administration for adjuvant therapy, 4) treatments during LR, 5) health state resource use and monitoring, 6) end-of-life care, 7) managing AEs, and 8) managing DM.

Figure 4.1: Model structure



(Source: Figure 26, CS)[1]

EAG comment: The modelled pathway was appropriate. The model structure was consistent with previous economic models of lung cancer (e.g. TA823).[5] The assumption that the DM health state was an absorbing state was consistent with previous TARs.[45,46] The EAG considers the cycle duration of three weeks to capture transitions across the different health states as appropriate.

The company assumed that three weekly probabilities of recurrence and death were an appropriate approximation of the hazard rates of recurrence and death (Company Clarification Response to Question B12).[15] The EAG incorporated the probability to hazard rate conversion functions, and the overall conclusions did not change: nivolumab + PDC dominated neoadjuvant CRT and adjuvant PDC, and had an ICER of £2627 compared with surgery alone. Therefore, the EAG accepts this approximation as adequate.

4.2.3 Population

The economic model was developed for a single population of adult patients with resectable (tumours ≥ 4 cm or node positive) NSCLC, 71.2% of which were male and had a mean age of 63.9 years based

on the population of the CheckMate-816 trial.[1] The company did not provide a subgroup analysis in their submission.

EAG comment:

Overall, the population in the economic model is consistent with the NICE scope. The NICE scope also mentioned it would be desirable to have subgroup analyses by stage if that were feasible. The company did not present the results of analyses by stage of disease.

As described in Section 3.2.3, the study population in CheckMate-816 may have greater proportion of patients in stage IIIB NSCLC than may be seen in England. The studies included in the NMA have predominantly either stages IB-II or stage IIA (see Table 3.21, Section 3.5).

Additionally, the EAG noted that the characteristics of patients enrolled in CheckMate-816 may not reflect the characteristics of patients see in clinical practice in England (see Section 3.2.8). The EAG considered that patients from Europe and North America may be more reflective of patients seen in England and noted that nivolumab + PDC may be less effective in patients from Europe and North America than those in Asia This assumption was verified with expert clinical opinion to the EAG.

The EAG asked the company to update the effectiveness and economic analyses by undertaking two subgroup analyses: 1) on disease stage (Stage IB-II versus Stage IIIA); and 2) using data from North America and Europe only in the points for clarification letter.[15] In their reply, the company argued that CheckMate-816 data were too immature to undertake a subgroup analyses due to low event count but that there was a possibility of revisiting these analyses using data from the next data cut (IA 2).[15] Although the EAG agrees that the data is limited for these subgroup analyses, they would still be beneficial as the data is arguably more applicable to England. The EAG presented subgroup analyses in Section 6 using the available evidence to estimate the effect of these analyses on the ICER and the uncertainty in the results.

Additionally, the EAG had concerns about the Carboplatin-based PDC regimens used in CheckMate-816 and their applicability to the clinical context in England (as previously discussed in Section 3.2.3). The EAG undertook exploratory sub-group analyses using data for patients receiving exclusively Cisplatin-based chemotherapy regimens, and patients receiving only Carboplatin-based treatments (see Table 3.2.3). These results are presented in Section 6.2.

4.2.4 Interventions and comparators

The intervention was nivolumab in combination with PDC (nivolumab + PDC) administered intravenously every three weeks per cycle of administration for three cycles, with a dose per administration of 360 mg for nivolumab and a combination of: cisplatin with either pemetrexed or gemcitabine; or a combination of carboplatin with either paclitaxel, pemetrexed, or gemcitabine. Distributions were based on the intervention arm of CheckMate-816.[1]

The comparators in the company's base-case model included neoadjuvant CRT), adjuvant PDC, and surgery alone. In CS Section B.2 the company report that carboplatin was used in combination with paclitaxel. However, a small number of other combinations were listed in CS Section B3.5.1. Neoadjuvant CRT and adjuvant PDC were modelled as a combination of cisplatin with either pemetrexed, vinorelbine or docetaxel, or a combination of carboplatin with either paclitaxel, pemetrexed, vinorelbine, gemcitabine, or docetaxel; with distributions based on the CheckMate-816

trial.[1] Paclitaxel in combination with gemcitabine was excluded from the bundle of neoadjuvant CRT treatments following clinical expert advice.[1]

Some patients did not receive surgery and the surgical approach was split between thoracotomy and minimally invasive surgery.

EAG comment: The intervention and comparators are consistent with the NICE scope.

4.2.5 Perspective, time horizon and discounting

The economic analysis was undertaken from an NHS perspective. The model followed a state transition (semi-Markov) structure, with a cycle duration of three weeks for a lifetime horizon of 35 years. Both costs and outcomes in the model were adjusted for a half cycle correction and discounted at 3.5% per year after the first year.

EAG comment: The lifetime horizon chosen in the base-case analysis of the model was sufficiently long to capture the healthcare resources use and health outcomes affected by the interventions. Costs and effects were discounted at 3.5%. The approach is in concordance with the NICE reference case. (NICE, 2022D, #54)

The company undertook analysis from the NHS perspective only. Although the PSS perspective is mentioned in the scope, there is no evidence provided by company that this perspective was considered or any justification for why it was not included.

4.2.6 Treatment effectiveness and extrapolation

The process to derive the effectiveness data for the model is summarised as follows.

1. Individual patient data from the CheckMate-816 trial was used to build a lifetime model for a hypothetical cohort of patients.
2. KM curves from the CheckMate-816 trial arms were obtained for EF to LR, EF to any progression, EF to dead, and LR to dead, these data were assessed for PHs and accelerated failure time (AFT).
3. Parametric survival models were fit to the KM curves to extrapolate beyond CheckMate-816 follow-up dates to the patient lifetime horizon, models were chosen primarily based on statistical fit and comparisons with data from the literature, along with clinical expert opinion.
4. Hazards ratios obtained from the NMA were applied to CheckMate-816 data to generate the progression probabilities between EF and LR, and EF and DM, for the valid comparators under NICE's scope. The PDC alone arm in CheckMate-816 was the common comparator in the NMA, therefore survival data for the comparators included within scope were derived from it.
5. The transition probability between LR and DM was derived from expert opinion.
6. The "cure assumption" was applied between years 5 and 7, so that 95% of patients were assumed to be cured by year 7.
7. DM was an absorbing state; there was no explicit transition to dead but as described above pay-offs in terms of costs, LYs and QALYs were applied to those who entered this state.

4.2.6.1 Survival analysis and extrapolation methods

This section surrounds the selection of parametric models that were fitted to the KM CheckMate-816 trial data which were used to derive state transition probabilities.[1] To extrapolate survival across EF and LR health states beyond the trial follow-up, the company followed the guidelines for survival analysis outlined in the NICE Decision Support Unit Technical Support Document 14.[47]

The parametric model selection was as follows: a set of seven parametric functions (exponential, Weibull, Gompertz, log-logistic, log-normal, gamma, and generalised gamma) were fitted to the data of both trial arms and spline models were fitted to the KM data if the seven parametric functions were not a good fit.[1] Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC), supported by a graphical assessment of diagnostic plots, were compared across parametric models to assess fit and PH and AFT assumptions between trial arms.

A further assessment of clinical plausibility between the extrapolated versus the KM curves was informed by expert clinical opinion to the company.[1] Finally, the extrapolations predicted by the model for both arms of the CheckMate-816 trial were compared with constructed conditional survival curves built using data from the literature.

Event-Free to Locoregional Recurrence

The assessment using diagnostic plots suggested that either the PH or the AFT assumptions could hold when fitting parametric models to the two arms of CheckMate-816 using observed data. Therefore, the company extrapolated the time-to-event curve using joint parametric models fitted with the intervention arm as the predictor. The company presented a graph with all of the survival curves in the CS (see CS Figures 32 and 33),[1] but only considered the log-normal and exponential distributions as they provided the best fit based on goodness of fit statistics. Both extrapolations generated substantially different long-term predictions. To address this concern, the company compared time from EF to LR predictions for the PDC arm with two literature sources (see Figure 4.2):

- estimates from a 2014 meta-analysis;[48] and
- the base-case extrapolation used in NICE TA761.[49]

Figure 4.2: Time to Locoregional Recurrence: comparison versus external data – nivolumab + PDC arm

(Source: Figure 34, CS)[1]
(Abbreviations: CM-816 = CheckMate-816; KM = Kaplan-Meier; NSCLC = non-small cell lung cancer; PDC = platinum doublet chemotherapy; SOC = standard of care; TA = technology appraisal)

Figure 4.3: Time to locoregional recurrence: long-term extrapolations (nivolumab + PDC)

(Source: Figure 32, CS)[1]
(Abbreviations: PDC = platinum doublet chemotherapy)

The comparison with the literature led to the company's conclusion that both extrapolations were generally more pessimistic. Nevertheless, predictions from the log-normal distribution for the PDC arm were closer to those in NICE TA761.[49] Therefore, a log-normal distribution was chosen for the company base-case to model time to LR in the EF state.

EAG comment: The EAG considers that the comparison of the survival curves with the literature sources presented adds very limited information, as both studies reported a lower proportion of patients with Stage IIIA disease relative to CheckMate-816.[1,48,50]

The survival curves presented in Figure 4.3 do not account for the cure assumption. The EAG has produced time-to-event curves including the cure assumption (see Figure 4.4). Although the company mentions that clinical expert opinion was consulted for the plausibility of the Log-normal extrapolation,[1] it remains unclear to the EAG which alternative survival curves were presented to the clinical experts and whether the cure assumption was included in these curves.

Figure 4.4: Models of TTLR for PDC alone with and without the cure assumption

(Source: recreated by the EAG using Figure 34, CS.[1]
(Abbreviations: TTLR = time to locoregional recurrence; PDC = platinum doublet chemotherapy; KM = Kaplan-Meier curves)

Finally, the EAG agrees that the selection of the Lognormal distribution over the Exponential distribution to model TTLR better reflects the opinion of clinical experts about likely recurrence outcomes when a cure assumption is not modelled. However, there are other survival curves not presented in Figure 4.4 that may more realistically model TTLR; the EAG presents these in Section 6.

Event-Free to Distant Metastasis

The company considered the time to distant metastasis (TTDM) data to be immature from the available CheckMate-816 data due to the relatively low event count. Instead, the company derived the TTDM curve from a DM hazard rate which was estimated as the difference between the hazard rate of any progression and the hazard rate of a locoregional progression at each time point.

EAG comment: The EAG considers this to be a sensible assumption given the lack of available data.

Time to any progression

Data on TTaP were derived from the CheckMate-816 trial data, with deaths censored. Assessments from diagnostic plots suggested that either the PH or the AFT assumptions could hold when fitting parametric models to the two arms of CheckMate-816 using observed data. Therefore, the company extrapolated the time-to-event curve by jointly fitting parametric models with treatment arm as the predictor. Based on BIC and AIC statistics, the log-normal distribution was the best fitting model. As TTaP (with deaths censored) was not widely reported in the literature, the company applied the chosen log-normal parametric model to CheckMate-816 EFS data (i.e. progression or death) and compared the

EFS long-term predictions across the literature. The company presented four survival curves using the following sources from the literature (see Figure 4.5).

- The previously used NSCLC 2014 meta-analysis.[48]
- A patient-level meta-analysis conducted by the company (see Appendix P in the CS)[6]
- An observational study by the company using real-world data for the USA (see Appendix P in the CS)[6]
- A weighted average of two RCTs, weighted by stage to match the distribution in CheckMate-816.[23,39]

Figure 4.5: Event-free survival: comparison versus external data – PDC alone arm

(Source: Figure 42, CS)[1]
(Abbreviations: BMS = Bristol Myers Squibb; CM-816 = CheckMate816; EFS = event-free survival; MA = meta-analysis; NSCLC = non-small cell lung cancer; PDC = platinum doublet chemotherapy; US = United States)

Finally, the company received input from six clinicians (CS, Appendix N),[6] who all agreed that the log-normal extrapolation provided clinically plausible long-term predictions of EFS (see Figure 4.6**Error! Reference source not found.**).

Figure 4.6: Time to any progression: long-term extrapolations (nivolumab + PDC)

Abbreviations: PDC = platinum doublet chemotherapy

EAG comment: The EAG considers the Log-normal distribution to be an appropriate model based on statistical fit to trial data. Regarding the supporting literature, the EAG notes there are differences in the populations in CheckMate-816 and the studies supplying the comparison time-to-event curves. As previously mentioned, there are considerable differences in disease Stage IIIA proportions across CheckMate-816 ( ) and the 2014 meta-analysis (24%),[48] as well as with the company's own meta-analysis (; CS Appendix P).[6]

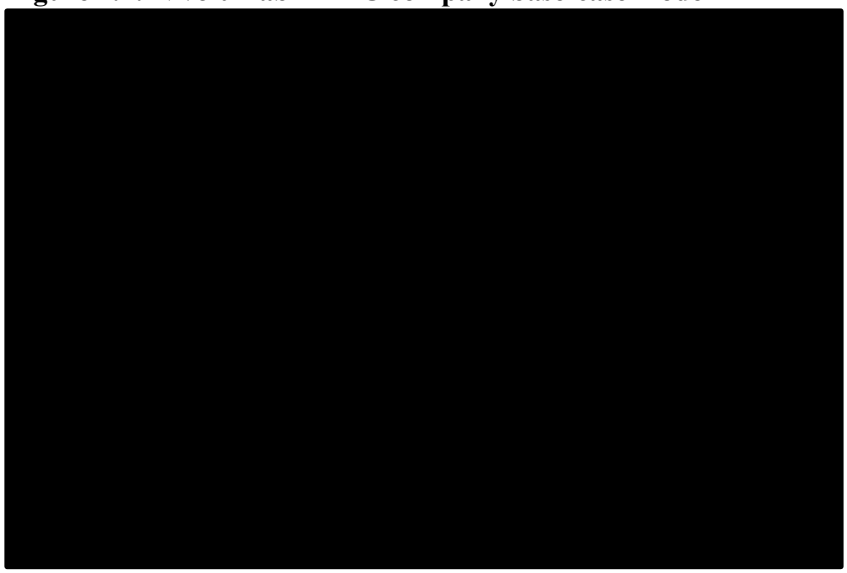
Time to distant metastasis

The approach outlined in Section B3.3.1.3 of the CS reported constructing the time to distant metastasis (TTDM) survival curve from a hazard function of DM as the result of the difference between the hazard rate of any progression and the hazard rate of LR, with both hazards derived directly from CheckMate-816 data.[1] The justification given for following this approach was that the current CheckMate-816 data cut was immature due to the low count of events.

When the hazard rate of LR was greater than the hazard rate of any progression, the hazard rate of DM was capped at 0 to avoid negative transition probabilities.

Figures 4.7 and 4.8 present the survival predictions of TTLR, TTaP, and TTDM made by the company base-case model, including the impact of the cure assumption.

Figure 4.7: Nivolumab + PDC company base-case model



(Source: recreated by the EAG using Figure 43, CS)[1]
(Abbreviations: Nivo = Nivolumab; PDC = platinum doublet chemotherapy; TTLR = time to locorregional recurrence; TTaP = time to any progression; TTDM = time to distant metastasis; KM = Kaplan-Meier curves)

Figure 4.8: PDC alone company base-case model

(Source: recreated by the EAG using Figure 44, CS)[1]
(Abbreviations: PDC = platinum doublet chemotherapy; TTLR = time to locorregional recurrence; TTaP = time to any progression; TTDM = time to distant metastasis; KM = Kaplan-Meier curves)

EAG comment: Given the available evidence, the EAG considers the approach used to derive the DM time-to-event curve to be appropriate. The same parametric distribution was selected for TTLR and TTaP, leading to a plausible time-to-event curve for DM. It is unclear to the EAG whether the plausibility of the TTDM curve, including the implications from the "cure assumption", was discussed with clinical experts.

Locoregional recurrence to distant metastasis

Time from locoregional disease to distant metastasis was not included in CheckMate-816 as a trial outcome. Therefore, the company sought this estimate from the literature and clinical opinion. The company obtained an estimate from the LuCaBIS study[51] and consulted its validity with a group of international clinicians. The clinicians rejected the literature estimate and provided their own set of estimates, which the company used in the base-case model.

EAG comment: The EAG note the average value of all the values provided by KOLs from all geographical regions was used in the base-case. However, the EAG consider the range of values provided by the UK KOLs, including the upper limit of 25%, could have been used in scenario analysis. The company used the LuCaBIS[51] estimates in the scenario analysis, which the EAG does not consider to be appropriate given that these values were rejected by the clinical experts.

Mortality at event-free

The company considered that overall survival data from the current data cut of the CheckMate-816 trial were immature. Furthermore, the company stated that the Kaplan-Meier curves for both treatment arms in **Error! Reference source not found.** (CS, page 111)[1] suggested no difference in mortality at the current trial follow-up, among EF patients between treatment arms. Therefore, both treatment arms were pooled for the parametric survival analysis. Considering the best fit by AIC and BIC, the company compared the parametric model predictions with a constructed survival curve based on the results of a separate patient-level meta-analysis conducted by the company (CS, Appendix P).[6] Mortality rates in the parametric models were capped by general mortality. The company base-case selected an Exponential model for mortality at EF after comparing extrapolations with their patient-level meta-analysis and considering the Exponential distribution to have a good statistical fit to trial data (see Figure 4.9).

Figure 4.9: Patient-level meta-analysis versus long-term event-free mortality extrapolations from CheckMate-816

(Source: Figure 49, CS)[1]

(Abbreviations: CM816 = CheckMate-816; KM = Kaplan-Meier curves)

EAG comment: The data are immature; therefore the extrapolation is highly uncertain. The selection of the parametric model was heavily reliant on the BMS patient-level meta-analysis due to the immature data.[1] It is not clear that the Exponential distribution was the best fit given that the CheckMate-816 KM curve is not as steep as the curve obtained from the BMS patient-level meta-analysis. The EAG uses an alternative model selection in Section 6.1. It is unclear from the CS whether expert opinion was elicited to compare the parametric distributions used to extrapolate overall survival at EF and the implications of the "cure assumption" on these curves.[6]

Mortality after locoregional recurrence

The company followed the same approach for mortality after LR as mortality at EF. The CheckMate-816 data on mortality after LR was pooled across trial arms and a single extrapolation was used to model mortality after LR in all arms. The company considered that Information co-efficient statistics across the models tested had small differences, while a graphical assessment suggested that the models being tested may not offer an appropriate fit to the shape of the KM curves. For this reason, the company used spline knot models to fit the data.

Extrapolations across models were compared with literature sources provided by the company.[1] The studies selected had patients with stages IIIA and IIIB disease,[4,52] rather than patients post-LR survival, due to lack of evidence on survival post LR. The graphical assessment suggests that spline models with 3 and 4 knots generated the most optimistic survival estimates, closer to the literature estimates, while all other models have more pessimistic predictions. A spline model with 3 knots was chosen based on information criterion statistics, although differences across spline models were not large.

EAG comment: The EAG considers the overall approach to model mortality at LR to be generally appropriate. Comparisons between trial data and the literature remain a point of concern, as CheckMate-816 KM curves show more pessimistic survival estimates compared with the literature selected. Differences in disease stage between the literature and the trial add more uncertainty about the usefulness of these comparisons.

4.2.6.2 Network meta-analysis data

Although the control in the CheckMate-816 trial, neoadjuvant PDC, was not a comparator within the scope, in the evidence network neoadjuvant PDC is used as the common comparator. The model applied indirect treatment comparison-derived HRs to generate the survival curves across the treatments relevant to the scope.

Network meta-analysis: TTLR and TTDM

Tables 4.6 and 4.7 report the TTLR and TTDM HRs estimated from the CheckMate-816 trial and the NMA; these values were extracted from the CEM. The company deemed evidence from the NMA to be highly uncertain, which was illustrated by the large CIs around the estimated HRs.

Considering that the base-case extrapolation of TTLR in the model followed a parametric log-normal distribution, the HR between treatment (neoadjuvant nivolumab + PDC) and comparator (neoadjuvant PDC alone) was not assumed constant over time. This also applied to the other treatments from the NMA, as they assumed PHs with the trial comparator (Neoadjuvant PDC alone). This was also the case in TTDM, as this was made of two survival functions with log-normal distributions.

Table 4.6: HRs for time to LR

Intervention	HR	95% CI	Source
Nivolumab + PDC	[redacted]	[redacted]	CheckMate-816
Neoadjuvant CRT	[redacted]	[redacted]	NMA
Neoadjuvant PDC	Reference		
Surgery alone	[redacted]	[redacted]	NMA
Adjuvant PDC	[redacted]	[redacted]	Expanded NMA

Source: Figure 23, CS.[1]
Abbreviations: HR = hazard ratio; LR = locoregional recurrence; CI = confidence interval; NMA = network meta-analysis; PDC = platinum doublet chemotherapy; CRT = chemoradiotherapy.

Table 4.7: HRs for time to DM

Intervention	HR	95% CI	Source
Nivolumab + PDC	[redacted]	[redacted]	CheckMate-816
Neoadjuvant CRT	[redacted]	[redacted]	NMA
Neoadjuvant PDC	Reference		
Surgery alone	[redacted]	[redacted]	NMA
Adjuvant PDC	[redacted]	[redacted]	Expanded NMA

Source: recreated by the EAG using Figure 25, CS.[1]
Abbreviations: CRT = chemoradiotherapy; HR = hazard ratio; DM = distant metastasis; CI = confidence interval; NMA = network meta-analysis; PDC = platinum doublet chemotherapy; CRT = chemoradiotherapy.

EAG comment: In the NMAs that were conducted to estimate the HRs of LR and DM, fewer studies with the most recent generation chemotherapy regimens reported LR and DM outcomes than EFS outcomes. The company reported that they considered the estimates to be uncertain. The 95% CrIs were wide. In addition, trial arm hazard rates were estimated using the proportion of patients experiencing LR or DM events, but not both. The HR estimates for LR and DM for the comparators were very different, far more different than the LR and DM HR estimates for nivolumab + PDC compared to PDC. This could be due to differences in the nature of the interventions. The company argues that neoCRT is more likely than other interventions to reduce LR than DM. But part of it could also be due in part to differences in data collection and the data reported (see section 3.3.1.3 above for further discussion). The EAG also considers these HR estimates to be highly uncertain.

The HR for the comparators versus neoadjuvant PDC was assumed to be constant over time. In contrast, the implied HR of any progression for nivolumab + PDC versus neoadjuvant PDC changed over time. On the one hand, a constant hazard ratio for the comparators could be a strong assumption- the implied hazard ratio for nivolumab gets closer to 1 over time. On the other hand, the implementation of a cure assumption limits that benefit and perhaps favours the lower hazard ratios for nivolumab + PDC early in the model. The implications and clinical justification for these assumptions were not discussed in the CS. However, while the company could have presented results for EFS using a model that would allow for time-varying hazard ratios, this is unlikely to have been possible for LR and DM outcomes given the available data.

The implied HR of any progression for nivolumab + PDC versus the model comparators are presented in Figures 4.10 and 4.11.

Figure 4.10: Hazard ratios for TTLR

(Source: recreated by the EAG using data from the CEM)
(Abbreviations: TTLR = time to locoregional recurrence; PDC = platinum doublet chemotherapy; HR = hazard ratio; CRT = chemoradiotherapy)

Figure 4.11: Hazard ratios for TTDM

(Source: recreated by the EAG using data from the CEM)
(Abbreviations: TTDM = time to distant metastasis; PDC = platinum doublet chemotherapy; HR = hazard ratio; CRT = chemoradiotherapy)

4.2.6.3 Distant metastasis

In the CEM, patients enter the DM health state after experiencing a progression to DM from the EF or LR health states and they remained in the DM health state until death. In the DM health state, patients were expected to receive a mix of therapies for first-line metastatic disease. Rather than modelling each of these treatments separately, the CEM applied 'one off' LYs, QALYs and costs. This means the DM state acts as an absorbing state like death. The CS states that this approach was used to reduce the complexity of the model and cite that this was considered pragmatic by the NICE appraisal committee

in TA544.[45] The CS also cites how this was considered appropriate by a Global HTA advisory board and in TA705,[46] where the CEM was criticised for being too complex.

In calculating the overall LYs, QALYs and costs using a 'one off' approach, three treatment options were considered: chemotherapy, immune-oncology therapies and no treatment. LYs, QALYs and costs were calculated for each of these treatment options and then multiplied by the proportion expected to be in each treatment following transition into the DM state. To reduce uncertainty in this part of the model, cost, LY and QALY data for the different treatment options were obtained from previous NICE STAs related to NSCLC (TA531, TA584, TA683, TA770),[53-56] which were supplied to the EAG by NICE. These results are presented in the confidential appendices.

The company sourced alternative 'placeholder' values for costs, LYs and QALYs, which were used in the base-case model in the CS.[1] These values were obtained from TA724.[57] As two relevant subsequent treatments were not available in TA724,[57] these were sourced from a submission of nivolumab + ipilimumab to the Scottish Medicines Consortium.[58] Due to a further absence of data, the value for atezolizumab monotherapy was set equal to the other monotherapy available to the UK, pembrolizumab. It was also assumed, based upon expert opinion, that some patients eligible for first line metastatic treatment would receive BSC only (25%), and that the HR compared with patients receiving PDC would be 0.9. This HR was used to generate the LYs and QALYs for the BSC treatment arm. These inputs are shown in Table 4.8 below.

Table 4.8: Inputs for Distant Metastasis health state

Outcome	Pembrolizumab	Pembrolizumab + carboplatin + paclitaxel (squamous)	Pembrolizumab + carboplatin + paclitaxel (nonsquamous)	Atezolizumab + carboplatin + paclitaxel (nonsquamous)	PDC	BSC
LYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Source: Figure 44, CS.[1]
Abbreviations: LYs = Life Years, QALYs = Quality-Adjusted Life Years, PDC = Platinum Doublet Chemotherapy, BSC = Best Supportive Care

In the CS, the distributions of treatment in the DM health state were taken from 'BMS market share data on file.'[1,59] The company provided no detail on how these market share figures were derived in the CS. Following the points for clarification, the company stated that these data were based on quantitative market research from a rolling sample of 50 UK-based physicians, where the clinicians are asked to provide details of the current treatments they use.[15] As previously mentioned, it was assumed that 25% of the patients eligible for first line metastatic treatment would receive BSC. These data are shown in Table 4.9 below.

Table 4.9: Distribution of treatment in Distant Metastasis health state in CS

Treatment	Pembrolizumab	Pembrolizumab + carboplatin + paclitaxel (squamous)	Pembrolizumab + carboplatin + paclitaxel (nonsquamous)	Atezolizumab + carboplatin + paclitaxel (nonsquamous)	PDC	BSC
Nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25.0%
PDC (Neoadjuvant)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25.0%
Neoadjuvant CRT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25.0%
PDC (Adjuvant)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25.0%
Surgery only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25.0%

Source: Figure 44, CS.[1]
Abbreviations: CS = Company Submission, PDC = Platinum Doublet Chemotherapy, BSC = Best Supportive Care, CRT = Chemoradiotherapy

In the CEM, immuno-oncology (I-O) therapy retreatment restrictions were applied for patients who received nivolumab + PDC as their initial treatment and progressed within six months. These patients were not considered eligible for further I-O treatment. Data from CheckMate-816 were used to adjust the distribution of treatment in the DM health state to account for the fact that 15.1% of patients in the nivolumab + PDC arm experienced an event while on treatment. Hence, these patients were not eligible for further treatment with I-O therapy for six months and their treatments were redistributed across the remaining treatment options. A scenario analysis was included by the company where this retreatment restriction was extended to 12 months and the percentage of those not considered for further I-O retreatment therefore increased to 23.6%. Another scenario analysis was conducted where the retreatment restriction was not included.

In the updated CEM provided to the EAG by the company following the points for clarification,[15] different distributions of treatment for those in the DM health state in the nivolumab + PDC arm were stated than what was presented in the CS.[1] The distributions for the other treatment arms remained the same as reported in the CS. The distributions for the nivolumab + PDC arm included in the CEM are shown in Table 4.10.

Table 4.10: Distribution of treatment in Distant Metastasis health state in CEM

Treatment	Pembrolizumab	Pembrolizumab + carboplatin + paclitaxel (squamous)	Pembrolizumab + carboplatin + paclitaxel (nonsquamous)	Atezolizumab + carboplatin + paclitaxel (nonsquamous)	PDC	BSC
Nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25.0%
Source: Updated CEM following points for clarification[15] Abbreviations: PDC = Platinum Doublet Chemotherapy, BSC = Best Supportive Care						

EAG comment: Overall, the EAG notes that the approach to modelling the DM state was appropriate. The EAG agrees that the 'one-off approach' for LYs, QALYs and costs incurred in the DM health state was a pragmatic decision by the company, which reduced the complexity of the CEM. The EAG also note that the placeholder values used by the company are subject to a significant level of uncertainty. However, this is noted by the company in the CS and justified by the collection of published committee papers from the NICE website to be used by the EAG in the confidential appendices.

The EAG note that the distributions of treatment in the DM state were based on 'BMS market share data on file.' No further information regarding this market share data was included in the CS and the EAG were therefore unable to scrutinise this further. The company also did not provide any information regarding the clinical expert opinion used to derive the figure of 25% for those only receiving supportive care and the HRs in relation to PDC. In response to the points for clarification letter.[15] the company clarified that the data were based on quantitative market research from a rolling sample of 50 UK-based physicians, where the clinicians are asked to provide details of the current treatments they use. Despite this clarification, given the lack of detail regarding what the clinical experts were asked exactly, the EAG considers the distributions of treatment and the estimated hazard ratio to be uncertain.

The EAG note that for the nivolumab + PDC treatment arm, the distributions of treatment for DM were adjusted using data from CheckMate-816 to consider the events experienced whilst on treatment and subsequent ineligibility for further treatment with I-O (15.1%). However, the EAG were unable to find the source for this figure in the CS and were therefore unable to scrutinise this issue further.

Furthermore, the EAG note that no retreatment restrictions were considered for the other treatment arms. Alternatives to this assumption were explored in the EAG analysis in Section 6.

The EAG note that no cost estimate was included for BSC (palliative care only). No explanation in the CS is given regarding this assumption. However, the EAG note that including a cost for palliative care reduces the ICER for the nivolumab + PDC treatment arm.

There were uncertainties associated with the placeholder values provided by the company in the CEM, although these uncertainties were addressed in the EAG analysis. The EAG also note that the distributions of treatment in the DM health state were not based on optimal evidence and are therefore subject to uncertainty and there is uncertainty regarding the retreatment restrictions for patients receiving I-O treatments.

4.2.6.4 Cure assumption

In the CEM, a cure assumption is implemented in the EF health state, defined as:

- no risk of progression;
- no excess cancer-related mortality compared with the age- and sex-matched population

The CS notes there are two potential methods that may be used to account for cure: the "uninformed" and "informed" approach. In the "uninformed" approach, the cure fraction is based on the long-term survival estimates from the relevant trial.[1] The CS states that, as no plateau suggesting cure was observed in the KM data from CheckMate-816 due its immaturity, this approach was ruled out, and an "informed" approach using long-term observations and clinical expert opinion was used.

The CS states that the evidence for the inclusion of the cure assumption rested on three key pillars:

- engagement with clinical experts;
- precedent from NICE appraisals TA761[49] and TA823;[5,60] and
- empirical evidence from Demicheli *et al.,* (2012)[61] and a variety of studies related to neoadjuvant PDC.

As described in Appendix N of the CS,[6] engagement with clinical experts took the form of a UK HTA clinical expert meeting in March 2022 and a Global HTA advisory board meeting in May 2022. In these meetings, both groups were asked about the plausibility of cure in NSCLC, as well as the timepoint and the proportion of patients achieving cure. The CS reports there was broad consensus that cure was plausible and that five years was an appropriate timepoint. There was no clear consensus on the percentage of patients achieving cure.[1]

The CS also cites two recent NICE appraisals in early-stage NSCLC which included a cure assumption (TA761 and TA823).[5,49] In NICE TA761, it was assumed that 95% of patients who were progression-free at five years would be cured and return to the mortality expected from an age- and sex-matched population without cancer.[49] The EAG on TA761 noted that the five-year timepoint was "too generous" and opted for an eight-year time point as their base case. In TA823, a cure proportion of 91.5% was assumed, based on published literature, and a five-year cure timepoint was again applied.[5] The NICE committee agreed there was uncertainty regarding both the timepoint and proportion but agreed that a cure timepoint of six or seven years would be plausible.

Two further bodies of evidence were cited in relation to the cure assumption. The first, Demicheli *et al.,* 2012,[61] investigated how the hazard of different types of progression changes over time among patients with resected, early-stage NSCLC. The CS notes that the results appear to suggest a fluctuating

risk of recurrence over the first five years after resection, which approaches zero at approximately five years.[1] The CS also cites several studies evaluating long term EFS outcomes for neoadjuvant PDC, which appear to show that EFS curves flatten after approximately five years.

The three inputs that are used in the CEM to take account of the cure assumption are the proportion of patients achieving cure, the time point in which cure is applied, and the period over which the cure occurs. The parameters used in the base case are shown in Table 4.11 below.

Table 4.11: Base-case cure parameters

Parameter	Input
Time at which patients in EFS begin to be considered cured	5 years
Time from beginning to end of cure process	2 years (Year 5 to Year 7)
Percentage of patients cured at completion of cure process	95%
Source: Table 46, CS.[1] Abbreviations: EFS = Event Free Survival	

In response to the clarification letter,[15] the company clarified that in reality, patients have been cured since surgery but clinicians cannot determine who will be cured after surgery. The company also stated that current clinical practice is to consider a patient cured if they have not had a recurrence at five years. However, even if a patient has not experience reoccurrence at five years, clinicians can only be certain that the probability of recurrence is low. The company used this as their rationale to assume that 5% of patients will remain at risk of recurrence after five years. The company also stated in their response that, although alternative modelling approaches could have been applied, fitting explicit cure models when limited data is available has previously been prone to biases.[62]

Given the uncertainty regarding this cure assumption, the percentage of those cured, the cure onset and the length of the cure process were tested as part of the company scenario analyses, with all analyses making very little difference to the ICER.

EAG comment: Given the immaturity of the data, there is considerable uncertainty in the extrapolations of time to recurrence. The EAG acknowledges that the use of long-term, applicable external data and clinical expert opinion would be useful in selecting time-to-event models and assumptions. The company described three pillars of evidence.

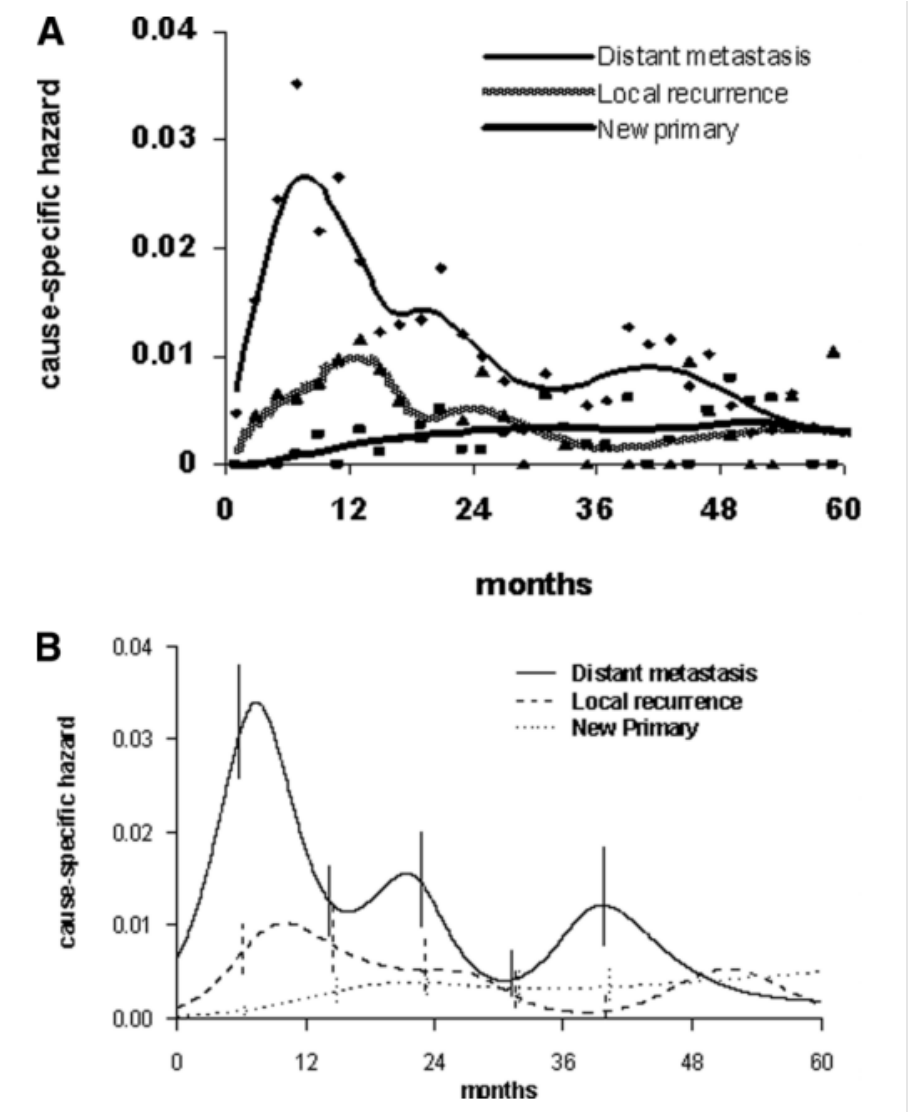
In relation to the first pillar of evidence, the EAG notes that although Appendix N states that there was a "consensus around a timepoint of 5 years" by clinical experts for the cure assumption, the meeting notes also state that proportion is more difficult to predict, and the model should include flexibility to test different thresholds.[6] Moreover, the EAG notes that in the UK HTA clinical expert meeting (March 2022), "the advisors disagreed on if, and when, a patient might be considered cured". It is unclear from both sets of meeting notes[63] what data the clinical experts were presented with and how the conclusions from the clinical experts were reached. The cure assumption was discussed with the EAG's clinical advisor, who agreed that it was reasonable but could not provide any data to support this assumption.

The second pillar on which the cure assumption is based is precedent from NICE appraisals TA761[49] and TA823.[5] The EAG notes that the cure assumption has been used in previous NICE appraisals. An example of an EAG critique in a previous appraisal is in TA761: 1) there is a lack of clinical evidence beyond expert opinion to support the cure assumption; 2) except for the Gompertz distribution none of the other models fitted to trial data seem consistent with the cure assumption as framed by the company;

and 3) the hazard function of distributions like Gompertz and Generalised-Gamma resemble the cure assumption (as framed by the company base-case) for TTLR and TT-any progression, therefore applying a cure assumption through the model settings has a limited impact on these distributions.[49]

The final pillar on which the cure assumption is based consists of two bodies of empirical evidence. In Demicheli *et al*., 2012,[61] a significant proportion (41%) of the study participants had Stage IA cancer. Consequently, HRs could potentially be higher in a Stage IB-IIA population. Furthermore, although the Figure presented by the company in the CS (Panel B in Figure 4.12 below) shows that the hazard of progression is low at five years, there are no data beyond 60 months with which to validate the cure assumption. There appears to be a multi-modal distribution of hazard rates. There could be another peak after 60 months.[61]

Figure 4.12: Hazard of progression in early-stage resected NSCLC



(Source: Demicheli *et al.,* (2012)[61] figure reproduced here without permission)
(Note: Panel A = Hazard Rate with Two Month Interval, Panel B = Smoothed Curves using Kernal Smoothing Procedure)
(Abbreviations: NSCLC = non-small cell lung cancer)

In the second body of evidence, the variety of studies cited by the company in Appendix P[6] evaluate long-term EFS outcomes in relation to neoadjuvant PDC to support the cure assumption. The EAG

notes that the studies include a variety of different countries, study populations and use different methodological approaches. Although comparable in relation to some patient characteristics (such as median age and the percentage of males included), both the NSCLC Collaborative Group[64] and BMS meta-analyses[63] cited were not comparable to CheckMate-816 in terms of cancer stage. Although the US oncology study[59] was comparable regarding cancer stage, it was a retrospective observational study and not comparable in terms of PS (i.e. activities of daily living).

The company also constructed separate survival curves from the Felip *et al*., 2010[39] and Pless *et al*., 2015[23] clinical trials, weighted to reflect the patient distribution in CheckMate-816. However, no further information regarding this curve construction was given in the CS and therefore the EAG are unable critique these methods further. Furthermore, in Figure 4.13 below, the studies that show a plateau have close to zero patients at risk at that point (for example Pless *et al*., 2015 and Scagliotti *et al*., 2012).[22,23] Studies with larger sample sizes (for example the BMS meta-analysis and the NSCLC Collaboration Group)[63,64] do not indicate a plateau within this timeframe.

Figure 4.13: Long-term EFS from neoadjuvant PDC studies

(Source: Figure 59, CS)[1]

(Abbreviations: BMS = Bristol-Myers Squibb; EFS = Event-free survival; NSCLC = Non small-cell lung cancer; CG = Collaboration Group)

Overall, no convincing clinical evidence was provided to support any of the three cure assumption pillars. There is consensus among clinical experts (both the company's and EAG's) who believe only a small percentage of patients alive and event free at a particular uncertain time point experience a recurrence. Patients who are cured are in fact cured since surgery and the recurrence events in the KM curve are the events for the patients who are not cured. Employing the company's approach to the cure assumption results in a sharp deviation from the time-to-recurrence curve associated with those not cured. A two-year period of moving from 0% cure assumption to a 95% cure assumption was not supported by evidence and was more pragmatic than assuming an immediate transition. The EAG

acknowledges that the company has taken a pragmatic approach to modelling the cure assumption but presents alternative modelling approaches in Section 6.2.

4.2.7 Adverse events

Costs and disutilities associated with the different treatments to manage adverse events (AEs) were included in the CEM. Lower grade AEs (Grade 1 and 2) were not considered in the CEM as these were not assumed to have a significant impact on costs or quality of life. These lower grade AEs were not reported in the CS and therefore the EAG were not able to assess these. Grade 3 and 4 AEs were considered in the CEM, specifically those events experienced by at least 5% or more of patients in at least one of the comparators included in the model. AEs experienced by less than 5% of the patients in at least one of the comparators were not included in the CS and therefore the EAG were unable to assess these. Furthermore, only AEs associated with initial (i.e. current line) treatments were considered, with the AEs associated with subsequent lines (e.g. second line) of treatment not considered.

The AE profiles of the different treatment arms were gathered from a variety of difference sources. The AE profiles of the nivolumab + PDC and neoadjuvant PDC arms were taken from CheckMate-816. The AE profile of the neoadjuvant CRT arm was assumed to be the same as neoadjuvant PDC. In response to the clarification letter,[15] the company explained that this assumption was based on a single paper from the SLR reporting AEs for RT. The AE profile of the adjuvant PDC was taken from an SLR previously undertaken by BMS. AEs were not considered to be applicable to the surgery alone arm as these patients did not receive a systemic therapy. No scenario analyses were conducted in relation to the AE profiles of the different treatment arms. A summary of Grade 3 and 4 AEs are presented in Table 4.12 below.

Table 4.12: Percentage of patients experiencing grade 3 or 4 adverse events

Event	NIVO+PDC	Neoadjuvant CRT	Adjuvant PDC	Surgery only
Anaemia	4.0%	5.1%	8.2%	0.0%
Neutropenia	16.5%	22.7%	51.1%	0.0%
Leukopenia	1.7%	3.4%	16.3%	0.0%
Thrombocytopenia	2.3%	0.6%	5.2%	0.0%
Fatigue or asthenia	0.6%	1.7%	10.9%	0.0%
Nausea and/or vomiting	2.2%	1.2%	13.7%	0.0%

Source: Table 47 CS.[1]
Abbreviations: CRT = chemoradiation; NIVO = nivolumab; PDC = platinum doublet chemotherapy

The CS stated that the CEM estimated the QALY loss due to AEs for each treatment arm using the treatment-specific AE rates, mean utility decrements and mean duration of each AE episode.[1] The total mean QALY loss and costs of AE management were applied once at the start of the model, assuming that AEs occurred only once during the first model cycle.

The disutility values for the AEs included in the model are presented in Table 4.13 below. Utility decrements associated with these AEs were not collected as part of the CheckMate-816 trial, and therefore were sourced from Nafees *et al*., (2008), which estimated utility values for AEs using the

standard gamble (SG) method.[65] If there were no data on specific AEs, utility decrements were based on assumptions. No scenario analyses were conducted in relation to the AE disutilities.

Table 4.13: Adverse event-related disutilities

Adverse Event	Disutility	Reference/Note
Anaemia	−0.08973	Assumed the same as neutropenia
Neutropenia	−0.08973	Nafees *et al*., (2008)[65]
Leukopenia	−0.08973	Assumed the same as neutropenia
Thrombocytopenia	−0.08973	Assumed the same as neutropenia
Fatigue or asthenia	−0.08973	Nafees *et al*., (2008)[65]
Nausea and/or vomiting	−0.07346	Nafees *et al*., (2008)[65]
Source: Table 51 CS.[1]		

EAG comment: The EAG consider the CheckMate-816 trial to be the most appropriate source of AE profile for the nivolumab and neoadjuvant PDC treatment arms. The EAG consider the assumption that the neoadjuvant CRT AE profile was the same as the neoadjuvant PDC AE profile to be reasonable. It is unclear from the BMS SLR[1] or Appendix D[6] how the AE profile for the adjuvant PDC treatment arm was calculated and therefore these values are associated with some uncertainty, particularly given the relatively high values for some of the AEs (for instance Neutropenia – 51.1%). The EAG consider the assumption of no AEs for the surgery treatment arm to be a strong assumption given the possible complications that may arise during surgery. Therefore, the CEM is potentially underestimating additional costs and disutilities associated with AEs from surgery, which could be important given the probability of surgery is different for each of the treatment arms. However, the EAG note that this is a conservative assumption.

The EAG consider restricting the AEs included to Grade 3 and 4 only to be a strong assumption, given that some common Grade 1 or Grade 2 AEs (such as diarrhoea) may be experienced for a high proportion of those in the model for an extended period of time. However, the EAG note that this is a typical assumption made in economic models of this nature. Data regarding the proportion of Grade 1 and 2 AEs in each treatment arm were not reported in the CS and therefore the EAG were unable to investigate this matter further. However, the EAG note that the inclusion of Grade 1 or 2 AEs or the inclusion of AEs from subsequent treatment lines is likely to have a minimal impact on the overall results.

It was assumed that AEs occurred once within the first cycle of the model and were associated with one-off costs and disutility values, multiplied by the incidence to calculate total disutility. This is a standard assumption made in economic models of this nature and previous TARs, for instance TA761.[49] However, this implies that these AEs are transitory and that there are no persisting impacts on individuals over time. Although this assumption may be valid for certain Grade 3 or 4 AEs, this may not be the case for others (e.g. fatigue). Therefore, it is possible that the CEM has underestimated the disutilities associated with the AEs. However, the EAG notes that this is unlikely to have a large impact on the overall results.

The EAG notes that the estimates of disutility sourced for neutropenia, fatigue/asthenia and nausea/vomiting from Nafees *et al*., (2008)[65] have been used in previous TARs and are likely to be the best available estimates for these conditions. The CS notes that there is a more recent study by Nafees *et al*., (2017),[66] which used the time-trade off (TTO) method which could have alternatively been used.

However, given the higher utilities generated by the SG method and the AE profiles of the different treatments, this was a conservative assumption. The EAG agrees with the use of these utility values (rather than the values from Nafees *et al*., 2017).[66] Following the points for clarification,[15] the company stated that because the AEs were expected to have a minimal effect on the results, alternative assumptions were not explored for these utilities.

In the CS, the disutility values for anaemia, leukopenia and thrombocytopenia were assumed to be the same as neutropenia.[1] In TA416 (Osimertinib for treating EGFR T790M mutation-positive advanced NSCLC)[67] and TA761 (Osimertinib for adjuvant treatment of EGFR mutation-positive NSCLC after complete tumour resection),[49] the disutility associated with neutropenia was estimated to be 0.09, in line with the estimate from Nafees *et al*., 2008.[65] In TA416[67] and TA761,[49] the disutility associated with anaemia was assumed to be 0.073. In TA761,[49] the disutility associated with thrombocytopenia was assumed to be 0.05. Therefore, it is possible that the disutilities for anaemia and thrombocytopenia have been slightly overestimated in the CEM. Following the points for clarification,[15] the company provided alternative utility decrements for anaemia and thrombocytopenia. These utility values were explored in the EAG analysis.

The durations of all AEs were assumed to be one week in length. This information was not provided in the CS but was in the CEM. No justification, either empirical or through expert clinical opinion, was given for this assumption. Following the points for clarification,[15] the company stated that, given the short duration of neoadjuvant treatments, a one week duration was considered reasonable. Previous TARs in this clinical area, such as TAR416,[67] have assumed longer time horizons for AEs (four weeks). This may be particularly pertinent for longer term conditions such as fatigue. Alternative assumptions were explored in the EAG analysis (see Section 6).

In summary, the EAG notes that several assumptions were made by the company regarding the AEs in relation to their profiles, disutility values and durations. Overall, the EAG considers the company's approach to including disutility values for AEs in the CEM to be consistent with previous TARs and economic models of this type. Furthermore, the EAG acknowledges that the effect of AEs on the ICER is likely to be negligible due to their relatively low frequency, short duration and relatively small utility decrements.

4.2.8 Health-related quality of life

4.2.8.1 Health-related quality of life data identified in the review

An SLR was undertaken to identify HRQOL studies associated with neoadjuvant, peri-adjuvant, and adjuvant treatment of early-stages (stages I-IIIa) NSCLC in Australia, Canada, France, Germany, Italy, Spain, the UK, and the US (see Section 4.1). As discussed in CS Appendix H, 10 eligible papers reporting PROs and QoL in patients with early-stage NSCLC in the UK (n = 1), US (n = 2), France (n = 2); Australia (n = 2 publications on 1 study population) and Canada (n = 3) were identified.[6]

The studies included the following HRQOL measures: Lung Cancer Symptom Scale (LCSS); Functional Assessment of Cancer Therapy–Lung (FACT-L) score; and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). In addition, one study reported the impact of side effect on patients' HRQOL. None of the studies reported utility data. The company specified in the CS that since no studies used the EQ-5D or undertook a mapping exercise to derive utilities, data extraction of the identified studies was not undertaken. Instead, utility values from the CheckMate-816 trial were used in the CEM.

EAG comment: The SLR identified a large range of studies in the targeted countries. The company only presented HRQOL data narratively in Appendix H because none of the studies identified estimated utility values.[6]

4.2.8.2 Health state utility values

Given that no utility values were identified from the SLR the company used utility values from the CheckMate-816 trial in the CEM.[1,13] These data were collected at various points over the treatment period depending on whether the patient was in the neoadjuvant or adjuvant period. Although not stated in the CS, it was by assumed by the EAG that the EQ-5D-3L value set currently recommended by NICE was used to convert responses into utility scores.[33] Non-treatment-specific utilities by health state were used for all comparators equally. These utility values are presented in Table 4.14.

Table 4.14: Summary of utility values for cost-effectiveness analysis

Health State	Mean Utility Value (Standard Error)	95% CI
Event-Free	[redacted]	[redacted]
Locoregional Recurrence	[redacted]	[redacted]

Source: Table 49 CS.[1]
Abbreviations: CI = Confidence Interval

To account for the fact the utility value for EF was higher than the mean age- and sex-adjusted utility value for the general population at age of entry into the model (63.9 years), the EF value was capped at this general population utility in the base-case, with the utility decrement from EF to LR estimated from the CheckMate-816 trial applied to this capped value. These adjusted utility values are shown in Table 4.15. A scenario analysis was conducted by the company using the unadjusted trial values.[68]

Table 4.15: Alternative utility estimates used in the base case and scenario analysis

	Source	EF	LR	LR to EF Decrement
Base case	CM-816 EF capped with general population, with LR decrement from CM-816	0.833	[redacted]	[redacted]
Scenario	Unadjusted values from CM-816	[redacted]	[redacted]	[redacted]

Source: Table 50 CS[1]
Abbreviations: CM-816 = CheckMate-816; EF = Event-Free; LR = Locoregional Recurrence.

An age adjustment was applied to all utility values in the CEM. This age-adjustment was based on the latest NICE DSU report specifically using values from the 2014 wave of the Health Survey for England (HSE).[44] Specifically, an age adjusted multiplier was assigned to each age in the model by comparing the EQ-5D estimate with the reference utility. A weighted average was calculated using information on the proportion of males and females in the model. The age-adjusted values in the model were therefore derived by multiplying the utility value for each health state by the age-specific adjustment value.

EAG comment: The utility values for EF and LR were originally sourced from the CheckMate-816 trial. Although this was in line with the NICE reference case, as only 23% of the participants in the trial were from Europe (with most participants from North America and Asia) it is unclear how generalisable these health state values are to the English population.

As the data from the CheckMate-816 trial showed no statistically significant difference between treatment arms, the CS assumed that the overall utilities were appropriate to be applied to all treatment arms, instead of using treatment-specific utilities. The overall and treatment-specific utilities are presented in Table 4.16.

Table 4.16: Utility values in model and patient numbers

	Model without Treatment	**Model with Treatment**		
Health State	**Overall**	**Overall**	**NIVO + PDC**	**PDC**
No. of patients/no. of observations				
Pre-progression or recurrence	[redacted]	[redacted]	[redacted]	[redacted]
LR	[redacted]	[redacted]	[redacted]	[redacted]
DM	[redacted]	[redacted]	[redacted]	[redacted]
Least squares means (95% CI)				
Pre-progression or recurrence	[redacted]	[redacted]	[redacted]	[redacted]
LR	[redacted]	[redacted]	[redacted]	[redacted]
DM	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 48 CS[1]

Abbreviations: CI = confidence interval; DM = Distant Metastasis; LR = Locoregional Recurrence; NIVO = nivolumab; PDC = platinum doublet chemotherapy; UK = United Kingdom.

The EAG does not consider this to be best practice, as this assumes that a lack of evidence is the same as evidence of no difference. Whilst the difference in utility values between EF and LR in the different trial arms are relatively small ([redacted] and [redacted] respectively), and therefore the impact on the overall results may be minimal, the different utility values should have been used for the different treatment arms and the imprecision explored in a probabilistic sensitivity analysis.

Furthermore, in the CEM, the other comparators in the model (neoadjuvant CRT, adjuvant PDC and surgery only) are assumed to have the same level of utility in both the EF and LR health states without any justification (either empirical or expert clinical opinion). The health state utility values for these other comparators are therefore associated with a substantial level of uncertainty. No scenario analyses were conducted in relation to these utility values, aside from setting them to the unadjusted value for LR.

The EAG notes that the SLR did not identify any eligible studies that had either used or mapped to the EQ-5D, in line with the NICE reference case,[13] and were therefore seen as being unsuitable. However, the EAG notes that 'surgery' was not included in the search terms for this SLR, The company was asked about the absence of surgery-related terms in the points for clarification (Question A26) and responded that all surgery-related economic evaluation studies would be expected to be captured as they would be picked up as part of studies looking at neoadjuvant or adjuvant treatments.[15] Despite this clarification, the EAG are concerned that potentially important studies related to HRQOL post-surgery could potentially have been missed.

The pooled unadjusted utility values from CheckMate-816 were reported as [redacted] for EF and [redacted] for LR. Given that the age-adjusted utility value for the general population at 63.9 years was 0.833, the CheckMate-816 data suggest that the utility of being in EF is higher than the average utility value of the general population at age 63.9 and the utility of being in LR is only [redacted] below this average utility value. Whilst the UK general population utility values include individuals with long-term health conditions and some individuals who are very ill, the EAG consider the utility values for EF and LR to be improbable and therefore subject to substantial uncertainty. This was acknowledged by clinical experts in the UK HTA clinical validation meeting in the CS Appendix N.[6] The EAG notes that no alternative utility values or value ranges were suggested by the clinical experts to be included in the scenario analyses. In their response to the points for clarification, the company confirmed that although clinical experts thought the utility value from CheckMate-816 for EF was 'marginally' higher than expected, they did not provide an alternative value that they thought would be more clinically plausible. The CS acknowledges that these values were higher than expected and states that there are "2 key reasons why utility values might be expected for patients with NSCLC in the UK." However, this sentence is not expanded upon in the CS.[1] This sentence was removed from company submission received after the points of clarification (CS2).[25] Clinical advice to the EAG agreed that this utility value was higher than expected and estimated that the true value was 10-20% lower.[25]

It is also worth noting that the UK HTA clinical validation panel were of the opinion that the decrement from EF to LR was smaller than expected. Expert advice gathered by the EAG also agreed with this conclusion and estimated the utility difference to be between 0.15-0.20. However, when the company capped the utility value of EF, as described above, they still assumed the observed utility decrement from EF to LR from CheckMate-816 ([redacted]). The EAG notes that this type of assumption has been made in previous TAR submissions (e.g. TA689).[69] The CS notes that, due to the clinical validation panel regarding this absolute decrement as lower than clinically expected, this can be considered a conservative assumption in relation to the treatment effect.[1] In their response to the points for clarification,[15] the company expanded upon this point, stating that one clinical advisor thought the utility value for LR would be around 0.75 and reiterating that this lower value was not used as it was a non-conservative assumption that may overestimate the benefit of nivolumab. Other potential adjustment methods, for example calculating the decrement as the relative difference between the EF and LR utilities from the CheckMate-816 trial rather than the absolute difference, were not considered in the CS.

In the presence of high and potentially implausible utility values, the EAG in TA653[60] explored the impact of using the utility values generated using the standard gamble method from Nafees *et al*., 2008[65] for 'Stable' (0.653) and 'Progressed' (0.470) disease in a scenario analysis, despite these utilities being taken from a general population sample and descriptors based on breast cancer health states. Despite the potential lack of robustness of utilities from Nafees *et al.,* 2008,[65] the use of these utility values was explored as part of the EAG scenario analysis in Section 6.

The EAG also notes that the utility values applied have been derived using linear mixed models (with repeated measures), which assume the normality of residuals. EQ-5D-3L utility data are known to have a non-normal distribution. Therefore, alternative models, such as the adjusted limited dependent variable mixture model,[70] may have been more appropriate to analyse these data. There is no evidence in the CS that other model types were applied to account for the probable non-normality in the EQ-5D data. The EAG notes that the impact of using alternative model types on the utility values, and therefore the overall results, is likely to be small.

In relation to the age-sex adjustment, it is unclear to what extent these adjustment multipliers calculated using data from the general population are appropriate for those with resectable NSCLC, especially those with more advanced Stage IIIA disease. However, the EAG notes there is currently no guidance from NICE on the preferred source of age adjustment in economic models.

Overall, the EAG considers the health state utility values used in the CEM to be associated with a degree of uncertainty, mainly due to the seemingly infeasible utility values derived from the CheckMate-816 trial for the EF and LR health states, which were assigned to all treatment arms. There are also several other minor issues with these utility values, such as the use of overall rather than treatment-specific utilities from CheckMate-816, the use of linear mixed models when analysis non-linear EQ-5D-3L data, and the age-sex adjustment process implemented in the CEM.

4.2.9 Resources and costs

4.2.9.1 Resource use and costs data identified in the review

According to Appendix G in the CS, the SLR identified 14 eligible studies (four reported costs and ten reported resource utilisation).[6]

Four studies reported cost data for patients with early-stages (stage I-IIIA) of NSCLC who received adjuvant treatment and presented a broad variety of costs from the US, UK, Canada, France and Germany.[51,71-73]Three studies reported total direct costs in the population,[51,71,72] while one also reported indirect costs.[51] Costs associated with medications and specific treatments to treat and manage recurrence in NSCLC were also reported, as well as those associated with secondary, primary and community care.[51,71,73]

Ten studies identified by the SLR reported healthcare resource use in the US (n = 6), UK (n = 1), Italy (n = 2), and Canada (n = 1) among patients with early-stage NSCLC receiving adjuvant treatments. Studies reported on proportions of hospitalised patients, mean number of hospitalisations and mean length of hospital stay, as well as emergency department ED and physician outpatient visits (oncologist and other specialist visits), and usage of other associated resources, both related and unrelated to adjuvant treatment. The results of the searches are described in CS Appendix G.[6]

EAG comment: As discussed in Section 4.1, the company searched a number of databases and other literature sources. However, they did not quantitatively analyse the results of the SLR and hence they did not use these costing values in their analysis. The company narratively provided a description of each study. Unit costs were then derived from national published reference costs.

4.2.9.2 Intervention and comparator drug costs

Unit costs of drugs were identified from both the Drugs and pharmaceutical electronic market information tool (eMIT, 2021)[74] and Monthly Index of Medical Specialities (MIMS)[75] – UK Drug

Database.[1] These unit costs were combined with dosing regimens to estimate total drug costs (further details below).

4.2.9.2.1 Dose, vial sharing and dose intensity

The dosing regimen for each treatment arm was based on the dosing regimen used in the CheckMate-816 trial. The dosing of some intravenous treatments was dependent on a patient's body surface area (BSA). A mean BSA of 1.84 m^2 was estimated based on patient characteristics in CheckMate-816 and the average height of the UK population.[1]

For treatments that depended on BSA, there was a potential for drug wastage if perfect vial sharing was not implemented. For the base-case, the model included drug wastage (no vial sharing). The details of the dosing regimens are provided in Table 4.17.

Table 4.17: Drug dosing regimens

Treatment	Dose/Vial Concentration	Pack Size/Vial Volume	Dose per administration	Cost per Pack/Vial	Cost per mg
Carboplatin	450 mg	1	900 mg	£13.51	£0.03
Cisplatin	100 mg	1	75 mg	£8.97	£0.09
Paclitaxel	300 mg	1	175 mg	£15.97	£0.05
Gemcitabine	38 mg/ml	26.3 ml	1250 mg	£9.37	£0.01
Pemetrexed	500 mg	1	500 mg	£800.00	£1.60
Docetaxel	80 mg	1	75 mg	£8.90	£0.11
Vinorelbine	10 mg	10	25 mg	£57.88	£0.58
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Produced by EAG based on CS Tables 56 and 58.[1]
Abbreviation: mg = milligramme; ml = millilitre

EAG comment: The EAG raised a concern in the clarification letter asking the company to provide alternative cost acquisition estimates if there were different dose/vial sizes. The company responded to the clarification letter[15] that nivolumab was administered based on a fixed dose and thus would not be affected by adjustments to BSA.

4.2.9.2.2 Acquisition costs

Drug acquisition costs were dependent on distribution of treatment for each of the comparators. The cost of neoadjuvant treatment reflected nivolumab and the combination of PDC received in CheckMate-816. The distribution of PDC for the neoadjuvant CRT comparator was assumed to be the same as the distribution from neoadjuvant PDC. However, during the UK HTA clinical validation meeting in August 2022, clinical experts advised that gemcitabine is not given concurrently with CRT and that vinorelbine is most widely used in the UK (see appendix N).[6] Patients incurred costs for three full cycles of neoadjuvant treatment. For patients who progressed before completing three cycles of treatment,

costs of neoadjuvant treatment were applied until the time of progression. The distribution of treatment regimens for adjuvant PDC was assumed to be the same as the regimen distribution for neoadjuvant PDC. Adjuvant PDC was also administered for three cycles.

Details of drug acquisition costs are provided in Table 4.18. The cost per dose for each comparator is calculated based on the dose per administration and cost per mg.

Table 4.18: Drug acquisition cost per treatment arm and model cycle

Treatment	Cost per Dose - Neoadjuvant	Cost per Dose - Adjuvant	Cost per Model Cycle - Neoadjuvant	Cost per Model Cycle - Adjuvant
Carboplatin	£27.02	£27.02	£27.02	£27.02
Cisplatin	£17.94	£17.94	£17.94	£17.94
Paclitaxel	£31.94	£31.94	£31.94	£31.94
Gemcitabine	£28.11	£28.11	£56.22	£56.22
Pemetrexed	£1,600.00	£1,600.00	£1,600.00	£1,600.00
Docetaxel	£17.80	£17.80	£17.80	£17.80
Vinorelbine	£57.88	£57.88	£115.76	£115.76
Treatment	**Cost per Dose**	**Cost per Model Cycle**	**--**	**--**
Nivolumab	[redacted]	[redacted]	---	---

Source: reproduced by EAG based on the CEM

EAG comment: Although details of drug acquisition costs were provided in the CS,[1] relevant tables with the specific information (e.g. drug acquisition cost per treatment arms or cost per mg) used to estimate total costs were not provided within the CS; the EAG used data in the model to populate this costing section.

The company assumed that the distribution of treatment regimens for adjuvant PDC was the same as the regimen distribution for neoadjuvant PDC but did not provide a justification for this. As such, the EAG asked them to clarify this in the points for clarification. The company responded that clinical experts were asked about the distribution of treatment regimens for neoadjuvant PDC and the model was updated based on their advice.[15] As part of this discussion, it was not explicitly asked if they agreed with the assumption of adjuvant PDC being equal to neoadjuvant PDC. However, the clinical experts consulted by the company considered PDCs to be similar in the adjuvant and neoadjuvant settings when validating data observed in CheckMate-816.

4.2.9.2.3 Administration costs

A drug administration cost was applied per administration for drugs administered intravenously. Unit costs for drug administration were obtained from the UK National Schedule of NHS Costs 2019-2020[76]

(inflated to 2020/2021values).[1] A cost of £363.09 was applied for the first treatment cycle and a cost of £261.58 was applied for subsequent cycles.

EAG comment: The EAG agree that the UK National Schedule of NHS Costs[76] was a suitable source for unit costs. However, the company does not explain why the cost of subsequent treatment cycles were lower than costs incurred during the first treatment cycle. It was noteworthy that the company did not provide the details of the inflation method in CS. In their response to the clarification letter,[15] the company provided the inflation details included in the model and they also corrected that the costs were inflated for one year, as opposed to the two years stated in the CS.

Cost of surgery

The proportion of patients undergoing surgery after nivolumab + PDC was informed by the CheckMate-816 trial. The proportion of patients undergoing surgery after neoadjuvant CRT was assumed to be the same as the proportion of patients in the neoadjuvant PDC arm in CheckMate-816. For adjuvant PDC, the proportion undergoing surgery was informed by the literature.[39] For patients in surgery alone, the proportion of potentially resectable patients who received surgery was assumed to be the same as that observed for adjuvant treatment given that, in both cases, patients would not receive any treatment between diagnosis and surgery.[1]

The costs of surgery were estimated as a weighted average of costs by surgery approach (minimally invasive surgery versus thoracotomy) and the proportion of patients undergoing each type of surgery. The proportion of invasive versus non-invasive surgery for the nivolumab + PDC arm was based on CheckMate-816 data. The distribution of surgical approaches for the other comparators (neoadjuvant CRT, adjuvant PDC and surgery alone) was assumed to be the same as the distribution for neoadjuvant PDC. Unit costs for each surgical approach were obtained from the UK National Schedule of NHS Costs 2019-2020[76] (inflated to 2020/2021 values).

EAG comment: The overall approach of estimating a cost of surgery for each treatment arm based on the proportion of patients undergoing surgery they type of surgery performed seems reasonable to the EAG. The company assumed that "the proportion of patients undergoing surgery after neoadjuvant CRT was assumed to be the same as the proportion of patients in the neoadjuvant PDC arm".[1] However, the EAG couldn't find any evidence in the CS to support this assumption. As such, this was raised by the EAG in the points for clarification. The company responded that clinical experts were asked about the distribution of surgical approaches but there was no consensus on this. Considering the lack of data and clinical advice, the company used the assumption that the distribution of surgery for neoadjuvant CRT, adjuvant PDC and surgery alone was the same as for neoadjuvant PDC in the base-case CEM. Given the uncertainty in this assumption, the company undertook additional scenario analyses on this.[15] Given the potential importance of the proportion of those undergoing surgery on costs and the ICER, the EAG undertook a scenario analysis based on the opinions obtained from a clinical expert.

It was mentioned in the CS that the proportion of patients undergoing surgery was taken from CkeckMate-816 trial for neoadjuvant CRT and surgery alone. However, for adjuvant PDC, a single study by Felip *et al*., 2010[39] was used to inform the proportion of patients undergoing surgery but the company they didn't provide further clarification as to why they used this study.

The EAG have noted that the latest version of the National Schedule of NHS Costs[76] was published in July 2022 and have used the updated costs for surgery in the EAG analyses as a scenario analysis. The EAG only used updated costs for surgery as there was a substantial difference in the unit costs between the two versions.

4.2.9.3 Monitoring and disease management costs

A micro-costing approach was applied to estimate costs for routine healthcare resource use for patients in the EF and LR health states.

The frequency of use for healthcare services used in both the EF and LR health states was informed by the LuCaBIS study, identified from the SLR.[51] The LuCaBIS study[51] was previously used to inform routine medical resource use (MRU) in EF and LR states in a previous TA submission for NSCLC (NICE TA761).[49] Unit costs for clinic visits, hospitalisation and diagnostics were obtained from the UK National Schedule of NHS Costs 2019-2020[76] (inflated to 2020/2021values).

EAG comment: The company noted in the CS that a micro-costing approach was used to estimate the monitoring and disease management costs.[1] However, they in fact extracted unit costs from the NHS Schedule of Costing(2019-2020)[76] and the frequency of health service use in both the EF and LR health states was informed by the literature.[51]

The frequency of use for healthcare services in EF and LR states was obtained from a single study, LuCaBIS,[51] despite ten studies being identified as eligible from the SLR using the healthcare resource use eligibility criteria. The company did not justify this in the CS and so the EAG sought clarification from the company. In their response,[15] the company stated that this study was the only paper which included UK settings and had the information by health states which made it suitable to be used in model. However, as the company identified eight countries as key markets of interest in the SLR, it is unclear why the company didn't use cost and resource use data from these countries in scenario analyses.

There is a cost category named 'adjuvant care after neoadjuvant' included in the CEM for the neoadjuvant PDC and neoadjuvant CRT comparators. However, it was not mentioned in the CS how this cost was calculated. As such, the EAG were unable to comment on the estimation of these costs.

4.2.9.4 Adverse effects costs

The cost of managing Grade 3 or 4 AEs occurring in ≥ 5% of patients in CheckMate-816 were considered in the model. Adverse event costs were applied as a one-time cost in the first model cycle when patients were receiving active treatments. Adverse event costs were estimated as a weighted average, based on the type of AE experienced and the treatment received for that AE.[1] Unit costs for each AE were extracted from National Schedule of NHS Costs for 2019-2020[76] (inflated to 2020/2021values). Details of the unit costs are presented in Table 4.19.

Table 4.19: Adverse event unit costs

Adverse event	Unit cost	Source
Anaemia	£1,276.17	NHS Schedule of Costing 2019-2020[76] (inflated to 2020/2021values)
Neutropenia	£1,840.60	
Leukopenia	£1,580.60	
Thrombocytopenia	£1,974.07	
Fatigue or Asthenia	£1,379.66	
Nausea and/or Vomiting	£1,537.62	
Source: Produced by EAG based on CS Table 69.[1]		

EAG comment: The EAG have no concerns in how AE costs were estimated.

Terminal care costs

A one-off cost of terminal care was applied to patients who entered the 'Dead' health state. The cost of terminal care was estimated as a weighted average of end-of-life costs based on care received in three different settings: hospice, hospital and at home. The proportion of patients receiving each type of end of life care was informed by sources used in the recent technology assessment submission (NICE TA761).[49] Unit costs for terminal care were extracted from standard costing databases and previous HTA submission (NICE TA761).[49]

EAG comment: The study used to estimate the proportion of patients in end-of-life care settings included a systematic review and economic evaluation to evaluate the clinical- and cost-effectiveness of first-line chemotherapy currently licensed in Europe and recommended by NICE.[77] Although it was a comprehensive review, it was not based in the UK and UK data sources for end life of care was not searched. As such, the EAG has concerns about the data used to estimate terminal care costs in the 'Dead' health state.

4.2.9.5 Health state costs

Four health states were defined in the model EF, LR, DM and dead. The costing of drug acquisition, drug administration and surgery were applied in all states dependent on the treatment arms, where applicable in all three treatment cycles. The cost of resource use and treatment monitoring were calculated for EF and LR state separately to reflect the amount of resources used in each health state. These data were based on LuCaBIS study.[51]

Treatment costs for managing recurrence for patients in the LR health state were estimated as a one-off cost. Treatment costs were estimated as a weighted average, based on the proportion of patients who had PDC, single-modality radiotherapy and surgery. The distribution of treatment modalities for patients in the LR health state was informed using interviews with clinical experts and reflected current clinical practice in the UK.[1]

Unit costs for each treatment modality in LR state were extracted from standard costing databases in the UK, including eMIT for cost of drugs and NHS Schedule of Costing[76] for other unit costs. Four cycles of cisplatin + pemetrexed were considered for the costing of PDC during the LR health state, aligned with the PDC regimen used for costing in a NICE appraisal of osimertinib in adjuvant non-metastatic NSCLC (NICE TA761).[49]

A one-off cost was applied upon entry to the DM health state, this included subsequent treatment costs (e.g., second line), resource use costs, and terminal care costs.

Patients were assumed to receive a mix of therapies for first-line metastatic disease, in line with UK clinical practice. The one-off modelling approach in the DM state was validated by clinical experts and health economists during the Global HTA advisory board meeting in May 2022, see CS Appendix N[6]

To populate costs associated with each of the first-line metastatic appraisals, other NICE STA submissions were used (NICE TA770, TA531, TA683, TA584).[53-56]

Due to data being redacted, it was not possible to extract the costs from the respective committee papers. Therefore, to ensure the DM costs in the CEM were reflective of published costs associated with the previously mentioned approved first-line metastatic NSCLC NICE TAs (NICE TA770, TA531, TA683, TA584),[53-56], the company proposed a collaboration with NICE. NICE was to provide this data to the EAG so it could be included in the EAG model and presented to NICE as a confidential appendix. This process also provided QALY and LY data for the DM health state.

In the CS, to act as a placeholder for the values that NICE would be providing to the EAG, the company sourced alternative input values for DM costs. These values were sourced from a previous NICE STA for nivolumab + ipilimumab in untreated advanced non-small cell lung cancer (TA724),[57] specifically using the ERG-preferred values from the appraisal consultation document (ACD).[1]

The only cost parameter included in the costing of the Dead health state was terminal care.

EAG comment: The company provided details on the unit costs and proportion of patients receiving treatments for most costing categories and provided additional detail on the costings for the LR, DM and Dead health states. However, the company did not provide enough explanation how these costs were applied to each health state. For example, the treatment monitoring and resource use costs is a source of difference in EF and LR states cost, which was not explicitly mentioned in the CS. The EAG has relied on the model inputs and other cost categories to explain the health state costs in EAG analyses.

Regarding the DM health state, the company tried to resolve the uncertainty around DM costs and QALYs by collaborating with NICE and requested that NICE provide the EAG with the confidential values to be included in the EAG model. As the company did not have access to these data the company used placeholder values, described above, and undertook an extreme scenario analysis assuming there was no cost associated with subsequent treatment in DM.

4.2.10 Summary of company assumptions applied in base-case analysis

Table 4.20 shows a summary of the key assumptions used in the base-case analysis of the CEM.

Table 4.20: Company model assumptions

Category	Assumption	Rationale
Long-term mortality risk	The CheckMate-816 population is assumed to be representative of patients receiving treatment for resectable non-metastatic NSCLC.	This is a necessary limitation of a cohort-level approach.
Treatment efficacy	All PDC regimens administered as neoadjuvant treatment have the same efficacy.	It is known to be the case that, across different practices, the use of specific combinations in PDC differ from CheckMate-816 (even in CheckMate-816, choice of PDC was based on physician discretion). Expert feedback suggested that no significant difference in efficacy would be expected between PDC combinations. Furthermore, data are not available to account for efficacy differences between specific PDC regimens, given the CheckMate-816 trial design where PDC regimen was based on investigator choice. Therefore, adjusting the distribution of PDC in the model can impact costs but will not impact estimated survival.

Treatment efficacy	The CEM compares multiple treatment strategies for resectable non-metastatic NSCLC. Each of these involves a sequence of treatments (e.g., neoadjuvant PDC, followed by surgery, followed by optional adjuvant PDC). Efficacy data in the CEM are based on an indirect treatment comparison of treatments. When comparing treatment strategies in the CEM, changes in the proportion of patients receiving a specific treatment within one strategy (e.g., percentage receiving surgery in the strategy outlined above) will only affect cost and utility but not survival.	Data to explicitly consider the clinical impact of changes within a treatment strategy, such as percentage of patients undergoing surgery or percentage receiving adjuvant treatment, are not available. These figures are implicitly considered in the existing data.
Comparators	In the adjuvant PDC arm, all patients are assumed to receive adjuvant treatment.	This assumption is made for logical consistency. Patients who do not receive adjuvant treatment should not be considered in the adjuvant comparator arms.
Disease progression	The probability of experiencing distant metastasis remains constant over time among patients with locoregional recurrence.	This is an assumption made to cover a lack of data necessary to characterise the time-dependency of this risk.
Occurrence of distant metastasis	Rather than extrapolating the likelihood of distant metastasis from EFS directly, it is computed as the difference between the hazard of any progression and the hazard of locoregional recurrence.	There were not enough distant metastasis events in CheckMate-816 to develop reliable extrapolations. This approach leverages the number of total and locoregional progression events, which are sufficient to develop extrapolations.
Mortality	Prior to progression to metastatic disease, patients' mortality is dependent only on the health state they occupy (EF or LR) and not on the non-metastatic NSCLC treatment strategy received.	This assumption is justified based on data from CheckMate-816 that show no difference in expected mortality across treatment arms among patients in the same health state. Furthermore, pooling the data across treatment arms increases the overall number of events upon which extrapolations may be based, increasing their predictive power. Clinical and economic experts noted that this assumption may overestimate mortality in the nivolumab + PDC arm, making this a conservative assumption.

Long-term mortality risk	Patients will not be able to achieve better mortality outcomes than would be expected among the general population. Accordingly, if the risk of mortality based on survival projections ever decreases below what would be expected based on published life tables, the estimate from the life table will be applied instead.	This is a common assumption in cost-effectiveness analysis and is based on the reasoning that the best possible outcome in terms of mortality impact for a given treatment would be a lack of any disease-specific or excess mortality.
Functional care	Ninety-five percent of patients who remain event-free for at least five years achieve functional cure, with no risk of progression and mortality equal to that expected for the general population.	This assumption follows available evidence in the literature suggesting a strong plateau in EFS starting at five years. It was validated by clinical experts who suggested that cure is a possibility after successful resection.
Distant metastasis cost and outcomes	It is assumed that weighted results from previous TAR appraisals of in first-line metastatic NSCLC treatments applied as a one-off impact to patients with distant metastasis can reasonably approximate the cost, survival and utility expectations for these patients.	This is a simplifying assumption made to reduce the complexity required in the model to capture treatments in metastatic NSCLC, especially in consideration of the understanding that these treatments fall outside the scope of the decision problem of treatment in resectable non-metastatic NSCLC. This approach has been used previously and deemed acceptable by NICE, specifically in the evaluation for dabrafenib with trametinib for adjuvant treatment of resected BRAF V600 mutation-positive melanoma (TA544).[45]
Treatment discontinuation	Discontinuation from neoadjuvant treatment is not explicitly considered. Therefore, all patients receiving neoadjuvant treatment and remaining in EFS are assumed to incur the cost of a full course of treatment.	Most patients in CheckMate-816 (93.8% in the nivolumab + PDC arm and 84.7% in the neoadjuvant PDC arm) completed the three cycles of neoadjuvant treatment. Given the relatively limited cost of any missed treatment cycles, this is unlikely to have a major impact on the model result. Further, this is a conservative assumption, given the relatively higher cost of nivolumab.
Treatment costs	Half-cycle correction is never applied to drug acquisition and administration costs in the neoadjuvant and adjuvant settings.	The objective of half-cycle correction is to distribute costs and benefits across a model cycle, rather than counting them

		all at the beginning of the cycle. However, it is known that patients will receive treatment at the beginning of each model cycle. Therefore, these costs should not be redistributed across the cycle.

Source: Table 71, CS.[1]
Abbreviations: CEM = company economic model; EF = Event free; EFS = Event free survival; LR = Locoregional recurrence; NICE = National Institute of Health and Care Excellence; NSCLC = Non-small cell lung cancer; PDC = platinum doublet chemotherapy

5 COST-EFFECTIVENESS RESULTS

5.1 Company's cost-effectiveness results

The company base-case discounted deterministic results, including the confidential patient access scheme (PAS) for nivolumab, are presented below. Three pairwise comparisons were undertaken, which estimated the incremental cost per QALY gained of nivolumab + PDC compared with: 1) surgery alone, 2) neoadjuvant CRT, and 3) adjuvant PDC.

The nivolumab PAS has changed since the company provided its submission. The ICERs in this section are based on the superseded PAS ([redacted]) and do not incorporate commercial arrangements for other products. The EAG analyses presented in Section 6 have been updated to incorporate the current PAS for nivolumab ([redacted]), the EAG also present the company base-case results incorporating this new PAS in Section 6.

Compared with surgery alone, nivolumab + PDC was more costly and more effective with a life year (LY) gain of [redacted], a QALY gain of [redacted], and an incremental cost of [redacted]. The associated incremental cost per QALY gained was £2,685. The results are presented in Table 5.1.

Compared with neoadjuvant CRT, nivolumab + PDC was dominant (i.e. less costly and more effective), with a LY gain of [redacted], a QALY gain of [redacted], and an incremental cost of [redacted]. The results are presented in Table 5.2.

Compared with adjuvant PDC, nivolumab + PDC was dominant, with a LY gain of [redacted], a QALY gain of [redacted], and an incremental cost of [redacted]. The results are presented in Table 5.3.

Table 5.1: Base-case deterministic economic analysis results (with PAS) – nivolumab + PDC versus surgery

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Surgery	[redacted]	[redacted]	[redacted]					1.54	2.56
NIVO+PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,685	2.56	3.63

Source: Tables 71 and 75, CS.[1]

This table reports discounted LYG, costs and QALYs.

Abbreviations: ICER = incremental cost effectiveness ratio; LYG = life year gained; PAS = patient access scheme; QALYs = quality-adjusted life years; NHB = net health benefit; NIVO+PDC = nivolumab + platinum doublet chemotherapy.

Table 5.2: Base-case deterministic economic analysis results (with PAS) – nivolumab + PDC versus neoadjuvant CRT

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
NeoCRT	[redacted]	[redacted]	[redacted]					2.22	3.31
NIVO+PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	2.56	3.63

Source: Tables 71 and 75, CS.[1]

This table reports discounted LYG, costs and QALYs.

Abbreviations: ICER = incremental cost effectiveness ratio; LYG = life year gained; PAS = patient access scheme; QALYs = quality-adjusted life years; NHB = net health benefit; NeoCRT = neoadjuvant chemoradiation; NIVO+PDC = nivolumab + platinum doublet chemotherapy.

Table 5.3: Base-case deterministic economic analysis results (with PAS) – nivolumab + PDC versus adjuvant PDC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Adj. PDC	[redacted]	[redacted]	[redacted]					1.85	2.92
NIVO+PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	2.56	3.63

Source: Tables 71 and 75, CS.[1]

This table reports discounted LYG, costs and QALYs.

Abbreviations: ICER = incremental cost effectiveness ratio; LYG = life year gained; PAS = patient access scheme; QALYs = quality-adjusted life years; NHB = net health benefit; Adj. PDC = adjuvant platinum doublet chemotherapy; NIVO+PDC = nivolumab + platinum doublet chemotherapy.

EAG comment: The EAG requested in the clarification letter that the cost-effectiveness results and the CEM should be provided as a full incremental analysis. The EAG's argument for this was that all relevant comparators should be compared against each other. However, the company responded that nivolumab was expected to specifically replace all the individual comparators and hence pairwise comparisons have been provided in accordance with the NICE technology appraisal manual.[15] The EAG was satisfied with this response.

The EAG also requested for the following subgroup analyses to be undertaken: 1) disease stage, and 2) race/ethnicity. The rationale for these subgroup analyses was that nivolumab may not be as effective in patients with an earlier stage of disease (Stage IB-II) and in patients not from an Asian population, based on the CheckMate-816 results. The company responded that there was currently insufficient data from CheckMate-816 to undertake the subgroup analysis by disease stage but that they would prepare an updated clinical section of the CS in late 2022, when further information was available.[15] While the EAG appreciate the lack of data available from CheckMate-816, the EAG still considers this to be an important subgroup analysis based on the resectable NSCLC disease profile in England. The company's justification for not originally providing a subgroup by ethnicity/region was that these were not stratification factors in CheckMate-816, hence potential imbalances are from unknown factors and should be interpreted with caution. In the PfC, the company provided summaries on potential differences between the two groups such as gender, PD-L1 and baseline ECOG PS to justify the need for the differences between Asian and white ethnicities to be interpreted with caution.[15] The EAG appreciates the limitation of the data available from CheckMate-816, especially since race and region were not stratifying factors. However, given the ethnic profile of England, the EAG still has concerns about the applicability of the results of CheckMate-816 to the English population.

The EAG also noted that there appeared to be uncertainty in the effectiveness of the different PDC regimens. Also, clinical advice to the EAG suggested that a cisplatin-based PDC would be more routinely used than carboplatin-based PDC in the UK. However, clinical recommendations for carboplatin may change if it was paired with nivolumab. Due to the uncertainty in the effectiveness of the different PDC regimens and the uncertainty in the difference of their effectiveness The EAG undertook scenario analyses for the different regimens. All subgroup analyses are presented in Section 6.1.3.

5.2 Company's sensitivity analyses

The company performed and presented the results of probabilistic sensitivity analyses (PSA), deterministic sensitivity analyses (DSA) and scenario analyses.[1]

5.2.1 Probabilistic sensitivity analysis

The PSA results for all pairwise comparisons were based on 1000 repeated simulations. The company PSA results for nivolumab + PDC compared with surgery are presented in Table 5.4. The average incremental costs were [redacted] and the average incremental QALYs were [redacted], generating a probabilistic incremental cost per QALY gained of £2,655.

Table 5.4: Mean PSA results (with PAS) – nivolumab + PDC versus surgery

Technologies	Total	Incremental	ICER (£/QALY)

	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Surgery	[redacted]	[redacted]	[redacted]				
NIVO+PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2,655

Source: Tables 71 and 75, CS.[1]

Abbreviations: ICER = incremental cost-effectiveness ratio; LYG = life year gained; PAS = patient access scheme; QALYs = quality-adjusted life years; NHB = net health benefit; NIVO+PDC = nivolumab + platinum doublet chemotherapy.

The company produced a cost-effectiveness plane and cost-effectiveness acceptability curves (CEACs), which are reproduced in Figures 5.1 and 5.2. The probability that nivolumab was cost-effective was [redacted] and [redacted] at NICE recommended thresholds of £20,000 and £30,000 per QALY gained.

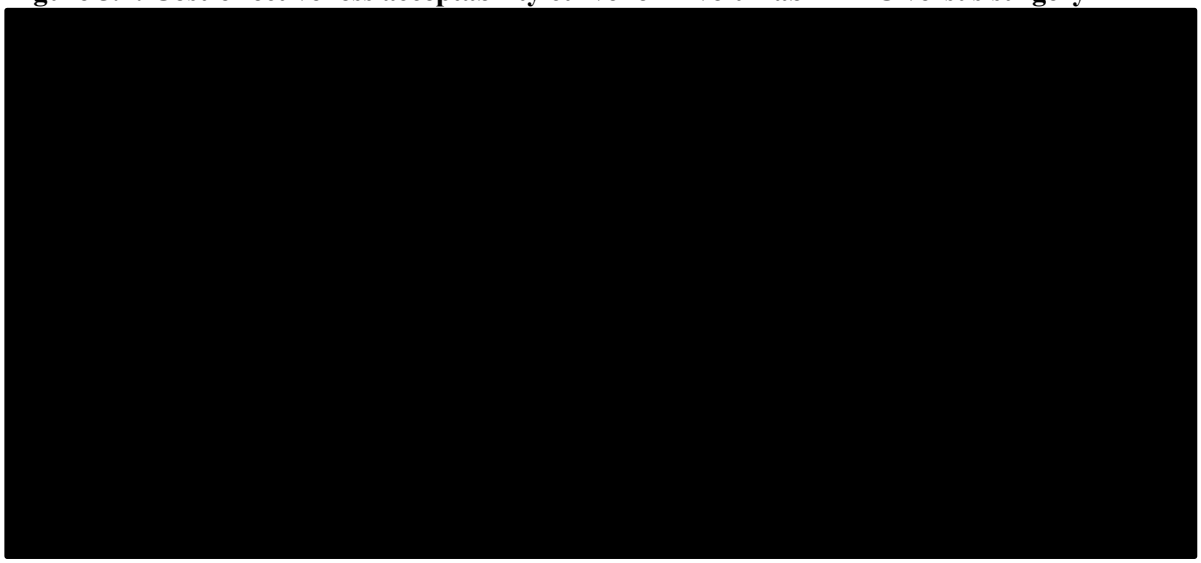
Figure 5.1: Cost-effectiveness plane for nivolumab versus surgery

[redacted]

(Source: Figure 61, CS)[1]

(Abbreviations: PDC, platinum doublet chemotherapy; CE, cost-effectiveness; QALYs, quality-adjusted life years)

Figure 5.2: Cost-effectiveness acceptability curve for nivolumab + PDC versus surgery



(Source: Figure 64, CS)[1]

(Abbreviations: CEAC, cost-effectiveness acceptability curve; PDC, platinum doublet chemotherapy)

The company PSA results for nivolumab + PDC compared with neoadjuvant CRT are presented in Table 5.5. The average incremental costs were [redacted] and the average incremental QALYs were [redacted], hence nivolumab + PDC was dominant.

Table 5.5: Mean PSA results (with PAS) – nivolumab + PDC versus neoadjuvant CRT

Technologies	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
NeoCRT	[redacted]	[redacted]	[redacted]				
NIVO+PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Source: Tables 71 and 75, CS[1]

Abbreviations: ICER: incremental cost effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life years; NHB: net health benefit; NeoCRT, neoadjuvant chemoradiation; NIVO+PDC, nivolumab + platinum doublet chemotherapy.

The company produced a cost-effectiveness plane and CEACs, which are reproduced in Figure 5.3 and Figure 5.4. The probability that nivolumab was cost-effective was [redacted] at NICE recommended thresholds of £20,000 and £30,000 per QALY gained.

Figure 5.3: Cost-effectiveness plane for nivolumab + PDC versus neoadjuvant CRT

(Source: Figure 62, CS)[1]

(Abbreviations: PDC = platinum doublet chemotherapy; CRT = chemoradiotherapy; CE = cost-effectiveness; QALYs = quality-adjusted life years)

Figure 5.4: Cost-effectiveness acceptability curve for nivolumab + PDC versus neoadjuvant CRT

(Source: Figure 65, CS)[1]

(Abbreviations: CEAC = cost-effectiveness acceptability curve; PDC = platinum doublet chemotherapy; CRT = chemoradiotherapy)

The company PSA results for nivolumab + PDC compared with adjuvant PDC are presented in Table 5.6. The average incremental costs were [redacted] and the average incremental QALYs were [redacted], hence nivolumab + PDC was dominant.

Table 5.6: Mean PSA results (with PAS) – nivolumab + PDC versus adjuvant PDC

Technologies	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Adj. PDC	[redacted]	[redacted]	[redacted]				
NIVO+PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Source: Tables 71 and 75, CS.[1]

Abbreviations: ICER = incremental cost-effectiveness ratio; LYG = life years gained; PAS = patient access scheme; QALYs = quality-adjusted life years; NHB = net health benefit; Adj. PDC = adjuvant platinum doublet chemotherapy; NIVO+PDC = nivolumab + platinum doublet chemotherapy.

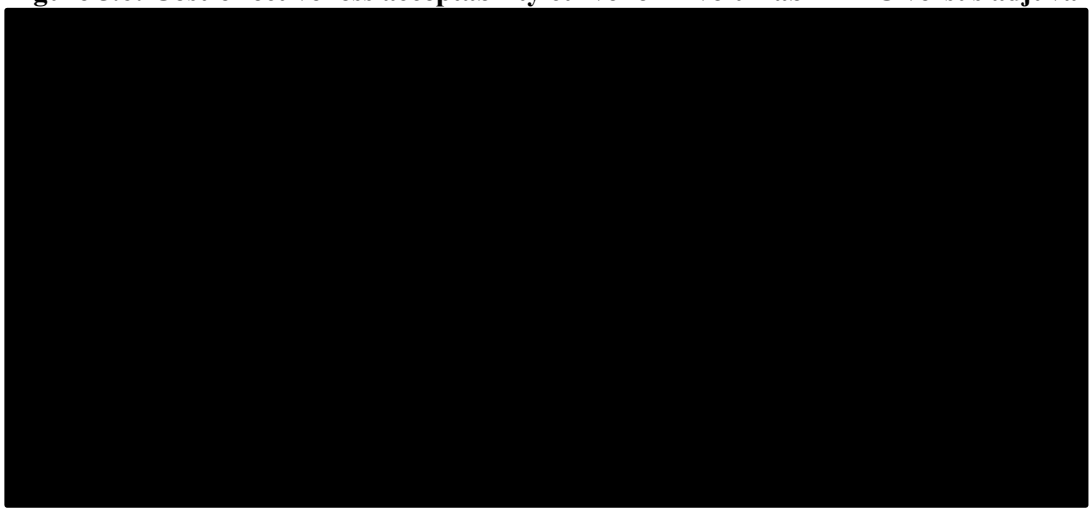
The company produced a CE plane and CEACs, which are reproduced in Figures 5.5 and 5.6. The probability that nivolumab was cost-effective was [redacted] and [redacted] at NICE recommended thresholds of £20,000 and £30,000 per QALY gained.

Figure 5.5: Cost-effectiveness plane for nivolumab + PDC versus adjuvant PDC

(Source: Figure 63, CS)[1]

(Abbreviations: PDC = platinum doublet chemotherapy; CRT = chemoradiation; CE = cost-effectiveness; QALYs = quality-adjusted life years)

Figure 5.6: Cost-effectiveness acceptability curve for nivolumab + PDC versus adjuvant PDC



(Source: Figure 66, CS)[1]
(Abbreviations: CEAC = cost-effectiveness acceptability curve; PDC = platinum doublet chemotherapy)

5.2.2 Scenario analysis

The company undertook several scenario analyses (CS Tables 81-83) to estimate the impact of certain model inputs and assumptions on the cost-effectiveness results.[1] The results of the scenario analyses are presented in Tables 5.7, 5.8 and 5.9. The list of parameters or assumptions changed in scenario analysis include the following:

- Source of utility values
- Cure assumption
- Costs associated with the DM health state
- Utilities associated with the DM health state
- PDC regimen
- I-O retreatment
- Proportion of patients receiving neoadjuvant treatment who continue with adjuvant treatment
- Transition probability from LR to DM
- The models chosen for extrapolation
- Treatment effect

Table 5.7: Scenario analysis results of nivolumab + PDC versus surgery

Scenario	Base-case	Alternative input	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
Base-case			[redacted]	[redacted]	£2,685
1	Utility values	Use unadjusted trial values from CM-816	[redacted]	[redacted]	£2,536
2	Cure assumption (% of patients cured)	No patients cured	[redacted]	[redacted]	£3,492
3	Cure assumption (onset)	Cure onset at 8 years	[redacted]	[redacted]	£2,857

4	Cure assumption (time from beginning to end of cure process)	Immediate cure	[redacted]	[redacted]	£2,665
5	DM QALY outcome	QALY of subsequent treatment = 5 QALYs	[redacted]	[redacted]	£4,356
6	DM cost outcome	No cost of subsequent treatment	[redacted]	[redacted]	£12,706
7	PDC regimen	Vinorelbine used instead of docetaxel and paclitaxel in PDC regimen	[redacted]	[redacted]	£2,823
8	I-O retreatment	I-O retreatment restriction extended to 12 months	[redacted]	[redacted]	£1,537
9	I-O retreatment	I-O retreatment restriction not included	[redacted]	[redacted]	£4,638
10	Patients on neoadjuvant treatments who continue with adjuvant treatments	5% radiotherapy based on UK clinical input	[redacted]	[redacted]	£2,629
11	LR to DR transition probability	7.7% from the LuCaBIS study[51]	[redacted]	[redacted]	£3,045
12	Distribution for TTLR extrapolation	Exponential	[redacted]	[redacted]	£3,306
13	Distribution for any disease progression extrapolation	Generalised gamma	[redacted]	[redacted]	£3,374
14	Distribution of event-free mortality	Generalised gamma	[redacted]	[redacted]	£2,864
15	Distribution for locoregional recurrence mortality	Log-logistic	[redacted]	[redacted]	£2,908
16	Treatment effect for local and distant recurrence	EFS ITC treatment effect for both TTLR and TTDM	[redacted]	[redacted]	£1,898

Source: Table 81 in the CS[1]
Abbreviations: CM-816 = CheckMate-816; PDC = platinum doublet chemotherapy; DM = distant metastasis; EFS = event free survival; I-O = immuno-oncology; ITC = indirect treatment comparison; LR = Locoregional Recurrence; QALY = quality-adjusted life-year; TTDM = time to distant metastases; TTLR = time to locoregional recurrence; UK = United Kingdom.

Table 5.8: Scenario analysis results of nivolumab + PDC versus neoadjuvant CRT

Scenario	Base-case	Alternative input	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
Base-case			[redacted]	[redacted]	Dominant
1	Utility values	Use unadjusted trial values from CM-816	[redacted]	[redacted]	Dominant
2	Cure assumption (% of patients cured)	No patients cured	[redacted]	[redacted]	Dominant
3	Cure assumption (onset)	Cure onset at 8 years	[redacted]	[redacted]	Dominant
4	Cure assumption (time from beginning to end of cure process)	Immediate cure	[redacted]	[redacted]	Dominant
5	DM QALY outcome	QALY of subsequent treatment = 5 QALYs	[redacted]	[redacted]	Dominant
6	DM cost outcome	No cost of subsequent treatment	[redacted]	[redacted]	£21,496
7	PDC regimen	Vinorelbine used instead of docetaxel and paclitaxel in PDC regimen	[redacted]	[redacted]	Dominant
8	I-O retreatment	I-O retreatment restriction extended to 12 months	[redacted]	[redacted]	Dominant
9	I-O retreatment	I-O retreatment restriction not included	[redacted]	[redacted]	£2,719
10	Patients on neoadjuvant treatments who continue with adjuvant treatments	5% radiotherapy based on UK clinical input	[redacted]	[redacted]	Dominant
11	LR to DR transition probability	7.7% from the LuCaBIS study[51]	[redacted]	[redacted]	Dominant
12	Distribution for TTLR extrapolation	Exponential	[redacted]	[redacted]	Dominant
13	Distribution for any disease progression extrapolation	Generalised gamma	[redacted]	[redacted]	Dominant
14	Distribution of event-free mortality	Generalised gamma	[redacted]	[redacted]	Dominant

15	Distribution for locoregional recurrence mortality	Log-logistic	[redacted]	[redacted]	Dominant
16	Treatment effect for local and distant recurrence	EFS ITC treatment effect for both TTLR and TTDM	[redacted]	[redacted]	Dominant

Source: Table 83 in the CS[1]

Abbreviations: PDC = platinum doublet chemotherapy; CRT = chemoradiotherapy; DM = distant metastasis; EFS = event free survival; I-O, immuno-oncology; ITC = indirect treatment comparison; LR = locoregional recurrence; QALY = quality-adjusted life-year; TTDM = time to distant metastases; TTLR = time to locoregional recurrence; UK = United Kingdom.

Table 5.9: Scenario analysis results of nivolumab + PDC versus adjuvant PDC

Scenario	Base-case	Alternative input	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
Base-case			[redacted]	[redacted]	Dominant
1	Utility values	Use unadjusted trial values from CM-816	[redacted]	[redacted]	Dominant
2	Cure assumption (% of patients cured)	No patients cured	[redacted]	[redacted]	Dominant
3	Cure assumption (onset)	Cure onset at 8 years	[redacted]	[redacted]	Dominant
4	Cure assumption (time from beginning to end of cure process)	Immediate cure	[redacted]	[redacted]	Dominant
5	DM QALY outcome	QALY of subsequent treatment = 5 QALYs	[redacted]	[redacted]	Dominant
6	DM cost outcome	No cost of subsequent treatment	[redacted]	[redacted]	£12,737
7	PDC regimen	Vinorelbine used instead of docetaxel and paclitaxel in PDC regimen	[redacted]	[redacted]	Dominant
8	I-O retreatment	I-O retreatment restriction extended to 12 months	[redacted]	[redacted]	Dominant
9	I-O retreatment	I-O retreatment restriction not included	[redacted]	[redacted]	£3,022

10	Patients on neoadjuvant treatments who continue with adjuvant treatments	5% radiotherapy based on UK clinical input	[redacted]	[redacted]	Dominant
11	LR to DR transition probability	7.7% from the LuCaBIS study[51]	[redacted]	[redacted]	£284
12	Distribution for TTLR extrapolation	Exponential	[redacted]	[redacted]	£602
13	Distribution for any disease progression extrapolation	Generalised gamma	[redacted]	[redacted]	£502
14	Distribution of event-free mortality	Generalised gamma	[redacted]	[redacted]	£143
15	Distribution for locoregional recurrence mortality	Log-logistic	[redacted]	[redacted]	Dominant
16	Treatment effect for local and distant recurrence	EFS ITC treatment effect for both TTLR and TTDM	[redacted]	[redacted]	Dominant

Source: Table 83 in the CS[1]

Abbreviations: CM-816 = CheckMate-816; PDC = platinum doublet chemotherapy = DM = distant metastasis; EFS = event free survival; I-O = immuno-oncology; ITC = indirect treatment comparison; LR = Locoregional Recurrence; QALY = quality-adjusted life-year; TTDM = time to distant metastases; TTLR = time to locoregional recurrence; UK = United Kingdom.

EAG comment: The results of the scenario analyses undertaken by the company had a small to moderate impact on the ICER for all pairwise comparisons. The largest difference to the company base-case results for all three comparators was assuming no subsequent treatment costs in the DM health state, followed by removing any restrictions on IO retreatments.

All ICERs estimated in the scenario analyses were below £20,000 for an additional QALY, except one analysis comparing nivolumab + PDC with neoadjuvant CRT. In this scenario analysis, where it was assumed that there were no subsequent treatment costs in the DM state, nivolumab + PDC had an ICER of £21,496.

While the company concluded that there is little uncertainty in the cost-effectiveness of the intervention based on the results of the DSA, PSA and scenario analyses, the EAG have identified potential sources of uncertainty that could impact the CE results, in particular the subgroup analyses by disease stage, region and PDC regimen. Furthermore, the EAG does not think uncertainty in the cure assumption, the choice of time-to-event models used to predict EFS and disease progression, and in the proportional hazards assumption made in estimating the comparator hazard ratios for LR and DM have been adequately represented in the scenario analyses.

5.2.3 Deterministic sensitivity analysis

The effect on the cost-effectiveness results by varying key model parameters over plausible ranges was evaluated using univariate DSA. The plausible range was determined by either upper and lower bounds

of the confidence interval (CI) or assumed a -/+ 20% variation in values where no estimates of precision were available. Lower and upper values of the discount rate were also used as part of the DSA (CS Figures 67-69).[1] Figures 5.7, 5.8 and 5.9 summarise the results of the DSA for each pairwise comparison.

Figure 5.7: DSA tornado plot for nivolumab + PDC versus surgery

(Source Figure 67, CS)[1]

(Abbreviations: CI = confidence interval; DM = distant metastasis; DSA = deterministic sensitivity analysis; EF = Event-Free; HR = hazard ratio; INHB = incremental net health benefit; LR = locoregional recurrence; PDC = platinum doublet chemotherapy)

Figure 5.8: DSA tornado plot for nivolumab + PDC versus neoadjuvant CRT

(Source Figure 69, CS)[1]

(Abbreviations: CI, confidence interval; DM, Distant Metastasis; DSA, deterministic sensitivity analysis; EF, Event-Free; HR = hazard ratio; INHB = incremental net health benefit; LR = locoregional recurrence; PDC = platinum doublet chemotherapy; CRT = chemoradiation)

Figure 5.9: DSA tornado plot for nivolumab + PDC versus adjuvant PDC

(Source Figure 68, CS)[1]

(Abbreviations: CI = confidence interval; DM = distant metastasis; DSA = deterministic sensitivity analysis; EF = Event-Free; HR = hazard ratio; INHB = incremental net health benefit; LR = locoregional recurrence; PDC = platinum doublet chemotherapy)

5.3 Severity of the condition

In response to a points for clarification question B.22,[15] the company stated that the QALY shortfall was less than that required for a QALY multiplier. Hence, the company did not include a severity analysis in the CS.

5.4 Model validation and face validity check

5.4.1 Face validity assessment and technical verification

In the CS, the company stated that the validity of the CEM was assessed by a health economist not otherwise involved in the programming of the model. This validity check included assessing the logical structure of the model and verifying the formulae, calculations, and model inputs. The company state that one error was found and corrected through this process.

Following this initial validation process, the model underwent another round of validation undertaken by an independent health economist. Again, the assessor focused on the model's conceptual validity and the internal technical validity. Additional technical validity tests were undertaken during this process, such as using extreme values, in line with Good Model Validation Practice guidance.[78,79]

5.4.2 Comparison with external data

The company compared model outcomes against two conditional survival curves, one for neoadjuvant nivolumab + PDC and one for neoadjuvant PDC. Several sources, CheckMate-816 trial data, BMS patient-level meta-analysis data and the Surveillance, Epidemiology, and End Results (SEER) data were used to construct the conditional survival curves.[1] CheckMate-816 provided the data for up to year 3, BMS patient-level meta-analysis provided data from years 3-15 and SEER provided data for years 15-

20.[1] Differences between the curves was estimated for the first three years, based on CheckMate-816 but subsequent years assumed the same survival predictions.

However, given the 'one-off approach' that was used by the company to estimate DM outcomes, it was not possible to generate an overall survival (OS) curve that would be suitable for direct comparison against external data. Therefore the company:

1) Compared aggregated LYs based on the conditional survival curve to the LYs model output over the same timeframe
2) used multiple approaches to generate an OS curve based on the total LYs accrued in DM in the model, this was done using three approaches:
    a) an exponential distribution of survival time in DM was produced so that the area under the curve produced the LYs in DM as the model
    b) an exponential distribution of survival time in DM was produced with the LYs associated with the assumption that 75% of patients were treated with PDC and 25% with BSC
    c) DM survival time was assumed to the same as the OS KM curve for PDC from the CheckMate-9LA study.

In the first comparison, the CEM estimated lower long-term LYs compared to the conditional survival curves for both neoadjuvant nivolumab + PCS and neoadjuvant PDC. The difference in the predicted survival curves was larger for neoadjuvant nivolumab + PDC hence the company concluded that this difference was unlikely to bias the incremental results and that the model results could be conservative.

A visual comparison was made between the conditional survival curves and OS curves, with patient survival in DM predicted over time using the three approaches listed above instead of the "one-off approach". All three approaches illustrated divergence between the conditional survival curves and the overall OS curves. The company generated additional curves based on annual conditional survival and stated that they showed approximately the same level of divergence. These additional curves were not included in the CS so the EAG could not comment on this conclusion. The company hypothesised that the difference between the two curves, particularly between years 4 and 14 was due to differences in the population (disease stage and age) of CheckMate-816 and the BMS patient level meta-analysis data.[1] The company stated that the differences in disease stage could be accounted for by splitting and re-weighting the OS curves however the difference (age divergence) could not be controlled for.

EAG comment Overall the EAG was satisfied with the external validation undertaken by the company. The company highlighted the potential issues with this validation due to the construction of the DM state and made three adjustments to DM survival to account for this. Based on the LYs comparison it is likely that the CEM is conservative.

The EAG have previously noted (see Section 4.2.6) that there are disparities in the populations of CheckMate-816 and BMS patient-level meta-analysis which the company have also stated as part of their external validation. However, the company was reliant on this data for choosing their extrapolation distributions due to the immaturity of the CheckMate-816 data and didn't raise their concerns. This provides further justification to the assumptions made by the EAG in the base-case and scenario analyses presented in Section 6.1.

The company also compared the long-term survival outcomes to the model OS predictions, under the assumption that the exponential distribution of DM survival was predicted with 75% of patients receiving PDC and 25% BSC. This comparison was done for neoadjuvant PDC only because nivolumab + PDC is a novel intervention in this population hence it was not feasible to valuate long-term OS of

nivolumab + PDC. Again, data were compared with external sources (BMS patient-level meta-analysis and Goldstraw).[1] Overall the predicted OS for neoadjuvant PDC aligned with Goldstraw for the first five years after which the BMS patient-level meta-analysis data were a better fit.[1]

EAG comment The EAG were satisfied with the external comparison of long-term OS survival in neoadjuvant PDC. While the EAG had the same concerns about the comparability of the BMS patient-level meta-analysis, these data suggest that the BMS patient-level meta-analysis is a comparable with the OS of neoadjuvant PDC after five years.

Finally, the company made comparisons between OS predicted from the model and CheckMate-816 data. OS curves were estimated for both nivolumab + PDC and neoadjuvant PDC using the first two assumptions (2a and 2b) to predict the exponential distribution of DM survival. There was more variation in the neoadjuvant PDC OS curves compared to the CheckMate-816 data relative to the nivolumab + PDC comparison. However, the company noted that this deviation meant that the CEM predicted higher survival for neoadjuvant PDC and thus was not likely to bias the model results in favour of nivolumab.

EAG comment The EAG were satisfied with the external comparison of short-term OS (<4years) using the CheckMate-816 data.

6 EVIDENCE ASSESSMENT GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

This section describes the EAG base-case and scenario analyses conducted on both the EAG and the company base-case analyses. The EAG base-case and scenario analyses use the company's economic model and adopts alternative assumptions.

6.1.1 EAG base-case

Table 6.1 summarises the key issues related to the cost effectiveness, categorised according to the sources of uncertainty as defined by Grimm *et al*., 2020.[80]

- Transparency (e.g., lack of clarity in presentation, description, or justification)
- Methods (e.g., violation of best research practices, existing guidelines, or the reference case)
- Imprecision (e.g., particularly wide CIs, small sample sizes, or immaturity of data)
- Bias and indirectness (e.g., a mismatch between the decision problem and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
- Unavailability (e.g., lack of data or insight)

Identifying the source of uncertainty can help determine what course of action can be taken (i.e., whether additional clarifications, evidence and/or analyses might help to resolve the key issue). Moreover, Table 6.1 lists suggested alternative approaches, expected effects on the cost-effectiveness and whether it is reflected in the EAG base-case, as well as additional evidence or analyses that might help to resolve the key issues.

Based on all considerations in the preceding Sections of this EAG report, the EAG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous sections. These adjustments made by the EAG form the EAG base-case and were subdivided into three categories (derived from Kaltenthaler 2016).[81]

1. Fixing errors (FE) (correcting the model where the company's submitted model was unequivocally wrong)
2. Fixing violations (FV) (correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to)
3. Matters of judgement (MJ) (amending the model where the EAG considers that reasonable alternative assumptions are preferred)

Adjustments made by the EAG to derive the EAG base-case (using the CS base-case as starting point) are listed below. Table 6.2 shows how individual adjustments impact the results, plus the combined effect of all abovementioned adjustments simultaneously, resulting in the EAG base-case. The 'fixing error' adjustments were combined and the other EAG analyses were performed also incorporating these 'fixing error' adjustments given the EAG considered that the 'fixing error' adjustments corrected unequivocally wrong issues.

The EAG found errors in the model but found no violations. After these errors were corrected in the company's model, the EAG base-case and scenario analyses were undertaken to assess the impact of alternative assumptions on the cost-effectiveness results.

6.1.1.1 Fixing errors

Coding error: Cells E41:H41 in the "DM State" spreadsheet contain different distributions of treatments to the figures presented in the CS.

Correction: The values in array E41:H41 were replaced by the values reported in Table 45 of the CS.[1]

During the factual accuracy check, the company clarified that the distributions in the CS did not account for the 25% of patients who would receive best supportive care and that the distributions in the CEM had been updated to account for this. The EAG analyses were based on the distributions in the CS and hence do not account for the 25% of patients receiving best supportive care. The EAG note that the difference in cost associated with the alternative subsequent treatment distribution has no effect on the overall conclusions. The ICER for nivolumab would be reduced by £0-£2000, depending on the scenario analysis.

6.1.1.2 Fixing violations

No violations were identified by the EAG.

6.1.1.3 Matters of judgement

An overview of the key issues related to the cost-effectiveness after fixing errors is presented in Table 6.1.

Table 6.1: Overview of key issues related to the cost-effectiveness (conditional on fixing errors highlighted in Section 5.1)

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
1. Effectiveness of nivolumab + PDC more uncertain for patients with Stage IB or II NSCLC	3.2.8/ 3.5/ 4.2.3	Methods, imprecision	A NMA for Stage IB-II patients and Stage IIIA patients with updated results included in the EAG CEM.	+	Explored in EAG subgroup analyses 1-2	Further CheckMate-816 evidence from a later data cut, which is not currently available, would help reduce uncertainty.
2. Applicability of the CheckMate-816 population to England	3.2.3/ 3.2.8/ 4.2.3	Methods, imprecision	A NMA for patients from Europe and North America with updated results included in the EAG CEM.	+	Explored in EAG subgroup analysis 3	Further CheckMate-816 evidence from a later data cut, which is not currently available, would help reduce uncertainty.
3. Uncertainty in the effectiveness of different nivolumab + PDC regimens	3.2.3/ 3.2.8/ 4.2.4	Methods, imprecision	A NMA for patients receiving cisplatin only and carboplatin only with updated results included in the EAG CEM.	+/-	Explored in EAG subgroup analyses 4-5	Further evidence is needed on the HRs for LR and DM for the comparators and further CheckMate-816 evidence from a later data cut, which is not currently available, would help reduce uncertainty.
4. Applicability of resection type and surgical approach used in CheckMate-816 to the English clinical setting	3.2.4/ 4.29	Imprecision	Assumed the same proportion of patients received minimally invasive surgery across arms and that surgery rates were the same across arms.	+	Explored in EAG scenario analyses 1-2	No
5. Uncertainty in extrapolation models used to estimate time to any progression (TTaP) and time to locoregional recurrence (TTLR)	4.2.6	Methods, unavailability	A log-logistic model was applied to both TTaP and TTLR.	+/-	Explored in EAG base-case, scenario analysis 4	No

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
6. Uncertainty in the cure assumption	4.2.6	Methods, imprecision	The cure assumption was removed and the Gompertz distribution was applied from month 60.	+/-	Explored in EAG-base-case and EAG scenario analyses 5-7	Longer follow-up of NSCLC patients is needed to provide evidence to support the cure assumption.
7. Uncertainty in the event-free utility estimate	4.2.8	Methods, imprecision	Additional values were inputted to the model using the literature and clinical advice.	+	Explored in EAG scenario analyses 8-11	No
8. Uncertainty in the immuno-oncology (I-O) retreatment restrictions and distribution of chemotherapies in the DM state	4.2.6	Methods, imprecision	All patients received the same chemotherapy regimens regardless of initial treatment and assumed no restrictions.	+/-	Explored in EAG scenario analyses 14-15	Further evidence on potential I-O restrictions when recurrence occurs within six-months of initial treatment is needed.
9. Uncertainty in the effectiveness of the comparators	4.2.6	Methods, imprecision	HRs for the intervention and comparators used as inputs in the CEM were adjusted for proportionality to EFS estimates from the NMA.	+/-	Explored in EAG sub-group analyses	Further evidence on the effectiveness of the comparators is needed.

[a] Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the EAG and '+' indicates that the EAG believes this issue likely induces bias in favour of the intervention versus at least one comparator; [b] Explored

Abbreviations: CEM = company economic model; DM = distant metastisis; EAG = Evidence Assessment Group; EFS = event free survival; FE = fixing errors; FV = fixing violations; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; I-O = immuno-oncology; LR = locoregional recurrence; MJ = matters of judgement; NSCLC = non-small cell lung cancer; NMA = network meta-analysis; TTaP = time to any progression; TTLR = time to locoregional recurrence

1. The company assumed that the AEs anaemia, leukopenia and thrombocytopenia incurred the same disutility value as neutropenia (see Section 4.2.7)

The company provided no justification for this assumption in the CS. However, after the EAG queried this in the clarification letter, the company provided alternative values for both anaemia and thrombocytopenia.[15]

2. The company used a log-normal extrapolation to estimate TTLR (see Section 4.2.6)

The company fitted seven parametric models to the data of both the CheckMate-816 trial arms (see Figures 6.1 and 6.2). Both the log-logistic and exponential distributions were considered by the company based on goodness of fit statistics. However, both these distributions produced sizeably different long-term predictions. The company chose the log-normal distribution for their base-case model after making comparisons to the literature (see Figure 6.3). The EAG have concerns that the literature sources used were not comparable with CheckMate-816 data in terms of disease staging. The company used the exponential function to predict TTLR in a scenario analysis.

Figure 6.1: Time to locoregional recurrence: long-term extrapolations (nivolumab + PDC arm)

(Source: Figure 32, CS)[1]
(Abbreviations: PDC = platinum doublet chemotherapy)

Figure 6.2: Time to locoregional recurrence: long-term extrapolations (PDC arm)

(Source: Figure 33, CS)[1]
(Abbreviations: PDC = platinum doublet chemotherapy)

Figure 6.3: Time to Locoregional Recurrence: comparison versus external data – nivolumab + PDC arm

(Source: Figure 34, CS)[1]
(Abbreviations: CM-816 = CheckMate-816; KM = Kaplan-Meier; NSCLC = non-small cell lung cancer; PDC = platinum doublet chemotherapy; SOC = standard of care; TA = technology appraisal)

The EAG agree that the lognormal distribution was a better selection for the base-case compared to the exponential distribution, based on clinical advice provided to the EAG. However, the EAG also considered other distributions not explored by the company in scenario analyses may more realistically model TTLR. The EAG's preferred distribution for TTLR was the log-logistic distribution, as it generated an in-between prediction relative to the log-normal and exponential distributions, which is also perhaps potentially more consistent with external validity evidence.

3. The company used an exponential extrapolation to estimate EF mortality (see Section 4.2.6)

The company fitted seven extrapolations capped by the general population mortality to EF mortality and compared these long-term predictions to the observed patient-level mortality in the BMS meta-analysis.[1] All seven models predicted lower mortality rates than what was observed in the BMS meta-analysis, however this comparison needs to be interpreted with caution as previously identified by the EAG the proportion of patients with later stages of disease in the BMS meta-analysis was higher than what was observed in CM-816. These predicted and observed survival curves were discussed with clinical experts and the exponential distribution was chosen as it was the most conservative. The company adopted a generalised gamma distribution in a scenario analysis as it was the best statistical fit and converged towards general population mortality which was in alignment with their cure assumption (see Figure 6.4).

Based on assessment of the graphical data, the EAG felt that the log-normal distribution was a better fit of EF mortality. This distribution predicted similar mortality rates as all the other models up to month 60 (5 years) but was a better longer-term fit of EF mortality as it followed the general population mortality distribution, which is what you would expect at 5 years, based on clinical advice provided to the EAG.

Figure 6.4: Patient-level meta-analysis versus long-term event-free mortality extrapolations from CheckMate-816

(Source: Figure 49, CS)[1]
(Abbreviations: BMS = Bristol Myers Squibb; CM816 = CheckMate-816; KM = Kaplan-Meier)

4. The company applied a cure assumption after 5 years EF (see Section 4.2.6)

The company, based on clinical advice and precedent from other TA reports,[49,60] applied a cure assumption to the hazard rates of TTLR, TTaP and EF mortality. The company assumed that 95% of patients would be cured from year 7 if they had not experienced progression. In the CEM, the company pragmatically applied this assumption by reducing the hazard rate linearly over a two-year period from year 5, so by year 7, 95% of patients in EF were 'cured'.

If 'cured' patients are cured from surgery, then the KM curves for LR and any progression reflect the events that occur for patients that are NOT cured. If 'cured' patients were removed from the KM curve by cutting off a section of the bottom of the KM curve, the KM curve would be stretched along the vertical axis and the KM curve would be the KM curve for patients who are not cured. The question then is, "what time-to-event analysis extrapolation is appropriate for this population of non-cured patients?"

If the follow-up time were sufficiently long then it is quite likely that the shape of KM curve could not be modelled by one of the standard parametric time-to-event models. A model with a different distribution or a more flexible model fitting different parametric curves at different points may be needed. The company adopted a pragmatic approach to ensure the model predicted outcomes consistent with clinical expert opinion. This resulted in a very sharp change in hazard rates and flattening of the TTLR and TTDM curves. To represent a flexible modelling approach but with a less sharp change in hazard rates, the EAG applied the Gompertz distribution to TTLR, TTaP, and EF mortality at month 60 and removed any additional adjustment to progression/mortality associated with the cure assumption.

The cure assumption was applied to the TTDM curve rather than the any progression curve. The company base-case and EAG base-case TTLR and TTDM curves for PDC are presented in Figures 6.5 and 6.7 along with time-to-event curves for EAG scenarios 5, 6 and 7 described in Section 6.1.2.1. Figure 6.7 does not include a KM curve because the TTDM curve was derived from the TTLR and TTaP curves. For TTLR, as described in Matters of Judgement (2), the EAG selected a log-logistic model instead of the log-normal model in the company base-case. Comparable Figures for nivolumab + PDC are presented in Appendix 1. The company base-case and EAG base-case LR and DM hazard rate curves for PDC are presented in Figures 6.6 and 6.8 along with hazard rate curves for EAG scenarios 5, 6 and 7 described in Section 6.1.2.1.

Figure 6.5 shows a sudden drop in the hazard rate of LR at 5 years in the EAG base-case model is due to the transition from the log-logistic model to the Gompertz model. This contrasts with a much greater drop in the hazard rate of LR in the company base-case model between 5 and 7 years. The lower hazard rates of DM in the EAG base-case model compared to the company base-case model was due to the selection of the log-logistic model for LR in the EAG base-case. The DM hazard rates were calculated from the any progression and LR hazard rates.

The predictive values of the percentage of the initial PDC cohort that were still EF (EFS/cohort) at years 5, 10 and 15, and of the percentage of patients still EF at years 5, 10 and 15 who do not go on to experience a recurrence (never recurrence/still EFS) for both the company base-case and EAG base-case are presented in Table 6.2. These predictive values for nivolumab + PDC are presented in Table 6.3.

Figure 6.5: TTLR curves for PDC for different models

(Source: Produced by EAG)

(Abbreviations: EAG = evidence assessment group; KM = Kaplan-Meier; PDC = platinum doublet chemotherapy; TTLR = time to locoregional recurrence)

Figure 6.6: LR hazard rate curves for PDC for different models

(Source: Produced by EAG)

(Abbreviations: EAG = evidence assessment group; LR = locoregional recurrence; PDC = platinum doublet chemotherapy)

Figure 6.7: TTDM curves for PDC for different models

(Source: Produced by EAG)

(Abbreviations: EAG = evidence assessment group; PDC = platinum doublet chemotherapy; TTDM = time to distant metastasis)

Figure 6.8: DM hazard rate curves for PDC for different models

(Source: Produced by EAG)

(Abbreviations: DM = distant metastasis; EAG = evidence assessment group; PDC = platinum doublet chemotherapy)

Table 6.2: Predictive values of EFS and never recurrence for PDC by scenario

Outcome	Company base case			EAG base case			EAG Gompertz 46 (Scenario 5)		
	Yr 5	Yr 10	Yr 15	Yr 5	Yr 10	Yr 15	Yr 5	Yr 10	Yr 15
EFS/cohort (%)	[redacted]								
never recurrence/ still EFS (%)	[redacted]								
	EAG Gompertz 60 at 46 (Scenario 6)			EAG no model (Scenario 7)					
	Yr 5	Yr 10	Yr 15	Yr 5	Yr 10	Yr 15			
EFS/cohort (%)	[redacted]								
never recurrence/ still EFS (%)	[redacted]								

(Source: Produced by EAG)

Abbreviations: EAG = evidence assessment group; EFS = event-free survival; Yr = Year; PDC = platinum doublet chemotherapy.

Table 6.3: Predictive values of EFS and never recurrence for nivolumab + PDC by scenario

Outcome	Company base case			EAG base case			EAG Gompertz 46 (Scenario 5)		
	Yr 5	Yr 10	Yr 15	Yr 5	Yr 10	Yr 15	Yr 5	Yr 10	Yr 15
EFS/cohort (%)	[redacted]								
never recurrence/ still EFS (%)	[redacted]								
	EAG Gompertz 60 at 46 (Scenario 6)			EAG no model (Scenario 7)					
	Yr 5	Yr 10	Yr 15	Yr 5	Yr 10	Yr 15			
EFS/cohort (%)	[redacted]								
never recurrence/ still EFS (%)	[redacted]								

(Source: Produced by EAG)

Abbreviations: EAG = evidence assessment group; EFS = event-free survival; Yr = Year; PDC = platinum doublet chemotherapy.

6.1.2 EAG exploratory scenario analyses

The EAG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the EAG base-case.

6.1.2.1 Exploratory scenario analyses

This section describes the scenario and sensitivity analyses conducted by the EAG. The EAG conducted the three scenario analyses included in the CS with the greatest impact on ICER estimates. In addition, the EAG conducted 13 scenario analyses not conducted by the company. All these scenario and sensitivity analyses are described below.

1. Distribution of surgery (see Section 4.2.6)
   The EAG consulted clinical expert opinion about the proportion of minimally invasive surgeries assigned to each treatment arm. The EAG were advised that this was lower than expected in the UK and so the EAG undertook two scenario analyses using the following assumptions: 1) 50% of patients receive minimally invasive surgery across all treatment arms (EAG Scenario 1), and 2) 50% of patients receive minimally invasive surgery across all treatment arms and the rates of surgery were the same as nivolumab + PDC for all the comparators (EAG Scenario 2). The second assumption was a conservative assumption made by the EAG given the uncertainty in the evidence to justify the surgery rates for the different comparators.

2. Surgery cost data was updated using more recent sources
   The National Schedule of Reference Costs,[76] which was used by the company, has been updated since the CS. The company consistently inflated costs where necessary to the 2019/2020 price year. The EAG noted that the 2019/2020 National Schedule of Reference Costs surgery unit costs were substantially different compared with the inflated 2019/2020 costs the company used in the CEM (other inflated costs did not appear to be markedly different to those in the updated National Schedule of Reference Costs).[76] The EAG updated the surgery unit costs in the EAG base-case analysis because this could affect the ICER (EAG Scenario 3).

3. Distribution for TTaP (see Section 4.2.6)
   The same distribution (log-logistic) was applied to both TTaP and TTLR (EAG Scenario 4).

4. Cure assumption (see Section 4.2.6)
   The EAG explored the effect on cost-effectiveness of alternative models extrapolating TTLR and TTaP curves. In none of these scenarios was the company approach to the cure assumption included. The EAG made the following assumptions: 1) the TTLR model switched from the log-logistic model to the Gompertz model at 46 months (EAG Scenario 5- Gompertz 46), 2) the TTLR model switched from the log-logistic model to the Gompertz model at 46 months, but applied the Gompertz hazard rates from month 60 onwards to month 46 onwards (EAG Scenario 6- Gompertz 60 at 46), and 3) TTLR was modelled for the entire time horizon using the log-logistic model (EAG Scenario 7- one model, which was #3 scenario analysis in the CS).[1]

5. Utility values associated with the EF and LR health states (see Section 4.2.8)
   The company noted there was uncertainty in the utility values for both the EF and LR health states, as they were higher than what would be expected in a population with NSCLC; this was verified with expert opinion. The company did not provide alternative values to be explored in scenario analysis. The EAG sought alternative absolute values for EF and LR and alternative

values for the decrement between EF and LR from the literature and clinical expert opinion.[65] The EAG assigned the following assumptions: 1) EF and LR utility values from the literature[65] (EAG Scenario 8), 2) EF values used in the CEM but assign a decrement between EF and LR based on clinical advice (EAG Scenario 9), 3) EF utility value is based on clinical advice the decrement to LR is the same as the CEM (EAG Scenario 10); EF and LR utility values are based on clinical advice (EAG Scenario 11).

6. Disutility value associated with the AE fatigue (see Section 4.2.7)
   The EAG assigned a larger disutility value to fatigue based on a previous TAR (TA653).[60] (EAG Scenario 12)

7. I-O retreatment restrictions (see Section 4.2.6)
   The company assumed there would be restrictions on patients who progressed after they received I-O as their initial treatment. There was little evidence to support this assumption and the company undertook scenario analysis to determine its effect on the ICER. The EAG assumed: 1) that the distribution of chemotherapies in the DM health state would be the same for those who initially received I-O treatments and those who did not (EAG Scenario 13), and 2) that there was no I-O retreatment restriction (as per scenario #10 in the CS).[1] (EAG scenario 14)

8. No subsequent treatment costs (see Section 4.3.9)
   The company assumed, in a scenario analysis (as per scenario #10 in the CS)[1] that there were no subsequent treatment costs (EAG Scenario 15). This extreme assumption was made due to the lack of evidence available to the company. The EAG replicated this scenario analysis as it had the greatest effect on the ICER. Alternative confidential estimates for the costs and QALYs accrued in the DM health state based on previous STA reports are included as a scenario analysis in the cPAS appendix. [46,53,55,56]

9. Assume AE proportions in adjuvant PDC were the same as neoadjuvant CRT (see Section 4.3.9)
   Given the uncertainty in the proportion of AEs for adjuvant PDC the same proportion of AEs for neoadjuvant CRT was applied to adjuvant PDC (EAG Scenario 16).

6.1.3 EAG subgroup analyses

This Section describes the subgroup analyses conducted by the EAG. The EAG conducted three subgroup analyses: 1) disease stage (Stage IB and II versus Stage IIIA); 2) using data from North America and Europe only; and 3) PDC regimen (cisplatin is more likely to be used in a UK setting than carboplatin). These subgroup analyses are described below.

1. Subgroup analysis by disease stage
   As previously highlighted by the EAG (see Section 3.2.8), there may be a slight difference in the effectiveness of nivolumab + PDC in the earlier stages of disease (Stages IB and II) compared with later stage disease (Stage IIIA). Whilst the EAG agrees with the company that the data available from the latest CheckMate-816 data cut is subject to uncertainty, the EAG considered this to be an important analysis (EAG Subgroup 1 and 2).

2. Subgroup analysis using data from North America and Europe
   The EAG has concerns about the applicability of the data from the CheckMate-816 trial, as the characteristics of patients enrolled in CheckMate-816 may not reflect the characteristics of

patients see in clinical practice in England. The EAG considers that patients from Europe and North America may be more reflective of patients seen in England and noted that nivolumab + PDC was less effective in patients from Europe and North America than those in Asia (see Section 3.2.8). This assumption was verified with expert clinical opinion to the EAG. This subgroup analysis was undertaken by the EAG with the caveat that the data available for this analysis was limited and hence subject to uncertainty. The EAG recommends that the company undertake this subgroup analysis using a later data cut from CM-816 to reduce this uncertainty (EAG subgroup 3).

3. Subgroup analysis based on the PDC regimens

   Based on clinical advice, the EAG noted that it was unlikely that carboplatin-based PDC regimens would be provided in England. Hence, the EAG undertook a subgroup analysis assuming the effectiveness of nivolumab + cisplatin-based PDC only (EAG subgroup 4 and 6).

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

6.2.1 The EAG base-case, scenario and subgroup analyses

In Section 6.1, the features of the EAG base-case were presented, which was based on various changes compared to the company base-case relating to both fixing of errors and matters of judgement (MJ). Tables 6.4, 6.5 and 6.6 show how each of the individual changes impact the results for each pairwise comparison, plus the combined effect of all changes simultaneously. The exploratory scenario analyses are listed in Table 6.7 with the results for each of the pairwise comparisons presented in Tables 6.8, 6.9 and 6.10. The exploratory subgroup analyses are presented in Tables 6.11, 6.12 and 6.13 for each pairwise comparison. The probabilistic results are presented in Tables 6.14, 6.15, and 6.16. Additional analyses determining the effect of the proportional HR assumption on the subgroup analysis are presented in Tables 6.17, 6.18 and 6.19. The probabilistic results are presented in Tables 6.20. 6.21, 6.22. These are all conditional on the EAG base-case.

The nivolumab PAS has changed since the company provided its submission. The ICERs presented in Section 6 are based on the latest PAS for nivolumab ([redacted]). The company base-case results have also been updated with the latest PAS for nivolumab and these results are presented within Tables 6.4, 6.5 and 6.6 for each of the pairwise comparisons.

Table 6.4: Deterministic EAG base-case results (unless otherwise stated) – nivolumab + PDC versus neoadjuvant CRT

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS base-case – Deterministic					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Neoadj CRT	[redacted]	[redacted]			
CS base-case – Probabilistic					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Neoadj CRT	[redacted]	[redacted]			
Fixing error 1					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Neoadj CRT	[redacted]	[redacted]			
CS base-case after fixing errors					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Neoadj CRT	[redacted]	[redacted]			
CS with updated PAS for nivolumab					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Neoadj CRT	[redacted]	[redacted]			
Matter of judgement 1 - Alternative AE disutilities					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Neoadj CRT	[redacted]	[redacted]			
Matter of judgement 2 log-logistic TTLR; Key issue 5, Section 2.4.6					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Neoadj CRT	[redacted]	[redacted]			
Matter of judgement 3 EF Mortality with log-normal extrapolation; Key issue 6, Section 2.4.6					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Neoadj CRT	[redacted]	[redacted]			
Matter of judgement 4 Gompertz cure assumption in TTLR; Key issue 7, Section 4.2.6					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Neoadj CRT	[redacted]	[redacted]			
Matter of judgement 4 Gompertz cure assumption in TTaP; Key issue 7, Section 4.2.6					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Neoadj CRT	[redacted]	[redacted]			
Matter of judgement 5 Gompertz cure assumption in EF mortality; Key issue 7, Section 4.2.6					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Neoadj CRT	[redacted]	[redacted]			
EAG base-case – Deterministic					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Neoadj CRT	[redacted]	[redacted]			
EAG base-case – Probabilistic					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Neoadj CRT	[redacted]	[redacted]			

Abbreviations: EAG = evidence assessment group; QALY = quality adjusted life-year; ICER = incremental cost-effectiveness ratio; CS = company submission; AE = adverse event; TTLR = time to locoregional recurrence; TTaP = time to any progression; EF = event-free; Nivo = nivolumab; PDC = platinum doublet chemotherapy; Neoadj. CRT = neoadjuvant chemoradiotherapy.

Table 6.5: Deterministic EAG base-case results (unless otherwise stated) – nivolumab + PDC versus adjuvant PDC

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS base-case – Deterministic					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Adj PDC	[redacted]	[redacted]			
CS base-case – Probabilistic					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Adj PDC	[redacted]	[redacted]			
Fixing error 1					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	£529
Adj PDC	[redacted]	[redacted]			
CS base-case after fixing errors					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	£529

Adj PDC	[redacted]	[redacted]			
CS with updated PAS for nivolumab					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	£207
Adj PDC	[redacted]	[redacted]			
Matter of judgement 1 - Alternative AE disutilities					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	£207
Adj PDC	[redacted]	[redacted]			
Matter of judgement 2 log-logistic TTLR; Key issue 5, Section 2.4.6					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	£831
Adj PDC	[redacted]	[redacted]			
Matter of judgement 3 EF Mortality with log-normal extrapolation; Key issue 6, Section 2.4.6					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	£401
Adj PDC	[redacted]	[redacted]			
Matter of judgement 4 Gompertz cure assumption in TTLR; Key issue 7, Section 4.2.6					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	£248
Adj PDC	[redacted]	[redacted]			
Matter of judgement 4 Gompertz cure assumption in TTaP; Key issue 7, Section 4.2.6					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Adj PDC	[redacted]	[redacted]			
Matter of judgement 5 Gompertz cure assumption in EF mortality; Key issue 7, Section 4.2.6					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	£307
Adj PDC	[redacted]	[redacted]			
EAG base-case – Deterministic					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	£879
Adj PDC	[redacted]	[redacted]			
EAG base-case – Probabilistic					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	£1,197
Adj PDC	[redacted]	[redacted]			

Abbreviations: EAG = evidence assessment group; QALY = quality adjusted life-year; ICER = incremental cost-effectiveness ratio; CS = company submission; AE = adverse event; TTLR = time to locoregional recurrence; TTaP = time to any progression; EF = event-free; Nivo = nivolumab; PDC = platinum doublet chemotherapy; Adj PDC = adjuvant platinum doublet chemotherapy.

Table 6.6: Deterministic EAG base-case results (unless otherwise stated) – nivolumab + PDC versus surgery alone

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS base-case – Deterministic					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	£2,685
Surgery alone	[redacted]	[redacted]			

CS base-case – Probabilistic					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	£2,560
Surgery alone	[redacted]	[redacted]			
Fixing error 1					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	£3,183
Surgery alone	[redacted]	[redacted]			
CS base-case after fixing errors					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	£3,183
Surgery alone	[redacted]	[redacted]			
CS with updated PAS for nivolumab					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	£2,991
Surgery alone	[redacted]	[redacted]			
Matter of judgement 1 - Alternative AE disutilities					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	£2,991
Surgery alone	[redacted]	[redacted]			
Matter of judgement 2 log-logistic TTLR; Key issue 5, Section 2.4.6					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	£3,455
Surgery alone	[redacted]	[redacted]			
Matter of judgement 3 EF Mortality with log-normal extrapolation; Key issue 6, Section 2.4.6					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	£3,054
Surgery alone	[redacted]	[redacted]			
Matter of judgement 4 Gompertz cure assumption in TTLR; Key issue 7, Section 4.2.6					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	£3,181
Surgery alone	[redacted]	[redacted]			
Matter of judgement 4 Gompertz cure assumption in TTaP; Key issue 7, Section 4.2.6					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	£2,398
Surgery alone	[redacted]	[redacted]			
Matter of judgement 5 Gompertz cure assumption in EF mortality; Key issue 7, Section 4.2.6					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	£3,017
Surgery alone	[redacted]	[redacted]			
EAG base-case – Deterministic					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	£3,478
Surgery alone	[redacted]	[redacted]			
EAG base-case – Probabilistic					
Nivo + PDC	[redacted]	[redacted]	[redacted]	[redacted]	£4,559
Surgery alone	[redacted]	[redacted]			

Abbreviations: EAG = evidence assessment group; QALY = quality adjusted life-year; ICER = incremental cost-effectiveness ratio; CS = company submission; AE = adverse event; TTLR = time to locoregional recurrence; TTaP = time to any progression; EF = event-free; Nivo = nivolumab; PDC = platinum doublet chemotherapy.

The EAG updated the EAG base-case deterministic and probabilistic analyses to reflect the updated nivolumab PAS discount which has increased from [redacted] to [redacted] since the CS. In the EAG base-case, nivolumab dominated neoadjuvant CRT and had a [redacted] probability of being considered cost-effective at a £20,000 threshold for an additional QALY. The ICER for nivolumab compared to adjuvant PDC was £879 and the probability of nivolumab being considered cost-effective was [redacted] at a £20,000 threshold for an additional QALY. In the comparison between nivolumab and surgery alone, the ICER was £3,478 and the probability of nivolumab being cost-effective at £20,000 for an additional QALY was [redacted].

Table 6.7: List of EAG scenario analyses

Scenario	Scenario description
1	Assume that 50% of patients receive minimally invasive surgery across all treatment arms
2	Assume that 50% of patients receive minimally invasive surgery across all treatment arms and no difference in surgery rates between nivolumab + PDC and other treatment arms (83.2% for all treatments)
3	Use the cost data from the updated National Schedule of NHS Costs (2020-2021)[76] for surgery
4	Log logistic distribution rather than log-normal distribution for TTLR and TTaP
5	Start of the cure assumption at 46 months instead of 60 months (switching to Gompertz from month 46)
6	Start of the cure assumption at 46 months instead of 60 months, using Gompertz hazards from month 60 onwards at month 46 onwards
7	No cure assumption (Sensitivity analysis #3 from CS)
8	Use utility values from Nafees *et al.,* (2008)[65] for the EF (0.653) and LR (0.473) health states
9	Retain the utility value for the EF health state used in the CEM (0.833) and set the utility decrement between the EF and LR health state to 0.2
10	Set the utility value for the EF health state to 0.75 and retain the utility decrement from EF to LR from the CS (0.62)
11	Set the utility value of the EF health state to 0.75 and the utility value of the LR health state to 0.55
12	Use the disutility value for fatigue from TA653 (-0.21)[60]
13	Assume that the distribution of chemotherapies in the DM state is the same for I-O and non-I-O therapies
14	I-O treatment restriction not included (Sensitivity analysis #10 from CS)
15	Assume no cost of subsequent treatment (Sensitivity analysis #7 from CS)
16	Assume the AE proportions in the adjuvant PDC treatment arm are equal to those in the neoadjuvant CRT treatment arm
Abbreviations: PDC = platinum doublet chemotherapy; TTLR = time to locoregional recurrence; TTaP = time to any progression; CS = company submission; EF = event-free; LR = locoregional recurrence; I-O = immune-oncology; AE = adverse event; CRT = chemoradiotherapy	

Table 6.8: Deterministic results of EAG scenario analyses (nivolumab + PDC versus neoadjuvant CRT)

Scenario	EAG base-case input	Alternative input	Incremental Costs (£)	Incremental QALYs	Incremental Cost Per QALY
	EAG base-case	N/A	[redacted]	[redacted]	Dominant
1	Minimally invasive surgery rates in CEM taken from Spicer e*t al.,* (2021).[82]	Minimally invasive surgery changed to up 50% of surgeries for all treatment arms	[redacted]	[redacted]	Dominant
2	Minimally invasive surgery rates in CEM taken from Spicer *et al.,* (2021).[82] Rates of patients receiving surgery in CEM taken from CM-816.	Minimally invasive surgery makes up 50% of surgeries for all treatments. Rates of patients receiving surgery assumed to be 83.2% across all treatments.	[redacted]	[redacted]	Dominant
3	Use surgery costs from CS	Use updated surgery costs	[redacted]	[redacted]	Dominant
4	Log-normal distribution for TTLR and TTaP	Log-logistic distribution for TTLR and TTaP	[redacted]	[redacted]	Dominant
5	Gompertz distribution applied at 60 months	Gompertz distribution applied at 46 months	[redacted]	[redacted]	Dominant
6	Gompertz distribution applied at 60 months	Gompertz distribution applied at 46 months with HRs from 60 months	[redacted]	[redacted]	Dominant
7	Cure assumption included	No cure assumption included	[redacted]	[redacted]	Dominant
8	Use utility values for the EF and LR health states from CS	Use utility values for the EF and LR health states from Nafees *et al.,* (2008)[65]	[redacted]	[redacted]	Dominant

9	Use utility values for the EF and LR health states from CS	Use utility value of 0.833 for EF and 0.633 for LR	[redacted]	[redacted]	Dominant
10	Use utility values for the EF and LR health states from CS	Use utility value of 0.750 for EF and [redacted] for LR	[redacted]	[redacted]	Dominant
11	Use utility values for the EF and LR health states from CS	Use utility value of 0.750 for EF and 0.550 for LR	[redacted]	[redacted]	Dominant
12	Disutility value for fatigue is -0.073	Disutility value for fatigue is –0.21	[redacted]	[redacted]	Dominant
13	Distribution of chemotherapies in the DM state is different for I-O and non-I-O therapies	Distribution of chemotherapies is the same	[redacted]	[redacted]	£8,046
14	I-O retreatment restrictions included	I-O retreatment restrictions not included	[redacted]	[redacted]	£6,429
15	Costs of subsequent treatment included	Assume no costs of subsequent treatments	[redacted]	[redacted]	£32,718
16	Use AE proportions from CS	Assume AE proportions in the adjuvant PDC arm are equal to those in the neoadjuvant CRT arm	[redacted]	[redacted]	Dominant

Abbreviations: EAG = evidence assessment group; PDC = platinum doublet chemotherapy; QALY = quality-adjusted life-year; ICER = incremental cost-effectiveness ratio; NA = not applicable; CEM = company economic model; CM-816 = CheckMate-816 CS = company submission; TTLR = time to locoregional recurrence; TTaP = time to any progression; EF = event-free; DM = distant metastasis; I-O = immuno-oncology; AE = adverse event; CRT = chemoradiotherapy

Table 6.9: Deterministic Results of EAG Scenario Analyses (nivolumab + PDC versus adjuvant PDC)

Scenario	EAG base-case input	Alternative input	Incremental Costs (£)	Incremental QALYs	Incremental Cost Per QALY
	EAG base-case	N/A	[redacted]	[redacted]	£879
1	Minimally invasive surgery rates in CEM taken from Spicer *et al.,* (2021)[82]	Minimally invasive surgery changed to up 50% of surgeries for all treatment arms	[redacted]	[redacted]	£1,881
2	Minimally invasive surgery rates in CEM taken from Spicer *et al.,* (2021).[82] Rates of patients receiving surgery in CEM taken from CM-816.	Minimally invasive surgery makes up 50% of surgeries for all treatments. Rates of patients receiving surgery assumed to be 83.2% across all treatments.	[redacted]	[redacted]	£3,094
3	Use surgery costs from CS	Use updated surgery costs	[redacted]	[redacted]	Dominant
4	Log-normal distribution for TTLR and TTaP	Log-logistic distribution for TTLR and TTaP	[redacted]	[redacted]	£185
5	Gompertz distribution applied at 60 months	Gompertz distribution applied at 46 months	[redacted]	[redacted]	£697
6	Gompertz distribution applied at 60 months	Gompertz distribution applied at 46 months with HRs from 60 months	[redacted]	[redacted]	£862
7	Cure assumption included	No cure assumption included	[redacted]	[redacted]	£1,603
8	Use utility values for the EF and LR health states from CS	Use utility values for the EF and LR health states from Nafees *et al*., (2008)[65]	[redacted]	[redacted]	£1,233
9	Use utility values for the EF and LR health states from CS	Use utility value of 0.833 for EF and 0.633 for LR	[redacted]	[redacted]	£887

10	Use utility values for the EF and LR health states from CS	Use utility value of 0.750 for EF and [redacted] or LR	[redacted]	[redacted]	£1,008
11	Use utility values for the EF and LR health states from CS	Use utility value of 0.750 for EF and 0.550 for LR	[redacted]	[redacted]	£1,020
12	Disutility value for fatigue is -0.073	Disutility value for fatigue is –0.21	[redacted]	[redacted]	£878
13	Distribution of chemotherapies in the DM state is different for I-O and non-I-O therapies	Distribution of chemotherapies is the same	[redacted]	[redacted]	£4,212
14	I-O retreatment restrictions included	I-O retreatment restrictions not included	[redacted]	[redacted]	£3,532
15	Costs of subsequent treatment included	Assume no costs of subsequent treatments	[redacted]	[redacted]	£12,498
16	Use AE proportions from CS	Assume AE proportions in the adjuvant PDC arm are equal to those in the neoadjuvant CRT arm	[redacted]	[redacted]	£2,623

Abbreviations: EAG = evidence assessment group; PDC = platinum doublet chemotherapy; QALY = quality-adjusted life-year; ICER = incremental cost-effectiveness ratio; NA = not applicable; CEM = company economic model; CM-816 = CheckMate-816 CS = company submission; TTLR = time to locoregional recurrence; TTaP = time to any progression; EF = event-free; DM = distant metastasis; I-O = immuno-oncology; AE = adverse event; CRT = chemoradiotherapy

Table 6.10: Deterministic results of EAG scenario analyses (nivolumab + PDC versus surgery alone)

Scenario	EAG base-case input	Alternative input	Incremental Costs (£)	Incremental QALYs	Incremental Cost Per QALY
	EAG base-case	N/A	[redacted]	[redacted]	£3,478
1	Minimally invasive surgery rates in CEM taken from Spicer *et al*., (2021)[82]	Minimally invasive surgery changed to up 50% of surgeries for all treatment arms	[redacted]	[redacted]	£4,037
2	Minimally invasive surgery rates in CEM taken from Spicer *et al*., (2021).[82] Rates of patients receiving surgery in CEM taken from CM-816.	Minimally invasive surgery makes up 50% of surgeries for all treatment. Rates of patients receiving surgery assumed to be 83.2% across all treatments.	[redacted]	[redacted]	£4,696
3	Use surgery costs from CS	Use updated surgery costs	[redacted]	[redacted]	£2,785
4	Log-normal distribution for TTLR and TTaP	Log-logistic distribution for TTLR and TTaP	[redacted]	[redacted]	£2,899
5	Gompertz distribution applied at 60 months	Gompertz distribution applied at 46 months	[redacted]	[redacted]	£3,224
6	Gompertz distribution applied at 60 months	Gompertz distribution applied at 46 months with HRs from 60 months	[redacted]	[redacted]	£3,273
7	Cure assumption included	No cure assumption included	[redacted]	[redacted]	£4,722
8	Use utility values for the EF and LR health states from CS	Use utility values for the EF and LR health states from Nafees *et al*., (2008)[65]	[redacted]	[redacted]	£4,706
9	Use utility values for the EF and LR health states from CS	Use utility value of 0.833 for EF and 0.633 for LR	[redacted]	[redacted]	£3,462

10	Use utility values for the EF and LR health states from CS	Use utility value of 0.750 for EF and [redacted] or LR	[redacted]	[redacted]	£3,962
11	Use utility values for the EF and LR health states from CS	Use utility value of 0.750 for EF and 0.550 for LR	[redacted]	[redacted]	£3,941
12	Disutility value for fatigue is -0.073	Disutility value for fatigue is –0.21	[redacted]	[redacted]	£3,478
13	Distribution of chemotherapies in the DM state is different for I-O and non-I-O therapies	Distribution of chemotherapies is the same	[redacted]	[redacted]	£5,508
14	I-O retreatment restrictions included	I-O retreatment restrictions not included	[redacted]	[redacted]	£4,949
15	Costs of subsequent treatment included	Assume no costs of subsequent treatments	[redacted]	[redacted]	£12,337
16	Use AE proportions from CS	Assume AE proportions in the adjuvant PDC arm are equal to those in the neoadjuvant CRT arm	[redacted]	[redacted]	£3,478

Abbreviations: EAG = evidence assessment group; PDC = platinum doublet chemotherapy; QALY = quality-adjusted life-year; ICER = incremental cost-effectiveness ratio; NA = not applicable; CEM = company economic model; CM-816 = CheckMate-816 CS = company submission; TTLR = time to locoregional recurrence; TTaP = time to any progression; EF = event-free; DM = distant metastasis; I-O = immuno-oncology; AE = adverse event; CRT = chemoradiotherapy

Table 6.11: Deterministic results of EAG subgroup analyses (nivolumab + PDC versus neoadjuvant CRT)

Subgroup Analysis	Base-case assumption	Subgroup assumption	Incremental Costs (£)	Incremental QALYs	Incremental Cost Per QALY
	EAG base-case	NA	[redacted]	[redacted]	Dominant
1	All stages of cancer	Stage IB&II only	Not able to estimate		
2	All stages of cancer	Stage III only	[redacted]	[redacted]	Dominant
3	All countries	North America/ Europe only	[redacted]	[redacted]	Dominated
4	All chemotherapies	Cisplatin only	[redacted]	[redacted]	£3,420*
5	All chemotherapies	Carboplatin only	[redacted]	[redacted]	Dominant

* ICER estimated for neoadjuvant CRT as nivolumab + PDC was less costly and less effective
Abbreviations: EAG = Evidence Assessment Group; PDC = platinum doublet chemotherapy; QALY = quality-adjusted life-year; ICER = incremental cost-effectiveness ratio; NA = not applicable

Table 6.12: Deterministic results of EAG subgroup analyses (nivolumab + PDC versus adjuvant PDC)

Subgroup Analysis	**Base-case assumption**	**Subgroup assumption**	**Incremental Costs (£)**	**Incremental QALYs**	**Incremental Cost Per QALY**
	EAG base-case	N/A	[redacted]	[redacted]	£879
1	All stages of cancer	Stage IB and II only	[redacted]	[redacted]	Dominated
2	All stages of cancer	Stage III only	Not able to estimate		
3	All countries	North America/ Europe only	Not able to estimate		
4	All chemotherapies	Cisplatin only	Not able to estimate		
5	All chemotherapies	Carboplatin only	[redacted]	[redacted]	Dominant

Abbreviations: EAG = Evidence Assessment Group; PDC = platinum doublet chemotherapy; QALY = quality-adjusted life-year; ICER = incremental cost-effectiveness ratio; NA = not applicable

Table 6.13: Deterministic results of EAG subgroup analyses (nivolumab + PDC versus surgery alone)

Subgroup Analysis	**Base-case assumption**	**Subgroup assumption**	**Incremental Costs (£)**	**Incremental QALYs**	**Incremental Cost Per QALY**

	EAG base-case	N/A	[redacted]	[redacted]	£3,478
1	All stages of cancer	Stage IB&II only	[redacted]	[redacted]	£16,143
2	All stages of cancer	Stage III only	[redacted]	[redacted]	£301
3	All countries	North America/ Europe only	[redacted]	[redacted]	£4,890
4	All chemotherapies	Cisplatin only	[redacted]	[redacted]	£2,627
5	All chemotherapies	Carboplatin only	[redacted]	[redacted]	£292

Abbreviations: EAG = Evidence Assessment Group; PDC = platinum doublet chemotherapy; QALY = quality-adjusted life-year; ICER = incremental cost-effectiveness ratio; NA = not applicable

Table 6.14: Probabilistic results of EAG subgroup analyses (nivolumab + PDC versus neoadjuvant CRT)

Subgroup Analysis	Base-case assumption	Subgroup assumption	Incremental Costs (£)	Incremental QALYs	Incremental Cost Per QALY
	EAG base-case	N/A	[redacted]	[redacted]	Dominant
1	All stages of cancer	Stage IB&II only	Not able to estimate		
2	All stages of cancer	Stage III only	[redacted]	[redacted]	Dominant
3	All countries	North America/ Europe only	[redacted]	[redacted]	£1,978*
4	All chemotherapies	Cisplatin only	[redacted]	[redacted]	Dominant
5	All chemotherapies	Carboplatin only	[redacted]	[redacted]	Dominant

* ICER estimated for neoadjuvant CRT as nivolumab + PDC was less costly and less effective
Abbreviations: EAG = Evidence Assessment Group; PDC = platinum doublet chemotherapy; CRT = chemoradiotherapy; QALY = quality-adjusted life-year; ICER = incremental cost-effectiveness ratio; NA = not applicable

Table 6.15: Probabilistic results of EAG subgroup analyses (nivolumab + PDC versus adjuvant PDC)

Subgroup Analysis	Base-case assumption	Subgroup assumption	Incremental Costs (£)	Incremental QALYs	Incremental Cost Per QALY
	EAG base-case	N/A	[redacted]	[redacted]	£1,197
1	All stages of cancer	Stage IB&II only	[redacted]	[redacted]	Dominated

2	All stages of cancer	Stage III only	Not able to estimate		
3	All countries	North America/ Europe only	Not able to estimate		
4	All chemotherapies	Cisplatin only	Not able to estimate		
5	All chemotherapies	Carboplatin only	[redacted]	[redacted]	Dominant
Abbreviations: EAG = Evidence Assessment Group; PDC = platinum doublet chemotherapy; QALY = quality-adjusted life-year; ICER = incremental cost-effectiveness ratio; NA = not applicable					

Table 6.16: Probabilistic results of EAG subgroup analyses (nivolumab + PDC versus surgery alone)

Subgroup Analysis	Base-case assumption	Subgroup assumption	Incremental Costs (£)	Incremental QALYs	Incremental Cost Per QALY
	EAG base-case	N/A	[redacted]	[redacted]	£4,559
1	All stages of cancer	Stage IB&II only	[redacted]	[redacted]	£23,607
2	All stages of cancer	Stage III only	[redacted]	[redacted]	£1,043
3	All countries	North America/ Europe only	[redacted]	[redacted]	£6,998
4	All chemotherapies	Cisplatin only	[redacted]	[redacted]	£3,836
5	All chemotherapies	Carboplatin only	[redacted]	[redacted]	£619
Abbreviations: EAG = Evidence Assessment Group; PDC = platinum doublet chemotherapy; QALY = quality-adjusted life-year; ICER = incremental cost-effectiveness ratio; NA = not applicable					

Given the quality of the evidence in the NMA for LR and DM outcomes, the EAG also investigated the sensitivity of the results to different values of the HR of LR and DM for the comparators. In these analyses, the same ratio of the HRs of LR and DM compared to HR of EFS for nivolumab + PDC are used for the HRs of LR and DM for the comparators. The EAG does not disagree with the company's approach to estimating the HRs of LR and DM for the comparators. The purpose was to explore the sensitivity of the results to these changes given uncertainty in the underlying evidence used to estimate the HRs of LR and DM for the comparators. Assuming HRs of LR and DM equal to the HR of EFS for the comparators significantly increases the cost-effectiveness of nivolumab + PDC. The cost-effectiveness of nivolumab + PDC could go up or down. The deterministic analysis results are reported in Tables 6.17, 6.18 and 6.19. The probabilistic analysis results are reported in Tables 6.20, 6.21 and 6.22.

Table 6.17: Deterministic results of EAG subgroup analyses (nivolumab + PDC versus neoadjuvant CRT) with the HR of LR and DM for comparators adjusted to have a similar ratio as for nivolumab + PDC

Sub-Group Analysis	Base-case assumption	Alternative assumption	Mean Incremental Costs (£)	Mean Incremental QALYs	Mean Incremental Cost Per QALY
	EAG base-case	N/A	[redacted]	[redacted]	Dominant
0	EAG base-case	HRs adjusted	[redacted]	[redacted]	Dominant
1	All stages of cancer	Stage IB&II only	Not able to estimate		
2	All stages of cancer	Stage III only	[redacted]	[redacted]	Dominant
3	All countries	North America/Europe only	[redacted]	[redacted]	Dominated
4	All chemotherapies	Cisplatin only	[redacted]	[redacted]	Dominated
5	All chemotherapies	Carboplatin only	[redacted]	[redacted]	Dominant

Abbreviations: EAG = Evidence Assessment Group; PDC = platinum doublet chemotherapy; CRT = chemoradiotherapy; QALY = quality-adjusted life-year; ICER = incremental cost-effectiveness ratio; NA = not applicable

Table 6.18: Deterministic results of EAG subgroup analyses (nivolumab + PDC versus adjuvant PDC) with the HR of LR and DM for comparators adjusted to have a similar ratio as for nivolumab + PDC

Sub-Group Analysis	Base-case assumption	Alternative assumption	Mean Incremental Costs (£)	Mean Incremental QALYs	Mean Incremental Cost Per QALY

	EAG base-case	N/A	[redacted]	[redacted]	£879
0	EAG base-case	HRs adjusted	[redacted]	[redacted]	£1,780
1	All stages of cancer	Stage IB&II only	[redacted]	[redacted]	Dominated
2	All stages of cancer	Stage III only	Not able to estimate		
3	All countries	North America/Europe only	Not able to estimate		
4	All chemotherapies	Cisplatin only	Not able to estimate		
5	All chemotherapies	Carboplatin only	[redacted]	[redacted]	Dominant
Abbreviations: EAG = Evidence Assessment Group; PDC = platinum doublet chemotherapy; QALY = quality-adjusted life-year; ICER = incremental cost-effectiveness ratio; NA = not applicable					

Table 6.19: Deterministic results of EAG subgroup analyses (nivolumab + PDC versus surgery alone) with the HR of LR and DM for comparators adjusted to have a similar ratio as for nivolumab + PDC

Sub-Group Analysis	Base-case assumption	Alternative assumption	Mean Incremental Costs (£)	Mean Incremental QALYs	Mean Incremental Cost Per QALY
	EAG base-case	N/A	[redacted]	[redacted]	£3,478
0	EAG base-case	HRs adjusted	[redacted]	[redacted]	£4,195
1	All stages of cancer	Stage IB&II only	[redacted]	[redacted]	£24,888
2	All stages of cancer	Stage III only	[redacted]	[redacted]	£468
3	All countries	North America/Europe only	[redacted]	[redacted]	£6,024
4	All chemotherapies	Cisplatin only	[redacted]	[redacted]	£3,107
5	All chemotherapies	Carboplatin only	[redacted]	[redacted]	£675
Abbreviations: EAG = Evidence Assessment Group; PDC = platinum doublet chemotherapy; QALY = quality-adjusted life-year; ICER = incremental cost-effectiveness ratio; NA = not applicable					

Table 6.20: Probabilistic results of EAG subgroup analyses (nivolumab + PDC versus neoadjuvant CRT) with the HR of LR and DM for comparators adjusted to have a similar ratio as for nivolumab + PDC

Sub-Group Analysis	Base-case assumption	Alternative assumption	Mean Incremental Costs (£)	Mean Incremental QALYs	Mean Incremental Cost Per QALY
	EAG base-case	N/A	[redacted]	[redacted]	Dominant
0	EAG base-case	HRs adjusted	[redacted]	[redacted]	Dominant
1	All stages of cancer	Stage IB&II only	Not able to estimate		
2	All stages of cancer	Stage III only	[redacted]	[redacted]	Dominant
3	All countries	North America/Europe only	[redacted]	[redacted]	£60*
4	All chemotherapies	Cisplatin only	[redacted]	[redacted]	£4,605*
5	All chemotherapies	Carboplatin only	[redacted]	[redacted]	Dominant

* ICER estimated for neoadjuvant CRT as nivolumab + PDC was less costly and less effective
Abbreviations: EAG = Evidence Assessment Group; PDC = platinum doublet chemotherapy; CRT = chemoradiotherapy; QALY = quality-adjusted life-year; ICER = incremental cost-effectiveness ratio; NA = not applicable

Table 6.21: Probabilistic results of EAG subgroup analyses (nivolumab + PDC versus adjuvant PDC) with the HR of LR and DM for comparators adjusted to have a similar ratio as for nivolumab + PDC

Sub-Group Analysis	Base-case assumption	Alternative assumption	Mean Incremental Costs (£)	Mean Incremental QALYs	Mean Incremental Cost Per QALY
	EAG base-case	N/A	[redacted]	[redacted]	£1,197
0	EAG base-case	HRs adjusted	[redacted]	[redacted]	£2,382
1	All stages of cancer	Stage IB&II only	[redacted]	[redacted]	Dominated
2	All stages of cancer	Stage III only	Not able to estimate		
3	All countries	North America/Europe only	Not able to estimate		

4	All chemotherapies	Cisplatin only	Not able to estimate		
5	All chemotherapies	Carboplatin only	[redacted]	[redacted]	Dominant
Abbreviations: EAG = Evidence Assessment Group; PDC = platinum doublet chemotherapy; QALY = quality-adjusted life-year; ICER = incremental cost-effectiveness ratio; NA = not applicable					

Table 6.22: Probabilistic results of EAG subgroup analyses (nivolumab + PDC versus surgery alone) with the HR of LR and DM for comparators adjusted to have a similar ratio as for nivolumab + PDC

Sub-Group Analysis	Base-case assumption	Alternative assumption	Mean Incremental Costs (£)	Mean Incremental QALYs	Mean Incremental Cost Per QALY
	EAG base-case	N/A	[redacted]	[redacted]	£4,559
0	EAG base-case	HRs adjusted	[redacted]	[redacted]	£5,560
1	All stages of cancer	Stage IB&II only	[redacted]	[redacted]	£41,341
2	All stages of cancer	Stage III only	[redacted]	[redacted]	£1,417
3	All countries	North America/Europe only	[redacted]	[redacted]	£8,499
4	All chemotherapies	Cisplatin only	[redacted]	[redacted]	£4,578
5	All chemotherapies	Carboplatin only	[redacted]	[redacted]	£1,106
Abbreviations: EAG = Evidence Assessment Group; PDC = platinum doublet chemotherapy; QALY = quality-adjusted life-year; ICER = incremental cost-effectiveness ratio; NA = not applicable					

6.2.2 Severity of the condition

No adjustments were made for the severity of the condition.

6.3 EAG's preferred assumptions

The estimated EAG base-case ICER (probabilistic), based on the EAG preferred assumptions highlighted in Section 6.1, was that:

- nivolumab + PDC dominated neoadjuvant CRT;
- the incremental cost per QALY gained was £1,609 compared with adjuvant PDC;
- the incremental cost per QALY gained was £4,795 compared with surgery alone.

The probabilistic EAG base-case analyses indicated cost-effectiveness probabilities of [redacted], [redacted], and [redacted] compared with neoadjuvant CRT, adjuvant PDC and surgery alone respectively at a willingness to pay threshold of £20,000 per QALY gained. These results are illustrated on the CEACs in Figures 6.9, 6.10 and 6.11.

Figure 6.9: Cost-effectiveness acceptability curve for nivolumab + PDC versus neoadjuvant CRT

(Source: Produced by EAG)
(Abbreviations: CEAC = cost-effectiveness acceptability curve; PDC = platinum doublet chemotherapy; CRT = chemoradiotherapy)

Figure 6.10: Cost-effectiveness acceptability curve for nivolumab + PDC versus adjuvant PDC

(Source: Produced by EAG)
(Abbreviations: CEAC = cost-effectiveness acceptability curve; PDC = platinum doublet chemotherapy)

Figure 6.11: Cost-effectiveness acceptability curve for nivolumab + PDC versus surgery alone

(Source: Produced by EAG)
(Abbreviations: CEAC = cost-effectiveness acceptability curve; PDC = platinum doublet chemotherapy)

As shown in Tables 6.8 and 6.10, the most influential scenario analyses to the EAG base-case when nivolumab + PDC was compared to neoadjuvant CRT, adjuvant PDC and surgery alone in ranked order were:

1. assuming the cost of subsequent treatment was £0 (Scenario analysis #7 in CS);
2. assuming the same distribution of chemotherapy for I-O and non-I-O therapies; and
3. assuming no I-O restrictions (Scenario analysis #10 in CS).

For all three scenarios nivolumab + PDC incurred a higher ICER compared to the EAG base-case. Only one scenario estimated an ICER greater than £20,000. In this scenario, nivolumab + PDC was compared to neoadjuvant CRT and it was assumed that there were no costs associated with subsequent treatment. In this scenario nivolumab + PDC had an ICER of £32,718.

As shown in Tables 6.11 – 6.22, the deterministic and probabilistic results from the subgroup analyses had a larger effect on the EAG base-case results than the scenario analyses.

Neoadjuvant CRT

The most influential adjustments to the EAG base-case when nivolumab + PDC was compared with neoadjuvant CRT in ranked order were:

1) subgroup analysis using data from North America and Europe only; and
2) subgroup analysis assuming cisplatin as the only PDC regimen.

In the subgroup analysis using data from North America and Europe only neoadjuvant CRT would be considered cost-effective compared to nivolumab + PDC in all scenarios as it either dominated nivolumab + PDC or had an ICER less than £2,000. There was more uncertainty when the assumption that cisplatin was the only PDC regimen was applied, this was due to the immaturity of the CheckMate-816 data and the uncertainty in the HRs of LR and DM (Key Issue 9). When the values of the HR of LR and DM were changed relative to each other neoadjuvant CRT dominated or had an ICER of £4,605 compared to nivolumab CRT. Using the original HR values for LR and DM for the comparators,

neoadjuvant CRT had an ICER of £3,420 compared with nivolumab + PDC; however, in the PSA the nivolumab + PDC was dominant but the probability of being considered cost-effective was close to [redacted].

Adjuvant PDC

The most influential adjustments to the EAG base-case when nivolumab + PDC was compared with adjuvant PDC in ranked order were:

1) subgroup analysis using data for Stage IB/II only.

In this subgroup analysis adjuvant PDC dominated nivolumab in all deterministic and probabilistic analyses.

Surgery alone

The most influential adjustments to the EAG base-case when nivolumab + PDC was compared with surgery alone in ranked order were:

1) subgroup analysis using data for Stage IB/II only,

In the subgroup analysis using data for Stage IB/II patients only the ICER for surgery alone increased from £16,143 to £41,341.

6.4 Conclusions of the cost-effectiveness section

A TLR was undertaken by the company to identify modelling approaches and structures used to estimate CEA in early-stage NSCLC. Four eligible studies were identified: two undertook retrospective analyses and two used semi-Markov models. The company did not use the results of the TLR to inform the structure of their CEM. An SLR was undertaken to identify HRQOL, cost and healthcare resource use data to populate the model. The economic SLR identified 10 publications on HRQOL and 13 publications on costs and healthcare resource use. Overall, the EAG was satisfied with the conduct of these reviews but believe the company could have provided additional information in the CS, particularly on the critique of studies in the TLR.

The EAG considers that the company appropriately complied with most of the elements present in the NICE reference case. The company did not provide details on how EQ-5D values were estimated. The company developed a de novo semi-Markov model, which consisted of four health states: EF, LR, DM and dead. Patients start in the EF health state and can stay in this state or move to having recurrence (LR or DM) or die. The patients in LR can stay there, move to DM, or die. Both the DM and dead health states were absorbing states and patients in these health states were assigned one-off costs, QALYs and LYs. The model cycle duration was three weeks, and the model was run for 35 years. The EAG had no concerns with model structure provided.

The population used in the CS base-model was patients with Stage IB-IIIA NSCLC and was based on the CheckMate-816 trial. The EAG were satisfied that this population is consistent with the population in the NICE scope. The NICE scope also mentioned subgroup analysis would be desirable by stage of disease if feasible. The company argued that data from CheckMate-816 were too immature for these subgroup analyses. The EAG considered these subgroup analyses by stage would be beneficial with the appropriate caveats. In terms of generalisability of effectiveness to clinical practice in England, the EAG also considered that an analysis based on the combined geographical region of North America and Europe would be useful given the potential, but uncertain, differences in effectiveness of nivolumab

+ PDC across regions,[1] although this may also have its limitations. The company did not present results by this combined region as they considered this analysis to be inappropriate.

The intervention was nivolumab (360 mg) + PDC administered intravenously every three weeks (one model cycle) for three cycles. There were three pairwise comparisons: neoadjuvant CRT, adjuvant PDC, and surgery alone. The EAG accepted the rationale for pairwise comparisons: individual patient decisions are made; all comparators are in use in current practice. There was evidence that nivolumab + PDC was associated with fewer surgical procedures, extended PFS and OS.

The company fitted seven parametric models to the CheckMate-816 data to estimate long-term predictions of EFS, TTLR and TTaP. Comparisons were made between estimated survival curves using goodness of fit measures, literature and clinical expert opinion. The data from CheckMate-816 were too immature to estimate TTDM, so the company derived this based on the difference between TTaP and TTLR at each timepoint. The EAG had some queries about the distributions chosen in the company base-case model, especially since the population of patients in the literature was different to that of CheckMate-816. It was also unclear to the EAG what data were presented to clinical experts to support their model choice.

In addition, the company applied a cure assumption based on clinical advice and previous TARs.[49,60] However, it was unclear to the EAG whether the clinical experts were presented survival curves with this cure assumption applied (95% of patients in EF were considered cured if they did not experience recurrence at year five). The assumption was also applied linearly over two years, but the company provided no justification for this. The EAG undertook additional analyses fitting different distributions to TTLR and TTaP and applying a Gompertz model in replacement of the cure assumption.

The model assumed that Grade 3 and 4 AEs, which occurred in at least 5% of patients, would be included in the model for the first cycle only. This assumption is consistent with other TARs.[49] Updated utility values were provided by the company after the initial submission,[15] though no evidence was provided for the duration of AEs (one week). While it is likely that these assumptions will have minimal effect on the overall results due to their transitory nature, it is likely that the CEM underestimates the potential impact of AEs.

The utility values for the health states (EF and LR) and the decrement between EF and LR were estimated using CheckMate-816 data and were higher than expected. The absolute utility values for the health states were capped at the age-sex matched general population utility values; no scenario analysis was undertaken by the company on the decrement in utilities between EF and LR. The company's clinical experts and the EAG's clinical advisor agreed that these utility values were still high. The EAG undertook additional analyses on these utility values.

The costs for each of the different health states were derived based on intervention costs, routine healthcare resource use, costs of managing recurrence and terminal care costs. The EAG raised some concerns about the lack of information provided in the CS for certain cost calculations. In addition, the EAG was unclear, even after the response to the points for clarification letter, as to why the company undertook an SLR specifying key markets yet only used one of the 13 eligible studies from the SLR to populate the model.[51] Despite this, the EAG was relatively confident in the costs provided by the company. The company highlighted the uncertainty in the costs provided for the DM health state and undertook an extreme scenario analysis assuming no costs associated with subsequent treatment. The EAG, as agreed between NICE and the company, updated the EAG base-case model with confidential values provided by NICE.

The company's CEM complied with the NICE reference case. There was one coding error, the distribution of treatments in DM. Once corrected, this increased the ICER by £500 for adjuvant PDC and surgery alone (£529, £3,183). The main points for critique were the distributions chosen for EF mortality, TTLR, and the cure assumption. Despite these critiques, the results were robust to changes made in the EAG base-case analysis. The company's base-case deterministic results were that nivolumab + PDC dominated neoadjuvant CRT and adjuvant PDC and had an ICER of £2,685 compared with surgery alone. The EAG base-case results, which incorporated the updated PAS for nivolumab, were that nivolumab + PDC dominated neoadjuvant CRT and nivolumab + PDC had an ICER of £879 and £3,478 compared with adjuvant PDC and surgery alone. While the results were robust across the scenario analyses, the probability of decision error was high for the neoadjuvant CRT comparison, with a nivolumab having a [redacted] probability of being cost-effective in the EAG base-case. This is likely due to the uncertainty in the comparator effectiveness estimates.

The greatest cause of uncertainty in the company's scenario analysis results surrounded costs associated with treatments in the DM health state. The EAG conducted 16 scenario analyses (replicating three of the company's scenario analyses with the biggest effect on the ICER). All these scenario analyses provided results favourable of nivolumab + PDC assuming a threshold of £20,000 for an additional QALY, except the only analysis highlighted above. Similarly to the CS, the EAG estimated that nivolumab was unlikely to be considered cost-effective at a £20,000/QALY threshold compared with neoadjuvant CRT using the assumption of no costs associated with subsequent treatment in DM. The company scenario analysis ICER was £21,496 for an additional QALY and the EAG scenario ICER was £32,718. However, the EAG considers this to be an extreme assumption. Alternative confidential estimates for the costs and QALYs accrued in the DM health state based on previous STA reports are included in a scenario analysis in the cPAS appendix.[46,53,55,56]

No subgroup analyses were provided by the company, but the EAG considered that cost-effectiveness may vary by: 1) disease stage, 2) geographical region, and 3) PDC regimen subgroups. The company argued that there was not enough data to produce robust results for these subgroups at the first interim analysis point for EFS. The results of the EAG subgroup probabilistic sensitivity analyses suggest that, compared to neoadjuvant CRT, nivolumab + PDC is cost-effective across all subgroups except when data from North America and Europe is used. Compared to adjuvant PDC, nivolumab + PDC is dominated in stage IB-II; otherwise, it is cost-effective. Compared to surgery alone, nivolumab + PDC has an ICER of £23,607 in stage IB-II; otherwise, it is cost-effective at a £20,000/QALY threshold.

In the subgroup analyses, the decision uncertainty increased further. There was greater uncertainty in the nivolumab + PDC effectiveness estimates, as well as closer effectiveness estimates for nivolumab + PDC and the comparators. Further uncertainty in the subgroup analyses is caused by the relatively weak evidence base used to estimate the HRs of LR and DM for the comparators. The EAG found that the cost-effectiveness results for the North America/Europe only subgroup and cisplatin subgroup compared to neoadjuvant CRT were particularly sensitive to changes to the HRs of LR and DM. The ICER of nivolumab + PDC could significantly increase or decrease. The probability that nivolumab + PDC was cost-effective compared to neoadjuvant CRT at a £20,000/QALY threshold was [redacted] in the North America/Europe only subgroup analysis and [redacted] in the cisplatin subgroup analysis. The decision uncertainty is very high in every scenario for every comparator. This is due to both the uncertainty in the nivolumab + PDC and comparator effectiveness evidence in these subgroups.

In summary, the EAG's base-case deterministic analysis resulted in nivolumab + PDC dominating neoadjuvant CRT and having an ICER of £879 and £3,478 compared with adjuvant PDC and surgery alone respectively. The EAG's base-case probabilistic analysis resulted in in nivolumab + PDC

dominating neoadjuvant CRT and having an ICER of £1,197 and £4,559 compared with adjuvant PDC and surgery alone. The probability of nivolumab + PDC being considered cost-effective at a £20,000/QALY threshold was [redacted], [redacted] and [redacted] compared with neoadjuvant CRT, adjuvant PDC, and surgery alone. The EAG base-case results were relatively robust to the scenario analyses. The EAG base-case was also robust to most subgroup analyses, although decision uncertainty increased. The only subgroup probabilistic analyses where nivolumab + PDC did not have an ICER estimate lower than the £20,000/QALY threshold was the comparisons with surgery alone and with adjuvant PDC in the stage IB-II subgroup. Compared with surgery alone, the ICER for nivolumab + PDC was £23,607. Compared with adjuvant PDC, nivolumab + PDC was dominated. Some of the uncertainty in these results is associated with the immaturity of the CheckMate-816 data; further data cuts could potentially resolve this issue. In addition, there is considerable uncertainty in the HR of LR and DM estimates for the comparators.

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7 Appendix 1: Nivolumab and PDC time-to-event and hazard rate curves

The graphs in this appendix are the time-to-event curves and HR curves for nivolumab + PDC. These match the graphs presented in Section 6.1.1 under Matters of Judgement 4.

The company base-case and EAG base-case TTLR and TTDM curves for nivolumab + PDC are presented in Figures 7.1 and 7.3 along with time-to-event curves for EAG scenarios 5, 6 and 7 described in Section 6.1.2.1. Figure 7.3 does not include a KM curve because the TTDM curve was derived from the TTLR and TTaP curves. For TTLR, as described in Matters of Judgement (2), the EAG selected a log-logistic model instead of the log-normal model in the company base-case. The company base-case and EAG base-case LR and DM hazard rate curves for PDC are presented in Figures 7.2 and 7.4 along with hazard rate curves for EAG scenarios 5, 6 and 7 described in Section 6.1.2.1.

Figure 7.1: TTLR curves for nivolumab + PDC for different models

(Source: Produced by the EAG)

(Abbreviations: KM = Kaplan-Meirer: PDC = platinum doublet chemotherapy; TTLR = time to locoregional recurrence)

Figure 7.2: LR hazard rate curves for nivolumab + PDC for different models

(Source: Produced by the EAG)

(Abbreviations: PDC = platinum doublet chemotherapy; LR = locoregional recurrence)

Figure 7.3: TTDM curves for nivolumab + PDC for different models

(Source: Produced by the EAG)

(Abbreviations: PDC = platinum doublet chemotherapy; TTDM = Time to distant metastasis)

Figure 7.4: DM hazard rate curves for nivolumab + PDC for different models

(Source: Produced by the EAG)

(Abbreviations: DM = distant metastasis; PDC = platinum doublet chemotherapy)

Nivolumab with chemotherapy for neoadjuvant treatment of resectable non-small cell lung cancer [ID3757]

Addendum to EAG report

Produced by Newcastle University

Authors Tara Homer, Senior Research Associate, Newcastle University
Eugenie Johnson, Research Assistant, Newcastle University
Louise Tanner, Research Associate, Newcastle University
Giovany Orozco-Leal, Research Assistant, Newcastle University
Tomos Robinson, Senior Research Associate, Newcastle University
Sedighe Hosseinijebeli, Research Associate, Newcastle University
Nick Meader, Principal Research Associate, Newcastle University
Ryan Kenny, Research Associate, Newcastle University
Sheila Wallace, Research Fellow, Newcastle University
Catherine Richmond, Research Assistant, Newcastle University
Claire Eastaugh, Research Assistant, Newcastle University
Alistair Greystoke, Clinical Senior Lecturer, Newcastle University
Stephen Rice, Senior Lecturer, Newcastle University

Correspondence to Stephen Rice, Newcastle University
Baddiley Clark Building,
Newcastle University,
Newcastle upon Tyne
NE2 4BN

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Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Confidential comparator prices are highlighted in green throughout the report.

Any de-personalised data are highlighted in pink throughout the report.

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

Stephen Rice acted as project lead. Louise Tanner acted as lead effectiveness reviewer. Tara Homer acted as lead health economist. Nick Meader and Ryan Kenny reviewed the network meta-analyses. Catherine Richmond acted as lead reviewer of the literature search methods. Eugenie Johnson acted as assistant effectiveness reviewer. Tomos Robinson, Giovany Orozco-Leal and Sedighe Hosseinijebeli acted as assistant health economics reviewers. Claire Eastaugh assisted in reviewing the literature search methods. Sheila Wallace assisted in reviewing the literature search methods and reviewing the effectiveness section. Alastair Greystoke provided clinical expert opinion.

Contents

1. Details of changes to the company base-case model to generate the EAG base-case 4

2. Details of changes to the EAG base-case model for sub-group analysis 7

3. Explanation of Sub-Group results for Adjuvant PDC and Neoadjuvant CRT 10

EAG base-case results: 10
Stages I-II only subgroup results for Adjuvant PDC: 11
Europe and North America only sub-group results for Neoadjuvant CRT: 13
Cisplatin only sub-group results for Neoadjuvant CRT: 15

4. Adjusting EAG subgroup analysis results for the proportionality assumption 18

1. Details of changes to the company base-case model to generate the EAG base-case

The model file submitted by the company after the points of clarification letter was used by the EAG to generate the EAG base-case model below.

Change #	Type	Description of Change	Rationale
1	Fixing errors	In Sheet "DM State" array E41:H41 values were replaced by using the formula "=E33*(1-F37)" in cell "E41" and dragging to "H41" so that the next formulas are: "=F33*(1-F37)"; (…); "=H33*(1-F37)" in "H41". Next, the values in I41 were replaced for the formula "=I33+SUM(E33:H33)*F37".	The values in the latest CEM file didn't match those reported in the CS Table 45. The fix implemented by the EAG generated the values reported in the CS while accounting for any changes made to the I-O treatment restriction assumptions in cell "F37"
2	Matters of judgement #1	In sheet "Utility" the values in cell "E39" was changed to -0.125, and the value in cell "E42" was change to -0.184	Alternative values for both anaemia and thrombocytopenia were provided by the company after the PfC letter (see Matter of judgement 1)
3	Matters of judgement #2	In sheet "Clinical inputs", cells "F18" and "F19", using the drop-down function in both cells, the Log-logistic function was selected.	The Log-logistic extrapolation was used to model hazards for TTLR (see Matters of judgement 2)
4	Matters of judgement #3	In sheet "Clinical inputs", cell "E74", using the drop-down function the Log-normal distribution was selected.	The Log-normal extrapolation was used to model hazards for mortality at EF (see Matters of judgement 3)
5	Matters of judgement #4	In sheet "Markov Details", using the Insert option in column "CJ" two new columns were generated next to "CJ". Starting in cell "CJ261" the array "CJ261:CJ911" was populated with values of survival per model cycle using the Gompertz extrapolation for Nivolumab. Next, array "CK261:CK911" was populated with survival values per cycle using the Gompertz extrapolation for PDC alone. In cell CV262 the formula was replaced for "=IF($D262<$CV$251,CV261*CN262/CN261,CV261*CJ262/CJ261)" and dragged to the next cell on the right "CW262". The formulas in cells CV262 and CW262 were then dragged down to cells CV911 and CW911 respectively. In cell CX262 the formula was replaced for "=$CW262^CP$248" and	The cure assumption was modelled for TTLR by having the hazards follow a Gompertz extrapolation after year 5 (see Matters of judgement 4). This modification will only produce the deterministic results for the EAG base-case. For the PSA further tweaks in the "Markov Details" and "Parameters" sheets to add uncertainty around the Gompertz curve were required.

		dragged across cells CY262 and CZ262. Finally, the formulas in array CX262:CZ262 were dragged down to CX911:CZ911.	
6	Matters of judgement #4	In sheet "Markov Details", the Insert option was used in column "DH" to generate two new columns. Starting in cell "DH261", array "DH261:DH911" was populated with survival per model cycle values from the Gompertz extrapolation for Nivolumab. The array "DI261:DI911" in the next column to the right was populated with survival per model cycle values, using the Gompertz extrapolation for PDC alone. In cell DL262 the formula was replaced for "=IF($D262<$CV$251,1-DF262/DF261,1-DH262/DH261)" and dragged to cell "DM262" on the right. The formulas in cells "DL262" and "DM262" were then dragged down to "DL911" and "DM911" respectively. In "DO262" the formula was replaced to "=1-CV262/CV261" and dragged to the next cell "DP262" on the right. The formulas in "DO262" and "DP262" were dragged down to "DO911" and "DP911" respectively. In cell "EC262" the formula was replaced for "=DU262", dragged from "EC262" to the right up to cell "EG262"; then these formulas were dragged down to "EC911", "ED911", (...), "EG911" respectively.	The cure assumption was modelled for TTaP by having the hazards follow a Gompertz extrapolation after year 5 (see Matters of judgement 4). This modification will only produce the deterministic results for the EAG base-case. For the PSA further tweaks in the "Markov Details" and "Parameters" sheets to add uncertainty around the Gompertz curve were required
7	Matters of judgement #4	In sheet "Markov Details", using Insert in "EN" a new column was generated. Starting in cell "EN261" array "EN261:EN911" was populated with survival per model cycle values using the Gompertz extrapolation for mortality. In cell "EO262" the formula was replaced for "=IF($D262<$CV$251,EO261*EM262/EM261,EO261*EN262/EN261)" and dragged down to cell "EF911".	The cure assumption was modelled for mortality at EF by having the hazards follow a Gompertz extrapolation after year 5 (see Matters of judgement 4). This modification will only produce the deterministic results for the EAG base-case. For the PSA further tweaks in the "Markov Details" and "Parameters" sheets to add uncertainty around the Gompertz curve were required

Abbreviations: CEM = company economic model; CS = company submission; DM = distant metastasis; EAG = Evidence Assessment Group; EF = event free; I-O = immuno-oncology; PDC = platinum doublet chemotherapy; PSA = probabilistic sensitivity analysis; TTaP = time to any progression; TTLR = time to locoregional recurrence

2. Details of changes to the EAG base-case model for sub-group analysis

The following changes were implemented in the EAG base-case model file to perform the sub-group analysis.

Change #	Type	Description of Change	Rationale
	Subgroup Analysis	In Sheet "Clinical Inputs" a table containing information on EFS data from the CS has been added in array "D12:K16". This table is used to generate adjustment weights to the mean and 95% CIs of the HR estimates used for time-to-progression from EF to LR and to DM in each arm, based on EFS data for each subgroup. EFS HR estimates and CIs for each subgroup analysis were added to the light blue cells in the table. The weights generated in this table are then fed to the TTLR mean HR and CIs in array E37:G39 and TTDM in array E67:E69. The model applies the subgroup weights to the survival functions of Nivo + PDC vs PDC alone (in TTLR and TTaP) stored in sheet "Markov Details". For this it was necessary to estimate the time-varying hazard ratios for each model cycle ("Markov Details" cells CW260:CW911 for TTLR and DO260:DO911 for TTaP), adjust them by the sub-group weight ("Markov Details" cells CX260:CX911 and DP260:DP911 for TTLR and TTaP respectively), and use that to reconstruct the survival function of Nivo + PDC ("Markov Details" cells CZ260:CZ911 DR260:DR911 for TTLR and TTDM respectively).	HR mean (and CIs) estimates for TTLR and for TTDM are adjusted by weighing mean (SEs) estimates in each arm by the ratio of EFS HR mean (SEs) in a particular subgroup obtained from the NMA over the overall EFS HR mean (SEs) estimate. The EAG acknowledges this to be a rudimentary approach to obtain sub-group estimates, which was used given the absence of better data.
Sub-group analysis 1	Stage I-II only	In Sheet "Clinical Inputs", row 13 the values in F13, I13 and J13 are replaced by [redacted] respectively. In the same table row 15, the values in F15, I15 and J15 are	As presented in the EAG Report Table 3.25, EFS HR estimates for the Stage I-II sub-group obtained for Nivolumab were [redacted]; for Adjuvant PDC were [redacted];

		replaced by [redacted] respectively. In the same sheet row 16, the values in F16, I16 and J16 are replaced by [redacted] respectively.	and for Surgery alone were [redacted]. Estimates could not be obtained for Neoadjuvant CRT.
Sub-group analysis 3	Europe and North America only	In Sheet "Clinical Inputs", row 13 the values in F13, I13 and J13 are replaced by [redacted] respectively. In the same table row 14, the values in F14, I14 and J14 are replaced by [redacted] respectively. In the same sheet row 16, the values in F16, I16 and J16 are replaced by [redacted] respectively.	As presented in the EAG Report Table 3.25, EFS HR estimates for the Europe and North America patient sub-group obtained for Nivolumab were [redacted]; for Neoadjuvant CRT were [redacted]; and for Surgery alone were [redacted]. Estimates could not be obtained for Adjuvant PDC.
Sub-group analysis 4	Cisplatin combination only	In Sheet "Clinical Inputs", row 13 the values in F13, I13 and J13 are replaced by [redacted] respectively. In the same table row 14, the values in F14, I14 and J14 are replaced by [redacted] respectively. In the same sheet row 16, the values in F16, I16 and J16 are replaced by [redacted] respectively. In Sheet "Treatment Pathway" array E23:M25 the proportions of patients receiving Carboplatin combinations (cells J23:M25) were added to their Cisplatin equivalents (cells E23:H25). The proportion of Patients receiving a Paclitaxel combination in I23:I25 were added to the proportion of Cisplatin + Permetrexed. Finally the proportion of patients receiving Carboplatin combination was assumed to be 0%.	As presented in the EAG Report Table 3.25, EFS HR estimates for the sub-group of Patients receiving only Cisplatin combinations of chemotherapy obtained for Nivolumab were [redacted]; for Neoadjuvant CRT were [redacted]; and for Surgery alone were [redacted]. Estimates could not be obtained for Adjuvant PDC. Patients were assumed to receive the equivalent combinations of Carboplatin with Cisplatin instead. Only patients receiving Paclitaxel + Carboplatin were assumed to receive Cisplatin + Pemetrexed as there was no equivalent Cisplatin combination and this was the most popular combination. This assumption had little impact on the total and incremental costs obtained.

Abbreviations: CI = confidence intervals; CRT = chemoradiotherapy; CS = company submission; DM = distant metastasis; EAG = Evidence Assessment Group; EF = event free; EFS = event free survival; HR = hazard ratio; LR = locoregional recurrence, Nivo = nivolumab; NMA = network meta-analysis; PDC = platinum doublet chemotherapy; SE = standard errors; TTaP = time to any progression; TTDM = time to distant metastasis; TTLR = time to locoregional recurrence

3. Explanation of Sub-Group results for Adjuvant PDC and Neoadjuvant CRT

The EAG base-case results have been reported here for reference when reviewing the subgroup analysis results.

EAG base-case results:

Figure 1: Time to locoregional recurrence hazard rates: EAG base-case

Figure 2: Time to locoregional recurrence hazard ratios: EAG base-case

Figure 3: Time to distant metastasis hazard rates: EAG base-case

Figure 4: Time to distant metastasis hazard ratios: EAG base-case

Stages I-II only subgroup results for Adjuvant PDC:

In the FAC document, issue 2, the company expressed their concern about the result of Adjuvant PDC having absolute dominance over Nivolumab + PDC in the sub-group analysis for patients with Stage I-II disease performed by the EAG. The core of the issue was that in the EAG NMA estimates obtained for EFS in this sub-group (Stage I-II disease), Adjuvant PDC is clinically inferior to Neoadjuvant PDC alone (HR: [redacted] for Adjuvant PDC vs Neoadjuvant PDC), and Neoadjuvant PDC alone is clinically inferior to Neoadjuvant Nivolumab + PDC (HR: [redacted] for Neoadjuvant Nivolumab + PDC vs Neoadjuvant PDC alone).

The company considers it illogical then, for Adjuvant PDC to generate more QALYs relative to Neoadjuvant Nivolumab + PDC. The EAG does not consider this to be illogical or an error, as sub-group EFS were not a direct input into the model but rather the proportion of sub-group EFS over overall EFS estimates were used to generate and adjustment parameter for time to LR HRs and time to DM HRs. As a result, the HR estimates of EF to LR and EF to DM for Adjuvant PDC went from [redacted] to

[redacted], and from [redacted] to [redacted] respectively; while the time-varying HR estimates of EF to LR and EF to any progression of Nivolumab + PDC versus Neoadjuvant PDC alone increased both by 38%.

This process has been detailed in Section 2; furthermore, the model file the EAG used to construct this scenario will also be provided.

Figure 6 and Figure 8 below show the impact of the sub-group adjustment parameter on the time-varying hazard rate functions for progressing from EF to LR and from EF to DM in Nivolumab + PDC versus Adjuvant PDC in contrast to the EAG base-case (see Figure 2 and Figure 4).

Figure 5: Time to locoregional recurrence hazard rates: Disease stage I-II only

[redacted]

Figure 6: Time to locoregional recurrence hazard ratios: Disease stage I-II only

[redacted]

In the subgroup of patients with Stage I-II disease, the risk of having LR is greater for patients receiving nivolumab + PDC relative to patients receiving adjuvant PDC over their lifetime.

Figure 7: Time to distant metastasis hazard rates: Disease stage I-II only

Figure 8: Time to distant metastasis hazard ratios: Disease stage I-II only

Although the risk of DM is lower for nivolumab + PDC, the difference with adjuvant PDC in DM is negligible after 3 years. Therefore, the QALY gains of adjuvant PDC are explained by the lower risk of LR recurrence.

Europe and North America only sub-group results for Neoadjuvant CRT:

In the FAC document, issue 2, the company expressed a similar concern about the result of Neoadjuvant CRT having absolute dominance over Nivolumab + PDC in the sub-group analysis for Europe and North America only patients performed by the EAG. The core of the issue was that in the EAG NMA estimates obtained for this sub-group (Europe and North America), Neoadjuvant Nivolumab + PDC generated a lower hazard ratio for EFS compared to Neoadjuvant CRT when both were compared against Neoadjuvant PDC alone (HR: [redacted] and [redacted] respectively).

The company considers it may be the product of an error that Neoadjuvant CRT generates more QALYs relative to Neoadjuvant Nivolumab + PDC. The EAG does not consider this to be an error, as sub-group EFS were not a direct input into the model but rather the proportion of sub-group EFS over overall EFS estimates were used to generate and adjustment parameter for time to LR HRs and time to DM HRs. As a result, the HR estimates of EF to LR and EF to DM for Neoadjuvant CRT went from [redacted] to [redacted], and from [redacted] to [redacted] respectively; while the time-varying HR estimates of EF to LR and EF to any progression of Nivolumab + PDC versus Neoadjuvant PDC alone increased both by 25%.

This process has been detailed in Section 2; furthermore, the model file the EAG used to construct this scenario will also be provided.

Figure 10 and Figure 12 below show the impact of the sub-group adjustment parameter on the time-varying hazard rate functions for progressing from EF to LR and from EF to DM in Nivolumab + PDC versus Neoadjuvant CRT in contrast to the EAG base-case (see Figure 2 and Figure 4).

Figure 9: Time to locoregional recurrence hazard rates: Europe and North America only

[redacted]

Figure 10: Time to locoregional recurrence hazard ratios: Europe and North America only

[redacted]

In the subgroup for the Europe and North America regions only, the risk of having LR is greater for patients receiving nivolumab + PDC compared with patients receiving neoadjuvant CRT over their lifetime.

Figure 11: Time to distant metastasis hazard rates: Europe and North America only

Figure 12: Time to distant metastasis hazard ratios: Europe and North America only

The risk of DM is lower for Nivolumab + PDC at the start of the treatment; however, the relative difference with neoadjuvant CRT narrows between 2 and 3 years. These variations in risk over time, the EAG argues, are driving the QALY gains of neoadjuvant CRT, specifically the relative differences in time to LR.

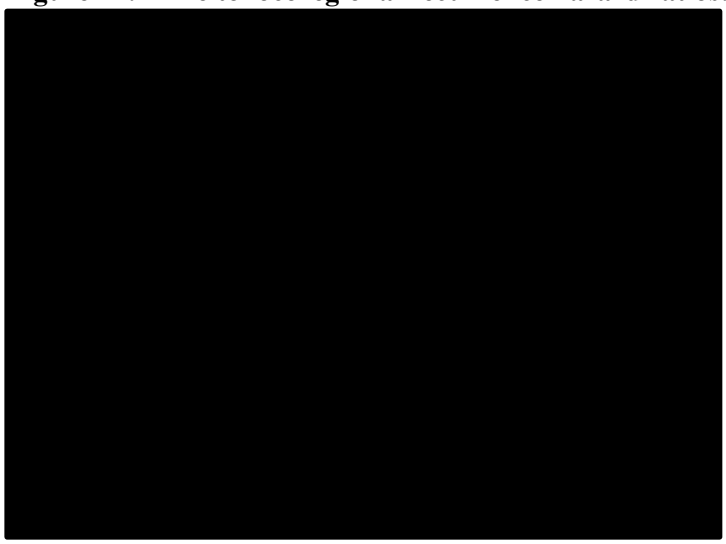
Cisplatin only sub-group results for Neoadjuvant CRT:

The sub-group analysis for patients receiving Cisplatin combination treatments only was another scenario carried out by the EAG where Neoadjuvant CRT generated more QALYs relative to Neoadjuvant Nivolumab + PDC despite the EFS HRs being better for Nivolumab + PDC relative to Neoadjuvant CRT when Neoadjuvant PDC alone was the comparator (and respectively).

The process of how this sub-group was modelled has been detailed in Section 2; furthermore, the model file the EAG used to construct this scenario will also be provided.

Figure 13: Time to locoregional recurrence hazard rates: Cisplatin combinations only

Figure 14: Time to locoregional recurrence hazard ratios: Cisplatin combinations only



In the subgroup of patients receiving Cisplatin combination treatments only, the risk of having LR is greater for patients receiving nivolumab + PDC relative to patients receiving neoadjuvant CRT over their lifetime.

Figure 15: Time to distant metastasis hazard rates: Cisplatin combinations only

Figure 16: Time to distant metastasis hazard ratios: Cisplatin combinations only

The risk of DM is lower for nivolumab + PDC, the difference with neoadjuvant CRT narrows between 2 and 3 years. Therefore, the QALY gains associated with neoadjuvant CRT are explained by the lower risk of LR recurrence.

4. Adjusting EAG subgroup analysis results for the proportionality assumption

Following the modifications implemented in the EAG base-case model file to perform the subgroup analysis, further modifications were made to the comparator hazard ratios to include the assumption for proportionality.

Change #	Type	Description of change	Rationale
	Proportionality adjustment	A proportionality adjustment weight was generated for the comparator HR estimates for TTLR and TTDM from EF. The weight applied to TTLR in the comparators was the result of dividing the CheckMate-816 HR of TTLR ([redacted]) by the HR of EFS ([redacted]). Similarly, the weight applied to TTDM in the comparators was the result of dividing the CheckMate-816 HR of TTDM ([redacted]) by the HR of EFS ([redacted]). In the model file sheet "Clinical Inputs" the trial HR values and SEs for EFS, TTLR and TTDM were stored in rows 13, 34, and 66 respectively. The comparator HRs for TTLR (array E39:E41) were multiplied by the weight "[redacted]". In the same sheet, the comparator HRs for TTDM (array E71:73) were multiplied by the weight "[redacted]". The SEs for the comparator HRs of TTLR and TTDM were also weighted by the trial SEs of TTLR divided by the trial EFS SEs, and the trial SEs of TTDM divided by the trial EFS SEs respectively, and then transformed into 95% CIs.	The EAG considers this to be an extreme scenario, therefore this adjustment was not included in the base-case. The justification for this scenario was the considerable uncertainty surrounding the HR estimates for the comparator interventions obtained from the NMA. This scenario was an exploration of such uncertainty by proportionally adjusting the EF to LR comparator HRs upwards and the EF to DM comparator HRs downwards.

Abbreviations: CI = confidence intervals; CRT = chemoradiotherapy; CS = company submission; DM = distant metastasis; EAG = Evidence Assessment Group; EF = event free; EFS = event free survival; HR = hazard ratio; LR = locoregional recurrence, Nivo = nivolumab; NMA = network meta-analysis; PDC = platinum doublet chemotherapy; SE = standard errors; TTaP = time to any progression; TTDM = time to distant metastasis; TTLR = time to locoregional recurrence

Single Technology Appraisal

Nivolumab with chemotherapy for neoadjuvant treatment of resectable non-small-cell lung cancer [ID3757]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG 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 **5pm on 7 December 2022** 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 '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Issue 1 Several 'key issues' that are presented are not key issues for decision making

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
BMS do not consider most of the key issues proposed by the EAG to be 'key' issues in determining whether neoadjuvant nivo+PDC should be reimbursed. Although we appreciate the conservative perspective and extent of critique that the EAG has provided throughout the report, the EAG-conducted scenarios for issues 3,4,5,6,7,8 and 9 do not produce ICERs that exceed [redacted] per QALY. Across all comparators, the highest ICER generated by the EAG analyses in issues 3-9 is [redacted] per QALY gained, where nivo+PDC is compared to neoadjuvant CRT in a scenario assuming no IO retreatment restrictions, in issue 8.	Key issues 3-9 should not be labelled as key issues.	BMS believe that 'key' issues should be those that could affect the committee's decision, i.e. whether an indication should be reimbursed.	This is not a Factual Accuracy Check issue. The EAG selected the main areas of uncertainty in the evidence for the Key Issues. The impact on cost-effectiveness has been indicated. The Key Issues form the basis of discussion for the NICE committee. If the majority of Key Issues are not likely to affect the Committee decision then this provides confidence in the decision.

Issue 2 Lack of information to assess analyses undertaken for key issues 1 and 2

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Generally, given the limited information provided in the EAG report on the exact methods used to generate several of the EAG scenarios, it has not been possible to validate the EAG-generated ICERs as we are unable to recreate these analyses. **EAG 'key issue' 1: 'Effectiveness of nivolumab + PDC more uncertain for patients with Stage IB or II NSCLC'** BMS believe that the CheckMate 816 Kaplan Meier data are currently too immature to consider conducting subgroup analyses for patients with stage IB-II vs IIIA disease; there are very few progression events. Our interim analysis 1 results show that, for patients using nivo+PDC with stage IB-II disease, [redacted] patients experienced a locoregional recurrence and [redacted] patients	The EAG should explain how the results of their NMA have been incorporated into the cost-effectiveness model to generate the ICERs presented.	Some of the EAG analyses appear to be incorrect and unreproducible.	Details of model changes had been included in the Excel model in one of the sheets. These should have been included in the economic model. The EAG have provided an addendum to the EAG report detailing the changes made to the EAG economic model and explaining the findings. Additionally, the EAG have provided information to help explain the results of some of the subgroup analyses: 1) stage IB/II, 2) Europe and North America, 3) PDC provided – cisplatin only and 4) the EAG base-case with the proportionality assumption explored.

experienced a distant metastatic recurrence. There are simply too few events to credibly predict the future outcomes of these patients without more events occurring. Additionally, the CM816 trial is not powered for subgroups. Despite the above, we understand that the EAG have conducted some exploratory subgroup scenario analyses for stage of disease. The EAG report states that neoadjuvant nivo+PDC is dominated by adjuvant PDC in the deterministic stage IB-II subgroup analysis that the EAG have generated. It is not possible for BMS to validate the results of this analysis without a more detailed description of the methodology. However, importantly, we believe the EAG has made an error when generating this result. In the EAG-generated (stage IB-II) NMA results, **adjuvant PDC is clinically inferior to neoadjuvant PDC** (HR: [redacted] for adjuvant PDC vs neoadjuvant PDC), **and neoadjuvant PDC is clinically inferior to neoadjuvant**			

nivo+PDC (HR: [redacted] for neoadjuvant nivo+PDC vs neoadjuvant PDC). Without a detailed description of the methods it is impossible to show where the error has occurred. However, it is not logically possible for adjuvant PDC to generate higher QALYs for stage IB-II patients than neoadjuvant nivo+PDC, based on the EAG-generated NMA results. Ultimately, this means that it is not possible for adjuvant PDC to dominate neoadjuvant nivo+PDC in cost-effectiveness analyses. **EAG 'key issue' 2: 'Applicability of the CheckMate-816 population to England'** BMS do not think it is appropriate to conduct analyses surrounding race/region for this appraisal. Race/ethnicity and region were not stratification factors of the CheckMate 816 trial, and as a result, any differences in treatment effect between these groups are confounded by imbalances in known or unknown prognostic factors. In			

Table 7 of the clarification response document we outline the differences in baseline characteristics between Asian, European and North American patients. Imbalances in the presented prognostic factors alone could explain some of the variation observed between these groups. In addition, and similar to the findings for issue 1 above, it is unclear to BMS how the EAG region analysis can result in neoadjuvant CRT dominating neoadjuvant nivo+PDC. **In the EAG-generated NMA, neoadjuvant nivo+PDC generates a lower hazard ratio for EFS compared to neoadjuvant CRT when both are compared against neoadjuvant PDC** (HR: [redacted] respectively). It is therefore unclear to BMS how the resulting ICERs for this scenario show that neoadjuvant CRT dominates neoadjuvant nivo+PDC. BMS believe there has been a calculation error made by the EAG, however as discussed above for issue 1, there are no presented EAG methods to allow us to reproduce the			

subgroup analyses, which would enable validation. **Other:** Errors could also be present for other subgroup analyses but are not possible to validate given a lack of information available in the EAG report.			

Issue 3 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 4.2.6.1 (page 97), in relation to mortality the EAG states "there was no evidence of a difference between the trial arms". There is evidence of a difference in overall survival between the two arms, there is a clear separation in the OS curves that widens over time, however this difference is not yet statistically significant.	Change wording to "there is evidence of overall survival benefit for nivo+PDC based on the separation of the OS KM curves, but this difference is not statistically significant"	This wording implies that BMS believes there is no evidence at all for an OS benefit for nivo+PDC.	The issue here is whether the EAG accurately reported the company justification for pooling the trial arms. The EAG have edited the statement to read, "The company stated that the Kaplan-Meier curves for both treatment arms in **Error! Reference source not found.** (CS, page 111) suggested no difference in mortality at the current trial follow-up, among EF

			patients between treatment arms.”
In Section 6.4 (page 178), the EAG states “the company did not present results by this combined region as they considered data from CheckMate-816 too immature for this regional analysis.” BMS do consider it inappropriate to conduct regional subgroup analysis as this is a non-stratified trial subgroup and any causal inference will be confounded by known and unknown prognostic differences between the regional populations, not because the data are immature.	The EAG report should state that regional subgroup analysis was considered ‘inappropriate’ by BMS rather than ‘immature’.	This wording implies that BMS believes that regional subgroup analysis will be appropriate with longer follow-up data, which is not the case.	The EAG have updated the text to the following: “The company did not present results by this combined region as they considered this analysis to be inappropriate.”
On page 34, the EAG state “The company reference their ‘in-house’ draft report of the wider SLR to which the EAG does not have access”. This report was provided by BMS in the reference pack and should therefore have been available to the EAG.	Remove this sentence.	This wording implies the company withheld information which is not true.	The EAG have replaced this statement with, “The EAG reference their ‘in-house’ draft report of the wider SLR. This may have been the SLR reported in the Appendix, but it was not 100% clear.”
We identified various errors with cross referencing in the report, all	We believe this example should read:	To ensure accuracy of the EAG report	The EAG have checked all cross references to the company submission and

should be checked and updated. For example: In Section 3.1.5 (page 41) of the EAG report some cross-references to the CS and appendices are wrong: “The SLR only reported on Grade 3 and 4 AEs (CS Section D.1.3.5.6)” and “In CS Section D.1.3.5.6 (Table D-19, p. 38-9) and CS Section M.3.2 (p.188)”	“The SLR only reported on Grade 3 and 4 AEs (CS Section D.1.2.5.6)” and “In CS Section D.1.2.5.6 (Table D-19, p. 38-9) and CS Section M.5.8 (p.170)” All similar cross-referencing should be checked.		made changes based on the company’s suggestion. The reference to the NMA appendix included in the company’s example has also been removed.
In Table 3.20 on page 64-65 is a typo 95% CI [redacted] [redacted] The upper confidence interval in the company response to clarification questions, as reported in the CSR, was [redacted].	Correct the upper confidence interval to [redacted]	The current value is incorrect	The EAG has made this change in the text.

Issue 4 Inaccurate wording relating to CheckMate-816 protocol amendment

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 3.2.1 (page 44) the EAG comment on amendments to the CheckMate-816 protocol in terms of the intervention arms and state "The company stated that Bristol Myers Squibb were blinded to the decision to add the nivolumab + PDC arm in light of promising results from the KEYNOTE-021 trial (in metastatic NSCLC), although it was unclear precisely which trial the company were referring to, and in the NADIM study (in resectable NSCLC)." This is inaccurate, in our response to clarification questions we noted that "BMS remained blinded to the CheckMate 816 study results while taking this decision". Therefore, risk of bias was minimized in that the decision to add the nivolumab + PDC arm was taken before any results had become available. BMS were not blind to the decision to add nivolumab + PDC as is currently stated in the EAG report.	Reword to: "The company stated that Bristol Myers Squibb were blinded *to the results of CheckMate-816 at the time of the* decision to add the nivolumab + PDC arm in light of promising results from the KEYNOTE-021 trial (in metastatic NSCLC), and in the NADIM study (in resectable NSCLC)."	The current wording is inaccurate	We have reworded to the following: "The company stated that the decision to add the nivolumab + PDC arm came in light of promising results from the KEYNOTE-021 trial (in metastatic NSCLC), and in the NADIM study (in resectable NSCLC); Bristol Myers Squibb were blinded to the results and allocation of CheckMate-816 during this process."

It is unclear what the EAG mean when they say “although it was unclear precisely which trial the company were referring to” in terms of the KEYNOTE-021 and NADIM trials, we therefore suggest removing this or explaining the statement.			

Issue 5 Inaccurate description of timing of statistical analyses

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 3.2.2 (page 45) the EAG states “Initial analyses were conducted at 30 months for the pathological complete response (pCR) outcome, followed by further interim analyses at 48 months (148 EFS events and 101 OS events). Results reported in the CS are from the 48-month interim analyses (first interim analysis of EFS).” It is important to be clear that, to date, the analyses have been driven by event numbers and not timing. The information in the EAG report is extracted from Figure 7 of the CS,	Revise sentence to read: “Initial analyses were planned to be conducted at approximately 30 months for the pathological complete response (pCR) outcome, followed by further interim analyses at approximately 48 months (after 148 EFS events and/or 101 OS events). Results reported in the CS are from the ~48-month interim analyses (first interim analysis of EFS).”	Current wording is inaccurate	The EAG accepts the company’s suggestion and have updated the text accordingly.

where the timings are presented as approximate (~30 months and ~48 months).			

Issue 6 Error in interpretation of comparator

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 89, the EAG state “Patients in the CM-816 trial are initially described as receiving Cisplatin in combination with Carboplatin and Paclitaxel in CS Section B.2.3.1, yet in CS Section B.3.5.1 patients are described as receiving either a Cisplatin-based or Carboplatin-based combination with other treatment”. We believe that this misinterpretation of the information in Section B.2.3.1 is due to an issue with formatting of sub-bullets in Table 7 of the CS which should clearly show the treatment options are either cisplatin + another chemotherapy agent OR carboplatin + paclitaxel	This sentence should be removed, we have amended Document B so the formatting is correct.	The current wording is inaccurate and the confusion due to a formatting error.	The company has clarified the apparent inconsistency. The EAG has removed the sentence.

Issue 7 Error in description of company base case analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 4.2.6.1 the EAG states the following "The EAG considers that values elicited from clinicians in the UK, which were arguably more applicable to the UK, should have informed the company's base-case CEM. These values were more conservative compared with the values used in the base-case model, hence the EAG considers the values from UK clinicians to be more appropriate given the lack of available data to inform TTDM from LR. The company used the LuCaBIS estimates in the scenario analysis, which the EAG does not consider to be appropriate given that these values were rejected by the clinical experts." The statement here is conflicting or not correct given that the values from the UK clinicians were used in the company base case.	We propose the following amendment: The EAG agrees that values elicited from clinicians in the UK, which were arguably more applicable to the UK, should informed the base-case CEM. These values were more conservative compared with the LuCaBIS estimates, hence the EAG considers the values from UK clinicians to be more appropriate given the lack of available data to inform TTDM from LR.	On the contrary to how the EAG text reads, the UK clinical values were used in the company base case.	The EAG has updated the EAG comment as follows: "The EAG note the average value of all the values provided by KOLs from all geographical regions was used in the base-case. However, the EAG consider the range of values provided by the UK KOLs, including the upper limit of 25%, could have been used in scenario analysis."

Issue 8 Error in fixing error in Excel model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG has implemented changes in the economic model due to differences in the distributions of subsequent treatments shown in the Excel model compared with values presented in Table 45 of the CS. We acknowledge this discrepancy between the economic model and the CS. However, we argue that the error was made in the CS and not within the Excel model. Section 6.1.1.1 of the EAG report (page 142-143) and Section 6.2.1 (page 157- 160)	It is suggested that updates are made in Table 45 of the CS and the formulas in sheet "DM State" array E41:I41 within the Excel model are restored to those in the original economic model. In addition, references to the issue "Fixing errors" are removed from the EAG report.	In the original submitted model, the proportion of patients not eligible for IO retreatment was calculated based on the proportion of those eligible for any retreatment. However, EAG changes to the formulas suggest that the distribution of IO retreatment should be based on the proportions of all patients (including those who receive best supportive care). As can be seen from the numbers presented in Table 45 of the CS, we had originally calculated the proportions in the same way as the EAG. However, we deliberately changed the formulas in the submitted economic model so that only patients eligible to receive any subsequent treatment would be candidates for IO	From the EAG perspective this is not a factual inaccuracy as it was based on the information provided by the company in the original CS and CS2 and the original CEM. As the company acknowledges, the distribution of subsequent treatments was in the CS and in the company model were different. The following has been added to Section 6.1.1.1: "During the factual accuracy check, the company clarified that the distributions in the CS did not account for the 25% of patients who would receive best supportive care and that the distributions in the CEM

		retreatment. This was done so that the 25% of patients assumed to only receive best supportive care based on clinical input would not influence the distribution of treatments given.	had been updated to account for this. The EAG analyses were based on the distributions in the CS and hence do not account for the 25% of patients receiving best supportive care. The EAG note that the difference in cost associated with the alternative subsequent treatment distribution has no effect on the overall conclusions. The ICER for nivolumab would be reduced by [redacted], depending on the scenario analysis.”

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 3.3.1 of the EAG report.	Content on the NMA should be marked AIC – currently only tables are highlighted	All values in text in section 3.3.1. that are confidential in the respective tables should be marked as academic in confidence.	We have marked the discussion of the NMA results as AIC
Section 3.2.2 of the EAG report (page 45)	Information on future database locks should be marked CIC	[redacted]	We have marked the suggested information as CIC

(Please add further lines to the table as necessary)