NICE National Institute for Health and Care Excellence

# Single Technology Appraisal

# Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma [ID972]

# Committee Papers

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**SINGLE TECHNOLOGY APPRAISAL**

# Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma [ID972]

**Contents:**



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

# Pre-meeting briefing

## Nivolumab for relapsed or refractory classical Hodgkin lymphoma (STA)

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting.

ID972 nivolumab pre-meeting briefing

# Abbreviations

| | | | |
|---|---|---|---|
| **Allo SCT** | Allogeneic stem cell transplant | **IRRC** | Independent Radiological Review Committee |
| **ASCT** | Autologous stem cell transplant | **OOR** | Objective overall response |
| **BCSH** | British Committee for Standards in Haematology | **OS** | Overall survival |
| **BOR** | Best overall response | **PAS** | Patient Access Scheme |
| **BTX** | Brentuximab vedotin | **PFS** | Progression-free survival |
| **cHL** | Classical Hodgkin lymphoma | **PR** | Partial response |
| **CR** | Complete response | **QALY** | Quality-adjusted life year |
| **HL** | Hodgkin lymphoma | **SD** | Stable disease |
| **ICER** | Incremental cost effectiveness ratio | **SOC** | Standard of care |

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## Key issues 1: clinical management

- What are the criteria used in clinical practice for stopping treatment with nivolumab?
  - SmPC states that 'Treatment ……should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.'
- Are mini-BEAM or DexaBeam commonly used as salvage regimens for HL in England?
- What proportion of people would be expected to proceed to alloSCT after:
  - Nivolumab?
  - SoC?

SmPC, Summary of product characteristics; HL, Hodgkin lymphoma; alloSCT, allogeneic stem cell treatment; SoC, standard of care

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Note:

Median duration of treatment in CA209-039 was [redacted]
Median duration of treatment not reached in CheckMate 205

**Source**: Company submission, section 4.7.1.8 (page 47) and 4.7.1.7 (page 60)

Appendix 6 (page 26) reports the following information for the overall nivolumab cohort:

Discontinuation due to any reason

Median time on treatment: [redacted]
Discontinuation excluding discontinuation due to progression

Median time on treatment: [redacted]

# Key Issues 2: clinical effectiveness

- How effective is nivolumab?
  - Phase I and II, non comparative, single arm trials.
  - Data immature. Follow-up of participants from both trials is continuing.
  - How robust is the indirect comparison of nivolumab with SoC?
  - How well do the populations in the comparator studies match those in the nivolumab studies, and reflect patients in clinical practice in England?
  - Is it appropriate to exclude the investigational agents from the Cheah data set?
  - To what extent do the benefits of nivolumab exceed those of potential comparator treatments?

# Key issues 3: cost effectiveness

- Which survival modelling for SoC is the most appropriate?
  - Company: modelling based on Cheah study excluding patients who have received investigational agents
  - ERG: modelling based overall population from the Cheah study
- Is the large difference in utility values for post-progression in the nivolumab and SoC treatment arms realistic?
- Is it appropriate to include the costs for mini-BEAM or DexaBEAM as part of the costs for SOC used in the cost effectiveness analysis?
- Is it appropriate for the company to include analyses of alloSCT as scenario analyses rather than in its base case given that nivolumab has the potential to act as a bridge to transplant?

# Key issues 4: cost effectiveness (cont.)

- What estimate should be used in the cost effectiveness analysis for the proportion of people who proceed to alloSCT after nivolumab or SoC?
  - The company assumeds that the proportion receiving alloSCT was ~~is~~ 22% for CR, 14.1% for PR and 5.56% for SD (taken from Perrot et al)
  - The ERG considered the proportion of patients receiving alloSCT to be ~~is~~ underestimated in the economic model compared with observed alloSCT in the studies
- Which of the company's scenario analyses incorporating alloSCT is more appropriate?
- Does nivolumab meet the criteria for life-extending treatments at the end of life?
- Does nivolumab represent an innovative treatment?

# Hodgkin lymphoma

- A haematological malignancy diagnosed in ~1,954 UK patients during 2013 (3 cases per 100,000 people).
- Bimodal age distribution; peak incidence in people aged 20-24 years and 75-79 years.
- 1 year survival 91%; 10 year survival 80%.
- Outcomes poor for those with relapsed or refractory disease following autologous stem cell transplant (ASCT) (median overall survival 19-29 months), and poorer following ASCT and brentuximab vedotin (BTX).

# Nivolumab (Opdivo)

## Bristol-Myers Squibb

| | |
|---|---|
| **Mechanism of action** | Human monoclonal antibody that blocks PD-1 (programmed cell death protein 1) to promote anti-tumour response |
| **Marketing authorisation** | ". . . for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin"<br>Designated Promising Innovative Medicine by MHRA |
| **Administration & dose** | 3 mg/kg every 2 weeks, administered intravenously |
| **Cost** | List price £439 (4 ml vial) or £1,097 (10 ml vial)<br>Average cost of a course of treatment £5,724 per month (not including administration costs)<br>Company has agreed a patient access scheme (PAS) with the Department of Health which provides a simple discount of [redacted].<br>PAS price £[redacted] (4 ml vial) or £[redacted] (10 ml vial) |
| MHRA, Medicines and Health products regulatory agency | |

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**Source**: Company submission, section 2.1 (page 22), section 2.2 (page 24), section 2.3 (page 25), section 5.5.1 (page 127)

# Patient and professional feedback

- Patients with relapsed or refractory lymphoma have symptoms which can be debilitating and distressing, including fever, drenching night sweats, breathlessness, unexplained weight loss, skin rash or itch, pains in the chest, abdomen or bones.
- Patients have to choose between treatments that may have little success or many side effects, or palliative care and short life expectancy.
- Many patients are young and fit with the potential for a long and active life if they can undergo transplant.
- Patients and carers would like to see a cure, or strong, durable remission, and treatments with lower toxicity profiles or reduced/manageable side effects.
- Nivolumab:
  - is a promising rescue salvage regime.
  - could potentially increase the proportion of patients eligible for allogeneic stem cell transplant.
  - has lower toxicity profile/is better tolerated compared with standard chemotherapy.



**Source**: Lymphoma Association (endorsed by Leukaemia CARE), Clinical experts, NCRI, ACP and RCP joint submission

# Decision problem
## Company's submission

| | NICE scope | Company submission |
|---|---|---|
| **Population** | People with relapsed or refractory classical Hodgkin lymphoma following:<br>• autologous stem cell transplant and brentuximab vedotin | |
| | • at least 2 prior therapies when autologous stem cell transplant is not a treatment option | • Not covered (not in marketing authorisation) |
| **Comparator** | • Established clinical management without nivolumab including chemotherapy such as gemcitabine or bendamustine<br>• Best supportive care | • Standard of Care comprising chemotherapy, brentuximab retreatment and bendamustine |
| **Outcomes** | • Overall survival<br>• Progression-free survival<br>• Response rates<br>• Adverse effects of treatment<br>• Health-related quality of life | • As per NICE scope<br>• Other outcomes also reported (for example, duration of response, time to response) |

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**Source**: Company submission, section 1.1, table 1 (page 13)

Brentuximab MA:
Adcetris is indicated for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL):
- following autologous stem-cell transplant (ASCT) or;
- following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.
Adcetris is indicated for the treatment of adult patients with CD30+ HL at increased risk of relapse or progression following ASCT.
Brentuximab on CDF:
The treatment of relapsed or refractory CD30+ Hodgkin's lymphoma where all the following criteria are met:
1. Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
2. Relapsed or refractory CD30+ Hodgkin lymphoma
3. a) Following autologous stem cell transplant (ASCT), OR,
b) Following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option
NOTE: If a patient has not achieved a partial or complete response after 6 cycles, then treatment with brentuximab should be discontinued
NOTE: No treatment breaks of more than 4 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or
in the case of intercurrent co-morbidities)

NOTE: Maximum of 16 cycles should be administered

# Decision problem

## ERG's critique

| | Company submission | ERG comment |
|---|---|---|
| **Population** | People with relapsed or refractory classical Hodgkin lymphoma following:<br>• autologous stem cell transplant and brentuximab vedotin | The population covered in the company's submission is acceptable.<br>The marketing authorisation does not cover the 2nd population in the final scope issued by NICE. |
| **Comparator** | • Standard of Care comprising chemotherapy, brentuximab retreatment and bendamustine (as per Cheah 2016 study) | • Cheah 2016 study conducted in USA. Unclear how well this reflects experience of ~~UK~~ patients in England, and there is a lack of detail about precise combinations of treatment regimens<br>• However, not aware of a more appropriate source of data |

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**Source**: ERG report, section 2.3 (page 23-4)

## Treatment pathway

- If ASCT fails to delay disease progression, no standard therapy.
- British Committee for Standards in Haematology (BCSH) guidelines recommend that treatment aims to attain sufficient response to allow allogeneic transplantation (alloSCT).
- BCSH guidelines recommend brentuximab vedotin (BTX) as an option for patients whose disease has relapsed after ASCT, and an option prior to ASCT for patients who are either ineligible for ASCT or whose disease has not achieved sufficient response.
- Clinical pathway subject to uncertainty and heterogeneity between patients because of limited treatment options, low patient numbers and short life expectancies.

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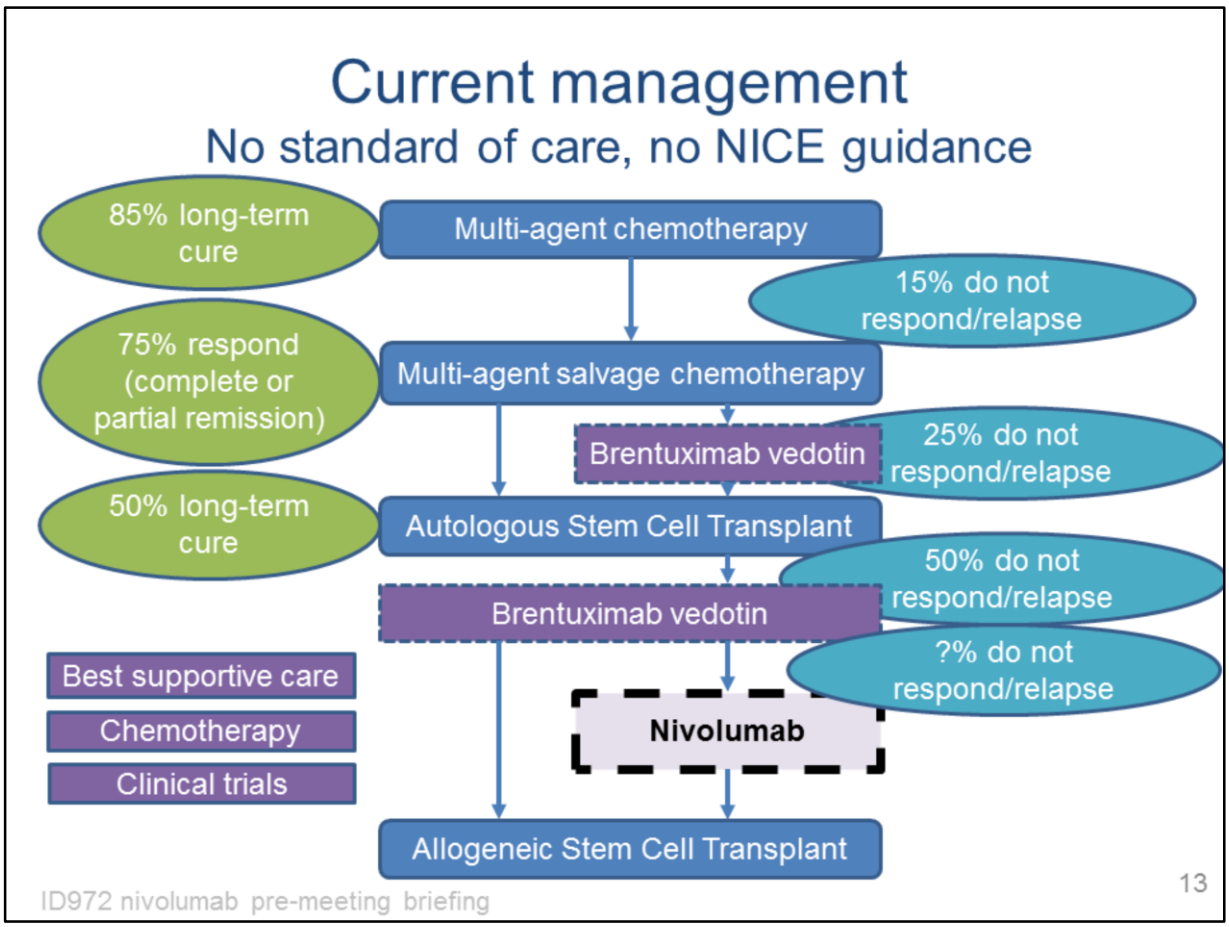
**Source**: Company submission, section 3.2 (pages 28-30); ERG report, section 4.3.5 (page 117)




**Source**: Adapted from Company submission, section 5.2.2.3 (page 103)

Brentuximab vedotin subject to ongoing NICE appraisal (ID722) but has been available through the Cancer Drugs Fund for 2 of its licensed indications:

2. Relapsed or refractory CD30+ Hodgkin lymphoma

3. a) Following autologous stem cell transplant (ASCT), OR,

b) Following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option

NOTE: If a patient has not achieved a partial or complete response after 6 cycles, then treatment with brentuximab should be discontinued

NOTE: No treatment breaks of more than 4 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or

in the case of intercurrent co-morbidities)

NOTE: Maximum of 16 cycles should be administered

## Company's clinical evidence

| Trial | CheckMate 205 | CA209-039 |
|---|---|---|
| Design | Non-comparative, single-arm | |
| | Phase 2 | Phase 1 |
| Population | Adults with cHL after ASCT failure:<br>Cohort A: BTX-naïve (63)<br>**Cohort B: Prior BTX after ASCT (80)**<br>**Cohort C: Prior BTX before or after ASCT (100)** | Adults with relapsed, refractory haematological malignancies (cHL n=23)<br>**15 had previously had ASCT and BTX** |
| Intervention | Nivolumab 3 mg/kg once every 2 weeks | |
| Primary outcomes | Objective response rate (best overall response) | |
| Duration | Median follow-up:<br>• Cohort B interim analysis (August 2015) 8.9 months<br>• Cohort B (April 2016) 15.7 months<br>• Cohort C (April 2016) 8.9 months | Median follow-up:<br>• Interim analysis (June 2014) 40 weeks<br>• August 2015 23.3 months |

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**Source**: Company submission, section 4.2 (page 36), section 4.7.1.1 (pages 39-40), section 4.7.1.4 (page 42), section 4.7.1.6 (page 43), section 4.7.1.9 (page 53), section 4.7.2.1 (page 57), section 4.7.2.4 (page 59), section 4.7.1.8 (page 46)

Note: CheckMate 205 Cohort C included 2 patients that had not received BTX; these were excluded from the Indirect Treatment Comparison and Cost Effectiveness Analysis

Both trials are ongoing.

No relevant randomised controlled trials identified.

ERG consider systematic review generally of good methodological quality, no key studies are missing. Searches generally comprehensive and reported transparently.

Overall, the ERG considers that the eligibility criteria used in the main systematic review were appropriate and matched the decision problem according to the proposed licensed indication of nivolumab **Source**: ERG report, section 3.1.1 (pages 28-9), section 3.1.2 (page 30)

Note: CheckMate 205 cohort C is not referenced in the Summary of Product Characteristics https://www.medicines.org.uk/emc/medicine/30476

# Company's clinical evidence

## Trial populations

| Trial | Previous treatment | No. |
|---|---|---|
| **CheckMate 205 Cohort A** | ASCT → Failure **NOT RELEVANT (BTX naïve)** | 63 |
| **CheckMate 205 Cohort B** | ASCT → BTX → Failure | 80 |
| **CheckMate 205 Cohort C** | ASCT → BTX → Failure<br>**OR**<br>BTX → ASCT → Failure<br>**OR**<br>BTX → ASCT → BTX → Failure | 57<br><br>33<br><br>8 |
| **CA209-039** | ASCT → BTX → Failure | 15 |
| **Total** | | 193 |

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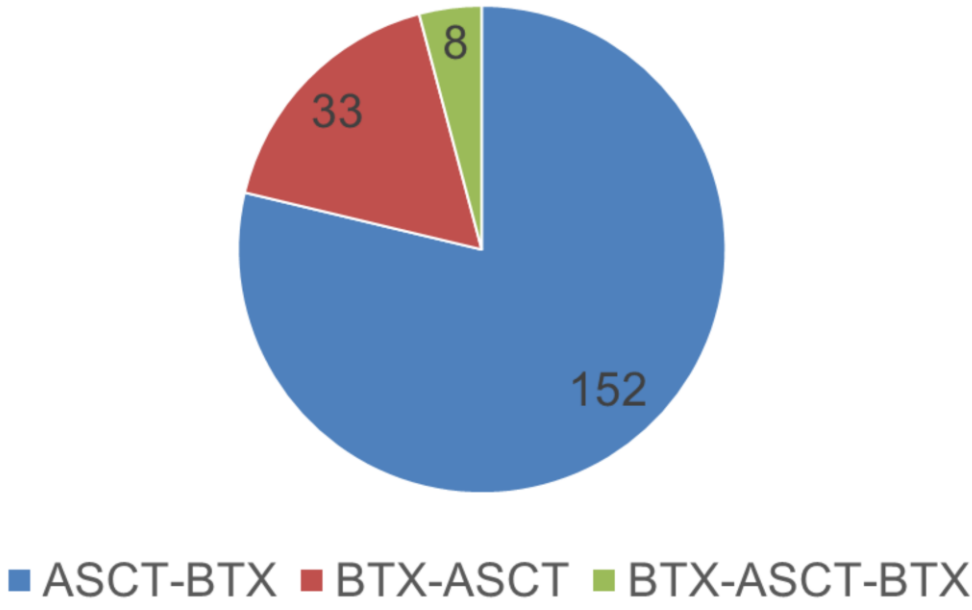
**Source**: Adapted from ERG report, Table 3 (page 32)

# Company's clinical evidence

## Composition of relevant population from trials

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# Company's clinical evidence

## Results: CheckMate 205, Aug 2015 interim analysis

| | Cohort B (n=80) | |
|---|---|---|
| | IRRC-assessed | Investigator-assessed |
| Objective response % (n)<br>95% confidence interval | 66.3% (53)<br>(54.8, 76.4) | 72.5% (58)<br>(61.4, 81.9) |
| Complete response % (n) | 8.8% (7) | 27.5% (22) |
| Partial response % (n) | 57.5% (46) | 45.0% (36) |
| Stable disease % (n) | 22.5% (18) | 22.5% (18) |
| Relapsed/progressed disease % (n) | 7.5% (6) | 3.8% (3) |
| Progression-free survival, median<br>95% confidence interval (2° outcome) | 9.99 months<br>(8.41, NA) | 10.94 months<br>(9.99, 11.56) |
| Overall survival at 6 months<br>95% confidence interval (2° outcome) | | 98.7%<br>(91.0, 99.8) |
| Median follow up: 8.9 months. Median OS not reached. | | |

IRRC, Independent Radiologic Review Committee

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**Source**: Company submission, section 4.7.1.8, table 9 (page 48)

Note: Later data cut-off point used in economic analysis; interim analysis presented for information

Objective Response Rate assessed by independent radiologic review committee (IRRC): defined as the proportion of patients with a best overall response of complete response or partial response, according to the 2007 International Working Group criteria. Investigator-assessed response also reported (defined in same way as IRRC-assessed response)

Best overall response (BOR) defined as best response designation recorded between date of first dose and date of initial objectively documented progression per 2007 IWG criteria or date of subsequent therapy, whichever occurred first. For patients without documented progression or subsequent anticancer therapy, all available response designations contributed to the BOR determination. For patients who continued treatment beyond progression, the BOR was determined based on response designations recorded up to the time of initial progression

PFS by IRRC: defined as the time from the first dosing date to the date of the first documented tumour progression or death due to any cause, whichever occurred first.

OS: defined as the time from first dosing date to the date of death.

**Source**: Company submission, section 4.7.1.4 (page 42)

Discordance between IRRC and investigator-assessments due to interpretation of FDG-PET scans needed for confirmation of complete response. Majority of investigator-assessed complete responses considered not complete by IRRC were assessed as partial responses by

IRRC. **Source**: Company submission, section 4.7.1.8 (page 47)

## Company's clinical evidence

### Results: CheckMate 205, April 2016

| | Cohort B (n=80) | | Cohort C (n=100) | |
|---|---|---|---|---|
| | IRRC | Investigator | IRRC | Investigator |
| ORR (95% CI) | 67.5% (54) (57.2, 77.8) | [redacted] | 73.0% (73) (64.3, 81.7) | **66.0% (66) (56.7, 75.3)** |
| CR | 7.5% (6) | [redacted] | 17.0% (17) | **26.0% (26)** |
| PR | 60.0% (48) | [redacted] | 56.0% (56) | **40.0% (40)** |
| SD | 21.3% (17) | [redacted] | 17.0% (17) | **24.0% (24)** |
| PD | 8.8% (7) | [redacted] | [redacted] | [redacted] |
| PFS, median (95% CI) | 14.78 months (11.33, NA) | [redacted] | 11.17 months (8.51, NA) | **11.40 months (11.17, NA)** |
| OS, 6 months (95% CI) | | **96.1% (92.0, 100)** | | **94.0% (89.1, 98.8)** |

Median follow up: cohort B 15.7 months; C 8.9 months. Median OS not reached.

IRRC, Independent Radiological Review Committee; ORR, Overall objective response; CR, Complete response; PR, Partial response; SD, Stable disease; PD, Progressed disease; PFS, Progression-free survival; OS, Overall survival

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**Source**: Company submission, section 4.7.1.9, table 13 (page 56)

April 2016 is the latest data cut-off; used in the economic analysis
Note: Cohort C only 98 patients had received both ASCT and BTX. These 2 patients were removed from further analysis

Cohort C: BTX before ASCT n=33; BTX after ASCT n=57; BTX before and after ASCT n=8; Sequence unclear n=2

Number of PFS events: Cohort B: 32 (IRRC-assessed), 28 (investigator-assessed); Cohort C: 28 (IRRC-assessed), 25 (investigator-assessed) Note: Investigator-assessed PFS used in model

Number of deaths: Cohort B: 5; Cohort C: 8 **Source**: Company submission, section 4.7.1, Table 13 (page 56)

Objective Response Rate assessed by independent radiologic review committee (IRRC): defined as the proportion of patients with a best overall response of complete response or partial response, according to the 2007 International Working Group criteria. Investigator-assessed response also reported (defined in same way as IRRC-assessed response). Best overall response (BOR) defined as best response designation recorded between date of first dose and date of initial objectively documented progression per 2007 IWG criteria or date of subsequent therapy, whichever occurred first. For patients without documented progression or subsequent anticancer therapy, all available response designations contributed to the BOR determination. For patients who continued treatment beyond progression, the BOR was determined based on response designations recorded up to the time of initial progression. PFS by IRRC: defined as the time from the first dosing date to the date of the first documented tumour progression or

death due to any cause, whichever occurred first. OS: defined as the time from first dosing date to the date of death. **Source**: Company submission, section 4.7.1.4 (page 42)

# Company's clinical evidence

## Results: CA209-039, June 2014, Aug 2015

| Post BTX & ACST (n=15) | June 2014 | August 2015 | |
|---|---|---|---|
| | | IRRC | Investigator |
| **Objective response 95% CI** | 87% (13) (60, 98) | 60% (9) | **87% (13)** |
| **Complete response** | 7% (1) | 0% (0) | **13% (2)** |
| **Partial response** | 80% (12) | 60% (9) | **73% (11)** |
| **Stable disease** | 13% (2) | 33% (5) | **13% (2)** |
| **Progression-free survival, median, 95% CI** *(2° outcome)* | 85% (52, 96)* | 12.65 (5.91, NA) | [redacted] |
| **Overall survival at 1 year, 95% CI** *(2° outcome)* | NA | | [redacted] |
| Median follow up: June 2014 40 weeks; August 2015 23.3 months<br>Median OS not reached | | | |
| *24 weeks, not median | | | |

BTX, brentuximab vedotin; ASCT, autologous stem cell transplant; IRRC, Independent Radiologic Review Committee; CI, confidence interval; NA, not available



**Source**: Company submission, section 4.7.1.9, table 16 (page 62), table 17 (page 63)

Note: Later data cut-off point used in economic analysis; interim analysis presented for information

Note: Investigator-assessed PFS used in model

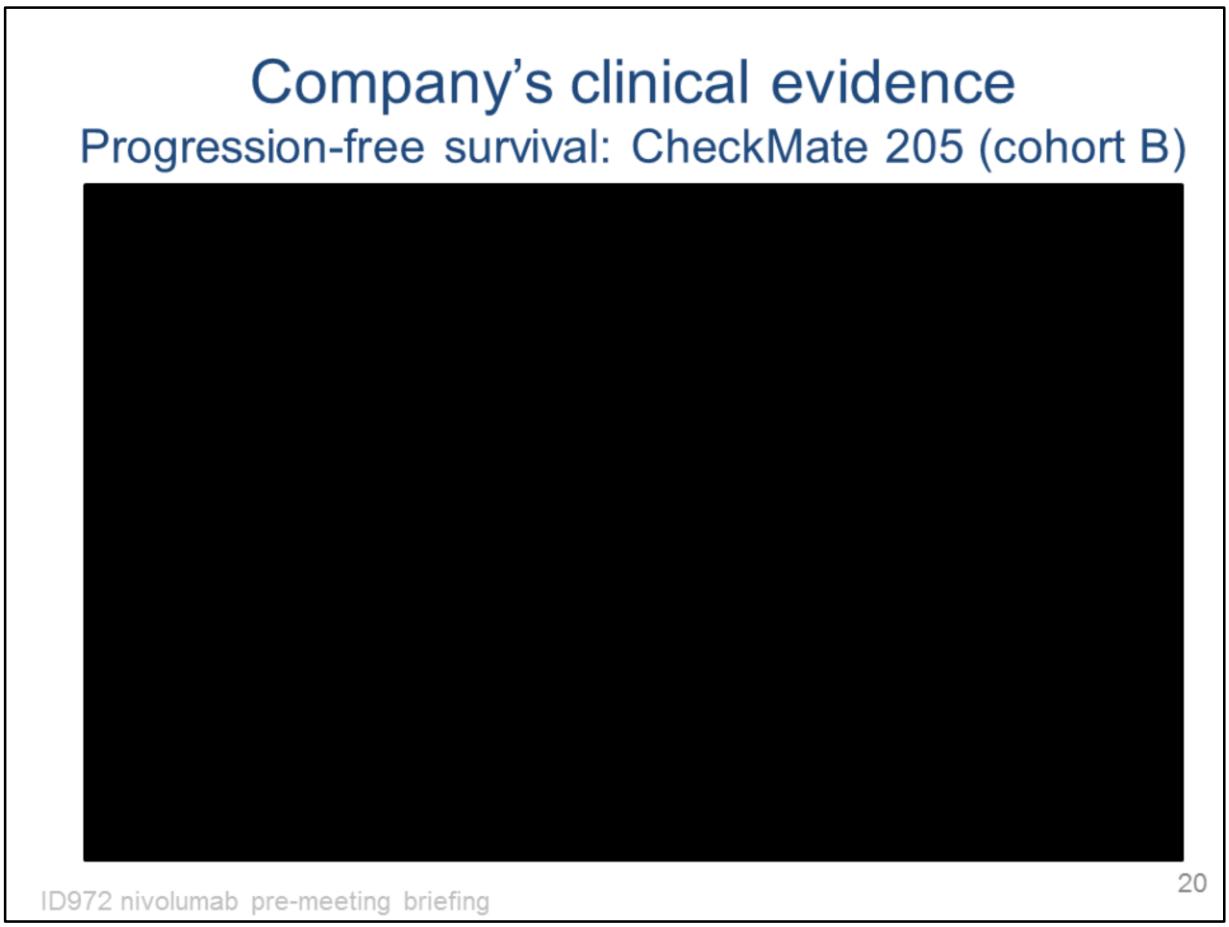
Objective Response Rate, investigator-assessed: defined as proportion of patients whose BOR was either Complete Response (CR) or Partial Response (PR), using protocol-defined International Workshop to Standardized Response Criteria for Lymphomas. A secondary efficacy endpoint was IRRC-assessed Objective Response Rate using 2007 International Working Group criteria.

BOR defined as the best response between the date of the first dose and the last efficacy assessment before subsequent therapy.

CR: defined as tumour regression to 1.5 cm or less in greatest diameter, if the tumour measured more than 1.5 cm before therapy, or a decrease in previously involved nodes measuring 1.1 to 1.5 cm in greatest diameter to 1 cm or less or a decrease of more than 75%, with negative results on PET scanning.

PFS: defined as the time from the date of the first dose of study medication to the date of first disease progression or the date of death.

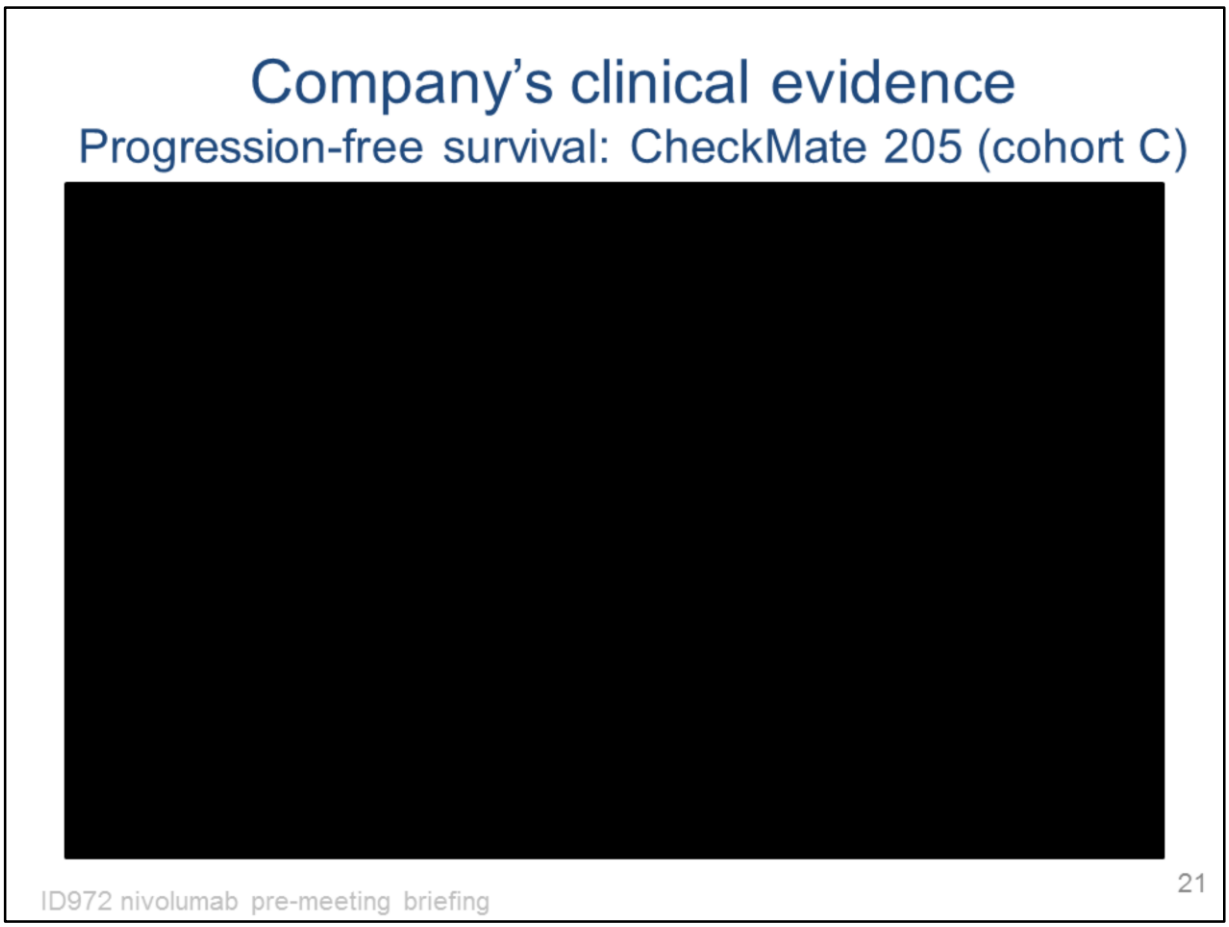
**Source**: Company submission, section 4.7.1.5 (page 59)




**Source**: Company submission, Appendix 6, Figure 3 (page 7)

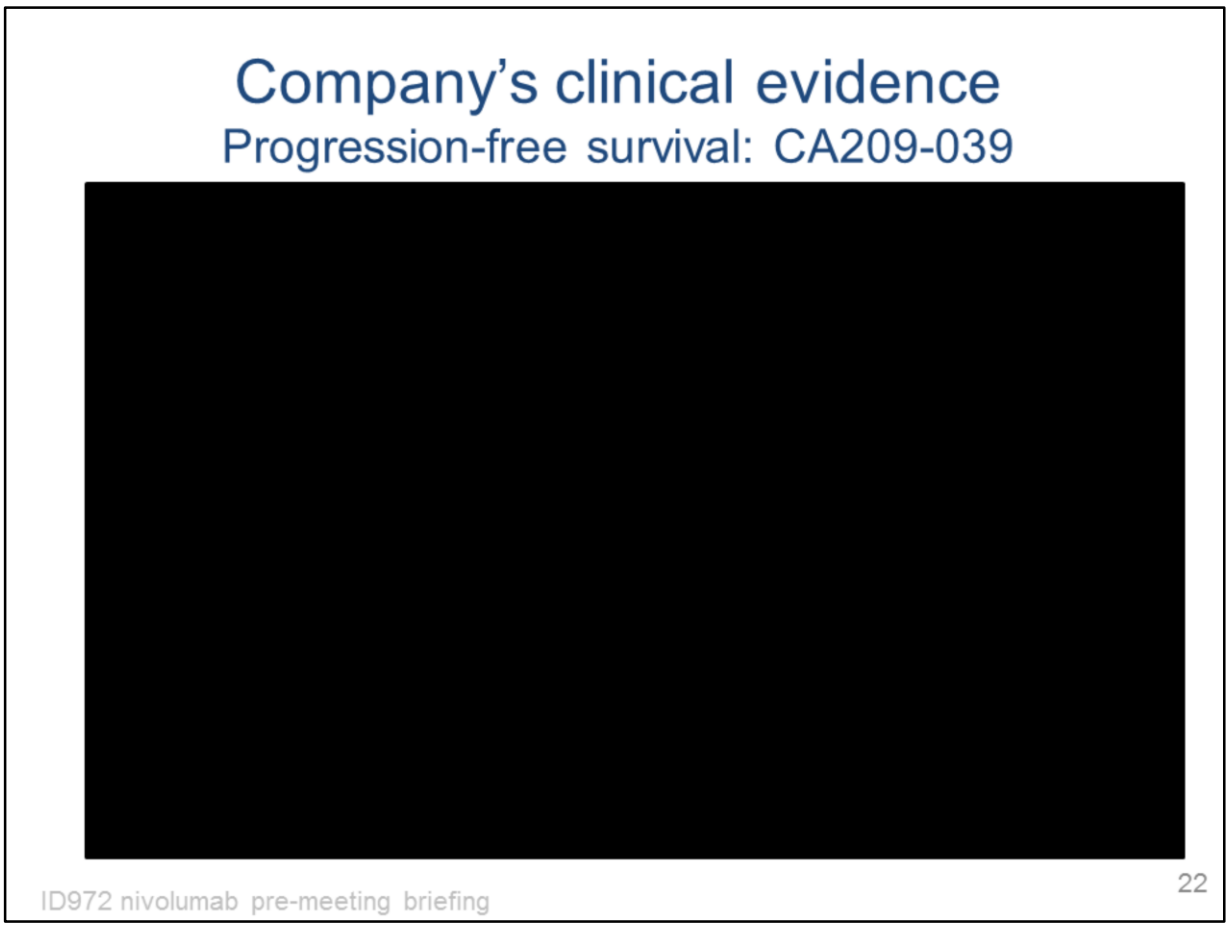
Investigator-assessed PFS

Later data cut-off point (April 2016)




**Source**: Company submission, Appendix 6, Figure 4 (page 7)

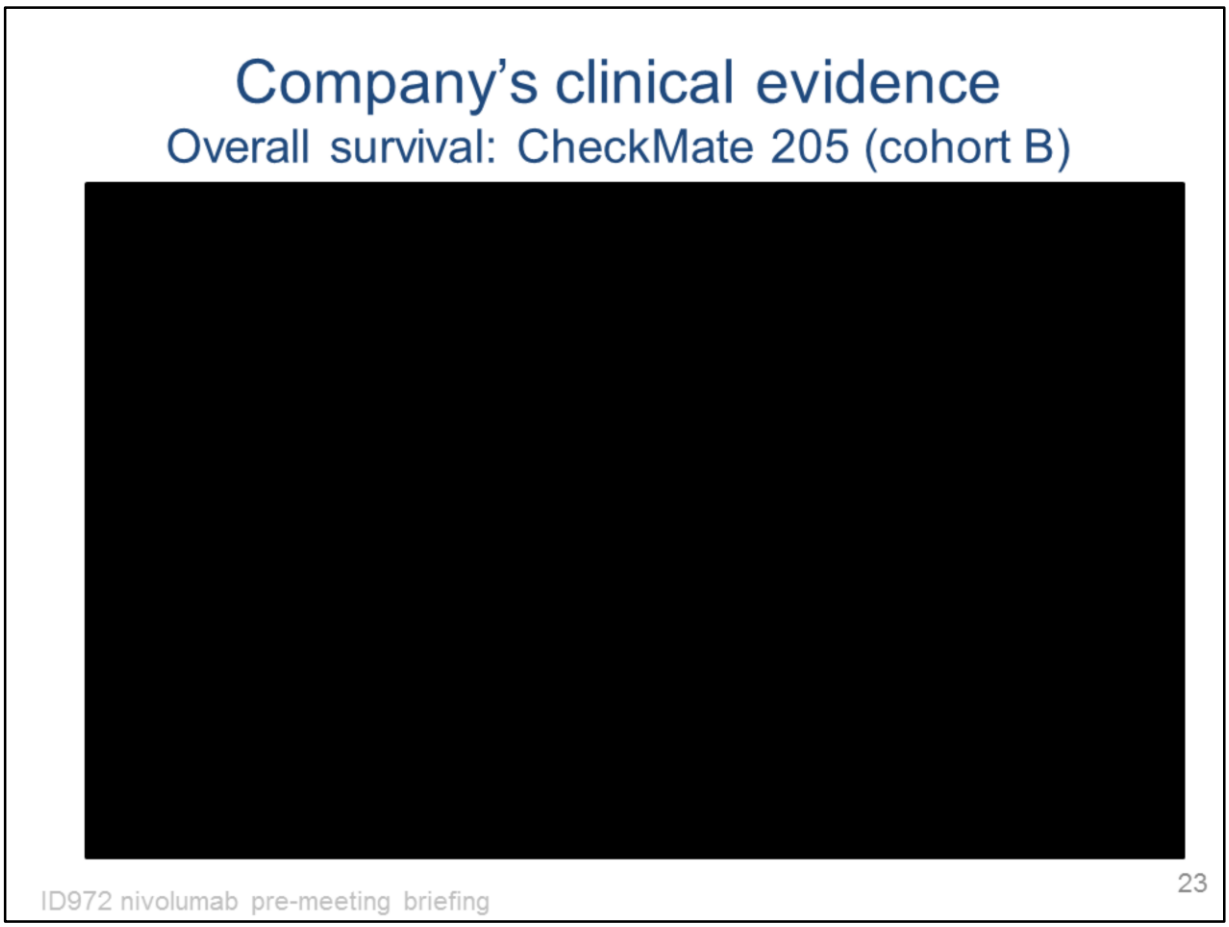
Investigator-assessed PFS




**Source**: Company submission, Appendix 6, Figure 2 (page 6)

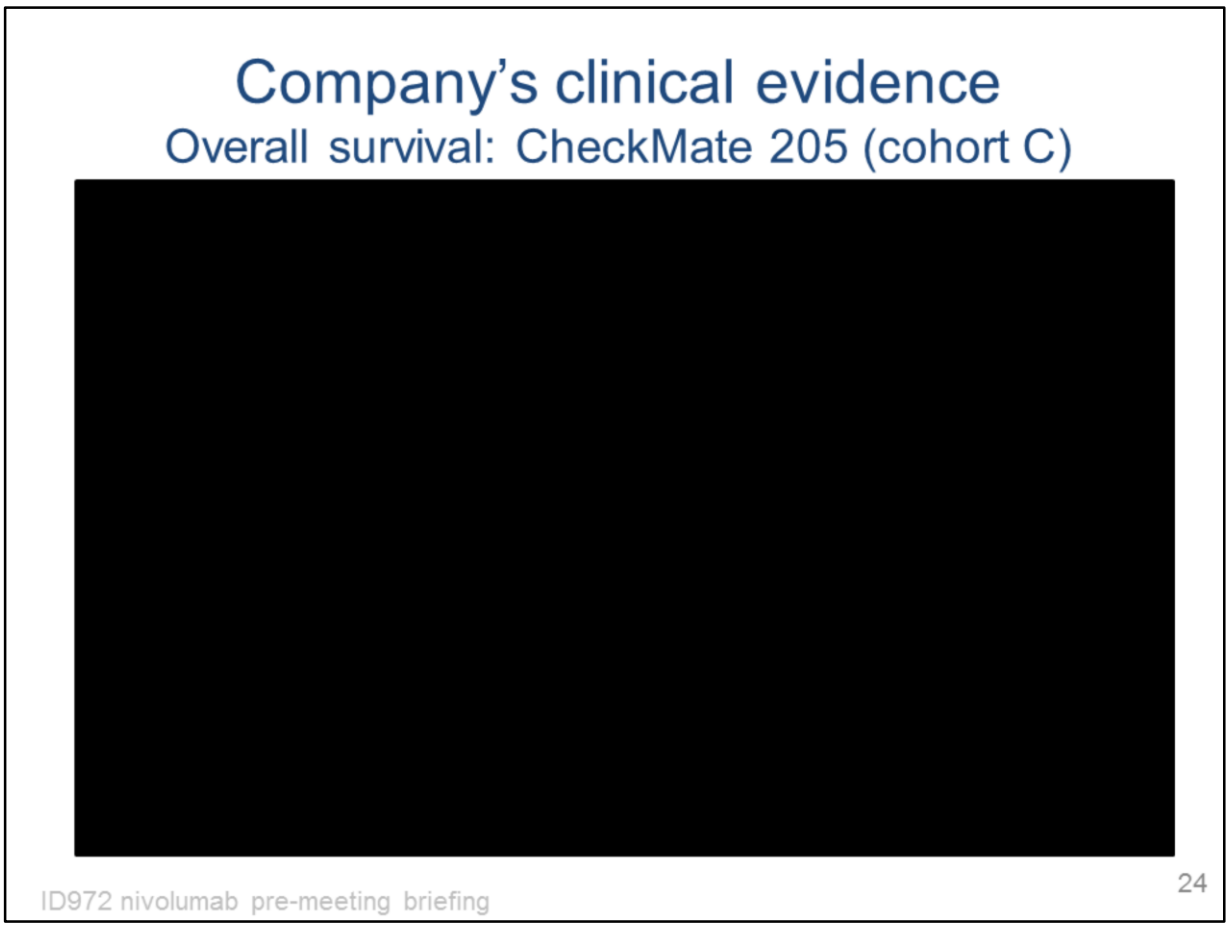
Investigator-assessed PFS

Later data cut-off point (August 2015)

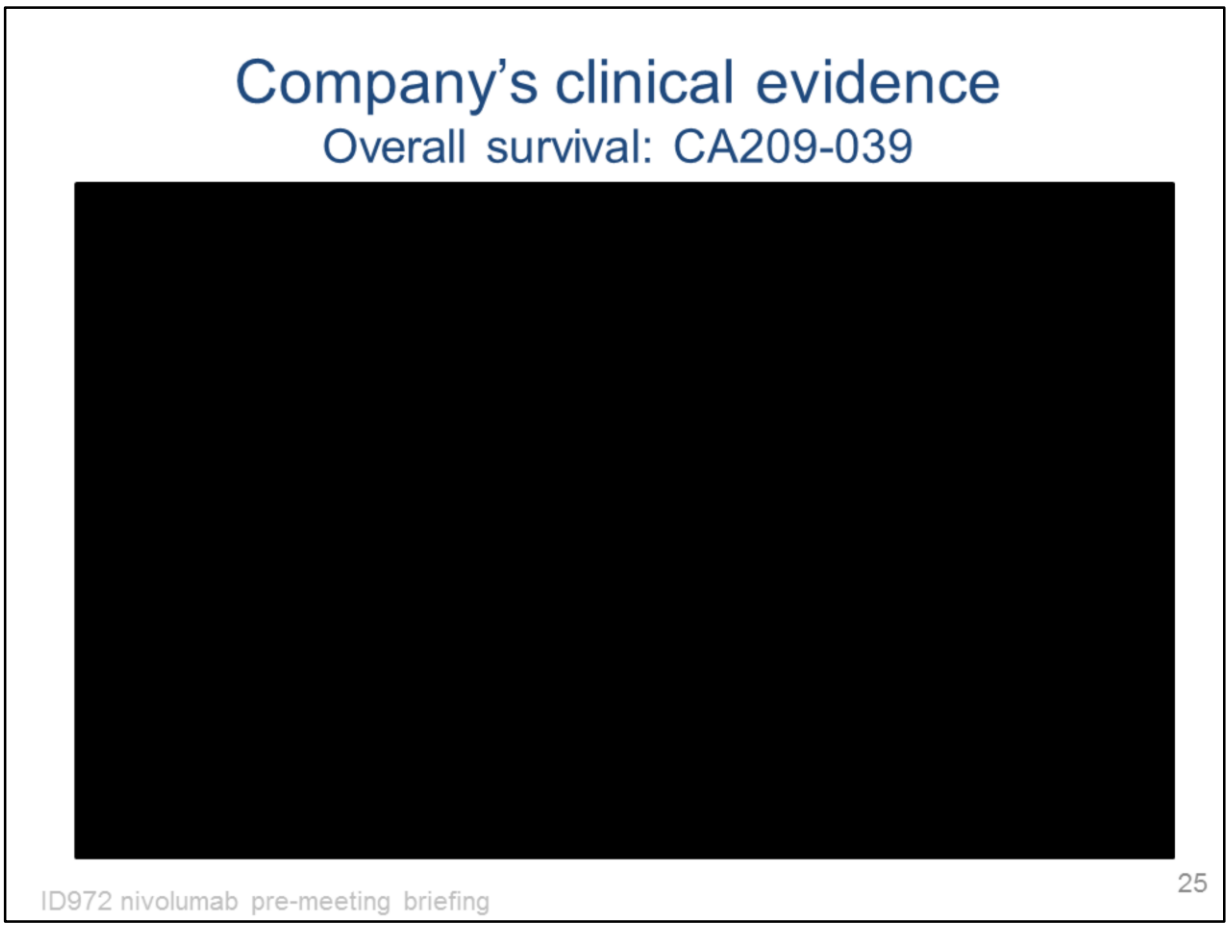



**Source**: Company submission, Appendix 6, Figure 18 (page 19)

Later data cut off point (April 2016)




**Source**: Company submission, Appendix 6, Figure 19 (page 20)




**Source**: Company submission, Appendix 6, Figure 17 (page 19)

Later data cut-off point (August 2015)

# ERG's critique

## Clinical effectiveness evidence for nivolumab

- Trial quality:
  - Agree with company's quality assessment of studies.
  - Trials of reasonable quality but have serious limitations by design.
  - Data are largely not peer-reviewed.
- Generalisability:
  - Details of size and demographics of source population not stated, so difficult to determine whether participants are representative of entire population.
  - Unknown whether there were differences between those who participated and those who did not.



**Source**: ERG report, section 3.1.3 (pages 35-8), section 3.1.4 (pages 39-43)

# Company's clinical evidence

## Subgroup analysis: CheckMate 205

- Post-hoc analysis of Cohort B results (IRRC-assessed ORR) according to multiple variables showed objective response remained consistent across subgroups
- Variables included:
  - Age
  - Gender
  - Race
  - Region
  - Smoking status
  - B-symptoms at initial diagnosis
  - Baseline ECOG performance status
  - Time from initial diagnosis to first ASCT
  - Time from most recent ASCT to first subsequent therapy
  - Number of prior lines of cancer therapy excluding preparative regimens

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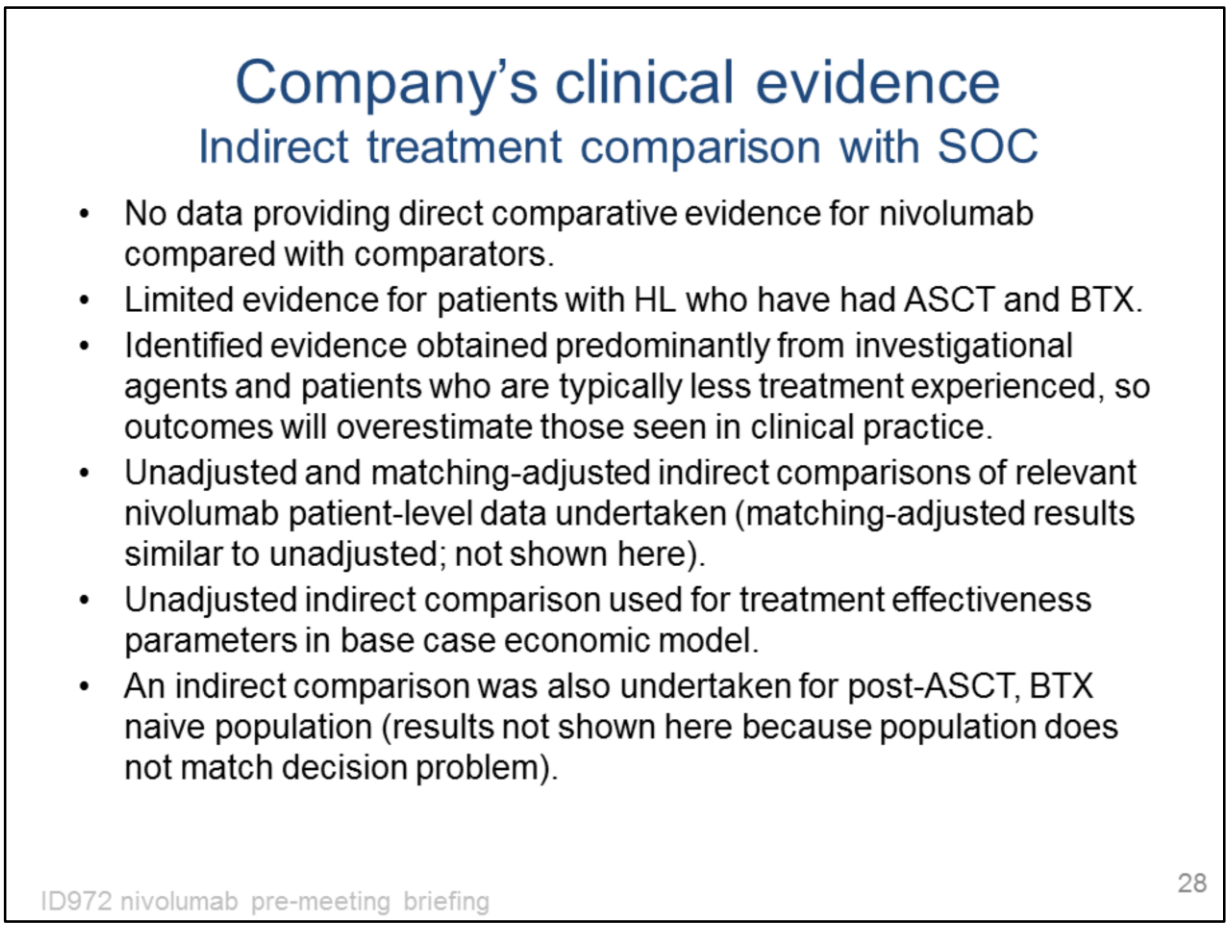
**Source**: Company submission, section 4.8.1 (page 67)

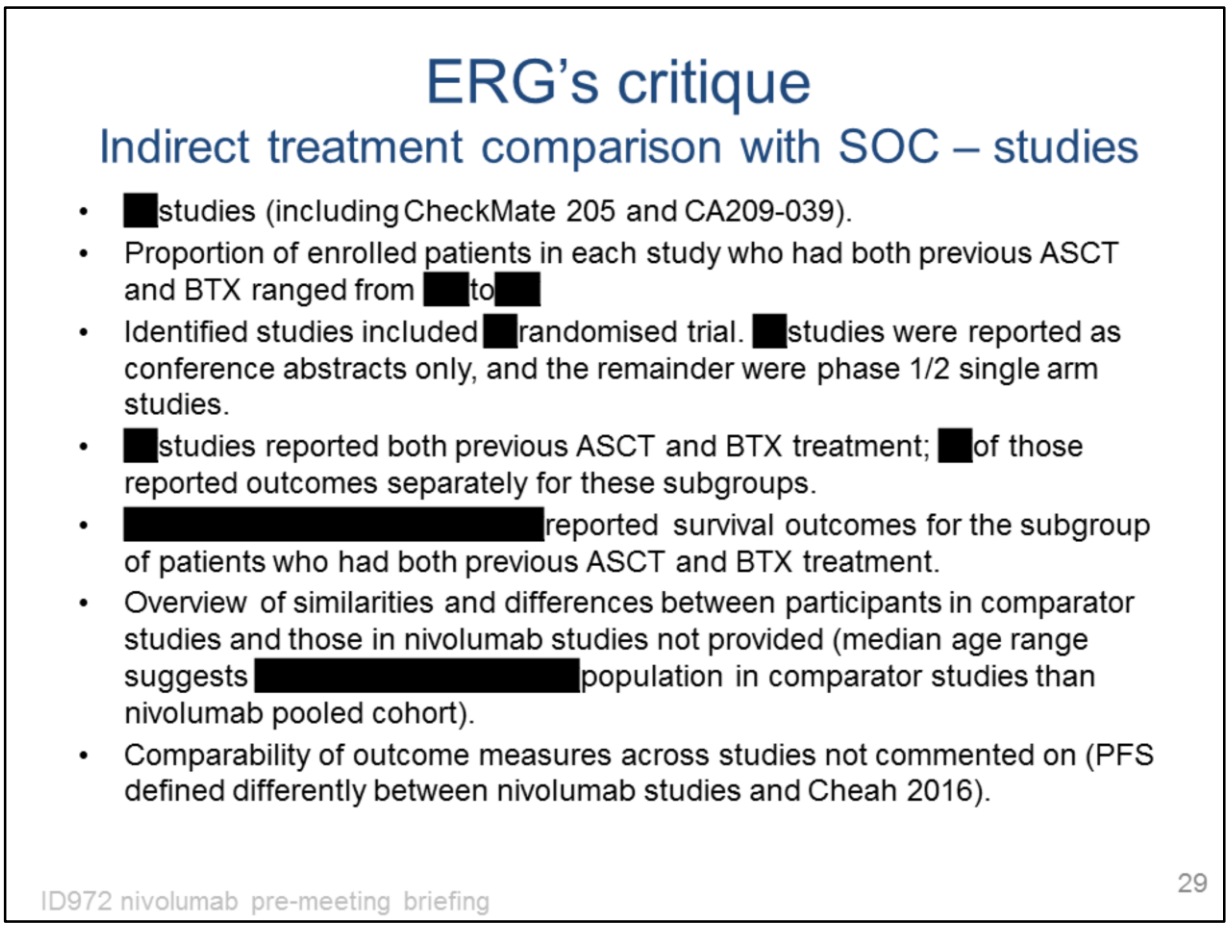



**Source**: Company submission, section 4.10 (page 70); ERG report, section 3.1.7 (pages 54-59)

Response results obtained from the MAIC were very similar to those obtained from the unadjusted indirect comparison.

[redacted] **Source**: ERG report, section 3.4 (pages 94-5)

Comparison for post-ASCT population only is supportive data only. It is not reflective of clinical practice and does not address decision problem.

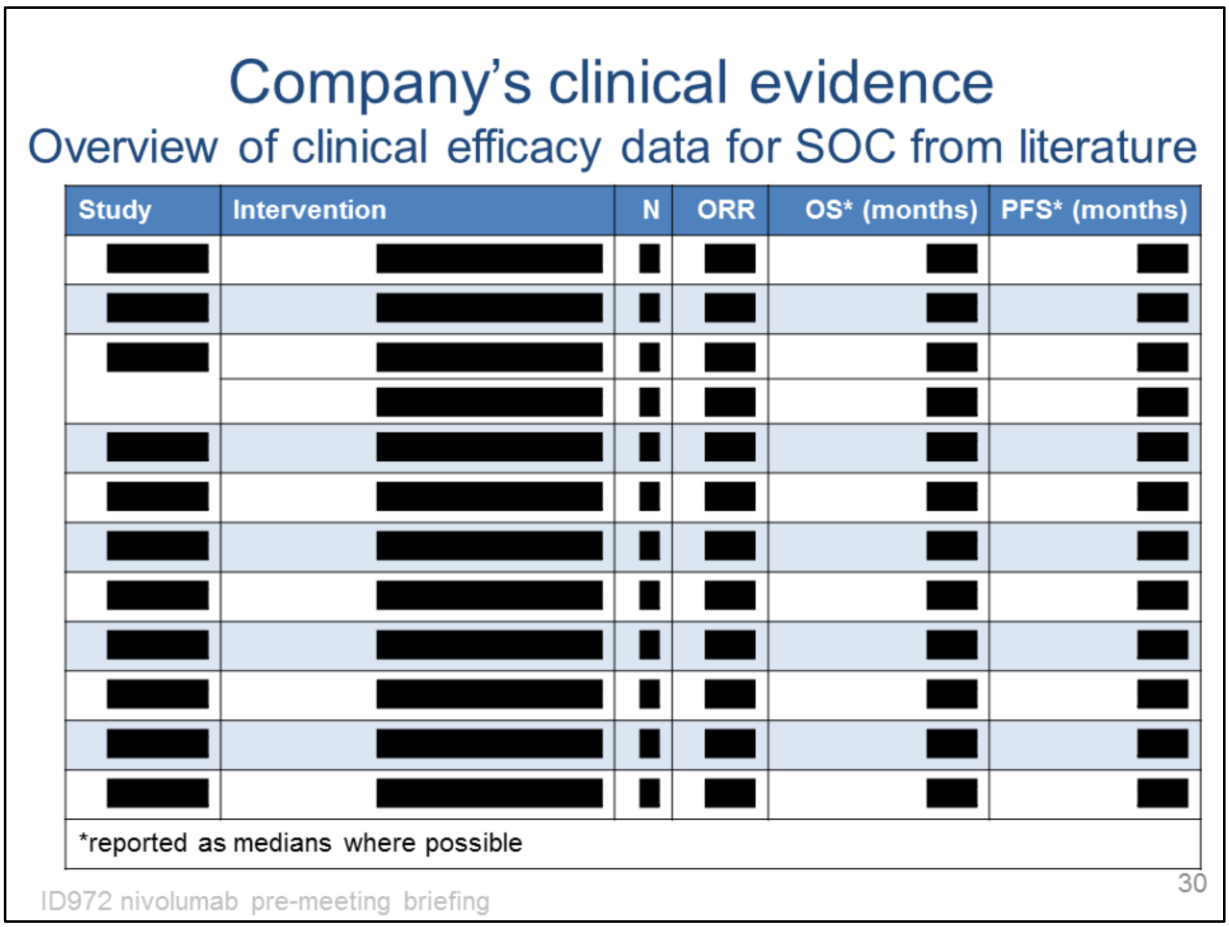



**Source**: Company submission, section 4.10.1.1 (pages 71-2); ERG report, section 3.1.7 (pages 49, 54-7)

Nivolumab studies define PFS as time from first dosing date to date of first documented tumour progression or death.

Cheah 2016 defines PFS as time measured from date of confirmed disease relapse following BTX to disease progression or death.

Information requested from the company at clarification stage showed that median time from BTX failure to nivolumab treatment in CheckMate 205 were [redacted] and [redacted]months.
If the nivolumab studies had used the Cheah 2016 PFS definition, PFS would have been higher.



# Company's clinical evidence

## Overview of clinical efficacy data for SOC from literature

| Study | Intervention | N | ORR | OS* (months) | PFS* (months) |
|---|---|---|---|---|---|
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
|  | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

*reported as medians where possible

**Source**: Company submission, section 4.10.1.2, Table 22 (page 74)

Note:

- Does not include CheckMate 205 Cohort B (interim analysis), CA209-039 (interim analysis) and Cheah 2016 (details on later slide)
- [redacted]

## ERG's critique

### Cheah 2016 as comparator evidence

- Identified as primary source of comparator evidence because:
  - majority of patients had both previous ASCT and BTX,
  - use of non-investigational agents reflective of clinical practice.
- Real world study (retrospective database review) conducted in USA:
  - Uncertain how well this reflects UK practice.
  - Authors noted potential selection bias.
  - 'Investigational agents' not described fully.
  - Composition of chemotherapies unclear.
- ~70% participants had received both previous ASCT and BTX

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**Source**: Company submission, section 4.10 (page 70); ERG report, section 3.1.7 (pages 55-7)

Note: 66/97 reported in full paper (68%) and 71/100 reported in abstract (71%)

To be included in the study patients had to meet the following criteria:

- A histologically confirmed diagnosis of classical Hodgkin lymphoma
- Treatment with brentuximab vedotin for relapsed Hodgkin lymphoma
- Disease progression at any time after treatment with brentuximab vedotin

The aim of the study was to determine PFS and OS following disease relapse after brentuximab vedotin therapy. Secondary outcomes were to analyse the efficacy of subsequent therapeutic strategies and to explore candidate prognostic factors for PFS and OS.

The Cheah study authors note that patient selection bias for patients willing and able to travel long distances to an academic centre may limit the generalisability of their findings and that outcomes among other patient groups (e.g. those in community settings), may be less favourable.

# Company's clinical evidence

## Results: Cheah 2016

| Intervention (n) | ORR | CR | PR | OS (months) | PFS (months) |
|---|---|---|---|---|---|
| Overall (79) | 27 | 12 | 15 | 25.2 | 3.5 |
| Investigational agent (28) | 7 | 4 | 3 | 47.7 | 2.4 |
| Gemcitabine (15) | 8 | 4 | 4 | NR | 2.1 |
| Bendamustine (12) | 6 | 2 | 4 | 34.0 | 3.7 |
| Other alkylator (6) | 2 | 1 | 1 | 9.5 | 5.0 |
| BTX retreatment (6) | 2 | 0 | 2 | 10.4 | 3.5 |
| Platinum based (4) | 1 | 0 | 1 | 25.2 | 0.9 |
| ASCT (3) | 1 | 1 | 0 | 11.9 | NR |
| Other (5) | 0 | 0 | 0 | 24.9 | NR |
| Note: Stable disease not reported | | | | | |

ORR, Objective response rate; CR, Complete response; PR, Partial response; OS, Overall survival; PFS, Progression-free survival; NR, Not reported; BTX, brentuximab vedotin; ASCT, autologous stem cell treatment

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**Source**: Company submission, section 4.10.1, Table 22 (page 74)

# ERG's critique

## Indirect treatment comparison

- Unadjusted indirect treatment comparison appropriate because no common comparator.
- However, will include sampling error and systematic error because of the imbalance in prognostic factors and effect modifiers.
- Unclear whether log scale was used for indirect comparison of response outcomes where comparison were reported as adjusted relative risk
- [redacted] may have been more appropriate to combine time to event data for comparators compared with nivolumab ([redacted])
- Matching-adjusted indirect comparison an improved method because it takes into account the different distributions of prognostic factors and effect modifiers, however
- Matching-adjusted indirect comparison results are not considered robust (results used in a scenario analysis by the company).

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**Source**: ERG report, section 3.1.7 (pages 58-9)

ERG notes that a NICE DSU Technical support document on methods for population-adjusted indirect comparisons was published during the course of the evidence review but was not available to the company as their submission was prepared.

[redacted]

[redacted] **Source**: ERG report, section 3.1.7 (page 59)

[redacted]

[redacted]

**Source**: ERG report, section 3.1.7 (pages 60, 62-3)

# Company's clinical evidence

## Nivolumab data pooled for indirect comparison

| | CheckMate 205 (B) | CheckMate 205 (C) | CA209-039 | Overall |
|---|---|---|---|---|
| Patients (n) | 80 | 98 | 15 | 193 |
| CR | [redacted] | [redacted] | [redacted] | [redacted] |
| PR | [redacted] | [redacted] | [redacted] | [redacted] |
| ORR | [redacted] | [redacted] | [redacted] | [redacted] |
| PFS events | [redacted] | [redacted] | [redacted] | [redacted] |
| Median PFS (months) | [redacted] | [redacted] | [redacted] | [redacted] |
| OS events | [redacted] | [redacted] | [redacted] | [redacted] |
| Median OS (months) | [redacted] | [redacted] | [redacted] | [redacted] |
| Median OS and PFS not reached so data extrapolated using parametric curves | | | | |

ITC, indirect treatment comparison; CR, complete response; PR, partial response; ORR, overall response rate; PFS, progression-free survival; OS, overall survival; NA, not available

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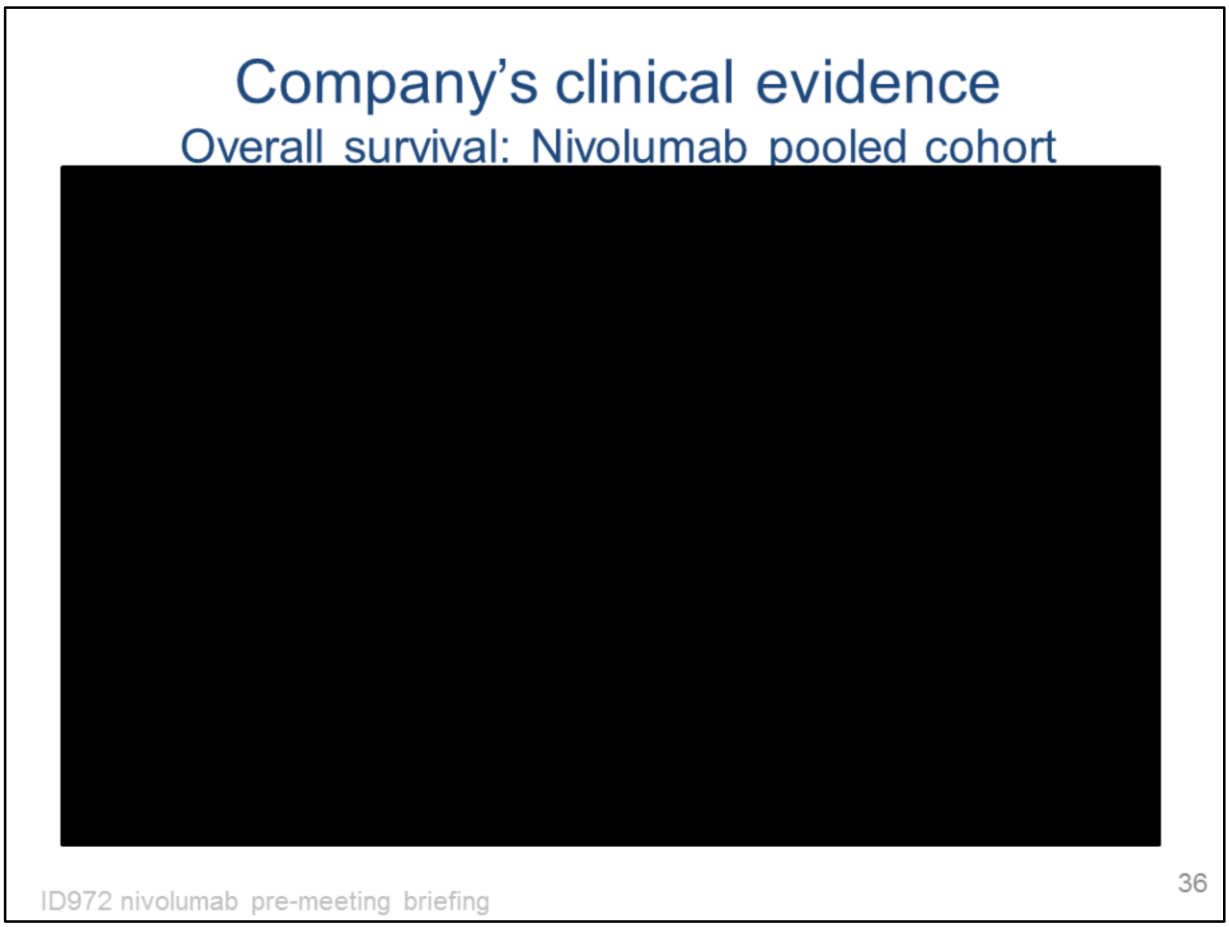
**Source**: Company submission, Appendix 3, Table 10 (page 20)

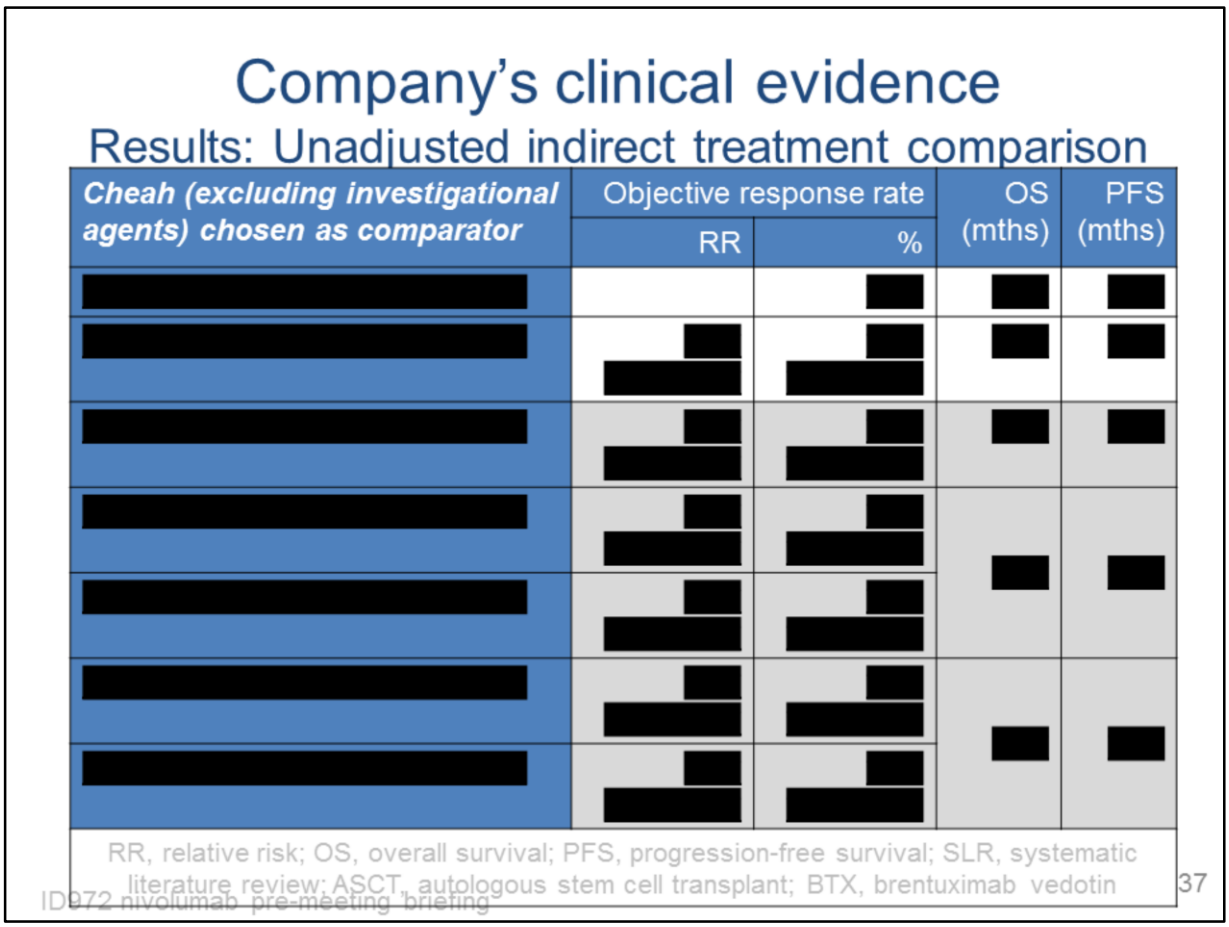
Parametric curves shown on later slides

Note that median PFS for CA209-039 differs from that reported for the individual study (slide 19). This was queried with the company who responded to say that the discrepancy is due to the different methods for calculating confidence intervals. The CSR applied a method based on the log of cumulative hazard while the survival analysis applied a method based on the cumulative hazard. BMS made the decision to use the method based on the cumulative hazard as this was the default output from the survfit function, which is part of the survival package in R.


**Source**: Company submission, Appendix 6, Figure 1 (page 6)




**Source**: Company submission, Appendix 6, Figure 16 (page 18)




**Source**: Company submission, section 4.10.1, Table 24 (page 75)

**Nivolumab pooled cohort (n=193)**

CheckMate 205 Cohort B:

BTX after ASCT n=80

CheckMate 205 Cohort C:

- BTX before ASCT n=33
- BTX after ASCT n=57
- BTX before and after ASCT n=8
- Sequence unclear n=2 (these patients had not had BTX and so were removed from analysis)

CA209-039:

BTX after ASCT n=15

4 scenarios evaluated (nivolumab versus):

[redacted]

**Source**: ERG report, section 3.4 (pages 96-7)

Company notes matching-adjusted indirect comparison showed similar results. ERG notes t[redacted]

OS and PFS for pooled nivolumab cohort was a predicted value based on extrapolation of

patient level data because median survival not reached in either study.

# ERG's critique

## Indirect treatment comparison – summary

- There is considerable uncertainty regarding the extent to which the benefits of nivolumab exceed those of potential comparator treatments because of:
  - immaturity of evidence base for nivolumab and comparators,
  - evidence base for comparators limited in quality and completeness,
  - the need to undertake indirect comparisons,
  - uncertainty about how well the comparator populations, particularly in Cheah 2016, match those in the nivolumab studies and UK patients,
  - uncertainty about specific treatment regimens in Cheah 2016.
- However, agreed that Cheah 2016 is the best available evidence for comparators.



**Source**: ERG report, section 3.1.7 (page 62), section 3.4 (page 96-7)

# Outcomes following alloSCT in patients having nivolumab

| Number of patients Total n=15 | Disease status at alloSCT | Disease status after alloSCT |
|---|---|---|
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | | |

Note: May include patients from CheckMate 205 cohort A, which is not of relevance to the appraisal.
[redacted] patients (in the relevant population) received post-nivolumab alloSCT (as at June 2016). Information on disease status following alloSCT only available for 15 patients from CheckMate 205, and not reported separately by cohort.

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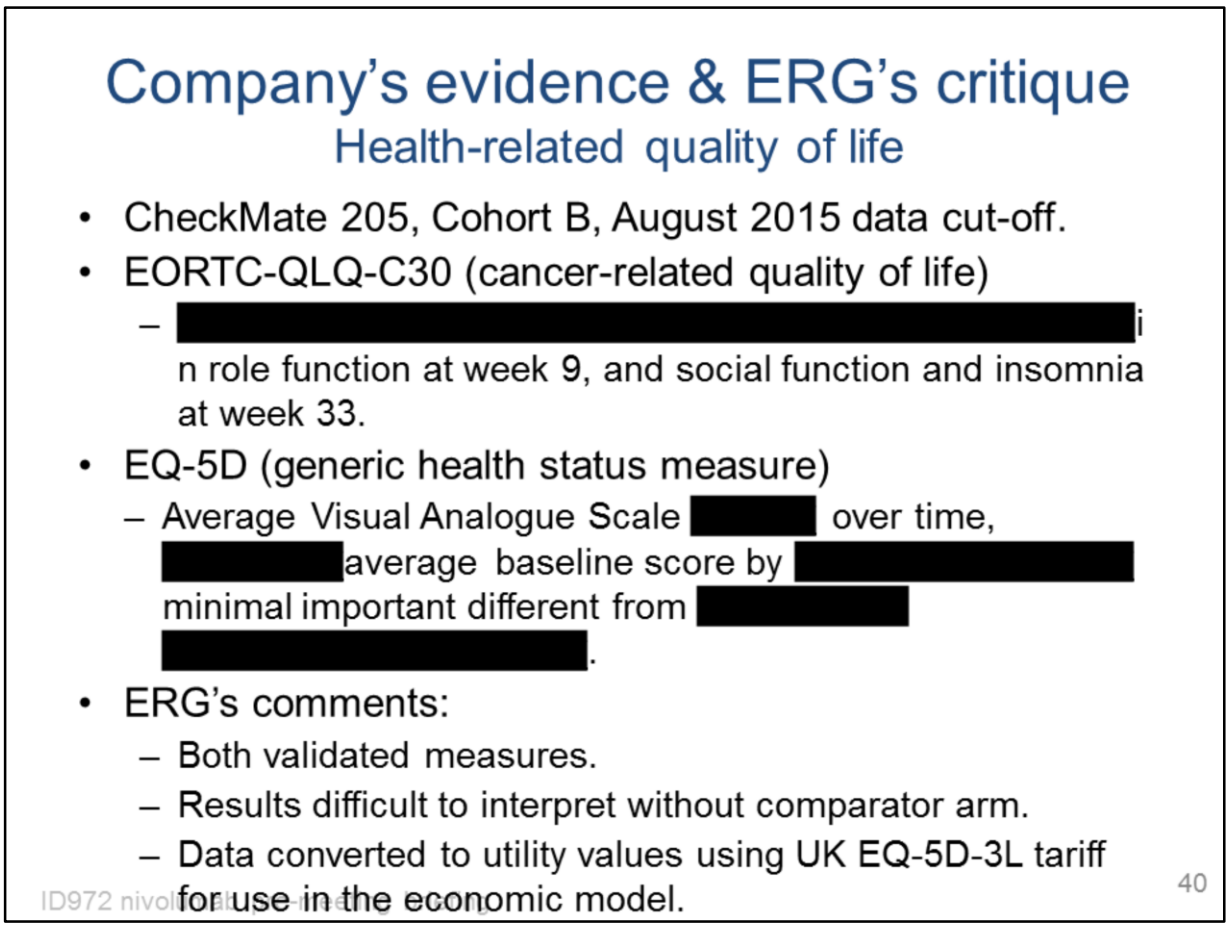
**Source**: Company submission, section 4.13.4.1 (page 93); ERG report, section 3.3.5 (pages 83-4)




**Source**: Company submission, section 4.7.1 (page 52); ERG report, section 3.3.6 (page 84)

# Company's clinical evidence

## Adverse events: CheckMate 205, August 2015

| | Cohort B (n=80) | | Total (n=240) | |
|---|---|---|---|---|
| | Any grade | Grade 3-4 | Any grade | Grade 3-4 |
| Diarrhoea | 8 (10.0%) | 0 | 26 (10.8%) | 1 (0.4%) |
| Nausea | 10 (12.5%) | 0 | 26 (10.8%) | 0 |
| Fatigue | 20 (25.0%) | 0 | 39 (16.3%) | 1 (0.4%) |
| Pyrexia | 11 (13.8%) | 0 | 21 (8.8%) | 0 |
| Rash | 13 (16.3%) | 1 (1.3%) | 23 (9.6%) | 2 (0.8%) |
| Pruritus | 8 (10.0%) | 0 | 20 (8.3%) | 0 |
| Arthralgia | 11 (13.8%) | 0 | 16 (6.7%) | 0 |
| Infusion related reaction | 16 (20.0%) | 0 | 31 (12.9%) | 1 (0.4%) |
| Any drug related adverse event (any grade) | 88% | | 70% | |
| Any drug related adverse event leading to discontinuation | 3 (3.8%) | | 9 (3.8%) | |

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**Source**: Company submission, section 4.12.1.2 (pages 82-3), adapted from table 30

Median follow-up 8.9 months. Updated data from April 2016 data cut-off will be presented when available.

# Company's clinical evidence

## Adverse events: CA209-039

| | Total population (n= 23) | |
|---|---|---|
| | Any grade | Grade 4-5 |
| Gastrointestinal disorders | [redacted] | [redacted] |
| General disorders, administration site conditions | [redacted] | [redacted] |
| Skin, subcutaneous tissue disorders | [redacted] | [redacted] |
| Musculoskeletal, connective tissue disorders | [redacted] | [redacted] |
| Respiratory, thoracic, mediastinal disorders | [redacted] | [redacted] |
| Metabolism, nutrition disorders | [redacted] | [redacted] |
| Endocrine disorders | [redacted] | [redacted] |
| Blood, lymphatic system disorders | [redacted] | [redacted] |
| Any drug related adverse event (any grade) | | [redacted] |
| Any drug related adverse event leading to discontinuation | | 2 (8.7%) |

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**Source**: Company submission, section 4.12.1.2, adapted from table 32 (pages 85-6)

Median follow-up 23.3 months

# ERG's critique

## Adverse events

- CheckMate 205 total population data included 63 patients not relevant to decision problem.
- CA209-039 total population data included 8 patients not relevant to decision problem (data not presented for relevant subgroup).
- Diarrhoea, nausea, fatigue, pyrexia, rash and pruritus were most common adverse events in both studies, affecting ≥10% patients.
- Infusion related reaction affected 20% in CheckMate 205 Cohort B and 12.9% of total CheckMate 205 population, compared with [redacted] in CA209-039.
- All patients in both studies received at least 1 dose of nivolumab, although median duration of study therapy not reached in CheckMate 205.
- Patients continued to be followed up so extent of exposure increasing and not fully captured by the data presented.

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**Source**: ERG report, section 3.1.5 (page 46), section 3.3.8 (pages 86-7), section 3.4 (page 95)

# Cost effectiveness analysis

## Company's model

*Consistent with NICE reference case*

| | |
|---|---|
| Type | Semi-Markov |
| Population | People with relapsed or refractory classical Hodgkin lymphoma following autologous stem cell transplant and brentuximab vedotin<br>CheckMate 205, cohorts B and C, and CA209-039 = 193 total |
| Comparators | Standard of Care |
| Time horizon | Lifetime (40 years) |
| Cycle length | 1 month with half-cycle correction |
| Measure of health effects | QALY |
| Discounting of utilities and costs | 3.5% |
| Perspective | NHS/PSS |

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**Source**: Company submission, section 5.2 – 5.22 (pages 96-8), section 5.2.2.4 (page 101)

**Nivolumab pooled cohort (n=193)**

CheckMate 205 Cohort B:

BTX after ASCT n=80

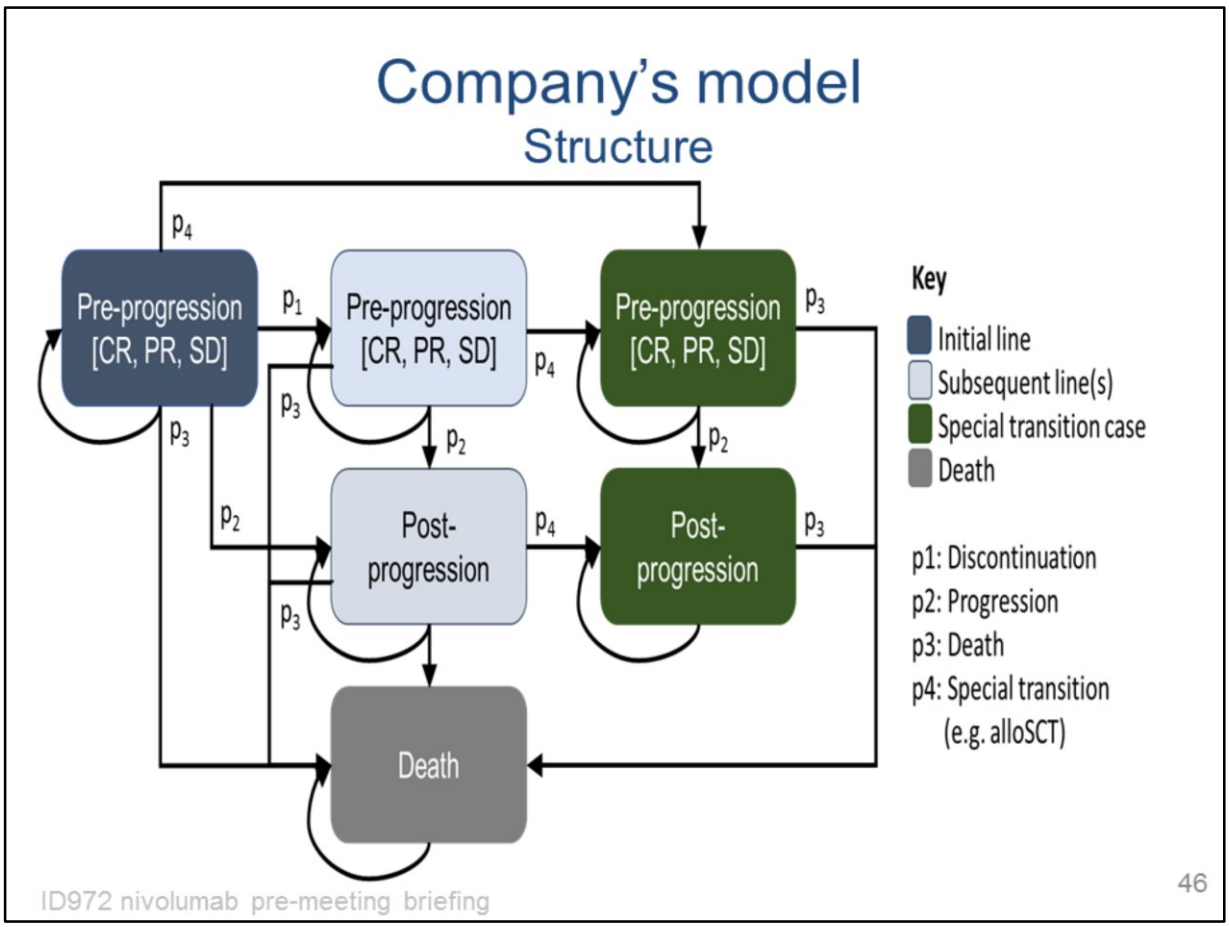
CheckMate 205 Cohort C:

- BTX before ASCT n=33
- BTX after ASCT n=57
- BTX before and after ASCT n=8

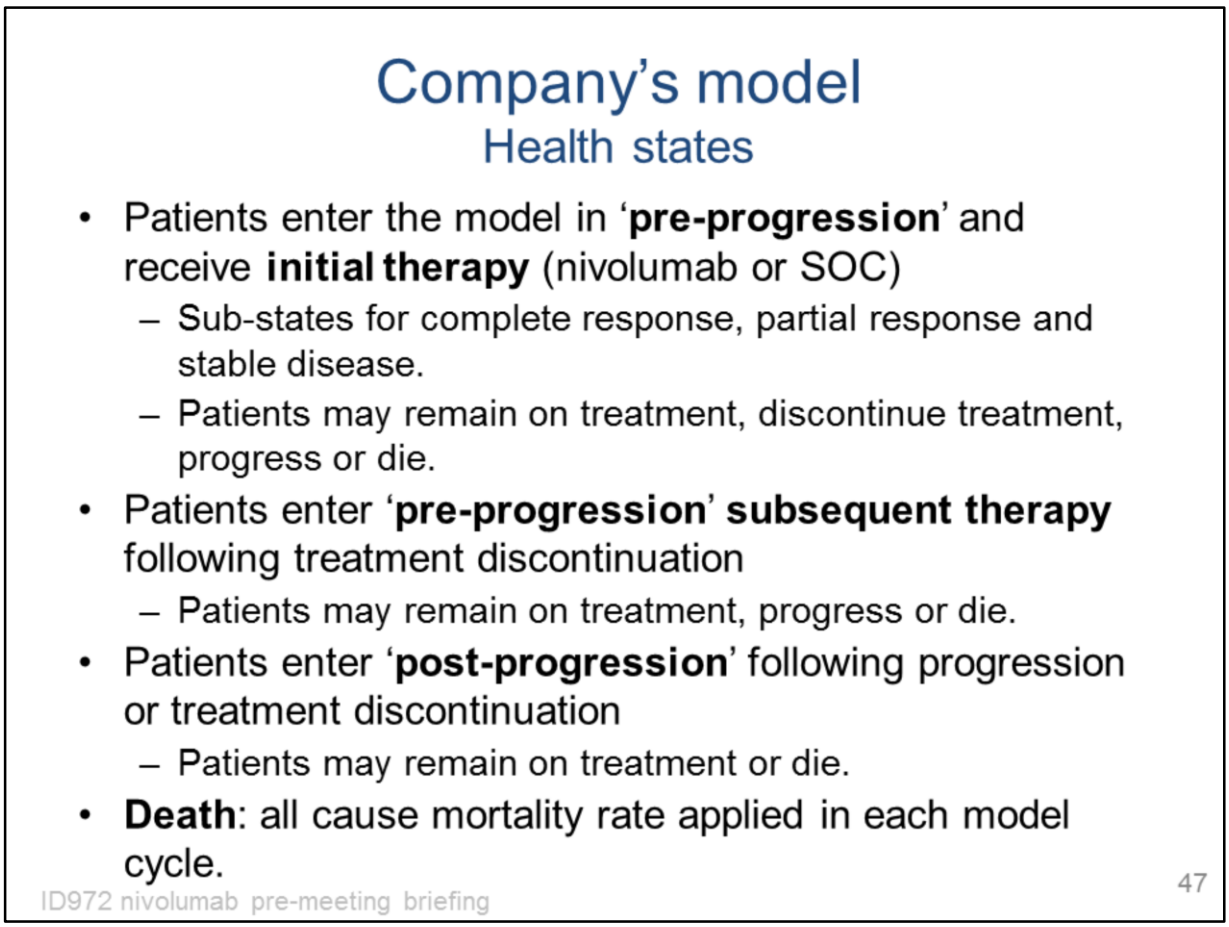
Sequence unclear n=2 (these patients had not had BTX and so were removed from analysis)

CA209-039:

BTX after ASCT n=15




**Source**: Company's clarification response B2, Figure 3 (page 17)




**Source**: Company submission, section 5.2.2 (pages 97-100); ERG report, section 4.3.2 (page 101)

All cause mortality rate uses age and gender-adjusted mortality from UK life tables, due to young age of population included in trials. Applied multiplicatively to each cycle in addition to disease-related mortality.

# ERG's critique

## Model structure

- Appropriate cycle length and half-cycle correction.
- Modelling approach appropriate.
- Model structure an adequate representation of treatment pathway.



**Source**: ERG report, section 4.3.2 (pages 101-2)

## Company's evidence and ERG's critique
### Population

- Company's evidence:
  - Nivolumab: CheckMate 205 and CA209-039.
  - Standard of Care: Cheah 2016.
- ERG's comments:
  - Sample population in Cheah 2016 not a complete match with population of interest (only 36% patients refractory prior to BTX treatment).
  - However, the most appropriate available studies are used to inform comparisons.



**Source**: ERG report, section 4.3.3 (pages 103-4)

# Company's model
## Comparators

- Standard of Care assumed equivalent to treatments in Cheah 2016, with amendments to better reflect clinical practice and enable calculation of costs and utilities:
  - 'other' category excluded.
  - ASCT excluded.
  - 'investigational agents' excluded (included PD-1 inhibitors so likely to include nivolumab).
  - 'gemcitabine', 'other alkylator' and 'platinum-based' regimens pooled for proportion having chemotherapy.
- Composition of standard of care assumed to be:
  - Chemotherapy 58.1% (compositions based on equal usage of regimens specified by BCSH guidelines),
  - Bendamustine 27.9%,
  - BTX retreatment 14.0%.

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**Source**: Company submission, section 5.2.3 (pages 102-3)

# Company's model

## Treatment effectiveness

- Comparative data derived from unadjusted indirect comparison of nivolumab (pooled data from CheckMate 205 and CA209-039 [n=193]) with SOC (Cheah 2016 data [excluding investigational agents]; n=51])
- Patient level survival data extrapolated using parametric survival functions, validated by clinical experts and goodness-of-fit statistics
- Progression-free survival defined as investigator-assessed:
  - Reflects real world clinician behaviour
  - Offsets 'pseudo-progression' effect attributed to immunotherapeutic treatments (whereby tumour appears enlarged when assessed in initial stages of therapy)
  - Better reflects accrual of costs and benefits (differences in management plans and quality of life between patients considered to have progressed by the clinician and those considered not to have progressed)

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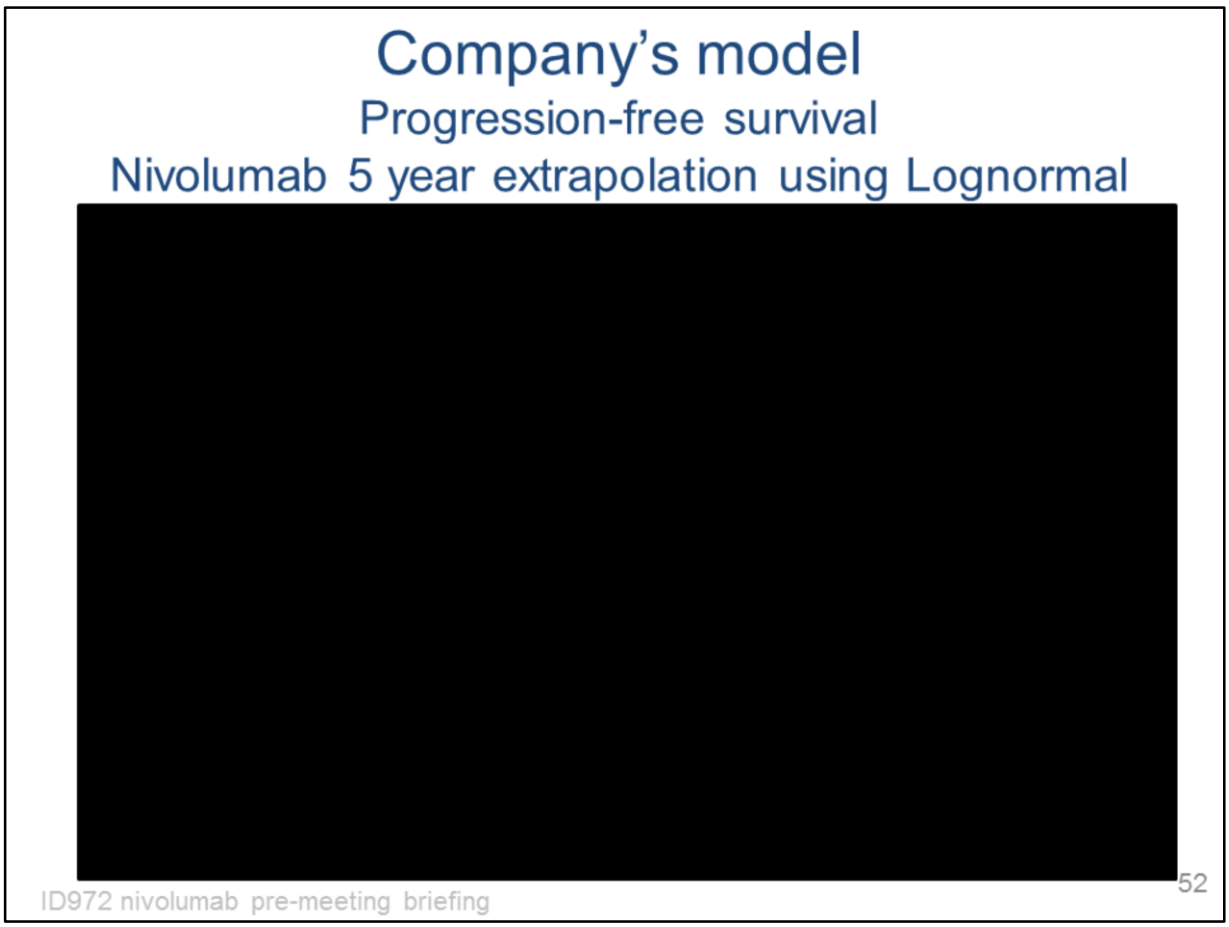
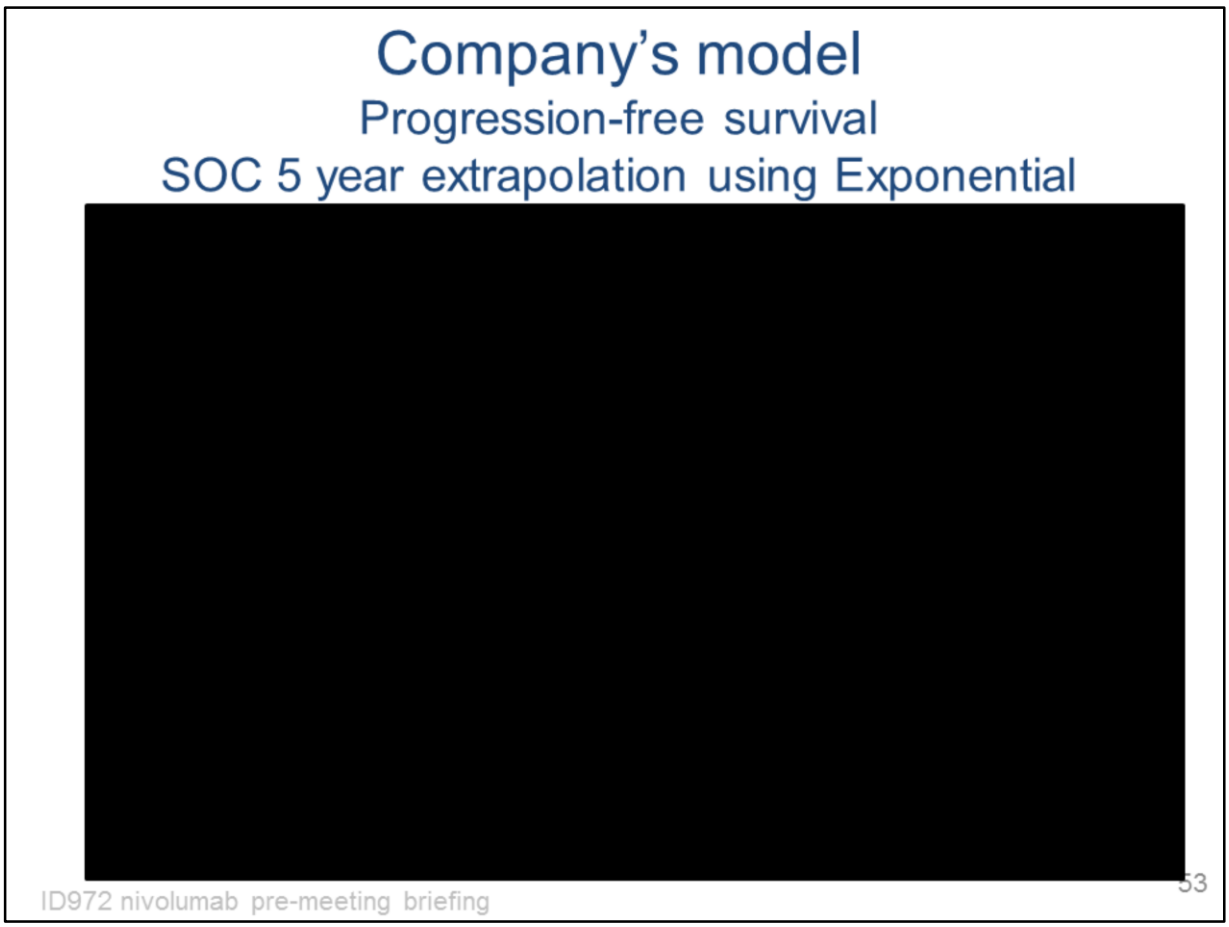
**Source**: Company submission, section 5.3.1 (pages 103-11), section 5.2.2.1 (page 99)



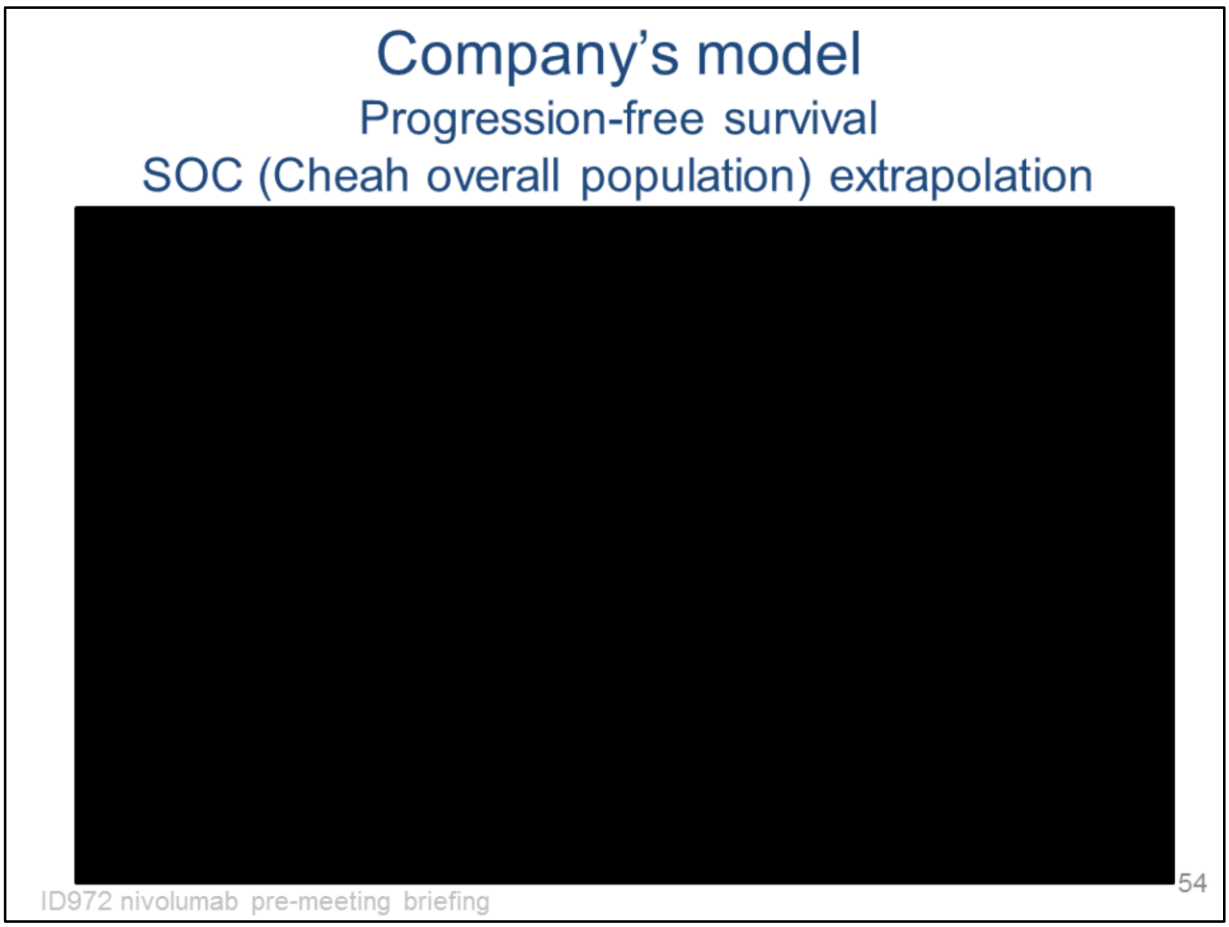

**Source**: Company submission, section 5.3.2, Figure 25 (page 106)

For longer term extrapolation, see the company submission, section 5.3.2, Figure 27 (page 107)

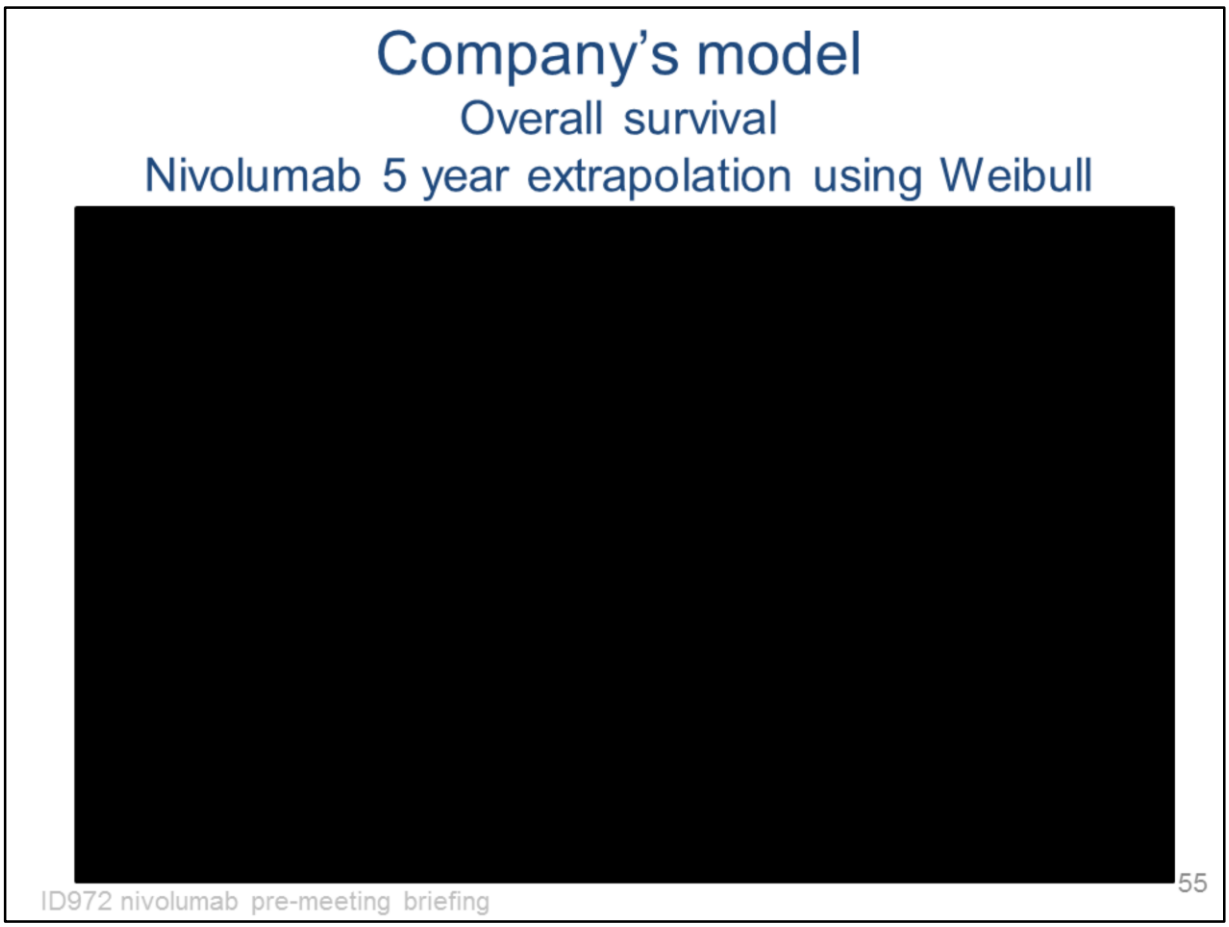



**Source**: Company submission, section 5.3.2, Figure 29 (page 109)

ERG: Choice of curve not sufficiently justified, company provided all curve fits at clarification, ERG concluded exponential correct **Source**: ERG report, section 4.3.5.1 (page 110)

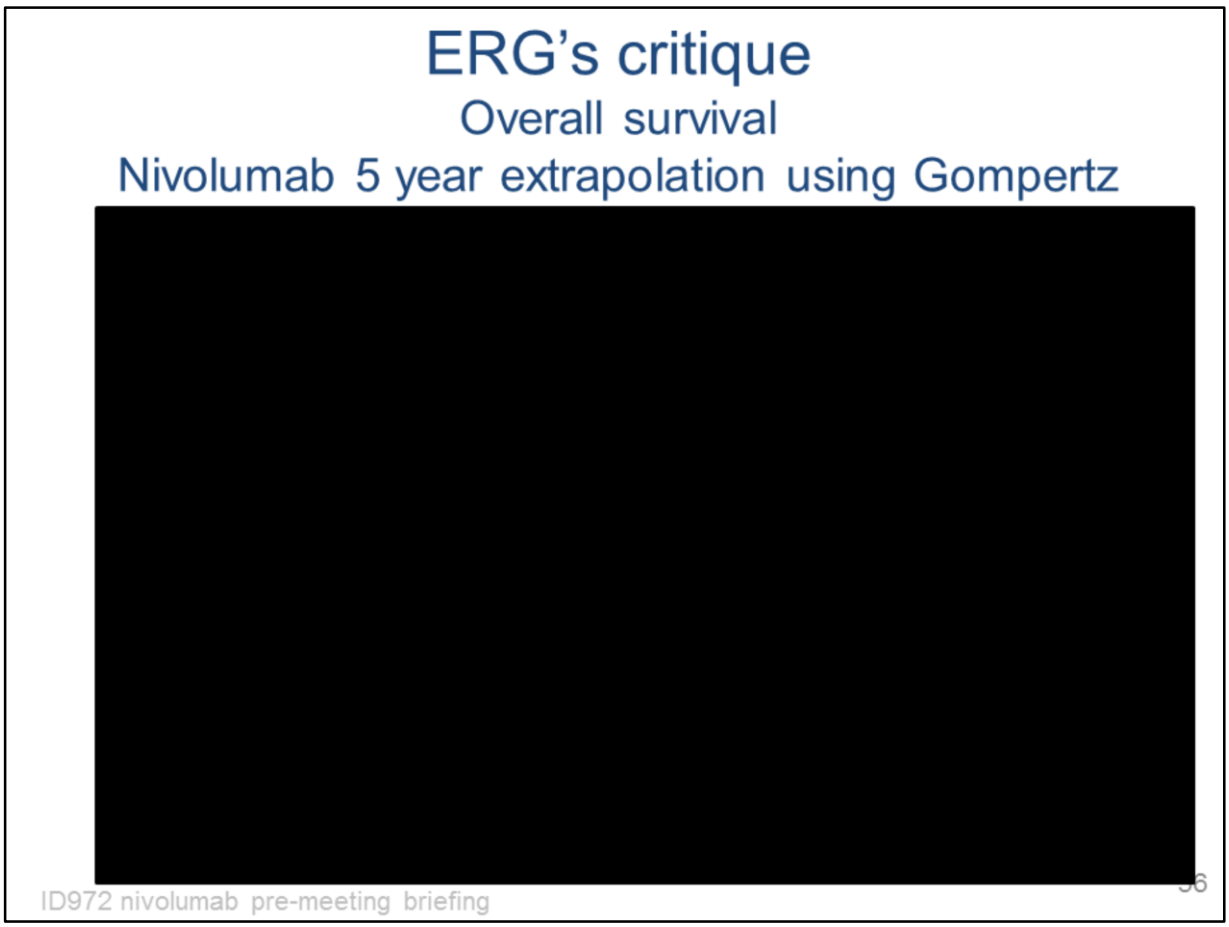



**Source**: Company clarification response, question B5 (page 22)




**Source**: Company submission, section 5.3.2, Figure 26 (page 107)

For longer term extrapolation, see the company submission, section 5.3.2, Figure 28 (page 108)

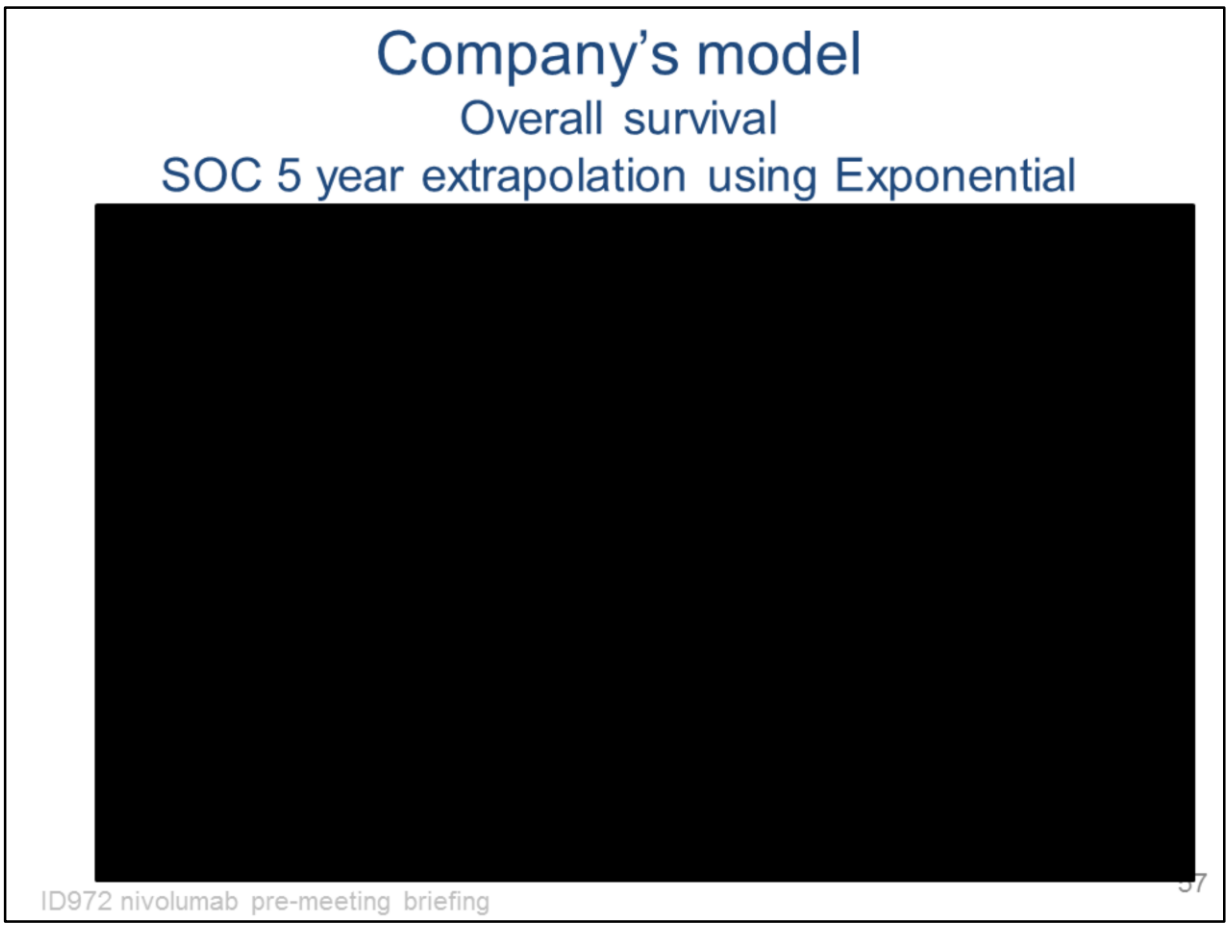



**Source**: ERG's addendum, Figure 4 (page 6)

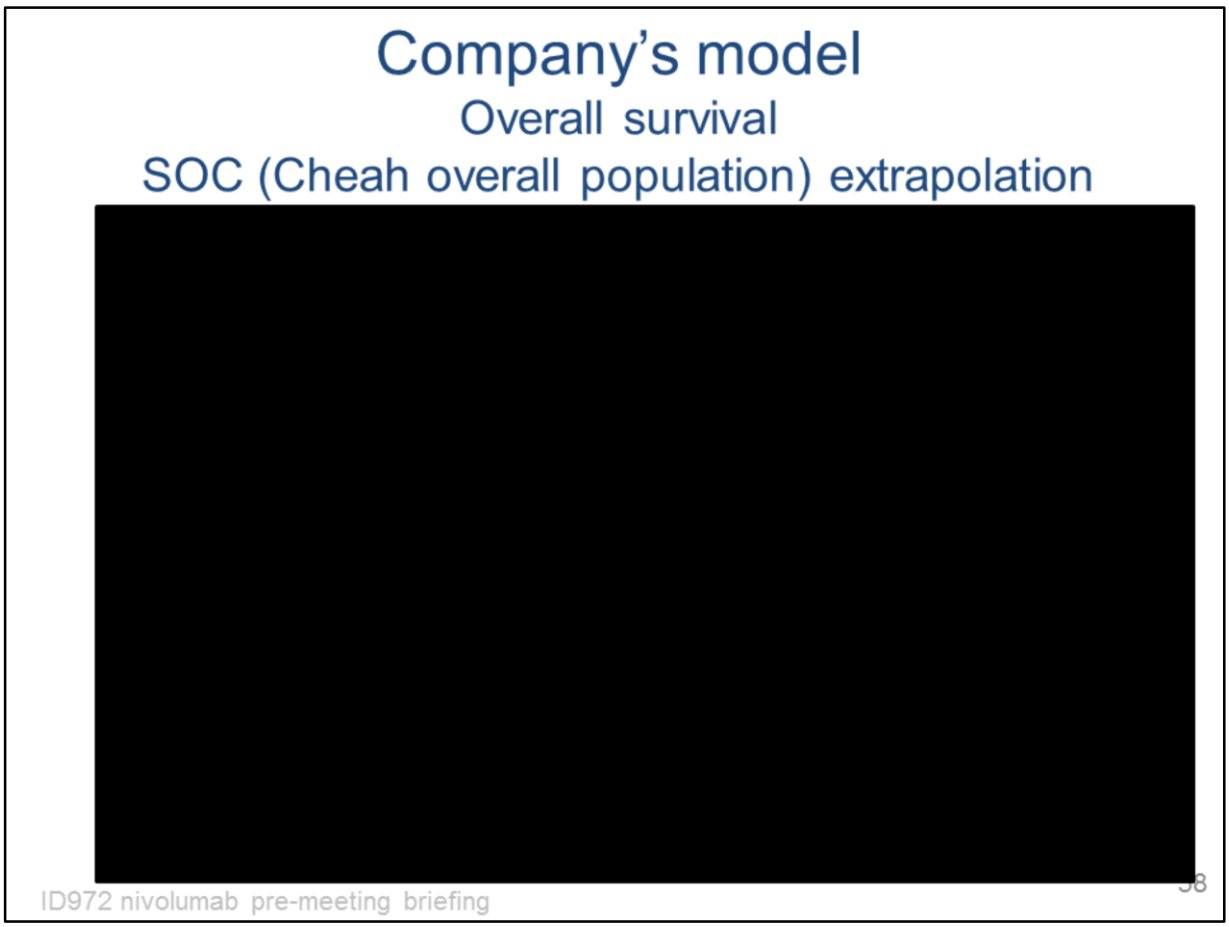
Additional analysis requested by committee lead team.

See Figure 3 (page 6) to see nivolumab OS hazard over time for Gompertz curve

The ERG did not conduct analyses using Gompertz curve for SOC as this would have improved survival for SOC, which their clinical experts did not find plausible.




**Source**: Company submission, section 5.3.2, Figure 30 (page 111)




**Source**: Company clarification response, question B5 (page 23)

# Company's model

## Response rates

| Treatment | Complete response | | Partial response | |
|---|---|---|---|---|
| | Value | Standard error | Value | Standard error |
| **Nivolumab** | [redacted] | [redacted] | [redacted] | [redacted] |
| **SOC** | 15.7% | 5.09 | 23% | 5.94 |

- Investigator-assessed.
- No direct impact on progression or survival (considered implicitly incorporated).
- Utility valued stratified by response not applied in base case because of low patient numbers, but used in scenario analysis

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**Source**: Company submission, section 5.3.3.1, Table 43 (pages 112-3)

# Company's model

## Treatment discontinuation

- Patients discontinued treatment because of:
  - Progression (as per PFS extrapolated data).
  - Median or recommended duration of treatment (SOC only).
  - Other reasons.
- Rates of 'treatment discontinuation because of other reasons' obtained from patient-level data from CheckMate 205 and CA209-039, extrapolated to longer term using lognormal parametric curve.
- Same rate of treatment discontinuation because of other reasons applied to SOC



**Source**: Company submission, section 5.3.3.2 (page 113)

# Company's model

## Adverse events

| Weighted monthly rate | Nivolumab | SOC |
|---|---|---|
| Anaemia | [redacted] | 8.2% |
| Diarrhoea | [redacted] | 0.5% |
| Dyspnoea | [redacted] | 0.1% |
| Fatigue | [redacted] | 0.6% |
| Leukopenia | [redacted] | 13.6% |
| Nausea | [redacted] | 2.0% |
| Neutropenia | [redacted] | 14.2% |
| Pyrexia | [redacted] | 0.3% |
| Thrombocytopenia | [redacted] | 16.8% |
| Vomiting | [redacted] | 2.3% |

- Treatment-related adverse events (grade 3-4)
- Nivolumab: pooled CheckMate 205 and CA209-039 data
- SOC: studies cited in BCSH guidelines
- Converted into monthly rate
- Applied to costs and benefits

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**Source**: Company submission, section 5.3.3.3 (page 113-18); ERG report, section 4.3.5.4, Table 36 (page 116)

# ERG's critique
## Clinical parameters

- Survival data
  - Cheah 2016 overall population should have been used (authors confirmed only 2 of those receiving investigational agents had received PD-1 inhibitors).
  - On balance, survival models used in base case were the most appropriate extrapolation choices.
- All cause mortality
  - Company acknowledged double counting but stated this only occurs in first few years (due to low baseline age), and effect applied equally to all comparators. ERG agreed unlikely to have significant impact on cost-effectiveness results.
- AlloSCT
  - Benefits captured as nivolumab and Cheah 2016 studies included small proportion of patients who received alloSCT.



**Source**: ERG report, section 4.3.5 (page 117), section 4.3.5.1 (page 109), section 4.3.5.5 (page 116), section 4.3.5.6 (page 117)

# Company's model

## Health state utility values

| Company's values | Nivolumab | Standard of care |
|---|---|---|
| Pre-progression | [redacted] | 0.76 |
| Post-progression | [redacted] | 0.38 |

- Nivolumab values obtained from EQ-5D data from CheckMate 205 Cohort B, converted to utility values using UK EQ-5D-3L tariff and stratified by progression status (investigator-assessed) and timing of progression.
- SOC values obtained from Swinburn 2015 paper, weighted by response rates in Cheah 2016.
- Age-dependent utility decrements applied (based on estimated health utility of the general UK population).
- Disutilities associated with grade 3-4 treatment-related adverse events applied as one off disutility in monthly cycle (sourced from NICE TA306).

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**Source**: Company submission, section 5.4.1 – 5.4.5 (pages 119-23)

Swinburn 2015: Swinburn P, Shingler S, Acaster S, et al. Health utilities in relation to treatment response and adverse events in relapsed/refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma. Leuk Lymphoma. 2015;56(6):1839-45.

Swinburn and colleagues reported utility values for patients with relapsed and refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma elicited from members of the public in several countries (including the 100 people from the UK) using the time trade off method. The study reported utility values for the pre-progression and post-progression health states.

TA306: Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma, published February 2014

# ERG's critique

## Heath state utility values

| ERG's values | Nivolumab | Standard of care |
|---|---|---|
| Pre-progression | [redacted] | [redacted] |
| Post-progression | [redacted] | [redacted] |

**Pre-progression utility**

- Utility values for complete response in nivolumab patients was slightly lower than Swinburn 2015, while those for partial response and stable disease were slightly higher.
- Therefore a more consistent approach would be to use response-specific utility values from CheckMate 205 data, and estimate values for SOC by applying them to SOC treatment response proportions.

**Post-progression utility**

- Company's rationale for significant difference between nivolumab and SOC arms, that post-progression benefit of nivolumab was because of its unique mechanism of action, was not considered plausible
- Ramsey 2016 paper shows higher utility values for placebo, suggesting Swinburn 2015 may be an outlier (also TTO method; may be inconsistent with EQ-5D)
- ERG's preferred approach to use same values for nivolumab and SOC

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**Source**: ERG report, section 4.3.6 (pages 119-20)

Ramsey 2016: Ramsey SD, Nademanee A, Masszi T, Holowiecki J, Abidi M, Chen A, et al. Quality of life results from a phase 3 study of brentuximab vedotin consolidation following autologous haematopoietic stem cell transplant for persons with Hodgkin lymphoma. *Br J Haematol* 2016.

Ramsey and colleagues reported EQ-5D values for patients with relapsed or refractory Hodgkin lymphoma post-ASCT for patients receiving brentuximab vedotin vs. placebo. The study shows utility values for progressed disease for the placebo group to be between 0.85 (after 3 months) to 0.7 (after 24 months).

# Company's model

## Resource use and costs – nivolumab

| Nivolumab acquisition costs | | | | |
|---|---|---|---|---|
| Dose: 3 mg/kg every 2 weeks | Dose per cycle | Cost (4ml vial) | Cost (10ml vial) | Cost per cycle |
| | | (each ml concentrate contains 10mg nivolumab) | | |
| | 240 mg | [redacted] | [redacted] | [redacted] |
| *Assumes remainder of vial is wasted | | | | |

| Nivolumab administration costs | |
|---|---|
| Initial – deliver complex chemotherapy including prolonged infusional treatment | Subsequent elements of chemotherapy cycle |
| £389.41 | £326.46 |
| *Source: NHS reference costs 2014-15* | |

| TOTAL COSTS PER CYCLE | |
|---|---|
| Initial | Subsequent |
| [redacted] | [redacted] |



**Source**: Company submission, section 5.5.2.1 (page 127)

# Company's model

## Resource use and costs – SOC

| | Nivolumab monthly costs | SOC Company's base case | SOC ERG's estimate |
|---|---|---|---|
| Month 1 | [redacted] | £4,729.43 | £3710.21 |
| Month 2 | [redacted] | £4,141.92 | £3204.80 |
| Month 3 | [redacted] | £3,037.50 | £2652.61 |
| Month 4 | [redacted] | £2,251.40 | £2251.40 |
| Month 5 | [redacted] | £2,218.97 | £2218.97 |
| Month 6 | [redacted] | £1,913.31 | £1913.32 |
| Month 7 | [redacted] | £331.52 | £331.52 |
| Month 8+ | [redacted] | £0.00 | £0 |

Based on costs for each component:

- Chemotherapy (assumed equal usage of all regimens specified in BCSH guidelines)
- BTX retreatment
- Bendamustine

Converted to monthly costs; weighted average based on Cheah 2016 usage

**ERG's estimate**: Excludes Mini-BEAM and DexaBEAM because of clinical advice that not commonly used

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**Source**: Company submission, section 5.5.2.2 (page 126-8), ERG report, section 4.3.7 (page 122-3)

# Company's model

## Resource use and costs – subsequent therapy

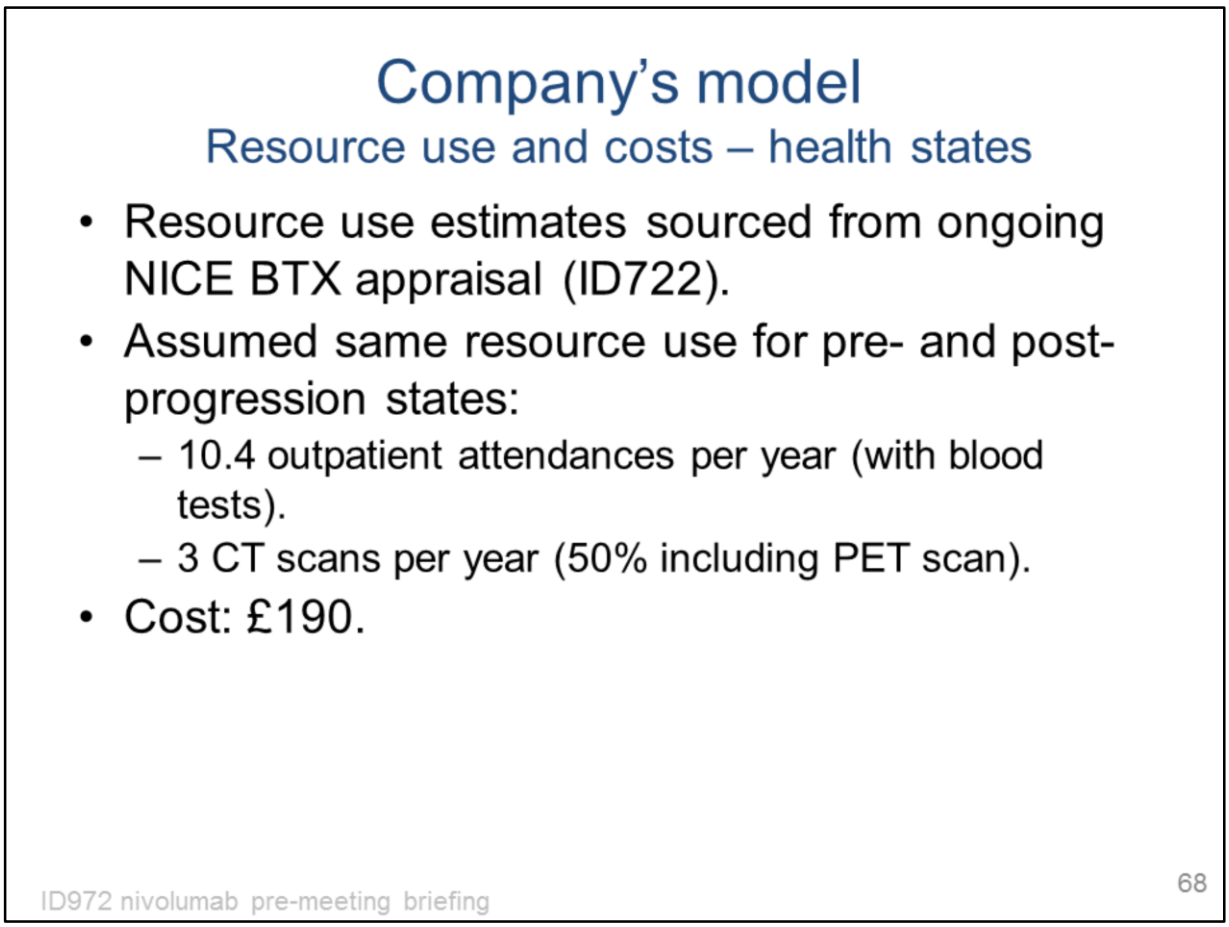
| | Pre-progression | Post-progression |
|---|---|---|
| Total cost | £4,161.26 | £4,544.94 |

- Subsequent therapy was best supportive care in the base case.
- Assumed to comprise chemotherapy and palliative care.
- Resource use and costs source from NICE TA306
- Applied as one-off cost on advent of treatment discontinuation.



**Source**: Company submission, section 5.5.2.3 (page 131)

TA306: Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma, published February 2014




**Source**: Company submission, sections 5.5.3.1, 5.5.3.2 (page 132)

NICE appraisal ID722 brentuximab vedotin for treating CD30-positive Hodgkin's lymphoma

TA306: Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma, published February 2014

TA251: Dasatinib, nilotinib and imatinib for chronic myeloid leukaemia, published April 2012

# Company's model

## Resource use and costs – adverse events

| Adverse event | Costs | Source |
|---|---|---|
| Anaemia | £205.50 | NICE TA306 |
| Diarrhoea | £0 | Assumption |
| Dyspnoea | £841.06 | NICE TA306 |
| Fatigue | £88.98 | NICE TA306 |
| Leukopenia | £1,723.21 | NICE TA306 |
| Nausea | £591.07 | NICE TA306 |
| Neutropenia | £779.62 | NICE TA306 |
| Pyrexia | £1,454.38 | NICE TA306 |
| Thrombocytopenia | £156.90 | NICE TA251 |
| Vomiting | £591.07 | NICE TA306 |

Inflated to 2014-5 costs

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**Source**: Company submission, section 5.5.4 (page 133)

# ERG's critique

## Resource use and costs

- Costs of alloSCT should be included in the base case analysis because patients in both nivolumab and SOC arms received alloSCT (and therefore benefits captured).
- Company's scenario analysis including alloSCT treatment underestimates costs (see later slide).
- Proportion of patients receiving alloSCT is underestimated compared to observed alloSCT procedures in the studies.



**Source**: ERG report, section 4.3.7 (page 125), 4.3.8 (pages 125-8)

## Company's base case (with PAS)

| Treatment | Total | | Incremental | | ICER per QALY gained |
|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | |
| **Standard of Care** | £21,090 | 0.932 | | | |
| **Nivolumab** | [redacted] | [redacted] | [redacted] | [redacted] | **£19,882** |

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**Source**: Company submission, section 5.7, table 63 (page 137)

# Company's sensitivity analyses

## Probabilistic and deterministic (with PAS)

| Probability of cost-effectiveness of nivolumab compared with SOC | Maximum acceptable ICER (cost/QALY) | |
|---|---|---|
| | £30,000/QALY | £50,000/QALY |
| Applying 10% standard error | 94.8% | 100% |
| Applying 20% standard error | 96.6% | 100% |

Deterministic sensitivity analyses showed that the most influential factors included health state utilities, therapy costs, rate of discounting and time horizon In all scenarios, ICER remained below £30,000 per QALY gained.

ERG's comments:

One-way sensitivity analysis

- ICER of nivolumab appears robust to alternative parameter assumptions
- Choice of parameters adequate.

Probabilistic sensitivity analysis

- Distributions chosen and assumptions reasonable
- Simulation with 20% uncertainty more realistic, but given paucity of data even larger estimates of uncertainty may be appropriate.



**Source**: Company submission, section 5.8.1.1 (page 142), section 5.8.2.1 (page 144); ERG report, section 4.3.10 (page 130), section 4.3.10.3 (pages 149-50)

# Company's scenario analyses (1)
## (with PAS)

| Scenario | | ICER/QALY gained | n |
|---|---|---|---|
| Alternative parametric fittings | Nivolumab (OS and PFS) | £10,718 - £20,132 | 16 |
| | SOC (OS) | £18,6013 - £22,742 | 2 |
| | Nivolumab applying KM data over trial period (OS and PFS) | £19,994 | 1 |
| | No half cycle correction | £19,730 | 1 |
| Alternative treatment sequences | Allogeneic stem cell therapy | £18,479 - £20,489 | 4 |
| | Subsequent chemotherapy | £22,095 | 1 |
| Alternative comparator composition | Cheah 2016 overall population | £22,855 | 1 |
| | Best supportive care | £21,580 | 1 |
| | Ongoing BTX TA | £12,452 | 1 |
| ITC-derived comparator efficacy | | £20,885 - £24,381 | 18 |
| Alternative baseline age | Older cohort | £22,226 | 1 |
| | Younger cohort | £16,037 | 1 |

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**Source**: Company submission, section 5.8.3 (pages 147-64)

Alternative parametric fittings: section 5.8.3.1 (page 147-51)

Alternative treatment sequences: section 5.8.3.2 (pages 152-7)

Alternative comparator composition: section 5.8.3.3 (pages 157-62)

Alternative baseline age: section 5.8.3.4 (pages 163-4)

# Company's scenario analyses (2)
## (with PAS)

| Scenario | | ICER/QALY gained | n |
|---|---|---|---|
| Alternative assumptions around treatment duration | Stopping rule (CR) | £17,436 | 1 |
| | Stopping rule (CR + PR) | £13,632 | 1 |
| | Post-progression treatment | £16,186 | 1 |
| | No discontinuation | £29,573 | 1 |
| Alternative assumptions around utilities | Comparator post-progression utility equal to nivolumab | £24,983 | 1 |
| | Nivolumab post-progression utility equal to comparator | £33,167 | 1 |
| | Swinburn 2015 for pre- and post-progression utility in both arms | £34,332 | 1 |
| | Response-specific pre-progression utilities | £19,930 | 1 |
| Alternative post-progression costs | | £21,218 | 1 |
| IRRC-assessed endpoint data (for nivolumab) | | £17,617 | 1 |
| TOTAL SCENARIO ANALYSES | | | 58 |

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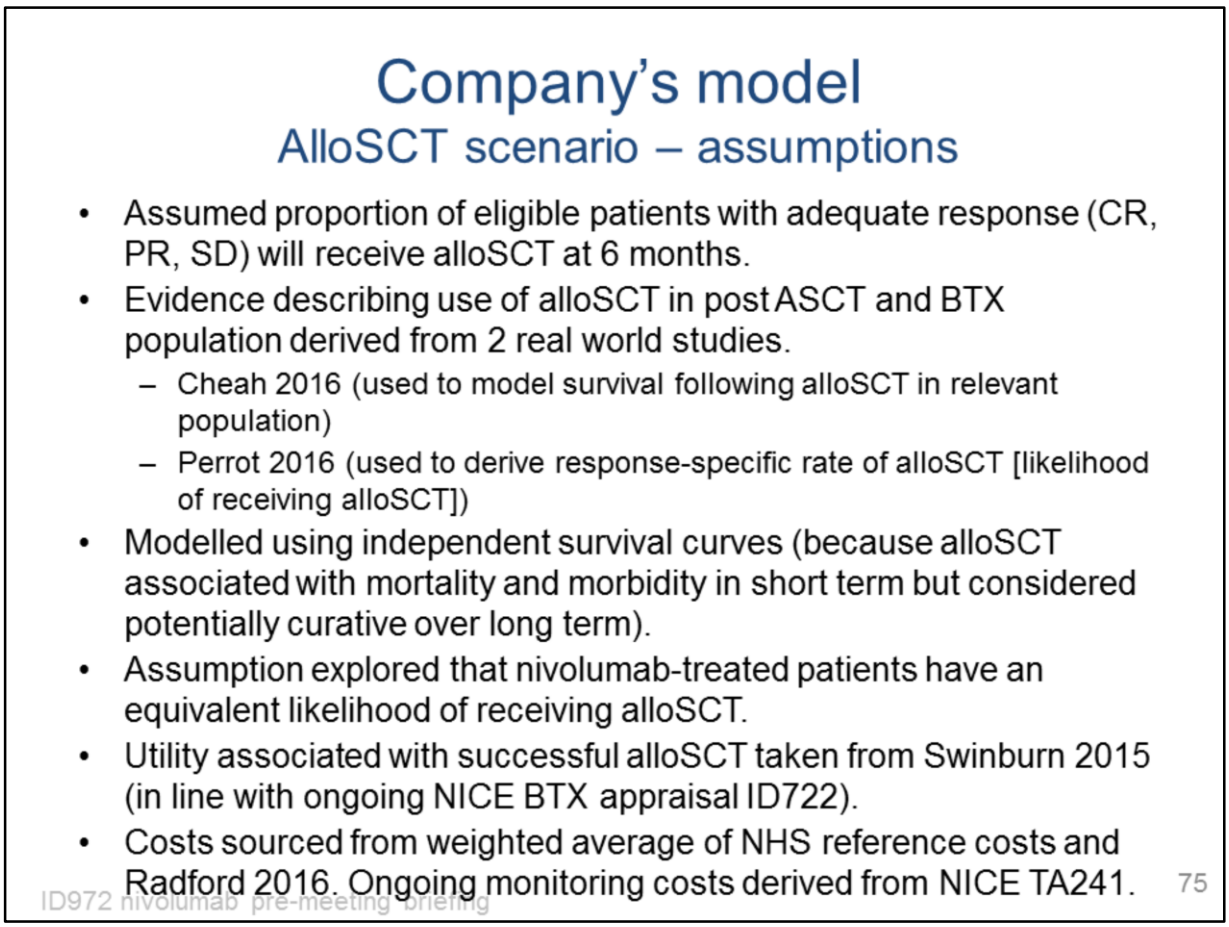
**Source**: Company submission, section 5.8.3 (pages 163-8)

Alternative assumptions around treatment duration: section 5.8.3.5 (pages 164-5)

Alternative assumptions around utilities: section 5.8.3.6 (pages 165-6)

Alternative post-progression costs: section 5.3.3.8 (pages 166-7)

Application of IRRC-assessed endpoints for nivolumab: section 5.8.3.9 (pages167-8)




**Source**: Company submission, section 5.8.3.2 (pages 152-4)

NICE appraisal ID722 brentuximab vedotin for treating CD30-positive Hodgkin's lymphoma

Perrot 2016: Perrot A, Monjanel H, Bouabdallah R, et al. Impact of post-brentuximab vedotin consolidation on relapsed/refractory CD30+ Hodgkin lymphomas: a large retrospective study on 240 patients enrolled in the French Named-Patient Program. Haematologica. 2016;101(4):466-73.
Study assessed outcomes in patients with HL who had previously received ASCT, followed by BTX consolidation treatment. Does not match population of interest and was conducted in France, but provides an indication of proportion of patients who would receive alloSCT in UK clinical practice.

Radford 2016: Radford J, Johnson R, McKay P, et al. Treatment pathways and resource use associated with the management of recurrent Hodgkin lymphoma after autologous stem cell transplantation. Haematologica. 2013.
Conducted a retrospective analysis on resource use in 5 centres for patients with relapsed or refractory Hodgkin lymphoma post-ASCT.

TA241: Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML) (part review of NICE technology appraisal guidance 70), and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance, published January 2012

# Company's model

## AlloSCT scenario – results

| | Total | | Incremental | | ICER per QALY gained |
|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | |
| 1) Perrot likelihood; NHS reference costs | | | | | |
| SOC | £22,866 | 1.076 | | | |
| Nivolumab | [redacted] | [redacted] | [redacted] | [redacted] | **£18,587** |
| 2) Perrot likelihood; Radford costs | | | | | |
| SOC | £24,880 | 1.076 | | | |
| Nivolumab | [redacted] | [redacted] | [redacted] | [redacted] | **£20,433** |
| 3) Perrot likelihood; Nivolumab equivalent; NHS reference costs | | | | | |
| SOC | £22,866 | 1.076 | | | |
| Nivolumab | [redacted] | [redacted] | [redacted] | [redacted] | **£18,479** |
| 4) Perrot likelihood; Nivolumab equivalent; Radford costs | | | | | |
| SOC | £24,880 | 1.076 | | | |
| Nivolumab | [redacted] | [redacted] | [redacted] | [redacted] | **£20,489** |

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**Source**: Company submission, section 5.8.3.2 (page 154), adapted from Table 76

# ERG's critique
## AlloSCT scenario

- Perrot 2016 underestimates proportion receiving alloSCT – estimated proportion does not match that observed in trials:

| Source | Observed proportion receiving alloSCT | Predicted proportion receiving alloSCT (Perrot) |
|---|---|---|
| Nivolumab trials | [redacted] | [redacted] |
| Cheah 2016 (SOC) | 17.72% | [redacted] |

- Modelled survival from Cheah 2016 included s 14 patients already included in overall survival data for SOC, who are therefore double counted
- Post-progression utility should be similar across all interventions
- Radford 2016 costs should be used to be consistent with ongoing NICE BTX appraisal ID722

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**Source**: ERG report, section 4.3.8 (pages 126-7), section 4.4 (page 153)

NICE appraisal ID722 brentuximab vedotin for treating CD30-positive Hodgkin's lymphoma

# ERG's base case

## Assumptions

| | Company's base case | ERG's base case |
|---|---|---|
| AlloSCT | Scenario analysis | Included in base case |
| AlloSCT rates | N/A | Derived from trials rather than Perrot 2016 predictions |
| SOC survival data Cheah 2016 | Population excluding investigational agents | Overall population |
| Pre-progression utilities (nivolumab) | CheckMate 205 non-response-specific | CheckMate 205 response-specific |
| Pre-progression utilities (SOC) | Swinburn 2015 | CheckMate 205 utilities weighted by response |
| Post-progression utilities | Swinburn 2015 for SOC | CheckMate 205 utilities for all interventions |
| alloSCT survival modelling | N/A | Original treatment OS curves instead of lognormal |
| SOC costs – miniBEAM, dexaBEAM | Included | Excluded |

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**Source**: ERG report, section 4.4 (pages 154-6), Table 65

# ERG's base case (with PAS)

| Treatment | Total | | Incremental | | ICER per QALY gained |
|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | |
| **Standard of Care** | £23,043 | 2.102 | | | |
| **Nivolumab** | [redacted] | [redacted] | [redacted] | [redacted] | **£36,525** |

Additional sensitivity and scenario analyses resulted in all ICERs below £50,000 per QALY gained, but several above £30,000 per QALY gained.

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**Source**: ERG report, section 4.4 (pages 158-9), Table 67

# ERG's base case (with PAS)

## Disaggregated

| Assumption | ICER per QALY |
|---|---|
| AlloSCT rates derived from trials | £20,616 |
| SOC survival data; using overall population from Cheah | £22,348 |
| Nivolumab overall survival data; using Gompertz | £122,825 |
| Pre-progression utilities (nivolumab) CheckMate 205 response-specific | £20,476 |
| Pre-progression utilities (SOC) CheckMate 205 utilities weighted by response | £20,603 |
| Post-progression utilities the same across all interventions | £25,209 |
| alloSCT survival modelling; using original OS treatment curves | £21,517 |
| Post-progression utility for alloSCT; the same across all interventions | £18,174 |
| SOC costs – miniBEAM, dexaBEAM excluded | £20,950 |



**Source**: ERG report, section 4.4, Table 67 (page 158)

# End of life

| Criterion | Data | ERG comments |
|---|---|---|
| Short life expectancy, normally less than 24 months | Cheah 2016 shows median overall survival ~2 years, which decreases to ~19 months when efficacy of investigational agents removed<br><br>Investigational agents do not reflect current practice, and including them may present an equality issue, as patients treated at smaller hospitals are unlikely to receive them | Mean life years (in model) is 2.3 years (excluding investigational agents) Consider overall population should be used where overall survival is 2.9 years |
| Extension to life, normally of at least 3 months, compared with current NHS treatment | CheckMate 205 and CA209-039 show nivolumab likely to increase overall survival to exceeding 42.9 months (median overall survival not reached in studies) | Agree likely to extend life expectancy by at least 3 months |

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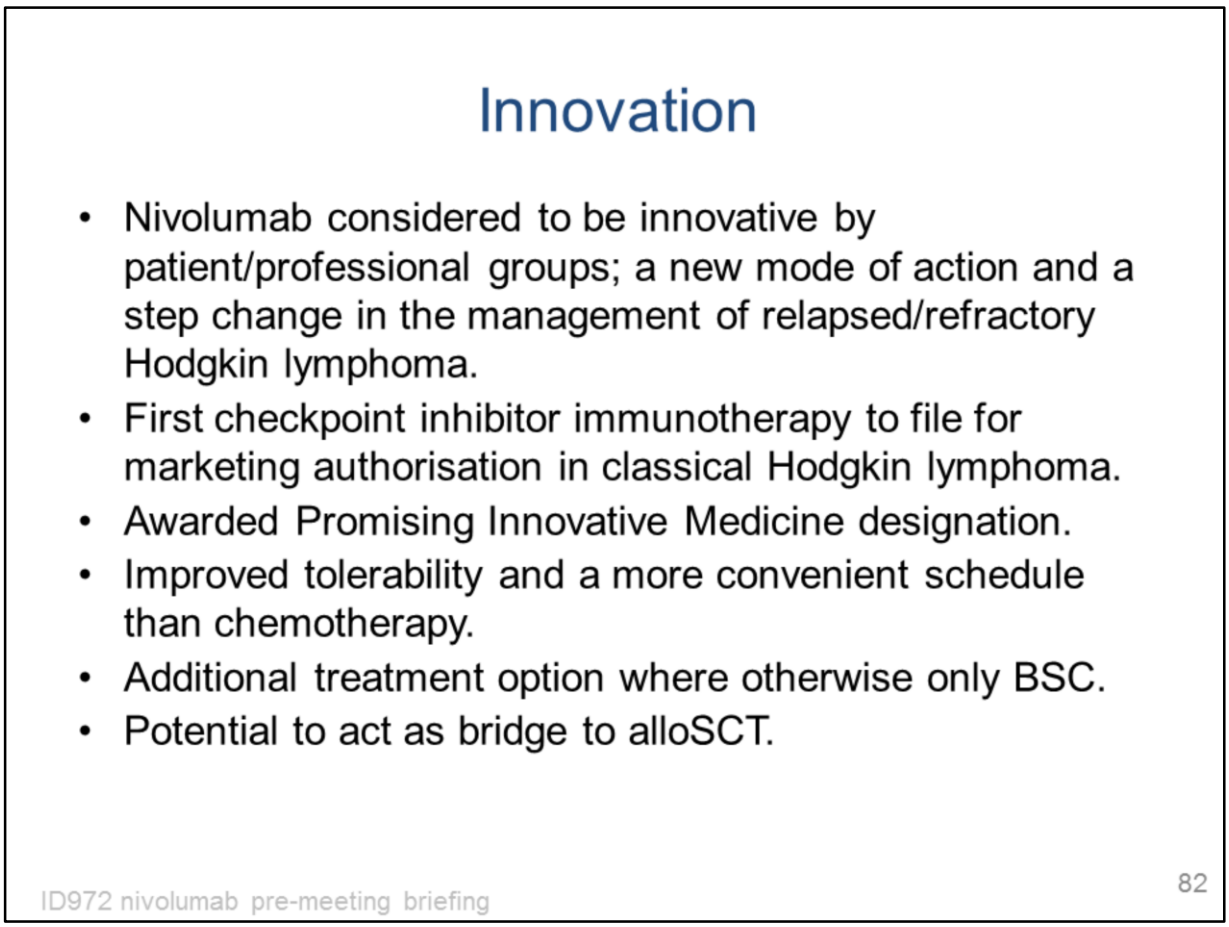
**Source**: Company submission, section 5.11 (pages 171-2); ERG report, section 5 (pages 161-2)




**Source**: Lymphoma Association (endorsed by Leukaemia CARE), Company submission, section 2.5 (pages 26-27)

Company scenario analysis explores assumption of allogeneic stem cell transplant following nivolumab, but limitations in the data may mean this benefit is not fully captured.

Company also suggest that the peak incidence of disease in people aged 20-24 means that nivolumab as a bridge to allogeneic stem cell transplant could provide significant economic and societal benefits that are not captured in the model.

Early access to medicines scheme (EAMS) granted 03 November 2016; expired 21 November 2016 https://www.gov.uk/government/publications/early-access-to-medicines-scheme-expired-scientific-opinions/expired-early-access-to-medicines-scheme-scientific-opinions#nivolumab-to-treat-a-type-of-cancer-of-the-lymph-system

## Equality considerations

- As a result of existing comorbidities, fewer patients aged 75-79 will have undergone salvage chemotherapy and ASCT. Patients in this group likely to have few, if any, treatment options. High unmet need for these patients (incidence peak at this age), an effective therapy that is well tolerated would be helpful. Little evidence for patients in this age category.
- Patients aged 20-24 years have a greater range of treatment options but onset of HL in this population restricts ability to study, work or participate in family life.
- No issues raised by ERG.



**Source**: Company submission, section 3.3 (page 32)

# Authors

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- with input from the Lead Team (Nigel Langford, Stephen O'Brien, Judith Wardle)

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal

## Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma

## Final scope

### Final remit/appraisal objective

To appraise the clinical and cost effectiveness of nivolumab within its marketing authorisation for treating relapsed or refractory classical Hodgkin lymphoma.

### Background

Hodgkin's lymphoma is a cancer of the lymphatic system. It can be classified into 2 main groups; the classical types, and the nodular lymphocyte predominant type. Classical Hodgkin lymphomas contain the Reed-Sternberg cells (which are cancerous B lymphocyte cells), whereas the nodular lymphocyte predominant type contains other abnormal cells, but not Reed-Sternberg cells. The initial symptom of Hodgkin lymphoma is often swelling of lymph nodes in the neck, armpit or groin. Other symptoms include recurring fever, night sweats, weight loss, cough, breathlessness, abdominal pain, and itching.

Hodgkin lymphoma accounts for around 20% of all diagnosed lymphomas. In England, there were 1634 people diagnosed with Hodgkin lymphoma in 2013[1] and 256 registered deaths from Hodgkin lymphoma in 2012.[2] The age-specific incidence of Hodgkin lymphoma shows two peaks, one in people aged 20–24 years and the second in people aged over 75 years.[1]

Current first-line treatment for Hodgkin lymphoma is chemotherapy alone or chemotherapy combined with radiotherapy. Between 15 and 30% of people with Hodgkin lymphoma do not achieve long-term remission with these therapies.[3] For these people, high-dose chemotherapy followed by autologous stem cell transplant is a potentially curative treatment that is effective in about 50% of people.[3] However, autologous stem cell transplant may not be an option in some circumstances; for example, when the disease is refractory to chemotherapy, or when the person's age or co-morbidities prohibit this intervention.

Brentuximab vedotin is indicated for relapsed or refractory CD30+ Hodgkin lymphoma (CD30 is an integral membrane antigen expressed by some tumours):

- after autologous stem cell transplant, or

- after at least 2 prior therapies when autologous stem cell transplant or multi-agent chemotherapy is not a treatment option (NICE guidance is in development, funded by the Cancer Drugs Fund in the interim).

There is no standard therapy administered after autologous stem cell transplant and brentuximab vedotin. The aim of treatment is generally to attain a sufficient response for allogeneic stem cell transplant. For people in whom allogeneic stem cell transplant is not considered suitable, therapy depends on individual circumstances, and may include chemotherapy such as gemcitabine or bendamustine, or best supportive care. Some chemotherapy regimens are used outside their marketing authorisation.

### The technology

Nivolumab (Opdivo, Bristol–Myers Squibb) is a monoclonal antibody that targets a receptor on the surface of lymphocytes known as PD-1. This receptor is part of the immune checkpoint pathway, and blocking its activity may promote an anti-tumour immune response. Nivolumab is given intravenously.

Nivolumab does not currently have a marketing authorisation in the UK for classical Hodgkin Lymphoma. It has been studied in a non-comparative clinical trial alone in adults with previously treated classical Hodgkin lymphoma.

| | |
|---|---|
| **Intervention(s)** | Nivolumab |
| **Population(s)** | • People with relapsed or refractory classical Hodgkin lymphoma following autologous stem cell transplant and brentuximab vedotin.<br>• People with relapsed or refractory classical Hodgkin lymphoma following at least 2 prior therapies when autologous stem cell transplant is not a treatment option. |

| | |
|---|---|
| **Comparators** | For people with relapsed or refractory classical Hodgkin lymphoma following autologous stem cell transplant and brentuximab vedotin:<br>• Established clinical management without nivolumab including chemotherapy such as gemcitabine or bendamustine<br>• Best supportive care<br>For people with relapsed or refractory classical Hodgkin lymphoma following at least 2 prior therapies when autologous stem cell transplant is not a treatment option:<br>• Brentuximab vedotin (NICE guidance is in development, funded by the CDF in the interim)<br>• Best supportive care |
| **Outcomes** | The outcome measures to be considered include:<br>• overall survival<br>• progression-free survival<br>• response rates<br>• adverse effects of treatment<br>• health-related quality of life. |
| **Economic analysis** | The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.<br>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.<br>Costs will be considered from an NHS and Personal Social Services perspective. |

| | |
|---|---|
| **Other considerations** | If the evidence allows, a scenario analysis including allogeneic stem cell transplant as a subsequent treatment after nivolumab or its comparators will be considered. This should reflect the proportion of people who proceed to allogeneic stem cell transplant after each treatment, as well as the costs and quality-adjusted life year benefits of the procedure.<br><br>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. |
| **Related NICE recommendations and NICE Pathways** | Appraisals in development (including suspended appraisals)<br><br>'Brentuximab vedotin for treating CD30-positive Hodgkin lymphoma' NICE technology appraisals guidance [ID722]. Publication expected January 2017.<br><br>Related Guidelines:<br><br>'Improving outcomes in haemato-oncology cancers' (2003). Cancer Service Guidance<br><br>http://www.nice.org.uk/nicemedia/live/10891/28786/28786.pdf |
| **Related National Policy** | Department of Health, NHS Outcomes Framework 2015-2016, Dec 2014. Domains 1 and 2. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/385749/NHS_Outcomes_Framework.pdf<br><br>NHS England, National Cancer Drugs Fund List, February 2016. https://www.england.nhs.uk/wp-content/uploads/2016/02/ncdf-list-01-02-16.pdf |

## References

1 Cancer Research UK (2013) Hodgkin lymphoma incidence statistics. Accessed May 2016.

2 Cancer Research UK (2013) Hodgkin lymphoma mortality statistics. Accessed May 2016.

3 National Institute for Health and Clinical Excellence (2015) Brentuximab vedotin for treating CD30-positive Hodgkin's lymphoma [ID722]. Final scope. Accessed May 2016.

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

## Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma [ID972]

## Matrix of consultees and commentators

| **Consultees** | **Commentators (no right to submit or appeal)** |
|---|---|
| Company<br>• Bristol–Myers Squibb (nivolumab)<br><br>Patient/carer groups<br>• African Caribbean Leukaemia Trust (ACLT)<br>• Anthony Nolan<br>• Black Health Agency<br>• Bloodwise<br>• Cancer Black Care<br>• Cancer Equality<br>• Cancer52<br>• Delete Blood Cancer<br>• HAWC<br>• Helen Rollason Cancer Charity<br>• Independent Cancer Patients Voice<br>• Leukaemia Cancer Society<br>• Leukaemia CARE<br>• Lymphoma Association<br>• Macmillan Cancer Support<br>• Maggie's Centres<br>• Marie Curie<br>• Muslim Council of Britain<br>• Rarer Cancers Foundation<br>• South Asian Health Foundation<br>• Specialised Healthcare Alliance<br>• Tenovus Cancer Care<br><br>Professional groups<br>• Association of Cancer Physicians<br>• British Committee for Standards in Haematology<br>• British Geriatrics Society<br>• British Institute of Radiology<br>• British Psychosocial Oncology Society | General<br>• Allied Health Professionals Federation<br>• Board of Community Health Councils in Wales<br>• British National Formulary<br>• Care Quality Commission<br>• Department of Health, Social Services and Public Safety for Northern Ireland<br>• Healthcare Improvement Scotland<br>• Medicines and Healthcare Products Regulatory Agency<br>• National Association for Primary Care<br>• National Pharmacy Association<br>• NHS Alliance<br>• NHS Commercial Medicines Unit<br>• NHS Confederation<br>• Scottish Medicines Consortium<br><br>Comparator companies<br>• Takeda UK (brentuximab vedotin)<br><br>Relevant research groups<br>• Cochrane Haematological Malignancies Group<br>• Institute of Cancer Research<br>• Leuka<br>• Leukaemia Busters<br>• Lymphoma Research Trust<br>• MRC Clinical Trials Unit<br>• National Cancer Research Institute<br>• National Cancer Research Network<br>• National Institute for Health Research<br><br>Associated Public Health Groups<br>• Public Health England |

| **Consultees** | **Commentators (no right to submit or appeal)** |
|---|---|
| • British Society for Haematology<br>• Cancer Research UK<br>• Royal College of General Practitioners<br>• Royal College of Nursing<br>• Royal College of Pathologists<br>• Royal College of Physicians<br>• Royal College of Radiologists<br>• Royal Pharmaceutical Society<br>• Royal Society of Medicine<br>• Society and College of Radiology<br>• UK Clinical Pharmacy Association<br>• UK Health Forum<br>• UK Oncology Nursing Society<br><br><u>Others</u><br>• Department of Health<br>• NHS Brighton and Hove CCG<br>• NHS England<br>• NHS Horsham and Mid Sussex CCG<br>• Welsh Government | • Public Health Wales |

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***PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS***

**Definitions:**

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies; Healthcare Improvement Scotland; other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the British National Formulary.

All non-company commentators are invited to nominate clinical specialists or patient experts.

[1] Non-company consultees are invited to submit statements relevant to the group they are representing.

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single technology appraisal

# Nivolumab for relapsed or refractory classical Hodgkin lymphoma

## ID972

## Company evidence submission

**November 2016**

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| | | Yes | |

# Contents

# Tables and figures

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# Abbreviations

| | |
|---|---|
| AE | Adverse Event |
| AIC | Akaike Information Criteria |
| AlloSCT | Allogenic Stem Cell Transplant |
| ASCT | Autologous Stem Cell Transplant |
| BCSH | British Committee for Standards in Haematology |
| BIC | Bayesian Information Criteria |
| BOR | Best Overall Response |
| BTX | Brentuximab |
| cHL | Classical Hodgkin Lymphoma |
| CHMP | Committee for Medicinal Products for Human Use |
| CR | Complete Response |
| CSR | Clinical Study Report |
| DoR | Duration of Response |
| ECOG | Eastern Cooperative Oncology Group |
| EMA | European Medicines Agency |
| EPAR | European Public Assessment Report |
| ERG | External Review Group |
| ESMO | European Society for Medical Oncology |
| HL | Hodgkin Lymphoma |
| HTA | Health Technology Assessment |
| IRRC | Independent Regulatory Review Committee |
| IWG | International Working Group |
| KM | Kaplan-Meier |
| MAIC | Matching-Adjusted Indirect Comparison |
| NCCN | National Comprehensive Cancer Network |
| NHL | Non-Hodgkin Lymphoma |
| NICE | National Institute for Health and Care Excellence |
| ORR | Objective Response Rate |

| | |
|---|---|
| OS | Overall Survival |
| PAS | Patient Access Scheme |
| PD | Progressive Disease |
| PFS | Progression-free Survival |
| PLD | Patient-level Data |
| PR | Partial Response |
| QoL | Quality of Life |
| R-S cells | Reed-Sternberg Cells |
| SCT | Stem Cell Transplant |
| SD | Stable Disease |
| SLR | Systematic Literature Review |
| SoC | Standard of Care |
| SPC | Summary of Product Characteristics |

# 1 Executive summary

### Disease background

Hodgkin lymphoma (HL) is a haematological malignancy diagnosed in around 1,954 patients in the UK during 2013, equivalent to 3.0 cases per 100,000 people.[1] HL is one of the most common cancers in young people, but shows a clear bimodal age distribution, with a sharp peak in people aged 20–24 years and another in patients aged 75–79. For patients in England and Wales diagnosed with HL during 2010-2011, one-year survival is predicted to be 91.4%, while ten-year survival declines to 80.4%.[1] Long-term remission can be achieved in the majority of HL patients receiving first line therapy; however, 15–30% do not achieve long-term remission.[2] In these patients, salvage therapy, comprising chemotherapy and/or radiotherapy, is used to achieve sufficient response to allow autologous stem cell transplantation (ASCT),[3] which is a potentially curative treatment that is effective in approximately 50% of people.[2] Outcomes for patients who relapse following ASCT have historically been very poor. Further, there is no standard therapy administered after ASCT failure to delay disease progression.[3] Following failure of ASCT, British Committee for Standards in Haematology (BCSH) guidelines recommend that the aim of treatment in patients is to attain sufficient response to allow consideration of allogeneic transplantation (alloSCT) in those deemed eligible and in those not deemed appropriate candidates for alloSCT, therapy should be individualised according to specific circumstance.[3]

### High unmet need

BCSH guidelines recommend that brentuximab (BTX) is considered for use as an option for patients who have relapsed after ASCT, and also as an option prior to ASCT for patients who are either ineligible for ASCT or who are eligible for ASCT but have not achieved sufficient response.[3] BTX has improved the prognosis of many patients with HL, particularly those who achieve complete response (CR).[4] However, the prognosis remains poor in patients with partial response (PR) or who do not achieve response (stable disease; SD), with median time to progression or death of up to 6.9 months and median overall survival (OS) of 18.3 months for SD and 39.4 months for PR.[4] In patients with relapsed or refractory cHL, outcomes are poor, although data describing this patient population is limited. Patients with relapsed or refractory cHL following ASCT had a median OS of 19-29 months, depending on therapies received and availability of BTX,[5,6] and this decreases further in patients who do not achieve an initial response following ASCT.[6] Further, in patients who receive palliative care, median OS decreases to 2.6 months.[5] During the pivotal study for BTX, patients with PR or who do not achieve response (SD) had a median time to progression or death of up to 6.9 months, while median OS was 18.3 months for patients achieving SD and 39.4 months for PR.[4]

Outcomes are known to be even poorer in relapsed or refractory patients who have received both ASCT and BTX, with estimates of median PFS that do not exceed 5 months. Estimates of OS are around two years, but this is obscured by inclusion of the efficacy of clinical trial therapies (47.4 months).[7] When the efficacy of investigational agents is removed, median OS is estimated to be around 19 months. Thus, there is a high degree of unmet medical need in this patient population.

Relapsed or refractory HL is associated with low patient numbers and short survival; thus, the need for individualised care is considerable. This renders the clinical pathway subject to uncertainty and heterogeneity between patients. This is particularly true in the post-ASCT, post-BTX setting, where there are limited treatment options and short life expectancies.

**Nivolumab**

Nivolumab is a human IgG4 monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with its ligands, PD-L1 and PD-L2.[8] In patients with HL, Hodgkin/Reed-Sternberg cells overexpress the PD-L1 and PD-L2 ligands of the PD-1 receptor, suppressing T-cell activation and actively downregulating the tumour-specific T-cell effector functions, enabling escape from immune surveillance.[9,10] Interruption of PD-1 binding to PD-L1 and PD-L2 (overexpressed as a hallmark of cHL), nivolumab allows potentiation of T-cell responses, including anti-tumour responses.[8] This submission outlines the beneficial impact of nivolumab for the treatment of relapsed and refractory HL in terms of patient-relevant outcomes, including improved survival, quality of life, symptom control, tolerability and convenience. In summary, nivolumab can be considered an effective treatment option in a patient group with limited alternative options and high unmet need. Thus, nivolumab offers a step-change in the management of patients with relapsed or refractory HL, and the adoption of nivolumab in this therapeutic indication in the National Health Service (NHS) would represent a further, significant advance in the management of this life-threatening condition.

## 1.1 Statement of decision problem

**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 | People with relapsed or refractory classical Hodgkin lymphoma following autologous stem cell transplant and brentuximab vedotin. | People with relapsed or refractory classical Hodgkin lymphoma following autologous stem cell transplant and brentuximab vedotin. | As NICE scope |
| Intervention | Nivolumab | Nivolumab | As NICE scope |
| Comparator (s) | • Established clinical management without nivolumab including chemotherapy such as gemcitabine or bendamustine.<br>• Best supportive care (BSC) | In the base case analysis, the comparator is based on Standard of Care (SoC), comprised of chemotherapy, BTX retreatment and bendamustine, based on a real world retrospective study.<br><br>Additional scenario analyses assess the impact of applying a comparator comprised of: SoC including investigational agents; chemotherapy only; or BSC. | In the specific context of relapsed or refractory HL, with low patient numbers, short survival and an ongoing NICE appraisal of BTX, the clinical pathway for HL patients is subject to considerable uncertainty and heterogeneity, particularly in the post-ASCT, post-BTX setting. Further, data describing treatment in the post ASCT, post-BTX setting is likely to describe investigational therapies rather than established clinical practice. For this reason, the base case analysis assumes that real world retrospective data would be representative of UK clinical practice, with scenario analyses to assess the impact of alternative assumptions. |
| Outcomes | The outcome measures to be considered include:<br>• overall survival<br>• progression-free survival<br>• response rates<br>• adverse effects of treatment<br>• health-related quality of life. | The outcome measures considered include:<br>• overall survival<br>• progression-free survival<br>• objective response rate<br>• complete response rate<br>• adverse effects of treatment<br>• health-related quality of life.<br>Additionally, rate of partial response and stable disease are considered as outcome measures of interest. | As NICE scope |
| Economic analysis | The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.<br>The reference case stipulates that the time horizon for estimating clinical and cost | The cost-effectiveness of treatments is expressed in terms of incremental cost per quality-adjusted life year. The time horizon for estimating clinical and cost effectiveness is life time, which is sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. | As NICE scope |

| | | | |
|---|---|---|---|
| | 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. | Costs are considered from an NHS and Personal Social Services perspective. | |
| Subgroups to be considered | None specified | Subgroups will be provided for analysis wherever data allows, including age-specific groupings. | Not applicable |
| Special considerations including issues related to equity or equality | None specified | HL shows a clear bimodal age distribution, with a sharp peak in people aged 20–24 years and another in patients aged 75–79.<br>Due to existing comorbidities and concerns around age, fewer patients aged 75-79 will have undergone salvage chemotherapy and ASCT following first line chemotherapy failure, so that data describing the effectiveness of therapies post-ASCT and post-BTX is more scarce for these patients. Patients in this group are likely to have few, if any, treatment options, and as such are more likely to be receiving BSC, which has limited impact on symptoms, progression or survival and is associated with more hospital admissions, impacting on quality of life. As such, these patients have a high unmet need, and an efficacious therapy that is well-tolerated would represent a much needed treatment option.<br>By contrast, patients aged 20-24 years have a greater range of treatment options available. However, onset of HL can restrict ability to study, work or participate in family life, and this is a particular issue in this patient group. Availability of a therapy that can provide a bridge to potentially curative allogenic stem cell transplant could allow patients in this age group with the potential to live long and active lives, with significant indirect economic benefits in terms of avoiding lost productivity.[11] | Not applicable |
| ASCT: autologous stem cell transplant; BSC: best supportive care; BTX: brentuximab; SoC: Standard of care. | | | |

## 1.2 Description of the technology being appraised

Programmed death-1 (PD-1) is an immune-system checkpoint protein receptor expressed at high levels on activated T-cells, which has been shown to control the inhibition of T-cell response at the effector stage of the immune response, in the setting of human malignancy. Tumour cells can exploit this pathway by up-regulating proteins that engage PD-1 with its ligands (programmed death ligand-1 [PD-L1] and programmed death ligand-2 [PD-L2]) to limit the activity of T-cells at the tumour site.

Nivolumab is a fully human, monoclonal immunoglobulin G4 antibody (IgG4 HuMAb) that acts as a PD-1 checkpoint-inhibitor, blocking the interaction of PD-1 with PD-L1 and PD-L2. Nivolumab stops the evasion of immune-mediated tumour destruction and stimulates the patient's own immune system to directly destroy cancer cells (in the same way that it would any other "foreign" cell), resulting in destruction of the tumour through pre-existing, intrinsic processes. The innovation of nivolumab is reflected in the Medicines and Healthcare products Regulatory Agency (MHRA) awarding nivolumab Promising Innovative Medicine (PIM) status.

Details of the technology being appraised in this submission are summarised in Table 2.

**Table 2. Technology being appraised**

| | |
|---|---|
| **UK approved name and brand name** | Nivolumab (Opdivo®) |
| **Marketing authorisation/CE mark status** | A Marketing Authorisation Application (MAA) was submitted to the European Medicines Agency (EMA) on 9 March 2016 and the product has been submitted for registration via the Centralised Procedure. A positive opinion for nivolumab (Opdivo®) from the Committee for Medicinal Products for Human Use (CHMP) was made available in October 2016.[12] |
| **Indications and any restriction(s) as described in the summary of product characteristics** | The proposed indication for nivolumab for the treatment of classical Hodgkin lymphoma (cHL) is as follows: OPDIVO as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL)after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin (BTX).[8] |
| **Method of administration and dosage** | The recommended dose of OPDIVO is 3 mg/kg administered intravenously over 60 minutes every 2 weeks. Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.[8] |

## 1.3 Summary of the clinical effectiveness analysis

Evidence to support the effectiveness of nivolumab for the treatment of relapsed or refractory cHL following ASCT and BTX therapy is primarily derived from two non-comparative, single-arm studies: CheckMate 205 and CA209-039.[13-15] In order to provide

evidence of the comparative clinical effectiveness of nivolumab, several indirect comparison have been undertaken. An overview of each is provided below, with full details provided in Section 4.

### 1.3.1 CheckMate 205

CheckMate 205 is a non-comparative, parallel-cohort, single-arm Phase 2 study in cHL patients ≥18 years old who failed ASCT.[13,16] Patients enrolled in the study may have been BTX-naïve (Cohort A), or may have had prior BTX treatment as a salvage therapy after failure of ASCT (Cohort B), while patients in Cohort C could have prior ASCT and BTX in any treatment order.

This study demonstrated that nivolumab was efficacious in terms of response rate, as well as OS, PFS, symptom control and tolerability, as described in Section 4. At a median follow-up of 15.7 months in Cohort B and 8.9 months in Cohort C, the objective response rate (ORR) was 75% and 66.0%, respectively, with many patients reporting CR (26.0% and 26.5%). Further, this high response rate has translated into lower incidence of progression and extended survival; only [redacted] of the [redacted] treated patients had died ([redacted] in Cohort B and [redacted] in Cohort C) indicating very high OS in these patients, and median PFS was in excess of 11 months in both cohorts. Further, the safety profile can be considered acceptable in the context of alternative therapies, such as standard chemotherapy regimens.[16] Additionally, nivolumab was associated with improvement from baseline in disease-specific patient quality of life (EORTC-QLQ-C30) and a generic health status measure (EQ-5D), demonstrating clinically significant benefits in quality of life using several of the scales.[16]

### 1.3.2 CA209-039

This is an open-label, non-comparative, single-arm Phase 1 study of nivolumab for the treatment of haematological malignancies, including cHL.[15,17] Patients with relapsed or refractory HL (n = 23) that had already been heavily treated received nivolumab (at a dose of 3 mg/kg) every 2 weeks; 15 of the patients had previously received both BTX and ASCT, 3 had previously received BTX (no ASCT) and 5 had received no BTX (2 had previously received ASCT, but 3 had not).[15,17]

This study demonstrated that nivolumab was efficacious in terms of response rate, as well as OS, PFS, symptom control and tolerability, as described in Section 4. At a median follow-up of 23.3 months in CA209-039, 87% of patients in the overall population achieved on objective response, of which 22% achieved CR, with similar levels of response in the post-BTX, post-ASCT group (ORR: 87%; CR: 13%).[15] Further, this high response rate has translated into lower incidence of progression and extended survival. Median PFS and median OS were not reached, with [redacted] PFS events and 5 OS events occurring in enrolled patients, and a one-year OS rate of 91.3%, indicating very high survival in these patients.[15] The rate of adverse events (AEs) was similar to that in trials of nivolumab in patients with solid tumours and AEs were mainly of grade 1 or 2.[14]

### 1.3.3 Indirect comparison in the post-ASCT, post-BTX setting

Several indirect comparisons were undertaken to inform the comparison of nivolumab versus SoC. Unadjusted and matching-adjusted indirect comparisons (MAICs) of relevant nivolumab patient-level data were undertaken and demonstrated that nivolumab is associated with improved rates of response [redacted] and survival outcomes [redacted]. Due to the paucity of evidence available in the post-ASCT, post-BTX setting, a further systematic literature review and indirect comparison of nivolumab versus available treatment options in a population that are post-ASCT (and not necessarily post-BTX) were undertaken; results are supportive of these conclusions.

### 1.3.4 Conclusions

- Nivolumab therapy has significant benefits in terms of patient-relevant outcomes, including high response rates, improved survival (both PFS and OS), symptom control and an acceptable safety profile.

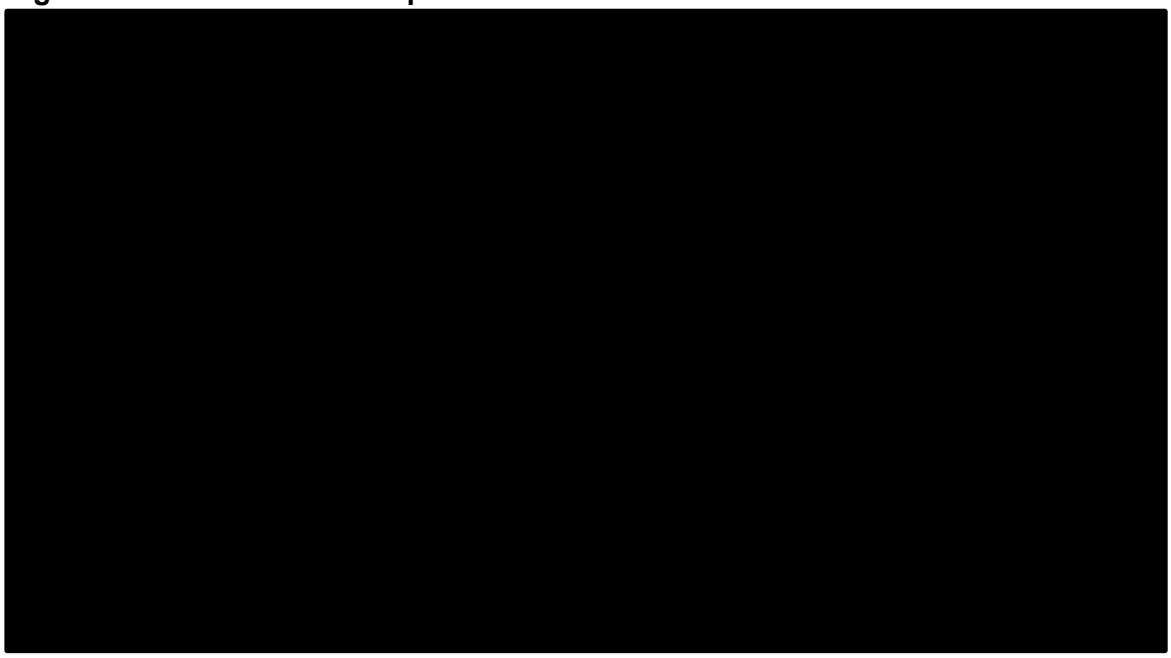
- Compared with standard of care (SoC), including chemotherapy, BTX re-treatment and investigational agents, nivolumab extends life expectancy, reduces progression and has improved tolerability.

## *1.4 Summary of the cost-effectiveness analysis*

### 1.4.1 Base case analysis

In the base case analysis, it was estimated that nivolumab use would result in an additional [redacted] discounted QALYs and 2.90 discounted LYs versus SoC. Further, it was estimated that patients receiving nivolumab would spend [redacted] years in the pre-progression state (versus 0.41 years for patients receiving SoC), with a subsequent [redacted] years in the post-progression state (versus 1.70 years for SoC), indicating a substantial benefit to survival in both the pre- and post-progression period. Incremental costs were expected to be [redacted] under base case assumptions (including availability of a nivolumab Patient Access Scheme [PAS]) and the resultant ICER was £19,882, which can be considered cost-effective at a willingness-to-pay threshold of £30,000/QALY.

**Figure 1. Cost-effectiveness plane**



### 1.4.2 Sensitivity analyses

In the specific context of relapsed or refractory HL, with low patient numbers, short survival and an ongoing NICE appraisal of BTX, the clinical pathway for HL patients is subject to considerable uncertainty and heterogeneity. This is particularly true in the post-ASCT, post-BTX setting, where there are limited treatment options, in addition to small patient numbers and short, highly uncertain life expectancy.

In order to assess the impact of this uncertainty, a large number of sensitivity analyses have been undertaken, assessing the impact of variation in all variables and assumptions applied within the model. In the deterministic analysis and PSA, nivolumab was cost-effective in the majority of scenarios at a WTP threshold of £30,000/QALY and in all scenarios at a WTP threshold of £50,000/QALY. Similarly, when plausible alternative inputs and assumptions were assessed as scenario analyses within Section 5.8.3, the majority of ICERs remain below the £30,000/QALY threshold, and was cost-effective in all scenarios at a WTP threshold of £50,000/QALY.

**Figure 2. Cost-effectiveness scatterplot**

**Figure 3. Scenario analysis: overview of all scenarios**

### 1.4.3 Conclusions

- Under base case assumptions, the ICER for nivolumab versus SoC was £19,882 (including PAS)

- Extensive sensitivity analyses were undertaken to assess the impact of the significant uncertainty around assumptions. The majority of these remained below a WTP threshold of £30,000/QALY, with all cost-effective at a WTP threshold of £50,000/QALY.

Nivolumab is a new, innovative, cost-effective and step-changing treatment option which meets an unmet medical need by offering durable clinical response and the potential for improved long-term survival in a population with a short life expectancy and lack of effective treatment options. The innovative nature of nivolumab has been recognised by the MHRA in through the granting of PIM status. In comparison with chemotherapy, nivolumab has improved tolerability and a more convenient schedule, which can potentially help maintain patient dignity and facilitate normal life, as well as enabling patients to spend less time at hospital and more at home.

Outcomes are known to be poor in relapsed or refractory patients who have received both ASCT and BTX, with estimates of median PFS that do not exceed 5 months and estimates of median OS of around 19 months (as described in Section 4.13). Thus, there is a high degree of unmet medical need in this patient population.

HL shows a sharp peak in incidence in people aged 20–24 years and restricts ability to study, work or participate in family life, impacting significantly on their quality of life. This can result in a loss of income and an increased expense as a result of their illness. The availability of a therapy that is efficacious in its own right and that may bridge to potentially curative alloSCT could allow patients in this age group to live long and active lives, with significant indirect economic benefits in terms of avoiding lost productivity.

Further, nivolumab provides an additional treatment option with proven efficacy and tolerability in patients who may otherwise have been receiving only best supportive care (BSC) due to limited alternative options, which would manage the patient's illness, but with limited impact on survival. This is of particular importance in the HL setting, where a large proportion of cases diagnosed are in elderly patients,[1] who may not be eligible to receive chemotherapies because of their age or comorbidities.

In summary, availability of nivolumab would provide an opportunity to make a significant and substantial impact on health-related benefits and address a current unmet need, and the adoption of nivolumab in this therapeutic indication in NHS England would represent a further, significant advance in the management of this life-threating condition.

# 2 The technology

## *2.1 Description of the technology*

**Brand name:** Opdivo®

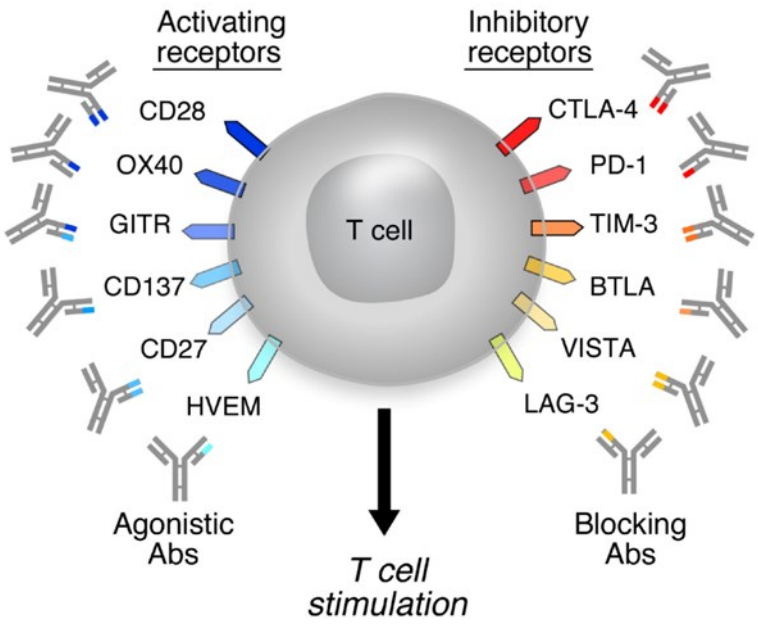
**UK approved name:** Nivolumab

**Therapeutic class:** Antineoplastic agents, monoclonal antibodies. ATC code: L01XC17. Programmed death-1 (PD-1) immune checkpoint inhibitor

**Overview of mechanism of action**

Immunotherapy has been at the forefront of therapeutic development in oncology since the discovery that cancer cells evade destruction by exploiting the signalling pathways that control the immune system. The typical immune response to foreign cells or antigens in the body is the activation of T-cells that can then destroy those foreign cells or antigens. T-cells proliferate and differentiate through various pathways, with T-cell activation regulated through a complex balance of positive and negative signals provided by co-stimulatory and co-inhibitory receptor interactions on the T-cell surface (Figure 4). Healthy, non-foreign cells ('self'-cells) avoid T-cell destruction by stimulating inhibitory receptors, known as checkpoints, to suppress the T-cell response; cancer cells can use these same inhibitory receptors to escape destruction by T-cell activity. Blocking antibodies designed to bind to these checkpoints (so called 'checkpoint-inhibitors') can prevent tumour driven T-cell suppression, as depicted in Figure 4, and increase immune activity against cancer cells.

**Figure 4. Receptors involved in the regulation of the T-cell immune response (from Mellman 2011[18])**



PD-1 is an immune checkpoint protein receptor expressed at high levels on activated T-cells, which has been shown to control the inhibition of T-cell response at the effector stage of the immune response, in the setting of human malignancy.[10,19-22] Tumour cells can exploit this pathway by up-regulating proteins that engage PD-1 with its ligands (programmed death ligand-1 [PD-L1] and programmed death ligand-2 [PD-L2]) to limit the activity of T-cells at the tumour site.

It has been widely demonstrated that biopsies obtained from cHL patients often have amplifications and alterations in the expression of PD-1 ligands, PD-L1 and PD-L2,[23-25] and this is often associated with progression or more advanced disease.[25] Through exploitation of the PD-1 immune checkpoint inhibitor pathway, as depicted in Figure 5, HL cells are able to escape immune surveillance.[9]

Nivolumab is a fully human, monoclonal immunoglobulin G4 antibody (IgG4 HuMAb) that acts as a PD-1 checkpoint-inhibitor, blocking the interaction of PD-1 with PD-L1 and PD-L2, as depicted in Figure 5 and Figure 6. Through interruption of PD-1 binding to PD-L1 and PD-L2, nivolumab stops the evasion of immune-mediated tumour destruction and actually potentiates this process by restoring T-cell activity; that is, nivolumab stimulates the patient's own immune system to directly destroy cancer cells (in the same way that it would any other "foreign" cell), resulting in destruction of the tumour through pre-existing, intrinsic processes (Figure 6).

**Figure 5. PD-1 pathway and blockade (from McDermott and Atkins 2013[26])**

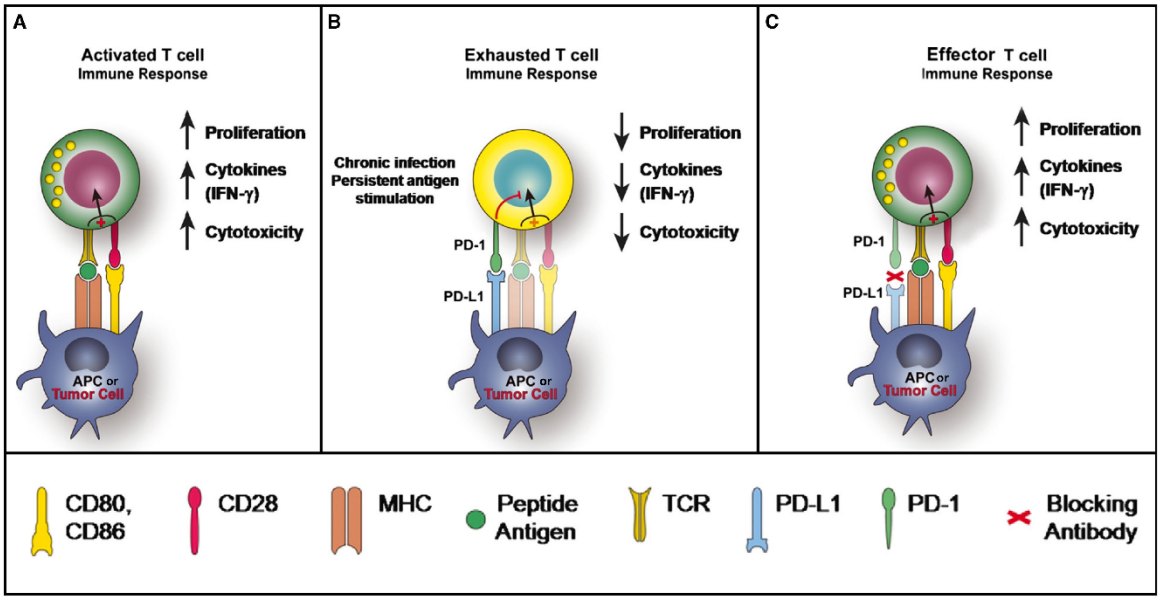
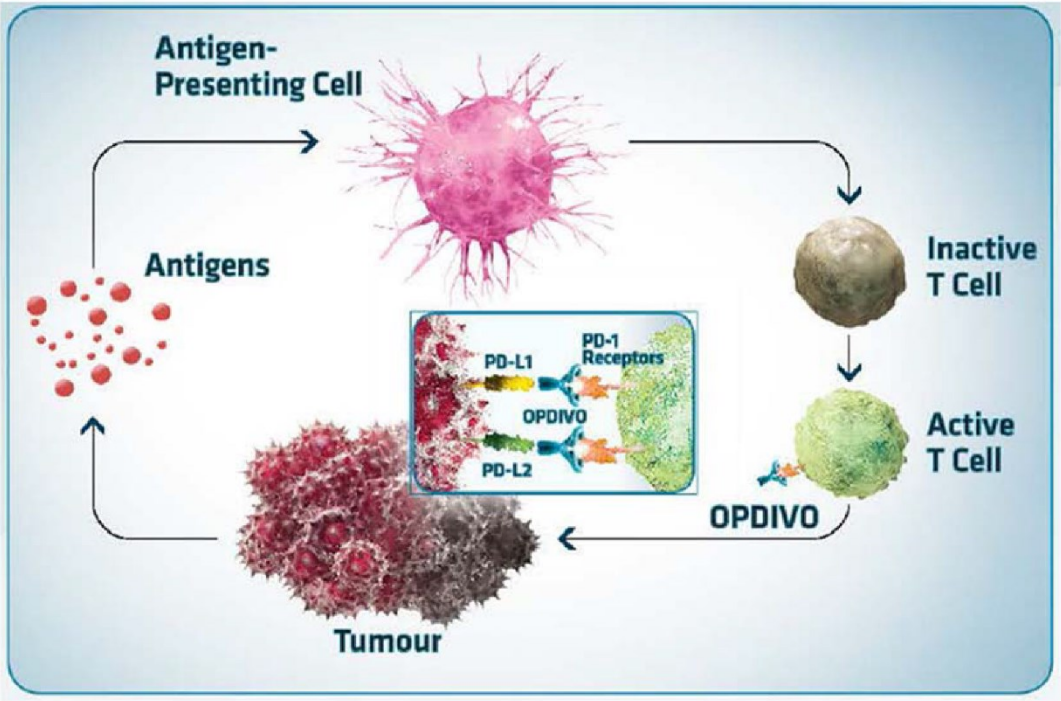


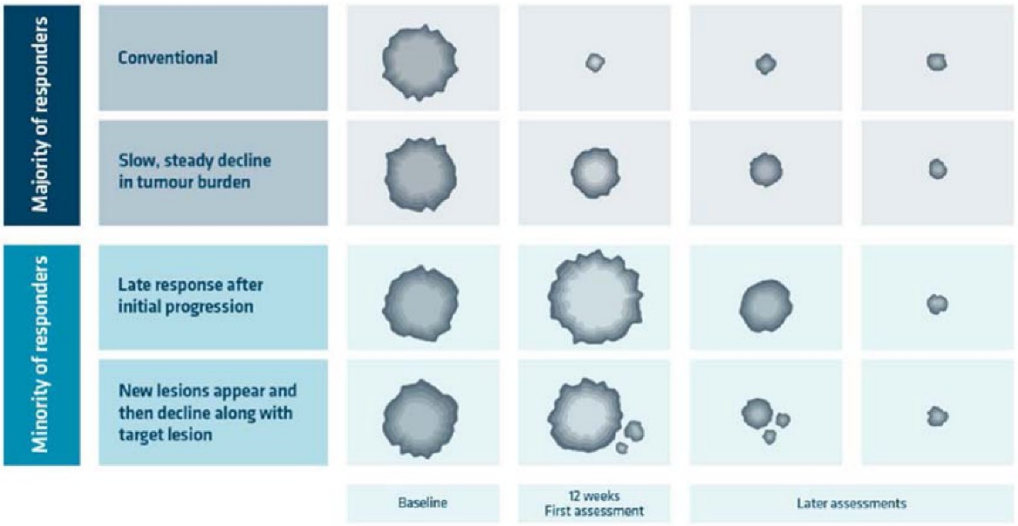

**Figure 1.** PD-1 in T-cell activation, exhaustion, and effector function. (A) T cells are activated via (1) binding of MHC plus peptide on an APC to the TCR and then (2) binding of APC CD80/86 to T-cell CD28. In patients with cancer, tumor cells can also serve as APCs. Upon T-cell activation, PD-1 expression is induced. (B) In situations of chronic infection or persistent stimulation, PD-L1 signals through T-cell PD-1 to "turn off" T cells in order to minimize damage to healthy tissue. Tumor cells can upregulate PD-L1 in order to "turn off" T cells that might destroy them. (C) Blocking the PD-1/PD-L1 signaling pathway allows T cells to maintain their effector functions. In patients with cancer, activated tumor-specific T cells can kill tumor cells and secrete cytokines that activate/recruit other immune cells to participate in the antitumor response. APC, antigen-presenting cell; IFN-γ, interferon gamma; MHC, major histocompatibility complex; PD-1, programmed death-1; PD-L1, PD ligand 1; TCR, T-cell receptor.

**Figure 6. Nivolumab stimulation of immune-mediation destruction**




Conventional anti-cancer therapies typically aim reduce the tumour burden through disruption of cell proliferation or induction of apoptosis. By contrast, there are key differences with immunotherapy agents such as nivolumab, as a result of their novel mechanism of action. One of these differences is the varying patterns of response that can be observed with immunotherapy agents, such that patients who ultimately achieve a positive clinical outcome may have tumours that appear to have enlarged when assessed in the early stages of treatment. Several approaches have been suggested to improve monitoring of efficacy in these promising, new immuno-oncology therapies, including development of specific response criteria and use of alternative endpoints, such as disease control and tumour growth rates.

**Figure 7. Typical patterns of response observed with immunotherapy**



Despite the potential for the varying pattern of response, data from clinical studies illustrate that nivolumab can be considered highly efficacious for the treatment of HL when evaluated using the standard response criteria currently applied in clinical practice.[27] Data provided within the submission reports the efficacy of nivolumab in terms of these standardised response criteria; supportive evidence describing the beneficial impact of nivolumab therapy beyond progression is reported as additional study outcomes where data are available.

## *2.2 Marketing authorisation/CE marking and health technology assessment*

Nivolumab (Opdivo®) received marketing authorisation on 19 June 2015 as a monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults.[8] Subsequently, the licensed indication was extended to include:[28]

- Treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) after prior chemotherapy in adults (28 October 2015)
- Treatment of locally advanced or metastatic non-squamous NSCLC after prior chemotherapy in adults (4 April 2016)
- Monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults (4 April 2016)
- In combination with ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma in adults. (11 May 2016)

This submission details evidence to support the use of nivolumab as monotherapy for the treatment of adult patients with relapsed or refractory cHL after ASCT and treatment with BTX. A regulatory submission was made to the EMA on 9 March 2016. A positive opinion for nivolumab (Opdivo®) from the Committee for Medicinal Products for Human Use (CHMP) was made available in October 2016.[12]

The draft Summary of Product Characteristics (SPC) has been provided in Appendix 1; however a draft European public assessment report (EPAR) is not yet available due to the timing of this submission. No other health technology assessments (HTAs) are currently ongoing within the UK setting for this indication, although submission to the Scottish Medicines Consortium is planned.

## 2.3 Administration and costs of the technology

Administration and costs associated with nivolumab are summarised in Table 3.

**Table 3. Costs of the technology being appraised**

| | Cost | Source |
|---|---|---|
| **Pharmaceutical formulation** | Concentrate for solution for infusion (sterile concentrate). | SPC[8] |
| **Acquisition cost (excluding VAT) *** | 10mg/ml concentrate for solution for infusion in vial; 4 ml vial: £439; 10 ml vial £1,097 | List price (MIMS[29]) |
| **Method of administration** | Intravenous infusion. | SPC[8] |
| **Doses** | 3mg/kg | SPC[8] |
| **Dosing frequency** | Every 2 weeks. | SPC[8] |
| **Average length of a course of treatment** | Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. | SPC[8] |
| **Average cost of a course of treatment** | £5,724 per month, assuming patient weight of 80kg and wastage of remainder of vial, in line with SPC (not including administration costs) | List price (MIMS[29]) |
| **Anticipated average interval between courses of treatments** | Nivolumab retreatment is not anticipated. | - |
| **Anticipated number of repeat courses of treatments** | Nivolumab retreatment is not anticipated | - |
| **Dose adjustments** | Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability. | SPC[8] |
| **Anticipated care setting** | Hospital or clinic setting. | SPC[8] |
| MIMS: Monthly Index of Medical Specialities; SPC: Summary of Product Characteristics. | | |

## 2.4 Changes in service provision and management

It is not anticipated that nivolumab use will require provision of additional tests or investigations outside of those required for the diagnosis and monitoring of advanced HL.

As specified in the SPC, nivolumab treatment must be initiated and supervised by physicians experienced in the treatment of cancer.[8] The staffing and infrastructure needed for the administration of cancer treatments is available at hospital oncology units, and it is anticipated that the administration of nivolumab would utilise this existing NHS infrastructure.

Nivolumab as a monotherapy is administered as an intravenous infusion over a period of 60 minutes every two weeks.[8] This dosing regimen is less frequent and less complex than many other commonly used combination regimens, for example those that require gemcitabine infusion on days 1 and 8 of a three-week cycle.[3,30-32] This dosing schedule is

fully accounted for in the economic modelling presented in Section 5; however, any potential benefits associated with this schedule, such as patient preference, are not reflected.

As with other immuno-oncology therapies, patients should also be regularly monitored for signs or symptoms of immune-related AEs; most immune-related AEs improved or resolved with appropriate management, including initiation of corticosteroids and treatment modifications.[8] Given the advanced nature of HL in this population, it is not anticipated that this will require additional monitoring from clinicians.

## *2.5 Innovation*

Nivolumab is a highly innovative therapy that has shown unprecedented single-agent activity in the treatment of relapsed or refractory cHL, with a unique mechanism of action and published data describing the beneficial impact of therapy in terms of efficacy and safety.

Nivolumab is the first checkpoint inhibitor immunotherapy to file for marketing authorisation in advanced cHL, providing an innovative mechanism of action that utilises the body's own immune system to destroy cancer cells (see Section 2.1). The innovation of nivolumab is reflected in the MHRA awarding nivolumab PIM status. Further, nivolumab will be the only treatment with European Medicines Agency (EMA) approval for patients with relapsed or refractory cHL following ASCT and BTX, and is viewed by physicians and patients as a 'step-change' in the management of this stage of the disease.

As described within Section 4, nivolumab therapy has significant benefits in terms of patient-relevant outcomes, including high response rates, improved survival (both PFS and OS), symptom control and a reassuring safety profile.

Those therapies that are available in patients with relapsed or refractory cHL are associated with poor outcomes, although data describing this patient population is limited. Patients with relapsed or refractory cHL following ASCT have a median OS of 19-29 months, depending on therapies received and availability of BTX,[5,6] and this decreases further in patients who do not achieve an initial response following ASCT.[6] Further, in patients who receive palliative care, median OS decreases to 2.6 months.[5] Outcomes are known to be even poorer in relapsed or refractory patients who have received both ASCT and BTX, with estimates of median PFS that do not exceed 5 months. Estimates of OS are around two years, but this is obscured by inclusion of the efficacy of clinical trial therapies (47.4 months).[7] When the efficacy of investigational agents is removed, median OS is estimated to be around 19 months. Thus, there is a high degree of unmet medical need in this patient population.

By contrast, clinical trial data presented within this submission demonstrates PFS in nivolumab-treated patients exceeding 11 months (Section 4), and although median OS has not yet been reached, analyses predict that median OS will reach almost five years (Section 5.3.2.1). Furthermore, nivolumab was associated with improvement in disease-specific patient quality of life (EORTC-QLQ-C30) as well as a generic health status measure (EQ-5D), demonstrating clinically significant benefits in quality of life using several of the scales (Section 4.7.1.9)

The safety and efficacy of nivolumab are of particular importance in the setting of relapsed or refractory HL following ASCT and BTX, where there is significant unmet need for new treatments, specifically those with a favourable safety profile, as well as improved efficacy. Following failure of both ASCT and BTX, therapeutic options are limited, and available chemotherapeutic options may not be available to all patients due tolerability issues. In this setting, nivolumab may be a well-tolerated therapeutic option with the potential to offer significant survival benefit and bridge to potentially curative alloSCT.

In summary, the key benefits of nivolumab that may not be captured in the economic model by the utility and QALY assessment include the following:

- In comparison with chemotherapy, nivolumab monotherapy has improved tolerability and a more convenient schedule, which can potentially help maintain patient dignity and facilitate normal life, as well as enabling patients to spend less time at hospital and more at home.

- Nivolumab provides an additional treatment option with proven efficacy and tolerability in patients who may otherwise have been receiving only BSC due to limited alternative options, which would manage the patient's illness, but with limited impact on survival. This is of particular importance in the HL setting, where a large proportion of cases diagnosed are elderly patients,[1] who may not be eligible to receive chemotherapies because of their age or comorbidities.

- The aim of treatment in HL patients following failure of prior ASCT is to attain sufficient response to allow consideration of alloSCT in those deemed eligible.[3] Given the high rates of response, there is significant potential for nivolumab to act as a bridge to curative transplant in some patients. Although this benefit may be partly captured by the economic assessment scenarios presented in Section 5, limitations in the data may prevent it fully reflecting the impact of a long and active life following alloSCT.

- HL shows a sharp peak in incidence in people aged 20–24 years[1] and restricts ability to study, work or participate in family life, impacting significantly on their quality of life. According to a recent patient group submission to NICE,[33] most people with blood cancer say that they suffer a loss of income and an increased expense as a result of their illness. Further, they may have problems continuing with work or have to take lots of time off due to regular hospital visits and feeling unwell. These effects are not taken into account in the economic model, in line with the NICE reference case.[34] However, the availability of a therapy that can provide a bridge to potentially curative alloSCT could allow patients in this age group to live long and active lives, with significant indirect economic benefits in terms of avoiding lost productivity.[11] Preliminary data describing outcomes following alloSCT in patients who have received nivolumab are provided in Section 4.13.4.1.

The introduction of nivolumab would change the treatment paradigm for this patient group and thus represents a 'step-change' in the management of cHL following failure of prior ASCT and BTX. Availability of nivolumab would provide an opportunity to make a significant and substantial impact on health-related benefits and address a current unmet need, and the adoption of nivolumab in this therapeutic indication in NHS England would represent a further, significant advance in the management of this life-threating condition.

# 3 Health condition and position of the technology in the treatment pathway

## *3.1 Disease background*

HL is a haematological malignancy originating from cancerous B lymphocyte cells, and diagnosis is based on the finding of Hodgkin/Reed-Sternberg cells in an appropriate cellular background of reactive leucocytes.[35] HL comprises around 1 in 5 lymphomas diagnosed[36] and can be classified into two distinct entities: classical HL (cHL), which comprises around 95% of cases; and nodular lymphocyte-predominant HL (5% of cases).[35] HL usually presents as a swelling of lymph nodes, but systemic symptoms (night sweats, weight loss and fever; termed B-symptoms) can also be present.[35]

During 2013, there were 1,954 new cases of HL in the UK, equivalent to 3.0 cases per 100,000 people.[1] Although around half of these (49%) were diagnosed in people aged 45 and over, HL shows a clear bimodal age distribution, with a sharp peak in people aged 20–24 years and another in patients aged 75–79. For patients in England and Wales diagnosed with HL during 2010-2011, one-year survival is predicted to be 91.4%, while ten-year survival declines to 80.4%.[1]

## *3.2 Clinical pathway of care*

The treatment of HL depends upon the disease stage; the size of affected lymph nodes and disease spread; and the patient's age and general health.[3,37] Current guidelines recommend the use of a combination of chemotherapy and radiotherapy for the first line treatment of HL,[37] which may include: doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD regimen) with 20Gy radiotherapy; or bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone (BEACOPP regimen) with ABVD and 20Gy radiotherapy. However, 15–30% of patients do not achieve long-term remission with these first line therapies.[2] In these patients, salvage therapy, comprising chemotherapy and/or radiotherapy, is used to achieve sufficient response to allow ASCT,[3] as depicted in Figure 8. In this population, high-dose chemotherapy followed by ASCT is a potentially curative treatment that is effective in approximately 50% of people.[2] However, ASCT may not be an option in some circumstances, such as those patients who are unable to achieve sufficient response or those whose age or co-morbidities prohibit this intervention.[2]

Outcomes for patients who relapse following ASCT have historically been very poor and there is no standard therapy administered after ASCT failure to delay disease progression.[3] The aim of treatment in these patients is to attain sufficient response to allow consideration of alloSCT in those deemed eligible. In those for whom alloSCT is not appropriate, therapy should be individualised according to specific circumstance.[3]

NICE are currently assessing the use of BTX for the treatment of: patients with CD30-positive HL following ASCT who have relapsed or refractory disease or who are at high risk of residual disease; and patients with CD30-positive HL following at least two previous therapies when ASCT or multi-agent chemotherapy is not a treatment option.[38] In the

absence of NICE guidelines, BCSH treatment guidelines form the best available evidence to inform current clinical practice for the treatment of HL in the UK.[3]

**Figure 8. British Committee for Standards in Haematology and British Society of Blood and Marrow Transplantation treatment guidelines[3]**

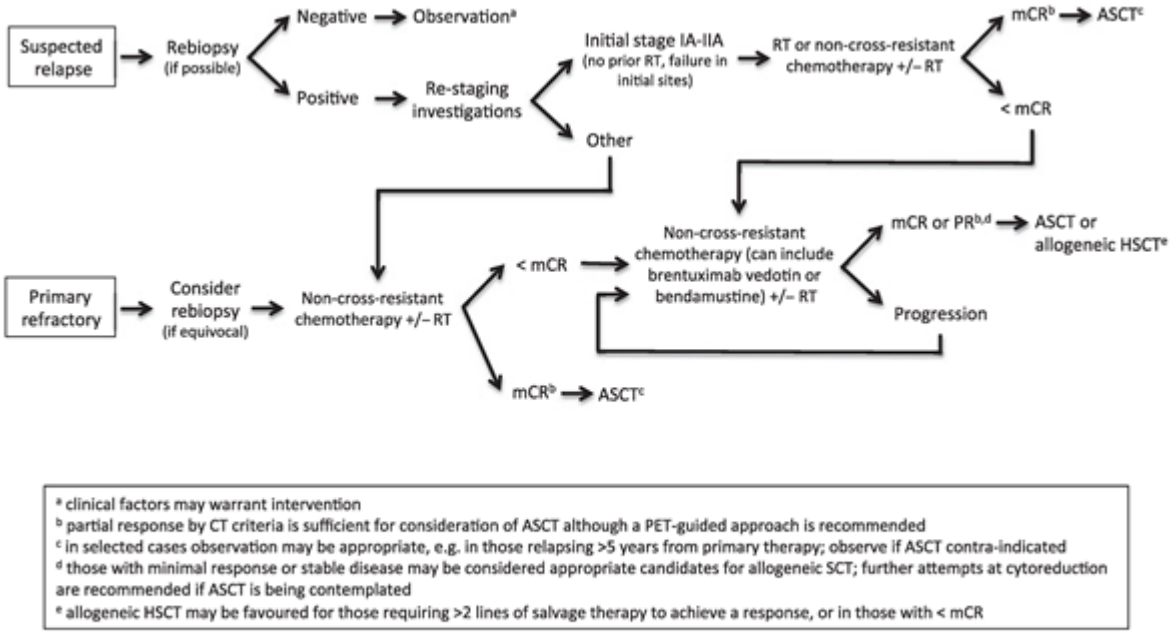



Fig 1. Flow diagram of recommended treatment pathway for patients deemed eligible for potential high dose consolidation therapy. RT, radiotherapy; CT, computerized tomography; PET, positron-emission tomography; mCR, metabolic complete response; PR, partial response; ASCT, autologous stem cell transplantation; HSCT, haematopoietic stem cell transplantation.

Guidelines produced by BCSH, European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN; USA) recommend that BTX is considered for use as an option for patients who have relapsed after ASCT, and also as an option prior to ASCT for patients who are either ineligible for ASCT or who are eligible for ASCT but have not achieved sufficient response.[3,31,39]

BTX has improved the prognosis of many patients with HL, particularly those who achieve CR.[4] However, the prognosis remains poor in patients with PR or who do not achieve response (SD), with median time to progression or death of up to 6.9 months and median OS of 18.3 months for SD and 39.4 months for PR.[4] In patients who have failed both ASCT and BTX, as well as poor outcomes, there are currently no recommended treatment options. Current options in patients with relapsed or refractory cHL following ASCT and BTX are associated with poorer outcomes; estimates of median PFS do not exceed 5 months, while median OS is predicted to be around 2 years, even when including the effects of clinical trial therapies.[7] When the efficacy of investigational agents is removed, median OS is imputed to be around 19 months (as described in Section 4.10). Thus, there is a high unmet medical need in this patient population.

## Issues with the current clinical pathway

In the specific context of relapsed or refractory HL, with low patient numbers, short survival and an ongoing NICE appraisal of BTX, the clinical pathway for HL patients is subject to considerable uncertainty and heterogeneity, particularly in the post-ASCT, post-BTX setting.

Following failure of ASCT and BTX, BCSH guidelines recommend that the aim of treatment in patients is to attain sufficient response to allow consideration of alloSCT in those deemed eligible and in those not deemed appropriate candidates for alloSCT, therapy should be individualised according to specific circumstance. Some patients will be most appropriately treated with a palliative approach, and early involvement of specialist palliative services is recommended. In the majority, further attempts to gain disease control are warranted, recognising that some will achieve prolonged periods of disease control. As such, there is no standard therapy administered in this patient population.

In the HL setting, a large proportion of cases diagnosed are in elderly patients,[1] who may not be eligible to receive chemotherapies because of their age or comorbidities. These patients may receive BSC due to limited alternative options, which would manage the patient's illness, but with limited impact on survival. Further, even in those patients eligible to receive chemotherapy and/or radiotherapy, the poor tolerability profile may impact on patient quality of life and increase the time spent in hospital.

## Nivolumab within the current clinical pathway

Nivolumab is a fully human, monoclonal immunoglobulin G4 antibody (IgG4 HuMAb) that acts as a PD-1 checkpoint-inhibitor. Through interruption of PD-1 binding to PD-L1 and PD-L2, nivolumab stops the evasion of immune-mediated tumour destruction and actually potentiates this process by restoring T-cell activity, so that the patient's own immune system is stimulated to directly destroy cancer cells (in the same way that it would any other "foreign" cell), resulting in destruction of the tumour through pre-existing, intrinsic processes (Figure 6).

Nivolumab is a highly innovative therapy that has shown unprecedented single-agent activity in the treatment of relapsed or refractory cHL, with a unique mechanism of action and published data describing the beneficial impact of therapy in terms of efficacy and safety. Nivolumab is the first checkpoint inhibitor immunotherapy to file for marketing authorisation in advanced cHL. Further, nivolumab will be the only treatment with EMA approval for patients with relapsed or refractory cHL following ASCT and BTX, and is viewed by physicians and patients as a 'step-change' in the management of this stage of the disease.

The benefits of nivolumab therapy include:

- **Improved survival outcomes:** Alternative options in patients with relapsed or refractory cHL following ASCT and BTX are associated with poorer outcomes; estimates of median PFS do not exceed 5 months, while median OS is predicted to be around 2 years, even when including the effects of clinical trial therapies.[7] By contrast, clinical trial data presented within this submission demonstrates PFS in

nivolumab-treated patients exceeding 11 months (Section 4), and although median OS has not yet been reached, analyses predict that median OS will reach almost five years (Section 5.3.2.1).

- **Improved quality of life:** nivolumab was associated with improvement from baseline in disease-specific patient quality of life (EORTC-QLQ-C30) and a generic health status measure (EQ-5D), demonstrating clinically significant benefits in quality of life using several of the scales (Section 4.7.1.9).

- **Rapid symptom control:** in the majority of patients with B-symptoms, complete resolution is achieved quickly, with a median time of 1.9 months.[16]

- **Improved tolerability**: in comparison with currently available treatments, such as chemotherapy, the safety profile for nivolumab can be considered acceptable to patients, as described in Section 4.12. Further, this safety profile is well-established based on that observed in other indications.[8]

- **More convenient administration schedule**: nivolumab monotherapy requires administration once every two weeks, enabling patients to schedule outpatient attendances into their lives in a predictable manner. This facilitates normal life, including work and family activities, and enables patients to spend less time at hospital and more at home.

- **Potential bridge to alloSCT:** The aim of treatment in HL patients following failure of prior ASCT is to attain sufficient response to allow consideration of alloSCT in those deemed eligible.[3] Given the high rates of response, there is significant potential for nivolumab to act as a bridge to curative transplant in some patients.

- **Additional treatment option:** Nivolumab provides an additional treatment option with proven efficacy and tolerability in patients who may otherwise have been receiving only BSC due to limited alternative options, which would manage the patient's illness, but with limited impact on survival. This is of particular importance in the HL setting, where a large proportion of cases diagnosed are in elderly patients,[1] who may not be eligible to receive chemotherapies because of their age or comorbidities.

In summary, availability of nivolumab would provide an opportunity to make a significant and substantial impact on health-related benefits and address a current unmet need, and the adoption of nivolumab in this therapeutic indication in NHS England would represent a further, significant advance in the management of this life-threating condition. This submission outlines the clinical efficacy of nivolumab for the treatment of relapsed and refractory HL, and details a cost-utility analysis outlining the cost-effectiveness of therapy.

## *3.3 Assessment of equality issues*

HL shows a clear bimodal age distribution, with a sharp peak in people aged 20–24 years and another in patients aged 75–79,[1] and each of these populations should be considered due to the divergence in their clinical pathways.

Due to existing comorbidities and concerns around age, fewer patients aged 75-79 will have undergone salvage chemotherapy and ASCT following first line chemotherapy failure, so that data describing the effectiveness of therapies post-ASCT and post-BTX is more scarce for these patients. Patients in this group are likely to have few, if any, treatment options, and as such are more likely to be receiving BSC, which has limited impact on symptoms, progression or survival and is associated with more hospital admissions, impacting on quality of life. As such, these patients have a high unmet need, and an efficacious therapy that is well-tolerated would represent a much needed treatment option. Nivolumab provides an additional treatment option with proven efficacy and tolerability, with the potential to impact on symptoms, progression and survival.

By contrast, patients aged 20-24 years have a greater range of treatment options available. However, onset of HL in this population restricts ability to study, work or participate in family life. Availability of a therapy that is efficacious in its own right and that may provide a bridge to potentially curative alloSCT could allow patients in this age group to live long and active lives, with significant indirect benefits to the patient, in terms of additional life years and freedom to achieve of life goals, as well as society, in terms of avoiding lost productivity.[11]

# 4 Clinical effectiveness

**Key points**

- Nivolumab therapy has significant benefits in terms of patient-relevant outcomes, including high response rates, improved survival (both PFS and OS) and rapid symptom control.
- Based on available evidence, the safety profile of nivolumab can be considered acceptable in the context of alternative therapies, such as standard chemotherapy regimens.[16] Further, this safety profile is well-established based on that observed in other indications.[8]
- Compared with standard of care, including chemotherapy, BTX re-treatment and investigational agents, nivolumab extends life expectancy, reduces progression and has improved tolerability.
- Unadjusted and matching-adjusted indirect comparisons (MAICs) of relevant nivolumab patient-level data were undertaken and demonstrated that nivolumab is associated with improved rates of response [redacted] and survival outcomes [redacted]

## *4.1 Identification and selection of relevant studies*

A systematic literature review (SLR) was conducted to identify studies that could inform the comparative effectiveness of nivolumab for the treatment of relapsed or refractory cHL after ASCT and treatment with BTX. Full methodology, including search strategies and eligibility criteria, is provided as Appendix 2.

In brief, electronic database searches in Embase, MEDLINE and the Cochrane Library were conducted in March 2016, in addition to manual searching of reference lists, systematic reviews and conference abstracts. Full eligibility criteria are reported in Appendix 2, but main inclusion criteria were:

- The study enrolled adult patients with relapsed or refractory cHL following prior ASCT and BTX
- Patients received any intervention aimed at managing cHL
- The study reported any outcome of interest, including OS, PFS, CR rate, PR rate, ORR or rate of SD.

**Figure 9. Flow diagram of included publications for systematic review**

**Table 4. Publications identified during SLR**

| Author | Study name | NCT identifier | Study type | Intervention | Dosing and administration |
|---|---|---|---|---|---|
| [redacted] | | | | | |

The study flow diagram is presented in Figure 9. Full details of excluded and included studies are presented in Appendix 2. Identified studies are described in Table 4. In total, [redacted] citations met the criteria for inclusion, encompassing [redacted] studies. Assessed therapies included:

[redacted]Additionally, a real world study provided evidence assessing the following therapies: investigational agents, chemotherapies (including gemcitabine, other alkylators and platinum-based therapy), bendamustine, brentuximab retreatment, ASCT and other therapies.[redacted] studies reported data describing

response rate (either ORR, CR or PR) for the [redacted]; however, survival outcomes were [redacted] reported, with [redacted] studies reporting median OS and [redacted] studies reporting median PFS.

[redacted]

In addition to CA209-039 and CheckMate 205 Cohort B, unpublished data from cohort B and C of CheckMate 205 are also available to inform the effectiveness of nivolumab in this indication and are detailed in this submission.

## *4.2 List of relevant randomised controlled trials*

Evidence to support the effectiveness of nivolumab for the treatment of relapsed or refractory cHL following ASCT and BTX therapy, the indication described in the regulatory application, is derived primarily from:

- CheckMate 205: a non-comparative, parallel-cohort, single-arm Phase 2 study in cHL patients ≥18 years old who failed ASCT. Patients enrolled into Cohort B and C are most relevant to the indication described in the regulatory submission (relapsed or refractory cHL after ASCT and treatment with BTX); however, supportive evidence from the total population is presented where possible.[13]
- CA209-039: an open-label, non-comparative, single-arm Phase 1 study of nivolumab for the treatment of haematological malignancies; data from the cohort of patients with cHL are presented.[14,15]

No relevant randomised controlled trials evaluating nivolumab for the treatment of HL were identified, so evidence from the single-arm studies is provided within Sections 4.3-4.8.

Although there are currently no data providing direct comparative evidence for nivolumab versus comparators, SLRs were conducted to identify any potentially relevant evidence, as described in Section 4.10.1. Data were summarised qualitatively to allow naïve indirect comparisons, and then two adjusted indirect comparisons were conducted, presented in Section 4.10, in order to inform comparative effectiveness decisions.

## 4.3 Summary of methodology of the relevant randomised controlled trials

A summary of methodology for each of the trials is provided in Section 4.7.

## 4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

An overview of statistical analysis methods and study group definitions are provided for each of the trials in Section 4.7.

## 4.5 Participant flow in the relevant randomised controlled trials

An overview of participant flow is provided for each of the trials in Section 4.7.

## 4.6 Quality assessment of the relevant randomised controlled trials

As previously described, no relevant randomised controlled trials evaluating nivolumab for the treatment of HL were identified, so evidence from the single-arm studies is provided within Sections 4.3-4.8.

**Table 5. Quality assessment of studies**

| | CheckMate 205 | CA209-039 |
|---|---|---|
| Was randomisation carried out appropriately? | Not applicable | Not applicable |
| Was the concealment of treatment allocation adequate? | Open-label study | Open-label study |
| Were the groups similar at the outset of the study in terms of prognostic factors? | Not applicable | Not applicable |
| Were the care providers, participants and outcome assessors blind to treatment allocation? | Open-label study | Open-label study |
| Were there any unexpected imbalances in drop-outs between groups? | Not applicable | Not applicable |
| Is there any evidence to suggest that the authors measured more outcomes than they reported? | Yes; the trial is ongoing, but data using additional follow-up will be made available as possible. | Yes; the trial is ongoing, but data using additional follow-up will be made available as possible. |
| Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data? | Efficacy analyses were performed for the treated population, defined as all patients who received at least 1 dose of nivolumab | All the patients who received at least one dose of nivolumab were included in the safety and efficacy analyses |

As studies assessing nivolumab were not randomised controlled trials, an assessment of the methodological quality was also conducted based on the Downs and Black instrument[58], as recommended by the Cochrane Handbook for Systematic Reviews of Interventions.[59]

**Table 6. Quality assessment of studies: Downs and Black instrument[58]**

| Description of criteria | Ansell (2015) | Younes (2016) |
|---|---|---|
| **Reporting** | | |
| Is the hypothesis/aim/objective of the study clearly described? | Yes | Yes |
| Are the main outcomes to be measured clearly described in the Introduction or Methods section? | Yes | Yes |
| Are the characteristics of the patients included in the study clearly described? | Yes | Yes |
| Are the interventions of interest clearly described? | Yes | Yes |
| Are the distributions of principal confounders in each group of subjects to be compared clearly described? | Not applicable | Not applicable |
| Are the main findings of the study clearly described? | Yes | Yes |
| Does the study provide estimates of the random variability in the data for the main outcomes? | Yes | Yes |
| Have all important adverse events that may be a consequence of the intervention been reported? | Yes | Yes |
| Have the characteristics of patients lost to follow-up been described? | Yes | Yes |
| Have actual probability values been reported (e.g.0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001? | Not applicable | Not applicable |
| **External validity** | | |
| Were the subjects asked to participate in the study representative of the entire population from which they were recruited? | Yes | Yes |
| Were those subjects who were prepared to participate representative of the entire population from which they were recruited? | Yes | Yes |
| Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive? | Yes | Yes |
| **Internal validity - bias** | | |
| Was an attempt made to blind study subjects to the intervention they have received? | No | No |
| Was an attempt made to blind those measuring the main outcomes of the intervention? | No | No |
| If any of the results of the study were based on “data dredging”, was this made clear? | Not applicable | Not applicable |
| In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls? | Not applicable | Not applicable |
| Were the statistical tests used to assess the main outcomes appropriate? | Not applicable | Not applicable |
| Was compliance with the intervention/s reliable? | Yes | Yes |
| Were the main outcome measures used accurate (valid and reliable)? | Yes | Yes |
| **Internal validity - confounding (selection bias)** | | |
| Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population? | Not applicable | Not applicable |
| Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time? | Not applicable | Not applicable |
| Were study subjects randomised to intervention groups? | No | No |
| Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable? | Not applicable | Not applicable |
| Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? | Not applicable | Not applicable |
| Were losses of patients to follow-up taken into account? | Not applicable | Yes |
| Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%? | Not applicable | Not applicable |

## 4.7 Clinical effectiveness results of the relevant randomised controlled trials

**Key points**

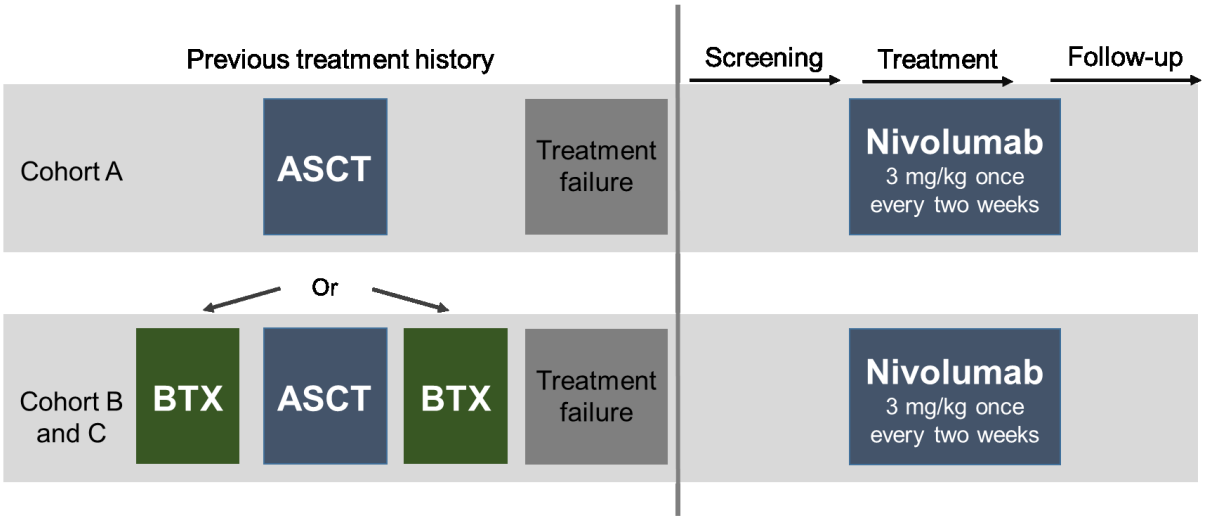
- Nivolumab therapy has significant benefits in terms of patient-relevant outcomes, including high response rates, improved survival (both PFS and OS), symptom control and an acceptable safety profile.
- Compared with standard of care, including chemotherapy, BTX re-treatment and investigational agents, nivolumab extends life expectancy, reduces progression and has improved tolerability.

### 4.7.1 CheckMate 205 (CA209-205)

#### *4.7.1.1 Study design*

CheckMate 205 is a non-comparative, parallel-cohort, single-arm Phase 2 study in cHL patients ≥18 years old who failed ASCT.[13] The study design schematic is presented as Figure 10. A single-arm (i.e. non-comparative) study design was chosen because of the small patient population, limiting patient recruitment, and because there is no appropriate, fully-approved active comparator for relapsed third-line or later cHL patients failing ASCT and BTX.

**Figure 10. Study design schematic for CheckMate 205[13]**




Patients enrolled in the study may have been BTX-naïve (Cohort A), or may have had prior BTX treatment as a salvage therapy after failure of ASCT (Cohort B), while patients in Cohort C could have prior ASCT and BTX in any treatment order.[13] Patients with a treatment history of BTX before first ASCT were not eligible for entry into Cohorts A and B.

Patients were independently enrolled for each cohort; as each cohort completed enrolment, other cohorts remained open until its complete accrual was reached. Due to the differing follow-up, two datasets for CheckMate 205 are presented within this submission:

- Cohort B as of the 20 August 2015 data cut-off date (clinical database lock: 05 October 2015; IRRC database lock: 20 October 2015), presenting a minimum of six months follow-up; available from published data and clinical study report (CSR)
- Cohort B and C as of the April 2016 data cut-off date, presenting a median follow-up of 15.7 months in Cohort B and 8.9 months in Cohort C. Data derived from preliminary analysis of patient-level data; further outcomes and data will be provided when available.

It is anticipated that additional follow-up from all cohorts will become available during the NICE appraisal process, and will be provided as evidence to support use of nivolumab in the population under consideration. It should be noted that data from Cohort A is less mature and will be the subject of separate regulatory filing in [redacted].

#### *4.7.1.2 Eligibility criteria*

Patients were considered eligible if they fulfilled the following key criteria:[13,60]

- Adult patients (at least 18 years of age).
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
- Received prior high-dose conditioning chemotherapy followed by ASCT as a part of salvage therapy for cHL.
- Confirmed documentation of cHL after failure of ASCT or after failure of ASCT and BTX.
- Cohort A: Patients who were naïve to BTX treatment and who met one of the following criteria according to the 2007 IWG criteria:
  - Documented absence of CR after 90 days from stem cell infusion for the most recent ASCT;
  - Documented relapsed disease (after CR) or disease progression (after PR or SD).
- Cohort B: Patients who failed treatment with BTX which was administered following failure of ASCT, and who met one of the following criteria according to the 2007 IWG criteria:
  - Documented failure to achieve at least PR after the most recent treatment;
  - Documented relapse disease (after CR) or disease progression (after PR or SD).
- Cohort C: Patients who failed ASCT and who received prior treatment with BTX at any time point (including BTX treatment as an initial therapy or salvage therapy before ASCT, and/or BTX treatment after ASCT), and who met one of the following criteria according to the 2007 IWG criteria:
  - Documented absence of CR after 90 days from stem cell infusion for the most recent ASCT;
  - Documented failure to achieve at least PR after the most recent chemotherapy or radiation therapy;
  - Documented relapse disease (after CR) or disease progression (after PR or SD).

Key exclusion criteria were:[13,60]

- Known central nervous system lymphoma or nodular lymphocyte-predominant HL.
- Active interstitial pneumonitis.
- Active, known or suspected autoimmune disease.
- A condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses >10 mg daily prednisone equivalents were permitted in the absence of active autoimmune disease.
- Patients with the following prior treatment history were excluded:
  - Prior treatment history with BTX administered before first ASCT, for Cohorts A and B.
  - ASCT ≤90 days prior to first dose of study drug.
  - Prior chemotherapy within 4 weeks, nitrosureas within 6 weeks, therapeutic anticancer antibodies within 4 weeks, radio- or toxin immunoconjugates (excluding BTX) within 10 weeks and BTX within 4 weeks or major surgery within 2 weeks prior to first dose of study drug.
  - Carmustine (BCNU) ≥600 mg/m² received as part of the pre-transplant conditioning regimen.
  - Prior radiation therapy within 3 weeks, or chest radiation ≤24 weeks prior to first dose of the study drug.
  - Prior treatment with an anti-programmed death-1 (PD-1), anti-PD-L1, anti-programmed death ligand 2 (PD-L2), anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
  - Prior alloSCT.

#### *4.7.1.3 Study medications*

All enrolled patients who met eligibility criteria were treated with nivolumab at 3 mg/kg, on day one of each two-week cycle, administered as an IV infusion over 60 minutes.[61] Patients were to be dosed no less than 12 days between doses and no more than three days after the scheduled dosing date.

Nivolumab dosing calculations were based on the patient's body weight, and dose reductions and escalations were not permitted. Dose delays were permitted of <6 weeks for all drug-related AEs according to pre-specified criteria. Treatment was permanently discontinued according to pre-specified criteria, due to AE, preparation for alloSCT or ASCT, or disease progression.[61]

**Treatment beyond disease progression**

Patients who met the criteria for progression defined by relapsed disease (after CR) or progressive disease (after PR or SD) were eligible to continue receiving study medication

beyond investigator-assessed progression as long as they met pre-specified criteria, including the following:[61]

- Investigator-assessed clinical benefit and do not have rapid disease progression
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression
- Tolerance of study drug.

#### *4.7.1.4 Study objectives*

**Primary endpoint**

The primary efficacy endpoint was ORR assessed by independent radiologic review committee (IRRC), defined as the proportion of patients with a best overall response (BOR) of CR or PR, according to the 2007 International Working Group (IWG) criteria.[13] The BOR was defined as the best response designation recorded between the date of first dose and the date of initial objectively documented progression per the 2007 IWG criteria or the date of subsequent therapy, whichever occurred first. For patients without documented progression or subsequent anticancer therapy, all available response designations contributed to the BOR determination. For patients who continued treatment beyond progression, the BOR was determined based on response designations recorded up to the time of initial progression.[13]

**Secondary and exploratory endpoints**

Relevant additional endpoints included:[13]

- Duration of response based on IRRC assessment: defined as the time from first response (CR or PR) to the date of the first documented tumour progression.
- CR rate and duration of CR based on IRRC assessment.
- PR rate and duration of PR based on IRRC assessment.
- ORR and duration of response based on investigator assessment.
- PFS by IRRC: defined as the time from the first dosing date to the date of the first documented tumour progression or death due to any cause, whichever occurred first.
- OS: defined as the time from first dosing date to the date of death.
- Safety: assessed as the frequency of deaths, AEs, SAEs, AEs leading to discontinuation of study drug and AEs leading to dose delay.
- Evaluation of quality of life changes: measured by mean changes from baseline in a generic measure (EQ-5D) or cancer-specific measure (EORTC-QLQ-C30).

#### *4.7.1.5 Statistical analyses*

For the interim data analysis, efficacy analyses were performed for the treated population, defined as all patients who received at least 1 dose of nivolumab.[13]

The primary endpoint (IRRC-assessed ORR) was estimated using a binomial response rate and its corresponding two-sided 95% exact CIs using the Clopper-Pearson method. The null hypothesis would be rejected if the 2-sided 95% CI lower bound was greater than 20%. The BOR was summarized by response category.[13]

Similarly, secondary endpoints assessing rate of response (IRRC-assessed CR rate, IRRC-assessed PR rate, and investigator-assessed ORR) were estimated using a binomial response rate and its corresponding two-sided 95% exact CIs using the Clopper-Pearson method.[13]

Times to event distributions, including duration of response, time to response, PFS, and OS, were estimated using Kaplan-Meier (K-M) methodology. When appropriate, the median along with 95% CI was provided using Brookmeyer and Crowley methodology. Rates at a fixed time point, such as OS or PFS at 6 months, were derived from the K-M estimate and corresponding CI was derived based on the Greenwood formula. CIs for binomial proportions were derived using the Clopper-Pearson method.[13]

#### *4.7.1.6 Sample size and power calculation*

The sample size for Cohorts A and B (n = 60) was determined based on two considerations: the ability to produce a CI which would exclude an ORR of 20%, which is not considered clinically relevant, and also provide sufficient information for a reliable understanding of the safety profile. Assuming the true ORR is 40%, each cohort has approximately 93% power to reject the null hypothesis that the true ORR is ≤20%, considering a 2-sided alpha of 5%.[13,61]

By contrast, the sample size for Cohort C (n=200) was empirically determined to support expanded assessment of the benefit-risk profile of nivolumab in cHL through observation of less common safety events.[13]

#### *4.7.1.7 Baseline demographics*

Table 7 summarises the demographics and baseline characteristics for patients enrolled into CheckMate 205. Within Cohort B, the majority of patients were white (88.8%) and male (63.8%), and the median age was 37 years, with three patients (3.8%) aged 65 years or older. All patients had a baseline ECOG PS of 0 or 1, with 52.5% having an ECOG PS of 1.[13]

At study entry, the majority of patients in Cohort B had Stage IV disease (67.5%) and extra lymphatic involvement and bone marrow involvement at baseline were reported in 45.0% and 10.0% of patients, respectively. The median time from initial diagnosis to the first dose of nivolumab was 6.2 years while the median time from the most recent transplant to the first dose of nivolumab was 3.4 years.[13]

All enrolled patients were heavily pre-treated, and previous treatments included radiotherapy, chemotherapy, ASCT, monoclonal immunotherapy, and steroids. Within Cohort B, the median number of prior systemic regimens was 4, with 48.8% receiving 5 or

more previous regimens. All patients had prior BTX and ASCT, with 6 patients undergoing ASCT twice. Best response to the most recent ASCT was CR or PR in 36.3% of patients and relapse/PD in 46.3%; 43 patients (53.8%) had no response (SD or PD/relapse) to most recent prior BTX treatment.[13]

**Table 7. CheckMate 205: Patient demographics and baseline characteristics[13,16]**

| | Cohort B | Total |
|---|---|---|
| N | 80 | 240 |
| Age (years) | | |
| Mean (SD) | 38.7 (13.00) | 37.1 (12.67) |
| Median (Min, Max) | 37.0 (18-72) | 34.0 (18-72) |
| < 30 | 27 (33.8%) | 88 (36.7%) |
| ≥30 and <65 | 50 (62.5%) | 145 (60.4%) |
| >= 65 | 3 (3.8%) | 7 (2.9%) |
| Gender, male (%) | 51 ( 63.8) | 141 ( 58.8) |
| Race (%) | | |
| White | 71 ( 88.8) | 208 ( 86.7) |
| Black Or African American | 4 ( 5.0) | 12 ( 5.0) |
| Asian | 1 ( 1.3) | 9 ( 3.8) |
| American Indian Or Alaska Native | 0 | 2 ( 0.8) |
| Other | 4 ( 5.0) | 9 ( 3.8) |
| Ethnicity (%) | | |
| Hispanic Or Latino | 1 ( 1.3) | 5 ( 2.1) |
| Not Hispanic Or Latino | 63 ( 78.8) | 147 ( 61.3) |
| Not Reported | 16 ( 20.0) | 88 ( 36.7) |
| Performance Status (ECOG) [%] | | |
| 0 | 42 ( 52.5) | 131 ( 54.6) |
| 1 | 38 ( 47.5) | 109 ( 45.4) |
| Disease Stage At Study Entry | | |
| Stage I | 1 ( 1.3) | 4 ( 1.7) |
| Stage II | 11 ( 13.8) | 51 ( 21.3) |
| Stage III | 14 ( 17.5) | 48 ( 20.0) |
| Stage IV | 54 ( 67.5) | 136 ( 56.7) |
| Not Reported | 0 | 1 ( 0.4) |
| Bulky Disease At Baseline | 17 ( 21.3) | 48 ( 20.0) |
| Extra Lymphatic Involvement At Baseline | 36 ( 45.0) | 99 ( 41.3) |
| Bone Marrow Involvement At Baseline | 8 ( 10.0) | 18 ( 7.5) |
| Median Time: Initial Diagnosis To First Dose Of Study Therapy (Years) [Min – Max] | 6.15 (1.3–25.1) | 4.43 (1.0–30.8) |
| Median Time: Most Recent Transplant To First Dose Of Study Therapy (Years) Min–Max | 3.37 (0.2–19.0) | 2.02 (0.2–19.0) |
| Number Of Prior Systemic Regimen Received | | |
| ≤2 | 0 | 37 (15.4) |
| 3 | 19 (23.8) | 66 (27.5) |
| 4 | 22 (27.5) | 65 (27.1) |
| ≥ 5 | 39 (48.8) | 72 (30.0) |
| Median (Min, Max) | 4 (3, 15) | 4 (1, 15) |
| Number Of Prior ASCT | | |
| 1 | 74 (92.5) | 233 (97.1) |
| ≥ 2 | 6 (7.5) | 7 (2.9) |
| Best Response To Most Recent ASCT | | |
| CR Or PR | 29 (36.3) | 107 (44.6) |
| SD | 6 (7.5) | 11 (4.6) |
| Relapse/PD | 37 (46.3) | 100 (41.7) |
| Unable To Determine/Not Reported | 8 (10.0) | 22 (9.2) |
| Best Response To Regimen Post Most Recent ASCT | | |
| CR Or PR | 37 (46.3) | 74 (30.8) |
| Stable disease | 10 (12.5) | 22 (9.2) |
| Relapse/PD | 25 (31.3) | 55 (22.9) |
| Unable To Determine/Not Reported | 8 (10.0) | 89 (37.1) |
| Prior Radiotherapy | 59 (73.8) | 161 (67.1) |
| Prior BTX Therapy | 80 (100.0) | 177 (73.8) |

ASCT: autologous stem cell transplant; BTX: brentuximab; CR: complete response; ECOG: Eastern Cooperative Oncology Group: PD: progressed disease; PR: partial response; SD: standard deviation

#### *4.7.1.8 Cohort B (Data cut-off: 20 August 2015)*

**Patient disposition**

For this interim analysis, the clinical database lock occurred on 5 October 2015 and the IRRC database lock occurred on 20 October 2015 for all 3 cohorts.[13] As of the data cut-off date for this report, 276 patients were enrolled in the study. Of the 276 patients enrolled, 240 were treated with nivolumab across the three cohorts (63 in Cohort A, 80 in Cohort B, and 97 in Cohort C). The most common reason given for not being treated was that the patient no longer met study entry criteria (25/276, 9.1%).[13]

Within Cohort B, the minimum follow-up in Cohort B was six months (median follow-up: 8.92 months). By contrast, there was insufficient follow-up to describe Cohorts A and C within this interim analysis (median follow-up: 5.09 and 2.83 months, respectively).[13]

Patient disposition in cohort B and in the total patient population is summarised in Table 8. In Cohorts B, the majority (51/80, 63.8%) of patients were still continuing in the treatment period and the most common reason for treatment discontinuation reported was disease progression (16.3%), followed by study drug toxicity (5.0%). Most patients (92.5%) were continuing in the study, either receiving study treatment or in survival follow-up.[13]

**Table 8. CheckMate 205: patient disposition[13]**

| | Cohort B | Total |
|---|---|---|
| Patients enrolled | - | 276 |
| Patients not entering the treatment period | - | 36 |
| Patients entering the treatment period | 80 | 240 |
| Patients continuing in the treatment period | 51 (63.8) | 195 (81.3) |
| Patients not continuing in the treatment period | 29 (36.3) | 45 (18.8) |
| Reason for not continuing in the treatment period (%) | | |
| Disease progression | 13 (16.3) | 20 (8.3) |
| Study drug toxicity | 4 (5.0) | 10 (4.2) |
| Patient request to discontinue study treatment | 2 (2.5) | 3 (1.3) |
| Lost to follow-up | 1 (1.3) | 1 (0.4) |
| Other | 8 (10.0) | 10 (4.2) |
| Not reported | 1 (1.3) | 1 (0.4) |
| Study | | |
| Patients continuing in the study | 74 (92.5) | 229 (95.4) |
| Patients not continuing in the study | 5 (6.3) | 10 (4.2) |
| Not reported | 1 (1.3) | 1 (0.4) |
| Reason for not continuing in the study | | |
| Death | 1 (1.3) | 5 (2.1) |
| Patient withdrew consent | 2 (2.5) | 3 (1.3) |
| Lost to follow-up | 2 (2.5) | 2 (0.8) |

In the study, all patients in the treated population had received at least one infusion of nivolumab. In Cohort B, the majority (76.3%) of patients received ≥90% of the planned dose

intensity, with a further 20.0% receiving 70% to <90% of the planned dose intensity. The median number of nivolumab doses received was 17; however the median duration of treatment was not reached.[13]

Dose delay occurred in 60.0% of patients in Cohort B, with 32.5% requiring more than 1 delay; however, the majority (84.5%) of delays lasted less than 14 days. The most common reasons for dose delay were reported as AEs (54.6%) and 'other' (45.4%). Infusion interruption was required in 5 (6.3%) patients; reasons given were hypersensitivity reaction (n=1) and other (n=4). Similarly, 4 (5.0%) patients required infusion rate reduction and reasons were reported as hypersensitivity reactions (n=2), infusion administration issues (n=1), and other (n=2).[13]

**Results**

Treatment with nivolumab resulted in robust antitumor activity in patients enrolled into Cohort B,[13] as summarised in Table 7. The primary endpoint of ORR as determined by IRRC was 66.3%, of which 7 patients achieved CR and 46 patients achieved PR. Investigator-assessed ORR was also high, achieved by 72.5% of patients (CR: 27.5%; PR: 45.0%). The rate of concordance between IRRC and investigator-assessments was 76.3% for objective response and discordance was due to interpretation of FDG-PET scans required for confirmation of CR. For this reason, IRRC-assessed CR rate was numerically lower than investigator-assessed CR (8.8% vs 27.5%), and the majority of investigator-assessed CRs considered not CRs by IRRC (13/19; 73.7%) were assessed as PRs by IRRC.[13]

These responses can also be considered durable; with minimum follow-up of 6 months and median follow-up of 8.9 months, the majority of the responders (62.3% as evaluated by IRRC) were continuing in response. However, 31/53 responders per IRRC and 37/58 per investigator were still on treatment at the time of analysis, and so estimates of the median duration of response are unstable due to early censoring.[13]

The median time to objective response (TTR) was 2.10 months (IRRC-assessed; investigator-assessed: 2.17 months), which increased to 4.44 months for time to CR (4.75 months for investigator-assessed CR). Of the 53 responders, 31 (58.5%) achieved their response by the time of first scan (9 weeks), and all of the responses were achieved within six months of treatment initiation.[13]

With 24 events (23 progressions and 1 death), IRRC-assessed PFS at six months was 76.9% and median PFS was 9.99 months; this increased to 82.6% for investigator-assessed PFS (16 progression events and 2 deaths), with a median PFS of 10.94 months. Rate of OS at six months was 98.7% (three events), and median OS was not reached.[13]

Of the 18 patients with B-symptoms (e.g. fever, night sweats, weight loss) present at baseline, 16 experienced complete resolution, with a mean time to resolution of 2.31 months (median: 1.91 months; range: 1.8-5.6 months), demonstrating that the majority of nivolumab-treated patients experience rapid symptom control.[13]

**Table 9. CheckMate 205: overview of efficacy endpoints (August 2015 data cut-off)[13]**

| | Cohort B, N=80 | |
|---|---|---|
| | **IRRC** | **Investigator** |
| **Primary endpoint** | | |
| Objective Response Rate (ORR), n (%) | 53 (66.3) | 58 (72.5) |
| (95% CI) | (54.8, 76.4) | (61.4, 81.9) |
| **Additional endpoints** | | |
| Duration of response: events | 11/53 | 9/58 |
| Median duration of response, months | 7.79 | 9.10 |
| Complete Remission (CR) | 7 (8.8) | 22 (27.5) |
| Partial Remission (PR) | 46 (57.5) | 36 (45.0) |
| Stable Disease (SD) | 18 (22.5) | 18 (22.5) |
| Relapsed or Progressive Disease (PD) | 6 (7.5) | 3 (3.8) |
| Unable to Determine (UTD) | 3 (3.8) | 1 (1.3) |
| Duration of CR: events | 1/7 | 1/22 |
| Median duration of CR, months | 4.63 | 8.74 |
| Duration of PR: events | 10/46 | 8/36 |
| Median duration of PR, months | 7.79 | 7.79 |
| PFS events | 24/80 | 18/80 |
| Median PFS, months (95% CI) | 9.99 (8.41, NA) | 10.94 (9.99, 11.56) |
| Six-month PFS rate, % (95% CI) | 76.9 (64.9, 85.3) | 82.6 (71.1, 89.8) |
| OS events | 3/80 | |
| Median OS, months (95% CI) | NA | |
| Six-month OS rate, % (95% CI) | 98.7 (91.0, 99.8) | |

CI: confidence interval; CR: complete response; IRRC: Independent Regulatory Review Committee; ORR: objective response rate; OS: overall survival; PD: progressed disease; PFS: progression-free survival; PR: partial response; SD: stable disease; UTD: unable to determine.

**Figure 11. CheckMate 205: Kaplan-Meier plot of IRRC-assessed PFS (Cohort B; 20 August 2015 data cut-off)[13]**

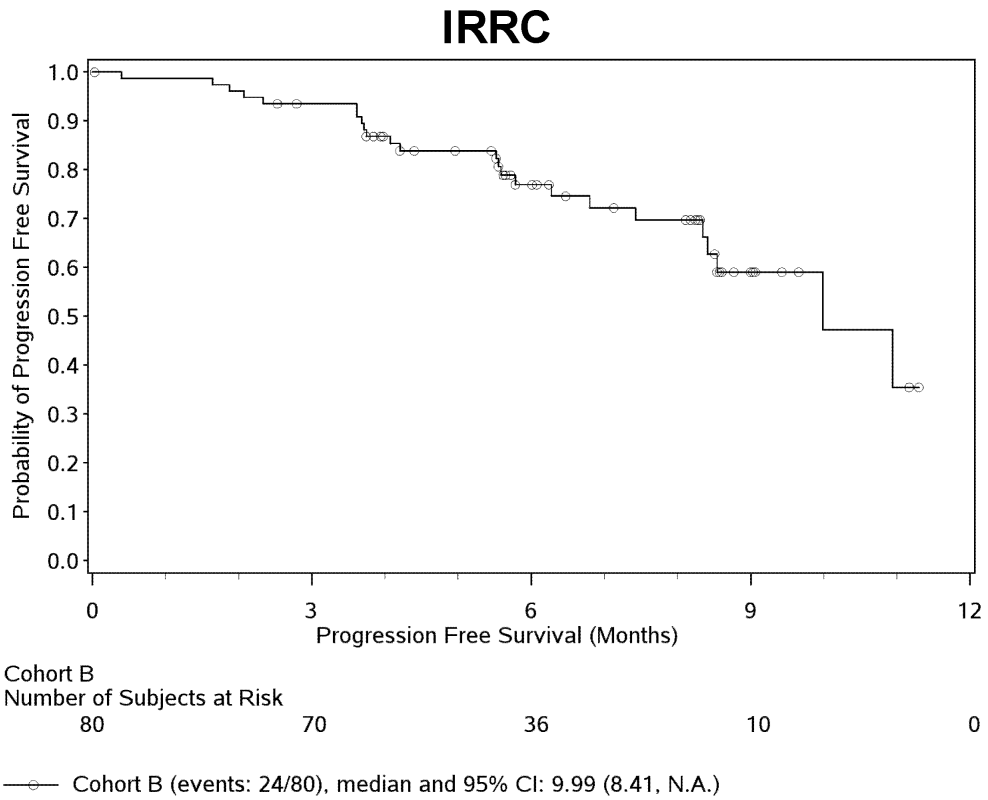



**Figure 12. CheckMate 205: Kaplan-Meier plot of investigator-assessed PFS (Cohort B; 20 August 2015 data cut-off)[13]**

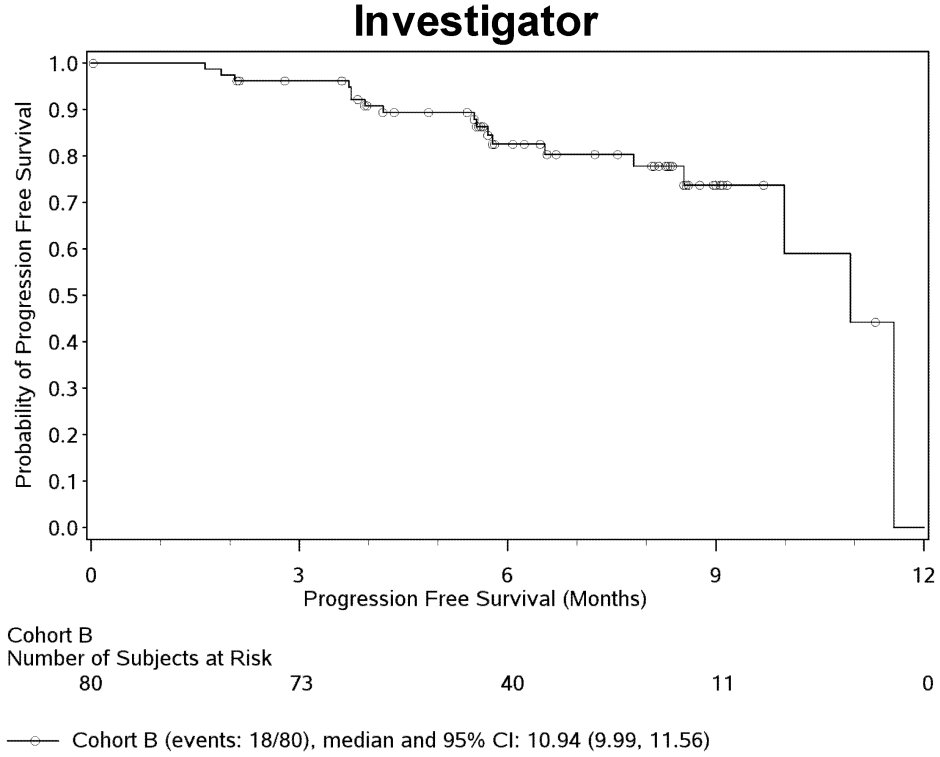
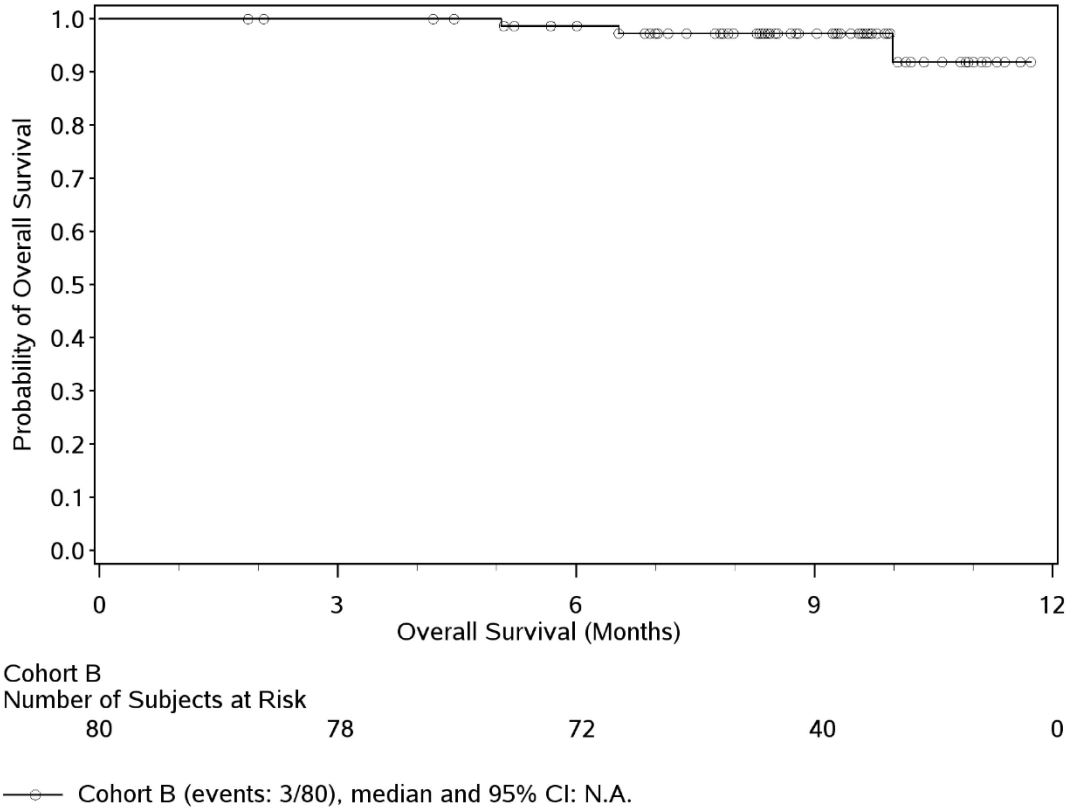


**Figure 13. CheckMate 205: Kaplan-Meier plot of overall survival (Cohort B)[13]**




*Efficacy of nivolumab following progression*

Patients could receive nivolumab treatment beyond progression according to specific criteria, described in Section 4.7.1.3.[13] [redacted] Cohort B patients who had progressed as assessed by the investigators were subsequently considered eligible to receive continued nivolumab therapy. Before treatment beyond progression was initiated, the investigator-assessed BOR was [redacted]. The number of doses received beyond progression ranged from [redacted] and the duration of treatment beyond progression ranged from [redacted]. Outcomes in terms of tumour burden are depicted in

Figure 14. Among these [redacted] patients treated beyond progression, [redacted] maintained tumour reduction in target lesion compared to baseline.[13]

**Figure 14. Investigator-assessed tumour burden change in patients receiving nivolumab beyond progression[13]**

*Graft-versus-host disease after post-study transplant*

Six patients in Cohort B elected to discontinue study drug and proceed to SCT (5 alloSCT and 1 ASCT). Grade 1-2 acute graft-versus-host disease was reported in three patients. All six patient remained alive at data cut-off.[13] Further information pertaining to outcomes following alloSCT in patients with HL is described in Section 4.13.1.

**Quality of life outcomes**

Two quality of life measures were utilised during CheckMate 205: EORTC-QLQ-C30 questionnaire version 3 was used to assess cancer-related quality of life, as well as the generic health status measure, EQ-5D.

*EORTC-QLQ-C30*

The EORTC-QLQ-C30 is made up of 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), a global health status/quality of life scale, 3 symptom scales (fatigue, nausea, and pain), and 6 individual items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). Analysis of EORTC-QLQ-C30 was performed on patients who had an assessment at baseline and at least one post baseline assessment. The scale scores range from 0 to 100, with higher scores for all functional scales and global health status/quality of life scale indicating better health-related quality of life (HRQoL); positive change scores indicate improvement in HRQoL compared to baseline. By contrast, lower scores for symptom scales indicate better status; negative change scores indicate improvement in symptoms compared to baseline. A score difference of 10 is used as an estimate of the minimal important difference (MID) for all subscales of the EORTC-QLQ C30, including the symptom scales.

Questionnaire completion rate at baseline for Cohort B patients was 93.8% and remained greater than 80% for each visit for patients that were still participating in the study, from baseline to visit at week 33.
[redacted]The EORTC-QLQ-C30 scores [redacted] over time with mean changes trending towards [redacted] across functional and symptom scales. [redacted]

- Role function at Week 9 (mean change=10.7, SD 29.0)
- Social function at Week 33 (mean change=10.6, SD 23.5)
- Insomnia at Week 33 (mean change=-12.2, SD 25.6)

*EQ-5D*

The EQ-5D visual analogue scale elicits patients' ratings of their health status on a 0 to 100 scale with 0 being the worst imaginable health state and 100 being the best imaginable health state. The baseline score for the EQ-5D VAS for the Cohort B patients was [redacted]. The average EQ-5D VAS score [redacted] over time and [redacted] the average baseline score by [redacted] minimal important difference from [redacted]. Utility valuation for application within the economic is described in Appendix 7.

#### *4.7.1.9 Cohort B and C (Data cut-off: April 2016)*

**Patient disposition**

As of the data cut-off date for this report, 243 patients have been treated with nivolumab across the three cohorts (63 in Cohort A, 80 in Cohort B, and 100 in Cohort C). Of these patients, 67 have discontinued treatment (37 in Cohort B and 30 in Cohort C), as described in **Error! Not a valid bookmark self-reference.**. Within Cohort C, two of the enrolled patients had previously received ASCT but not BTX; of these patients (Table 11), one had discontinued therapy at the time of the data cut. Data presented for Cohort C include the two patients who had previously received ASCT but not BTX. Baseline characteristics for Cohort C, including patients enrolled following the previous data cut-off, are presented in Table 12.

**Table 10. CheckMate 205: patient disposition (April 2016 data cut-off)**

| | Cohort B | Cohort C | Total |
|---|---|---|---|
| Patients entering the treatment period | 80 | 100 | [redacted] |
| Patients continuing in the treatment period | 43 (53.8) | 70 (70.0) | [redacted] |
| Patients not continuing in the treatment period | 37 (46.3) | 30 (30.0) | [redacted] |

**Table 11. CheckMate 205: Treatment history (April 2016 data cut-off)**

| | Cohort B | Cohort C | Total |
|---|---|---|---|
| BTX after ASCT | 79 | 57 | 136 |
| BTX before ASCT | 0 | 33 | 33 |
| BTX both before and after ASCT | 0 | 8 | 8 |
| ASCT both before and after BTX | 1 | 0 | 1 |
| Other | 0 | 1* | 65** |
| Total | | | 243 |

ASCT: autologous stem cell transplant; BTX: brentuximab.
* includes ASCT but not BTX
** includes 64 patients with prior ASCT only i.e. Cohort A, which is not detailed here.

**Table 12. CheckMate 205: Patient demographics and baseline characteristics (April 2016 data cut-off)**

| | Cohort B | Cohort B | Cohort C |
|---|---|---|---|
| N | 80 | | |
| Age (years) | | | |
| Mean (SD) | 38.7 (13.00) | | |
| Median (Min, Max) | 37.0 (18-72) | | |
| < 30 | 27 (33.8%) | | |
| ≥30 and <65 | 50 (62.5%) | | |
| >= 65 | 3 (3.8%) | | |
| Gender, male (%) | 51 ( 63.8) | | |
| Race (%) | | | |
| White | 71 ( 88.8) | | |
| Black Or African American | 4 ( 5.0) | | |
| Asian | 1 ( 1.3) | | |
| American Indian Or Alaska Native | 0 | | |
| Native Hawaiian Or Other Pacific Islander | 0 | | |
| Other | 4 ( 5.0) | | |
| Ethnicity (%) | | | |
| Hispanic Or Latino | 1 ( 1.3) | | |
| Not Hispanic Or Latino | 63 ( 78.8) | | |
| Not Reported | 16 ( 20.0) | | |
| Performance Status (ECOG) [%] | | | |
| 0 | 42 ( 52.5) | | |
| 1 | 38 ( 47.5) | | |
| Disease Stage At Study Entry | | | |
| Stage I | 1 ( 1.3) | | |
| Stage II | 11 ( 13.8) | | |
| Stage III | 14 ( 17.5) | | |
| Stage IV | 54 ( 67.5) | | |
| Not Reported | 0 | | |
| Bulky Disease At Baseline | 17 ( 21.3) | | |
| Extra Lymphatic Involvement At Baseline | 36 ( 45.0) | | |
| Bone Marrow Involvement At Baseline | 8 ( 10.0) | | |
| Median Time: Initial Diagnosis To First Dose Of Study Therapy (Years) [Min – Max] | 6.15 (1.3–25.1) | | |
| Median Time: Most Recent Transplant To First Dose Of Study Therapy (Years) Min–Max | 3.37 (0.2–19.0) | | |
| Number Of Prior Systemic Regimen Received | | | |
| ≤2 | 0 | | |
| 3 | 19 (23.8) | | |
| 4 | 22 (27.5) | | |
| ≥ 5 | 39 (48.8) | | |
| Median (Min, Max) | 4 (3, 15) | | |
| Number Of Prior ASCT | | | |
| 1 | 74 (92.5) | | |
| ≥ 2 | 6 (7.5) | | |
| Best Response To Most Recent ASCT | | | |
| CR Or PR | 29 (36.3) | | |
| SD | 6 (7.5) | | |
| Relapse/PD | 37 (46.3) | | |
| Unable To Determine/Not Reported | 8 (10.0) | | |
| Best Response To Regimen Post Most Recent ASCT | | | |
| CR Or PR | 37 (46.3) | | |
| SD | 10 (12.5) | | |
| Relapse/PD | 25 (31.3) | | |
| Unable To Determine/Not Reported | 8 (10.0) | | |
| Prior Radiotherapy | 59 (73.8) | | |
| Prior Brentuximab Therapy | 80 (100.0) | | |

**Results**

Similar to the August 2015 data cut-off, interim data analysis from the April 2016 data cut-off demonstrated that treatment with nivolumab resulted in robust antitumor activity in patients enrolled into both Cohorts B and C, as summarised in Table 13. The primary endpoint of ORR as determined by IRRC was 67.5% in Cohort B (CR: 7.5%; PR: 60.0%) and 73.0% in Cohort C (CR: 17.0%; PR: 56.0%). Investigator-assessed ORR was also high, achieved by 75.0% of patients in Cohort B (CR: 32.5%; PR: 42.5%) and 66.0% of patients in Cohort C (CR: 26.0%; PR: 40.0%). These responses can also be considered durable; with median follow-up of 15.7 months and 8.9 months, the majority of the responders (66.7% in Cohort B and 80.8% in Cohort C, as evaluated by IRRC) were continuing in response.

Within Cohort B, there were [redacted] IRRC-assessed PFS events, resulting in a median PFS of 14.8 months and PFS at six months of 79.8%. Similarly in Cohort C, there were [redacted] IRRC-assessed PFS events so that PFS at six months was 74.4% and median PFS was 11.2 months. However, investigator-assessed PFS at six months was higher in both cohorts [redacted] and 79.2% in cohort C), resulting in longer median PFS (Cohort B: not available; Cohort C: 11.2 months).

There were few deaths in both cohorts, so that median OS was not reached; at six months rate of OS was 97.5% in Cohort B [redacted] events at database lock) and 94.0% in Cohort C [redacted] events at database lock).

**Table 13. CheckMate 205: overview of efficacy endpoints (April 2016 data cut-off)**

| | Cohort B, N=80 | | Cohort C, N=100 | |
|---|---|---|---|---|
| | IRRC | Investigator | IRRC | Investigator |
| **Primary endpoint** | | | | |
| Objective Response Rate (ORR), n (%) | 54 (67.5) | [redacted] | 73 (73.0) | 66 (66.0) |
| (95% CI) | (57.2, 77.8) | [redacted] | (64.3, 81.7) | (56.7, 75.3) |
| **Additional endpoints** | | | | |
| Duration of response: events | 18/54 | [redacted] | 14/73 | 9/66 |
| Median duration of response, months | [redacted] | [redacted] | 4.17 | 4.17 |
| Complete Remission (CR) | 6 (7.5) | [redacted] | 17 (17.0) | 26 (26.0) |
| Partial Remission (PR) | 48 (60.0) | [redacted] | 56 (56.0) | 40 (40.0) |
| Stable Disease (SD) | 17 (21.3) | [redacted] | [redacted] | [redacted] |
| Relapsed or Progressive Disease (PD) | 7 (8.8) | [redacted] | [redacted] | [redacted] |
| Unable to Determine (UTD)/NA | 2 (2.5) | [redacted] | [redacted] | [redacted] |
| Duration of CR: events | 1/6 | [redacted] | [redacted] | [redacted] |
| Median duration of CR, months | [redacted] | [redacted] | [redacted] | [redacted] |
| Duration of PR: events | 17/48 | [redacted] | [redacted] | [redacted] |
| Median duration of PR, months | [redacted] | [redacted] | [redacted] | [redacted] |
| PFS events | 32/80 | [redacted] | [redacted] | [redacted] |
| Median PFS, months (95% CI) | 14.78 (11.33, NA) | [redacted] | 11.17 (8.51, NA) | 11.40 (11.17, NA) |
| Six-month PFS rate, % (95% CI) | 79.7 (71.2, 89.4) | [redacted] | 74.4 (65.5, 84.4) | 79.2 (71.0, 88.4) |
| OS events | [redacted] | | [redacted] | |
| Median OS, months (95% CI) | NA | | NA | |
| Six-month OS rate, % (95% CI) | 96.1 (92.0, 100) | | 94.0 (89.1, 98.9) | |

CI: confidence interval; CR: complete remission; IRRC: independent radiological review committee; NA: not available; ORR: objective response rate; OS: overall survival; PD: progressed disease; PFS: progression-free survival; PR: partial remission; SD: stable disease; UTD: unable to determine.

### 4.7.2 CA209-039

#### *4.7.1.1 Study design*

This is an open-label, non-comparative, single-arm Phase 1 study of nivolumab for the treatment of haematological malignancies, including cHL.[15,17] A single-arm (i.e. non-comparative) study design was chosen because of the small patient population, limiting patient recruitment, and because there is no appropriate, fully-approved active comparator for relapsed third-line or later cHL patients failing ASCT and BTX.

The dose escalation phase of the study assessed patients with relapsed/refractory haematological malignancies who received nivolumab 1 mg/kg and 3 mg/kg); this was followed by four expansion cohorts studying different types of haematological malignancy, with evidence from the HL population presented within this submission.

While this study allowed enrolment for any type of HL, including nodular lymphocyte predominant Hodgkin disease, all HL patients who enrolled in the nivolumab monotherapy cohort (n = 23) were treated with 3 mg/kg and had cHL.[15] Of these 23 patients, 15 had previously received both ASCT and BTX, and so are most relevant to the patient population of interest.

Data presented within this submission is derived from published data based on a database lock on 16 June 2014 (median follow-up: 40 weeks),[14] as well as unpublished evidence from the most recent database lock (11 August 2015; median follow-up: 23.3 months).[15]

#### *4.7.1.2 Eligibility criteria*

While the study enrolled and treated patients with relapsed refractory haematological malignancies (HL, multiple myeloma, non-HL (NHL) and T-cell lymphoma), only the patients with relapsed or refractory cHL and treated with nivolumab monotherapy are presented within this submission. While this study allowed enrolment for any type of HL, all HL patients (n =23) had cHL. Patients with prior alloSCT transplant or autoimmune disorders were excluded.[15]

Patients were considered eligible if they fulfilled the following key criteria:[15,17]

- Adult patients (≥18 years of age).
- ECOG performance status 0 or 1.
- Histological confirmation of relapsed or refractory hematologic malignancy
- Patients with HL must have had at least one measureable lesion > 1.5 cm as defined by lymphoma response criteria. Patients must also have had an additional lesion that was amenable for biopsy. Patients with lesions in a previously radiated field as the sole site of measurable disease were permitted to enrol provided the lesion had demonstrated clear progression and could be measured accurately.
- More than 100 days post-ASCT
- At least one prior chemotherapy regimen; patients had been off therapy for at least 3 weeks (3 weeks for subcutaneous, 2 weeks for oral agents, 1 week for topical agents) prior to Day 1

- Prior palliative radiation must have been completed at least 2 weeks prior to study Day 1
- History of BTX treatment or could be BTX naive to be eligible. Patients were not required to have failed BTX treatment to be eligible for the study

Key exclusion criteria were:[15,17]

- Myelodysplasia, polycythaemia vera, idiopathic thrombocythaemia, myelofibrosis, acute leukaemias, chronic myeloid leukaemia, T-cell lymphoblastic or Burkitt lymphoma
- History of central nervous system involvement by haematological malignancy or symptoms suggestive of central nervous system involvement
- History of chest radiation ≤24 weeks prior to first dose of study medication
- Active autoimmune disease or a history of known or suspected autoimmune disease, or history of a syndrome that requires systemic corticosteroids or immunosuppressive medications
- A serious uncontrolled medical disorder or active infection
- Deep vein thrombosis not adequately controlled
- Uncontrolled or significant cardiovascular disease
- Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137 or anti CTLA-4 antibody (or any other antibody or drug specifically targeting T-cell stimulation or checkpoint pathways).
- History of Grade 4 anaphylactic reaction to monoclonal antibody therapy

#### *4.7.1.3 Study medications*

All cHL patients enrolled in the extension phase of the study received nivolumab 3 mg/kg by IV infusion.[14,15] The first dose was followed by a three-week evaluation period, with subsequent doses administered every 2 weeks.

Therapy was continued for up to 2 years, with the potential for retreatment in eligible patients; dose reductions and escalations were not permitted.[15] Dose delays were permitted of <6 weeks for all drug-related AEs according to pre-specified criteria. Treatment was permanently discontinued due to AEs according to pre-specified criteria. Patients with a CR may have continued to receive study therapy until response confirmation or for an additional 16 weeks (whichever is longer) and then enter the follow-up period.[15]

**Treatment beyond disease progression**

Patients who met the criteria for disease progression may have continued to receive study medication beyond investigator-assessed progression as long as they met pre-specified criteria, including the following:[15]

- Investigator-assessed clinical benefit
- Disease progression is not rapid
- Stable performance status

- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression
- Tolerance of study drug.
- Patients have provided written informed consent prior to receiving additional treatment

#### *4.7.1.4 Study objectives*

The primary objective was to evaluate the safety and side-effect profile of nivolumab, while secondary objectives included characterising the efficacy of nivolumab in patients with relapsed/refractory hematologic malignancy.[15] The primary efficacy endpoint was investigator-assessed ORR using the protocol-defined International Workshop to Standardized Response Criteria for Lymphomas. The secondary efficacy endpoint was IRRC-assessed ORR using 2007 IWG criteria, while additional endpoints included TTR, time to CR, time to PR, duration of response, PFS and OS.[15]

#### *4.7.1.5 Statistical analyses*

All the patients who received at least one dose of nivolumab were included in the safety and efficacy analyses.[14] All efficacy and safety analyses in cHL patients were performed on three populations: all patients; patients with prior ASCT/BTX failure (Post-ASCT/BTX); and patients with other treatment histories (Other).[15]

BOR was defined as the best response between the date of the first dose and the last efficacy assessment before subsequent therapy.[14] ORR was defined as the proportion of the total number of patients whose BOR was either CR or PR. CR was defined as tumour regression to 1.5 cm or less in greatest diameter, if the tumour measured more than 1.5 cm before therapy, or a decrease in previously involved nodes measuring 1.1 to 1.5 cm in greatest diameter to 1 cm or less or a decrease of more than 75%, with negative results on PET scanning. PFS was defined as the time from the date of the first dose of study medication to the date of first disease progression or the date of death, and was estimated with the use of Kaplan–Meier methods. The time to a response was defined as the time from the date of the first dose to the date of the first response. The duration of a response was defined as the time between the date of the first response and the date of first progression or the date of death.[14]

ORR, CR and PR were estimated using a binomial response rate and its corresponding two-sided 95% exact CIs using the Clopper-Pearson method.[15] Time to event distributions, including PFS, OS and duration of response, were estimated using the K-M method. When appropriate, the median along with 95% CI was provided using Brookmeyer and Crowley methodology (using log-log transformation for constructing the confidence intervals). Rates at fixed time points, such as PFS at 6 months or OS at 12 months, were derived from the K-M estimate and corresponding confidence interval were derived based on the Greenwood formula. Confidence intervals for binomial proportions were derived using the Clopper-Pearson method.[15]

#### *4.7.1.6 Sample size and power calculation*

Approximately 23 patients were expected to be enrolled in the expansion phase, and if 4 (17.4%) or 5 (21.7%) responses were observed among 23 patients, then the lower limit of the 90% one-sided confidence intervals for ORR would be 7.8% and11.0% respectively.[15] In addition, if the true ORR in an expansion cohort is 20%, then with 23 patients, there was 86.7% chance of observing at least 3 responses or 13.3% chance of observing 0, 1 or 2 responses (false negative rate). If the true ORR in a tumour type is 5% rather than 20%, then there is 10.5% chance that there would be at least 3 responses in 23 patients (false positive rate).[15]

#### *4.7.1.7 Patient disposition*

For the unpublished analysis, the database lock occurred on 11 August 2015.[15] At this follow-up time, 20 of the 23 cHL patients were off study treatment at the time of this report for reasons of disease progression (n=6), maximum clinical benefit (n=6; defined as achieving CR or completing two years of therapy), study drug toxicity (n=2), patient request (n=2), or other reasons, such as transplant (n=4). An overview of patient disposition is provided in Table 14.[15]

**Table 14. CA209-039: patient disposition**

| | Post ASCT/BTX | Other | All |
|---|---|---|---|
| Number of patients | 15 | 8 | 23 |
| Patients continuing in the treatment period | 2 (13.3) | 1 (12.5) | 3 (13.0) |
| Patients not continuing in the treatment period | 13 (86.7) | 7 (87.5) | 20 (87.0) |
| **Reason for not continuing in the treatment period (%)** | | | |
| Disease progression | 5 (33.3) | 1 (12.5) | 6 (26.1) |
| Study drug toxicity | 2 (13.3) | 0 | 2 (8.7) |
| Patient request to discontinue study treatment | 2 (13.3) | 0 | 2 (8.7) |
| Maximum clinical benefit | 3 (20.0) | 3 (37.5) | 6 (26.1) |
| Other | 1 (6.7) | 3 (37.5) | 4 (17.4) |
| Patients continuing in the study | 14 (93.3) | 8 (100.0) | 22 (95.7) |
| Patients not continuing in the study | 1 (6.7) | 0 | 1 (4.3) |
| **Reason for not continuing in the study** | | | |
| Death | 1 (6.7) | 0 | 1 (4.3) |

ASCT: autologous stem cell transplant; BTX: brentuximab.

In the study, all patients in the treated population had received at least one infusion of nivolumab.[15] The majority of patients (78.3%) received ≥ 90% of the planned dose intensity and the remaining patients (21.7%) received 70% to <90%. The median number of nivolumab doses received for all patients was 18 (range: 6-48 doses). Patients achieving CR (n=5) were eligible to discontinue therapy, and in these patients, the number of doses ranged from 10 to 40. The median duration of study therapy was 8.2 months (95% CI: 5.29, 15.87).[15]

#### *4.7.1.8 Baseline demographics*

Table 15 summarises the demographics and baseline characteristics for patients enrolled into CA209-039. The median age was 35 years (range: 20 to 54), and 17 patients (74%) had an ECOG performance-status score of 1.[14] Extranodal disease involving bone, lung, pelvis, peritoneum or pleura was found in 17% of the patients. With one exception, all the patients had the nodular sclerosis type of HL; the remaining patient had mixed cellularity.[14]

All the patients had been extensively pre-treated, with 87% having received three or more previous treatment regimens; 78% of the patients had received BTX previously, and 78% had undergone ASCT.[14] Among the 23 cHL patients, 15 received prior BTX treatment as a salvage therapy after failure of ASCT (post-ASCT/BTX); 8 patients had treatment histories categorised as other, including those who had failed ASCT and were BTX-naïve (n=2), failed BTX and ASCT-naïve (n=2), failed BTX prior to ASCT failure (n=1) or naïve to both ASCT and BTX (n=3).[15]

**Table 15. CA209-039: Patient demographics and baseline characteristics[14]**

| Characteristic | All patients |
|---|---|
| N | 23 |
| Median age (years) | 35 |
| Range | 20–54 |
| Gender, male (%) | 12 (52) |
| Race (%) | |
| White | 20 (87) |
| Black | 2 (9) |
| Other | 1 (4) |
| Performance Status (ECOG) [%] | |
| 0 | 6 (26) |
| 1 | 17 (74) |
| Histologic findings (%) | |
| Nodular sclerosis | 22 (96) |
| Mixed cellularity | 1 (4) |
| Number Of Prior Systemic Regimen Received | |
| 2 or 3 | 8 (35) |
| 4 or 5 | 7 (30) |
| ≥ 6 | 8 (35) |
| Previous treatments (%) | |
| Brentuximab | 18 (78) |
| ASCT | 18 (78) |
| Radiotherapy | 19 (83) |
| Extranodal involvement | 4 (17) |
| ASCT: autologous stem cell transplant; ECOG: Eastern Cooperative Oncology Group | |

#### *4.7.1.9 Results*

Nivolumab monotherapy had clinically meaningful anti-tumour activity in patients with cHL, and this was independent of BTX and ASCT history, as demonstrated by the high ORRs presented in Table 16 and Table 17. At 40 weeks median follow-up, ORR as assessed by

the investigator was 87%, with CR occurring in 4 patients (17%), PR in 16 patients (70%), and SD in 3 patients (13%).[14] Response rates at 23.3 months median follow-up were similarly high (87% per investigator and 61% per IRRC), with a rapid median time to response (1.7 months per investigator and 1.2 months per IRRC).[15] Further, median duration of response, PFS and OS were not reached.

**Table 16. CA209-039: efficacy at 40 weeks follow-up[14]**

| Variable | Post BTX/ASCT | Post BTX (no ASCT) | No BTX | Total |
|---|---|---|---|---|
| N | 15 | 3 | 5 | 23 |
| **Best overall response — no. (%)** | | | | |
| Complete response | 1 (7) | 0 | 3 (60) | 4 (17) |
| Partial response | 12 (80) | 3 (100) | 1 (20) | 16 (70) |
| Stable disease | 2 (13) | 0 | 1 (20) | 3 (13) |
| Progressive disease | 0 | 0 | 0 | 0 |
| **Objective response** | | | | |
| No. of patients | 13 | 3 | 4 | 20 |
| Percent of patients (95% CI) | 87 (60–98) | 100 (29-100) | 80 (28–99) | 87 (66–97) |
| **Survival** | | | | |
| Progression-free survival at 24 wk % (95% CI) | 85 (52–96) | NC* | 80 (20–97) | 86 (62–95) |
| Overall survival — wk | | | | |
| Median | NR | NR | NR | NR |
| Range at data cutoff† | 21–75 | 32–55 | 30–50 | 21–75 |

ASCT: autologous stem cell transplant; BTX: brentuximab; CI: confidence interval; NC: not calculated; NR: not reached.
* The estimate was not calculated when the percentage of data censoring was above 25%.
† Responses were ongoing in 11 patients.

**Table 17. CA209-039: efficacy at 23.3 months follow-up[15]**

| | Post-BTX/ASCT, N=15 | | Other, N=8 | | All, N=23 | |
|---|---|---|---|---|---|---|
| | IRRC | Investigator | IRRC | Investigator | IRRC | Investigator |
| ORR, n (%) | 9 (60) | 13 (87) | 5 (63) | 7(88) | 14 (61) | 20 (87) |
| CR, n (%) | 0 | 2 (13) | 3 (38) | 3 (38) | 3 (13) | 5 (22) |
| PR, n (%) | 9 (60) | 11(73) | 2 (25) | 4 (50) | 11 (48) | 15 (65) |
| SD, n (%) | 5 (33) | 2 (13) | 2 (25) | 1 (13) | 7 (30) | (3) |
| Median duration of response, months | 12.0 | NA | NA | NA | NA | NA |
| Median time to response, months | 0.8 | 1.7 | 1.6 | 2.6 | 1.2 | 1.7 |
| Median time to CR, months | - | 10.8 | 12.4 | 5.3 | 12.5 | 5.3 |
| Median time to PR, months | 0.82 | 1.7 | 1.17 | 3.5 | 0.8 | 1.7 |
| PFS events | 6/15 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Median PFS, months (95% CI) | 12.65 (5.91, NA) | [redacted] | [redacted] | [redacted] | NA (8.97, NA) | NA (18.56, NA) |
| One-year PFS rate, % (95% CI) | NC | [redacted] | [redacted] | [redacted] | NC | NC |
| OS events | [redacted] | | [redacted] | | [redacted] | |
| Median OS, months (95% CI) | [redacted] | | [redacted] | | NA | |
| One-year OS rate, % (95% CI) | [redacted] | | [redacted] | | 91.3 (69.5, 97.8) | |

ASCT: autologous stem cell transplant; BTX: brentuximab; CR: complete response; IRRC: Independent Regulatory Review Committee; NA: Not available; NC: not calculated; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PR: partial response; SD: stable disease.

**Figure 15. CA209-039: Kaplan-Meier plot of investigator-assessed progression-free survival in all cHL patients receiving nivolumab[15]**

**Figure 16. CA209-039: Kaplan-Meier plot of overall survival in all cHL patients receiving nivolumab[15]**

**Efficacy of nivolumab following progression**

Patients could receive nivolumab treatment beyond progression according to pre-specified criteria.[15] [redacted] patients met the criteria for treatment beyond progression during CA209-039,

of which [redacted] Of these, [redacted] patient achieved [redacted] before disease progression was recorded; [redacted] Outcomes in terms of tumour burden are depicted in

Figure 17 (responders) and

Figure 18 (non-responders).[15]

**Figure 17. CA209-039: investigator-assessed tumour burden change in patients receiving nivolumab beyond progression (responders)[15]**

[redacted]

**Figure 18. CA209-039: investigator-assessed tumour burden change in one non-responder patient receiving nivolumab beyond progression[15]**

## *4.8 Subgroup analysis*

### 4.8.1 CheckMate 205 Cohort B subgroup analysis of the primary endpoint: IRRC-assessed ORR

Post-hoc subgroup analyses were conducted in CheckMate 205, to assess the impact of multiple factors on ORR, as assessed by IRRC.[13] These variables included: age; gender; race; region; smoking status; B-symptoms at initial diagnosis; baseline ECOG performance status; time from initial diagnosis to first ASCT; time from most recent ASCT to first subsequent therapy, and; number of prior lines of cancer therapy excluding preparative regimens. **Error! Not a valid bookmark self-reference.** summarises the subgroup analysis of Cohort B, which showed that ORR remained consistent across subgroups.

**Table 18. CheckMate 205: Subgroup analysis of objective response rate by IRRC in Cohort B (n=80)[13]**

| | | ORR (%) | 95% CI |
|---|---|---|---|
| **Age categorisation (years)** | <65 | 51/77 (66.2) | 54.6, 76.6 |
| | ≥65 and <75 | 2/3 (66.7) | 9.4, 99.2 |
| | ≥65 | 2/3 (66.7) | 9.4, 99.2 |
| | <30 | 18/27 (66.7) | 46.0, 83.5 |
| | ≥30 and <45 | 18/28 (64.3) | 44.1, 81.4 |
| | ≥45 and <60 | 13/18 (72.2) | 46.5, 90.3 |
| | ≥60 | 4/7 (57.1) | 18.4, 90.1 |
| **Region** | USA/Canada | 33/47 (70.2) | 55.1, 82.7 |
| | Europe | 20/33 (60.6) | 42.1, 77.1 |
| **Gender** | Male | 33/51 (64.7) | 50.1, 77.6 |
| | Female | 20/29 (69.0) | 49.2, 84.7 |
| **Race** | White | 47/71 (66.2) | 54.0, 77.0 |
| | Black or African American | 2/4 (50.0) | 6.8, 93.2 |
| | Asian | 0/1 | 0.0, 97.5 |
| | Other | 4/4 (100) | 39.8, 100.0 |
| **Smoking status** | Current/former | 22/32 (68.8) | 50.0, 83.9 |
| | Never smoked | 29/45 (64.4) | 48.8, 78.1 |
| | Unknown | 2/3 (66.7) | 9.4, 99.2 |
| **Performance status** | 0 | 26/42 (61.9) | 45.6, 76.4 |
| | 1 | 27/38 (71.1) | 54.1, 84.6 |
| **B-symptoms (e.g. fever, night sweats, weigh loss) at initial diagnosis** | Present | 31/46 (67.4) | 52.0, 80.5 |
| | Absent | 22/34 (64.7) | 46.5, 80.3 |
| **Time from initial diagnosis to first ASCT (years)** | <1 | 15/21 (71.4) | 47.8, 88.7 |
| | 1-2 | 25/37 (67.6) | 50.2, 82.0 |
| | ≥2 | 13/22 (59.1) | 36.4, 79.3 |
| **Number of prior lines of cancer therapy received excluding preparative regimens** | ≤3 | 12/19 (63.2) | 38.4, 83.7 |
| | 4-6 | 26/38 (68.4) | 51.3, 82.5 |
| | ≥7 | 15/23 (65.2) | 42.7, 83.6 |
| **Time from most recent ASCT to first subsequent cancer therapy (months)** | <6 | 15/22 (68.2) | 45.1, 86.1 |
| | 6-12 | 10/16 (62.5) | 35.4, 84.8 |
| | ≥12 | 28/42 (66.7) | 50.5, 80.4 |

ASCT: autologous stem cell transplant; CI: confidence interval; ORR: objective response rate.

**Figure 19. CheckMate 205: Subgroup analysis of objective response rate by IRRC in Cohort B (n=80)[13]**

### 4.8.2 CheckMate 205 Cohort B: Efficacy by prior response to BTX therapy

Post-hoc analysis of Cohort B showed that objective responses following nivolumab treatment are durable, regardless of the response to most recent prior BTX.[13] Among 43 patients in Cohort B who had no response (SD or PD/relapse) to prior BTX treatment, 31 (72.1%) achieved an IRCC-assessed objective response during nivolumab therapy. Of the 31 responders in this subgroup, 19 (61.3%) had continued to respond at the time of analysis. **Error! Not a valid bookmark self-reference.** summarises the BOR to nivolumab treatment according to best response to most recent BTX therapy.

**Table 19. CheckMate 205: Best overall response with nivolumab by best response to prior BTX in Cohort B (n=80)[13]**

| Best overall response to nivolumab (IRRC) | Best response to prior BTX (medical records) | | | | |
|---|---|---|---|---|---|
| | CR (n=6) | PR (n=17) | SD (n=9) | Relapse/PD (n=34) | Unable to determine (n=14) |
| CR | 0 | 1 (5.9) | 2 (22.2) | 3 (8.8) | 1 (7.1) |
| PR | 4 (66.7) | 8 (47.1) | 4 (44.4) | 22 (64.7) | 8 (57.1) |
| SD | 2 (33.3) | 7 (41.2) | 1 (11.1) | 5 (14.7) | 3 (21.4) |
| PD | 0 | 1 (5.9) | 1 (11.1) | 3 (8.8) | 1 (7.1) |
| Unable to determine | 0 | 0 | 1 (11.1) | 1 (2.9) | 1 (7.1) |

IRRC: independent radiologic review committee; CR: complete remission; PR: partial remission; SD: stable disease; PD: progressive disease.

### 4.8.3 CheckMate 205: Efficacy by baseline PD-L1 expression status

Of 80 patients in Cohort B of CheckMate 205, PD-L1 expression in Hodgkin/Reed-Sternberg cells was quantifiable in 63 patients. In 57 patients with PD-L1 expression ≥1% at baseline, the ORR to nivolumab treatment was 66.7%. The ORR was 83.3% in patients with PD-L1 expression <1% at baseline (6 patients), and 58.8% in patients without quantifiable PD-L1 (17 patients). **Error! Not a valid bookmark self-reference.** summarises the BOR and ORR to nivolumab treatment according to baseline PD-L1 status.

**Table 20. CheckMate 205: BOR and ORR by IRRC for baseline PD-L1 expression status in Cohort B (n=80)[13]**

| Baseline PD-L1 status | n (%) | BOR to nivolumab (IRRC) | | | | | ORR (%) (95% CI) |
|---|---|---|---|---|---|---|---|
| | | CR | PR | SD | Relapse/ PD | Unable to determine | |
| ≥1% | 57 (71.3) | 4 (5.0) | 34 (42.5) | 11 (13.8) | 5 (6.3) | 3 (3.8) | 38/57 (66.7) (52.9, 78.6) |
| <1% | 6 (7.5) | 0 | 5 (6.3) | 1 (1.3) | 0 | 0 | 5/6 (83.3) (35.9, 99.6) |
| Not quantifiable | 17 (21.3) | 3 (3.8) | 7 (8.8) | 6 (7.5) | 1 (1.3) | 0 | 10/17 (58.8) (32.9, 81.6) |

IRRC: independent radiologic review committee; CR: complete remission; PR: partial remission; SD: stable disease; PD: progressive disease.

### 4.8.4 CheckMate 205: Efficacy by 9p24.1 alteration

In cHL, alterations in the expression of PD-1 ligands (PD-L1 and PD-L2) are commonly observed, particularly through polysomy, copy gain or amplification of chromosome 9p24.1, which is associated with shorter PFS in HL patients.[23]

Of 80 patients in Cohort B of CheckMate-205, chromosome 9p24.1 in Reed-Sternberg cells was quantifiable in 45 patients (56.3%). Of these, all quantifiable patients showed one or more of the following chromosome alterations: amplification (27.7%); copy gain (57.8%), and; polysomy (15.6%). Table 21 shows that ORR per IRCC was similar across the three chromosome 9p24.1 alteration categories.

**Table 21. CheckMate 205: ORR by IRRC for chromosome 9p24.1 status in Cohort B (n=80)[13]**

| Chromosome 9p24.1 alteration category | Reported in quantifiable patients (n=45) | Responders per category (ORR %) |
|---|---|---|
| Amplification | 12/45 (27.7) | 10/12 (83.3%) |
| Copy gain | 26/45 (57.8) | 17/26 (65.4) |
| Polysomy | 7/45 (15.6) | 5/7 (71.4) |

## *4.9 Meta-analysis*

All indirect comparison evidence is provided within Section 4.10.

## *4.10 Indirect and mixed treatment comparisons*

**Key points**

- A systematic literature review highlighted that there are limited data available for patients with HL in the post-ASCT and post-BTX setting. This is reflective of the fact that there are very few treatment options in these patients, and the associated outcomes are highly uncertain.
- SLR-identified evidence is predominantly derived from investigational agents, so that outcomes will overestimate that seen in clinical practice. Further, the evidence identified is derived from patients who are typically less treatment experienced and so can be considered to have an improved prognosis versus those enrolled in the nivolumab studies.
- Unadjusted and matching-adjusted indirect comparisons (MAICs) of relevant nivolumab patient-level data were undertaken and demonstrated that nivolumab is associated with improved rates of response [redacted] and survival outcomes [redacted]
- A further systematic literature review and indirect comparison of nivolumab versus available treatment options in a population that are post-ASCT (and not necessarily post-BTX) were undertaken; results are supportive of these conclusions.
- Of the identified evidence, the Cheah (2016)[7] study reports the most complete data set (i.e. both response data and survival data) and can be considered relevant to the decision problem, due to the high proportion of patients enrolled who had previously received both ASCT and BTX, as well as the use of non-investigational agents (in line with clinical practice, as well as the scope of this appraisal).

There are currently no data providing direct comparative evidence for nivolumab versus comparators. In order to provide evidence to inform comparative effectiveness decisions, indirect comparisons were undertaken, using SLR-derived data.

### 4.10.1 Post-ASCT, post-BTX population

#### *4.10.1.1 Systematic literature review*

As previously described, an SLR was conducted to identify studies that could inform the comparative effectiveness of nivolumab for the treatment of relapsed or refractory cHL after ASCT and treatment with BTX. Full methodology, including search strategies and eligibility criteria, is provided as Appendix 2.

In brief, electronic database searches in Embase, MEDLINE and the Cochrane Library were conducted in March 2016, in addition to manual searching of reference lists, systematic reviews and conference abstracts. Full eligibility criteria are reported in Appendix 2, but main inclusion criteria were:

- The study enrolled adult patients with relapsed or refractory cHL following prior ASCT and BTX
- Patients received any intervention aimed at managing cHL
- The study reported any outcome of interest, including OS, PFS, CR rate, PR rate, ORR or rate of SD.

**Figure 20. PRISMA flow diagram: post-ASCT, post-BTX SLR**

In total, [redacted] citations met the criteria for inclusion, encompassing [redacted] studies. For [redacted] of the studies, evidence was reported only via conference abstracts, limiting the available data. The [redacted] of clinical studies were non-comparative studies [redacted], while [redacted], and [redacted] were based on real-world data. [redacted] studies recruited treatment experienced HL patients [redacted] Assessed therapies included: [redacted] Additionally, a real world study provided evidence assessing the following therapies: investigational agents, chemotherapies (including gemcitabine, other alkylators and platinum-based therapy), bendamustine, BTX retreatment, ASCT and other therapies.

As previously described, there was a paucity of data in this population. [redacted] studies reported data describing response rate (either ORR, CR or PR) for the [redacted]; however, survival

outcomes were [redacted] reported, with [redacted] studies reporting median OS and [redacted] studies reporting median PFS.

[redacted]

Of the identified evidence, the Cheah (2016)[7] study reports the most complete data set (i.e. both response data and survival data) and can be considered relevant to the decision problem, due to the high proportion of patients enrolled who had previously received both ASCT and BTX.

#### *4.10.1.2 Unadjusted indirect treatment comparison*

An overview of efficacy data from the SLR is provided in Table 22 [redacted] and Table 23 [redacted] ORR ranged from [redacted] to [redacted], while median OS was reported as [redacted] and median PFS was [redacted] Only studies assessing the efficacy of [redacted] reported survival outcomes in the [redacted]. However, [redacted] studies reported data describing [redacted] in the [redacted], while [redacted] study ([redacted]) reported outcomes for the [redacted]. Noting this discrepancy between populations, the objective response was [redacted] in the [redacted] compared to those receiving [redacted]. [redacted] study assessing use of [redacted] in a study cohort of [redacted] identified an ORR of [redacted]; however, [redacted]. Similar to objective response rate, rates of [redacted] for [redacted] were also [redacted] in patients who had [redacted], achieved by [redacted], compared with those receiving [redacted] These estimates of efficacy were then simply combined to evaluate the beneficial impact of nivolumab on cHL treatment; full methodology and results are provided in Appendix 3. Four scenarios were evaluated:

[redacted]

Outcomes are summarised in Table 24. SLR-identified evidence is predominantly derived from [redacted] Despite this, **rates of response were [redacted], and this was reflected in [redacted] survival outcomes** [redacted]

#### *4.10.1.3 Matching-adjusted indirect comparison*

Where there is a lack of common anchor arms, precluding traditional indirect comparison methodology, the MAIC method allows comparison between interventions by matching and adjusting for differences in patient baseline characteristics across separate study populations.

Full methodology is provided within Appendix 3; in brief, this method, as described by Signorovitch (2010)[62], reweights individual patient data in the intervention trial such that the weighted summary statistics match the summary statistics reported for the comparator cohort. The patient-level outcomes are then similarly weighted by these values, such that the effect of the nivolumab treatment regimen on the parts of the cohort most similar to that of the comparator study may be estimated, and thus the relative treatment effect may be estimated. Outcomes from the MAIC are summarised in Table 25. As previously described, SLR-identified evidence is predominantly derived from [redacted]. However, **rates of response were [redacted], and this was reflected in [redacted] survival outcomes [redacted]**

**Table 22. Post-ASCT, post-BTX population: overview of clinical efficacy data from systematic review - overall population**

| Study | Intervention | Cohort size (N) | ORR | ORR | CR | PR | SD | OS* | PFS* |
|---|---|---|---|---|---|---|---|---|---|
| | | | n | % | n | n | n | | |
| [redacted] | | | | | | | | | |
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CR: complete response; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PR: partial response; NR: not reported; SCT: stem cell transplant; SD: stable disease.
*Survival outcomes reported as medians where possible (months).
** Comprised of all cHL patients from CheckMate 205 and CA209-039 who previously received ASCT and BTX

## Table 23. Post-ASCT, post-BTX population: overview of clinical efficacy data from systematic review - prior ASCT and brentuximab subgroup

| Author | Intervention | Prior ASCT and BTX (n) | ORR | | CR | | PR | | SD | OS* | PFS* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | n | % | n | % | n | % | n | | |
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CR: complete response; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PR: partial response; NR: not reported; SCT: stem cell transplant; SD: stable disease.
*Survival outcomes reported as medians where possible (months).
** Comprised of all cHL patients from CheckMate 205 and CA209-039 who previously received ASCT and BTX

## Table 24. Post-ASCT, post-BTX population: overview of unadjusted indirect treatment comparison evidence

| Author | ORR | | CR | | PR | | OS* | PFS* |
|---|---|---|---|---|---|---|---|---|
| | RR | % | RR | % | RR | % | | |
| | | | | | | | | |
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CR: complete response; NR: not reported; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PR: partial response; RR: relative risk; SCT: stem cell transplant; SD: stable disease.
*Survival outcomes based on parameterisation of available data
** Comprised of all cHL patients from CheckMate 205 and CA209-039 who previously received ASCT and BTX
Subgroup of SLR studies based on those studies where subgroup of post-ASCT post-BTX population is reported or where >70% of patients match this criteria; this includes efficacy of investigational agents.

**Table 25.Post-ASCT, post-BTX population: overview of matching-adjusted indirect treatment comparison evidence**

| Comparator source | Analysis | Endpoint | Nivolumab cohort | Comparator endpoint | Relative risk/Time Acceleration* |
|---|---|---|---|---|---|
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | | [redacted] | [redacted] | [redacted] | [redacted] |
| | | [redacted] | [redacted] | [redacted] | [redacted] |
| | | [redacted] | [redacted] | [redacted] | [redacted] |
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| [redacted] | | | | | |

### 4.10.2 Post-ASCT population

Due to the relative lack of data identified within the SLR described within Section 4.1, the eligibility criteria for the studies was expanded to treatments for relapsed or refractory HL in patients who have previously received prior ASCT (i.e. prior BTX treatment was not a requirement) in an attempt to provide additional supportive data in a patient population whose treatment options and outcomes are subject to considerable uncertainty. This can be considered a highly conservative analysis, as the evidence identified from this SLR will be derived from patients who are less treatment experienced and so can be considered to have an improved prognosis. As such, this analysis can be considered supportive to the analyses set out in Section 4.10.1, but should not be considered representative of clinical practice.

#### *4.10.2.1 Systematic literature review*

Full methodology, including search strategies and eligibility criteria, is provided as Appendix 4. In brief, electronic database searches in Embase, MEDLINE and the Cochrane Library were conducted in March 2016, in addition to manual searching of reference lists, systematic reviews and conference abstracts. Main inclusion criteria were:

- The study enrolled adult patients with relapsed or refractory cHL following prior ASCT
- Patients received any intervention aimed at managing cHL
- The study reported any outcome of interest, including OS, PFS, CR, PR, ORR or rate of SD.

The study design, baseline characteristics and results from the eligible studies are provided in Appendix 4.

**Figure 21. PRISMA flow diagram: post-ASCT SLR**

As depicted in Figure 21, [redacted] citations met the criteria for inclusion, encompassing [redacted] studies. The interventions assessed in these studies included: [redacted] Interventions with [redacted] were most heavily represented.

#### *4.10.2.2 Unadjusted indirect treatment comparison*

These estimates of efficacy were then simply combined to evaluate the beneficial impact of nivolumab on cHL treatment; full methodology and results are provided in Appendix 3. Two scenarios were considered: [redacted] Outcomes are summarised in Table 26. [redacted]

#### *4.10.2.3 Matching-adjusted indirect comparison*

Where there is a lack of common anchor arms, precluding traditional indirect comparison methodology, the MAIC method allows comparison between interventions by matching and adjusting for differences in patient baseline characteristics across study populations.

Full methodology is provided within Appendix 3; in brief, this method, as described by Signorovitch (2010)[62], reweights individual patient data in the intervention trial such that the weighted summary statistics match the summary statistics reported for the comparator cohort. The patient-level outcomes are then similarly weighted by these values, such that the effect of nivolumab on the parts of the cohort most similar to that of the comparator study may be estimated, and thus the relative treatment effect may be estimated.

Outcomes from the MAIC are summarised in Table 27. [redacted]

## Table 26. Post-ASCT population: overview of unadjusted indirect treatment comparison evidence

| | Analysis | ORR | | CR | | PR | | PFS* | OS* |
|---|---|---|---|---|---|---|---|---|---|
| | | RR | % | RR | % | RR | % | | |
| | | | | | | | | | |
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CR: complete response; NR: not reported; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PR: partial response; RR: relative risk; SCT: stem cell transplant; SD: stable disease.
*Survival outcomes based on parameterisation of available data
** Comprised of all cHL patients from CheckMate 205 and CA209-039 who previously received ASCT and BTX
Subgroup of SLR studies based on those studies where subgroup of post-ASCT post-BTX population is reported or where >70% of patients match this criteria; this includes efficacy of investigational agents.

## Table 27.Post-ASCT population: overview of matching-adjusted indirect treatment comparison evidence

| Comparator source | Analysis | Endpoint | Nivolumab cohort | Comparator endpoint | Relative risk/Time Acceleration* |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |

### 4.10.3 Summary and conclusions from indirect comparison evidence

An overview of the indirect comparison evidence is provided in Table 28. As previously discussed,

[redacted]

**Table 28. Overview of indirect comparison evidence**

| Data source | | Model | PFS* | OS* | ORR | CR | PR |
|---|---|---|---|---|---|---|---|
| [redacted] | | | | | | | |
| [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] | | | | | | | |

## *4.11 Non-randomised and non-controlled evidence*

Non-randomised and non-controlled evidence was identified in the SLR reported within Section 4.1. All available clinical evidence to support use of nivolumab in the HL population has been presented within Section 4.7.

## *4.12 Adverse reactions*

**Key points**

- Based on available evidence, the safety profile of nivolumab can be considered acceptable in the context of alternative therapies, such as standard chemotherapy regimens.[16]
- Further, this safety profile is well-established based on that observed in other indications.[8]

Safety data for nivolumab in cHL are available from the following studies:

- CheckMate 205: a non-comparative, parallel-cohort, single-arm Phase 2 study in cHL patients ≥18 years old who failed ASCT. Data from the August 2015 data cut-off are presented, comprising Cohort B and the total population where possible.[13]
- CA209-039: an open-label, non-comparative, single-arm Phase 1 study of nivolumab for the treatment of haematological malignancies; data from the cohort of patients with cHL are presented.[14,15]

### 4.12.1 CheckMate 205

Safety data from CheckMate 205 is available from 8.9 month follow up data, described in Section 4.7.1, presented for both Cohort B and the total population below.[13] Updated safety data reflecting the April 2016 data cut-off will be presented when available.

#### *4.12.1.1 Extent of exposure*

All patients received at least one dose of nivolumab.[13] In all cohorts, the majority (>76%) of patients received ≥90% of the planned dose intensity, and the median number of nivolumab doses received was highest in Cohort B. The median duration of study therapy was not reached in any cohort. Dose intensity, extent of follow up and duration of therapy for Cohort B and the total study population are summarised in Table 29.[13]

**Table 29. CheckMate 205: extent of nivolumab exposure[13]**

| Variable | Cohort B | Total population |
|---|---|---|
| N | 80 | 240 |
| **Number of doses received** | | |
| Mean (SD) | 16.1 (5.82) | 10.9 (6.57) |
| Median (Range) | 17.0 (3, 25) | 10.0 (1, 25) |
| **Cumulative dose (mg/kg)** | | |
| Mean (SD) | 47.91 (17.295) | 32.26 (19.487) |
| Median (Range) | 50.88 (9.0, 75.8) | 29.68 (2.9, 75.8) |
| **Relative dose intensity (n)** | | |
| ≥110% | 0 | 1 (0.4%) |
| 90-110% | 61 (76.3%) | 198 (82.5%) |
| 70-90% | 16 (20.0%) | 34 (14.2%) |
| 50-70% | 3 (3.8%) | 7 (2.9%) |
| <50% | 0 | 0 |
| **Time between date of first dose date and last known date alive or death (months)** | | |
| Mean (SD) | 8.62 (2.017) | 5.44 (3.251) |
| Median (Range) | 8.92 (1.9, 11.7) | 5.09 (0.3, 11.7) |

#### *4.12.1.2 Overall adverse events*

Drug-related AEs were reported by 88% and 70% of patients in Cohort B and the total study population, respectively, while grade 3-4 AEs were reported by 25.0% and 15.4% of patients.[13] Drug-related AEs of Grade 3-4 were experienced by no more than two patients in each cohort.[13] A drug-related Grade 5 AE of multi-organ failure was reported in one patient in Cohort B, in addition to two patients in the total study population that experienced Grade 5 AEs of atypical pneumonia and dyspnoea.[13] Table 30 summarises the AE profile of nivolumab treatment in Cohort B and the total study population.

**Table 30. CheckMate 205: Summary of drug-related adverse event profile impacting ≥10% of population (August 2015 data cut-off)[13]**

| | Cohort B (n=80) | | Total population (n=240) | |
|---|---|---|---|---|
| | Any grade | Grade 3-4 | Any grade | Grade 3-4 |
| Diarrhoea | 8 (10.0) | 0 | 26 (10.8) | 1 (0.4) |
| Nausea | 10 (12.5) | 0 | 26 (10.8) | 0 |
| Fatigue | 20 (25.0) | 0 | 39 (16.3) | 1 (0.4) |
| Pyrexia | 11 (13.8) | 0 | 21 (8.8) | 0 |
| Rash | 13 (16.3) | 1 (1.3) | 23 (9.6) | 2 (0.8) |
| Pruritus | 8 (10.0) | 0 | 20 (8.3) | 0 |
| Arthralgia | 11 (13.8) | 0 | 16 (6.7) | 0 |
| Infusion related reaction | 16 (20.0) | 0 | 31 (12.9) | 1 (0.4) |
| **Laboratory parameters** | | | | |
| Haemoglobin (anaemia) | 62 (77.5) | 1 (1.3) | 183 (76.3) | 6 (2.5) |
| Platelets (thrombocytopenia) | 36 (45.0) | 3 (3.8) | 95 (39.6) | 6 (2.5) |
| Leukocytes | 32 (40.0) | 2 (2.5) | 83 (34.6) | 7 (2.9) |
| Lymphocytes | 58 (72.5) | 15 (18.8) | 145 (60.4) | 31 (12.9) |
| Absolute neutrophil count | 31 (38.8) | 5 (6.3) | 62 (27.1) | 9 (3.8) |
| ALT | 25 (31.3) | 2 (2.5) | 69 (28.8) | 4 (1.7) |
| ALP | 36 (45.0) | 5 (6.3) | 96 (40.0) | 10 (4.2) |
| AST | 32 (40.0) | 3 (3.8) | 63 (26.3) | 5 (2.1) |

AEs: adverse events; ALT: alanine aminotransferase; ALP: alkaline phosphatase; AST: aspartate aminotransferase.

#### *4.12.1.3 Discontinuation due to adverse events*

Drug-related AEs of any grade led to the discontinuation of nivolumab treatment in 3 (3.8%) patients in Cohort B, compared with 9 (3.8%) patients in the total study population.[13] In Cohort B, study discontinuation was due to Grade 3-4 autoimmune hepatitis (1 patient), Grade 3-4 increases in alanine aminotransferase and aspartate aminotransferase (1 patient) and Grade 5 multi-organ failure (1 patient). In the total study population, drug-related AEs that led to study discontinuation were of Grade 3-4 in 5 (2.1%) patients, and Grade 5 in 2 (0.8%) patients; however, AEs in these toxicity grades were reported by single patients.[13]

#### *4.12.1.4 Deaths*

Seven deaths (2.9%) were reported in all patients treated with nivolumab during the study, four of which were attributed to disease progression.[13] Three patients in Cohort B died during the study. One of these patients died due to disease progression, while one patient was lost to follow up and their cause of death was undetermined. The third death was attributed to a drug-related Grade 5 AE of multi-organ failure 13 days from the last dose of nivolumab; however, the event was changed by the investigator to Epstein-Barr virus positive peripheral T-cell lymphoma, and was considered unrelated to the study drug.[13]

#### *4.12.1.5 Serious adverse events*

Drug-related serious AEs (SAEs) of any grade were reported in 6.3% and 9.6% of patients in Cohort B and the total study population, respectively.[13] The most frequently reported drug-related SAE was infusion related reaction, which was reported in 2.5% of patients in Cohort B and 2.1% of the total study population.

#### *4.12.1.6 Laboratory parameters*

Laboratory parameter abnormalities are summarised in Table 30. Abnormalities in haematology tests performed during nivolumab treatment or within 30 days of last treatment dose were mostly Grade 1-2 in Cohort B and the total study population.[13] Grade 3-4 haematological abnormalities reported in at least 5% of each cohort were decreased lymphocytes (18.8% in Cohort B and 13.4% in the total population) and neutropenia (6.3% in Cohort B) and 3.3% in the total population.[13]

Abnormal increase in hepatic parameters during nivolumab treatment or within 30 days of last treatment dose were mostly Grade 1-2. Grade 3-4 abnormalities were reported in alanine aminotransferase (2.5% in Cohort B), alkaline phosphatase (6.3% in Cohort B and 4.2% in the total population), and aspartate aminotransferase (3.8% in Cohort B and 2.5% in the total population).[13]

#### *4.12.1.7 Adverse events of special interest*

Identification of AEs of special clinical interest was conducted to characterise those events that are potentially associated with the use of nivolumab, and this was based on the following criteria:[13]

- AEs that may differ in type, frequency, or severity from AEs caused by non-immunotherapies.
- AEs that may require immunosuppression (eg, corticosteroids) as part of their management.
- AEs whose early recognition and management may mitigate severe toxicity.
- AEs for which multiple event terms may be used to describe a single type of AE, thereby necessitating the pooling of terms for full characterisation.

Using these criteria, and taking into account the safety profile associated with nivolumab monotherapy, endocrinopathies, diarrhoea/colitis, hepatitis, pneumonitis, interstitial nephritis, and rash are currently considered to be 'Select AEs' (defined as AEs with potential immunological cause that is of special clinical interest with the use of nivolumab).[13] Multiple event terms that may describe each of these were grouped into endocrine, gastrointestinal (GI), hepatic, pulmonary, renal, and skin Select AE categories, respectively. Additionally, hypersensitivity/infusion reactions were analysed, as multiple event terms that may be used to describe such events and pooling of terms was therefore necessary for full characterisation.[13]

In Cohort B, the most frequently reported adverse events of special interest, irrespective of causality, were skin abnormalities (33 patients [41%]); gastrointestinal abnormalities (21 [26%]); hypersensitivity or infusion-related reaction (17 [21%]); and endocrine (14 [18%]), hepatic (eight [10%]), renal (four [5%]), and pulmonary (one [1%]) events.[16] Pneumonitis (irrespective of cause) was reported in two (3%) patients (one grade 2 and one grade 3) between the first dose and 35 days after the last dose; both cases were judged to be drug related and both resolved with corticosteroid treatment. One of these patients had grade 3 pneumonitis 35 days after the last dose of nivolumab, which was discontinued because of autoimmune hepatitis. Most select adverse events of special interest reported were of grades 1 or 2, and most were considered by the investigators to be drug related.[16]

### 4.12.1 CA209-039

The published 40-week follow-up data[14] and unpublished [redacted]-month follow up data are presented here.[15]

#### *4.12.1.1 Extent of exposure*

All patients received at least one dose of nivolumab.[15] The majority (78.3%) of patients received ≥90% of the planned dose intensity and the remaining patients (21.7%) received 70-90%. The median number of nivolumab doses received for all patients was 18 [redacted] The median duration of study therapy for all patients was

[redacted][15] Dose intensity, extent of follow up and duration of therapy for the total study population are summarised in Table 31.

**Table 31. CA209-039: extent of exposure at 23.3-month follow-up[15]**

| Variable | Total population |
|---|---|
| N | 23 |
| **Number of doses received** | |
| Mean (SD) | [redacted] |
| Median (Range) | 18.0 [redacted] |
| **Cumulative dose (mg/kg)** | |
| Mean (SD) | [redacted] |
| Median (Range) | [redacted] |
| **Relative dose intensity (n)** | |
| ≥110% | 0 |
| 90-110% | 18 (78.3) |
| 70-90% | 5 (21.7) |
| 50-70% | 0 |
| <50% | 0 |
| **Time between date of first dose date and last known date alive or death (months)** | |
| Mean (SD) | [redacted] |
| Median (Range) | [redacted] |

#### *4.12.1.2 Overall adverse events*

At the 40-week follow-up[14], drug-related AEs of any grade were reported in 18 (78.3%) patients. The most common drug-related AEs of any grade were thrombocytopaenia (17.4%) and rash (21.7%). Drug-related Grade 3 AEs, which were reported in 5 (21.7%) patients, included myelodysplastic syndrome, pancreatitis, pneumonitis, stomatitis, colitis, gastrointestinal inflammation, thrombocytopenia, an increased lipase level, a decreased lymphocyte count, and leukopaenia. Grade 3 AEs were not reported in more than 1 patient, and there were no drug-related Grade 4 or 5 AEs.

At 23.3 months follow-up [15], drug-related AEs of any grade were reported in [redacted] patients. The most common were [redacted]. As stated above, [redacted] patients reported Grade 3-4 drug-related AEs, in addition to a[redacted]. Table 32 summarises the AE profile of nivolumab treatment throughout the study and for 100 days after the last dose was administered.

**Table 32. CA209-039: Summary of drug-related adverse event profile at 40-week follow-up[14] and 23.3-month follow-up[15]**

| N=23 | 40-week follow-up* | | | 23.3-month follow-up | | |
|---|---|---|---|---|---|---|
| | Any grade | Grade 3 | Grade 4-5 | Any grade | Grade 3 | Grade 4-5 |
| Any drug-related AE | 18 (78.3) | 5 (21.7) | 0 | [redacted] | [redacted] | [redacted] |
| Gastrointestinal disorders | | | 0 | [redacted] | [redacted] | [redacted] |
| Diarrhoea | 3 (13.0) | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Nausea | 3 (13.0) | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Stomatitis | 2 (8.7) | 1 (4.3) | 0 | [redacted] | [redacted] | [redacted] |

| N=23 | 40-week follow-up* | | | 23.3-month follow-up | | |
|---|---|---|---|---|---|---|
| | Any grade | Grade 3 | Grade 4-5 | Any grade | Grade 3 | Grade 4-5 |
| Colitis | 1 (4.3) | 1 (4.3) | 0 | [redacted] | [redacted] | [redacted] |
| Gastrointestinal inflammation | 1 (4.3) | 1 (4.3) | 0 | [redacted] | [redacted] | [redacted] |
| Gastro-oesophageal reflux disease | | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Pancreatitis | 1 (4.3) | 1 (4.3) | 0 | [redacted] | [redacted] | [redacted] |
| Vomiting | | 0 | 0 | [redacted] | [redacted] | [redacted] |
| General disorders and administration site conditions | | | 0 | [redacted] | [redacted] | [redacted] |
| Fatigue | 3 (13.0) | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Pyrexia | 3 (13.0) | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Asthenia | | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Chills | | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Pain | | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Skin and subcutaneous tissue disorders | | | 0 | [redacted] | [redacted] | [redacted] |
| Rash | 5 (21.7) | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Pruritus | 3 (13.0) | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Acne | | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Dry skin | | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Rash pruritic | | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Skin hypopigmentation | | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Musculoskeletal and connective tissue disorders | | | 0 | [redacted] | [redacted] | [redacted] |
| Myalgia | | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Arthralgia | | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Groin pain | | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Respiratory, thoracic and mediastinal disorders | | | 0 | [redacted] | [redacted] | [redacted] |
| Bronchospasm | | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Cough | 2 (8.7) | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Dyspnoea exertional | | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Pneumonitis | 1 (4.3) | 1 (4.3) | 0 | [redacted] | [redacted] | [redacted] |
| Injury, poisoning and procedural complications | | | 0 | [redacted] | [redacted] | [redacted] |
| Infusion related reaction | | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Procedural headache | | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Nervous system disorders | | | 0 | [redacted] | [redacted] | [redacted] |
| Neuropathy peripheral | | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Immune system disorders | | | 0 | [redacted] | [redacted] | [redacted] |
| Cytokine release syndrome | | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Infections and infestations | | | 0 | [redacted] | [redacted] | [redacted] |
| Lung infection | | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Neoplasms (benign, malignant and unspecified) | | | 0 | [redacted] | [redacted] | [redacted] |
| Myelodysplastic syndrome | 1 (4.3) | 1 (4.3) | 0 | [redacted] | [redacted] | [redacted] |
| Metabolism and nutrition disorders | | | 0 | [redacted] | [redacted] | [redacted] |
| Hypercalcaemia | 2 (8.7) | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Hypophosphataemia | 2 (8.7) | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Decreased appetite | | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Hyperglycaemia | | 0 | 0 | [redacted] | [redacted] | [redacted] |

| N=23 | 40-week follow-up* | | | 23.3-month follow-up | | |
|---|---|---|---|---|---|---|
| | Any grade | Grade 3 | Grade 4-5 | Any grade | Grade 3 | Grade 4-5 |
| Hyperuricaemia | | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Hypocalcaemia | | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Endocrine disorders | | | 0 | [redacted] | [redacted] | [redacted] |
| Hypothyroidism | 2 (8.7) | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Hyperthyroidism | | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Blood and lymphatic system disorders | | | 0 | [redacted] | [redacted] | [redacted] |
| Lymph node pain | 1 (4.3) | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Laboratory abnormalities | | | | | | |
| Haemoglobin (anaemia) | | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Platelets (thrombocytopaenia) | 4 (17.4) | 1 (4.3) | 0 | [redacted] | [redacted] | [redacted] |
| Leukocytes | 1 (4.3) | 1 (4.3) | 0 | [redacted] | [redacted] | [redacted] |
| Lymphocyte decreased | 2 (8.7) | 1 (4.3) | 0 | [redacted] | [redacted] | [redacted] |
| Absolute neutrophil count (neutropaenia) | | 0 | 0 | [redacted] | [redacted] | [redacted] |
| ALT | | | 0 | [redacted] | [redacted] | [redacted] |
| ALP | | | 0 | [redacted] | [redacted] | [redacted] |
| AST | | | 0 | [redacted] | [redacted] | [redacted] |
| Lipase increased | 2 (8.7) | 1 (4.3) | 0 | [redacted] | [redacted] | [redacted] |
| Weight increased | 2 (8.7) | 0 | 0 | [redacted] | [redacted] | [redacted] |

AE: adverse event; ALT: alanine aminotransferase; ALP: alkaline phosphatase; AST: aspartate aminotransferase.
Drug-related AEs were reported between first dose and 100 days after last dose of study therapy. AE terms were coded and grouped according to system organ class using Medical Dictionary for Regulatory Activities (MedDRA) version 18.0, and toxicity grade using the Common Terminology Criteria for Adverse Events (CTCAE version 4.0). Some terms were remapped for the purpose of complying with regulatory guidance for reporting adverse reactions, and avoiding exhaustive lists of every reported AE, including those that were minor, commonly observed in the absence of drug therapy, or not plausibly related to drug therapy.
* Blank cells were not reported at 40-week follow-up. At this time point, only serious AEs or drug-related AEs reported in ≥5% of patients were presented. No Grade 4 or 5 drug-related AEs were reported.

#### *4.12.1.3 Discontinuation due to adverse events*

Drug-related AEs of any grade led to the discontinuation of nivolumab treatment in 2 (8.7%) patients.[15] One patient entered the study after [redacted] prior systemic cancer regimens, and was discontinued after [redacted] cycles of study treatment due to [redacted]. One [redacted] patient entered the study after [redacted] prior regimens, and was discontinued after [redacted] cycles due to [redacted].[15]

#### *4.12.1.4 Deaths*

In CA209-039, 5 (21.7%) deaths were reported following nivolumab treatment.[15] All 5 deaths occurred >100 days after the last dose of nivolumab and following subsequent therapy. Patients died from disease progression (2 patients), pulmonary compromise (1 patient) or following complications of alloSCT (2 patients). None of the deaths were deemed to be drug-related.[15]

#### *4.12.1.5 Serious adverse events*

During CA209-039, drug-related SAEs of any grade were reported in 3 (13.0%) patients.[15] These included Grade 2 lymph node pain (1 patient); Grade 3 pancreatitis (1 patient) and Grade 3 myelodysplastic syndrome (1 patient).
[redacted]. No Grade 4 or 5 drug-related SAEs were reported in this study.[15]

#### *4.12.1.6 Laboratory parameters*

Laboratory parameter abnormalities are summarised in Table 32. [redacted] laboratory abnormalities reported during nivolumab treatment or within [redacted] of last treatment dose were [redacted].[15] At [redacted] follow-up, the most common [redacted] haematological abnormality reported was [redacted]. Grade 3-4 hepatic abnormalities reported were
[redacted]
15

#### *4.12.1.7 Adverse events of special interest*

Identification of AEs of special clinical interest was conducted to characterise those events that are potentially associated with the use of nivolumab, and this was based on the following criteria:[15]
[redacted]

Using these criteria and taking into account the safety profile associated with nivolumab monotherapy,
[redacted] are currently considered to be select AEs. Multiple event terms that may describe each of these were grouped into [redacted], respectively. Additionally,
[redacted]
*
[redacted]

Table 33 summarises the select AEs reported by all patients within [redacted]. The [redacted] of select AEs reported were Grade 1-2, and [redacted] were considered not drug-related by the investigator. The most frequently reported (>10% of patients) drug-related select AE category was [redacted] The Grade 3-4 drug-related select AE categories were [redacted]. The most frequently reported immune-mediated AE was [redacted] were reported for any select AE category. Across Select AE categories, the [redacted] of events were

manageable, with resolution occurring for [redacted].
The [redacted] Select AEs were [redacted] and only [redacted] was not considered resolved due to the continuing need for [redacted]

**Table 33. CA209-039: Summary of select adverse events at 23.3-month follow-up[15]**

| | 23.3 month follow-up | | |
|---|---|---|---|
| | Any grade | Grade 3-4 | Grade 5 |
| [redacted] | | | |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | | | |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | | | |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | | | |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | | | |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | | | |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | | | |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | | | |

## *4.13 Interpretation of clinical effectiveness and safety evidence*

### 4.13.1 Principal findings from the clinical evidence

The clinical evidence supporting use of nivolumab for relapsed or refractory HL patients following prior ASCT or BTX is primarily derived from CheckMate 205 and CA209-039.

CheckMate 205 demonstrated that nivolumab was efficacious in terms of response rate, as well as OS, PFS, symptom control and tolerability, as described in Section 4. At a median follow-up of 15.7 months in Cohort B and 8.9 months in Cohort C, the ORR was 75% and 66.0%, respectively, with many patients reporting CR (26.0% and 26.5%). Further, this high response rate has translated into lower incidence of progression and extended survival; only [redacted] of the [redacted] treated patients had died ([redacted] in Cohort B and [redacted] in Cohort C) indicating very high OS in these patients, and median PFS was in excess of 11 months in both cohorts. Further, the safety profile can be considered acceptable in the context of alternative therapies, such as standard chemotherapy regimens.[16] Additionally, nivolumab was associated with improvement from baseline in disease-specific patient quality of life (EORTC-QLQ-C30) and a generic health status measure (EQ-5D), demonstrating clinically significant benefits in quality of life using several of the scales.[16]

Similarly, CA209-039 also demonstrated that nivolumab was efficacious in terms of response rate, as well as OS, PFS, symptom control and tolerability, as described in Section 4. At a median follow-up of 23.3 months in CA209-039, 87% of patients in the overall population achieved on objective response, of which 22% achieved CR, with similar levels of response in the post-BTX, post-ASCT group (ORR: 87%; CR: 13%).[15] Further, this high response rate has translated into lower incidence of progression and extended survival. Both median PFS and OS were not reached, with [redacted] PFS events and 5 OS events occurring in enrolled patients, and a one-year OS rate of 91.3%, indicating very high survival in these patients.[15] The rate of adverse events was similar to that in trials of nivolumab in patients with solid tumours and adverse events were mainly of grade 1 or 2.[14]

In patients with relapsed or refractory HL following ASCT, the prognosis following BTX therapy remains poor in patients with PR or who do not achieve response (SD), with median time to progression or death of up to 6.9 months and median OS of 18.3 months for SD and 39.4 months for PR.[4] In patients who have failed both ASCT and BTX, as well as poor outcomes, there are currently no recommended treatment options. Alternative options in patients with relapsed or refractory cHL following ASCT and BTX are associated with poorer outcomes; estimates of median PFS do not exceed 5 months, while median OS is predicted to be around 2 years, even when including the effects of clinical trial therapies.[7] Thus, there is a high unmet medical need in this patient population.

By contrast, clinical trial data presented within this submission demonstrates PFS in nivolumab-treated patients exceeding 11 months (Section 4), and although median OS has not yet been reached, analyses predict that median OS will reach almost five years (Section 5.3.2.1). Furthermore, nivolumab was associated with improvement in disease-specific patient quality of life (EORTC-QLQ-C30) as well as a generic health status measure (EQ-5D), demonstrating clinically significant benefits in quality of life using several of the scales (Section 4.7.1.9)

Several indirect comparisons (both unadjusted and MAIC) are also presented within this submission as evidence of comparative clinical effectiveness. These comparisons underscore the beneficial impact of nivolumab, and demonstrate that nivolumab can be considered a step-change versus alternative therapies.

### 4.13.2 Strengths and limitations of the clinical evidence base

The main limitations of the clinical evidence base are short-term follow-up available and the prevalence of non-comparative studies, so that there is no opportunity for blinding or a control arm, with the potential to cause bias in terms of outcome reporting. A single-arm (i.e. non-comparative) study design was chosen because of the small patient population, limiting patient recruitment, and because there is no appropriate, fully-approved active comparator for relapsed third-line or later cHL patients failing ASCT and BTX. Further, it should be noted that this potential to cause bias is blunted by the dramatic benefits in terms of PFS and OS attributable to nivolumab therapy. These endpoints can be considered independent of patients and/or clinicians, particularly in the case of OS, limiting the opportunity for bias.

Additionally, these limitations should be set within the context of relapsed or refractory HL, which is associated with low patient numbers, short survival and an ongoing NICE appraisal of BTX; thus, the need for individualised care is considerable and data describing care are scarce. This renders the clinical pathway subject to uncertainty and heterogeneity between patients. This is particularly true in the post-ASCT, post-BTX setting. Alternative options in patients with relapsed or refractory cHL following ASCT and BTX are associated with poorer outcomes; estimates of median PFS do not exceed 5 months, while median OS is predicted to be around 2 years, even when including the effects of clinical trial therapies.[7] Thus, there is a high unmet medical need in this patient population.

The safety and efficacy of nivolumab are of particular importance in the setting of relapsed or refractory HL following ASCT and BTX, where there is significant unmet need for new treatments, specifically those with a favourable safety profile, as well as improved efficacy. Following failure of both ASCT and BTX, therapeutic options are limited, and available chemotherapeutic options may not be available to all patients due tolerability issues. In this setting, nivolumab may be a well-tolerated therapeutic option with the potential to offer significant survival benefit and bridge to potentially curative alloSCT.

The most important treatment outcomes for most HL patients include survival (progression free and overall), reduced side effects, improved symptom control and quality of life, and nivolumab provides significant benefits for each of these outcomes:

- **Improved survival outcomes:** Alternative options in patients with relapsed or refractory cHL following ASCT and BTX are associated with poorer outcomes; estimates of median PFS do not exceed 5 months, while median OS is predicted to be around 2 years, even when including the effects of clinical trial therapies.[7] When the efficacy of investigational agents is removed, median OS is estimated to be around 19 months. Thus, there is a high degree of unmet medical need in this patient population. By contrast, clinical trial data presented within this submission demonstrates PFS in nivolumab-treated patients exceeding 11 months (Section 4),

and although median OS has not yet been reached, analyses predict that median OS will reach almost five years (Section 5.3.2.1).

- **Improved quality of life:** nivolumab was associated with improvement from baseline in disease-specific patient quality of life (EORTC-QLQ-C30) and a generic health status measure (EQ-5D), demonstrating clinically significant benefits in quality of life using several of the scales (Section 4.7.1.9).

- **Rapid symptom control**: in the majority of patients, symptom control is rapid, with a median time to complete resolution of 1.91 months.

- **Improved tolerability**: in comparison with currently available treatments, such as chemotherapy, the safety profile for nivolumab can be considered acceptable to patients, as described in Section 4.12. Further, this safety profile is well-established based on that observed in other indications.[8]

In summary, availability of nivolumab would provide an opportunity to make a significant and substantial impact on health-related benefits and address a current unmet need.

### 4.13.3 Relevance of the evidence base to the decision problem

The submission presents two non-comparative studies evaluating the efficacy of nivolumab in patients with relapsed or refractory cHL following ASCT and BTX, in line with the decision problem. Further, a number of indirect comparisons applying different methodologies versus alternative comparators are presented in order to provide evidence of comparative effectiveness. Further, outcomes considered closely mirror the decision problem set out by NICE.

Thus, it can be considered that the evidence base presented within this submission is directly relevant to the decision problem, and can be considered the best available evidence.

### 4.13.4 External validity of study results to patients in routine clinical practice

Patients enrolled in the available studies can be considered broadly representative of UK practice, in terms of baseline characteristics, with subgroups provided for analysis where possible.

It should be noted that enrolment into CheckMate 205 Cohort B required treatment failure with BTX, which was administered following failure of ASCT. Treatment guidelines recommend that BTX is considered for use as an option for patients who have relapsed after ASCT, and also as an option prior to ASCT for patients who are either ineligible for ASCT or who are eligible for ASCT but have not achieved sufficient response.[3,31,39] Clinical expert opinion suggests the majority of HL patients within clinical practice in the UK will receive BTX prior to ASCT. However, it is not anticipated that the sequencing of BTX and ASCT will impact on the efficacy of nivolumab, and this is supported by data from Cohort C, where 33% of patients had received BTX prior to ASCT.

As previously described, relapsed or refractory HL is associated with low patient numbers, short survival and an ongoing NICE appraisal of BTX; thus, the need for individualised care is considerable. This renders the clinical pathway subject to uncertainty and heterogeneity between patients. This is particularly true in the post-ASCT, post-BTX setting, where there are limited treatment options and short life expectancies.

The safety and efficacy of nivolumab are of particular importance in the setting of relapsed or refractory HL following ASCT and BTX, where there is significant unmet need for new treatments, specifically those with a favourable safety profile, as well as improved efficacy. Following failure of both ASCT and BTX, therapeutic options are limited, and available chemotherapeutic options may not be available to all patients due tolerability issues. In this setting, nivolumab may be a well-tolerated therapeutic option with the potential to offer significant survival benefit and bridge to potentially curative alloSCT.

#### *4.13.4.1 Outcomes following alloSCT*

Following failure of ASCT, current guidelines recommend that the aim of treatment in cHL patients is to attain sufficient response to allow consideration of alloSCT in those deemed eligible.[3] Given the high levels of response achieved following nivolumab therapy (as described in Sections 4.7 and 4.10), there is significant potential for nivolumab to act as a bridge to curative transplant in some patients.

AlloSCT is typically offered to patients who have achieved at least PR. Patients in this population are not able to achieve the required level of disease control without the use of an active treatment, such as nivolumab. However, there are typically few efficacious treatment options remaining for patients who have failed prior ASCT and BTX, particularly in those patients who are older or have comorbidities.[7]

As of June 2016, 40 patients with cHL have received post-nivolumab alloSCT (five patients from CA209-039; within CheckMate 205, six from Cohort A, 11 from Cohort B and 18 from Cohort C), and there have been no deaths due to disease progression. Disease status after allogeneic HSCT was [redacted] from CA209-039, but was [redacted] from Cohorts A, B and C in CheckMate 205. [redacted] patients with [redacted] at transplant [redacted] after transplant, and [redacted] with [redacted] at transplant have [redacted] after transplant, although [redacted]. [redacted] patient with [redacted] at transplant has [redacted] to CR after transplant. The remaining [redacted] patients who underwent alloSCT at [redacted] after transplant. Although based on preliminary evidence, this suggests that responses in nivolumab-treated patients are [redacted] following alloSCT.

Of the 40 patients undergoing alloSCT, 18 (45%) have experienced acute graft versus host disease, but in only 7 (17.5%) patients was this considered to be a grade 3 event or above. Further, there were six deaths, all of which were due to transplant-related mortality, which is in line with initial mortality observed for post-alloSCT patients during Cheah (2016).[7]

### *4.13.5 Application of NICE end-of-life criteria to nivolumab use in HL*

Despite a paucity of data, outcomes are known to be even poorer in relapsed or refractory patients who have received both ASCT and BTX, with highly limited treatment options and estimates of median OS of around 19 months. Thus, there is a high degree of unmet medical need in this patient population, which would be addressed by availability of nivolumab.

The case for application of NICE end-of-life criteria to nivolumab use in HL is set out in Table 33, and based on this evidence, it can be considered that nivolumab meets both criteria for end-of-life.

**Table 34. End-of-life criteria**

| Criterion | Data available |
|---|---|
| The treatment is indicated for patients with a short life expectancy, normally less than 24 months | Those therapies that are available in patients with relapsed or refractory cHL are associated with poor outcomes, although data describing this patient population is limited. Patients with relapsed or refractory cHL following ASCT had a median OS of 19-29 months, depending on therapies received and availability of BTX,[5,6] and this decreases further in patients who do not achieve an initial response following ASCT.[6] Further, in patients who receive palliative care, median OS decreases to 2.6 months.[5] During the pivotal study for BTX, patients with PR or who do not achieve response (SD) had a median time to progression or death of up to 6.9 months, while median OS was 18.3 months for patients achieving SD and 39.4 months for PR.[4]<br>Outcomes are known to be even poorer in relapsed or refractory patients who have received both ASCT and BTX, with estimates of median PFS that do not exceed 5 months. Estimates of OS are around two years, but this is obscured by inclusion of the efficacy of clinical trial therapies (47.4 months).[7] When the efficacy of investigational agents is removed, median OS is estimated to be around 19 months. Thus, there is a high degree of unmet medical need in this patient population. |
| There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment | Median OS was not reached during CheckMate 205 or CA209-039, but the small number of deaths occurring during these studies indicate a substantially longer median survival than that offered by current therapies. Fitting of parametric functions to this data indicate median OS exceeding 42.9 months, potentially reaching 156 months, which would be a substantial survival benefit in this patients group. |

## *4.14 Ongoing studies*

CheckMate 205 is an ongoing, non-comparative, parallel-cohort, single-arm Phase 2 study in cHL patients who failed ASCT, while CA209-039 is an open-label, non-comparative, single-arm Phase 1 study of nivolumab. All available data from these studies are presented in this submission, with further data cuts from these studies to be presented as it becomes available.

# 5 Cost effectiveness

**Base case analysis**

- In line with estimates of short life expectancy in patients receiving SoC, the model predicts a median OS of 1.5 years (mean: 2.1 years)
- Use of nivolumab will result in an additional [redacted] discounted QALYs (total: [redacted] QALYs) and 2.90 discounted LYs (total: 5.01 LYs).
- Incremental costs were expected to be [redacted] under base case assumptions and the resultant ICER was £19,882, which can be considered cost-effective at a willingness-to-pay threshold of £30,000/QALY.

**Sensitivity analysis**

- In the deterministic analysis and PSA, nivolumab was cost-effective in the majority of scenarios at a WTP threshold of £20,000/QALY and in all scenarios at a WTP threshold of £50,000/QALY.
- Extensive scenario analyses were undertaken, reflecting the assumptions required to undertaken a plausible, robust and transparent base case analysis.
- Within these scenario analyses, the majority of ICERs remain below the £20,000/QALY threshold, and in all scenarios at a WTP threshold of £50,000/QALY.

## *5.1 Published cost-effectiveness studies*

### 5.1.1 Identification of studies

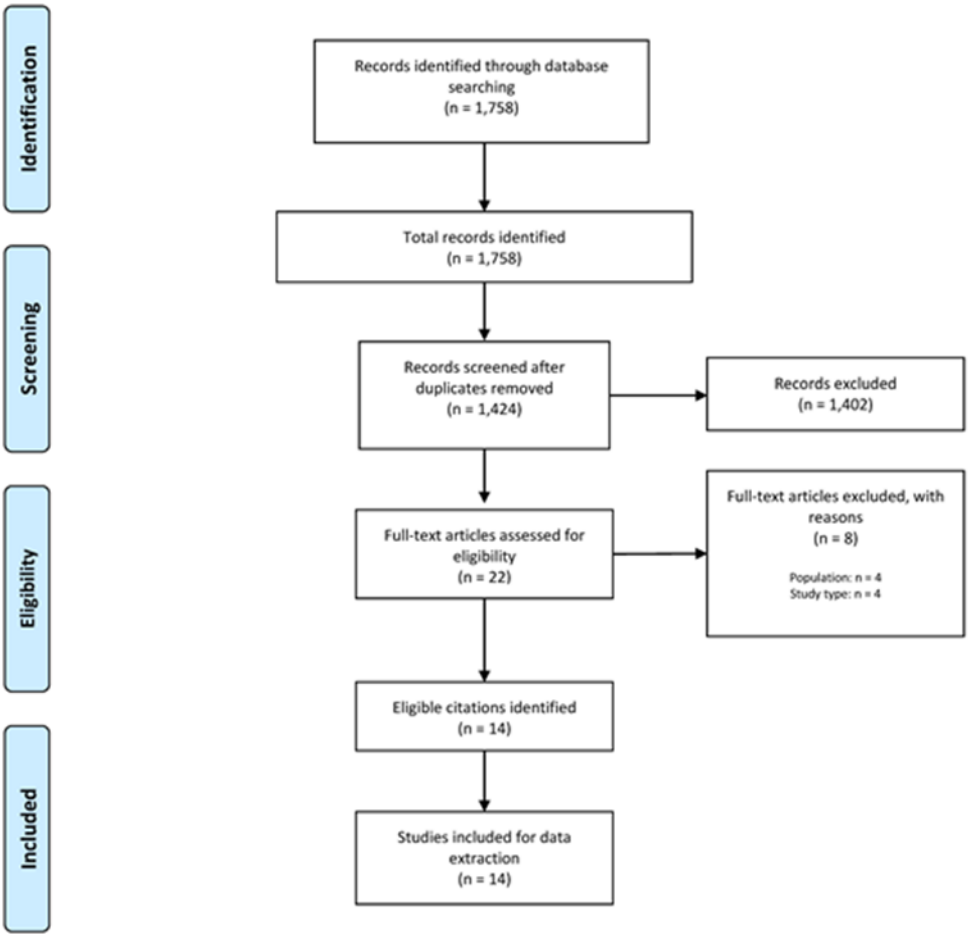
In line with the NICE Guide to the methods of technology appraisal 2013,[34] an SLR was conducted to identify cost-effectiveness studies for the treatment of HL. In brief, electronic database searches (MEDLINE, Embase, the Cochrane library and EconLit) and additional manual searches of conference proceedings (American Society for Clinical Oncology [ASCO], American Society of Haematology [ASH], ESMO, and the European Haematology Association [EHA]) were conducted in March 2016. Publications describing full economic evaluations of interventions aimed at managing HL were included. Full methodology and a detailed search strategy is presented in Appendix 5.

### 5.1.2 Description of identified studies

The database searches identified 1,758 citations, of which 1,424 were screened on first pass, as depicted in Figure 22. Following this, 1,402 citations were excluded and the remaining 22 studies proceeded to secondary screening and, following full text assessment 8 further studies were excluded on the basis of study type (n=4) and population (n=4). Data describing the studies were extracted from the remaining 14 studies, as described in

Appendix 5. These studies were used to inform the approach taken with the de novo model, in conjunction with previous HL submissions to UK HTA bodies.

**Figure 22. Identification of relevant economic evaluation studies**




### *5.1.3 Quality assessment*

In accordance with the NICE recommended checklist, the quality of the papers was assessed using the checklist developed by Drummond and Jefferson[64] and has been presented in Appendix 5.

## *5.2 De novo analysis*

The economic case presented in this submission is based on conventional cost-utility analysis, assessing use of nivolumab versus Standard of Care (SoC) for the treatment of relapsed refractory cHL in patients following prior ASCT and BTX, taking into account a PAS discount for nivolumab. This analysis uses a similar approach to that utilised by analyses[65-71] identified within the SLR described in Section 5.1, as well as previous submissions to UK HTA bodies.[72]

A Markov structure has been deemed appropriate due to the need to model multiple lines of treatments as well as the need to implement time-specific costs and utilities. In addition, as

previously noted, there is a precedent for use of a Markov approach for modelling in HL, as well as NHL, facilitating review and transparency. Similarly, the model applies three health states in order to reflect the cost and utility of post-progression patients, but it also enables the model to discontinue treatment upon progression, which is likely to occur in clinical practice.

The model structure has been chosen to reflect the most important treatment outcomes for most HL patients: survival (progression free and overall), side effects, symptom control and quality of life. Survival curves have been applied to estimate PFS and OS in each treatment arm, while AE rates are used to derive the costs associated with each treatment arm and disutilities experienced by the patients. Further, treatment-specific health state utilities have been applied to reflect the symptom control and quality of life experienced by patients receiving nivolumab or SoC.

In the specific context of relapsed or refractory HL, with low patient numbers, short survival and an ongoing NICE appraisal of BTX, the clinical pathway for HL patients is subject to considerable uncertainty and heterogeneity, particularly in the post-ASCT, post-BTX setting. This translates to a paucity of evidence describing clinical practice on which to base economic evaluation. In general, where no evidence has been identified, simple assumptions have been made based on independent sources, such as published literature, British HL guidelines or previous NICE appraisals in the field of HL or NHL. These assumptions were then assessed for clinical plausibility, and alternative assumptions were assessed in scenario analyses. Further information is provided in Section 5.6, with scenario analyses provided in Section 5.8.

A Markov model also appropriately accommodates treatment discontinuation and subsequent lines of therapy. This is of particular importance in the appraisal of nivolumab, where therapies may be discontinued on progression, or may be continued following progression due to post-progression benefit. Additionally, given the uncertainties around the treatment pathway for patients with cHL, a Markov model allows the flexibility to model several scenarios assessing the impact of alternative treatment sequences based on response or patient characteristics. It is acknowledged that a Markov model may not replicate survival outcomes with the same degree of accuracy as a partitioned survival model; however, a Markov model populated with appropriately flexible survival equations would not be expected to produce significantly different results. Analyses have been undertaken to assess the impact of model choice on replication of survival outcomes, and these are presented within Section 5.10.

### 5.2.1 Patient population

This economic evaluation considers the use of nivolumab as monotherapy for the treatment of adult patients with refractory or relapsed cHL following ASCT and BTX in the base case analysis. All scenarios and analyses assume that the heterogeneous treatment history of patients enrolled into CheckMate 205 and CA209-039 is adequately reflective of the heterogeneity observed in clinical practice.

Baseline patient parameters are derived from the baseline characteristics of patients enrolled into the CheckMate 205 (cohorts B and C) and CA209-039 studies (n = 193), as is detailed in Table 35. Sensitivity analyses will assess the impact of alternative baseline patient parameters.

**Table 35. Baseline patient parameters**

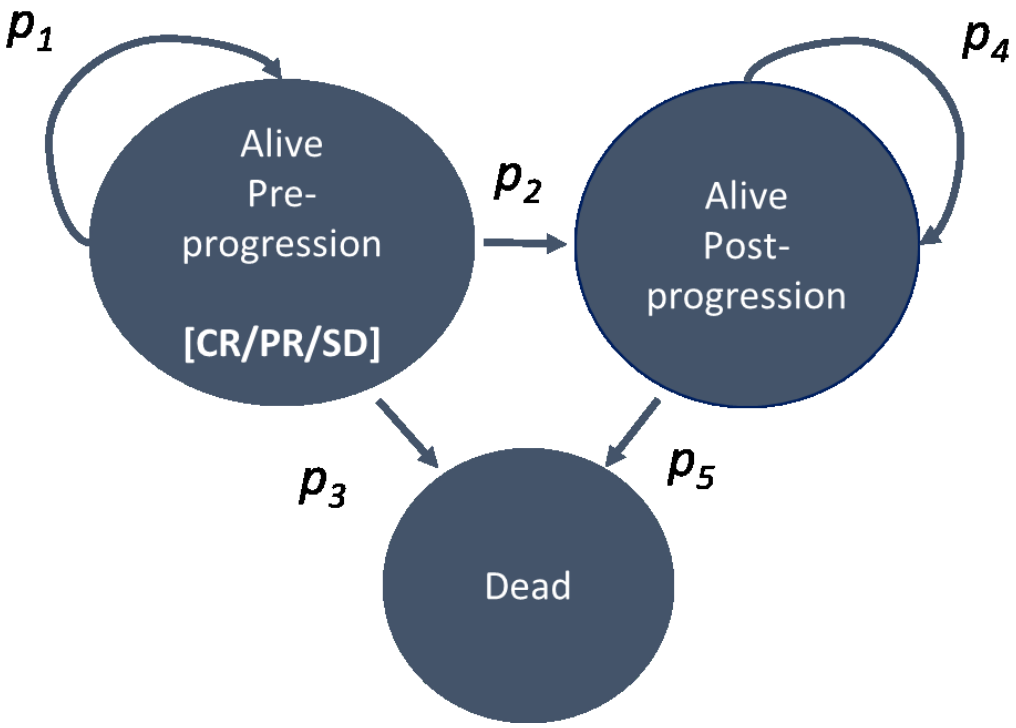
| Parameter | Mean | SE | Source |
|---|---|---|---|
| Baseline age (years) | [redacted] | [redacted] | Eligible population from CheckMate 205 (B and C) and CA209-039 |
| Proportion of cohort male | [redacted] | [redacted] | |
| Cohort size | 1000 | | |

### 5.2.2 Model structure

A de novo semi-Markov survival model was developed, applying health states representing pre-progression, post-progression and death, as depicted in Figure 23. These health states reflect disease severity and determine use of healthcare resources, health-related quality of life and mortality rates. To reflect the nature of HL and available evidence, the model assumes that cHL phases are consecutive, so that patients cannot revert to pre-progression from more advanced phases of the disease; this assumption has been validated by clinicians.

Using a monthly cycle length, and applying half-cycle correction, the model predicts the proportion of the population who experience a progression or death event. Monthly cycles were considered appropriate because they reflect the frequency of follow-up of cHL patients and a realistic minimum time during which the symptoms or response can change.

**Figure 23. Markov states used in model**



#### *5.2.2.1 Derivation of health state occupancy estimates*

Health state occupancy is defined by treatment-specific PFS and OS extrapolation, derived from available data (as described in Section 5.3.1). As these PFS and OS data implicitly include the effects of any subsequent treatment that may have been administered, the need to explicitly incorporate the effects of these subsequent treatments is negated. As an exception, scenarios considering the use of alloSCT as subsequent therapy are modelled using independent survival curves, as alloSCT is associated with morbidity and mortality in the short-term but can be considered potentially curative over the long-term.[7]

For nivolumab, parametric curves for PFS and OS were fitted using patient-level data from the CheckMate 205 and CA209-039 studies. Data for a real-world comparator is derived from the Cheah 2016 real-world data, where Kaplan-Meier data and published survival estimates were used to inform OS and PFS curves. Full details are provided in Section 5.3.1.

**Definition of progression events**

Conventional anti-cancer therapies typically aim reduce the tumour burden through disruption of cell proliferation or induction of apoptosis. By contrast, immuno-oncology therapies demonstrate a varied pattern of response, including the appearance of larger tumours due to the increased immune cell activity in the tumour environment. This pattern of response is a well-recognised challenge associated with immuno-oncology therapies, and can result in dissociated responses, delayed responses and pseudo-progressions, where patients who ultimately achieve a positive clinical outcome may have tumours that appear to have enlarged when assessed in the early stages of treatment. These challenges are exacerbated by PET scan limitations,[73] in the context of increased activation of immune cells due to the nivolumab mechanism of action.

Several approaches have been suggested to improve monitoring of efficacy in these promising, new immuno-oncology therapies, including development of specific response criteria and use of alternative endpoints, such as disease control and tumour growth rates.[74] However, the extent to which these approaches have been incorporated into clinical practice is unclear.

For this reason, progression within the model is applied based on investigator-assessed PFS from clinical studies, as clinical experts suggest that this is likely to reflect clinician behaviour in a real world setting. Similarly, this may better reflect the accrual of costs and QALYs of HL patients, as a patient considered not to have progressed by the clinician is likely to have a different quality of life and management plan compared with a patient considered to have progressed. The impact of applying IRRS-derived PFS data is assessed using sensitivity analyses.

#### *5.2.2.2 Derivation of Treatment Line Occupancy*

Patients enter the model following failure of prior therapies and can receive nivolumab or SoC. Following treatment cessation or progression, patients can receive subsequent therapy; however, it is assumed that patients may not discontinue the final line of therapy (BSC, comprised of palliative care/chemotherapy). Thus, in the base case analysis, the proportion of patients on initial or subsequent treatment lines is based on the following criteria:

- All-cause discontinuation
- Treatment cessation (where treatment duration is specified)
- The probability of progression

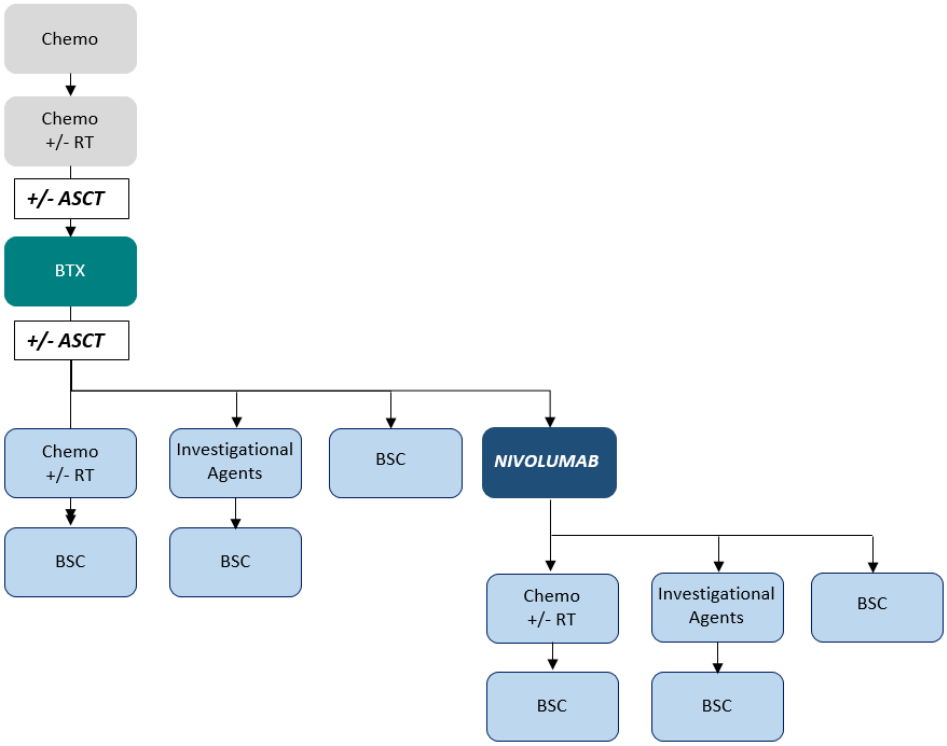
Although the model has the capacity to model response-specific stopping rules, this is not implemented within the base case analysis; however, scenario analyses assess the impact of applying these stopping rules.

#### *5.2.2.3 Treatment sequences*

A summary of clinical practice, based on BCSH guidelines and clinician advice, is presented in Figure 24. Using these guidelines, as well as clinical expert opinion, a base case treatment pathway has been developed for application within the model, taking into account potential comparators and future clinical practice, depicted in Figure 24. Patients enter the model following failure of prior therapies, including ASCT and BTX, and can receive nivolumab or SoC. Following treatment discontinuation or progression, patients can receive subsequent therapy, which in the base case analysis is applied as BSC. Composition of BSC is assumed to be chemotherapy, palliative care and clinical trials; further information is provided in Section 5.5.2.3.

A number of alternative comparators and treatment sequences were also considered as scenario analysis; further information is provided in Section 5.8.

**Figure 24. Current treatment pathways (determined by BCSH guidelines and clinician advice) and the potential place in therapy of nivolumab**




### *5.2.2.4 Outcome measures*

The primary model output is the incremental cost-effectiveness ratio (ICER) expressed as costs per QALY gained. Additionally, the model expresses outcomes as LYs gained, as well as clinically relevant outcomes, such as predicted median OS and PFS.

**Table 36. Features of the de novo analysis**

| Factor | Values | Justification |
|---|---|---|
| Time horizon | 40 years | Life time horizon reflecting all important costs and outcomes, in line with NICE Guide to the Methods of Technology Appraisal;[34] a 60-year time horizon is available to simulate cohorts with extended survival. |
| Were health effects measured in QALYs? | Yes | In line with the NICE Guide to the Methods of Technology Appraisal[34] |
| Discount of 3.5% for utilities and costs | Yes | |
| Perspective (NHS/PSS) | NHS and PSS | |
| PSS: personal social services; QALYs: quality-adjusted life years | | |

### 5.2.3 Intervention technology and comparators

The NICE scope for this appraisal specified the following comparators to be included in the analysis:[75]

- Established clinical management without nivolumab, including chemotherapy such as gemcitabine or bendamustine.
- Best supportive care.

In the specific context of relapsed or refractory HL, with low patient numbers, short survival and an ongoing NICE appraisal of BTX, the clinical pathway for HL patients is subject to considerable uncertainty and heterogeneity, particularly in the post-ASCT, post-BTX setting. Further, data describing treatment in the post ASCT, post-BTX setting is likely to apply investigational therapies rather than established clinical practice.

In light of this uncertainty and the lack of data surrounding comparator composition, the general approach has been to use simple assumptions based on independent sources, such as the published literature, British HL guidelines or previous NICE appraisals in the field of HL or NHL. These assumptions were then assessed for clinical plausibility, and alternative assumptions were assessed in scenario analyses. In line with this approach, the base case analysis assumes that established clinical management is equivalent to the therapies described within the Cheah 2016 real world data.[7] Patients in this study had previously received BTX (100%) and ASCT (71%) and so can be said to adequately represent the post-ASCT, post-BTX HL population. The study was conducted at the at MD Anderson Cancer Center in the USA; however, it is unlikely that there are significant differences in patients from study compared with those in CheckMate 205 or those likely to be seen in UK clinical practice.

Treatments administered within Cheah 2016 and the outcomes from these therapies are presented in Table 37. In order to provide the most robust base case analysis, these therapies are assumed to comprise SoC, with the following assumptions and amendments to reflect clinical practice and enable calculation of costs and utilities:

- The “Other” category does not provide enough detailed information to allocate costs and utilities, consequently the composition of SoC has been weighted excluding these therapies, as detailed in Table 38.
- Second ASCT is not considered to be a relevant comparator in this patient population, as typically patients are only considered for ASCT following adequate response to salvage therapy. By contrast, patients considered for nivolumab therapy would have relapsed or refractory cHL, and so ASCT would not be an option in these patients. Therefore, composition of SoC has been weighted excluding this therapy, as detailed in Table 38.
- Investigational agents within the Cheah 2016 study[7] were highly beneficial in terms of increased median OS, but included PD-1 inhibitor agents and this is likely to have included nivolumab, limiting the relevance of this treatment category as a comparator for the assessment of the clinical benefits of nivolumab. However, within UK clinical practice, a proportion of patients are likely to receive investigational agents as part of clinical trials following failure of prior therapies; a scenario analysis is provided to examine the impact of inclusion of investigational agents within SoC.

- Use of the “Gemcitabine”, “Other alkylator”, and “platinum based” regimens have been pooled to inform the proportion of patients receiving chemotherapy; composition of chemotherapy in UK clinical practice has been assumed based on equal usage of regimens specified by the BCSH guidelines.[3]

**Table 37. Cheah 2016: therapies administered and outcomes**

| Treatment | *n* | Eval | CR (%) | PR (%) | ORR (%) | mPFS (m) | mOS (m) |
|---|---|---|---|---|---|---|---|
| Investigational agent | 28 | 28 | 4 (14) | 3 (11) | 7 (25) | 2.4 | 47.7 |
| Gemcitabine | 15 | 12 | 4 (27) | 4 (27) | 8 (53) | 2.1 | NR |
| Bendamustine | 12 | 11 | 2 (17) | 4 (33) | 6 (50) | 3.7 | 34.0 |
| Other alkylator | 6 | 4 | 1 (17) | 1 (17) | 2 (33) | 5.0 | 9.5 |
| BTX retreatment | 6 | 4 | 0 (0) | 2 (33) | 2 (33) | 3.5 | 10.4 |
| Platinum based | 4 | 4 | 0 (0) | 1 (25) | 1 (25) | 0.9 | 25.2 |
| ASCT | 3 | 3 | 1 (33) | 0 (0) | 1 (33) | - | 11.9 |
| Other | 5 | 1 | 0 (0) | 0 (0) | 0 (0) | - | 24.9 |
| **Total** | **79** | **67 (85)** | **12 (15)** | **15 (19)** | **27 (34)** | **3.5** | **25.2** |

ASCT: autologous stem cell transplant; BTX: brentuximab; CR: complete response; mOS: median overall survival; mPFS: median progression-free survival; ORR: objective response rate; PR: partial response.

**Table 38. Composition of comparator (Standard of Care) based on Cheah 2016[7]**

| | Percentage | Composition |
|---|---|---|
| Chemotherapy | 58.1% | The following regimens based on BCSH Table 1[3] and appraisal scope[75]: ASHAP, DexaBEAM, DHAOx, DHAP, ESHAP, GDP, GEM-P, GVD, ICE, IGEV, IVE, IVOx, MINE, Mini-BEAM |
| Bendamustine | 27.9% | - |
| BTX retreatment | 14.0% | - |

ASHAP: doxorubicin, methylprednisolone, cytarabine, cisplatin; BTX: brentuximab; DexaBEAM: dexamethasone, carmustine, etoposide, cytarabine, melphalan; DHAOx: dexamethasone, cytarabine, oxaliplatin; DHAP: dexamethasone, cytarabine, cisplatin; ESHAP: etoposide, methylprednisolone, cytarabine, cisplatin; GDP: gemcitabine, dexamethasone, cisplatin; GEM-P: gemcitabine, cisplatin, methylprednisolone; GVD: gemcitabine, vinorelbine, liposomal doxorubicin; ICE: ifosfamide, carboplatin, etoposide; IGEV: ifosfamide, gemcitabine, vinorelbine; IVE: ifosfamide, epirubicin, etoposide; IVOx: ifosfamide, etoposide, oxaliplatin; MINE: mitoxantrone, ifosfamide, vinorelbine, etoposide; Mini-BEAM: carmustine, etoposide, cytarabine, melphalan;

Based on BCSH guidelines[3] and clinician opinion, it is believed that use of BSC is minimal at this stage in the treatment pathway, as eligible patients are likely to receive therapy where feasible. As such, BSC has been applied within the model as a subsequent therapy in the base case analysis, with the composition derived from a recent NHL NICE Technology Appraisal (TA306[72]).

In order to provide cost-effectiveness evidence with direct relevance to the NICE scope, scenario analyses have been provided assessing the impact of chemotherapy (as specified within the NICE scope) and BSC as comparators.

## *5.3 Clinical parameters and variables*

### 5.3.1 Evidence synthesis

As discussed in Section 4, no direct comparative evidence is available for nivolumab versus SoC. In order to identify data describing SoC, several SLRs have been undertaken, and

using this data a MAIC has been conducted. However, these analyses have inherent limitations, not least with regard to the applicability of the patient population to the decision problem. With this in mind, a naïve indirect comparison of nivolumab versus SoC has been used to inform the base case analysis; the impact of using alternative data sources, including the MAIC, has been assessed by scenario analyses.

In order to provide an assessment of the efficacy of SoC, the base case analysis applies comparator efficacy derived from the Cheah 2016 real world data.[7] Patients in this study had previously received BTX (100%) and ASCT (71%) and so can be said to adequately represent the post-ASCT, post-BTX HL population. In the base case scenario, efficacy inputs are derived from the population of patients who did not receive investigational agents; scenario analyses assess the impact of applying efficacy based on the overall population, as well as applying the shortest and longest survival estimates.

Nivolumab efficacy is derived from a pooled analysis of the CheckMate 205 and CA209-039 studies; an overview of these studies is provided in Sections 4.7.1 and 4.7.2. Data from all patients who had previously received both ASCT and BTX were pooled and considered representative of the overall effect of nivolumab. As such, unless specified otherwise, nivolumab efficacy data are derived from patients within Cohort B and Cohort C (excluding two patients who had not previously received BTX) from CheckMate 205 and the 15 patients from CA209-039 who had previously received both ASCT and BTX.

Evidence to describe the efficacy of BSC in this population has not been identified; scenario analyses describing BSC as a comparator have been based on the efficacy of SoC, in order to provide a highly conservative analysis of the benefits of nivolumab versus BSC. Composition of BSC has been derived from a recent NICE appraisal in the NHL population.[72]

### 5.3.2 Parameterisation of overall survival and progression-free survival

#### *5.3.2.1 Nivolumab*

Clinical data to inform nivolumab PFS and OS can be derived from Cohort B (n = 80) and Cohort C (n = 98; two patients who had not received BTX excluded) of the CheckMate 205 study (total: 178) and the post-ASCT/BTX patients from CA209-039 (n = 15). However, median follow-up during CheckMate 205 was 15.7 months for Cohort B, 8.9 months for Cohort C, and 23.3 months during CA209-039, which is below the 40-year time horizon of the model. Therefore parametric extrapolation of survival data from the study was required to inform long-term outcomes, undertaken with reference to the guidance from the NICE Decision Support Unit (DSU)[76] and Bagust and Beale (2014)[77] within the context of only using single-arm data. Full methodology is outlined in Appendix 6.

In brief, the parametric functions that inform survival curves were developed using patient-level data from Cohorts B and C of CheckMate 205 and the post-ASCT+BTX patients from CA209-039; due to the relatively low number of patients enrolled in both studies, data from these studies were pooled. Progression events were based on investigator-assessed outcomes, as described in Section 5.2.2.1, and were derived from PFS data, defined as in

CheckMate 205 and CA209-039. Death events from CheckMate 205 and CA209-039 were used to inform OS modelling.

Parametric survival functions were fitted to the extracted pooled data using the R statistics environment, including exponential, Weibull, log-logistic, lognormal, Gompertz and generalised-gamma survival distributions. Goodness-of-fit was evaluated using the Akaike and Bayesian Information Criteria (AIC and BIC, respectively); minimisation of these measures is used to indicate goodness-of-fit whilst penalising overfitting, so that a smaller value demonstrates a more appropriate fit.

It is worth noting that while the above methods for validating the extrapolation of progression and death events are appropriate, they are also necessarily constrained by derivation from observed data which is, as previously indicated, limited by short duration of follow-up. Therefore in order to inform the clinical plausibility of the long-term extrapolation of parametric functions, clinical experts visually assessed the resulting survival curves and the corresponding evolution of the hazards over time. Clinicians determined that lognormal PFS curves were most clinically plausible, due to the initial increase in hazard following by a gradual decline in risk over time, but noted the paucity of data to inform OS. In order to overcome this limitation, clinicians considered that PFS and OS hazards would have similar long-term extrapolation. Of the available OS curves, Weibull provided the most similar hazards over time, and so this was applied within the model; it should be noted however that in comparison with other survival distributions, the Weibull may be considered one of the most conservative.

Survival function parameters applied in the model are detailed in Table 39; Kaplan-Meier data and short term survival functions are illustrated in Figure 25 and Figure 26, while long-term extrapolations are illustrated in Figure 27 and Figure 28

**Table 39. Parameters describing PFS and OS for nivolumab**

| | **Nivolumab** |
|---|---|
| PFS | Lognormal;<br>μ: 2.825<br>σ: 1.109 |
| OS | Weibull<br>Scale (A): 76.74<br>Shape (B): 1.326 |
| OS: overall survival; PFS: progression-free survival.<br>Lognormal survival equation takes the form: S(t) = 0.5-0.5*erf((ln(t)-mu)/(sqrt(2)*sigma))<br>Weibull survival equation takes the form: S(t) = exp(-(t/A)^B) | |

**Table 40. Goodness of fit statistics and median survival estimates**

| | PFS | | | OS | | |
|---|---|---|---|---|---|---|
| | AIC | BIC | Median (months) | AIC | BIC | Median (months) |
| Exponential | 493.6 | 496.8 | 19.0 | 203.0 | 206.3 | 94.2 |
| Weibull | 486.8 | 493.3 | 15.7 | 203.5 | 210.0 | 58.2 |
| Log-logistic | 484.8 | 491.3 | 15.9 | 203.5 | 210.0 | 70.1 |
| Lognormal | 483.2 | 489.7 | 16.9 | 203.1 | 209.6 | 108.7 |
| Gompertz | 492.1 | 498.6 | 16.3 | 204.0 | 210.6 | 42.7 |
| G Gamma | 485.2 | 495.0 | 17.1 | 205.0 | 214.8 | 156.5 |
| AIC: Akaike Information Criteria; BIC: Bayesian Information Criteria; OS: overall survival; PFS: progression-free survival. | | | | | | |

**Figure 25. Parameterisation of progression-free survival: nivolumab (years 0-5)**

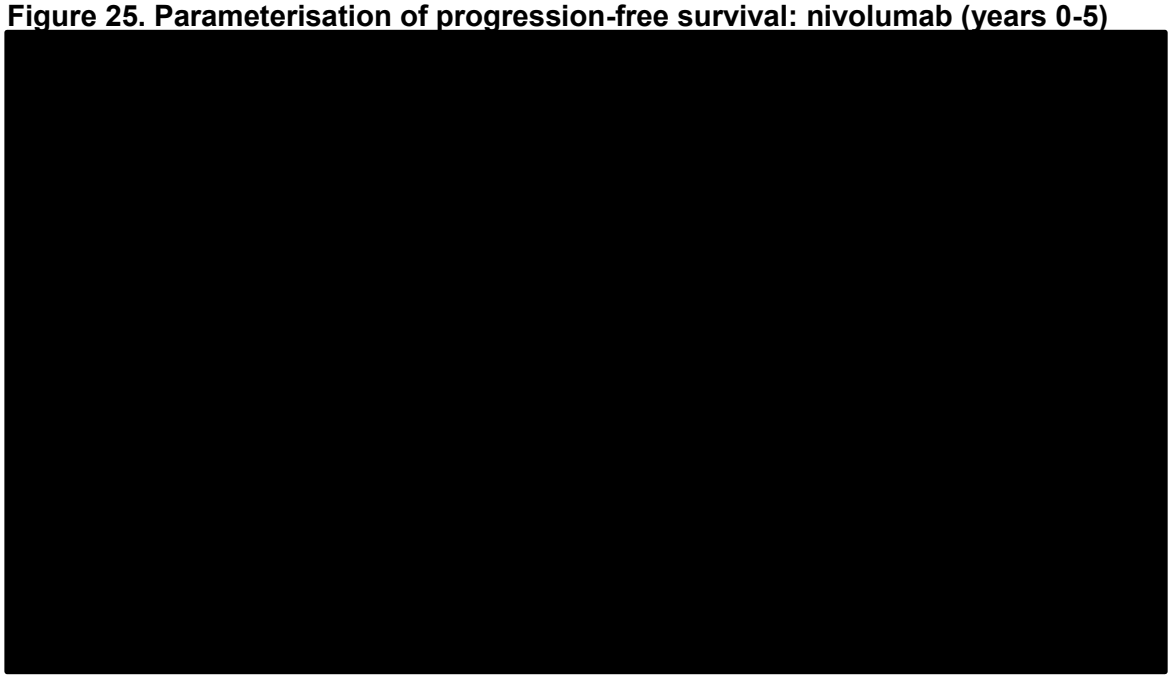


**Figure 26. Parameterisation of overall survival: nivolumab (years 0-5)**

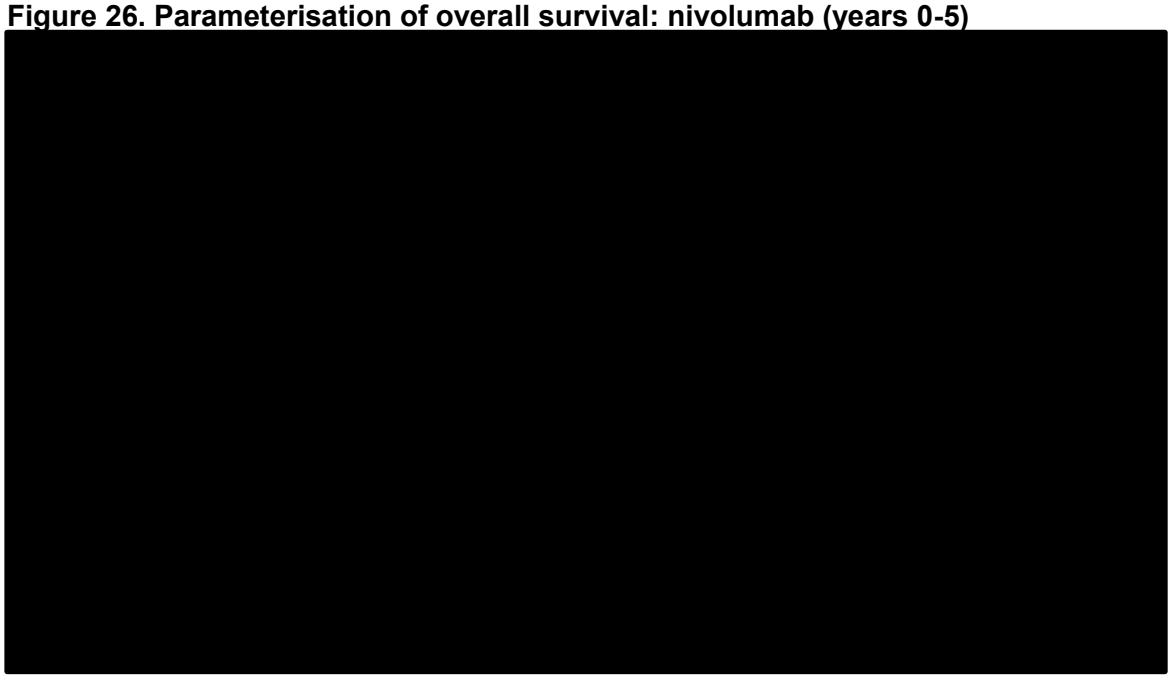


**Figure 27. Long-term parameterisation of progression-free survival: nivolumab**

**Figure 28. Long-term parameterisation of overall survival: nivolumab**

#### *5.3.2.2 Standard of care*

In order to provide an unbiased assessment of the efficacy of SoC, the base case analysis applies comparator efficacy derived from the Cheah 2016 real world data.[7] Patients in this study had previously received BTX (100%) and ASCT (71%) and so can be said to adequately represent the post-ASCT, post-BTX HL population. In the base case scenario, efficacy inputs are derived from the population of patients who did not receive investigational agents.

A full description of the derivation of survival curves for SoC has been provided in Appendix 6; however, an overview is provided below.

**Progression-free survival**

Kaplan-Meier data describing PFS is provided within Cheah 2016 for the overall population (n = 79),[7] providing a median PFS of 3.5 months. Median PFS for specific therapy categories ranged from 0.9 months (platinum based therapies) to 5.0 (other alkylator therapies), with investigational agents reporting a median PFS of 2.4 months. As PFS associated with investigational agents appears to be comparable to that of other therapy categories, it has been assumed that the Kaplan-Meier data describing PFS for the overall population is representative of SoC (i.e. without investigational agents).

Given the paucity of data, a conservative approach was taken and an exponential curve was fitted to the available data, in line with the Bagust and Beale (2014)[77] rationale that an exponential distribution should be considered the default parametric function for long-term survival projection. Survival function parameters applied in the model are detailed in Table 41; Kaplan-Meier data and survival functions are illustrated in Figure 29.

The “all therapy” PFS curve was considered to be a proportional sum of the investigational and the non-investigational survival curves, where the median intercept of the total and the investigational curves was reported, but the non-investigational was unknown.

**Figure 29. Parameterisation of progression-free survival: SoC**

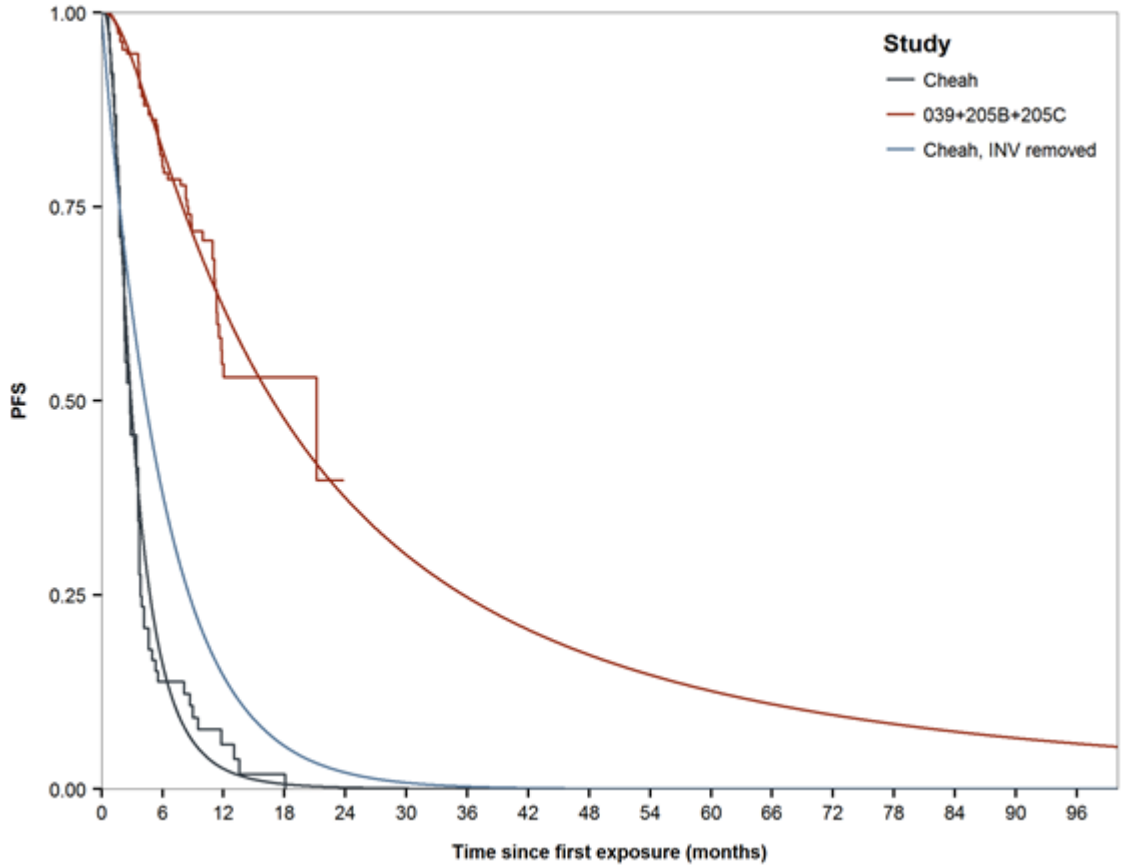



**Table 41. Parameters describing PFS and OS for standard of care**

| | SoC |
|---|---|
| PFS | Exponential<br>λ: 0.160 |
| OS | Exponential<br>λ: 0.036 |
| OS: overall survival; PFS: progression-free survival; SoC: standard of care<br>Exponential survival equation takes the form: S(t) = exp(lambda*t) | |

## Overall survival

As with PFS, Kaplan-Meier data describing OS is available for the overall population (n = 79) reported by Cheah 2016,[7] providing a median OS of 25.2 months. Median OS for specific therapy categories ranged from 9.5 months (other alkylator therapies) to 34.0 (bendamustine), with investigational agents reporting a median OS of 47.7 months. It can be concluded that OS associated with investigational agents appears to be far greater than that reported for other therapy categories, and likely contains patients receiving nivolumab. In order to avoid a scenario where the beneficial effects of nivolumab are compared against those of a SoC where benefits are driven by patients receiving investigational agents, including nivolumab, it has been necessary to derive an OS curve where the impact of investigational agents has been removed.

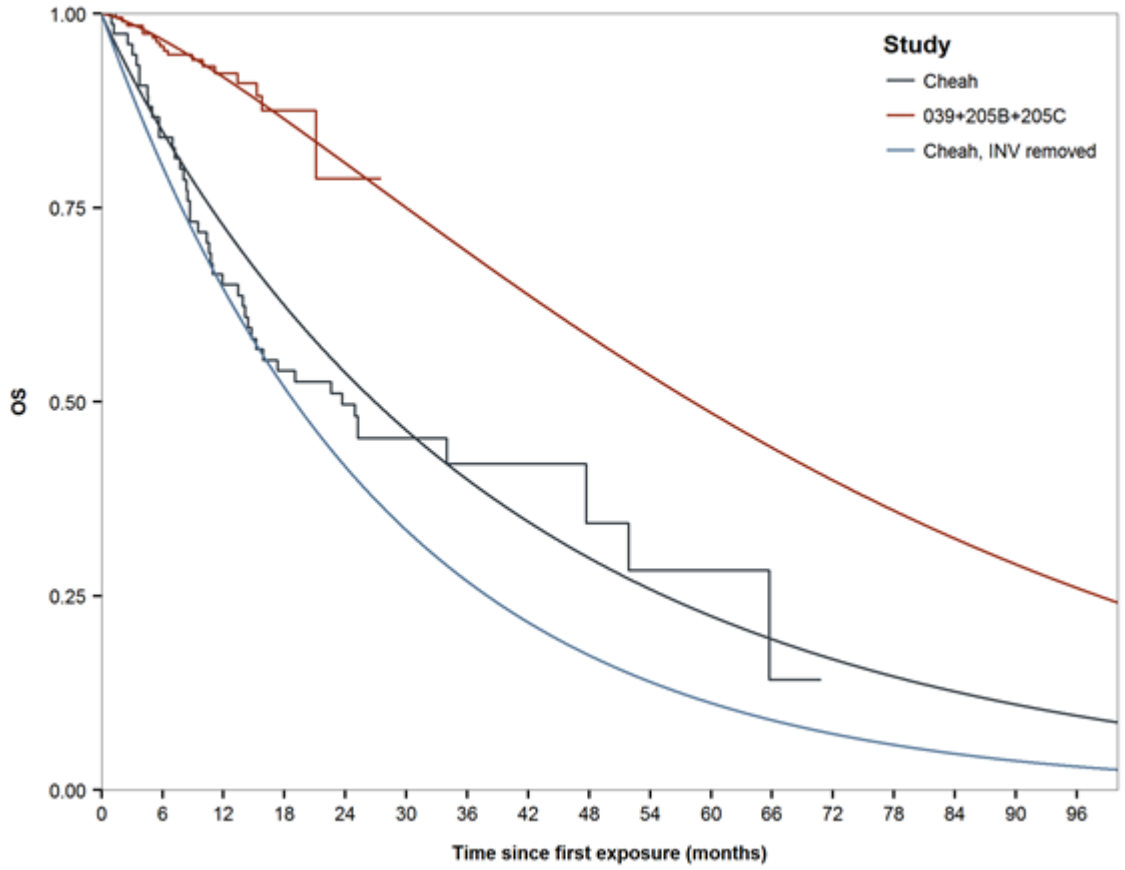
As some therapy categories do not report median OS, and there are no Kaplan-Meier data available to describe each individual therapy category, it has been assumed that an exponential fit would be an appropriate parametric fit for the overall population, as well as each therapy category. An exponential parametric fit was applied to the overall population OS median (25.2 months) and the investigational agent OS median (47.7 months). The investigational agent exponential curve was then used to adapt the overall population exponential curve using the following equation:

$$lambda\_OTH = - ln(( 0.5 - p*exp(-lambda\_INV * t\_m) )/(1-p)) / t\_m$$

where: p is the proportion of the overall cohort receiving investigational agents; t_m is the median OS in the overall population, and lambda_INV is the rate of the exponential fitted through the investigation agent median OS.

Survival function parameters applied in the model are detailed in Table 41; Kaplan-Meier data and survival functions are illustrated in Figure 30.

**Figure 30. Parameterisation of overall survival: SoC**




### *5.3.2.3 All-cause mortality*

Individuals randomised into clinical trials are likely to be younger and healthier than the overall HL patient population in the UK. The average age of patients in CheckMate 205[13] and CA209-039[14] was 37 years and 35 years, respectively, increasing the likelihood that most deaths observed over the trial period were HL-related.

Therefore, the model includes age and gender-adjusted mortality based on information from UK life tables,[78] described in Table 42. These values are included in every cycle in addition to the disease-related mortality values and are applied multiplicatively. While some form of double counting occurs in the first few years, due to the low baseline age, this effect applies equally to all comparators and is likely to have a minimal impact on predicted survival (and hence cost-effectiveness).

**Table 42. Excerpt from England and Wales life tables[78]**

| Age | Annual probability of mortality | |
|---|---|---|
| | Males | Females |
| 50 | 0.003101 | 0.002156 |
| 51 | 0.003423 | 0.002344 |
| 52 | 0.003702 | 0.002558 |
| 53 | 0.004067 | 0.002780 |
| 54 | 0.004528 | 0.002977 |
| 55 | 0.004865 | 0.003402 |
| - | - | - |
| 95 | 0.259055 | 0.219153 |
| 96 | 0.286001 | 0.251076 |
| 97 | 0.308416 | 0.267500 |
| 98 | 0.330830 | 0.289642 |
| 99 | 0.347717 | 0.315701 |
| 100 | 0.355920 | 0.329873 |

### 5.3.3 Therapy effects

#### *5.3.3.1 Response rates*

Within the model, rate of response does not impact directly on progression or survival, as impact on patient survival is assumed to be implicitly incorporated into reported survival data. Similarly, costs associated with follow-up and treatment are applied based on health state, and are not directly impacted by response rate. However, it is plausible that response rates could impact on pre-progression utility, as well as application of stopping rules or switching to subsequent therapies such as alloSCT.

Response rates within the model are derived from investigator-assessed BOR rates, because as previously discussed, clinical experts suggest that this is likely to reflect clinician behaviour in a real world setting. The impact of applying IRRS-derived response rate data is assessed using sensitivity analyses. Patients with a BOR of progressed disease (PD) were included within the SD population at baseline, as this is most likely to represent their utility and treatment decisions in the pre-progression state.

Patient-level data from Cohorts B and C from CheckMate205 were pooled with that from CA209-039 and this comprises the primary data source for nivolumab rates of response. Response rate for SoC was derived from the Cheah 2016 study[7] after adjustment for exclusion of patients receiving investigational agents. Table 43 summarises response rates applied within the base case analysis.

**Table 43. Treatment response: base case analysis**

| Treatment | CR | | PR | | Source population |
|---|---|---|---|---|---|
| | Value | SE | Value | SE | |
| Nivolumab* | [redacted] | [redacted] | [redacted] | [redacted] | Eligible population from CheckMate 205 (B and C) and CA209-039 |
| SoC | 15.7% | 5.09 | 23% | 5.94 | Cheah 2016[7] (excluding investigational agents) |

CR: complete response; PR: partial response; SD: stable disease; SE: standard error: SoC: standard of care.
Patients with best overall response of progressed disease included within SD at baseline. SD assumed to be the residual of 'N – CR – PR'.
For probabilistic analysis, the relative response rate between the nivolumab cohort response and the SoC response, as calculated by the Mantel-Haenszel Fixed Effects Model, was sampled and used to inform the distribution of the SoC response.

#### *5.3.3.2 Treatment discontinuation*

For both nivolumab and SoC, it was assumed that patients switched to subsequent treatment following progression; while nivolumab therapy was maintained until the progression event, the median or recommended duration of treatment was applied when costing components of SoC, based on pivotal trials or those specified within BCSH guidelines.[3]

In addition to applying treatment switching on progression, the model applies discontinuation rates to reflect discontinuation due to AEs or other reasons, such as patient preference. The timing of these discontinuations were assumed to impact on incidence of AEs, treatment costs and resource use.

Patient-level data describing patients discontinuing for reasons other than death or progression were obtained from CheckMate205 (Cohorts B and C) and CA209-039. These data were used to derive the rate of discontinuation during nivolumab treatment, with a lognormal curve fitted to available data. It was assumed that patients receiving comparator chemotherapy regimens would receive a similar rate of discontinuation. Inputs are summarised in Table 44.

**Table 44. CheckMate 205 discontinuations (applied to nivolumab and SoC)**

| | Parameter |
|---|---|
| Fitting | Lognormal |
| μ | 3.283 |
| σ | 1.252 |
| Lognormal survival equation takes the form: S(t) = 0.5-0.5*erf((ln(t)-mu)/(sqrt(2)*sigma)) | |

#### *5.3.3.3 Adverse events*

Treatment-related AEs are an inevitable consequence of any intervention, and these events are applied in the model, affecting the costs and benefits accrued by patients on each intervention. In order to reflect clinical practice, haematological AEs are included in the model; additional AEs have been identified based on a subsection of those considered clinically relevant within a recent NICE appraisal of an NHL therapy.[72]

**Nivolumab**

Data from Cohorts A, B and C from CheckMate205 were pooled with that from the overall CA209-039 population, and this was assumed to comprise all available evidence describing the safety profile of nivolumab for the treatment of cHL. Treatment-related grade 3-4 AE rates were sourced for each study, and incidence rates were converted into monthly equivalents based on follow-up time using standard formulae and applied to all patients in the model in all cycles. Monthly rates from each study have then been used to create a weighted mean monthly rate. Inputs are summarised in Table 45.

**Table 45. Nivolumab adverse event rates**

| | | CheckMate205 overall cohort | CA209-039 overall cohort | Weighted monthly rate | SE |
|---|---|---|---|---|---|
| **Study characteristics** | | | | | |
| Number of patients | | 240 | 23 | - | |
| Follow-up | | Median [redacted] months | Median 23.26 months | | |
| Source | | Table S.6.4BT and Table S.7.1BT-SI Whole cohort | Table S.6.3 and table S.7.1-SI | | |
| **Adverse events** | | | | | |
| Anaemia | N | [redacted] | [redacted] | [redacted] | [redacted] |
| | % | [redacted] | [redacted] | | |
| | Rate | [redacted] | [redacted] | | |
| Diarrhoea | N | [redacted] | [redacted] | [redacted] | [redacted] |
| | % | [redacted] | [redacted] | | |
| | Rate | [redacted] | [redacted] | | |
| Dyspnoea | N | [redacted] | [redacted] | [redacted] | [redacted] |
| | % | [redacted] | [redacted] | | |
| | Rate | [redacted] | [redacted] | | |
| Fatigue | N | [redacted] | [redacted] | [redacted] | [redacted] |
| | % | [redacted] | [redacted] | | |
| | Rate | [redacted] | [redacted] | | |
| Leukopenia | N | [redacted] | [redacted] | [redacted] | [redacted] |
| | % | [redacted] | [redacted] | | |
| | Rate | [redacted] | [redacted] | | |
| Nausea | N | [redacted] | [redacted] | [redacted] | [redacted] |
| | % | [redacted] | [redacted] | | |
| | Rate | [redacted] | [redacted] | | |
| Neutropenia | N | [redacted] | [redacted] | [redacted] | [redacted] |
| | % | [redacted] | [redacted] | | |
| | Rate | [redacted] | [redacted] | | |
| Pyrexia | N | [redacted] | [redacted] | [redacted] | [redacted] |
| | % | [redacted] | [redacted] | | |
| | Rate | [redacted] | [redacted] | | |
| Thrombocytopenia | N | [redacted] | [redacted] | [redacted] | [redacted] |
| | % | [redacted] | [redacted] | | |
| | Rate | [redacted] | [redacted] | | |
| Vomiting | N | [redacted] | [redacted] | [redacted] | [redacted] |
| | % | [redacted] | [redacted] | | |
| | Rate | [redacted] | [redacted] | | |
| Incidence rates have been converted into monthly equivalents based on follow-up time using standard formulae and applied to all patients in the model in all cycles. Monthly rates from each study have then been used to create a weighted mean monthly rate. | | | | | |

## Standard of care

In the base case analysis, SoC is assumed to be comprised of a combination of therapies: bendamustine, BTX re-treatment and chemotherapy.

Chemotherapy regimens used to treat relapsed or refractory cHL in clinical practice were assumed to be those specified by BCSH guidelines, with usage assumed to be equally shared. In order to provide AE rates relevant to these regimens, treatment-related grade 3-4 AE rates were sourced for each study, using the study specifically cited within the BCSH guidelines. Incidence rates were converted into monthly equivalents based on follow-up time (as detailed in Table 46) and these were then combined into a set of weighted mean chemotherapy monthly AE rates (Table 47). It should be noted that these cohorts were less heavily pre-treated than those patients enrolled in CheckMate 205 and CA209-039; however, the safety profile can be anticipated to be similar between these groups.

The monthly incidence of AEs for SoC was calculated similarly. AE rates were sourced from relevant studies, and converted into monthly equivalents based on follow-up time. These were then combined into a set of weighted mean chemotherapy monthly AE rates, using predicted usage from Cheah 2016 (Table 47).[7]

As the comparator composition is based on a series of assumptions, scenario analyses examined the impact of different comparator compositions. AE rates applied in these analyses are described in Section 5.8.3 and were calculated similarly.

**Table 46. Adverse event rates for BCSH-specified chemotherapy regimens**

| | | ICE | IVE | MINE | IVOx | IGEV | GEM-P | GDP | GVD | Mini-BEAM | DexaBEAM | ESHAP | ASHAP | DHAP | DHAOx |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study characteristics** | | | | | | | | | | | | | | | |
| Number of patients | | NR | 145 | 207 | NR | 313 | % | 23 | 37 | NR | NR | 22 | NR | 201 | 70 |
| Follow-up | | NR | Results reported in terms of cycles impacted. 21 day cycle | Results reported in terms of cycles impacted. 28 day cycle | NR | Results reported in terms of cycles impacted. 21 day cycle | Median 11.7 months | Median 2 cycles (six weeks) | NR. Six cycles | NR | NR | 50 months | NR | Results reported in terms of cycles impacted. 21 day cycle | Median 21 months |
| Source | | Moskowitz 2001[79] | Zinzani 2002[80] | Ferme 1995[81] | Sibon 2011[82] | Santoro 2007[83] | Chau 2003[84] | Baetz 2003[85] | Bartlett 2007[86] | Girouard 1997[87] | Schmitz 2002[88] | Aparicio 1999[89] | Rodriguez 1999[90] | Josting 2002[91] | Rigacci 2010[92] |
| **Adverse event rates** | | | | | | | | | | | | | | | |
| Anaemia | N | NR | NR | 25 | NR | 57 | - | 2 | 6 | NR | NR | 6 | NR | 34 | 4 |
| | % | NR | NR | 12.1% | NR | 18.2% | 9.5% | 8.7% | 16.2% | NR | NR | 27.3% | NR | 16.9% | 5.7% |
| | Rate | NR | NR | 13.1% | NR | 25.3% | 0.8% | 12.4% | 4.2% | NR | NR | 0.6% | NR | 23.6% | 0.3% |
| Diarrhoea | N | NR | NR | 2 | NR | NR | - | NR | 1 | NR | NR | 7 | NR | NR | NR |
| | % | NR | NR | 1.0% | NR | NR | 0.0% | NR | 2.7% | NR | NR | 31.8% | NR | NR | NR |
| | Rate | NR | NR | 1.0% | NR | NR | 0.0% | NR | 0.7% | NR | NR | 0.8% | NR | NR | NR |
| Dyspnoea | N | NR | NR | NR | NR | NR | NR | 1 | NR | NR | NR | NR | NR | NR | NR |
| | % | NR | NR | NR | NR | NR | NR | 4.3% | NR | NR | NR | NR | NR | NR | NR |
| | Rate | NR | NR | NR | NR | NR | NR | 6.2% | NR | NR | NR | NR | NR | NR | NR |
| Fatigue | N | NR | NR | NR | NR | NR | NR | 2 | 4 | NR | NR | NR | NR | NR | NR |
| | % | NR | NR | NR | NR | NR | NR | 8.7% | 10.8% | NR | NR | NR | NR | NR | NR |
| | Rate | NR | NR | NR | NR | NR | NR | 12.4% | 2.7% | NR | NR | NR | NR | NR | NR |
| Leukopenia | N | NR | NR | NR | NR | NR | - | NR | 6 | NR | NR | NR | NR | 136 | NR |
| | % | NR | NR | NR | NR | NR | 61.9% | NR | 16.2% | NR | NR | NR | NR | 67.7% | NR |
| | Rate | NR | NR | NR | NR | NR | 7.9% | NR | 4.2% | NR | NR | NR | NR | 80.5% | NR |
| Nausea | N | NR | NR | 8 | NR | 5 | - | 0 | 0 | NR | NR | NR | NR | 26 | 0 |
| | % | NR | NR | 3.9% | NR | 1.6% | 0.0% | 0.0% | 0.0% | NR | NR | NR | NR | 12.9% | 0.0% |
| | Rate | NR | NR | 4.2% | NR | 2.3% | 0.0% | 0.0% | 0.0% | NR | NR | NR | NR | 18.2% | 0.0% |
| Neutropenia | N | NR | 36 | 92 | NR | 89 | - | 2 | 19 | NR | NR | 7 | NR | NR | 25 |

| | | ICE | IVE | MINE | IVOx | IGEV | GEM-P | GDP | GVD | Mini-BEAM | DexaBEAM | ESHAP | ASHAP | DHAP | DHAOx |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | % | NR | 24.8% | 44.4% | NR | 28.4% | 71.4% | 8.7% | 51.4% | NR | NR | 31.8% | NR | NR | 35.7% |
| | Rate | NR | 46.2% | 47.2% | NR | 38.4% | 10.1% | 12.4% | 16.0% | NR | NR | 0.8% | NR | NR | 2.1% |
| Pyrexia | N | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | % | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | Rate | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| Thrombocytopenia | N | NR | 25 | 37 | NR | 63 | - | 3 | 16 | NR | NR | 7 | NR | 139 | 26 |
| | % | NR | 17.2% | 17.9% | NR | 20.1% | 47.7% | 13.0% | 43.2% | NR | NR | 31.8% | NR | 69.2% | 37.1% |
| | Rate | NR | 33.7% | 19.3% | NR | 27.8% | 5.4% | 18.3% | 12.8% | NR | NR | 0.8% | NR | 81.8% | 2.2% |
| Vomiting | N | NR | NR | 8 | NR | 5 | - | 3 | 1 | NR | NR | NR | NR | 26 | 0 |
| | % | NR | NR | 3.9% | NR | 1.6% | 0.0% | 13.0% | 2.7% | NR | NR | NR | NR | 12.9% | 0.0% |
| | Rate | NR | NR | 4.2% | NR | 2.3% | 0.0% | 18.3% | 0.7% | NR | NR | NR | NR | 18.2% | 0.0% |

ASHAP: doxorubicin, methylprednisolone, cytarabine, cisplatin; DexaBEAM: dexamethasone, carmustine, etoposide, cytarabine, melphalan; DHAOx: dexamethasone, cytarabine, oxaliplatin; DHAP: dexamethasone, cytarabine, cisplatin; ESHAP: etoposide, methylprednisolone, cytarabine, cisplatin; GDP: gemcitabine, dexamethasone, cisplatin; GEM-P: gemcitabine, cisplatin, methylprednisolone; GVD: gemcitabine, vinorelbine, liposomal doxorubicin; ICE: ifosfamide, carboplatin, etoposide; IGEV: ifosfamide, gemcitabine, vinorelbine; IVE: ifosfamide, epirubicin, etoposide; IVOx: ifosfamide, etoposide, oxaliplatin; MINE: mitoxantrone, ifosfamide, vinorelbine, etoposide; Mini-BEAM: carmustine, etoposide, cytarabine, melphalan; NR: not reported.
Incidence rates have been converted into monthly equivalents based on follow-up time using standard formulae and applied to all patients in the model in all cycles. Monthly rates from each study have then been used to create a weighted mean monthly rate.

## Table 47. SoC adverse event rates

| | | Chemotherapy | Bendamustine | BTX | SoC overall weighted mean | SoC SE |
|---|---|---|---|---|---|---|
| **Study characteristics** | | | | | | |
| Number of patients | | - | % | 167 | - | - |
| Follow-up | | | Median 19 months | Minimum 24 months | | |
| Source | | | Moskowitz 2013[93] | Moskowitz 2015 AETHERA[94] | | |
| Usage (Cheah 2016[7]) | | 58.14 | 27.91 | 13.95 | | |
| **Adverse events** | | | | | | |
| Anaemia | N | 11.7% | - | NR | 8.2% | 5.1% |
| | % | | 14.0% | NR | | |
| | Rate | | 0.8% | NR | | |
| Diarrhoea | N | 0.9% | - | 3 | 0.5% | 0.43% |
| | % | | 0.0% | 1.8% | | |
| | Rate | | 0.0% | 0.1% | | |
| Dyspnoea | N | 0.1% | - | 11 | 0.1% | 0.1% |
| | % | | 0.0% | 6.6% | | |
| | Rate | | 0.0% | 0.3% | | |
| Fatigue | N | 0.5% | - | 3 | 0.6% | 0.4% |
| | % | | 20.0% | 1.8% | | |
| | Rate | | 1.2% | 0.1% | | |
| Leukopenia | N | 13.6% | NR | NR | 13.6% | 2.8% |
| | % | | NR | NR | | |
| | Rate | | NR | NR | | |
| Nausea | N | 3.3% | - | 5 | 2.0% | 1.5% |
| | % | | 3.0% | 3.0% | | |
| | Rate | | 0.2% | 0.1% | | |
| Neutropenia | N | 23.9% | - | 49 | 14.2% | 11.5% |
| | % | | 8.0% | 29.3% | | |
| | Rate | | 0.4% | 1.4% | | |
| Pyrexia | N | NR | - | 25 | 0.3% | 0.2% |
| | % | | 3.0% | 15.0% | | |
| | Rate | | 0.2% | 0.7% | | |
| Thrombocytopenia | N | 24.4% | - | NR | 16.8% | 10.9% |
| | % | | 20.0% | NR | | |
| | Rate | | 1.2% | NR | | |
| Vomiting | N | 3.6% | - | 11 | 2.3% | 1.6% |
| | % | | 8.0% | 6.6% | | |
| | Rate | | 0.4% | 0.3% | | |

Incidence rates have been converted into monthly equivalents based on follow-up time using standard formulae and applied to all patients in the model in all cycles. Monthly rates from each study have then been used to create a weighted mean monthly rate.

## 5.4 Measurement and valuation of health effects

### 5.4.1 Health-related quality-of-life data from clinical trials

Two quality of life measures were utilised during CheckMate 205: EORTC-QLQ-C30 questionnaire version 3 was used to assess cancer-related quality of life, as well as the generic health status measure, EQ-5D. As described in Section 4.7.1, outcomes for nivolumab-treated patients demonstrated improvements using both scales. The EORTC-QLQ-C30 scores remained relatively stable over time with mean changes trending towards an improvement on-treatment across functional and symptom scales. No clinically meaningful deterioration was observed in any of the EORTC-QLQ-C30 scales, while clinically meaningful improvements from baseline were observed for several scales. Similarly, the average EQ-5D VAS score increased over time and exceeded the average baseline score by more than the 7-point minimal important difference from Week 9 through Week 33.

Questionnaires were completed at several time points within CheckMate 205: baseline (prior to first dose on day 1), week 9, every 8 weeks up to week 25, week 33 and every 12 weeks thereafter; following discontinuation, questionnaires were completed on each of the two subsequent follow-up visits, with EQ-5D assessments also completed on subsequent visits.

Appendix 7 provides a full description of the methods used to derive utilities by health state. In summary, a utility was assigned to each completed questionnaire using the UK EQ-5D-3L tariff[95], and these questionnaires were stratified by the progression status of the patient and the timing of progression in order to create a weighted mean score for the pre- and post-progression health states, detailed in Table 48. Within the model, assessment of utility has been linked to investigator-assessed progression (i.e. pre-progression state versus post-progression state), as this may better reflect clinical practice, including the accrual of QALYs in HL patients, as a patient considered not to have progressed by the clinician is likely to have a different quality of life and management plan compared with a patient considered to have progressed.

Utility stratified by response (i.e. CR, PR or SD in the pre-progression state) is provided in Table 48 but this has not been applied in the base case analysis due to relatively low patient numbers; a scenario analysis has been conducted to assess the impact of applying response-specific utility.

**Table 48. EQ-5D utility estimates derived from CheckMate 205**

| | | Investigator-assessed endpoints | | IRRC-assessed endpoints | |
|---|---|---|---|---|---|
| | | Mean value | SE | Mean value | SE |
| Pre-progression | CR | [redacted] | [redacted] | [redacted] | [redacted] |
| | PR | [redacted] | [redacted] | [redacted] | [redacted] |
| | SD | [redacted] | [redacted] | [redacted] | [redacted] |
| | Overall | [redacted] | [redacted] | [redacted] | [redacted] |
| Post-progression | | [redacted] | [redacted] | [redacted] | [redacted] |

### 5.4.2 Mapping

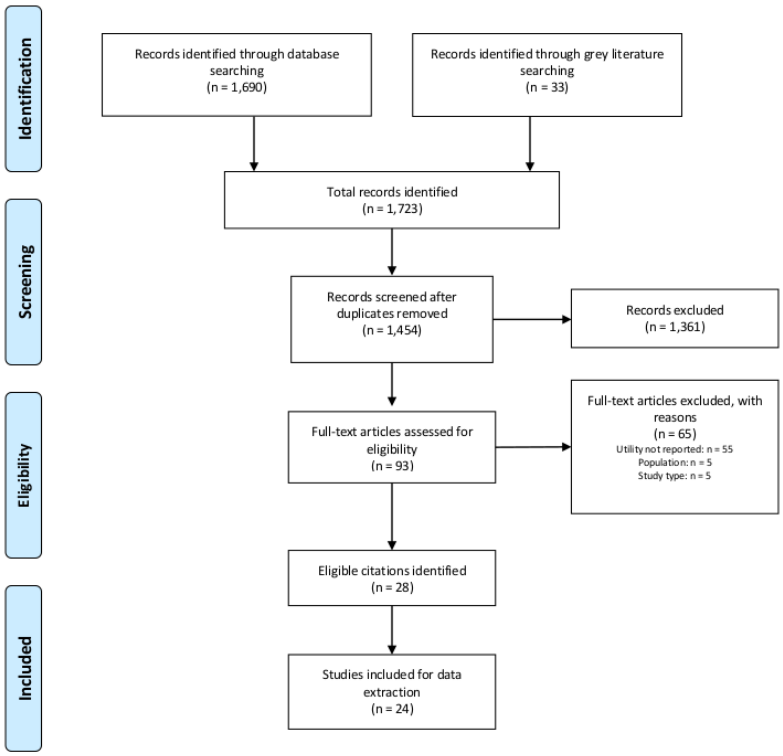
As previously discussed, EQ-5D data were obtained from CheckMate 205, and converted to utilities using the UK EQ-5D-3L tariff[95] Further details are available within Appendix 7.

### 5.4.3 Health-related quality-of-life studies

In line with the NICE Guide to the methods of technology appraisal 2013,[34] an SLR was conducted to identify studies reporting HRQoL utilities for the treatment of HL. In brief, electronic database searches (MEDLINE, Embase, the Cochrane library and EconLit) and additional manual searches of conference proceedings (American Society for Clinical Oncology [ASCO], American Society of Haematology [ASH], ESMO, and the European Haematology Association [EHA]) were conducted in March 2016. Publications describing full economic evaluations of interventions aimed at managing HL were included. Full methodology and a detailed search strategy is presented in Appendix 5.

Searches identified 1,723 studies, of which 269 were removed due to duplication. Of the remaining 1,454 studies, 1,361 were excluded during phase one screening, as depicted in Figure 31. The remaining 93 studies proceeded to secondary screening and, following full text assessment 65 further studies were excluded on the basis of study type (n=5), population (n=5) and utility values not being reported (n=55). Data describing the remaining studies were extracted from the remaining 28 studies, as described in Appendix 5.

**Figure 31. Identification of relevant Health-related quality-of-life studies**



### 5.4.4 Adverse reactions

Disutilities associated with grade 3-4 treatment-related AEs were based on those applied in a recent NICE appraisal of a NHL therapy,[72] with additional inputs sourced where required. Inputs applied in the model are summarised in Table 49.

**Table 49. Adverse event disutilities**

| Adverse event | Disutility | SE | Source |
|---|---|---|---|
| Anaemia | 0.090 | 0.0021 | Beusterian 2010[96] |
| Diarrhoea | 0.080 | 0.0021 | Beusterian 2010[96] |
| Dyspnoea | 0.050 | 0.0120 | Doyle 2008[97] |
| Fatigue | 0.073 | 0.0185 | Nafees et al 2008[98] |
| Leukopenia | 0.090 | 0.0154 | Assumed as neutropenia |
| Nausea | 0.048 | 0.0162 | Nafees et al 2008[98] |
| Neutropenia | 0.090 | 0.0154 | Nafees et al 2008[98] |
| Pyrexia | 0.110 | 0.0021 | Beusterian 2010[96] |
| Thrombocytopenia | 0.108 | 0.0108 | Tolley 2013[99] |
| Vomiting | 0.048 | 0.0162 | Nafees et al 2008[98] |
| SE: standard error | | | |

### 5.4.5 Health-related quality-of-life data used in cost-effectiveness analysis

The health utility of patients is dependent upon their disease state and so consequently, during each cycle, patients are assigned the health utility value equivalent to their current disease state.

Age-dependent quality of life decrements are applied to patients relative to their age at model initiation, with decrements based on the estimated health utility of the general UK population.[100] The age-dependent decrement is calculated as in the following equation:

$$UD = HU_b - HU_t$$

where: UD = Utility decrement; $HU_b$ = Health utility at baseline; and $HU_t$ = Health utility at time t.

Utility estimates associated with cHL by progression status are available for the nivolumab treatment arm based on EQ-5D data reported in Section 5.4.1. In order to estimate utility for patients receiving SoC, response-specific utilities from Swinburn (2015)[101] have been used to derive pre- and post-progression utilities weighted by response rates reported within Cheah 2016.[7]

**Table 50. Health state utilities applied in the economic model**

| | | SoC | | | Nivolumab | |
|---|---|---|---|---|---|---|
| **Health state** | **Response** | **Utility** | **Rate** | **Input*** | **Input** | **SE** |
| Pre-progression | CR | 0.91 | 15.7% | 0.76 | [redacted] | [redacted] |
| | PR | 0.79 | 23.5% | | | |
| | SD | 0.71 | 60.8% | | | |
| Post-progression | | 0.39 | - | 0.38 | [redacted] | [redacted] |
| Source | | Swinburn 2015[101] | Cheah 2016[7] | - | CheckMate 205 Cohort B/C | |

CR: complete response; PR: partial response; SD: stable disease; SE: standard error; SoC: standard of care.
* SE assumed equivalent to 10% and 20% for probabilistic sensitivity analysis

**Table 51. Summary of utility values for cost-effectiveness analysis**

| State | Utility value: mean (standard error) | Reference in submission | Justification |
|---|---|---|---|
| **Health state utilities** | | | |
| Nivolumab: pre-progression | [redacted] | Table 50 | Based on CheckMate 205 data |
| Nivolumab: post-progression | | Table 50 | |
| SoC: pre-progression | 0.76 (NA*) | Table 50 | HL response-specific utilities |
| SoC: post-progression | 0.38 (NA*) | Table 50 | |
| **Adverse event disutilities** | | | |
| Anaemia | 0.090 (0.0021) | Table 49 | Disutilities associated with grade 3-4 treatment-related AEs were based on those applied in a recent NICE appraisal of an NHL therapy,[72] with additional inputs sourced where required |
| Diarrhoea | 0.080 (0.0021) | Table 49 | |
| Dyspnoea | 0.050 (0.0120) | Table 49 | |
| Fatigue | 0.073 (0.0185) | Table 49 | |
| Leukopenia | 0.090 (0.154) | Table 49 | |
| Nausea | 0.048 (0.0162) | Table 49 | |
| Neutropenia | 0.090 (0.0154) | Table 49 | |
| Pyrexia | 0.110 (0.0021) | Table 49 | |
| Thrombocytopenia | 0.108 (0.0108) | Table 49 | |
| Vomiting | 0.048 (0.0162) | Table 49 | |

It should be noted that post-progression utility applied in the model is significantly lower for SoC than for nivolumab (0.38 versus [redacted]), with SoC input derived from the published literature and the nivolumab input derived from patient-level utility data. Although contrary to standard assumptions around the impact of therapies on utility following progression, this can be expected given the unique nivolumab mechanism of action. In contrast to common oncology therapies, nivolumab stimulates the patient's own immune system to directly destroy cancer cells (in the same way that it would any other "foreign" cell), resulting in destruction of the tumour through pre-existing, intrinsic processes. The clinical benefits of nivolumab are described in Section 4, but in brief there are several benefits that impact directly on patient quality of life during therapy in the pre-progression phase, including rapid symptom control in the majority of patients and a tolerable AE profile. Further, there are several indirect benefits on patient quality of life, including improved PFS and OS, with a significant impact on post-progression survival. Thus, the quality of life data derived from patients during CheckMate 205 reflects the expected benefits of nivolumab in the post-progression phase, even following cessation of therapy. This includes the potential for immune system stimulation following progression and continued B-symptom control. Additionally, it should be noted that immuno-oncology therapies demonstrate a varied

pattern of response, and can result in dissociated responses, delayed responses and pseudo-progressions. This potential post-progression benefit is also reflected in the increased survival for nivolumab-treated patients during the post-progression state, which is predicted to be substantially improved versus SoC.

Despite the expectation of improved health state utilities for the nivolumab arm, scenario analyses have been undertaken to evaluate the impact of alternative utility assumptions in the post-progression state (Section 5.8.3.6).

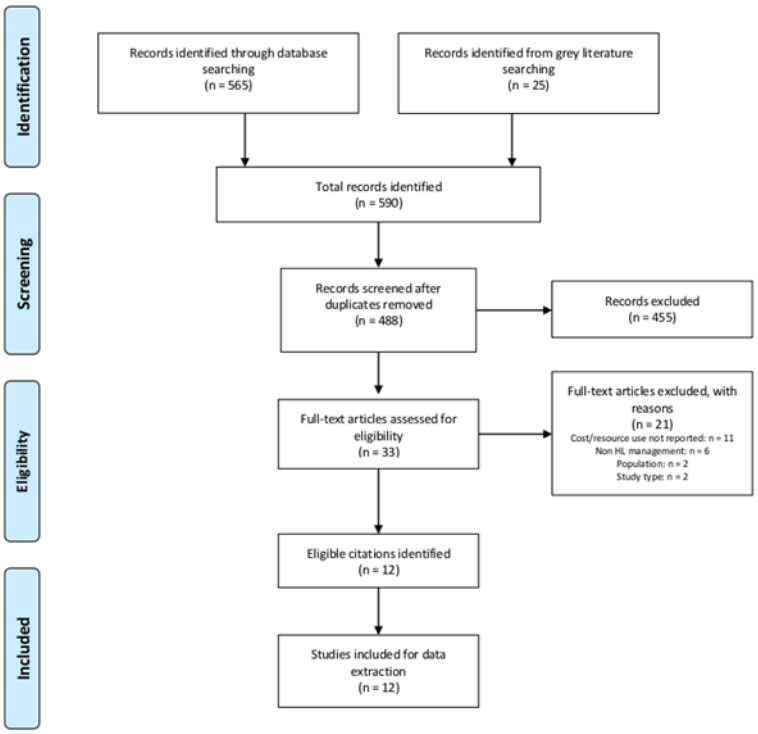
## *5.5 Cost and healthcare resource use identification, measurement and valuation*

### 5.5.1 Resource identification, measurement and valuation studies

In line with the NICE Guide to the methods of technology appraisal 2013,[34] an SLR was conducted to identify studies reporting costs and healthcare resource use in patients with HL. A full description is provided in Appendix 5; in brief, electronic database searches (MEDLINE, Embase, the Cochrane library and EconLit) and additional manual searches of conference proceedings (American Society for Clinical Oncology [ASCO], American Society of Haematology [ASH], ESMO, and the European Haematology Association [EHA]) were conducted in March 2016. Publications describing full economic evaluations of interventions aimed at managing HL were included. Full methodology and a detailed search strategy is presented in Appendix 5.

Searches identified 590 studies of which 102 were removed due to duplication. Of the remaining 488 studies, 455 were excluded during phase one screening (references available upon request) as depicted in Figure 32. The remaining 33 studies proceeded to secondary screening and, following full text assessment 21 further studies were excluded on the basis of study type (n=2), population (n=2), non HL management (n=6) and cost/resource use not being reported (n=11). Data describing the studies were extracted from the remaining 12 studies, as described in Appendix 5.

**Figure 32. Identification of relevant cost and healthcare resource studies**



### 5.5.2 Intervention and comparators' costs and resource use

#### *5.5.2.1 Nivolumab costs*

The costs of nivolumab, including drug procurement and administration, are applied each cycle, based on acquisition costs detailed in Table 52.

**Table 52. Nivolumab dosing and acquisition cost**

| | |
|---|---|
| **Dosing** | 3mg/kg by iv inf over 60 mins every 2 weeks |
| **Dose per cycle** | 240 mg |
| **Cost** | 10mg/ml conc for soln for inf in vial, 4ml=£439.00; 10ml=£1097.00. |
| **Cost per cycle** | £2,633 (assuming wastage of remainder of vial). |
| **Administration costs** | Initial: £389.41; Subsequent: £326.46 (derived from costs detailed in Table 53) |
| **Total** | Initial: £3,022.41; subsequent: £2,959.46 |

**Table 53. Administration costs**

| Component | NHS reference cost 2014-2015 code | Cost |
|---|---|---|
| Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance | Weighted average of SB14Z codes (DCRDN: Daycase and Regular Day/Night; OP: Outpatient; Oth: Other) | £389.41 |
| Deliver subsequent elements of a chemotherapy cycle | Weighted average of SB14Z codes (DCRDN: Daycase and Regular Day/Night; OP: Outpatient; Oth: Other) | £326.46 |

**Patient Access Scheme**

A Patient Access Scheme (PAS) has been proposed with approval by the Department of Health anticipated [redacted], and comprises a discount of [redacted] from the nivolumab list price. In order to best replicate the true economic impact of a positive recommendation for nivolumab, the economic evaluation presented in this submission applies the PAS in the base case analysis. Scenario analyses were used to assess the cost-effectiveness of nivolumab where no PAS is available.

**Table 54. Acquisition cost of nivolumab following application of PAS**

| | 4 ml vial | 10 ml vial | Cycle cost |
|---|---|---|---|
| No PAS | £439.00 | £1,097.00 | £2,633.00 |
| PAS | [redacted] | [redacted] | [redacted] |
| PAS: patient access scheme | | | |

#### *5.5.2.2 Standard of care*

Costs of SoC are based on the costs required for each of the components:

- Chemotherapy: assumed to be equal usage of all regimens specified for the treatment of relapsed or refractory HL within BCSH guidelines.
- BTX retreatment
- Bendamustine

For each component, the intervention cost, comprising acquisition cost and administration cost, was calculated on a per cycle basis (Table 55 and Table 57). This was subsequently converted to a monthly costs over the course of each regimen, and used to create a weighted average based on the Cheah 2016[7] usage (Table 56).

**Table 55. Standard of care costs**

| Regimen | Cost per cycle | Dosing instructions | Cycle length | Number of cycles |
|---|---|---|---|---|
| ICE | £1,993.51 | every 14 d for two cycles | 14 | 2 |
| IVE | £2,833.51 | 21 day cycle; 2 cycles | 21 | 2 |
| MINE | £1,683.20 | every 28 days; 2 courses | 28 | 2 |
| IVOx | £3,128.47 | 21 day cycle; 3 cycles | 21 | 3 |
| IGEV | £3,703.72 | 21 day cycle; 4 cycles | 21 | 4 |
| GEM-P | £2,198.83 | 28 day cycle; three cycles | 28 | 3 |
| GDP | £1,484.32 | 21 days; 2 cycles | 21 | 2 |
| GVD | £3,020.85 | 21 days; 2 cycles | 21 | 2 |
| Mini-BEAM | £11,221.91 | 28 day cycle; three cycles | 28 | 3 |
| DexaBEAM | £11,355.50 | 28 day cycle; 2 cycles | 28 | 2 |
| ESHAP | £1,056.87 | every 21-28 d for 4 cycles | 28 | 4 |
| ASHAP | £1,058.87 | Assumed 28 day cycle; 3 cycles | 28 | 3 |
| DHAP | £1,204.27 | every 21 days for two cycles | 21 | 2 |
| DHAOx | £2,004.77 | 21 day cycle; 4 cycles | 21 | 4 |
| Bendamustine | £2,096.91 | every 28d for 6 cycles | 28 | 6 |
| BTX | £7,889.41 | 3 week cycle for 9 cycles | 21 | 9 |

ASHAP: doxorubicin, methylprednisolone, cytarabine, cisplatin; BTX: brentuximab; DexaBEAM: dexamethasone, carmustine, etoposide, cytarabine, melphalan; DHAOx: dexamethasone, cytarabine, oxaliplatin; DHAP: dexamethasone, cytarabine, cisplatin; ESHAP: etoposide, methylprednisolone, cytarabine, cisplatin; GDP: gemcitabine, dexamethasone, cisplatin; GEM-P: gemcitabine, cisplatin, methylprednisolone; GVD: gemcitabine, vinorelbine, liposomal doxorubicin; ICE: ifosfamide, carboplatin, etoposide; IGEV: ifosfamide, gemcitabine, vinorelbine; IVE: ifosfamide, epirubicin, etoposide; IVOx: ifosfamide, etoposide, oxaliplatin; MINE: mitoxantrone, ifosfamide, vinorelbine, etoposide; Mini-BEAM: carmustine, etoposide, cytarabine, melphalan.
Dosing and cost per cycle derivation provided in Table 57

**Table 56. Intervention and comparator costs: model inputs**

| | SoC (£) | Nivolumab (£) | |
|---|---|---|---|
| | | No PAS | PAS |
| Month 1 | 4,729.43 | 6,497.18 | [redacted] |
| Month 2 | 4,141.92 | 6,434.18 | [redacted] |
| Month 3 | 3,037.50 | 6,434.18 | [redacted] |
| Month 4 | 2,251.40 | 6,434.18 | [redacted] |
| Month 5 | 2,218.97 | 6,434.18 | [redacted] |
| Month 6 | 1,913.31 | 6,434.18 | [redacted] |
| Month 7 | 331.52 | 6,434.18 | [redacted] |
| Month 8+ | 0.00 | 6,434.18 | [redacted] |

PAS: patient access scheme; SoC: standard of care.

## Table 57. Dosing and derivation of regimen costs comprising Standard of Care

| Regimen | Component | Dosing Instructions | Dose | Cost | No. of vials | Cost per vial | Cost per day | Cost per cycle |
|---|---|---|---|---|---|---|---|---|
| ICE[79] | Ifosfamide | 5 g/m$^2$ continuous infusion IV on day 2 | 9.8 g | 1g powder in vial, 1=£91.32. 2g powder in vial, 1=£179.88. | 5 x 2g vial | £179.88 | £899.40 | £899.40 |
| | Mesna | 5 g/m$^2$ continuous infusion IV on day 2 | 9.8 g | 100mg/ml soln in amps, 15 x 4ml=£201.15; 15 x 10ml=£441.15. | 10 | £29.41 | £294.10 | £294.10 |
| | Carboplatin | Area under the curve of 5 (not to exceed 800 mg/dose) on day 1 | 800 mg | 10mg/ml soln for inf in vial, 5ml=£22.04; 15ml=£56.29; 45ml=£168.85; 60ml=£260.00. | - | - | £337.70 | £337.70 |
| | etoposide | 100 mg/m$^2$/day IV on days 1-3 | 196 mg | 100mg/5ml conc for soln for inf in vial, 1=£12.15. | 2 | £12.15 | £24.30 | £72.90 |
| | Admin | | | | | | | £389.41 |
| | **Total** | | | | | | | **£1,993.51** |
| IVE[80,102] | Ifosfamide | 3 g/m$^2$ on days 1-3 | 5.88 g | 1g powder in vial, 1=£91.32. 2g powder in vial, 1=£179.88. | 3 | £179.88 | £539.64 | £1,618.92 |
| | Mesna | 3 g/m$^2$ on days 1-3 | 5.88 g | 100mg/ml soln in amps, 15 x 4ml=£201.15; 15 x 10ml=£441.15. | 6 x10 ml vial | £29.41 | £176.46 | £529.38 |
| | epirubicin | 50 mg/m$^2$ on day 1 | 98 mg | 2mg/ml soln for inj in vial, 5ml=£15.00; 25ml=£75.00; 50ml=£150.00; 100ml=£300.00. | 1 x 50 ml vial | £150.00 | £150.00 | £150.00 |
| | etoposide | 200 mg/m$^2$ on days 1-3 | 392 mg | 100mg/5ml conc for soln for inf in vial, 1=£12.15. | 4 | £12.15 | £48.60 | £145.80 |
| | Admin | | | | | | | £389.41 |
| | **Total** | | | | | | | **£2,833.51** |
| MINE[81] | Mitoxantrone | 8 mg/m$^2$ IV on day 1 | 15.7 mg | 2 mg/mL, net price 10-mL vial = £100.00 | 1 | £100.00 | £100.00 | £100.00 |
| | Ifosfamide | 1.33 g/m$^2$/day IV on days 1-3 | 2.61 g | 1g powder in vial, 1=£91.32. 2g powder in vial, 1=£179.88. | 1.5 | £179.88 | £271.20 | £813.60 |
| | Mesna | 1.33 g/m$^2$/day IV on days 1-3 | 2.61 g | 100mg/ml soln in amps, 15 x 4ml=£201.15; 15 x 10ml=£441.15. | 2 x 10 ml vial and 2 x 4 ml vial | NA | £85.64 | £256.92 |
| | Mesna | 500 mg PO 4hrs after each ifosfamide dose on days 1-3 | 500 mg | 400mg white oblong f-c tab, 10=£134.30. 600mg white oblong f-c tab, 10=£190.60 | 1.25 x 400 mg tab | £13.43 | £16.79 | £50.36 |
| | etoposide | 65 mg/m$^2$/day IV on days 1-3 | 127.4 mg | 100mg/5ml conc for soln for inf in vial, 1=£12.15. | 2 | £12.15 | £24.30 | £72.90 |
| | Admin | | | | | | | £389.41 |
| | **Total** | | | | | | | **£1,683.20** |
| IVOx[82] | Ifosfamide | 1500 mg/m$^2$ IV on days 1–3 (1-h infusion) | 2.94 g | 1g powder in vial, 1=£91.32. 2g powder in vial, 1=£179.88. | 1.5 | £179.88 | £271.20 | £813.60 |
| | Mesna | 1500 mg/m$^2$ IV on days 1–3 | 2.94 g | 100mg/ml soln in amps, 15 x 4ml=£201.15; 15 x 10ml=£441.15. | 3 | £29.41 | £88.23 | £264.69 |
| | Etoposide | 150 mg/m$^2$ on days 1-3 | 294 mg | 100mg/5ml conc for soln for inf in vial, 1=£12.15. | 3 | £12.15 | £36.45 | £109.35 |
| | oxaliplatin | 130 mg/m$^2$ on day 1 | 254.8 mg | Powder for soln for inf in vial, 50mg=£150.00; 100mg=£299.50. 5mg/ml conc for soln for inf in vial, 10ml=£156.75; 20ml=£313.50. | 3 | £299.50 | £898.50 | £898.50 |
| | Admin | | | | | | | £1,042.33 |
| | **Total** | | | | | | | **£3,128.47** |
| IGEV[83] | Ifosfamide | 2000 mg/m$^2$ IV on days 1-4 | 3.92 g | 1g powder in vial, 1=£91.32. 2g powder in vial, 1=£179.88. | 2 | £179.88 | £359.76 | £1,439.04 |
| | Mesna | 2600 mg/m$^2$ IV on days 1-4 | 5.096 g | 100mg/ml soln in amps, 15 x 4ml=£201.15; 15 x 10ml=£441.15. | 6 | £29.41 | £176.46 | £705.84 |
| | gemcitabine | 800 mg/m$^2$ on days 1-4 | 1568 mg | Conc for soln for inf: 200mg vial, 1=£32.00. 1g vial, 1=£162.00. 2g vial, 1=£324.00. | 1 x 1 g vial and 3 x 200 mg vial | £162.00 | £258.00 | £1,032.00 |
| | Vinorelbine | 20 mg/m$^2$ on day 1 | 39.2 mg | 10 mg/mL, net price 1-mL vial = £29.00, 5-mL vial = £139.00 | 4 | £29.00 | £116.00 | £116.00 |
| | Prednisolone | 100 mg on days 1-4 | 100 mg | 1mg tab, 28=77p. 5mg tab, 28=86p. 25mg tab, 56=£75.00. | 4 | £1.34 | £5.36 | £21.43 |

| Regimen | Component | Dosing Instructions | Dose | Cost | No. of vials | Cost per vial | Cost per day | Cost per cycle |
|---|---|---|---|---|---|---|---|---|
| | Admin | | | | | | | £389.41 |
| | **Total** | | | | | | | **£3,703.72** |
| GEM-P[84] | gemcitabine | 1000 mg/m$^2$ on day 1, 8 and 15 | 1960 mg | Conc for soln for inf: 200mg vial, 1=£32.00. 1g vial, 1=£162.00. 2g vial, 1=£324.00. | 2 x 1 g vial | £162.00 | £324.00 | £972.00 |
| | cisplatin | 100 mg/m$^2$ on day 15 | 196 mg | 1mg/ml conc for soln for inf in vial, 10ml=£5.85; 50ml=£24.50; 100ml=£50.22. | 4 | £24.50 | £98.00 | £98.00 |
| | Methyl-prednisolone | 1000 mg on days 1-5 | 1000 mg | 40mg, 1=£1.58. 125mg, 1=£4.75. 500mg, 1=£9.60. 1g, 1=£17.30. | 1 | £17.30 | £17.30 | £86.50 |
| | Admin | | | | | | | £1,042.33 |
| | **Total** | | | | | | | **£2,198.83** |
| GDP[85] | gemcitabine | 1000 mg/m$^2$ on day 1 and 8 | 1960 mg | Conc for soln for inf: 200mg vial, 1=£32.00. 1g vial, 1=£162.00. 2g vial, 1=£324.00. | 2 x 1 g vial | £162.00 | £324.00 | £648.00 |
| | dexamethasone | 40 mg on days 1-4 | 40 mg | 500 microgram tab, 28=£54.20. 2mg tab, 50=£49.00. | 20 | £0.98 | £19.60 | £78.40 |
| | Cisplatin | 75 mg on day 1 | 75 mg | 1mg/ml conc for soln for inf in vial, 10ml=£5.85; 50ml=£24.50; 100ml=£50.22. | 1 50 ml vial and 3 10 ml vials | £24.50 | £42.05 | £42.05 |
| | Admin | | | | | | | £715.87 |
| | **Total** | | | | | | | **£1,484.32** |
| GVD[86] | gemcitabine | 1000 mg/m$^2$ on days 1 and 8 | 1960 mg | Conc for soln for inf: 200mg vial, 1=£32.00. 1g vial, 1=£162.00. 2g vial, 1=£324.00. | 2 x 1 g vial | £162.00 | £324.00 | £648.00 |
| | vinorelbine | 20 mg/m$^2$ IV on days 1 and 8 | 39.2 mg | 10 mg/mL, net price 1-mL vial = £29.00, 5-mL vial = £139.00 | 4 | £29.00 | £116.00 | £232.00 |
| | Pegylated liposomal doxorubicin (Caelyx®) | 15 mg/m$^2$ IV on days 1 and 8 | 29.4 mg | 2mg/ml (in pegylated liposomes) conc for soln for inf in vial, 10ml=£360.23; 25ml=£712.49. | 1 x 25 ml vial | £712.49 | £712.49 | £1,424.98 |
| | Admin | | | | | | | £715.87 |
| | **Total** | | | | | | | **£3,020.85** |
| Mini-BEAM[87] | carmustine | 60 mg/m$^2$ on day 1 | 117.6 | 7.7mg implants, 8=£5203.00. | 15.28 | £650.38 | £9,755 | £9,755.63 |
| | etoposide | 75 mg/m$^2$/day IV on days 2-5 | 147 mg | 100mg/5ml conc for soln for inf in vial, 1=£12.15. | 2 | £12.15 | £24.30 | £97.20 |
| | cytarabine | 100 mg/m$^2$ twice per day on days 2-5 | 196 mg | 20mg/ml soln for inj or inf, 5 x 5ml=£20.98. 100mg/ml soln for inj or inf, 5 x 1ml=£30.00; 1 x 10ml=£39.00. | 2 x 20 mg/ml (5 ml vials) per dose | £4.20 | £16.78 | £67.14 |
| | melphalan | 30 mg/m$^2$ IV on day 6 | 58.8 mg | net price 50-mg vial (with solvent-diluent) = £129.81 | 2 | £129.81 | £259.62 | £259.62 |
| | Admin | | | | | | | £1,042.33 |
| | **Total** | | | | | | | **£11,221.91** |
| DexaBEAM[88] | dexamethasone | 8 mg every 8hs orally on days 1–10 | 8 mg | 500 microgram tab, 28=£54.20. 2mg tab, 50=£49.00. | 4 | £0.98 | £3.92 | £117.60 |
| | carmustine | 60 mg/m$^2$ IV on day 2 | 117.6 mg | 7.7mg implants, 8=£5203.00. | 15.28 | £650.38 | £9,756 | £9,755.63 |
| | etoposide | 250 mg/m$^2$ IV on days 4–7 | 490 mg | 100mg/5ml conc for soln for inf in vial, 1=£12.15. | 5 | £12.15 | £60.75 | £243.00 |

| Regimen | Component | Dosing Instructions | Dose | Cost | No. of vials | Cost per vial | Cost per day | Cost per cycle |
|---|---|---|---|---|---|---|---|---|
| | cytarabine | 100 mg/m$^2$ IV every 12hs on days 4–7 | 196 mg | 20mg/ml soln for inj or inf, 5 x 5ml=£20.98. 100mg/ml soln for inj or inf, 5 x 1ml=£30.00; 1 x 10ml=£39.00. | 2 x 20 mg/ml (5 ml vials) per dose | £4.20 | £16.78 | £67.14 |
| | melphalan | 20 mg/m$^2$ IV on day 3 | 39.2 mg | net price 50 mg vial (with solvent-diluent) = £129.81 | 1 | £129.81 | £129.81 | £129.81 |
| | Admin | | | | | | | £1,042.33 |
| | **Total** | | | | | | | **£11,355.50** |
| ESHAP[89] | etoposide | 40 mg/m$^2$/day IV on days 1-4 | 78.4 mg | 100mg/5ml conc for soln for inf in vial, 1=£12.15. | 1 | £12.15 | £12.15 | £48.60 |
| | methylprednisolone | 500 mg/day IV on days 1-4 | 500 mg | 40mg, 1=£1.58. 125mg, 1=£4.75. 500mg, 1=£9.60. 1g, 1=£17.30. | 1 | £9.60 | £9.60 | £38.40 |
| | cytarabine | 2 g/m$^2$ on day 5 | 3920 mg | 20mg/ml soln for inj or inf, 5 x 5ml=£20.98. 100mg/ml soln for inj or inf, 5 x 1ml=£30.00; 1 x 10ml=£39.00. | 4 x 100 mg/ml soln (10 ml vials) per dose | £39.00 | £156.00 | £156.00 |
| | cisplatin | 25 mg/m$^2$/day continuous IV infusion on days 1-4 | 49 mg | 1mg/ml conc for soln for inf in vial, 10ml=£5.85; 50ml=£24.50; 100ml=£50.22. | 1 x 50 ml vial | £24.50 | £24.50 | £98.00 |
| | Admin | | | | | | | £715.87 |
| | **Total** | | | | | | | **£1,056.87** |
| ASHAP[90] | doxorubicin | 10 mg/m$^2$/day continuous infusion IV over 24hrs on days 1-4 | 19.6 mg | 2mg/ml conc for soln for inf in vial, 5ml=£10.00; 50ml=£100.00. | 2 x 5 ml vial per dose | £10.00 | £20.00 | £80.00 |
| | Methylprednisolone | 500 mg IV over 15 mins daily for 5 days. | 500 mg | 40mg, 1=£1.58. 125mg, 1=£4.75. 500mg, 1=£9.60. 1g, 1=£17.30. | 1 | £9.60 | £9.60 | £48.00 |
| | cytarabine | cytosine arabinoside 1.5 g/m$^2$ IV over 2 hrs after completion of cisplatinum (day 5) | 2940 mg | 20mg/ml soln for inj or inf, 5 x 5ml=£20.98. 100mg/ml soln for inj or inf, 5 x 1ml=£30.00; 1 x 10ml=£39.00. | 3 x 100 mg/ml (10 ml vials) per dose | £39.00 | £117.00 | £117.00 |
| | Cisplatin | 25 mg/m$^2$/day continuous infusion IV over 24hrs on days 1 to 4 | 49 mg | 1mg/ml conc for soln for inf in vial, 10ml=£5.85; 50ml=£24.50; 100ml=£50.22. | 1 x 50 ml vial | £24.50 | £24.50 | £98.00 |
| | Admin | | | | | | | £715.87 |
| | **Total** | | | | | | | **£1,058.87** |
| DHAP[91] | dexamethasone | 40 mg on days 1-4 | 40 mg | 500 microgram tab, 28=£54.20. 2mg tab, 50=£49.00. | 20 x 2 mg tab | £0.98 | £19.60 | £78.40 |
| | cytarabine | 2 g/m$^2$ IV every 12hrs for two doses on day 2 | 3920 mg | 20mg/ml soln for inj or inf, 5 x 5ml=£20.98. 100mg/ml soln for inj or inf, 5 x 1ml=£30.00; 1 x 10ml=£39.00. | 4 x 100 mg/ml 10 ml vials per dose | £39.00 | £312.00 | £312.00 |
| | Cisplatin | 100 mg/m$^2$ IV on day 1 | 196 mg | 1mg/ml conc for soln for inf in vial, 10ml=£5.85; 50ml=£24.50; 100ml=£50.22. | 4 | £24.50 | £98.00 | £98.00 |
| | Admin | | | | | | | £715.87 |
| | **Total** | | | | | | | **£1,204.27** |
| DHAOx[92] | dexamethasone | orally on days 1-4. | 40 mg | 500 microgram tab, 28=£54.20. 2mg tab, 50=£49.00. | 20 x 2 mg tab | £0.98 | £19.60 | £78.40 |
| | Cytarabine | 2g/m$^2$ IV (1$^{st}$ dose: 3-hour infusion on day 2 at 3pm; 2$^{nd}$ dose 3-hour infusion on day 3 at 8am) on days 2 and 3 | 3920 mg | 20mg/ml soln for inj or inf, 5 x 5ml=£20.98. 100mg/ml soln for inj or inf, 5 x 1ml=£30.00; 1 x 10ml=£39.00. | 4 x 100 mg/ml (10 ml vials) per dose | £39.00 | £156.00 | £312.00 |

| Regimen | Component | Dosing Instructions | Dose | Cost | No. of vials | Cost per vial | Cost per day | Cost per cycle |
|---|---|---|---|---|---|---|---|---|
| | oxaliplatin | 130 mg/m$^2$ (2-hr IV) on day 1 | 254.8 mg | Powder for soln for inf in vial, 50mg=£150.00; 100mg=£299.50. 5mg/ml conc for soln for inf in vial, 10ml=£156.75; 20ml=£313.50. | 3 x 100 mg vial | £299.50 | £898.50 | £898.50 |
| | Admin | | | | | | | £715.87 |
| | **Total** | | | | | | | **£2,004.77** |
| Bendamustine[93] | Bendamustine | 120 mg/m$^2$ on days 1-2 every 28 days for 6 cycles | 235.2 mg | 25mg vial, 5=£347.26. 100mg vial, 5=£1379.04. | 2x 100 mg vial and 2 x 25 mg vial | NA | £690.52 | £1,381.04 |
| | Admin | | | | | | | £715.87 |
| | **Total** | | | | | | | **£2,096.91** |
| BTX[94,103] | BTX | 1.8mg/kg IV (30 mins) – 3 week cycle for 9 cycles | 144 mg | 50mg powder for conc for soln for inf in vial, 1=£2500.00. | 3 | £2,500 | £7,500 | £7,500.00 |
| | Admin | | | | | | | £389.41 |
| | **Total** | | | | | | | **£7,889.41** |

ASHAP: doxorubicin, methylprednisolone, cytarabine, cisplatin; BTX: brentuximab; DexaBEAM: dexamethasone, carmustine, etoposide, cytarabine, melphalan; DHAOx: dexamethasone, cytarabine, oxaliplatin; DHAP: dexamethasone, cytarabine, cisplatin; ESHAP: etoposide, methylprednisolone, cytarabine, cisplatin; GDP: gemcitabine, dexamethasone, cisplatin; GEM-P: gemcitabine, cisplatin, methylprednisolone; GVD: gemcitabine, vinorelbine, liposomal doxorubicin; ICE: ifosfamide, carboplatin, etoposide; IGEV: ifosfamide, gemcitabine, vinorelbine; IVE: ifosfamide, epirubicin, etoposide; IVOx: ifosfamide, etoposide, oxaliplatin; MINE: mitoxantrone, ifosfamide, vinorelbine, etoposide; Mini-BEAM: carmustine, etoposide, cytarabine, melphalan.
Assumes weight 80 kg based on CheckMate 205 mean baseline weight, and body surface area 1.97m$^2$ derived from mean weight and average UK height (175cm)
Costs derived from MIMS and BNF.
Lowest acquisition costs applied where possible.
Administration cost derived using weighted average (Table 53)

#### *5.5.2.3 Best supportive/palliative care*

There is significant uncertainty around the composition of BSC in the context of cHL, partly due to the low patient numbers and evolving nature of the cHL treatment pathway in the UK. Depending on patient and disease characteristics, BSC may include subsequent chemotherapy, palliative care and/or hospital-based management.

In order to provide an assessment of the costs associated with BSC in the UK, costs were sourced from a recent NICE appraisal of a NHL therapy.[72]. BSC costs comprise both subsequent chemotherapy and palliative care, including drug procurement and administration, and this cost is applied as a one-off cost on the advent of treatment discontinuation in the pre-progression state or following progression (i.e. entry into the post-progression state).

**Figure 33. Excerpt from ERG report TA306[72]**

Table 43. Total costs associated with subsequent therapy and palliative care used in the manufacturer's model

| Therapy | Distribution of patients across therapies (%)[a] | | Number of cycles | Drug cost per administration (£)[b] | Administration cost (£) |
|---|---|---|---|---|---|
| | PFS, discontinued on 3rd (or 4th) line treatment | PD | | | |
| Gemcitabine monotherapy (administered over 4 weeks) | 1.67 | 8.33 | 4.00 | 860.71 | 643.00 |
| Gemcitabine monotherapy (administered over 3 weeks) | 8.33 | 0.00 | 3.50 | 573.81 | 437.00 |
| Rituximab monotherapy | 5.00 | 0.00 | 8.00 | 1,249.83 | 302.00 |
| CVP | 15.00 | 0.00 | 6.00 | 61.05 | 231.00 |
| IVE | 8.33 | 0.00 | 5.00 | 1,226.25 | 920.00 |
| RVIG | 0.00 | 16.67 | 4.50 | 2,531.67 | 920.00 |
| DHAP | 0.00 | 11.67 | 6.00 | 204.15 | 508.00 |
| CHOP | 0.00 | 1.67 | 6.00 | 234.46 | 231.00 |
| IVAC | 1.67 | 3.33 | 3.50 | 1,115.52 | 1,126.00 |
| Weekly therapy[c] | 10.00 | 8.33 | 7.00 | 238.32 | 437.00 |
| GEM-P | 20.00 | 0.00 | 3.50 | 1,003.11 | 643.00 |
| Palliative care | 23.33 | 46.67 | – | | |
| Clinical trial | 6.67 | 3.33 | | | |
| **Total cost (£)[d]** | **3,928.42** | **4,290.63** | | | |

[a] Based on expert clinical opinion.

[b] Including wastage.

[c] Weekly therapy includes prednisolone, mitoxantrone, cyclophosphamide, etoposide, bleomycin, vincristine and methotrexate.

[d] Calculated as the sum of the weighted average of treatment costs and the weighted average of administration costs; weighted by proportion of patients receiving each treatment regimen.

Abbreviations used in table: CHOP, cyclophosphamide, prednisolone, doxorubicin and vincristine; CVP, cyclophosphamide, vincristine and prednisolone; DHAP, dexamethasone, cytarabine and cisplatin; GEM-P, gemcitabine, cisplatin and prednisolone; IVAC, etoposide, cytarabine, mesna and ifosfamide; IVE, ifosfamide, etoposide, mesna and epirubicin; PD, progressive disease; PFS, progression-free survival; RVIG, rituximab, vinorelbine, ifosfamide and gemcitabine.

Using this composition of BSC, the associated costs have been updated and costs applied in the model are summarised in Table 58.

**Table 58. Cost of subsequent treatment and palliative care**

| | Pre-progression | Post-progression |
|---|---|---|
| Total cost (£) | 4,161.26 | 4,544.94 |

### 5.5.3 Health-state unit costs and resource use

#### *5.5.3.1 Pre-progression*

Resource use estimates for the pre-progression state were derived from those applied during the ongoing NICE appraisal of BTX,[33] where clinical expert opinion was elicited to estimate resource use for long-term follow-up of relapsed or refractory HL patients. This is summarised in Table 59. Within the base case analysis, it was assumed that the year 1 resource use would apply throughout the treatment period for both nivolumab and SoC.

**Table 59. Pre- and post-progression resource use applied in the economic model**

| Resource | Item | Value | Source |
|---|---|---|---|
| Outpatient attendance | Rate | 10.40 | BTX TA[33] |
| | Cost (£) | 150.38 | NHS reference costs 2014-15[104] |
| | Total (£) | 1,563.94 | - |
| Blood count | Rate | 10.40 | BTX TA[33] |
| | Cost (£) | 3.01 | NHS reference costs 2014-15[104] |
| | Total (£) | 31.26 | - |
| Biochemistry | Rate | 10.40 | BTX TA[33] |
| | Cost (£) | 1.19 | NHS reference costs 2014-15[104] |
| | Total (£) | 12.37 | - |
| CT scan (with assumption that 50% will include PET scan) | Rate | 3.00 | BTX TA[33] |
| | Cost (£) | 224.44 | NHS reference costs 2014-15[104] |
| | Total (£) | 673.33 | - |
| Overall cost | Annual (£) | 2,280.91 | - |
| | Monthly (£) | 190.08 | - |

#### *5.5.3.2 Post-progression*

In line with the pre-progression state, assumptions surrounding resource use in the post-progression state were derived from those applied during the ongoing NICE appraisal of BTX.[33] BSC is assumed to be administered during the post-progression state, comprising chemotherapy and palliative care (see Section 5.5.2.3), which can be considered in line with the assumptions applied during the BTX appraisal, where a one-off cost of chemotherapy was applied. Similarly, follow-up costs during post-progression therapy were assumed to be equal to those associated with pre-progression therapy, based on the assumptions applied within the BTX appraisal, so that monthly costs of £190 were applied during the post-progression phase. Scenario analyses have been conducted to assess the impact of increasing post-progression resource use in line with alternative assumptions.

### 5.5.4 Adverse reaction unit costs and resource use

In order to provide an assessment of the costs associated with AEs, costs were sourced from recent NICE appraisals where possible,[72,105] and inflated to 2014-2015 costs.[106] These costs are summarised in Table 60.

**Table 60. Adverse event costs**

| Adverse event | Costs | Source |
|---|---|---|
| Anaemia | £205.50 | NICE TA306 [72] |
| Diarrhoea | £0 | Assumption |
| Dyspnoea | £841.06 | NICE TA306 [72] |
| Fatigue | £88.98 | NICE TA306 [72] |
| Leukopenia | £1,723.21 | NICE TA306 [72] |
| Nausea | £591.07 | NICE TA306 [72] |
| Neutropenia | £779.62 | NICE TA306 [72] |
| Pyrexia | £1,454.38 | NICE TA306 [72] |
| Thrombocytopenia | £156.90 | NICE TA251 [105] |
| Vomiting | £591.07 | NICE TA306 [72] |

### 5.5.5 Miscellaneous unit costs and resource use

All costs and resource use has been detailed in Sections 5.5.1-5.5.4.

## 5.6 Summary of base-case de novo analysis inputs and assumptions

### 5.6.1 Summary of base-case de novo analysis inputs

**Table 61. Summary of variables applied in the economic model**

| Variable | Value | Measurement of uncertainty and distribution | Section |
|---|---|---|---|
| **Baseline parameters** | | | |
| Baseline parameters | Table 35 | SE (age: normal; sex: beta) | 5.2.1 |
| **Survival and progression functions** | | | |
| Overall survival | Table 39 | SE (coefficients of functional form: normal) | 5.3.2.1-5.3.2.2 |
| Progression-free survival | Table 39 | SE (coefficients of functional form: normal) | |
| All-cause mortality | Table 39 | SE (coefficients of functional form: normal) | 5.3.1.3 |
| **Clinical parameters** | | | |
| Response rates | Table 43 | SE (beta) | 5.3.3.1 |
| Discontinuations | Table 44 | SE (beta) | 5.3.3.2 |
| AE rates | Table 45; Table 47 | SE (beta) | 5.3.3.3 |
| **Utilities** | | | |
| Health state utilities | Table 50 | SE (beta) | 5.4.5 |
| AE disutilities | Table 49 | SE (beta) | 5.4.4 |
| **Costs** | | | |
| Medication costs | Table 56 | Not applicable | 5.5.2 |
| Health state costs | Table 59 | SE (gamma) | 5.5.3 |
| AE costs | Table 60 | SE (gamma) | 5.5.4 |
| BSC costs | Table 58 | SE (gamma) | 5.5.2.3 |
| AE: adverse events; BSC: best supportive care; SE: standard error. | | | |

### 5.6.2 Assumptions

A summary of the main assumptions applied within the economic model is provided with Table 62.

**Table 62. Assumptions applied within the economic model**

| Assumption | Rationale | Section |
|---|---|---|
| All scenarios and analyses assume that the heterogeneous treatment history of patients enrolled into CheckMate 205, CA209-039 and Cheah 2016[7] is adequately reflective of the heterogeneity observed in clinical practice. | In the specific context of relapsed or refractory HL, with low patient numbers, short survival and an ongoing NICE appraisal of BTX, the clinical pathway for HL patients is subject to considerable uncertainty and heterogeneity, particularly in the post-ASCT, post-BTX setting. CheckMate 205, CA209-039 and Cheah 2016[7] appear to be equally heterogeneous and as such are reflective of patients in clinical practice. | 5.3.1 |
| Baseline parameters are derived from CheckMate 205 and CA209-039, which is assumed to be reflective of patients seen in UK clinical practice. | Sensitivity analyses (probabilistic and deterministic) have been conducted to assess the impact of variability in these parameters, while scenarios assessed the impact of the differing clinical pathway on outcomes. | 5.2.1 |
| To reflect the nature of HL and available evidence, the model assumes that cHL phases are consecutive, so that patients cannot revert to pre-progression from more advanced phases of the disease. | This assumption has been validated by clinicians and is line with other HTAs and economic analyses assessing the lymphoma population. | 5.2.2 |

| Assumption | Rationale | Section |
|---|---|---|
| In the base case, for simplicity it is assumed that patients moving from initial therapy will receive BSC, comprising chemotherapy and palliative care | It is likely that clinicians will determine subsequent therapy on a per patient basis, so that some patients will receive palliative care following discontinuation of treatment, while others will be considered eligible to receive chemotherapy or clinical trial therapies. As such, the composition of BSC likely reflects that applied in clinical practice. However, scenario analyses have been conducted assuming alternative treatment pathways that could be received in some patient groups, including alloSCT. | 5.2.2.3 |
| Comparator composition and efficacy is assumed based on Cheah 2016[7] therapy usage, as well as BCSH guidelines[3] and NICE scope | In the specific context of relapsed or refractory HL, with low patient numbers, short survival and an ongoing NICE appraisal of BTX, the clinical pathway for HL patients is subject to considerable uncertainty and heterogeneity, particularly in the post-ASCT, post-BTX setting. As such, the base case is based on a simple assumption likely to represent clinical practice in the UK. Alternative comparators and alternative sources of efficacy data have been considered within scenario analysis. | 5.2.3 |
| Patients in both treatment arms discontinue therapy at the time of progression or due to the rate of discontinuation derived from nivolumab patient-level data. | This is likely to reflect clinical practice in most patients and with most therapies, and also provides a conservative assessment of incidence of discontinuation due to AEs during SoC. However, clinical practice may vary, particularly with the use of nivolumab, where treatment may be continued following progression due to the novel mechanism of action. Additionally, clinicians may wish to stop treatment in patients responding at one year. Alternative treatment duration assumptions have been examined as scenario analyses. | 5.3.3.2 |
| Efficacy has been based on investigator-assessed data, rather than IRRS data | As previously discussed, clinical experts suggest that investigator-assessed response and progression is likely to reflect clinician behaviour in a real world setting, as well as accrual of costs and QALYs in clinical practice. However, scenario analysis have been conducted to assess the impact of deriving efficacy inputs from IRRS-assessed data. | 5.2.2.1 |
| The proportion of patients comprising SD at baseline was assumed to be the residual of N-CR - PR | When HL patients start receiving therapy, they may either achieve a response or progress; SD is defined as patients who neither respond nor progress. This is reflected in the model, in that patients without response enter the model in SD, and subsequently progress. | 5.3.3.1 |
| Long-term pre- and post-progression health state costs were based on year 1 management costs in the pre-progression state | Resource use estimates for the pre-progression state were derived from those applied during the ongoing NICE appraisal of BTX, where clinical expert opinion was elicited to estimate resource use for long-term follow-up of relapsed or refractory HL patients. While the original study determined that resource use would decline following the first year, year 1 costs were applied in all subsequent years, as the basis of a conservative estimate of long-term follow-up in more advanced disease. Similarly, this resource use was assumed to apply to the post-progression state. Scenario analyses have been conducted to assess the impact of increased post-progression resource use in line with alternative assumptions. | 5.5.3 |

## *5.7 Base-case results*

The results of the base case analysis are summarised in Table 63 and Figure 34.

In line with estimates of short life expectancy in patients receiving SoC, the model predicts a median OS of 1.5 years (mean: 2.1 years), with accrual of 0.93 QALYs over the model time horizon. By comparison, it was predicted that use of nivolumab will result in an additional [redacted] discounted QALYs (total: [redacted] QALYs) and 2.90 discounted LYs (total: 5.01 LYs). It was estimated that patients receiving nivolumab would spend [redacted] years in the pre-progression state (versus 0.41 years for patients receiving SoC), with a subsequent [redacted] years in the post-progression state (versus 1.70 years for SoC), indicating a substantial benefit to survival in both the pre- and post-progression period.

Total costs associated with nivolumab therapy (with PAS) were predicted to be [redacted], with the [redacted]. By comparison, costs associated with SoC were predicted to be £21,090, and this was [redacted] mainly due to treatment costs (£10,477 for initial modelled therapy). Incremental costs were expected to be [redacted] under base case assumptions and the resultant ICER was £19,882, which can be considered cost-effective at a willingness-to-pay threshold of £30,000/QALY.

Table 64 presents the base case analysis where no nivolumab PAS is available. Total costs associated with nivolumab therapy (without PAS) were predicted to be [redacted], with the [redacted]. Incremental costs were thus expected to be [redacted] under base case assumptions and the resultant ICER was [redacted]; which can be considered to be cost-effective at a threshold £30,000/QALY.

**Figure 34. Cost-effectiveness plane**

[redacted]

**Table 63. Base case analysis results (with PAS)**

| | Comparator | Nivolumab | Incremental |
|---|---|---|---|
| **Patient-level progression** | | | |
| **Time in pre-progression (years)** | **0.405** | [redacted] | [redacted] |
| - Time in 4th line (years) | 0.369 | [redacted] | [redacted] |
| - Time in post 4th line (years) | 0.036 | [redacted] | [redacted] |
| **Time in post-progression (years)** | **1.704** | [redacted] | [redacted] |
| **Patient-level utility breakdown** | | | |
| **Health state utility** | **0.956** | [redacted] | [redacted] |
| - CR | 0.048 | [redacted] | [redacted] |
| - PR | 0.073 | [redacted] | [redacted] |
| - SD | 0.187 | [redacted] | [redacted] |
| - Progressed disease | 0.648 | [redacted] | [redacted] |
| **AE disutility** | **0.020** | **0.003** | **-0.017** |
| **Age based disutility** | **0.005** | **0.057** | **0.052** |
| **Total utilities** | **0.932** | [redacted] | [redacted] |
| **Patient-level cost breakdown (All figures in £)** | | | |
| **Health state costs** | **4,813** | **11,434** | **6,621** |
| - CR | 145 | 1,065 | 920 |
| - PR | 218 | 1,657 | 1,439 |
| - SD | 562 | 1,085 | 523 |
| - Progressed disease | 3,888 | 7,627 | 3,739 |
| **Treatment costs** | **14,420** | [redacted] | [redacted] |
| - Initial line | 10,477 | [redacted] | [redacted] |
| - Subsequent line | 3,943 | [redacted] | [redacted] |
| **AE costs** | **1,857** | **257** | **-1,600** |
| **Total costs** | **21,090** | [redacted] | [redacted] |
| **Patient-level CE results** | | | |
| **Total QALYs** | **0.932** | [redacted] | [redacted] |
| **Total LYs** | **2.110** | **5.013** | **2.903** |
| - Median ToT (years) | 0.263 | 0.801 | 0.538 |
| - Mean ToT (years) | 0.369 | 1.134 | 0.765 |
| - Median PFS (years) | 0.282 | 1.128 | 0.847 |
| - Mean PFS (years) | 0.405 | [redacted] | [redacted] |
| - Median OS (years) | 1.461 | 4.042 | 2.581 |
| - Mean OS (years) | 2.110 | 5.013 | 2.903 |
| **Total Costs (£)** | **21,090** | [redacted] | [redacted] |
| **ICER (Cost/QALY)** | | | **19,882** |

AE: Adverse event; CR: Complete remission; ICER: incremental cost-effectiveness ratio; LY: Life year; OS: Overall survival; PFS: Progression-free survival; PR: Partial response; QALY: Quality-adjusted life year; SD: Stable disease; ToT: Time on Treatment.

**Table 64. Base case analysis results (without PAS)**

| | Comparator | Nivolumab | Incremental |
|---|---|---|---|
| **Patient-level progression** | | | |
| **Time in pre-progression (years)** | **0.405** | [redacted] | [redacted] |
| - Time in 4th line (years) | 0.369 | [redacted] | [redacted] |
| - Time in post 4th line (years) | 0.036 | [redacted] | [redacted] |
| **Time in post-progression (years)** | **1.704** | [redacted] | [redacted] |
| **Patient-level utility breakdown** | | | |
| **Health state utility** | **0.956** | [redacted] | [redacted] |
| - CR | 0.048 | [redacted] | [redacted] |
| - PR | 0.073 | [redacted] | [redacted] |
| - SD | 0.187 | [redacted] | [redacted] |
| - Progressed disease | 0.648 | [redacted] | [redacted] |
| **AE disutility** | **0.020** | **0.003** | **-0.017** |
| **Age based disutility** | **0.005** | **0.057** | **0.052** |
| **Total utilities** | **0.932** | [redacted] | [redacted] |
| **Patient-level cost breakdown (All figures in £)** | | | |
| **Health state costs** | **4,813** | **11,434** | **6,621** |
| - CR | 145 | 1,065 | 920 |
| - PR | 218 | 1,657 | 1,439 |
| - SD | 562 | 1,085 | 523 |
| - Progressed disease | 3,888 | 7,627 | 3,739 |
| **Treatment costs** | **14,420** | [redacted] | [redacted] |
| - Initial line | 10,477 | [redacted] | [redacted] |
| - Subsequent line | 3,943 | [redacted] | [redacted] |
| **AE costs** | **1,857** | **257** | **-1,600** |
| **Total costs** | **21,090** | [redacted] | [redacted] |
| **Patient-level CE results** | | | |
| **Total QALYs** | **0.932** | [redacted] | [redacted] |
| **Total LYs** | **2.110** | **5.013** | **2.903** |
| - Median ToT (years) | 0.263 | 0.801 | 0.538 |
| - Mean ToT (years) | 0.369 | 1.134 | 0.765 |
| - Median PFS (years) | 0.282 | 1.128 | 0.847 |
| - Mean PFS (years) | 0.405 | [redacted] | [redacted] |
| - Median OS (years) | 1.461 | 4.042 | 2.581 |
| - Mean OS (years) | 2.110 | 5.013 | 2.903 |
| **Total Costs (£)** | **21,090** | [redacted] | [redacted] |
| **ICER (Cost/QALY)** | | | [redacted] |

AE: Adverse event; CR: Complete remission; ICER: incremental cost-effectiveness ratio; LY: Life year; OS: Overall survival; PFS: Progression-free survival; PR: Partial response; QALY: Quality-adjusted life year; SD: Stable disease; ToT: Time on Treatment.

### 5.7.1 Clinical outcomes from the model

The proportion of the cohort in each health state over the modelled time horizon is provided in Figure 35. As can be seen, the impact of longer pre- and post-progression survival in the nivolumab arm increases the accrual of both LYs and QALYs.

Further, a comparison of clinical trial versus modelled outcomes is provided in Table 65. As can be seen, undiscounted model outputs closely represent survival observed during clinical trials as well as survival curves used as model inputs.

**Figure 35. Proportion of the cohort in each health state over time**

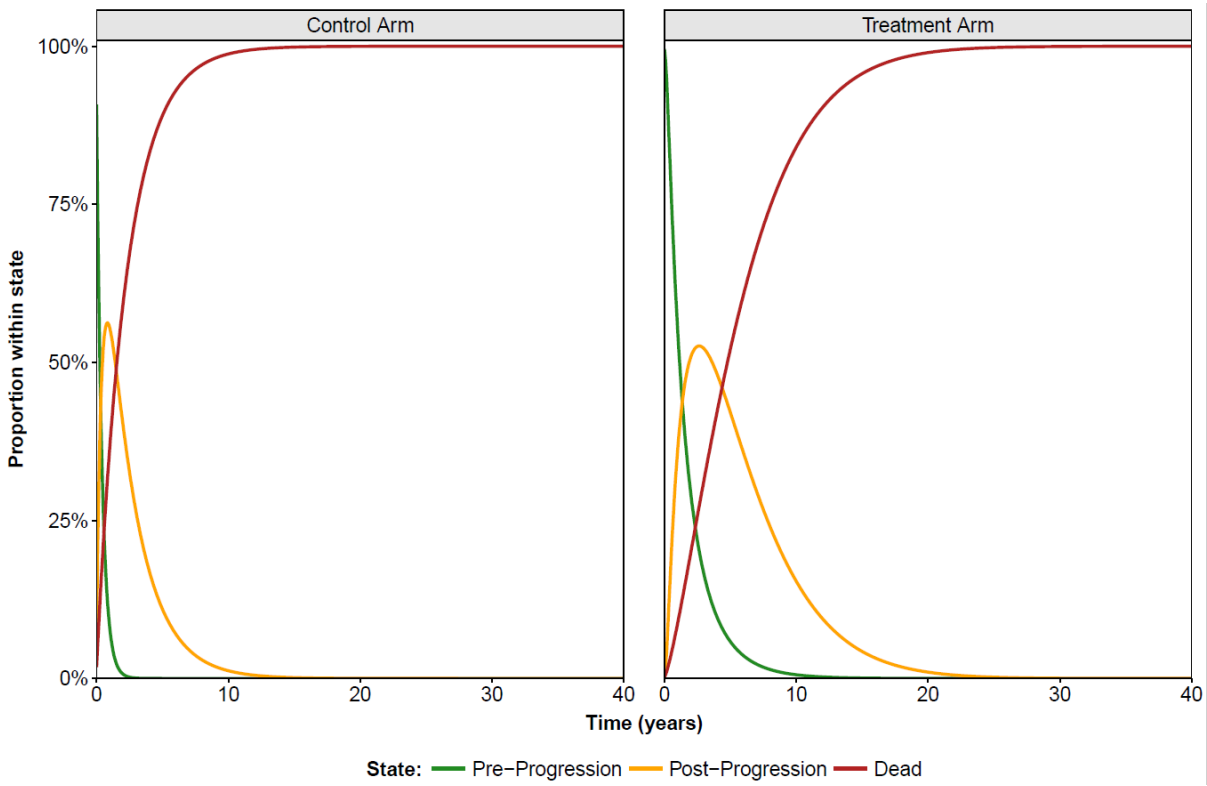



**Table 65. Comparison of clinical trial inputs and modelled outputs**

| | Nivolumab | SoC | Incremental |
|---|---|---|---|
| **Overall survival** | | | |
| Survival curve median (mean) OS (years) | 4.8 (5.9) | 1.6 (2.3) | 3.3 (3.6) |
| Model output median (mean) OS (years) | 4.0 (5.0) | 1.5 (2.1) | 2.6 (2.9) |
| **Progression-free survival** | | | |
| Clinical trial (Median) PFS (years) | 1.4 | 0.4 | 1.0 |
| Survival curve median (mean) PFS (years) | 1.4 (2.6) | 0.4 (0.5) | 1.0 (2.1) |
| Model output median (mean) PFS (years) | 1.1 ([redacted]) | 0.3 (0.4) | 0.8 ([redacted]) |
| **Modelled output** | | | |
| QALYs | [redacted] | 0.93 | [redacted] |
| LYs | 5.01 | 2.11 | 2.90 |

LY: life year; OS: overall survival; PFS: progression-free survival; QALY: quality-adjusted life year; SoC: standard of care.

### 5.7.2 Disaggregated results of the base case incremental cost effectiveness analysis

A breakdown of costs and QALYs by comparator and by health state is provided in Table 66.

**Table 66. Summary of QALY gain and costs by health state**

| | Comparator | Nivolumab | Incremental |
|---|---|---|---|
| **Patient-level utility breakdown** | | | |
| **Health state utility** | **0.956** | [redacted] | [redacted] |
| - CR | 0.048 | [redacted] | [redacted] |
| - PR | 0.073 | [redacted] | [redacted] |
| - SD | 0.187 | [redacted] | [redacted] |
| - Progressed disease | 0.648 | [redacted] | [redacted] |
| **AE disutility** | **0.020** | **0.003** | **-0.017** |
| **Age based disutility** | **0.005** | **0.057** | **0.052** |
| **Total utilities** | **0.932** | [redacted] | [redacted] |
| **Patient-level cost breakdown (All figures in £)** | | | |
| **Health state costs** | **4,813** | **11,434** | **6,621** |
| - CR | 145 | 1,065 | 920 |
| - PR | 218 | 1,657 | 1,439 |
| - SD | 562 | 1,085 | 523 |
| - Progressed disease | 3,888 | 7,627 | 3,739 |
| **Treatment costs** | **14,420** | [redacted] | [redacted] |
| - Initial line | 10,477 | [redacted] | [redacted] |
| - Subsequent line | 3,943 | [redacted] | [redacted] |
| **AE costs** | **1,857** | **257** | **-1,600** |
| **Total costs** | **21,090** | [redacted] | [redacted] |

AE: Adverse event; CR: Complete remission; ICER: incremental cost-effectiveness ratio; LY: Life year; OS: Overall survival; PFS: Progression-free survival; PR: Partial response; QALY: Quality-adjusted life year; SD: Stable disease; ToT: Time on Treatment.

## *5.8 Sensitivity analyses*

In the specific context of relapsed or refractory HL, with low patient numbers, short survival and an ongoing NICE appraisal of BTX, the clinical pathway for HL patients is subject to considerable uncertainty and heterogeneity, particularly in the post-ASCT, post-BTX setting. This translates to a paucity of evidence describing clinical practice on which to base economic evaluation. In general, where no evidence has been identified, simple assumptions have been made based on independent sources, such as published literature, British HL guidelines or previous NICE appraisals in the field of HL or NHL. These assumptions were then assessed for clinical plausibility; uncertainty has been characterised through the use of sensitivity analyses.

In order to assess the impact of parameters on the model outcomes, deterministic sensitivity analyses have been used to vary the data inputs by a set amount. Uncertainty around the input data has been assessed using probabilistic analyses, while alternative assumptions have been examined in scenario analyses.

### 5.8.1 Probabilistic sensitivity analysis

In the probabilistic sensitivity analysis (PSA), a non-parametric bootstrapping approach was taken, sampling values from distributions around the means of input parameters in the model. Sampling utilises information on the mean and standard error of parameters to derive an estimated value using an appropriate distribution (costs: gamma distributions; age: normal distribution; proportions and percentages: beta distributions). These analyses are used to estimate the overall uncertainty that exists in the model results due to uncertainty in the chosen input parameters.

In general, each parameter included in the PSA is sampled independently; however, there are several exceptions to this approach. The model allows health state costs to be specified by treatment and response state; however, the base case analysis applies pre-progression and post-progression cost regardless of response or therapy arm. Thus, within the PSA, treatment arm-specific and response-state specific health state costs are not sampled independently, but are linked so that health state costs are varied similarly.

Similarly, response and survival parameters are sampled differently to other parameters, due to the paucity of data around SoC. Mean PFS and OS associated with SoC are sampled according to a normal distribution based on the specified SE level, due to a lack of confidence bounds on the fit. The mean PFS and OS data are then transformed to the exponential rate required for the parametric survival curve generation. When sampling SoC response rates, the inverse relative risk of response versus nivolumab is sampled according to a lognormal distribution, and then the nivolumab mean response rate is divided by this deviate to provide the SoC response rate sample.

Several inputs are derived from sources where it has not been possible to ascertain SEs. To assess uncertainty around these inputs, two sets of PSAs have been conducted: one assuming SEs of 10% and a second assuming SEs of 20%.

#### *5.8.1.1 PSA Results*

Scatterplots for the base case analyses, arising from 1,000 simulations of the model with all parameters sampled are presented in ***[redacted]
Figure 36 and cost-effectiveness acceptability curves (CEACs) are presented in Figure 37. Applying a SE of 10% where exact SEs are unknown, the probability that nivolumab is cost-effective versus SoC is 94.8% at a WTP threshold of £30,000, increasing to 100% at a £50,000 threshold; applying a SE of 20%, the probability is 96.6% and 100%, respectively.

Over the course of the two PSAs, nivolumab was always predicted to be clinically beneficial versus SoC, with incremental QALYs ranging from [redacted]. Accrual of costs was reassuringly stable, resulting in incremental costs of [redacted]

**Figure 36. Cost-effectiveness scatterplot**

**Figure 37. Cost-effectiveness acceptability curve**

### 5.8.2 Deterministic sensitivity analysis

A range of one-way (deterministic) sensitivity analyses have been conducted, regarding the following assumptions and parameters:

- Rates of discounting (0% and 6%)
- Time horizon (10 and 20 years)
- Baseline patient age (18 and 60 years)
- Sex (0% and 100% male)
- Health state costs: complete remission (± 20%)
- Health state costs: partial remission (± 20%)
- Health state costs: stable disease (± 20%)
- Health state costs: progressed disease (initial month) (± 20%)
- Health state health state utility: CR (± 20%)
- Health state health state utility: PR (± 20%)
- Health state health state utility: SD (± 20%)
- Health state health state utility: post-progression (± 20%)

- Pre-progression therapy costs: nivolumab (± 20%)
- Pre-progression therapy costs: SoC (± 20%)
- Pre-progression therapy costs: BSC (± 20%)
- Pre-progression therapy costs: BSC (± 20%)

#### *5.8.2.1 Deterministic sensitivity analysis results*

Results of the univariate sensitivity analyses are presented in Figure 38 to Figure 40 and demonstrate the impact of particular parameters upon incremental costs and QALYs and ICERs. In all scenarios, the ICER for nivolumab versus SoC remained below the £30,000/QALY WTP threshold. The most influential factors included health state utilities, therapy costs, rate of discounting and the time horizon.

Plausible alternative scenarios have been further investigated in Section 5.8.3, in order to assess the impact of the uncertainty in the analysis, with relatively little impact on cost-effectiveness outcomes.

**Figure 38. Univariate sensitivity analysis (ICERs)**

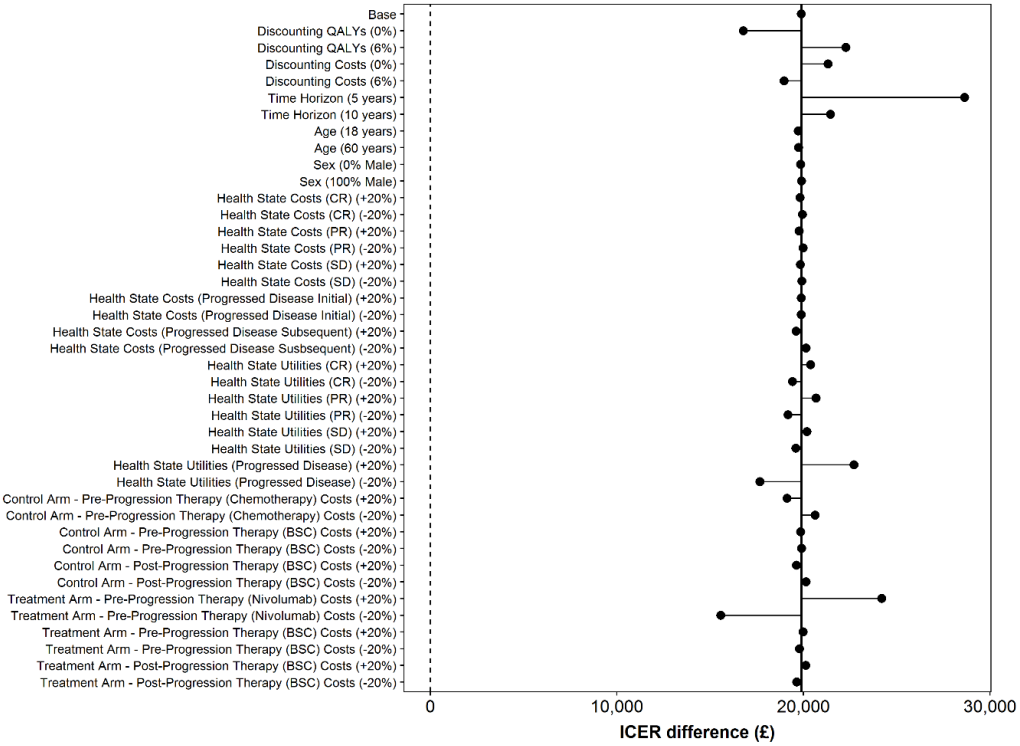


**Figure 39. Univariate sensitivity analysis (incremental costs)**

**Figure 40. Univariate sensitivity analysis (incremental QALYs)**

### 5.8.3 Scenario analysis

#### *5.8.3.1 Alternative parametric fittings*

**Alternative nivolumab parametric fittings**

Survival modelling using long-term extrapolation of parametric functions is subject to considerable uncertainty despite efforts to robustly and transparently provide survival curves that best represent patients in clinical practice. In order to assess the impact of alternative parametric fittings on the cost-effectiveness of nivolumab, survival curves described in Section 5.3.2 have been applied within the model as scenario analyses. As described in Table 67 and depicted in Figure 41, predicted incremental LYs ranged from 2.9 to 7.4 and QALYs ranged from [redacted], with an associated variation in costs ([redacted]). However, the ICERs remained relatively stable, ranging between £10,718/QALY and £20,132/QALY. It should be noted that the survival curves applied in the base case scenario

can be considered the least beneficial to the ICER, but as discussed in Section 5.3.2, can be considered most clinically plausible on the basis of clinician advice.

**Figure 41. Scenario analysis: impact of alternative survival modelling on base case analysis**

Colour denotes alternative PFS parametric fits; shape denotes alternative OS parametric fits.

**Table 67. Scenario analysis: impact of alternative survival modelling on base case analysis**

| | Nivolumab | | | | | | | | | | | | | | | | SoC |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Survival modelling** | | | | | | | | | | | | | | | | | |
| PFS fitting | E | W | LL | LN | E | W | LL | LN | E | W | LL | LN | E | W | LL | LN | E |
| OS fitting | E | E | E | E | W | W | W | W | LL | LL | LL | LL | LN | LN | LN | LN | E |
| Median PFS (months) | 14.71 | 13.38 | 13.23 | 13.56 | 14.64 | 13.38 | 13.23 | 13.54 | 14.63 | 13.37 | 13.22 | 13.53 | 14.62 | 13.35 | 13.19 | 13.51 | 3.38 |
| Median OS (months) | 66.41 | 66.41 | 66.41 | 66.41 | 48.51 | 48.51 | 48.51 | 48.51 | 53.72 | 53.72 | 53.72 | 53.72 | 67.77 | 67.77 | 67.77 | 67.77 | 17.53 |
| **Absolute outcomes** | | | | | | | | | | | | | | | | | |
| QALYs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 0.932 |
| LYs | 7.884 | 7.884 | 7.884 | 7.884 | 5.013 | 5.013 | 5.013 | 5.013 | 7.148 | 7.148 | 7.148 | 7.148 | 9.508 | 9.508 | 9.508 | 9.508 | 2.110 |
| Costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 21,090 |
| **Incremental outcomes** | | | | | | | | | | | | | | | | | |
| QALYs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | - |
| LYs | 5.774 | 5.774 | 5.774 | 5.774 | 2.903 | 2.903 | 2.903 | 2.903 | 5.039 | 5.039 | 5.039 | 5.039 | 7.398 | 7.398 | 7.398 | 7.398 | - |
| Costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | - |
| ICER | 13,764 | 12,199 | 13,202 | 13,642 | 20,132 | 17,984 | 19,264 | 19,882 | 14,842 | 13,252 | 14,245 | 14,697 | 12,015 | 10,718 | 11,562 | 11,926 | - |

ICER: incremental cost-effectiveness ratio; LY: life year; OS: overall survival; PFS: progression-free survival; QALY: quality-adjusted life year; SoC: standard of care.
Parametric fittings: E: Exponential; W: Weibull; LL: Log-logistic; LN: Lognormal

## Alternative SoC parametric fittings

In the base case, the SoC OS curve has been derived from Cheah 2016 with the impact of investigational agents removed. In order to assess the impact of variation in the survival associated with SoC, alternative SoC parametric fittings for OS have been considered, based on the highest and lowest reported OS reported within Cheah 2016,[7] described in Table 68. As demonstrated in Table 79, alternative assumptions around SoC OS parametrisation impact on the nivolumab ICER, but it remains below the £30,000/QALY WTP threshold.

**Table 68. Alternative parametric fittings for SoC OS**

| | Nivolumab | SoC | |
|---|---|---|---|
| | | Low (9.5 months OS) | High (34.0 months OS) |
| PFS | Lognormal;<br>μ: 2.825<br>σ: 1.109 | Exponential<br>λ: 0.160 | |
| OS | Weibull<br>Scale (A): 76.742<br>Shape (B): 1.326 | Exponential<br>λ: 0.036 | Exponential<br>λ: 0.073 |
| OS: overall survival; PFS: progression-free survival; SoC: standard of care.<br>Lognormal survival equation takes the form: S(t) = 0.5-0.5*erf((ln(t)-mu)/(sqrt(2)*sigma))<br>Weibull survival equation takes the form: S(t) = exp(-(t/A)^B)<br>Exponential survival equation takes the form: S(t) = exp(lambda*t) | | | |

**Table 69. Scenario analysis: alternative SoC OS parametric fittings**

| | Scenario 1 | Scenario 2 |
|---|---|---|
| | High SoC OS from Cheah 2016 | Low SoC OS from Cheah 2016 |
| **Nivolumab** | | |
| Costs (£) | [redacted] | [redacted] |
| QALYs | [redacted] | [redacted] |
| LYs | 5.013 | 5.013 |
| **SoC** | | |
| Costs (£) | 25,287 | 17,135 |
| QALYs | 1.468 | 0.528 |
| LYs | 3.554 | 1.098 |
| **Incremental** | | |
| Costs (£) | [redacted] | [redacted] |
| QALYs | [redacted] | [redacted] |
| LYs | 1.458 | 3.915 |
| ICER (£) | 22,742 | 18,613 |
| ICER: incremental cost-effectiveness ratio; LY: life year; QALY: quality-adjusted life year; SoC: standard of care. | | |

## Application of nivolumab Kaplan-Meier data over trial period

As previously descried, it is acknowledged that survival modelling using long-term extrapolation of parametric functions is subject to considerable uncertainty despite efforts to

robustly and transparently provide survival curves that best represent patients in clinical practice. In order to assess the impact of these fittings on the cost-effectiveness of nivolumab, a scenario analysis was conducted applying nivolumab Kaplan-Meier data over the trial period, followed by long-term extrapolation based on parametric fitting applied in the base case. Survival data applied in the analysis are depicted in Figure 42 and Figure 43.

As can be seen in Table 70, LYs and QALYs in the nivolumab arm are slightly improved in this scenario, with an associated increase in costs. However, the resulting ICER can still be considered cost-effective at a WTP of £30,000 per QALY gained.

**Table 70. Scenario analyses: application of nivolumab Kaplan-Meier data over trial period**

| | Nivolumab | SoC | Incremental |
|---|---|---|---|
| Costs (£) | [redacted] | 21,090 | [redacted] |
| QALYs | [redacted] | 0.932 | [redacted] |
| LYs | 5.060 | 2.110 | 2.950 |
| ICER (£/QALY) | 19,994 | | |

**Figure 42. Application of nivolumab Kaplan-Meier data over trial period: overall survival**

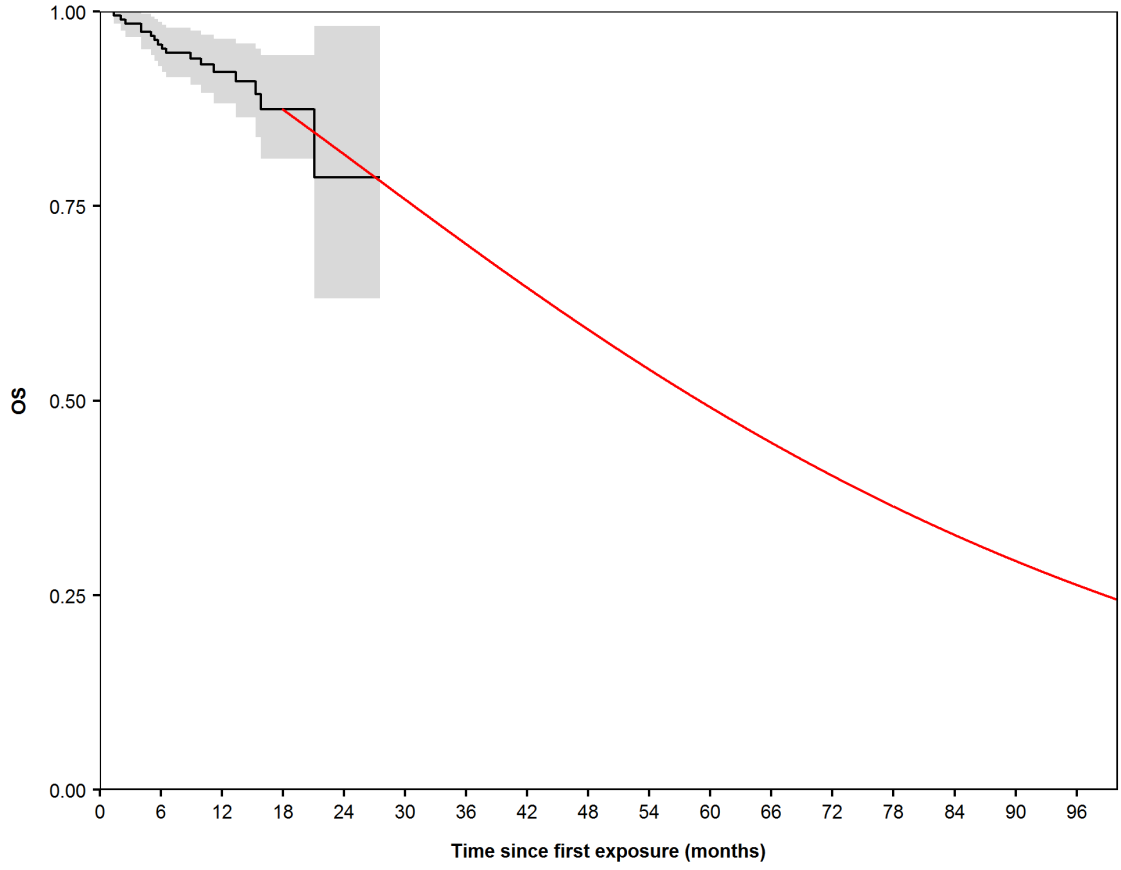
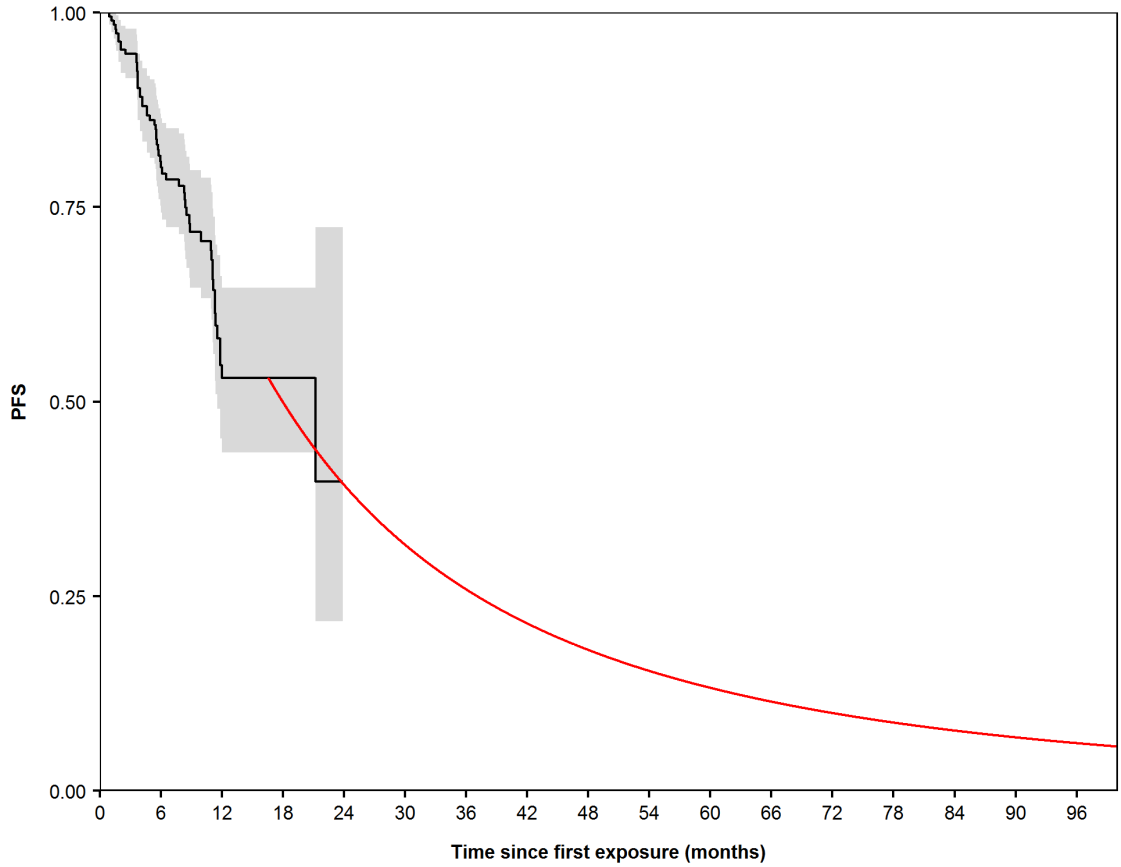


**Figure 43. Application of nivolumab Kaplan-Meier data over trial period: progression-free survival**




## No half-cycle correction applied

In the base case, a half cycle correction has been applied in order to best reflect cost and QALY accrual. A scenario has been conducted to assess the impact of removing this half-cycle correction. As can be seen in Table 71, there is minimal impact on the cost-effectiveness of nivolumab.

**Table 71. Scenario analysis: no half-cycle correction**

| | Nivolumab | Comparator | Incremental |
|---|---|---|---|
| Costs (£) | [redacted] | 23,732 | [redacted] |
| QALYs | [redacted] | 0.960 | [redacted] |
| LYs | 5.047 | 2.149 | 2.899 |
| ICER (£/QALY) | 19,730 | | |

#### *5.8.3.2 Alternative treatment sequences*

**Allogenic stem cell therapy**

Following failure of ASCT, BCSH guidelines recommend that the aim of treatment in patients is to attain sufficient response to allow consideration of alloSCT in those deemed eligible. Given the responses achieved within CheckMate 205 and CA209-039, it is possible that clinicians will use nivolumab as a bridge to alloSCT.

In order to model scenarios where patients with adequate response receive subsequent alloSCT, evidence describing use of alloSCT in the post-ASCT, post-BTX population was derived from two real-world studies. As previously described, Cheah 2016 can be said to represent real-world clinical practice in the UK,[7] and so Kaplan-Meier data from this population is used to model survival following alloSCT in this patient population. The likelihood of receiving alloSCT in patients responding to initial therapy is derived from real world data from a study by Perrot et al (2016).[107] This study assessed outcomes in patients with HL who had previously received ASCT, followed by BTX consolidation treatment. While this patient population does not match the population of interest (patients with relapsed or refractory HL following prior ASCT and BTX) and was conducted in France, it does provide an indication of the proportion of patients who would receive alloSCT in UK clinical practice.

As alloSCT is associated with morbidity and mortality in the short-term but can be considered potentially curative over the long-term,[7] scenarios considering the use of alloSCT as subsequent therapy are modelled using independent survival curves. Kaplan-Meier data describing OS post-alloSCT were obtained from Cheah 2016,[7] and a lognormal parametric fitting was applied. Median PFS in the post-alloSCT population was also obtained from Cheah 2016,[7] and an exponential parametric fitting was applied, based on the absence of information suggesting that a contrary fit would be more appropriate. Where patients experience progression following alloSCT, it is assumed that patients experience costs, utilities and survival comparable to the SoC arm, regardless of initial therapy.

**Table 72. Parameters describing PFS and OS for alloSCT**

| | **alloSCT** |
|---|---|
| OS | Lognormal;<br>μ: 9.252<br>σ: 3.551 |
| PFS | Exponential<br>λ: 0.037 |
| Lognormal survival equation takes the form: S(t) = 0.5-0.5*erf((ln(t)-mu)/(sqrt(2)*sigma))<br>Exponential survival equation takes the form: S(t) = exp(lambda*t) | |

The utility associated with successful alloSCT in the model is 0.856, applying utilities derived from Swinburn 2015,[101] in line with the BTX NICE TA.[33] Two alternative scenarios have been used to estimate cost of alloSCT: the first was based on a weighted average of NHS reference costs (described in Table 73), while the second is based on the cost of alloSCT put forward by Radford 2016.[108] The cost of ongoing monitoring costs has been derived from a previous NICE TA, using the method put forward by the Assessment Group, during NICE

TA241,[109] based on the cost of a quarterly specialist appointment and immunosuppressive therapies.

**Table 73. Estimation of ongoing drug and monitoring costs after alloSCT**

| Resource | Mean | Source | |
|---|---|---|---|
| AlloSCT | £21,672.64 | National Schedule of Reference Costs 2014-15 - Total HRGs: weighted average of total adult bone marrow transplantation costs [codes: SA19A, SA20A, SA21A, SA22A, SA23A] [104]. | |
| Monthly cost of AlloSCT | £91.69 | Derivation based on Assessment Group method NICE TA241[109] set out below | |
| **Unit** | **Unit cost** | **Source** | **Monthly cost** |
| **Quarterly specialist appointment** | | | |
| Clinical Haematology consultant-led outpatient attendance | £150.38 per appointment | NHS Reference Costs 2014-15 [104] | £50.13 |
| **Immunosuppressive therapies** | | | |
| Ciclosporin 50 mg twice daily plus prednisolone 20 mg once daily (60% of patients) | Ciclosporin: 30 x 50 mg capsules £25.50<br>Prednisolone: 100 x 5 mg tablet £2.20 | MIMS [29] | £54.42 |
| Mycophenolate mofetil 1g twice daily plus prednisolone 20 mg once daily (40% of patients) | Mycophenolate mofetil: 50 x 500 mg tablets £8.05<br>Prednisolone: 100 x 5 mg tablet £2.20 | MIMS [29] | £22.28 |
| **Total management costs** | | | |
| Quarterly specialist appointment plus weighted average of two immunosuppressive regimens | | | £91.69 |

**Resource costs:** AlloSCT, allogenic stem cell transplant.
**Drug and monitoring costs:** Length of month assumed to be 30.475 days
National Schedule of Reference Costs 2014-15 – Consultant-led outpatient attendance: Clinical Haematology; Currency code: WF01A; Service code: 303

Based on CheckMate 205 and the published literature, it has been assumed that a proportion of eligible patients with an adequate response will receive alloSCT at six months; the response-specific rate of alloSCT has been derived from Perrot 2016,[107] as described in Table 74. However, scenario analyses have been undertaken where nivolumab-treated patients have an equivalent likelihood of receiving alloSCT. Table 75 describes the scenario analyses undertaken to ascertain the impact of inclusion of alloSCT as a therapy option.

**Table 74. Patients receiving alloSCT in the model based on response category**

| | Proportion who received alloSCT (Perrot 2016[107]) | Proportion receiving alloSCT (Model input) |
|---|---|---|
| CR | 18/81 | 22.2% |
| PR | 9/64 | 14.1% |
| SD | 1/18 | 5.56% |

AlloSCT: allogenic stem cell therapy; CR: complete response; PR: partial response: SD: stable disease.

**Table 75. AlloSCT scenarios modelled as scenario analyses**

| | Proportion of patients receiving alloSCT | | | Cost of alloSCT |
|---|---|---|---|---|
| | CR | PR | SD | |
| Scenario 1: likelihood of alloSCT from Perrot 2016[107] and costs from NHS reference costs[104] | 22.2% | 14.1% | 5.56% | £33,072 as initial cost, followed by 91.69 monthly cost |
| Scenario 2: likelihood of alloSCT from Perrot 2016[107] and costs derived from Radford 2016[108] | 22.2% | 14.1% | 5.56% | £110,374 as initial cost, followed by £91.69 monthly cost |
| Scenario 3: likelihood of alloSCT from Perrot 2016[107], but nivolumab patients with CR and PR assumed equivalent; costs from NHS reference costs[104] | 18.62% | 18.62% | 5.56% | £33,072 as initial cost, followed by 91.69 monthly cost |
| Scenario 2: likelihood of alloSCT from Perrot 2016[107], but nivolumab patients with CR and PR assumed equivalent; costs derived from Radford 2016[108] | 18.62% | 18.62% | 5.56% | £110,374 as initial cost, followed by £91.69 monthly cost |

The results of these scenarios are presented in Table 76, and demonstrate that alloSCT extends overall life expectancy by up to 1.3 years and improves QALYs in both treatment arms versus the base case. Costs can be increased versus the base case analysis, depending on assumptions around procedure cost; however, the ICER for nivolumab improves following availability of alloSCT, suggesting that the base case analysis may undervalue the benefits of nivolumab in clinical practice.

**Table 76. Scenario analyses: alloSCT**

| | Scenario 1 | Scenario 2 | Scenario 3 | Scenario 4: |
|---|---|---|---|---|
| | Perrot 2016 likelihood and NHS ref cost | Perrot 2016 likelihood and Radford 2016 cost | Perrot 2016 likelihood (Nivo CR/PR equivalent) and NHS ref cost | Perrot 2016 likelihood (Nivo CR/PR equivalent) and Radford 2016 cost |
| **Nivolumab** | | | | |
| Costs | [redacted] | [redacted] | [redacted] | [redacted] |
| QALYs | [redacted] | [redacted] | [redacted] | [redacted] |
| LYs | 6.241 | 6.241 | 6.327 | 6.327 |
| **SoC** | | | | |
| Costs | 22,866 | 24,880 | 22,866 | 24,880 |
| QALYs | 1.076 | 1.076 | 1.076 | 1.076 |
| LYs | 2.512 | 2.512 | 2.512 | 2.512 |
| **Incremental** | | | | |
| Costs | [redacted] | [redacted] | [redacted] | [redacted] |
| QALYs | [redacted] | [redacted] | [redacted] | [redacted] |
| LYs | 3.729 | 3.729 | 3.816 | 3.816 |
| ICER | 18,587 | 20,433 | 18,479 | 20,489 |

**Subsequent chemotherapy**

In the base case analysis, it is assumed that patients with progression or discontinuation switch to BSC, comprised of several therapies including chemotherapy and palliative care, dependent on progression status. However, this is a simplification, and in clinical practice, patients are likely to receive chemotherapy in the pre-progression phase if it is clinically feasible. On this basis, a scenario analysis was conducted whereby patients discontinuing therapy (either nivolumab or SoC) in the pre-progression phase receive subsequent SoC, subject to the same assumptions and costs as the initial therapy line; BSC is still received as the post-progression therapy.

As can be seen in Table 77, costs in the nivolumab arm are increased due to longer pre-progression survival incurring additional costs. However, the ICER can be considered cost-effective at a WTP threshold of £30,000.

**Table 77. Scenario analysis: subsequent chemotherapy**

| | Nivolumab | SoC | Incremental |
|---|---|---|---|
| Costs (£) | [redacted] | 21,988 | [redacted] |
| QALYs | [redacted] | 0.930 | [redacted] |
| LYs | 5.013 | 2.110 | 2.903 |
| ICER (£) | 22,095 | | |

### *5.8.3.3 Alternative comparator composition*

**Cheah 2016 overall population (naïve indirect comparison)**

As previously stated, the Cheah 2016 real world data[7] can be suggested to adequately represent the treatment of the post-ASCT, post-BTX HL population in clinical practice. A scenario analysis was conducted to examine the impact of including the use of investigational agents into SoC, based on efficacy reported in the Cheah 2016 study.[7,72]

Kaplan-Meier data describing PFS and OS for the overall population enrolled in Cheah 2016 were digitised, and parametric survival functions were fitted to the extracted data using the R statistics environment. As described in Section 5.3.2.1, goodness-of-fit was evaluated using the Akaike and Bayesian Information Criteria, and a visual assessment of parametric fittings was conducted to ensure that long-term extrapolation reflected what could be expected in clinical practice. Due to the high rate of inclusion of nivolumab-treated patients, it can be inferred that parametric fittings would reflect similar evolution of hazard over time, and on this basis, parametric fittings applied within the analysis were equivalent to those applied for nivolumab (PFS: lognormal; OS: Weibull).

Response and pre-progression utilities in the SoC arm were updated to reflect the responses achieved by the overall population during Cheah (2016). Further, SoC AE rates were updated to included investigational agents, which was assumed to be equivalent to those reported for nivolumab. Further, costs for SoC were updated to include administration of investigational agents, which was assumed to be the costs associated with one intravenous infusion every two weeks; it was assumed that there would be no therapy acquisition costs.

Table 79 demonstrates that despite longer survival in the SoC arm, nivolumab can still be considered cost-effective at a WTP threshold of £30,000/QALY.

**Table 78. Parameters describing PFS and OS for nivolumab and standard of care (Cheah 2016)**

| | Nivolumab | SoC |
|---|---|---|
| PFS | Lognormal;<br>μ: 2.831<br>σ: 1.147 | Lognormal;<br>μ: 1.074<br>σ: 0.728 |
| OS | Weibull<br>Scale (A): 76.742<br>Shape (B): 1.326 | Weibull<br>Scale (A): 39.438<br>Shape (B): 0.959 |
| Lognormal survival equation takes the form: S(t) = 0.5-0.5*erf((ln(t)-mu)/(sqrt(2)*sigma))<br>Weibull survival equation takes the form: S(t) = exp(-(t/A)^B) | | |

**Table 79. Scenario analysis: Cheah 2016 overall population (naïve indirect comparison)**

| | Nivolumab | SoC | Incremental |
|---|---|---|---|
| Median PFS | 1.128 | 0.224 | 0.904 |
| Median OS | 4.042 | 1.996 | 2.047 |
| Costs (£) | [redacted] | 18,988 | [redacted] |
| QALYs | [redacted] | 1.204 | [redacted] |
| LYs | 5.013 | 2.970 | 2.043 |
| ICER (£) | 22,855 | | |

**Best supportive care**

In order to provide cost-effectiveness evidence with direct relevance to the NICE scope, scenario analyses have been provided assessing the impact of BSC as a comparator. Assumptions around the composition of BSC have been carried forward from the base case; patients are assumed to receive a combination of therapies including chemotherapy and palliative care, with the availability of therapies dependent on the health state where BSC is received.

No evidence was identified to support the efficacy of BSC, and so it was assumed that all patients would enter the model in SD, with OS derived from the lowest reported by Cheah 2016[7] for chemotherapies (exponential parametric fit; λ: 0.07296); PFS was assumed to be equivalent to the PFS applied in the base case for SoC, due to the evidence supporting comparable PFS for non-investigational agents.[7] Utilities for BSC were derived based on Swinburn 2015,[101] weighted to assume 100% occupancy of the SD response rate. As a conservative assumption, the rate of AEs and discontinuation was assumed to be zero, and patients remained receiving BSC until death.

Results from this scenario are provided in Table 80, and demonstrate that LYs and QALYs for BSC decrease dramatically under these assumptions, reflecting the clinical reality that BSC will not impact on disease progression, survival or symptom control in cHL patients.

However, the incremental costs for nivolumab increases, as a result of reduced BSC costs for the comparator, but the ICER remains below a WTP threshold of £30,000/QALY.

**Table 80. Scenario analyses: BSC**

| | Nivolumab | BSC | Incremental |
|---|---|---|---|
| Costs (£) | [redacted] | 7,630 | [redacted] |
| QALYs | [redacted] | 0.528 | [redacted] |
| LYs | 5.013 | 1.098 | 3.915 |
| ICER (£/QALY) | 21,580 | | |

**SoC composition equivalent to ongoing BTX TA**

As previously described, the composition of SoC is subject to a set of assumptions, particularly with regard to the chemotherapy element. A scenario analysis was conducted to examine the impact of varying SoC composition by applying the composition used during the ongoing NICE appraisal of BTX,[33] which is set out in Table 81.

**Table 81. Chemotherapy composition during BTX appraisal**

| Component | Usage |
|---|---|
| GEM-Ox: gemcitabine and oxaliplatin | 15% |
| GEM-P: gemcitabine ,cisplatin, methylprednisolone | 15% |
| BEACOPP: Cyclophosphamide, doxorubicin, etoposide, procarbazine, prednisolone, vincristine, bleomycin | 10% |
| DHAP: dexamethasone, cytarabine, cisplatin | 10% |
| Bendamustine | 20% |
| Investigational agents | 5% |
| ChIVPP: chlorambucil, vinblastine, procarbazine, prednisolone | 25% |

Due to inclusion of chemotherapy, bendamustine and investigational agents, it was assumed that the efficacy of the BTX comparator would be equivalent to that for the overall population from Cheah 2016, so that response rates, PFS and OS were as applied for that scenario. Therapy costs and rate of AEs were calculated as specified within Sections 5.5.2.2 and 5.3.3.3, respectively, with inputs outlined in Table 82 and Table 83.

**Table 82. Rate of adverse events for SoC (composition derived from BTX appraisal)**

| Adverse event | Rate |
|---|---|
| Anaemia | 0.052852 |
| Diarrhoea | 0.014965 |
| Dyspnoea | 0.0000374 |
| Fatigue | 0.002373 |
| Leukopenia | 0.12179 |
| Nausea | 0.031132 |
| Neutropenia | 0.11337 |
| Pyrexia | 0.00032 |
| Thrombocytopenia | 0.147947 |
| Vomiting | 0.054733 |

**Table 83. Cost of SoC (composition derived from BTX appraisal)**

| Month | Monthly cost (£) |
|---|---|
| Month 1 | 2041.17 |
| Month 2 | 1932.93 |
| Month 3 | 1780.49 |
| Month 4 | 1508.09 |
| Month 5 | 1027.86 |
| Month 6 | 512.19 |
| Month 7 | 38.91 |
| Month 8+ | 0 |

Results from this scenario are provided in Table 84, and demonstrate that costs for SoC increase dramatically under these assumptions, reflecting the conservative comparator costs applied in the base case analysis. Thus, the ICER is reduced versus the base case, and can be considered cost-effective at a WTP threshold of £30,000/QALY.

**Table 84. Scenario analyses: SoC composition equivalent to ongoing BTX TA**

| | Nivolumab | SoC | Incremental |
|---|---|---|---|
| Costs (£) | [redacted] | 45,274 | [redacted] |
| QALYs | [redacted] | 1.204 | [redacted] |
| LYs | 5.013 | 2.970 | 2.043 |
| ICER (£/QALY) | 12,452 | | |

**Indirect treatment comparison derived comparator efficacy and composition**

In the specific context of relapsed or refractory HL, with low patient numbers, short survival and an ongoing NICE appraisal of BTX, there is significant uncertainty around the clinical pathway for HL patients in the post-ASCT, post-BTX setting, with an associated lack of data

to inform the efficacy of therapies. Although Cheah 2016 real world data[7] can be suggested to adequately represent the treatment of the post-ASCT, post-BTX HL population in clinical practice, scenario analyses were conducted to assess the impact of applying alternative assumptions around comparator composition and efficacy. Table 85 details model inputs for SoC based on indirect comparisons detailed in Section 4. As can be seen, choice of comparator composition and efficacy impacts significantly on incremental costs and QALYs. However, nivolumab can be considered clinically beneficial in all scenarios, and the ICER is below the £30,000 WTP threshold (as depicted in Figure 41), so that nivolumab can be considered cost-effective in this indication.

**Figure 44. Scenario analysis: impact of applying SoC data derived from indirect treatment comparisons**

**Table 85. Summary of indirect treatment comparison scenario results**

| Data source | | Model | SoC model inputs | | | | | SoC model outputs | | | Incremental | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | PFS* | OS* | CR | PR | Pre-progression utility | LYs | QALYs | Costs | LYs | QALYs | Costs | ICER |
| **Post-ASCT, Post-BTX SLR studies** | | | | | | | | | | | | | | |
| Unadjusted | All studies | Fixed | 0.1134 | 0.0204 | [redacted] | [redacted] | [redacted] | 3.551 | 1.532 | 23,379 | 1.462 | [redacted] | [redacted] | 24,277 |
| | | Random | 0.1134 | 0.0204 | [redacted] | [redacted] | [redacted] | 3.551 | 1.540 | 23,379 | 1.462 | [redacted] | [redacted] | 24,361 |
| | Subgroup** | Fixed | 0.1576 | 0.0261 | [redacted] | [redacted] | [redacted] | 2.862 | 1.229 | 20,149 | 2.151 | [redacted] | [redacted] | 22,626 |
| | | Random | 0.1576 | 0.0261 | [redacted] | [redacted] | [redacted] | 2.862 | 1.236 | 20,149 | 2.151 | [redacted] | [redacted] | 22,686 |
| MAIC | All studies | Fixed | 0.1169 | 0.0222 | [redacted] | [redacted] | [redacted] | 3.299 | 1.435 | 22,554 | 1.714 | [redacted] | [redacted] | 23,605 |
| | | Random | 0.1169 | 0.0222 | [redacted] | [redacted] | [redacted] | 3.299 | 1.442 | 22,554 | 1.714 | [redacted] | [redacted] | 23,681 |
| | Subgroup** | Fixed | 0.1602 | 0.0277 | [redacted] | [redacted] | [redacted] | 2.709 | 1.170 | 19,651 | 2.304 | [redacted] | [redacted] | 22,298 |
| | | Random | 0.1602 | 0.0277 | [redacted] | [redacted] | [redacted] | 2.709 | 1.177 | 19,651 | 2.304 | [redacted] | [redacted] | 22,357 |
| | Cheah (overall) | | 0.2064 | 0.0292 | [redacted] | [redacted] | [redacted] | 2.585 | 1.086 | 18,349 | 2.428 | [redacted] | [redacted] | 22,079 |
| | Cheah (no investigational agents) | | 0.1673 | 0.0387 | [redacted] | [redacted] | [redacted] | 1.996 | 0.886 | 17,338 | 3.017 | [redacted] | [redacted] | 20,885 |
| **Post-ASCT SLR studies** | | | | | | | | | | | | | | |
| Unadjusted | All studies | Fixed | 0.0640 | 0.0246 | [redacted] | [redacted] | [redacted] | 3.012 | 1.456 | 23,970 | 2.001 | [redacted] | [redacted] | 23,204 |
| | | Random | 0.0640 | 0.0246 | [redacted] | [redacted] | [redacted] | 3.012 | 1.462 | 23,970 | 2.001 | [redacted] | [redacted] | 23,262 |
| | Subgroup*** | Fixed | 0.0928 | 0.0305 | [redacted] | [redacted] | [redacted] | 2.486 | 1.163 | 20,953 | 2.527 | [redacted] | [redacted] | 21,733 |
| | | Random | 0.0928 | 0.0305 | [redacted] | [redacted] | [redacted] | 2.486 | 1.167 | 20,953 | 2.527 | [redacted] | [redacted] | 21,764 |
| MAIC | All studies | Fixed | 0.0615 | 0.0239 | [redacted] | [redacted] | [redacted] | 3.096 | 1.500 | 24,384 | 1.917 | [redacted] | [redacted] | 23,477 |
| | | Random | 0.0615 | 0.0239 | [redacted] | [redacted] | [redacted] | 3.096 | 1.506 | 24,384 | 1.917 | [redacted] | [redacted] | 23,540 |
| | Subgroup*** | Fixed | 0.0881 | 0.0294 | [redacted] | [redacted] | [redacted] | 2.568 | 1.206 | 21,400 | 2.445 | [redacted] | [redacted] | 21,918 |
| | | Random | 0.0881 | 0.0294 | [redacted] | [redacted] | [redacted] | 2.568 | 1.209 | 21,400 | 2.445 | [redacted] | [redacted] | 21,951 |

* PFS and OS exponential rate

** Subgroup of SLR studies based on those studies where subgroup of post-ASCT post-BTX population is reported or where >70% of patients match this criteria; this includes efficacy of investigational agents.

***Subgroup of SLR studies based on those studies where subgroup of post-ASCT population is reported or where >70% of patients match this criteria; this includes efficacy of investigational agents.

#### *5.8.3.4 Alternative baseline age*

HL shows a clear bimodal age distribution, with a sharp peak in people aged 20–24 years and another in patients aged 75–79.

Due to existing comorbidities and concerns around age, fewer patients aged 75-79 will have undergone salvage chemotherapy and ASCT following first line chemotherapy failure, so that data describing the effectiveness of therapies post-ASCT and post-BTX is more scarce for these patients. Patients in this group are likely to have few, if any, treatment options, and as such are more likely to be receiving BSC, which has limited impact on symptoms, progression or survival and is associated with more hospital admissions, impacting on quality of life. As such, these patients have a high unmet need, and an efficacious therapy that is well-tolerated would represent a much needed treatment option.

By contrast, patients aged 20-24 years have a greater range of treatment options available. However, onset of HL can restrict ability to study, work or participate in family life, and this is a particular issue in this patient group. Availability of a therapy that can provide a bridge to potentially curative alloSCT could allow patients in this age group with the potential to live long and active lives, with significant indirect economic benefits in terms of avoiding lost productivity.[11]

Based on this rationale, two scenarios were undertaken to provide an indication of the impact these differing clinical perspective could have on outcomes:

- Younger cohort: baseline age assumed to be 20 years; alloSCT assumed to be an option in these patients, with inputs reflecting scenario 1 from Section 5.8.3.2.
- Older cohort: baseline age assumed to be 70 years; BSC is assumed to be the most appropriate comparator, with model inputs as described in Section 5.8.3.3.

It should be noted that these economic analyses do not fully reflect the benefits outlined above, which are highly relevant to patients, as it is not possible to reflect these within the QALY calculations. However, results from these scenarios are provided in Table 86. For both scenarios, nivolumab use results in increased accrual of LYs and QALYs, demonstrating the potential benefits that could be made available in clinical practice. Similarly, the ICERs in both scenarios are below the £30,000/QALY WTP threshold, so that nivolumab can be considered cost-effective in both scenarios.

**Table 86. Scenario analyses: Alternative baseline age**

| | Older Cohort | Younger Cohort |
|---|---|---|
| **Nivolumab** | | |
| Costs (£) | [redacted] | [redacted] |
| QALYs | [redacted] | [redacted] |
| LYs | 4.562 | 6.137 |
| **Comparator** | | |
| Costs (£) | 7,561 | 22,193 |
| QALYs | 0.518 | 1.101 |
| LYs | 1.076 | 2.531 |
| **Incremental** | | |
| Costs (£) | [redacted] | [redacted] |
| QALYs | [redacted] | [redacted] |
| LYs | 3.486 | 3.786 |
| ICER (£) | 23,226 | 18,037 |

#### *5.8.3.5 Alternative assumptions around treatment duration*

In the base case analysis, it is assumed that patients in both treatment arms discontinue therapy at the time of progression or due to the rate of discontinuation, which was derived from nivolumab patient-level data. This is likely to reflect clinical practice in most patients and with most therapies, and also provides a conservative assessment of incidence of discontinuation due to AEs during SoC. However, clinical practice may vary, particularly with the use of nivolumab, where treatment may be continued following progression due to the novel mechanism of action. Additionally, clinicians may wish to stop treatment in patients responding at one year.

The following scenario analyses were conducted:

- Patients in the nivolumab arm achieving CR and remaining on initial therapy at 12 months cease to receive therapy costs and incur AEs until discontinuation or progression.
- Patients in the nivolumab arm achieving CR or PR and remaining on initial therapy at 12 months cease to receive therapy costs and incur AEs until discontinuation or progression.
- Patients in the nivolumab arm no longer switch treatment at progression. Additionally, the nivolumab patient-level data-derived treatment discontinuation curve was adjusted to include discontinuation due to all causes, including progression, with the intent of reflecting potential nivolumab use in clinical practice (lognormal curve; μ: 2.732; σ: 1.057)
- Patient discontinuation for reasons other than death or progression was assumed to be zero; on progression, patients were assumed to switch to therapies in line with base case assumptions.

It should be noted that these analyses assume that the clinical benefit of nivolumab remains the same when applying these assumptions around treatment duration; this can be considered conservative, as treatment guidelines and clinicians are unlikely to use these

treatment durations where efficacy is impacted. Results from these analyses are detailed in Table 87. As can be expected, shortening the nivolumab treatment period through application of a stopping rule in responders improves the cost-effectiveness versus SoC. By contrast, extending the treatment period incurs additional costs associated with nivolumab therapy, resulting in an increased ICER; however, this is still below a WTP threshold of £30,000/QALY.

**Table 87. Scenario analyses: Alternative assumptions around treatment duration**

| | Stopping rule (CR) | Stopping rule (CR + PR) | Post-progression treatment | No discontinuation |
|---|---|---|---|---|
| **Nivolumab** | | | | |
| **Costs (£)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **QALYs** | [redacted] | [redacted] | [redacted] | [redacted] |
| **LYs** | 5.013 | 5.013 | 5.013 | 5.013 |
| **Comparator** | | | | |
| **Costs (£)** | 21,090 | 21,090 | 21,090 | 21,174 |
| **QALYs** | 0.932 | 0.932 | 0.932 | 0.932 |
| **LYs** | 2.110 | 2.110 | 2.110 | 2.110 |
| **Incremental** | | | | |
| **Costs (£)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **QALYs** | [redacted] | [redacted] | [redacted] | [redacted] |
| **LYs** | 2.903 | 2.903 | 2.903 | 2.903 |
| **ICER (£/QALY)** | 17,436 | 13,632 | 16,186 | 29,573 |

#### *5.8.3.6 Alternative assumptions around utilities*

In the base case analysis, utility for SoC was derived from the published literature and the nivolumab input was derived from patient-level utility data, resulting in post-progression utility significantly lower for SoC than for nivolumab (0.38 versus [redacted]). Although contrary to standard assumptions around the impact of therapies on utility following progression, this can be expected given the unique nivolumab mechanism of action. However, in order to assess the impact of alternative derivation of utility inputs, several scenarios were undertaken. As can be seen, alternative utility inputs has a fairly large impact on the cost-effectiveness of nivolumab; however, all ICERs remained below a WTP threshold of £50,000/QALY.

**Table 88. Scenario analyses: Alternative utility inputs**

| | Scenario 1 | Scenario 2 | Scenario 3 | Scenario 4 |
|---|---|---|---|---|
| | Comparator post-progression utility set equal to nivolumab post-progression utility | Nivolumab post-progression utility set equal to comparator post-progression utility | Swinburn 2015 used to derive utility for pre- and post-progression in both arms | Response-specific pre-progression utilities applied |
| **Nivolumab** | | | | |
| Costs | [redacted] | [redacted] | [redacted] | [redacted] |
| QALYs | [redacted] | [redacted] | [redacted] | [redacted] |
| LYs | 5.013 | 5.013 | 5.013 | 5.013 |
| **SoC** | | | | |
| Costs | 21,090 | 21,090 | 21,090 | 21,090 |
| QALYs | 1.503 | 0.932 | 0.932 | 0.932 |
| LYs | 2.110 | 2.110 | 2.110 | 2.110 |
| **Incremental** | | | | |
| Costs | [redacted] | [redacted] | [redacted] | [redacted] |
| QALYs | [redacted] | [redacted] | [redacted] | [redacted] |
| LYs | 2.903 | 2.903 | 2.903 | 2.903 |
| ICER | 24,983 | 33,167 | 34,332 | 19,930 |

#### *5.8.3.7 Alternative assumptions around incidence of AEs*

The safety profile associated with nivolumab therapy can be considered acceptable in the context of alternative therapies in this setting, such as chemotherapy. Additionally, it is plausible that the available utilities account for the toxicity of therapies, so that AE-associated disutilities may be double counting. Thus a conservative scenario analysis was conducted where it was assumed that neither nivolumab nor SoC were associated with AEs. The results of this analysis are provided in Table 89.

**Table 89. Scenario analyses: no AEs**

| | Nivolumab | SoC | Incremental |
|---|---|---|---|
| Costs (£) | [redacted] | 19,233 | [redacted] |
| QALYs | [redacted] | 0.951 | [redacted] |
| LYs | 5.013 | 2.110 | 2.903 |
| ICER (£/QALY) | 20,580 | | |

#### *5.8.3.8 Alternative post-progression costs*

The base case analysis applies health state costs derived from resource use estimates for the pre-progression state based on those applied during the ongoing NICE appraisal of BTX.[33] In line with this appraisal, an assumption was made that post-progression costs would be equivalent to pre-progression costs. However, it is possible that this underestimates resource use in the post-progression phase, and so a scenario analysis has been conducted where resource usage was assumed to be increased to double that of the pre-progression state. As can be seen from Table 90, the costs associated with nivolumab

treatment are increased in comparison with the base case, with health state costs now accounting for £19,061 (versus £11,434 in the base case). SoC health state costs see a similar increase (£4,813 to £8,700); however, the shorter survival in this patient arm results in less accrual of health state costs, causing incremental costs to increase so the ICER is no longer below a WTP threshold of £20,000/QALY but is below a WTP threshold of £30,000/QALY.

**Table 90. Scenario analyses: alternative post-progression costs**

| | Nivolumab | SoC | Incremental |
|---|---|---|---|
| Costs (£) | [redacted] | 24,978 | [redacted] |
| QALYs | [redacted] | 0.932 | [redacted] |
| LYs | 5.013 | 2.110 | 2.903 |
| ICER (£/QALY) | 21,218 | | |

#### *5.8.3.9 Application of IRRC-assessed endpoints for nivolumab*

Within the base case analysis, progression and response are applied based on investigator-assessed endpoints from clinical studies, as clinical experts suggest that this is likely to reflect clinician behaviour in a real world setting. Similarly, this may better reflect the accrual of costs and QALYs of HL patients, as a patient considered not to have progressed by the clinician is likely to have a different quality of life and management plan compared with a patient considered to have progressed.

The impact of applying IRRC-derived data for nivolumab was assessed using sensitivity analyses. Table 91 describes IRRC-derived data applied within this scenario analysis.

**Table 91. IRRC-derived endpoint data (nivolumab)**

| Parameter | IRRC-derived nivolumab input |
|---|---|
| Progression-free survival parametric fit | Lognormal;<br>μ: 2.656<br>σ: 1.121 |
| Response rates | CR: [redacted]<br>PR: [redacted] |
| Health state utilities | Pre-progression: [redacted]<br>Post-progression: [redacted] |

As can be seen from Table 89, the costs associated with nivolumab treatment are reduced in comparison with the base case, with an associated increase in QALYs gained. This causes an overall reduction in incremental costs and increase in incremental QALYs, so that the ICER is reduced, improving cost-effectiveness.

**Table 92. Scenario analyses: IRRC-assessed endpoint data**

| | Nivolumab | SoC | Incremental |
|---|---|---|---|
| Costs (£) | [redacted] | 21,090 | [redacted] |
| QALYs | [redacted] | 0.932 | [redacted] |
| LYs | 5.013 | 2.110 | 2.903 |
| ICER (£/QALY) | 17,617 | | |

### 5.8.4 Summary of sensitivity analyses results

A large number of sensitivity analyses have been undertaken, assessing the impact of variation in all variables and assumptions applied within the model. In the deterministic analysis and PSA, nivolumab was cost-effective in the majority of scenarios at a WTP threshold of £30,000/QALY and in all scenarios at a WTP threshold of £50,000/QALY.

Plausible alternative inputs and assumptions were assessed as scenario analyses within Section 5.8.3 as depicted in Figure 45. Reflecting the PSA and deterministic sensitivity analysis, the majority of ICERs remain below the £30,000/QALY threshold, and in all scenarios at a WTP threshold of £50,000/QALY.

**Figure 45. Scenario analysis: overview of all scenarios**

## *5.9 Subgroup analysis*

All available subgroup analyses are provided in Section 5.8.3.

## *5.10 Validation*

### 5.10.1 Validation of de novo cost-effectiveness analysis

In the specific context of relapsed or refractory HL, with low patient numbers, short survival and an ongoing NICE appraisal of BTX, the clinical pathway for HL patients is subject to considerable uncertainty and heterogeneity, particularly in the post-ASCT, post-BTX setting. This translates to a paucity of evidence describing clinical practice on which to base economic evaluation. In general, where no evidence has been identified, simple assumptions have been made based on independent sources, such as published literature, British HL guidelines or previous NICE appraisals in the field of HL or NHL. These assumptions were then assessed for clinical plausibility; rationales for each assumption are provided in Section 5.6.2. Extensive sensitivity analyses were then undertaken, and the majority of ICERs remain below the £30,000/QALY threshold, with only one exceeding the £50,000/QALY threshold.

A technical review of the cost-effectiveness model was conducted by an independent consultant. This allowed the model approach to be validated and permitted areas of disagreement to be resolved prior to generation of model results. It also enabled any issues which may be raised by reimbursement authorities or model critics to be pre-empted and addressed in advance. In addition, quality control was undertaken, whereby a cell-by-cell verification process was conducted to allow checking of all input calculation, formulae and visual basic code.

### 5.10.2 Comparison of clinical trial inputs and modelled outputs

A comparison of clinical trial inputs versus modelled outputs is provided in Table 93. As can be seen, undiscounted model outputs closely represent survival observed during clinical trials as well as survival curves used as model inputs.

**Table 93. Comparison of clinical trial inputs and modelled outputs (undiscounted)**

| | Nivolumab | SoC | Incremental |
|---|---|---|---|
| **Overall survival** | | | |
| Survival curve median (mean) OS (years) | 4.8 (5.9) | 1.6 (2.3) | 3.3 (3.6) |
| Model output median (mean) OS (years) | 4.8 (5.8) | 1.5 (2.3) | 3.3 (3.6) |
| **Progression-free survival** | | | |
| Clinical trial (Median) PFS (years) | 1.4 | 0.4 | 1.0 |
| Survival curve median (mean) PFS (years) | 1.4 (2.6) | 0.4 (0.5) | 1.0 (2.1) |
| Model output median (mean) PFS (years) | 1.2 ([redacted]) | 0.3 (0.4) | 0.9 ([redacted]) |

## 5.11 Interpretation and conclusions of economic evidence

**Base case analysis**

- In line with estimates of short life expectancy in patients receiving SoC, the model predicts a median OS of 1.5 years (mean: 2.1 years)
- Use of nivolumab will result in an additional [redacted] discounted QALYs (total: [redacted] QALYs) and 2.90 discounted LYs (total: 5.01 LYs).
- Incremental costs were expected to be [redacted] under base case assumptions and the resultant ICER was £19,882, which can be considered cost-effective at a willingness-to-pay threshold of £30,000/QALY.

**Sensitivity analysis**

- In the deterministic analysis and PSA, nivolumab was cost-effective in the majority of scenarios at a WTP threshold of £20,000/QALY and in all scenarios at a WTP threshold of £50,000/QALY.
- Extensive scenario analyses were undertaken, reflecting the assumptions required to undertaken a plausible, robust and transparent base case analysis.
- Within these scenario analyses, the majority of ICERs remain below the £20,000/QALY threshold, and in all scenarios at a WTP threshold of £50,000/QALY.

As previously discussed, in the specific context of relapsed or refractory HL, with low patient numbers, short survival and an ongoing NICE appraisal of BTX, the clinical pathway for HL patients is subject to considerable uncertainty and heterogeneity, particularly in the post-ASCT, post-BTX setting. This translates to a paucity of evidence describing clinical practice on which to base economic evaluation. In general, where no evidence has been identified, simple assumptions have been made based on independent sources, such as published literature, British HL guidelines or previous NICE appraisals in the field of HL or NHL. These assumptions were then assessed for clinical plausibility; rationales for each assumption are provided in Section 5.6.2. Extensive sensitivity analyses were then undertaken, and the conclusions from these represent the best evidence of cost-effectiveness available.

As previously noted, this current analysis has been designed to be comparable with previous health economic analysis and HTAs in HL, as well as NHL, facilitating review and transparency. Further, the approach has been chosen to reflect the most important treatment outcomes for most HL patients: survival (progression free and overall), side effects, symptom control and quality of life.

In the base case analysis, it was estimated that nivolumab use would result in an additional [redacted] discounted QALYs and 2.90 discounted LYs versus SoC. Further, it was estimated that patients receiving nivolumab would spend [redacted] years in the pre-progression state (versus 0.4

years for patients receiving SoC), with a subsequent [redacted] years in the post-progression state (versus 1.7 years for SoC), indicating a substantial benefit to survival in both the pre- and post-progression period. Incremental costs were expected to be [redacted] under base case assumptions and the resultant ICER was £19,882, which can be considered cost-effective at a willingness-to-pay threshold of £30,000/QALY.

A large number of sensitivity analyses have been undertaken, assessing the impact of variation in all variables and assumptions applied within the model. In the deterministic analysis and PSA, nivolumab was cost-effective in the majority of scenarios at a WTP threshold of £30,000/QALY and in all scenarios at a WTP threshold of £50,000/QALY. Similarly, when plausible alternative inputs and assumptions were assessed as scenario analyses within Section 5.8.3, and the majority of ICERs remain below the £30,000/QALY threshold, with all scenarios producing ICERs below the £50,000/QALY threshold.

NICE appraisal of BTX is ongoing, but outputs of analyses conducted by the manufacturer and ERG are available for comparison. It should be noted that the patient population of interest is less treatment experienced than that for nivolumab (relapsed or refractory patients with cHL following ASCT) and so clinical outcomes can be anticipated to be slightly better. Reflecting this, in the manufacturer's base case analysis (discounted) patients receiving the comparator are predicted to accrue 4.16 LYs and 1.80 QALYs, which is around twice as many predicted for SoC in the current submission (2.11 LYs and 0.93 QALYs). Absolute costs accrued were comparable (£27,416 versus £20,831), but reflect the difference in survival. By comparison, clinical benefits predicted for BTX is [redacted] to that predicted for nivolumab (5.45 LYs and 3.35 QALYs); total costs predicted for BTX were £61,173, which is [redacted] than for nivolumab ([redacted]), reflecting the ongoing nature of nivolumab treatment. The breakdown of costs and utilities by health state can also be considered broadly similar, while reflecting the differences in survival time and treatment costs.

**Application of NICE end of life criteria to nivolumab use in HL**

End of life criteria as applied by NICE are summarised as follows:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months; and
- There is sufficient evidence to indicate that the treatment offers an extension to life,

Those therapies that are available in patients with relapsed or refractory cHL are associated with poor outcomes, although data describing this patient population is limited. Patients with relapsed or refractory cHL following ASCT had a median OS of 19-29 months, depending on therapies received and availability of BTX,[5,6] and this decreases further in patients who do not achieve an initial response following ASCT.[6] Further, in patients who receive palliative care, median OS decreases to 2.6 months.[5] During the pivotal study for BTX, patients with PR or who do not achieve response (SD) had a median time to progression or death of up to 6.9 months, while median OS was 18.3 months for patients achieving SD and 39.4 months for PR.[4]

Outcomes are known to be even poorer in relapsed or refractory patients who have received both ASCT and BTX, with estimates of median PFS that do not exceed 5 months. Estimates

of OS are around two years, but this is obscured by inclusion of the efficacy of clinical trial therapies (47.4 months).[7] When the efficacy of investigational agents is removed, median OS is estimated to be around 19 months. Thus, there is a high degree of unmet medical need in this patient population.

Median OS was not reached during CheckMate 205 or CA209-039, but the small number of deaths occurring during these studies indicate a substantially longer median survival than that offered by current therapies. Fitting of parametric functions to this data indicate median OS exceeding 42.9 months, potentially reaching 156 months, which would be a substantial survival benefit in this patients group.

Based on available evidence, it can be considered that nivolumab meets both criteria for end of life, as specified by NICE.

**Relevance of the analysis to NHS England**

The analyses presented in this submission have been conducted in line with the NICE reference case and guidance on the completion of the Single Technology Appraisal template; inputs used were specific to the UK or England wherever available and appropriate. Further, evidence and analyses have been completed with specific reference to the scope set out by NICE. Therefore it can be concluded that results presented can be considered relevant to NHS England.

# 6 Assessment of factors relevant to the NHS and other parties

## 6.1 Eligible population

The incidence of HL in the UK is around 1,954 new cases, equivalent to 3.0 cases per 100,000 people.[1] During 2014, 123 ASCT procedures were carried out in UK patients with HL,[110] which when scaled to the population of England, is approximately 103 procedures.[111] Of these 103 patients who receive ASCT, around 50% (51.7 patients) will fail to respond or will relapse, and so will receive BTX therapy. In patients failing to respond to BTX (i.e. less than CR; 59.8%), median progression is short;[4] thus, these patients can be considered to be most likely to fail BTX treatment and require treatment with nivolumab. This would equate to around 30.9 patients eligible for nivolumab treatment each year, or 154.7 patients over a five year period. The estimated number of patients eligible for nivolumab over the next five years is summarised in Table 94.

**Table 94. Expected number of treatment eligible cases of cHL over five years**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| **Estimated HL population treated with ASCT** | | | | | |
| UK (based on 2014) | 123 | | | | |
| England only | 103.5 | | | | |
| **Sub-population of eligible patient cohort (%)** | | | | | |
| Patients failing ASCT | 50% | | | | |
| Patients failing BTX | 59.8% | | | | |
| Estimated total eligible sub-population treated each year | 30.9 | 61.9 | 92.8 | 123.8 | 154.7 |
| ASCT: autologous stem cell transplant; BTX: brentuximab. | | | | | |

## 6.2 Current treatment options and uptake assumptions

In the specific context of relapsed or refractory HL, with low patient numbers, short survival and an ongoing NICE appraisal of BTX, the clinical pathway for HL patients is subject to considerable uncertainty and heterogeneity, particularly in the post-ASCT, post-BTX setting. In light of this uncertainty and the lack of data surrounding comparator composition, the base case analysis assumes that established clinical management is comprised of standard chemotherapy (assumed to be equivalent to BCSH regimens), bendamustine and BTX retreatment. Table 96 details the current treatment options, market share assumptions and regimen costs.

## 6.3 Assumed market share

Market share assumptions are detailed in Table 95; for the purpose of the analysis, current chemotherapies are assumed to have equal market share. Nivolumab is assumed to replace

other chemotherapies once introduced, applying an assumption of 100% market share in order to provide a highly conservative estimation of the potential budget impact.

**Table 95. Standard of care: market share assumptions**

| | Percentage | Patients |
|---|---|---|
| Chemotherapy | 58.1% | 18 |
| Bendamustine | 27.9% | 4 |
| BTX retreatment | 14.0% | 9 |

## *6.4 Technology costs*

Costs for nivolumab and displaced regimens were calculated applying the assumptions outlined in Section 5.5.2, with regimen costs outlined in Table 96 and Table 97.

**Table 96. Standard of care: composition, usage and costs**

| Regimen | Usage | Total regimen cost | |
|---|---|---|---|
| Bendamustine | 27.90% | 12,581.46 | |
| BTX | 14% | 70,501.07 | |
| Chemotherapy | 58.10% | ICE | 3,987.03 |
| | | IVE | 5,667.03 |
| | | MINE | 3,366.39 |
| | | IVOx | 9,385.40 |
| | | IGEV | 14,814.89 |
| | | GEM-P | 6,596.48 |
| | | GDP | 2,968.64 |
| | | GVD | 6,041.70 |
| | | Mini-BEAM | 33,665.73 |
| | | DexaBEAM | 22,711.00 |
| | | ESHAP | 4,227.48 |
| | | ASHAP | 3,176.61 |
| | | DHAP | 2,408.54 |
| | | DHAOx | 8,019.08 |
| | | **Overall** | **9,074.00** |
| Weighted total regimen cost | | | 18,652.37 |

ASHAP: doxorubicin, methylprednisolone, cytarabine, cisplatin; BTX: brentuximab; ChlVPP: chlorambucil, vinblastine, procarbazine and prednisolone; DexaBEAM: dexamethasone, carmustine, etoposide, cytarabine, melphalan; DHAOx: dexamethasone, cytarabine, oxaliplatin; DHAP: dexamethasone, cytarabine, cisplatin; ESHAP: etoposide, methylprednisolone, cytarabine, cisplatin; GDP: gemcitabine, dexamethasone, cisplatin; GEM-P: gemcitabine, cisplatin, methylprednisolone; GVD: gemcitabine, vinorelbine, liposomal doxorubicin; ICE: ifosfamide, carboplatin, etoposide; IGEV: ifosfamide, gemcitabine, vinorelbine; IVE: ifosfamide, epirubicin, etoposide; IVOx: ifosfamide, etoposide, oxaliplatin; MINE: mitoxantrone, ifosfamide, vinorelbine, etoposide; Mini-BEAM: carmustine, etoposide, cytarabine, melphalan;

**Table 97. Nivolumab annual cost**

| | No PAS | PAS |
|---|---|---|
| Nivolumab cost | 77,273.08 | [redacted] |
| Applies assumptions as in Table 52 and Table 53, and includes cost of administration | | |

## 6.5 Resource savings and other significant costs

In clinical practice, there may be cost savings associated with nivolumab therapy due to the simplified administration schedule. However, in order to provide a robust, conservative analysis, it is assumed that there are no significant savings associated with the use of nivolumab.

## 6.6 Estimated annual budget impact

Based on assumptions surrounding the number of patients eligible for treatment, market share and uptake, the estimated budget impact to the NHS over the next 5 years associated with the use of nivolumab in this setting is reported in Table 98.

**Table 98. Expected budget impact**

| Year | SoC (£) | Nivolumab (£) | | Net Impact (£) | |
|---|---|---|---|---|---|
| | | No PAS | With PAS | No PAS | With PAS |
| Year 1 | 577,211 | 2,391,271 | [redacted] | 1,814,060 | [redacted] |
| Year 2 | 1,154,422 | 4,782,542 | [redacted] | 3,628,120 | [redacted] |
| Year 3 | 1,731,633 | 7,173,813 | [redacted] | 5,442,180 | [redacted] |
| Year 4 | 2,308,844 | 9,565,085 | [redacted] | 7,256,240 | [redacted] |
| Year 5 | 2,886,055 | 11,956,356 | [redacted] | 9,070,300 | [redacted] |

## 6.7 Alternative budget impact scenarios

No alternative scenarios are provided.

# 7 References


1. Cancer Research UK. Hodgkin lymphoma incidence statistics. 2016. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/hodgkin-lymphoma/incidence#heading-Zero [accessed 16/05/2016].
2. National Institute for Health and Care Excellence. ID722. Brentuximab vedotin for treating CD30-positive Hodgkin's lymphoma: final scope. 2016. Available from: https://www.nice.org.uk/guidance/GID-TAG467/documents/lymphoma-hodgkins-cd30positive-brentuximab-vedotin-final-scope2 [accessed 16/05/2016].
3. Collins GP, Parker AN, Pocock C, et al. Guideline on the management of primary resistant and relapsed classical Hodgkin lymphoma. Br J Haematol. 2014;164(1):39-52.
4. Chen R, Gopal AK, Smith SE, et al. Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma. Blood. 2016.
5. Martinez C, Canals C, Sarina B, et al. Identification of prognostic factors predicting outcome in Hodgkin's lymphoma patients relapsing after autologous stem cell transplantation. Ann Oncol. 2013;24(9):2430-4.
6. Bair SM, Strelec LE, Nasta S, et al. Outcomes in patients with relapsed/refractory Hodgkin lymphoma (RR-HL) with progression after autologous stem cell transplantation in the current era of novel therapeutics. J Clin Oncol. 2016;31(suppl):Abstr 2543.
7. Cheah CY, Chihara D, Horowitz S, et al. Patients with classical Hodgkin lymphoma experiencing disease progression after treatment with brentuximab vedotin have poor outcomes. Ann Oncol. 2016;27(7):1317-23.
8. Bristol-Myers Squibb Pharmaceuticals Ltd. Summary of Product Characteristics. OPDIVO 10 mg/mL concentrate for solution for infusion. 2016. Available from: http://www.medicines.org.uk/emc/medicine/30476 [accessed 12/10/2016].
9. Villasboas JC, Ansell SM. Nivolumab for the treatment of classical Hodgkin lymphoma after failure of autologous stem cell transplant and brentuximab. Expert Rev Anticancer Ther. 2016;16(1):5-12.
10. Ansell SM. Targeting immune checkpoints in lymphoma. Curr Opin Hematol. 2015;22(4):337-42.
11. Bradley CJ, Yabroff KR, Dahman B, et al. Productivity costs of cancer mortality in the United States: 2000-2020. J Natl Cancer Inst. 2008;100(24):1763-70.
12. Committee for Medicinal Products for Human Use (CHMP). EMA/CHMP/671272/2016: Summary of opinion (post authorisation). Nivolumab (Opdivo). 2016. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion/human/003985/WC500214219.pdf [accessed 19/10/2016].
13. Bristol-Myers Squibb Pharmaceuticals Ltd. Interim Clinical Study Report for Study CA209205. Non-Comparative, Multi-Cohort, Single-Arm, Open-Label, Phase 2 Study of Nivolumab (BMS-936558) in Classical Hodgkin Lymphoma (cHL) Subjects After Failure of Autologous Stem Cell Transplant (ASCT). 2016.
14. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med. 2015;372(4):311-9.
15. Bristol-Myers Squibb Pharmaceuticals Ltd. Interim Clinical Study Report for Study CA209039: A Phase 1 Dose Escalation Study to Investigate the Safety, Pharmacokinetics, Immunoregulatory Activity, and Preliminary Antitumor Activity of Anti-Programmed-Death 1 (PD-1) Antibody (Nivolumab, BMS-936558) and the Combinations of Nivolumab and Ipilimumab or Nivolumab and Lirilumab in Subjects with Relapsed or Refractory Hematologic Malignancy. 2016.

16. Younes A, Santoro A, Shipp M, et al. Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial. Lancet Oncol. 2016.
17. Bristol-Myers Squibb Pharmaceuticals Ltd. NCT01592370: A Phase I Dose Escalation Study to Investigate the Safety, Pharmacokinetics, Immunoregulatory Activity, and Preliminary Antitumor Activity of Anti-Programmed-Death 1 (PD-1) Antibody (Nivolumab, BMS936558) and the Combination of Nivolumab and Ipilimumab or Nivolumab and Lirilumab in Subjects With Relapsed or Refractory Hematologic Malignancy. 2016. Available from: https://clinicaltrials.gov/ct2/show/NCT01592370 [accessed 30/05/2016].
18. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature. 2011;480(7378):480-9.
19. Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol. 2010;28(19):3167-75.
20. Freeman GJ, Long AJ, Iwai Y, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med. 2000;192(7):1027-34.
21. Blank C, Gajewski TF, Mackensen A. Interaction of PD-L1 on tumor cells with PD-1 on tumor-specific T cells as a mechanism of immune evasion: implications for tumor immunotherapy. Cancer Immunol Immunother. 2005;54(4):307-14.
22. Latchman Y, Wood CR, Chernova T, et al. PD-L2 is a second ligand for PD-1 and inhibits T cell activation. Nat Immunol. 2001;2(3):261-8.
23. Roemer MG, Advani RH, Ligon AH, et al. PD-L1 and PD-L2 Genetic Alterations Define Classical Hodgkin Lymphoma and Predict Outcome. J Clin Oncol. 2016;34(23):2690-7.
24. Villasboas JC, Ansell S. Checkpoint Inhibition: Programmed Cell Death 1 and Programmed Cell Death 1 Ligand Inhibitors in Hodgkin Lymphoma. Cancer J. 2016;22(1):17-22.
25. Green MR, Monti S, Rodig SJ, et al. Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. Blood. 2010;116(17):3268-77.
26. McDermott DF, Atkins MB. PD-1 as a potential target in cancer therapy. Cancer Med. 2013;2(5):662-73.
27. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25(5):579-86.
28. European Medicines Agency. OPDIVO. Procedural steps taken and scientific information after the authorisation. 2016. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/003985/WC500197949.pdf [accessed 12/05/2016].
29. Haymarket Media Group Ltd. Monthly Index of Medical Specialities (MIMS). 2016. Available from: http://www.mims.co.uk/ [accessed 13/05/2016].
30. Haymarket Media Inc. Cancer Therapy Advisor: Hodgkin Lymphoma Treatment Regimens. 2016. Available from: http://www.cancertherapyadvisor.com/hematologic-cancers/hodgkin-lymphoma-treatment-regimens/article/218176/ [accessed 15/05/2016].
31. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Hodgkin Lymphoma. Version 2.2016. 2016. Available from: https://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf [accessed 16/05/2016].
32. South West Strategic Clinical Network. (R) GDP - Gemcitabine, Dexamethasone and Cisplatin +/- Rituximab. 2014. Available from: http://www.swscn.org.uk/wp/wp-content/uploads/2014/12/R-GDP.pdf [accessed 16/05/2016].

33. National Institute for Health and Care Excellence. Single Technology Appraisal. Brentuximab vedotin for treating CD30-positive Hodgkin's lymphoma. Committee Papers. 2016. Available from: https://www.nice.org.uk/guidance/GID-TAG467/documents/committee-papers [accessed 03/09/2016].
34. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. 2013. Available from: https://www.nice.org.uk/article/pmg9 [accessed 03/06/2016].
35. Yung L, Linch D. Hodgkin's lymphoma. Lancet. 2003;361(9361):943-51.
36. Cancer Research UK. What is Hodgkin lymphoma? 2016. Available from: http://www.cancerresearchuk.org/about-cancer/type/hodgkins-lymphoma/about/what-is-hodgkins-lymphoma [accessed 15/05/2016].
37. Follows GA, Ardeshna KM, Barrington SF, et al. Guidelines for the first line management of classical Hodgkin lymphoma. Br J Haematol. 2014;166(1):34-49.
38. National Institute for Health and Care Excellence. NICE in development [GID-TAG467]. Lymphoma (Hodgkin's, CD30-positive) - brentuximab vedotin [ID722]. 2016. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-tag467 [accessed 16/05/2016].
39. Eichenauer DA, Engert A, Andre M, et al. Hodgkin's lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25 Suppl 3:iii70-5.
40. Armand P, Ansell SM, Lesokhin AM, et al. Nivolumab in patients with relapsed or refractory hodgkin lymphoma-preliminary safety, efficacy and biomarker results of a phase I study. Blood. 2014;124(21).
41. Timmerman J, Armand P, Lesokhin AM, et al. Nivolumab in Patients With Relapsed or Refractory Lymphoid Malignancies and Classical Hodgkin Lymphoma: Updated Results of a Phase 1 Study (CA209-039) Hematological Oncology. 2015;33(S1):8-9.
42. Armand P, Shipp MA, Ribrag V, et al. PD-1 blockade with pembrolizumab in patients with classical hodgkin lymphoma after brentuximab vedotin failure: Safety, efficacy, and biomarker assessment. Blood. 2015;126(23):584.
43. Moskowitz CH, Ribrag V, Michot JM, et al. PD-1 blockade with the monoclonal antibody pembrolizumab (MK-3475) in patients with classical hodgkin lymphoma after brentuximab vedotin failure: Preliminary results from a phase 1B study (KEYNOTE-013). Blood. 2014;124(21).
44. Bartlett NL, Chen R, Fanale MA, et al. Retreatment with brentuximab vedotin in patients with CD30-positive hematologic malignancies. Journal of Hematology and Oncology. 2014;7(1).
45. Batlevi CL, Kasamon Y, Bociek RG, et al. ENGAGE- 501: phase II study of entinostat (SNDX-275) in relapsed and refractory Hodgkin lymphoma. Haematologica. 2016;101(8):968-75.
46. Chen RW, Zinzani PL, Fanale MA, et al. Pembrolizumab for relapsed/refractory classical Hodgkin lymphoma (R/R cHL): phase 2 KEYNOTE-087 study. Journal of Clinical Oncology. 2016;34.
47. Moskowitz C, Zinzani P, Fanale M, et al. Multicohort phase 2 study of pembrolizumab for relapsed/refractory classical Hodgkin lymphoma (R/R CHL): KEYNOTE-087. 21st Congress of the European Hematology Association June 9–12, 2016; Copenhagen, Denmark.
48. Christian B, Kopko A, Fehniger TA, et al. A phase I trial of the histone deacetylase (HDAC) inhibitor, panobinostat, in combination with lenalidomide in patients with relapsed/refractory hodgkin's lymphoma (HL). Blood. 2012;120(21).
49. Falchi L, Sawas A, Deng C, et al. Rate of complete metabolic responses to immune checkpoint inhibitors in extremely heavily pre-treated patients with classical Hodgkin's lymphoma and immunoepigenetic priming. Journal of Clinical Oncology. 2016;34.
50. Forero-Torres A, Barr P, Diefenbach C, et al. A phase 1 study of patients with relapsed or refractory classical hodgkin lymphoma treated with a PI3K delta inhibitor

(INCB040093) alone or in combination with a selective JAK1 inhibitor (INCB039110). Haematologica. 2015;100:112.
51. Forero-Torres A, Barr PM, Magid Diefenbach CS, et al. A phase 1 study of PI3Kδ inhibitor INCB040093 alone or in combination with selective JAK1 inhibitor INCB039110 in patients with relapsed/refractory hodgkin lymphoma. Hematological Oncology. 2015;33:157.
52. Jasielec J, Kimball AS, Cohen KS, et al. Temsirolimus (TEM) and lenalidomide (LEN) in relapsed/refractory Hodgkin lymphoma including in patients with prior exposure to brentuximab vedotin (BV). Journal of Clinical Oncology. 2014;32(15).
53. Pinto A, Pavone V, Angrilli F, et al. Lenalidomide in combination with bendamustine for patients with chemorefractory hodgkin lymphoma: Final results of the leben multicenter phase 1/2 study. Blood. 2015;126(23):1541.
54. Ugocsai P, Klobuch S, Zaiss S, et al. Targeting the tumors' systems biology: Combined biomodulatory therapy in refractory Hodgkin's lymphoma. Oncology Research and Treatment. 2014;37:12.
55. Younes A, Santoro A, Zinzani PL, et al. Checkmate 205: Nivolumab (nivo) in classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (ASCT) and brentuximab vedotin (BV)-A phase 2 study. Journal of Clinical Oncology. 2016;34.
56. Engert A, Santoro A, Shipp M, et al. CheckMate 205: A Phase 2 Study of Nivolumab in Patients With Classical Hodgkin Lymphoma Following Autologous Stem Cell Transplantation and Brentuximab Vedotin. 21st Congress of the European Hematology Association June 9–12, 2016; Copenhagen, Denmark.
57. Zinzani PL, Vitolo U, Viviani S, et al. Safety and efficacy of single-agent bendamustine after failure of brentuximab vedotin in patients with relapsed or refractory Hodgkin's lymphoma: Experience with 27 patients. Clinical Lymphoma, Myeloma and Leukemia. 2015;15(7):404-8.
58. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health. 1998;52(6):377-84.
59. The Cochrane Collaboration. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0. 2011; updated March 2011. Available from: www.cochrane-handbook.org. [accessed 03/11/2014].
60. Bristol-Myers Squibb Pharmaceuticals Ltd. NCT02181738: Non-Comparative, Multi-Cohort, Single Arm, Open-Label, Phase 2 Study of Nivolumab (BMS-936558) in Classical Hodgkin Lymphoma (cHL) Subjects. 2016. Available from: https://clinicaltrials.gov/ct2/show/NCT02181738 [accessed 30/05/2016].
61. Bristol-Myers Squibb Pharmaceuticals Ltd. Clinical Protocol CA209205: Non-Comparative, Multi-Cohort, Single Arm, Open-Label, Phase 2 Study of Nivolumab (BMS-936558) in classical Hodgkin Lymphoma (cHL) Subjects (CheckMate 205: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 205). 2014.
62. Signorovitch JE, Wu EQ, Yu AP, et al. Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept. Pharmacoeconomics. 2010;28(10):935-45.
63. Armand P, Shipp MA, Ribrag V, et al. Programmed Death-1 Blockade With Pembrolizumab in Patients With Classical Hodgkin Lymphoma After Brentuximab Vedotin Failure. J Clin Oncol. 2016.
64. Drummond M, Jefferson T. Guidelines for authors and peer reviewers of economic submissions to the BMJ. Bmj. 1996;313(7052):275-83.
65. Barosi G, Marchetti M, Alessandrino P, et al. A model for analysing the cost of autologous peripheral blood progenitor cell (PBPC) transplantation. Bone Marrow Transplantation. 1999;23(7):719-25.
66. Chen AB, Punglia RS, Kuntz KM, et al. Cost effectiveness and screening interval of lipid screening in Hodgkin's lymphoma survivors. Journal of Clinical Oncology. 2009;27(32):5383-9.

67. Engstrom A. The cost-effectiveness of brentuximab vedotin in hodgkin lymphoma in Sweden. Value in Health. 2014;17(7):A639.
68. Gallamini A, Marchetti M, Borra A, et al. Cost-effectiveness of interim PET response adapted therapy in ABVD-treated, advanced-stage Hodgkin lymphoma. Blood. 2011;118(21).
69. Guadagnolo BA, Punglia RS, Kuntz KM, et al. Cost-effectiveness analysis of computerized tomography in the routine follow-up of patients after primary treatment for Hodgkin's disease. Journal of Clinical Oncology. 2006;24(25):4116-22.
70. Meza-Torres B, Gay JG, Jakouloff DE. Cost-effectiveness evaluation of brentuximab vedotin for refractory/relapsed hodgkin lymphoma: A comparative analysis of the results of Mexico and Venezuela. Value in Health. 2014;17(7):A637.
71. Ng AK, Kuntz KM, Mauch PM, et al. Costs and effectiveness of staging and treatment options in early-stage Hodgkin's disease. International Journal of Radiation Oncology Biology Physics. 2001;50(4):979-89.
72. National Institute for Health and Care Excellence. NICE technology appraisal guidance [TA306]. Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B‐ cell lymphoma. 2014. Available from: https://www.nice.org.uk/guidance/ta306 [accessed 07/06/2016].
73. Ansell SM, Armitage JO. Positron emission tomographic scans in lymphoma: convention and controversy. Mayo Clin Proc. 2012;87(6):571-80.
74. Postel-Vinay S, Aspeslagh S, Lanoy E, et al. Challenges of phase 1 clinical trials evaluating immune checkpoint-targeted antibodies. Ann Oncol. 2016;27(2):214-24.
75. National Institute for Health and Care Excellence. Single Technology Appraisal. Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma: Final scope. 2016. Available from: https://www.nice.org.uk/guidance/GID-TA10100/documents/final-scope [accessed 12/10/2016].
76. National Institute for Health and Care Excellence Decision Support Unit. Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2013. Available from: http://www.nicedsu.org.uk/NICE%20DSU%20TSD%20Survival%20analysis.updated%20March%202013.v2.pdf [accessed 07/06/2016].
77. Bagust A, Beale S. Survival analysis and extrapolation modeling of time-to-event clinical trial data for economic evaluation: an alternative approach. Med Decis Making. 2014;34(3):343-51.
78. Office for National Statistics. National Life Tables, United Kingdom, 2012–2014. 2015. Available from: http://www.ons.gov.uk/ons/rel/lifetables/national-life-tables/2012-2014/stb-life-tables-2012-2014.html [accessed 20/10/2016].
79. Moskowitz CH, Nimer SD, Zelenetz AD, et al. A 2-step comprehensive high-dose chemoradiotherapy second-line program for relapsed and refractory Hodgkin disease: analysis by intent to treat and development of a prognostic model. Blood. 2001;97(3):616-23.
80. Zinzani PL, Tani M, Molinari AL, et al. Ifosfamide, epirubicin and etoposide regimen as salvage and mobilizing therapy for relapsed/refractory lymphoma patients. Haematologica. 2002;87(8):816-21.
81. Ferme C, Bastion Y, Lepage E, et al. The MINE regimen as intensive salvage chemotherapy for relapsed and refractory Hodgkin's disease. Ann Oncol. 1995;6(6):543-9.
82. Sibon D, Ertault M, Al Nawakil C, et al. Combined ifosfamide, etoposide and oxalipatin chemotherapy, a low-toxicity regimen for first-relapsed or refractory Hodgkin lymphoma after ABVD/EBVP: a prospective monocentre study on 34 patients. Br J Haematol. 2011;153(2):191-8.
83. Santoro A, Magagnoli M, Spina M, et al. Ifosfamide, gemcitabine, and vinorelbine: a new induction regimen for refractory and relapsed Hodgkin's lymphoma. Haematologica. 2007;92(1):35-41.

84. Chau I, Harries M, Cunningham D, et al. Gemcitabine, cisplatin and methylprednisolone chemotherapy (GEM-P) is an effective regimen in patients with poor prognostic primary progressive or multiply relapsed Hodgkin's and non-Hodgkin's lymphoma. Br J Haematol. 2003;120(6):970-7.
85. Baetz T, Belch A, Couban S, et al. Gemcitabine, dexamethasone and cisplatin is an active and non-toxic chemotherapy regimen in relapsed or refractory Hodgkin's disease: a phase II study by the National Cancer Institute of Canada Clinical Trials Group. Ann Oncol. 2003;14(12):1762-7.
86. Bartlett NL, Niedzwiecki D, Johnson JL, et al. Gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD), a salvage regimen in relapsed Hodgkin's lymphoma: CALGB 59804. Ann Oncol. 2007;18(6):1071-9.
87. Girouard C, Dufresne J, Imrie K, et al. Salvage chemotherapy with mini-BEAM for relapsed or refractory non-Hodgkin's lymphoma prior to autologous bone marrow transplantation. Ann Oncol. 1997;8(7):675-80.
88. Schmitz N, Pfistner B, Sextro M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. Lancet. 2002;359(9323):2065-71.
89. Aparicio J, Segura A, Garcera S, et al. ESHAP is an active regimen for relapsing Hodgkin's disease. Ann Oncol. 1999;10(5):593-5.
90. Rodriguez J, Rodriguez MA, Fayad L, et al. ASHAP: a regimen for cytoreduction of refractory or recurrent Hodgkin's disease. Blood. 1999;93(11):3632-6.
91. Josting A, Rudolph C, Reiser M, et al. Time-intensified dexamethasone/cisplatin/cytarabine: an effective salvage therapy with low toxicity in patients with relapsed and refractory Hodgkin's disease. Ann Oncol. 2002;13(10):1628-35.
92. Rigacci L, Fabbri A, Puccini B, et al. Oxaliplatin-based chemotherapy (dexamethasone, high-dose cytarabine, and oxaliplatin)+/-rituximab is an effective salvage regimen in patients with relapsed or refractory lymphoma. Cancer. 2010;116(19):4573-9.
93. Moskowitz AJ, Hamlin PA, Jr., Perales MA, et al. Phase II study of bendamustine in relapsed and refractory Hodgkin lymphoma. J Clin Oncol. 2013;31(4):456-60.
94. Moskowitz CH, Nademanee A, Masszi T, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2015;385(9980):1853-62.
95. Kind P, Hardman G, Macran S. UK Population norms for EQ-5D. Discussion Paper 172. 1999. Available from: http://www.york.ac.uk/che/pdf/DP172.pdf [accessed 31/08/2016].
96. Beusterien KM, Davies J, Leach M, et al. Population preference values for treatment outcomes in chronic lymphocytic leukaemia: a cross-sectional utility study. Health Qual Life Outcomes. 2010;8:50.
97. Doyle S, Lloyd A, Walker M. Health state utility scores in advanced non-small cell lung cancer. Lung Cancer. 2008;62(3):374-80.
98. Nafees B, Stafford M, Gavriel S, et al. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes. 2008;6:84.
99. Tolley K, Goad C, Yi Y, et al. Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia. Eur J Health Econ. 2013;14(5):749-59.
100. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health. 2010;13(5):509-18.
101. Swinburn P, Shingler S, Acaster S, et al. Health utilities in relation to treatment response and adverse events in relapsed/refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma. Leuk Lymphoma. 2015;56(6):1839-45.
102. Proctor SJ, Taylor PR, Angus B, et al. High-dose ifosfamide in combination with etoposide and epirubicin (IVE) in the treatment of relapsed/refractory Hodgkin's

disease and non-Hodgkin's lymphoma: a report on toxicity and efficacy. Eur J Haematol Suppl. 2001;64:28-32.
103. Younes A, Bartlett NL, Leonard JP, et al. Brentuximab Vedotin (SGN-35) for Relapsed CD30-Positive Lymphomas. New England Journal of Medicine. 2010;363(19):1812-21.
104. Department of Health. NHS reference costs 2014 to 2015. 2015. Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015 [accessed 07/09/2016].
105. National Institute for Health and Care Excellence. NICE Technology Appraisal Guidance 251. Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia (part review of technology appraisal guidance 70). 2012. Available from: https://www.nice.org.uk/guidance/ta251 [accessed 03/06/2016].
106. Curtis L. Unit Costs of Health and Social Care 2015. 2015. Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2015/index.php [accessed 07/09/2016].
107. Perrot A, Monjanel H, Bouabdallah R, et al. Impact of post-brentuximab vedotin consolidation on relapsed/refractory CD30+ Hodgkin lymphomas: a large retrospective study on 240 patients enrolled in the French Named-Patient Program. Haematologica. 2016;101(4):466-73.
108. Radford J, Johnson R, McKay P, et al. Treatment pathways and resource use associated with the management of recurrent Hodgkin lymphoma after autologous stem cell transplantation. Haematologica. 2013.
109. National Institute for Health and Care Excellence. Technology appraisal guidance [TA241]. Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML) (part review of NICE technology appraisal guidance 70), and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance. 2012. Available from: https://www.nice.org.uk/guidance/ta241 [accessed 26/10/2016].
110. British Society of Blood and Marrow Transplantation. 2014 Activity: Table 1. 2014 UK & ROI Transplant Table Indications. 2016. Available from: http://bsbmt.org/2014-activity/ [accessed 12/10/2016].
111. Office for National Statistics. Population estimates. 2016. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates [accessed 12/10/2016].

**Single technology appraisal**

**Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma [ID972]**

Dear James,

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The ERG and the technical team at NICE will be addressing these issues in their reports.

Please note that priority question B9 and the accompanying Table 3, refers to problems that the ERG have encountered when using the economic model to validate data in the company submission, specifically:

- All scenario analyses have to be manually run
- When inputs from the company submission are replicated, the results produced do not always match those reported (this may be a simple rounding error)
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Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Anna Brett, Technical Lead (anna.brett@nice.org.uk). Any procedural questions should be addressed to Stephanie Yates, Project Manager (Stephanie.yates@nice.org.uk).

Yours sincerely

Nicola Hay
Technical Adviser – Appraisals
Centre for Health Technology Evaluation

On behalf of
Dr Frances Sutcliffe
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

## Section A: Clarification on effectiveness data

A1. **Priority question** *Company submission page 39, Figure 10*: Patients in cohort C could have prior autologous stem cell transplant (ASCT) and brentuximab vedotin (BTX) in any treatment order, including BTX treatment as an initial therapy. Please clarify if any patients in Cohort C received BTX as their initial therapy and if so how many.

A2. **Priority question** *Company submission page 42*: Progression-free survival (PFS) and overall survival (OS) are defined as time from first dosing with nivolumab to the event(s) of interest. Please clarify the time period between earlier treatment failure (e.g. failure of BTX for those in cohort B) to first dose with nivolumab and how variable this was between patients and studies.

A3. **Priority question** *Company submission page 45, Table 7*: Please supply separate demographic and baseline characteristic data for cohort B and cohort C (either 100 patients, or the 98 who contribute data to the indirect comparisons), including all the baseline characteristics that were used for matching with Cheah data and listed in Table 19 of Appendix 3.

A4. **Priority question** *Company submission pages 47-48, Table 9*: Please clarify the information reported in the following paragraph on page 47:

*'With 24 events (23 progressions and 1 death), IRRC-assessed PFS at six months was 76.9% and median PFS was 9.99 months; this increased to 82.6% for investigator-assessed PFS (16 progression events and 2 deaths), with a median PFS of 10.94 months. Rate of OS at six months was 98.7% (three events), and median OS was not reached'*

a. If the Independent Regulatory Review Committee (IRRC)-assessed and investigator-assessed PFS are both for a 6 month time-point please explain why the number of deaths contributing to PFS events is different

b. Please explain why the 3 overall deaths reported in Table 9 (page 48) are not contributing to the PFS events.

A5. **Priority question** *Company submission page 61, Table 15*: Please supply separate demographic and baseline characteristic data for the relevant 15 patients in CA209-039, including all the baseline characteristics that were used for matching with Cheah data and listed in Table 19 of Appendix 3.

A6. **Priority question** *Appendix 3 pages 43-51 Matching-Adjusted Indirect Comparison (MAIC)*: Please clarify why the complete response (CR) and partial response (PR) relative risks for the proportional improvement in response of nivolumab over the comparators in the Cheah study reported in Table 20 do not match:

a. those provided in Table 24

b. those provided in Figures 19 to 26.

A7. **Priority question** *Appendix 3 page 43, Table 19*: Please clarify why the data for disease stage 4 was not included in the matching of baseline characteristics. If disease stage 4 was included in the matching, what would the size of the weighted nivolumab cohort be reduced to?

A8. *Company submission page 33*: For this (and other) systematic reviews described in the submission, please clarify the process for:

a. screening records and full papers (for example, conducted independently and results compared or conducted by one person and checked by another [if so was every record checked or a percentage]).

b. data extractions (for example, conducted independently or extracted by one person and checked by another).

A9. *Company submission page 34*: Please clarify whether the 'other sources' used to identify 53 additional records were conference abstracts (as reported in Appendix 2 6.4 n=51).

A10. *Company submission page 46, Table* 8: Please clarify what the 'Other' reasons were for 'Not continuing in the treatment period' in cohort B, equating to 10%.

A11. *Company submission pages 45, 54, 61, Tables 7, 12, 15*: Please provide the disease classification method used to stage disease in the nivolumab studies. In addition, please provide disease stage information for patients in the CA209-039 study.

A12. *Company submission page 47*: Please provide the range of dose delays for the 15.5% of patients who had delays that lasted 14 days or more, and the number of patients who were affected.

A13. *Company submission page 47*: Please clarify the types of event that were captured by the 'Other' category which accounts for 45.4% of dose delays.

A14. *Company submission page 56, Table 13*: Please provide a definition of the following outcomes and clarify what is being reported for each:

a. Duration of response: events

b. Duration of CR: events

c. Duration of PR: events.

A15. *Company submission pages 61-62*: Text describing treatment histories of patients in CA209-039 are difficult to reconcile with the groups of patients in Table 16. Please indicate whether our understanding (as shown in the table below) is correct, and if so, explain why one participant in the Post BTX (no ASCT) group has failed BTX prior to ASCT failure (that is, they received ASCT). If not, please clarify using the format of the table below.

**Table 1 Treatment histories of patients in CA209-039**

| **Cohort** | **Number enrolled (n=23)** | **Groups described in text (page 61)** | **Groups described in Table 16 (page 62)** |
|---|---|---|---|
| nivolumab monotherapy | 15 | received prior BTX treatment as a salvage therapy after failure of ASCT (post-ASCT/BTX) | Post BTX/ASCT (n=15) |
| | 8 | had treatment histories categorised as other: | |
| | 2 | failed BTX and ASCT naive | Post BTX (no ASCT) (n=3) |
| | 1 | failed BTX prior to ASCT failure | |
| | 2 | failed ASCT and BTX naive | No BTX (n=5) |
| | 3 | naive to both ASCT and BTX | |

A16. *Appendix 3 page 44 (MAIC)*: Two analyses are described: the first (5.2.2.2) reporting the MAIC of the adjusted nivolumab cohort against all the data from the Cheah study (overall population). The second analysis (5.2.2.3) excludes data for patients who received 'investigational agents' in the Cheah study because it was likely that some of these people received PD-1 inhibitor agents which likely included nivolumab. Logically one might expect that removing the data for those who received investigational agents

(including nivolumab) would decrease the observed CR, PR, median PFS and Median OS in the Cheah study. However CR, PR and PFS increase. Please provide an explanation for these counter-intuitive results.

**Section B: Clarification on cost-effectiveness data**

B1. **Priority question** *Company submission page 105, Table 37 (Cheah study)*: The number of patients in the Cheah study is totalled as 79. However, this includes 28 patients who received investigational agents. As these have been excluded in the base case analysis, the actual sample from the Cheah study is 51 patients. Please confirm whether 51 patients is correct.

B2. **Priority question** *Company submission page 100, Figure 23*: The diagram does not adequately represent the complexity of the model, because it does not include treatment switching and special transitions such as allogeneic stem cell transplant (alloSCT). Please provide a full diagram of the model with all possible and optional transitions (alloSCT, pre-progression chemotherapy, etc…) illustrated for all arms.

B3. **Priority question** *Company submission pages 108-9, Figures 25, 26*: Please clarify whether these figures represent the whole trial data for cohorts B and C from the CheckMate 205 trial and the post-ASCT/BTX patients from CA209-039 (n=80 + n=98 + n=15), or an adjusted subgroup.

B4. **Priority question** *Company submission page109, Figure 29:* Please clarify whether the patients who have received alloSCT are included in the data presented in Figure 26. Please confirm the numbers who received alloSCT which the ERG believe to be 11/80 from CheckMate 025 cohort B, 18/98 from CheckMate 025 cohort C and 5/15 from post-ASCT/BTX CA209-039.

B5. **Priority question** *Company submission pages 111, 113, Figures 29, 30*: Please provide full diagnostics for alternative parametric fittings of PFS and OS for standard of care (SoC). Please use the table below, and provide alternatives for Figures 29 and 30 that are formatted in the same way as Figures 25 and 26. The parameters used for the displayed curves should be incorporated in the figures as in Figures 25 and 26 (pages 108-109), or should be in a separate table.

**Table 2 Diagnostics for alternative parametric fittings**

| | PFS | | | OS | | |
|---|---|---|---|---|---|---|
| | **AIC** | **BIC** | **Median (months)** | **AIC** | **BIC** | **Median (months)** |
| Exponential | | | | | | |
| Weibull | | | | | | |
| Log-logistic | | | | | | |
| Lognormal | | | | | | |
| AIC: Akaike Information Criteria; BIC: Bayesian Information Criteria; OS: overall survival; PFS: progression-free survival. | | | | | | |

B6. **Priority question** *Company submission page 128, Table 55*: Please provide details of the proportion of patients on each of the treatments for SoC. Please provide the calculations used to obtain the comparator costs in Table 56 in an Excel spreadsheet.

B7. **Priority question** *Company submission pages 154-6*: It is unclear how alloSCT or other treatments that require changes to subsequent therapies are incorporated in the model. For example, the subsequent chemotherapy analysis (page 156), states that patients discontinuing or progressing will switch to the comparator therapy. Setting 5$^{th}$ line to Comparator instead of BSC for the reference treatment in the model produces an ICER of £45,947/QALY instead of the reported £22,095/QALY ICER. Please provide a full explanation of how these treatment switches work in the model and provide instructions or model modifications that allow running of analyses using the model mechanics as explained, preferably with simple switches or buttons.

B8. **Priority question** *Company submission, section 5.8.*3: Please provide a spreadsheet that contains the exact (unrounded) model parameters for each of the 58 scenario analyses conducted. Only the parameters that are different from the base case need reporting in this manner.

B9. **Priority question:** In total, 58 scenario analyses were conducted in Section 5.8.3 of the company submission. However, the ERG was only able to fully conduct and validate 19 analyses: the 15 analyses utilising alternative survival curves for PFS and OS for nivolumab, the analysis examining SOC overall survival, the analysis without half-cycle correction, the analysis using alternative utility for SOC (utility scenario 1), and the analysis with adverse events excluded from both treatment arms. Some model scenarios, such as the alloSCT scenarios and pre-progression chemotherapy scenario, were unable to be verified because the explanation of methods was unclear. One scenario did not have input data available (Kaplan Meier survival). Several other analyses did not produce the results reported in the company submission.

The following Table 3 provides a list of analyses that we were unable to confirm, with reasons and the action needed from the company. Please note that some analyses have been designated as priority analyses.

**Table 3 Scenario analyses that could not be confirmed using the model**

| Priority | # | Company Submission Table/Page | Analysis | Action |
|---|---|---|---|---|
| **Alternative Treatment Sequences (alloSCT)** | | | | |
| **Priority** | 20-23 | Table 75 (page 156) | Scenario 1: likelihood of alloSCT from Perrot 2016 and costs from NHS reference costs<br><br>Scenario 2: likelihood of alloSCT from Perrot 2016 and costs derived from Radford 2016<br><br>Scenario 3: likelihood of alloSCT from Perrot 2016, but nivolumab patients with CR and PR assumed equivalent; costs from NHS reference costs<br><br>Scenario 4: likelihood of alloSCT from Perrot 2016, but nivolumab patients with CR and PR assumed equivalent; costs derived from Radford 2016 | Provide full textual explanation of the mechanics of these analyses within the model. Build the capability to conduct these analyses in the model with the push of a button, and the ability to combine these analyses with other analyses. |
| **Alternative Treatment Sequences (subsequent chemotherapy)** | | | | |
| **Priority** | 24 | Table 77 (page 157) | Patients receive chemotherapy pre-progression after discontinuing treatment (nivolumab or SoC) | Provide full textual explanation of the mechanics of this analysis within the model. Build the capability to conduct this analysis in the model with the push of a button, and the ability to combine this analysis with other analyses. |
| **Alternative Comparator Composition** | | | | |
| | 27 | Table 84 (page 160) | SoC composition and AE equivalent to ongoing BTX TA | The text and tables for this analysis (CS pp. 158-9) do not provide the alternative |

| Priority | # | Company Submission Table/Page | Analysis | Action |
|---|---|---|---|---|
| | | | | costs and AE profile for the alternative SoC composition, which makes validating the analysis not possible. |
| **Alternative ITC comparisons** | | | | |
| **Priority** | 28-45 | Table 85 (page 162) | All analyses in Table 85, including Alternative ITC comparisons Post-ASCT, Post-BTX studies and Alternative ITC comparisons Post-ASCT studies | When these simulations are run with the parameters defined in Table 85, there are consistent cost and QALY discrepancies. Costs for SoC are generally £3,100 to £3,500 more and QALYs 0.002 to 0.011 less when we run the simulations. Can you explain these discrepancies? |
| **Alternative baseline age** | | | | |
| | 46 | Table 86 (page 164) | Age 20, alloSCT likelihood of alloSCT from Perrot 2016 and costs from NHS reference costs | As with analyses 20-23, the mechanics to implement this analysis are not clearly defined. Additionally, it does not appear that survival was changed to reflect the patient age, please confirm this. |
| | 47 | Table 86 (page 164) | Age 70, BSC assumed to be the most appropriate comparator, (OS derived from the lowest reported by Cheah 2016 for chemotherapies (exponential parametric fit; λ: 0.07296); PFS was assumed to be equivalent to the PFS applied in the base case for SoC, due to the evidence supporting comparable PFS for non-investigational agent) | It does not appear that survival was changed to reflect patient age, please confirm this. Additionally, please provide full details of the settings necessary to replicate this analysis. Changing survival, and changing comparator costs to BSC did not replicate the analysis results reported. |

| Priority | # | Company Submission Table/Page | Analysis | Action |
|---|---|---|---|---|
| **Alternative assumptions around utilities** | | | | |
| **Priority** | 53 | Table 88 (page 166) | Nivolumab post-progression utility set equal to comparator post-progression utility | Analyses do not produce results consistent with those reported. Please explain to which specific treatment lines (nivolumab, SoC, BSC (treatment), BSC (control)) the utility values were applied to. |
| **Priority** | 54 | Table 88 (page 166) | Swinburn 2015 used to derive utility for pre- and post-progression in both arms | |
| **Priority** | 55 | Table 88 (page 166) | Response-specific pre-progression utilities applied | |
| **Alternative Post-progression Costs** | | | | |
| | 57 | Table 90 (page 167) | Resource use doubles post progression | Unclear how increase in state costs is applied only to post-progression, as health state costs are not defined by progression status. Treatment costs, are defined by progression status. |
| **Application of IRRC-assessed endpoints for nivolumab** | | | | |
| | 58 | Table 91 (page 167) | PFS<br>μ: 2.656<br>σ: 1.121<br><br>Response rates<br>CR: 11.4%<br>PR: 58.0%<br><br>Utilities<br>Pre-progression: 0.834<br>Post-progression: 0.746 | When running the model using the specified parameters, our results were not consistent with those reported in the CS. Total costs for nivolumab matched, but total QALYs were 3.705, which is significantly lower than the 3.811 QALY result reported in the CS. Please explain this discrepancy. |

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B10. **Priority question:** Changing the utility score in the economic model does not always replicate the reported results of the analysis with a changed utility score. For the utility specific analyses, only Scenario 1 (Company submission page 166, Table 88) produced results consistent with those reported. Please explain these discrepancies.

B11. *Company submission page 121, Table 48*: Please provide the total number of observations for each of the utility classification categories (CR pre-progression, PR pre-progression, stable disease (SD) pre-progression, progressed disease). Please also provide the 95% confidence interval range for these data.

B12. *Company submission page 123, Table 49*: Please clarify the duration used for the adverse event disutility in the economic model and whether the adverse event rate is assumed to be the same for patients with CR, PR and SD.

B13. *Company submission page 134, Table 56*: Please provide the HRG codes for the resources.

B14. *Company submission page 135, Table 60*: The adverse event costs do not appear to match the references given. For example, there are no values reported in NICE Technology appraisal guidance (TA) 306 for nausea and leukopenia. Please clarify where these values are obtained from. Please also clarify whether the values used for adverse event costs were from the company's analysis in TA 306 or from the ERG's sensitivity analysis.

B15. *Company submission page 140, Table 64*: Please provide an explanation of how age based disutilities have been calculated and a rationale for their use.

B16. *Company submission page 151, Table 68*: The lower λ value for SoC OS (0.036) appears to be an error as inputting this value into the model produces an ICER of £19,921/QALY, not £22,742/QALY. Please provide the correct lower λ value for this scenario analysis.

**Section C: Textual clarifications and additional points**

C1. *Company submission pages 46 and 53*: Please clarify whether the difference in numbers for Cohort C (page 46 n=97; page 53 n=100) is due to continued enrolment into Cohort C between the data cut-off points (August 2015 and April 2016) or is an error.

C2. *Company submission page 62, Table 16*: Please clarify whether the footnote 'responses were ongoing in 11 patients' applies to the total population (n=23) or the subgroup (n=15).

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C3. *Appendix 3 pages 57-59, Figures 27-30*: It is not possible to match references to the studies listed in Figures 27-30. Please provide these references.

**Single technology appraisal**

**Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma [ID972]**

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Yours sincerely

Nicola Hay
Technical Adviser – Appraisals
Centre for Health Technology Evaluation

On behalf of
Dr Frances Sutcliffe
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Encl. checklist for confidential information

## Section A: Clarification on effectiveness data

**A1. Priority question Company submission page 39, Figure 10: Patients in cohort C could have prior autologous stem cell transplant (ASCT) and brentuximab vedotin (BTX) in any treatment order, including BTX treatment as an initial therapy. Please clarify if any patients in Cohort C received BTX as their initial therapy and if so how many.**

Of the [redacted] Cohort C patients included within indirect comparisons, three patients received BTX as initial treatment, and these patients comprised 1.6% of the pooled nivolumab cohort used to inform the submission.

It should be noted that patients in the UK typically receive the ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) regimen as a first line therapy,[1] and this is reflected in the CheckMate 205 and CA209-039 patient population, where over 80% of patients received this therapy.[2,3] However, patients in clinical practice are subject to substantial heterogeneity in terms of baseline characteristics (e.g. age, performance score and treatment history) and it is useful to provide evidence to demonstrate the effectiveness of nivolumab across these patient groups.

**A2. Priority question Company submission page 42: Progression-free survival (PFS) and overall survival (OS) are defined as time from first dosing with nivolumab to the event(s) of interest. Please clarify the time period between earlier treatment failure (e.g. failure of BTX for those in cohort B) to first dose with nivolumab and how variable this was between patients and studies.**

Table 1 provides an overview of the time between prior treatment failure and nivolumab treatment. For cohort B, [redacted] end dates for most recent prior regimen were available without imputation; [redacted] end dates were available without imputation for Cohort C.

**Table 1. CheckMate 205: time from completion of most recent prior regimen to nivolumab treatment**

| | Cohort B | Cohort B: time from BTX failure | Cohort C | Cohort C: time from BTX failure |
|---|---|---|---|---|
| N | [redacted] | [redacted] | [redacted] | [redacted] |
| Median (months) | [redacted] | [redacted] | [redacted] | [redacted] |
| Range | [redacted] | [redacted] | [redacted] | [redacted] |
| < 3 months | [redacted] | [redacted] | [redacted] | [redacted] |
| 3-6 months | [redacted] | [redacted] | [redacted] | [redacted] |
| >=6 months | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | | | | |

It should be noted that the majority (98.8%) of patients in Cohort B received systemic therapy regimens after BTX and prior to initiating nivolumab. Most patients received either one (45.0%) to two (27.5%) subsequent systemic therapy regimens; however, 6 patients (7.5%) received at

least five subsequent systemic therapy regimens before initiating nivolumab.[2] [redacted] This demonstrates that outcomes are favourable in nivolumab treated patients, despite substantial pre-treatment, in a group of patients that likely have no further treatment options.

**A3. Priority question *Company submission page 45, Table 7*: Please supply separate demographic and baseline characteristic data for cohort B and cohort C (either 100 patients, or the 98 who contribute data to the indirect comparisons), including all the baseline characteristics that were used for matching with Cheah data and listed in Table 19 of Appendix 3.**

Demographic and baseline characteristics for Cohort B and C are provided within the submission as Table 12, and are reproduced below as Table 2 for ease of use. Further, the baseline characteristics used for matching with Cheah 2016 data are provided below in Table 3.

**Table 2. CheckMate 205: Patient demographics and baseline characteristics**

| | Cohort B | Cohort C | Total[1] | Pooled[2] |
|---|---|---|---|---|
| N | 80 | [redacted] | [redacted] | [redacted] |
| Age (years) | | | | |
| Mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] |
| Median (Min, Max) | 37.0 (18-72) | [redacted] | [redacted] | [redacted] |
| < 30 | 27 (33.8%) | [redacted] | [redacted] | [redacted] |
| ≥30 and <65 | [redacted] | [redacted] | [redacted] | [redacted] |
| >= 65 | [redacted] | [redacted] | [redacted] | [redacted] |
| Gender, male (%) | 51 ( 63.8) | [redacted] | [redacted] | [redacted] |
| Race (%) | | | | |
| White | [redacted] | [redacted] | [redacted] | [redacted] |
| Black Or African American | [redacted] | [redacted] | [redacted] | [redacted] |
| Asian | [redacted] | [redacted] | [redacted] | [redacted] |
| American Indian Or Alaska Native | [redacted] | [redacted] | [redacted] | [redacted] |
| Native Hawaiian Or Other Pacific Islander | [redacted] | [redacted] | [redacted] | [redacted] |
| Other | [redacted] | [redacted] | [redacted] | [redacted] |
| Ethnicity (%) | | | | |
| Hispanic Or Latino | [redacted] | [redacted] | [redacted] | [redacted] |
| Not Hispanic Or Latino | [redacted] | [redacted] | [redacted] | [redacted] |
| Not Reported | [redacted] | [redacted] | [redacted] | [redacted] |
| Performance Status (ECOG) [%] | | | | |
| 0 | 42 ( 52.5) | [redacted] | [redacted] | [redacted] |
| 1 | 38 ( 47.5) | [redacted] | [redacted] | [redacted] |
| Disease Stage At Study Entry | | | | |
| Stage I | 1 ( 1.3) | [redacted] | [redacted] | [redacted] |

| | Cohort B | Cohort C | Total[1] | Pooled[2] |
|---|---|---|---|---|
| Stage II | 11 ( 13.8) | [redacted] | [redacted] | [redacted] |
| Stage III | 14 ( 17.5) | [redacted] | [redacted] | [redacted] |
| Stage IV | 54 ( 67.5) | [redacted] | [redacted] | [redacted] |
| Not Reported | 0 | [redacted] | [redacted] | [redacted] |
| Bulky Disease At Baseline | [redacted] | [redacted] | [redacted] | [redacted] |
| Extra Lymphatic Involvement At Baseline | [redacted] | [redacted] | [redacted] | [redacted] |
| Bone Marrow Involvement At Baseline | [redacted] | [redacted] | [redacted] | [redacted] |
| Median Time: Initial Diagnosis To First Dose Of Study Therapy (Years) [Min – Max] | [redacted] | [redacted] | [redacted] | [redacted] |
| Median Time: Most Recent Transplant To First Dose Of Study Therapy (Years) Min–Max | [redacted] | [redacted] | [redacted] | [redacted] |
| Number Of Prior Systemic Regimen Received | | | | |
| ≤2 | [redacted] | [redacted] | [redacted] | [redacted] |
| 3 | [redacted] | [redacted] | [redacted] | [redacted] |
| 4 | [redacted] | [redacted] | [redacted] | [redacted] |
| ≥ 5 | [redacted] | [redacted] | [redacted] | [redacted] |
| Median (Min, Max) | 4 [redacted] | [redacted] | [redacted] | [redacted] |
| Number Of Prior ASCT | | | | |
| 1 | 74 (92.5) | [redacted] | [redacted] | [redacted] |
| ≥ 2 | 6 (7.5) | [redacted] | [redacted] | [redacted] |
| Best Response To Most Recent ASCT | | | | |
| CR Or PR | [redacted] | [redacted] | [redacted] | [redacted] |
| SD | [redacted] | [redacted] | [redacted] | [redacted] |
| Relapse/PD | [redacted] | [redacted] | [redacted] | [redacted] |
| Unable To Determine/Not Reported | [redacted] | [redacted] | [redacted] | [redacted] |
| Best Response To Regimen Post Most Recent ASCT | | | | |
| CR Or PR | [redacted] | [redacted] | [redacted] | [redacted] |
| SD | [redacted] | [redacted] | [redacted] | [redacted] |
| Relapse/PD | [redacted] | [redacted] | [redacted] | [redacted] |
| Unable To Determine/Not Reported | [redacted] | [redacted] | [redacted] | [redacted] |
| Prior Radiotherapy | 59 (73.8) | [redacted] | [redacted] | [redacted] |
| Prior Brentuximab Therapy | 80 (100.0) | [redacted] | [redacted] | [redacted] |

1 Includes Cohort A, Cohort B and Cohort C from CheckMate 205
2 Includes pooled post-ASCT, post-BTX population (Cohort B, Cohort C [excluding two patients] and CA209-039 [post-ASCT, post-BTX population)

**Table 3. Baseline characteristics used for matching with Cheah 2016**

| | Pooled (B+C98+039) | | 039 | | Overall** | | B | | C | | C98 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % |
| N | | | | | | | 80 | | | | | |
| Female | | | | | | | | | | | | |
| Median age | | | | | | | | | | | | |
| Age >45 years | | | | | | | | | | | | |
| Disease stage* | | | | | | | | | | | | |
| 1 | | | | | | | | | | | | |
| 2 | | | | | | | | | | | | |
| 3 | | | | | | | | | | | | |
| 4 | | | | | | | | | | | | |
| B symptoms* | | | | | | | | | | | | |
| Haemoglobin <$10^5$ g/l* | | | | | | | | | | | | |
| Lymphocytes <0.6 x $10^9$/L* | | | | | | | | | | | | |
| White cell count > 15 x $10^9$/L* | | | | | | | | | | | | |
| Albumin <40g/L* | | | | | | | | | | | | |
| Any extranodal site* | | | | | | | | | | | | |
| ECOG <1 | | | | | | | | | | | | |
| Max tumour diameter ≥4cm* | | | | | | | | | | | | |
| Median prior lines | | | | | | | | | | | | |

* data unavailable for 039 – imputed from 205 data for combined
** Includes data from CheckMate 205 Cohort A, Cohort B and Cohort C.

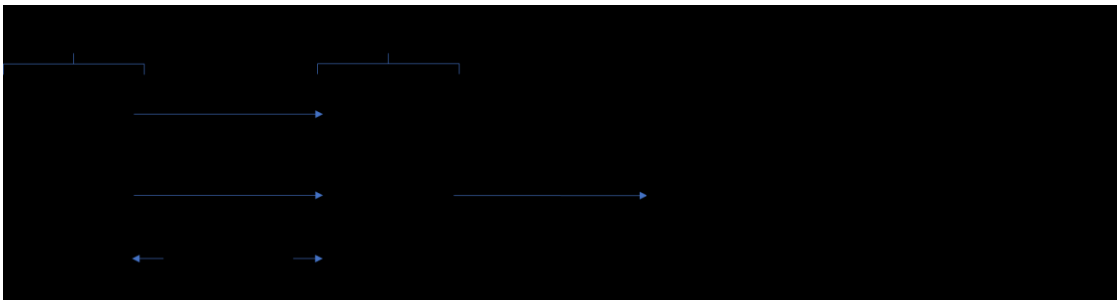
**A4. Priority question *Company submission pages 47-48, Table 9*: Please clarify the information reported in the following paragraph on page 47:**

***'With 24 events (23 progressions and 1 death), IRRC-assessed PFS at six months was 76.9% and median PFS was 9.99 months; this increased to 82.6% for investigator-assessed PFS (16 progression events and 2 deaths), with a median PFS of 10.94 months. Rate of OS at six months was 98.7% (three events), and median OS was not reached'***

a. **If the Independent Regulatory Review Committee (IRRC)-assessed and investigator-assessed PFS are both for a 6 month time-point please explain why the number of deaths contributing to PFS events is different**
b. **Please explain why the 3 overall deaths reported in Table 9 (page 48) are not contributing to the PFS events.**

As is common for oncology studies,[4] PFS was defined as the time from the first dosing date to the date of the first documented tumour progression or death due to any cause, whichever occurred first. As such, if a patient progresses prior to death, the progression event will be classed as a PFS event while the death event will not, as the progression occurred first. Conversely, where a patient dies (but has not progressed), the death event will be classed as a PFS event. A simplified definition of PFS is provided in Figure 1.

**Figure 1. Simplified illustration of progression-free survival definition**



Thus, as noted in Question A4B, there were three death events that had occurred prior to the data lock:

- One death occurred in a patient who had previously progressed (as assessed by both IRRC and investigator) and so was not included as a progression event in either analysis.
- One death occurred in a patient who had previously progressed as assessed by the IRRC but not the investigator; thus the event was classed as a progression event in the investigator-assessed PFS analysis but not the IRRC-assessed analysis.
- One death occurred in a patient who had not previously progressed and so was included as a progression event in both the investigator-assessed and IRRC-assessed analyses.

In summary, the clarifications requested in this question are:

a. As described above, only one death event was eligible as a progression event within the IRRC-assessed PFS analysis as the other two death events occurred following progression. By contrast, two death events were eligible as progression events within the IRRC-assessed PFS analysis as only one of the death events occurred in a patient considered by the investigator to have already progressed.
b. As described above, a death event eligible for inclusion within the PFS analysis was required to have happened prior to progression. This was not the case for all three deaths, leading to this discrepancy.

**A5. Priority question *Company submission page 61, Table 15*: Please supply separate demographic and baseline characteristic data for the relevant 15 patients in CA209-039, including all the baseline characteristics that were used for matching with Cheah data and listed in Table 19 of Appendix 3.**

The demographic and baseline characteristics from the post-ASCT, post-BTX subgroup of CA209-039 are reproduced in Table 4. As can be seen, the patient population is not significantly different from the overall population, with the exception of the prior treatment history, as can be expected.

**Table 4. CA209-039: Patient demographics and baseline characteristics[5]**

| Characteristic | Post-ASCT, post-BTX | Pooled population* |
|---|---|---|
| N | 15 | 193 |
| Median age (years) | 40 | 35 |
| Range | 24-54 | 18-72 |
| Gender, male (%) | 10 (67) | 115 (59.6%) |
| Race (%) | | |
| White | 12 (80) | 168 (87.0) |
| Black | 2 (13) | 12 (6.2) |
| Other | 1 (7) | 7 (3.6) |
| Performance Status (ECOG) [%] | | |
| 0 | 7 (47) | 98 (50.8) |
| 1 | 8 (53) | 95 (49.2) |
| Histologic findings (%) | | |
| Nodular sclerosis | 15 (100) | NA |
| Mixed cellularity | 0 | NA |
| Number Of Prior Systemic Regimen Received | | |
| 2 or 3 | 3 (20) | 57 (29.5) |
| 4 or 5 | 6 (40) | 79 (40.9) |
| ≥ 6 | 6 (40) | 57 (29.5) |
| Previous treatments (%) | | |
| Brentuximab | 15 (100) | 193 (100) |
| ASCT | 15 (100) | 193 (100) |
| Radiotherapy | 13 (87) | 140 (72.5) |
| Extranodal involvement | 2 (13) | 80 (41.5) |

ASCT: autologous stem cell transplant; ECOG: Eastern Cooperative Oncology Group; NA: not available.
* Includes patients from CheckMate 205 Cohorts B and C (excluding two patients) and the post-ASCT, Post-BTX CA209-039 population.

**A6. Priority question *Appendix 3 pages 43-51 Matching-Adjusted Indirect Comparison (MAIC)*: Please clarify why the complete response (CR) and partial response (PR) relative risks for the proportional improvement in response of nivolumab over the comparators in the Cheah study reported in Table 20 do not match:**

**a. those provided in Table 24**

b. **those provided in Figures 19 to 26.**

Table 20 of Appendix 3 incorrectly provides unadjusted data. The correct, adjusted data is presented within Appendix 3 as Table 4, Table 24 and Figures 19-26. Further, the correct, adjusted data is presented within the submission as Table 25, Table 28 and Table 85. For clarity, a corrected version of Table 20 from Appendix 3 is provided as Table 5, below.

**Table 5. Adjusted relative risk of response for nivolumab versus alternative treatment options (Cheah 2016)[6]**

| | Nivolumab cohort | Cheah (2016)* | Relative risk |
|---|---|---|---|
| **CR** | 28.0% | 15.0% ( 8.5 - 26.6) | 1.86 (1.05 - 3.30) |
| **PR** | 43.5% | 19.6% (12.0 - 31.8) | 2.23 (1.37 - 3.62) |
| CR: complete response; PR: partial response<br>* Includes investigational agents | | | |

**A7. Priority question *Appendix 3 page 43, Table 19*: Please clarify why the data for disease stage 4 was not included in the matching of baseline characteristics. If disease stage 4 was included in the matching, what would the size of the weighted nivolumab cohort be reduced to?**

Disease stage 4 was implicitly included within the matching of baseline characteristics, due to the requirement within the methodology that all states be mutually exclusive and complete. As such, disease stage 4 would naturally be matched by the remainder from the weighting of those patients in stages 1-3. An updated Table 19 is provided below as Table 6, in order to provide this information. As in Appendix 3, the weighted cohort had an effective size of 81, versus an original cohort of 193.

There were 15 patients within the nivolumab cohort for whom disease stage was not reported. As stated within Appendix 3, in the case of a missing value for the nivolumab cohort, the mean cohort value was used. In line with this approach, these patients were weighted according to the assumption that their disease stage would be equivalent to the overall population.

**Table 6: Matching of baseline characteristics between nivolumab and Cheah (2016) data[6]**

| Baseline characteristics | Nivolumab cohort | | Cheah 2016 |
|---|---|---|---|
| | Before matching | After matching | |
| Female | [redacted] | [redacted] | 47% |
| Median age (years) | [redacted] | [redacted] | 32 |
| Age > 45 | [redacted] | [redacted] | 14% |
| Disease stage 1* | [redacted] | [redacted] | 3% |
| Disease stage 2* | [redacted] | [redacted] | 30% |
| Disease stage 3* | [redacted] | [redacted] | 21% |
| Disease stage 4 | [redacted] | [redacted] | 46% |
| B-symptoms | [redacted] | [redacted] | 8% |
| Haemoglobin < $10^5$ g/l | [redacted] | [redacted] | 35% |
| Lymphocytes < 0.6 x$10^9$/l | [redacted] | [redacted] | 41% |
| White cell count > 15 x$10^9$/l | [redacted] | [redacted] | 5% |
| Albumin < 40g/l | [redacted] | [redacted] | 28% |
| Any extranodal site | [redacted] | [redacted] | 35% |
| ECOG ≥ 1 | [redacted] | [redacted] | 59% |
| Max tumour diameter ≥ 4cm | [redacted] | [redacted] | 26% |
| Median prior lines | [redacted] | [redacted] | 6 |

* Disease classification methods not specified in Cheah (2016). Assumed equivalent to methods applied in nivolumab studies, or equivalent prognosis between staging methods.

**A8. *Company submission page 33*: For this (and other) systematic reviews described in the submission, please clarify the process for:**

**a. screening records and full papers (for example, conducted independently and results compared or conducted by one person and checked by another [if so was every record checked or a percentage]).**

b. **data extractions (for example, conducted independently or extracted by one person and checked by another).**

a. First and second passes were conducted by one reviewer with all results checked by a second reviewer. Where results differed, a third reviewer was used to provide resolution.

b. Similarly, data extractions were undertaken by one reviewer and checked by a second reviewer. Where discrepancies were identified, these were discussed to provide resolution, with a third reviewer included if required.

**A9. *Company submission page 34*: Please clarify whether the 'other sources' used to identify 53 additional records were conference abstracts (as reported in Appendix 2 6.4 n=51).**

Search terms provided in the table detailed in Section 6.4 of Appendix 2 refer to those identified through searching of clinicaltrials.gov, and resulted in 51 results. Manual searching of the ASCO,

ASH, ESMO and EHA conference proceedings resulted in very few additional studies (n = 2). This reflects the general paucity of data in this setting, as well as the fact that conference abstracts presented at these conferences are frequently indexed on PubMed and Embase, and so were already captured in the SLR ahead of manual searching of these conference proceedings.

### A10. *Company submission page 46, Table* 8: Please clarify what the 'Other' reasons were for 'Not continuing in the treatment period' in cohort B, equating to 10%.

A complete listing of reasons for not continuing in the treatment period is provided in Table 7. As can be seen, in Cohort B, the most common 'Other' reason for not continuing in the treatment period was alloSCT (6 patients; 7.5%).

Following failure of ASCT, current guidelines recommend that the aim of treatment in cHL patients is to attain sufficient response to allow consideration of alloSCT in those deemed eligible.[7] Given the high levels of response achieved following nivolumab therapy (as described in Sections 4.7 and 4.10), there is significant potential for nivolumab to act as a bridge to curative transplant in some patients. Thus, high rates of patient discontinuation to pursue alloSCT can be expected within the nivolumab studies, and indeed this can be seen as evidence of a further beneficial impact of nivolumab. As of June 2016, 40 patients with cHL have received post-nivolumab alloSCT (five patients from CA209-039; within CheckMate 205, six from Cohort A, 11 from Cohort B and 18 from Cohort C), and there have been no deaths due to disease progression.[8] Further outcomes following alloSCT are provided in Section 4.13.4.1 of the submission; it should be noted that patients receiving alloSCT were considered to be receiving a subsequent anticancer therapy, and were censored from assessments of the efficacy of nivolumab, including response and PFS, in order to ensure that efficacy outcomes were not overestimated.[9]

**Table 7. CheckMate 205: Reasons for not continuing in the treatment period**

| | Cohort B | Total |
|---|---|---|
| Total number of patients entering treatment period | 80 | 240 |
| Disease progression | 13 (16.3) | 20 (8.3) |
| Study drug toxicity | 4 (5.0) | 10 (4.2) |
| Patient request to discontinue study treatment | 2 (2.5) | 3 (1.3) |
| Lost to follow-up | 1 (1.3) | 1 (0.4) |
| Other | 8 (10.0) | 10 (4.2) |
| Other – Allogeneic Transplant | 6 (7.5) | 7 (2.9) |
| Other – Unspecified Transplant | 1 (1.3) | 1 (0.4) |
| Oher – Lack of response | 1 (1.3) | 1 (0.4) |
| Other – Primary Investigator discretion | 0 | 1 (0.4) |
| Not reported | 1 (1.3) | 1 (0.4) |

**A11.** ***Company submission pages 45, 54, 61, Tables 7, 12, 15*: Please provide the disease classification method used to stage disease in the nivolumab studies. In addition, please provide disease stage information for patients in the CA209-039 study.**

CheckMate 205 and CA209-039 utilised the Ann Arbor staging system with Cotswolds modifications.[10] Disease stage information for patients in the CA209-039 study are not available.

**A12.** ***Company submission page 47*: Please provide the range of dose delays for the 15.5% of patients who had delays that lasted 14 days or more, and the number of patients who were affected.**

The range of delay for the twelve (15.5%) patients that had a delay of more than 14 days was 15–106 days (mean: 31.2 days; median: 28 days). Only three patients were delayed more than once by more than 14 days. Each of these three patients achieved a response using investigator-assessed outcomes (1 patient achieved each of CR, PR and SD), with no progressions or deaths. Applying IRRC-assessed outcomes, one patient achieved SD, one achieved PR and the third progressed on day 11, but was followed-up and had not progressed by day 220 according to investigator-assessment.

**A13.** ***Company submission page 47*: Please clarify the types of event that were captured by the 'Other' category which accounts for 45.4% of dose delays.**

**Table 8. Reasons captured for 'other' category of dose delay**

| 'Other' reason for dose delay | Number of events (n) |
|---|---|
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |

**A14.** ***Company submission page 56, Table 13*: Please provide a definition of the following outcomes and clarify what is being reported for each:**

**a. Duration of response: events**

**b. Duration of CR: events**

c. **Duration of PR: events.**

a. This is the number of events informing the duration of response endpoint. Duration of response was defined as the time from first response (CR or PR, as defined in Figure 2) to the date of the first documented tumour progression using the 2007 IWG criteria or death due to any cause, whichever occurred first. For patients who neither progressed nor died, the duration of response were censored on the date of their last evaluable tumour assessment. Patients who started subsequent therapy without a prior reported progression were censored at the last evaluable tumour assessment prior to initiation of the subsequent anticancer therapy. This endpoint was only to be evaluated in patients who achieved CR or PR. For clarity, Table 13 of the submission provides data describing the investigator-assessed outcomes as well as the IRRC-assessed outcomes.

b. This is the number of events informing the duration of CR endpoint. The duration of CR was only evaluated in patients who achieved CR (as defined in Figure 2) and was defined as the time from first documentation of CR (the date of first negative FDG-PET scan or the date of first documentation of no disease involvement in the bone marrow [if required], whichever occurred later) to the date of initial objectively documented progression as determined using the 2007 IWG criteria or death due to any cause, whichever occurred first. Censoring was applied as per duration of response definition. For clarity, Table 13 of the submission provides data describing the investigator-assessed outcomes as well as the IRRC-assessed outcomes.

c. This is the number of events informing the duration of PR endpoint. The duration of PR was only evaluated in patients who achieved PR (as defined in Figure 2) and was defined as the time from first documentation of PR to the date of initial objectively documented progression as determined using the 2007 IWG criteria or death due to any cause, whichever occurred first. Censoring was applied as per the duration of response definition. For clarity, Table 13 of the submission provides data describing the investigator-assessed outcomes as well as the IRRC-assessed outcomes.

**Figure 2. IWG criteria for response**[11]

**Table 2.** Response Definitions for Clinical Trials

| Response | Definition | Nodal Masses | Spleen, Liver | Bone Marrow |
|---|---|---|---|---|
| CR | Disappearance of all evidence of disease | (a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative<br>(b) Variably FDG-avid or PET negative; regression to normal size on CT | Not palpable, nodules disappeared | Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative |
| PR | Regression of measuable disease and no new sites | ≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes<br>(a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site<br>(b) Variably FDG-avid or PET negative; regression on CT | ≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen | Irrelevant if positive prior to therapy; cell type should be specified |
| SD | Failure to attain CR/PR or PD | (a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET<br>(b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT | | |
| Relapsed disease or PD | Any new lesion or increase by ≥ 50% of previously involved sites from nadir | Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis<br>Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy | > 50% increase from nadir in the SPD of any previous lesions | New or recurrent involvement |

Abbreviations: CR, complete remission; FDG, [$^{18}$F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

**A15. *Company submission pages 61-62*: Text describing treatment histories of patients in CA209-039 are difficult to reconcile with the groups of patients in Table 16. Please indicate whether our understanding (as shown in the table below) is correct, and if so, explain why one participant in the Post BTX (no ASCT) group has failed BTX prior to ASCT failure (that is, they received ASCT). If not, please clarify using the format of the table below.**

**Table 1 Treatment histories of patients in CA209-039**

| Cohort | Number enrolled (n=23) | Groups described in text (page 61) | Groups described in Table 16 (page 62) |
|---|---|---|---|
| nivolumab monotherapy | 15 | received prior BTX treatment as a salvage therapy after failure of ASCT (post-ASCT/BTX) | Post BTX/ASCT (n=15) |
| | 8 | had treatment histories categorised as other: | |
| | 2 | failed BTX and ASCT naive | Post BTX (no ASCT) (n=3) |
| | 1 | failed BTX prior to ASCT failure | |
| | 2 | failed ASCT and BTX naive | No BTX (n=5) |
| | 3 | naive to both ASCT and BTX | |

The information produced by the ERG is correct. An updated table describing outcomes at [redacted] for the groups identified by the ERG is provided below.

**Table 9. Clinical outcomes from CA209-039**

| Variable | All Patients (N = 23) | Failure of ASCT followed by Brentuximab (N = 15) | Post BTX (no ASCT) (n=3) | | No BTX (n=5) | |
|---|---|---|---|---|---|---|
| | | | Failure of Brentuximab, no ASCT (N = 2) | Failure of Brentuximab followed by ASCT (N = 1) | Neither Brentuximab nor ASCT (N = 3) | Failure of ASCT, no Brentiximab (N = 2) |
| **Best overall response – n (%)** | | | | | | |
| Complete response | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Partial response | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Stable disease | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Progressive disease | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Objective response** | | | | | | |
| No. of patients | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Percent of patients (95% CI) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Progression-free survival at 24 weeks - % (95% CI)** | | | | | | |
| | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Overall survival - weeks** | | | | | | |
| Median | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Range at data cutoff | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**A16.** ***Appendix 3 page 44 (MAIC)*: Two analyses are described: the first (5.2.2.2) reporting the MAIC of the adjusted nivolumab cohort against all the data from the Cheah study (overall population). The second analysis (5.2.2.3) excludes data for patients who received 'investigational agents' in the Cheah study because it was likely that some of these people received PD-1 inhibitor agents which likely included nivolumab. Logically one might expect that removing the data for those who received investigational agents (including nivolumab) would decrease the observed CR, PR, median PFS and Median OS in the Cheah study. However CR, PR and PFS increase. Please provide an explanation for these counter-intuitive results.**

Since baseline characteristics for subgroups of the Cheah data are unavailable, all relative effects received the same adjustment, regardless of subgroup; thus, effectively, unadjusted data can be considered to address this query:

- When removing the impact of investigational agents, CR increased slightly. The whole cohort had a CR rate of 15.2% (12/79). The removal of the investigational agents (n = 28) left 51 patients, of which 8 (15.7%) had CR.
- When removing investigational agents, PR increased. The whole cohort had a PR rate of 19.0% (15/79), versus 23.5% (12/51) when investigational agents were removed.
- When removing investigational agents, PFS increased. The whole cohort had a median PFS of 3.5 months. The investigational agent subgroup had a median PFS of 2.4 months. Therefore removal of the investigational agent subgroup results in a higher median PFS.

The counterintuitive results noted are nevertheless consistent with the available data. Since the data available for the investigational agent group is limited, we are not able to provide a clear rationale for the effects, other than to hypothesise that investigational agents comprised a great variety of agents, of which some were highly efficacious (as per nivolumab) and some were less efficacious than available chemotherapy regimens. Regardless, we consider it logical to remove these data from the analysis, since the inclusion of agents that may be unlicensed, and for which we have no information, is not appropriate.

## Section B: Clarification on cost-effectiveness data

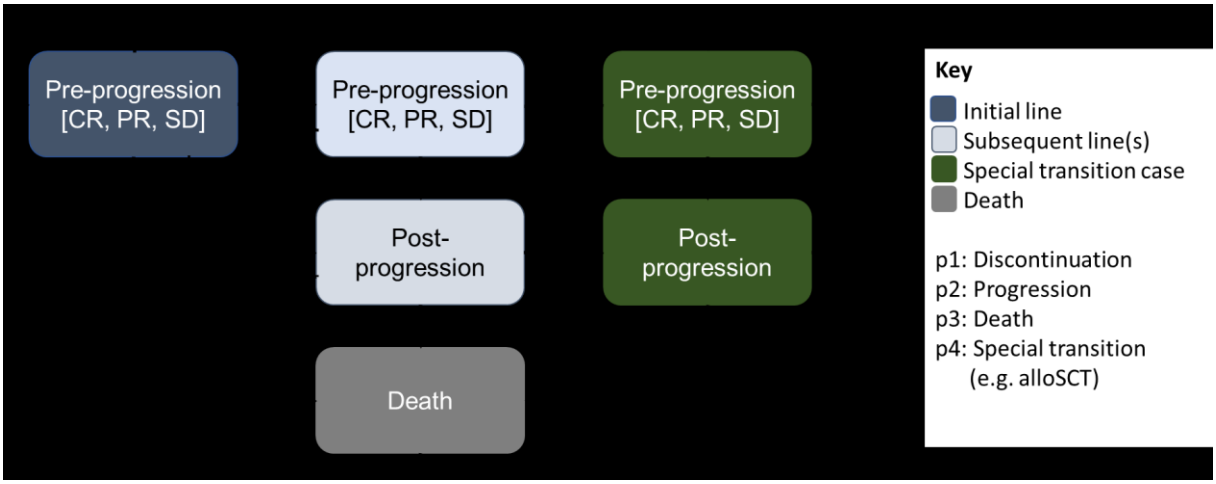
**B1. Priority question Company submission page 105, Table 37 (Cheah study): The number of patients in the Cheah study is totalled as 79. However, this includes 28 patients who received investigational agents. As these have been excluded in the base case analysis, the actual sample from the Cheah study is 51 patients. Please confirm whether 51 patients is correct.**

This is correct: after exclusion of the 28 patients who received investigational agents, 51 patients were assessed from the Cheah data. This has been reflected in the calculation of outcomes, including CR, PR and SEs, described in Table 43 of the submission.

**B2. Priority question Company submission page 100, Figure 23: The diagram does not adequately represent the complexity of the model, because it does not include treatment switching and special transitions such as allogeneic stem cell transplant (alloSCT). Please provide a full diagram of the model with all possible and optional transitions (alloSCT, pre-progression chemotherapy, etc…) illustrated for all arms.**

An updated figure is provided as Figure 3, modified to visualise both multiple treatment lines and where applicable the special transition case used for patients who receive alloSCT. Colours have been used to reflect the different treatment options, while transitions are indicated by numbers, with a key provided to aid clarity.

**Figure 3. Amended Markov model flow diagram**




Patients enter the model in the pre-progression state, receiving initial therapy (i.e. nivolumab or SoC in the base case analysis). Following discontinuation, they may enter the state represented as subsequent therapy within the pre-progression state; in the base case analysis, this is BSC, but in scenarios this may be subsequent chemotherapy. Additionally, they may receive a third therapy on the basis of a special transition case; this is not used as part of the base case analysis, but is used within scenarios to model alloSCT. Following progression, patients move to

a post-progression state, with a subsequent therapy specified; in the base case, this is BSC. Reflecting clinical practice, patients may move to the death state from all other states within the model.

**B3. Priority question *Company submission pages 108-9, Figures 25, 26*: Please clarify whether these figures represent the whole trial data for cohorts B and C from the CheckMate 205 trial and the post-ASCT/BTX patients from CA209-039 (n=80 + n=98 + n=15), or an adjusted subgroup.**

As described in Section 5.3.2.1 and Appendix 6, the Kaplan-Meier data and associated extrapolations depicted in Figures 25 and 26 are based upon a total of 193 patients, derived from the following cohorts:

- Cohort B of the CheckMate 205 study (n = 80); median follow-up: [redacted]
- Cohort C of the CheckMate 205 study (n = 98; two patients who had not received BTX excluded); median follow-up: [redacted]
- Post-ASCT/BTX patients from CA209-039 (n = 15); median follow-up: [redacted]

**B4. Priority question *Company submission page109, Figure 29:* Please clarify whether the patients who have received alloSCT are included in the data presented in Figure 26. Please confirm the numbers who received alloSCT which the ERG believe to be 11/80 from CheckMate 025 cohort B, 18/98 from CheckMate 025 cohort C and 5/15 from post-ASCT/BTX CA209-039.**

The data cited by the ERG refers to the overall nivolumab-treated HL population (i.e. Cohorts A, B and C of CheckMate 205 and the overall CA209-039 cohort) as of June 2016. Data used to inform survival within the submission is based on the April 2016 data cut-off, due to the requirement for complete data (i.e. including sufficient efficacy follow-up for all patients, including those without alloSCT) and is based on subgroups that match the population under consideration (i.e. patients that had received prior ASCT and brentuximab). Of the patients included within the pooled nivolumab cohort at that time, alloSCT was received by:

- [redacted] from CheckMate 205 Cohort B
- [redacted] from CheckMate 205 Cohort C
- [redacted] from the post-ASCT, post-BTX subgroup of CA209-039
- [redacted] from the overall pooled nivolumab cohort

As stated within the submission, OS data implicitly include the effects of any subsequent treatment that may have been administered, enabling the survival parameterisation to implicitly incorporate the effects of these subsequent therapies. This includes alloSCT, and of the [redacted] OS events in the pooled nivolumab cohort, [redacted] occurred in patients who has received alloSCT ([redacted]).

As of June 2016, 40 patients with cHL have received post-nivolumab alloSCT (five patients from CA209-039; within CheckMate 205, six from Cohort A, 11 from Cohort B and 18 from Cohort C) (Table 10), and there have been no deaths due to disease progression.[8]

**Table 10. Patients included in the pooled nivolumab cohort and who received subsequent alloSCT at April and June 2016 database locks**

| Patients included in pooled nivolumab cohort as of: | Total | 039 | 205: A | 205: B | 205: C |
|---|---|---|---|---|---|
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| June 2016 | 40 | 5 | 6 | 11 | 18 |

[redacted]Disease status after alloSCT was not available from CA209-039, but was available in [redacted] patients from Cohorts A, B and C in CheckMate 205.

[redacted]Of the 40 patients undergoing alloSCT, 18 (45%) have experienced acute graft versus host disease, but in only 7 (17.5%) patients was this considered to be a grade 3 event or above. Further, there were six deaths, all of which were due to transplant-related mortality, which is in line with initial mortality observed for post-alloSCT patients during Cheah (2016).[6,8]

**B5. Priority question *Company submission pages 111, 113, Figures 29, 30*: Please provide full diagnostics for alternative parametric fittings of PFS and OS for standard of care (SoC). Please use the table below, and provide alternatives for Figures 29 and 30 that are formatted in the same way as Figures 25 and 26. The parameters used for the displayed curves should be incorporated in the figures as in Figures 25 and 26 (pages 108-109), or should be in a separate table.**

In line with the methodology described in the submission document (Section 5.3 and Appendix 6), Kaplan-Meier data was obtained by digitisation of Kaplan-Meier plots from the Cheah 2016 overall population[6]. Parametric survival functions were subsequently fitted to the extracted pooled data, including exponential, Weibull, log-logistic, lognormal, Gompertz and generalised-gamma survival distributions, based on the NICE DSU guidelines;[12] functional forms are described in Table 2 of Appendix 6.

Parametric fits for the Cheah 2016 overall population data and the goodness-of-fit statistics (AIC and BIC) are provided in Figure 4 and Figure 5. It is worth noting that while the above methods for validating the extrapolation of progression and death events are appropriate, these measures only provide a numerical measure of the match between observed data and model estimates across the available trial follow-up but give no indication of the relative merits of competing models when used for extrapolation[13]. Thus, in line with guidance from the NICE Decision Support Unit (DSU)[12] and Bagust and Beale (2014),[13] the progression of the hazard profile

should also be assessed for clinical plausibility. For instance, the Gompertz fit of OS presented in Figure 5 has a negative shape parameter, and as a result of the hazard of mortality will always decrease with time. This might be acceptable if other mechanisms suggest that this will reflect OS during the extrapolation period, but highlights the problem that the plausibility of the progression of hazards must be assessed along with the mathematical goodness of fit recommendations.

It should be noted that the survival extrapolations provided in Figure 4 and Figure 5 are based on Kaplan-Meier data for the Cheah 2016 overall population, which reported a median OS of 25.2 months.[6] Median OS for specific therapy categories ranged from 9.5 months (other alkylator therapies) to 34.0 (bendamustine), with investigational agents reporting a median OS of 47.7 months. It can be concluded that OS associated with investigational agents appears to be far greater than that reported for other therapy categories; however, this therapy group included PD-1 inhibitor agents and which is likely to have included nivolumab. In order to avoid a scenario where the beneficial effects of nivolumab are compared against those of a SoC where benefits are driven by patients receiving investigational agents, including nivolumab, it has been necessary to derive an OS curve where the impact of investigational agents has been removed.

As some therapy categories do not report median OS, and there are no Kaplan-Meier data available to describe each individual therapy category, it has been assumed that a parametric fit can be applied to the overall population, as well as each therapy category. Given the paucity of data, a conservative approach was taken and it was assumed that the most appropriate parametric fit was an exponential curve, in line with the Bagust and Beale (2014)[13] rationale that an exponential distribution should be considered the default parametric function for long-term survival projection.

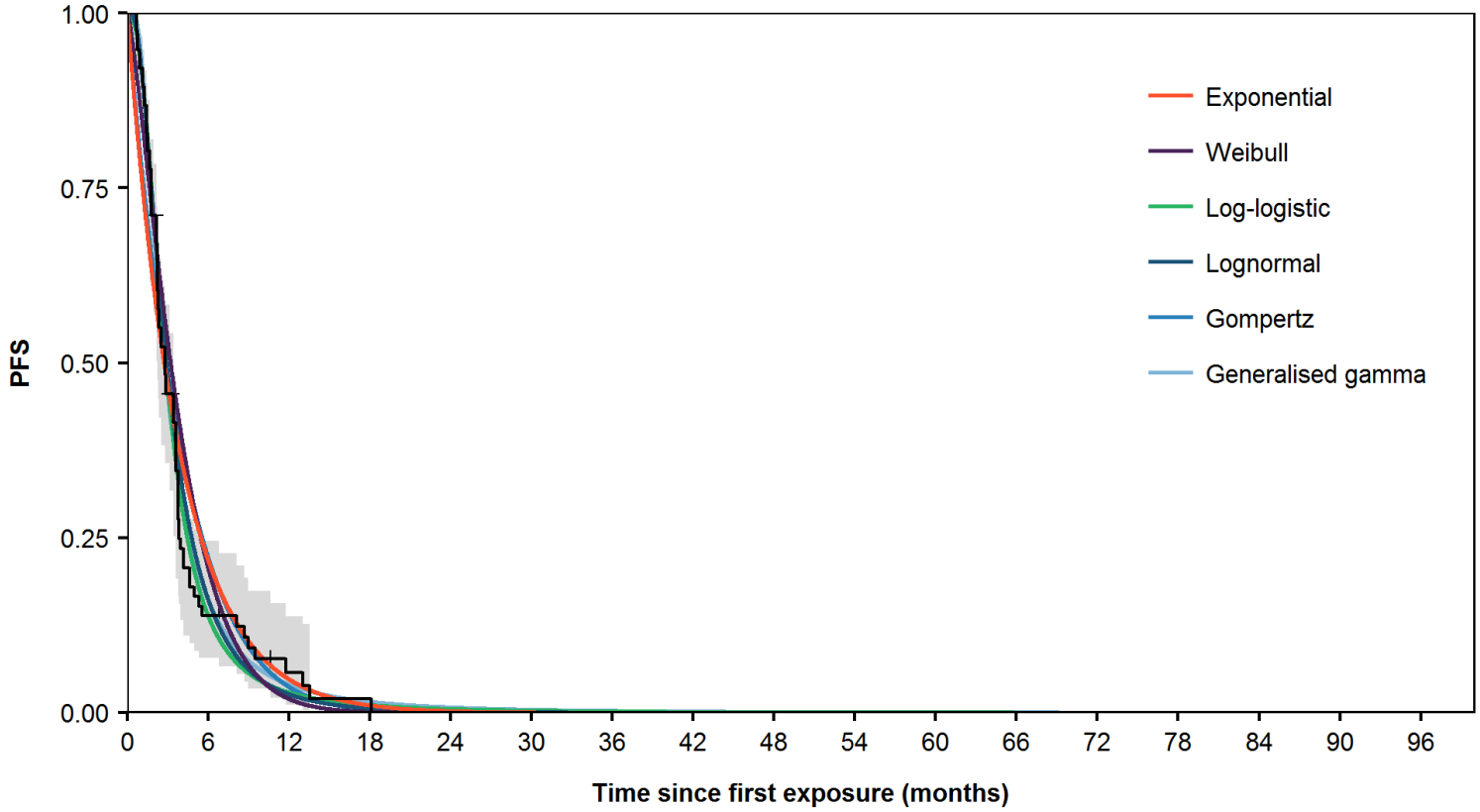
Applying the same methodology as that described for the base case analysis, it is possible to adjust the Cheah 2016 overall population alternative parametric fits to exclude the impact of investigational agents. However, it should not be considered methodologically sound. Any parametric fit that allows for a time-varying hazard when fitted to data composed of various subgroups with distinct survival profiles will tend to be dominated by the most long-lived subgroups in the tail. Simple scaling of these parameterisations to represent the removal of these long-lived subgroups is therefore not representative of the long-term survival characteristics of the remaining subgroups. Due to the high median of the investigational agents in OS compared to the other subgroups, it is likely that it maintains a lower hazard profile into the extrapolated region; thus in removing this subgroup, we encounter the aforementioned issue.

The assumption of constant hazard for each subgroup, fitting to the medians, ameliorates this problem. The lower long-term hazards are entirely accounted for by the more long-lived subgroups, whilst those that have a more severe survival profile are not forced to reduce their hazard with time to coincide with the shape of the combined fit. The result of combining these constant hazard models is nonetheless very similar to a fit with varying hazards.

Thus, parametric fitting to the Cheah 2016 overall population Kaplan-Meier data is provided. This can be considered to overestimate the survival in the SoC arm, but can be considered

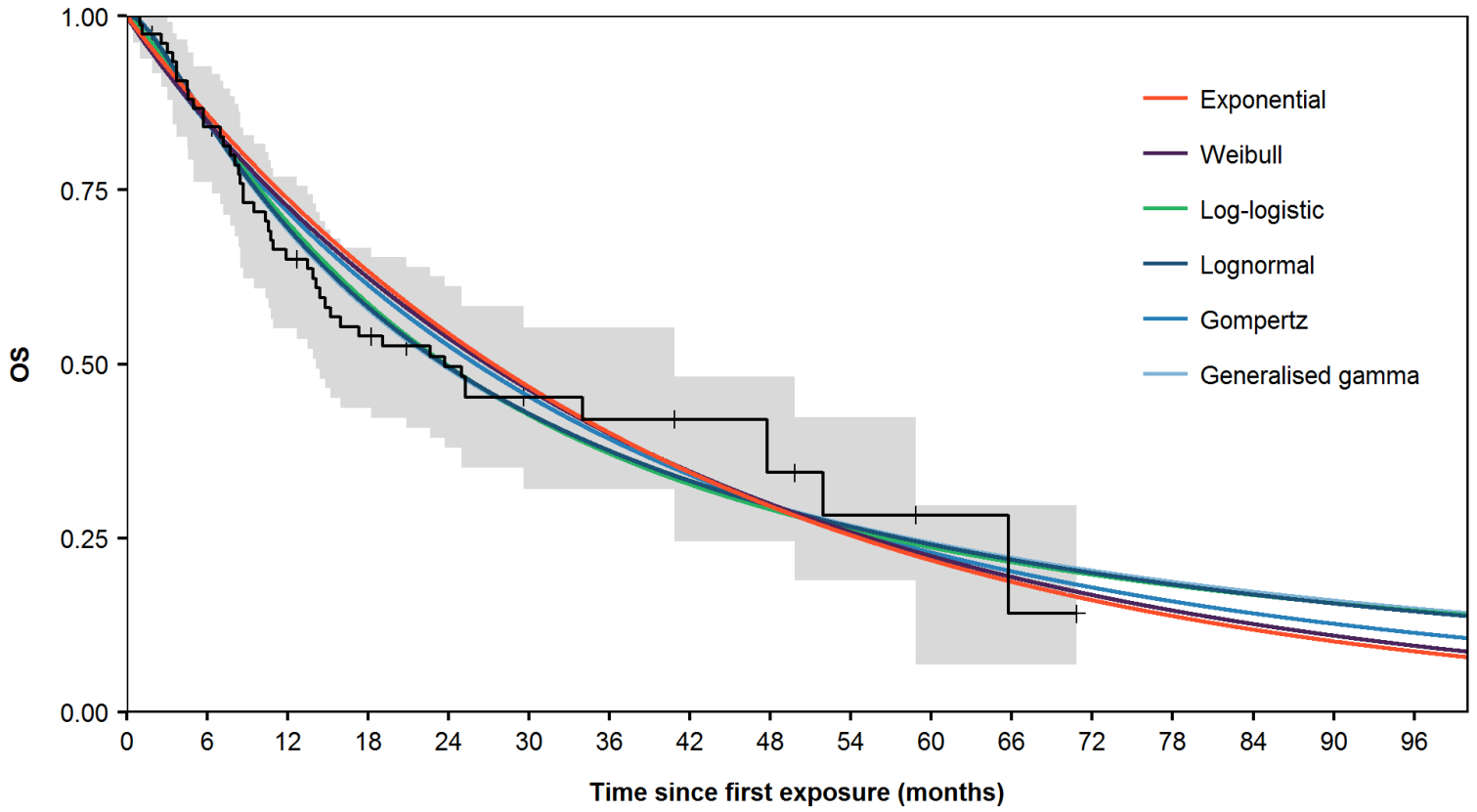
indicative of the variation in survival parameters that would result from alternative parametric fits. It should also be noted that available parametric extrapolation do not impact greatly on predicted survival outcomes, with median PFS predicted to be 27-3.2 months and median OS predicted to be 23.7-27.3 months based on the Cheah 2016 overall population (i.e. including investigational agents). It is anticipated that would have minimal impact on cost-effectiveness outcomes, as greater variation in survival has been assessed as part of scenarios described in the submission document, particularly those in Sections 5.8.3.1 and 5.8.3.3.

**Figure 4. Parameterisation of progression-free survival: Cheah 2016 overall population (including investigational agents)**




| Fit Name | AIC | BIC | Parameters | Median (Months) | Mean (Months) |
|---|---|---|---|---|---|
| Exponential | 343.67 | 346.02 | lambda: 0.2534 | 2.7 | 3.9 |
| Weibull | 336.33 | 341.04 | shape: 1.320; scale: 4.257 | 3.2 | 3.9 |
| Log-logistic | 317.17 | 321.88 | shape: 2.439; scale: 2.838 | 2.8 | 3.8 |
| Lognormal | 317.19 | 321.90 | mu: 1.0743; sigma: 0.7281 | 2.9 | 3.8 |
| Gompertz | 344.86 | 349.57 | shape: 0.02987; rate: 0.22873 | 2.9 | 3.9 |
| Generalised gamma | 316.76 | 323.83 | mu: 0.9063; sigma: 0.6981; Q: -0.4749 | 2.8 | 4.0 |

**Figure 5. Parameterisation of overall survival: Cheah 2016 overall population (including investigational agents)**




| Fit Name | AIC | BIC | Parameters | Median (Months) | Mean (Months) |
|---|---|---|---|---|---|
| Exponential | 506.82 | 509.16 | lambda: 0.02537 | 27.3 | 39.4 |
| Weibull | 508.68 | 513.36 | shape: 0.9591; scale: 39.4382 | 26.9 | 40.2 |
| Log-logistic | 507.21 | 511.89 | shape: 1.264; scale: 23.768 | 23.8 | 96.7 |
| Lognormal | 504.87 | 509.56 | mu: 3.164; sigma: 1.324 | 23.7 | 56.8 |
| Gompertz | 508.41 | 513.10 | shape: -0.004893; rate: 0.028328 | 26.1 | 44.2 |
| Generalised gamma | 506.85 | 513.88 | mu: 3.12157; sigma: 1.33678; Q: -0.07549 | 23.5 | 60.3 |

**B6. Priority question *Company submission page 128, Table 55*: Please provide details of the proportion of patients on each of the treatments for SoC. Please provide the calculations used to obtain the comparator costs in Table 56 in an Excel spreadsheet.**

As requested, Table 55 of the submission has been reproduced below as Table 11, providing the proportion of patients receiving each SoC component. Additionally, the calculations used to obtain comparator costs in Table 56 are provided within the spreadsheet labelled 'B6. Calculation of chemotherapy costs'.

In light of uncertainty and the lack of data surrounding comparator composition, the general approach has been to use simple assumptions based on independent sources, such as the published literature, British HL guidelines or previous NICE appraisals. As stated within the submission, the Cheah 2016 real world data[6] can be suggested to adequately represent the treatment of the post-ASCT, post-BTX HL population in clinical practice. Based on this real-world data, it has been assumed that chemotherapy and bendamustine comprise the majority of usage, in line with NICE scope, with some BTX retreatment. Composition of chemotherapy in UK clinical practice has then been assumed based on equal usage of regimens specified by the BCSH guidelines.[7] Several alternative assumptions were assessed in scenario analyses, such as the inclusion of investigational agents into SoC, comparator composition based on the BTX TA and BSC as a comparator. It should be noted that these alternative assumptions had minimal impact on cost-effectiveness analysis and did not impact on cost-effectiveness conclusions at threshold of £30,000 per QALY.

**Table 11. Proportion of patients receiving comparator therapies**

| Regimen | Cost per cycle | Dosing instructions | Cycle length | Number of cycles | Proportion received |
|---|---|---|---|---|---|
| ICE | £1,993.51 | every 14 d for two cycles | 14 | 2 | 4.15% |
| IVE | £2,833.51 | 21 day cycle; 2 cycles | 21 | 2 | 4.15% |
| MINE | £1,683.20 | every 28 days; 2 courses | 28 | 2 | 4.15% |
| IVOx | £3,128.47 | 21 day cycle; 3 cycles | 21 | 3 | 4.15% |
| IGEV | £3,703.72 | 21 day cycle; 4 cycles | 21 | 4 | 4.15% |
| GEM-P | £2,198.83 | 28 day cycle; three cycles | 28 | 3 | 4.15% |
| GDP | £1,484.32 | 21 days; 2 cycles | 21 | 2 | 4.15% |
| GVD | £3,020.85 | 21 days; 2 cycles | 21 | 2 | 4.15% |
| Mini-BEAM | £11,221.91 | 28 day cycle; three cycles | 28 | 3 | 4.15% |
| DexaBEAM | £11,355.50 | 28 day cycle; 2 cycles | 28 | 2 | 4.15% |
| ESHAP | £1,056.87 | every 21-28 d for 4 cycles | 28 | 4 | 4.15% |
| ASHAP | £1,058.87 | Assumed 28 day cycle; 3 cycles | 28 | 3 | 4.15% |
| DHAP | £1,204.27 | every 21 days for two cycles | 21 | 2 | 4.15% |
| DHAOx | £2,004.77 | 21 day cycle; 4 cycles | 21 | 4 | 4.15% |
| Bendamustine | £2,096.91 | every 28d for 6 cycles | 28 | 6 | 27.91% |
| BTX | £7,889.41 | 3 week cycle for 9 cycles | 21 | 9 | 13.95% |

ASHAP: doxorubicin, methylprednisolone, cytarabine, cisplatin; BTX: brentuximab; DexaBEAM: dexamethasone, carmustine, etoposide, cytarabine, melphalan; DHAOx: dexamethasone, cytarabine, oxaliplatin; DHAP: dexamethasone, cytarabine, cisplatin; ESHAP: etoposide, methylprednisolone, cytarabine, cisplatin; GDP: gemcitabine, dexamethasone, cisplatin; GEM-P: gemcitabine, cisplatin, methylprednisolone; GVD: gemcitabine, vinorelbine, liposomal doxorubicin; ICE: ifosfamide, carboplatin, etoposide; IGEV: ifosfamide, gemcitabine, vinorelbine; IVE: ifosfamide, epirubicin, etoposide; IVOx: ifosfamide, etoposide, oxaliplatin; MINE: mitoxantrone, ifosfamide, vinorelbine, etoposide; Mini-BEAM: carmustine, etoposide, cytarabine, melphalan.

**B7. Priority question *Company submission pages 154-6*: It is unclear how alloSCT or other treatments that require changes to subsequent therapies are incorporated in the model. For example, the subsequent chemotherapy analysis (page 156), states that patients discontinuing or progressing will switch to the comparator therapy. Setting 5th line to Comparator instead of BSC for the reference treatment in the model produces an ICER of £45,947/QALY instead of the reported £22,095/QALY ICER. Please provide a full explanation of how these treatment switches work in the model and provide instructions or model modifications that allow running of analyses using the model mechanics as explained, preferably with simple switches or buttons.**

As described in the answer to question B2, subsequent treatment options are available within the model based one of two methods. The first is via use of the decision tree within the model and is applicable to almost all treatments, except for alloSCT. The second is specific to alloSCT and makes use of the special transition case, as an added layer of functionality was required due to the special properties associated with alloSCT (i.e. treatment switching in a specific proportion of patients in the pre-progression health state at a single point in time based on level of response). As such the subsequent chemotherapy scenario is applied in the model differently to that of the alloSCT scenarios.

In the base case analysis, it is assumed that

- Following discontinuation in the pre-progression phase, patients switch to BSC, comprised of several therapies including chemotherapy, clinical study therapies and palliative care.
- Following progression, patients enter the post-progression phase and received BSC, which has a different composition to that received in pre-progression, and has a greater proportion of patients receiving palliative care.

Although composition of pre-progression BSC is based on a previous NICE appraisal, and contains chemotherapy, this assumption can still be considered a simplification. In clinical practice, patients are more likely to receive chemotherapy in the pre-progression phase if it is clinically feasible, particularly where a patient is considered fit enough or where comorbidities allow. Thus, as stated within the submission document, a scenario analysis was conducted whereby patients discontinuing therapy (either nivolumab or SoC) in the pre-progression phase receive subsequent SoC, subject to the same assumptions and costs as the initial therapy line; BSC is still received as the post-progression therapy. As a clarification, the treatment pathways applied in the scenario are outlined below:

- Following discontinuation in the pre-progression phase, patients switch to a second set of SoC, with composition of SoC as described for the initial therapy in the base case analysis.
- Following progression, patients enter the post-progression phase and received BSC, as in the base case analysis.

It should be noted that post-progression BSC includes some chemotherapy costs, but with more patients receiving palliative care, reflecting the heterogeneous nature and declining health status in post-progression patients, so that palliative care will be the most appropriate therapy in the majority of patients.

We believe that the approach that the ERG have taken to implement their noted scenario is technically correct and produces the ICER quoted. However, this scenario applies chemotherapy as the exclusive post-progression therapy, which is not clinically plausible and does not take into account the declining health status of these patients. Therefore, the ICER cited in the submission reflects the scenario as outlined, and represents a more clinically plausible account of patient experience.

Independent of the two methods outlined above, the user also has the option of applying a new survival profile when moving to a subsequent treatment. Within each treatment module, setting the 'use in subsequent treatment lines' switch to 1 will load the survival profile specific to that treatment. In terms of the model mechanics, at the time in which patients move to that treatment, they will receive a hazard relating to the s(t) where t corresponds to the time they have spent within that treatment (i.e. t = 0 when they arrive). To cater for this functionality, for each time-point, the patients arriving at a treatment are simulated up until horizon and this process is repeated until no more time points remain. Examples of scenarios which use this functionality include the alloSCT scenarios described within the submission document.

**B8. Priority question *Company submission, section 5.8.*3: Please provide a spreadsheet that contains the exact (unrounded) model parameters for each of the 58 scenario analyses conducted. Only the parameters that are different from the base case need reporting in this manner.**

A spreadsheet is provided ('B8. Unrounded model parameters'), and unrounded values have been incorporated into the models provided for B9.

**B9. Priority question: In total, 58 scenario analyses were conducted in Section 5.8.3 of the company submission. However, the ERG was only able to fully conduct and validate 19 analyses: the 15 analyses utilising alternative survival curves for PFS and OS for nivolumab, the analysis examining SOC overall survival, the analysis without half-cycle correction, the analysis using alternative utility for SOC (utility scenario 1), and the analysis with adverse events excluded from both treatment arms. Some model scenarios, such as the alloSCT scenarios and pre-progression chemotherapy scenario, were unable to be verified because the explanation of methods was unclear. One scenario did not have input data available (Kaplan Meier survival). Several other analyses did not produce the results reported in the company submission.**

**The following Table 3 provides a list of analyses that we were unable to confirm, with reasons and the action needed from the company. Please note that some analyses have been designated as priority analyses.**

A response column has been included in the table below to provide clarification for each issue raised.

Models for all scenarios are provided, including those already validated for completeness. To aid the process of validation, a read-me tab has been incorporated within each, which

outlines the scenario name, how the scenario was implemented, as well as the specific (non-rounded) parameters that were integrated into the model (i.e. priority question B8).

Please refer back to email correspondence on the 2 December 2016, which provided agreement from the ERG that the above approach would be sufficient in addressing the requests for model adaptations and clarifications.

Amendments

Whilst conducting this task, two errors were noted in the models:

- In the 'SoC composition equivalent to ongoing BTX TA' scenario, the cost of BTX has been applied as opposed to the cost of the BTX comparator. This has been addressed in the amended model and has not impacted cost-effectiveness conclusions.
- In the scenario assessing the impact of post-progression nivolumab use, a modification has been made directly within the VBA code to implement this behaviour, as the functionality did not exist to allow for treatment-specific behaviour. However, results reported within the NICE submission did not incorporate this modification correctly. This has been addressed in the provided model and has not impacted cost-effectiveness conclusions.

These errors have been corrected in the enclosed models, and full details of how the scenarios have been conducted are available in the enclosed pre-loaded models.

**Table 12. ERG Table 3: Scenario analyses that could not be confirmed using the model**

| Priority | # | Company Submission Table/Page | Analysis | Action | Company response |
|---|---|---|---|---|---|
| **Alternative Treatment Sequences (alloSCT)** | | | | | |
| **Priority** | 20-23 | Table 75 (page 156) | Scenario 1: likelihood of alloSCT from Perrot 2016 and costs from NHS reference costs<br><br>Scenario 2: likelihood of alloSCT from Perrot 2016 and costs derived from Radford 2016<br><br>Scenario 3: likelihood of alloSCT from Perrot 2016, but nivolumab patients with CR and PR assumed equivalent; costs from NHS reference costs<br><br>Scenario 4: likelihood of alloSCT from Perrot 2016, but nivolumab patients with CR and PR assumed equivalent; costs derived from Radford 2016 | Provide full textual explanation of the mechanics of these analyses within the model. Build the capability to conduct these analyses in the model with the push of a button, and the ability to combine these analyses with other analyses. | As agreed with the ERG on 2/12/16, individual models are provided that have been validated and contain descriptions of parameter implementation, and Figure 3 has been provided to describe how the alloSCT therapy is incorporated into the model.<br><br>AlloSCT has been incorporated as a subsequent treatment. For both treatment and comparator arm, a special transition case has been applied used to switch treatment to alloSCT in a proportion of patients based on response status of pre-progression patients at 6 months. |
| **Alternative Treatment Sequences (subsequent chemotherapy)** | | | | | |
| **Priority** | 24 | Table 77 (page 157) | Patients receive chemotherapy pre-progression after discontinuing treatment (nivolumab or SoC) | Provide full textual explanation of the mechanics of this analysis within the model. Build the capability to conduct this analysis in the model with the push of a button, and the ability to combine this analysis with other analyses. | As agreed with the ERG on 2/12/16, individual models that have been validated and contain descriptions of parameter implementation are provided. A full description of implementation is provided in the response to Question B8 and Figure 3 has been provided. |
| **Alternative Comparator Composition** | | | | | |

| Priority | # | Company Submission Table/Page | Analysis | Action | Company response |
|---|---|---|---|---|---|
| | 27 | Table 84 (page 160) | SoC composition and AE equivalent to ongoing BTX TA | The text and tables for this analysis (CS pp. 158-9) do not provide the alternative costs and AE profile for the alternative SoC composition, which makes validating the analysis not possible. | In response to B8, further detail has been included within the spreadsheet of inputs, as well as an amended model, which should allow for validation of this scenario. |
| **Alternative ITC comparisons** | | | | | |
| **Priority** | 28-45 | Table 85 (page 162) | All analyses in Table 85, including Alternative ITC comparisons Post-ASCT, Post-BTX studies and Alternative ITC comparisons Post-ASCT studies | When these simulations are run with the parameters defined in Table 85, there are consistent cost and QALY discrepancies. Costs for SoC are generally £3,100 to £3,500 more and QALYs 0.002 to 0.011 less when we run the simulations. Can you explain these discrepancies? | We believe that the discrepancy observed in terms of QALYs is due to input rounding; full unrounded parameters are provided in response to Question B8. We believe that the discrepancies seen in the costs are due to the use of alternative comparator treatment costs, which included investigational agents. It is assumed that these treatments were provided as part of a clinical trial; therefore, comprise only administration costs. |
| **Alternative baseline age** | | | | | |
| | 46 | Table 86 (page 164) | Age 20, alloSCT likelihood of alloSCT from Perrot 2016 and costs from NHS reference costs | As with analyses 20-23, the mechanics to implement this analysis are not clearly defined. Additionally, it does not appear that survival was changed to reflect the patient age, please confirm this. | As described above, individual models are provided that have been validated and contain descriptions of parameter implementation, and Figure 3 has been provided to describe how the alloSCT therapy is incorporated into the model. The mechanics of subsequent treatments are discussed in response to B7. In regards to adjustments for age on |

| Priority | # | Company Submission Table/Page | Analysis | Action | Company response |
|---|---|---|---|---|---|
| | | | | | patient survival, we have insufficient data to stratify by age. However, based on data presented within Section 4.8 of the submission document, it can be demonstrated that response is not anticipated to be different when stratified by age. |
| | 47 | Table 86 (page 164) | Age 70, BSC assumed to be the most appropriate comparator, (OS derived from the lowest reported by Cheah 2016 for chemotherapies (exponential parametric fit; λ: 0.07296); PFS was assumed to be equivalent to the PFS applied in the base case for SoC, due to the evidence supporting comparable PFS for non-investigational agent) | It does not appear that survival was changed to reflect patient age, please confirm this. Additionally, please provide full details of the settings necessary to replicate this analysis. Changing survival, and changing comparator costs to BSC did not replicate the analysis results reported. | The amended models provided should allow for validation. Please refer to read me tabs for an explanation of how they were implemented.<br><br>The mechanics of subsequent treatments are discussed in response to B7. In regards to adjustments for age on patient survival, we have insufficient data to stratify by age. However, based on data presented within Section 4.8 of the submission document, it can be demonstrated that response is not anticipated to be different when stratified by age. |
| **Alternative assumptions around utilities** | | | | | |
| **Priority** | 53 | Table 88 (page 166) | Nivolumab post-progression utility set equal to comparator post-progression utility | Analyses do not produce results consistent with those reported. Please explain to which specific treatment lines (nivolumab, SoC, BSC (treatment), BSC (control)) the utility values were applied to. | Utilities are specific to each arm of the analysis, and so utilities specific to the nivolumab arm must be applied in the nivolumab initial therapy as well as the post-nivolumab pre-progression BSC therapy line. |
| **Priority** | 54 | Table 88 (page 166) | Swinburn 2015 used to derive utility for pre- and post-progression in both arms | | |
| **Priority** | 55 | Table 88 (page 166) | Response-specific pre-progression utilities applied | | |

| Priority | # | Company Submission Table/Page | Analysis | Action | Company response |
|---|---|---|---|---|---|
| | | | | | The amended models provided should allow for validation. Please refer to read me tabs for an explanation of how they were implemented. Further, in response to B8, further detail has been included within the spreadsheet of inputs, as well as an amended model, which should allow for validation of this scenario. |
| **Alternative Post-progression Costs** | | | | | |
| | 57 | Table 90 (page 167) | Resource use doubles post progression | Unclear how increase in state costs is applied only to post-progression, as health state costs are not defined by progression status. Treatment costs, are defined by progression status. | Health state costs are treatment-specific and stratified by CR, PR, SD, progressed disease (initial month), progressed disease (subsequent month), disease death (initial month), general death (initial month). In the base case analysis (and scenarios), health state costs are assumed to be the same between treatments and pre-progression response states; further, no costs of death are applied.<br><br>In the base case, it is assumed that pre-progression health state costs are equivalent to post-progression health state costs (independent of treatment). In this scenario, the health state costs for progressed disease states (190.08) were doubled (380.16). Using the base case model submitted to NICE, an |

| Priority | # | Company Submission Table/Page | Analysis | Action | Company response |
|---|---|---|---|---|---|
| | | | | | example of where this is implemented for nivolumab is in cells H232:H233. |
| **Application of IRRC-assessed endpoints for nivolumab** | | | | | |
| | 58 | Table 91 (page 167) | PFS<br>μ: 2.656<br>σ: 1.121<br><br>Response rates<br>CR: 11.4%<br>PR: 58.0%<br><br>Utilities<br>Pre-progression: 0.834<br>Post-progression: 0.746 | When running the model using the specified parameters, our results were not consistent with those reported in the CS. Total costs for nivolumab matched, but total QALYs were [redacted], which is [redacted] than the [redacted] QALY result reported in the CS. Please explain this discrepancy. | Utilities are specific to each arm of the analysis, and so utilities specific to the nivolumab arm must be applied in the nivolumab initial therapy as well as the post-nivolumab pre-progression BSC therapy line.<br><br>The amended models provided should allow for validation. Please refer to read me tabs for an explanation of how they were implemented. |

**B10. Priority question: Changing the utility score in the economic model does not always replicate the reported results of the analysis with a changed utility score. For the utility specific analyses, only Scenario 1 (Company submission page 166, Table 88) produced results consistent with those reported. Please explain these discrepancies.**

Please refer to B9, which contains the models applicable to this query. Please note that alternate utilities must be implemented for **all** treatments in the arm. Utilities are specific to each arm of the analysis, and so utilities specific to the nivolumab arm must be applied in the nivolumab initial therapy, as well as the post-nivolumab pre-progression BSC therapy line.

**B11. *Company submission page 121, Table 48*: Please provide the total number of observations for each of the utility classification categories (CR pre-progression, PR pre-progression, stable disease (SD) pre-progression, progressed disease). Please also provide the 95% confidence interval range for these data.**

Table 13 provides the number of questionnaires completed stratified by classification category, as well as the 95% confidence interval range.

**Table 13. Utilities by response category**

| | N (questionnaires) | Mean value | 95% confidence interval |
|---|---|---|---|
| Complete response | [redacted] | [redacted] | [redacted] |
| Partial response | [redacted] | [redacted] | [redacted] |
| Stable disease | [redacted] | [redacted] | [redacted] |
| Post progression | [redacted] | [redacted] | [redacted] |

**B12. *Company submission page 123, Table 49*: Please clarify the duration used for the adverse event disutility in the economic model and whether the adverse event rate is assumed to be the same for patients with CR, PR and SD.**

The adverse event disutility is assumed to be applied as a one-off disutility in the monthly cycle, in line with usage from previous HTAs.[14-16] Further, this is applied regardless of response category, as there is no evidence to suggest that adverse event rates are response-dependent.

**B13. *Company submission page 134, Table 56*: Please provide the HRG codes for the resources.**

Table 56 has been reproduced below as Table 14, including HRG codes.

**Table 14. Pre- and post-progression resource use applied in the economic model**

| Resource | Item | Value | Source |
|---|---|---|---|
| Outpatient attendance | Rate | 10.40 | BTX TA[17] |
| | Cost (£) | 150.38 | NHS reference costs 2014-15[18] Consultant led follow-up attendance, non-admitted face to face, Clinical Haematology 303 |
| | Total (£) | 1,563.94 | - |
| Blood count | Rate | 10.40 | BTX TA[17] |
| | Cost (£) | 3.01 | NHS reference costs 2014-15[18] Haematology DAPS05 |
| | Total (£) | 31.26 | - |
| Biochemistry | Rate | 10.40 | BTX TA[17] |
| | Cost (£) | 1.19 | NHS reference costs 2014-15[18] Clinical Biochemistry DAPS04 |
| | Total (£) | 12.37 | - |
| CT scan (with assumption that 50% will include PET scan) | Rate | 3.00 | BTX TA[17] |
| | Cost (£) | 224.44 | NHS reference costs 2014-15[18]: Computerised Tomography Scan, three areas with contrast RD26Z<br>Positron Emission Tomography with Computed Tomography (PET-CT) of more than three areas, 19 years and over RN03A |
| | Total (£) | 673.33 | - |
| Overall cost | Annual (£) | 2,280.91 | - |
| | Monthly (£) | 190.08 | - |

**B14. *Company submission page 135, Table 60*: The adverse event costs do not appear to match the references given. For example, there are no values reported in NICE Technology appraisal guidance (TA) 306 for nausea and leukopenia. Please clarify where these values are obtained from. Please also clarify whether the values used for adverse event costs were from the company's analysis in TA 306 or from the ERG's sensitivity analysis.**

As noted within the submission AE costs were sourced from recent NICE appraisals where possible,[14,15] and inflated to 2014-2015 costs.[19] Table 15 provides detailed analysis of how these costs were sourced and calculated. Further, please note that where there was a discrepancy between the ERG's preferred analysis and the company analysis, the ERG input was applied. It should be noted that AE costs and utilities are not a driver of the cost-effectiveness analysis, and alternative assumptions in the scenario analysis did not impact cost-effectiveness conclusions.

**Table 15. Adverse event costs**

| Adverse event | 2010/11 costs | Source | 2014/15 costs |
|---|---|---|---|
| Anaemia | £194.00 | TA306 ERG report, Table 44 (p116-117), ERG's SA[14] | £205.50 |
| Dyspnoea | £794.00 | TA306 ERG report, Table 44 (p116-117), ERG's SA[14] | £841.06 |
| Fatigue | £84.00 | TA306 ERG report, Table 44 (p116-117), ERG's SA[14] | £88.98 |
| Leukopaenia | £1,626.79 | TA306 ERG report, Table 45 (p117)[14] | £1,723.21 |
| Nausea | £558.00 | TA306 ERG report, Table 44 (p116-117), ERG's SA, assumed same as vomiting[14] | £591.07 |
| Neutropaenia | £736.00 | TA306 ERG report, Table 44 (p116-117), ERG's SA[14] | £779.62 |
| Pyrexia | £1,373.00 | TA306 ERG report, Table 44 (p116-117), ERG's SA[14] | £1,454.38 |
| Thrombocytopaenia | £155.51 | TA 251[15] | £156.90 |
| Vomiting | £558.00 | TA306 ERG report, Table 44 (p116-117), ERG's SA[14] | £591.07 |

**B15. *Company submission page 140, Table 64*: Please provide an explanation of how age based disutilities have been calculated and a rationale for their use.**

It is stated within the NICE Guide to the methods of technology appraisal (Section 5.3.7) that in some circumstances adjustments to utility values, for example for age or comorbidities, may be needed.[20] There are several publications that support this recommendation, stating that there will be a natural decline in utility relating to age.[21,22]

As modelling of HL requires a lifetime horizon, it can be considered that adjustment of utility values based on age is appropriate.

Within the model, the adjustment of utility due to age is applied as a decrement, calculated using the following equation:

$$UD = HU_b - HU_t$$[21]

Where: UD = Utility decrement; $HU_b$ = Health utility at baseline age; and $HU_t$ = Health utility at time t.

The age-based utility decrements applied can be found in the model within the life table tab. Column G contains the index utility associated with age.[23] Column M contains the calculation, based on patient age over the time horizon modelled.

The decrement calculated is applied within the VBA simulation. Due to the static nature of the calculation, this is performed after the trace is established, and is multiplied by the number of people in the pre-progression and post-progression states.

In addition to providing a more accurate representation of the clinical reality of patients, age-adjusted utilities can be considered conservative. As patients have longer survival in the nivolumab arm, the impact of age-related utility decline will be greater compared with the SoC arm.

**B16.** ***Company submission page 151, Table 68*: The lower λ value for SoC OS (0.036) appears to be an error as inputting this value into the model produces an ICER of £19,921/QALY, not £22,742/QALY. Please provide the correct lower λ value for this scenario analysis.**

Incorrect parameterisations were provided in the submission document. Correct values are provided in Table 16. These were implemented in the original analysis, and therefore the ICER is unaffected; ICERs provided in Table 69 of the submission document are reproduced below for clarity.

**Table 16. Alternative parametric fittings for SoC OS**

| | Nivolumab | SoC | |
|---|---|---|---|
| | | Low (9.5 months OS) | High (34.0 months OS) |
| PFS | Log-normal;<br>μ: 2.825<br>σ: 1.109 | Exponential<br>λ: 0.160 | |
| OS | Weibull<br>Scale (A): 76.742<br>Shape (B): 1.326 | Exponential<br>λ: 0.073 | Exponential<br>λ: 0.020 |
| ICER (£/QALY) | - | 18,613 | 22,742 |
| Log-normal survival equation takes the form: S(t) = 0.5-0.5*erf((ln(t)-mu)/(sqrt(2)*sigma))<br>Weibull survival equation takes the form: S(t) = exp(-(t/A)^B)<br>Exponential survival equation takes the form: S(t) = exp(lambda*t) | | | |

**Section C: Textual clarifications and additional points**

**C1. *Company submission pages 46 and 53*: Please clarify whether the difference in numbers for Cohort C (page 46 n=97; page 53 n=100) is due to continued enrolment into Cohort C between the data cut-off points (August 2015 and April 2016) or is an error.**

Three patients had been enrolled in Cohort C prior to August 2015 data cut-off, but had yet to receive initial treatment, and as such were not included in the Cohort C analysis population, in line with the analysis plan. However, at the April 2016 data cut-off point, all three patients had received initial nivolumab therapy and so were included as part of the analysis population.

**C2. *Company submission page 62, Table 16*: Please clarify whether the footnote 'responses were ongoing in 11 patients' applies to the total population (n=23) or the subgroup (n=15).**

Responses were ongoing in 11 patients from the overall CA209-039 population, of which 7 were in the post-ASCT, post-BTX subgroup.[5]

[redacted]

**C3. *Appendix 3 pages 57-59, Figures 27-30*: It is not possible to match references to the studies listed in Figures 27-30. Please provide these references.**

The references listed in Figures 27-30 from Appendix 3 are provided in Table 17 to Table 20.

**Table 17. References applying to Appendix 3 Figure 27**

| Study in Figure 27 | Reference |
|---|---|
| ***SCT** | |
| Streetly (2004) | Streetly M, Kazmi M, Radia D, et al. Second autologous transplant with cyclosporin/interferon α-induced graft versus host disease for patients who have failed first-line consolidation. Bone Marrow Transplantation. 2004;33(11):1131-5. |
| Smith (2008) | Smith SM, van Besien K, Carreras J, et al. Second Autologous Stem Cell Transplantation for Relapsed Lymphoma after a Prior Autologous Transplant. Biology of Blood and Marrow Transplantation. 2008;14(8):904-12. |
| Lin (2002) | Lin TS, Avalos BR, Penza SL, et al. Second autologous stem cell transplant for multiply relapsed Hodgkin's disease. Bone Marrow Transplantation. 2002;29(9):763-7. |
| Anderlini (2011) | Anderlini P, Acholonu S, Okoroji GJ, et al. Donor leukocyte infusions (DLIs) for recurrent hodgkin lymphoma (HL) following allogeneic stem cell transplantation (allo-SCT): Ten-year experience at the M.D. anderson cancer center. Blood. 2011;118(21). |
| **Radiotherapy** | |
| Tsang (2010) | Tsang RW, Goda JS, Massey C, et al. What can be expected from salvage radiation therapy when an autologous stem cell transplant (ASCT) fails to control Hodgkin lymphoma? Haematologica. 2010;95:S27. |
| Goda (2012) | Goda JS, Massey C, Kuruvilla J, et al. Role of salvage radiation therapy for patients with relapsed or refractory Hodgkin lymphoma who failed autologous stem cell transplant. International Journal of Radiation Oncology Biology Physics. 2012;84(3):e329-e35. |
| **<70% post−ASCT** | |
| Zinzani (2015a) | Zinzani PL, Gandolfi L, Casadei B, et al. Long-term responders after brentuximab vedotin: Experience on 57 patients with relapsed and refractory hodgkin and anaplastic large cell lymphoma. Blood. 2015;126(23):2725. |
| Zinzani (2000) | Zinzani PL, Bendandi M, Stefoni V, et al. Value of gemcitabine treatment in heavily pretreated Hodgkin's disease patients. Haematologica. 2000;85(9):926-9. |
| Walweski (2011) | Walewski J, Paszkiewicz-Kozik E, Warszewska A, et al. Final results of the phase II SAPHIRE trial of resminostat (4SC-201) in patients with relapsed/refractory Hodgkin lymphoma. Blood. 2011;118(21). |
| Validire (2008) | Validire P, Ferme C, Brice P, et al. A multicenter study of gemcitabine-containing regimen in relapsed or refractory Hodgkin's lymphoma patients. Anti-cancer drugs. 2008;19(3):309-15. |
| Ricciuti (2014) | Ricciuti G, Finolezzi E, Falorio S, et al. Salvage treatment with single-agent bendamustine for relapsed/refractory hodgkin lymphoma: An Italian monocentric experience. Haematologica. 2014;99:677-8. |
| Pugliese (2013a) | Pugliese N, Cerchione C, Grimaldi F, et al. Bendamustine-based therapy is effective and has a favourable toxicity profile in the treatment of refractory and relapsed hodgkin lymphoma. Haematologica. 2013;98:571. |
| Pinto (2015) | Pinto A, Pavone V, Angrilli F, et al. Lenalidomide in combination with bendamustine for patients with chemorefractory hodgkin lymphoma: Final results of the leben multicenter phase 1/2 study. Blood. 2015;126(23):1541. |
| Oki (2008) | Oki Y, Pro B, Fayad LE, et al. Phase 2 study of gemcitabine in combination with rituximab in patients with recurrent or refractory Hodgkin lymphoma. Cancer. 2008;112(4):831-6. |
| Majhail (2006)b | Majhail NS, Weisdorf DJ, Wagner JE, et al. Comparable results of umbilical cord blood and HLA-matched sibling donor hematopoietic stem cell transplantation after reduced-intensity preparative regimen for advanced Hodgkin lymphoma. Blood. 2006;107(9):3804-7. |
| Kalyoannidis (2011) | Kaloyannidis P, Voutiadou G, Baltadakis I, et al. Outcomes of Hodgkin's Lymphoma Patients with Relapse or Progression following Autologous Hematopoietic Cell Transplantation. Biology of Blood and Marrow Transplantation. 2012;18(3):451-7. |
| Johnston (2013) | Johnston PB, Pinter-Brown L, Rogerio J, et al. Phase 2 study everolimus for relapsed/refractory classical Hodgkin Lymphoma (CHL). Haematologica. 2013;98:44. |
| Jasielec (2014) | Jasielec J, Kimball AS, Cohen KS, et al. Temsirolimus (TEM) and lenalidomide (LEN) in relapsed/refractory Hodgkin lymphoma including in patients with prior exposure to brentuximab vedotin (BV). Journal of Clinical Oncology. 2014;32(15). |

| Study in Figure 27 | Reference |
|---|---|
| Gibb (2013) | Gibb A, Jones C, Bloor A, et al. Brentuximab vedotin in refractory CD30+ lymphomas: a bridge to allogeneic transplantation in approximately one quarter of patients treated on a Named Patient Programme at a single UK center. Haematologica. 2013;98(4):611-4. |
| Garciaz (2014b) | Garciaz S, Coso D, Peyrade F, et al. Brentuximab vedotin followed by allogeneic transplantation as salvage regimen in patients with relapsed and/or refractory Hodgkin's lymphoma. Hematological Oncology. 2014;32(4):187-91. |
| Gandolfi (2015) | Gandolfi L, Celli M, Pellegrini C, et al. Long-term responders after brentuximab vedotin: Experience on 57 patients with relapsed and refractory hodgkin and anaplastic large cell lymphoma. Haematologica. 2015;100:3. |
| Fehniger (2012) | Fehniger TA, Larson S, Trinkaus K, et al. A phase 2 multicenter study of continuous dose lenalidomide in relapsed or refractory classical hodgkin lymphoma. Blood. 2012;120(21). |
| Clozel (2013) | Clozel T, Deau B, Benet C, et al. Pegylated liposomal doxorubicin: an efficient treatment in patients with Hodgkin lymphoma relapsing after high dose therapy and stem cell transplation. British Journal of Haematology. 2013;162(6):846-8. |
| Christian (2012) | Christian B, Kopko A, Fehniger TA, et al. A phase I trial of the histone deacetylase (HDAC) inhibitor, panobinostat, in combination with lenalidomide in patients with relapsed/refractory hodgkin's lymphoma (HL). Blood. 2012;120(21). |
| Anastasia (2014)b | Anastasia A, Carlo-Stella C, Corradini P, et al. Bendamustine for Hodgkin lymphoma patients failing autologous or autologous and allogeneic stem cell transplantation: A retrospective study of the Fondazione Italiana Linfomi. British Journal of Haematology. 2014;166(1):140-2. |
| Anastasia (2014)a | Anastasia A, Carlo-Stella C, Corradini P, et al. Bendamustine for relapsed/refractory classical hodgkin lymphoma after high dose chemotherapy and or allogeneic transplant: A study of fondazione italiana linfomi (FIL). Blood. 2012;120(21). |
| **Lenalidomide** | |
| Rueda (2015) | Rueda A, García-Sanz R, Pastor M, et al. A phase II study to evaluate lenalidomide in combination with metronomic-dose cyclophosphamide in patients with heavily pretreated classical Hodgkin lymphoma. Acta Oncologica. 2015;54(6):933-8. |
| Fehniger (2011) | Fehniger TA, Larson S, Trinkaus K, et al. A phase 2 multicenter study of lenalidomide in relapsed or refractory classical Hodgkin lymphoma. Blood. 2011;118(19):5119-25. |
| **Investigational** | |
| Younes (2012b) | Younes A, Sureda A, Ben-Yehuda D, et al. Panobinostat in patients with relapsed/refractory Hodgkin's lymphoma after autologous stem-cell transplantation: Results of a phase II study. Journal of Clinical Oncology. 2012;30(18):2197-203. |
| Younes (2011b)a | Younes A, Oki Y, Bociek RG, et al. Mocetinostat for relapsed classical Hodgkin's lymphoma: An open-label, single-arm, phase 2 trial. The Lancet Oncology. 2011;12(13):1222-8. |
| Smith (2013) | Smith SM, Schöder H, Johnson JL, et al. The anti-CD80 primatized monoclonal antibody, galiximab, is well-tolerated but has limited activity in relapsed Hodgkin lymphoma: Cancer and Leukemia Group B 50602 (Alliance). Leukemia and Lymphoma. 2013;54(7):1405-10. |
| Schnell (2005) | Schnell R, Dietlein M, Staak JO, et al. Treatment of refractory Hodgkin's lymphoma patients with an iodine-131–labeled murine anti-CD30 monoclonal antibody. Journal of Clinical Oncology. 2005;23(21):4669-78. |
| Forero Torres (2015)b | Forero-Torres A, Barr PM, Magid Diefenbach CS, et al. A phase 1 study of PI3Kδ inhibitor INCB040093 alone or in combination with selective JAK1 inhibitor INCB039110 in patients with relapsed/refractory hodgkin lymphoma. Hematological Oncology. 2015;33:157. |
| Forero Torres (2015)a | |
| Armand (2015) | Armand P, Shipp MA, Ribrag V, et al. PD-1 blockade with pembrolizumab in patients with classical hodgkin lymphoma after brentuximab vedotin failure: Safety, efficacy, and biomarker assessment. Blood. 2015;126(23):584. |
| Ansell (2007)e | Ansell SM, Horwitz SM, Engert A, et al. Phase I/II study of an anti-CD30 monoclonal antibody (MDX-060) in Hodgkin's lymphoma and anaplastic large-cell lymphoma. Journal of Clinical Oncology. 2007;25(19):2764-9. |
| Ansell (2007)b | |
| Aloj (2014) | Aloj L, D'Ambrosio L, Aurilio M, et al. Radioimmunotherapy with Tenarad, a 131I-labelled antibody fragment targeting the extra-domain A1 of tenascin-C, in patients with refractory Hodgkin's lymphoma. European Journal of Nuclear Medicine and Molecular Imaging. 2014;41(5):867-77. |
| **Everolimus** | |

| Study in Figure 27 | Reference |
|---|---|
| Johnston (2010) | Johnston PB, Inwards DJ, Colgan JP, et al. A Phase II trial of the oral mTOR inhibitor everolimus in relapsed Hodgkin lymphoma. American Journal of Hematology. 2010;85(5):320-4. |
| **Chemotherapy** | |
| Ozdemir (2015a) | Ozdemir E, Aslan A, Turker A, et al. Single agent gemcitabine as a salvage regimen in patients with relapsed/refractory Hodgkin's lymphoma after autologous stem cell transplantation. Blood. 2015;126(23):5090. |
| Ozdemir (2015b) | Ozdemir E, Aslan A, Turker A, et al. Gemcitabine in combination with oxaliplatin (GEMOX) as a salvage regimen in patients with relapsed/refractory hodgkin's lymphoma. Blood. 2015;126(23):1517. |
| Moskowitz (2009) | Moskowitz AJ, Perales MA, Kewalramani T, et al. Outcomes for patients who fail high dose chemoradiotherapy and autologous stem cell rescue for relapsed and primary refractory Hodgkin lymphoma. Br J Haematol. 2009;146(2):158-63. |
| Little (1998) | Little R, Wittes RE, Longo DL, et al. Vinblastine for recurrent Hodgkin's disease following autologous bone marrow transplant. Journal of Clinical Oncology. 1998;16(2):584-8. |
| Czyz (2013) | Czyz A, Romejko-Jarosinska J, Knopinska-Posluszny W, et al. Treatment strategy based on gemcitabine-containing salvage chemotherapy used with intent to proceed to second stem cell transplant for patients with Hodgkin lymphoma relapsing after a prior autologous transplant. Leukemia and Lymphoma. 2013;54(5):973-8. |
| Czyz (2010) | Czyz A, Nowicki A, Gil L, et al. Gemcitabine-based salvage chemotherapy as a bridge to allogeneic hematopoietic stem cell transplantation for the patients with relapse of hodgkin lymphoma after autologous hematopoietic stem cell transplantation. Blood. 2010;116(21). |
| Bartlett (2007) | Bartlett NL, Niedzwiecki D, Johnson JL, et al. Gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD), a salvage regimen in relapsed Hodgkin's lymphoma: CALGB 59804. Annals of Oncology. 2007;18(6):1071-9. |
| **Brentuximab vedotin** | |
| Younes (2010a) | Younes A, Bartlett NL, Leonard JP, et al. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. New England Journal of Medicine. 2010;363(19):1812-21. |
| Viviani (2015) | Viviani S, Guidetti A, Dalto S, et al. Brentuximab vedotin (BV) an effective treatment for transplant ineligible patients with relapsed/refractory (R/R) hodgkin lymphoma (HL). Haematologica. 2015;100:455-6. |
| Tsirigotis (2015) | Tsirigotis P, Vassilakopoulos T, Bousiou Z, et al. Salvage treatment of patients with relapsed/refractory hodgkin lymphoma with brentuximab vedotin: The greek experience. Haematologica. 2015;100:454-5. |
| Pellegrini(2012) | Pellegrini C, Viviani S, Anastasia A, et al. Brentuximab vedotin in 65 relapsed/refractory hodgkin's lymphoma: Preliminary report of a multicenter italian retrospective study. Haematologica. 2012;97:84. |
| Monjanel (2014) | Monjanel H, Malphettes M, Deville L, et al. Brentuximab vedotin in heavily treated hodgkin and anaplastic lymphoma, a single center study on 45 patients. Hematological Oncology. 2013;31:268. |
| Minga (2014) | Minga P, Meli E, Rusconi C, et al. Efficacy and toxicity of brentuximab vedotin monotherapy in relapsed or refractory CD30+ classical hodgkin lymphoma patients outside clinical trials. Haematologica. 2014;99:679. |
| Kuruvilla (2015) | Kuruvilla J, Connors JM, Sawas A, et al. A phase 1 study of brentuximab vedotin (BV) and bendamustine (B) in relapsed or refractory hodgkin lymphoma (HL) and anaplastic large T-cell lymphoma (ALCL). Hematological Oncology. 2015;33:148. |
| Gopal (2015) | Gopal AK, Chen R, Smith SE, et al. Durable remissions in a pivotal phase 2 study of brentuximab vedotin in relapsed or refractory Hodgkin lymphoma. Blood. 2015;125(8):1236-43. |
| Fanale (2012) | Fanale MA, Bartlett NL, Forero-Torres A, et al. Retrospective analysis of the safety and efficacy of brentuximab vedotin in patients aged 60 years or older with relapsed or refractory CD30+ hematologic malignancies. Blood. 2012;120(21). |
| Erdem (2013a) | Erdem G, Karadurmus N, Ozaydin S, et al. Brentuximab vedotin (SGN-35) in Hodgkin Lymphoma patients with relapsed after autologous peripheral blood stem-cell transplantation. Haematologica. 2013;98:53. |
| Chen (2012a) | Chen R, Palmer JM, Thomas SH, et al. Brentuximab vedotin enables successful reduced-intensity allogeneic hematopoietic cell transplantation in patients with relapsed or refractory Hodgkin lymphoma. Blood. 2012;119(26):6379-81. |

| Study in Figure 27 | Reference |
|---|---|
| Bartlett (2014) | Bartlett NL, Chen R, Fanale MA, et al. Retreatment with brentuximab vedotin in patients with CD30-positive hematologic malignancies. Journal of Hematology and Oncology. 2014;7(1). |
| **Bendamustine** | |
| Zinzani (2015b) | Zinzani PL, Vitolo U, Viviani S, et al. Safety and efficacy of single-agent bendamustine after failure of brentuximab vedotin in patients with relapsed or refractory Hodgkin's lymphoma: Experience with 27 patients. Clinical Lymphoma, Myeloma and Leukemia. 2015;15(7):404-8. |
| Moskowitz (2013) | Moskowitz AJ, Hamlin Jr PA, Perales MA, et al. Phase ii study of bendamustine in relapsed and refractory hodgkin lymphoma. Journal of Clinical Oncology. 2013;31(4):456-60. |
| Ghesquières (2013) | Ghesquières H, Stamatoullas A, Casasnovas O, et al. Clinical experience of bendamustine in relapsed or refractory Hodgkin lymphoma: A retrospective analysis of the French compassionate use program in 28 patients. Leukemia and Lymphoma. 2013;54(11):2399-404. |
| Corazzelli (2013) | Corazzelli G, Angrilli F, D'Arco A, et al. Efficacy and safety of bendamustine for the treatment of patients with recurring Hodgkin lymphoma. British Journal of Haematology. 2013;160(2):207-15. |
| Brice (2012) | Brice P, Ghesquieres H, Stamatoullas A, et al. Bendamustine in heavily treated hodgkin lymphoma, a retrospective French study in 28 patients. Haematologica. 2012;97:86. |
| **Allogeneic SCT** | |
| Thomson (2008) | Thomson KJ, Peggs KS, Smith P, et al. Superiority of reduced-intensity allogeneic transplantation over conventional treatment for relapse of Hodgkin's lymphoma following autologous stem cell transplantation. Bone Marrow Transplantation. 2008;41(9):765-70. |
| Thompson (2015a) | Thompson PA, Perera T, Marin D, et al. Double umbilical cord blood transplant is effective therapy for relapsed or refractory Hodgkin lymphoma. Leukemia and Lymphoma. 2015:1-9. |
| Sarina (2010) | Sarina B, Castagna L, Farina L, et al. Allogeneic transplantation improves the overall and progression-free survival of Hodgkin lymphoma patients relapsing after autologous transplantation: A retrospective study based on the time of HLA typing and donor availability. Blood. 2010;115(18):3671-7. |
| Robinson (2009) | Robinson SP, Sureda A, Canals C, et al. Reduced intensity conditioning allogeneic stem cell transplantation for Hodgkin's lymphoma: Identification of prognostic factors predicting outcome. Haematologica. 2009;94(2):230-8. |
| Porter (2001) | Porter DL, Luger SM, Duffy KM, et al. Allogeneic cell therapy for patients who relapse after autologous stem cell transplantation. Biology of Blood and Marrow Transplantation. 2001;7(4):230-8. |
| Majhail (2006)a | Majhail NS, Weisdorf DJ, Wagner JE, et al. Comparable results of umbilical cord blood and HLA-matched sibling donor hematopoietic stem cell transplantation after reduced-intensity preparative regimen for advanced Hodgkin lymphoma. Blood. 2006;107(9):3804-7. |
| Dey (2001) | Dey BR, McAfee S, Sackstein R, et al. Successful allogeneic stem cell transplantation with nonmyeloablative conditioning in patients with relapsed hematologic malignancy following autologous stem cell transplantation. Biology of Blood and Marrow Transplantation. 2001;7(11):604-12. |
| Cooney (2003) | Cooney JP, Stiff PJ, Toor AA, et al. BEAM allogeneic transplantation for patients with Hodgkin's disease who relapse after autologous transplantation is safe and effective. Biol Blood Marrow Transplant. 2003;9(3):177-82. |
| Chen (2011) | Chen R, Palmer JM, Popplewell L, et al. Reduced intensity allogeneic hematopoietic cell transplantation can induce durable remission in heavily pretreated relapsed Hodgkin lymphoma. Annals of Hematology. 2011;90(7):803-8. |
| Armand (2008) | Armand P, Kim HT, Ho VT, et al. Allogeneic Transplantation with Reduced-Intensity Conditioning for Hodgkin and non-Hodgkin Lymphoma: Importance of Histology for Outcome. Biology of Blood and Marrow Transplantation. 2008;14(4):418-25. |
| Anderlini (2008) | Anderlini P, Saliba R, Acholonu S, et al. Fludarabine-melphalan as a preparative regimen for reduced-intensity conditioning allogeneic stem cell transplantation in relapsed and refractory Hodgkin's lymphoma: The updated M.D. Anderson Cancer Center experience. Haematologica. 2008;93(2):257-64. |
| Anderlini (2005) | Anderlini P, Saliba R, Acholonu S, et al. Reduced-intensity allogeneic stem cell transplantation in relapsed and refractory Hodgkin's disease: Low transplant-related mortality and impact of intensity of conditioning regimen. Bone Marrow Transplantation. 2005;35(10):943-51. |
| Alvarez (2006) | Alvarez I, Sureda A, Caballero MD, et al. Nonmyeloablative stem cell transplantation is an effective therapy for refractory or relapsed Hodgkin lymphoma: Results of a Spanish prospective cooperative protocol. Biology of Blood and Marrow Transplantation. 2006;12(2):172-83. |

**Table 18. References applying to Appendix 3 Figure 28**

| Study in Figure 28 | Reference |
|---|---|
| ***SCT** | |
| Smith (2008) | Smith SM, van Besien K, Carreras J, et al. Second Autologous Stem Cell Transplantation for Relapsed Lymphoma after a Prior Autologous Transplant. Biology of Blood and Marrow Transplantation. 2008;14(8):904-12. |
| Anderlini (2011) | Anderlini P, Acholonu S, Okoroji GJ, et al. Donor leukocyte infusions (DLIs) for recurrent hodgkin lymphoma (HL) following allogeneic stem cell transplantation (allo-SCT): Ten-year experience at the M.D. anderson cancer center. Blood. 2011;118(21). |
| **Radiotherapy** | |
| Tsang (2010) | Tsang RW, Goda JS, Massey C, et al. What can be expected from salvage radiation therapy when an autologous stem cell transplant (ASCT) fails to control Hodgkin lymphoma? Haematologica. 2010;95:S27. |
| Goda (2012) | Goda JS, Massey C, Kuruvilla J, et al. Role of salvage radiation therapy for patients with relapsed or refractory Hodgkin lymphoma who failed autologous stem cell transplant. International Journal of Radiation Oncology Biology Physics. 2012;84(3):e329-e35. |
| **<70% post−ASCT** | |
| Zinzani (2000) | Zinzani PL, Bendandi M, Stefoni V, et al. Value of gemcitabine treatment in heavily pretreated Hodgkin's disease patients. Haematologica. 2000;85(9):926-9. |
| Younes (1996) | Younes A, Cabanillas F, McLaughlin PW, et al. Preliminary experience with paclitaxel for the treatment of relapsed and refractory Hodgkin's disease. Ann Oncol. 1996;7(10):1083-5. |
| Walweski (2011) | Walewski J, Paszkiewicz-Kozik E, Warszewska A, et al. Final results of the phase II SAPHIRE trial of resminostat (4SC-201) in patients with relapsed/refractory Hodgkin lymphoma. Blood. 2011;118(21). |
| Validire (2008) | Validire P, Ferme C, Brice P, et al. A multicenter study of gemcitabine-containing regimen in relapsed or refractory Hodgkin's lymphoma patients. Anti-cancer drugs. 2008;19(3):309-15. |
| Ricciuti (2014) | Ricciuti G, Finolezzi E, Falorio S, et al. Salvage treatment with single-agent bendamustine for relapsed/refractory hodgkin lymphoma: An Italian monocentric experience. Haematologica. 2014;99:677-8. |
| Pugliese (2013a) | Pugliese N, Cerchione C, Grimaldi F, et al. Bendamustine-based therapy is effective and has a favourable toxicity profile in the treatment of refractory and relapsed hodgkin lymphoma. Haematologica. 2013;98:571. |
| Pinto (2015) | Pinto A, Pavone V, Angrilli F, et al. Lenalidomide in combination with bendamustine for patients with chemorefractory hodgkin lymphoma: Final results of the leben multicenter phase 1/2 study. Blood. 2015;126(23):1541. |
| Oki (2008) | Oki Y, Pro B, Fayad LE, et al. Phase 2 study of gemcitabine in combination with rituximab in patients with recurrent or refractory Hodgkin lymphoma. Cancer. 2008;112(4):831-6. |
| Moskowitz (2012) | Moskowitz CH, Younes A, De Vos S, et al. CSF1R inhibition by PLX3397 in patients with relapsed or refractory hodgkin lymphoma: Results from a phase 2 single agent clinical trial. Blood. 2012;120(21). |
| Kalyoannidis (2011) | Kaloyannidis P, Voutiadou G, Baltadakis I, et al. Outcomes of Hodgkin's Lymphoma Patients with Relapse or Progression following Autologous Hematopoietic Cell Transplantation. Biology of Blood and Marrow Transplantation. 2012;18(3):451-7. |
| Johnston (2013) | Johnston PB, Pinter-Brown L, Rogerio J, et al. Phase 2 study everolimus for relapsed/refractory classical Hodgkin Lymphoma (CHL). Haematologica. 2013;98:44. |
| Jasielec (2014) | Jasielec J, Kimball AS, Cohen KS, et al. Temsirolimus (TEM) and lenalidomide (LEN) in relapsed/refractory Hodgkin lymphoma including in patients with prior exposure to brentuximab vedotin (BV). Journal of Clinical Oncology. 2014;32(15). |
| Guidetti (2012) | Guidetti A, Viviani S, Marchianò A, et al. Dual targeted therapy with the AKT inhibitor perifosine and the multikinase inhibitor sorafenib in patients with relapsed/refractory lymphomas: Final results of a phase II trial. Blood. 2012;120(21). |
| Gibb (2013) | Gibb A, Jones C, Bloor A, et al. Brentuximab vedotin in refractory CD30+ lymphomas: a bridge to allogeneic transplantation in approximately one quarter of patients treated on a Named Patient Programme at a single UK center. Haematologica. 2013;98(4):611-4. |

| Study in Figure 28 | Reference |
|---|---|
| Garciaz (2014b) | Garciaz S, Coso D, Peyrade F, et al. Brentuximab vedotin followed by allogeneic transplantation as salvage regimen in patients with relapsed and/or refractory Hodgkin's lymphoma. Hematological Oncology. 2014;32(4):187-91. |
| Fehniger (2012) | Fehniger TA, Larson S, Trinkaus K, et al. A phase 2 multicenter study of continuous dose lenalidomide in relapsed or refractory classical hodgkin lymphoma. Blood. 2012;120(21). |
| Clozel (2013) | Clozel T, Deau B, Benet C, et al. Pegylated liposomal doxorubicin: an efficient treatment in patients with Hodgkin lymphoma relapsing after high dose therapy and stem cell transplation. British Journal of Haematology. 2013;162(6):846-8. |
| Christian (2012) | Christian B, Kopko A, Fehniger TA, et al. A phase I trial of the histone deacetylase (HDAC) inhibitor, panobinostat, in combination with lenalidomide in patients with relapsed/refractory hodgkin's lymphoma (HL). Blood. 2012;120(21). |
| Anastasia (2014)b | Anastasia A, Carlo-Stella C, Corradini P, et al. Bendamustine for Hodgkin lymphoma patients failing autologous or autologous and allogeneic stem cell transplantation: A retrospective study of the Fondazione Italiana Linfomi. British Journal of Haematology. 2014;166(1):140-2. |
| Anastasia (2014)a | Anastasia A, Carlo-Stella C, Corradini P, et al. Bendamustine for relapsed/refractory classical hodgkin lymphoma after high dose chemotherapy and or allogeneic transplant: A study of fondazione italiana linfomi (FIL). Blood. 2012;120(21). |
| **Lenalidomide** | |
| Rueda (2015) | Rueda A, García-Sanz R, Pastor M, et al. A phase II study to evaluate lenalidomide in combination with metronomic-dose cyclophosphamide in patients with heavily pretreated classical Hodgkin lymphoma. Acta Oncologica. 2015;54(6):933-8. |
| Fehniger (2011) | Fehniger TA, Larson S, Trinkaus K, et al. A phase 2 multicenter study of lenalidomide in relapsed or refractory classical Hodgkin lymphoma. Blood. 2011;118(19):5119-25. |
| **Investigational** | |
| Younes (2012b) | Younes A, Sureda A, Ben-Yehuda D, et al. Panobinostat in patients with relapsed/refractory Hodgkin's lymphoma after autologous stem-cell transplantation: Results of a phase II study. Journal of Clinical Oncology. 2012;30(18):2197-203. |
| Younes (2011b)b | Younes A, Oki Y, Bociek RG, et al. Mocetinostat for relapsed classical Hodgkin's lymphoma: An open-label, single-arm, phase 2 trial. The Lancet Oncology. 2011;12(13):1222-8. |
| Younes (2011b)a | |
| Smith (2013) | Smith SM, Schöder H, Johnson JL, et al. The anti-CD80 primatized monoclonal antibody, galiximab, is well-tolerated but has limited activity in relapsed Hodgkin lymphoma: Cancer and Leukemia Group B 50602 (Alliance). Leukemia and Lymphoma. 2013;54(7):1405-10. |
| Schnell (2005) | Schnell R, Dietlein M, Staak JO, et al. Treatment of refractory Hodgkin's lymphoma patients with an iodine-131–labeled murine anti-CD30 monoclonal antibody. Journal of Clinical Oncology. 2005;23(21):4669-78. |
| Kuruvilla (2006) | Kuruvilla J, Song K, Mollee P, et al. A phase II study of thalidomide and vinblastine for palliative patients with Hodgkin's lymphoma. Hematology. 2006;11(1):25-9. |
| Forero Torres (2015)b | Forero-Torres A, Barr PM, Magid Diefenbach CS, et al. A phase 1 study of PI3Kδ inhibitor INCB040093 alone or in combination with selective JAK1 inhibitor INCB039110 in patients with relapsed/refractory hodgkin lymphoma. Hematological Oncology. 2015;33:157. |
| Forero Torres (2015)a | |
| Dickinson (2009) | Dickinson M, Ritchie D, Deangelo DJ, et al. Preliminary evidence of disease response to the pan deacetylase inhibitor panobinostat (LBH589) in refractory Hodgkin Lymphoma. British Journal of Haematology. 2009;147(1):97-101. |
| Armand (2015) | Armand P, Shipp MA, Ribrag V, et al. PD-1 blockade with pembrolizumab in patients with classical hodgkin lymphoma after brentuximab vedotin failure: Safety, efficacy, and biomarker assessment. Blood. 2015;126(23):584. |
| Ansell (2007)c | Ansell SM, Horwitz SM, Engert A, et al. Phase I/II study of an anti-CD30 monoclonal antibody (MDX-060) in Hodgkin's lymphoma and anaplastic large-cell lymphoma. Journal of Clinical Oncology. 2007;25(19):2764-9. |
| Ansell (2007)b | |
| Aloj (2014) | Aloj L, D'Ambrosio L, Aurilio M, et al. Radioimmunotherapy with Tenarad, a 131I-labelled antibody fragment targeting the extra-domain A1 of tenascin-C, in patients with refractory Hodgkin's lymphoma. European Journal of Nuclear Medicine and Molecular Imaging. 2014;41(5):867-77. |
| **Everolimus** | |
| Johnston (2010) | Johnston PB, Inwards DJ, Colgan JP, et al. A Phase II trial of the oral mTOR inhibitor everolimus in relapsed Hodgkin lymphoma. American Journal of Hematology. 2010;85(5):320-4. |

| Study in Figure 28 | Reference |
|---|---|
| **Chemotherapy** | |
| Ozdemir (2015a) | Ozdemir E, Aslan A, Turker A, et al. Single agent gemcitabine as a salvage regimen in patients with relapsed/refractory Hodgkin's lymphoma after autologous stem cell transplantation. Blood. 2015;126(23):5090. |
| Ozdemir (2015b) | Ozdemir E, Aslan A, Turker A, et al. Gemcitabine in combination with oxaliplatin (GEMOX) as a salvage regimen in patients with relapsed/refractory hodgkin's lymphoma. Blood. 2015;126(23):1517. |
| Moskowitz (2009) | Moskowitz AJ, Perales MA, Kewalramani T, et al. Outcomes for patients who fail high dose chemoradiotherapy and autologous stem cell rescue for relapsed and primary refractory Hodgkin lymphoma. Br J Haematol. 2009;146(2):158-63. |
| Little (1998) | Little R, Wittes RE, Longo DL, et al. Vinblastine for recurrent Hodgkin's disease following autologous bone marrow transplant. Journal of Clinical Oncology. 1998;16(2):584-8. |
| Czyz (2013) | Czyz A, Romejko-Jarosinska J, Knopinska-Posluszny W, et al. Treatment strategy based on gemcitabine-containing salvage chemotherapy used with intent to proceed to second stem cell transplant for patients with Hodgkin lymphoma relapsing after a prior autologous transplant. Leukemia and Lymphoma. 2013;54(5):973-8. |
| Czyz (2010) | Czyz A, Nowicki A, Gil L, et al. Gemcitabine-based salvage chemotherapy as a bridge to allogeneic hematopoietic stem cell transplantation for the patients with relapse of hodgkin lymphoma after autologous hematopoietic stem cell transplantation. Blood. 2010;116(21). |
| Bartlett (2007) | Bartlett NL, Niedzwiecki D, Johnson JL, et al. Gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD), a salvage regimen in relapsed Hodgkin's lymphoma: CALGB 59804. Annals of Oncology. 2007;18(6):1071-9. |
| **Brentuximab vedotin** | |
| Younes (2010a) | Younes A, Bartlett NL, Leonard JP, et al. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. New England Journal of Medicine. 2010;363(19):1812-21. |
| Viviani (2015) | Viviani S, Guidetti A, Dalto S, et al. Brentuximab vedotin (BV) an effective treatment for transplant ineligible patients with relapsed/refractory (R/R) hodgkin lymphoma (HL). Haematologica. 2015;100:455-6. |
| Tsirigotis (2015) | Tsirigotis P, Vassilakopoulos T, Bousiou Z, et al. Salvage treatment of patients with relapsed/refractory hodgkin lymphoma with brentuximab vedotin: The greek experience. Haematologica. 2015;100:454-5. |
| Pellegrini(2012) | Pellegrini C, Viviani S, Anastasia A, et al. Brentuximab vedotin in 65 relapsed/refractory hodgkin's lymphoma: Preliminary report of a multicenter italian retrospective study. Haematologica. 2012;97:84. |
| Monjanel (2014) | Monjanel H, Malphettes M, Deville L, et al. Brentuximab vedotin in heavily treated hodgkin and anaplastic lymphoma, a single center study on 45 patients. Hematological Oncology. 2013;31:268. |
| Minga (2014) | Minga P, Meli E, Rusconi C, et al. Efficacy and toxicity of brentuximab vedotin monotherapy in relapsed or refractory CD30+ classical hodgkin lymphoma patients outside clinical trials. Haematologica. 2014;99:679. |
| Kuruvilla (2015) | Kuruvilla J, Connors JM, Sawas A, et al. A phase 1 study of brentuximab vedotin (BV) and bendamustine (B) in relapsed or refractory hodgkin lymphoma (HL) and anaplastic large T-cell lymphoma (ALCL). Hematological Oncology. 2015;33:148. |
| Gopal (2015) | Gopal AK, Chen R, Smith SE, et al. Durable remissions in a pivotal phase 2 study of brentuximab vedotin in relapsed or refractory Hodgkin lymphoma. Blood. 2015;125(8):1236-43. |
| Fanale (2012) | Fanale MA, Bartlett NL, Forero-Torres A, et al. Retrospective analysis of the safety and efficacy of brentuximab vedotin in patients aged 60 years or older with relapsed or refractory CD30+ hematologic malignancies. Blood. 2012;120(21). |
| Erdem (2013a) | Erdem G, Karadurmus N, Ozaydin S, et al. Brentuximab vedotin (SGN-35) in Hodgkin Lymphoma patients with relapsed after autologous peripheral blood stem-cell transplantation. Haematologica. 2013;98:53. |
| Chen (2012a) | Chen R, Palmer JM, Thomas SH, et al. Brentuximab vedotin enables successful reduced-intensity allogeneic hematopoietic cell transplantation in patients with relapsed or refractory Hodgkin lymphoma. Blood. 2012;119(26):6379-81. |
| Bartlett (2014) | Bartlett NL, Chen R, Fanale MA, et al. Retreatment with brentuximab vedotin in patients with CD30-positive hematologic malignancies. Journal of Hematology and Oncology. 2014;7(1). |

| Study in Figure 28 | Reference |
|---|---|
| **Bendamustine** | |
| Zinzani (2015b) | Zinzani PL, Vitolo U, Viviani S, et al. Safety and efficacy of single-agent bendamustine after failure of brentuximab vedotin in patients with relapsed or refractory Hodgkin's lymphoma: Experience with 27 patients. Clinical Lymphoma, Myeloma and Leukemia. 2015;15(7):404-8. |
| Moskowitz (2013) | Moskowitz AJ, Hamlin Jr PA, Perales MA, et al. Phase ii study of bendamustine in relapsed and refractory hodgkin lymphoma. Journal of Clinical Oncology. 2013;31(4):456-60. |
| Ghesquières (2013) | Ghesquières H, Stamatoullas A, Casasnovas O, et al. Clinical experience of bendamustine in relapsed or refractory Hodgkin lymphoma: A retrospective analysis of the French compassionate use program in 28 patients. Leukemia and Lymphoma. 2013;54(11):2399-404. |
| Corazzelli (2013) | Corazzelli G, Angrilli F, D'Arco A, et al. Efficacy and safety of bendamustine for the treatment of patients with recurring Hodgkin lymphoma. British Journal of Haematology. 2013;160(2):207-15. |
| Brice (2012) | Brice P, Ghesquieres H, Stamatoullas A, et al. Bendamustine in heavily treated hodgkin lymphoma, a retrospective French study in 28 patients. Haematologica. 2012;97:86. |
| **Allogeneic SCT** | |
| Thomson (2008) | Thomson KJ, Peggs KS, Smith P, et al. Superiority of reduced-intensity allogeneic transplantation over conventional treatment for relapse of Hodgkin's lymphoma following autologous stem cell transplantation. Bone Marrow Transplantation. 2008;41(9):765-70. |
| Thompson (2015a) | Thompson PA, Perera T, Marin D, et al. Double umbilical cord blood transplant is effective therapy for relapsed or refractory Hodgkin lymphoma. Leukemia and Lymphoma. 2015:1-9. |
| Robinson (2009) | Robinson SP, Sureda A, Canals C, et al. Reduced intensity conditioning allogeneic stem cell transplantation for Hodgkin's lymphoma: Identification of prognostic factors predicting outcome. Haematologica. 2009;94(2):230-8. |
| Porter (2001) | Porter DL, Luger SM, Duffy KM, et al. Allogeneic cell therapy for patients who relapse after autologous stem cell transplantation. Biology of Blood and Marrow Transplantation. 2001;7(4):230-8. |
| Cooney (2003) | Cooney JP, Stiff PJ, Toor AA, et al. BEAM allogeneic transplantation for patients with Hodgkin's disease who relapse after autologous transplantation is safe and effective. Biol Blood Marrow Transplant. 2003;9(3):177-82. |
| Alvarez (2006) | Alvarez I, Sureda A, Caballero MD, et al. Nonmyeloablative stem cell transplantation is an effective therapy for refractory or relapsed Hodgkin lymphoma: Results of a Spanish prospective cooperative protocol. Biology of Blood and Marrow Transplantation. 2006;12(2):172-83. |

**Table 19. References applying to Appendix 3 Figure 29**

| Study in Figure 29 | Reference |
|---|---|
| **Radiotherapy** | |
| Tsang (2010) | Tsang RW, Goda JS, Massey C, et al. What can be expected from salvage radiation therapy when an autologous stem cell transplant (ASCT) fails to control Hodgkin lymphoma? Haematologica. 2010;95:S27. |
| Goda (2012) | Goda JS, Massey C, Kuruvilla J, et al. Role of salvage radiation therapy for patients with relapsed or refractory Hodgkin lymphoma who failed autologous stem cell transplant. International Journal of Radiation Oncology Biology Physics. 2012;84(3):e329-e35. |
| **Lenalidomide** | |
| Rueda (2015) | Rueda A, García-Sanz R, Pastor M, et al. A phase II study to evaluate lenalidomide in combination with metronomic-dose cyclophosphamide in patients with heavily pretreated classical Hodgkin lymphoma. Acta Oncologica. 2015;54(6):933-8. |
| Fehniger (2011) | Fehniger TA, Larson S, Trinkaus K, et al. A phase 2 multicenter study of lenalidomide in relapsed or refractory classical Hodgkin lymphoma. Blood. 2011;118(19):5119-25. |
| **Investigational** | |
| Younes (2012b) | Younes A, Sureda A, Ben-Yehuda D, et al. Panobinostat in patients with relapsed/refractory Hodgkin's lymphoma after autologous stem-cell transplantation: Results of a phase II study. Journal of Clinical Oncology. 2012;30(18):2197-203. |
| Younes (2011b)a | Younes A, Oki Y, Bociek RG, et al. Mocetinostat for relapsed classical Hodgkin's lymphoma: An open-label, single-arm, phase 2 trial. The Lancet Oncology. 2011;12(13):1222-8. |
| Smith (2013) | Smith SM, Schöder H, Johnson JL, et al. The anti-CD80 primatized monoclonal antibody, galiximab, is well-tolerated but has limited activity in relapsed Hodgkin lymphoma: Cancer and Leukemia Group B 50602 (Alliance). Leukemia and Lymphoma. 2013;54(7):1405-10. |
| Schnell (2005) | Schnell R, Dietlein M, Staak JO, et al. Treatment of refractory Hodgkin's lymphoma patients with an iodine-131–labeled murine anti-CD30 monoclonal antibody. Journal of Clinical Oncology. 2005;23(21):4669-78. |
| Forero Torres (2015)b | Forero-Torres A, Barr PM, Magid Diefenbach CS, et al. A phase 1 study of PI3Kδ inhibitor INCB040093 alone or in combination with selective JAK1 inhibitor INCB039110 in patients with relapsed/refractory hodgkin lymphoma. Hematological Oncology. 2015;33:157. |
| Forero Torres (2015)a | |
| Armand (2015) | Armand P, Shipp MA, Ribrag V, et al. PD-1 blockade with pembrolizumab in patients with classical hodgkin lymphoma after brentuximab vedotin failure: Safety, efficacy, and biomarker assessment. Blood. 2015;126(23):584. |
| Ansell (2007)e | Ansell SM, Horwitz SM, Engert A, et al. Phase I/II study of an anti-CD30 monoclonal antibody (MDX-060) in Hodgkin's lymphoma and anaplastic large-cell lymphoma. Journal of Clinical Oncology. 2007;25(19):2764-9. |
| Ansell (2007)b | |
| Aloj (2014) | Aloj L, D'Ambrosio L, Aurilio M, et al. Radioimmunotherapy with Tenarad, a 131I-labelled antibody fragment targeting the extra-domain A1 of tenascin-C, in patients with refractory Hodgkin's lymphoma. European Journal of Nuclear Medicine and Molecular Imaging. 2014;41(5):867-77. |
| **Everolimus** | |
| Johnston (2010) | Johnston PB, Inwards DJ, Colgan JP, et al. A Phase II trial of the oral mTOR inhibitor everolimus in relapsed Hodgkin lymphoma. American Journal of Hematology. 2010;85(5):320-4. |
| **Chemotherapy** | |
| Ozdemir (2015a) | Ozdemir E, Aslan A, Turker A, et al. Single agent gemcitabine as a salvage regimen in patients with relapsed/refractory Hodgkin's lymphoma after autologous stem cell transplantation. Blood. 2015;126(23):5090. |
| Ozdemir (2015b) | Ozdemir E, Aslan A, Turker A, et al. Gemcitabine in combination with oxaliplatin (GEMOX) as a salvage regimen in patients with relapsed/refractory hodgkin's lymphoma. Blood. 2015;126(23):1517. |
| Moskowitz (2009) | Moskowitz AJ, Perales MA, Kewalramani T, et al. Outcomes for patients who fail high dose chemoradiotherapy and autologous stem cell rescue for relapsed and primary refractory Hodgkin lymphoma. Br J Haematol. 2009;146(2):158-63. |

| Study in Figure 29 | Reference |
|---|---|
| Little (1998) | Little R, Wittes RE, Longo DL, et al. Vinblastine for recurrent Hodgkin's disease following autologous bone marrow transplant. Journal of Clinical Oncology. 1998;16(2):584-8. |
| Czyz (2013) | Czyz A, Romejko-Jarosinska J, Knopinska-Posluszny W, et al. Treatment strategy based on gemcitabine-containing salvage chemotherapy used with intent to proceed to second stem cell transplant for patients with Hodgkin lymphoma relapsing after a prior autologous transplant. Leukemia and Lymphoma. 2013;54(5):973-8. |
| Czyz (2010) | Czyz A, Nowicki A, Gil L, et al. Gemcitabine-based salvage chemotherapy as a bridge to allogeneic hematopoietic stem cell transplantation for the patients with relapse of hodgkin lymphoma after autologous hematopoietic stem cell transplantation. Blood. 2010;116(21). |
| Bartlett (2007) | Bartlett NL, Niedzwiecki D, Johnson JL, et al. Gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD), a salvage regimen in relapsed Hodgkin's lymphoma: CALGB 59804. Annals of Oncology. 2007;18(6):1071-9. |
| **Bendamustine** | |
| Zinzani (2015b) | Zinzani PL, Vitolo U, Viviani S, et al. Safety and efficacy of single-agent bendamustine after failure of brentuximab vedotin in patients with relapsed or refractory Hodgkin's lymphoma: Experience with 27 patients. Clinical Lymphoma, Myeloma and Leukemia. 2015;15(7):404-8. |
| Moskowitz (2013) | Moskowitz AJ, Hamlin Jr PA, Perales MA, et al. Phase ii study of bendamustine in relapsed and refractory hodgkin lymphoma. Journal of Clinical Oncology. 2013;31(4):456-60. |
| Ghesquières (2013) | Ghesquières H, Stamatoullas A, Casasnovas O, et al. Clinical experience of bendamustine in relapsed or refractory Hodgkin lymphoma: A retrospective analysis of the French compassionate use program in 28 patients. Leukemia and Lymphoma. 2013;54(11):2399-404. |
| Corazzelli (2013) | Corazzelli G, Angrilli F, D'Arco A, et al. Efficacy and safety of bendamustine for the treatment of patients with recurring Hodgkin lymphoma. British Journal of Haematology. 2013;160(2):207-15. |
| Brice (2012) | Brice P, Ghesquieres H, Stamatoullas A, et al. Bendamustine in heavily treated hodgkin lymphoma, a retrospective French study in 28 patients. Haematologica. 2012;97:86. |

**Table 20. References applying to Appendix 3 Figure 30**

| Study in Figure 30 | Reference |
|---|---|
| **Radiotherapy** | |
| Tsang (2010) | Tsang RW, Goda JS, Massey C, et al. What can be expected from salvage radiation therapy when an autologous stem cell transplant (ASCT) fails to control Hodgkin lymphoma? Haematologica. 2010;95:S27. |
| Goda (2012) | Goda JS, Massey C, Kuruvilla J, et al. Role of salvage radiation therapy for patients with relapsed or refractory Hodgkin lymphoma who failed autologous stem cell transplant. International Journal of Radiation Oncology Biology Physics. 2012;84(3):e329-e35. |
| **Lenalidomide** | |
| Rueda (2015) | Rueda A, García-Sanz R, Pastor M, et al. A phase II study to evaluate lenalidomide in combination with metronomic-dose cyclophosphamide in patients with heavily pretreated classical Hodgkin lymphoma. Acta Oncologica. 2015;54(6):933-8. |
| Fehniger (2011) | Fehniger TA, Larson S, Trinkaus K, et al. A phase 2 multicenter study of lenalidomide in relapsed or refractory classical Hodgkin lymphoma. Blood. 2011;118(19):5119-25. |
| **Investigational** | |
| Younes (2012b) | Younes A, Sureda A, Ben-Yehuda D, et al. Panobinostat in patients with relapsed/refractory Hodgkin's lymphoma after autologous stem-cell transplantation: Results of a phase II study. Journal of Clinical Oncology. 2012;30(18):2197-203. |
| Younes (2011b)b | Younes A, Oki Y, Bociek RG, et al. Mocetinostat for relapsed classical Hodgkin's lymphoma: An open-label, single-arm, phase 2 trial. The Lancet Oncology. 2011;12(13):1222-8. |
| Younes (2011b)a | |
| Smith (2013) | Smith SM, Schöder H, Johnson JL, et al. The anti-CD80 primatized monoclonal antibody, galiximab, is well-tolerated but has limited activity in relapsed Hodgkin lymphoma: Cancer and Leukemia Group B 50602 (Alliance). Leukemia and Lymphoma. 2013;54(7):1405-10. |
| Schnell (2005) | Schnell R, Dietlein M, Staak JO, et al. Treatment of refractory Hodgkin's lymphoma patients with an iodine-131–labeled murine anti-CD30 monoclonal antibody. Journal of Clinical Oncology. 2005;23(21):4669-78. |
| Kuruvilla (2006) | Kuruvilla J, Song K, Mollee P, et al. A phase II study of thalidomide and vinblastine for palliative patients with Hodgkin's lymphoma. Hematology. 2006;11(1):25-9. |
| Forero Torres (2015)b | Forero-Torres A, Barr PM, Magid Diefenbach CS, et al. A phase 1 study of PI3Kδ inhibitor INCB040093 alone or in combination with selective JAK1 inhibitor INCB039110 in patients with relapsed/refractory hodgkin lymphoma. Hematological Oncology. 2015;33:157. |
| Forero Torres (2015)a | |
| Dickinson (2009) | Dickinson M, Ritchie D, Deangelo DJ, et al. Preliminary evidence of disease response to the pan deacetylase inhibitor panobinostat (LBH589) in refractory Hodgkin Lymphoma. British Journal of Haematology. 2009;147(1):97-101. |
| Armand (2015) | Armand P, Shipp MA, Ribrag V, et al. PD-1 blockade with pembrolizumab in patients with classical hodgkin lymphoma after brentuximab vedotin failure: Safety, efficacy, and biomarker assessment. Blood. 2015;126(23):584. |
| Ansell (2007)c | Ansell SM, Horwitz SM, Engert A, et al. Phase I/II study of an anti-CD30 monoclonal antibody (MDX-060) in Hodgkin's lymphoma and anaplastic large-cell lymphoma. Journal of Clinical Oncology. 2007;25(19):2764-9. |
| Ansell (2007)b | |
| Aloj (2014) | Aloj L, D'Ambrosio L, Aurilio M, et al. Radioimmunotherapy with Tenarad, a 131I-labelled antibody fragment targeting the extra-domain A1 of tenascin-C, in patients with refractory Hodgkin's lymphoma. European Journal of Nuclear Medicine and Molecular Imaging. 2014;41(5):867-77. |
| **Everolimus** | |
| Johnston (2010) | Johnston PB, Inwards DJ, Colgan JP, et al. A Phase II trial of the oral mTOR inhibitor everolimus in relapsed Hodgkin lymphoma. American Journal of Hematology. 2010;85(5):320-4. |
| **Chemotherapy** | |
| Ozdemir (2015a) | Ozdemir E, Aslan A, Turker A, et al. Single agent gemcitabine as a salvage regimen in patients with relapsed/refractory Hodgkin's lymphoma after autologous stem cell transplantation. Blood. 2015;126(23):5090. |

| Study in Figure 30 | Reference |
|---|---|
| Ozdemir (2015b) | Ozdemir E, Aslan A, Turker A, et al. Gemcitabine in combination with oxaliplatin (GEMOX) as a salvage regimen in patients with relapsed/refractory hodgkin's lymphoma. Blood. 2015;126(23):1517. |
| Moskowitz (2009) | Moskowitz AJ, Perales MA, Kewalramani T, et al. Outcomes for patients who fail high dose chemoradiotherapy and autologous stem cell rescue for relapsed and primary refractory Hodgkin lymphoma. Br J Haematol. 2009;146(2):158-63. |
| Little (1998) | Little R, Wittes RE, Longo DL, et al. Vinblastine for recurrent Hodgkin's disease following autologous bone marrow transplant. Journal of Clinical Oncology. 1998;16(2):584-8. |
| Czyz (2013) | Czyz A, Romejko-Jarosinska J, Knopinska-Posluszny W, et al. Treatment strategy based on gemcitabine-containing salvage chemotherapy used with intent to proceed to second stem cell transplant for patients with Hodgkin lymphoma relapsing after a prior autologous transplant. Leukemia and Lymphoma. 2013;54(5):973-8. |
| Czyz (2010) | Czyz A, Nowicki A, Gil L, et al. Gemcitabine-based salvage chemotherapy as a bridge to allogeneic hematopoietic stem cell transplantation for the patients with relapse of hodgkin lymphoma after autologous hematopoietic stem cell transplantation. Blood. 2010;116(21). |
| Bartlett (2007) | Bartlett NL, Niedzwiecki D, Johnson JL, et al. Gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD), a salvage regimen in relapsed Hodgkin's lymphoma: CALGB 59804. Annals of Oncology. 2007;18(6):1071-9. |
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| Zinzani (2015b) | Zinzani PL, Vitolo U, Viviani S, et al. Safety and efficacy of single-agent bendamustine after failure of brentuximab vedotin in patients with relapsed or refractory Hodgkin's lymphoma: Experience with 27 patients. Clinical Lymphoma, Myeloma and Leukemia. 2015;15(7):404-8. |
| Moskowitz (2013) | Moskowitz AJ, Hamlin Jr PA, Perales MA, et al. Phase ii study of bendamustine in relapsed and refractory hodgkin lymphoma. Journal of Clinical Oncology. 2013;31(4):456-60. |
| Ghesquières (2013) | Ghesquières H, Stamatoullas A, Casasnovas O, et al. Clinical experience of bendamustine in relapsed or refractory Hodgkin lymphoma: A retrospective analysis of the French compassionate use program in 28 patients. Leukemia and Lymphoma. 2013;54(11):2399-404. |
| Corazzelli (2013) | Corazzelli G, Angrilli F, D'Arco A, et al. Efficacy and safety of bendamustine for the treatment of patients with recurring Hodgkin lymphoma. British Journal of Haematology. 2013;160(2):207-15. |
| Brice (2012) | Brice P, Ghesquieres H, Stamatoullas A, et al. Bendamustine in heavily treated hodgkin lymphoma, a retrospective French study in 28 patients. Haematologica. 2012;97:86. |

## References


1. Follows GA, Ardeshna KM, Barrington SF, et al. Guidelines for the first line management of classical Hodgkin lymphoma. Br J Haematol. 2014;166(1):34-49.
2. Bristol-Myers Squibb Pharmaceuticals Ltd. Interim Clinical Study Report for Study CA209205. Non-Comparative, Multi-Cohort, Single-Arm, Open-Label, Phase 2 Study of Nivolumab (BMS-936558) in Classical Hodgkin Lymphoma (cHL) Subjects After Failure of Autologous Stem Cell Transplant (ASCT). 2016.
3. Bristol-Myers Squibb Pharmaceuticals Ltd. Interim Clinical Study Report for Study CA209039: A Phase 1 Dose Escalation Study to Investigate the Safety, Pharmacokinetics, Immunoregulatory Activity, and Preliminary Antitumor Activity of Anti-Programmed-Death 1 (PD-1) Antibody (Nivolumab, BMS-936558) and the Combinations of Nivolumab and Ipilimumab or Nivolumab and Lirilumab in Subjects with Relapsed or Refractory Hematologic Malignancy. 2016.
4. U.S. Food and Drug Administration. Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. 2007. Available from: http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071590.pdf [accessed 01/12/2016].
5. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med. 2015;372(4):311-9.
6. Cheah CY, Chihara D, Horowitz S, et al. Patients with classical Hodgkin lymphoma experiencing disease progression after treatment with brentuximab vedotin have poor outcomes. Ann Oncol. 2016;27(7):1317-23.
7. Collins GP, Parker AN, Pocock C, et al. Guideline on the management of primary resistant and relapsed classical Hodgkin lymphoma. Br J Haematol. 2014;164(1):39-52.
8. Armand P, Zinzani PL, Collins GP, et al. 3502: Outcomes of Allogeneic Hematopoietic Stem Cell Transplantation After Treatment With Nivolumab for Relapsed/Refractory Hodgkin Lymphoma. 58th American Society of Hematology (ASH) Annual Meeting & Exposition; 2016; San Diego, CA.
9. Bristol-Myers Squibb Pharmaceuticals Ltd. Clinical Protocol CA209205: Non-Comparative, Multi-Cohort, Single Arm, Open-Label, Phase 2 Study of Nivolumab (BMS-936558) in classical Hodgkin Lymphoma (cHL) Subjects (CheckMate 205: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 205). 2014.
10. Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol. 1989;7(11):1630-6.
11. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25(5):579-86.
12. National Institute for Health and Care Excellence Decision Support Unit. Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2013. Available from: http://www.nicedsu.org.uk/NICE%20DSU%20TSD%20Survival%20analysis.updated%20March%202013.v2.pdf [accessed 07/06/2016].
13. Bagust A, Beale S. Survival analysis and extrapolation modeling of time-to-event clinical trial data for economic evaluation: an alternative approach. Med Decis Making. 2014;34(3):343-51.
14. National Institute for Health and Care Excellence. NICE technology appraisal guidance [TA306]. Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B‑cell lymphoma. 2014. Available from: https://www.nice.org.uk/guidance/ta306 [accessed 07/06/2016].
15. National Institute for Health and Care Excellence. NICE Technology Appraisal Guidance 251. Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia (part review of technology appraisal

guidance 70). 2012. Available from: https://www.nice.org.uk/guidance/ta251 [accessed 03/06/2016].
16. National Institute for Health and Care Excellence. Technology appraisal guidance [TA241]. Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML) (part review of NICE technology appraisal guidance 70), and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance. 2012. Available from: https://www.nice.org.uk/guidance/ta241 [accessed 26/10/2016].
17. National Institute for Health and Care Excellence. Single Technology Appraisal. Brentuximab vedotin for treating CD30-positive Hodgkin's lymphoma. Committee Papers. 2016. Available from: https://www.nice.org.uk/guidance/GID-TAG467/documents/committee-papers [accessed 03/09/2016].
18. Department of Health. NHS reference costs 2014 to 2015. 2015. Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015 [accessed 07/09/2016].
19. Curtis L. Unit Costs of Health and Social Care 2015. 2015. Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2015/index.php [accessed 07/09/2016].
20. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. 2013. Available from: https://www.nice.org.uk/process/pmg9/chapter/foreword [accessed 06/12/16].
21. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health. 2010;13(5):509-18.
22. Dolan P, Gudex C, Kind P, et al. The time trade-off method: results from a general population study. Health Econ. 1996;5(2):141-54.
23. The University of York Centre for Health Economics. UK Population Norms for EQ-5D. 1999. Available from: https://www.york.ac.uk/media/che/documents/papers/discussionpapers/CHE%20Discussion%20Paper%20172.pdf [accessed 07/12/16].

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Patient/carer organisation submission (STA)

## Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma [ID972]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

## 1. *About you and your organisation*

**Your name:** [redacted]
**Name of your organisation:** Lymphoma Association
**Your position in the organisation:** [redacted]
**Brief description of the organisation:**

The Lymphoma Association is a national charity registered in England and Wales and in Scotland.

Our primary aim and objective is to provide information, advice, support and training to everyone affected by lymphoma. We work throughout the UK, publishing leading, quality-assured written information on lymphoma, operating a clinical trials information service (Lymphoma TrialsLink at www.lymphomas.org.uk/lymphoma-trialslink) and providing a national helpline, a network of support groups and a buddy scheme. We are also in the process of developing a survivorship and well-being programme specifically designed for those with lymphoma (*Live Your Life*) and have just launched a clinical psychology service. We also provide education and training courses for healthcare professionals, as part of their CPD.

***About this submission***

In compiling this patient organisation submission, we gathered information from our network of patients and carers who are linked to us through our role as a national lymphoma information, support and training charity in the UK, and via access to international networks as part of our membership of the global Lymphoma Coalition. We have access to people affected by lymphoma via our national helpline, network of support groups, buddy schemes, programme of conferences and events, the readers of our "Lymphoma Matters" magazine, people who contribute to our online forums, and via the circulation of surveys/feedback forms.

(For example: who funds the organisation? How many members does the organisation have?)

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

**Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:** None

## 2. *Living with the condition*

**What is it like to live with the condition or what do carers experience when caring for someone with the condition?**

Patients with relapsed or refractory lymphoma often have many symptoms, which can be debilitating and distressing. They also know that, despite all the treatment they have been through, their life-expectancy is severely limited. They are faced with a choice between:

- treatments that they know have little chance of success (particularly in the long term) but risk them developing significant side effects and/or spending large parts of their remaining life away from family and friends in hospital, or
- purely palliative care, which is likely to give them a life-expectancy of a few months only and potentially with a number of symptoms.

Even those who are fit enough and have the possibility of a donor to enable them to undergo an allogeneic transplant may not be able to do so if their lymphoma cannot be controlled again with effective treatment first.

Achieving a cure in these patients can allow them to return to work and make an active contribution to society as well as having a profound positive impact on physical and psychological health.

Many patients with relapsed or refractory Hodgkin lymphoma are young with the potential for a long and active life if they can undergo transplant. Patients unsuitable for transplant can also benefit from palliative treatment giving significant and prolonged symptom reduction which cannot be achieved with standard chemotherapy options.

Following transplant, patients, who are often in their prime childbearing and family years, can have a long and healthy life.

## 3. *Current practice in treating the condition*

**Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.**

Patients or carers would like to see a cure to their Hodgkin lymphoma or failing that a strong, durable remission, or for those in palliative care a life-extending treatment that keeps their lymphoma under control. In addition, whatever the outcome patients or carers would like treatments to have lower toxicity profiles and reduced or manageable side effects of after effects.

Most patients in this situation know their life-expectancy is severely limited and that the current treatments offer little chance of success (particularly in the long term) but risk significant side effects and/or may require large amounts of time to be spent in hospital. The alternative is palliative care, which allows them to spend the time they have left with family and friends as much as possible.

Patients want more effective therapy that still offers them a good chance of spending time at home.

**What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?**

For relapsed/refractory disease, chemotherapy will be the usual treatment, with patients reporting experience of a number of different regimens, such as gemcitabine, vinblastine, vinorelbine, alone or in combination. Such treatments will carry a higher toxicity profile and significant side effects and after affects.

Some patients may have been able to access brentuximab vedotin via a clinical trial or the Cancer Drugs Fund, which represents a step-change in the treatment and management of Hodgkin lymphoma for a small group of patients whose treatment options would otherwise be limited. This treatment may be used as either a bridge to a transplant or post-transplant, and is currently undergoing its own appraisal.

## *4. What do patients or carers consider to be the advantages of the treatment being appraised?*

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

**Please list the benefits that patients or carers expect to gain from using the treatment being appraised.**

There is no standard of care for Hodgkin lymphoma patients who progress after an autologous stem cell transplant and subsequent brentuximab vedotin treatment. Thus, the reality is that patient expectations at this point may be low, particularly given that they are likely to have been through numerous lines of treatment to reach this stage. However, given the innovative nature of nivolumab, patients and carers will hope or expect that the treatment will either cure their disease or give them a speedy, strong and durable remission. At the same time, they will be hoping for or expecting a manageable or acceptable side-effects profile. For a small number of patients, they may expect successful treatment will lead to an allogeneic stem cell transplant, which may offer the hope of a cure.

**Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.**

The main advantage for patients and carers is the lower toxicity profile of nivolumab compared to standard chemotherapy regimes. At the point at which patients will be offered nivolumab, they are likely to be in a debilitating and distressed condition, with poor quality of life.

*"I was fairly underweight due to treatment and disease-related complications that impacted my ability to both keep down and digest food."*

*Female patient in her 20s*

Generally patients report that the treatment has few and/or manageable side-effects. The most common (in at least 20% of people) are fatigue, upper respiratory tract infection, cough, pyrexia and diarrhoea. Other common reactions (in at least 10% of people) might include rash, pruritus, musculoskeletal pain, nausea, vomiting, abdominal pain, headache, peripheral neuropathy, arthralgia and hypothyroidism or thyroiditis.

However, for many patients these sorts of side effects are manageable compared to other treatments and compared to their current quality of life. Indeed many patients report how their quality of life significantly improved with the treatment.

*"But all the while, I felt great. I wasn't experiencing any fatigue from the drug. I wasn't watching my hair fall out bit by bit. I was able to start eating more and gain muscle mass. But mostly importantly: for the first time in a long time, I was able to start taking care of myself."*

*Female patient in her 20s*

**If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.**

Although the treatment is effective for many patients, for a small percentage of patients there are some serious adverse effects, such as pneumonia, pleural effusion, pneumonitis, pyrexia, etc.

## *5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?*

| Disadvantages of a treatment might include: |
|---|

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

**Please list any concerns patients or carers have about current NHS treatments in England.**

The higher levels of toxicity of existing chemotherapy treatments, along with significant side effects and after effects.

**Please list any concerns patients or carers have about the treatment being appraised.**

There are some side effects to the treatment (see answers to earlier questions), but they are generally seen as manageable and some of them will already be known to most patients from their experience of harsher chemotherapy regimes. For some, there can be serious side-effects, as noted in an earlier answer. For those who are receiving the treatment as part of palliative care, the side effects will be seen as a reasonable trade-off for the benefit of extra time with family and loved ones.

**If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.**

Not aware of any, although experience of side-effects will vary from patient to patient.

## *6. Patient population*

**Are there any groups of patients who might benefit more from the**

**treatment than others? If so, please describe them and explain why.**

Given the age profile for Hodgkin lymphoma, many younger people will benefit from the treatment and be able to return to normal or near normal lives.

**Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.**

Not aware of any.

## *7. Research evidence on patient or carer views of the treatment*

**Is your organisation familiar with the published research literature for the treatment?**

☐X Yes ☐ No

**If you answered 'no', please skip the rest of section 7 and move on to section 8.**

**Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.**

n/a

**Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?**

Yes, we believe the trials have captured the outcomes that are important to patients.

We're not aware of any limitations in how the treatment has been assessed in the clinical trials, although the trial population is low and there is more data to be collected. However, given the group of patients at which this drug is targeted and the high level of unmet need, it's important that there is flexibility in reviewing and assessing the clinical evidence.

**If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?**

n/a

**Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?**

☐ Yes ☐X No

**If yes, please provide references to the relevant studies.**

## *8. Equality*

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

**Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.**

Don't believe there are any particular equality issues.

**Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.**

Please see above for comments on current treatments and this new treatment.

## 9. *Other issues*

**Do you consider the treatment to be innovative?**

☐X Yes ☐ No

**If yes, please explain what makes it significantly different from other treatments for the condition.**

As a novel immunotherapy agent, nivolumab is innovative, with a new mode of action and represents a step change in the management of relapsed/refractory Hodgkin lymphoma for this group of patients

**Are there any other issues that you would like the Appraisal Committee to consider?**

No

## 10. *Key messages*

**In no more than 5 bullet points, please summarise the key messages of your submission.**

- Nivolumab represents a step-change in treatment for this group of patients, where there is no current standard of care.
- Efficacy of treatment means improved life-expectancy for many patients compared with the current alternatives.
- Fewer side effects than other chemotherapy that may be offered in this situation, which are manageable and usually familiar to patients who have had previous treatment for lymphoma.

**Appendix G - professional organisation submission template**

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Single Technology Appraisal (STA)**

# Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma [ID972]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

**About you**

**Your name:** [redacted]
**Name of your organisation:**
**Are you (tick all that apply): NCRI-ACP-RCP**

**Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None**

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Single Technology Appraisal (STA)**

# Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma [ID972]

**What is the expected place of the technology in current practice?**

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

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Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

*Around 85% of cases of classical Hodgkin lymphoma is cured with front line treatment. For the rare cases that relapse, standard of care is to administer 2$^{nd}$ line chemotherapy and aim for an autologous stem cell transplant (ASCT). This cures around 50% of patients. For those who relapse after ASCT, the most commonly used treatment is brentuximab vedotin. This shows high response rates (approx. 70%) but many of those responses are short lived. As most patients are young and fit, the aim is to bridge them to a potentially curative allogeneic (from a donor) stem cell transplant. A short lived response is not ideal for this as it takes time to organise an allogeneic transplant.*

*The current scope is assessing nivolumab in those who relapse after ASCT and brentuximab vedotin. Most of these patients would be heading to an allogeneic stem cell transplant. The data for nivolumab suggests a high response rate (approx. 70%) and, crucially, mostly durable responses. This is ideal to act as a bridge to transplant. There is some concern that nivolumab may make subsequent transplant more risky, but very recent data does not support this. Using nivolumab as a bridge is important as it will reduce the cycles of nivolumab used. If used in the UK for this indication we would therefore expect significantly fewer cycles of nivolumab to be used compared to the published trials, in which only a minority proceeded to transplant.*

*The other population which is part of the scope are those who are not fit for transplant and have failed 2 lines of treatment. This is a rare patient group but one with high unmet need. There are no curative options in this group and a drug which leads to durable remissions with low toxicity risk would be extremely useful. Even palliative options are very limited in this group.*

**The advantages and disadvantages of the technology**

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

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*Nivolumab is fairly easy to give. 1 hour iv infusion with no pre-medication. It is given every 2 weeks which is comparable to chemotherapy. No specific concomitant medications are required. Quality of life studies in the phase II trial suggest an improvement in scores associated with treatment.*

*In terms of UK practise, nivolumab would be a very useful treatment to have access to in those failing ASCT and brentuximab (assuming we will be allowed to continue giving brentuximab in this setting after the current NICE appraisal reports).The phase II trial did therefore reflect UK clinical practise. However a significant area of unmet need in relapsed Hodgkin is those who fail to reach a remission PRIOR to their ASCT. It would be helpful to have a drug like nivolumab in that setting. This is being assessed in a proposed clinical trial. The UK try to bridge all patient with relapse after ASCT (and who are fit enough) to allogeneic SCT. This is NOT typical of practise elsewhere in the world. Therefore it would be expected that nivolumab in this situation would be used as a bridge to a potentially curative therapy. As stated before this would reduce the number of cycles given (and therefore cost).*

*There are 2 important outcomes in the published phase II trial:*
*1. Response rate of around 70%. Perhaps more important though is:*
*2. Durable responses. This is a key outcome when trying to bridge patients to allogeneic stem cell transplants which take time to arrange. Furthermore, for the other group of patients who are not fit for transplant, this is a key outcome in producing sustained quality and quantity of life. The trial suggests that many remissions are durable. However follow up for the trial is relatively short and it would be expected that the reported durability of remission will increase with increasing follow up.*

*Nivolumab is associated with a different set of side effects from 'standard' chemotherapy. In particular, 5-10% may suffer from autoimmune side effects. These can be relatively trivial (e.g. hypothyroidism) or very serious (e.g. pneumonitis, colitis). Although uncommon they can cause morbidity and even mortality (deaths have been seen with nivolumab in trials involving other tumour types). More common side effects include fatigue and rash which can in some instances be troublesome. Infection risk is not a significant issue with this drug. My experience with this drug though is that its significantly better tolerated than chemotherapy in this setting.*

*Note: the primary endpoint was ORR. PFS is a more relevant endpoint which was collected. Perhaps the most relevant is overall survival. However much longer follow up will be needed before this can be fully assessed.*

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Single Technology Appraisal (STA)**

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**Any additional sources of evidence**

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

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Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

*The drug is easy to deliver: 1 hour iv infusion with no premed. This would no impact on resources significantly. However as the drug works well, patients will be on treatment for longer coming in every 2 weeks. These patients are rare though, so we would not expect significant implications for NHS resources.*

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Single Technology Appraisal (STA)**

# Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma [ID972]

**Equality**
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
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- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

## Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma [ID972]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

**About you**

**Your name: Cathy Burton**

**Name of your organisation: Leeds Teaching Hospitals NHS Trust**

**Are you (tick all that apply):**

- a specialist in the treatment of people with the condition for which NICE is considering this technology? yes
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? yes
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? NHS, NCRI Hodgkin lymphoma subgroup member
- other? (please specify)

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Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Approximately 200 patients in the UK per year will relapse with Hodgkin lymphoma (HL) and, due to the demographics of the population affected by cHL, most will be young and fit. Relapsed and primary refractory HL has a bleak outlook with standard chemotherapy alone, overall survival rates are between 10 and 20% (Longo et al. 1992). This is significantly improved by treatment with non cross-reacting salvage regimes and high intensity chemotherapy followed by autologous stem cell transplant (ASCT) (Linch et al., 1993, Schmitz et al. 2002). 5 year freedom from second failure (FF2F) in patients treated with this approach was reported as 42% by the German Hodgkins lymphoma study group (GHSG). However, a minority of this relapsed/ refractory cohort (33%) actually made it to ASCT, resulting in poor outcomes overall (17% 5 year FF2F), due to progressive disease, therapy related toxicity, failure of stem cell harvest and poor performance status (Josting et al. 2000). A number of factors have been identified as predictive of poor prognosis: shorter time to relapse or primary refractory disease; advanced stage at relapse; anaemia; extra-nodal disease; presence of B symptoms (Josting et al. 2002, Moskowitz et al. 2001). The most discriminatory factor is achievement of PET negativity following salvage therapy. In patients achieving PET negativity following salvage, 3-5 year PFS following ASCT is > 70%, whereas in those not achieving this, PFS is 25-30% (Jabbour et al. 2007, Moskowitz et al. 2010).
A number of strategies have been explored to optimise outcomes post ASCT, particularly for patients with poor prognostic factors. Post ASCT consolidation with radiotherapy and/or cytotoxic chemotherapy has so far yielded disappointing results (Rapoport et al. 2004). The Aethera trial (Moskowitz et al. 2014) demonstrated some

benefit of using the anti-CD30 monoclonal antibody-drug conjugate brentuximab vedotin (BV) in this context. Median PFS was 42.9 months versus 24.1 months compared with placebo when BV was given to high risk patients (primary refractory or relapsing within 12 months of first line therapy) post ASCT. Tandem ASCT has also been tested in a non-randomised trial setting: outcomes for the poor risk group remained inferior (Morschhauser et al. 2008). Allogeneic SCT is an alternative approach. Treatment related mortality (TRM) has improved significantly with reduced intensity (RIC) conditioning regimes (Peggs et al. 2007), but remains significantly higher than for ASCT, and confers significant morbidity especially from graft versus host disease. It is therefore usually still reserved for patients relapsing post auto-ASCT or who are ineligible for ASCT because of chemo-refractory disease or failure of stem cell harvest (BCSH 2014 guidelines).

Brentuximab vedotin (BV) is used in relapsed/refractory HL, although there is a paucity of evidence for this, and it is not currently licensed in the UK. The largest data set is a retrospective, observational study of 30 relapsed, refractory cHL patients, not responding to first line salvage therapy, in whom BV was given pre ASCT (Zinzani et al., 2015). The overall response rate (ORR) was 40% with a complete response (CR) rate of 30%. However, trials of BV in the setting of relapse post ASCT demonstrate that median PFS with BV is relatively short (5.7 months) (Younes et al., 2012). This is problematic for patients being considered for allo-SCT, because of the time it can take for donor matching and work-up. Moreover, BV is associated with significant peripheral neuropathy and neutropenia. The use of BV in the salvage setting is the subject of a current clinical trial, BRaVE, which combines BV with DHAP up-front. This trial does not use PET stratification to change therapy.

Nivolumab, as one of the immune checkpoint inhibitor drugs, has emerged as a new class of drug with promising results in relapsed, refractory cHL. This suggests that they could also be used to good effect in the salvage setting. These drugs have been pioneered, and are now licensed, in solid tumours, eg. melanoma and non small cell lung cancer (Borhaei et al., 2015; Faron et al. , 2015). They have also shown considerable promise in haematological malignancies, with the most promising results of all in cHL (Ansell et al. 2014, Moskowitz et al., 2014). Indeed, the response of cHL to PD1 inhibitors far exceeds the response rates seen in any other tumour type.

There are several reasons why nivolumab is particularly effective in cHL:

- PDL-1, the ligand for PD-1, is over-expressed by the cancerous cell (the Hodgkin / Reed-Sternberg cell) of cHL due to polysomy of chromosome 9p, 9p copy gain, and 9p24.1a amplification, on which PDL-1 is located (Ansell et al. 2009).
- The 9p24.1 locus also encodes janus kinase 2 (JAK2), which further increases PD-L1 transcription through gene-dose dependent JAK-STAT signalling. (Green et al. 2010)
- Epstein Barr virus (EBV) which is implicated in the pathogenesis of 10-40% of cHL, varying by subtype, also increases the expression of PDL-1. (Green et al. 2012)
- Histologically, cHL is characterised by a particularly extensive immune infiltrate, mainly consisting of CD4+ T helper 2 cells (Th2) and T regulatory cells (TRegs). These Th2 cells provide continuous CD40L stimulation and release cytokines that promote RS cell survival and proliferation. Therapeutic blockade of

PD-1 may alter the proliferation and behaviour of different T cell subsets, disrupting this protective effect of the immune environment. (Steidl et al. 2011).

Trial evidence for immune checkpoint inhibitors in cHL

Three key studies have demonstrated the efficacy of PD-1 inhibitors in relapsed/ refractory cHL. Ansell et al., 2015, reported on a cohort of 23 patients with relapsed/ refractory cHL, 18 of whom had had prior BV and 18 prior ASCT, treated with nivolumab. Response rates were remarkably high given how heavily pre-treated the population was: 87% achieved an ORR with 26% achieving a CR. Younes et al., 2016, reported at 66% response rate to nivolumab in 80 patients with cHL, treated across 34 centres, who had failed ASCT and were relapsed after or refractory to BV. An ongoing phase 1b trial of pembrolizumab in haematological malignancies, has reported on 31 patients with relapsed, refractory cHL, all of whom had failed prior treatment with BV and 71% of whom had failed prior ASCT. 65% achieved an ORR, with 16% achieving a CR (Moskowitz et al. Blood 2014).

Nivolumab would be used in haematology clinics.

BCSH guideline on the management of primary resistant and relapsed classical Hodgkin lymphoma published October 2013 and therefore did not include use of checkpoint inhibitors.

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## Single Technology Appraisal (STA)

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Use of nivolumab is potentially advantageous for a number of reasons:

- Response rates appear to be at least as good as for cytotoxic chemotherapy and BV, despite being tested in a more heavily pre-treated cohort, making nivolumab a very promising rescue salvage regime. This would potentially increase the proportion of patients eligible for ASCT, and reduce the risk of failure of this invasive and costly procedure.
- Using nivolumab in a more upfront context might avoid the need for exposure to multiple successive lines of cytotoxic chemotherapy, which impact negatively on the patient's fitness for ASCT, and on the success of stem cell harvest.

There are also theoretical arguments why nivolumab might specifically be preferable to cytotoxic chemotherapy or BV in the salvage setting:

- It is less likely to induce neutropenia and peripheral neuropathy, well established side effects of BV and chemotherapy.
- Responses tend to be more durable, regardless of whether PR or CR is achieved (Ansell et al. and Younes 2016), in contrast to BV in which long lasting responses are generally only seen in those achieving CR. Longer duration of response would allow time to plan for allograft, if this is the preferred treatment option, or potentially even obviate the need for ASCT, in patients in whom this procedure is deemed high risk.
- Use of BV prior to nivolumab may make nivolumab less effective, as CD30+ cells may be important for optimal response (Ansell et al.). This would allow BV to be reserved as a subsequent rescue therapy.

## NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Safety of nivolumab in the salvage context

In the Ansell et al. study, nivolumab was reasonably well-tolerated with most side effects being grade 1-2. Most frequently reported side effects were rash, thrombocytopenia. Grade 3-4 events included decreased lymphocytes count, increased serum lipase, stomatitis, pancreatitis, myelodysplasia (likely related to previous treatment rather than nivolumab). Patients in the pembrolizumab study suffered more grade 3 adverse events, including grade 3 transaminitis, colitis, pneumonitis, nephrotic syndrome, with 2 patients discontinuing therapy (Armand et al. 2015). However, on balance, this side effect profile is probably less severe than that seen with BV: 28% grade 3 with BV (Younes et al.) compared with 16- 22% with nivolumab (Armand et al., Ansell et al.).
There are particular concerns about potential autoimmune complications of nivolumab for patients who may be candidates for subsequent allo-SCT, in terms of increased risk of severe GVHD. The extent of this problem is unclear as there is a lack of published data and experience. One small study reported on 12 relapsed/ refractory cHL patients treated with nivolumab post allo-HSCT. 2 patient developed grade III-IV skin acute GVHD (although one had a prior history of grade 2 skin GVHD). 1 patient developed grade IV neutropenia and 1 patient developed grade III thrombocytopenia (Herbaux et al., 2015). There is clearly more exploration to be done in this area, although it does not seem to be as great a problem as anticipated at present. This concern also lends weight to the argument for using nivolumab in a more upfront setting, rather than reserving it as a treatment of last resort post allo-HSCT.

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- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities No

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts
All patients with relapsed/refractory cHL should be able to be considered for this agent

**Any additional sources of evidence**

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Updated data due to be presented at American Society of Haematology meeting Dec 2016 which will shows ongoing impressive response rates and prolonged response. Initial data led to approval by FDA in US May 2016.

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Please do not exceed the 8-page limit.

**About you**

**Your name: Dr Graham Collins**

**Name of your organisation : Oxford University Hospitals NHS Foundation Trust**

**Are you (tick all that apply):**

- a specialist in the treatment of people with the condition for which NICE is considering this technology? – yes, I am the Thames Valley Lymphoma MDT lead.
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*There are 2 important outcomes in the published phase II trial:*
*1. Response rate of around 70%. Perhaps more important though is:*
*2. Durable responses. This is a key outcome when trying to bridge patients to allogeneic stem cell transplants which take time to arrange. Furthermore, for the other group of patients who are not fit for transplant, this is a key outcome in producing sustained quality and quantity of life. The trial suggests that many remissions are durable. However follow up for the trial is relatively short and it would be expected that the reported durability of remission will increase with increasing follow up.*

*Nivolumab is associated with a different set of side effects from 'standard' chemotherapy. In particular, 5-10% may suffer from autoimmune side effects. These can be relatively trivial (e.g. hypothyroidism) or very serious (e.g. pneumonitis, colitis). Although uncommon they can cause morbidity and even mortality (deaths have been seen with nivolumab in trials involving other tumour types). More common side effects include fatigue and rash which can in some instances be troublesome. Infection risk is not a significant issue with this drug. My experience with this drug though is that its significantly better tolerated than chemotherapy in this setting.*

*Note: the primary endpoint was ORR. PFS is a more relevant endpoint which was collected. Perhaps the most relevant is overall survival. However much longer follow up will be needed before this can be fully assessed.*

## NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

**Equality and Diversity**

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

*I cannot think of any impact in these areas.*

**Any additional sources of evidence**

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

*I cannot think of any relevant evidence.*

## NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

**Implementation issues**

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

*The drug is easy to deliver: 1 hour iv infusion with no premed. This would no impact on resources significantly. However as the drug works well, patients will be on treatment for longer coming in every 2 weeks. These patients are rare though, so I would not expect significant implications for NHS resources.*

## NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Patient/carer expert statement (STA)

## Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma [ID972]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

## *1. About you*

**Your name:** Ellie Philpotts
**Name of your nominating organisation:** Leukaemia CARE
**Do you know if your nominating organisation has submitted a statement?**

☐ Yes ☐ No

**Do you wish to agree with your nominating organisation's statement?**

☐ Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

**Are you:**

- a patient with the condition?

☑ Yes ☐ No

- a carer of a patient with the condition?

☐ Yes ☐ No

- a patient organisation employee or volunteer?

☐ Yes ☐ No

**Do you have experience of the treatment being appraised?**

☐ Yes ☑ No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

**Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:**

n/a

## *2. Living with the condition*

**What is your experience of living with the condition as a patient or carer?**

I was diagnosed with Hodgkin Lymphoma Stage 2B in January 2011, aged 15. My treatment plan was four cycles of chemotherapy – two of COPP and two of OEPA, alongside steroids. I'm now 21, and have been in remission since May 2011, but remain passionate in improving the treatments and survivorships of those diagnosed with lymphoma.

## *3. Current practice in treating the condition*

**Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.**

I would like treatment to achieve full remission from lymphoma, which in time results in being considered completely cured. I would also like treatment to entail minimal side and after effects, creating a positive quality of life and promoting emotional wellbeing as well as physical health.

**What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?**

I primarily underwent COPP and OEPA chemotherapy and steroids on the NHS. Collectively and individually, they worked very well for me personally, with my PET Scan halfway through treatment showing no signs of active lymphoma, and I have remained in remission and in time cured ever since. I have been treated in NHS hospitals as both outpatient and inpatient, and believe the NHS is essential for patients with a range of illnesses across the UK.

## *4. What do you consider to be the advantages of the treatment being appraised?*

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

**Please list the benefits that you expect to gain from using the treatment being appraised.**

The treatment being appraised should increase the likelihood of greater responses to Hodgkin Lymphoma treatments. This could include more long-term survivors, with a heightened quality of life, for example being able to return to work or family routine more quickly, thus benefitting wider society. Mental health and the emotional effects of diagnosis would have room for improvement, but the physical side of lymphoma – symptoms, pain management, after or late effects – could also be managed more effectively.

**Please explain any advantages that you think this treatment has over other NHS treatments in England.**

I think it has the advantage to reach a range of Hodgkin Lymphoma patients across the country, offering hope and moving closer in the direction of kinder treatments and higher rates of remission.

**If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.**

## *5. What do you consider to be the disadvantages of the treatment being appraised?*

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

**Please list any concerns you have about current NHS treatments in England.**

**Please list any concerns you have about the treatment being appraised.**

**If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.**

## *6. Patient population*

**Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.**

**Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.**

## *7. Research evidence on patient or carer views of the treatment*

**Are you familiar with the published research literature for the treatment?**

☐ Yes ☐ No

**If you answered 'no', please skip the rest of section 7 and move on to section 8.**

**Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.**

**Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?**

**If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?**

**Are you aware of any relevant research on patient or carer views of the condition or existing treatments?**

☐ Yes ☐ No

**If yes, please provide references to the relevant studies.**

## *8. Equality*

**NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.**

## *9. Other issues*

**Do you consider the treatment to be innovative?**

☑ Yes ☐ No

**If yes, please explain what makes it significantly different from other treatments for the condition.**

This treatment seems to have the potential to reach a broader amount of Hodgkin Lymphoma patients across the country, a positive and new development for those diagnosed with this form of cancer.

**Is there anything else that you would like the Appraisal Committee to consider?**

## *10. Key messages*

**In no more than 5 bullet points, please summarise the key messages of your submission.**

- I was diagnosed with classical Hodgkin Lymphoma in January 2011, and was treated with chemotherapy and steroids until May 2011.
- Since then, I have remained cancer-free, but am conscious of the fact that not every Hodgkin Lymphoma patient has the same outlook as me.
- One of my areas of interest is youth lymphoma. Having undergone treatment at the age of 15, I am aware of the risk of future after-effects and the emotional burden that can be paired with physical cancer.
- I am passionate in getting involved with blood cancer organisations such as Leukaemia CARE, to help my fellow patients both of present and future.
- I am interested to attend the meeting and hear the eventual verdicts of the appraisal. I hope it will be of benefit to those diagnosed with Hodgkin Lymphoma.

**NHS England submission into the NICE appraisal for the use of nivolumab in Hodgkin's lymphoma February 2017**

1. Nivolumab is licensed in adult patients with relapsed/refractory classical Hodgkin's lymphoma (cHL) following autologous stem cell transplantation (auto-SCT) and treatment with brentuximab. Although the SPC does not state this directly, the main published evidence base for nivolumab in CHL on which the EMA approved nivoumab in this indication is in patients who progressed following auto-SCT and then also treatment with brentuximab (cohort B in the nivolumab phase 2 study). In addition, the EPAR describes a cohort of patients who received brentuximab pre- and/or post- auto-SCT (cohort C) but follow-up on this latter cohort is very short.

2. NHS England is mainly describing in its submission to NICE the published evidence and that set out in the SPC. The SPC describes evidence from a phase 2 study with just cHL patients previously treated with auto-SCT and post-auto-SCT brentuximab (n=80) combined with 15 cHL patients similarly treated but in a study which recruited other types of lymphoma. The SPC has a combined analysis of these 95 patients who were all of performance status 0 or 1. 52% had received 5 or more lines of treatment, 92% had been treated with one auto-SCT and 8% with 2 or more auto-SCTs. Despite this heavily pre-treated population of patients, there was a median of 3.5 years from the most recent transplant to treatment with nivolumab, the range being 0.2 to 19 years. This median 3.5 year figure suggests that many of the patients in this combined study had a more indolent course to their cHL and thus had a better prognosis.

3. The duration of follow-up was 15.8 mo in the combined 95 patient study. The overall response rate was 66% (the primary end point), the complete remission rate was 6% and the median duration of response was 13 mo. The rate of progression free survival (PFS) was 57% at 12 months and the median PFS duration was 14.8 mo but the number of events was still low (38 of 95). So far reported, 9 of the 95 patients have undergone further SCT. The OS rate at 12 mo was 95%.

4. Of the 63 patients who had a quantifiable PD-L1 expression result, 91% had a PD-L1 expression of ≥1%.

5. Of interest in a post hoc exploratory analysis is that 37 of the 80 patients in the cHL only phase 2 study had previously been non-responders to brentuximab and the overall response rate in these 37 patients was 60% and the median duration of response was 13 mo. The response rate and duration in this group were therefore very similar to the whole group.

6. The main toxicities from nivolumab were fatigue, infusion-related reactions, rash, fever and neutropenia, as well as a range of uncommon but serious immune-mediated toxicities such as pneumonitis, colitis, hepatitis, renal dysfunction and endocrinopathies. Nevertheless, most patients tolerated treatment with nivolumab reasonably well and maintained active life styles and good quality of life.

7. In the 80 patient phase 2 study, mean EQ-5D VAS scores increased over time with nivolumab but EORTC QLQ-C30 scores remained stable over time.

8. Cohort C patients are described in the EPAR, there being 100 patients in all, 57 having brentuximab post-auto-SCT (as in cohort B), 33 having brentuximab only prior to auto-SCT, 8 having brentuximab both before and after auto-SCT and 2 patients in whom the sequence of brentuximab in relation to auto-SCT was impossible to determine. 29% of cohort C received 5 or more previous systemic therapy regimens. The median duration of follow-up was only 8.9 mo. The overall response rate was 73% with 17% attaining a complete response. Other data are too immature.

Comment on the use of nivolumab in cHL

9. The data for the use of nivolumab is still immature with a median duration of follow-up of only about 16 months. Its early impact as palliative treatment is evident as the response rate is high and this is reasonably tolerated treatment. It is unclear as to how many patients achieve a sufficient response to nivolumab which can then lead to salvage with an allo-SCT.

10. It is usual for clinicians to seek to only offer SCTs in England to those patients achieving PET-CT negative scans with pre-SCT treatment. The mode of action of nivolumab and other PD-L1 drugs is such that one might expect there to be residual PET avidity on the scans despite a very satisfactory response to treatment. Thus, the potential rate of a further SCT is likely to be higher than the rate of complete responses seen in the above 95 patient combined study.

11. It was initially reported that patients treated with nivolumab who subsequently had an allo-SCT had a high rate of transplant-related complications such as graft versus host disease, steroid-requiring febrile syndrome, hepatic dysfunction and other immune-related problems. NHS England is informed that there is much greater awareness of such issues and that treatment strategies are now in place for their mitigation.

12. The license for nivolumab is limited to adults. Relapsed/refractory HL is also seen in patients aged less than 18 years and there is no biological reason why any NICE recommendation as to the clinical and cost effectiveness of nivolumab for its indication in cHL would not be valid in paediatric and teenager populations. In this situation, NHS England would ensure that the funding of nivolumab within baseline commissioning is extended to relevant patients under the age of 18 years.

13. NHS England wishes to note that the use of nivolumab in HL is only licensed after use of brentuximab and that the evidence base in its licensing is mainly in patients who received brentuximab after auto-SCT. In terms of any use of nivolumab as assessed by NICE in cHL, this would be contingent on the recommendation by NICE of brentuximab as being required to have been administered before and/or after auto-SCT.

14. As an alternative to nivolumab treatment in cHL, re-treatment with brentuximab is a theoretical possibility but the only published evidence is in 20 patients. Such re-use has not been considered by NICE and nor would NHS England commission it.

Prof Peter Clark
Chair of NHS England Chemotherapy Clinical Reference Group and National Clinical Lead for the Cancer Drugs Fund
February 2017

# CONFIDENTIAL UNTIL PUBLISHED

## Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

# Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma


**Produced by** Southampton Health Technology Assessments Centre (SHTAC)

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**Declared competing interests of the authors**

None from the authors and none from the two clinical advisors.

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**Rider on responsibility for report**

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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**Contributions of authors**

Keith Cooper (Senior Research Fellow) critically appraised the health economic systematic review, critically appraised the economic evaluation and drafted the report; Micah Rose (Research Fellow) critically appraised the health economic systematic review, critically appraised the economic evaluation and drafted the report; Petra Harris (Research Fellow) critically appraised the clinical effectiveness systematic review and drafted the report; Maria Chorozoglou (Senior Research Fellow) critically appraised the health economic systematic review, critically appraised the economic evaluation and drafted the report; Joanna Picot (Senior

Research Fellow) critically appraised the clinical effectiveness systematic review, drafted the report, project managed the review and is the project guarantor.

Word count: 48, 957

**Key to colour highlighting used in report**
*Commercial in confidence (CIC) information in blue*
*Academic in confidence (AIC) information in yellow.*

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| | |
|---|---|
| AE | Adverse events |
| AIC | Academic in Confidence |
| alloSCT | Allogeneic stem cell transplant |
| ASCT | Autologous stem cell transplant |
| ASHAP | Doxorubicin, methylprednisolone, cytarabine and cisplatin |
| BMS | Bristol-Myers Squibb |
| BOR | Best overall response |
| BSC | Best supportive care |
| BCSH | British Committee for Standards in Haematology |
| BTX | Brentuximab vedotin |
| CEAC | Cost-effectiveness acceptability curve |
| CHMP | Committee for Medicinal Products for Human Use |
| cHL | classical Hodgkin lymphoma |
| CI | Confidence interval |
| CIC | Commercial in confidence |
| CR | Complete response |
| CRD | Centre for Reviews and Dissemination |
| CS | Company's submission |
| CSR | Clinical study report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DexaBEAM | Dexamethasone, carmustine, etoposide, cytarabine and melphalan |
| DHAOx | Dexamethasone, cytarabine and oxaliplatin |
| DHAP | Dexamethasone, cytarabine and cisplatin |
| DSU | Decision Support Unit |
| ECOG | Eastern Cooperative Oncology Group |
| EPAR | European Public Assessment Report |
| EQ-5D | EuroQoL five dimension questionnaire |
| ERG | Evidence Review Group |
| ESHAP | Etoposide, methylprednisolone, cytarabine and cisplatin |
| FDA | Food and Drug Administration |
| GDP | Gemcitabine, vinorelbine and liposomal doxorubicin |
| GEM-P | Gemcitabine, cisplatin and methylprednisolone |
| GVD | Gemcitabine, vinorelbine and liposomal doxorubicin |
| HL | Hodgkin lymphoma |
| HR | Hazard ratio |
| HRQoL | Health-related quality of life |
| ICE | Ifosfamide, carboplatin and etoposide |
| ICER | Incremental cost-effectiveness ratio |
| IGEV | Ifosfamide, gemcitabine and vinorelbine |
| IPD | Individual patient data |
| IRRC | Independent regulatory review committee |
| ITC | Indirect treatment comparison |
| ITT | Intention-to-treat |
| IGEV | Ifosfamide, gemcitabine and vinorelbine |
| IWG | International Working Group |
| MAIC | Matching-adjusted indirect comparison |
| MedDRA | Medical Dictionary for Regulatory Activities |

| | |
|---|---|
| MHRA | Medicines and Healthcare products Regulatory Agency |
| MINE | Mitoxantrone, ifosfamide, vinorelbine and etoposide |
| MIMS | Monthly Index of Medical Specialities |
| Mini-BEAM | Carmustine, etoposide, cytarabine and melphalan |
| mOS | Median overall survival |
| mPFS | Median progression-free survival |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NMA | Network meta-analysis |
| OR | Odds ratio |
| ORR | Objective response rate |
| OS | Overall survival |
| PAS | Patient Access Scheme |
| PET | Positron emission tomography |
| PFS | Progression free survival |
| PIM | Promising Innovative Medicine |
| PR | Partial response |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| PSA | Probabilistic sensitivity analysis |
| PSS | Personal Social Services |
| QoL | Quality of life |
| QALY | Quality-adjusted life year |
| RCT | Randomised controlled trial |
| ScHARRHUD | School of Health and Related Research Health Utilities Database |
| SD | Stable disease |
| SLR | Systematic literature review |
| SmPC | Summary of product characteristics |
| SoC | Standard of Care |
| STA | Single technology appraisal |
| TA | Technology appraisal |
| VAS | Visual analogue scale |
| VBA | Visual Basic for Applications |

## SUMMARY

### Scope of the company submission

The company's submission (CS) on the whole reflects the scope of the appraisal issued by the National Institute for Health and Care Excellence (NICE), although evidence is presented for only one of the patient groups included in the NICE scope. The submission focuses on assessing the clinical effectiveness and cost effectiveness of nivolumab for the treatment of adults with relapsed or refractory classical Hodgkin lymphoma following autologous stem cell transplant (ASCT) and brentuximab vedotin. The second population specified in the final scope issued by NICE, "People with relapsed or refractory classical Hodgkin lymphoma following at least 2 prior therapies when autologous stem cell transplant is not a treatment option", is not considered by the CS (presumably because the second population is not encompassed by the proposed indication for nivolumab). Nivolumab therapy is compared to 'Standard of Care' (SoC), which the company defines as being comprised of chemotherapy, brentuximab vedotin retreatment and bendamustine, based on a real-world retrospective study because only single-arm studies of nivolumab are available. The comparator broadly matches one of the comparators described in the NICE scope: "Established clinical management without nivolumab including chemotherapy such as gemcitabine or bendamustine." However, the Evidence Review Group (ERG) notes that there is some uncertainty, due to differences in treatment practices, about how well the real-world retrospective study data based on patients from the USA presented in the submission to represent SoC reflects the experience of patients treated in the UK. In the economic model, patients may receive best supportive care (BSC) as subsequent therapy following nivolumab treatment or the comparator SoC. BSC consists primarily of palliative care, including palliative chemotherapy.

### Summary of submitted clinical effectiveness evidence

The company's systematic review of clinical effectiveness identified two relevant non-comparative single-arm studies of nivolumab. In these, nivolumab was administered by intravenous infusion at a dosage of 3mg/kg every two weeks.

- The CheckMate 205 parallel cohort study (phase II) included classical Hodgkin lymphoma patients ≥ 18 years old who failed ASCT. The study has three cohorts: A, B and C. Only patients in cohorts B (n=80) and C (n=100) meet the inclusion criteria for the CS systematic review. The difference between cohorts B and C is that patients in cohort B had brentuximab vedotin treatment after failure of ASCT, whereas patients in Cohort C could have brentuximab vedotin either before or after ASCT. Patients in cohort

A (n=63) were brentuximab vedotin-naïve and therefore they are outside the NICE scope.

- The CA209-039 open-label study (phase I) included 23 patients with classical Hodgkin lymphoma, but only 15 of these patients had received prior ASCT and brentuximab vedotin. Therefore it is the subgroup of 15 patients from this study who meet the population defined in the NICE scope.

The primary outcome in both studies was the objective response rate (ORR) as assessed by the independent regulatory review committee (IRRC) in CheckMate 205, but as assessed by investigators in CA209-039 (both IRRC and investigator assessments of ORR were reported by both studies). Additional outcomes included those listed in the NICE scope [overall survival (OS); progression-free survival (PFS); response rates; adverse effects; health-related quality of life (HRQoL)] as well as outcomes not specified in the NICE scope (e.g. duration of complete response, time to complete response). Both of these single-arm non-comparative studies appear to be of reasonable quality (though by design they are inherently weak) and the ERG believes that it is likely that the company has identified all relevant studies on nivolumab and potential comparators.

CheckMate 205 and CA209-039 are still ongoing and continuing to generate evidence on longer-term outcomes, including OS and PFS. Published and unpublished results are reported in the CS for each study. For CheckMate 205, results have been published for Cohort B [follow-up ≥6 months; insufficient follow-up for interim analysis of cohort C (median follow-up of 2.83 months)] and unpublished results are presented at a later follow-up point for cohort B (median follow-up 15.7 months) and cohort C (median follow-up 8.9 months). For study CA209-039, results from an analysis at median follow-up of 40 weeks have been published and unpublished results are also presented (median follow-up 23.3 months). A large proportion of the clinical effectiveness evidence is academic in confidence (AIC).

Due to the lack of head-to-head data from randomised controlled trials of nivolumab, an indirect comparison approach was required to compare nivolumab to comparators defined in the NICE scope and decision problem. The overall effect of nivolumab was obtained by pooling data from all patients in the CheckMate 205 and CA209-039 studies who had previously received both ASCT and brentuximab vedotin. The nivolumab pooled cohort included data from 193 patients

[CheckMate 205 Cohort B n=80 (median follow-up 15.7 months); CheckMate 205 Cohort C n=98 (median follow-up 9.0 months); CA209-039 n=15 (median follow-up 23.5 months)].

Comparator data were drawn from [redacted] potential comparator studies that were identified by one of the company's systematic reviews. However, of these, [redacted] studies were reported only as conference abstracts and [redacted] The remainder were [redacted]. One retrospective USA database study published in 2016 by Cheah and colleagues was identified in the CS as providing evidence on the outcomes of interest in a population where the majority of patients had received prior ASCT and had failed brentuximab vedotin. This study was used as the primary source of comparator evidence. In this study the [redacted] patients with disease progression either did not receive any further treatment [redacted] or were reported as having received one of the following types of therapy: investigational agent; gemcitabine; bendamustine; other alkylator; brentuximab vedotin retreatment; platinum based; ASCT; and 'other'. The CS speculates that the some of the 'investigational agent' group were likely to have received nivolumab and for this reason the 'investigational agent' group was excluded from some analyses as shown below. The comparator studies contribute to indirect comparisons that were made for four scenarios:





1a) [redacted]

1b) [redacted]

2a) [redacted]

2b) [redacted]

The company conducted both unadjusted indirect comparisons and matching-adjusted indirect comparisons (MAICs) for each of the four scenarios for the outcomes of ORR, CR rate, PR rate, OS, and PFS.

The primary outcome, ORR, was [redacted] for the study defined primary endpoints at the longest follow-up points in both nivolumab studies. The median duration of objective response is reported for cohort B [redacted] at median follow-up of 15.7 months) and cohort C [redacted] at median follow-up of 8.9 months), but as the CheckMate 205 study is still ongoing this is likely to change as more data accrue. [redacted]

[redacted] In the indirect comparisons the ORR for the nivolumab pooled cohort (n=193) was [redacted] compared to [redacted] for the Cheah 2016 study [redacted]). Across all the indirect comparisons conducted (either unadjusted or MAIC and for the four scenarios) the range of values for the comparator ORR range from the [redacted] obtained for the Cheah 2016 study [redacted] to [redacted]. Response outcomes from the unadjusted indirect comparison were used in the economic model base case to stratify pre-progression utility based on response and outcomes from both the unadjusted indirect comparison and the MAIC are used in scenario analyses. IRRS-derived response data are used in a sensitivity analysis.

OS data are not yet complete and median OS has not been reached in either CheckMate 205 cohorts B and C or the CA209-039 study at the longest follow-up periods reported in the CS. In CheckMate 205 Cohort B, there had been [redacted] deaths among the 80 patients at median follow-up of 15.7 months, in Cohort C [redacted] deaths among 100 patients at median follow-up of 8.9 months and in CA209-039 [redacted] deaths among 15 patients at a median follow-up of 23.3 months. The six-month OS for Cohorts B and C are 96.1% (95% CI 92.0 to 100) and 94.0% (95% CI 89.1 to 98.9) respectively and in CA209-039 the one year OS rates [redacted] In the indirect comparisons a median OS period was predicted for the nivolumab pooled cohort of [redacted] (based on extrapolation of the patient level data). In comparison the median OS obtained by unadjusted indirect comparison with the overall Cheah data set was [redacted] (range of values for comparator OS across the different indirect comparisons is [redacted] to [redacted] Overall survival is included in the economic model.



Similarly to OS, PFS data are not yet complete. Median PFS ranges from just over 11 months (CheckMate 205 cohort C, median follow-up 8.9 months) to 14.78 months (CheckMate 205 cohort B IRRC assessment, median follow-up 15.7 months). For the investigator assessments of CheckMate 205 Cohort B and CA209-039 median PFS had not been reached at these time points. In all the indirect comparisons investigator assessments were used, hence in the unadjusted indirect comparison a median PFS was predicted for the nivolumab pooled cohort of [redacted] In comparison the median PFS with the overall Cheah data set was [redacted] (range of values for comparator PFS across the different indirect comparisons, both unadjusted and MAIC, is [redacted] to [redacted] Progression-free survival is included in the economic model.

In both nivolumab studies, patients were able to continue treatment beyond progression if they met pre-specified criteria. The number of patients reported in the CS who have received such treatment is low (CheckMate 205 cohort B at median follow-up of 8.92 months: [redacted] patients; CA209-039 at median follow-up of 23.3 months: [redacted] patients). In all, [redacted] of the [redacted] patients treated beyond progression maintained tumour reduction in the target lesion.

Of the post-ASCT, post-brentuximab vedotin patients who received nivolumab, [redacted] went on to receive allogeneic stem cell transplant (alloSCT). The CS states that there have been no deaths due to disease progression and preliminary evidence available from all patients (i.e. including those in the included studies who are not relevant to this appraisal) who have received post-nivolumab alloSCT suggests that [redacted]. Transplant-related mortality is not reported for the separate cohorts but overall (including those who are not of relevance to this appraisal), among 40 patients undergoing alloSCT, there were six deaths due to transplant-related mortality.

Limited data for health-related quality of life (HRQoL) are presented in the CS from CheckMate 205 cohort B after a minimum follow-up of six months (median follow-up 8.92 months). HRQoL data are not reported for cohort C. In the absence of a comparator arm, these data are difficult to interpret. For the EORTC-QLQ-C30 a minimal important difference (a score difference of 10) is reported in role function at week 9 and in social function and insomnia at week 33. The average EQ-5D visual analogue score (VAS) [redacted] over time and the CS states that it [redacted] the average baseline score by [redacted] minimal important difference from [redacted]

Adverse event data are presented in the CS for the total CheckMate 205 study population [n=240 in cohorts A (not relevant to the decision problem), B and C] and separately for Cohort B, in both cases at the 8.9 month follow-up. For study CA209-039 data are presented for the total population (n=23, so includes eight patients not relevant to the decision problem) from the published 40-week follow up point and the unpublished 23.3 month follow-up. All patients in both studies received at least one dose of nivolumab.

Drug related AEs of any severity grade were reported for 70% of the overall CheckMate 205 population (88% of Cohort B) and 82.6% of CA209-039. Diarrhoea, nausea, fatigue, pyrexia,

rash and pruritus were the most common adverse events in both studies affecting 10% or more of the participants. The majority of these events were of grade 1 or 2. Infusion related reaction stood out as differing between the two studies affecting 20% of participants in CheckMate 205 Cohort B and 12.9% of the overall population in comparison to [redacted] of participants in CA209-039. In CheckMate 205 there were three Grade 5 AEs (multi-organ failure and two patients with atypical pneumonia and dyspnoea) but no Grade 5 AEs were reported for CA208-039. Laboratory parameter abnormalities were also reported which were mostly Grade 1-2. The most common grade 3-4 haemotological abnormality was decreased lymphocytes in [redacted] (CheckMate 205 18.8% in Cohort B and 13.4% in the overall population[redacted]. The proportion of patients who discontinued nivolumab treatment due to a drug-related adverse event was 3.8% in CheckMate 205 (overall population and Cohort B) and 8.7% in CA209-039. A serious drug-related adverse event was experienced by 9.6% of the CheckMate 205 study (6.3% of Cohort B) and 13.0% of CA209-039.

Identification of AEs of special clinical interest was conducted to characterise any AEs that are potentially associated with the use of nivolumab. Skin abnormalities were the most frequently reported of these adverse events, irrespective of causality, in CheckMate 205 Cohort B (41%). The other categories where more than 10% of the participants experienced an event were: Gastrointestinal abnormalities (26%), hypersensitivity or infusion-related reaction (21%) and endocrine (18%). Most adverse events of special interest were of grades 1 or 2 and no grade 5 events were reported. In CA209-039[redacted]

**Summary of submitted cost effectiveness evidence**

The CS includes:

i) A review of published economic evaluations of the management of Hodgkin lymphoma in adult patients,

ii) An economic evaluation undertaken for the NICE STA process. The cost effectiveness of nivolumab is compared with that of SoC, comprised of chemotherapy, brentuximab vedotin treatment and bendamustine.

A systematic search of the literature was conducted by the company to identify economic evaluations of the management of Hodgkin lymphoma in adult patients. The review identified 14

studies, but none of them report on nivolumab as an intervention for patients with Hodgkin lymphoma or report on interventions in patients with relapsed or refractory Hodgkin lymphoma following ASCT and treatment with brentuximab vedotin.

The economic evaluation used a semi-Markov survival model (developed in Microsoft Excel) to assess the cost effectiveness of nivolumab compared with SoC in adult patients with relapsed or refractory Hodgkin lymphoma following ASCT and brentuximab vedotin. The model adopted a time horizon of 50 years to capture lifetime costs and health outcomes, with a cycle length of one month and half-cycle correction. The model consisted of three health states: pre-progression, progression and death. Analyses were presented from the NHS and Personal Social Services perspective.



The model uses pooled efficacy data (PFS, OS, treatment response, adverse events) from the CheckMate 205 and CA209-039 studies for the nivolumab arm and from Cheah and colleagues for the SoC arm. The company fitted parametric survival curves to these data for progression free survival and overall survival and selected the most appropriate curves on the basis of the goodness of fit and clinical plausibility. The log-normal function was selected for progression-free survival and the Weibull function for overall survival for the nivolumab arm. The exponential function was selected for progression-free survival and overall survival for the SoC arm. Utility estimates were taken from EQ-5D data obtained from the company's CheckMate 205 study for the nivolumab arm, and from a study by Swinburn and colleagues that used time-trade off methods for the SoC arm.



Nivolumab is administered intravenous and the recommended dose, based on patient weight, is 3.0 mg/kg given once every two weeks. Nivolumab has been provided with a confidential patient access scheme (PAS) price discount in the company analyses.

The results of the economic model were presented as incremental cost effectiveness ratios (ICERs), measured as the incremental cost per quality-adjusted life-years (QALYs). In the base analysis, the model estimated that there would be an additional 2.8 discounted QALYs for nivolumab compared to SoC. The results of the cost effectiveness analyses with the PAS discount price for nivolumab showed an incremental cost effectiveness ratio (ICER) of £19,882 per QALY compared to SoC (Table 1).

**Table 1 Company base case analysis results**

| Parameters | Costs | Incremental costs | QALYs | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|
| **SoC** | £21,090 | - | 0.932 | - | - |
| **Nivolumab** | [redacted] | [redacted] | [redacted] | [redacted] | £19,882 |

The ICER with a list price for nivolumab was [redacted] per QALY. In probabilistic sensitivity analyses, the probability that nivolumab is cost-effective versus SoC was 94.8% at a willingness-to-pay threshold of £30,000 per QALY.

The company conducted a large number of scenario analyses. The ERG was unable to replicate some analyses, which led to requests for clarification on how analyses were run and updated analysis parameters from the company. In general, all analyses produced results under £50,000 per QALY and two analyses, that assessed alternative post-progression utility scores, produced results above £30,000 per QALY.

**Commentary on the robustness of submitted evidence**

**Strengths**

The company's systematic review of clinical effectiveness was generally of good methodological quality. The ERG does not consider that any key studies of nivolumab or of potential comparators are missing. Two single-arm studies provide evidence for the effectiveness of nivolumab for adults with relapsed or refractory classical Hodgkin lymphoma following ASCT and brentuximab vedotin. Twelve studies provide evidence on outcomes following treatments that are considered potential comparators for nivolumab.

The company conducted systematic reviews to identify cost-effectiveness, HRQoL and cost studies and values from this review were utilised in the model. The model structure is generally representative of the clinical pathway for patients with Hodgkin lymphoma.

**Weaknesses and Areas of uncertainty**

The evidence base for potential comparators is limited in terms of quality (the studies were predominantly phase 1 or 2 single-arm studies), and completeness of reporting (seven only reported as conference abstracts, limited follow-up up periods, outcomes of PFS and OS often not reported). The degree to which the populations in the 12 comparator studies match those in the nivolumab studies and reflect the UK population is also uncertain. As the modelled

comparison between nivolumab and SoC is based on this evidence, rather than a randomised controlled trial, there is considerable uncertainty around modelled efficacy.

There is considerable uncertainty regarding the extent to which the clinical benefits of nivolumab exceed those of potential comparator treatments. This uncertainty is due to the immaturity of the evidence base for nivolumab and comparators and because indirect comparisons are needed due to the absence of direct evidence. The CS base case used a population for SoC that excluded patients that received investigational agents, rather than using the overall population from the Cheah study. Including investigational agents reflects clinical practice and improves the efficacy of SoC.

Additionally, there is uncertainty around the composition of treatments used for patients receiving SoC and therefore the treatment costs for this group are uncertain. The costs for alloSCT have not been included in the base case analysis even though patients received alloSCT in the nivolumab and SoC arms.

**Summary of additional work undertaken by the ERG**

In order to address the issues identified above we undertook a series of scenario analyses that adapted a company scenario wherein patients could have alloSCT and used the company's higher estimate for alloSCT costs.

Our base case contained the following elements (see Table 2 for results):

- A structure that allowed patients to receive alloSCT treatment, and included both costs and benefits for alloSCT
- alloSCT rates derived from the trials (CheckMate 205 and Cheah and colleagues)
- Pre-progression survival derived from Cheah and colleagues for patients receiving SoC
- Alternative pre-progression utilities based on CheckMate 205 (EQ-5D) and weighted by treatment response for each intervention independently
- Post-progression utilities based on CheckMate 205 (EQ-5D) for all interventions, including alloSCT
- Survival curves modelled using the initial treatment curves for each intervention independently
- SoC treatment costs that assume that patients do not receive treatment with mini-BEAM or DexaBeam

**Table 2 ERG base case analysis results**

| Parameters | Costs | Incremental costs | QALYs | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|
| **SoC** | £23,043 | - | 2.102 | - | - |
| **Nivolumab** | [redacted] | [redacted] | [redacted] | [redacted] | £36,525 |

The resultant ICER of the ERG base case was £36,525 per QALY gained. The ERG conducted sensitivity analyses on the ERG base case varying treatment costs for SoC, assumptions about the survival curve parameterisations, and the assumptions about treatment response and associated utilities. The ICERs for these additional analyses varied between £25,647 per QALY and £42,226 per QALY.

# 1 Introduction to the ERG Report

This report is a summary and critique of the company's submission (CS) to NICE from Bristol-Myers Squibb (BMS) on the clinical effectiveness and cost effectiveness of nivolumab (OPDIVO®) for treating relapsed or refractory classical Hodgkin lymphoma. It identifies the strengths and weakness of the CS. Clinical experts were consulted to advise the ERG and to help inform this review.

Clarification on some aspects of the CS was requested from the company by NICE and the ERG on 29 November 2016. A response from the company via NICE was received by the ERG on 15 December 2016 and this can be seen in the NICE committee papers for this appraisal.

The ERG found that there were inconsistencies in the marking of data as academic in confidence (AIC) or commercial in confidence (CIC). The same data could be found unmarked in some places, but marked as AIC or CIC in other places in the submission. The ERG has taken a conservative approach and marked up, as AIC or CIC, any unmarked data whenever we were aware it was marked as AIC or CIC elsewhere in the submitted evidence.

# 2 BACKGROUND

## 2.1 Critique of company's description of underlying health problem

The ERG considers that the CS provides a clear and accurate overview of classical Hodgkin lymphoma in section 3 (CS p. 28-32).

Classical Hodgkin lymphoma is a subtype of Hodgkin lymphoma which is a haematological malignancy that accounts for approximately one in five lymphomas diagnosed. The classical Hodgkin lymphoma type of Hodgkin lymphoma accounts for about 95% of Hodgkin lymphoma with the remaining 5% of Hodgkin lymphoma being nodular lymphocyte-predominant Hodgkin lymphoma. Hodgkin lymphoma has been reported to have a bi-modal age distribution with peaks of cases among people aged 20-24 years and people aged 75-79 years. During 2013 there were 1,954 new cases of Hodgkin lymphoma in the UK and just under half of these (49%) were diagnosed in people aged 45 years or over. The one year survival rate for patients diagnosed in

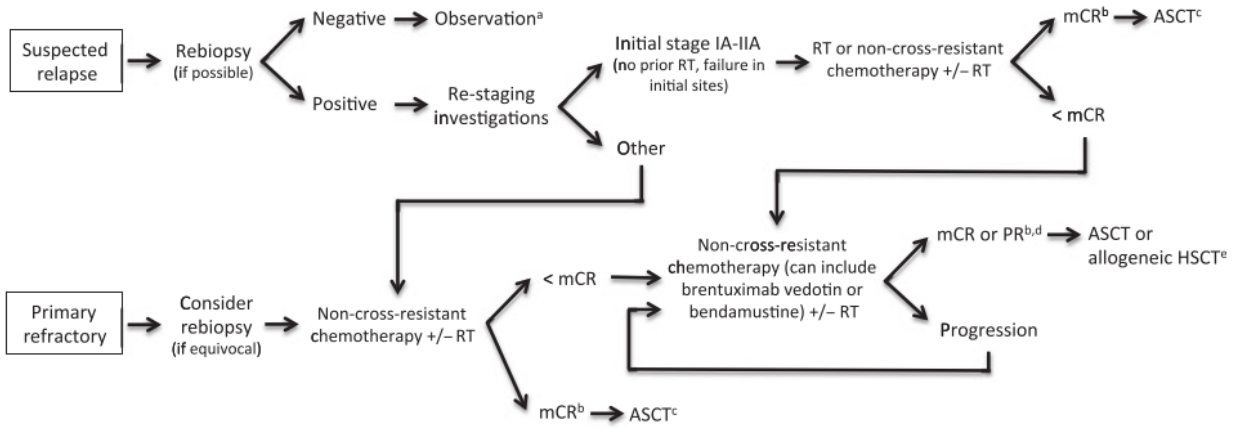
England and Wales during 2010-2011 is predicted to be 91.4%, with ten-year survival estimated at 80.4%.

## 2.2 Critique of company's overview of current service provision

The CS provides a clear and accurate overview of current treatment options for people with classical Hodgkin lymphoma (CS section 3.2 p. 28) and cites the British Committee for Standards in Haematology (BCSH) treatment guidelines,[1] stating that these form the best available evidence to inform current clinical practice for the treatment of Hodgkin lymphoma in the UK. The CS notes that NICE are currently appraising the use of brentuximab vedotin for the treatment of two groups of patients with CD30-positive Hodgkin lymphoma: those who have relapsed or refractory disease following ASCT or who are at high risk of residual disease following ASCT; those who have had at least two previous therapies when ASCT or multi-agent chemotherapy is not a treatment option. This guidance is expected to be published in February 2017. The ERG notes that NICE intend to appraise Pembrolizumab for classical Hodgkin lymphoma (expected guidance publication February 2018), but a scope for this STA is not available at the time of writing (December 2016).



The company describes current first-line treatment options for Hodgkin lymphoma and highlights that 15-30% of patients do not achieve long-term remission following first-line therapy, either due to primary refractory disease or relapse. Based on the information provided about the number of new cases of Hodgkin lymphoma in the UK in 2013, this would mean approximately 278-558 of the classical Hodgkin lymphoma patients diagnosed in the UK in 2013 would require salvage therapy at some point in the future. The goal of salvage therapy (chemotherapy and/or radiotherapy) is to achieve a sufficient response such that ASCT can be carried out. The recommended treatment pathway for those who do not achieve long-term remission and who are eligible for ASCT is presented in the CS (Figure 8, p. 29) based on BCSH treatment guidelines[1] and this is reproduced below (Figure 1). However, ASCT is not a treatment option for patients who are unable to achieve a sufficient response or for those who age or co-morbidities prevent ASCT being a treatment option. The clinical experts we consulted suggested that, of those who do not achieve long-term remission following first-line therapy, about 30% would not be eligible for ASCT (due to age or co-morbidities). For the remaining 70%, there would probably be a 70-80% change of achieving a good enough remission for transplant.




[a] clinical factors may warrant intervention
[b] partial response by CT criteria is sufficient for consideration of ASCT although a PET-guided approach is recommended
[c] in selected cases observation may be appropriate, e.g. in those relapsing >5 years from primary therapy; observe if ASCT contra-indicated
[d] those with minimal response or stable disease may be considered appropriate candidates for allogeneic SCT; further attempts at cytoreduction are recommended if ASCT is being contemplated
[e] allogeneic HSCT may be favoured for those requiring >2 lines of salvage therapy to achieve a response, or in those with < mCR

Fig 1. Flow diagram of recommended treatment pathway for patients deemed eligible for potential high dose consolidation therapy. RT, radiotherapy; CT, computerized tomography; PET, positron-emission tomography; mCR, metabolic complete response; PR, partial response; ASCT, autologous stem cell transplantation; HSCT, haematopoietic stem cell transplantation.

**Figure 1 BCSH and British Society of Blood and Marrow Transplantation treatment guidelines diagram of the recommended treatment pathway for patients deemed eligible for potential high dose consolidation therapy[1]**

ASCT is a potentially curative treatment and it will be effective for about 50% of the people who are eligible to receive it. However, the CS states that outcomes for patients who relapse following ASCT have historically been very poor. The aim of treatment in these patients is to attain a sufficient response to allow consideration of allogeneic stem cell transplant (alloSCT), but again not all patients will be eligible for this route and the most appropriate option for some will be a palliative approach. The BCSH guidelines do not indicate a standard therapy at this point but do indicate that brentuximab vedotin should be considered as a possible treatment option. As noted above, NICE are currently assessing the use of brentuximab vedotin with guidance due to be published in February 2017.

For patients who have failed ASCT and who subsequently receive brentuximab but who do not achieve a response or who achieve only a partial response, there are no currently recommended treatment options and the prognosis remains poor for these patients. It is this patient group who would be eligible to receive nivolumab.

The ERG believes the company has presented an accurate description of current service provision and the treatment options available to patients with Hodgkin lymphoma at different points in the treatment pathway.

## 2.3 Critique of company's definition of decision problem

The decision problem is summarised in CS Table 1 (p. 13).

Population

The population is defined in the company's decision problem as people with relapsed or refractory classical Hodgkin lymphoma following autologous stem cell transplant and brentuximab vedotin. This is one of two populations specified in the final scope issued by NICE and the ERG believes that this population is appropriate for the potential use of nivolumab in the NHS. The second population specified in the final scope issued by NICE "People with relapsed or refractory classical Hodgkin lymphoma following at least 2 prior therapies when autologous stem cell transplant is not a treatment option" are not considered by the CS. The CS does not provide a reason for this but the ERG believes that this is because the proposed wording of the license indication for nivolumab is "OPDIVO as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin (BTX)" as described in CS Table 2 (CS p. 15). Thus the second population specified in the final scope issued by NICE is not encompassed by the proposed indication for nivolumab. These patients would predominantly be those over 70 years who are not eligible for transplants and a small proportion of patients under 70 years of age. The clinical experts were not certain how many patients this might be, but estimated perhaps around 300 patients each year.

Intervention

The intervention described in the company's decision problem is nivolumab (brand name: Opdivo®), and this is in line with the final scope issued by NICE. Nivolumab first received marketing authorisation on 19th June 2015 as a monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults. Since then the licensed indication has been extended to four other indications (CS p. 24) and a positive opinion for nivolumab as monotherapy for the treatment of adult patients with relapsed or

refractory classical Hodgkin lymphoma after ASCT and treatment with brentuximab vedotin was made available by the Committee for Medicinal Products for Human Use (CHMP) on 13 October 2016. Nivolumab is a monoclonal antibody that acts as a programmed death-1 (PD-1) immune checkpoint inhibitor and, according to the company, "stimulates the patient's own immune system to directly destroy cancer cells" (CS p. 15).

As outlined in the CS Table 3 (p. 25), nivolumab is provided as an intravenous infusion at a dosage of 3mg/kg over a period of 60 minutes every two weeks. Treatment should be continued as long as a clinical benefit is observed or until treatment is no longer tolerated by the patient. An anticipated duration of treatment is not reported in the CS. Dose escalations or dose reductions are not recommended, but dosing delay or discontinuation may be required based on individual safety and tolerability issues. No retreatment with nivolumab is anticipated.

Comparators

The NICE scope describes comparators according to the populations set out in the decision problem. As the CS has only considered the population of people with relapsed or refractory classical Hodgkin lymphoma following autologous stem cell transplant and brentuximab vedotin, it consequently only considers the comparators relevant for this population. The CS describes the base case comparator as:

- Standard of Care (SoC) - comprised of chemotherapy, brentuximab vedotin retreatment and bendamustine, based on a real world retrospective study by Cheah and colleagues.[2]

This comparator broadly matches one of the comparators described in the NICE scope: "Established clinical management without nivolumab including chemotherapy such as gemcitabine or bendamustine." However the ERG notes that there is some uncertainty about how well the Cheah study,[2] which drew on data from patients treated in the USA and which provides the base case comparator data, reflects the experience of patients treated in the UK. There is a lack of detail in the Cheah and colleagues publication about the precise composition of the treatment regimens received by patients who had received ASCT and brentuximab vedotin. Many patients for whom outcome evaluations were available (28/67; 42%) were enrolled onto trial protocols and received what is described as 'Investigational agent', but there is no further detail about which therapies may have been classified under this heading. To find

out whether PD-1 inhibitors (such as nivolumab) were included among the 'Investigational agent' treatments, the ERG contacted the authors of the Cheah and colleagues study and were informed that only a couple of patients in the study received PD-1 inhibitors. The next most common regimens received by patients in the Cheah and colleagues study were gemcitabine-based (12/67; 18%) or bendamustine-based (11/67; 16%).

Clinical advice to the ERG suggests that gemcitabine regimens such as GDP (gemcitabine, dexamethasone, cisplatin) are commonly used in this patient population in the UK but platinum-containing regimens such as ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) and DHAP (dexamethasone, cytarabine, cisplatin) are also in common use. In the Cheah study 12/67 (18%) of patients with outcome evaluations received gemcitabine and just 4/67 (6%) of patients received platinum-based regimens.

However, despite the uncertainty about how closely the experience of patients from the USA may match that of patients in the UK, the ERG is not aware of a more appropriate source of data for the comparator population.

In addition to the base case analysis with SoC comparator the model includes scenario analyses comprising:

- SoC including investigational agents
- Chemotherapy only
- Best supportive care (BSC) (Due to the uncertainty around the composition of BSC for the patient group relevant to this STA the composition of BSC is assumed to be chemotherapy, palliative care and participation in clinical trials (CS Section 5.2.2.3 p. 102 and Section 5.5.2.3 p. 131).

Evidence for the clinical efficacy of BSC is not presented within the clinical effectiveness section of the CS (CS section 4, p. 33) and the CS states that evidence to describe the efficacy of BSC in the post-ASCT post brentuximab vedotin classical Hodgkin lymphoma population has not been identified (CS Section 5.3.1, p. 103). The scenario analyses describing BSC were therefore based on the efficacy of SoC.

Outcomes

The company has listed all the outcomes specified in the final scope in their decision problem:

- Overall survival (OS)
- Progression-free survival (PFS)
- Response rates [in the CS decision problem this is covered by objective response rate (ORR) and complete response/remission rate (CR) with a note stating that rate of partial response (PR) and stable disease (SD) are also considered of interest]
- Adverse effects of treatment
- Health-related quality of life (HRQoL)

These outcomes are appropriate and clinically meaningful to patients. The ERG considers that the company has included all important outcomes in the decision problem.

Economic analysis

The economic analysis specified in the decision problem matches the final scope and is appropriate for the NHS. The company have conducted a cost-utility analysis with a lifetime horizon which is appropriate for considering differences in costs and outcomes between treatments for patients with relapsed or refractory classical Hodgkin lymphoma following ASCT and brentuximab vedotin. Costs are considered from the NHS and Personal Social Services perspective.

On CS page 127 the company state that a Patient Access Scheme (PAS) has been proposed. Approval by the Department of health is stated to have been given in [redacted] for a discount of [redacted] from the nivolumab list price. The economic evaluation presented in the CS applies the PAS in the base case analysis. The comparator is not subject to a PAS.

Other relevant factors

The CS states that no subgroups are specified in the NICE scope and indicates that the CS will provide subgroups for analysis wherever data allows (including age-specific groupings). The CS presents subgroup analysis (two of which are clearly indicated to be post-hoc) in section 4.8 (CS p. 67-68).

The ERG notes that the NICE scope requests that, if the evidence allows, a scenario analysis including alloSCT as a subsequent treatment after nivolumab or its comparators should be considered. The CS does include modelling of scenarios including alloSCT (CS section 5.8.3.2, p. 152).

No equity or equality issues were specified in the final scope or identified by the company. The ERG is not aware of any issues related to equity or equality in the use of nivolumab in patients with relapsed or refractory classical Hodgkin lymphoma following ASCT and brentuximab vedotin.

The company highlights that few patients in the 75-79 years age category undergo ASCT so therefore there is very little evidence for patients in this age category who are post-ASCT and post-brentuximab vedotin. Treatment options are stated to be fewer in this age group (which is one of the peaks of Hodgkin lymphoma incidence), so there is a high level of unmet need.

The other peak of Hodgkin lymphoma incidence is in people aged 20-24 years, who would benefit from a therapy that could act as a bridge to alloSCT.

# 3 CLINICAL EFFECTIVENESS

## 3.1 Critique of company's approach to systematic review

### 3.1.1 Description of company's search strategy

The CS reports five systematic literature searches.

- Clinical Effectiveness Search 1 (Appendix 2) (searched from database inception to October 2016)
- Clinical Effectiveness Search 2 (Appendix 4) (searched from database inception to March 2016)
- Cost Effectiveness (Appendix 5) (searched from database inception to March 2016)
- Measurement and valuation of health effects (Appendix 5) (searched from database inception to April 2016)
- Resource identification, measurement and valuation review (Appendix 5) (searched from database inception to April 2016)

The ERG considers the searches overall to be fit for purpose, despite an apparent error in one of the clinical effectiveness strategies. They are reasonably well designed, well documented and transparent (e.g. the numbers of references returned by each line of the search is reported).

The first clinical effectiveness search covered Hodgkin lymphoma linked to post-ASCT and post-brentuximab vedotin interventions. The CS reported this yielded a "paucity" of evidence and undertook a second clinical effectiveness search aimed to identify all treatment options in Hodgkin lymphoma post-ASCT to provide a basis for indirect comparison. Consequently, brentuximab vedotin not overtly linked to ASCT, as in the first search. Core databases were searched for both clinical effectiveness reviews: Embase, Pubmed and the Cochrane Library. Conference proceedings were recorded as searched. Company in-house databases were not recorded as searched. The only ongoing trials databases documented as examined was clinicaltrials.gov.

The searches were constructed with a balance of descriptors and free text terms, including the use of search filters e.g. to limit the results to English Language publications. There is an error in combining sets in the first search documented in Appendix 2 at line 26 " #24 or #25 or #25", this would leave line #23 (which represents the search terms for brentuximab) redundant. It is noted

that these lines are correctly linked in the Pubmed and Cochrane search strategies. The ERG checked Embase with the sets correctly linked and deemed the error in the documented search to be a mere transcription error. Additionally, in mitigation, the second search was designed to retrieve any treatment which would therefore have obviated the error had it occurred. The choice of descriptors and free text and use of truncation were satisfactory. Search filters to identify specific types of trial such as RCTs were not applied to either search. This was in line with the wide trial inclusion criteria of RCTs, non-randomised controlled trials, longitudinal cohort studies and registries. PRISMA (Preferred Reporting Items for Systematic review and Meta-Analysis) charts were provided for both reviews separately and the text matched the numbers in the diagram. The first search has an end date of October 2016 and the second March 2016 which is inconsistent. The ERG searched Medline, Medline in Process and Embase for nivolumab, since it did not appear in either strategy linked to Hodgkin disease. This did not retrieve additional relevant results that were not already documented in the CS.

The three economic searches to identify cost effectiveness, valuation of health and resource use, contained a balance of free text and descriptor terms with correct truncation and linked sets. Core databases searched included Pubmed, Embase, Cochrane and Econlit. It is noted that NHSEED was not searched separately on the CRD website. It appears from a quick check that it was searched via the Cochrane Library (of which it is one of the constituent databases). It may have been useful to search using only the Hodgkin lymphoma terms specifically on NHSEED since this part of the database just covers economic papers. The same conferences were searched as for the clinical effectiveness searches. The ERG additionally searched ScHARRHUD (the School of Health and Related Research Health Utilities Database) to identify any HRQoL utility papers relating to Hodgkin lymphoma, however nothing further of relevance was identified that was not already referenced in the CS.

In summary, it is considered that the searches conducted by the company to support the systematic reviews in the submission are generally comprehensive and are reported transparently.

### 3.1.2 Statement of the inclusion/exclusion criteria used in the study selection.

The CS clearly states what are described as the “main inclusion criteria” and these are “adult patients with relapsed or refractory cHL following prior ASCT and BTX” (CS p. 33) receiving any

intervention aimed at managing classical Hodgkin lymphoma. Studies could assess any outcome of interest including OS, PFS, CR rate, PR rate, ORR or rate of SD. Unlike the NICE final scope, the inclusion criteria do not explicitly list HRQoL or adverse events (AE) as required outcomes. An overview of the inclusion/exclusion criteria is available in the appendices (CS Appendix 2). The included population is in line with the decision problem and the proposed licensed indication of nivolumab, but as stated earlier only relates to one of the populations listed in the final NICE scope. The company did not specify treatment setting as an inclusion criterion nor place any limits on inclusion relating to the quality of the RCTs, which is appropriate.

The CS includes a flow diagram (CS Figure 9, p. 34) illustrating the number of records included and excluded at each stage of the main systematic literature review (SLR), based on adult patients with relapsed or refractory classical Hodgkin lymphoma and prior ASCT and brentuximab vedotin treatment. The flowchart records 53 additional records identified through other sources, but the nature of the sources is unclear. The company response to clarification request A9 about the nature of the sources, identifies these as conference proceedings. Reasons for the exclusion of full-text publications are detailed in the flow diagram and associated papers are referenced appropriately (CS Appendix 7).

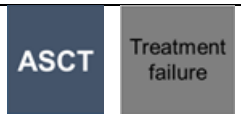
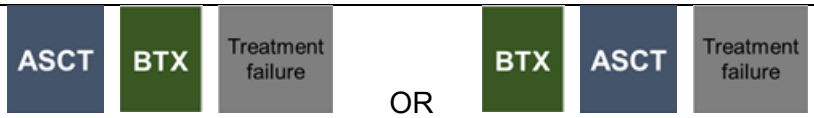
Overall, the ERG considers that the eligibility criteria used in the main systematic review were appropriate and matched the decision problem according to the proposed licensed indication of nivolumab. The SLR is also utilised to inform an indirect treatment comparison (CS Appendix 3). In addition, the company conducted a SLR for the treatment of relapsed or refractory Hodgkin lymphoma with prior ASCT only, i.e. without brentuximab vedotin (CS Appendix 4). This population is not relevant to the decision problem (nor does it meet the proposed licensed indication for nivolumab) and it is therefore not discussed any further by the ERG.

### 3.1.3 Identified studies

No relevant RCTs evaluating nivolumab for the treatment of patients with relapsed or refractory classical Hodgkin lymphoma after ASCT and treatment with brentuximab vedotin were identified. The SLR identified [redacted]. Two of these studies were described as relevant evidence for the effectiveness of nivolumab for the treatment of relapsed or refractory classical Hodgkin lymphoma following ASCT and brentuximab vedotin therapy. Both studies are non-comparative, single-arm studies. All of the [redacted] are included in an indirect treatment comparison presented in the CS (Section3.1.7).

The first study presented in the CS using nivolumab as an intervention is a phase II parallel-cohort study named CheckMate 205,[3,4] which included classical Hodgkin lymphoma patients ≥ 18 years old who failed ASCT, either because of refractory disease or because of disease relapse after ASCT. The study has three cohorts (see Table 3), with patients in cohort B (n=80) and C (n=100) said to be most relevant to the submission (CS section 4.2 p. 36). The ERG agrees that both of these cohorts are of interest, as the NICE final scope does not specify a particular order of treatment with regard to ASCT or brentuximab vedotin. Patients in cohort A (n=63) were brentuximab vedotin-naïve. The study [redacted][3] and is still ongoing. Published and unpublished interim results are available with a data cut-off as of August 2015[3,4] for cohort B (follow-up ≥6 months; insufficient follow-up for interim analysis of cohort C with a median follow-up of 2.83 months) and unpublished results available for cohort B and C with a data cut-off as of April 2016 (median follow-up of 15.7 months and 8.9 months respectively). The CS notes that it is anticipated that additional follow-up results from all cohorts will become available during the NICE appraisal process (CS p. 40).

**Table 3 Previous treatment history of cohorts in CheckMate 205**

| Cohort | Previous treatment history of patient cohorts |
|---|---|
| A n=63 |  <br>• Cohort A patients were brentuximab vedotin-naïve (being naïve to brentuximab vedotin treatment was part of the eligibility criteria for cohort A). |
| B n=80 |  <br>• Cohort B patients had received prior brentuximab vedotin treatment as a salvage therapy after failure of ASCT. Patients with a treatment history of brentuximab vedotin before first ASCT were not eligible for entry into cohort B. |
| C n=100 |  <br>• Cohort C patients could have received prior ASCT and brentuximab vedotin in any treatment order (it was also possible for these patients to have received BTX both before and after ASCT). |

ASCT, autologous stem cell transplant; BTX, Brentuximab vedotin.
Table is based on CS Figure 10 p. 39.

The second included study (CA209-039[5,6]) was an open-label, phase I study of nivolumab for the treatment of haematological malignancies, including classical Hodgkin lymphoma. Of the included 23 patients, all had classical Hodgkin lymphoma, but only 15 patients had received previous treatment with both ASCT and brentuximab vedotin and were therefore relevant to the submission (see Table 4). This study was based in the USA and included no UK patients. Published results are available with a cut-off as of 16 June 2014[5] (median follow-up 40 weeks) and unpublished results from the most recent database cut-off (11 August 2015; median follow-up 23.3 months).[6]

**Table 4 Summary of study details of the CS included non-RCTs**

| Parameters | CheckMate 205[3,7,8]<br>Cohort B n=80; Cohort C n=100* | CA209-039[4,6,9]<br>Subgroup n=15 |
|---|---|---|
| *Eligibility criteria (CS p. 40 & p. 57)* | • Adults, age ≥18 years<br>• ECOG status 0 or 1<br>• Prior chemotherapy followed by ASCT as a part of salvage therapy for cHL<br>• Confirmed cHL after failure of ASCT or after ASCT and BTX<br>*Cohort B:*<br>• Failed BTX treatment after failure of ASCT<br>*Cohort C*:<br>• Failed ASCT and prior treatment with BTX at any time point (including as an initial therapy or salvage therapy before ASCT, and/or BTX treatment after ASCT | • Adults, age ≥18 years<br>• ECOG status 0 or 1<br>• Histological confirmation of relapsed or refractory hematologic malignancy<br>• HL patients ≥1 lesion >1.50 cm + additional lesion for biopsy<br>• >100 days post-ASCT<br>• ≥1 prior chemotherapy, off therapy ≥3 weeks<br>• Prior palliative radiation, completed ≥2 weeks prior study<br>• Prior BTX treatment or BTX-naïve (not required to have failed treatment) |
| *Nivolumab treatment (CS p. 41 & p. 57)* | Nivolumab at 3 mg/kg patient's body weight (by IV infusion over 60 minutes) on day one of each two-week cycle (no less than 12 days between doses and no more than three days after the scheduled dosing date). Dose reductions and escalations were not permitted. Dose delays were permitted of <6 weeks for all drug-related AEs according to pre-specified criteria. Treatment was permanently discontinued according to pre-specified criteria, due to AE, | Nivolumab 3 mg/kg (by IV infusion).The first dose was followed by a three-week evaluation period, with subsequent doses administered every 2 weeks. Dose reductions and escalations were not permitted. Dose delays were permitted of <6 weeks for all drug-related AEs according to pre-specified criteria. |

| | | |
|---|---|---|
| | preparation for alloSCT or ASCT, or disease progression. | |
| *Design (CS p. 39 & p. 57)* | Non-comparative, parallel-cohort, single-arm phase II study | Non-comparative, escalating dose, open-label, single-arm, phase I study |
| *Treatment beyond investigator-assessed disease progression (CS p. 41 & p. 58/59)* | Defined by relapsed disease (after CR) or progressive disease. Based on pre-specified criteria, including:<br>• Investigator-assessed clinical benefit and do not have rapid disease progression<br>• Stable performance status<br>• Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression<br>• Tolerance of study drug. | Pre-specified criteria:<br>• Investigator-assessed clinical benefit<br>• Disease progression is not rapid<br>• Stable performance status<br>• Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression<br>• Tolerance of study drug.<br>• Patients have provided written informed consent prior to receiving additional treatment |
| *Length of follow-up (CS p. 45/52 & p. 56)* | • Cohort B as of the 20 August 2015 data cut-off date - minimum of six months<br>• Cohort B and C as of the April 2016 data cut-off date - a median follow-up of 15.7 months in cohort B and 8.9 months in cohort C (preliminary analysis of patient-level data) | • Up to 2 years, with the potential for retreatment in eligible patients. Patients with a CR may have continued to receive study therapy until response confirmation or for an additional 16 weeks (whichever is longer) and then enter the follow-up period.<br>• Published data based on a database lock on 16 June 2014 (median follow-up: 40 weeks)[5]<br>• Unpublished data from the most recent database lock (11 August 2015; median follow-up: 23.3 months)[6] |

AE, adverse events; alloSCR, allogenic stem cell transplant; ASCT, autologous stem cell transplant; BTX, brentuximab vedotin; cHL, classical hodgkin lymphoma; CR, complete response; ECOG, Eastern Cooperative Oncology Group; PR, partial response.
* Cohort C included 2 patients that had not previously received Brentuximab vedotin (CS p. 53)

Evidence from the two included studies is provided consecutively in the CS. The ERG has presented the evidence from the two studies side-by-side for a clearer overview where possible.

The CS presents demographics/baseline characteristics and patient disposition for cohort B at data cut-off 20 August 2015 (not reported by the ERG) and at a second later data cut-off April 2016 (see Table 5). For the later data cut-off, the majority of the information is marked AIC. The CS presents the same information for the total population of CA209-039, which includes eight patients who do not meet the licenced indication for nivolumab; all of the patient disposition data is marked AIC. Following a clarification request, the company provided patient demographics and baseline characteristics for the subgroup of 75 patients who do meet the licenced indication for nivolumab (Clarification response A5). The ERG reports on the subgroup of 15 patients from CA209-039 who are relevant to the decision problem.



The median age in the two cohorts of the CheckMate 205 study and the post-ASCT post-brentuximab vedotin subgroup of the CA209-039 study varies between [redacted] years and [redacted] years, with mean age only reported in CheckMate 205. The maximum age of patients in CheckMate 205 was higher ([redacted] to 72 years) compared to CA209-039 ([redacted] years). The majority of patients in the two cohorts of CheckMate 205 were aged between 30 and 65 years (cohort C [redacted] in cohort B), and [redacted] of patients are aged 65 or over. A break-down by age groups was not reported in CA209-039. The majority of patients included were white ([redacted] to [redacted]) and predominantly male ([redacted]). The Eastern Cooperative Oncology Group (ECOG) status was fairly similar across the cohorts and subgroup, and nearly equally divided between grade 0 (Fully active, able to carry on all pre-disease performance without restriction) and grade 1 (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work) in the cohorts. Details for the number of prior systemic regimen received by patients was grouped differently in the two studies, but cohort B of CheckMate 205 had the highest proportion of patients ([redacted]) that had received ≥5 prior systemic regimens [redacted] Patients who had received with prior radiotherapy ranged between 70% to 87%.

Cohort B of CheckMate 205 appears to have had a slightly higher proportion of patients with a higher disease stage at study entry and more prior systemic treatments compared to cohort C, which may be related to patients in cohort B being slightly older. However, the ERG notes that there is very little evidence in the CS for the 75 to 79 year age group, as acknowledged in the CS.

**Table 5 Baseline characteristics of patients in CheckMate 205 and CA209-039**

| **Parameters n (%)** | **CheckMate 205 (April 2016 data cut-off)** | | **CA209-039** |
|---|---|---|---|
| | **Cohort B** (n=80) | **Cohort C** (n=100) | **Post-ASCT, post-BTX subgroup (n=15)** |
| Age (years), mean (standard deviation) | 38.7 (13.00) | [redacted] | NR |
| Median (Min, Max) | 37.0 (18-72) | [redacted] | [redacted] |
| < 30 | 27 (33.8%) | [redacted] | NR |
| ≥30 and <65 | 50 (62.5%) | [redacted] | NR |
| 3 (3.8%) | 3 (3.8%) | [redacted] | NR |
| Gender, male | 51 ( 63.8) | [redacted] | [redacted] |
| Race | | | |
| White | 71 ( 88.8) | [redacted] | [redacted] |
| Black or African American | 4 ( 5.0) | [redacted] | [redacted] |
| Asian | 1 ( 1.3) | [redacted] | [redacted] |
| American Indian Or Alaska Native | 0 | [redacted] | [redacted] |
| Native Hawaiian Or Other Pacific Islander | 0 | [redacted] | [redacted] |
| Other | 4 ( 5.0) | [redacted] | [redacted] |
| Ethnicity | | | |
| Hispanic Or Latino | 1 ( 1.3) | [redacted] | NR |
| Not Hispanic Or Latino | 63 ( 78.8) | [redacted] | NR |
| Not Reported | 16 ( 20.0) | [redacted] | NR |
| Performance Status - ECOG | | | |

| Parameters n (%) | CheckMate 205 (April 2016 data cut-off) | | CA209-039 |
|---|---|---|---|
| | **Cohort B** (n=80) | **Cohort C** (n=100) | **Post-ASCT, post-BTX subgroup (n=15)** |
| 0 | 42 ( 52.5) | [redacted] | [redacted] |
| 1 | 38 ( 47.5) | [redacted] | [redacted] |
| Disease Stage At Study Entry | | | |
| Stage I | 1 ( 1.3) | [redacted] | NR |
| Stage II | 11 ( 13.8) | [redacted] | NR |
| Stage III | 14 ( 17.5) | [redacted] | NR |
| Stage IV | 54 ( 67.5) | [redacted] | NR |
| Not Reported | 0 | [redacted] | NR |
| Bulky Disease At Baseline | 17 ( 21.3) | [redacted] | NR |
| Extra Lymphatic Involvement At Baseline | 36 ( 45.0) | [redacted] | NR |
| Bone Marrow Involvement At Baseline | 8 ( 10.0) | [redacted] | NR |
| Median Time: Initial Diagnosis To First Dose Of Study Therapy, Years (Min – Max) | 6.15 (1.3–25.1) | [redacted] | NR |
| Median Time: Most Recent Transplant To First Dose Of Study Therapy, Years (Min–Max) | 3.37 (0.2–19.0) | [redacted] | NR |
| Number Of Prior Systemic Regimen Received | | | |
| ≤2 | 0 | [redacted] | [redacted] |
| 3 | 19 (23.8) | [redacted] | |
| 4 | 22 (27.5) | [redacted] | [redacted] |
| ≥ 5 | 39 (48.8) | [redacted] | |
| ≥ 6 | NR | [redacted] | [redacted] |
| Median (Min, Max) | 4 (3, 15) | [redacted] | NR |
| Number Of Prior ASCT | | | |
| 1 | 74 (92.5) | [redacted] | NR |

| Parameters n (%) | CheckMate 205 (April 2016 data cut-off) | | CA209-039 |
|---|---|---|---|
| | **Cohort B** (n=80) | **Cohort C** (n=100) | **Post-ASCT, post-BTX subgroup (n=15)** |
| ≥ 2 | 6 (7.5) | [redacted] | NR |
| Prior ASCT | 80 (100) | 100 (100) | [redacted] |
| Best Response To Most Recent ASCT | | | |
| CR Or PR | 29 (36.3) | [redacted] | NR |
| Stable disease | 6 (7.5) | [redacted] | NR |
| Relapse/PD | 37 (46.3) | [redacted] | NR |
| Unable To Determine/Not Reported | 8 (10.0) | [redacted] | NR |
| Best Response To Regimen Post Most Recent ASCT | | | |
| CR Or PR | 37 (46.3) | [redacted] | NR |
| Stable disease | 10 (12.5) | [redacted] | NR |
| Relapse/PD | 25 (31.3) | [redacted] | NR |
| Unable To Determine/Not Reported | 8 (10.0) | [redacted] | NR |
| Prior Radiotherapy | 59 (73.8) | [redacted] | [redacted] |
| Prior BTX Therapy | 80 (100.0) | [redacted] | [redacted] |
| Extranodal involvement | NR | NR | [redacted] |
| Histologic findings | | | |
| Nodular sclerosis | NR | NR | [redacted] |
| Mixed cellularity | NR | NR | [redacted] |

ASCT: autologous stem cell transplant; BTX: brentuximab vedotin; ECOG: Eastern Cooperative Oncology Group CI: confidence interval; CR: complete remission; IRRC: independent radiological review committee; NA: not available; ORR: objective response rate; OS: overall survival; PD: progressed disease; PFS: progression-free survival; PR: partial remission.
Table based on CS Table 12, p.54 and Table 15, p. 61.

We agree that the three populations presented from the two studies (cohort B and C from CheckMate 205, and the subgroup from CA209-039) meet the inclusion criteria of the review. There are some differences between the studies (and between the two cohorts of CheckMate 205) in patient's baseline characteristics as noted above. However, the ERG is not aware that any of these would have a major impact on the response of the participants to treatment with nivolumab.

Both of the studies were sponsored by the company and copies of all the cited references were received electronically.

### 3.1.4 Description and critique of the approach to validity assessment

The CS provides two quality assessments for the included non-RCTs, one based on the RCT criteria in the NICE report template[10] and another based on criteria for non-RCTs. The assessments appear to have been based on published data (Younes and colleagues[4] and Ansell and colleagues[5]), which in the case of the CheckMate 205 study only encompasses cohort B, as no cohort C data have been fully published. The ERG assessed both of the studies using the Downs and Black instrument[11] as utilised in the CS, which is one of two methods recommended by Cochrane for the assessment of methodological quality or risk of bias in non-RCTs,[12] based on a systematic review by Deeks and colleagues[13] published in 2003.[12]

The ERG generally agrees with the CS assessment of the studies (Table 6). As the studies are as yet not fully published, there are some minor points of note. Both the studies are ongoing and therefore outcome data will change; the data in the assessed Younes publication (CheckMate 205) was for cohort B only with a cut-off date of August 2015, whereas the CS also provided data for cohort B and C with a later data cut-off (April 2016); and the adverse events data available in the Ansell publication (CA209-039) is for the whole cohort (n=23) and not the subgroup of interest (n=15), although the number of participants in the study is small. The interim clinical study report (CSR)[6] for CA209-039 does report adverse event data for the smaller subgroup, but with a much earlier data cut-off ([redacted]) than the data in the CS. The ERG judged that the external validity of the studies was difficult to determine because details were not reported about the source populations that study participants were recruited from, and it is not known whether there were differences between those who agreed to participate in the studies and those who did not. Most of the criteria for internal validity and confounding are not applicable to one-armed studies (see Table 6).The ERG agrees with the CS in that results of the quality assessment suggest that the two non-comparative, single-arm studies appear to be of reasonable quality (but by design they have serious limitations), although data is largely not peer-reviewed.

**Table 6 Company and ERG assessment of trial quality**

| Description of criteria | | Younes (2016) [4] (CheckMate 205, Cohort B) | Ansell (2015) [5] (CA209-039) |
|---|---|---|---|
| Is the hypothesis/aim/objective of the study clearly described? | CS | Yes | Yes |
| | ERG | Yes | Yes |
| Are the main outcomes to be measured clearly described in the Introduction or Methods section? | CS | Yes | Yes |
| | ERG | Yes | Yes |
| Are the characteristics of the patients included in the study clearly described? | CS | Yes | Yes |
| | ERG | Yes | Yes |
| Are the interventions of interest clearly described? | CS | Yes | Yes |
| | ERG | Yes | Yes |
| Are the distributions of principal confounders in each group of subjects to be compared clearly described? | CS | Not applicable | Not applicable |
| | ERG | Not applicable | Not applicable |
| Are the main findings of the study clearly described? | CS | Yes | Yes |
| | ERG | Yes | Yes |
| ERG comment: While both studies are clearly described both studies are ongoing. Published data are based on the pre-specified minimum follow-up period of 6 months for CheckMate 205 cohort B and for a median follow-up of 40 weeks for CA209-039. | | | |
| Does the study provide estimates of the random variability in the data for the main outcomes? | CS | Yes | Yes |
| | ERG | Yes | Yes |
| ERG comment: Complete 95% CIs are not always available due to the immaturity of the data. | | | |
| Have all important adverse events that may be a consequence of the intervention been reported? | CS | Yes | Yes |
| | ERG | Yes | Yes |
| ERG comment: Ansell – data available only for the whole population (n=23) not the n=15 post-ASCT post-brentuximab vedotin patients. Data for the subgroup are not reported in the CS but are available in the interim CSR (cut-off date August 2015).[6] | | | |
| | CS | Yes | Yes |

| Description of criteria | | Younes (2016) [4] (CheckMate 205, Cohort B) | Ansell (2015) [5] (CA209-039) |
|---|---|---|---|
| Have the characteristics of patients lost to follow-up been described? | ERG | Yes | Yes |
| Have actual probability values been reported (e.g.0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001? | CS | Not applicable | Not applicable |
| | ERG | Not applicable | Not applicable |
| **External validity** | | | |
| Were the subjects asked to participate in the study representative of the entire population from which they were recruited? | CS | Yes | Yes |
| | ERG | Unable to determine | Unable to determine |
| ERG comment: Details of the size and demographics of the source population are not stated, so unable to determine whether participants are representative of the entire population from which they were recruited. | | | |
| Were those subjects who were prepared to participate representative of the entire population from which they were recruited? | CS | Yes | Yes |
| | ERG | Unable to determine | Unable to determine |
| ERG comment: The proportion of the eligible population who agreed to participate was not stated. It is not known whether there were differences between those who agreed to participate and those who did not. | | | |
| Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive? | CS | Yes | Yes |
| | ERG | Yes | Yes |
| **Internal validity – bias** | | | |
| Was an attempt made to blind study subjects to the intervention they have received? | CS | No | No |
| | ERG | No | No |
| Was an attempt made to blind those measuring the main outcomes of the intervention? | CS | No | No |
| | ERG | No | No |

| Description of criteria | | Younes (2016) [4] (CheckMate 205, Cohort B) | Ansell (2015) [5] (CA209-039) |
|---|---|---|---|
| If any of the results of the study were based on “data dredging”, was this made clear? | CS | Not applicable | Not applicable |
| | ERG | Not applicable | Not applicable |
| In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls? | CS | Not applicable | Not applicable |
| | ERG | Not applicable | Not applicable |
| Were the statistical tests used to assess the main outcomes appropriate? | CS | Not applicable | Not applicable |
| | ERG | Not applicable | Not applicable |
| Was compliance with the intervention/s reliable? | CS | Yes | Yes |
| | ERG | Yes | Yes |
| Were the main outcome measures used accurate (valid and reliable)? | CS | Yes | Yes |
| | ERG | Yes | Yes |
| **Internal validity - confounding (selection bias)** | | | |
| Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population? | CS | Not applicable | Not applicable |
| | ERG | Not applicable | Not applicable |
| Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time? | CS | Not applicable | Not applicable |
| | ERG | Not applicable | Not applicable |
| Were study subjects randomised to intervention groups? | CS | No | No |
| | ERG | No | No |
| Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable? | CS | Not applicable | Not applicable |
| | ERG | Not applicable | Not applicable |
| | CS | Not applicable | Not applicable |

| Description of criteria | | Younes (2016) [4] (CheckMate 205, Cohort B) | Ansell (2015) [5] (CA209-039) |
|---|---|---|---|
| Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? | ERG | Not applicable | Not applicable |
| Were losses of patients to follow-up taken into account? | CS | Not applicable | Yes[a] |
| | ERG | Not applicable | Not applicable |
| Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%? | CS | Not applicable | Not applicable |
| | ERG | Not applicable | Not applicable |
| ERG comment: The Younes publication (Cohort B) states the planned sample size of 60 patients provided roughly 93% power to reject the null hypothesis. | | | |

[a] In the assessment of methodological quality of studies presented in CS appendix 2, the judgement differs and is 'not applicable'.
Table based on CS Table 6 p. 38.

### 3.1.5 Description and critique of company's outcome selection

The outcomes in the CS match those listed in the final NICE scope (CS Table 1, p. 13). The CS lists rate of partial response and stable disease as outcome measures of interest in association with response rates, although objective response rate and complete response rate cover the specified outcome of response rates in the final NICE scope. Other outcomes reported in the CS but not specified in the NICE final scope were:

CheckMate 205:

- Duration of complete response (CR)
- Six-month progression-free survival (PFS) rate
- Six-month overall survival (OS) rate
- Tumour burden change in patients receiving nivolumab beyond progression
- Graft-versus-host disease after post-study transplant

For CA209-039:

- Time to objective response (TTR)
- Time to CR
- Time to PR

Outcome assessments were carried out by investigators, an independent regulatory review committee (IRRC) or both. The primary efficacy endpoint of CheckMate 205 was IRRC-assessed ORR, whereas the primary endpoint of CA209-039 was investigator assessed ORR.

**Outcome Definitions**

ORR

- IRRC-assessed ORR for CheckMate 205 (primary endpoint) and CA209-039 (secondary endpoint) was defined as the proportion of patients with a best overall response (BOR) of CR or PR, when response was assessed according to the 2007 International Working Group (IWG) criteria.[16]
- Investigator-assessed ORR was a secondary endpoint in CheckMate 205 but ORR was defined in the same way as IRRC-assessed ORR. For CA209-039 investigator assessed ORR was the primary endpoint and also defined as the proportion of the total number of patients whose BOR was either CR or PR however in this case the International Workshop to Standardized Response Criteria for Lymphomas[17] were used for evaluation of response.
- BOR definitions differed
  - CheckMate 205 defined BOR as the best response designation recorded between the date of first dose and the date of initial objectively documented progression per the 2007 IWG criteria or the date of subsequent therapy, whichever occurred first. For patients without documented progression or subsequent anticancer therapy, all available response designations contributed to the BOR determination. For patients who continued treatment beyond progression, the BOR was determined based on response designations recorded up to the time of initial progression (CS p.42).
  - CA209-039 defined BOR as the best response between the date of the first dose and the last efficacy assessment before subsequent therapy (CS p. 59).

Duration of response

- CheckMate 205: the time from first response (CR or PR) to the date of the first documented tumour progression (IRRC assessment)
- CA209-039: time between the date of the first response and the date of first progression or the date of death.

PFS

- CheckMate 205: the time from the first dosing date to the date of the first documented tumour/disease progression or death due to any cause, whichever occurred first (IRRC-assessment)
- CA209-039 the time from the date of the first dose of study medication to the date of first disease progression or the date of death.

OS

- CheckMate 205: the time from first dosing date to the date of death.

TTR

- CheckMate 205: not defined
- CA209-039: The time from the date of the first dose to the date of the first response.

Duration of a response

- CA209-039: The time between the date of the first response and the date of first progression or the date of death.

Health-related quality of life (HRQoL) was only measured in CheckMate 205 and only reported for Cohort B (August 2015 data cut-off). Two measures were used, the EORTC-QLQ-C30 questionnaire version 3 to assess cancer-related quality of life (QoL) and the generic health status measure EQ-5D. Both are validated measures. The CS provides a full description of the EORTC-QLQ-C30 items/scales and data interpretation, as well as details for the EQ-5D. Some of the information is marked AIC, although most of the details are freely available.

The EORTC-QLQ-C30 has:

- 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning) - higher scores = better HRQoL

- a global health status/quality of life scale: higher scores = better HRQoL
- 3 symptom scales (fatigue, nausea, and pain) - lower scores = better status
- 6 individual items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties)

Positive change scores indicate improvement in HRQoL compared to baseline. By contrast, lower scores for symptom scales indicate better status; negative change scores indicate improvement in symptoms compared to baseline. The scale scores range from 0 to 100 and a score difference of 10 is used as an estimate of the minimal important difference (MID) for all subscales of the EORTC-QLQ C30 including the symptom scales (analysis was performed on patients who had an assessment at baseline and ≥1 post baseline assessment).

EQ-5D

The EQ-5D visual analogue scale elicits patients' ratings of their health status on a 0 to 100 scale with 0 being the worst imaginable health state and 100 being the best imaginable health state. Utility valuation for application within the economic section is described in Appendix 7 (CS p. 51).

Adverse events

The format of presenting AEs for the two studies in the CS differs, and makes comparisons difficult. For CheckMate 205, a summary of drug-related AEs impacting on ≥10% of the population is presented. However, AEs are only reported for cohort B (n=80, data cut-off August 2015) or the total population (n=240) which includes the cohort A patients who were brentuximab vedotin naive and therefore not relevant to the decision problem. Data are reported for AEs and laboratory parameters, categorised as any grade or grade three to four AEs. Grade five AEs are discussed in text format. For CA209-039, a more detailed account of AEs is provided. A summary of drug-related AEs at the 40-week and the 23.3-month follow-up is provided, albeit for all the twenty-three participants of the study and not the subgroup of 15 post-ASCT post-brentuximab vedotin patients of interest to this submission. AE terms were coded and grouped according to system organ class using Medical Dictionary for Regulatory Activities (MedDRA) version 18.0, and toxicity grade using the Common Terminology Criteria for Adverse Events (CTCAE version 4.0). Identification of AEs of special clinical interested was conducted to characterise any AEs that are potentially associated with the use of nivolumab. The criteria for identifying these adverse events were:

[redacted]

The adverse events that were identified as being of special interest [redacted]. These were reported under the following group headings [redacted] For CA209-039 these outcomes were tabulated separately in the CS for all patients within 100 days of the last dose of nivolumab at 23.3-months follow-up.

Not all of the outcomes reported in the clinical effectiveness section contributed data to the economic model. Response rates were mostly restricted to use in scenario analyses.

### 3.1.6 Description and critique of the company's approach to trial statistics

The CS reports the results for all the measured outcomes listed in CS Section 4.7.1.4 (CheckMate, 205, p. 42) and CS Section 4.7.1.4 (CA209-039, p. 57-58). All the data presented are based on interim data and cut-off dates (and relevant population/s in case of CheckMate 205) are clearly stated. The CS notes that further data cuts from these studies are going to be presented as they become available.

The CS reports the statistical methods used to analyse data and the power calculations (CS p. 43-58) that were used to determine sample size. For CheckMate 205, the sample size for cohort B (n=60) was determined in order to produce a confidence interval (CI) which would exclude an ORR of 20% (because an ORR of 20% is not considered clinically relevant) and to provide sufficient safety information (CS p.43). As 80 patients were recruited to cohort B this was adequately powered. The sample size for cohort C however, was empirically determined with the aim of capturing less common safety events. For CA209-039, approximately 23 patients were expected to be enrolled and the possible lower limits for the 90% one-sided CI for ORR, false negative rates and false positive rates were calculated. As the nivolumab studies were single-arm studies there were no within-study comparisons to make with comparator data.

Results are reported narratively and consecutively for the two included studies and summarised using descriptive statistics (e.g. percentages, medians, ranges). Indirect comparisons were conducted to compare the efficacy of nivolumab with comparator data (further details of this reported in Section 3.1.7 below).

With regards to HRQoL, we note that the CS presents limited data for EORTC-QLQ-C30, restricted to weeks with clinically meaningful improvements from baseline for role functioning, social functioning and insomnia. The CS states that [redacted]

There are also limited results reported for the EQ-5D in the clinical effectiveness section, but the CS states that utility valuation for application within the economic model is described in CS Appendix 7.

### 3.1.7 Description and critique of the company's approach to the evidence synthesis

As stated earlier no randomised trials of nivolumab were identified by the systematic review (CS p. 36), only single-arm studies are available so consequently pairwise meta-analysis is not possible.



A narrative review of the evidence from the key nivolumab studies, CheckMate 205 (cohorts B and C) and study CA209-039 is presented in the CS Section 4 (p. 33 – 69). Where possible the ERG has checked key data presented in the CS against those in the publications[4,5] and found only one minor discrepancy



To enable comparison of nivolumab against the comparators defined in the NICE scope and decision problem, for which there is no direct evidence, the company conducted an unadjusted indirect comparison and a matching-adjusted indirect comparison (MAIC) (CS p. 70 – 76 and CS Appendix 3).

Evidence on nivolumab was obtained from patient-level data for:

- Cohort B of the CheckMate 205 study (n = 80); median follow-up (OS): 15.7 months.
- Cohort C of the CheckMate 205 study (n = 98; two patients who had not received brentuximab vedotin excluded); median follow-up (OS): 9.0 months.
- Post-ASCT/brentuximab vedotin patients from CA209-039 (n = 15); median follow-up (OS):

23.5 months.

The patient-level data from the patients in each of these groups was combined to create a nivolumab pooled cohort (n=193) (CS Appendix 3 p. 20). The median follow-up period for the nivolumab pooled cohort was not reported.

A systematic review was undertaken to identify studies that could provide comparative effectiveness data on adult patients with relapsed or refractory classical Hodgkin lymphoma, following prior ASCT and brentuximab vedotin, who had subsequently received any intervention aimed at managing classical Hodgkin lymphoma. The identified studies had to report on any outcome of interest including OS, PFS, CR rate, PR rate, ORR or rate of SD (CS p.71).

A total of [redacted] studies (represented by [redacted] citations) met the inclusion criteria for the systematic review, these [redacted] studies included the [redacted] accounting for [redacted] citations). Therefore there were [redacted] studies that met the inclusion criteria and provided information on potential comparator interventions. [redacted] of the [redacted] studies of potential comparators in the post-ASCT post-brentuximab vedotin population were reported only as conference abstracts (the majority from 2014 to 2016 but one dates back to 2012) which present limited data. [redacted] study was [redacted], the remainder were [redacted]. The [redacted] studies published as full papers are:

[redacted]

[redacted]

An overview of the [redacted] comparator studies is provided in Table 7.

**Table 7 Overview of the potential comparator studies identified by systematic review**

| First Author (year) | PT | Study design (name) | Cohort size (N) | Patients | Median age (range) | % Male | ECOG, % | | | Intervention |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | 0 | 1 | ≥2 | |
| | | | | | | | | | | |
| | | | | | | | | | | |
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| | | | | | | | | | | |
| | | | | | | | | | | |

[redacted]

[redacted]

The ERG notes that the company did not provide an overview of the similarities and differences between the participants in the comparator studies and those in the nivolumab studies. As can be seen from Table 7 the median age of participants in the comparator studies (where reported) ranges from [redacted] to [redacted] years, which likely represents a [redacted] population than the nivolumab pooled cohort which had a median age of [redacted] years. The proportion of males in the comparator studies ranges from [redacted] to [redacted] (where reported) resulting in an overall proportion of [redacted] male (comparator studies combined) in comparison to [redacted] in the pooled nivolumab cohort which is [redacted]. Data on ECOG performance status was [redacted] of the comparator studies. In the remainder, [redacted] had an ECOG performance status [redacted] which is [redacted] pooled nivolumab cohort, where [redacted] had an ECOG status of [redacted] and [redacted] of [redacted].

All the participants in the nivolumab studies had received a prior ASCT and prior brentuximab. [redacted] the systematic review inclusion criteria to identify comparator studies specified that patients must previously have received ASCT and brentuximab [redacted]

[redacted] of the studies reporting on potential comparators reported survival outcomes for the subgroup of patients who had received prior ASCT and brentuximab. One study, by Cheah and colleagues,[2] was identified in the CS as providing evidence on the outcomes of interest in a population where the majority had received prior ASCT and had failed brentuximab vedotin and was used as the primary source of comparator evidence. Due to the importance of the Cheah and colleagues[2] study within the CS the ERG have summarised its key aspects below.

Cheah and colleagues[2] conducted a retrospective review of their institutional database (at the MD Anderson Cancer Center, Texas) to identify patients who had been treated with brentuximab vedotin

between June 2007 and January 2015. To be included in the study patients had to meet the following criteria:

- A histologically confirmed diagnosis of classical Hodgkin lymphoma
- Treatment with brentuximab vedotin for relapsed Hodgkin lymphoma
- Disease progression at any time after treatment with brentuximab vedotin

The aim of the study was to determine PFS and OS following disease relapse after brentuximab vedotin therapy. Secondary outcomes were to analyse the efficacy of subsequent therapeutic strategies and to explore candidate prognostic factors for PFS and OS.

There is a discrepancy between the abstract and main text of the paper which report either 100 or 97 patients respectively meeting the inclusion criteria for the study. The abstract states that 71/100 patients had prior ASCT [whereas the main text of the paper reports 66/97 (68%) ASCT and 4 (4%) allo-SCT conducted at the time of second remission]. Data were available on subsequent therapy for 83 patients with disease progression following brentuximab vedotin therapy and these data are reproduced below in Table 8. The proportion of patients who had prior ASCT among the 83 patients with disease progression is not reported.

**Table 8 Therapies received by patients in the Cheah and colleagues study[2] who had disease progression following brentuximab vedotin therapy (based on CS Table 37, p. 103)**

| Treatment | n | Evaluated | CR (%) | PR (%) | ORR (%) | mPFS (months) | mOS (months) |
|---|---|---|---|---|---|---|---|
| Investigational agent | 28 | 28 | 4 (14) | 3 (11) | 7 (25) | 2.4 | 47.7 |
| Gemcitabine | 15 | 12 | 4 (27) | 4 (27) | 8 (53) | 2.1 | NR[b] |
| Bendamustine | 12 | 11 | 2 (17) | 4 (33) | 6 (50) | 3.7 | 34.0 |
| Other alkylator | 6 | 4 | 1 (17) | 1 (17) | 2 (33) | 5.0 | 9.5 |
| BTX retreatment | 6 | 4 | 0 (0) | 2 (33) | 2 (33) | 3.5 | 10.4 |
| Platinum based | 4 | 4 | 0 (0) | 1 (25) | 1 (25) | 0.9 | 25.2 |
| ASCT | 3 | 3 | 1 (33) | 0 (0) | 1 (33) | [a] | 11.9 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Other | 5 | 1 | 0 (0) | 0 (0) | 0 (0) | [a] | 24.9 |
| **Overall** | **79** | **67 (85%)** | **12 (15)** | **15 (16)** | **27 (34)** | **3.5** | **25.2** |
| No treatment received | 4 due to poor performance status and/or patient decision | | | | | | |
| **TOTAL** | **83** | | | | | | |

ASCT, autologous stem cell transplant; BTX, brentuximab vedotin; CR, complete response; mOS, median overall survival; mPFS, median progression-free survival; ORR, objective response rate; PR, partial response.

The CS used the data on outcomes from subsequent therapy (Table 8) in two ways in their analyses: using the overall Cheah population (i.e. including efficacy from all the treatments listed above) or using the Cheah population but excluding efficacy data for the n=28 patients who received investigational agents. Because the Cheah study reported an OS Kaplan-Meier curve only for the overall Cheah population, the company had to derive an OS Kaplan-Meier curve for Cheah excluding investigational agents (this is further described in section 4.3.5). It is worth noting that the Cheah study authors did not describe the interventions that constituted their 'Investigational Agent' grouping, however they do indicate that the study period included brief overlap with the availability of PD-1 inhibitors on investigational protocols at their centre. The CS speculates that the 'Investigational Agent' group was therefore likely to have included nivolumab (CS p. 102 and 110). The ERG contacted the authors of the Cheah study and was informed that only a couple of patients in the study received PD-1 inhibitors (although numerical data to support this statement were not provided). The Cheah study authors note that patient selection bias for patients willing and able to travel long distances to an academic centre may limit the generalisability of their findings and that outcomes among other patient groups (e.g. those in community settings), may be less favourable.

As already indicated above, all the participants in the nivolumab studies had received an ASCT in comparison to 68% of participants in the Cheah and colleagues study. In CheckMate 205 cohort C, 33 patients received brentuximab vedotin before ASCT and 8 patients received brentuximab vedotin both before and after ASCT, whereas in the Cheah and colleagues study brentuximab vedotin was only received after relapse of classical Hodgkin lymphoma (Patients' treated with brentuximab vedotin as part of frontline classical Hodgkin lymphoma therapy were excluded).

Indirect comparison was conducted for the outcomes of OS, PFS, CR rate, PR rate and ORR [redacted] The rationale for the selection of outcomes for which indirect comparison was

conducted is not described in the CS or Appendix 3. The comparability of outcome measures across studies was also not reported on and the ERG notes that there were differences in how PFS was defined between the nivolumab studies and Cheah and colleagues.[2] In the two nivolumab studies, PFS was defined as the time from the first dosing date to the date of the first documented tumour progression or death. In contrast, the PFS definition in Cheah and colleagues[2] was the time in months measured from date of confirmed disease relapse following brentuximab vedotin to disease progression or death. NICE and the ERG therefore asked for clarification from the company regarding the time between earlier treatment failure and the first does of nivolumab (clarification questions A2). The company response indicates that the median times from brentuximab vedotin failure to nivolumab treatment in CheckMate 205 cohorts B and C were [redacted] and [redacted] respectively. If the company's definition of PFS had been the same as that reported in Cheah and colleagues (i.e. from date of disease relapse instead of from dates of first nivolumab dosing) then [redacted]. A NICE DSU Technical support document on methods for population-adjusted indirect comparisons was published during the course of this evidence review[30] but it was not available to the company as their submission was prepared.

[redacted]

The data extracted from the [redacted] studies providing comparative effectiveness data for use in indirect comparisons, were used in four scenarios (CS p. 72; Appendix 3 p.21).

1a) [redacted]

[redacted]

**The unadjusted indirect comparison (Appendix 3 p. 21)**

An unadjusted indirect comparison compares the outcomes from the individual arms of two different studies as if they had been arms in the same RCT. It is generally considered an inappropriate method when an adjusted indirect comparison is possible because a common control group is available. However, in this case the nivolumab studies are single-arm trials and no common comparator is available. The NICE DSU Technical Support Document[30] highlights that an unadjusted indirect comparison will include sampling error plus systematic error due to the imbalance in both prognostic factors and effect modifiers. Outcomes from unadjusted indirect comparisons were used in the base case of the economic model.

For response rates the unadjusted indirect comparison for scenarios 1a and 1b, where evidence came from [redacted] For scenarios 2a and 2b where [redacted] The NICE DSU Technical Support Document[30] indicates that indirect comparisons should be made on a log transformed scale but it is not clear from the CS whether a log scale was used for the indirect comparison of response outcomes where the comparison is reported as an adjusted relative risk.

[redacted]

[redacted]

**The MAIC**

MAICs use individual patient data (IPD) from a study of one treatment (in this case pooled data from the single-arm nivolumab studies) to match aggregate (summary) baseline statistics reported from trials of another treatment (in this case from the potential comparator studies). MAIC is a form of propensity score weighting in which individuals in the IPD population are weighted to balance the covariate distribution with that of the aggregate population, so that treatment outcomes can then be compared across balanced study populations. In the CS there are only single-arm studies for both the intervention and comparator, and in this case the indirect comparison is said to be "unanchored" (in contrast, if there is a common comparator arm in each trial in a network the indirect comparison is said to be "anchored"). In theory an unanchored MAIC (i.e. an MAIC where only single-arm study data are available) could improve on an unadjusted indirect comparison by taking into account the different distributions of prognostic factors and effect modifiers in the two studies that are being compared. However, to have confidence that this is the case the MAIC method needs to be used appropriately. [redacted]

[redacted]MAIC outcomes were not used in the base case of the economic model but were used in scenario analyses.

[redacted]

[redacted] The NICE DSU Technical Support Document[30] indicates that MAIC, in common with other types of indirect comparisons, should be made on a log transformed scale, [redacted]

As noted above indirect comparisons, were made for four scenarios:

- [redacted]

[redacted]

[redacted]

**Summary of the company's approach to the evidence synthesis**

The ERG agrees that, in the absence of data from randomised or controlled trials of nivolumab, an indirect comparison approach is required to compare outcomes of interest following nivolumab treatment to those obtained from the comparators defined in the NICE scope and decision problem.

The ERG also agrees that there is not currently a better published data source for the comparator population than the Cheah and colleagues study.

During the course of the evidence review by the ERG a NICE DSU Technical support document on methods for population-adjusted indirect comparisons was published,[30] but this was not available to the company when the submission was prepared.

The CS has conducted both unadjusted indirect comparisons and MAICs for four scenarios. A MAIC could improve on an unadjusted indirect comparison by taking into account the different distributions of prognostic factors and effect modifiers in the two studies that are being compared.

However, the ERG does not believe that the MAICs reported in the CS are likely to be robust because:

[redacted]

### 3.2 Summary statement of company's approach

The ERG's quality assessment of the review in the CS is summarised in Table 9. Processes for inclusion or exclusion of studies and for data extraction for the systematic reviews were not described in the CS so NICE and the ERG requested clarification from the company about this (clarification A8). The company responded indicating that both screening and data extraction were conducted by one reviewer and checked by a second reviewer. Where there were discrepancies a third reviewer was involved to provide resolution. The systematic reviews would have been methodologically more rigorous if the first and second reviewer had conducted their screening and data extractions independently (instead of the second reviewer checking what the first reviewer had done) but the ERG accepts that the process that was used was adequate. Included studies were subject to critical appraisal. Overall, the ERG considers the study selection, data extraction and critical appraisal processes to have been adequate and they followed standard accepted review methodology

The ERG concludes that the submitted evidence reflects the decision problem defined in the CS, although the ERG notes that the CS decision problem omits one of the population groups listed in the NICE scope. The ERG considers the overall risk of systematic error in the systematic review to be low.

**Table 9 Quality assessment (CRD criteria) of CS review**

| CRD Quality Item: score Yes/ No/ Uncertain with comments | |
|---|---|
| 1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question? | Yes. Inclusion and exclusion criteria are clearly stated. |
| 2. Is there evidence of a substantial effort to search for all relevant research? Ie all studies identified | Yes. There was a substantial effort to search for all relevant studies. The restriction of the evidence to English Language only is unlikely to have resulted in any missed studies. |
| 3. Is the validity of included studies adequately assessed? | Yes. Quality assessment (using the Downs and Black instrument) of the two included nivolumab studies is presented in the CS. The ERG assessment agreed with the company assessment. Quality assessment for the comparator studies is presented in CS Appendix 2 (the ERG did not independently check these assessments). As eight of 12 comparator studies were reported as conference abstracts the details necessary for comprehensive quality assessment are likely to be lacking. |
| 4. Is sufficient detail of the individual studies presented? | Yes. Methodology, patient characteristics and outcomes of the included studies are presented in sufficient detail. NICE and the ERG asked the company for details of the subgroup of 15 patients in study CA209-039 (clarification question A5) who had received previous treatment with ASCT and brentuximab vedotin and who were therefore relevant to the decision problem because much of the reporting for this study was for the whole population (n=23). The company provided this information. |
| 5. Are the primary studies summarised appropriately? | Yes. The primary studies are summarised appropriately both for the studies of nivolumab and for the comparator studies with details provided in tables and figures in the main body of the CS or appendices. |

## 3.3 Summary of submitted evidence

In this section the ERG focuses on the main outcomes of the included single-arm studies CheckMate 205 and CA209-039 and the indirect comparisons made with potential comparator studies. There are two data cut-off points for each of the included nivolumab studies as shown in Table 10. The results from the first data cut off dates are published for CheckMate 205, cohort B[4] and CA209-039[5] but other results are not yet published and consequently are still AIC. The CS presents the results of the CheckMate 205 study first, and then the results of the CA209-039 study. For the CA209-039 study the results are reported for the whole population (n=23) instead of for the population that matches that described in the scope for this appraisal (n=15). Where available, the ERG report presents results for the later time points of the studies (i.e. longest follow-up periods), which are based on the interim CSRs.[3,6] Where evidence feeds into the economic model this is indicated and cross-references are provided to the economic section of the ERG report.

**Table 10 Data analysis points and duration of follow-up for the included studies**

| Parameter | CheckMate 205 | | | CA209-039 | |
|---|---|---|---|---|---|
| | Cohort B | | Cohort C | | |
| **Database lock** | Clinical: 05/10/2015<br>IRRC: 20/10/2015 | | | 16/06/2014 (CS p. 57) | 11/08/2015 (CS p. 57) |
| **Data cut-off date** | 20/08/2015 (CS p. 40) | April 2016 (CS p. 40) | April 2016 (CS p. 40) | | |
| **Median follow-up** | 8.92 months (minimum of 6 months follow-up) (CS p. 46) | 15.7 months (CS p. 40) | 8.9 months (CS p. 40) | 40 weeks (CS p. 57) | 23.3 months (CS p. 57) |

### 3.3.1 Summary of response outcomes from CheckMate 205 and CA209-039

The objective response rate assessed by the IRRC was the primary efficacy endpoint of the CheckMate 205 study whereas the primary efficacy endpoint of CA209-039 was the investigator assessed objective response rate.

The objective response rate was [redacted] at the later time points in both studies and [redacted] for the study defined primary endpoints (Table 11). There were slight differences [redacted] between the IRRC and investigator assessed objective response rates for cohorts B and C of the

CheckMate 205 study, whereas [redacted] in the CA209-039 study where investigators and IRRC used different versions of response criteria to assess response outcomes. Differences between investigator and IRRC assessments were greater in the CheckMate 205 study when considering complete and partial remission outcomes individually.

[redacted]

Median time to response in CA209-039 [redacted] For CheckMate 205 median time to response was only reported for Cohort B at the earlier follow-up period (median 8.92 months, minimum of 6 months) where the median time to objective response was just over 2 months (2.10 months by IRRC assessment and 2.17 month by investigator assessment). The time to complete remission was approximately 4.5 months (4.44 months by IRRC assessment and 4.75 months for investigator assessment). All responses were achieved within six months of treatment initiation and 58.5% of the 53 responders had achieved a response by the time of their first scan (8 weeks).



**Table 11 Response outcomes from CheckMate 205 and CA209-039**

| Parameter | CheckMate 205 | | | | CA209-039 | |
|---|---|---|---|---|---|---|
| | Cohort B (n=80) Median follow-up 15.7 months | | Cohort C, (n=100) Median follow-up 8.9 months | | Post BTX/ASCT (n=15) Median follow-up 23.3 months | |
| **Primary endpoint (in bold type)** | **IRRC** | **Investigator** | **IRRC** | **Investigator** | **IRRC** | **Investigator** |
| Objective response rate, n (%) | **54 (67.5)** | [redacted] | **73 (73.0)** | [redacted] | 9 (60) | **13 (87)** |
| (95% CI) | **(57.2, 77.8)** | [redacted] | **(64.3, 81.7)** | [redacted] | [redacted] | |
| **Additional endpoints** | | | | | | |
| Duration of response: events | [redacted] | [redacted] | [redacted] | [redacted] | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Median duration of response, months | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Median time to response, months | | | | | [redacted] | [redacted] |
| CR, n (%)[a] | 6 (7.5) | [redacted] | 17 (17.0) | [redacted] | 0 | 2 (13) |
| PR, n (%)[a] | 48 (60.0) | [redacted] | 56 (56.0) | [redacted] | 9 (60) | 11(73) |
| SD, n (%)[a] | 17 (21.3) | [redacted] | 17 (17.0) | [redacted] | 5 (33) | 2 (13) |
| Relapsed or PD, n (%)[a] | 7 (8.8) | [redacted] | [redacted] | [redacted] | | |
| UTD/NA, n (%)[a] | [redacted] | [redacted] | [redacted] | [redacted] | | |
| Duration of CR: events | [redacted] | [redacted] | [redacted] | [redacted] | | |
| Median duration of CR, months | [redacted] | [redacted] | [redacted] | [redacted] | | |
| Median time to CR, months | | | | | [redacted] | [redacted] |
| Duration of PR: events | [redacted] | [redacted] | [redacted] | [redacted] | | |
| Median duration of PR, months | [redacted] | [redacted] | [redacted] | [redacted] | | |
| Median time to PR, months | | | | | [redacted] | [redacted] |



BTX, brentuximab vedotin; CI, confidence interval; CR, complete remission; IRRC, independent radiological review committee; NA, not available; ORR, objective response rate; OS, overall survival; PD, progressed disease; PFS, progression-free survival; PR, partial remission; SD, stable disease; UTD, unable to determine.
[a] Outcomes not annotated as n (%) in CS table 13 (p. 55), but % reported in text.

Indirect comparisons for response outcomes of objective response rate, complete remission and partial remission were made with potential comparator data identified by the systematic literature review. Response outcomes from the unadjusted indirect comparison were used in the economic model base case to stratify pre-progression utility based on response (CR, PR or SD) and outcomes from both the unadjusted indirect comparison and the MAIC are used in scenario analyses, including the scenario analyses on alloSCT (see below for cross references to the cost-effectiveness section of this report). IRRS-derived response rate data are used in a sensitivity analysis (ERG Table 64).

[redacted]

[redacted]

[redacted] Results obtained from the MAIC were very similar to those obtained from the unadjusted indirect comparison.

**Table 12 Indirect comparison outcomes for objective response rate**

| Scenario | Objective response rate | | | |
|---|---|---|---|---|
| | Unadjusted indirect comparison | | MAIC | |
| | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |



MAIC, matching-adjusted indirect comparison; SLR, Systematic literature review.

[redacted]

In addition to conducting indirect comparisons for the outcome of objective response rate, the CS also presented indirect comparison evidence for complete remission and partial remission (the two categories of response that contribute to the objective response rate). The results of these indirect comparisons can be seen in Table 13 and Table 14. Data from Table 13 and Table 14 can also be

found in the cost-effectiveness section in ERG Table 32 and Table 40. These data are also used in model scenarios #27 to #36 reported in ERG Table 59.

**Table 13 Indirect comparison outcomes for complete remission**

| Scenario | Complete Remission | | | |
|---|---|---|---|---|
| | Unadjusted indirect comparison | | MAIC | |
| | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |



MAIC, matching-adjusted indirect comparison; SLR, Systematic literature review.

[redacted]

**Table 14 Indirect comparison outcomes for partial remission**

| Scenario | Partial remission | | | |
|---|---|---|---|---|
| | Unadjusted indirect comparison | | MAIC | |
| | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |



MAIC, matching-adjusted indirect comparison; SLR, Systematic literature review.

[redacted]

### 3.3.2 Summary of overall survival results from CheckMate 205 and CA209-039

The CS presents the overall survival results for both data cut-off points of each study (CheckMate 205 cohort B CS p.47-48 and p. 50; cohorts B and C CS p. 55-56; CA209-039

CS p. 62-63 and p. 65). In the CS the results for each study and each data cut-off are presented in separate tables. The ERG presents an overview of the two studies at the latest time point (longest follow-up) for each study.

In CheckMate 205 Cohort B there had been [redacted] deaths among the 80 patients enrolled over a median follow-up of 15.7 months and in Cohort C [redacted] deaths among 100 patients over a median follow-up of 8.9 months. Median survival had not been reached in either cohort at these follow-up points. The six-month overall survival for Cohorts B and C is 96.1% (95% CI 92.0 to 100) and 94.0% (95% CI 89.1 to 98.9) respectively. Median overall survival was'not available' (which the ERG takes to mean not reached) for the 15 participants in CA209-039 study who are relevant to the scope of this appraisal. At a median follow-up of 23.3 months there had been [redacted] deaths and [redacted]. The One year overall survival rate is [redacted]

**Table 15 Overall survival results for CheckMate 205 and CA209-039 at the longest reported follow-up**

| Additional endpoints | CheckMate 205 | | CA209-039 |
|---|---|---|---|
| | Cohort B (n=80) Median follow-up 15.7 months | Cohort C, (n=100) Median follow-up 8.9 months | Post BTX/ASCT (n=15) Median follow-up 23.3 months |
| Overall survival events | [redacted] | [redacted] | [redacted] |
| Median overall survival (95% CI), months | [redacted] | [redacted] | [redacted] |
| Six-month overall survival rate (95% CI), % | 96.1 (92.0, 100) | 94.0 (89.1, 98.9) | NR |
| One-year overall survival rate (95% CI), % | NR | NR | [redacted] |

ASCT, Autologous stem cell transplant; BTX, brentuximab vedotin; NA, Not available; NR, Not reported
[a] Percentage value calculated by reviewer

The CS presents Kaplan-Meier plots for overall survival for CheckMate 205 Cohort B at the earlier follow-up period of 8.92 months (minimum of 6 months follow-up, Figure 2) and for CA209-039 at 23.3 months follow-up (Figure 3).

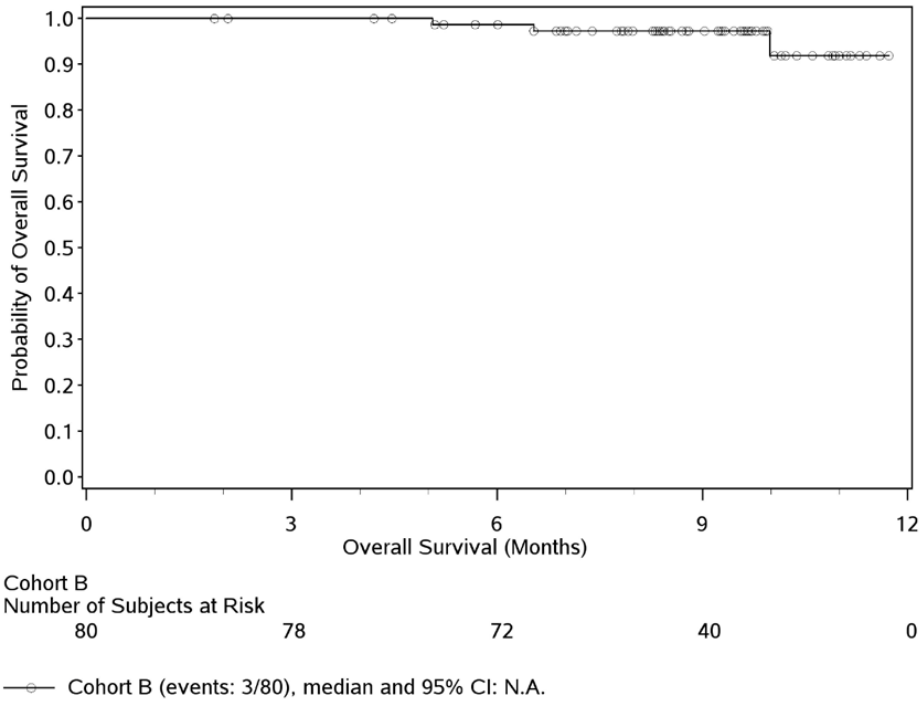


**Figure 2 Overall survival CheckMate 205 Cohort B (CS Figure 13, p. 50)**


**Figure 3 Overall survival CA209-039 subgroup of 15 patients with prior failure of ASCT and brentuximab vedotin (CS Figure 16 top panel, p. 65)**

To provide an indication of comparative effectiveness, indirect comparisons were made with potential comparator data identified by the SLR (Table 16). Overall survival is included in the economic model (ERG report section 4.3.5 page 104, Table 30 and Table 31).

[redacted]

**Table 16 Indirect comparisons for overall survival**

| Scenario | Overall Survival | | |
|---|---|---|---|
| | Unadjusted indirect comparison [redacted] | MAIC [redacted] | [redacted] |
| [redacted] | [redacted] | | |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | | | [redacted] |
| [redacted] | | | |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | | [redacted] | [redacted] |



MAIC, matching-adjusted indirect comparison; NR, Not reported; SLR, Systematic literature review.

[redacted]

### 3.3.3 Summary of Progression-free survival results from CheckMate 205 and CA209-039

The CS presents the progression-free survival results for both data cut-off points of each study (CheckMate 205 cohort B CS p.47-49; cohorts B and C CS p. 55-56; CA209-039 CS p. 62-64).

The CS reports progression-free survival for cohorts B and C of CheckMate 205 and for the 15 patients in study CA209-039 who meet the population defined in the scope for this appraisal (Table 17). Progression-free survival was assessed both by the IRRC and by the investigator and results are provided for both assessments. For each study the IRRC identified a slightly greater number of PFS events than investigators did. Clinical advice to the ERG was that this slight difference in IRRC and investigator assessments was not surprising.

Median PFS ranged from just over 11 months (CheckMate 205 cohort C, median follow-up 8.9 months) to 14.78 months (CheckMate 205 cohort B IRRC assessment, median follow-up 15.7 months. [redacted] CA209-039 study [at the 40 week follow-up period PFS at 24 weeks was 85% (95% CI 52 to 96)].

**Table 17 Progression-free survival results for CheckMate 205 and CA209-039 at the longest reported follow-up**

| Additional endpoints | CheckMate 205 | | | | CA209-039 | |
|---|---|---|---|---|---|---|
| | Cohort B (n=80) Median follow-up 15.7 months | | Cohort C (n=100) Median follow-up 8.9 months | | Post BTX/ASCT (n=15) Median follow-up 23.3 months | |
| | IRRC | Investigator | IRRC | Investigator | IRRC | Investigator |
| PFS, events | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Median PFS, months (95% CI) | 14.78 (11.33, NA) | [redacted] | 11.17 (8.51, NA) | 11.40 (11.17, NA) | 12.65 (5.91. NA) | NA (8.87, NA) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Six-month PFS rate, % (95% CI) | 79.7 (71.2, 89.4) | [redacted] | 74.4 (65.5, 84.4) | 79.2 (71.0, 88.4) | [redacted] | [redacted] |
| One-year PFS rate, % | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

ASCT, Autologous stem-cell transplant; BTX, brentuximab vedotin; IRRC, Independent radiological review committee; NA, not available; NC, Not calculated; NR, Not reported; PFS, Progression-free survival.

The CS presents Kaplan-Meier plots for progression-free survival assessed by either the investigators (reproduced from the CS as Figure 4 in this report) or the IRRC (Figure 5) for CheckMate 205 Cohort B at the earlier follow-up period of 8.92 months (minimum of 6 months follow-up) and for CA209-039 assessed by the investigators at 23.3 months follow-up (Figure 6).

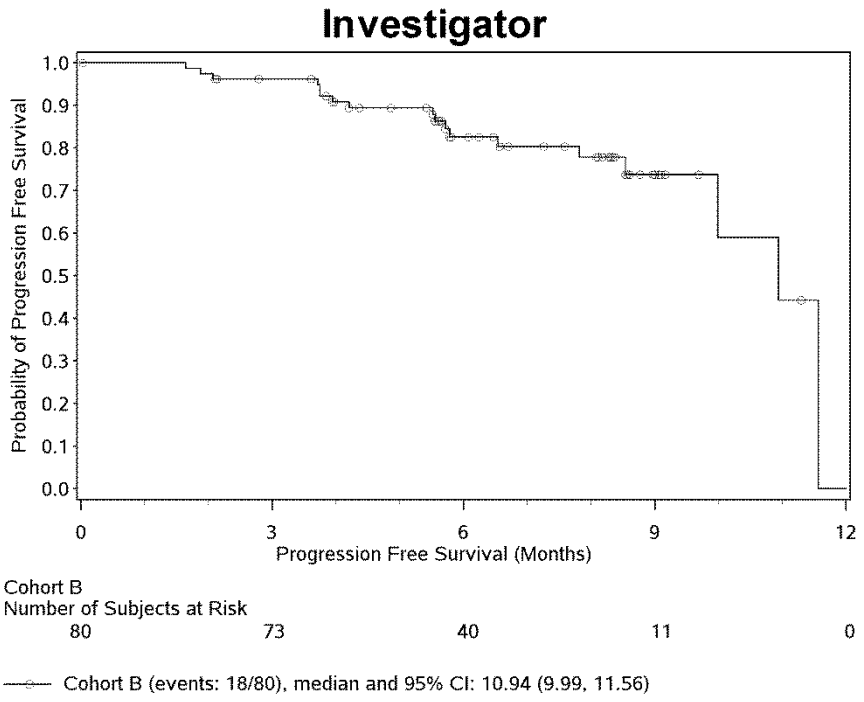


**Figure 4 Investigator-assessed progression-free survival CheckMate 205 Cohort B (CS Figure 12, p. 49)**

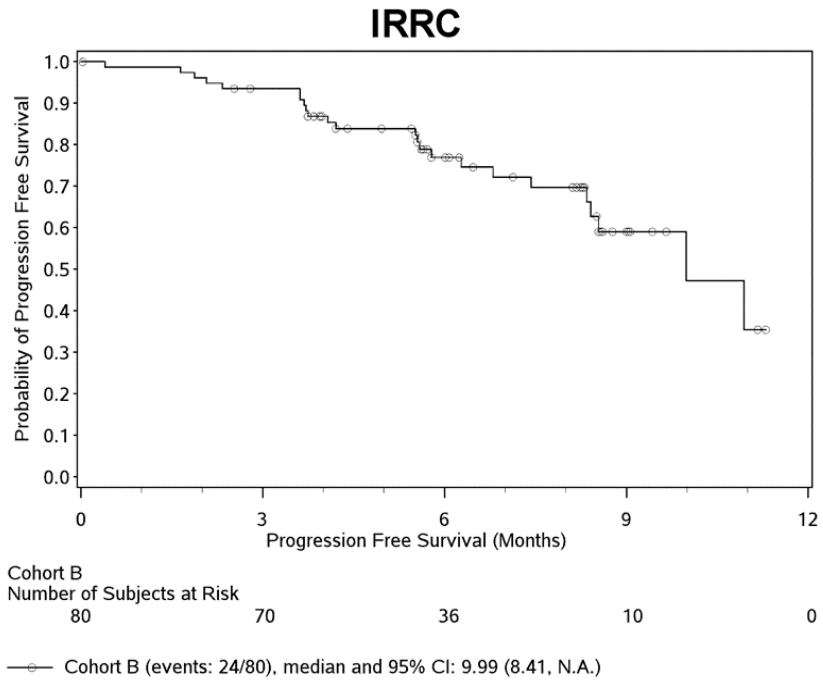


**Figure 5 IRRC-assessed progression-free survival CheckMate 205 Cohort B (CS Figure 11, p. 49)**


**Figure 6 Investigator-assessed progression-free survival CA209-039 for the subgroup of patients post-ASCT and post-brentuximab vedotin (CS Figure 15 top panel, p. 64)**

Similarly to overall survival already described (section 3.3.1) indirect comparisons for progression-free survival were made with potential comparator data identified by the systematic literature review (Table 18). Progression-free survival is included in the economic model (ERG report section 4.3.5 page 104, Table 30 and Table 31).

[redacted]

**Table 18 Indirect comparison outcomes for progression-free survival**

| Scenario | Progression-free survival (Investigator assessed) | | |
|---|---|---|---|
| | Unadjusted indirect comparison [redacted] | MAIC [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | | [redacted] | [redacted] |
| [redacted] | | [redacted] | [redacted] |
| [redacted] | | [redacted] | [redacted] |



MAIC, matching-adjusted indirect comparison; NR, Not reported; SLR, Systematic literature review.

[redacted]

### 3.3.4 Investigator-assessed tumour burden change in patients receiving nivolumab beyond progression

In both CheckMate 205 and CA209-039, patients who met the criteria for progression were eligible to continue receiving nivolumab providing they met pre-specified criteria (CS p. 42 and CS p.58). The number of patients who continued to receive treatment beyond progression were only reported for CheckMate 205 cohort B at median follow-up of 8.92 months [redacted] patients) and for CA209-039 at median follow-up of 23.3 months [redacted] patients) (Table 19). These data do not contribute to the modelling of cost-effectiveness.

**Table 19 Patients from CheckMate 205 and CA209-039 treated beyond progression**

| Parameter | CheckMate 205 Cohort B (n=80) Median follow-up 8.92 months (minimum 6 months) | | | CA209-039 Post BTX/ASCT (n=15) Median follow-up 23.3 months | |
|---|---|---|---|---|---|
| Investigator best overall response before progression | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Patients on treatment beyond progression, n | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Number of doses received after progression, range | [redacted] | | | [redacted] | |
| Duration of treatment beyond progression, months | [redacted] | | | [redacted] | |

[a] Data from CSR, [redacted]
ASCT, Autologous stem cell transplant; BTX, Brentuximab vedotin; NR, Not reported.

The investigator-assessed tumour burden change in patients who were treated beyond progression was shown in graphical format in the CS and the plots are reproduced below. In CheckMate 205 Cohort B, [redacted] patients treated beyond progression maintained tumour reduction in the target lesion in comparison to baseline (Figure 7) and in CA209-039 [redacted] treated beyond progression maintained tumour reduction with respect to baseline (Figure 8).


**Figure 7 Investigator-assessed tumour burden change in patients receiving nivolumab beyond progression in CheckMate 205 Cohort B (CS Figure 14, p. 51)**


**Figure 8 Investigator-assessed tumour burden change in patients receiving nivolumab beyond progression in CA209-039 (CS Figure 17 left panel, p. 66)**

### 3.3.5 Outcomes following alloSCT: CheckMate 205 and CA209-039

The CS summarises outcomes following alloSCT within CS section 4.13.4.1 p. 93 (Interpretation of clinical effectiveness and safety evidence). The CS states that there is 'significant potential for nivolumab to act as bridge to curative transplant in some patients' due to the high levels of responses achieved as either partial or complete remission. AlloSCT is modelled in a scenario analysis based on response data from the nivolumab trials (ERG report section 4.3.5).

Among the patient groups relevant to this appraisal (i.e. post-ASCT and post-brentuximab vedotin), the number of patients who had received post-nivolumab alloSCT as of June 2016 was [redacted] from CheckMate 205 Cohort B and [redacted] from Cohort C, and [redacted] for the post-ASCT post-brentuximab vedotin subgroup of CA209-039 (clarification response to question B4 from the company indicates that [redacted] patients in this subgroup had received alloSCT). Thus at least [redacted] patients of relevance to this appraisal have received post-nivolumab alloSCT. The CS states that there have been no deaths due to disease progression. Disease status after alloSCT is not available in the CS

from study CA209-039 and was not reported separately for Cohorts B and C (CS p. 93). The CS states that the preliminary evidence available from all patients who have received post-nivolumab alloSCT suggests that [redacted]. Similarly transplant-related mortality is not reported for the separate cohorts but overall (including those in Cohort A, who are not of relevance to this appraisal); among 40 patients undergoing alloSCT there were six deaths due to transplant-related mortality.

### 3.3.6 Summary of health related quality of life

The CS presents limited data for HRQoL (CS p. 52) from CheckMate 205 Cohort B (minimum follow-up six months; median follow-up 8.92 months), and most of the data are AIC. Although HRQoL data from CheckMate 205 are used in the economic model the model uses the UK EQ-5D 3l with the UK tariff and not the EQ-5D VAS which is reported here.

The analysis of EORTC-QLQ-C30 was performed on cohort B patients, who had an assessment at baseline (93.8%) and at least one post-baseline assessment (completion rates remained >80% for each visit for patients that were still participating in the study recorded from baseline to the week 33 visit). The CS states that [redacted] The CS states that EORTC-QLQ-C30 scores [redacted] but with mean changes described as 'trending towards [redacted] across functional and symptom scales'. The CS reports a minimal important difference (a score difference of 10) in role function at week 9 (mean change=10.7, SD 29.0) and in social function (mean change = 10.6, SD 23.5) and insomnia (mean change = -12.2, SD 25.6) at week 33.

The average EQ-5D VAS score for CheckMate 205 Cohort B [redacted] over time and the CS states that it [redacted] the average baseline score [redacted] minimal important difference [redacted].

It should be noted that results for both HRQoL measures are difficult to interpret without a data from a comparator arm.

### 3.3.7 Sub-group analyses results: CheckMate 205 Cohort B

A variety of subgroup analyses were conducted in CheckMate 205 Cohort B in CS Section 4.8 (CS p. 67 - 69) and summarised in Table 20 below. The follow-up period for these analyses is not reported. These results do not feed into the economic model.

**Table 20 Summary of sub-group analyses conducted on CheckMate 205 Cohort B data**

| Subgroup analyses | Outcome | Finding |
|---|---|---|
| Post-hoc analyses of 10 variables | IRRC-assessed objective response rate | Objective response rate remained constant across subgroups. |
| Post-hoc analysis of efficacy by prior response to brentuximab vedotin therapy | IRRC-assessed best overall response to nivolumab | Objective responses following nivolumab are durable regardless of the response to most recent prior brentuximab vedotin. |
| Efficacy by baseline PD-L1 expression status | IRRC-assessed best overall response to nivolumab | Objective responses for three subgroups are reported: PD-L1 expression at baseline ≥1% (n=57 patients); PD-L1 expression <1% at baseline (n=6 patients); PD-L1 was not quantifiable (n=17). |
| Efficacy by 9p24.1 alteration | IRRC-assessed objective response rate | Objective response rate was similar across three categories of chromosome 9p24.1 alteration (amplicfication; copy gain; polysomy). |

### 3.3.8 Summary of adverse events

The CS presents data on AEs in CS section 4.12 (p. 81). In this section of the CS data are presented for cohort B (n=80) and the total CheckMate 205 study population (n=240 in cohorts A, B and C). The 63 patients in cohort A had not received brentuximab vedotin prior to nivolumab therapy and so are not relevant to the decision problem. Data from Cohort C are not presented separately. The CheckMate 205 data comes from the 8.9 month follow-up although the company have stated that they will present updated safety data reflecting the April 2016 cut-off when it is available (CS p. 82). For study CA209-039 data are presented for the total population (n=23) from the published 40-week follow up point[5] (which is not reproduced in this ERG report) and the unpublished 23.3 month follow-up. The CA209-039 data therefore include the eight patients who

had not received both prior ASCT and prior brentuximab vedotin, and who are not relevant to the decision problem.

When considering AE data it is worth bearing in mind the extent of exposure to nivolumab that patients had in the CheckMate 205 and CA209-039 studies. The CS states that the median duration of study therapy was not reached in any cohort of the CheckMate 205 study [redacted] All patients in both studies received at least one dose of nivolumab. The extent of nivolumab exposure is summarised in Table 21, but note that this will change with increasing length of follow-up.

**Table 21 Extent of nivolumab exposure (based on CS Table 29 p. 82 and CS Table 31 p. 85)**

| Parameter | CheckMate 205 (8.9 months follow-up)[3] | | CA209-039 (23.3 months follow-up)[6] |
|---|---|---|---|
| | Cohort B (n=80) | Total population (n=240) | Total population (n=23) |
| **Number of doses received** | | | |
| Mean (standard deviation) | 16.1 (5.82) | 10.9 (6.57) | [redacted] |
| Median (Range) | 17.0 (3 to 25) | 10.0 (1, 25) | [redacted] |
| **Cumulative dose (mg/kg)** | | | |
| Mean (standard deviation) | 47.91 (17.295) | 32.26 (19.487) | [redacted] |
| Median (Range) | 50.88 (9.0 to 75.8) | 29.68 (2.9, 75.8) | [redacted] |
| **Relative dose intensity (n)** | | | |
| ≥110% | 0 | 1 (0.4%) | [redacted] |
| 90-110% | 61 (76.3%) | 198 (82.5%) | [redacted] |
| 70-90% | 16 (20.0%) | 34 (14.2%) | [redacted] |
| 50-70% | 3 (3.8%) | 7 (2.9%) | [redacted] |
| <50% | 0 | 0 | [redacted] |
| **Time between date of first dose date and last known date alive or death (months)** | | | |
| Mean (standard deviation) | 8.62 (2.02) | 5.44 (3.251) | [redacted] |
| Median (Range) | 8.92 (1.9 to 11.7) | 5.09 (0.3, 11.7) | [redacted] |

**Overall adverse events**

For CheckMate 205, the CS presents a summary of any grade and grade 3-4 drug-related AEs occurring in ≥10% of the population for cohort B (n=80) and the total population (n=240), using data from the August 2015 data cut-off (8.9 months follow-up) (CS Table 30, p. 82). Grade 5 AEs are not included in the CS table, but are reported in the text: one drug related Grade 5 AE of multi-organ failure in Cohort B, two patients in the overall study population with Grade 5 AEs of atypical pneumonia and dyspnoea. For CA209-039, a more detailed summary (CS Table 32, p. 85-87) reporting any grade, grade 3 and grade 4 - 5 AEs relating to published (40 weeks) and unpublished data (23.3-month follow-up) is presented for the total population. The ERG notes that neither table indicates what format the data are being presented in, but the ERG assumes it is number and percentage of participants affected. The ERG presents an overview of the two CS overall adverse events tables (ERG Table 22) reporting only data for the longer follow-up period of study CA209-039. In addition, for ease of comparison, only percentage data are reported for those AEs that affected ≥10% of either of the study populations. The incidence of treatment-related grade 3-4 AEs feeds through to the cost-effectiveness section (ERG report Table 36).

Drug related AEs of any grade and of grades 3 or above were reported in similar proportions in the two studies (for AEs of any grade 88% of CheckMate 205 Cohort B and 70% of the overall population versus 82.6% of CA209-039). In both studies the individual adverse events affecting 10% or more of participants were diarrhoea, nausea, fatigue, pyrexia, rash and pruritus. The majority of these events were of grade 1 or 2. One adverse event stands out as differing between the two studies and that is infusion related reaction, which affected 20% of participants in CheckMate 205 Cohort B and 12.9% of the overall population in comparison to [redacted] of participants in CA209-039 (Table 22).

Laboratory parameter abnormalities in CheckMate 205 (identified from tests during nivolumab treatment or within 30 days of the last treatment dose) were mostly Grade 1-2 in both Cohort B and the overall study population. The grade 3-4 haematological abnormalities that were reported in ≥5% of each study cohort were decreased lymphocytes (18.8% in Cohort B and 13.4% in the overall population) and neutropenia (6.3% in Cohort B and 3.3% in the overall population). The ERG notes that although there appear to be minor discrepancies between CS text in section 4.12.1.6 p. 83 and CS Table 30 p. 82 (the latter data being reproduced in ERG Table 22) this may be due to differences in the outcomes being reported (i.e. 'decreased lymphocytes' reported in the text may not be the same outcome as 'Lymphocytes' reported in the table). In study CA209-039 laboratory

abnormalities (reported during nivolumab treatment or within 100 days of the last treatment dose) were also mostly of [redacted]. At the 23.3-month follow-up, [redacted] was the most common [redacted] haematological abnormality. Grade 3-4 hepatic abnormalities reported were [redacted]

**Table 22 Summary of drug-related adverse events affecting ≥10% of CheckMate 205 participants or ≥5% of CA209-039 participants**

| Parameters | CheckMate 205 8.9 month follow-up[3] | | | | CA209-039 23.3 month follow-up[6] | | |
|---|---|---|---|---|---|---|---|
| | Cohort B (n=80) | | Overall (n=240) | | Overall n=23 | | |
| **Grade of event** | **Any** | **3-4** | **Any** | **3-4** | **Any** | **3** | **4-5** |
| Any drug-related AE, % | 88 | 25.0 | 70 | 15.4 | [redacted] | [redacted] | [redacted] |
| Gastrointestinal disorders,[a] % | NR | NR | NR | NR | [redacted] | [redacted] | [redacted] |
| Diarrhoea, % | 10.0 | 0 | 10.8 | 0.4 | [redacted] | [redacted] | [redacted] |
| Nausea, % | 12.5 | 0 | 10.8 | 0 | [redacted] | [redacted] | [redacted] |
| General disorders & administration site conditions, % | NR | NR | NR | NR | [redacted] | [redacted] | [redacted] |
| Fatigue, % | 25.0 | 0 | 16.3 | 0.4 | [redacted] | [redacted] | [redacted] |
| Pyrexia, % | 13.8 | 0 | 8.8 | 0 | [redacted] | [redacted] | [redacted] |
| Skin & subcutaneous tissue disorders, % | NR | NR | NR | NR | [redacted] | [redacted] | [redacted] |
| Rash, % | 16.3 | 1.3 | 9.6 | 0.8 | [redacted] | [redacted] | [redacted] |
| Pruritus, % | 10.0 | 0 | 8.3 | 0 | [redacted] | [redacted] | [redacted] |
| Musculoskeletal & connective tissue disorders, % | NR | NR | NR | NR | [redacted] | [redacted] | [redacted] |
| Respiratory, thoracic & mediastinal disorders, % | NR | NR | NR | NR | [redacted] | [redacted] | [redacted] |
| Injury, poisoning & procedural complications, % | NR | NR | NR | NR | [redacted] | [redacted] | [redacted] |
| Infusion related reaction, % | 20.0 | 0 | 12.9 | 0.4 | [redacted] | [redacted] | [redacted] |
| Metabolism & nutrition disorders, % | NR | NR | NR | NR | [redacted] | [redacted] | [redacted] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Endocrine disorders, % | NR | NR | NR | NR | [redacted] | [redacted] | [redacted] |
| Blood & lymphatic system disorders, % | NR | NR | NR | NR | [redacted] | [redacted] | [redacted] |
| Laboratory abnormalities | | | | | | | |
| Haemoglobin (anaemia), % | 77.5 | 1.3 | 76.3 | 2.5 | [redacted] | [redacted] | [redacted] |
| Platelets (thrombocytopaenia), % | 45.0 | 3.8 | 39.6 | 2.5 | [redacted] | [redacted] | [redacted] |
| Leukocytes, % | 40.0 | 2.5 | 34.6 | 2.9 | [redacted] | [redacted] | [redacted] |
| Lymphocytes, % | 72.5 | 18.8 | 60.4 | 13.4 | NR | NR | NR |
| Lymphocyte decreased, % | NR | NR | NR | NR | [redacted] | [redacted] | [redacted] |
| Absolute neutrophil count (neutropaenia), % | 38.8 | 6.3 | 27.1 | 3.8 | [redacted] | [redacted] | [redacted] |
| ALT, % | 31.3 | 2.5 | 28.8 | 1.7 | [redacted] | [redacted] | [redacted] |
| ALP, % | 45.0 | 6.3 | 40.0 | 4.2 | [redacted] | [redacted] | [redacted] |
| AST, % | 40.0 | 3.8 | 26.3 | 2.1 | [redacted] | [redacted] | [redacted] |
| Lipase increased, % | NR | NR | NR | NR | [redacted] | [redacted] | [redacted] |

AE, adverse event; ALT, alanine aminotransferase, ALP, alkaline phosphatase; AST, aspartate aminotransferase, NR, Not reported.

[a] Grey shaded lines indicate summary data for a group of adverse events. If any of the adverse events contributing to the group were experienced by 10% or more of either study population then these are shown in the unshaded rows below.

[b] [redacted], this summary value is reported here because infusion related reaction appears under this heading and this was reported by >10% of participants in CheckMate 205.

**Discontinuation due to adverse events**

Some drug-related AEs did cause patients to discontinue nivolumab treatment, however the proportion of patients affected was low (Table 23).

**Table 23 Discontinuation due to adverse events**

| Parameters | CheckMate 205 8.9 month follow-up | | CA209-039 23.3 month follow-up |
|---|---|---|---|
| | Cohort B (n=80) | Overall (n=240) | Overall n=23 |
| Discontinuation due to drug-related AE of any grade | 3 (3.8%)[a] | 9 (3.8%)[b] | [redacted] |

The AEs that caused discontinuation were:
[a] Grade 3-4 autoimmune hepatitis (n=1); Grade 3-4 increases in ALT and AST (n=1); Grade 5 multi-organ failure (n=1)
[b] Grade 3-4: n=5 (2.1%); Grade 5: n=2 (0.8%)
[c] [redacted]

**Deaths**

During the follow-up periods reported, only 2.9% of the overall CheckMate 205 study died in comparison to [redacted] of the CA209-039 overall study population (Table 24).

**Table 24 Deaths**

| Parameters | CheckMate 205 8.9 month follow-up | | CA209-039 23.3 month follow-up |
|---|---|---|---|
| | Cohort B (n=80) | Overall (n=240) | Overall n=23 |
| Deaths | 3 | 7 (2.9%)[a] | [redacted] |
| - due to disease progression | 1 | 4 | |
| - due to undetermined cause (patient lost to follow-up) | 1 | | |
| - Grade 5 AE of multi-organ failure | 1[c] | | |

[a] The reason for one death is not given (the 4 deaths due to disease progression presumably included one death for this reason in Cohort B, 2 other patients in Cohort B died due to other reasons leaving 1 patient in the overall study whose reason for death is not given).
[b] [redacted]
[c] The CS notes that this event was changed by the investigator to Epstein-Barr virus positive peripheral T-cell lymphoma, and was considered unrelated to the study drug.

**Drug-related serious adverse events**

In CheckMate 205 (at 8.9 months follow-up) 6.3% of Cohort B experienced a drug-related serious adverse event in comparison to 9.6% of the overall study population. The most common drug-

related serious adverse event was infusion related reaction (Cohort B 2.5%; overall 2.1%). In CA209-039 (at 23.3 month follow-up) 13.0% of the overall study population had a drug-related serious adverse event. These were a Grade 2 lymph node pain (n=1), Grade 3 pancreatitis (n=1) and Grade 3 myelodysplastic syndrome (n=1).

**Adverse events of special interest**

In CheckMate 205 Cohort B most adverse events of special interest were of grades 1 or 2, and most were considered to be drug related No grade 5 events were reported for any category of select AEs in CheckMate 205 cohort . The most frequently reported of these adverse events, irrespective of causality was skin abnormalities (41%) (Table 25). Gastrointestinal abnormalities (26%), hypersensitivity or infusion-related reaction (21%) and endocrine (18%) events were the other categories in CheckMate 205 Cohort B, where more than 10% of the participants experienced an event. In CheckMate 205, cohort B pneumonitis was reported in two patients (one grade 2 and one grade 3) and both cases were considered to be drug related (which resolved with corticosteroid treatment). It is therefore not clear why only one event was reported for the pulmonary of select AEs in this study. Full details of adverse events of special interest are reported in the CS, pages 84 and 88-89.

**Table 25 Adverse events of special interest**

| Parameters | CheckMate 205 8.9 month follow-up Cohort B (n=80) | CA209-039 23.3 month follow-up overall n=23 | | |
|---|---|---|---|---|
| | Any grade | Any grade | Grade 3-4 | Grade 5 |
| Endocrine | | | | |
| All-causality | 14 (18%) | [redacted] | [redacted] | [redacted] |
| Drug-related | | [redacted] | [redacted] | [redacted] |
| Gastrointestinal | | | | |
| All causality | 21 (26%) | [redacted] | [redacted] | [redacted] |
| Drug-related | | [redacted] | [redacted] | [redacted] |
| Hepatic | | | | |
| All-causality | 8 (10%) | [redacted] | [redacted] | [redacted] |
| Drug-related | | [redacted] | [redacted] | [redacted] |
| Pulmonary | | | | |
| All causality | 1 (1%) | [redacted] | [redacted] | [redacted] |
| Drug-related | | [redacted] | [redacted] | [redacted] |
| Renal | | | | |
| All-causality | 4 (5%) | [redacted] | [redacted] | [redacted] |
| Drug-related | | [redacted] | [redacted] | [redacted] |
| Skin | | | | |
| All-causality | 33 (41%) | [redacted] | [redacted] | [redacted] |
| Drug-related | | [redacted] | [redacted] | [redacted] |
| Hypersensitivity/infusion reaction | | | | |
| All-causality | 17 (21%) | [redacted] | [redacted] | [redacted] |
| Drug-related | | [redacted] | [redacted] | [redacted] |

## 3.4 Summary

The systematic review of clinical effectiveness evidence in the CS identified two single-arm studies for nivolumab as a treatment for people with relapsed or refractory classical Hodgkin lymphoma following ASCT and brentuximab vedotin (CheckMate 205, Cohorts B and C; CA209-039). The decision problem in the CS did not include the second of the populations specified in the NICE

scope which was people with relapsed or refractory classical Hodgkin lymphoma following at least two prior therapies when ASCT is not a treatment option. The company provided supporting evidence from a population who had received ASCT only, but the ERG has not assessed this because the population does not meet the NICE scope (or the company's own decision problem).

The two single-arm nivolumab studies were judged to be of reasonable methodological quality but clearly the single-arm study design has inherent methodological limitations, the most obvious being that there is no comparator group against which to judge the efficacy of the study drug. Follow-up of participants from both studies is continuing and patients are still being recruited to the CA209-039 study.[36] The chief clinical efficacy outcomes reported in the CS are OS, PFS and response rates which are reported for both of the nivolumab single-arm studies.

As there is no direct evidence comparing the efficacy of nivolumab against the comparator (SoC comprised of chemotherapy, brentuximab vedotin retreatment and bendamustine) the company conducted indirect comparisons. The data from the nivolumab studies were pooled to create a nivolumab pooled cohort in these comparisons. A systematic review identified [redacted] studies of potential comparator treatments but [redacted] of these studies were reported only as conference abstracts and therefore limited data were reported. In [redacted] of the studies [redacted] One study (a retrospective database review), by Cheah and colleagues,[2] was identified as providing evidence on the outcomes of interest in a population where the majority had received prior ASCT and had failed brentuximab vedotin so this study was used as the primary source of comparator evidence. One subgroup of the patients (n=28) identified in the Cheah and colleagues study had received what were described as 'investigational agents'. The interventions that constituted investigational agents were not described but the CS speculates that it was likely to have included nivolumab and on this basis, conducted an indirect comparison using the full Cheah and colleagues data set and in a second scenario omitted the subgroup of patients who had received investigational agents. The ERG have been informed that only a couple of patients in the Cheah study received PD-1 inhibitors. The [redacted] studies providing comparative effectiveness data for use in indirect comparisons, were used in four scenarios

[redacted]

[redacted]

The objective response rate as the primary efficacy endpoint of both the CheckMate 205 study (when assessed by the IRRC) and the CA209-039 study (investigator assessed objective response rate). The objective response rate was [redacted] for the study defined primary endpoints. Median time to response was [redacted] and was just over 2 months (2.10 months by IRRC assessment and 2.17 month by investigator assessment) in Cohort B at median 8.92 months follow-up. The time to complete remission in Cohort B at this same time point was approximately 4.5 months. Indirect comparisons [redacted]



[redacted] Results obtained from the MAIC were very similar to those obtained from the unadjusted indirect comparison. Indirect comparisons were also conducted for complete remission and partial remission, the two categories of response that contribute to the objective response rate outcome.



Median overall survival had not been reached in CheckMate 205 Cohort B (median follow-up 15.7 months) or in Cohort C (median follow-up 8.9 months). The six-month overall survival for Cohorts B and C was 96.1% (95% CI 92.0 to 100) and 94.0% (95% CI 89.1 to 98.9) respectively. Median overall survival had also not been reached for the 15 post-ASCT post-brentuximab vedotin patients in study CA209-039 at median follow-up of 23.3 months. The one-year OS rate is [redacted] A predicted value for median overall survival of [redacted] was calculated for the nivolumab pooled cohort which was used in indirect comparisons. The median OS from unadjusted indirect comparison [redacted] in the four scenarios (1a, 1b, 2a, 2b) with comparator data. The overall survival estimates obtained by MAIC were [redacted] than those obtained by the unadjusted indirect comparison for each scenario.

PFS was assessed both by the IRRC and by the investigators and results are provided for both assessments. In CheckMate 205 [redacted] (Cohort C, median follow-up 8.9 months) to 14.78 months (Cohort B IRRC assessment, median follow-up 15.7 months. Median PFS was not reached using data from the investigator assessments of CheckMate 205 Cohort B and was also not reached in study CA209-039. Indirect comparisons of PFS utilised the investigator assessments of PFS and therefore a predicted value for median PFS had to be calculated for the nivolumab pooled cohort. The predicted value was [redacted] and in comparison the median PFS obtained by unadjusted indirect comparison with [redacted] The overall median progression-free survival estimates obtained by MAIC were [redacted] than those obtained by the unadjusted indirect comparison for each scenario.

Response rates, OS and PFS outcomes provide data which is used to inform clinical effectiveness parameters in the economic model.

Results were also presented on tumour burden change in patients receiving nivolumab beyond progression, outcomes following alloSCT, and a very limited amount of data on HRQoL but the data presented were not used in the economic model. A variety of subgroup analyses were conducted and reported for CheckMate 205 Cohort B.

Adverse events are reproduced in the ERG report for cohort B (n=80) and the total CheckMate 205 study population (n=240 in cohorts A, B and C) after 8.9 months follow-up. The 63 patients in cohort A are not relevant to the decision problem. AEs for CA209-039 are presented for the total population (n=23, at the 23.3 month follow up point). The CA209-039 data therefore also include the eight patients who are not relevant to the decision problem. All patients in both studies received at least one dose of nivolumab but, as patients are still being followed up the extent of nivolumab exposure is increasing and not fully captured by the data presented in the CS.

Drug related AEs of any grade were reported for 70% of the overall CheckMate 205 population (88% of Cohort B) and 82.6% of CA209-039. Diarrhoea, nausea, fatigue, pyrexia, rash and pruritus were the most common adverse events in both studies. The majority of these events were of grade

1 or 2. Infusion related reaction stood out as differing between the two studies affecting 20% of participants in CheckMate 205 Cohort B and 12.9% of the overall population in comparison to [redacted] of participants in CA209-039. In CheckMate 205 there were three Grade 5 AEs (multi-organ failure and two patients with atypical pneumonia and dyspnoea) but no Grade 5 AEs were reported for CA208-039. Laboratory parameter abnormalities were also reported which were mostly Grade 1-2. The most common grade 3-4 haemotological abnormality was [redacted] The proportion of patients who discontinued nivolumab treatment due to a drug-related adverse event was [redacted]. A serious drug-related adverse event was experienced by 9.6% of the CheckMate 205 study population (6.3% of Cohort B) and 13.0% of those in study CA209-039.



Identification of AEs of special clinical interested was conducted to characterise any AEs that are potentially associated with the use of nivolumab. Skin abnormalities were the most frequently reported of these adverse events, irrespective of causality, in CheckMate 205 Cohort B [redacted]



There is uncertainty about the effectiveness of nintedanib in comparison to alternative treatment options because the two key studies of nivolumab are single-arm studies. In its interpretation of the clinical evidence, the company highlights that ORR in both studies has been good. [redacted] patients have achieved complete response in CheckMate 205 and [redacted] in CA209-039, when response was assessed by investigators. At the follow-up times reported in the CS the median progression-free survival was at least 11 months in CheckMate 205 Cohorts B and C and had not been reached in CA209-039[redacted]

To compare the efficacy of nivolumab with potential comparators an indirect comparison approach was used. The company undertook a systematic review to identify evidence on potential comparators and found 12 studies that provided data in a population, at least some of whom had received prior ASCT and prior brentuximab vedotin. The ERG believes it is likely that the company's systematic review identified all the relevant evidence, but this is limited in terms of quality (the studies were predominantly phase 1 or 2 single-arm studies), and completeness of reporting (seven only reported as conference abstracts, limited follow-up up periods, outcomes of PFS and OS often not reported). [redacted]

[redacted] Therefore the ERG believes that at present, there is considerable uncertainty regarding the extent to which the benefits of nivolumab exceed those of potential comparator treatments. This uncertainty should reduce as data for the nivolumab studies and the potential comparator studies at increased lengths of follow-up becomes available. One of the comparator studies, by Cheah and colleagues, was identified as providing evidence on the outcomes of interest in a population where the majority had received prior ASCT and had failed brentuximab vedotin and was used as the primary source of comparator evidence. This study reported data from a retrospective review of an institutional database in the USA. Following disease progression after brentuximab vedotin, patients had received a variety of treatments but there is some uncertainty about how well these reflect the treatments that patients might receive in the UK and how well the Cheah patients match those in the nivolumab studies.

The two key issues that the ERG has identified can therefore be summarised as:

- considerable uncertainty regarding the extent to which the benefits of nivolumab exceed those of potential comparator treatments. This uncertainty is due to the immaturity of the evidence base for nivolumab and comparators and the need to undertake indirect comparisons.
- Uncertainty about how well the comparator populations, particularly those in the Cheah study, match those in the nivolumab studies and UK patients.

# 4 COST EFFECTIVENESS

## 4.1 Overview of company's economic evaluation

The company's submission to NICE includes:

i) a review of published economic evaluations of the management of Hodgkin lymphoma in adult patients.

ii) a report of an economic evaluation undertaken for the NICE STA process. The cost effectiveness of nivolumab is compared with standard of care for adults with refractory Hodgkin lymphoma following ASCT and brentuximab vedotin.

## 4.2 Company's review of published economic evaluations

A systematic search of the literature was conducted by the company to identify economic evaluations of adult patients with Hodgkin lymphoma. See section 3.1.1 of this report for the ERG critique of the search strategy. The inclusion and exclusion criteria for the systematic review are listed in appendix 5 of the CS. The inclusion criteria state that economic evaluations of the management of Hodgkin lymphoma in adult patients would be included.

Twenty two studies were identified from screening 1424 titles and abstracts. Fourteen of the studies were included for full review and the remaining eight studies were excluded, mainly because the population (4) or study type (4) did not meet the inclusion criteria.

The checklist suggested by NICE[37] has been applied to the included references. The CS does not discuss the quality assessment of the studies or comment on which studies are of most relevance to this appraisal. The studies identified are shown in Table 26 (CS Table 5, appendix 5). Of the 14 studies identified, none of them are for nivolumab for patients with Hodgkin lymphoma or for interventions in patients with relapsed or refractory Hodgkin lymphoma following ASCT and treatment with brentuximab vedotin.

**Table 26 Study characteristics of economic modelling studies in CS review**

| Study | Intervention and management strategy | Patient population |
|---|---|---|
| Barosi (1999) | CVD (cyclophosphamide, carmustine and etoposide) | Patients who first underwent a ASCT between August 1994 and May 1997. |
| Cerci (2010) | Fluorine-18–fluorodeoxyglucose positron emission tomography (FDG-PET) | Patients with Hodgkin lymphoma with unconfirmed complete remission (CRu) or partial remission (PR) after first-line treatment |
| Chen (2009) | Lipid screening | Survivors of Hodgkin lymphoma |
| Engstrom (2014) | Brentuximab vedotin compared to standard chemotherapy and allogeneic stem cell transplant | Swedish patients with relapsed or refractory Hodgkin lymphoma |
| Gallamini (2011) | Interim PET response adapted therapy | Patients with ABVD-treated, advanced-stage Hodgkin lymphoma |
| Guadagnolo (2006) | Computerized Tomography (CT) scan in the Routine Follow-Up of Patients After Primary Treatment for Hodgkin lymphoma. | Patients who have had a complete response (CR) to primary treatment for Hodgkin lymphoma. |
| Hatam (2015) | IEV (ifosfamide, epirubicin and etoposide) Drug Regimen Versus ESHAP (etoposide, methylprednisolone, high-dose cytarabine, and cisplatin) Drug Regimen | Patients with Relapsed and Refractory Hodgkin and Non-Hodgkin lymphoma in Iran |
| Meza-Torres (2014) | Brentuximab Vedotin | Patients with Refractory/Relapsed Hodgkin lymphoma |
| NG (2001) | Staging and treatment options in early-stage Hodgkin lymphoma | Patients with early-stage, favourable prognosis Hodgkin lymphoma |
| Norun (1996) | Stages I and II HL treated with ChlVPP (chlorambucil, vinblastine, procarbazine and prednisone), ABOD (doxombicin (or epirubicin), bleomycin, vincristine and dacarbazine) or ABVP [doxorubicin (or epirubicin), bleomycin, vinblastine and prednisone]<br>Stages III and IV treated with ABOD, ChlVPP or alternating ABOD/ChlVPP regimens | Patients with Hodgkin lymphoma |
| Ramsey (2015) and Roth (2014) | Brentuximab Vedotin Vs. Best Supportive Care Following Autologous Stem Cell Transplant | Adult Hodgkin lymphoma patients at high risk of relapse following ASCT |
| Wattson (2013) and Wattson (2014) | Low-Dose Chest Computed Tomography for Lung Cancer Screening | Hodgkin lymphoma Survivors |

## 4.3 Critical appraisal of the company's submitted economic evaluation

### 4.3.1 NICE reference case

The NICE reference case requirements have been considered for critical appraisal of the submitted economic evaluation, in Table 27.

**Table 27 NICE reference case requirements**

| NICE reference case requirements: | Included in submission | Comment |
|---|---|---|
| Decision problem: As per the scope developed by NICE | Yes | Described in CS Table 1, p. 13 |
| Comparator: As listed in the scope developed by NICE | Yes | |
| Perspective on costs: NHS and PSS | Yes | CS Table 36, p. 101 |
| 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 | |
| Perspective on outcomes: All direct health effects, whether for patients or, when relevant, carers | Yes | |
| Type of economic evaluation: Cost utility analysis with fully incremental analysis | Yes | |
| Synthesis of evidence on outcomes: Based on a systematic review | Yes | |
| Time horizon: Long enough to reflect all important differences in costs or outcomes between the technologies being compared | Yes | 40 years. CS Table 36, p. 101 |
| Measuring and valuing health effects: Health effect should be expressed in QALYs. The EQ-5D is the preferred measure of health related quality of life. | Yes | Health effects measured in QALYs; EQ-5D used for nivolumab arm and TTO for SoC arm. |
| Source of data for measurement of health related quality of life: Reported directly by patients and/or carers. | Yes | For nivolumab arm; utility estimated from general public for SoC arm. |
| Source of preference data: Representative sample of the UK population | Yes | |
| Equity considerations: An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit. | Yes | |
| Discount rate: 3.5% p.a. for costs and health effects | Yes | CS Table 36, p. 101 |

### 4.3.2 Model structure

The company presented a Markov model consisting of three primary health states. The model has a time horizon of 40 years (lifetime), monthly cycle length, applies appropriate discounting (3.5% per annum for costs and benefits), and half-cycle correction is run as a sensitivity analysis. The company did not include half-cycle correction in the base case analysis. We found the cycle length sufficiently short to represent transitions and that the company's approach to half-cycle correction was appropriate given the marginal effect of transition timing when cycles are short.

The model is built in Microsoft Excel, however, the model is executed almost entirely in the Visual Basic (VBA) programming language. The spreadsheets cannot be used to generate any calculations or model results independently of the VBA code — macros are required to produce all types of results: base-case, deterministic sensitivity analyses, scenario analyses, and probabilistic sensitivity analyses. Inputs into the model must take very specific forms or risk crashing the VBA code that is responsible for producing results. These limitations of the model rendered the model opaque and difficult to validate. All scenario analyses required manual modification of input parameters and not all analyses could be replicated, due either to insufficient explanation of methods or due to potential parameter discrepancies. NICE and the ERG requested clarification for the modelling methods and parameters used in scenario analyses. The company provided an adequate response to the clarification request.



A model schematic is presented in the CS (see CS Figure 23 p. 98), but more complex transitions are not included in the model schematic. The base case model is similar to the standard three state cancer model seen in many STAs. Patients enter the model in the pre-progression state, receiving initial therapy (i.e. nivolumab or SoC in the base case analysis). Within the pre-progression state, there are sub-states for alternative levels of response: complete response, partial response, and stable disease (CR, PR, and SD in Figure 9). Patients in the pre-progression state may remain on treatment in the pre-progression state, discontinue treatment in the pre-progression state, progress, or die. Following discontinuation, patients may enter the state represented as subsequent therapy within the pre-progression state; in the base case analysis, this is best supportive care (BSC), but in scenario analyses this may be subsequent chemotherapy. BSC consists primarily of palliative care, including palliative chemotherapy. Once patients have progressed they receive BSC. In the progressed state patients may either remain in that state or die.

The model allows several treatment switches to occur, with additional options either having their own overall survival curves or continuing the survival curve of the baseline therapy. In the base case, overall survival is derived from baseline therapy for all future treatments. However, more complicated transitions are modelled when incorporating allogenic stem cell transplant (alloSCT) into the model and when changing whether patients may continue receiving SoC after discontinuation. The structural means to execute these analyses were not clearly described in the CS, therefore additional clarification was requested from the company on the methods and parameters used in scenario analyses. In response to clarification question B2, the company presented an updated Markov flow diagram with further explanation on how therapies subsequent to the initial line of therapy are modelled. Figure 9 shows this diagram.

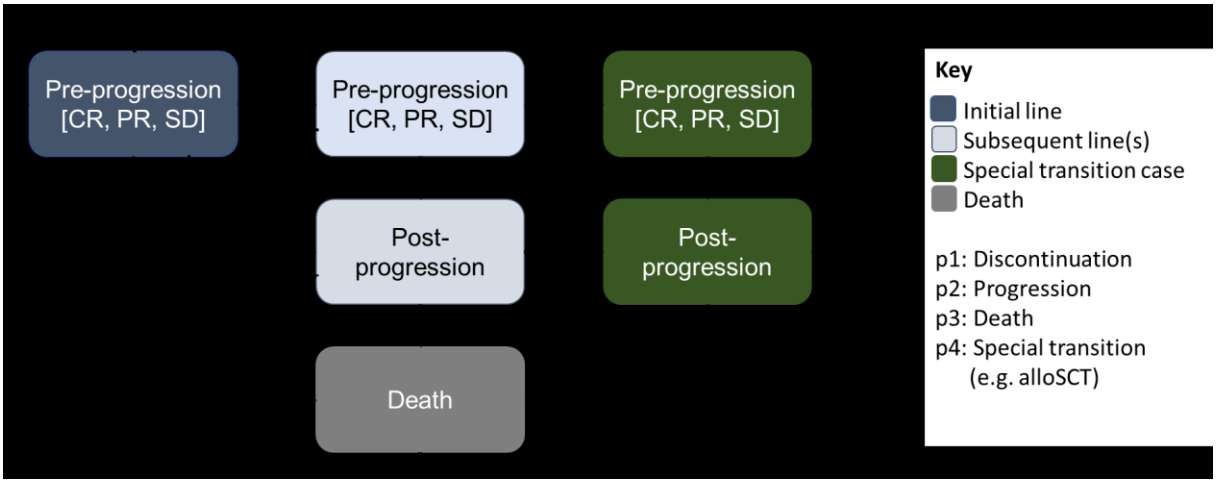


**Figure 9 Amended Markov flow diagram in response to clarification question B2 (Company Clarification Response Figure 3)**

The model uses survival modelling to predict PFS and OS. Alternative survival curve parameterisations are explored and presented as scenario analyses. The ERG discusses the survival modelling in section 4.3.5.

The ERG considers the model structure to be an adequate representation of the biological processes of relapsed or refractory classical Hodgkin lymphoma and adequately represents the treatment pathway. The company presented the model structure with sufficient justification for their methodological and structural choices (CS Section 5.2). In general, the modelling approach appears appropriate.

### 4.3.3 Population

In accordance with the final scope issued by NICE, the population of interest is people with relapsed or refractory classical Hodgkin lymphoma following ASCT (post-ASCT) and brentuximab vedotin (post-brentuximab vedotin). This is in accordance with the marketing authorisation for nivolumab. However, as described in Section 2.3, this is only one of the two populations specified in the final scope issued by NICE.

The company uses data from the CheckMate 205 and CA209-039 studies for the clinical parameters for nivolumab in the economic model. According to the CS, pooled data for 193 patients from Cohorts B (n=80) and Cohort C (n=98) of the CheckMate 205 study and a sub-group (n=15) from the CA209-039 study, matching the population of interest were used. As discussed in the clinical effectiveness section 3.1 above, these studies were single-arm, non-randomised, non-comparative, parallel cohort studies. Nivolumab efficacy data were derived from these studies while SoC efficacy data was derived from the Cheah and colleagues study[2]. In Cheah and colleagues, between 68% (66/97 reported in full paper) and 71% (71/100 reported in abstract) of the sample population were both post-ASCT and post-brentuximab vedotin patients (see Section 3.1.3).

**Table 28 Comparison of patient characteristics**

| Parameter | | CheckMate 205[a] | | CA209-039 (n=23)[a] | Cheah et al. (n=89)[b] |
|---|---|---|---|---|---|
| | | Cohort B (n=80) | Cohort C (n=100) | | |
| Age(years), median | | [redacted] | [redacted] | [redacted] | 32 |
| Disease Stage | Stage I | 1 | [redacted] | not reported | 2 |
| | Stage II | 11 | [redacted] | | 25 |
| | Stage III | 14 | [redacted] | | 18 |
| | Stage IV | 54 | [redacted] | | 39 |

[a] Nivolumab treatment
[b] Standard of care (SoC) treatment

Table 28, shows the patients' characteristics in terms of age and disease stage from the three studies used in this assessment (intervention and comparator studies). The median age of the population in these studies is similar ranging from 32 to 37 years. The Cheah study also states that details regarding the outcome of the last therapy before brentuximab vedotin were available in 84 patients, of whom only 31 (36%) were refractory. Therefore, the sample population in the Cheah

study is not a complete match with the population of interest in this appraisal. However, the ERG agrees with the company that due to the paucity of evidence available for nivolumab and its comparators in the relevant population, the two nivolumab single-arm trials (CheckMate 205 and CA209-039) and the single-arm comparator trial, Cheah and colleagues, are the most appropriate studies to inform comparisons.

### 4.3.4 Interventions and comparators

The CS compares nivolumab to SoC, in line with the NICE scope for this appraisal. SoC is defined as established clinical management without nivolumab, including chemotherapy such as gemcitabine and bendamustine. The base case analysis assumes that SoC comprises the therapies described within the Cheah study,[2] as shown in Table 29. These are: investigational agents, gemcitabine, bendamustine, brentuximab vedotin retreatment, platinum based therapies, ASCT and other alkylator therapies. The composition of SoC in terms of the actual chemotherapies used is unclear, and the regimens used are described in more detail in section 4.3.7 and shown in Table 42. The company conducts a scenario analysis that compares nivolumab to BSC, which is comprised of palliative care and chemotherapy (CS page 156).

The modelled doses and administration schedule of nivolumab are in line with the marketing authorisation. The Cheah study was conducted in the USA. The CS makes the assumption that the patient characteristics and the clinical management observed in this Cheah study are generalisable to UK clinical practice. The company states that it was considered unlikely that there are significant differences to patients seen in UK clinical practice. The ERG, advised by clinical experts, agrees that the Cheah study currently is the best available evidence for this assessment.

### 4.3.5 Treatment effectiveness and extrapolation

As described above (section 4.3.2) the economic model incorporates three health states which represent pre-progression, post-progression and death. The model predicts the proportion of patients who experience a progression or death event in monthly cycles.

In the company's base case analysis, patients enter the model following failure of prior therapies (post-ASCT and post–brentuximab vedotin) and receive either nivolumab or SoC. Patients may discontinue treatment from their initial therapy and these patents then receive BSC (comprised of

palliative care/chemotherapy). For the base case analysis, BSC is the final line of therapy and it is assumed that patients do not discontinue BSC.

Survival outcomes were modelled using survival equations fitted to data from the two studies for nivolumab and for the SoC arm, were derived from the Cheah study.[2] Survival curves were applied to estimate PFS and OS in each treatment arm. AE rates were used to derive the costs associated with each treatment arm and the disutilities experienced by the patients. This section outlines the PFS, OS, response rates, time to treatment discontinuation and AEs rates for both nivolumab and SoC.

#### 4.3.5.1 Survival outcomes (clinical events)

Parametric extrapolation of survival data from the studies was used to inform the long-term economic model. Parametric survival functions were fitted to the patient-level pooled nivolumab data (total n=193) and fitted to a number of different distributions, including exponential, Weibull, log-logistic, lognormal, Gompertz and generalised gamma survival distribution. The Akaike and Bayesian Information Criteria were implemented evaluating the goodness-of-fit, with smaller values demonstrating a more appropriate fit. The clinical plausibility of extrapolation was assessed by clinical experts. Clinicians visually assessed the survival curves and the corresponding hazards over time and determined the most plausible distribution.

Clinical data informing OS and PFS for patients treated with nivolumab were derived from Cohort B and Cohort C of the CheckMate 205 (n=178) and the post-ASCT / post-brentuximab vedotin patients from the CA209-038 (n=15) study. These studies provide follow-up data for 15.7, 8.9 and 23.3 months respectively. There is little available data for the SoC comparator. The company used data from Cheah and colleagues to inform SoC therapy in the model.[2] A proportion of 71% of patients within the Cheah study had previously received both ASCT and brentuximab vedotin. The company states that in the base case, efficacy inputs for SoC are derived from the population of patients who did not receive investigational agents (n=51). Despite this, tables and data within the CS refer to the full sample (n=79). The treatments administered within the Cheah and colleagues study[2] and the outcomes from these therapies are presented in Table 29 for the whole population (n=79). The company also conducted scenario analyses assessing the impact of applying efficacy from the overall population, and using the shortest and longest survival estimates. Whilst data is available on comparators, the company considered Cheah and colleagues the best available evidence believing that it is the most representative study of the SoC treatment (a mix of

chemotherapy) whereas other studies used in the ITC are single-arm studies consisting entirely of investigational agents. Whilst we agree that the ITC comparators are as representative of SoC as Cheah and colleagues, we stress that Cheah and colleagues data is best used including investigational agents, and that there are still significant limitations of the data given the single-arm nature of the study (see Section 3.1.3 for further critique).

**Table 29 Therapies administered and outcomes - Cheah study (2016), (CS Table 37, p. 103)**

| Treatment | *n* | Eval | CR (%) | PR (%) | ORR (%) | mPFS (m) | mOS (m) |
|---|---|---|---|---|---|---|---|
| Investigational agent | 28 | 28 | 4 (14) | 3 (11) | 7 (25) | 2.4 | 47.7 |
| Gemcitabine | 15 | 12 | 4 (27) | 4 (27) | 8 (53) | 2.1 | NR |
| Bendamustine | 12 | 11 | 2 (17) | 4 (33) | 6 (50) | 3.7 | 34.0 |
| Other alkylator | 6 | 4 | 1 (17) | 1 (17) | 2 (33) | 5.0 | 9.5 |
| BTX retreatment | 6 | 4 | 0 (0) | 2 (33) | 2 (33) | 3.5 | 10.4 |
| Platinum based | 4 | 4 | 0 (0) | 1 (25) | 1 (25) | 0.9 | 25.2 |
| ASCT | 3 | 3 | 1 (33) | 0 (0) | 1 (33) | - | 11.9 |
| Other | 5 | 1 | 0 (0) | 0 (0) | 0 (0) | - | 24.9 |
| **Total** | **79** | **67 (85)** | **12 (15)** | **15 (19)** | **27 (34)** | **3.5** | **25.2** |

ASCT, autologous stem cell transplant; BTX, brentuximab vedotin; CR, complete response; mOS, median overall survival; mPFS, median progression-free survival; ORR, objective response rate; PR, partial response.

## Nivolumab survival outcomes

### *Progression free survival*

Progression events derived from the PFS data are based on the investigator-assessed outcomes. Figure 10 presents the parametric survival functions fitted to the patient-level data. The lognormal was considered the most appropriate fit, on the basis that the Akaike and Bayesian Information Criteria, had the smallest values (Figure 10). Clinicians also determined that the lognormal distribution for PFS was the most plausible describing long-term outcomes in clinical practice. This was based on the assumption that there would be an initial increase in hazard, followed by a gradual decline over time. Alternative distributions were assessed in scenario analyses. Figure 10, shows the Kaplan-Meier data for the nivolumab pooled cohort (n=193), survival functions and extrapolations. Communication with our clinical experts confirmed their agreement to the approach chosen by the company. On balance, the ERG considered that the choices made by the company in the base case were the most appropriate extrapolation choices. The choice of lognormal for PFS appears reasonable. The parameters describing investigator-assessed PFS for nivolumab and SoC applied in the model are shown in Table 30. The CS presents scenario analyses for alternative survival models for nivolumab (Table 50).


**Figure 10 Extrapolation of PFS curves (years 0-5): nivolumab, (CS, Figure 25)**

**Table 30 Parameters describing PFS and OS for nivolumab (CS, Table 39)**

| | Nivolumab |
|---|---|
| PFS | Lognormal;<br>μ: 2.825<br>σ: 1.109 |
| OS | Weibull<br>Scale (A): 76.74<br>Shape (B): 1.326 |
| OS overall survival PFS: progression-free survival. | |

*Overall survival*

For the nivolumab arm the company stated that the exponential parametric function provides the best fit, based on Akaike and Bayesian Information Criteria values (Figure 11). However, as this

distribution would predict survival beyond 60 years for a proportion of patients, the company decided that a more conservative approach was appropriate. Clinicians considered that the PFS and OS hazards would have similar long-term extrapolation, however given the paucity of data to inform OS, the Weibull distribution was considered to provide a more appropriate fit for OS. The survival functions fitted are presented in Table 30. Kaplan-Meier data, the long-term extrapolations and the median survival estimates are shown in Figure 11.

The ERG considered that the choice of Weibull for OS to be an appropriate choice. We noted that there was a large range in the OS outcome, from 41.7 months for the Gompertz distribution to 394 months for the lognomal distribution (Figure 11), due to the short follow-up of the study. The CS provided scenario analyses varying the distributions used for survival (CS Table 67) but changing the distribution used for OS did not appear to have a large effect on the model results (Table 50).


**Figure 11 Extrapolation of OS curves (years 0-5): nivolumab, (CS, Figure 26)**

### SoC survival outcomes

*Progression free survival*

The Cheah and colleagues study[2] provides Kaplan-Meier data describing PFS for the overall population. The median PFS for the specific therapies ranged from 0.9 to 5.0 months, with investigational agents reporting a median PFS of 2.4 months. Figure 12, shows the PFS for the overall population from the Cheah study and the Cheah population excluding investigational agents compared to the PFS from the two studies for nivolumab.

The CS used the population from Cheah excluding the group of 28 patients who received investigational agents. The justification given by the company is that the group of patients who received investigational agents is likely to contain patients receiving nivolumab. The ERG contacted the authors of Cheah and colleagues, and were informed that there was only a small number of patients who received PD-1 inhibitors, such as nivolumab, in the 'investigational agents' group [personal communication]. The ERG considers that the company should have used the overall population from Cheah, i.e. including those patients receiving investigational agents.


**Figure 12 Long-term extrapolation of PFS: SoC (CS, Figure 29)**

Given the limited evidence for this population, the company used an exponential curve fitted to these data, based on the rationale that an exponential distribution should be considered the default parametric function for long term extrapolation. The CS stated that this was in line with the method proposed by Bagust and Beale.[38] This methodological recommendation from Bagust and Beale is not without debate. An alternative method is the one recommended by the NICE Decision Support Unit guide by Latimer.[39] The company follows the systematic testing of alternative survival curves recommended by Latimer for all nivolumab curves but did not do so for SoC curves. We did not feel that the choice of survival model was sufficiently justified for SoC in the CS, which led NICE and the ERG to request clarification on the model fit of alternative survival curves (Clarification question B5). The company provided survival curves and fit statistics comparable to CS Figure 25 and CS Figure 26 for all patients from Cheah and colleagues (including those patients receiving investigational agents). The parameters used in the model for the SoC PFS survival curve are shown in Table 31. We consider that the exponential is an appropriate choice of survival model for PFS of SoC

**Table 31 Parameters describing OS and PFS for SoC (CS, Table 41; App. 6, Table 13)**

| Parameter | SoC |
|---|---|
| PFS | Exponential<br>λ: 0.160 |
| OS | Exponential<br>λ: 0.036 |

OS, overall survival; PFS, progression-free survival.

*Overall survival*

Figure 13 shows the OS for SoC based on the population excluding investigational agents and for the overall population from the Cheah study compared to the OS from the two studies for nivolumab. Kaplan-Meier data from the Cheah study provided a median estimate of OS of 25.2 months. Median OS for specific therapies ranged from 9.5 months to 34 months with investigational agents reporting a median OS of 47.7 months. As discussed above, the CS considered that some of the investigational agents were likely to be nivolumab and so chose to use the patients not receiving investigational agents. Clarification from the Cheah study authors suggests this is not the case and the ERG considers the company should have used the overall population from Cheah. The ERG notes that by choosing the population not receiving investigational agents, the model produces results that are more favourable to nivolumab.

The company fit survival curves for the patients not receiving investigational agents by adapting the Kaplan-Meier data for the overall population according to the median OS observed from the two populations. NICE and the ERG requested that the company provide data for additional SoC survival models, which the company provided (Clarification question B5). The ERG considered that the exponential survival curve fitted for the overall population was appropriate (Table 31).

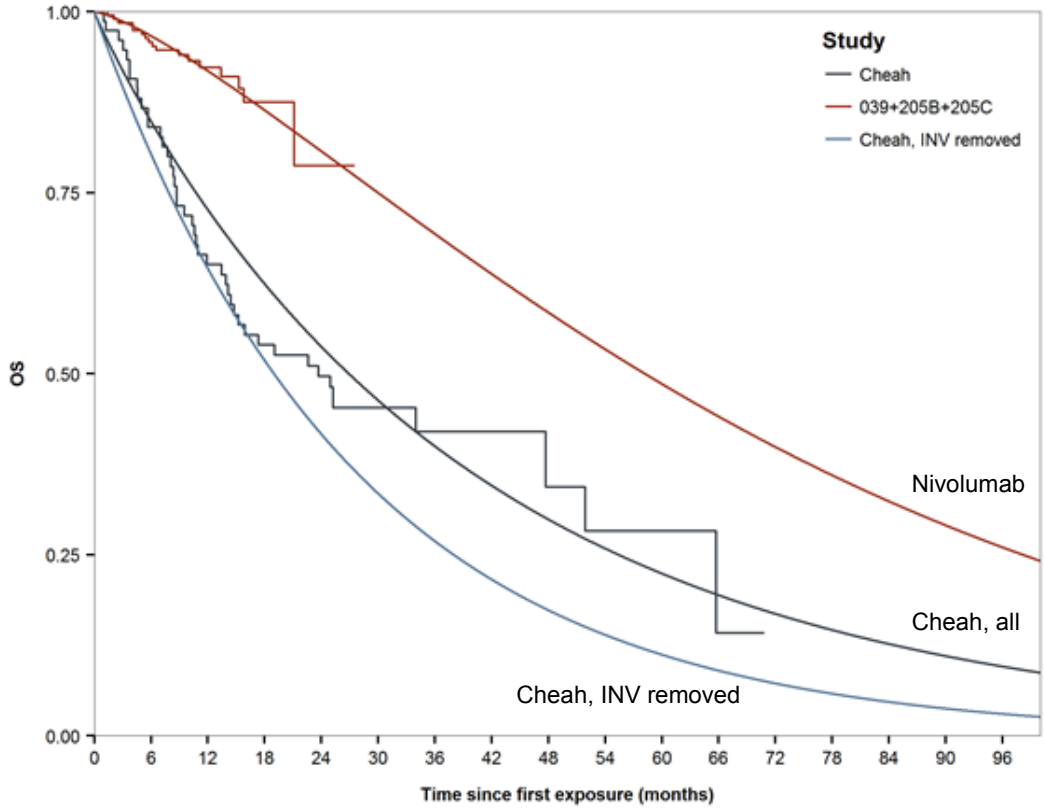


**Figure 13 Overall survival: SoC, (CS, Figure 30)**

#### 4.3.5.2 Response rates



The response rates or best overall response (BOR) rates, within this submission, have no direct impact on progression or survival, in the economic model. This is due to the use of survival data that implicitly incorporates any impact on patients' survival. However, response rates are used to estimate utility values (details in section 4.3.6). Response rates are also applied in stopping rules and switching to subsequent therapies such as alloSCT.



Within the company model, the response rates used for nivolumab are derived from investigator-assessments from the two nivolumab studies and the impact of applying IRRS-derived response rates are assessed in sensitivity analyses. Response rates for the SoC arm are derived from the Cheah study after adjustment for exclusion of patients receiving investigational agents. Table 32, summarises the response rates applied within the base case analysis of the economic model.

**Table 32 Treatment response: base case analysis (CS, Table 43)**

| Treatment | CR | | PR | | Source population |
|---|---|---|---|---|---|
| | Value | Standard error | Value | Standard error | |
| Nivolumab | [redacted] | [redacted] | [redacted] | [redacted] | Eligible population from CheckMate 205 (B and C) and CA209-039 |
| SoC | 15.7% | 5.09 | 23.5% | 5.94 | Cheah 2016[2] (excluding investigational agents) |

CR, complete response; PR, partial response; SD, stable disease; SoC, standard of care.

#### 4.3.5.3 Time to treatment discontinuation

The structure of the economic model assumes that patients in both nivolumab and SoC arms switch to subsequent treatment following progression (BSC for the base case). Nivolumab treatment is maintained until progression or discontinuation due to other reasons, while the SoC arm uses the recommended duration of SoC treatment which varies between 1 and 7 months, depending on the treatment (Table 42).

Patients discontinue treatment due to disease progression, AEs or other reasons such as patient preference. Table 33 shows the clinical data used to inform the parametric functions for time to treatment discontinuation. The approach taken in the economic model is for patients to discontinue treatment due to disease progression using the PFS curves described above and additionally for patients to discontinue treatment for reasons other than progression. The discontinuation rate for reasons other than progression is assumed to be the same for the nivolumab and SoC arms.

**Table 33 Discontinuation due to any reason: nivolumab (CS, App.6 Table 9)**

| Parameter | N | Median follow-up (months) | 6 Months | 12 Months | Median Time on Treatment (months) |
|---|---|---|---|---|---|
| Overall, discontinuation any reason | 193 | 12.1 | 76.7% | 59.5% | 20.0 |
| Overall, excluding discontinuation due to progression | 193 | 11.1 | 84.1% | 74.2% | 23.9 |

The survival function parameters and the Akaike and Bayesian Information Criteria for discontinuation curves are presented in Table 34 and the long-term survival functions presented in

Figure 14. The company concludes that the most appropriate distribution is the lognormal and the parameters for this are shown in Table 35. The ERG notes that there is a discrepancy in the description of the derivation of the survival function used in Appendix 6 and the survival function used in the economic model. Both functions are shown in Table 35.

**Table 34 Discontinuation (excluding discontinuations due to progression) (CS, App.6, Table 12)**

| Parameters | | Akaike Information Criteria | Bayesian Information Criteria | Median Time to Discontinuation (months) |
|---|---|---|---|---|
| Exponential | lambda: 0.01605 | 258.6 | 261.9 | 43.2 |
| Weibull | Shape: 1.378<br>Scale: 37.75 | 257.4 | 263.9 | 29.0 |
| Log-logistic | Shape: 1.437<br>Scale: 33.47 | 257.7 | 264.3 | 33.5 |
| Lognormal | mu: 3.708<br>sigma: 1.383 | 256.5 | 263.1 | 40.8 |
| Gompertz | Shape: 0.07401<br>Rate: 0.01021 | 257.7 | 264.2 | 24.3 |
| G Gamma | mu: 3.558<br>sigma: 1.801<br>Q: -0.7575 | 258.3 | 268.1 | 56.9 |


**Figure 14 Discontinuation (excluding discontinuation due to progression): nivolumab (CS, App.6 Figure 34)**

**Table 35 CheckMate 205 discontinuation: nivolumab and SoC (CS, Table 44)**

| | Discontinuation Parameter, economic model | Discontinuation Parameter, described in appendix 6[a] |
|---|---|---|
| Fitting | Lognormal | Lognormal |
| μ | 3.283 | 3.708 |
| σ | 1.252 | 1.383 |

[a] CS, App.6 – Table 13.

#### 4.3.5.4 Adverse events

AEs applied in the economic model affect costs and benefits accrued by patients in both arms. To identify AEs and assess the safety profile of nivolumab the company used pooled overall data from both the CheckMate 205 (including Cohort A patients who do not meet the decision problem criteria) and the CA209-39 studies (full sample which includes 8 patients who do not meet the decision problem criteria). The company used the incidence of treatment-related grade 3-4 AE rates,

converted to monthly equivalents based on follow-up times, and applied them to all patients in the model in all cycles. The nivolumab AEs rates are presented in Table 36.

The monthly incidence of AEs for SoC was calculated in a similar way using studies cited within the BCSH guidelines. These rates were then combined into a set of weighted mean chemotherapy monthly AE rates (CS, Table 46) using the proportions receiving each treatment from Cheah (2016). Table 36 presents the AE rates for SoC. The ERG notes that generally the adverse event profile for nivolumab is better than for SoC and in particular [redacted]

**Table 36 Adverse Event rates: nivolumab and SoC (CS, Table 45, Table 47)**

| Adverse events | Weighted monthly rate, nivolumab | Weighted monthly rate, SoC |
|---|---|---|
| Anaemia | [redacted] | 8.2% |
| Diarrhoea | [redacted] | 0.5% |
| Dyspnoea | [redacted] | 0.1% |
| Fatigue | [redacted] | 0.6% |
| Leukopenia | [redacted] | 13.6% |
| Nausea | [redacted] | 2.0% |
| Neutropenia | [redacted] | 14.2% |
| Pyrexia | [redacted] | 0.3% |
| Thrombocytopenia | [redacted] | 16.8% |
| Vomiting | [redacted] | 2.3% |

#### 4.3.5.5 All-cause mortality

The company states that due to the young age of the population enrolled in the clinical trials, the economic model includes age and gender adjusted mortality from the UK life tables. These values are included in every model cycle and are applied multiplicatively. While the company acknowledges some form of double counting, they state that this only occurs in the first few years, due to the low baseline age, and this effect applies equally to all comparators, and therefore is likely to have a minimal impact on predicted survival and cost-effectiveness. The ERG agrees that this approach is unlikely to have a significant impact on the cost-effectiveness results.

#### 4.3.5.6 AlloSCT

In the base case analysis, there is no consideration of patients who receive alloSCT. The CS states the company conducted scenario analyses that explored alternative treatment pathways including alloSCT. Patients were allocated to alloSCT according to evidence describing the use of alloSCT in the Perrot and colleagues (2016) study[40] (Section 4.3.10.2, for details). AlloSCT is allocated according to the proportion of patients in each response category. AlloSCT is associated with morbidity and mortality in the short-term but could be considered potentially curative over the long-term. Scenarios considering the use of alloSCT were modelled using the Kaplan-Meier data describing OS and PFS in the post-alloSCT population from the Cheah study. The description of the PFS and OS parameters used in the scenario analyses are presented in Table 37 and the alloSCT scenario analyses are presented in Section 4.3.10.2.

**Table 37 Parameters describing PFS and OS for alloSCT (CS, Table 72)**

| Parameter | alloSCT |
|---|---|
| OS | Lognormal;<br>μ: 9.252<br>σ: 3.551 |
| PFS | Exponential<br>λ: 0.037 |

The ERG notes that in the nivolumab trials and the Cheah study, a small proportion of patients received alloSCT. Therefore the survival for these studies already includes patients receiving alloSCT.

**Summary**

One of the main weaknesses of this appraisal is the lack of head-to-head evidence between nivolumab and SoC and the paucity of evidence in patients with relapsed or refractory Hodgkin lymphoma (post-ASCT, post-BTX setting). Therefore, the clinical pathway for Hodgkin lymphoma patients is subject to considerable uncertainty and heterogeneity. Given this, the clinical effectiveness for both the intervention and the comparators is based on assumptions and clinical plausibility. The ERG considers the company should have used the overall population from the Cheah study, rather than the excluding patients who received investigational agents. On balance, we found that the survival models used by the company in the base case were the most appropriate extrapolation choices for nivolumab and SoC.

### 4.3.6 Health related quality of life

The company conducted a literature search for utility values for adult patients with Hodgkin lymphoma. The search included Embase, Medline In-process, the Cochrane library and EconLit. The inclusion criteria specified generic QoL instruments or direct elicitation in adult patients with Hodgkin lymphoma, who may or may not have been treated previously. Twenty nine studies were included (CS Appendix 5, Table 11). The CS does not discuss the results of the literature search of the relevance of the studies identified. Of the studies included, the economic model uses values from the study by Swinburn and colleagues for the SoC arm.[41]

Swinburn and colleagues[41] reported utility values for patients with relapsed and refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma elicited from members of the public in several countries (including the 100 people from the UK) using the time trade off method. The study reported utility values for the pre-progression and post-progression health states.

HRQoL is incorporated in the model using utility estimates dependent upon the patients' disease state. A disutility is applied for adverse events and age-dependent utility decrements are applied.

The health state utility values used in the model are shown in Table 38 (CS Table 51, p. 122). The utility values for patients treated with nivolumab were based on the CheckMate 205 study. The EQ-5D questionnaire was completed by patients within CheckMate 205 at several time points: baseline (prior to first dose), week 9, every 8 weeks up to week 25, week 33 and every 12 weeks thereafter; following discontinuation, questionnaires were completed at two subsequent follow-ups. The EQ-5D questionnaire used the UK EQ-5D 3L tariff.

**Table 38 Summary of utility values for the cost-effectiveness analysis (CS Table 51, p. 122)**

| State | Utility value: mean (standard error) | Reference |
|---|---|---|
| Health state utilities | | |
| Nivolumab: pre-progression | [redacted] | Based on CheckMate 205 data |
| Nivolumab: post-progression | [redacted] | |
| SoC: pre-progression | 0.76 | HL response-specific utilities, Swinburn and colleagues.[41] |
| SoC: post-progression | 0.38 | |

The EQ-5D utility values from CheckMate 205 were stratified by response for the pre-progression health state. In the base case analysis, the economic model uses the same utility values for patients in the pre-progression health state, i.e. does not use different utility values for those in CR, PR or SD.

The health state utility values from CheckMate 205 and Swinburn and colleagues are shown in Table 39 (CS Appendix 7, Table 1). The CS commented that the utility associated with CR in nivolumab-treated patients is slightly lower than that described in Swinburn and colleagues, while that for PR and SD are higher. The values for post-progression are considerably lower for Swinburn and colleagues (0.39) than for CheckMate 205 ([redacted]).

**Table 39 Summary of nivolumab-specific utilities compared to those from Swinburn (CS Table 50, page 122)**

| Health-state | Response | Nivolumab-specific utility | Swinburn 2015[41] |
|---|---|---|---|
| Pre-progression | CR | [redacted] | 0.91 |
| | PR | [redacted] | 0.79 |
| | SD | [redacted] | 0.71 |
| | Overall | [redacted] | - |
| Post-progression | | [redacted] | 0.39 |

CR, complete response; PR, partial response; SD, stable disease.

In the base case analysis, the economic model uses pre-progression utility values from the CheckMate 205 study for patients treated with nivolumab and from Swinburn and colleagues for patients receiving SoC. This equates to a difference in utility of [redacted]between the arms. The ERG does not consider that this difference in utility between these patients has been proven and considers a more consistent approach would be to estimate the pre-progression utility values for patients on SoC from CheckMate 205. Applying the response-specific utilities from CheckMate 205 (Table 32) to the SoC treatment response proportions (Table 40) generates a pre-progression utility of [redacted], whilst applying response-specific utilities to nivolumab results in a utility of [redacted].

**Table 40 Response weighted utility values for nivolumab and SoC**

| Health State | % in state, Nivolumab | % in state SoC | Swiftburn 2015 | Nivolumab utility data |
|---|---|---|---|---|
| Complete Remission | [redacted] | 15.69% | 0.910 | [redacted] |
| Partial Remission | [redacted] | 23.53% | 0.790 | [redacted] |
| Stable Disease | [redacted] | 60.78% | 0.710 | [redacted] |
| **Nivolumab utility (weighted average)** | | | 0.801 | [redacted] |
| **SoC utility (weighted average)** | | | 0.760 | [redacted] |

The CS acknowledges that the large difference in utility for post-progression patients in the nivolumab and SoC arms may be considered counter-intuitive; however the company suggests that nivolumab has a unique mechanism of action that stimulates the patient's immune system and this would extend into benefits in quality of life in the post-progression phase, even though patients have discontinued treatment. The ERG is sceptical whether this large difference in utility is realistic.



The ERG identified a study by Ramsey and colleagues[42] that reported EQ-5D values for patients with relapsed or refractory Hodgkin lymphoma post-ASCT for patients receiving brentuximab vedotin vs. placebo. The study shows utility values for progressed disease for the placebo group to be between 0.85 (after 3 months) to 0.7 (after 24 months). Therefore, we suggest that the results from Swinburn and colleagues' are outliers and may not be realistic. The Swinburn study used TTO methodology using estimates from the general public and it may be that their perception of the disease is not consistent with EQ-5D valuation. In summary, therefore we conclude that our preferred approach is for the economic model to use the post-progression utility values from the CheckMate 205 study for the patients treated with nivolumab and with SoC. The ERG investigates the effect of changing these utility values in the ERG analyses reported in section 4.4.



<u>Age dependent disutility</u>

Age dependent disutility has been applied to patients according to patient age, based on the estimated health utility of the general population (Ara and Brazier[43]). The age-dependent decrement is calculated using the difference in utility between patients' age-related utility and the age-related utility at the age of patients at baseline. The ERG is unable to match the age related disutility to the study by Ara and Brazier and suggests the data is from the report by Kind and colleagues.[44]

Adverse event disutility

Disutilities were included in the model for grade 3-4 treatment-related AEs and are shown in Table 41 (CS Table 49, p. 121). The AE disutility values were based on those applied in the NICE appraisal for pixantrone for refractory aggressive non-Hodgkin's lymphoma (TA306)[45] and are listed in Table 41. In answer to a clarification question (B12), the company stated that the adverse event disutility is assumed to be applied as a one-off disutility in the monthly cycle.

**Table 41 Adverse event disutilities (CS Table 49, p. 121)**

| Adverse event | Disutility | Standard Error | Source |
|---|---|---|---|
| Anaemia | 0.090 | 0.0021 | Beusterian 2010[46] |
| Diarrhoea | 0.080 | 0.0021 | Beusterian 2010[46] |
| Dyspnoea | 0.050 | 0.0120 | Doyle 2008[47] |
| Fatigue | 0.073 | 0.0185 | Nafees et al 2008[48] |
| Leukopenia | 0.090 | 0.0154 | Assumed as for neutropenia |
| Nausea | 0.048 | 0.0162 | Nafees et al 2008[48] |
| Neutropenia | 0.090 | 0.0154 | Nafees et al 2008[48] |
| Pyrexia | 0.110 | 0.0021 | Beusterian 2010[46] |
| Thrombocytopenia | 0.108 | 0.0108 | Tolley 2013[49] |
| Vomiting | 0.048 | 0.0162 | Nafees et al 2008[48] |

### 4.3.7 Resource use and costs

The company conducted a literature search for resource use in Hodgkin lymphoma. The inclusion criteria specified that studies had to report resource use and/or costs associated with the management of Hodgkin lymphoma at the patient level where the study had been conducted in the UK or EU. The review identified 10 studies (shown in Appendix 5, Table 16). The ERG notes that the CS reports a different number of identified studies (i.e 12 studies, p. 124). The CS does not discuss the studies found or comment on whether any of them are relevant to this appraisal.

The nivolumab dosing schedule is stated in CS Table 52, p. 125. The recommended daily dose for nivolumab for patients with Hodgkin lymphoma is 3mg/kg by IV every 2 weeks, administered over 60 minutes. The dosage schedule is consistent with that used in the CheckMate 205 study. The unit cost for nivolumab is £1,097 for a 10 ml vial (10mg/mL) and £439 for 4ml vial. The cost per cycle is £5,724 per month, assuming wastage and a patient weight of 80kg. The administration costs are

£389.41[50] for the first administration and £326.41 for subsequent administrations. Nivolumab has been provided by the company with a patient access scheme discount of [redacted].

The cost calculation of SoC, comprised of chemotherapy, brentuximab vedotin retreatment and bendamustine, is based upon the proportion of patients who received each treatment in the Cheah and colleagues study. The dosage schedules of the treatments for SoC are shown in CS Table 57, p. 127. This table also shows the proportions of each treatment that comprise SoC (received by NICE and the ERG in response to a clarification question, B6). The proportions of patients that received bendamustine and brentuximab vedotin were specified in the Cheah and colleagues study. The CS calculated the proportions of patients on bendamustine and brentuximab vedotin using these data but excluded patients receiving investigational agents, ASCT and 'other'. For the chemotherapy agents, the company assumed an equal proportion of patients received each regimen. These regimens were chosen according to BCSH guidelines.[1] Clinical advice to the ERG suggested that mini-BEAM or DexaBEAM are not commonly used salvage regimens for Hodgkin lymphoma in the UK. The ERG therefore suggests that SoC should not contain these regimens. We investigate the effects of changing the SoC costs in the ERG analyses (section 4.4).

The unit costs and dose frequency for treatments comprising SoC and the proportion of patients receiving them are shown in Table 42. The monthly cost of SoC is as follows: £4,729 month 1, £4,141 month 2, £3,057 month 3, £2,251 month 4, £2,219 month 5, £1,913 month 6, £332 month 7, £0 month 8+.

**Table 42 SoC costs and dosing schedule (CS Table 55, p. 126)**

| Regimen | Cost per cycle | Dosing instructions | Cycle length | Number of cycles | Proportion received |
|---|---|---|---|---|---|
| ICE | £1,993.51 | every 14 d for two cycles | 14 | 2 | 4.15% |
| IVE | £2,833.51 | 21 day cycle; 2 cycles | 21 | 2 | 4.15% |
| MINE | £1,683.20 | every 28 days; 2 courses | 28 | 2 | 4.15% |
| IVOx | £3,128.47 | 21 day cycle; 3 cycles | 21 | 3 | 4.15% |
| IGEV | £3,703.72 | 21 day cycle; 4 cycles | 21 | 4 | 4.15% |
| GEM-P | £2,198.83 | 28 day cycle; three cycles | 28 | 3 | 4.15% |
| GDP | £1,484.32 | 21 days; 2 cycles | 21 | 2 | 4.15% |

| | | | | | |
|---|---|---|---|---|---|
| GVD | £3,020.85 | 21 days; 2 cycles | 21 | 2 | 4.15% |
| Mini-BEAM | £11,221.91 | 28 day cycle; three cycles | 28 | 3 | 4.15% |
| DexaBEAM | £11,355.50 | 28 day cycle; 2 cycles | 28 | 2 | 4.15% |
| ESHAP | £1,056.87 | every 21- 28 d for 4 cycles | 28 | 4 | 4.15% |
| ASHAP | £1,058.87 | Assumed 28 day cycle; 3 cycles | 28 | 3 | 4.15% |
| DHAP | £1,204.27 | every 21 days for two cycles | 21 | 2 | 4.15% |
| DHAOx | £2,004.77 | 21 day cycle; 4 cycles | 21 | 4 | 4.15% |
| Bendamustine | £2,096.91 | every 28d for 6 cycles | 28 | 6 | 27.91% |
| BTX | £7,889.41 | 3 week cycle for 9 cycles | 21 | 9 | 13.95% |

ASHAP: doxorubicin, methylprednisolone, cytarabine, cisplatin; BTX: brentuximab vedotin; DexaBEAM: dexamethasone, carmustine, etoposide, cytarabine, melphalan; DHAOx: dexamethasone, cytarabine, oxaliplatin; DHAP: dexamethasone, cytarabine, cisplatin; ESHAP: etoposide, methylprednisolone, cytarabine, cisplatin; GDP: gemcitabine, dexamethasone, cisplatin; GEM-P: gemcitabine, cisplatin, methylprednisolone; GVD: gemcitabine, vinorelbine, liposomal doxorubicin; ICE: ifosfamide, carboplatin, etoposide; IGEV: ifosfamide, gemcitabine, vinorelbine; IVE: ifosfamide, epirubicin, etoposide; IVOx: ifosfamide, etoposide, oxaliplatin; MINE: mitoxantrone, ifosfamide, vinorelbine, etoposide; Mini-BEAM: carmustine, etoposide, cytarabine, melphalan.

We conferred with clinical experts who confirmed that mini-BEAM and DexaBeam would not be expected to be used in the UK. In light of this, we have calculated alternative costs that exclude these treatments. Table 43 reports these treatment costs.

**Table 43 SoC costs excluding mini-BEAM and DexaBeam**

| Parameter | SoC (£) CS base case | SoC (£) ERG estimate |
|---|---|---|
| Month 1 | 4,729.43 | 3710.21 |
| Month 2 | 4,141.92 | 3204.80 |
| Month 3 | 3,037.50 | 2652.61 |
| Month 4 | 2,251.40 | 2251.40 |
| Month 5 | 2,218.97 | 2218.97 |
| Month 6 | 1,913.31 | 1913.32 |
| Month 7 | 331.52 | 331.52 |
| Month 8+ | 0.00 | 0 |

Resource use estimated for the health states were derived from those previously used for the NICE appraisal of brentuximab vedotin,[51] shown in CS Table 59, p. 132. The company assumed the same resource use for the pre-progression and post-progression health states. The resources used were 10.4 outpatient attendances per year with blood tests and 3 CT scans per year. Fifty per cent of the CT scans included a PET scan. The costs for these resources are shown in Table 44 (CS Table 59, p. 132). The monthly costs of pre-progression and post-progression health states are £190.

**Table 44 Pre- and post-progression resource use applied in the economic model (CS Table 59, p. 132)**

| Resource | Item | Value | Source |
|---|---|---|---|
| Outpatient attendance | Rate | 10.40 | BTX STA,[51] |
| | Cost (£) | 150.38 | NHS reference costs 2014-15[50] Clinical Haematology 303 |
| | Total (£) | 1,563.94 | - |
| Blood count | Rate | 10.40 | BTX STA,[51] |
| | Cost (£) | 3.01 | NHS reference costs 2014-15[50] Haematology DAPS05 |
| | Total (£) | 31.26 | - |
| Biochemistry | Rate | 10.40 | BTX STA,[51] |
| | Cost (£) | 1.19 | NHS reference costs 2014-15[50] Clinical Biochemistry DAPS04 |
| | Total (£) | 12.37 | - |
| CT scan (with assumption that 50% will include PET scan) | Rate | 3.00 | BTX STA,[51] |
| | Cost (£) | 224.44 | NHS reference costs 2014-15[50] RD26Z; RN03A |
| | Total (£) | 673.33 | - |
| Overall cost | Annual (£) | 2,280.91 | - |
| | Monthly (£) | 190.08 | - |

BTX, brentuximab vedotin.

The costs of treating treatment-related adverse events are shown in CS Table 60, page 133. These are taken from NICE appraisals for Pixantrone for non-Hodgkin's lymphoma (TA306)[45] and dasatinib, nilotinib and imatinib for chronic myeloid leukaemia (TA251)[52] and inflated to 2014-2015 costs. The company clarified (in answer to a clarification question, B14) that the adverse event costs from TA306 are from the ERG report for the TA306 NICE appraisal, rather than from the manufacturer submission.

In the company's base case, patients did not receive alloSCT. The ERG considers that the company should have included costs for alloSCT within the base case analysis because some patients in the nivolumab and SoC arms received alloSCT. The company conducted a scenario analysis where a proportion of patients received alloSCT at six months; the probability of receiving alloSCT was dependent on treatment respons. In this scenario, there were costs included for the alloSCT and subsequent immunosuppresion therapies. The company assumes that the proportion receiving alloSCT is based on the response category, derived from Perrot and colleagues,[40] where the proportion receiving alloSCT is 22.2% for CR, 14.1% for PR and 5.56% for SD. Patients receive immunosuppression therapies (ciclosporin and mycophenolate mofetil) and haematology outpatients appointments every 3 months. The cost of alloSCT is £21,672[50] and the monthly cost of immunosuppression therapies and outpatient appointments are £91.69.[53] The company varies the assumption around the costs and proportion of patients receiving alloSCT in scenario analyses.

The company conducts a scenario analysis using a cost of alloSCT of £110,374 as reported by Radford and colleagues[54] who conducted a retrospective analysis on resource use in 5 centres for patients with relapsed or refractory Hodgkin lymphoma post-ASCT. The ERG notes that the cost of alloSCT used in the appraisal of brentuximab vedotin was £108,052 based upon a study by the BMT Unit at the Beatson West of Scotland Cancer Centre.[51] We suggest that the company is therefore underestimating the cost of alloSCT and suggest that the cost of £110,374 should be used to be consistent with the NICE appraisal for brentuximab vedotin.

### 4.3.8 Model validation

**Internal consistency**

The company commissioned a technical review of the cost-effectiveness model conducted by an independent consultant. The technical review was designed to validate the modelling approach, illuminate areas of disagreement to be resolved prior to generating model results, and enable pre-emption of issues that reimbursement agencies and model critics may raise. The company also indicated that quality control was undertaken, whereby a cell-by-cell verification process was conducted to allow checking of all input calculations, formulae and visual basic code.

The company conducted additional internal validation assessing the fit of modelled survival to observed trial outcomes. These comparisons showed that modelled survival and observed survival closely matched. The results of these assessments of fit are reported in Table 45.

**Table 45 Comparison of clinical trial inputs and modelled outputs (CS Table 65, p. 139)**

| Parameter | Nivolumab | SoC | Incremental |
|---|---|---|---|
| **Overall survival in years** | | | |
| Survival curve median (mean) | 4.8 (5.9) | 1.6 (2.3) | 3.3 (3.6) |
| Model output median (mean) | 4.0 (5.0) | 1.5 (2.1) | 2.6 (2.9) |
| **Progression-free survival in years** | | | |
| Clinical trial (Median) | 1.4 | 0.4 | 1.0 |
| Survival curve median (mean) | 1.4 (2.6) | 0.4 (0.5) | 1.0 (2.1) |
| Model output median (mean) | 1.1 ([redacted]) | 0.3 (0.4) | 0.8 ([redacted]) |
| **Modelled output** | | | |
| QALYs | [redacted] | 0.93 | [redacted] |
| Life year | 5.01 | 2.11 | 2.90 |

QALY, quality-adjusted life year; SoC, standard of care.
No formal validation reports or procedures were reported.

The ERG replicated model outputs, checked inputs and outputs for consistency, and checked model code. Whilst the model was ostensibly in Excel; however, health state transitions and the utilities and costs associated with them are all calculated within and output from the VBA as values. The core outputs of the model are completely reliant on execution of VBA code — the model is more of a VBA model in an Excel graphical interface than a true spreadsheet model. The company conducted 58 scenario analyses, in total. Scenario analyses were manually run by the ERG to the extent that scenarios were sufficiently described. Some scenarios did not have sufficient explanation for their methods whilst others did not produce the results reported in the CS. The company's response to clarification question B9 enabled further scenario analysis checking. We identified discrepancies between the CS description of CS Analysis 26 and the parameters shown in the model provided for checking. When the ERG ran the analysis with parameters as reported, the ICER was £23,608 per QALY rather than £12,452 per QALY. Additionally, the reduction in the ICER reported by the company is illogical, as decreasing costs for SoC should not decrease the ICER of nivolumab. We were unable to identify the precise nature of the error, as the models provided in response to clarification did not produce the CS result, and had parameter discrepancies.

The ERG conducted additional validation of the company's alloSCT scenario 2 to verify that the numbers of people having alloSCT were consistent with those in the trials. Briefly, the alloSCT

scenarios implement a transition at six months to alloSCT as a new treatment for a proportion of patients with CR, PR and SD. To validate the use of Perrot and colleagues we multiplied the proportion of patients in each response state (CR, PR, SD) at the start of the model by the proportions of patients that Perrot and colleagues estimated would have alloSCT in each of these respective response states.[40] Table 46 compares the proportion of patients in each treatment who have alloSCT using the Perrot algorithm compared to the observed results of the treatment effectiveness trials. We note that the proportion of patients receiving alloSCT is underestimated in the economic model compared to observed alloSCT procedures in the studies. We investigate the effect on the model results of using the observed proportion of patients receiving alloSCT in the ERG analyses (section 4.4).

**Table 46 Modelled versus observed proportion of patients receiving alloSCT**

| Source | Proportion observed with alloSCT | Proportion predicted using Perrot and colleagues |
|---|---|---|
| Nivolumab trials | [redacted] | [redacted] |
| SoC (Cheah and colleagues) | 17.72% | [redacted] |

alloSCT, Allogeneic stem cell transplant; SoC, Standard of Care.

Additionally, we have compared the predicted survival in the model to predicted survival from observed data and from parametric curves for both nivolumab and alloSCT. We found that there was substantial variation in the data, primarily concerning whether SoC patients received the benefits of investigational therapies. Table 47 shows the results of these comparisons on mean and median survival. It should be noted, that there is substantial uncertainty with regards to long term survival in this patient population because data are immature for nivolumab and derived from a small population that may not be representative for SoC. There is substantial uncertainty around overall survival for nivolumab. Experts consulted by the ERG stated that there were insufficient data to estimate nivolumab OS, but that the recently published Younes and colleagues study estimate of 10 months median PFS seemed plausible.[4]

**Table 47 Comparison of company survival models**

| Analysis | Nivolumab median (mean) years OS | SoC median (mean) years OS |
|---|---|---|
| Survival curve estimate | 4.8 (5.9) | 1.6 (2.3) |
| CS base case output | 4.0 (5.0) | 1.5 (2.1) |
| CS Analysis 20 (alloSCT Scenario 2, CS p. 153) | [redacted] | [redacted] |

OS: overall survival; PFS: progression-free survival; SoC: standard of care.

**External consistency**

There is a lack of data on the patient population for patients who have failed brentuximab vedotin and ASCT with classical Hodgkin lymphoma. A NICE Technology Appraisal for brentuximab vedotin after the failure ASCT in classical Hodgkin lymphoma is in progress at the time of submission of this report.[51] As noted in the CS for nivolumab, the population in the brentuximab vedotin STA is at an earlier stage of the disease with greater expected survival, making the two STA populations not comparable.

The results presented were consistent with the data presented. Unfortunately, neither the company nor the ERG were able to identify a suitable model for external validation.

### 4.3.9 Cost effectiveness results

The results from the economic model are presented as incremental cost per QALY gained (CS Section 5.7, pp. 136-140). The company presented results for the base case analysis, with and without a PAS. Results for one-way sensitivity analyses, probabilistic sensitivity analyses, and the 58 scenario analyses reported by the company were conducted with the confidential PAS included.

The results of the list price base case analysis are reported in Table 48. Total costs for nivolumab were [redacted] whilst total costs for SoC were £21,090 [redacted] incremental). Total QALYs for nivolumab were [redacted] whilst total QALYs for SoC were 0.932 ([redacted] incremental QALYs). The base case ICER for nivolumab at list price was [redacted] per QALY compared to SoC. Base results with a [redacted] discount for nivolumab are reported in Table 49. The ICER for nivolumab (with PAS) compared to SoC was £19,882 per QALY.

**Table 48 Base case cost-effectiveness results (list price)**

| Parameter | Costs | Incremental costs | QALYs | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|
| **SoC** | £21,090 | - | 0.932 | - | - |
| **Nivolumab** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Table 49 Base case cost-effectiveness results (with PAS)**

| | Costs | Incremental costs | QALYs | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|
| **SoC** | £21,090 | - | 0.932 | - | - |
| **Nivolumab** | [redacted] | [redacted] | [redacted] | [redacted] | £19,882 |

ICER, Incremental cost-effectiveness ratio; SoC, Standard of Care; QALY, Quality-adjusted life year.

### 4.3.10 Assessment of uncertainty

#### 4.3.10.1 One-way sensitivity analyses

The company conducted a range of one-way sensitivity analyses (CS Section 5.8.2, pp. 144 to 146). The following parameters were varied in one-way deterministic sensitivity analyses:

- Rates of discounting
- Time horizon
- Baseline patient age
- Proportion male
- Health state costs: complete remission
- Health state costs: partial remission
- Health state costs: stable disease
- Health state costs: progressed disease (initial month)
- Health state health state utility: CR
- Health state health state utility: PR
- Health state health state utility: SD
- Health state health state utility: post-progression
- Pre-progression therapy costs: nivolumab
- Pre-progression therapy costs: SoC
- Pre-progression therapy costs: BSC
- Pre-progression therapy costs: BSC

Figure 15 shows the effect of the analyses on the ICERs. The most influential parameters were shortening the time horizon to 5 or 10 years, raising or lowering nivolumab pre-progression therapy costs by 20%, followed by lowering or raising post-progression utility by 20%. No analyses raised the ICER above £30,000 per QALY. The ICER of nivolumab, in comparison to SoC, appears robust to the alternative parameter assumptions in one-way sensitivity analyses. We considered that the choice of parameters for one-way sensitivity analyses were adequate.

The company did not make any conclusions with regards to the one-way sensitivity analyses except in the company's overall conclusions on sensitivity analyses.


**Figure 15 Univariate sensitivity analysis, ICERs (PAS price)(CS Figure 38, p. 145)**

#### 4.3.10.2 Scenario Analysis

A total of 58 scenario analyses were conducted (CS Section 5.8.3, pp. 147-165). For this section of the report we will break the section into the following categories:

- A. Alternative parameterisations of both PFS and OS nivolumab survival (16 analyses)
- B. Alternative parameterisations of SoC OS (2 analyses)
- C. Analyses with alternative treatment sequences (5 analyses)
- D. Analyses with alternative comparator arm treatment composition (3 analyses)
- E. Analyses using alternative synthesis methods for indirect treatment comparisons (18 analyses)
- F. Analyses with alternative baseline age (2 analyses)
- G. Explorations of treatment stopping rules (4 analyses)
- H. Explorations of alternative utility values (4 analyses)
- I. Analyses testing other modelling assumptions (4 analyses)
    - A scenario with no adverse events modelled (1 analysis)
    - A scenario doubling resource use in the post-progression health state (1 analysis)
    - A scenario that applies IRRC-assessed endpoints for nivolumab (1 analysis)
    - Analysis without half-cycle correction (1 analysis)

To maintain a consistent flow and allow convenient referencing between analyses, we have numbered the scenario analyses conducted by the company from 0-58. Analysis 0 corresponds to the company base case.

**A. Alternative parameterisations of both PFS and OS nivolumab survival**

The company ran a wide variety of alternative survival analyses for PFS and OS in nivolumab patients (see CS Figure 25 and CS Figure 26, pp. 106-107). The alternative survival curves tested for nivolumab in the model included the following: exponential, Weibull, lognormal, and log-logistic. Generalised gamma and Gompertz curves were assessed for goodness of fit in survival modelling, but not utilised in any cost-effectiveness model parameterisations. Analyses 1 to 15 assess alternative parametric forms, whilst Analysis 16 applies Kaplan-Meier curves during the trial follow-up and extrapolates using the survival models selected for the base case.

**Table 50 Alternative nivolumab survival models (PAS Price)**

| # | Analysis parameters[a,b] | Nivolumab Costs | Nivolumab QALYs | SoC Costs | SoC QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|
| 0 | Base Case<br>Lognormal PFS<br>Weibull OS | [redacted] | [redacted] | £21,090 | 0.932 | £19,882 |
| 1 | Exponential PFS<br>Exponential OS | [redacted] | [redacted] | £21,090 | 0.932 | £13,764 |
| 2 | Weibull PFS<br>Exponential OS | [redacted] | [redacted] | £21,090 | 0.932 | £12,199 |
| 3 | Log-logistic PFS<br>Exponential OS | [redacted] | [redacted] | £21,090 | 0.932 | £13,202 |
| 4 | Lognormal PFS<br>Exponential OS | [redacted] | [redacted] | £21,090 | 0.932 | £13,642 |
| 5 | Exponential PFS<br>Weibull OS | [redacted] | [redacted] | £21,090 | 0.932 | £20,132 |
| 6 | Weibull PFS<br>Weibull OS | [redacted] | [redacted] | £21,090 | 0.932 | £17,984 |
| 7 | Log-logistic PFS<br>Weibull OS | [redacted] | [redacted] | £21,090 | 0.932 | £19,264 |
| 8 | Exponential PFS<br>Log-logistic OS | [redacted] | [redacted] | £21,090 | 0.932 | £14,842 |
| 9 | Weibull PFS<br>Log-logistic OS | [redacted] | [redacted] | £21,090 | 0.932 | £13,252 |
| 10 | Log-logistic PFS<br>Log-logistic OS | [redacted] | [redacted] | £21,090 | 0.932 | £14,245 |
| 11 | Lognormal PFS<br>Log-logistic OS | [redacted] | [redacted] | £21,090 | 0.932 | £14,697 |
| 12 | Exponential PFS<br>Lognormal OS | [redacted] | [redacted] | £21,090 | 0.932 | £12,015 |
| 13 | Weibull PFS<br>Lognormal OS | [redacted] | [redacted] | £21,090 | 0.932 | £10,718 |
| 14 | Log-logistic PFS<br>Lognormal OS | [redacted] | [redacted] | £21,090 | 0.932 | £11,562 |
| 15 | Lognormal PFS<br>Lognormal OS | [redacted] | [redacted] | £21,090 | 0.932 | £11,926 |
| 16 | Kaplan-Meier over trial, with lognormal PFS and Weibull OS extrapolation (as in base case) | [redacted] | [redacted] | £21,090 | 0.932 | £19,994 |

ICER, Incremental cost-effectiveness ratio; OS: overall survival; PFS: progression-free survival; SoC: standard of care; QALY, Quality-adjusted life year.

[a] For Analyses 1 to 15, parameters from CS Figure 25 and CS Figure 26 (CS pp.106-107), Results from CS Table 67 (CS p. 148). [b] For Analysis 16, results derived from CS Table 70 (CS p. 150); Kaplan-Meier data was not provided with the CS, but was provided in the answers to clarification questions.

Analysis of goodness of fit for the various survival models showed that there was little difference between the models for PFS on the Akaike Information Criterion and the Bayesian Information Criterion. Figure 11 shows the assessments of survival model fits for PFS and OS.

In the scenario analyses conducted by the company, the survival model chosen for OS was a key driver of cost effectiveness. Alternative models for PFS had a modest impact on ICERs. Analyses 1 to 16 produced ICERs between £10,718 per QALY and £20,132 per QALY. The company stated that the survival curves utilised for the base case could be considered the least beneficial to nivolumab's cost-effectiveness but the most clinically plausible. We found that the choices made by the company in the base case were appropriate extrapolation choices as noted in Section 4.3.5.

**B. Scenarios evaluating alternative models for SoC OS**

The company conducted two analyses that tested the high and low estimates for OS using the exponential curve from data in Cheah and colleagues excluding investigational agents. Table 51 reports the alternative survival curves used and the results of the analysis.

**Table 51 Alternative SoC survival models (PAS Price) (CS Table 69, p. 149)**

| # | Analysis parameters | Nivolumab Costs | Nivolumab QALYs | SoC Costs | SoC QALYs | ICER (£/QALY) | Source |
|---|---|---|---|---|---|---|---|
| 0 | Base Case | [redacted] | [redacted] | £21,090 | 0.932 | £19,882 | Table 63 (p. 136) |
| 17 | High SoC OS from Cheah 2016 (exponential model) λ: 0.0204 | [redacted] | [redacted] | £25,287 | 1.468 | £22,742 | Table 69 (p. 149) |
| 18 | Low SoC OS from Cheah 2016 (exponential model) λ: 0.07296 | [redacted] | [redacted] | £17,135 | 0.528 | £18,613 | |

OS: overall survival; SoC: standard of care.

**C. Analyses with alternative treatment sequences**

The company conducted several analyses where alloSCT was modelled as a 'special transition case'. In this case, a proportion of patients transitioned at six months to a new alloSCT treatment arm. This treatment arm was identical whether patients transitioned from SoC or nivolumab. In the base case, patients' survival after initial therapy is determined by the survival curve for their initial therapy. In the special transition case, the proportion of patients that receive alloSCT have a new

survival curve that is not based on initial treatment. This new survival curve for patients receiving alloSCT was modelled based on data from Cheah and colleagues[2] using the parameters in Table 37. Patients who progressed after alloSCT were assumed to have costs, utilities and survival comparable to the SoC arm, regardless of initial therapy.

Whilst alloSCT survival was derived from Cheah and colleagues,[2] the probability of having an alloSCT was externally derived and applied to both arms using data from Perrot and colleagues,[40] under two assumptions. The first assumption based proportions of patients on probability of alloSCT by the level of response in Perrot and colleagues, whilst the second assumption assumed patients who had complete remission and partial remission had an equivalent probability of alloSCT. The second assumption is based on pooling response across patients with a complete or partial remission in Table 52, resulting in 18.6% of complete and partial responders receiving alloSCT.

**Table 52 Patients receiving alloSCT in the model based on response category (CS Table 74, p. 153)**

| Parameter | Proportion who received alloSCT in CS Scenario Analyses 19 and 20 (Perrot 2016)[40] | Proportion who received alloSCT in CS Scenario Analyses 21 and 22 (pooled CR and PR) |
|---|---|---|
| CR | 18/81 (22.1%) | 27/145 (18.6%) |
| PR | 9/64 (14.1%) | 27/145 (18.6%) |
| SD | 1/18 (5.56%) | 1/18 (5.56%) |

AlloSCT, allogenic stem cell transplant; CR, complete remission; PR, partial remission: SD: stable disease.

The cost of alloSCT was estimated in two ways: using pooled NHS Reference Costs (as in Analyses 19 and 21), and using costs estimated by Radford and colleagues (as in Analyses 20 and 22).[54] Details of the Reference Cost based calculation are reported in Table 53. Radford and colleagues estimated that the cost of alloSCT was £110,374. Under both alloSCT cost assumptions, the monthly cost of treatment after the alloSCT procedure is £91.69, as calculated in TA241.[55] We present further analysis of the cost of alloSCT in Section 4.3.7.

**Table 53 Estimation of ongoing drug and monitoring costs after alloSCT (CS Table 73, p. 153)**

| Resource | Mean | Source | |
|---|---|---|---|
| AlloSCT | £21,672.64 | National Schedule of Reference Costs 2014-15 - Total HRGs: weighted average of total adult bone marrow transplantation costs [codes: SA19A, SA20A, SA21A, SA22A, SA23A].[50] | |
| Monthly cost of AlloSCT | £91.69 | Derivation based on Assessment Group method NICE TA241[55] set out below | |
| **Unit** | **Unit cost** | **Source** | **Monthly cost** |
| **Quarterly specialist appointment** | | | |
| Clinical Haematology consultant-led outpatient attendance | £150.38 per appointment | NHS Reference Costs 2014-15[50] | £50.13 |
| **Immunosuppressive therapies** | | | |
| Ciclosporin 50 mg twice daily plus prednisolone 20 mg once daily (60% of patients) | Ciclosporin: 30 x 50 mg capsules £25.50<br>Prednisolone: 100 x 5 mg tablet £2.20 | MIMS[53] | £54.42 |
| Mycophenolate mofetil 1g twice daily plus prednisolone 20 mg once daily (40% of patients) | Mycophenolate mofetil: 50 x 500 mg tablets £8.05<br>Prednisolone: 100 x 5 mg tablet £2.20 | MIMS[53] | £22.28 |
| **Total management costs** | | | |
| Quarterly specialist appointment plus weighted average of two immunosuppressive regimens | | | £91.69 |
| **Resource costs:** AlloSCT, allogenic stem cell transplant.<br>**Drug and monitoring costs:** Length of month assumed to be 30.475 days<br>National Schedule of Reference Costs 2014-15 – Consultant-led outpatient attendance: Clinical Haematology; Currency code: WF01A; Service code: 303 | | | |

In addition to scenario analyses modelling alloSCT as a separate treatment, the company modelled pre-progression therapy (after discontinuation) using an alternative method. In the base case analysis, it is assumed that patients with progression or discontinuation switch to BSC, comprised of several therapies including chemotherapy and palliative care, dependent on progression status. The company argues that this is a simplification, and in clinical practice, patients are likely to receive chemotherapy in the pre-progression phase if it is clinically feasible. Based on this, the company conducted a scenario analysis where patients discontinuing therapy (either nivolumab or SoC) in the pre-progression phase receive subsequent SoC, subject to the same assumptions and costs as the initial therapy line; BSC is still received as the post-progression therapy.

Table 54 presents the results of the analyses with alternative treatment sequences. In Section 4.4 we have undertaken analyses using Analysis 20, as we believe that this scenario is most representative of the expected costs of alloSCT.

**Table 54 Parameters and results from analyses of alternative treatment sequences**

| # | Analysis parameters[a,b] | Nivolumab Costs | Nivolumab QALYs | SoC Costs | SoC QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|
| 0 | Base Case | [redacted] | [redacted] | £21,090 | 0.932 | £19,882 |
| 19 | Scenario 1: likelihood of alloSCT from Perrot 2016[107] and costs from NHS reference costs,[104] utility = 0.856 | [redacted] | [redacted] | £22,866 | 1.076 | £18,587 |
| 20 | Scenario 2: likelihood of alloSCT from Perrot 2016[107] and costs derived from Radford 2016,[108] utility = 0.856 | [redacted] | [redacted] | £24,880 | 1.076 | £20,433 |
| 21 | Scenario 3: likelihood of alloSCT from Perrot 2016[107], but nivolumab patients with CR and PR assumed equivalent; costs from NHS reference costs,[104] utility = 0.856 | [redacted] | [redacted] | £22,866 | 1.076 | £18,479 |
| 22 | Scenario 2: likelihood of alloSCT from Perrot 2016[107], but nivolumab patients with CR and PR assumed equivalent; costs derived from Radford 2016,[108] utility = 0.856 | [redacted] | [redacted] | £24,880 | 1.076 | £20,489 |
| 23 | Patients receive chemotherapy pre-progression after discontinuing treatment (nivolumab or SoC) | [redacted] | [redacted] | £21,988 | 0.930 | £22,095 |

alloSCT, allogenic stem cell transplant; CR, complete response; ICER, Incremental cost-effectiveness ratio; PR, partial response; SoC: standard of care; QALY, Quality-adjusted life year.
[a] Results derived from CS Table 63 (CS p. 136).
[b] Parameters and results derived from CS Table 75 (CS p. 153).

**D. Analyses with alternative comparator arm treatment composition**

The company conducted several analyses evaluating alternative compositions of SoC treatment. In the base case, OS was modelled with investigational agents excluded. Analysis 24 used digitised Kaplan-Meier data from Cheah and colleagues to fit survival curves for SoC. The company assumed that a lognormal parametric curve was the best model for PFS and Weibull was the best model for OS. They assumed this based on the assumption that a high number of patients in Cheah would have been taking nivolumab. As stated earlier, contact with the authors of Cheah and colleagues revealed that few patients received nivolumab.

An analysis was also conducted that compared nivolumab to SoC wherein SoC consisted only of BSC treatment. The company identified no evidence supporting the efficacy of BSC, so assumed that all patients would enter the model with stable disease and OS derived from the lowest reported by Cheah and colleagues for chemotherapies (exponential parametric fit; λ: 0.07296).[2] PFS was assumed equivalent to base case SoC PFS. Utilities for BSC were derived based on Swinburn and colleagues,[41] weighted to assume 100% occupancy of the stable disease response rate (utility = 0.71). Adverse events and discontinuation were assumed to be zero with patients remaining on BSC until death.

An additional analysis was undertaken where the make-up of SoC, and corresponding costs, were derived from the in-progress STA of brentuximab vedotin.[52] Efficacy was assumed to be equivalent to survival for the entire Cheah and colleagues population (including investigational agents). PFS was modelled using a lognormal curve (μ: 1.074, σ: 0.728) and OS was modelled using a Weibull curve (Scale: 39.438; Shape: 0.959). The make-up of chemotherapy in the brentuximab vedotin appraisal is reported in Table 55.

**Table 55 Chemotherapy composition during brentuximab vedotin appraisal (CS Table 81, p. 157)**

| Component | Usage |
|---|---|
| GEM-Ox: gemcitabine and oxaliplatin | 15% |
| GEM-P: gemcitabine ,cisplatin, methylprednisolone | 15% |
| BEACOPP: Cyclophosphamide, doxorubicin, etoposide, procarbazine, prednisolone, vincristine, bleomycin | 10% |
| DHAP: dexamethasone, cytarabine, cisplatin | 10% |
| Bendamustine | 20% |
| Investigational agents | 5% |
| ChIVPP: chlorambucil, vinblastine, procarbazine, prednisolone | 25% |

Adverse events for the alternative SoC make-up in Analysis 26 were derived from the brentuximab vedotin appraisal (see Table 56). Costs accorded to the new SoC treatment composition are reported in Table 57.

**Table 56 Rate of adverse events for SoC, derived from brentuximab vedotin appraisal (CS Table 82, p. 157)**

| Adverse event | Rate |
|---|---|
| Anaemia | 0.052852 |
| Diarrhoea | 0.014965 |
| Dyspnoea | 0.0000374 |
| Fatigue | 0.002373 |
| Leukopenia | 0.12179 |
| Nausea | 0.031132 |
| Neutropenia | 0.11337 |
| Pyrexia | 0.00032 |
| Thrombocytopenia | 0.147947 |
| Vomiting | 0.054733 |

**Table 57 Costs of SoC in Analysis 26, derived from brentuximab vedotin appraisal (CS Table 83, p. 158)**

| Month | Monthly cost (£) |
|---|---|
| Month 1 | 2041.17 |
| Month 2 | 1932.93 |
| Month 3 | 1780.49 |
| Month 4 | 1508.09 |
| Month 5 | 1027.86 |
| Month 6 | 512.19 |
| Month 7 | 38.91 |
| Month 8+ | 0 |

Table 58 reports the results of Analyses 24-26, in which alternative treatment compositions for SoC are examined. The ERG found an error in CS Analysis 26. When we input the parameters described by the company (CS pp. 155-156), the analysis produced an ICER of £23,608 per QALY not the value reported in Table 58. Examining further models provided by the company in response to clarification questions produced no further insight as to why total SoC costs more than double from the CS base case in an analysis that lowers the cost of SoC.

**Table 58 Analyses using alternative SoC treatment composition**

| # | Analysis parameters | Nivolumab Costs | Nivolumab QALYs | SoC Costs | SoC QALYs | ICER (£/QALY) | Source |
|---|---|---|---|---|---|---|---|
| 0 | Base Case | [redacted] | [redacted] | £21,090 | 0.932 | £19,882 | Table 63 (p. 136) |
| 24 | Including investigational interventions (naive ITC):<br>SoC survival,<br>PFS = Lognormal;<br>μ: 1.074<br>σ: 0.728<br>OS = Weibull;<br>Scale (A): 39.438<br>Shape (B): 0.959<br>Utilities for response and preprogression reflect Cheah whole population. | [redacted] | [redacted] | £18,988 | 1.204 | £22,855 | Table 79 (p. 156) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 25 | Best Supportive Care only<br>OS Exponential<br>λ: 0.07296<br>Utility (SoC)<br>0.71<br>No AE or discontinuation. | [redacted] | [redacted] | £7,630 | 0.528 | £21,580 | Table 80 (p. 157) |
| 26 | SoC composition and AE equivalent to ongoing BTX TA<br>SoC survival<br>PFS = Lognormal;<br>μ: 1.074<br>σ: 0.728<br>OS = Weibull;<br>Scale (A): 39.438<br>Shape (B): 0.959<br>AE derived from BTX appraisal | [redacted] | [redacted] | £45,274 | 1.204 | £12,452 | Table 84 (p. 158), the reported value is incorrect. The correct value is £23,608 per QALY |

BTX, brentuximab vedotin; OS, overall survival; PFS, progression-free survival; SoC: standard of care; QALY, Quality-adjusted life year.

**E. Analyses using alternative synthesis methods for indirect treatment comparisons**

The company conducted analyses modelling SoC based on indirect treatment comparisons described in Section 3.1.7. Table 59 reports parameters and results for analyses for studies in a post-ASCT, post-BTX population, whilst Table 60 reports parameters and results for studies with post-ASCT populations. Analyses adjusted PFS, OS, and composition of treatment response for SoC. As utility scores are based on treatment response, this also changes pre-progression utilities for SoC.

For the purposes of this assessment, the group of studies that is derived from a population that have not necessarily had brentuximab vedotin (Table 60), is not the most relevant population. ICERs for the alternative indirect treatment comparisons ranged between £20,885 per QALY and £24,361 per QALY. We believed that of the analyses conducted in this section, CS Analysis 30 is the most relevant. CS Analysis 30 is derived from the subgroup of studies where 70% of patients or more have had ASCT and brentuximab vedotin, better accounts for uncertainty by using a random effects model, and includes investigative agents in the estimates of efficacy. For these reasons, we have used CS Analysis 30 (in combination with CS Analysis 20) for some scenario analyses in our investigation of uncertainty in Section 4.4.

**Table 59 Alternative ITC comparisons (CS Table 85, p. 160) Post-ASCT, Post-brentuximab vedotin studies, SoC parameters and results**

| # | Analysis parameters[a,b] | Nivolumab Costs | Nivolumab QALYs | SoC Costs | SoC QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|
| 0 | Base Case | [redacted] | [redacted] | £21,090 | 0.932 | £19,882 |
| 27 | Unadjusted ITC, all studies, fixed effects.<br>PFS = λ: 0.1134<br>OS= λ: 0.0204<br>Complete response= [redacted]<br>Partial response= [redacted]<br>Utility (pre-progression)= [redacted] | [redacted] | [redacted] | £23,379 | 1.532 | £24,277 |
| 28 | Unadjusted ITC, all studies, random effects<br>PFS = λ: 0.1134<br>OS= λ: 0.0204<br>Complete response= [redacted]<br>Partial response= [redacted]<br>Utility (pre-progression)= [redacted] | [redacted] | [redacted] | £23,379 | 1.540 | £24,361 |
| 29 | Unadjusted ITC, subgroup,[c] fixed effects<br>PFS = λ: 0.1576<br>OS= λ: 0.0261<br>Complete response= [redacted]<br>Partial response= [redacted]<br>Utility (pre-progression)= [redacted] | [redacted] | [redacted] | £20,149 | 1.239 | £22,626 |
| 30 | Unadjusted ITC, subgroup,[c] random effects<br>PFS = λ: 0.1576<br>OS= λ: 0.0261<br>Complete response= [redacted]<br>Partial response= [redacted]<br>Utility (pre-progression)= [redacted] | [redacted] | [redacted] | £20,149 | 1.236 | £22,686 |
| 31 | MAIC ITC, all studies, fixed effects.<br>PFS = λ: 0.1169<br>OS= λ: 0.0222<br>Complete response= [redacted]<br>Partial response= [redacted]<br>Utility (pre-progression)= [redacted] | [redacted] | [redacted] | £22,554 | 1.435 | £23,605 |
| 32 | MAIC ITC, all studies, random effects<br>PFS = λ: 0.1169<br>OS= λ: 0.0222 | [redacted] | [redacted] | £22,554 | 1.442 | £23,681 |

| # | Analysis parameters[a,b] | Nivolumab Costs | Nivolumab QALYs | SoC Costs | SoC QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|
| | Complete response= [redacted]<br>Partial response= [redacted]<br>Utility (pre-progression)= [redacted] | | | | | |
| 33 | MAIC ITC, subgroup,[c] fixed effects<br>PFS = λ: 0.1602<br>OS= λ: 0.0277<br>Complete response= [redacted]<br>Partial response= [redacted]<br>Utility (pre-progression)= [redacted] | [redacted] | [redacted] | £19,651 | 1.170 | £22,298 |
| 34 | MAIC ITC, subgroup,[c] random effects<br>PFS = λ: 0.1602<br>OS= λ: 0.0277<br>Complete response= [redacted]<br>Partial response= [redacted]<br>Utility (pre-progression)= [redacted] | [redacted] | [redacted] | £19,651 | 1.177 | £22,357 |
| 35 | MAIC ITC, Cheah (overall)<br>PFS = λ: 0.2064<br>OS= λ: 0.0292<br>Complete response= [redacted]<br>Partial response= [redacted]<br>Utility (pre-progression)= [redacted] | [redacted] | [redacted] | £18,349 | 1.086 | £22,079 |
| 36 | MAIC ITC, Cheah (no investigational agents)<br>PFS = λ: 0.1673<br>OS= λ: 0.0387<br>Complete response= [redacted]<br>Partial response= [redacted]<br>Utility (pre-progression)= [redacted] | [redacted] | [redacted] | £17,338 | 0.886 | £20,885 |

ICER, Incremental cost-effectiveness ratio; MAIC ITC, matching-adjusted indirect comparisons Indirect treatment comparison; OS, overall survival; PFS, progression-free survival SoC: standard of care; QALY, Quality-adjusted life year.

[a] Results for the base case from CS Table 63 (CS p. 136)

[b] Parameters and results for CS Analyses 27-36 derived from CS Table 85 (CS p. 159)

[c] Subgroup of SLR studies based on those studies where subgroup of post-ASCT post-BTX population is reported or where >70% of patients match this criteria; this includes efficacy of investigational agents.

**Table 60 Alternative ITC comparisons (CS Table 85, p. 160) Post-ASCT studies, SoC parameters and results**

| # | Analysis parameters[a,b] | Nivolumab Costs | Nivolumab QALYs | SoC Costs | SoC QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|
| 0 | Base Case | [redacted] | [redacted] | £21,090 | 0.932 | £19,882 |
| 37 | Unadjusted ITC, all studies, fixed effects<br>PFS = λ: 0.0640<br>OS= λ: 0.0246<br>Complete response= [redacted]<br>Partial response= [redacted]<br>Utility (pre-progression)= [redacted] | [redacted] | [redacted] | £23,970 | 1.456 | £23,204 |
| 38 | Unadjusted ITC, all studies, random effects<br>PFS = λ: 0.0640<br>OS= λ: 0.0246<br>Complete response= [redacted]<br>Partial response= [redacted]<br>Utility (pre-progression)= [redacted] | [redacted] | [redacted] | £23,970 | 1.462 | £23,262 |
| 39 | Unadjusted ITC, subgroup,[c] fixed effects<br>PFS = λ: 0.0928<br>OS= λ: 0.0305<br>Complete response= [redacted]<br>Partial response= [redacted]<br>Utility (pre-progression)= [redacted] | [redacted] | [redacted] | £20,953 | 1.163 | £21,733 |
| 40 | Unadjusted ITC, subgroup,[c] random effects<br>PFS = λ: 0.0928<br>OS= λ: 0.0305<br>Complete response= [redacted]<br>Partial response= [redacted]<br>Utility (pre-progression)= [redacted] | [redacted] | [redacted] | £20,953 | 1.167 | £21,764 |
| 41 | MAIC ITC, all studies, fixed effects.<br>PFS = λ: 0.0615<br>OS= λ: 0.0239<br>Complete response= [redacted]<br>Partial response= [redacted]<br>Utility (pre-progression)= [redacted] | [redacted] | [redacted] | £24,384 | 1.500 | £23,477 |

| # | Analysis parameters[a,b] | Nivolumab Costs | Nivolumab QALYs | SoC Costs | SoC QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|
| 42 | MAIC ITC, all studies, random effects<br>PFS = λ: 0.0615<br>OS= λ: 0.0239<br>Complete response= [redacted]<br>Partial response= [redacted]<br>Utility (pre-progression)= [redacted] | [redacted] | [redacted] | £24,384 | 1.506 | £23,540 |
| 43 | MAIC ITC, subgroup,[c] fixed effects<br>PFS = λ: 0.0881<br>OS= λ: 0.0294<br>Complete response= [redacted]<br>Partial response= [redacted]<br>Utility (pre-progression)= [redacted] | [redacted] | [redacted] | £21,400 | 1.206 | £21,918 |
| 44 | MAIC ITC, subgroup,[c] random effects<br>PFS = λ: 0.0881<br>OS= λ: 0.0294<br>Complete response= [redacted]<br>Partial response= [redacted]<br>Utility (pre-progression)= [redacted] | [redacted] | [redacted] | £21,400 | 1.209 | £21,951 |



ICER, Incremental cost effectiveness ratio; MAIC ITC, matching adjusted indirect comparisons Indirect treatment comparison; OS, overall survival; PFS, progression-free survival SoC: standard of care; QALY, Quality-adjusted life year.

[a] Results for the base case from CS Table 63 (CS p. 137)

[b] Parameters and results for CS Analyses 37-44 derived from CS Table 85 (CS p. 158)

[c] Subgroup of SLR studies based on those studies where subgroup of post-ASCT population is reported or where >70% of patients match this criteria; this includes efficacy of investigational agents.

A full critique of the alternative synthesis methods used in Analysis 27-44 is reported in Section 3.1.7. In brief, the MAIC methods lacked sufficient power and it was unclear how the matching criteria were chosen or whether only the most relevant criteria were included. Additionally, all survival analyses assume an exponential curve, which was insufficiently justified.

**F. Analyses with alternative baseline age**

The company undertook two analyses to represent the bimodal age distribution of classical Hodgkin lymphoma. The parameters of these cohorts and the results of the analyses are reported in Table 61.

**Table 61 Alternative baseline age (CS Table 86, p. 162)**

| # | Analysis parameters[a,b] | Nivolumab Costs | Nivolumab QALYs | SoC Costs | SoC QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|
| 0 | Base Case | [redacted] | [redacted] | £21,090 | 0.932 | £19,882 |
| 45 | Age 20, alloSCT likelihood of alloSCT from Perrot 2016 and costs from NHS reference costs | [redacted] | [redacted] | £22,193 | 1.101 | £18,037 |
| 46 | Age 70, BSC assumed to be the most appropriate comparator, (OS derived from the lowest reported by Cheah 2016 for chemotherapies (exponential parametric fit; λ: 0.07296); PFS was assumed to be equivalent to the PFS applied in the base case for SoC, due to the evidence supporting comparable PFS for non-investigational agent) | [redacted] | [redacted] | £7,561 | 0.518 | £23,226 |

alloSCT, allogenic stem cell transplant; ICER, Incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; SoC: standard of care; QALY, Quality-adjusted life year.
[a] Results for the base case from CS Table 63 (CS p. 137).
[b] Parameters and results for CS Analyses 45-46 derived from CS Table 86 (CS p. 162).

**G. Explorations of treatment stopping rules**

In the base case analysis, it is assumed that patients in both treatment arms discontinue therapy at the time of progression or due to the rate of discontinuation, which was derived from nivolumab patient-level data. This is likely to reflect clinical practice in most patients and with most therapies, and also provides a conservative assessment of incidence of discontinuation due to AEs during SoC. However, clinical practice may vary, particularly with the use of nivolumab, where treatment may be continued following progression due to the novel mechanism of action. Additionally, clinicians may wish to stop treatment in patients responding at one year.

The following scenario analyses were conducted:

- Patients in the nivolumab arm achieving CR and remaining on initial therapy at 12 months cease to receive therapy costs and incur AEs until discontinuation or progression.
- Patients in the nivolumab arm achieving CR or PR and remaining on initial therapy at 12 months cease to receive therapy costs and incur AEs until discontinuation or progression.
- Patients in the nivolumab arm no longer switch treatment at progression. Additionally, the nivolumab patient-level data-derived treatment discontinuation curve was adjusted to include

discontinuation due to all causes, including progression, with the intent of reflecting potential nivolumab use in clinical practice (lognormal curve; μ: 2.732; σ: 1.057)

- Patient discontinuation for reasons other than death or progression was assumed to be zero; on progression, patients were assumed to switch to therapies in line with base case assumptions.

It should be noted that these analyses assume that the clinical benefit of nivolumab remains the same when applying these assumptions around treatment duration; the company argued that this can be considered conservative, as treatment guidelines and clinicians are unlikely to use these treatment durations where efficacy is impacted. Results from these analyses are detailed in Table 62.

**Table 62 Alternative assumptions around treatment duration (stopping rules) (CS Table 87, p.163)**

| # | Analysis parameters[a,b] | Nivolumab Costs | Nivolumab QALYs | SoC Costs | SoC QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|
| 0 | Base Case | [redacted] | [redacted] | £21,090 | 0.932 | £19,882 |
| 47 | Patients in the nivolumab arm achieving CR and remaining on initial therapy at 12 months cease to receive therapy costs and incur AEs until discontinuation or progression. | [redacted] | [redacted] | £21,090 | 0.932 | £17,436 |
| 48 | Patients in the nivolumab arm achieving CR or PR and remaining on initial therapy at 12 months cease to receive therapy costs and incur AEs until discontinuation or progression. | [redacted] | [redacted] | £21,090 | 0.932 | £13,632 |
| 49 | Patients in the nivolumab arm no longer switch treatment at progression. Additionally, the nivolumab patient-level data-derived treatment discontinuation curve was adjusted to include discontinuation due to all causes, including progression, with the intent of reflecting potential nivolumab | [redacted] | [redacted] | £21,090 | 0.932 | £16,186 |

| # | Analysis parameters[a,b] | Nivolumab Costs | Nivolumab QALYs | SoC Costs | SoC QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|
| | use in clinical practice (lognormal curve; μ: 2.732; σ: 1.057) | | | | | |
| 50 | Patient discontinuation for reasons other than death or progression were assumed to be zero; on progression, patients were assumed to switch to therapies in line with base case assumptions. | [redacted] | [redacted] | £21,090 | 0.932 | £29,573 |

AE, adverse events; CR, complete response; ICER, Incremental cost-effectiveness ratio; PR, partial response; SoC: standard of care; QALY, Quality-adjusted life year.
[a] Results for the base case from CS Table 63 (CS p. 137)
[b] Parameters and results for CS Analyses 47-50 derived from CS Table 87 (CS p. 163)

**H. Explorations of alternative utility values**

Table 63 provides alternative utility parameters and the results of analyses using these parameters. The ERG considered that Analysis 51 presents the most realistic representation of post-progression utility for SoC. In ERG scenario analyses conducted in Section 4.4 we assume that SoC post-progression utility is equivalent to that of nivolumab, as in Analysis 51.

**Table 63 Alternative utility scores (CS Table 88, p. 164)**

| # | Analysis parameters[a,b] | Nivolumab Costs | Nivolumab QALYs | SoC Costs | SoC QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|
| 0 | Base Case | [redacted] | [redacted] | £21,090 | 0.932 | £19,882 |
| 51 | Comparator post-progression utility set equal to nivolumab post-progression utility<br>Post progression = [redacted] | [redacted] | [redacted] | £21,090 | 1.503 | £24,983 |
| 52 | Nivolumab post-progression utility set equal to comparator post-progression utility<br>Post progression = 0.38 | [redacted] | [redacted] | £21,090 | 0.932 | £33,167 |
| 53 | Swinburn 2015 used to derive utility for pre- and post-progression in both arms | [redacted] | [redacted] | £21,090 | 0.932 | £34,332 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Pre-progression = 0.76<br>Post-progression = 0.38 | | | | | |
| 54 | Response-specific pre-progression utilities applied<br>Nivolumab<br>CR = [redacted]<br>PR = [redacted]<br>SD = [redacted]<br>post-progression = [redacted]<br>SoC<br>CR = 0.91<br>PR = 0.79<br>SD = 0.71<br>post-progression = 0.38 | [redacted] | [redacted] | £21,090 | 0.932 | £19,930 |

CR, complete response; ICER, Incremental cost-effectiveness ratio; PR, partial response; SD, stable disease; SoC, standard of care; QALY, Quality-adjusted life year

[a] Results for the base case from CS Table 63 (CS p. 137).

[b] Parameters and results for CS Analyses 51-54 derived from CS Table 88 (CS p. 164).

**I. Analyses testing other modelling assumptions**

Several analyses that did not fall under other classifications were conducted by the company. Analysis 55 presents results without half-cycle correction. Analysis 56 assumes that neither SoC nor nivolumab have adverse events. The company postulated that available utilities may already account for the toxicity of therapies, which might make utilising disutilities for adverse events double counting, so conducted Analysis 56. Analysis 57 doubles post-progression costs. Analysis 58 applies RRC-assessed endpoints for nivolumab. Table 64 reports the results of these analyses.





**Table 64 CS Analyses testing other modelling assumptions**

| # | Analysis parameters | Nivolumab Costs | Nivolumab QALYs | SoC Costs | SoC QALYs | ICER (£/QALY) | Source |
|---|---|---|---|---|---|---|---|
| 0 | Base Case | [redacted] | [redacted] | £21,090 | 0.932 | £19,882 | Table 63 (p. 137) |
| 55 | No half-cycle correction | [redacted] | [redacted] | £23,732 | 0.960 | £19,730 | Table 70 (p. 150) |
| 56 | Assume that utility scores from studies include disutilities for AE, no AEs modelled | [redacted] | [redacted] | £19,233 | 0.951 | £20,580 | Table 89 (p.164) |
| 57 | Alternative post-progression costs: resource use doubles post progression | [redacted] | [redacted] | £24,978 | 0.932 | £21,218 | Table 90 (p.165) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 58 | Application of IRRC-assessed endpoints for nivolumab<br>PFS<br>μ: 2.656<br>σ: 1.121<br>Response rates<br>CR: [redacted]<br>PR: [redacted]<br>Utilities<br>Pre-progression: [redacted]<br>Post-progression: [redacted] | [redacted] | [redacted] | £21,090 | 0.932 | £17,617 | Table 91 (p. 165) |

AE, adverse events; CR, complete response; ICER, Incremental cost-effectiveness ratio; IRRC, independent regulatory review committee; PR, partial response; SoC: standard of care;

**Summary**

The company conducted a large number of scenario analyses. All 58 scenario analyses required manual modification of input parameters in order to run and validate analyses. The ERG was unable to replicate some analyses, which led to requests for clarification on how analyses were run and updated analysis parameters were received from the company. The company complied with the clarification requests, providing both unrounded input values and versions of the model that allowed running alternative analyses with full explanation of the methods. All analyses produced results under £50,000 per QALY (end-of-life cost-effectiveness threshold) and only two analyses produced results above £30,000 per QALY (Analysis 52 and Analysis 53), both analyses assessed alternative post-progression utility scores. In the CS exploratory analyses Nivolumab appears robust to parameter uncertainty. There are some unresolved uncertainties that we explore in Section 4.4.



#### 4.3.10.3 Probabilistic Sensitivity Analysis (PSA)

The company undertook assessment of joint parameter uncertainty using a PSA. All relevant parameters, including costs and survival were included in the PSA. Costs were sampled using gamma distributions. Age was sampled using the normal distribution. Proportions and percentages were sampled using the beta distribution.

In general, each parameter included in the PSA is sampled independently; however, there are several exceptions to this approach. The model allows health state costs to be specified by treatment and response state; however, the base case analysis applies pre-progression and post-progression cost regardless of response or therapy arm. Thus, within the PSA, treatment arm-

specific and response-state specific health state costs are not sampled independently, but are linked so that health state costs are varied similarly.

Similarly, response and survival parameters are sampled differently to other parameters, due to the paucity of data around SoC. Mean PFS and OS associated with SoC are sampled according to a normal distribution based on the specified standard error level, due to a lack of confidence bounds on the fit. The mean PFS and OS data are then transformed to the exponential rate required for the parametric survival curve generation. When sampling SoC response rates, the inverse relative risk of response versus nivolumab is sampled according to a lognormal distribution, and then the nivolumab mean response rate is divided by this deviate to provide the SoC response rate sample.

The company conducted probabilistic sensitivity analyses under two sets of assumptions: one where unknown standard errors were assumed to be 10% of the parameter mean, and one where unknown standard errors were assumed to be 20% of the parameter mean. We believe that of these two sets of simulations, the simulation with 20% uncertainty is more realistic. However, we note that given the paucity of data in the treatment population even larger estimates of uncertainty may be appropriate. In general, the distributions chosen and assumptions for the PSA were reasonable.

Due to the considerable time (4 hours 40 minutes) needed to run the PSA, the ERG has not tested larger uncertainty assumptions. At a willing-to-pay of £30,000 per QALY, nivolumab was cost-effective in 94.8% (10% SE) to 96.6% (20% SE) of simulations. If the willingness-to-pay threshold is £50,000 per QALY, nivolumab is cost-effective in 100% of simulations. Probabilistic ICERs were not

reported. Figure 16 shows cost-effectiveness planes for nivolumab compared to SoC.


Figure 17  shows cost-effectiveness acceptability curves (CEAC) for nivolumab compared to SoC.


**Figure 16 Cost-effectiveness plane (CS Figure 36, p. 143)**


**Figure 17 Cost-effectiveness acceptability curve (CEAC) (CS Figure 37, p. 143)**

## 4.4 Additional work undertaken by the ERG

There were a number of areas where the ERG considered the CS base case to be limited. It included the survival benefits of alloSCT, but none of the costs of alloSCT; the population for SoC did not include those patients that received; utility scores were not based on EQ-5D values for all interventions; response weighted utilities were not precisely calculated; and post-progression utilities produced exaggerated differences between nivolumab and SoC. The ERG believes that CS Analysis 20 (CS alloSCT Scenario B, p.153) addresses concerns about the costs of alloSCT not being adequately represented in the base case, but this analysis carries forward some issues of the base case and introduces other issues. CS Analysis 20 allows alloSCT as a treatment administered as a special transition at six months wherein patients have the full costs and benefits of alloSCT and survival modelled independently from the baseline treatment curve. We have used CS Analysis 20 as the structural basis for additional analysis by the ERG. In each analysis conducted in this section,

parameters within CS Analysis 20 are substituted for alternative values, resulting in analyses that are combinations of CS Analysis 20 and other data, including data from other company analyses.

CS Analysis 20 uses response based estimates from Perrot and colleagues to assign the proportion of patients that have an alloSCT at six months. The model assumes that all alloSCTs happen at this time. In order for this assumption to be valid, the estimated proportion of patients receiving alloSCT treatment should be similar to that observed in the trials. As Section 4.3.8 shows, the estimates produced by Perrot and colleagues underestimate alloSCTs. Additionally, the company assumes that the post alloSCT survival can be defined by the post alloSCT survival in patients receiving alloSCT in the Cheah study. These data are based on 14 patients that are already included in OS data for SoC, so this is a form of double counting. Finally, the post-progression utility estimate for alloSCT is only 0.38. As we have discussed in Section 4.3.6, we would expect post-progression utility to be similar across all interventions, and an independent study found that utility values for brentuximab vedotin were similar to placebo after ASCT at all time points.[42]

Table 65 lists the analyses carried out by the ERG, along with their justifications, and how these analyses changed parameters from the CS. These analyses culminate in the ERG base case (ERG 10), which we believe is the most representative analysis for the cost-effectiveness of nivolumab compared to SoC.

In the company model for CS Analysis 20, only one survival curve may be applied at a time and this curve is applied to both interventions. In the CS Analysis 20, this curve is derived from Cheah and colleagues survival data for patients who have alloSCT (see Table 54). In order to analyse separate curves for each intervention (ERG6, ERG9, ERG17, ERG18) the model must be run twice, and the necessary results data (costs and QALYs) extracted and ICERs calculated.

The ERG base case (ERG10) uses data derived from all patients in Cheah and colleagues, including those who received investigational agents. We have chosen to use Cheah and colleagues data for our base case SoC efficacy data instead of data from the ITC because the other single-arm trials in the ITC (see Section 3.1.7) consist primarily of trials exploring purely investigational agents. This can be expected to bias the comparisons against nivolumab as current SoC consists of a mix of standard chemotherapies and investigational agents. We have investigated using efficacy data from the ITC in several scenario analyses (ERG9, ERG17, ERG18).

In ERG4, ERG9, ERG17, and ERG18, utilities are derived from EQ-5D data from CheckMate 205. Utilities are weighted by the proportions of people in each of the complete remission, partial remission and stable disease states for pre-progression utilities (see Section 4.3.6). In ERG9, ERG17, and ERG18, the health state weightings are derived from CS Analysis 30 (see Table 59). ERG9, ERG 17, and ERG18 also use parametric survival curves derived from CS Analysis 30 in combination with structural assumptions from CS Analysis 20 and other parameter estimates.

**Table 65 Assumptions for ERG exploratory analyses subsequent to CS analysis 20 (alloSCT scenario B)**

| # | Analysis Description | Analysis 20 parameters | ERG analysis parameters | Justification |
|---|---|---|---|---|
| 0 | Base Case | See CS Table 63, p. 137 | -- | |
| 20 | CS alloSCT Scenario B (CS Table 75, p. 153) | See CS Table 75, p. 153 | -- | |
| ERG1 | Alternative special transition case, alloSCT rates derived from trials | Both nivolumab and SoC have transitions based on Perrot 2016<br><br>Special transition case (all)<br>Complete remission: 22.22%<br>Partial remission: 14.06%<br>Stable disease: 5.56% | Special transition case based on observed alloSCT in Cheah for SoC and in nivolumab trials for nivolumab<br><br>Special transition case (nivolumab)<br>All levels of response: [redacted]<br><br>Special transition case (SoC)<br>All levels of response: 17.72% (14/79) | The company analysis underestimates the proportion of patients receiving alloSCT compared to observed alloSCT procedures in the studies. (see Section 4.3.8) |
| ERG2 | Alternative SoC survival population (including investigational agents) | PFS Exponential<br>λ: 0.160<br><br>OS Exponential<br>λ: 0.036 | PFS Exponential<br>λ: 0.0253<br><br>OS Exponential<br>λ: 0.025 | The company's base case does not include investigational agents. The ERG considered it more appropriate to use the overall population |

| # | Analysis Description | Analysis 20 parameters | ERG analysis parameters | Justification |
|---|---|---|---|---|
| | | | | (including investigational agents) (section 4.3.5) |
| ERG3 | Alternative nivolumab pre-progression utilities | [redacted] | [redacted] | The utilities based on the weighted average of response states are lower than the average value reported in the CS. |
| ERG4 | Alternative SoC pre-progression utilities (CheckMate 205 utilities weighted by response in Cheah) | 0.76 | [redacted] | The Swinburn utility values were based on the Time Trade Off method and not derived from patients with HL. CheckMate 205 utilities are EQ-5D and derived from patients. Response weighting allows for showing treatment effect of nivolumab. |
| ERG5 | SoC post-progression utility same as nivolumab post-progression utility | 0.38 | [redacted] | The difference in post-progression utility is not plausible (section 4.3.6). |
| ERG6 | alloSCT survival modelled using original treatment OS curves instead of lognormal curve from Cheah | All Treatments<br>OS Lognormal<br>μ: 9.252<br>σ: 3.551 | Nivolumab<br>OS Weibull<br>A (Scale): 76.742<br>B (Shape): 1.326<br><br>SoC<br>OS Exponential<br>λ: 0.025 | Using the lognormal curve provides an estimate of survival that is significantly greater than the original estimates based on the trial data. As the original survival modelling included patients having alloSCT, there should not be a significant boost in projected survival. (see Section 4.3.5) |
| ERG7 | Alternative post-progression utility for alloSCT intervention | 0.38 | [redacted] | This allows post-progression utility to be consistent between all treatments. (see Section 4.3.6) |
| ERG8 | ERG calculated costs for SoC (omitting miniBEAM and dexaBEAM) | Section 4.3.7Table 43 | Table 43 | miniBEAM and dexaBEAM are expensive and not commonly used in UK clinical practice. Their inclusion is not likely to be appropriate (see Section 4.3.7) |
| ERG9 | SoC pre-progression OS, | PFS Exponential<br>λ: 0.160 | PFS Exponential | As discussed in Section 3.1.7 and Section 4.3.10.2 |

| # | Analysis Description | Analysis 20 parameters | ERG analysis parameters | Justification |
|---|---|---|---|---|
| | PFS, and response from CS Analysis 30, utilities weighted using CheckMate 205 values) | OS Exponential λ: 0.036<br><br>Response Complete Remission: [redacted]<br>Partial Remission: [redacted]<br><br>Pre-progression Utility [redacted] | λ: 0.158<br><br>OS Exponential λ: 0.026<br><br>Response Complete Remission: [redacted]<br>Partial Remission: [redacted]<br><br>Pre-progression Utility [redacted] | that ITC methods are appropriate, but are less representative of the composition of SoC than Cheah and colleagues. The primary purpose of this analysis is to explore methodological uncertainty, as the most appropriate method of extrapolation is not entirely clear for this population. |
| ERG10 | ERG Base case combines ERG1 to ERG8 | -- | As above | As stated above |

alloSCT, allogenic stem cell transplant; dexaBEAM, Dexamethasone, carmustine, etoposide, cytarabine and melphalan; miniBEAM, Carmustine, etoposide, cytarabine and melphalan; OS, overall survival; PFS, progression-free survival; SoC, standard of care

We identified a number of further areas of uncertainty that we have explored through sensitivity analyses carried out by modifying some parameters in the ERG base case (ERG10). The additional analyses are as follows:

- There is uncertainty in the cost of SoC. ERG11 examines the ERG base case with costs derived from CS Analysis 20. ERG12 uses costs derived from the brentuximab vedotin STA.
- We conducted additional analyses to investigate uncertainty in survival parameters post-alloSCT, as the data from the nivolumab studies were immature and the data for SoC were based on a small number of patients from an observational dataset. Four additional analyses (ERG13 to ERG16) were conducted that modified alloSCT OS assumptions to account for structural uncertainty in alloSCT OS. PFS was not altered by the ERG analyses undertaken subsequent to the ERG base case.
- As noted in ERG9, there is some uncertainty in the methods that are most appropriate for estimating efficacy. ERG17 and ERG18 analyse the impact on cost-effectiveness of using efficacy (survival, response, utility score) estimates derived from CS Analysis 30.

The assumptions and justifications for ERG Analyses 11-18 are reported in Table 66.

**Table 66 Assumptions for ERG exploratory analyses subsequent to the base case**

| # | Analysis Description | Justification |
|---|---|---|
| ERG11 | ERG Base case with SoC costs derived from CS | As above |
| ERG12 | ERG Base case with SoC costs derived from brentuximab vedotin STA | As above |
| ERG13 | ERG Base case, alloSCT survival from CS Scenario 20 | See CS Table 75, p. 153 |
| ERG14 | ERG Base case, alloSCT survival from nivolumab | OS Weibull<br>A (Scale): 76.742<br>B (Shape): 1.326 |
| ERG15 | ERG Base case, alloSCT survival from SoC including investigational agents | PFS Exponential (λ: 0.0253)<br>OS Exponential (λ: 0.025) |
| ERG16 | ERG Base case, SoC without investigational agents (including alloSCT) | SoC PFS (λ: 0.160)<br>SoC OS (λ: 0.036)<br>SoC alloSCT OS (λ: 0.036) |
| ERG17 | ERG Base Case, SoC survival (PFS, OS before and OS after alloSCT) and response derived from CS Analysis 30, utilities reweighted as in ERG4 | SoC PFS Exponential (λ: 0.158)<br>SoC OS Exponential (λ: 0.026)<br>SoC alloSCT OS (λ: 0.026)<br>Response<br>Complete Remission: [redacted]<br>Partial Remission: [redacted]<br>SoC Pre-progression Utility<br>[redacted] |
| ERG18 | As ERG17, SoC survival (PFS, OS before and OS after alloSCT) and response derived from CS Analysis 30; utilities reweighted as in ERG4; but post alloSCT survival from CS Analysis 30 for all interventions. | SoC PFS Exponential (λ: 0.158)<br>SoC OS Exponential (λ: 0.026)<br>All interventions alloSCT OS (λ: 0.026)<br>SoC Response<br>Complete Remission: [redacted]<br>Partial Remission: [redacted]<br>SoC Pre-progression Utility<br>[redacted] |

alloSCT, allogenic stem cell transplant; OS, overall survival; PFS, progression-free survival; SoC, standard of care

The results of all analyses conducted by the ERG are reported in Table 67. ICERs for the ERG analyses ranged between £18,174 per QALY and £42,226 per QALY with the ERG base case analysis (ERG10) producing an ICER of £36,525 per QALY. The ERG analyses that used alternative survival assumptions for alloSCT whilst maintaining other assumptions of the ERG base case produced ICERs ranging between £25,647 per QALY and £42,226 per QALY. All analyses produced ICERs below the £50,000 per QALY threshold for end-of-life treatments, but several

analyses, including the ERG base case produced ICERs above £30,000 per QALY, the upper bound of the NICE threshold range for cost-effectiveness.

**Table 67 Results of ERG exploratory analyses**

| # | Analysis | Nivolumab | | SoC | | |
|---|---|---|---|---|---|---|
| | | Costs | QALY | Costs | QALY | ICER |
| 0 | Base Case | [redacted] | [redacted] | £21,090 | 0.932 | £19,882 |
| 20 | CS alloSCT Scenario B (CS Table 75, p. 153) | [redacted] | [redacted] | £24,880 | 1.076 | £20,433 |
| ERG1 | Alternative special transition case population | [redacted] | [redacted] | £27,692 | 1.184 | £20,616 |
| ERG2 | Alternative SoC survival (including investigational agents) | [redacted] | [redacted] | £23,756 | 1.278 | £22,348 |
| ERG3 | Alternative nivolumab pre-progression utilities | [redacted] | [redacted] | £24,880 | 1.076 | £20,476 |
| ERG4 | Alternative SoC pre-progression utilities (CheckMate 205 utilities weighted by response in Cheah) | [redacted] | [redacted] | £24,880 | 1.101 | £20,603 |
| ERG5 | SoC post-progression utility same as nivolumab post-progression utility | [redacted] | [redacted] | £24,880 | 1.633 | £25,209 |
| ERG6 | alloSCT survival modelled using original treatment OS curves instead of lognormal curve from Cheah | [redacted] | [redacted] | £23,952 | 0.952 | £21,517 |
| ERG7 | Alternative post-progression utility for alloSCT intervention | [redacted] | [redacted] | £24,380 | 1.212 | £18,174 |
| ERG8 | ERG calculated costs for SoC (omitting miniBEAM and dexaBEAM) | [redacted] | [redacted] | £23,360 | 1.076 | £20,950 |
| ERG9 | SoC OS, PFS, and response from CS Analysis 30, utilities weighted using CheckMate 205 values) | [redacted] | [redacted] | £28,806 | 2.227 | £31,392 |
| ***ERG10*** | ***ERG Base case combines ERG1 to ERG8*** | [redacted] | [redacted] | ***£23,043*** | ***2.102*** | ***£36,525*** |
| ERG11 | ERG Base case with SoC costs derived from CS | [redacted] | [redacted] | £24,465 | 2.102 | £35,684 |
| ERG12 | ERG Base case with SoC costs derived from BTX STA | [redacted] | [redacted] | £19,791 | 2.102 | £38,451 |
| ERG13 | ERG Base case, alloSCT survival from Cheah for both arms | [redacted] | [redacted] | £24,027 | 2.363 | £25,647 |
| ERG14 | ERG Base case, alloSCT survival from nivolumab | [redacted] | [redacted] | £23,233 | 2.150 | £37,489 |

| # | Analysis | Nivolumab | | SoC | | |
|---|---|---|---|---|---|---|
| | | Costs | QALY | Costs | QALY | ICER |
| ERG15 | ERG Base case, alloSCT survival from as SoC including investigational agents | [redacted] | [redacted] | £23,043 | 2.102 | £42,226 |
| ERG16 | ERG Base case, SoC without investigational agents (including alloSCT) | [redacted] | [redacted] | £24,446 | 1.534 | £26,712 |
| ERG17 | ERG Base Case, SoC survival (PFS, OS before and after alloSCT) and response derived from CS Analysis 30, utilities reweighted as in ERG4 | [redacted] | [redacted] | £27,255 | 2.068 | £33,370 |
| ERG18 | ERG Base Case, SoC survival (PFS, OS before and OS after alloSCT) and response derived from CS Analysis 30, utilities reweighted as in ERG5, post alloSCT survival from CS Analysis 30 for all interventions. | [redacted] | [redacted] | £27,255 | 2.068 | £38,575 |

BTX, brentuximab vedotin; alloSCT, allogenic stem cell transplant; dexaBEAM, Dexamethasone, carmustine, etoposide, cytarabine and melphalan; ICER, ICER, Incremental cost-effectiveness ratio; miniBEAM, Carmustine, etoposide, cytarabine and melphalan; OS, overall survival; PFS, progression-free survival; QALY, Quality-adjusted life year; SoC, standard of care.

We compared survival curve estimated OS, CS estimates for OS and the estimates produced by the ERG analyses. As the CS base case did not include investigational agents in the SoC arm, we believe that the ERG base case (Analysis 10) is the closest to a direct estimate of survival from Cheah and colleagues relevant to the decision problem. Table 68 provides the results of the ERG's comparisons.

**Table 68 Comparison of ERG analysis results**

| Analysis | Nivolumab mean years OS | SoC mean years OS |
|---|---|---|
| Survival curve estimate | 5.9 | 2.3 |
| CS base case output | 5.0 | 2.1 |
| CS Analysis 20 (alloSCT Scenario 2, p. 153) | [redacted] | [redacted] |
| ERG Analysis 2 (SoC survival with investigational agents) | [redacted] | [redacted] |
| ERG Analysis 10 (ERG base case) | [redacted] | [redacted] |
| ERG Analysis 13 (alloSCT survival as in CS Analysis 20) | [redacted] | [redacted] |
| ERG Analysis 14 (alloSCT survival with nivolumab OS curve for both interventions) | [redacted] | [redacted] |

| | | |
|---|---|---|
| ERG Analysis 15 (alloSCT survival with SoC OS curve for both interventions) | [redacted] | [redacted] |
| ERG Analysis 16 (SoC without investigational agents, including on alloSCT) | [redacted] | [redacted] |
| ERG Analysis 17 (SoC survival, response from CS Analysis 30) | [redacted] | [redacted] |
| ERG Analysis 18 (SoC survival/response as in ERG Analysis 18, all interventions have SoC OS) | [redacted] | [redacted] |

alloSCT, allogenic stem cell transplant; OS, overall survival; SoC, standard of care.

As can be seen, the CS base case produces significantly lower overall survival estimates for nivolumab than the survival curve estimate. For nivolumab survival, CS Analysis 20 produces a mean OS estimate closest to the survival curve estimate. As the data from the nivolumab study are immature, there is a large amount of uncertainty about extrapolation of overall survival. Clinical experts we consulted were not able to estimate overall survival for patients receiving nivolumab treatment. For SoC, the ERG base case (Analysis 10) should be considered the base comparison for estimating SoC survival as this survival curve includes investigational agents and is derived directly from Cheah and colleagues.

## 4.5 Conclusions of cost effectiveness

The company used a model structure commonly used for economic models of cancer treatments with health states for progression-free survival, progression and death. In addition, patients may discontinue treatment whilst in the progression-free state. The ERG considers the model structure to be appropriate for the decision problem.

The company used methods that are consistent with NICE methodological guidelines. The population, intervention and comparators used in the economic evaluation are consistent with the NICE scope.

The core clinical evidence for nivolumab was from single-arm studies and there are no direct head-to-head trials between nivolumvab and SoC. There is a paucity of evidence available for SoC for patients who have been previously treated with ASCT and brentuximab vedotin. The ERG considers the company has selected the most appropriate study for SoC but cautions that there is considerable uncertainty surrounding the comparison between nivolumab and SoC.

The SoC comparator has been based upon a study by Cheah and colleagues. Some patients within this study received investigational agents. The company has used the population excluding patients

receiving investigational agents. The ERG considers PFS and OS survival should be based upon the total population of Cheah and colleagues, including patients with investigational agents.

The results in the CS are presented with a patient access scheme discount. The CS base case analysis comparing nivolumab to SoC had an ICER of £19,888 per QALY gained. The company provides a large number of scenario analyses to test alternative modelling assumptions including the choice of survival parametric distributions used, utilities, treatment sequences and SoC composition. In general the results from the scenario analyses were robust with only two analyses producing results above £30,000 per QALY gained. The ERG preferred base case produced an ICER of £36,525 per QALY gained.

# 5 End of life

According to the NICE criteria for End of life, the following criteria should be satisfied:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

The company considers the two criteria for end of life. They state that 'patients with relapsed or refractory classical Hodgkin lymphoma following ASCT had a median OS of 19-29 months, depending on therapies received and availability of brentuximab vedotin,[56,57] and this decreases further in patients who do not achieve an initial response following ASCT.[57] OS in relapsed or refractory patients who have received both ASCT and brentuximab vedotin is around two years for OS, but this is obscured by inclusion of the efficacy of clinical trial therapies (47.4 months).[2] When the efficacy of the investigational agents is removed, median OS is estimated to be around 19 months.

The CS states that based on CheckMate 205 or CA209-039 nivolumab is likely to increase survival substantially to an estimated median OS exceeding 42.9 months, although median OS was not reached during these studies.

Based upon this evidence, the company considers that nivolumab meets the criteria for end of life.

The ERG notes that the mean life years of the patients with SoC in the economic model is 2.3 years which is greater than the 24 months specified in the NICE end of life criteria. However, the company base case excludes investigational agents in patients treated with SoC. The ERG considers that the full population of Cheah (i.e. including those treated with investigational agents) to be more representative and for this population OS is 3.3 years. We agree that the results from CheckMate 205 and CA 209-039 are likely to increase the life expectancy of these patients by at least three months. Whilst there is uncertainty around the life expectancy of patients in the non-treated population, the ERG considers, based on the evidence provided by the company, that the NICE criteria for end of life has not been met.

# 6 Innovation

The CS highlights that the innovative nature of nivolumab has already been recognised by the Medicines and Healthcare products Regulatory Agency (MHRA) which awarded nivolumab Promising Innovative Medicine (PIM) status (CS p. 15 and p. 20).

Nivolumab will also be the only treatment with European Medicines Agency (EMA) approval for patients with relapsed or refractory classical Hodgkin lymphoma who have received both ASCT and brentuximab vedotin. Treatment options for this group of patients are limited, and estimates of median PFS and OS are short (The CS indicates not more than 5 months for PFS or 19 months to 2 years for OS depending on whether investigative agents are included when estimating OS).

In comparison to the other chemotherapeutic treatment options for this patient group, which not all patients may tolerate, nivolumab has a fortnightly treatment schedule that patients may find convenient and which may be a well-tolerated therapeutic option.

There is also the potential for nivolumab to act as a bridge to alloSCT in eligible patients. Although there is a mortality risk with alloSCT, it can be a curative treatment option for some patients.

# 7 DISCUSSION

## 7.1 Summary of clinical effectiveness

Two relevant non-comparative single-arm studies of nivolumab were identified and described in the CS providing evidence on a total of 193 patients with classical Hodgkin lymphoma who had failed prior ASCT and brentuximab vedotin. Available follow-up extends to 15.7 months for 80 patients, 8.9 months for 98 patients and 23.3 months for the remaining 15 patients. Median overall survival has not yet been reached in either study.

To obtain an estimate of the comparative effectiveness of nivolumab in comparison to potential comparators indirect comparisons were conducted. A systematic review identified 12 studies reporting data for potential comparators but these data were limited in terms of quality and outcomes reported. Comparator studies were predominantly phase 1 or 2 single-arm studies and over half of them were only reported as conference abstracts.

The extent to which the benefits of nivolumab exceed those of potential comparator treatments is very uncertain due to absence of direct head-to-head comparisons and the immaturity of the evidence base both for nivolumab and for the potential comparator treatments.

No evidence was presented for people with relapsed or refractory classical Hodgkin lymphoma following at least two prior therapies when ASCT is not a treatment option.

## 7.2 Summary of cost effectiveness

The CS includes evidence on the cost-effectiveness of nivolumab compared to SoC in patients with refractory or relapsed Hodgkin lymphoma following ASCT and brentuximab vedotin. The model structure adopted for the economic evaluation is generally appropriate and consistent with the clinical disease pathway. The model contains health states of progression-free, progressed and death and uses survival curves based upon the clinical evidence. The clinical evidence comprises of single-arm studies. There is a paucity of evidence available for SoC for patients who have been previously treated with ASCT and brentuximab vedotin. The ERG considers that there is considerable uncertainty surrounding the comparison between nivolumab and SoC.

The CS presents results with a PAS discount for nivolumab. The CS model results produce an ICER of £19,888 per QALY for nivolumab compared to SoC. The company conducted deterministic

sensitivity analyses for the input parameters and a large number of scenario analyses varying model assumptions. The model results were robust to changes in input values and assumptions. The company's probabilistic sensitivity analyses showed there is a probability of 94.8% and 100% that nivolumab is cost effective at a willingness to pay of £30,000 and £50,000 respectively.

The ERG conducted sensitivity analyses evaluating alternative overall survival for SoC, utility estimates, lower costs for SoC, and including the effects and costs of alloSCT. The ERG's alternative base case analysis for nivolumab compared to SoC produces an ICER of £36,525 per QALY.

# 8 REFERENCES

1. Collins GP, Parker AN, Pocock C, Kayani I, Sureda A, Illidge T, et al. Guideline on the management of primary resistant and relapsed classical Hodgkin lymphoma. *Br J Haematol* 2014;164(1):39-52.
2. Cheah CY, Chihara D, Horowitz S, Sevin A, Oki Y, Zhou S, et al. Patients with classical Hodgkin lymphoma experiencing disease progression after treatment with brentuximab vedotin have poor outcomes. *Ann Oncol* 2016;27(7):1317-23.
3. Bristol-Myers Squibb Pharmaceuticals Ltd. Interim Clinical Study Report for Study CA209205. Non-Comparative, Multi-Cohort, Single-Arm, Open-Label, Phase 2 Study of Nivolumab (BMS-936558) in Classical Hodgkin Lymphoma (cHL) Subjects After Failure of Autologous Stem Cell Transplant (ASCT). 2016.
4. Younes A, Santoro A, Shipp M, Zinzani PL, Timmerman JM, Ansell S, et al. Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial. *Lancet Oncol* 2016;17(9):1283-94.
5. Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med* 2015;372(4):311-9.
6. Bristol-Myers Squibb Pharmaceuticals Ltd. Interim Clinical Study Report for Study CA209039: A Phase 1 Dose Escalation Study to Investigate the Safety, Pharmacokinetics, Immunoregulatory Activity, and Preliminary Antitumor Activity of Anti-Programmed-Death 1 (PD-1) Antibody (Nivolumab, BMS-936558) and the Combinations of Nivolumab and Ipilimumab or Nivolumab and Lirilumab in Subjects with Relapsed or Refractory Hematologic Malignancy. 2016.

7. Bristol-Myers Squibb Pharmaceuticals Ltd. NCT02181738: Non-Comparative, Multi-Cohort, Single Arm, Open-Label, Phase 2 Study of Nivolumab (BMS-936558) in Classical Hodgkin Lymphoma (cHL) Subjects. 2016.
8. Bristol-Myers Squibb Pharmaceuticals Ltd. Clinical Protocol CA209205: Non-Comparative, Multi-Cohort, Single Arm, Open-Label, Phase 2 Study of Nivolumab (BMS-936558) in classical Hodgkin Lymphoma (cHL) Subjects (CheckMate 205: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 205). 2014.
9. Bristol-Myers Squibb Pharmaceuticals Ltd. NCT01592370: A Phase I Dose Escalation Study to Investigate the Safety, Pharmacokinetics, Immunoregulatory Activity, and Preliminary Antitumor Activity of Anti-Programmed-Death 1 (PD-1) Antibody (Nivolumab, BMS936558) and the Combination of Nivolumab and Ipilimumab or Nivolumab and Lirilumab in Subjects With Relapsed or Refractory Hematologic Malignancy. 2016.
10. Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care. York Publishing Services Ltd.: CRD, 2009.
11. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* 1998;52(6):377-84.
12. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]: The Cochrane Collaboration, 2011.
13. Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, et al. Evaluating non-randomised intervention studies. *Health Technol Assess* 2003;7(27):iii-x, 1-173.
14. Armand P, Shipp MA, Ribrag V, Michot J-M, Zinzani PL, Kuruvilla J, et al. Programmed Death-1 Blockade With Pembrolizumab in Patients With Classical Hodgkin Lymphoma After Brentuximab Vedotin Failure. *Journal of Clinical Oncology* 2016;34(31):3733-39.
15. Armand P, Shipp MA, Ribrag V, Michot J-M, Zinzani PL, Gutierrez M, et al. PD-1 Blockade with Pembrolizumab in Patients with Classical Hodgkin Lymphoma after Brentuximab Vedotin Failure: Safety, Efficacy, and Biomarker Assessment. *Blood* 2015;126(23):584-84.
16. Moskowitz CH, Ribrag V, Michot J-M, Martinelli G, Zinzani PL, Gutierrez M, et al. PD-1 Blockade with the Monoclonal Antibody Pembrolizumab (MK-3475) in Patients with Classical Hodgkin Lymphoma after Brentuximab Vedotin Failure: Preliminary Results from a Phase 1b Study (KEYNOTE-013). *Blood* 2014;124(21):290-90.
17. Bartlett NL, Chen R, Fanale MA, Brice P, Gopal A, Smith SE, et al. Retreatment with brentuximab vedotin in patients with CD30-positive hematologic malignancies. *J Hematol Oncol* 2014;7:24.

18. Batlevi CL, Kasamon Y, Bociek RG, Lee P, Gore L, Copeland A, et al. ENGAGE- 501: phase II study of entinostat (SNDX-275) in relapsed and refractory Hodgkin lymphoma. *Haematologica* 2016;101(8):968-75.
19. Zinzani PL, Vitolo U, Viviani S, Corradini P, Motta G, Tani M, et al. Safety and efficacy of single-agent bendamustine after failure of brentuximab vedotin in patients with relapsed or refractory hodgkin's lymphoma: experience with 27 patients. *Clinical lymphoma, myeloma & leukemia* 2015;15(7):404-8.
20. Chen RW, Zinzani PL, Fanale MA, Armand P, Johnson N, Ribrag V, et al. Pembrolizumab for relapsed/refractory classical Hodgkin lymphoma (R/R cHL): phase 2 KEYNOTE-087 study. *2016 ASCO Annual Meeting* 2016.
21. Moskowitz C, Zinzani PL, Fanale MA, Armand P, Johnson N, Ribrag V, et al. Multicohort phase 2 study of pembrolizumab for relapsed/refractory classical Hodgkin lymphoma (R/R CHL): KEYNOTE-087 *21st Congress of the European Hematology Association June 9-12, 2016; Copenhagen, Denmark.*; 2016.
22. Christian B, Kopko A, Fehniger TA, Bartlett NL, Blum KA. A Phase I Trial of the Histone Deacetylase (HDAC) Inhibitor, Panobinostat, in Combination with Lenalidomide in Patients with Relapsed/Refractory Hodgkin's Lymphoma (HL) *Blood*; 2012.
23. Falchi L, Sawas A, Deng C, Amengual JF, Colbourn DS, Lichtenstein E, et al. Rate of complete metabolic responses to immune checkpoint inhibitors in extremely heavily pre-treated patients with classical Hodgkin's lymphoma and immunoepigenetic priming. *J Clin Oncol* 2016;34(suppl; abstr e19012).
24. Forero-Torres A, Barr P, Diefenbach C, Sher T, Schaub R, Zhou L, et al. A phase 1 study of patients with relapsed or refractory classical Hodgkin lymphoma treated with a P13K delta Inhibitor (INCB040093) alone or in combination with a Selective JAK1 inhibitor (INCB039110) *20th Congress of the European Hematology Association, Vienna, Austria*: Haematologica; 2015.
25. Forero-Torres A, Barr PM, Magid Diefenbach CS, Sher T, Schaub R, Zhou L, et al. A phase 1 study of PI3Kδ inhibitor INCB040093 alone or in combination with selective JAK1 inhibitor INCB039110 in patients with relapsed/refractory hodgkin lymphoma *Hematological Oncology*; 2015.
26. Jasielec J, Kimball AS, Cohen KS, Kline JP, Rapoport A, Petrich AM, et al. Temsirolimus (TEM) and lenalidomide (LEN) in relapsed/refractory Hodgkin lymphoma including in patients with prior exposure to brentuximab vedotin (BV) *Journal of Clinical Oncology*; 2014.

27. Pinto A, Pavone V, Angrilli F, Saggese M, Crisci S, Patti C, et al. Lenalidomide in Combination with Bendamustine for Patients with Chemorefractory Hodgkin Lymphoma: Final Results of the Leben Multicenter Phase 1/2 Study *Blood*; 2015.
28. Corazzelli G, Saggese M, Pavone V, Angrilli F, Zinzani PL, Spina M, et al. A phase 1/2 study of lenalidomide and bendamustine (LEBEN) in chemorefractory Hodgkin lymphoma *J Clin Oncol 32:5s, 2014 (suppl; abstr 8566)*; 2014.
29. Ugocsai P, Klobuch S, Zaiss S, Dietz D, Wolff D, Holler E, et al. Targeting the tumors' systems biology: Combined biomodulatory therapy in refractory Hodgkin´s lymphoma *Oncology Research and Treatment*; 2014.
30. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. Methods for population-adjusted indirect comparisons in submission to NICE. *NICE DSU Technical Support Document*, 2016:81.
31. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;8:16.
32. Jansen JP, Trikalinos T, Cappelleri JC, Daw J, Andes S, Eldessouki R, et al. Indirect treatment comparison/network meta-analysis study questionnaire to assess relevance and credibility to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. *Value Health* 2014;17(2):157-73.
33. Signorovitch JE, Wu EQ, Yu AP, Gerrits CM, Kantor E, Bao Y, et al. Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept. *Pharmacoeconomics* 2010;28(10):935-45.
34. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol* 2007;25(5):579-86.
35. Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, et al. Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas. *Journal of Clinical Oncology* 1999;17(4):1244-44.
36. Bristol-Myers Squibb. *Safety Study of Nivolumab by Itself or in Combination in Patients With Lymphoma or Multiple Myeloma*. https://clinicaltrials.gov/ct2/show/NCT01592370 (accessed 17/01/2017).
37. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* 1996;313(7052):275-83.

38. Bagust A, Beale S. Survival analysis and extrapolation modeling of time-to-event clinical trial data for economic evaluation: an alternative approach. *Med Decis Making* 2014;34(3):343-51.
39. Latimer NR. Survival analysis for economic evaluations alongside clinical trials--extrapolation with patient-level data: inconsistencies, limitations, and a practical guide. *Med Decis Making* 2013;33(6):743-54.
40. Perrot A, Monjanel H, Bouabdallah R, Quittet P, Sarkozy C, Bernard M, et al. Impact of post-brentuximab vedotin consolidation on relapsed/refractory CD30+ Hodgkin lymphomas: a large retrospective study on 240 patients enrolled in the French Named-Patient Program. *Haematologica* 2016;101(4):466-73.
41. Swinburn P, Shingler S, Acaster S, Lloyd A, Bonthapally V. Health utilities in relation to treatment response and adverse events in relapsed/refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma. *Leuk Lymphoma* 2015;56(6):1839-45.
42. Ramsey SD, Nademanee A, Masszi T, Holowiecki J, Abidi M, Chen A, et al. Quality of life results from a phase 3 study of brentuximab vedotin consolidation following autologous haematopoietic stem cell transplant for persons with Hodgkin lymphoma. *Br J Haematol* 2016.
43. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health* 2010;13(5):509-18.
44. Kind P, Hardman G, Macran S. Population norms for EQ-5D. *Discussion paper 172*. The Centre for Health Economics: University of York, 1999.
45. National Institute for Health and Care Excellence. TA 306 Single Technology Appraisal. Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B‐cell lymphoma. 2014. 2016.
46. Beusterien KM, Davies J, Leach M, Meiklejohn D, Grinspan JL, O'Toole A, et al. Population preference values for treatment outcomes in chronic lymphocytic leukaemia: a cross-sectional utility study. *Health Qual Life Outcomes* 2010;8:50.
47. Doyle S, Lloyd A, Walker M. Health state utility scores in advanced non-small cell lung cancer. *Lung Cancer* 2008;62(3):374-80.
48. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. *Health Qual Life Outcomes* 2008;6:84.
49. Tolley K, Goad C, Yi Y, Maroudas P, Haiderali A, Thompson G. Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia. *Eur J Health Econ* 2013;14(5):749-59.

50. Department of Health. NHS reference costs 2014-2015. *http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_122803* 2016.
51. National Institute for Health and Care Excellence. Single Technology Appraisal. Brentuximab vedotin for treating CD30-positive Hodgkin's lymphoma. Committee Papers. 2016. . 2016.
52. National Institute for Health and Care Excellence. TA 251 Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia (part review of technology appraisal guidance 70). 2012. 2016.
53. MIMS. Presciption drug database and drug prescribing guide. *http://www.mims.co.uk/* 2016.
54. Radford JJ, R,; McKay,P, et a;.;. reatment pathways and resource use associated with the management of recurrent Hodgkin lymphoma after autologous stem cell transplantation. *Haematologica* 2013.
55. National Institute for Health and Care Excellence. Technology appraisal guidance [TA241]. Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML) (part review of NICE technology appraisal guidance 70), and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance. 2012:333. https://www.nice.org.uk/guidance/GID-TAG467/documents/committee-papers.
56. Martinez C, Canals C, Sarina B, Alessandrino EP, Karakasis D, Pulsoni A, et al. Identification of prognostic factors predicting outcome in Hodgkin's lymphoma patients relapsing after autologous stem cell transplantation. *Ann Oncol* 2013;24(9):2430-4.
57. Bair SM, Stelec LM, Nasta S. Outcomes in patients with relapsed/refractory Hodgkin lymphoma (RR-HL) with progression after autologous stem cell transplantation in the current era of novel therapeutics. *J Clin Oncol.* 2016;31:A2543.

# National Institute for Health and Care Excellence
# Centre for Health Technology Evaluation

## Pro-forma Response

## ERG report

## Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma [ID972]

You are asked to check the ERG report from Southampton Health Technology Assessments Centre (SHTAC) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Monday 30 January 2017** using the below proforma 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 Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Dear Members of the Evidence Review Group,

Thank you for providing Bristol-Myers Squibb Pharmaceuticals Ltd (BMS) the opportunity to review the factual accuracy of the ERG report for nivolumab for the treatment of relapsed or refractory classical Hodgkin lymphoma (cHL).

As acknowledged within the company submission and the ERG's report, the prognosis is currently poor for patients with relapsed or refractory cHL who have previously received both autologous stem cell transplant (ASCT) and brentuximab vedotin (BTX). Though specific data are not currently available to describe survival in relapsed or refractory cHL patients following ASCT and BTX in clinical practice, median overall survival (OS) has been described as 19-29 months in cHL patients post-ASCT.[1, 2] This was supported by clinical experts attending the first Appraisal Committee meeting for the ongoing BTX appraisal [ID722], who suggested that life expectancy without BTX is likely to be less than 24 months.[3] In light of this evidence, it is highly unlikely that life expectancy would exceed 24 months in cHL patients who are more treatment-experienced and eligible for nivolumab (i.e., previously received both ASCT and BTX therapy), and who have no remaining treatment option, as proposed by the ERG in their revised base case analysis.

An estimated life expectancy of 3.3 years in post-ASCT, post-BTX cHL patients, as considered by the ERG in their revised base case analysis, represents an overestimate when considering current clinical practice. This longer survival estimate has been obscured by efficacy evidence from patients treated with "investigational agents", for which median survival was 47.7 months (3.98 years).[4] The "investigational agents" included cannot be identified, and as such may comprise unlicensed products and those not recommended by NICE. The approach taken by the ERG of including "investigational agents" as a relevant comparator in its analyses is inconsistent with both the NICE assessment process (see Guide to the methods of technology appraisal[5]), and therefore previous assessments undertaken by NICE, as well as the final scope issued for this appraisal.[6] **"Investigational agents", by definition, do not reflect established clinical practice for the treatment of relapsed and refractory cHL patients following ASCT and BTX, and cannot be considered an appropriate comparator in this population.**

This approach also presents an important equality issue, in that patients treated at smaller hospitals are unlikely to be provided access to "investigational agents".

In contrast to the ERG report, **established standard of care applied within the company submission is confirmed to comprise therapies that represent UK clinical practice, and is consistent with the scope of this appraisal and clinical expert opinion**.[6, 7]

When considering standard of care in this context, median life expectancy in post-ASCT, post-BTX cHL patients was 19 months. Though it is acknowledged that this estimate is subject to uncertainty, it indicates the **very short survival and the high unmet need for this group of patients.** Further, it is consistent with conclusions arrived at during the recent discussion of BTX, who considered a less heavily refractory population.[3] As acknowledged by the ERG, nivolumab is likely to increase the life expectancy of these patients by at least three months. Based on this evidence, BMS considers **nivolumab to meet end-of-life criteria.**

In order to conduct robust economic modelling in a population not well characterised in the literature, it has been necessary to acknowledge areas where data are not available, make simple and transparent assumptions based on independent sources, validate these assumptions through discussion with clinical experts, and assess the

impact of these assumptions using extensive sensitivity analyses. **It is heartening that the ERG agree that most of the assumptions applied in the company submission comprise the best available evidence.** In instances where BMS and the ERG differed in their assumptions, even the most pessimistic estimations of cost-effectiveness result in an incremental cost-effectiveness ratio below the appropriate threshold, further emphasising the favourable cost-effectiveness profile of nivolumab in this setting.

Nivolumab has been granted Promising Innovative Medicine status by the Medicines and Healthcare Products Regulatory Agency, and offers durable clinical responses and the potential for improved long-term survival in a population with a short life expectancy and lack of effective treatment options. In comparison with chemotherapy, nivolumab has improved tolerability and a convenient dosing schedule, which preserves patient dignity and facilitates normal life by enabling patients to spend less time at hospital and more at home. **Nivolumab is a novel, innovative, cost-effective and step-changing treatment option for patients with relapsed and refractory cHL following ASCT and BTX.**

In summary, BMS strongly believe that the availability of nivolumab would address the current unmet need for the treatment of relapsed and refractory cHL patients following ASCT and BTX, and meets end-of-life criteria in this patient population. The adoption of nivolumab for this therapeutic indication within NHS England would represent a significant advance in the management of this life-threating condition.

Please do not hesitate to contact BMS if any further information is required.

Kind regards,

Peter Dale

HEOR Consultant

Bristol-Myers Squibb Pharmaceuticals Ltd

## Issue 1 End of life criteria

| Description of problem | Description of proposed amendment | Justification for amendment | ERG Response |
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| **Section 5**<br><br>The estimate of life expectancy in the post-ASCT, post-BTX population put forth by the ERG may not be scientifically credible in the context of current clinical practice in the UK. | In the interest of scientific validity, we suggest that the ERG provide accurate context for their suggestion that life expectancy in the post-ASCT, post-BTX population exceeds 24 months, acknowledging that observations in current practice suggest that survival is highly likely to be under 24 months. | The ERG report notes that mean life years when including investigational agents increases to 3.3 years, indicating that life expectancy in the post-ASCT, post-BTX population exceeds 24 months.<br><br>The estimate of life expectancy provided by the ERG is not supported by the published literature or clinical expert opinion, and is counterintuitive based on conclusions drawn recently by the NICE Appraisal Committee. As such, the estimate provided is suggested to be inaccurate and misleading.<br><br>Though specific evidence to describe survival in cHL patients following ASCT and BTX in clinical practice is not available, median OS has been described as 19–29 months in cHL patients who are post-ASCT.[1, 2] This was supported by clinical experts attending the first Appraisal Committee meeting for the ongoing BTX appraisal [ID722], who suggested that life expectancy without BTX is likely to be less than 24 months.[3] Based on this evidence, it is highly unlikely that life expectancy would exceed 24 months in cHL patients who are more treatment-experienced and eligible for nivolumab therapy (i.e., having previously received both ASCT and BTX therapy).<br><br>The life expectancy of post-ASCT, post-BTX cHL patients as suggested by the ERG in their revised base case analysis is 3.3 years, which is longer than that described by clinical experts and in the | Not a factual inaccuracy. The ERG reports the mean results from the company's model for SoC. |

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| | | published literature for a less treatment-experienced post-ASCT population. After removal of efficacy data for "investigational agents" that do not reflect established clinical practice, median life expectancy associated with standard of care was 19 months. As this is based on calculation rather than observation, it can be acknowledged that this estimate cannot provide an accurate representation of life expectancy in cHL patients following ASCT and BTX, but it is indicative of the very short survival and the high unmet need experienced by this patient population. This life expectancy estimate is based on clinical expert opinion and published literature, and highlights that nivolumab meets end-of-life criteria for this patient population. By contrast, the ERG estimation of life expectancy in clinical practice is counterintuitive and unsupported. | |

## Issue 2 Inclusion of investigational agents within standard of care

| Description of problem | Description of proposed amendment | Justification for amendment | ERG Response |
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| **Throughout ERG report**<br><br>Inconsistently with the NICE process, previous technology assessments and the final scope issued, the ERG suggests that standard of care | Text throughout the report should be corrected to remove "investigational agents" from the base case comparison. | The inclusion of inappropriate comparator treatments diminishes the validity of the ERG base case. This approach subsequently results in factually inaccurate and misleading conclusions of cost-effectiveness.<br><br>The scope for this appraisal details the following comparators as appropriate: established clinical management without nivolumab including chemotherapy such as gemcitabine or bendamustine; and best supportive care.[6] Further, the NICE guide to the methods of | Not a factual inaccuracy. The ERG's opinion, as stated in the ERG report, is that the population including investigational agents is representative of established NHS clinical practice in England. |

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| should encompass "investigational agents". | | technology appraisal states several criteria applied when determining appropriate comparators for Technology Appraisal, including consideration of **established** NHS practice in England.[5]<br><br>The "investigational agents" described by Cheah and colleagues,[4] by definition, do not reflect established practice within the NHS in England. Data pertaining to relevant and established comparator therapies are outlined within other cohorts in this study.<br><br>The ERG claims that study authors specified that "only a couple" of the 28 patients within the "investigational agents" cohort received PD-1 inhibitors, but provided no further details regarding the composition of this group. It is likely that "investigational agents" will predominantly comprise unlicensed products and those not recommenced by NICE, thus limiting the relevance of this category to simulation of clinical practice.<br><br>This additionally raises an important equality issue, in that patients treated at smaller centres would not have access to "investigational agents".<br><br>The inclusion of "investigational agents" by the ERG in their revised base case analysis is inappropriate and inconsistent with both the scope defined for this appraisal, and the assessment of other therapies.[3, 5] Therefore, conclusions based on these revised analyses are inaccurate. | |

## Issue 3 Inclusion of allogeneic stem cell transplant in the base case analysis

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| **Section 4 (Cost-effectiveness)**<br>Inclusion of allogeneic stem cell transplant (alloSCT) in base case analysis. | AlloSCT should be excluded from the revised base case analysis throughout. | The scope for this appraisal states that "if the evidence allows, a **scenario analysis** including alloSCT as a subsequent treatment after nivolumab or its comparators will be considered. This should reflect the proportion of people who proceed to allogeneic stem cell transplant after each treatment, as well as the costs and QALY benefits of the procedure".[6]<br>In line with this scope, as well as the ongoing NICE BTX appraisal[3], the company submission outlines an approach where several scenario analyses assessed the impact of alloSCT as a subsequent treatment. By contrast, the ERG has included alloSCT in their revised base case analysis, which is inconsistent with the scope for this appraisal. | Not a factual inaccuracy.<br>If this is true, the health benefits of alloSCT should be excluded from the company base case. For consistency, the appropriate method is to include all downstream costs and benefits related to the treatment. The company base case potentially includes the survival benefits of alloSCT without including the costs.<br>AlloSCT is both a downstream cost and benefit of treatment in this population, so therefore should be included in the economic evaluation. |
| **Section 4 (Cost-effectiveness)**<br>Assumptions applied do not appropriately reflect survival profile of alloSCT patients. | The assumption regarding alloSCT survival should be corrected or placed into the context of the overwhelming evidence supporting alternative survival profiles in patients receiving alloSCT. | AlloSCT is typically considered to be associated with high morbidity and mortality in the short-term, but potentially curative in the long-term; this therefore necessitates alternative survival profiles. This has been acknowledged in other HTAs conducted by NICE, including the ongoing BTX appraisal, but has not been applied within the ERG analysis.[3]<br>It is acknowledged that both CheckMate 205 and the Cheah 2016 datasets included patients who subsequently received alloSCT. However, ERG analyses assume that the CheckMate 205 and Cheah 2016 datasets can be used to model the long-term survival of patients who subsequently | Not a factual inaccuracy.<br>It was the opinion of the ERG that the survival data provided from the pivotal trials included patients who received alloSCT, therefore, the tail of the survival curve already captures survival in patients who have alloSCT. As previously indicated by the company, patients on BSC do not survive long, so any additional survival would likely be attributable to alloSCT. |

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| | | undergo alloSCT, such that no new survival curves are necessary when patients transition in the model.<br><br>Using this approach, the long-term benefits of alloSCT will not be apparent over the trial periods of CheckMate 205 and Cheah 2016, and will not be accurately reflected in the parametric forms applied in the ERG's analyses. | |

## Issue 4 Derivation of utility inputs

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| **Section 4.3.6 (Health related quality of life)**<br><br>Pre-progression utilities are applied as response-specific inputs rather than treatment-specific utilities, based on EQ-5D data from the CheckMate 205 study. | The assumption that response-specific utilities are equivalent between nivolumab and SoC in the pre-progression phase should be amended. | The approach taken by the ERG assumes that the outcomes associated with complete response (CR) are equivalent between therapies; this is inappropriate due to the novel response profile associated with immunotherapies such as nivolumab.<br><br>Conventional anti-cancer therapies typically aim to reduce the tumour burden through disruption of cell proliferation or induction of apoptosis. By contrast, through interruption of PD-1 binding to PD-L1 and PD-L2, nivolumab stimulates the patient's own immune system to directly destroy cancer cells through pre-existing, intrinsic processes. As a result of this novel mechanism of action, immuno-oncology agents, including nivolumab, display varying patterns of response when compared to conventional chemotherapeutic agents. Therefore, it cannot be assumed that a given level of response with conventional chemotherapies will | Not a factual inaccuracy. As stated in the ERG report, the ERG believes that the most consistent approach is to use the same data source for both treatment arms. Using this approach does indicate that the utility value associated with SoC treatment is lower than for patients treated with nivolumab. Further the ERG notes that differences in adverse events are incorporated using adverse event disutilities. |

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| | | have an equivalent outcome or utility as that for an immunotherapy, or vice versa.<br><br>The utility associated with CR in nivolumab-treated patients is lower than observed in the literature[8] (as applied within the ERG base case for the ongoing BTX appraisal[3]), whereas those for PR and SD are higher. This may be due to differing long-term outcomes in patients achieving these levels of response. The company submission additionally recognised several benefits that impact directly on patient quality of life during therapy in the pre-progression phase, including rapid symptom control in the majority of patients and a tolerable AE profile, all of which underscore the differences in the utility profile between nivolumab and conventional chemotherapies. | |
| **Section 4.3.6 (Health related quality of life)**<br><br>Post-progression utilities have been assumed to be equivalent between nivolumab and SoC based on use of the CheckMate 205 data. | The assumption that post-progression utilities are equivalent between nivolumab and SoC should be amended. | As noted within the submission, there are several indirect benefits of nivolumab therapy on patient quality of life, including improved OS and post-progression survival. This includes the potential for immune system stimulation following progression and continued B-symptom control. Furthermore, immuno-oncology therapies demonstrate a varied pattern of response, and can result in dissociated responses, delayed responses and pseudo-progressions. As such, the quality of life data derived from patients during CheckMate 205 reflects the expected benefits of nivolumab in the post-progression phase, even following cessation of therapy.<br><br>Based on the above rationale, it is inappropriate to assume equivalency between quality of life in | Not a factual inaccuracy. As stated in the ERG report, the ERG considers the correct approach is to use equivalent post-progression utilities for the nivolumab and SoC arms. |

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| | | nivolumab-treated patients and that for its comparators. | |

## Issue 5 Indirect comparison

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| Page 54-55<br>The rationale for the selection of outcomes for which indirect comparison was conducted is not described in the CS or Appendix 3. | We request that text pertaining to lack of clarity in outcomes is removed. | It is unclear why the ERG has raised this, since these outcomes are consistent with those specified by NICE and are patient-relevant; therefore, ongoing justification of their use in the CS would be superfluous. | Not a factual inaccuracy. A justification of the use of these outcomes is not required but there should have been an indication of why these outcomes were selected for indirect comparison (should or could indirect comparison have been conducted for other outcomes but wasn't?). |
| Page 56, 59, 61<br>The NICE DSU Technical Support Document indicates that indirect comparisons should be made on a log transformed scale but it is not clear from the CS whether a log | We request that this is amended to reflect the fact that log transformations were utilised, consistent with the DSU Technical Support Document. | Log transformations were utilised; this is evidenced by the symmetry in log-space of the confidence intervals for relative risk, demonstrating that they have been transformed. We consider it inaccurate to state that the CS lacks clarity. | Not a factual inaccuracy. The CS does not state that log transformations were utilised. |

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| scale was used for the indirect comparison of response outcomes where the comparison is reported as an adjusted relative risk. | | | |
| Page 64<br><br>The choice of matching variables was based on availability of common characteristics in the studies rather than on a priori identification of effect modifiers justified on the basis of empirical evidence or clinical expertise. There may prognostic factors and effect modifiers that could not be accounted for in the analyses due to a lack of data, but this possibility has not been discussed. | We request that the following statement be removed:<br><br>"rather than on a priori identification of effect modifiers justified on the basis of empirical evidence or clinical expertise". | This is misleading and therefore may result in inaccurate interpretation. No definitive covariates have been identified as impacting the outcomes in question in the literature. Matching against uncertain covariates cannot bias the estimators, so a pragmatic decision was made. Evidence-based support should be provided for the ERG's statement. | Not a factual inaccuracy. Neither the CS nor Appendix 3 discusses whether covariates impacting on outcomes are known or not. |

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| Pages 58-68 and 142<br><br>Discussion of indirect comparison method. | We request that statements pertaining to the methodology lacking clarity are removed and that text is amended to acknowledge that a comprehensive approach was adopted, given limitations in the data available. | The methodology is clear and transparent in the CS, and as comprehensive an approach as possible was utilised. BMS followed the Bagust and Beale guidelines to support survival modelling whenever there was insufficient evidence to support alternative parametric forms.[9] We suggest that the ERG report should acknowledge that best efforts were made to provide as comprehensive and methodologically sound analysis as possible. | Not a factual inaccuracy. The ERG queries the page range of 58-68 as this extends beyond the part of the ERG report that discusses the indirect comparison. For pages 58 to 61 the ERG only raises 2 issues which have already been discussed in the two rows above in this table. These same issues are reiterated on p.142. |
| Page 65-66<br><br>The analysis used the investigator assessments for response (CS Appendix 3 p. 20 states that the 2007 IWG criteria were used whereas the main CS report indicates that the investigator assessments of response used the International Workshop to Standardized Response Criteria for Lymphomas for assessment). | We request that this is corrected. | We consider the submission clear and therefore this should be clearly reported in the ERG report.<br><br>Outcomes (CR, PR, ORR, PFS) were defined according to 2007 IWG criteria, based on investigator assessment.<br><br>CS, p59: "The primary efficacy endpoint was investigator-assessed ORR using the protocol-defined International Workshop to Standardized Response Criteria for Lymphomas. The secondary efficacy endpoint was IRRC-assessed ORR using 2007 IWG criteria, while additional endpoints included TTR, time to CR, time to PR, duration of response, PFS and OS." | Not a factual inaccuracy. The ERG is not clear which version of the response criteria were used because the text on p.59 states the investigator-assessed ORR used the International Workshop to Standardized Response Criteria for Lymphomas (which the ERG believes to be Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, et al. Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas. Journal of Clinical Oncology 1999;17(4):1244-44) whereas CS Appendix 3 p.20 states the 2007 IWG criteria were used (Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579-86). It is the ERG's understanding that the revised 2007 criteria incorporate the use of PET scans in response assessment which were not part of assessment in the earlier version of the response assessment criteria. |

## Issue 6 Population

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| Page 10<br>The CS on the whole reflects the scope of the appraisal issued by NICE, although evidence is presented for only one of the patient groups included in the NICE scope. | We suggest text relating to the second population is removed in the interest of ensuring compliance with the marketing authorisation. | NICE was informed of the licensed indication at the decision problem meeting; however, the scope produced was not reflective of this.<br>The second population stated in the scope is outside of the licensed indication for nivolumab and its inclusion may be misleading to readers in terms of how nivolumab may be used. We therefore suggest that the text should be removed. | Not a factual inaccuracy. The NICE scope includes two populations. The ERG does indicate that the second population specified in the final scope issued by NICE is not encompassed by the proposed indication for nivolumab on p.23 of the ERG report. |

## Issue 7 Cost-effectiveness modelling

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| Page 99<br>The model is built in Microsoft Excel, however, the model is executed almost entirely in VBA programming language. The spreadsheets cannot be used to generate any | We request that a more balanced description of the model is included and the necessity for VBA coding is acknowledged. Further, we request that text to describe the model as opaque and difficult to validate are removed, as well as being unable to replicate scenarios. | We consider the current text to adopt a biased view, and does not adequately convey the pragmatic requirement for VBA coding and efforts made to provide transparency.<br>There was a necessity to investigate the effects of a number of scenarios that required additional modelling complexity over the base case analyses (including combinations of time-dependent discontinuation, therapy escalation and survival). Therefore, it was necessary to implement the modelling process in VBA. | Not a factual inaccuracy. The ERG does not consider it necessary to implement all the modelling process using VBA. As stated in the ERG report, we believe that using this approach makes the model opaque and difficult to validate. |

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| calculations or model results independently of the VBA code — macros are required to produce all types of results: base-case, deterministic sensitivity analyses, scenario analyses, and probabilistic sensitivity analyses. Inputs into the model must take very specific forms or risk crashing the VBA code that is responsible for producing results. These limitations of the model rendered the model opaque and difficult to validate. All scenario analyses required manual modification of input parameters and not all analyses could be replicated, due either to insufficient | | Such implementation has resulted in a more concise and less convoluted model structure, with a much faster runtime; a purely Excel-based model would have required a hugely increased number of calculations to allow the model to maintain 'memory' of the time-dependent aspects.<br><br>In order to maintain transparency, BMS has ensured that the model code is structured in an intuitive way and that detail surrounding the purpose of each subroutine is provided within the code itself, in the form of textual comments.<br><br>Further, we have ensured that the model structure adheres to NICE guidelines, and all modelling approaches remain consistent with previous NICE cost-effectiveness submissions. | |

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| explanation of methods or due to potential parameter discrepancies. | | | |
| Page 101<br>The company did not include half-cycle correction in the base case analysis. We found the cycle length sufficiently short to represent transitions and that the company's approach to half-cycle correction was appropriate given the marginal effect of transition timing when cycles are short". | We request that this statement is rectified in the report. | This is factually inaccurate as the base case and all scenario analyses within the CS included half cycle correction (except for the one scenario to test the impact of excluding half cycle correction). | This is an error which the ERG has now corrected. |
| Page 103<br>The company states that in the base case, efficacy inputs for SoC are derived from the population of patients who did not receive | We request that the statement read:<br>"The company states that in the base case, efficacy inputs for SoC are derived from the population of patients who did not receive investigational agents. Tables and data within the CS refer to the without investigational agents group (n=51) and the full sample (n=79)." | This is incorrect. The groups are clearly labelled in terms of which agents they comprise, and methods for determining this data are set out. However, logically, when describing the overall study, the whole data set is also provided. | Not a factual inaccuracy. For example in Table 28 of the ERG report, the age and disease stage described are for the overall population, rather than for those who did not receive investigational agents. |

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| investigational agents (n=51). Despite this, tables and data within the CS refer to the full sample (n=79). | | | |
| Page 102<br>The composition of SoC in terms of the actual chemotherapies used is unclear, and the regimens used are described in more detail in section 4.3.7 and shown in Table 42. | We suggest the text is amended to read:<br>"The composition of SoC in terms of the actual chemotherapies/regimens used are described in more detail in section 4.3.7 and shown in Table 42. | It is factually inaccurate to say this is unclear.<br>The base case analysis assumes that SoC comprises the therapies described within the Cheah study, as shown in Table 29. These are: investigational agents, gemcitabine, bendamustine, brentuximab vedotin retreatment, platinum based therapies, ASCT and other alkylator therapies. | Not a factual inaccuracy. As stated in the company's submission, the composition of the chemotherapy agents is unclear.and required the company to make assumptions about the make-up of the regimens (CS section 5.5.2.2). |
| Page 120<br>For the chemotherapy agents, the company assumed an equal proportion of patients received each regimen. These regimens were chosen according to BCSH guidelines. Clinical advice to the ERG suggested that mini-BEAM or DexaBEAM are not | We request that this statement is amended to acknowledge the heterogeneity in treatment, rather than to suggest some should be definitely excluded. | As stated within the submission and above, the overarching approach has been to acknowledge where are gaps in the evidence and provide simple, transparent assumptions in order to enable robust examination. The composition of the chemotherapies available to patients was based exclusively on those listed within BCSH guidelines.<br>Based on evidence from clinical experts, it can be concluded that treatment of cHL in this setting is highly heterogeneous, due to the differing nature of the patients seen in clinical practice (i.e. age, comorbidities, prior therapies) as well as differing treatment practices between clinicians. It is suggested that the ERG ensure | Not a factual inaccuracy. |

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| commonly used salvage regimens for Hodgkin lymphoma in the UK. The ERG therefore suggests that SoC should not contain these regimens. We investigate the effects of changing the SoC costs in the ERG analyses (section 4.4). | | that the report acknowledges the heterogeneity in treatment in this setting. | |
| Page 17<br>In general, all analyses produced results under £50,000 per QALY and two analyses, that assessed alternative post-progression utility scores, produced results above £30,000 per QALY. | We request that “in general” is removed | All analyses were under £50,000 per QALY. “In general” is inaccurate. | Not a factual inaccuracy. |

## Issue 8 Typographical/transcription errors

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Page 11-12<br>Page 48-49<br>Page 69, Table 12<br>Page 70, Table 13<br>Page 71, Table 14<br>Page 75, Table 16<br>Page 80, Table 18<br>Incorrect follow-up times reported. | Median follow-up times should be amended to read:<br>CheckMate 205 Cohort B (n=80): 15.7 months<br>CheckMate 205 Cohort C (n=98): 8.9 months<br>CA209-039 (n=15): 23.3 months | Transcription error throughout ERG report. | The ERG agrees that in some places median follow-up times are incorrect.<br>Page 11 – no error identified<br>Page 12 – errors corrected<br>Page 48 – errors corrected<br>Page 49 – no error identified<br>Table 12 footnotes - errors corrected<br>Table 13 footnotes - errors corrected<br>Table 14 footnotes - errors corrected<br>Table 16 footnotes - errors corrected<br>Table 18 footnotes - errors corrected |
| Page 13<br>Incomplete description of results. | Text should be amended to read:<br>In the **unadjusted** indirect comparisons the ORR for the nivolumab pooled cohort (n=193) was [redacted] compared to [redacted] for the Cheah 2016 study [redacted] Across all the indirect comparisons conducted (either unadjusted or MAIC and for the four scenarios) the range of values for the comparator ORR range from [redacted] obtained for the | Results reported in ERG report lack clarity. | Text amended |

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| | Cheah 2016 study [redacted] to [redacted] **obtained for** [redacted] | | |
| Page 13<br>Page 67<br>Page 112<br>Typographical error. | Instances of “IRRS” should be amended to read “IRRC” throughout. | Typographical error throughout ERG report. | The three typographical errors have been corrected. |
| Page 16<br>Incorrect time horizon reported. | Text should be amended to read:<br>The model adopted a time horizon of **40** years to capture lifetime costs and health outcomes, with a cycle length of one month and half-cycle correction. | Typographical error in ERG report. | We agree with the amendment. The text has been changed to **40** years. |
| Page 16<br>Unmarked confidential information reported. | Commercial in confidence data should be marked as follows:<br>In the base analysis, the model estimated that there would be an additional [redacted] discounted QALYs for nivolumab compared to SoC.” | Text contains results of cost-effectiveness analyses based on a confidential patient access scheme (PAS) offered by BMS. These results are therefore confidential, as their publication would allow determination of the nivolumab PAS which remains confidential. | We agree. Text has been changed to commercial in confidence. |
| Page 21 | Text should be amended to read: For the remaining 70%, there | Typographical error in ERG report. | Typographical error corrected |

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|---|---|---|---|
| Typographical error | would probably be a 70-80% **chance** of achieving a good enough remission for transplant. | | |
| Page 35<br>Incorrect results reported. | Text should be amended to read:<br>Patients who had received with prior radiotherapy ranged between [redacted] to [redacted]. | Transcription error in ERG report. | Transcription error corrected. |
| Page 66 Table 11<br>Unmarked academic information reported | Academic in confidence data should be marked as follows:<br>Median follow-up 8.9 months | Text contains Academic in confidence data. | The ERG apologies for this inadvertent omission of AIC marking (text was underlined but had not been highlighted appropriately). This has now been corrected. |
| Page 70, Table 13<br>Incorrect results reported. | MAIC Relative risk cell for Scenario 2b should be amended to read:<br>[redacted] | Typographical error in the company submission, carried forward in the ERG report. | The ERG thanks the company for providing the correct values which have now been added to the report. The footnote describing the error has also been removed. |
| Page 71, Table 14<br>Incorrect results reported. | MAIC Relative risk cell for Scenario 2b should be amended to read:<br>[redacted] | Typographical error in the company submission, carried forward in the ERG report. | The ERG thanks the company for providing the correct values which have now been added to the report. The footnote describing the error has also been removed. |
| Page 94<br>Typographical error. | Text should be amended to read:<br>The objective response rate **was** the primary efficacy endpoint of both the CheckMate 205 study (when assessed by the IRRC) and | Typographical error in ERG report. | Typographical error corrected |

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| | the CA209-039 study (investigator assessed objective response rate) | | |
| Page 96<br>Typographical error. | Text should be amended to read:<br>There is uncertainty about the effectiveness of **nivolumab** in comparison to alternative treatment<br>Identification of AEs of special clinical **interest** was conducted | Typographical error in ERG report. | We agree. Text changed in the report, as suggested. |
| Page 119, Table 39<br>Incorrect reference to company submission. | Amended the title of Table 39 to reflect that it is adapted from "CS Appendix 4, Table 4". | Typographical error in ERG report. | Appendix 4, Table 4 does not appear to have any relevance to Table 39 of the ERG report. |
| Page 120, Table 40<br>Typographical error. | Amend "Swiftburn" to "Swinburn" | Typographical error in ERG report. | We agree. Text has been changed to 'Swinburn', as suggested. |
| Page 141, Table 59<br>Incorrect data reported. | "Nivolumab costs" column should be amended to [redacted] throughout the table.<br>"Nivolumab QALYs" column should be amended to [redacted] throughout the table. | Transcription errors in ERG report. | We agree. Table text has been corrected. |
| Page 141, Table 59 | Parameter cell for analysis 29 should be amended to read: Unadjusted ITC, subgroup,[c] fixed | Transcription errors in ERG report. | We agree. Table text has been corrected. |

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| Incorrect data reported. | effects<br>PFS = λ: 0.1576<br>OS= λ: 0.0261<br>Complete response= [redacted]<br>Partial response= [redacted]<br>Utility (pre-progression)= [redacted] | | |
| Page 141, Table 59<br>Incorrect data reported. | Parameter cell for analysis 30 should be amended to read:<br>Unadjusted ITC, subgroup,[c] random effects<br>PFS = λ: 0.1576<br>OS= λ: 0.0261<br>Complete response= [redacted]<br>Partial response= [redacted]<br>Utility (pre-progression)= [redacted] | Transcription errors in ERG report. | We agree. Table text has been corrected. |
| Page 144, Table 60<br>Incorrect data reported. | Parameter cell for analysis 42 should be amended to read:<br>MAIC ITC, all studies, random effects<br>PFS = λ: 0.0615<br>OS= λ: 0.0239<br>Complete response= [redacted]<br>Partial response= [redacted]<br>Utility (pre-progression)= [redacted] | Transcription error in ERG report. | We agree. Table text has been corrected. |
| Page 148, Table 64<br>Incorrect reference to company submission. | Source cell for analysis 55 should be amended to read “Table 71 (p. 151)”.<br>An additional source for analysis 58 should be noted: “Table 92 (p. 166)”. | Typographical errors in ERG report. | We agree. Table text has been corrected. |

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| Page 158, Table 67<br>Incorrect data reported. | Nivolumab costs in ERG12 should be amended to [redacted] | Typographical error in ERG report. | We agree. Table text has been corrected. |

## References


1. Martinez C, Canals C, Sarina B, Alessandrino EP, Karakasis D, Pulsoni A, et al. Identification of prognostic factors predicting outcome in Hodgkin's lymphoma patients relapsing after autologous stem cell transplantation. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2013;24(9):2430-4.
2. Bair SM, Strelec LE, Nasta S, Mato AR, Landsburg DJ, Stadtmauer EA, et al. Outcomes in patients with relapsed/refractory Hodgkin lymphoma (RR-HL) with progression after autologous stem cell transplantation in the current era of novel therapeutics. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2016;31(suppl):Abstr 2543.
3. National Institute for Health and Care Excellence. Appraisal consultation document: Brentuximab vedotin for treating CD30-positive Hodgkin's lymphoma. 2016. Available from: https://www.nice.org.uk/guidance/GID-TAG467/documents/appraisal-consultation-document [Accessed 25 January, 2017].
4. Cheah CY, Chihara D, Horowitz S, Sevin A, Oki Y, Zhou S, et al. Patients with classical Hodgkin lymphoma experiencing disease progression after treatment with brentuximab vedotin have poor outcomes. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2016;27(7):1317-23.
5. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. 2013. Available from: https://www.nice.org.uk/process/pmg9/chapter/foreword [Accessed 25 January, 2017].
6. National Institute for Health and Care Excellence. Final scope for the appraisal of nivolumab for treating relapsed or refractory classical Hodgkin lymphoma. September 2016.
7. National Institute for Health and Care Excellence. Consultation comments on the draft remit and draft scope for the technology appraisal of nivolumab for treating relapsed or refractory classical Hodgkin lymphoma. September 2016.
8. Swinburn P, Shingler S, Acaster S, Lloyd A, Bonthapally V. Health utilities in relation to treatment response and adverse events in relapsed/refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma. Leukemia & lymphoma. 2015;56(6):1839-45.
9. Bagust A, Beale S. Survival analysis and extrapolation modeling of time-to-event clinical trial data for economic evaluation: an alternative approach. Medical decision making : an international journal of the Society for Medical Decision Making. 2014;34(3):343-51.

**Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE**

# Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma

## ERRATUM

**Replacement pages for factual inaccuracies in Evidence Review Group report**

**06 February 2017**

**Produced by** Southampton Health Technology Assessments Centre (SHTAC)

[CheckMate 205 Cohort B n=80 (median follow-up 15.7 months); CheckMate 205 Cohort C n=98 (median follow-up 8.9 months); CA209-039 n=15 (median follow-up 23.3 months)].

Comparator data were drawn from [redacted] potential comparator studies that were identified by one of the company's systematic reviews. However, of these, [redacted] studies were reported only as conference abstracts and [redacted]The remainder were [redacted]One retrospective USA database study published in 2016 by Cheah and colleagues was identified in the CS as providing evidence on the outcomes of interest in a population where the majority of patients had received prior ASCT and had failed brentuximab vedotin. This study was used as the primary source of comparator evidence. In this study the [redacted] patients with disease progression either did not receive any further treatment [redacted]or were reported as having received one of the following types of therapy: investigational agent; gemcitabine; bendamustine; other alkylator; brentuximab vedotin retreatment; platinum based; ASCT; and 'other'. The CS speculates that the some of the 'investigational agent' group were likely to have received nivolumab and for this reason the 'investigational agent' group was excluded from some analyses as shown below. The comparator studies contribute to indirect comparisons that were made for four scenarios:

[redacted]

The company conducted both unadjusted indirect comparisons and matching-adjusted indirect comparisons (MAICs) for each of the four scenarios for the outcomes of ORR, CR rate, PR rate, OS, and PFS.

The primary outcome, ORR, was [redacted] for the study defined primary endpoints at the longest follow-up points in both nivolumab studies. The median duration of objective response is reported for cohort B [redacted]at median follow-up of 15.7 months) and cohort C [redacted]at median follow-up of 8.9 months), but as the CheckMate 205 study is still ongoing this is likely to change as more data accrue[redacted]

[redacted]In the unadjusted indirect comparisons the ORR for the nivolumab pooled cohort (n=193) was [redacted] compared to [redacted]for the Cheah 2016 study [redacted]Across all the indirect comparisons conducted (either unadjusted or MAIC and for the four scenarios) the range of values for the comparator ORR range from the [redacted]obtained for the Cheah 2016 study [redacted]) to [redacted] obtained for the subgroup of SLR-identified studies that reported outcomes separately for post-ASCT and post-brentuximab vedotin patients or where >70% of the patients matched that criterion. Response outcomes from the unadjusted indirect comparison were used in the economic model base case to stratify pre-progression utility based on response and outcomes from both the unadjusted indirect comparison and the MAIC are used in scenario analyses. IRRC-derived response data are used in a sensitivity analysis.

OS data are not yet complete and median OS has not been reached in either CheckMate 205 cohorts B and C or the CA209-039 study at the longest follow-up periods reported in the CS. In CheckMate 205 Cohort B, there had been [redacted]deaths among the 80 patients at median follow-up of 15.7 months, in Cohort C [redacted]deaths among 100 patients at a median follow-up of 8.9 months and in CA209-039 [redacted] deaths among 15 patients at a median follow-up of 23.3 months. The six-month OS for Cohorts B and C are 96.1% (95% CI 92.0 to 100) and 94.0% (95% CI 89.1 to 98.9) respectively and in CA209-039 the one year OS rate is [redacted]In the indirect comparisons a median OS period was predicted for the nivolumab pooled cohort of [redacted](based on extrapolation of the patient level data). In comparison the median OS obtained by unadjusted indirect comparison with the overall Cheah data set was [redacted](range of values for comparator OS across the different indirect comparisons is [redacted]to [redacted] Overall survival is included in the economic model.

Similarly to OS, PFS data are not yet complete. Median PFS ranges from just over 11 months (CheckMate 205 cohort C, median follow-up 8.9 months) to 14.78 months (CheckMate 205 cohort B IRRC assessment, median follow-up 15.7 months). For the investigator assessments of CheckMate 205 Cohort B and CA209-039 median PFS had not been reached at these time points. In all the indirect comparisons investigator assessments were used, hence in the unadjusted indirect comparison a median PFS was predicted for the nivolumab pooled cohort of [redacted]. In comparison the median PFS with the overall Cheah data set was [redacted](range of values for comparator PFS across the different indirect comparisons, both unadjusted and MAIC, is [redacted] to [redacted] Progression-free survival is included in the economic model.

studies, but none of them report on nivolumab as an intervention for patients with Hodgkin lymphoma or report on interventions in patients with relapsed or refractory Hodgkin lymphoma following ASCT and treatment with brentuximab vedotin.

The economic evaluation used a semi-Markov survival model (developed in Microsoft Excel) to assess the cost effectiveness of nivolumab compared with SoC in adult patients with relapsed or refractory Hodgkin lymphoma following ASCT and brentuximab vedotin. The model adopted a time horizon of 40 years to capture lifetime costs and health outcomes, with a cycle length of one month and half-cycle correction. The model consisted of three health states: pre-progression, progression and death. Analyses were presented from the NHS and Personal Social Services perspective.

The model uses pooled efficacy data (PFS, OS, treatment response, adverse events) from the CheckMate 205 and CA209-039 studies for the nivolumab arm and from Cheah and colleagues for the SoC arm. The company fitted parametric survival curves to these data for progression free survival and overall survival and selected the most appropriate curves on the basis of the goodness of fit and clinical plausibility. The lognormal function was selected for progression-free survival and the Weibull function for overall survival for the nivolumab arm. The exponential function was selected for progression-free survival and overall survival for the SoC arm. Utility estimates were taken from EQ-5D data obtained from the company's CheckMate 205 study for the nivolumab arm, and from a study by Swinburn and colleagues that used time-trade off methods for the SoC arm.

Nivolumab is administered intravenous and the recommended dose, based on patient weight, is 3.0 mg/kg given once every two weeks. Nivolumab has been provided with a confidential patient access scheme (PAS) price discount in the company analyses.

The results of the economic model were presented as incremental cost effectiveness ratios (ICERs), measured as the incremental cost per quality-adjusted life-years (QALYs). In the base analysis, the model estimated that there would be an additional [redacted] discounted QALYs for nivolumab compared to SoC. The results of the cost effectiveness analyses with the PAS discount price for nivolumab showed an incremental cost effectiveness ratio (ICER) of £19,882 per QALY compared to SoC (Table 1).

England and Wales during 2010-2011 is predicted to be 91.4%, with ten-year survival estimated at 80.4%.

## 1.1 Critique of company's overview of current service provision

The CS provides a clear and accurate overview of current treatment options for people with classical Hodgkin lymphoma (CS section 3.2 p. 28) and cites the British Committee for Standards in Haematology (BCSH) treatment guidelines,[1] stating that these form the best available evidence to inform current clinical practice for the treatment of Hodgkin lymphoma in the UK. The CS notes that NICE are currently appraising the use of brentuximab vedotin for the treatment of two groups of patients with CD30-positive Hodgkin lymphoma: those who have relapsed or refractory disease following ASCT or who are at high risk of residual disease following ASCT; those who have had at least two previous therapies when ASCT or multi-agent chemotherapy is not a treatment option. This guidance is expected to be published in February 2017. The ERG notes that NICE intend to appraise Pembrolizumab for classical Hodgkin lymphoma (expected guidance publication February 2018), but a scope for this STA is not available at the time of writing (December 2016).

The company describes current first-line treatment options for Hodgkin lymphoma and highlights that 15-30% of patients do not achieve long-term remission following first-line therapy, either due to primary refractory disease or relapse. Based on the information provided about the number of new cases of Hodgkin lymphoma in the UK in 2013, this would mean approximately 278-558 of the classical Hodgkin lymphoma patients diagnosed in the UK in 2013 would require salvage therapy at some point in the future. The goal of salvage therapy (chemotherapy and/or radiotherapy) is to achieve a sufficient response such that ASCT can be carried out. The recommended treatment pathway for those who do not achieve long-term remission and who are eligible for ASCT is presented in the CS (Figure 8, p. 29) based on BCSH treatment guidelines[1] and this is reproduced below (Figure 1). However, ASCT is not a treatment option for patients who are unable to achieve a sufficient response or for those who age or co-morbidities prevent ASCT being a treatment option. The clinical experts we consulted suggested that, of those who do not achieve long-term remission following first-line therapy, about 30% would not be eligible for ASCT (due to age or co-morbidities). For the remaining 70%, there would probably be a 70-80% chance of achieving a good enough remission for transplant.

AE, adverse events; alloSCR, allogenic stem cell transplant; ASCT, autologous stem cell transplant; BTX, brentuximab vedotin; cHL, classical hodgkin lymphoma; CR, complete response; ECOG, Eastern Cooperative Oncology Group; PR, partial response.
* Cohort C included 2 patients that had not previously received Brentuximab vedotin (CS p. 53)

Evidence from the two included studies is provided consecutively in the CS. The ERG has presented the evidence from the two studies side-by-side for a clearer overview where possible.

The CS presents demographics/baseline characteristics and patient disposition for cohort B at data cut-off 20 August 2015 (not reported by the ERG) and at a second later data cut-off April 2016 (see Table 5). For the later data cut-off, the majority of the information is marked AIC. The CS presents the same information for the total population of CA209-039, which includes eight patients who do not meet the licenced indication for nivolumab; all of the patient disposition data is marked AIC. Following a clarification request, the company provided patient demographics and baseline characteristics for the subgroup of 15 patients who do meet the licenced indication for nivolumab (Clarification response A5). The ERG reports on the subgroup of 15 patients from CA209-039 who are relevant to the decision problem.

The median age in the two cohorts of the CheckMate 205 study and the post-ASCT post-brentuximab vedotin subgroup of the CA209-039 study varies between [redacted] years and [redacted] years, with mean age only reported in CheckMate 205. The maximum age of patients in CheckMate 205 was higher ([redacted] to 72 years) compared to CA209-039 ([redacted] years). The majority of patients in the two cohorts of CheckMate 205 were aged between 30 and 65 years (cohort C [redacted] in cohort B), and [redacted] of patients are aged 65 or over. A break-down by age groups was not reported in CA209-039. The majority of patients included were white ([redacted] to [redacted]) and predominantly male ([redacted]). The Eastern Cooperative Oncology Group (ECOG) status was fairly similar across the cohorts and subgroup, and nearly equally divided between grade 0 (Fully active, able to carry on all pre-disease performance without restriction) and grade 1 (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work) in the cohorts. Details for the number of prior systemic regimen received by patients was grouped differently in the two studies, but cohort B of CheckMate 205 had the highest proportion of patients ([redacted]) that had received ≥5 prior systemic regimens[redacted] Patients who had received with prior radiotherapy ranged between 69% to 87%.

Results are reported narratively and consecutively for the two included studies and summarised using descriptive statistics (e.g. percentages, medians, ranges). Indirect comparisons were conducted to compare the efficacy of nivolumab with comparator data (further details of this reported in Section 0 below).

With regards to HRQoL, we note that the CS presents limited data for EORTC-QLQ-C30, restricted to weeks with clinically meaningful improvements from baseline for role functioning, social functioning and insomnia. The CS states that [redacted]

There are also limited results reported for the EQ-5D in the clinical effectiveness section, but the CS states that utility valuation for application within the economic model is described in CS Appendix 7.

### 3.1.7 Description and critique of the company's approach to the evidence synthesis

As stated earlier no randomised trials of nivolumab were identified by the systematic review (CS p. 36), only single-arm studies are available so consequently pairwise meta-analysis is not possible.

A narrative review of the evidence from the key nivolumab studies, CheckMate 205 (cohorts B and C) and study CA209-039 is presented in the CS Section 4 (p. 33 – 69). Where possible the ERG has checked key data presented in the CS against those in the publications[4,5] and found only one minor discrepancy.

To enable comparison of nivolumab against the comparators defined in the NICE scope and decision problem, for which there is no direct evidence, the company conducted an unadjusted indirect comparison and a matching-adjusted indirect comparison (MAIC) (CS p. 70 – 76 and CS Appendix 3).

Evidence on nivolumab was obtained from patient-level data for:

- Cohort B of the CheckMate 205 study (n = 80); median follow-up (OS): 15.7 months.
- Cohort C of the CheckMate 205 study (n = 98; two patients who had not received brentuximab vedotin excluded); median follow-up (OS): 8.9 months.
- Post-ASCT/brentuximab vedotin patients from CA209-039 (n = 15); median follow-up (OS):

CheckMate 205 study, whereas [redacted] in the CA209-039 study where investigators and IRRC used different versions of response criteria to assess response outcomes. Differences between investigator and IRRC assessments were greater in the CheckMate 205 study when considering complete and partial remission outcomes individually.

[redacted]

Median time to response in CA209-039 [redacted] For CheckMate 205 median time to response was only reported for Cohort B at the earlier follow-up period (median 8.92 months, minimum of 6 months) where the median time to objective response was just over 2 months (2.10 months by IRRC assessment and 2.17 month by investigator assessment). The time to complete remission was approximately 4.5 months (4.44 months by IRRC assessment and 4.75 months for investigator assessment). All responses were achieved within six months of treatment initiation and 58.5% of the 53 responders had achieved a response by the time of their first scan (9 weeks).

**Table 11 Response outcomes from CheckMate 205 and CA209-039**

| Parameter | CheckMate 205 | | | | CA209-039 | |
|---|---|---|---|---|---|---|
| | Cohort B (n=80) Median follow-up 15.7 months | | Cohort C, (n=100) Median follow-up 8.9 months | | Post BTX/ASCT (n=15) Median follow-up 23.3 months | |
| **Primary endpoint (in bold type)** | **IRRC** | **Investigator** | **IRRC** | **Investigator** | **IRRC** | **Investigator** |
| Objective response rate, n (%) | **54 (67.5)** | [redacted] | **73 (73.0)** | 66 (66.0) | 9 (60) | **13 (87)** |
| (95% CI) | **(57.2, 77.8)** | [redacted] | **(64.3, 81.7)** | (56.7, 75.3) | [redacted] | |
| **Additional endpoints** | | | | | | |
| Duration of response: events | [redacted] | [redacted] | [redacted] | 9/66 | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Median duration of response, months | [redacted] | [redacted] | [redacted] | 4.17 | [redacted] | [redacted] |
| Median time to response, months | | | | | [redacted] | [redacted] |
| CR, n (%)[a] | 6 (7.5) | [redacted] | 17 (17.0) | 26 (26.0) | 0 | 2 (13) |
| PR, n (%)[a] | 48 (60.0) | [redacted] | 56 (56.0) | 40 (40.0) | 9 (60) | 11(73) |
| SD, n (%)[a] | 17 (21.3) | [redacted] | 17 (17.0) | 24 (24.0) | 5 (33) | 2 (13) |
| Relapsed or PD, n (%)[a] | 7 (8.8) | [redacted] | [redacted] | [redacted] | | |
| UTD/NA, n (%)[a] | [redacted] | [redacted] | [redacted] | [redacted] | | |
| Duration of CR: events | [redacted] | [redacted] | [redacted] | [redacted] | | |
| Median duration of CR, months | [redacted] | [redacted] | [redacted] | [redacted] | | |
| Median time to CR, months | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Duration of PR: events | [redacted] | [redacted] | [redacted] | [redacted] | | |
| Median duration of PR, months | [redacted] | [redacted] | [redacted] | [redacted] | | |
| Median time to PR, months | | | | | [redacted] | [redacted] |

BTX, brentuximab vedotin; CI, confidence interval; CR, complete remission; IRRC, independent radiological review committee; NA, not available; ORR, objective response rate; OS, overall survival; PD, progressed disease; PFS, progression-free survival; PR, partial remission; SD, stable disease; UTD, unable to determine.

[a] Outcomes not annotated as n (%) in CS table 13 (p. 55), but % reported in text.

Indirect comparisons for response outcomes of objective response rate, complete remission and partial remission were made with potential comparator data identified by the systematic literature review. Response outcomes from the unadjusted indirect comparison were used in the economic model base case to stratify pre-progression utility based on response (CR, PR or SD) and outcomes from both the unadjusted indirect comparison and the MAIC are used in scenario analyses, including the scenario analyses on alloSCT (see below for cross references to the cost-effectiveness section of this report). IRRC-derived response rate data are used in a sensitivity analysis (ERG Table 64).

[redacted]

**Table 12 Indirect comparison outcomes for objective response rate**

| Scenario | Objective response rate | | | |
|---|---|---|---|---|
| | Unadjusted indirect comparison | | MAIC | |
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MAIC, matching-adjusted indirect comparison; SLR, Systematic literature review.

In addition to conducting indirect comparisons for the outcome of objective response rate, the CS also presented indirect comparison evidence for complete remission and partial remission (the two categories of response that contribute to the objective response rate). The results of these indirect comparisons can be seen in Table 13 and Table 14. Data from Table 13 and Table 14 can also be

found in the cost-effectiveness section in ERG Table 32 and Table 40. These data are also used in model scenarios #27 to #36 reported in ERG Table 59.

**Table 13 Indirect comparison outcomes for complete remission**

| Scenario | Complete Remission | | | |
|---|---|---|---|---|
| | Unadjusted indirect comparison | | MAIC | |
| | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

MAIC, matching-adjusted indirect comparison; SLR, Systematic literature review.

[redacted]

**Table 14 Indirect comparison outcomes for partial remission**

| Scenario | Partial remission | | | |
|---|---|---|---|---|
| | Unadjusted indirect comparison | | MAIC | |
| | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

MAIC, matching-adjusted indirect comparison; SLR, Systematic literature review.

[redacted]

### 3.3.2 Summary of overall survival results from CheckMate 205 and CA209-039

The CS presents the overall survival results for both data cut-off points of each study (CheckMate 205 cohort B CS p.47-48 and p. 50; cohorts B and C CS p. 55-56; CA209-039

[redacted]

**Table 16 Indirect comparisons for overall survival**

| Scenario | Overall Survival | | |
|---|---|---|---|
| | Unadjusted indirect comparison [redacted] | MAIC [redacted] | [redacted] |
| [redacted] | [redacted] | | |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | | [redacted] | [redacted] |
| [redacted] | | [redacted] | [redacted] |

MAIC, matching-adjusted indirect comparison; NR, Not reported; SLR, Systematic literature review.

[redacted]

[redacted]

**Table 18 Indirect comparison outcomes for progression-free survival**

| Scenario | Progression-free survival (Investigator assessed) | | |
|---|---|---|---|
| | Unadjusted indirect comparison [redacted] | MAIC | |
| | | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |

MAIC, matching-adjusted indirect comparison; NR, Not reported; SLR, Systematic literature review.

[redacted]

[redacted]

The objective response rate was the primary efficacy endpoint of both the CheckMate 205 study (when assessed by the IRRC) and the CA209-039 study (investigator assessed objective response rate). The objective response rate was [redacted] for the study defined primary endpoints. Median time to response was [redacted] and was just over 2 months (2.10 months by IRRC assessment and 2.17 month by investigator assessment) in Cohort B at median 8.92 months follow-up. The time to complete remission in Cohort B at this same time point was approximately 4.5 months. Indirect comparisons [redacted]

Results obtained from the MAIC were very similar to those obtained from the unadjusted indirect comparison. Indirect comparisons were also conducted for complete remission and partial remission, the two categories of response that contribute to the objective response rate outcome.

Median overall survival had not been reached in CheckMate 205 Cohort B (median follow-up 15.7 months) or in Cohort C (median follow-up 8.9 months). The six-month overall survival for Cohorts B and C was 96.1% (95% CI 92.0 to 100) and 94.0% (95% CI 89.1 to 98.9) respectively. Median overall survival had also not been reached for the 15 post-ASCT post-brentuximab vedotin patients in study CA209-039 at median follow-up of 23.3 months. The one-year OS rate is [redacted] A predicted value for median overall survival of [redacted] was calculated for the nivolumab pooled cohort which was used in indirect comparisons. The median OS from unadjusted indirect comparison [redacted] in the four scenarios (1a, 1b, 2a, 2b) with comparator data. The overall survival estimates obtained by MAIC were [redacted] than those obtained by the unadjusted indirect comparison for each scenario.

1 or 2. Infusion related reaction stood out as differing between the two studies affecting 20% of participants in CheckMate 205 Cohort B and 12.9% of the overall population in comparison to [redacted] of participants in CA209-039. In CheckMate 205 there were three Grade 5 AEs (multi-organ failure and two patients with atypical pneumonia and dyspnoea) but no Grade 5 AEs were reported for CA208-039. Laboratory parameter abnormalities were also reported which were mostly Grade 1-2. The most common grade 3-4 haemotological abnormality was [redacted] The proportion of patients who discontinued nivolumab treatment due to a drug-related adverse event was [redacted] A serious drug-related adverse event was experienced by 9.6% of the CheckMate 205 study population (6.3% of Cohort B) and 13.0% of those in study CA209-039.

Identification of AEs of special clinical interest was conducted to characterise any AEs that are potentially associated with the use of nivolumab. Skin abnormalities were the most frequently reported of these adverse events, irrespective of causality, in CheckMate 205 Cohort B [redacted]

There is uncertainty about the effectiveness of nivolumab in comparison to alternative treatment options because the two key studies of nivolumab are single-arm studies. In its interpretation of the clinical evidence, the company highlights that ORR in both studies has been good. [redacted] patients have achieved complete response in CheckMate 205 and [redacted] in CA209-039, when response was assessed by investigators. At the follow-up times reported in the CS the median progression-free survival was at least 11 months in CheckMate 205 Cohorts B and C and had not been reached in CA209-039. [redacted]

To compare the efficacy of nivolumab with potential comparators an indirect comparison approach was used. The company undertook a systematic review to identify evidence on potential comparators and found 12 studies that provided data in a population, at least some of whom had received prior ASCT and prior brentuximab vedotin. The ERG believes it is likely that the company's systematic review identified all the relevant evidence, but this is limited in terms of quality (the studies were predominantly phase 1 or 2 single-arm studies), and completeness of reporting (seven only reported as conference abstracts, limited follow-up up periods, outcomes of PFS and OS often not reported). [redacted]

### 4.3.2 Model structure

The company presented a Markov model consisting of three primary health states. The model has a time horizon of 40 years (lifetime), monthly cycle length, applies appropriate discounting (3.5% per annum for costs and benefits), and the impact of half-cycle correction is included as a sensitivity analysis. The company included half-cycle correction in the base case analysis.

The model is built in Microsoft Excel, however, the model is executed almost entirely in the Visual Basic (VBA) programming language. The spreadsheets cannot be used to generate any calculations or model results independently of the VBA code — macros are required to produce all types of results: base-case, deterministic sensitivity analyses, scenario analyses, and probabilistic sensitivity analyses. Inputs into the model must take very specific forms or risk crashing the VBA code that is responsible for producing results. These limitations of the model rendered the model opaque and difficult to validate. All scenario analyses required manual modification of input parameters and not all analyses could be replicated, due either to insufficient explanation of methods or due to potential parameter discrepancies. NICE and the ERG requested clarification for the modelling methods and parameters used in scenario analyses. The company provided an adequate response to the clarification request.

A model schematic is presented in the CS (see CS Figure 23 p. 98), but more complex transitions are not included in the model schematic. The base case model is similar to the standard three state cancer model seen in many STAs. Patients enter the model in the pre-progression state, receiving initial therapy (i.e. nivolumab or SoC in the base case analysis). Within the pre-progression state, there are sub-states for alternative levels of response: complete response, partial response, and stable disease (CR, PR, and SD in Figure 9). Patients in the pre-progression state may remain on treatment in the pre-progression state, discontinue treatment in the pre-progression state, progress, or die. Following discontinuation, patients may enter the state represented as subsequent therapy within the pre-progression state; in the base case analysis, this is best supportive care (BSC), but in scenario analyses this may be subsequent chemotherapy. BSC consists primarily of palliative care, including palliative chemotherapy. Once patients have progressed they receive BSC. In the progressed state patients may either remain in that state or die.

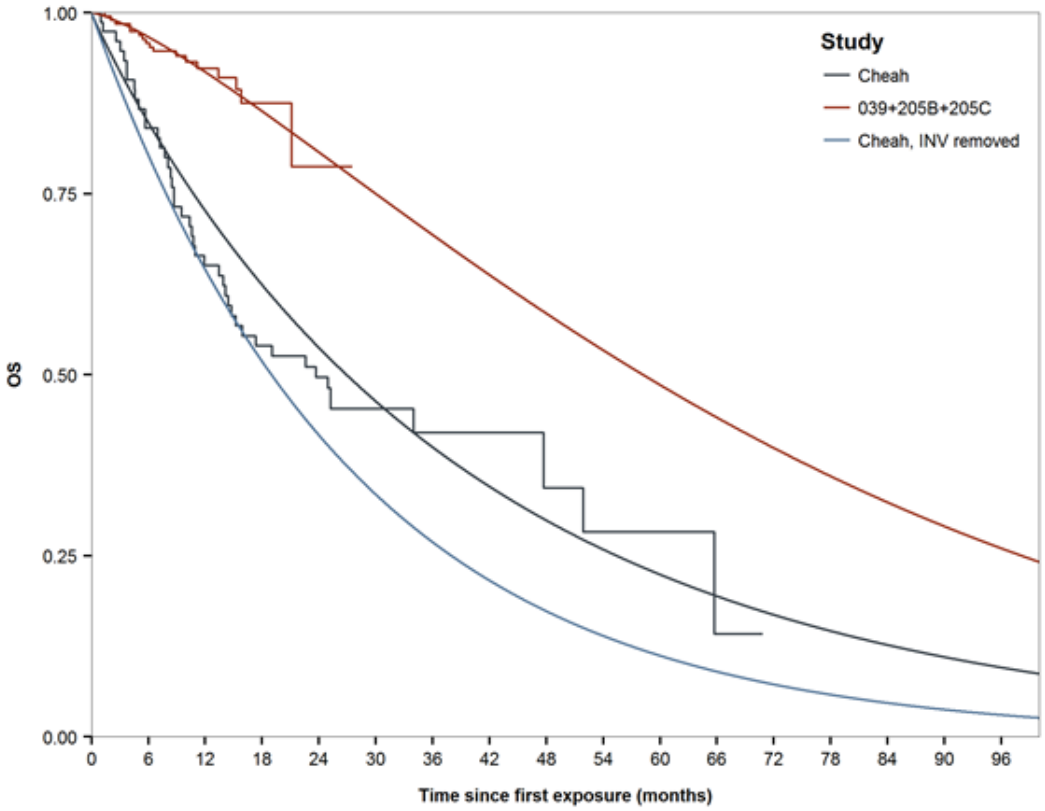


**Figure 13 Overall survival: SoC, (CS, Figure 30)**

#### 1.1.1.1 Response rates

The response rates or best overall response (BOR) rates, within this submission, have no direct impact on progression or survival, in the economic model. This is due to the use of survival data that implicitly incorporates any impact on patients' survival. However, response rates are used to estimate utility values (details in section 4.3.6). Response rates are also applied in stopping rules and switching to subsequent therapies such as alloSCT.

Within the company model, the response rates used for nivolumab are derived from investigator-assessments from the two nivolumab studies and the impact of applying IRRC-derived response rates are assessed in sensitivity analyses. Response rates for the SoC arm are derived from the Cheah study after adjustment for exclusion of patients receiving investigational agents. Table 32, summarises the response rates applied within the base case analysis of the economic model.

**Table 40 Response weighted utility values for nivolumab and SoC**

| Health State | % in state, Nivolumab | % in state SoC | Swinburn 2015 | Nivolumab utility data |
|---|---|---|---|---|
| Complete Remission | [redacted] | 15.69% | 0.910 | [redacted] |
| Partial Remission | [redacted] | 23.53% | 0.790 | [redacted] |
| Stable Disease | [redacted] | 60.78% | 0.710 | [redacted] |
| **Nivolumab utility (weighted average)** | | | 0.801 | [redacted] |
| **SoC utility (weighted average)** | | | 0.760 | [redacted] |

The CS acknowledges that the large difference in utility for post-progression patients in the nivolumab and SoC arms may be considered counter-intuitive; however the company suggests that nivolumab has a unique mechanism of action that stimulates the patient's immune system and this would extend into benefits in quality of life in the post-progression phase, even though patients have discontinued treatment. The ERG is sceptical whether this large difference in utility is realistic.

The ERG identified a study by Ramsey and colleagues[42] that reported EQ-5D values for patients with relapsed or refractory Hodgkin lymphoma post-ASCT for patients receiving brentuximab vedotin vs. placebo. The study shows utility values for progressed disease for the placebo group to be between 0.85 (after 3 months) to 0.7 (after 24 months). Therefore, we suggest that the results from Swinburn and colleagues[41] are outliers and may not be realistic. The Swinburn study used TTO methodology using estimates from the general public and it may be that their perception of the disease is not consistent with EQ-5D valuation. In summary, therefore we conclude that our preferred approach is for the economic model to use the post-progression utility values from the CheckMate 205 study for the patients treated with nivolumab and with SoC. The ERG investigates the effect of changing these utility values in the ERG analyses reported in section 4.4.

<u>Age dependent disutility</u>

Age dependent disutility has been applied to patients according to patient age, based on the estimated health utility of the general population (Ara and Brazier[43]). The age-dependent decrement is calculated using the difference in utility between patients' age-related utility and the age-related utility at the age of patients at baseline. The ERG is unable to match the age related disutility to the study by Ara and Brazier and suggests the data is from the report by Kind and colleagues.[44]

**Table 59 Alternative ITC comparisons (CS Table 85, p. 160) Post-ASCT, Post-brentuximab vedotin studies, SoC parameters and results**

| # | Analysis parameters[a,b] | Nivolumab Costs | Nivolumab QALYs | SoC Costs | SoC QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|
| 0 | Base Case | [redacted] | [redacted] | £21,090 | 0.932 | £19,882 |
| 27 | Unadjusted ITC, all studies, fixed effects.<br>PFS = λ: 0.1134<br>OS= λ: 0.0204<br>Complete response= [redacted]<br>Partial response= [redacted]<br>Utility (pre-progression)= [redacted] | [redacted] | [redacted] | £23,379 | 1.532 | £24,277 |
| 28 | Unadjusted ITC, all studies, random effects<br>PFS = λ: 0.1134<br>OS= λ: 0.0204<br>Complete response= [redacted]<br>Partial response= [redacted]<br>Utility (pre-progression)= [redacted] | [redacted] | [redacted] | £23,379 | 1.540 | £24,361 |
| 29 | Unadjusted ITC, subgroup,[c] fixed effects<br>PFS = λ: 0.1576<br>OS= λ: 0.0261<br>Complete response= [redacted]<br>Partial response= [redacted]<br>Utility (pre-progression)= [redacted] | [redacted] | [redacted] | £20,149 | 1.229 | £22,626 |
| 30 | Unadjusted ITC, subgroup,[c] random effects<br>PFS = λ: 0.1576<br>OS= λ: 0.0261<br>Complete response= [redacted]<br>Partial response= [redacted]<br>Utility (pre-progression)= [redacted] | [redacted] | [redacted] | £20,149 | 1.236 | £22,686 |
| 31 | MAIC ITC, all studies, fixed effects.<br>PFS = λ: 0.1169<br>OS= λ: 0.0222<br>Complete response= [redacted]<br>Partial response= [redacted]<br>Utility (pre-progression)= [redacted] | [redacted] | [redacted] | £22,554 | 1.435 | £23,605 |
| 32 | MAIC ITC, all studies, random effects<br>PFS = λ: 0.1169<br>OS= λ: 0.0222 | [redacted] | [redacted] | £22,554 | 1.442 | £23,681 |

| # | Analysis parameters[a,b] | Nivolumab Costs | Nivolumab QALYs | SoC Costs | SoC QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|
| 42 | MAIC ITC, all studies, random effects<br>PFS = λ: 0.0615<br>OS= λ: 0.0239<br>Complete response= [redacted]<br>Partial response= [redacted]<br>Utility (pre-progression)= [redacted] | [redacted] | [redacted] | £24,384 | 1.506 | £23,540 |
| 43 | MAIC ITC, subgroup,[c] fixed effects<br>PFS = λ: 0.0881<br>OS= λ: 0.0294<br>Complete response= [redacted]<br>Partial response= [redacted]<br>Utility (pre-progression)= [redacted] | [redacted] | [redacted] | £21,400 | 1.206 | £21,918 |
| 44 | MAIC ITC, subgroup,[c] random effects<br>PFS = λ: 0.0881<br>OS= λ: 0.0294<br>Complete response= [redacted]<br>Partial response= [redacted]<br>Utility (pre-progression)= [redacted] | [redacted] | [redacted] | £21,400 | 1.209 | £21,951 |

ICER, Incremental cost-effectiveness ratio; MAIC ITC, matching-adjusted indirect comparisons Indirect treatment comparison; OS, overall survival; PFS, progression-free survival SoC: standard of care; QALY, Quality-adjusted life year.

[a] Results for the base case from CS Table 63 (CS p. 137)

[b] Parameters and results for CS Analyses 37-44 derived from CS Table 85 (CS p. 158)

[c] Subgroup of SLR studies based on those studies where subgroup of post-ASCT population is reported or where >70% of patients match this criteria; this includes efficacy of investigational agents.

A full critique of the alternative synthesis methods used in Analysis 27-44 is reported in Section 3.1.7. In brief, the MAIC methods lacked sufficient power and it was unclear how the matching criteria were chosen or whether only the most relevant criteria were included. Additionally, all survival analyses assume an exponential curve, which was insufficiently justified.

**F. Analyses with alternative baseline age**

The company undertook two analyses to represent the bimodal age distribution of classical Hodgkin lymphoma. The parameters of these cohorts and the results of the analyses are reported in Table 61.

| | | | | | | |
|---|---|---|---|---|---|---|
| | Pre-progression = 0.76<br>Post-progression = 0.38 | | | | | |
| 54 | Response-specific pre-progression utilities applied<br>Nivolumab<br>CR = [redacted]<br>PR = [redacted]<br>SD = [redacted]<br>post-progression = [redacted]<br>SoC<br>CR = 0.91<br>PR = 0.79<br>SD = 0.71<br>post-progression = 0.38 | [redacted] | [redacted] | £21,090 | 0.932 | £19,930 |

CR, complete response; ICER, Incremental cost-effectiveness ratio; PR, partial response; SD, stable disease; SoC, standard of care; QALY, Quality-adjusted life year

[a] Results for the base case from CS Table 63 (CS p. 137).

[b] Parameters and results for CS Analyses 51-54 derived from CS Table 88 (CS p. 164).

**I. Analyses testing other modelling assumptions**

Several analyses that did not fall under other classifications were conducted by the company. Analysis 55 presents results without half-cycle correction. Analysis 56 assumes that neither SoC nor nivolumab have adverse events. The company postulated that available utilities may already account for the toxicity of therapies, which might make utilising disutilities for adverse events double counting, so conducted Analysis 56. Analysis 57 doubles post-progression costs. Analysis 58 applies IRRC-assessed endpoints for nivolumab. Table 64 reports the results of these analyses.

**Table 64 CS Analyses testing other modelling assumptions**

| # | Analysis parameters | Nivolumab Costs | Nivolumab QALYs | SoC Costs | SoC QALYs | ICER (£/QALY) | Source |
|---|---|---|---|---|---|---|---|
| 0 | Base Case | [redacted] | [redacted] | £21,090 | 0.932 | £19,882 | Table 63 (p. 137) |
| 55 | No half-cycle correction | [redacted] | [redacted] | £23,732 | 0.960 | £19,730 | Table 71 (p. 151) |
| 56 | Assume that utility scores from studies include disutilities for AE, no AEs modelled | [redacted] | [redacted] | £19,233 | 0.951 | £20,580 | Table 89 (p.164) |
| 57 | Alternative post-progression costs: resource use doubles post progression | [redacted] | [redacted] | £24,978 | 0.932 | £21,218 | Table 90 (p.165) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 58 | Application of IRRC-assessed endpoints for nivolumab<br>PFS<br>μ: 2.656<br>σ: 1.121<br>Response rates<br>CR: [redacted]<br>PR: [redacted]<br>Utilities<br>Pre-progression: [redacted]<br>Post-progression: [redacted] | [redacted] | [redacted] | £21,090 | 0.932 | £17,617 | Table 91 (p. 165), Table 92 (p. 166) |

AE, adverse events; CR, complete response; ICER, Incremental cost-effectiveness ratio; IRRC, independent regulatory review committee; PR, partial response; SoC: standard of care;

**Summary**

The company conducted a large number of scenario analyses. All 58 scenario analyses required manual modification of input parameters in order to run and validate analyses. The ERG was unable to replicate some analyses, which led to requests for clarification on how analyses were run and updated analysis parameters were received from the company. The company complied with the clarification requests, providing both unrounded input values and versions of the model that allowed running alternative analyses with full explanation of the methods. All analyses produced results under £50,000 per QALY (end-of-life cost-effectiveness threshold) and only two analyses produced results above £30,000 per QALY (Analysis 52 and Analysis 53), both analyses assessed alternative post-progression utility scores. In the CS exploratory analyses, Nivolumab appears robust to parameter uncertainty. There are some unresolved uncertainties that we explore in Section 4.4.

#### 4.3.10.3 Probabilistic Sensitivity Analysis (PSA)

The company undertook assessment of joint parameter uncertainty using a PSA. All relevant parameters, including costs and survival were included in the PSA. Costs were sampled using gamma distributions. Age was sampled using the normal distribution. Proportions and percentages were sampled using the beta distribution.

In general, each parameter included in the PSA is sampled independently; however, there are several exceptions to this approach. The model allows health state costs to be specified by treatment and response state; however, the base case analysis applies pre-progression and post-progression cost regardless of response or therapy arm. Thus, within the PSA, treatment arm-

analyses, including the ERG base case produced ICERs above £30,000 per QALY, the upper bound of the NICE threshold range for cost-effectiveness.

**Table 67 Results of ERG exploratory analyses**

| # | Analysis | Nivolumab | | SoC | | |
|---|---|---|---|---|---|---|
| | | Costs | QALY | Costs | QALY | ICER |
| 0 | Base Case | [redacted] | [redacted] | £21,090 | 0.932 | £19,882 |
| 20 | CS alloSCT Scenario B (CS Table 75, p. 153) | [redacted] | [redacted] | £24,880 | 1.076 | £20,433 |
| ERG1 | Alternative special transition case population | [redacted] | [redacted] | £27,692 | 1.184 | £20,616 |
| ERG2 | Alternative SoC survival (including investigational agents) | [redacted] | [redacted] | £23,756 | 1.278 | £22,348 |
| ERG3 | Alternative nivolumab pre-progression utilities | [redacted] | [redacted] | £24,880 | 1.076 | £20,476 |
| ERG4 | Alternative SoC pre-progression utilities (CheckMate 205 utilities weighted by response in Cheah) | [redacted] | [redacted] | £24,880 | 1.101 | £20,603 |
| ERG5 | SoC post-progression utility same as nivolumab post-progression utility | [redacted] | [redacted] | £24,880 | 1.633 | £25,209 |
| ERG6 | alloSCT survival modelled using original treatment OS curves instead of lognormal curve from Cheah | [redacted] | [redacted] | £23,952 | 0.952 | £21,517 |
| ERG7 | Alternative post-progression utility for alloSCT intervention | [redacted] | [redacted] | £24,880 | 1.212 | £18,174 |
| ERG8 | ERG calculated costs for SoC (omitting miniBEAM and dexaBEAM) | [redacted] | [redacted] | £23,360 | 1.076 | £20,950 |
| ERG9 | SoC OS, PFS, and response from CS Analysis 30, utilities weighted using CheckMate 205 values) | [redacted] | [redacted] | £28,806 | 2.227 | £31,392 |
| ***ERG10*** | ***ERG Base case combines ERG1 to ERG8*** | [redacted] | [redacted] | ***£23,043*** | ***2.102*** | ***£36,525*** |
| ERG11 | ERG Base case with SoC costs derived from CS | [redacted] | [redacted] | £24,465 | 2.102 | £35,684 |
| ERG12 | ERG Base case with SoC costs derived from BTX STA | [redacted] | [redacted] | £19,791 | 2.102 | £38,451 |
| ERG13 | ERG Base case, alloSCT survival from Cheah for both arms | [redacted] | [redacted] | £24,027 | 2.363 | £25,647 |
| ERG14 | ERG Base case, alloSCT survival from nivolumab | [redacted] | [redacted] | £23,233 | 2.150 | £37,489 |

# CONFIDENTIAL UNTIL PUBLISHED

## Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

## Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma

## ADDENDUM

Additional information requested by the National Institute for Health and Care Excellence

**Produced by** Southampton Health Technology Assessments Centre (SHTAC)

**Addendum date** 07 February 2017

**Key to colour highlighting used in addendum**

*Academic in confidence (AIC) information in yellow.*

*Commercial in confidence (CIC) information in blue.*

**TABLE OF CONTENTS**

# 1 Introduction

This is an addendum to the Evidence Review Group (ERG) report for the single technology appraisal (STA) "Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma". At the request of the National Institute for Health and Care Excellence (NICE), the ERG has provided the following additional information to inform the Appraisal Committee Meeting:

- Methods and results of generating a Gompertz overall survival (OS) curve for nivolumab
- Analyses applying the Gompertz OS curve to nivolumab survival in the ERG base case (analysis ERG10 in the ERG report)

# 2 Generating a Gompertz curve for nivolumab OS

In the company submission, the company fits survival curves to OS using the following curves: exponential, lognormal, log-logistic, Weibull, Gompertz and generalised gamma. In the base case, the Weibull was used to model OS, whilst the exponential, lognormal, and log-logistic curves were explored in sensitivity analyses. As can be seen in Figure 1, the curve with shortest mean survival is the Gompertz curve, predicting mean OS of [redacted] months.


**Figure 1 Parameterisation of overall survival (CS Figure 26 , page 106)**

There is a great deal of uncertainty in the OS estimates for nivolumab patients in the trial population as the OS data are immature. AiC and BiC data showed that all curves were a reasonable fit for nivolumab survival and therefore the choice of curve has been based on clinical plausibility. In order to further explore the uncertainty around OS, the committee lead team requested that the ERG conduct analyses using the Gompertz curve to estimate overall survival for nivolumab, as a clinician on the lead team believed that mean OS was likely to be shorter than the [redacted] years predicted by the Weibull OS model.

$$S(t) = e^{-a(e^{bt}-1)}$$ (Equation 1, Gompertz survival function)

In order to replicate the Gompertz OS curve (Equation 1, above) for nivolumab we attempted to build a curve using the rate (*a*) and shape (*b*) statistics reported in Figure 1 (CS Figure 26, p. 106). This curve did not match the Gompertz curve in Figure 1 and the CS did not provide details of the Gompertz survival function used. However, because the Gompertz curve is a two

parameter model and because we know that the mean survival for the curve is 41.7 months, we were able to provide plausible parameters (*a* = [redacted], and *b*=[redacted]) for use with the Gompertz equation above which produced a curve that matched Figure 1. The survival curve for this recreated Gompertz curve is presented in Figure 2, below. This curve is used in this addendum.


**Figure 2 Gompertz curve recreated by the ERG**

The ERG has reservations about the use of the Gompertz distribution for modelling nivolumab. Figure 3 shows the hazard for nivolumab overall survival over time. The gradual increase in hazard, with greatest risk at four years and hazard declining quickly thereafter, may not be clinically plausible. Additionally comparing the Gompertz curve to SoC survival curves in the CS and ERG base cases shows that the SoC survival curves cross the Gompertz curve of nivolumab (see Figure 4), which appears unlikely to the ERG.


**Figure 3 Nivolumab OS hazard over time for Gompertz curve**

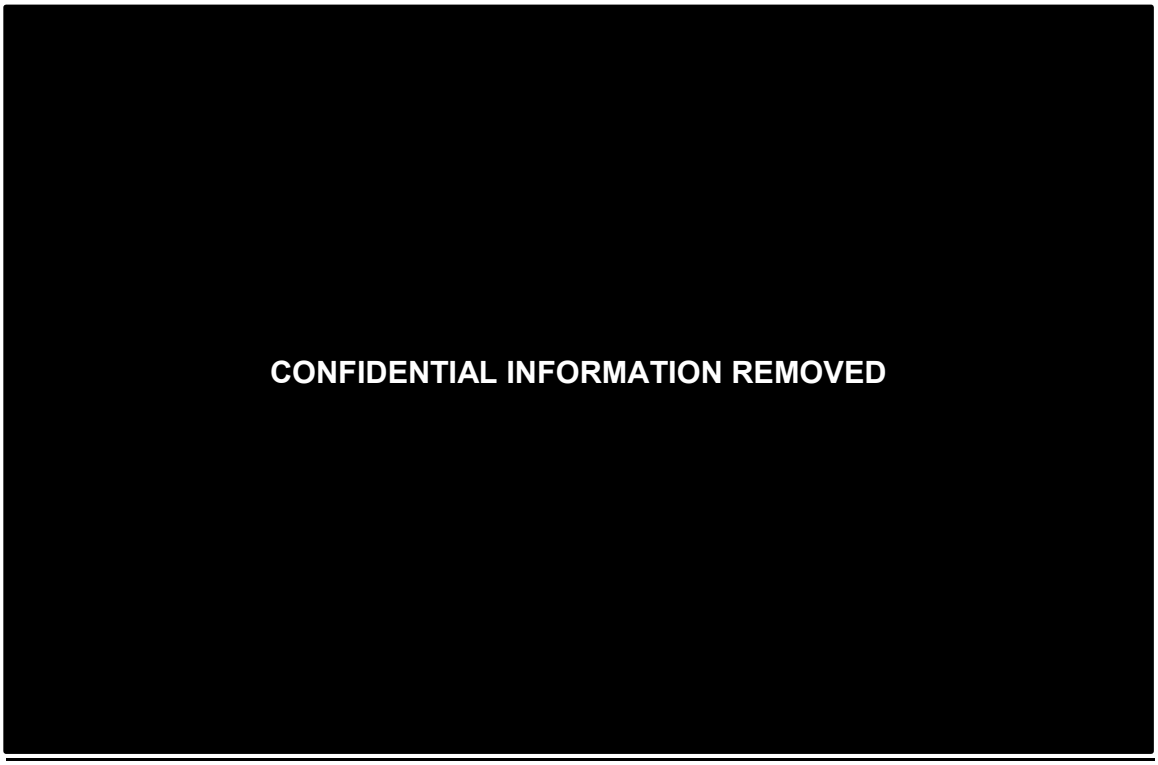


**Figure 4 Nivolumab and SoC survival curves**

The ERG did not conduct analyses using Gompertz curves for SoC as using the Gompertz curves would have improved survival for SoC. Clinical experts did not find this plausible.

# 3 Analyses applying the Gompertz OS curve to nivolumab survival in the ERG base case (analysis ERG10 in the ERG report)

The ERG conducted analyses using the ERG Base Case (for assumptions and justifications see Section 4.4 of the ERG report). The ERG ran an analysis replacing all OS curves for nivolumab (pre-progression, post-progression, and alloSCT OS on nivolumab) with the Gompertz survival curve. Table 1 reports the results of this analysis.

**Table 1 Results of ERG Addendum analyses containing alloSCT**

| | | Nivolumab | | SoC | | |
|---|---|---|---|---|---|---|
| **#** | **Analysis** | **Costs** | **QALY** | **Costs** | **QALY** | **ICER £/QALY)** |
| ERG10 | ERG Base Case[a] | [redacted] | [redacted] | £23,043 | 2.102 | £36,525 |
| ERGADD1 | ERG Base Case, Nivolumab OS using Gompertz | [redacted] | [redacted] | £23,043 | 2.102 | £122,825 |

[a] see Table 65, p. 152-153 in ERG report

# 4 Conclusions

There is substantial uncertainty on the long-term effectiveness of nivolumab and its comparator, SoC. NICE requested that the ERG produce an analysis using the Gompertz curve for overall survival for nivolumab. The ERG have produced this analysis although they have reservations about how clinically plausible the Gompertz curve may be. Unfortunately, the uncertainty around overall survival is unlikely to be resolved without further empirical data.