Public observer slides

# Lead team presentation

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

1st Appraisal Committee meeting

Background and Clinical Effectiveness

Committee C

Lead team: Nigel Langford, Stephen O'Brien, Judith Wardle

ERG: Southampton Health Technology Assessments Centre

NICE technical team: Anna Brett, Nicola Hay

Company: Bristol-Myers Squibb

15 February 2017

# Key clinical issues preview

- Is there a ‘standard of care’ for patients post autoSCT & brentuximab?
- What criteria are used in clinical practice for stopping nivolumab treatment?
  - SmPC states ‘Treatment …should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.’
- What proportion of people would be expected to proceed to alloSCT after nivolumab? After standard of care?
- How effective is nivolumab?
  - Phase I and II, non comparative, single arm trials
  - Data immature; follow-up continuing
- How robust is indirect comparison of nivolumab with standard of care?
  - How well do populations in comparator studies match those in nivolumab studies, and reflect patients in UK?
  - Is it appropriate to exclude investigational agents from Cheah data set?
  - To what extent do benefits of nivolumab exceed those of comparators?

# 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 20-34 years and over 70 years
- 1 year survival 91%; 10 year survival 80%
- Outcome poor for those with relapsed or refractory disease following autologous stem cell transplant (autoSCT) (median overall survival 19-29 months), and poorer following autoSCT and brentuximab (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 (autoSCT) 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

# Patient, professional & CDF clinical lead feedback

- Patients with relapsed or refractory lymphoma can have debilitating and distressing symptoms 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 young and fit with potential for 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 reduced/manageable side effects
- Nivolumab is a promising rescue salvage regime, could potentially increase proportion of patients eligible for allogeneic stem cell transplant (allo-SCT), and is better tolerated compared with standard chemotherapy
- Statement from Cancer Drugs Fund clinical lead:
  - Data for nivolumab immature, although early impact as palliative treatment evident because response rate is high and treatment is reasonably tolerated
  - Unclear how many patients achieve sufficient response to allow salvage with allo-SCT
  - Potential rate of further SCT likely to be higher than rate of complete responses seen in studies

# Decision problem
## Company's submission

| | NICE scope | Company submission |
|---|---|---|
| **Population** | People with relapsed or refractory classical Hodgkin lymphoma following:<br>• **autologous SCT 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) |

# Decision problem
## ERG's critique

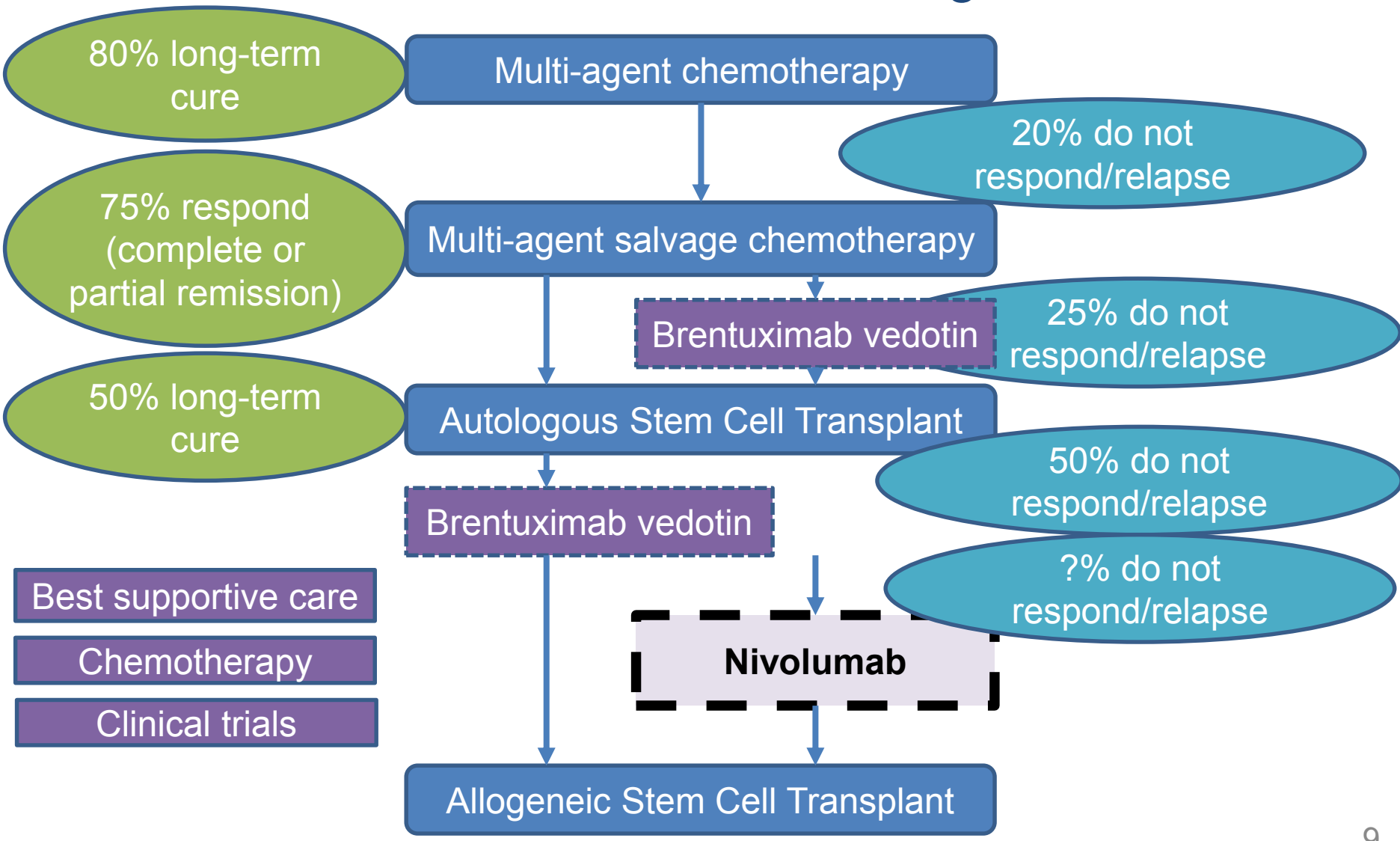
| | Company submission | ERG comment |
|---|---|---|
| **Population** | People with relapsed or refractory classical Hodgkin lymphoma following:<br>• autologous stem cell transplant and brentuximab vedotin | • Population covered in the company's submission is acceptable.<br>• Nivolumab's marketing authorisation does not cover the 2nd population. |
| **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, and there is a lack of detail about precise combinations of treatment regimens<br>• However, not aware of a more appropriate source of data |

# Treatment pathway

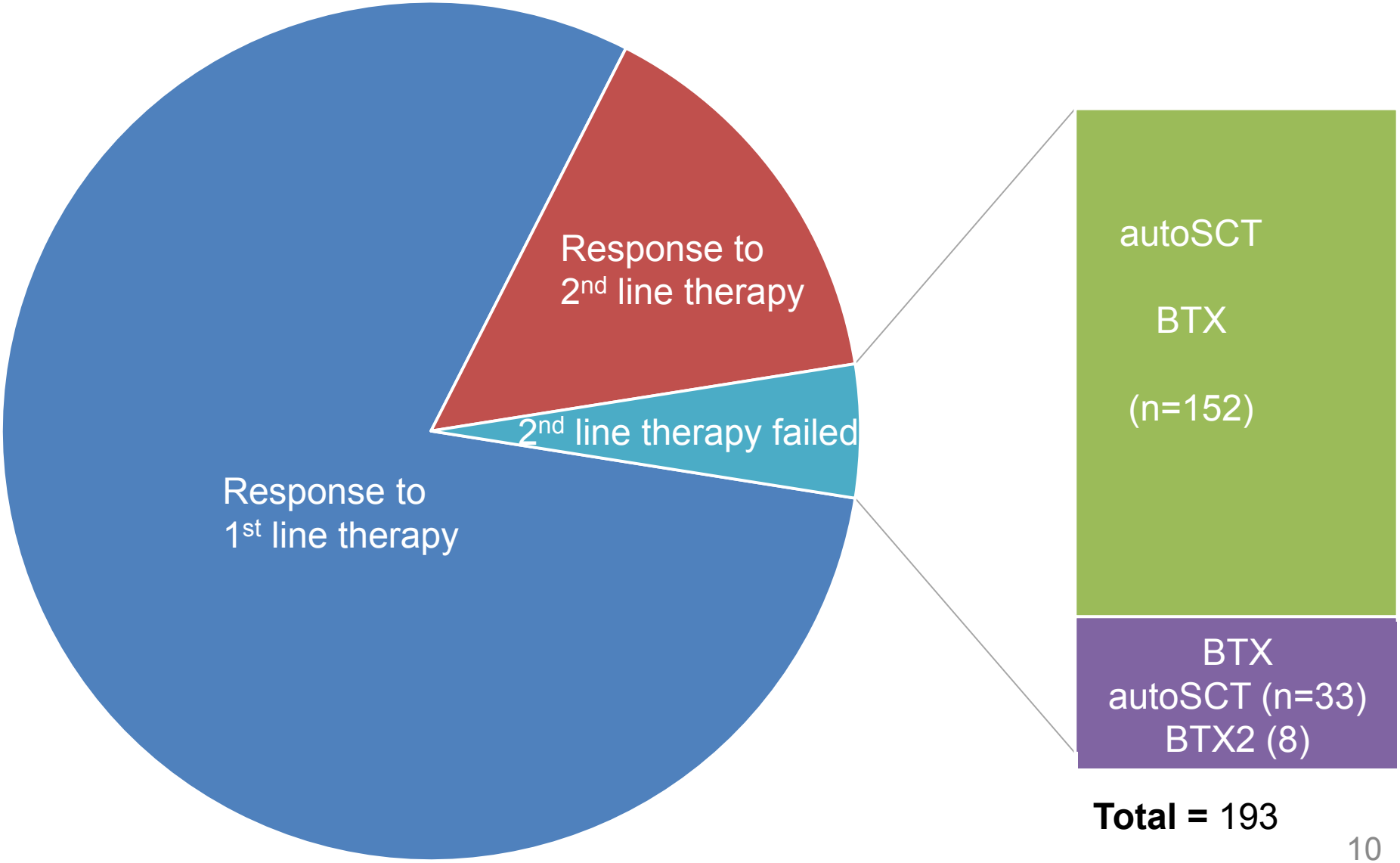
- If autoSCT fails to delay disease progression, there's no standard therapy
- British Committee for Standards in Haematology (BCSH) guidelines recommend that treatment aims to attain sufficient response to allow allogeneic transplantation (alloSCT)
- BCSH guidelines recommend brentuximab (BTX) as an option for patients whose disease has relapsed after autoSCT, and an option prior to autoSCT for patients who are either ineligible for autoSCT 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

# Current management

## No standard of care, no NICE guidance



# Clinical response & trial populations




**Total =** 193

# Company's clinical evidence

| Trial | CheckMate 205 | CA209-039 |
|---|---|---|
| Design | Non-comparative, single-arm | |
| | Phase 2 | Phase 1 |
| Population | Adults with cHL after autoSCT failure:<br>Cohort A: BTX-naïve (63)<br>**Cohort B: Prior BTX after autoSCT (80)**<br>**Cohort C: Prior BTX before or after autoSCT (98)** | Adults with relapsed, refractory haematological malignancies (cHL n=23)<br>**15 had previously had autoSCT 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 |

# 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 |

# Company's clinical evidence

## Results: CheckMate 205, August 2015

| | 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 | | |

# Company's clinical evidence

## Results: CheckMate 205, April 2016

| | Cohort B (n=80) | | Cohort C (n=98) | |
|---|---|---|---|---|
| | 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

# 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

# Company's clinical evidence

## Progression-free survival: CheckMate 205 (cohort B)

# Company's clinical evidence

## Progression-free survival: CheckMate 205 (cohort C)

# Company's clinical evidence

## Progression-free survival: CA209-039

# Company's clinical evidence

## Overall survival: CheckMate 205 (cohort B)

# Company's clinical evidence

## Overall survival: CheckMate 205 (cohort C)

# Company's clinical evidence
## Overall survival: CA209-039

# 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

# Company's clinical evidence
## Indirect treatment comparison with SOC

- No data providing direct comparative evidence for nivolumab versus comparators
- Limited evidence for patients with HL who have had ASCT and BTX
- Identified evidence predominantly derived from investigational agents and patients who are typically less treatment experienced, so outcomes will overestimate those seen in clinical practice
- Unadjusted and matching-adjusted indirect comparisons of relevant nivolumab patient-level data undertaken (matching-adjusted results similar to unadjusted; not shown here)
- Unadjusted indirect comparison used for treatment effectiveness parameters in base case economic model
- Indirect comparison also undertaken for post-ASCT population only (results not shown here)

# ERG's critique

## Indirect treatment comparison with SOC – studies

- [redacted] studies (including CheckMate 205 and CA209-039)
- Proportion of enrolled patients in each study who had both previous ASCT and BTX ranged from [redacted] to [redacted]
- Identified studies included [redacted] randomised trial. [redacted] studies reported as conference abstracts only; remainder phase 1/2 single arm studies
- [redacted] studies reported both previous ASCT and BTX treatment; [redacted] of those reported outcomes separately for these subgroups
- [redacted] reported survival outcomes for patients who had both previous ASCT and BTX treatment.
- Overview of similarities and differences between participants in comparator studies and those in nivolumab studies not provided (median age range suggests [redacted] population in comparator studies than nivolumab pooled cohort)
- Comparability of outcome measures across studies not commented on (PFS defined differently between nivolumab studies and Cheah)

# ERG's critique

## Cheah 2016 as comparator evidence

- Cheah 2016 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

# 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 |
| AutoSCT (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; AutoSCT, autologous stem cell treatment

# ERG's critique
## Indirect treatment comparison

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

# 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

# Company's clinical evidence

## Progression-free survival: Nivolumab pooled cohort

# Company's clinical evidence

## Overall survival: Nivolumab pooled cohort

# Company's clinical evidence

## Results: Unadjusted indirect treatment comparison

| ***Cheah (excluding investigational agents) chosen as comparator*** | Objective response rate | | OS (mths) | PFS (mths) |
|---|---|---|---|---|
| | RR | % | | |
| [redacted] | | [redacted] | [redacted] | [redacted] |
| [redacted] | | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | | |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | | |

RR, relative risk; OS, overall survival; PFS, progression-free survival; SLR, systematic literature review; ASCT, autologous stem cell transplant; BTX, brentuximab vedotin

# 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, agree Cheah 2016 best available evidence for comparators

# Key clinical issues

- Is there a ‘standard of care’ for patients post autoSCT & brentuximab?
- What criteria are used in clinical practice for stopping nivolumab treatment?
  - SmPC states ‘Treatment …should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.’
- What proportion of people would be expected to proceed to alloSCT after nivolumab? After standard of care?
- How effective is nivolumab?
  - Phase I and II, non comparative, single arm trials
  - Data immature; follow-up continuing (CA209-039 still recruiting)
- How robust is indirect comparison of nivolumab with standard of care?
  - How well do populations in comparator studies match those in nivolumab studies, and reflect patients in UK?
  - Is it appropriate to exclude investigational agents from Cheah data set?
  - To what extent do benefits of nivolumab exceed those of comparators?

Public observer slides

# Lead team presentation

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

1st Appraisal Committee meeting

Cost Effectiveness

Lead team: Nigel Langford, Stephen O'Brien, Judith Wardle

15 February 2017

# Key issues preview

- Uncertainty in the absence of head-to-head comparison
- Survival modelling for SOC: Cheah study excluding people who had received investigational agents or overall population from Cheah study?
- Survival modelling for nivolumab: Weibull, Gompertz, other?
- Widely different utility values post progression?
- AlloSCT as a scenario or base case?
- Does nivolumab meet criteria for life-extending treatments at end of life?
- Does nivolumab represent an innovative treatment?

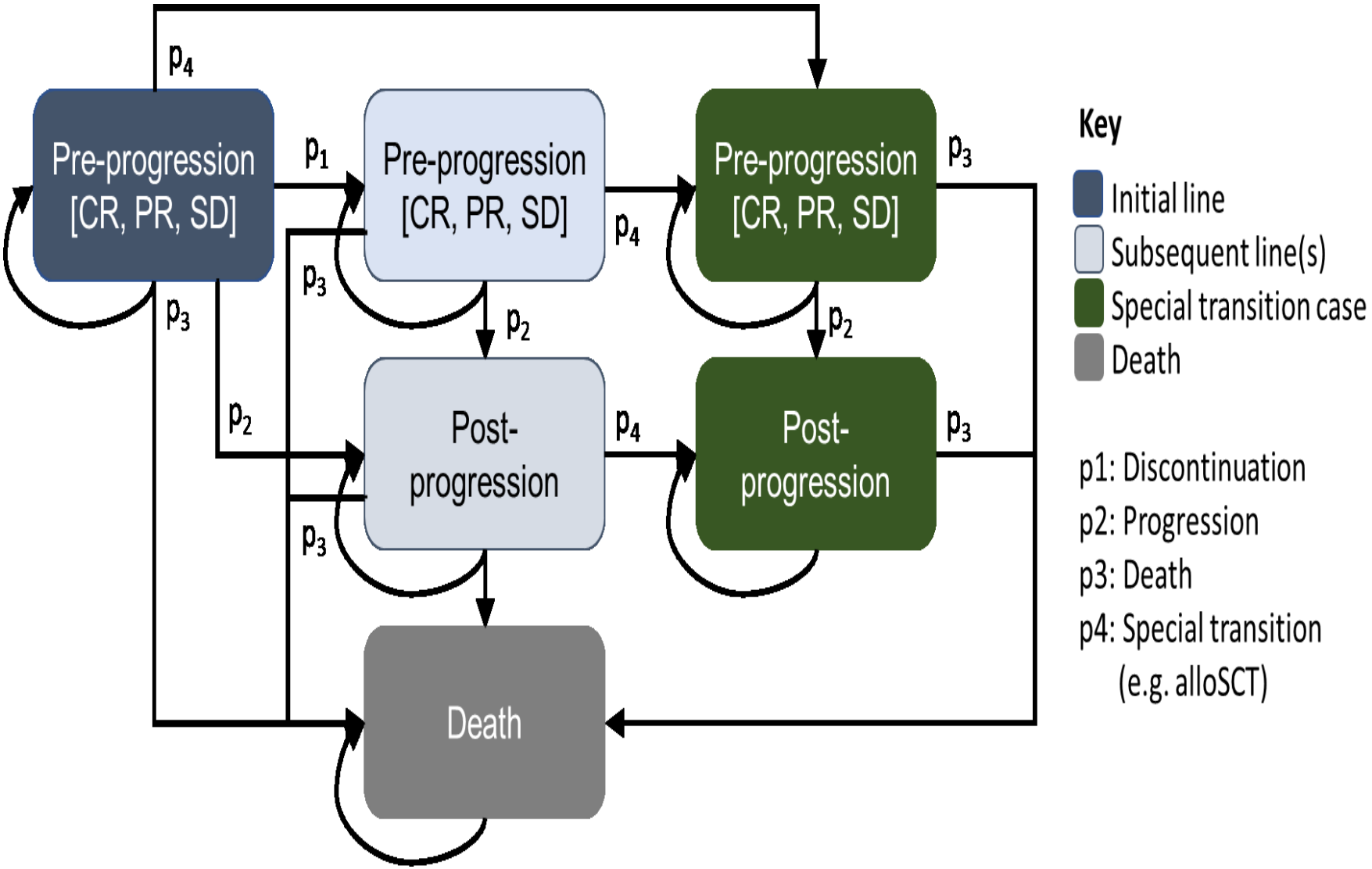
# Company's model

## *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 |

# Company's model

## Structure



# 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
  - AutoSCT 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%

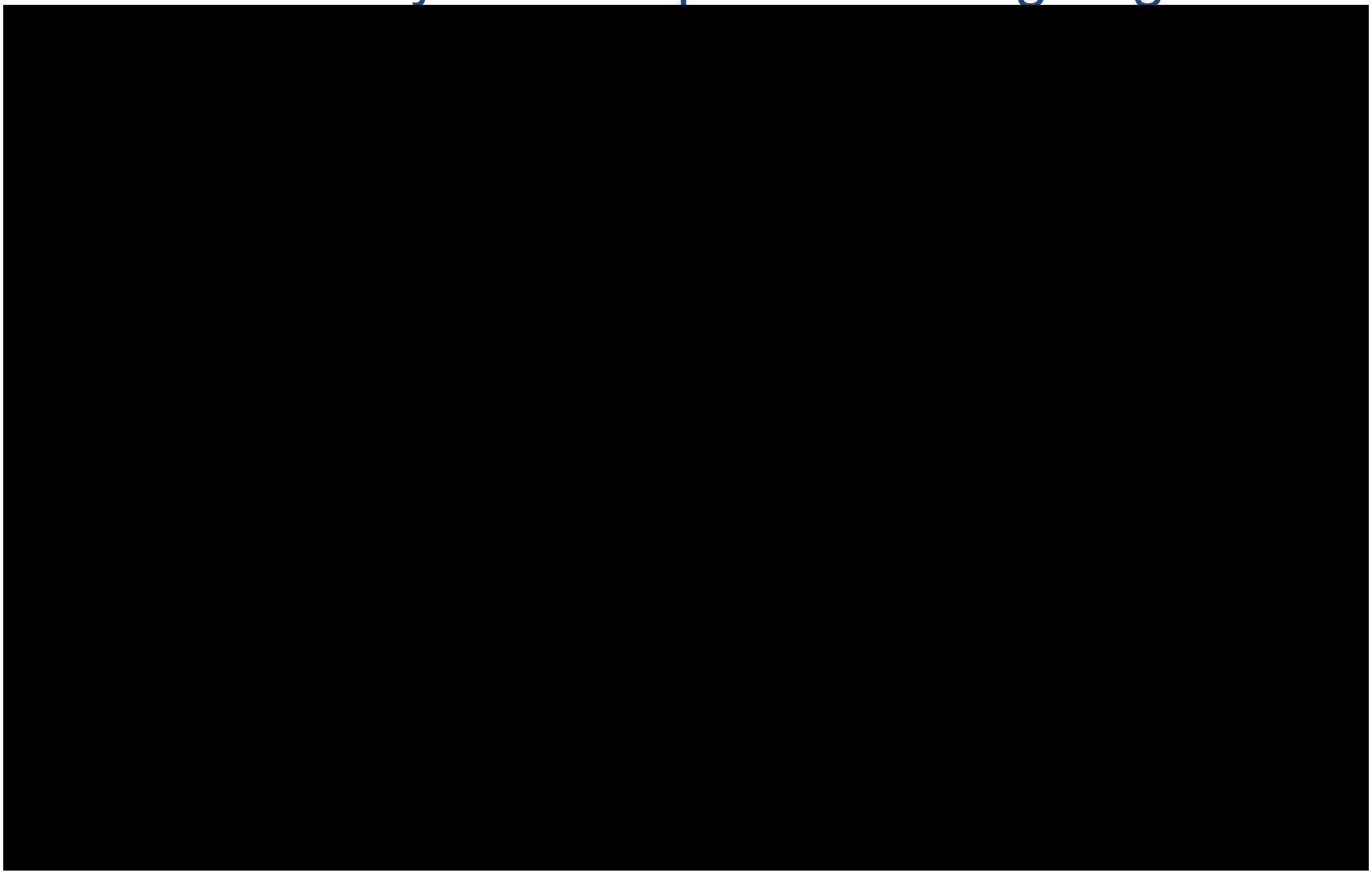
# Company's model
## Treatment effectiveness

- 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)

# Company's model

## Progression-free survival

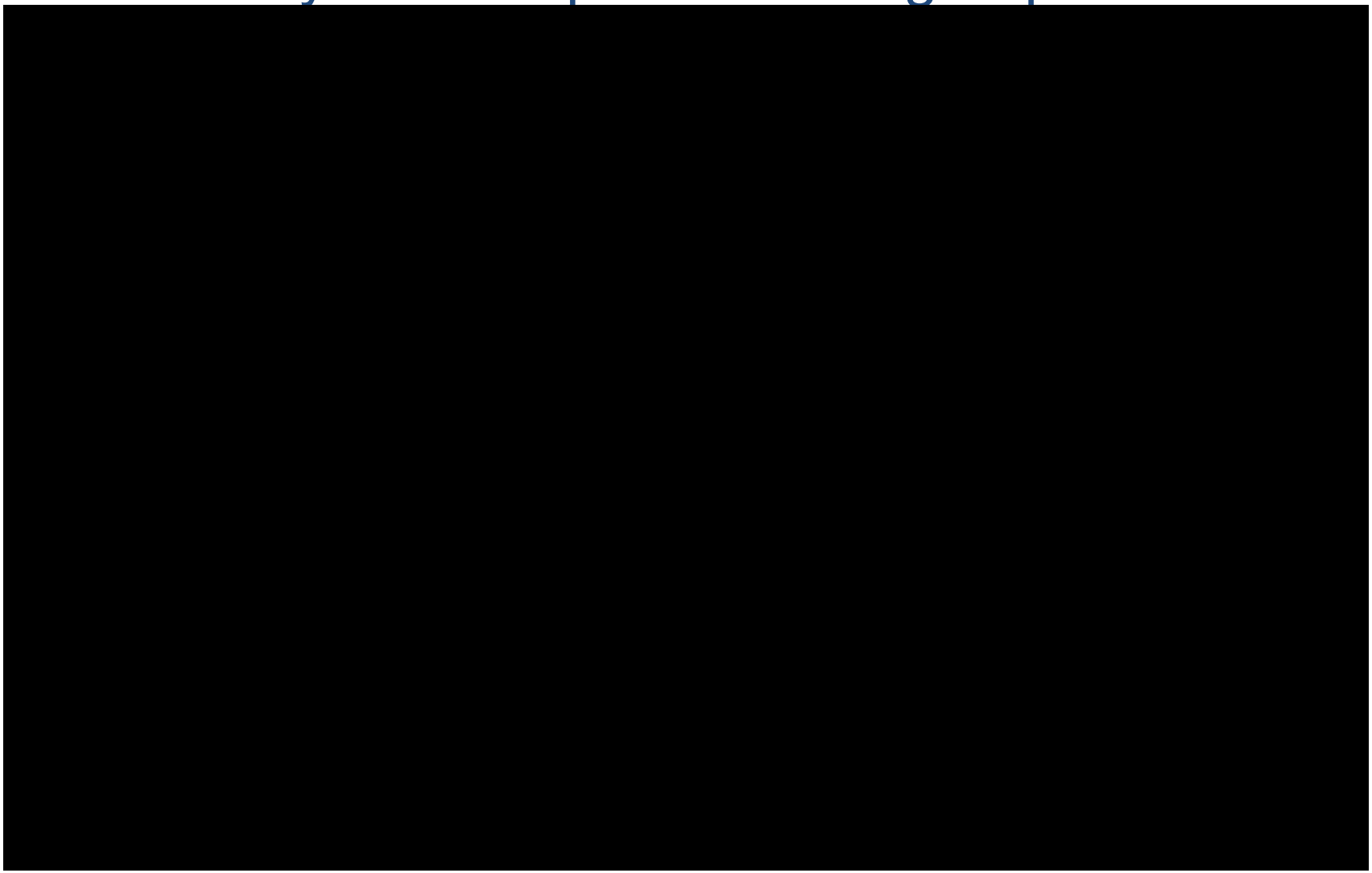
## Nivolumab 5 year extrapolation using Lognormal



# Company's model

## Progression-free survival

## SOC 5 year extrapolation using Exponential



# Company's model

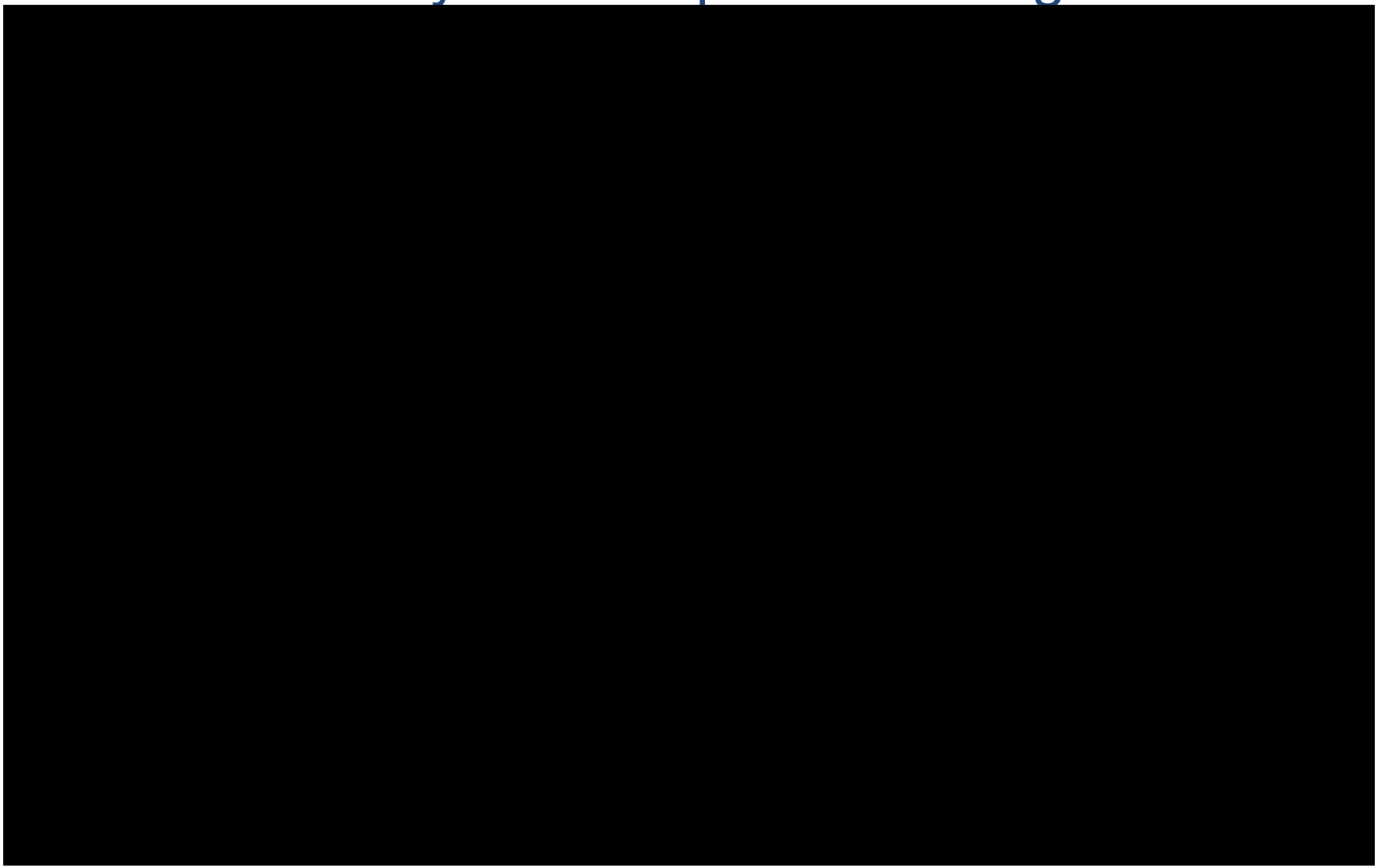
## Progression-free survival

## SOC (Cheah overall population) extrapolation

# Company's model

## Overall survival

## Nivolumab 5 year extrapolation using Weibull



# ERG's critique

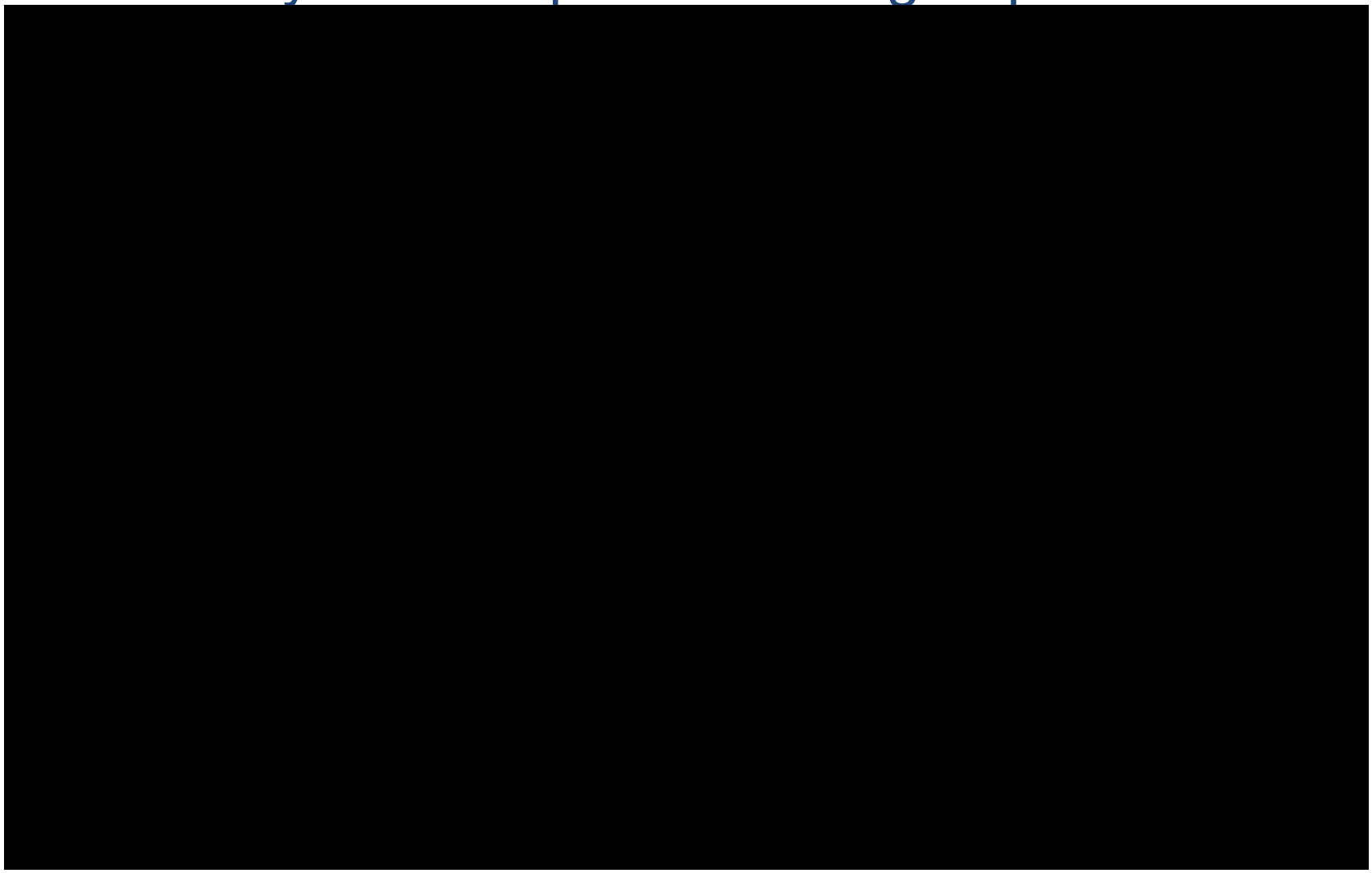
## Overall survival

## Nivolumab 5 year extrapolation using Gompertz

# Company's model

## Overall survival

## SOC 5 year extrapolation using Exponential



# Company's model

## Overall survival

## SOC (Cheah overall population) extrapolation

# 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 most appropriate extrapolation choices
- All cause mortality
  - Company acknowledges double counting but state this only occurs in first few years (due to low baseline age), and effect applies equally to all comparators. ERG agree unlikely to have significant impact on cost-effectiveness results
- AlloSCT
  - Benefits are captured because nivolumab and Cheah studies included small proportion of patients who received alloSCT (and so costs should be included)

# 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 derived from EQ-5D data from CheckMate 205 Cohort B, converted to utilities using UK EQ-5D-3L tariff and stratified by progression status (investigator-assessed) and timing of progression
- SOC values derived 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)

# 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**

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

**Post-progression utility**

- Company's rationale for large difference between nivolumab and SOC arms, that post-progression benefit of nivolumab is due to its unique mechanism of action, is not considered plausible
- Ramsey 2016 paper shows higher utilities 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

# 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** |

# 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:

<u>One-way sensitivity analysis</u>

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

<u>Probabilistic sensitivity analysis</u>

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

# 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 |

# 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 |

# Company's model
## AlloSCT scenario – assumptions

- Assumed proportion of eligible patients with adequate response (CR, PR, SD) will receive alloSCT at 6 months
- Evidence describing use of alloSCT in post ASCT and BTX population derived from 2 real world studies
  - Cheah 2016 (used to model survival following alloSCT in relevant population)
  - Perrot 2016 (used to derive response-specific rate of alloSCT [likelihood of receiving alloSCT])
- Modelled using independent survival curves (because alloSCT associated with mortality and morbidity in short term but considered potentially curative over long term)
- Assumption explored that nivolumab-treated patients have an equivalent likelihood of receiving alloSCT
- Utility associated with successful alloSCT taken from Swinburn 2015 (in line with ongoing NICE BTX appraisal)
- Costs sourced from weighted average of NHS reference costs and Radford 2016. Ongoing monitoring costs derived from NICE TA241.

# 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** |

# ERG's critique
## AlloSCT scenario

- Perrot 2016 underestimates proportion receiving alloSCT, compared with proportion 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 includes 14 patients already included in overall survival data for SOC, who are therefore double counted
- Post-progression utility should be similar across all interventions
- Costs are underestimated; Radford 2016 should be used for consistency with ongoing NICE BTX appraisal

# 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 |

# 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

# ERG's base case (with PAS)
## Disaggregated

| Assumption | ICER/QALY |
|---|---|
| Company's base case | £19,882 |
| 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 |
| *not in ERG's base case | |

# 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) Overall population 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) | Likely to extend life expectancy by at least 3 months |

# Innovation

- Nivolumab considered to be innovative by patient/professional groups; a new mode of action and a step change in the management of relapsed/refractory Hodgkin lymphoma
- First checkpoint inhibitor immunotherapy to file for marketing authorisation in classical Hodgkin lymphoma
- MHRA awarded Promising Innovative Medicine designation
- Improved tolerability and a more convenient schedule than chemotherapy
- Additional treatment option where otherwise only BSC
- Potential to act as bridge to alloSCT

# Equality considerations

- Due to 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

# Key issues

- Uncertainty in the absence of head-to-head comparison
- Survival modelling for SOC: Cheah study excluding people who had received investigational agents or overall population from Cheah study?
- Survival modelling for nivolumab: Weibull, Gompertz, other?
- Widely different utility values post progression?
- AlloSCT as a scenario or base case?
- Does nivolumab meet criteria for life-extending treatments at end of life?
- Does nivolumab represent an innovative treatment?