NICE National Institute for Health and Care Excellence

# Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refactory diffuse large B-cell lymphoma

**2nd Appraisal Committee meeting**

# Chair presentation

Lead team: Stephen Sharp, Sumithra Maheswaran, Richard Ballerand

ERG: KSR

Chair: Jane Adam

Technical team: Albany Meikle, Zoe Charles, Janet Robertson

Company: Roche

12th May 2020

# Key issues

- Which method for PFS and OS extrapolation is most appropriate?
- Have the differences between the company's deterministic and probabilistic results been adequately resolved?
- Do the company's scenario analyses on long-term remission rates give confidence in the assumed cure rate?
- Would further data collection address the remaining uncertainty?

# Disease Background – DLBCL

- Diffuse large B-cell lymphoma (DLBCL) is a high grade lymphoma
- Around 5,510 new cases of DLBCL pa in UK, some do not respond to first line treatment or relapse later (R/R)
- Approximately 600 pa treated for relapsed or refractory (R/R) DLBCL are not suitable for hematopoietic stem cell transplant (potentially curative option)
- R/R DLBCL has a poor prognosis - median survival 10 months. Approximately 41% survive for 12 months.
- Outcomes particularly poor for those refractory to first-line therapy. In the SCHOLAR-1 study, (largest pooled retrospective analysis of patients with refractory DLBCL), median overall survival was 6.3 months in refractory disease, 22% alive at 2 years.
- Age an important prognostic indicator: patients ≥65 years have a poorer prognosis than younger patients

# Polatuzumab vedotin

| | |
|---|---|
| **Marketing authorisation** | In combination with bendamustine and rituximab for adults with relapsed / refractory diffuse large B-cell lymphoma (DLBCL) ***who are not candidates for haematopoietic stem cell transplant.*** |
| **Additional tests** | None |
| **Administration and dosage** | Polatuzumab vedotin<br>• 1.8 mg/kg intravenously (IV) on day 1 over 1 hour<br>• subsequent doses 30-minute infusion<br>Bendamustine - 90 mg/$m^2$ IV on days 1 and 2<br>Rituximab - 375 mg/$m^2$ IV on day 1 |
| **Patient Access Scheme (PAS)** | Confidential PAS approved |

# Clinical trial evidence – GO29365

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|---|---|
| **Trial design** | Phase Ib/II, multicentre, open-label study |
| **Population** | Patients with R/R DLBCL<br>• ECOG PS 0–2<br>• At least 1 measurable lesion ≥1.5 cm in its longest dimension<br>• If received prior bendamustine, response duration >1 year<br>• 40 patients in each arm |
| **Intervention** | Polatuzumab vedotin plus bendamustine and rituximab (pola vedotin+BR) |
| **Comparator** | Bendamustine with rituximab (BR) |
| **Outcomes** | • Complete response (CR) – primary outcome<br>• Overall survival<br>• Progression-free survival<br>• Duration of response<br>• Adverse effects of treatment<br>• Health-related quality of life<br>Data for PFS and OS are from [redacted] data cut (submitted at clarification stage and used in model). For other endpoints 30th Apr 2018 data cut is reported |

# Results

| Outcome | Pola vedotin+BR (n=40) | BR (n=40) |
|---|---|---|
| **Complete response rate with PET-CT at primary response assessment (IRC-assessed)** | | |
| Complete response, n (%)<br>95% CI | 16 (40.0)<br>24.86, 56.67 | 7 (17.5)<br>7.34, 32.78 |
| Difference in response rates, (95% CI)<br>p value | 22.5% (2.62, 40.22)<br>p=0.0261 | |
| **Progression-free survival (IRC-assessed) – [redacted] cut-off** | | |
| Patients with event, n (%) | [redacted] | [redacted] |
| Median time to event, months<br>95% CI | [redacted] | [redacted] |
| Stratified HR %<br>(95% CI)<br>p value (log-rank) | [redacted] | |
| **Progression-free survival (IRC-assessed) – [redacted] cut-off** | | |
| Median time to event, months 95% CI | [redacted] | [redacted] |

# Kaplan-Meier Curve for PFS by IRC, cut-off date [redacted]

[redacted] months median follow up

**Figure redacted – academic in confidence**

# Kaplan-Meier Curve for PFS by IRC, cut-off date [redacted]

[redacted](BR) or [redacted] (Pola+BR) months median follow up

**Figure redacted – academic in confidence**

# Overall survival

| Outcome | Polatuzumab vedotin+BR (n=40) | BR (n=40) |
|---|---|---|
| **Overall survival – [redacted] cut-off** | | |
| Patients with event, n (%) | [redacted] | [redacted] |
| Median time to event, months (95% CI) | [redacted] | [redacted] |
| Stratified HR % (95% CI) p value (log-rank) | [redacted] | |
| **Overall survival – [redacted] cut-off** | | |
| Median time to event, months 95% CI | [redacted] | [redacted] |

# Kaplan-Meier Curve for OS cut-off date [redacted]

[redacted] months median follow up

**Figure redacted – academic in confidence**

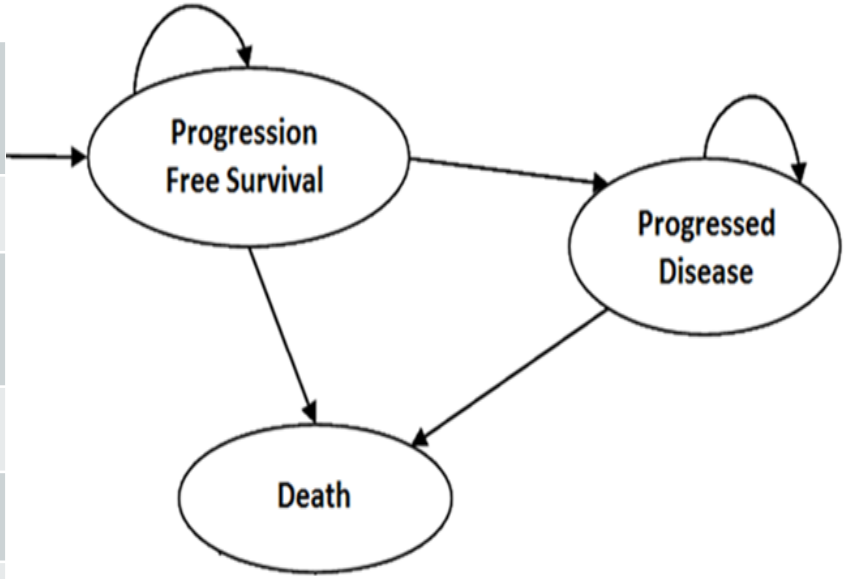
# Kaplan-Meier Curve for OS cut-off date [redacted]

[redacted] (BR) or [redacted] (Pola+BR) months median follow up

**Figure redacted – academic in confidence**

# Cost-effectiveness model

| | |
|---|---|
| **Model type** | Partitioned survival analysis model with three mutually exclusive health states |
| **Health states** | PFS, PD, Death |
| **Population** | Patients with R/R DLBCL ineligible for SCT |
| **Intervention** | Polatuzumab vedotin + BR (Pola+BR) |
| **Comparators** | BR |
| **Time horizon** | 45 years |
| **Model cycle** | 1 week |
| **Discount rates** | 3.5% for both cost and health outcomes |
| **Utility values** | EQ-5D-5L data (ZUMA-1 study),cross-walked to 3L values |




Progression free survival (PFS), Progressed disease (PD), Stem cell transplant (SCT), Bendamustine with rituximab (BR), Personal Social Services (PSS)

# ACD: preliminary recommendation

1.1 Polatuzumab vedotin with rituximab and bendamustine is not recommended, within its marketing authorisation, as an option for treating relapsed or refractory diffuse large B-cell lymphoma in adults who cannot have a haematopoietic stem cell transplant.

# Committee considerations at ACM1 (1)

- There is high unmet need for effective treatments and no standard of care for treating the disease in people who cannot have a HSCT
- Rituximab with bendamustine (comparator in clinical trial) is a reasonable proxy for standard care
- Clinical trial is generalisable to UK clinical practice
- Company's adjustments for imbalances between treatment arms are appropriate
- Polatuzumab vedotin is a promising new treatment with evidence suggesting it extends PFS and OS
- Lack of robust evidence on long-term remission and cure with polatuzumab vedotin but trial data so far suggest a small proportion of people may have a durable response that could indicate cure

# Committee considerations at ACM1 (2)

- Company and ERG used different methods to extrapolate PFS and OS which was the key driver of the cost-effectiveness results
  - Company cure-mixture model assumed a 'cured' population (2/3 of those who were progression-free at 2 years) and a population whose disease would progress
  - Cure rate assumed by company was not sufficiently justified
  - Sensitivity analysis with varied cure rates would be informative
- Large unexplained difference between company's deterministic and probabilistic analysis
- Company's probabilistic results suggested that the number of life years estimated for comparator arm was more than 2 years (end of life criteria), did not correlate with the clinical opinions received
- Company developed its own code for modelling which was not transparent and could not be verified by the ERG

# Committee considerations at ACM1 (3)

- ERG's standard parametric survival modelling is uncertain due to the mismatch in the predications for PFS and OS:
  - % predicted to be alive at 5 or 10 years much higher than the % predicted to be progression free (inconsistent with feedback that survival benefit is mediated through lack of progression, not post progression benefit)
  - Did not capture the potential cure aspect and therefore may be a conservative interpretation of the evidence
- Modelling of background mortality:
  - Company's use of different methods to model disease progression and mortality (cohort-based) and background mortality (individual patient-level based) is not appropriate
  - ERG's cohort-based approach preferred, in line with PFS and OS

The most plausible ICER was highly uncertain due to the robustness of the models – therefore not recommended for routine use or CDF

# ACD consultation responses

- Consultee comments from:
  - Lymphoma Action
  - Company (Roche)

- Web comments from:
  - The Christie Hospital, Manchester

# Comments from Lymphoma Action

- Patient testimonials: the disease and its current treatments have huge physical, psychological and financial impact
- There are limited options and this is a potentially curative treatment
- Concerns that ERG's cost effectiveness analysis is given more weight than company's even though the committee acknowledges that ERG's analysis is flawed
- Questions if flaws in economic modelling are enough to justify a negative recommendation for a life extending, potentially curative treatment in a disease with such a poor prognosis

# Web comments – The Christie

- Experience of treating 9 patients with Pola-BR: useful treatment for palliating people with relapsed DLBCL who are unsuitable for intensive chemotherapy and for bridging to potentially curative treatments
- Only other option in this population is BR, which has been shown to be inferior to Pola+BR in a recent RCT
- There is unmet need for treatment options in this population, particularly in current climate where access to other options may be restricted because of COVID-19
- Acknowledges uncertainty on the curative potential and cost-effectiveness – but highlight that evidence shows a clear PFS and OS benefit for Pola+BR

# Company comments – summary

To demonstrate the robustness of the company's model, the following steps were reported:

- Justification for using a cure-mixture model (CMM) and selection of appropriate CMM for survival modelling
- Alternative extrapolation models: standard parametric, hybrid and change-point models
- Scenario analysis with alternative long-term remission and survival ('cure') rates
- Revised model reducing difference between deterministic and probabilistic results
- An updated base case
- Validation of the in-house cure-mixture code versus other packages (ERG gained confidence in code based on validation exercise)

# Company comments – survival modelling

Committee conclusions at CM1: the cure rate assumed by the company was not sufficiently justified and it was difficult to infer the plausibility of long-term remission from the PFS data

- Standard survival parametric models may not be able to provide plausible fits and long-term extrapolations – cure-mixture models (CMM) are more suitable
- A significant proportion of people who achieve 2-year remission are expected to remain in long-term remission (based on clinical expert opinion and observations in studies with long-term follow-up of R/R DLBCL patients treated with R-chemo)
- Most progression events occur within the first 12 months in both arms of GO29365 and patients are at very low risk of progression after 24 months
- This natural history of the disease formed the basis of modelling for CAR-Ts, where committee accepted a cure point between 2 and 5 years

# Company comments – selection of appropriate cure-mixture model base case

- Company selected a Log-Normal function CMM for the revised base case which, compared with the Generalised Gamma function used in the original submission, provides:
  - reduced parameter uncertainty
  - similar visual fit
  - plausible long-term extrapolation
  - statistically better fits based on AIC and BIC values

# Company comments – survival modelling

## Revised base case extrapolation for PFS and OS (Log-Normal cure-mixture model, adjusted analysis)

**Figure redacted – academic in confidence**

Source: company response to ACD (March 2020), figure 2

# ERG response – survival modelling

ERG's concerns at CM1 regarding the use of a CMM remain unresolved:

- Observational data showing long-term remission after 2-year remission is not in R/R population, it's based on newly diagnosed DLBCL patients
- Further evidence (Howlader et al. 2017) suggests excess mortality up to 5 years
- Questions appropriateness of comparing polatuzumab with CAR-Ts
- Assuming a CMM needs 2 prerequisites from the data - identifiability of the cure fraction and sufficient follow-up:
  - Sample size in GO29365 is small, so the proportion of people entering long-term remission cannot be reliably estimated (at 30 month median follow-up 23% pola+BR vs 5% BR were in remission, but n=9)
  - Unlikely that 6 additional months after 24 months (=30 month median follow-up) is long enough to reliably estimate cure fraction

"The results of fitting a CMM to current data would be very uncertain"

# ERG response – selection of appropriate cure-mixture model base case

- Company did not provide any criteria that can be used to validate the plausibility of the updated long-term extrapolations using log-normal.
- The exponential CMM could have also been an appropriate choice (explored in ERG scenario 1)
- An OS benefit is shown for up to 20 years

# Company comments – alternative models (standard parametric)

- Company conducted a standard parametric Generalized Gamma model for PFS and OS
- Resulted in 5-year PFS rate of 16% and OS rate of 19% - smaller difference between PFS and OS than other parametric models

**ERG response:**

- Smaller difference between PFS and OS compared with ERG approach at CM1 which addresses committee concerns, but log-normal or log-logistic models result in smaller difference – explored in ERG analyses

# Company comments – alternative models (hybrid and change-point)

- Further alternative models were conducted:
  - 2 hybrid models using Generalised Gamma and Log-normal distributions
  - A change-point model which allows more complex hazard functions

**ERG response:**

- Hybrid models: assuming hybrid models needs the same 2 main prerequisites as for CMMs: identifiability of the cure fraction and sufficient follow-up (previously described as limitations of this data)
- Change-point model: given limited events to make estimates, agree long-term extrapolation is a concern for these models

# Company comments – scenario analyses on long-term remission rates

| | Long-term remission rate fitted | |
|---|---|---|
| | Pola+BR | BR |
| Base case | 22.8% | [redacted]% |
| Scenario 1 | 22.0% | 10.0% |
| Scenario 2 | 20.0% | 8.0% |

- Company: scenarios presented are conservative; smaller differences between Pola+BR and BR long-term remission rates are implausible
- Scenarios increase the ICERs by approx £7000

**ERG response**:
- Unclear what criteria the company has used to decide on the percentages in the scenarios
- ERG explore 2 further scenarios with lower and higher external remission rates

# Company comments – differences in deterministic and probabilistic results

Committee conclusions at CM1:
- Large unexplained difference in company's deterministic and probabilistic results

- Cure-mixture models may result in wider distributions around mean estimates compared to a standard parametric model
- For OS, deterministic estimates are bounded within a range deemed plausible by clinical experts; probabilistic scenarios were not bounded
- Probabilistic distribution is skewed towards higher values than deterministic mean OS values

**ERG response:**
Wide range of probabilistic estimates shows there is uncertainty associated with the data

**Difference in probabilistic/deterministic ICERs are smaller in company's revised base case**

# Company's updated base case

- Summary of changes to company's base case:
  - Log-Normal instead of Generalised Gamma function used for extrapolating PFS and OS using cure-mixture model to reduce probabilistic uncertainty
  - Background mortality: single age cohort used (69 years) in line with committee preference in ACD
  - Survival limited by general population mortality for all scenarios, using conditional background survival

# Company's revised economic modelling results

Revised base case deterministic results (with PAS)

| Intervention | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (Δ£/ΔQALY) |
|---|---|---|---|---|---|---|---|
| Pola+BR | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 31,808 |
| BR | 18,471 | 1.55 | [redacted] | - | - | - | - |

Mean probabilistic results (with PAS)

| Intervention | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (Δ£/ΔQALY) |
|---|---|---|---|---|---|---|---|
| Pola+BR | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 36,337 |
| BR | 27,729 | 2.04 | [redacted] | - | - | - | - |

Cost-effectiveness acceptability curve shows the probability of Pola+BR being cost effective was 82% at a threshold ICER of £50,000 per QALY gained

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Source: company response to ACD (March 2020), table 7, table 9

# Company's scenario analysis results

| Scenario | LY Pola+BR | LY BR | Incremental LY | Incremental costs (£) | Incremental QALYs | ICER (Δ£/ΔQALY) |
|---|---|---|---|---|---|---|
| Base case (Pola-BR 22.8%, BR [redacted]%) | [redacted] | 1.55 | [redacted] | [redacted] | [redacted] | 31,808 |
| CMM – (Pola-BR 22%, BR 10%) | [redacted] | 1.84 | [redacted] | [redacted] | [redacted] | 39,015 |
| CMM – (Pola-BR 20%, BR 8%) | [redacted] | 1.70 | [redacted] | [redacted] | [redacted] | 38,873 |
| CMM – (Pola-BR 24%, BR 6%) | [redacted] | 1.57 | [redacted] | [redacted] | [redacted] | 29,351 |
| Standard parametric, Generalized Gamma | [redacted] | 1.43 | [redacted] | [redacted] | [redacted] | 35,510 |
| Hybrid with Generalized Gamma for PFS and OS | [redacted] | 1.67 | [redacted] | [redacted] | [redacted] | 33,919 |
| Hybrid with Log-Normal for PFS and Generalized Gamma for OS | [redacted] | 1.54 | [redacted] | [redacted] | [redacted] | 37,678 |
| Change-point model | [redacted] | 1.68 | [redacted] | [redacted] | [redacted] | 45,247 |

Source: company response to ACD (March 2020), table 13

# ERG base case with revised model

Company's and ERG's preferred assumptions are now closely aligned, except for the choice of PFS and OS extrapolation models

- Company extrapolated PFS and OS using CMM with the Log-Normal function
- ERG assumed an independent Generalised Gamma distribution for OS and an independent Log-Normal distribution for PFS extrapolation

ERG:
- remain concerned about the lack of robust long-term evidence to support the cure assumptions
- with the current data, using standard parametric survival modelling to extrapolate PFS and OS is the most appropriate approach

**ERG base case deterministic results (with PAS) – using revised model**

| Intervention | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (Δ£/ΔQALY) |
|---|---|---|---|---|---|---|---|
| Pola+BR | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 48,837 |
| BR | 25,026 | [redacted] | [redacted] | - | - | - | - |

Source: ERG Addendum 2 (April 2020), table 10

# ERG exploratory analyses

| | | |
|---|---|---|
| **ERG scenario 1** | Exponential CMM<br>- provides the lowest BIC value and similar AIC to the other models; reduced parameter uncertainty was a criteria used to select company's model<br>- simplest form of distribution | |
| **ERG scenario 2** | Lower external remission rates<br>- lowering long-term remission rates in both arms, maintaining the difference (external cure rates 20% Pola+BR and 6% BR) | |
| **ERG scenario 3** | Higher external remission rates<br>- increasing long-term remission rates in both arms, maintaining the difference (external cure rates 24% Pola+BR and 10% BR) | |
| **ERG scenario 4** | Standard parametric modelling Log-logistic for OS | Gives smaller difference in OS and PFS in BR arm at 5-years than company's exploratory Generalised Gamma model:<br>• Log-logistic: 3.3% PFS and 5.1% OS<br>• Log-normal: 3.3% PFS and 5.2% OS<br>• Generalised Gamma: 3.3% PFS and 6.6% OS |
| **ERG scenario 5** | Standard parametric modelling Log-normal for OS | |

# ERG scenario analysis results

| Scenario | LY Pola+BR | LY BR | Incremental LY | Incremental costs (£) | Incremental QALYs | ICER (Δ£/ΔQALY) |
|---|---|---|---|---|---|---|
| Company base case | [redacted] | 1.55 | [redacted] | [redacted] | [redacted] | 31,808 |
| ERG base case | [redacted] | 1.43 | [redacted] | [redacted] | [redacted] | 48,837 |
| ERG scenario 1 | [redacted] | 1.66 | [redacted] | [redacted] | [redacted] | 33,546 |
| ERG scenario 2 | [redacted] | 1.57 | [redacted] | [redacted] | [redacted] | 35,279 |
| ERG scenario 3 | [redacted] | 1.84 | [redacted] | [redacted] | [redacted] | 35,159 |
| ERG scenario 4 | [redacted] | 1.29 | [redacted] | [redacted] | [redacted] | 47,796 |
| ERG scenario 5 | [redacted] | 1.30 | [redacted] | [redacted] | [redacted] | 49,744 |

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Source: ERG Addendum 2 (April 2020), table 11

# Company response – further data collection can address uncertainty

- Longer-term follow up of GO29365 will reduce remaining uncertainty on long-term extrapolations
- Further data will validate the current model and reduce uncertainty in parameter estimates due to large numbers of patients

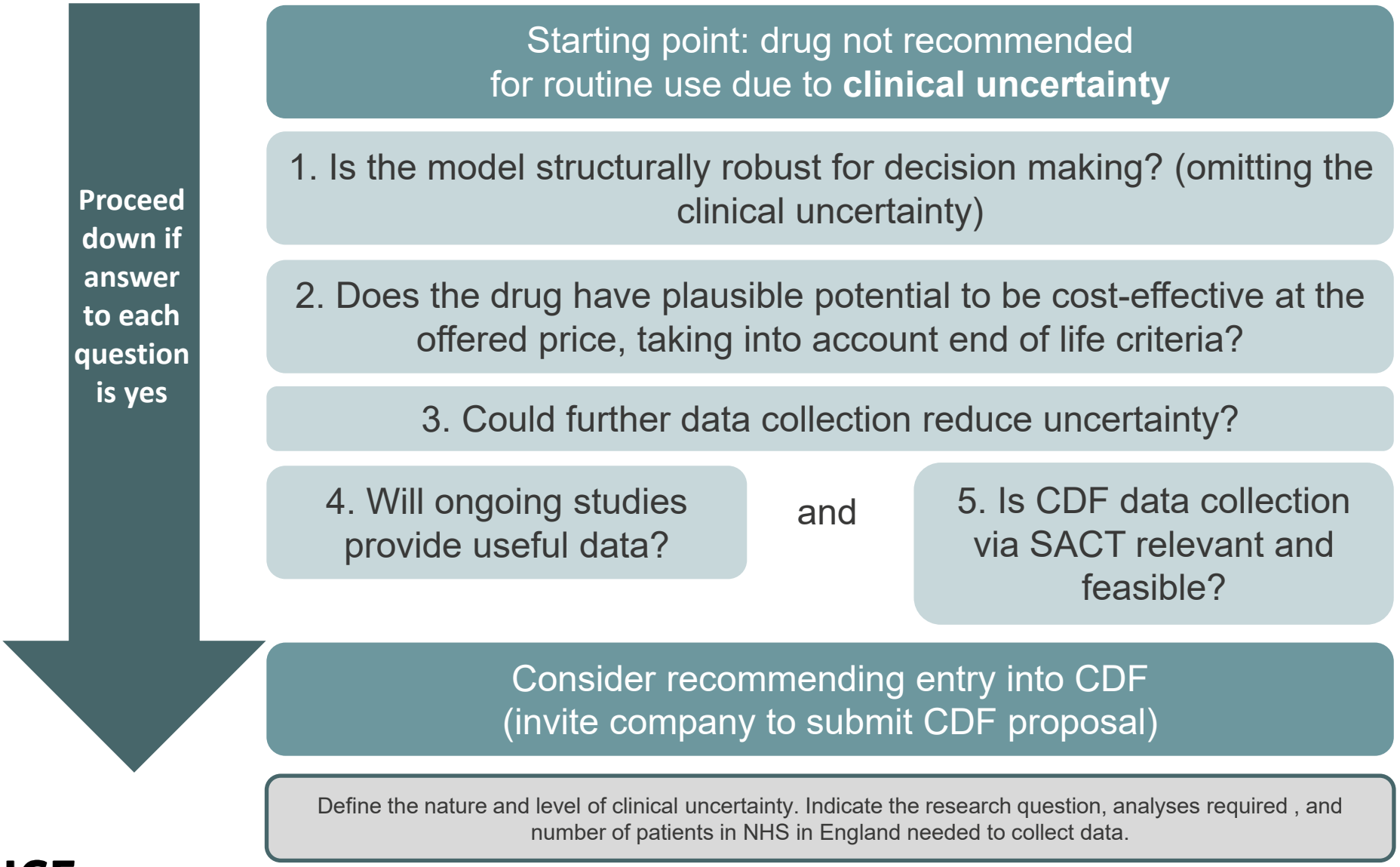
ERG agrees with the company that further data collection is needed to address the remaining uncertainty

# Key issues

- Which method for PFS and OS extrapolation is most appropriate?
- Have the differences between the company's deterministic and probabilistic results been adequately resolved?
- Do the company's scenario analyses on long-term remission rates give confidence in the assumed cure rate?
- Would further data collection address the remaining uncertainty?

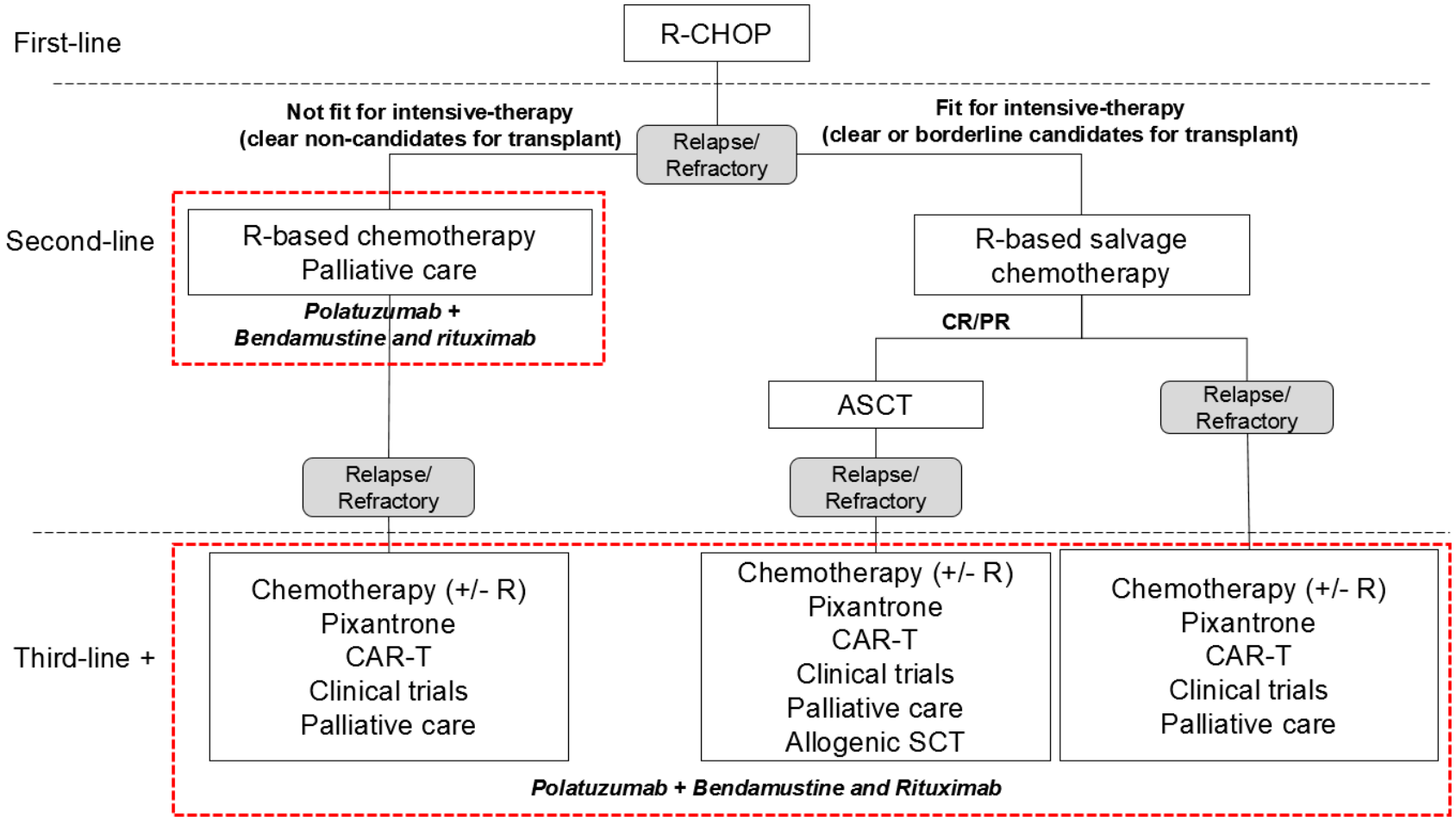
# Reserve

# Committee decision making: CDF recommendation criteria



# Treatment pathway and proposed positioning of polatuzumab vedotin in combination with bendamustine and rituximab

- No consensus on best treatment for R/R DLBCL
- Standard chemotherapy for first-line treatment of DLBCL is rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP)

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