# Lead team presentation

## Venetoclax with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia [ID1097] – STA

1st Appraisal Committee meeting

Committee C

Lead team: Derek Ward and David Chandler

ERG: Warwick Evidence

Technical team: Julia Sus and Sally Doss

27 September 2018

# Key Issues - clinical

- **Clinical Pathway:**

- Restricting the population to people post chemotherapy may exclude patients with del(17p) and/or TP53 mutation

- **Clinical evidence**

- Are the results generalisable to clinical practice in England?

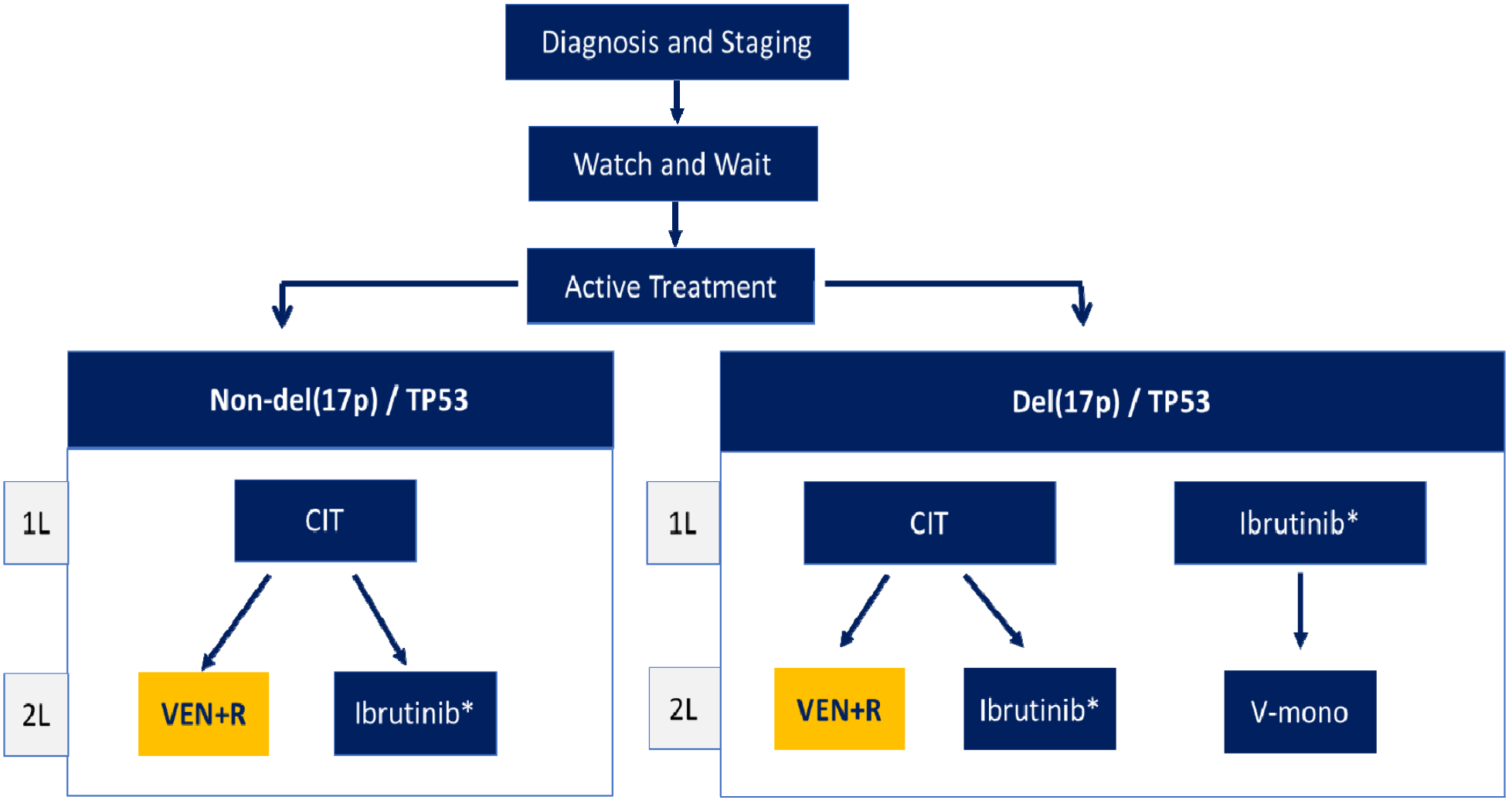
- Appropriateness of matched-adjusted indirect comparison (MAIC) data comparing VEN+R with ibrutinib and IDELA+R

- Clinical uncertainties and data collection

# Disease Background

- Chronic lymphocytic leukaemia (CLL) is a common form of leukaemia, with an estimated 3,515 new diagnoses in England each year.
- Risk increases with age and is more common in men
- 5%-10% of people are considered to have ‘high risk’ disease
- British Committee for Standards in Haematology defines people as ‘high-risk’, if:
  - they have **17p deletion** or **TP53 mutation** (this increases the rate of cell growth and the resistance of the disease to treatment)
  - their disease relapses/is refractory to chemotherapy
- The most common symptoms encountered by patients are fatigue, swollen lymph nodes, weakness or breathlessness, night sweats, weight loss, fever and repeated infections.

# Clinical pathway of care




*Ibrutinib is depicted in this figure as it is the preferred B-cell receptor inhibitor therapy because of its effectiveness and because of the AE associated with idelalisib with rituximab (idela+R) as per clinical experts' opinion as stated in NICE TA429.

NICE

# Related NICE Guidance (1)

**TA487**

Venetoclax is recommended for use within the Cancer Drugs Fund, within its marketing authorisation, as an option for treating chronic lymphocytic leukaemia, that is, in adults:

- with a 17p deletion or TP53 mutation and when a B-cell receptor pathway inhibitor is unsuitable, or whose disease has progressed after a B-cell receptor pathway inhibitor **or**
- without a 17p deletion or TP53 mutation, and whose disease has progressed after both chemo-immunotherapy and a B-cell receptor pathway inhibitor **and**
- only if the conditions in the managed access agreement are followed

**TA429**

Ibrutinib alone is recommended within its marketing authorisation as an option for treating chronic lymphocytic leukaemia in adults:

- who have had at least 1 prior therapy or
- who have a 17p deletion or TP53 mutation, and in whom chemo-immunotherapy is unsuitable and
- only when the company provides ibrutinib with the discount agreed in the patient access scheme.

# Related NICE Guidance (2)

**TA359**

Idelalisib with rituximab is recommended:

- for untreated chronic lymphocytic leukaemia in adults with a 17p deletion or TP53 mutation or
- for chronic lymphocytic leukaemia in adults when the disease has been treated but has relapsed within 24 months.
- Idelalisib is recommended only if the company provides the drug with the discount agreed in the simple discount agreement.

# Comments from patient groups* (1)

- CLL is rare and currently incurable for the majority
- Average age of patents is 72
- Usually develops slowly often without significant symptoms
- Most common symptoms
  - Fatigue, increased lymphocyte count, enlarged lymph nodes frequent infections, night sweats, enlarged spleen or discomfort, shortness of breath, anaemia, thrombocytopenia, neutropenia, rapid weight loss, pain and fever.
- Being diagnosed with CLL
  - Shock, distress, anxiety, difficulty sleeping and depression
    *"I was by myself for my appointment and told 'you have leukaemia' which immediately scared me to death, I thought, this is it, I am going to die, soon."*
- No recent progress in treatments

*Bloodwise , Leukaemia CARE, and Chronic Lymphocytic Leukaemia Support Association

# Comments from patient groups (2)

- Patients consider current treatments have limitations
  - *“one bucket fits all approach”*
- There is a need for targeted personalised medicine
- They want:
  - Tolerable side-effects and safety profile
  - High response, minimal disease residue and longest possible remission
  - An oral therapy
  - Limited treatment course
- Views of venetoclax
  - The therapy can be intense initially
  - Treatment option for patients with cardiac and anticoagulant comorbidity issues that are unsuitable for Ibrutinib.

# Comments from professional groups**

- Venetoclax with rituximab is a very effective combination in relapsed CLL.
- The combination achieves deep remissions and improves progression free survival and overall survival as compared to Bendamustine and rituximab.
- It is very difficult to compare clinical outcome data to current standard of therapy which is B-cell receptor antagonists. There is no available data for comparison at present.
- The strength of the combination is the finite duration of therapy and depth of response. The data will hopefully mature in time to reflect whether the improved depth in response translates into improved clinical outcomes. However, the follow up on trial is short at present to reflect that desired outcome.
- In short, this therapy offers very good and comparable treatment option to relapsing CLL patients and should be available as a choice of therapy in this cohort of patients.

**National Cancer Research Institute, Royal College of Physicians, British Society of Haematology-Royal College of Pathologists Association of Cancer Physicians

# NHS England's Comments (1)

- Treatment should be for 2 years maximum, in line with the key phase III MURANO trial.
- CLL charities, clinicians and patients welcome venetoclax with rituximab as it is a fixed duration of treatment rather than ibrutinib, which is given until disease progression. 10-15% of patients cannot tolerate ibrutinib, others suffer low grade toxicities for extensive durations with decrease in quality of life.
- The progression free survival results of the MURANO trial are immature and uncertain especially durability of response when treatment discontinues at 2 years. Follow up information are vital to help guide patients and clinicians in context of the treatment pathway.
- Venetoclax plus rituximab is a promising candidate for the CDF on the basis of its clinical uncertainties.
- The clinically relevant comparator to venetoclax plus rituximab is ibrutinib and Idelalisib plus rituximab. Idelalisib plus rituximab is perceived to be less active than ibrutinib yet more toxic.
- The results of the unanchored matched-adjusted indirect comparison need to be considered with caution since the populations in MURANO and RESONATE trials are very different. Also the results of comparison of MURANO and HELIOS showed no statistically significant difference and addition of bendamustine plus rituximab to ibrutinib in HELIOS added toxicity but no benefit.

# NHS England's Comments (2)

- The MURANO population is generalisable to the population of patients who would receive venetoclax plus rituximab in England. Especially patients who:
  - were treated with 1 prior systemic therapy. The majority of patients in the MURANO trial (59%) had only 1-prior treatment, of which 77% received an anti-CD-20 antibody and only 2% had previously received ibrutinib/idelalisib
  - have ECOG PS 0 or 1, as 57% of patients in the MURANO trial were of ECOG performance status 0 and 42% of PS 1.
- Post-progression costs of venetoclax plus rituximab are not included in the economic model. This is inappropriate as ibrutinib will potentially be used after venetoclax plus rituximab is stopped. Venetoclax monotherapy is currently available via the CDF for those who fail ibrutinib.

# Venetoclax, AbbVie

| | |
|---|---|
| **Marketing authorisation** | CHMP opinion received September 2018.<br>Venetoclax in combination with rituximab is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy |
| **Mechanism of action** | Selective small molecule inhibitor of B-cell lymphoma 2, anti- apoptotic protein overexpressed in 95% of people with CLL |
| **Administration and dose** | • **Titration phase**<br>  • Venetoclax, taken orally, dose escalates from 20 mg/day to 400 mg/day over 5 weeks<br>• **Post-titration phase**<br>  • Venetoclax, taken orally, 400 mg/day<br>  • Rituximab 375 mg/m$^2$ IV on day one of one cycle (a cycle is 28 days) followed by 500 mg/m$^2$ on day one of cycles two to six |
| **List price** | Venetoclax:<br>112 tab pack (100 mg) = £4,789.47 (Week five onwards, 400 mg per day for 28 days)<br>The company has a confidential commercial access agreement with NHS England which makes venetoclax available at a reduced cost<br>Rituximab:<br>500 mg/50 ml concentrate for solution for infusion vial = £785.84<br>The average cost of VEN+R for the course of 2-years when assuming 100% compliance and no progression or mortality events is £129,513 |

# Decision problem

| | Final scope issued by NICE | Company submission |
|---|---|---|
| **Population** | Adults with relapsed or refractory chronic lymphocytic leukaemia who have had at least 1 therapy | Adults with relapsed or refractory chronic lymphocytic leukaemia in the following population:<br>• Post chemoimmunotherapy |
| **Intervention** | Venetoclax with rituximab | Venetoclax with rituximab |
| **Comparator** | • Ibrutinib<br>• Idelalisib with rituximab<br>• Best supportive care (including but not limited to regular monitoring, blood transfusions, infection control, corticosteroids with or without rituximab and psychological support). | • Ibrutinib<br>• Idelalisib with rituximab<br>• BSC is not an appropriate comparator for this appraisal |
| **Outcomes** | The outcome measures to be considered include:<br>• overall survival<br>• progression-free survival<br>• disease-free survival<br>• minimal residual disease negative rate<br>• adverse effects of treatment<br>• health-related quality of life | Same as final scope issued by NICE |

# ERG's comments on decision problem

| Area | ERG's comments |
|---|---|
| Population | • Restricting the target population to patients post chemo-immunotherapy potentially excludes CLL patients with del(17p) and/or TP53 mutation<br>• Patients may never receive chemoimmunotherapy, given that they receive ibrutinib as first-line in clinical practice |
| Comparator | • Single-agent ibrutinib or idelalisib-rituximab combination (IDELA+R) are the main comparators<br>• No head-to-head trials comparing VEN+R against single-agent ibrutinib or IDELA+R were identified<br>• BSC is not relevant in this appraisal |
| Outcome | • Data from the key trial evidence (MURANO) was not mature enough to estimate the overall survival, so progression free survival was a reasonable primary endpoint<br>• The company did not provide MAIC analyses of the MRD status |

# Clinical evidence: MURANO

| | |
|---|---|
| **Design** | • Phase 3 open-label parallel-arm RCT |
| **Location (sites)** | • 109 sites in 20 countries: 4 sites in the UK |
| **Population** | • Adults (18yrs +) with R/R CLL treated with at least one but not more three lines of therapy |
| **Intervention and comparator** | • ITT=389: VEN+R (n=194) and BR (n=195)<br>• Patients from UK: VEN+R (n=6) and BR (n=4)<br>• BR was selected as the comparator arm for the MURANO trial as it was considered the most effective regimen for relapsed CLL when the study was initiated<br>• VEN+R is given for a maximum of 2 years, or until disease progression or unacceptable toxic effects, whichever occurred sooner |
| **Primary outcome measures** | • Investigator-assessed PFS median follow-up at recent data cut: 23.8 |
| **Secondary outcome measures** | • IRC-assessed PFS, investigator- and IRC-assessed PFS in patients with del(17p), protocol-defined investigator and IRC–assessed ORR, MRD, Duration of response, OS, event-free survival and time to next anti-CLL treatment, HRQoL |

# Baseline characteristics in MURANO trial (1)

| Characteristic | VEN+R (n=194) | BR (n=195) |
|---|---|---|
| **Age, years, median (range)** | 64.5 (28-83) | 66.0 (22–85) |
| **Male n (%** | 136 (70.1) | 151 (77.4) |
| **ECOG score, n (%)** | | (n=194) |
| 0 | 111(57.2) | 108 (55.7) |
| 1 | 82 (42.3) | 82 (42.3) |
| 2 | 1 (0.5) | 2 (1.0) |
| **Del(17p) status, n (%)** | (n=173) | (n=169) |
| Present | 46 (26.6) | 46 (27.2) |
| Absent | 127 (73.4) | 123 (72.8) |
| **TP53 mutation status, n (%)** | (n=192) | (n=184) |
| Mutated | 48 (25.0) | 51 (27.7) |
| Unmutated | 144 (75.0) | 133 (72.3) |
| **Del(17p) vs.TP53 mutation, n/N (%)** | (n=192) | (n=192) |
| Only del(17p) | 24 (14.0) | 18 (11.4) |
| TP53 mutation only | 19 (11.1) | 23 (14.6) |
| Del(17p) and TP53 mutated | 22 (12.9) | 22 (13.9) |
| Del(17p) and TP53 mutated | 53 (27.8) | 50 (26.6)[d] |
| Non-del(17p) andTP53 mutated[d] | 141 (72.7) | 138 (73.4)[d] |
| [d] Outcomes based on n=188. | | |

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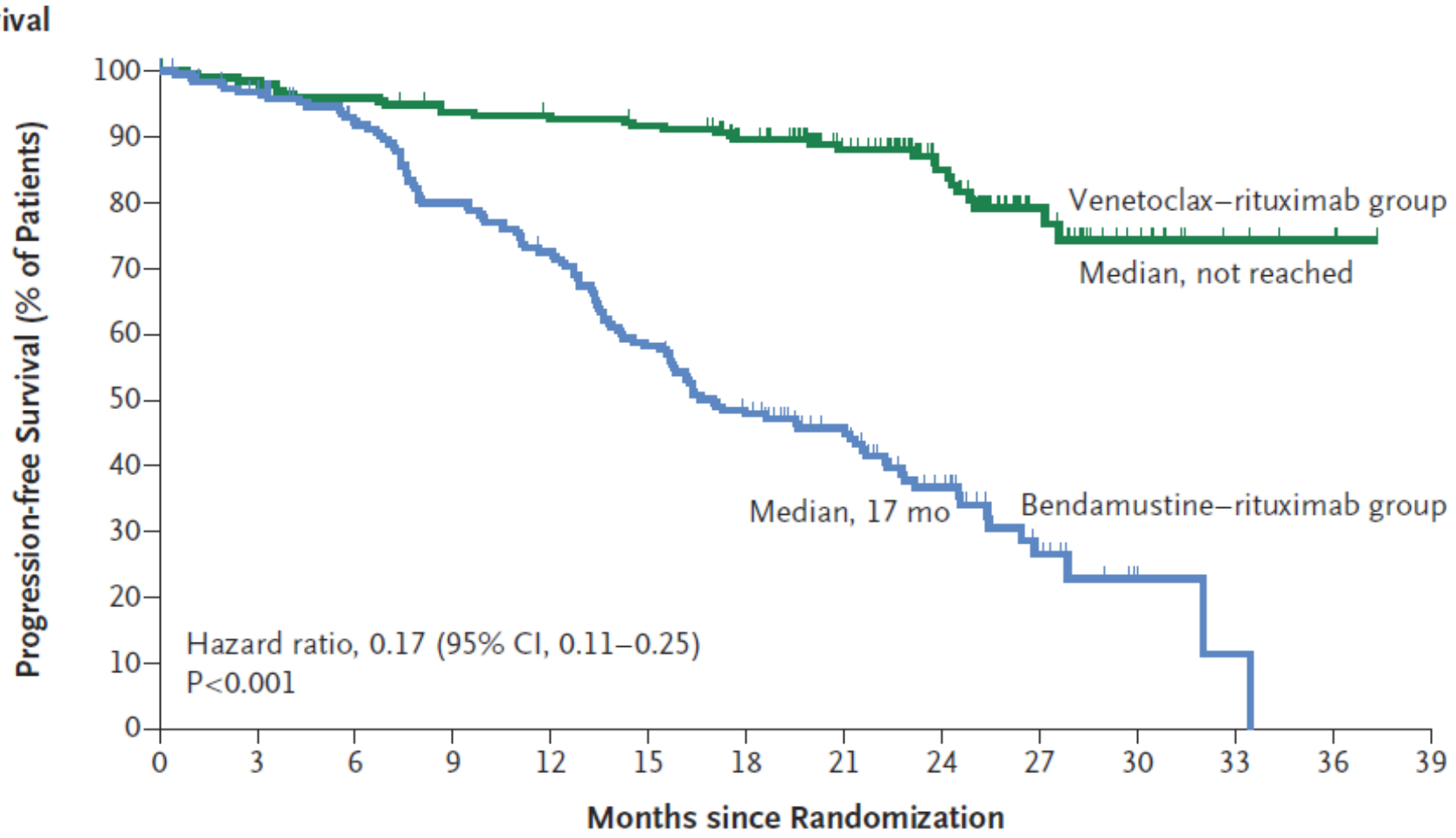
# Baseline characteristics in MURANO trial (2)

| Characteristic | VEN+R (n=194) | BR (n=195) |
|---|---|---|
| **Stratification factor: risk status (derived), n (%)** | | |
| N | 194 | 195 |
| High | 109 (56.2) | 118 (60.5) |
| Low | 84 (43.3) | 75 (38.5) |
| **Number of prior CLL therapies, n (%)** | | |
| N | 194 | 195 |
| 1 | 111 (57.2) | 117 (60.0) |
| 2 | 57 (29.4) | 43 (22.1) |
| 3 | 22 (11.3) | 34 (17.4) |
| >3 | 4 (2.1) | 1 (0.5) |
| **Type of prior CLL therapies, n (%)** | | |
| Alkylating agent | 182 (93.3) | 185 (95.4) |
| Purine analogue | 157 (80.5) | 158 (81.4) |
| Anti-CD20 antibody | 153 (78.5) | 148 (76.3) |
| B-cell receptor inhibitor | 3 (1.5) | 5 (2.6) |

# Progression free survival (investigator assessed)

PFS
VEN+R: the median was not reached.
BR: 17 months
HR= 0.17 (95% CI 0.11 to 0.25)
p<0.0001




**No. at Risk**

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Venetoclax–rituximab group | 194 | 190 | 185 | 179 | 176 | 173 | 157 | 115 | 76 | 33 | 14 | 5 | 3 |
| Bendamustine–rituximab group | 195 | 177 | 163 | 141 | 127 | 102 | 81 | 57 | 35 | 12 | 3 | 1 | |

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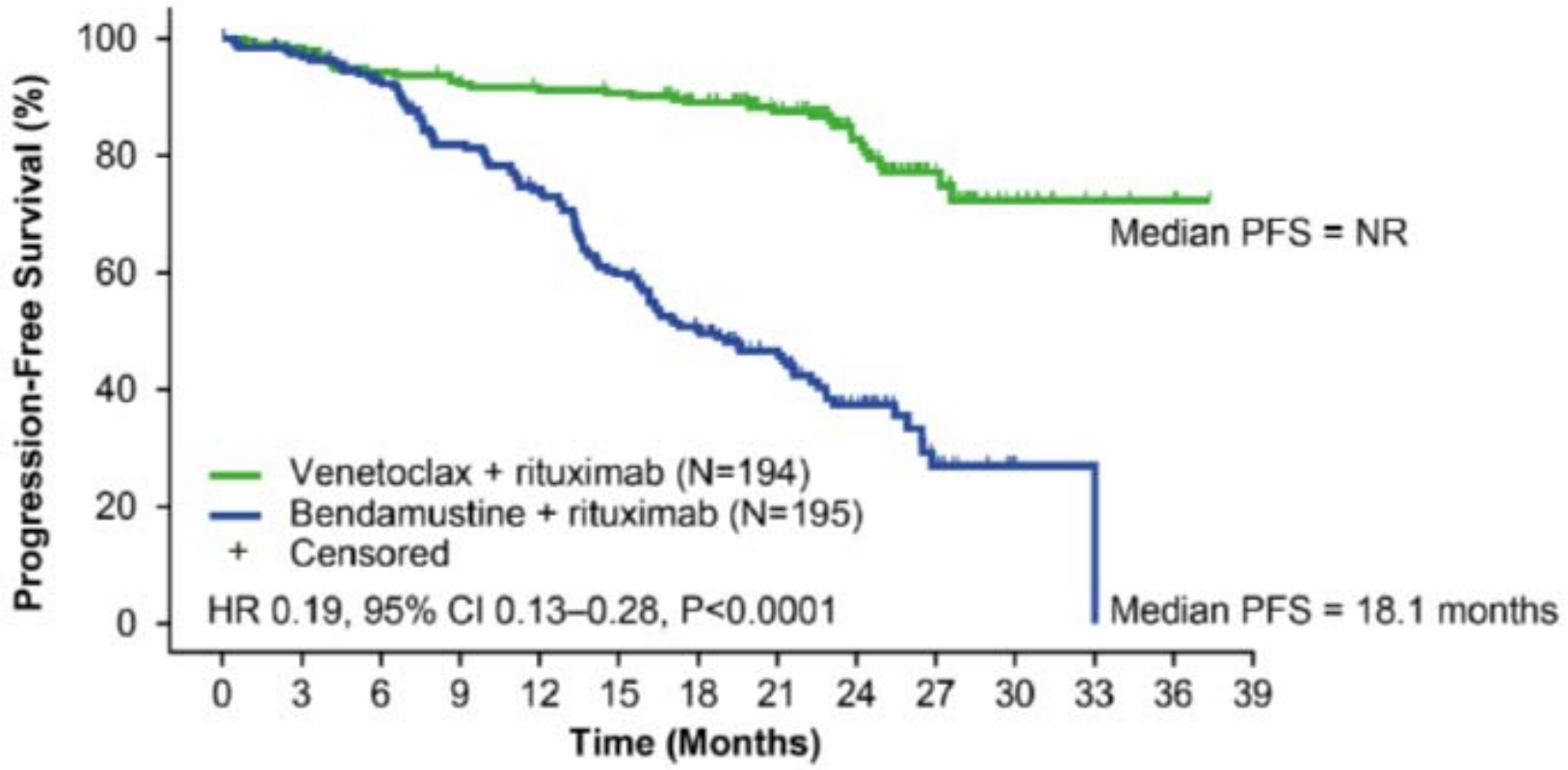
# Progression free survival (Independent review committee assessed)

PFS
VEN+R: the median was not reached
BR: 18.1 months
HR= 0.19 (95% CI 0.13 to 0.28)
p<0.0001




**No. of patients at risk**

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Venetoclax + rituximab | 194 | 190 | 182 | 177 | 173 | 171 | 157 | 116 | 75 | 34 | 14 | 5 | 3 |
| Bendamustine + rituximab | 195 | 178 | 162 | 138 | 124 | 100 | 82 | 56 | 34 | 11 | 2 | 1 | |

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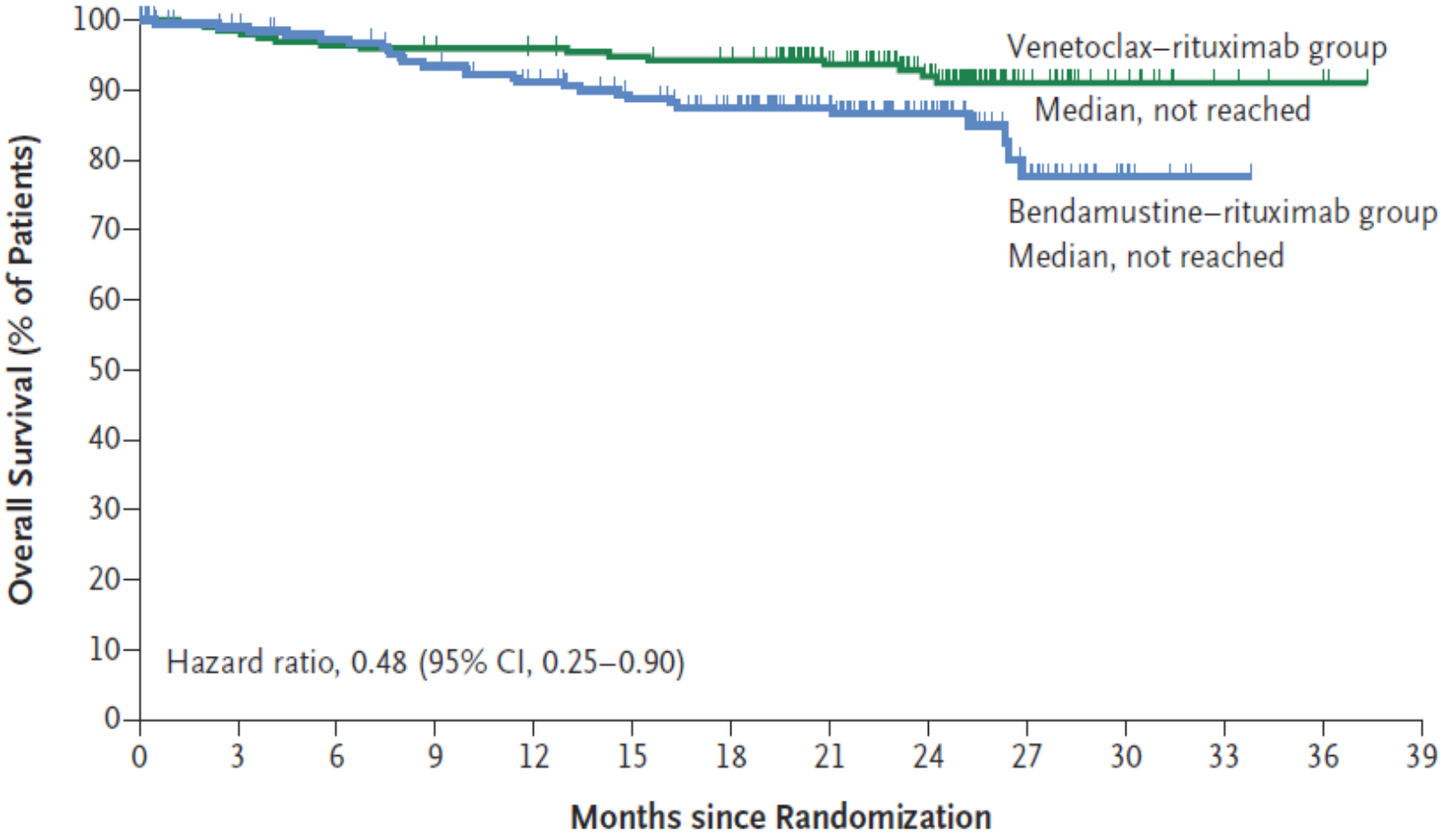
# Overall survival

OS
VEN+R: the median was not reached
BR: the median was not reached
HR= 0.48 (95% CI 0.25 to 0.90)




**No. at Risk**

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Venetoclax–rituximab group | 194 | 190 | 185 | 183 | 181 | 178 | 175 | 142 | 102 | 36 | 15 | 5 | 3 |
| Bendamustine–rituximab group | 195 | 181 | 175 | 166 | 158 | 146 | 134 | 102 | 66 | 29 | 8 | 2 | |

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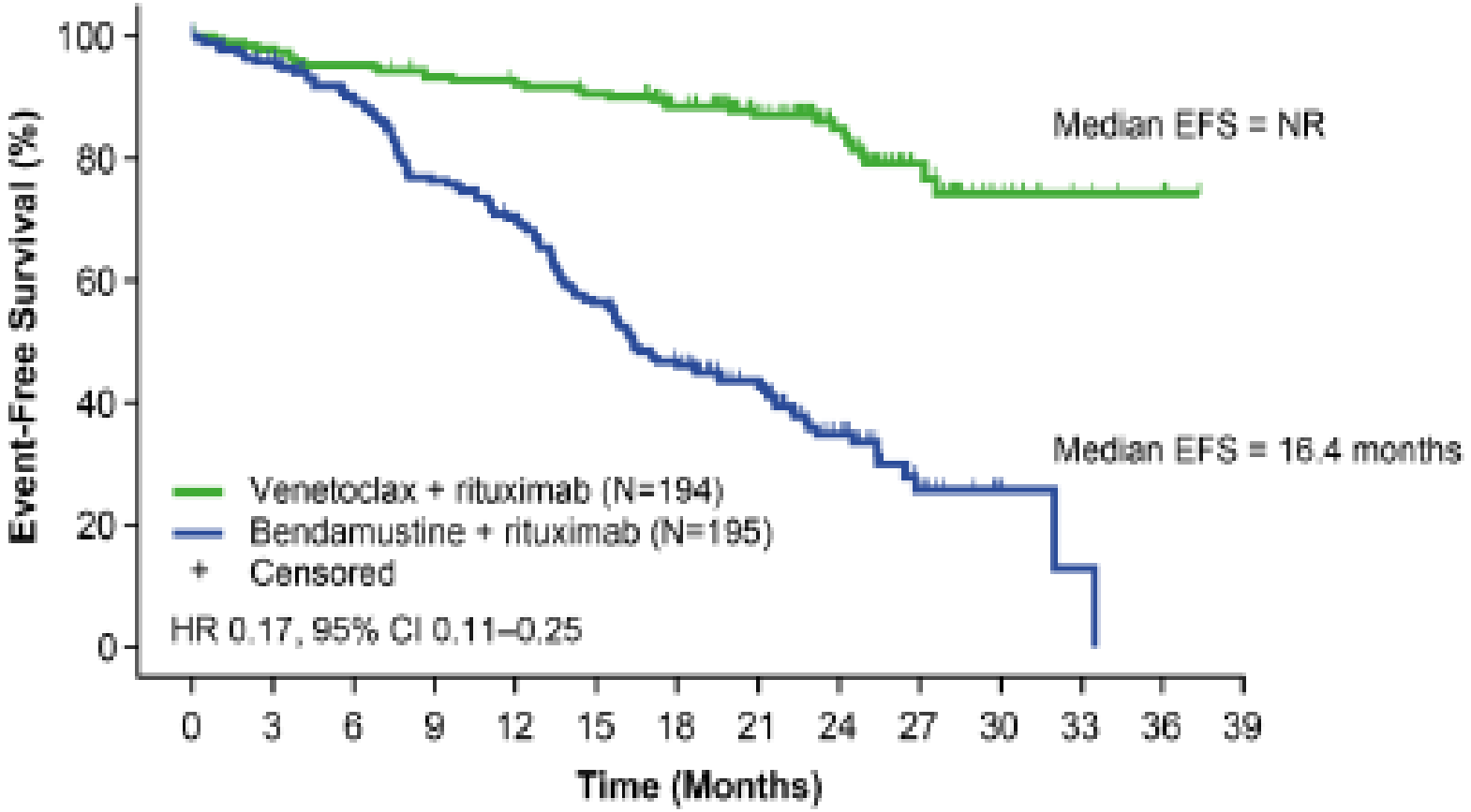
# Event-free survival

EFS
VEN+R: the median was not reached
BR: 16.4 months
Is VEN+R
HR= 0.17 (95% CI 0.11 to 0.25)




| No. of patients at risk | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Venetoclax + rituximab | 194 | 189 | 184 | 178 | 175 | 171 | 155 | 113 | 75 | 33 | 14 | 5 | 3 |
| Bendamustine + rituximab | 195 | 177 | 162 | 138 | 126 | 101 | 80 | 56 | 34 | 11 | 3 | 1 | |

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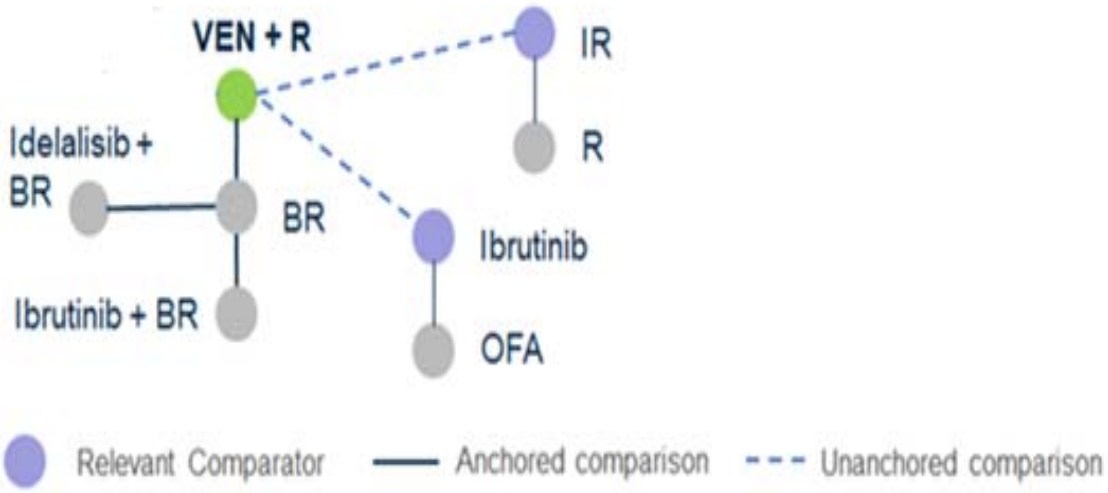
# Company's indirect treatment comparison (1)

- Since there was no common comparator connecting all the treatments in the MURANO trial (VEN+R, ibrutinib, IDELA+R), the company performed an unanchored matched-adjusted indirect comparison (MAIC) analysis using data from MURANO for VEN+R, RESONATE for ibrutinib and Study 116 for Ideal+R
- The company also performed an anchored MAIC which was conducted only for Ibrutinib+BR, assuming that the relative efficacy of VEN+R vs. ibrutinib+BR can be extended to VEN+R vs. ibrutinib monotherapy. Data was used from MURANO for VEN+R and HELIOS for ibrutinib+BR




| Treatment | Trial | ITT (N) |
|---|---|---|
| **VEN +R** | MURANO | VEN+R: 194<br>BR: 195 |
| **Ibrutinib** | RESONATE | Ibrutinib:195<br>OFA:196 |
| **Idela +R** | Study 116 | Idela+R:110<br>Rituximab:110 |
| **Ibrutinib** | HELIOS | Ibrutinib+BR:289<br>BR:289 |

# ERG's comments on indirect treatment comparison trial baseline characteristics

| Characteristics | Before matching | | After matching | |
|---|---|---|---|---|
| | VEN+R MURANO | Ibrutinib RESONATE | VEN+R MURANO | Ibrutinib RESONATE |
| | (N=169)[a] | (N=195) | (N=62)[b] | (N=195) |
| **Age ≥65** | 50.89% | 60.51% | 60.51% | 60.51% |
| **Rai stage III-IV** | 27.22% | 55.90% | 55.90% | 55.90% |
| **Bulky disease ≥5cm** | 43.79% | 63.59% | 63.59% | 63.59% |
| **Prior therapy >1** | 43.79% | 82.05% | 82.05% | 82.05% |
| **ECOG=1** | 45.56% | 59.49% | 59.49% | 59.49% |
| **β2-microglobulin>3.5 mg/L** | 64.50% | 83.71% | 83.71% | 83.71% |

[a] 25 patients with prior B-cell receptor inhibitor therapy, ECOG>1, and no central lab measurement for assessing del(17p) status were excluded from the VEN+R IPD population (N = 194) before matching. [b] About two-thirds of the VEN+R IPD population were unmatched to the ibrutinib arm of RESONATE.

- The ERG is concerned about the differences in the matched sample characteristics such as age, Rai stage, bulky disease status, prior therapy status, ECOG score, and Beta-2 microglobulin concentration.
- The population in the RESONATE trial seemed healthier at the offset than population in the MURANO trial.

# Company's indirect treatment comparisons (2)

| Anchored | | | |
|---|---|---|---|
| **VEN+R vs.** | HR PFS (95% CI) | HR OS (95% CI) | Sample Size |
| **Ibrutinib +BR (Unadjusted)** | [redacted] | 0.703 (0.270 – 1.829) | [redacted] |
| **Ibrutinib +BR (Adjusted)** | [redacted] | [redacted] | VEN+R= 71.5 [redacted] |

| Unanchored (Adjusted Comparison) | | | |
|---|---|---|---|
| | HR PFS (95% CI) | HR OS (95% CI) | Sample Size |
| **VEN+R vs. Ibrutinib** | [redacted] | [redacted] | [redacted] |
| **Unadjusted Comparison** | | | |
| **VEN+R vs. Ibrutinib** | [redacted] | [redacted] | [redacted] |

- The company also conducted a scenario analysis using HRs from the anchored MAIC where they assumed that [redacted]. The ERG explored impact of using this assumption in the cost effectiveness analysis (slide 42 and 43)

# ERG's comments on results from the company's MAIC analyses

- The ERG believes that the company MAIC produced implausible OS HRs estimates, since there is usually a correlation between PFS and OS. Within the company submission results are opposite, PFS showed higher HR than OS. Nothing in the mechanism of action of VEN+R could explain such results.

| Comparison of PFS and OS outcomes in patients with R/R CLL | | | | |
|---|---|---|---|---|
| **Study** | Treatment 1 | Treatment 2 | PFS HR $_{1 \text{ vs } 2}$ | OS HR $_{1 \text{ vs } 2}$ |
| **HELIOS** | Ibrutinib+BR | BR | 0.20 | 0.63 |
| **MURANO** | VEN+R | BR | 0.19 | 0.48 |
| **RESONATE** | Ibrutinib | Ofatumumab | 0.22 | 0.43 |
| **Company's MAIC** | VEN+R | Ibrutinib | XXXX | XXXX |

- Therefore the ERG conducted a network-meta analysis to produce alternative OS and PFS estimates for ibrutinib and VEN+R.

# ERG's network–meta analysis

- The ERG agrees that there is not sufficient evidence to indirectly compare ibrutinib with VEN+R using results from RCTs. However they identified an abstract by Hillmen et al. that compared single-agent ibrutinib to BR and they used it as a common comparator.
- The ERG believes that results from the NMA are more consistent because the benefit observed on PFS is associated with a lower benefit on OS.

| Comparison of PFS and OS outcomes in R/R CLL using the MAIC or the ERG's exploratory NMA | | | | |
|---|---|---|---|---|
| **Study** | Treatment 1 | Treatment 2 | PFS HR $_{1 \text{ vs } 2}$ | OS HR $_{1 \text{ vs } 2}$ |
| **Company's MAIC** | VEN+R | Ibrutinib | [redacted] | [redacted] |
| **ERG's NMA** | | | 1.43 (0.78-2.61) | 1.08 (0.42-2.73) |

- It is the ERG preference to model the OS and PFS of ibrutinib using HR from exploratory network meta-analysis undertaken by ERG rather than the company's MAIC .

# Summary of AEs and SAEs

| Event | VEN+R (n=194) | BR (n = 188) | ERG-calculated p-values |
|---|---|---|---|
| Grade 3 or 4 AE — with at least 2% difference in incidence between groups — no. of patients (%) | 159 (82.0) | 132 (70.2) | 0.01 |
| Total no. of events | 335 | 255 | |
| Discontinuations due to AEs | 24 | 11 | 0.03 |
| Grade 3 or 4 AEs with at least 2% difference in incidence between groups — no. of patients (%) | 130 (67.0) | 104 (55.3) | 0.02 |
| SAEs — with at least 2% incidence in either group- no. of patients (%) | 90 (46.4) | 81 (43.1) | 0.52 |

Overall, there were more AEs in the VEN+R arm (n = 335) than in the BR arm (n = 255). However, it is not specified in the company submission or the CSR if AEs were treatment-related.

# Key Issues - clinical

- **Clinical Pathway:**

- Restricting the population to people post chemotherapy may exclude patients with del(17p) and/or TP53 mutation

- **Clinical evidence**

- Are the results generalisable to clinical practice in England?

- Appropriateness of matched-adjusted indirect comparison (MAIC) data comparing VEN+R with ibrutinib and IDELA+R

- Clinical uncertainties and data collection

# Lead team presentation

## Venetoclax with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia [ID1097] – STA

1st Appraisal Committee meeting

Committee C

Lead team: Prithwiraj Das

ERG: Warwick Evidence

Technical team: Julia Sus and Sally Doss

27 September 2018

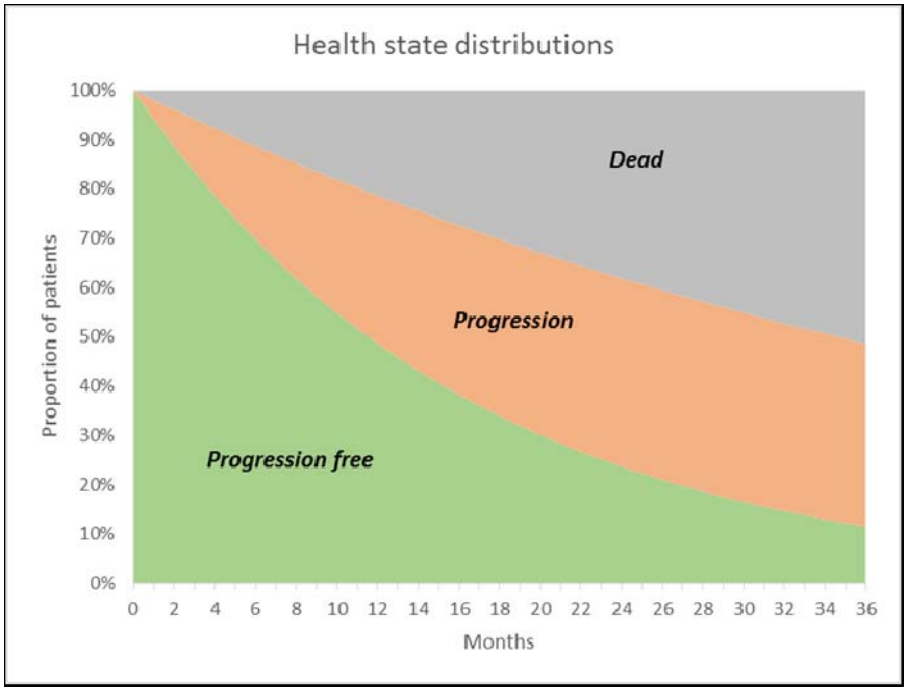
# Key issues- cost

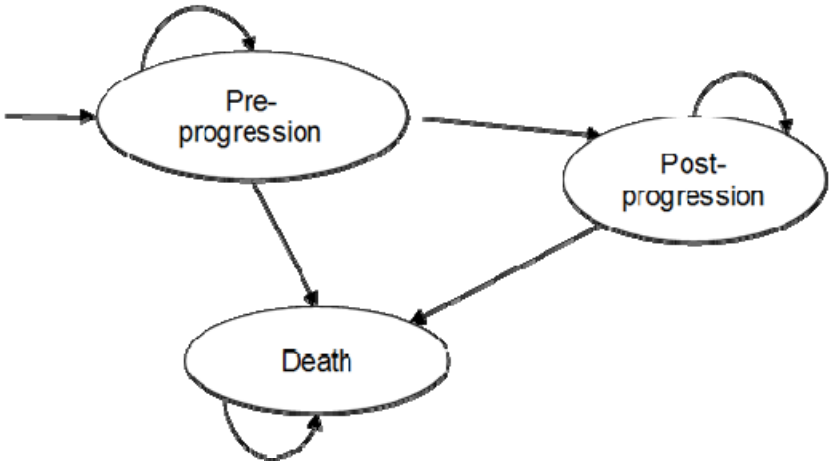
- Methods for estimating relative benefit of VEN+R compared with ibrutinib; company used MAIC, ERG used NMA
- Survival extrapolation for VEN+R and comparators; immature OS data
- What is the most plausible ICER for decision making?
- **Other:**

- Is VEN+R an innovative treatment?
- Are there any equality issues?
- End of life considerations
- CDF considerations

# Company's economic model

- De novo partitioned survival model
- Based on data from MURANO trial
- Discount rate of 3.5% per annum was applied
- Lifetime horizon – estimated 30 years



# Company's model: Summary

| Input | Source/assumption |
|---|---|
| Population | Full population include refractory and relapsed (R/R) CLL patients.<br>The company provided subgroup analysis for R/R CLL population:<br>•Patients WITH a deletion of chromosome 17p (del(17p) and/or TP53 mutation)<br>•Patients WITHOUT a deletion of chromosome 17p (non-del(17p) and/or TP53 mutation) |
| Intervention/ comparator | Venetoclax with rituximab is compared with ibrutinib or idelalisib with rituximab |
| Treatment effectiveness | Clinical outcomes included were response (CR/PR), PFS, RFS and OS, minimal residual disease negative rate, HRQoL, adverse events of treatment, del(17p)/TP53 status. |
| | The company modelled PFS and OS jointly across both arms, assuming proportionality and the same parametric form between OS and PFS. |
| | OS and PFS endpoints based on the investigator assessment and IRC assessment, clinical cut off data May 2017. |
| Adverse Events | Grade 3 and 4 treatment related events that occurred in at least 5% of patients in any of the three main trials (MURANO, RESONATE and Study 116) were included. |
| HRQoL | EQ-5D-3L data were collected in MURANO trial. However, the health state utility values used in the economic model are taken from literature sources that were used in TA487 (venetoclax monotherapy) and TA359 (idela+R). |

# Overall survival for VEN+R

The Company base case model selection for the extrapolation of VEN+R PFS and OS is the Weibull.

# Progression-free survival for VEN+R

The base case model selection for the extrapolation of VEN+R PFS and OS is the Weibull.

# ERG's Overall survival for VEN+R - jointly fitted parametric models

# Company's and ERG's method of fitting comparator survival curves

- In order to estimate the comparator survival curves, estimates of relative treatment efficacy (PFS and OS hazard ratios) obtained through the MAIC were combined with the VEN+ R parametric survival curves.
- The KM data from the MAIC was taken and separate models were parameterised using the Weibull distribution.
- The graph shows company's and ERG's OS predictions of ibrutinib in MURANO population alongside observed effect of ibrutinib on OS from RESONATE.

# ERG's comments on jointly fitted curves (1)

- The ERG preferred curve is Gamma for both OS and PFS rather than Weibull as it provides greater difference in the estimates between the pre- and post- progression life years. It also provides better estimates in comparison to other models, it falls within the range of estimates from the clinical experts and has a lower AIC than the Log-logistic.
- To fit a curve for ibrutinib the company used HR obtained from the MAIC to the parametric curves fitted to the VEN+R arm of the MURANO. It is the preference of the ERG to model the OS and PFS of ibrutinib using HR from the ERG's NMA as it results in a plausible balance of PFS and PPS life years for ibrutinib.
- There was no comparisons of IDELA+R to BR to generate alternative HRs. The ERG maintained the HRs estimated by the company, but applied them to the Gamma PFS and OS curves.

**Undiscounted LY estimates for VEN+R**

| | PFS | OS | PFS LY (% of total LY) | PPS LY (% of total LY) | Total LY |
|---|---|---|---|---|---|
| **Company base-case** | Weibull | Weibull | [redacted] | [redacted] | [redacted] |
| **ERG preferred assumptions** | Gamma | Gamma | [redacted] | [redacted] | [redacted] |
| **ERG scenario** | Log-logistic | Log-logistic | [redacted] | [redacted] | [redacted] |

# ERG's comments on jointly fitted curves (2)

| Undiscounted Life Year (LY) estimates of ibrutinib | | | | | |
|---|---|---|---|---|---|
| | PFS and OS Curves and HR | HR Source | PFS LY (% of total LY) | PPS LY (% of total LY) | Total LY |
| **Company base-case** | Weibull [redacted] | Company MAIC | [redacted] | [redacted] | [redacted] |
| **ERG preferred assumptions** | Weibull [redacted] | ERG NMA | [redacted] | [redacted] | [redacted] |
| **ERG scenario** | Gamma [redacted] | ERG NMA | [redacted] | [redacted] | [redacted] |
| **Undiscounted LY estimates of IDELA+R** | | | | | |
| **Company base-case** | Weibull | MAIC (IDELA+R) | [redacted] | [redacted] | [redacted] |
| **ERG preferred assumptions** | Gamma | MAIC (IDELA +R) | [redacted] | [redacted] | [redacted] |
| **ERG scenario** | Gamma | MAIC (IDELA +BR, adjusted) | [redacted] | [redacted] | [redacted] |

# Company's model: Health-related quality of life

- Health-state utility values derived from the MURANO trial were not used in the economic model as they were heavily skewed and lacked face validity compared with general UK adult population utility norms.
- The company used utility values from the literature source used in previous NICE technology appraisals including venetoclax monotherapy (TA487) and IDELA+R (TA359).
- The company included disutility associated with adverse events in the model and adjusted for age-related utility deterioration.

| State | Utility value: mean (standard error) | 95% CI (assuming SE=10% of the mean) | Literature Source |
|---|---|---|---|
| **Pre-progression** | 0.748 | 0.589-0.879 | Data from Study 116 |
| **Post-progression** | 0.600 | 0.480-0.714 | An ERG report by Dretzke et al. on the cost effectiveness of rituximab |

ERG comments:

- Source and approach to choosing utility values by the company is appropriate and consistent with the previous estimates of health utility in R/R CLL patients.
- Patient population in the current appraisal of VEN+R is likely to be similar to the populations considered in TA487 and TA359.
- The company disutility values and approach to adjusting for age-related utility deterioration is appropriate.

# Costs and resource use

- Model includes following costs:
  - Intervention and comparators' costs and resource use **(**active treatment costs: venetoclax, rituximab, ibrutinib, drug acquisition costs, drug administration costs (accounting for overheads, qualifications, and salary on costs, hospital-based scientific and professional staff, pharmacist time) no drug wastage costs were included in the model)
  - A two-year stopping rule was applied when calculating intervention costs for VEN+R, whereas treatment with ibrutinib and IDELA+R continued until disease progression
  - Treatment specific monitoring (the costs of Tumour Lysis Syndrome prophylaxis)
  - Health-state unit costs and resource use (routine care and monitoring unit costs: Full blood count, LDH, Chest X-ray, Bone marrow exam, Haematologist visit, Inpatient non-surgical/medical visit, Full blood transfusion)
  - Adverse reaction unit costs and resource use (anaemia, autoimmune haemolytic anaemia, neutropenia, pneumonia, thrombocytopenia)
  - Terminal Care costs (these are applied to all patients who transition to the death health state as a one-off cost)
  - Other healthcare costs (other adverse events, 'routine care and monitoring' including hospital visits, investigations and procedures undertaken during a CLL patient's treatment pathway)

ERG comment:
Uncertainty exists around the sources used to estimate adverse event costs in the economic model. The ERG have performed scenario analyses using estimates for adverse events from other sources identified in the literature.

NICE

# Company's base-case results

The Company analysis used:

- PFS and OS hazard ratios from the unanchored MAIC,
- 2-year maximum treatment duration applied to the VEN+R when estimating treatment costs
- Health-state utility values of 0.748 and 0.600 used for the pre-progression and post-progression health states respectively.

| Technologies | Total Costs, £ | Total QALYs | Inc. Costs, £ | Inc QALYs | ICER vs baseline (£/QALY) | Pairwise ICER vs. VEN+R (£/QALY) |
|---|---|---|---|---|---|---|
| **With CAA for VEN+R** | | | | | | |
| IDELA+R | xxxxxxx | 2.307 | - | - | - | £2,625 |
| VEN+R | xxxxxxx | 5.666 | -£8,816 | -3.358 | £2,625 | - |
| Ibrutinib | xxxxxxxx | 3.067 | -£147,377 | -0.759 | £194,048 | VEN+R dominates ibrutinib |

ERG comment: In the company base-case, the PFS is restricted to being equal or lower than OS, resulting in zero post-progression period for ibrutinib.

- The company also conducted the total of 51 scenario analyses for R/R CLL using both list and net prices.
- The company found the model predictions were generally robust with VEN+R continuing to dominate ibrutinib in the majority of the scenario analyses undertaken.

# Company's corrected base case model:

## corrections to the dosing regimen and treatment costs for VEN+R

- During the clarification stage, the ERG highlighted that the dosing regimen for rituximab needed correcting since it is given in cycles 2 to 7 and not 1 to 6 as it was in the original company model. The company corrected the error and provided updated base-case results generated from the corrected model for the R/R CLL population.

| **Company base–case corrected model: Company base-case discounted results after ERG applied the corrections to the dosing regimen and treatment costs for VEN+R for R/R CLL population** | | | | | |
|---|---|---|---|---|---|
| **Technologies** | Total Costs, £ | Total QALYs | Inc. Costs, £ | Inc. QALYs | ICER vs. VEN+R (£/QALY) |
| **With CAA for VEN+R** | | | | | |
| **VEN+R** | [redacted] | 5.666 | - | - | |
| **Ibrutinib** | [redacted] | 3.067 | -£135,650 | 2.599 | VEN+R dominates ibrutinib |
| **IDELA+R** | [redacted] | 2.307 | £11,726 | 3.358 | £3,492 |

# ERG scenario analysis (1)

## corrected model and using population data from RESONATE and Study 116

- The ERG believes that the modelled population should be taken form the comparator trial population (RESONATE and Study 116) when using the MAIC estimates and not from the MURANO trial since HRs were taken from the adjusted MAIC, for both Ibrutinib and idela+R.

| Technologies | Total Costs, £ | Total QALYs | Inc. Costs, £ | Inc. QALYs | ICER vs. VEN+R (£/QALY) |
|---|---|---|---|---|---|
| **Changed modelled population to RESONATE compared with ibrutinib (R/R CLL population)** | | | | | |
| **With CAA for VEN+R** | | | | | |
| **VEN+R** | xxxxxxxx | 5.55 | - | - | |
| **Ibrutinib** | xxxxxxxx | 3.017 | -£133,765 | 2.533 | VEN+R dominates ibrutinib |
| **Changed modelled population to Study 116 cohorts compared with IDELA+R (R/R CLL population)** | | | | | |
| **With CAA for VEN+R** | | | | | |
| **VEN+R** | xxxxxxxx | 5.24 | £102,033 | - | |
| **IDELA+R** | xxxxxxxx | 2.156 | £13,815 | 3.084 | £4,480 |

Minimal impact on the cost-effectiveness estimates

# ERG scenario analysis (2)

## corrected model and change to OS HR compared with ibrutinib

- The anchored MAIC analyses was conducted by the company assuming that relative efficacy of VEN+R vs. ibrutinib+BR could be extended to VEN+R vs. ibrutinib single-agent.
- Based on that assumption the ERG estimated scenario applying the mean, lower and higher 95% CI estimates of the OS HR in comparison with ibrutinib in R/R CLL population.

| Technologies | Total Costs, £ | Total QALYs | Inc. Costs, £ | Inc. QALYs | Pairwise ICER (£/QALY) |
|---|---|---|---|---|---|
| **Mean OS HR from company's anchored MAIC (adjusted) analysis** | | | | | |
| **With CAA for VEN+R** | | | | | |
| **Ibrutinib** | XXXXXXXX | 4.191 | | | |
| **VEN + R** | XXXXXXXX | 5.666 | -£149,447 | 1.475 | VEN+R dominates ibrutinib |
| **Lower 95%CI estimate of the OS HR (0.201) from anchored MAIC (adjusted) analysis** | | | | | |
| **With CAA for VEN+R** | | | | | |
| **Ibrutinib** | XXXXXXXX | 2.397 | | | |
| **VEN + R** | XXXXXXXX | 5.666 | -£84,647 | 3.269 | VEN+R dominates ibrutinib |
| **Minimal impact on the cost-effectiveness estimates** | | | | | |
| **Upper 95% CI estimate of the OS HR (1.534) from anchored MAIC (adjusted) analysis** | | | | | |
| **With CAA for VEN+R** | | | | | |
| **Ibrutinib** | XXXXXXXX | 6.546 | | | |
| **VEN + R** | XXXXXXXX | 5.666 | -£172,056 | -0.88 | £195,564 (SW quadrant) |
| **This suggests that VEN+R is cheaper but also generated fewer QALYs than ibrutinib** | | | | | |

# ERG scenario analysis (3)

## corrected model and change to OS HR compared with IDELA+R

- The company provided HRs for OS and PFS for VEN+R vs IDELA+BR based on adjusted anchored MAIC analysis but there is no published evidence to suggest IDELA+R and IDELA+BR have similar efficacy.
- In the absence of reliable comparative evidence, the ERG conducted a sensitivity analyses assuming similar effect for VEN+R and IDELA+R.

| **Assumed an OS HR of 1 for VEN+R vs. IDELA+R (R/R CLL population)** | | | | | |
|---|---|---|---|---|---|
| **Technologies** | Total Costs, £ | Total QALYs | Inc. Costs, £ | Inc. QALYs | Pairwise ICER (£/QALY) |
| **With CAA for VEN+R** | | | | | |
| **IDELA+R** | xxxxxxxx | 5.154 | | | |
| **VEN + R** | xxxxxxxx | 5.666 | -£14,944 | 0.512 | VEN+R dominates IDELA+R |

Under this assumption, VEN+R was cheaper and generated more QALYs than IDELA+R

# ERG scenario analysis (4)

## alternative method of estimating hazard ratio for VEN+R vs. ibrutinib

- The ERG conducted an alternative indirect comparison using a fixed-effect NMA to compare survival outcomes for VEN+R vs. ibrutinib as they found OS HRs from adjusted unanchored MAIC analysis highly uncertain.
- ERG applied HRs from the indirect comparison to corrected base-case model.

| Corrected model: used central estimate of PFS and OS HR for VEN+R vs. ibrutinib from ERG's NMA (R/R CLL population) | | | | | |
|---|---|---|---|---|---|
| **Technologies** | Total Costs, £ | Total QALYs | Inc. Costs, £ | Inc. QALYs | Pairwise ICER (£/QALY) |
| **With CAA for VEN+R** | | | | | |
| **Ibrutinib** | xxxxxxxx | 6.019 | | | |
| **VEN + R** | xxxxxxxx | 5.666 | -£279,766 | -0.354 | £790,988 (SW quadrant) |

VEN+R was cheaper but also generated fewer QALYs compared with ibrutinib

# Summary of ERG's scenario analysis

| Assumptions | VEN+R ICER |
|---|---|
| Changed modelled population to the RESONATE compared with ibrutinib (R/R CLL population) | Dominant |
| Changed modelled population to Study 116 cohorts compared with IDELA+R (R/R CLL population | £4,480 |
| Mean OS HR from company's anchored MAIC (adjusted) analysis (R/R CLL population) | Dominant |
| Lower 95%CI estimate of the OS HR from anchored MAIC (adjusted) analysis (R/R CLL population) | Dominant |
| Upper 95% CI estimate of the OS HR from anchored MAIC (adjusted) analysis (R/R CLL population) | £195,564 (SW quadrant) |
| Assumed an OS HR of 1 for VEN+R vs. IDELA+R (R/R CLL population) | Dominant |
| *Corrected model: used central estimate of PFS and OS HR for VEN+R vs. ibrutinib from ERG's indirect comparison analysis (R/R CLL population) | £790,988 (SW quadrant) |

* This is the only assumption used in the ERG preferred base case

# Further exploratory analyses undertaken by ERG

The ERG conducted a series of exploratory analysis based on:

- the corrected model to investigate the impact of assuming alternative parametric modelling of PFS and OS and
- use of higher estimates of routine care costs and TLS prophylaxis costs based on the figures in TA487 and adverse events costs based on figures reported in TA439.

| *Changed PFS and OS parametric curves from joint-Weibull to joint-Gamma: VEN+R vs ibrutinib (R/R CLL population) | | | | | |
|---|---|---|---|---|---|
| **Technologies** | Total Costs, £ | Total QALYs | Inc. Costs, £ | Inc. QALYs | ICER vs. VEN+R (£/QALY) |
| **With CAA for VEN+R** | | | | | |
| **VEN+R** | [redacted] | 6.04 | - | - | |
| **Ibrutinib** | [redacted] | 3.157 | -£142,716 | 2.884 | VEN+R dominates ibrutinib |
| **IDELA+R** | [redacted] | 2.351 | £10,711 | 3.69 | £2,903 |
| **Corrected model: changed TLS prophylaxis, adverse events costs and routine care costs (R/R CLL population)** | | | | | |
| **With CAA for VEN+R** | | | | | |
| **VEN+R** | [redacted] | 5.666 | - | - | |
| **Ibrutinib** | [redacted] | 3.157 | -£142,716 | 2.884 | VEN+R dominates ibrutinib |
| **IDELA+R** | [redacted] | 2.307 | £19,123 | 3.358 | £5,694 |

Implementing all these changes together had minimal impact on the ICER

* This is the only assumption used in the ERG preferred base case

# ERG's preferred base-case model for the ibrutinib comparison

- The ERG's preferred base-case model for the ibrutinib comparison involves making the following assumptions and changes to the company corrected base-case model:
  - Changing the parametric survival curves from joint-Weibull to joint-Gamma for both PFS and OS (slide 20)
  - Changing the unanchored MAIC PFS and OS HRs to ERGs indirect comparison using estimates of PFS and OS for ibrutinib vs BR reported in Hillmen (2015) and for VEN+R vs BR based on the MURANO data (slide 18)

| Technologies | Total Costs, £ | Total QALYs | Inc. Costs, £ | Inc. QALYs | ICER vs. VEN+R (£/QALY) |
|---|---|---|---|---|---|
| **Using Gamma curves and data from ERGs NMA** | | | | | |
| **With CAA for VEN+R** | | | | | |
| **VEN+R** | xxxxxxxx | 6.04 | - | - | |
| **Ibrutinib** | xxxxxxxx | 6.431 | -£322,979 | -0.39 | £827,252 (SW quadrant) |

VEN+R was cheaper but also generated on average fewer QALYs compared with ibrutinib
The ERG preferred base-case corrected model produced similar estimate of incremental costs as the company's base-case corrected model but differed in the direction of incremental QALYs generated

*ICER including the ibrutinib PAS will be shown in Part 2 slides

# Company's Subgroup analysis

The company explained that del(17p) and TP53 mutation are known to negatively affect a patient's prognosis, thus patients with this mutation would generally have a lower survival than the whole R/R CLL population and those patients who do not have this deletion or mutation.

| Technologies | Total Costs, £ | Total QALYs | Inc Costs, £ | Inc QALYs | ICER vs. baseline (£/QALY) | Pairwise ICER VS. VEN+R (£/QALY) |
|---|---|---|---|---|---|---|
| **Company's base-case results for subgroup of patients with del(17p)/TP53 mutation** | | | | | | |
| **With CAA for VEN+R** | | | | | | |
| **IDELA+R** | xxxxxxxx | 2.045 | - | - | - | £6,013 |
| **VEN + R** | xxxxxxxx | 5.132 | -£18,558 | -3.087 | £6,013 | - |
| **Ibrutinib** | xxxxxxxxx | 2.726 | -£127,669 | -0.681 | £187,556 | VEN+R dominates ibrutinib |
| **Company's base-case results for subgroup of patients without del(17p)/TP53 mutation** | | | | | | |
| **With CAA for VEN+R** | | | | | | |
| **IDELA+R** | xxxxxxxx | 2.411 | - | - | - | £1,333 |
| **VEN + R** | xxxxxxxxx | 5.869 | -£4,608 | -3.458 | £1,333 | - |
| **Ibrutinib** | xxxxxxxxx | 3.193 | -£152,538 | -0.782 | £194,985 | VEN+R dominates ibrutinib |

# **ERG's preferred base-case analysis** including subgroup of patients with and without del(17p)/TP53 mutation for the ibrutinib comparison

| **ERG preferred base–case corrected model (del(17p)/TP53 mutation) compared with ibrutinib** | | | | | |
|---|---|---|---|---|---|
| **Technologies** | Total Costs, £ | Total QALYs | Inc. Costs, £ | Inc. QALYs | ICER vs. VEN+R (£/QALY) |
| **With CAA for VEN+R** | | | | | |
| **VEN+R** | [redacted] | 5.494 | - | - | |
| **Ibrutinib** | [redacted] | 5.87 | -£269,728 | -0.376 | £718,043 (SW quadrant) |
| **ERG preferred base–case corrected model (nondel(17p)/TP53 mutation)) compared with ibrutinib** | | | | | |
| **With CAA for VEN+R** | | | | | |
| **VEN+R** | [redacted] | 6.245 | - | - | |
| **Ibrutinib** | [redacted] | 6.638 | -£343,718 | -0.393 | £873,858 (SW quadrant) |

The results of these analyses were similar to the ERGs preferred base-case results with VEN+R being cheaper but also generating fewer QALYs compared with ibrutinib in both list and net prices comparison

## ERG's preferred base-case model for the IDELA+R comparison

- The ERG was unable to conduct a preferred base-case model for the comparison with IDELA+R because no robust estimates of relative efficacy between VEN+R vs. IDELA+R was available.

# End of life considerations

End of life criteria:

- 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 has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared with current NHS treatment.

In addition, the Appraisal Committees will need to be satisfied that:

- the estimates of the extension to life are sufficiently robust and can be shown or reasonably inferred from either progression-free survival or overall survival (taking account of trials in which crossover has occurred and been accounted for in the effectiveness review) and
- the assumptions used in the reference case economic modelling are plausible, objective and robust.

The company and ERG agree that this intervention does not meet the end of life criteria because the patient life expectancy is more than 24 months (4.64 years).

# Innovation and equality

- Venetoclax plus rituximab is a breakthrough therapy offering a step change for patients with relapsed CLL who have received at least one prior therapy.
- This treatment offers patients a good chance of achieving an enduring remission and MRD negative status without the associated risks of repeated lines of chemotherapy or other agents that do not offer a chance of MRD negativity.
- The current standard treatments have failed or caused severe side effects, there is a need for a more innovative treatment with less significant side effects like venetoclax plus rituximab.
- Chemoimmunotherapy is unsuitable in most cases in an elderly population or those with 17p or TP53 mutation. Chemoimmunotherapy is associated with a higher risk of febrile neutropenia , lower overall response rates and shorter progression free survival than venetoclax plus rituximab.

- No issues equality issues raised during scoping or company submission/ patient professional statements.

# Key issues- cost

- Methods for estimating relative benefit of VEN+R compared with ibrutinib; company used MAIC, ERG used NMA
- Survival extrapolation for VEN+R and comparators; immature OS data
- What is the most plausible ICER for decision making?
- **Other:**

- Is VEN+R an innovative treatment?
- Are there any equality issues?
- End of life considerations
- CDF considerations