NICE National Institute for Health and Care Excellence

# Acalabrutinib for treating chronic lymphocytic leukaemia

## ACM 2

ERG: ScHARR

Technical team: Stephen O'Brien, Zain Hussain, Ross Dent

Company: AstraZeneca

ACM 2: 9th February 2021

# Draft recommendations

- Recommended for people with **untreated CLL** and a **17p deletion or TP53 mutation**

- Recommended for people **who have had at least 1 previous treatment**, only if ibrutinib is their only suitable treatment option

- Not recommended for people with **untreated CLL without a 17p deletion or TP53 mutation, for whom BR and FCR unsuitable**

- n.b. company did not submit evidence for people with untreated CLL and for whom BR and FCR are suitable

BR – bendamustine plus rituximab; FCR - fludarabine, cyclophosphamide, and rituximab

# Key issues

**People who have had at least 1 prior therapy**

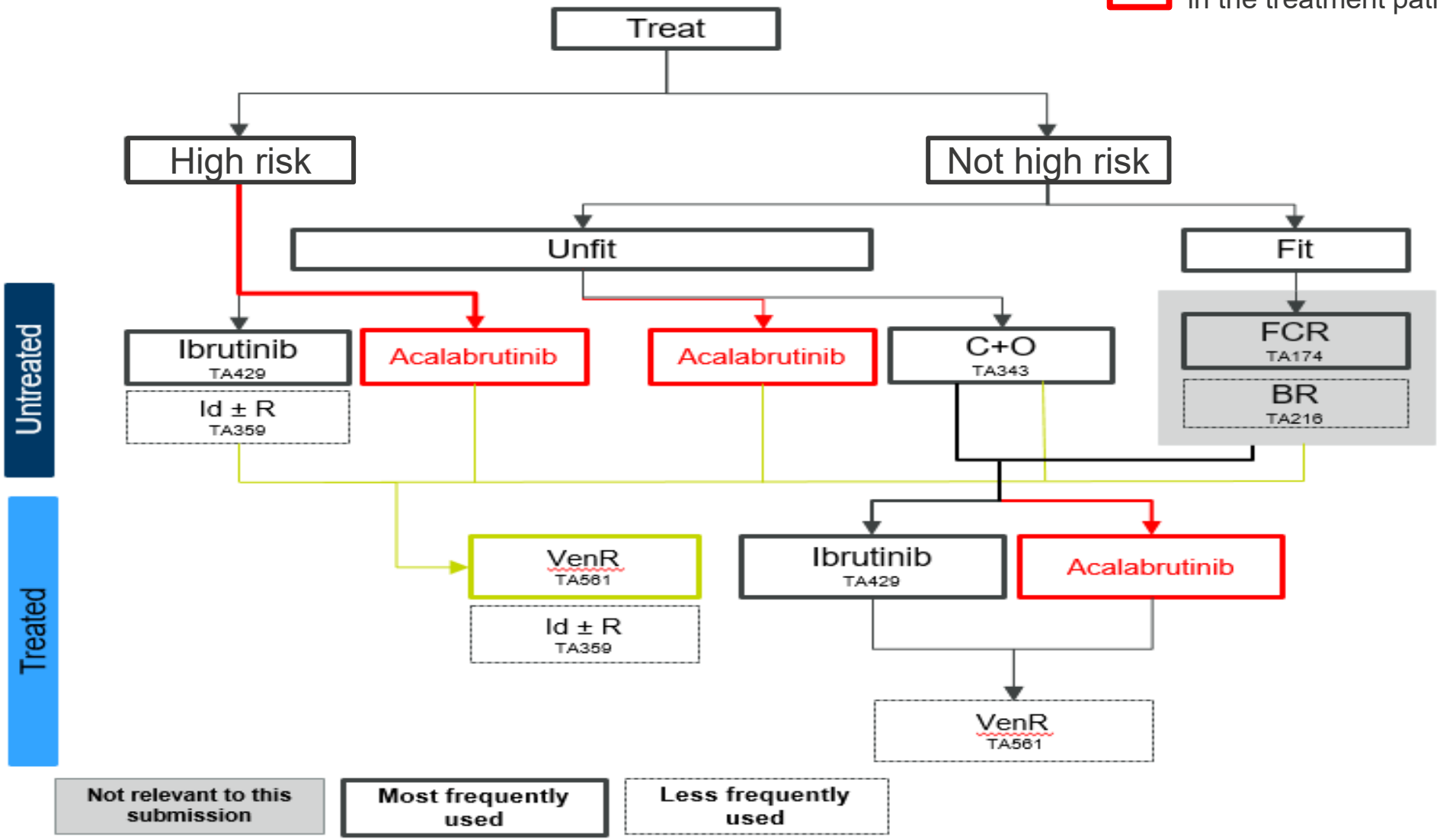
- Stipulation that ibrutinib must be their only suitable treatment option

**Untreated population**

- Proportion of patients having venetoclax plus rituximab following treatment with chlorambucil plus obinutuzumab
- Treatment duration of second-line ibrutinib following progression with chlorambucil plus obinutuzumab
- Survival benefit with acalabrutinib

# Treatment pathway

Represents proposed position in the treatment pathway




High-risk, defined as mutation status of TP53 or del17p; BR – bendamustine plus rituximab; C+O - chlorambucil plus obinutuzumab; FCR - fludarabine, cyclophosphamide, and rituximab; Id ± R - idelalisib ± rituximab; VenR – venetoclax plus rituximab

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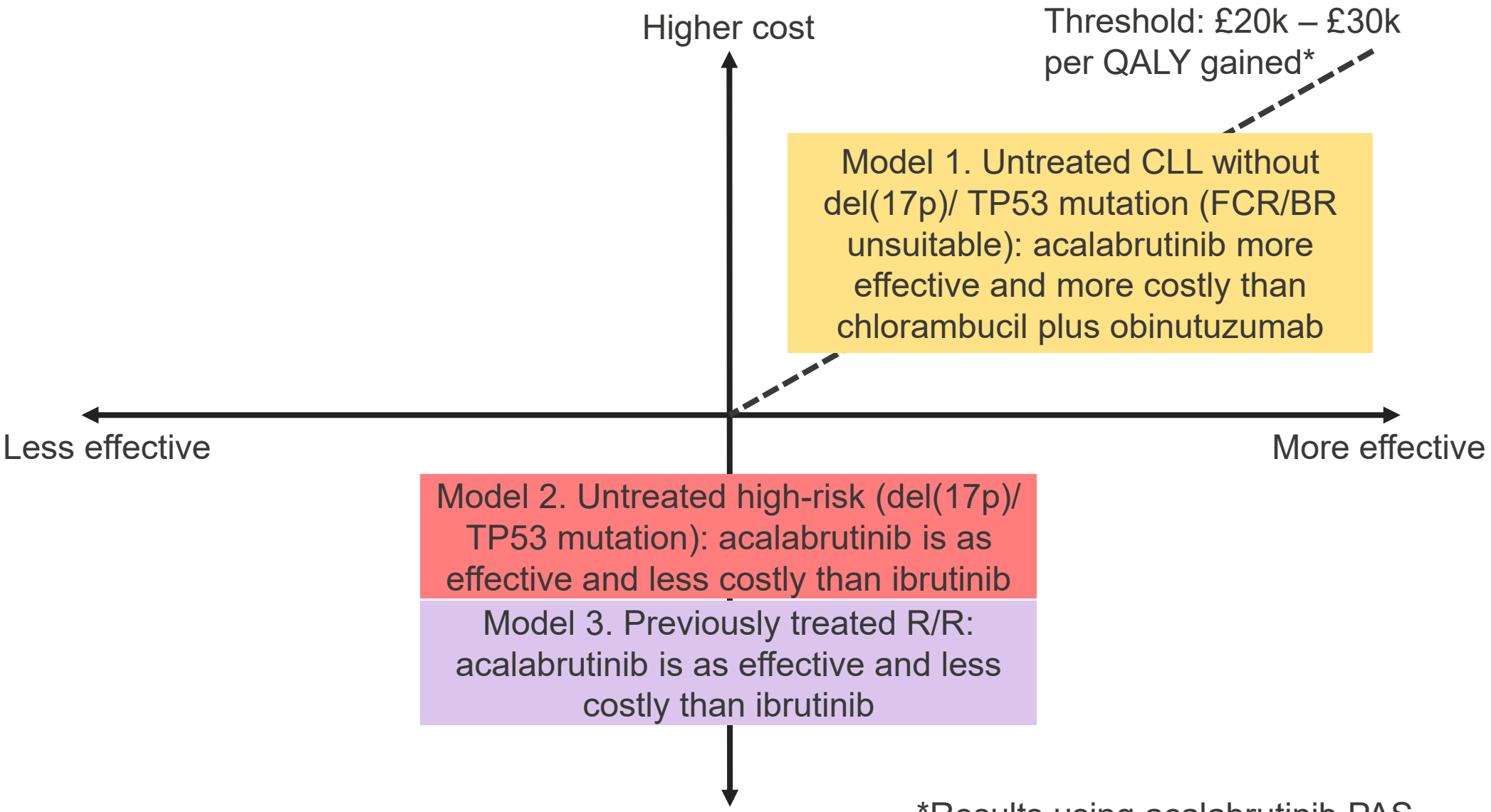
**Source: company submission** Figure 1, p31

# Acalabrutinib total costs lower than comparators in 2 of the subgroups over the model time horizon




*Results using acalabrutinib PAS & list price for comparators

# Acalabrutinib (Calquence, AstraZeneca)

| | |
|---|---|
| **Description of technology** | Acalabrutinib is a selective small-molecule inhibitor of Bruton's Tyrosine Kinase (BTK). It forms a bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. |
| **Marketing authorisation** | • Calquence as monotherapy or in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated CLL.<br>• Calquence as monotherapy is indicated for the treatment of adult patients with CLL who have received at least one prior therapy. |
| **Dosage and administration** | 100 mg taken orally twice daily. |
| **Price** | List price of acalabrutinib is £5,059 per 30-day pack.<br>A simple PAS discount has been approved for acalabrutinib – **updated in response to consultation** |

# Consultation comments

- Company
- 2x comparator companies
- National Cancer Research Institute, endorsed by Royal College of Physicians
- UK CLL forum/ British Society for Haematology/ Royal College of Pathology
- Chronic Lymphocytic Leukaemia Support and Lymphoma Action
- Leukaemia Care

# Themes from comments

- Unmet need for alternative first line therapies for people for whom BR/FCR is unsuitable
- ELEVATE-TN demonstrated significant PFS benefit compared with standard care
- Acalabrutinib has favourable toxicity profile, and unlike C+O is oral, so does not require chair time – important with and without COVID
- Concerned that infection risk is not taken into full consideration
  - anti-CD20 antibody therapy exacerbates hypogammaglobulinaemia and low immunoglobulin associated with increased risk of infection
- If the evidence allows people with unmutated IgHV disease should be considered – FCR may also be unsuitable for them

# Recommendation for people after 1 therapy (1)

Recommended for people who have had at least 1 previous treatment, **only if ibrutinib is their only suitable treatment option**

**Rationale for recommendation:**

- Treatment options are ibrutinib or venetoclax + rituximab (venR)
- Company assumed acalabrutinib and ibrutinib equally effective
- Total costs of acalabrutinib less than ibrutinib
- No analyses compared with venR – cost-effectiveness unknown

**Comments from patient organisations:**

- Ibrutinib will not be suitable for patients with cardiac issues or those on anticoagulant therapy so acalabrutinib will not be available to that group
  - clinically this is one of the main advantages of acalabrutinib over Ibrutinib

# Recommendation for people after 1 therapy (2)

Recommended for people who have had at least 1 previous treatment, **only if ibrutinib is their only suitable treatment option**

**Company comments:**

- does not allow clinicians to treat patients who are intolerant to ibrutinib with a BTKi
- Suggested wording: ***only if a BTKi is their most suitable treatment option***

**Comparator company comments:**

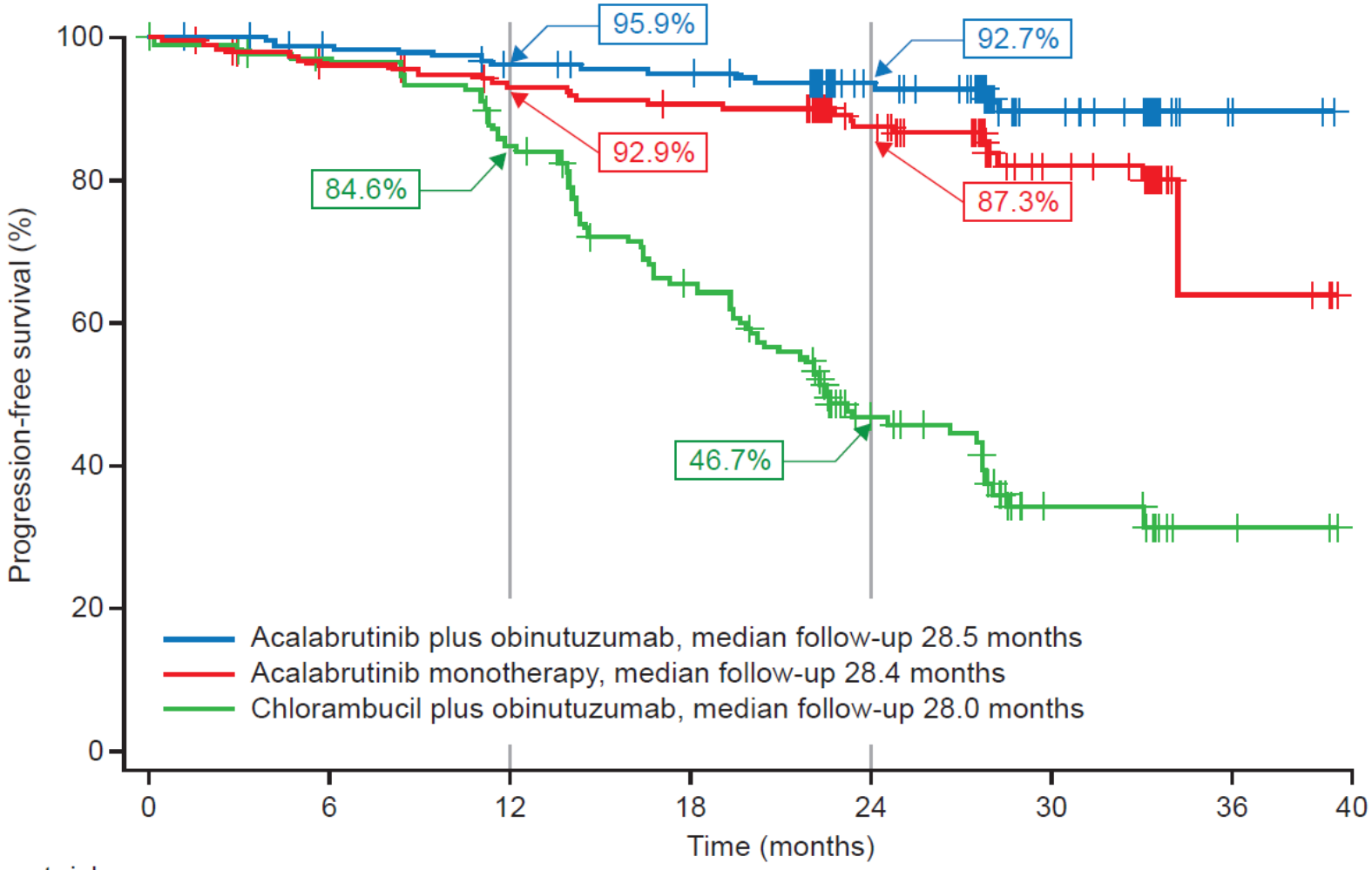
- **Company 1:** could be read as acalabrutinib can be used in patients that could have ibrutinib (broad interpretation) or for patients whose only option is ibrutinib (narrow interpretation). In second case, patients that are suitable for VenR could not receive acalabrutinib but could receive ibrutinib – can wording be clarified?
- **Company 2:** To clarify population suitable for acalabrutinib and ensure VenR is duly considered suggest: ***only if venetoclax plus rituximab is not a suitable treatment option***

n.b. acalabrutinib and ibrutinib are both BTKis

# Untreated population

- Company only submitted evidence for people ineligible for fludarabine, cyclophosphamide and rituximab-based (FCR) therapy
  - this matched population in key clinical trial
- Consultation comments urged committee to consider the Cancer Drugs Fund for people who are eligible for FCR while data on this population is collected
  - company have not made such a proposal

# ELEVATE-TN: PFS Kaplan-Meier plot




| Number at risk | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Acalabrutinib plus obinutuzumab | 179 | 176 | 170 | 168 | 163 | 160 | 159 | 155 | 109 | 104 | 46 | 41 | 4 | 2 |
| Acalabrutinib monotherapy | 179 | 166 | 161 | 157 | 153 | 150 | 148 | 147 | 103 | 94 | 43 | 40 | 4 | 3 |
| Chlorambucil plus obinutuzumab | 177 | 162 | 157 | 151 | 136 | 113 | 102 | 86 | 46 | 41 | 13 | 13 | 3 | 2 |

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reproduced from CS Figure 2

# ELEVATE-TN: OS Kaplan-Meier plot

reproduced from ERG report Figure 14

# ELEVATE-TN: PFS & OS results

**Progression-free survival**

| | Acalabrutinib | C+O |
|---|---|---|
| Events | 26 (14.5%) | 93 (52.5%) |
| Median | Not reached | 22.6 months |
| 1-year KM | 92.9% | 84.6% |
| 2-year KM | 87.3% | 46.7% |
| 3-year KM | 63.9% | 31.3% |
| HR | 0.20 (0.13–0.30) p<0.0001 | |

**Overall survival**

| | Acalabrutinib | C+O |
|---|---|---|
| Events | [redacted] | [redacted] |
| Median | Not reached | Not reached |
| 1-year KM | 98.3% | 96.5% |
| 2-year KM | 94.7% | 91.7% |
| 3-year KM | 93.5% | 88.1% |
| HR | 0.60 (0.28-1.27) p=0.1556 | |

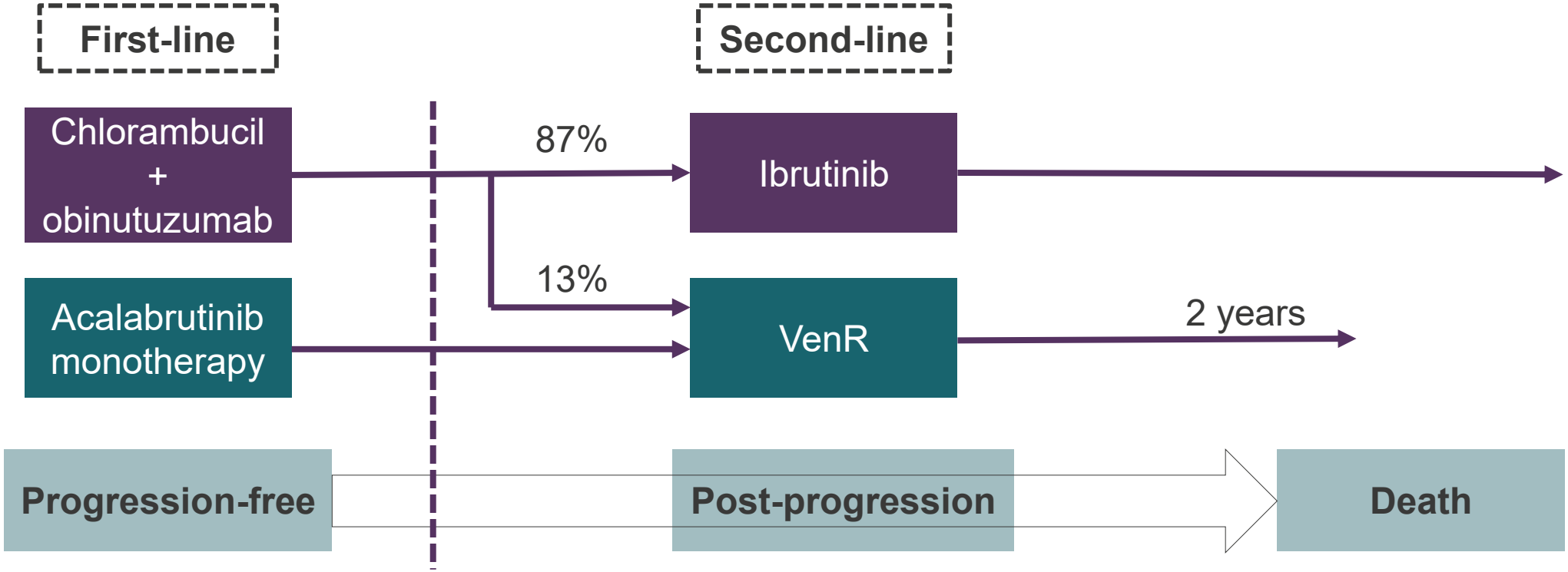
# Modelled survival benefit with acalabrutinib

## Company's modelled OS compared with general population OS

GClb – obinutuzumab plus chlorambucil; OS – overall survival

Figure 24, ERG report

# Company modelling of subsequent treatments




**Background:** company modelled 13% based on IQVIA data

**ACD:** Clinical experts noted VenR was a recent treatment option, likely to account for 20%-50% of second-line treatment after C+O and would increase over time. Committee concluded proportion at least 20% and possibly up to 40%.

# Company comments: VenR after C+O

**Company comments: no data suggests VenR proportion exceeds 20%**

- Experts misquoted: 1 agreed with 13%, other said proportion would **not** reach 50%
- Data from a retrospective chart review of 202 UK patients with CLL showed that between October 2019 and September 2020 only [redacted] had VenR
- UK data collected by IQVIA in September 2020, indicated 14% of second- and subsequent line (2L+) BTKi-naïve patients (n=164) had venetoclax-based regimen
  - removing the 20% having venetoclax monotherapy, which is outside the scope of this appraisal (as its only recommended in CDF) → VenR proportion is 11%
  - Overall proportion has not increased: March 20, 20%; July 20, 16%; Sept 20, 14%
  - Data also shows those who have had a BTKi mainly go on to venetoclax regimen – important that relevant population (BTKi-naive) is considered rather than entire 2L+ pop
- ERG supported company's modelling assumption and ERG clinical adviser stated:
  - "*there's a general preference for 2nd -line ibrutinib over VenR, with more than 80% of patients having ibrutinib and less than 20% of patients receiving VenR*"
  - and they did not expect split to change in *"next few years"* as *"there is no need to ramp up dosage or monitor for TLS with ibrutinib and fewer hospital attendances required*

# ERG comments: VenR after C+O

**ERG comments**

- The ERG's clinical advisors agreed that less than 20% of patients currently receive VenR, but did not fully agree whether this proportion would remain stable in the future
  - 1 clinical adviser comments are quoted by company on previous slide
  - other adviser: during COVID pandemic, continued preference for ibrutinib (don't need to attend hospital as frequently) but some units have developed outpatient dose escalation for VenR. Also emerging data suggest that ibrutinib works well in people who have had VenR without a prior BTKi, which may lead to an increase in the use of VenR
- ERG uses 13% in base case, as reflects data rather than assumption
- ERG agrees with the company that if committee wishes to make recommendations on the basis of current NHS practice, it would be inappropriate to assume higher levels of second-line VenR use

Note: in recently published TA663 venetoclax + obinutuzumab for CLL company assumed a 50:50 split between subsequent venR and ibrutinib

# Duration of 2nd-line treatments

**Committee preferred the ERG's second-line treatment costing model:**

- Weibull model fitted to data on patients that had 1-2 prior therapies in RESONATE
- Company preferred a lognormal fitted to same data → predicted 5.56 years of subsequent treatment vs. 4.78 years using Weibull
- ACD notes the committee considered the log-normal parametric model to be plausible but preferred the Weibull as it was less constrained by mortality constraint

**Consultee comments**

- The average length treatment with ibrutinib has been discussed in previous appraisals, such as VenR, so there is precedence that should be considered
- We believe 5 years to be a reasonable assumption
  - both the clinical experts agreed with in the committee meeting but does not seem to have been taken into account in the decision-making

# Company comments: Duration of 2L ibrutinib

**Company comments:**

- Treatment duration of 2L ibrutinib after C+O is underestimated and does not consider confounding effect of previous lines of therapy
- Using Weibull results in treatment duration with ibrutinib of 4.78 years
- Company prefers log-normal, accepted as clinically plausible in ACD: 5.56 years
- In TA561, VenR, subsequent ibrutinib duration was 5.18 years, based on RESONATE ITT population, where median line of previous therapy = 3
- Committee's assumptions mean that after 1L C+O, people have lower PFS on ibrutinib than in RESONATE for population who had median 3 prior lines of therapy

| Median PFS by prior line of therapy, RESONATE | | | | | |
|---|---|---|---|---|---|
| **Lines of therapy** | 1 (n=35) | 2 (n=57) | 3 (n=32) | 4 (n=27) | ≥5 (n=44) |
| **Median PFS, months (95% CI)** | NR (44.4 – NE) | 67.3 (36.0 – NE) | 44.1 (25.4 – NE) | 33.0 (13.6 – NE) | 27.3 (22.0 – 40.8) |

# ERG comments: Duration of 2L ibrutinib

**ERG comments**

- ERG agrees second-line treatment duration is uncertain
- Duration in TA561 is model-based estimate, not observed data
- ERG chose Weibull as this was company's preferred model in TA561 and, unlike other distributions, it was not strongly influenced by the mortality constraint in the model
  - extrapolated PFS using log-normal curtailed by mortality constraint
- Population starting 2L treatment in acalabrutinib older (~73 years) than TA561 (64 years), so treatment duration expected to be shorter (see figure →)

**Age patients start 2L therapy in TA561 (VenR for R/R CLL) vs. acalabrutinib model for untreated**

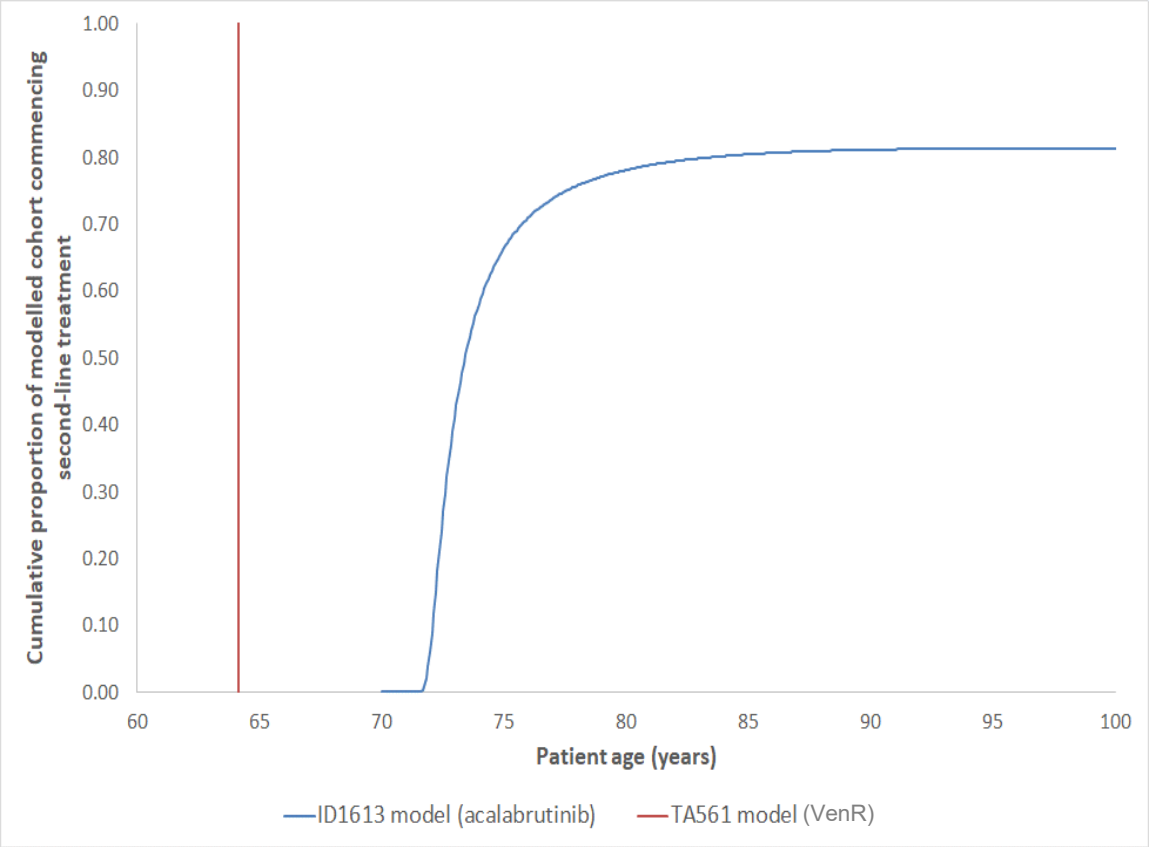



Figure 1, ERG critique of ACD response

# Overall survival benefit for acalabrutinib

**Background**

- Current OS data from ELEVATE-TN are immature → highly uncertain survival estimates
- **Company** estimate OS using PFS from ELEVATE-TN & PPS from MURANO & RESONATE
- **ERG noted this produced highly optimistic OS estimates, implying large proportion having acalabrutinib are cured**
- ERG prefer to use RESONATE for both groups → leads to less optimistic projections of OS
- **Committee** considered ERG's approach appropriate

**Consultee comments:**

- Uncertainty about overall survival is common in appraisals of CLL treatments due to the nature of the disease
- ACD states that the clinical experts supported the company's modelling for survival after acalabrutinib and that life expectancy could match the general population
  - unclear how this clinical advice impacted upon the committee's decision making
- Uncertainty could be resolved by use of the CDF as clinical trials are ongoing.

# Company comments on overall survival

**Company comments:**

- Committee's approach assumes risk of death after acalabrutinib and C+O is equivalent, but:
  - Clinical experts at ACM1 supported assumption that patients having acalabrutinib followed by VenR would have longer survival compared to C+O followed by ibrutinib
  - Having more efficacious treatments earlier in pathway will improve long-term survival
    - PFS HR for acalabrutinib is 0.2 and data from other novel agents, such as ibrutinib and VenR, shows that an early PFS benefit translates into a long-term survival benefit
    - C+O is very toxic; clinicians suggest non-DNA damaging treatments like acalabrutinib likely to result in a less aggressive cancer that is easier to treat at subsequent lines → leading to improved survival
  - Patients are modelled as having VenR after acalabrutinib, but using only RESONATE and not MURANO data means that outcomes are those associated with ibrutinib and not VenR → divorces costs and efficacy data
- Scenario analyses in which the OS gain for acalabrutinib compared to C+O is reduced by 50% is not supported by clinical rationale and is clinically implausible
  - Combined with using RESONATE for PPS in both treatment arms, scenario results in higher risk of death after acalabrutinib than after C+O → no clinical rationale for this

# ERG comments on overall survival

- The ERG's concerns regarding the limitations of the clinical evidence and the company's approach to modelling OS remain unchanged
  - e.g. company's model implies that a large proportion (> [redacted]) treated with acalabrutinib are cured and that uncured patients do not lose much life expectancy (predicted OS for acalabrutinib group is similar to general population)
- In TA663 (VenG for untreated CLL), the OS data were also immature but the model assumed zero survival gain between VenG and C+O, despite a statistically significant difference in PFS
- Both the ERG's preferred analysis and the Committee's preferred base case assume a survival gain for the acalabrutinib group

# Equalities issues

- 1 consultee highlights “it is this very group of vulnerable elderly or comorbid patients without high risk cytogenetics who would benefit most from access to acalabrutinib… for untreated CLL when BR/FCR [and venetoclax with obinutuzumab] are unsuitable”.

# Cost-effectiveness results

- **No cost-effectiveness results can be shown in part 1 because of confidential discounts**
- The table below is reproduced to illustrate the scenarios that the committee will consider in part 2

| ICER (£/QALY) | 2L PFS extrapolation | Base case | Scenarios | |
|---|---|---|---|---|
| | | 13% VenR | 20% VenR | 40% VenR |
| Company base case | Log-normal | Company base case | | - |
| RESONATE PPS for both groups | Weibull | ERG base case | | - |
| | Log-normal | | | - |
| RESONATE PPS for both groups + OS gain halved | Weibull | | | |
| | Log-normal | | | |

# Key issues

**People who have had at least 1 prior therapy**

- Stipulation that ibrutinib must be their only suitable treatment option

**Untreated population**

- Proportion of patients having venetoclax plus rituximab following treatment with chlorambucil plus obinutuzumab
- Treatment duration of second-line ibrutinib following progression with chlorambucil plus obinutuzumab
- Survival benefit with acalabrutinib