Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia

Redacted
PART 1 for public
Post cmte – FAC
Post company ACIC check

Technology appraisal committee C [14 March 2023]

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Company: Janssen-Cilag

Background on Chronic Lymphocytic Leukaemia

Causes, Epidemiology, Diagnosis & Classification, Prognosis

- Chronic lymphocytic leukaemia (CLL) is a malignant disorder of white blood cells (lymphocytes)
- Symptoms are not usually present at time of diagnosis and develop later which include:
    - anaemia, increased infections, swollen glands, spleen enlargement, and weight loss
- CLL is the most common type of leukaemia with 3,803 new cases diagnosed in England each year
- Risk of CLL increases with age and is more common in men
- High risk of CLL progression and poor prognosis is commonly caused by:
    - deletion of chromosome 17p (del(17p)), or
    - mutation of the tumour protein p53 (TP53)

Source: 2016-2018 average, Cancer Research UK, 2021

Technology (Imbruvica, Janssen-Cilag)

Table: Technology details

Marketing authorisation	Extended for ibrutinib plus venetoclax for adults with chronic lymphocytic leukaemia who are previously untreated. • 'Imbruvica (ibrutinib) is authorised for use in Great Britain as a single agent or in combination with rituximab or obinutuzumab **or venetoclax** for adults with chronic lymphocytic leukaemia who are previously untreated' • Note appraisal is only assessing the intervention 'ibrutinib plus venetoclax'
Mechanism of action	Ibrutinib: Bruton's tyrosine kinase (BTK) inhibitor Venetoclax: Selective inhibitor of B-cell lymphoma 2 (Bcl2)
Administration	Oral (Tablet)

Price	• Ibrutinib 28-tab pack (420 mg) list price = £4,292.40
	• At list price, the total cost of the fixed duration (FD) I+V regimen (15 cycles of ibrutinib and 12 cycles of venetoclax, including the ramp-up) is £118,177.73
	  • Completed treatment in CAPTIVATE trial: Ibrutinib ~ XX% venetoclax ~ XX%
	  • Completed treatment in GLOW trial: I+V ~ 77% OClb ~ 95%
	• A patient access scheme is applicable

I+V, ibrutinib plus venetoclax; OClb, Obinutuzumab plus chlorambucil

Patient and clinical perspectives

Submissions from Leukaemia Care, Lymphoma Action CLL Support Association, UK CLL Forum and British Society of Haematology

Patient perspectives

- Living with untreated CLL can cause physical side-effects
- Current active treatments for CLL like intensive chemotherapy cause short and long term side-effects (for example fatigue, fever, night sweats, weakness)
- Ibrutinib plus venetoclax (I+V) is an oral (tablet) treatment with a fixed duration and has a better safety profile than standard care. This is highly valued as a treatment option for people with CLL.

"To live with CLL, every day you know you cannot be cured of this cancer"

"There needs to be more therapies for the high risk CLL patients"

Leukaemia Care, Lymphoma Action and CLL Support Association

Clinical perspectives

- CLL treatment is challenging when all existing drug-classes are unsuccessful. There remains an unmet need for people with high risk CLL.
- Strong rationale for combining two highly effective drug classes and benefiting from their combined effect
- The responses and depth of remission achieved by I+V is encouraging, particularly for people with high risk CLL
- Advantages to having a fixed duration treatment option

"I+V regimen, provided early results are confirmed with longer follow-up, will help to fill an unmet need for the poor risk disease group (TP53 aberrant and IGHV unmutated)"
UK CLL Forum

NICE

CLL, Chronic lymphocytic leukaemia; I+V, ibrutinib plus venetoclax; IGHV, immunoglobulin heavy chain; TP53,tumour protein 53

Key issues for discussion

Comparator selection, indirect treatment comparison and model assumptions

	ICER impact
Comparators: Company excluded idelalisib plus rituximab and bendamustine plus rituximab	Unknown
Uncertain indirect comparison outcomes: • Immature trial data impacts the proportional hazards and treatment effect waning assumptions • FCR unsuitable cohort: The hazard ratio (HR) of I+V versus VenO derived from the indirect comparison remains uncertain and not statistically significant	Treatment effect waning assumptions vary across populations: • ↑ ICER for FCR suitable cohort • Key conclusions remain same for FCR unsuitable cohort HR I+V vs VenO: unknown
Model structure results in inconsistent model outcomes: • Inconsistent risk of progression for the surviving FCR unsuitable cohort compared with the FCR suitable cohort	Small impact/unknown

FCR, Fludarabine plus cyclophosphamide plus rituximab; ICER, Incremental cost-effectiveness ratio; I+V, ibrutinib plus venetoclax; HR, Hazard ratio; VenO, venetoclax plus obinutuzumab

Other issues for consideration

Immature trial data and utility assumptions

	ICER impact
Immature trial data: • Median PFS and OS not reached for I+V arm in both trials (CAPTIVATE and GLOW) resulting in uncertainty in model outcomes	Unknown 
Utility values not generalisable to NHS practice and may lack face validity: • Overestimation of utility estimate for person with CLL in routine NHS practice • Applying the same utility value to the PF 2L and PP state lacks face validity	Small 

- ✓ Slides per issue included in back up slides
- ✓ A number of issues were resolved at technical engagement. Please also see back up slides for further details.

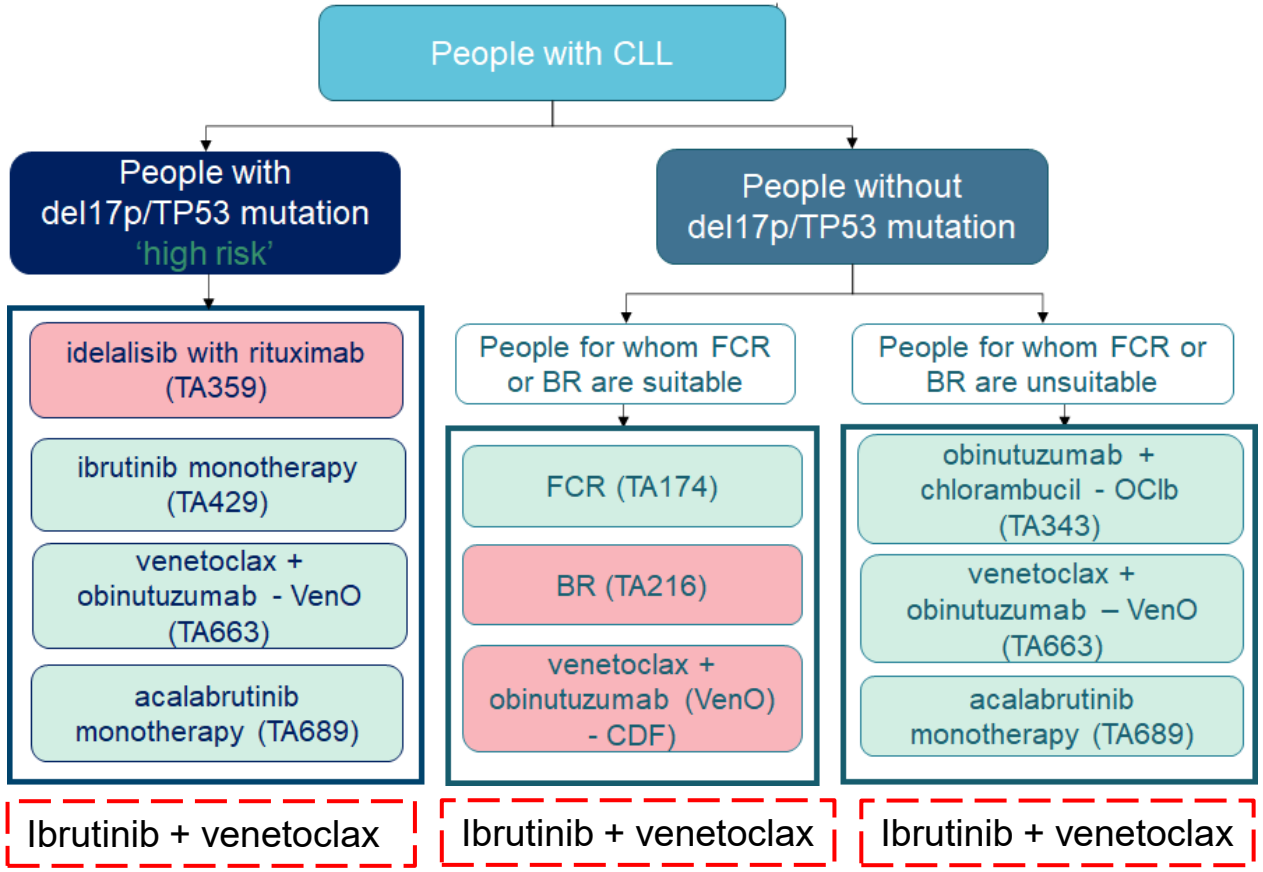
CLL, Chronic lymphocytic leukaemia; ICER, Incremental cost-effectiveness ratio; I+V, ibrutinib plus venetoclax; OS, Overall survival; PFS, Progression free survival; PF 2L, Progression free second line; PP, Post-progression

Key issue: Comparators

Comparators in green are considered relevant by the company

Company excluded idelalisib plus rituximab and bendamustine plus rituximab

Figure: CLL treatment pathway



Company

- Idel-R: rarely used in clinical practice because of risk of infection and death. Assumption accepted in TA689 and TA663. Validated by clinical expert opinion
- BR: rarely used in clinical practice, excluded from 2022 BSH guidelines. Assumption accepted in TA663. Clinical experts agreed

EAG comments

- The EAG agrees with company's comparators

Other considerations

- Clinical experts agree the included comparators reflect UK practice, all are considered equally relevant and efficacious. Excluded comparators are rarely used

What are the most appropriate comparators for the technology per cohort?

BR, bendamustine plus rituximab; BSH, British Society for Haematology; CDF, Cancer drugs fund; CLL,chronic lymphocytic leukaemia; del17p,17p deletion; FCR, fludarabine plus cyclophosphamide plus rituximab; Idel-R, Idelalisib plus rituximab; TP53,tumour protein 53

Source: company evidence submission Table 5, Pg 23

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Key clinical trials

Table: Clinical trial designs and outcomes

	CAPTIVATE (informs FCR suitable cohort)	GLOW (informs FCR unsuitable and high risk cohort)
Design	International, multi-centre, phase 2, 2 cohort clinical trial (with fixed duration (FD) cohort)	International, multi-centre, open-label, phase 3 randomised clinical trial
Population*	People aged between ≥18 and ≤70 years with a diagnosis of CLL and active disease with no prior therapy for CLL. Enrolled = 159; del 17p/TP53 = 27; no-del17p = 136; unknown del17p/TP53 mutation status = 3. Mean age (no-del 17p) (SD) = 57.9 (8.68)	People with a diagnosis of CLL and active disease with no prior therapy for CLL aged: ≥65 years, **or** 18 to 64 years with CIRS score >6 and/or estimated CrCl <70 mL/min. Enrolled = 211. Mean age (total intention to treat population) (standard deviation (SD)): 71.5 (7.15)
Intervention	Ibrutinib plus venetoclax (I+V)	I+V
Comparator(s)	None	Obinutuzumab plus chlorambucil (OClb)
Dosage	Ibrutinib: 15 cycles-420mg/day, venetoclax ramp-up to 400mg/day for 12 cycles	I+V: Same as CAPTIVATE; OClb (Clb: 0.5mg/kg D1+D15 for 6 cycles. O: Cycle 1-1000mg D1/2,D8,D15; Cycle2-6:D1
Primary outcome	Complete response / complete response with incomplete bone marrow recovery	Progression free survival (PFS)
Key secondary outcomes	PFS, overall survival (OS), adverse events (AEs)	Time to next treatment, OS, AEs and health-related quality of life (HRQoL)
Locations	Europe, North America and Asia-Pacific	Europe (including UK) and North America
Used in model?	Yes (PFS, OS (for validation), AEs)	Yes (PFS investigator assessed, AEs, HRQoL)

*Note: Trial includes SLL which is considered to be the same as CLL. CLL/SLL referred to as only CLL from now on. CIRS, Cumulative Illness Rating Scale; CLL, chronic lymphocytic leukaemia; CrCl, Creatine clearance; FCR, fludarabine plus cyclophosphamide plus rituximab; FD, fixed duration; kg, kilogram; mg, milligram; mL/min, millilitre per minute; MRD, minimal residual disease; ORR, overall response rate; TP53 , tumour protein 53.

CAPTIVATE FD cohort trial results (FCR suitable no del17p)

Median progression free or overall survival was not reached

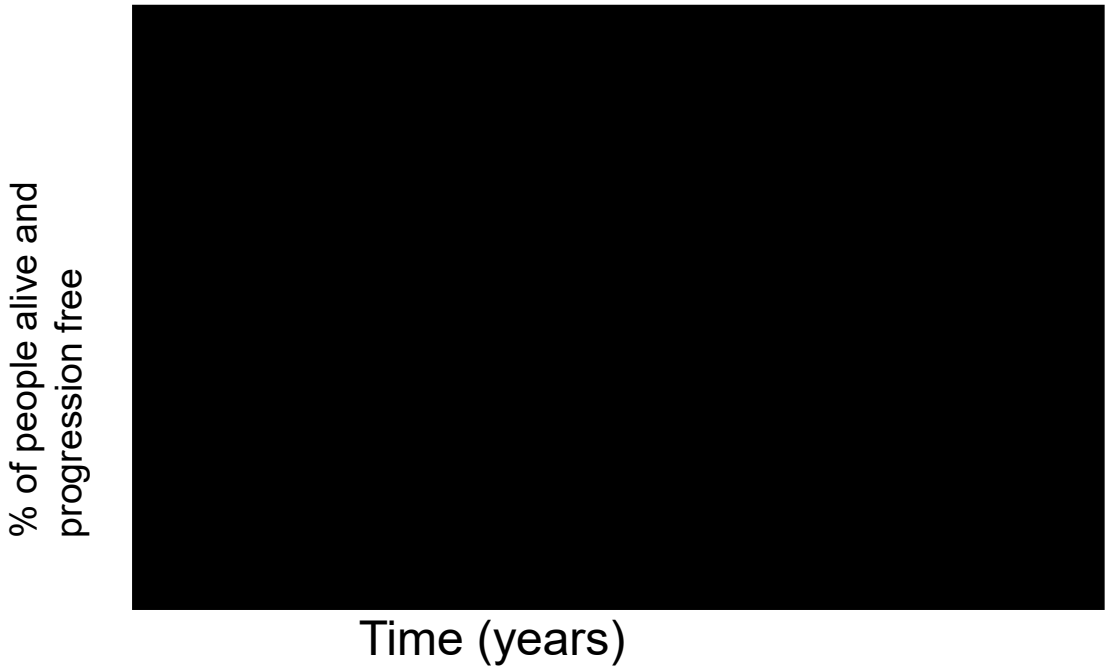


Figure: Comparison of PFS KM data from original (38.7m) and updated (xxxxm) data cuts

- At xx months investigator assessed PFS rates were xxxx% for people without del17p

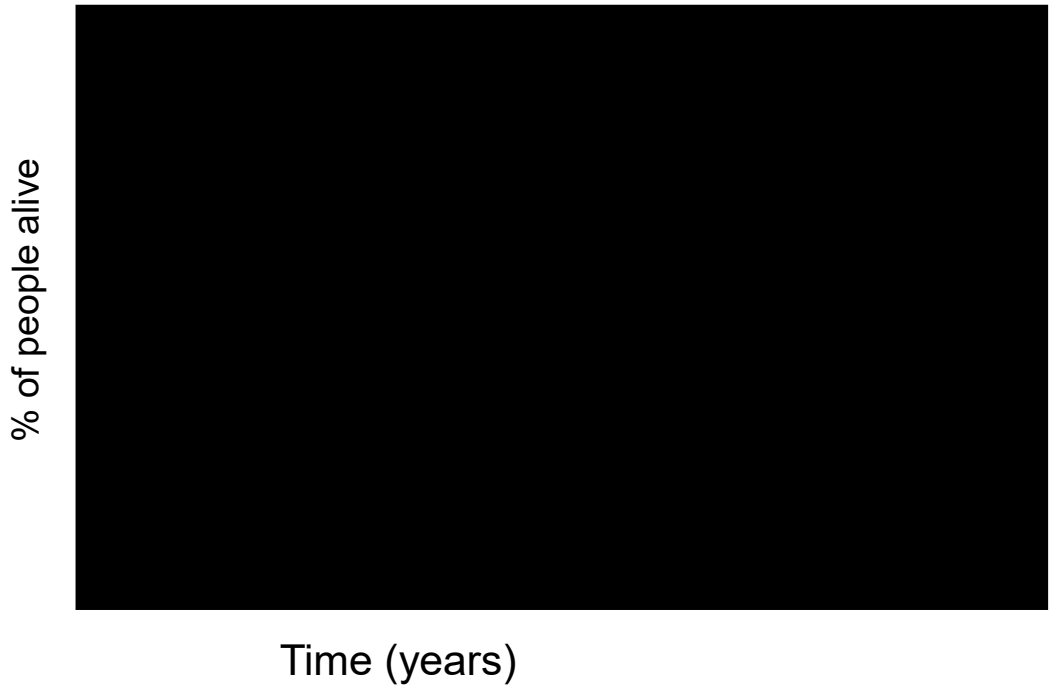


Figure: OS KM data from original and updated data cuts

- At xx months OS rates were xxxx % for people without del17p

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FCR, Fludarabine plus cyclophosphamide plus rituximab; FD, Fixed duration; del17p,17p deletion; I+V, ibrutinib plus venetoclax; KM, Kaplan-Meier; OS, Overall survival; PFS, Progression free survival. Source: For the numbers at risk please refer to Figure 1 and 2 Section 2.2.1 (Efficacy) company submission new appendix

GLOW clinical trial results (FCR unsuitable and high risk)

Median progression free survival (PFS) not reached for I+V, reached for OClb at xx months

At median follow-up of 46 months statistically significant PFS observed for I+V compared with OClb

The xx-month PFS rate as reported by the company:

- xxxx % for I+V
- xxxx % for OClb

I+V vs. OClb hazard ratio (HR): xxxx (95% CI: xxxx, xxxx, nominal p xxxxxxx

Figure: GLOW – Investigator assessed PFS KM data updated (ITT 46month follow-up)

I+V, Ibrutinib plus venetoclax; ITT, Intention-to-treat; KM, Kaplan-Meier; OClb, Obinutuzumab plus chlorambucil; CI, confidence interval

GLOW clinical trial results (FCR unsuitable and high risk)

Median overall survival not reached for either treatment arm

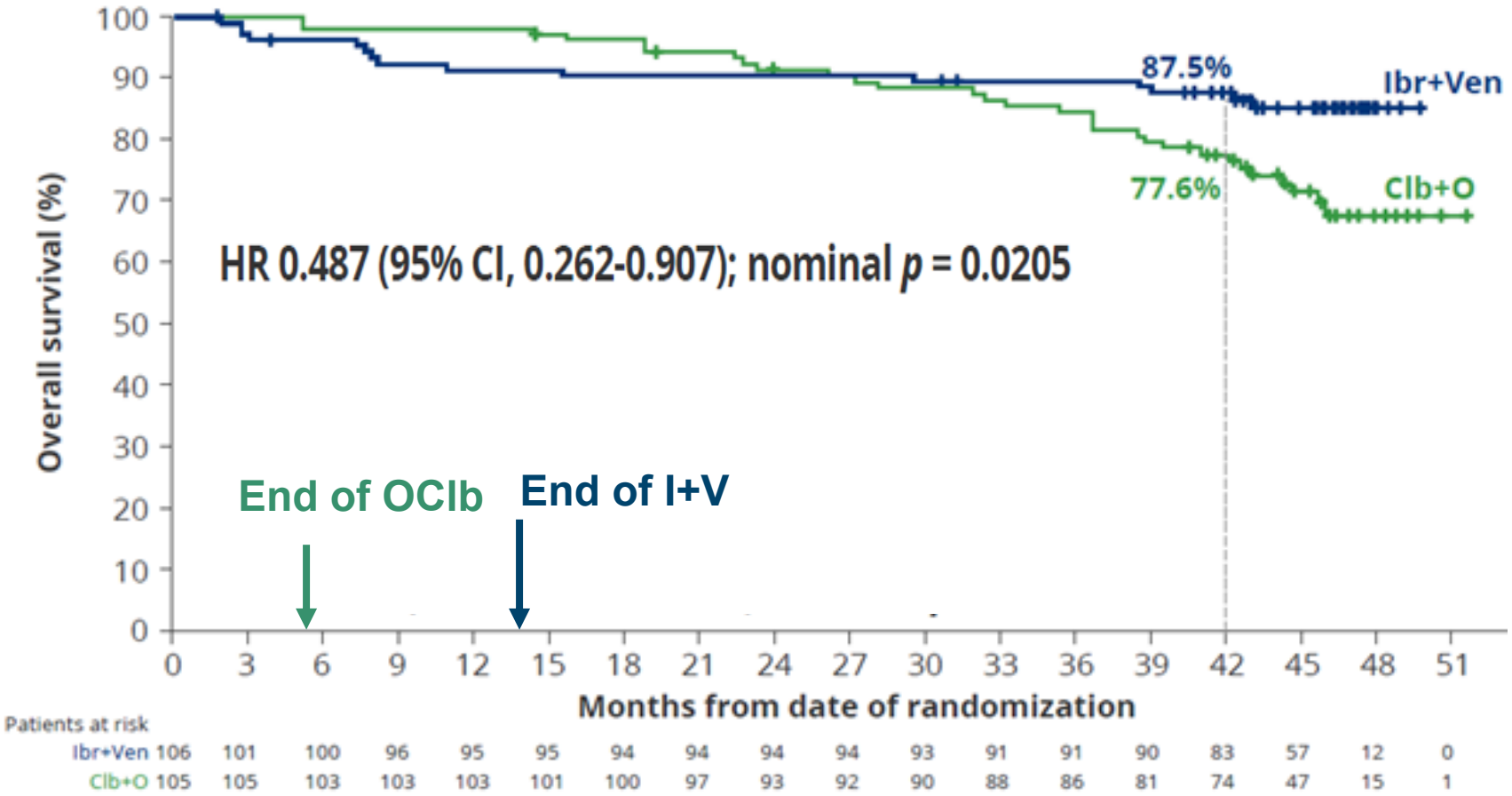

Figure: KM plot of OS (GLOW; ITT 46 months follow-up analysis)

At median follow-up of 46 months statistically significant OS observed for I+V compared with OClb

<u>The 42-month OS rate as reported by the company</u>:

- 87.5% for I+V
- 77.6% for OClb

CI, confidence interval; Clb+O/OClb, obinutuzumab plus chlorambucil; HR, hazard ratio; Ibr+Ven, ibrutinib + venetoclax, ITT, intent-to-treat; KM, Kaplan-Meier; OS, overall survival

Indirect treatment comparison methodology

1 indirect treatment comparison and 2 anchored MAICs used

- No head-to-head data available for the comparisons of I+V with FCR, VenO or acalabrutinib. The company did indirect treatment comparisons (ITC) for the FCR suitable and FCR unsuitable cohorts.
- GLOW provides head-to-head data for I+V versus OClb. Parametric survival analysis done on the trial data
- Ibrutinib efficacy assumed same as acalabrutinib in the high risk population (accepted in TA689)*

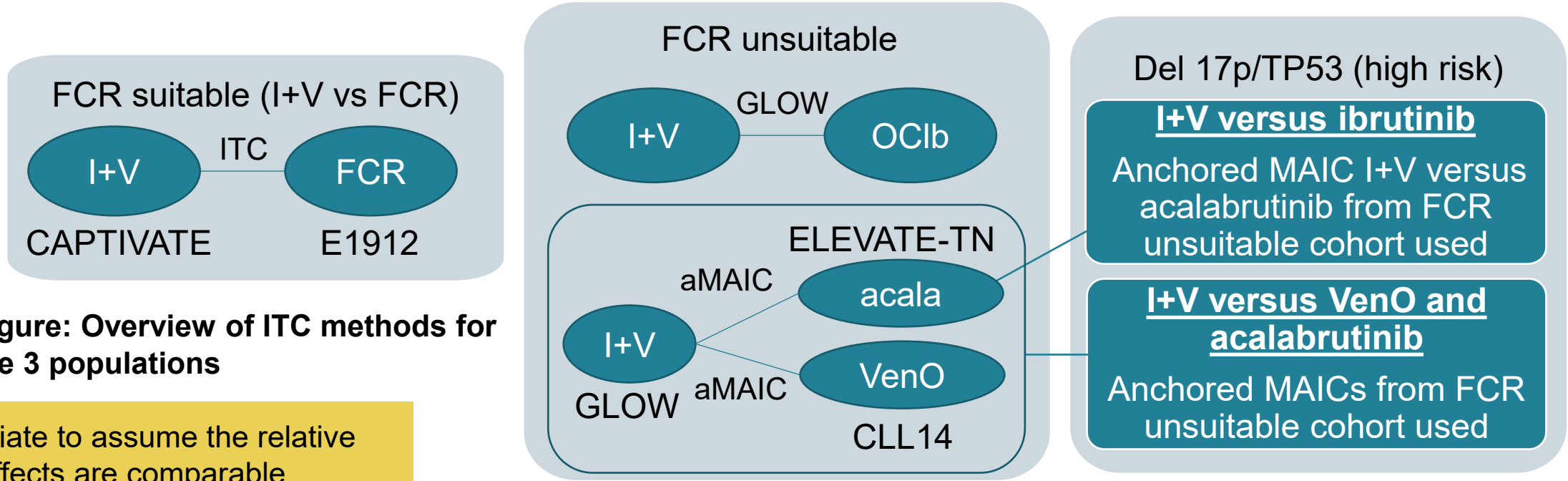

Figure: Overview of ITC methods for the 3 populations

Is it appropriate to assume the relative treatment effects are comparable between the FCR unsuitable and the high risk del17p/TP53 cohorts?

Acala, acalabrutinib; aMAIC, anchored MAIC; Del17p/TP53,17p deletion/Tumour protein 53; FCR, fludarabine plus cyclophosphamide plus rituximab; MAIC, Matching-adjusted indirect comparison; ITC, indirect treatment comparison; OClb, obinutuzumab plus chlorambucil; I+V, ibrutinib plus venetoclax; VenO, venetoclax plus obinutuzumab

*Supporting external evidence included by company in TE response (Additional issue 1)

ITC methodology

Figure: Detailed ITC methods for the 3 populations and external comparators

FCR suitable cohort ITC: I+V compared with FCR	FCR unsuitable and del17p/TP53 cohorts Anchored MAIC: I+V compared with VenO	FCR unsuitable and del17p/TP53 cohorts Anchored MAIC: I+V compared with acalabrutinib
• Data: I+V (CAPTIVATE FD); FCR (E1912 trial) • Used in economic model: Inverse probability for treatment weighting (IPTW) weighted to the covariate distribution of the FCR control group (ATC) • Other approaches: average treatment effect in the treated population (ATT) weighting and Average treatment effect in the combined/overall population (ATO)	• Data: I+V (GLOW); VenO (CLL14 trial) • Used in economic model: MAIC with CLL14 exclusion criteria and matching of four characteristics (age, ECOG status, CIRS, TP53 status) • PFS proportional hazards assumption violated in GLOW and CLL14. Time-varying hazard ratio (HR) sensitivity analysis done	• Data: I+V (GLOW); acalabrutinib (ELEVATE-TN trial) • Used in economic model: MAIC with ELEVATE-TN exclusion criteria and matching of four characteristics (age, ECOG status, CIRS-G score, mutated TP53) • PFS proportional hazards assumption violated in GLOW and ELEVATE-TN. Time-varying HR sensitivity analysis done

GLOW, CLL14 and ELEVATE-TN include OCIb as a common comparator. Anchored MAICs were preferred over other ITCs because of differences in inclusion/criteria between these 3 trials.

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CIRS (-G), Cumulative Illness Rating Scale (Geriatric); ECOG, European Cooperative Oncology Group; ITC, Indirect treatment comparison; MAIC, Matching-adjusted indirect comparison; FCR, fludarabine plus cyclophosphamide plus rituximab; I+V, ibrutinib plus venetoclax; OCIb, obinutuzumab plus chlorambucil; PFS, Progression free survival; VenO, venetoclax plus obinutuzumab

ITC results (with updated data cuts)

I+V PFS and OS is only statistically significant versus FCR

Figure: ITC results for the three external comparators

ITC: I+V versus FCR (ATC approach)

- *PFS: [redacted]
- OS: [redacted]
- PFS and OS in favour of I+V and statistically significant
  - Note - ATT approach not used in model shows [redacted]:
    - PFS: [redacted]

Anchored MAIC: I+V versus VenO

- *PFS: [redacted]
- OS: [redacted]
- TTNT: [redacted]
- PFS, OS, TTNT in favour of I+V. PFS and OS not statistically significant
- Consistency in the treatment effect of I+V shown over time

Anchored MAIC: I+V versus acalabrutinib:

- *PFS: [redacted]
- OS: [redacted]
- PFS and OS favours I+V. PFS not statistically significant

*PFS HR used in the economic model to inform transition probabilities. Mortality rates assumed from clinical trials (FCR arm E1912 trial, GLOW, ibrutinib arm RESONATE trial).

ATC, Average treatment effect in the control population; ATT, average treatment effect in the treated population; CI, Confidence interval; FCR, fludarabine plus cyclophosphamide plus rituximab; ITC, Indirect treatment comparison; I+V, ibrutinib plus venetoclax; MAIC, Matching-adjusted indirect comparison; OS, Overall survival; PFS, Progression free survival; TTNT, Time to next treatment; VenO, venetoclax plus obinutuzumab.

Unresolvable?

Key issue: Uncertain indirect comparison outcomes

Company: ITCs updated with longer PFS and OS data from CAPTIVATE and GLOW. Updated analysis reduces the uncertainty in I+V treatment effect. ITC and MAIC results remain consistent across the two data cuts. Treatment effect waning (waning) scenarios explored were as follows:
a) Waning start 5 years from treatment (tx) stop; Waning period = 10 years b) Waning start 5 years from tx stop; Waning period = 5 years c) Waning start 10 years from tx stop; Waning period = 10 years

EAG - Proportional hazards assumption: PFS HR applied in model relies on assumption that proportional hazards hold over model time horizon

- Company assumes proportional hazards hold indefinitely beyond 12 months
- Immature trial data impacts proportional hazards assumption. HRs derived from MAIC are relevant to the observed follow-up period of included studies (medians of ~XXX-XXX months). Their longer term application is uncertain
- The company's waning scenario increase the ICER vs FCR

EAG - FCR unsuitable cohort

- **Study differences:** Comparisons of I+V with VenO and acalabrutinib, rely on PFS HR from the anchored MAICs. Estimates are uncertain because of potential differences between studies
- **Non-significant results**: The PFS HR of I+V versus VenO remains not statistically significant Point estimates are close to 1 for I+V versus VenO and acalabrutinib
- A scenario with equal efficacy is worth considering

- ✓ Are the treatment waning scenarios explored relevant. Should alternative treatment waning scenarios be explored?
- ✓ Does the uncertainty with the indirect comparison cause considerable uncertainty to the model outcomes?

FCR, fludarabine plus cyclophosphamide plus rituximab; HR, Hazard ratio; ICER, Incremental cost-effectiveness ratio; ITC, Indirect treatment comparison; MAIC, Matching-adjusted indirect comparison; I+V, ibrutinib plus venetoclax; OS, Overall survival; PFS, Progression free survival; TE, Technical engagement; VenO, venetoclax plus obinutuzumab

Cost effectiveness

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Company's model overview

A 4 state semi-Markov model was used with a 30-40 year time horizon

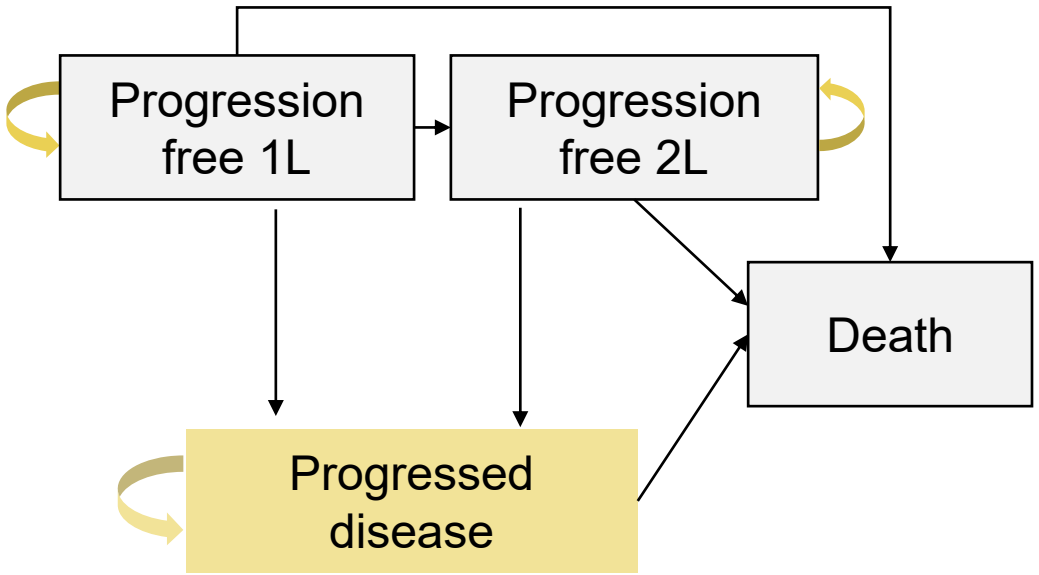

Figure: Model Structure

For further details on input assumptions: please see back up slide on 'How company incorporated evidence into model'

Technology affects costs by:

- Drug acquisition and administration costs compared with comparators
- Delaying or preventing disease progression which incur further treatment and disease management costs
- Incidence of adverse events which incur management costs

Technology affects QALYs by:

- Delaying or preventing disease progression
- Reducing mortality associated with disease progression

Assumptions with greatest ICER effect:

- The comparative effectiveness of the technology on progression free survival compared to the alternative treatments over the model time horizon

 1L, first line; 2L, second line, ICER, Incremental cost-effectiveness ratio; QALYs, quality adjusted life years

Unresolvable/small impact?

Key issue: Inconsistent model outcomes

Continued risk of progression modelled in FCR suitable cohort and not in the FCR unsuitable cohort

Background

- Transition probabilities for progression free first line (PF 1L) to PF 2L or PP are estimated by subtracting the hazards of general population mortality from the hazards of progression (from the PFS curve)
- The **FCR unsuitable** cohort model predicts that after XX-XX years from start of I+V and acalabrutinib treatment there is a 0% risk of CLL progression. Suggesting XX% in I+V arm and XX% in acalabrutinib arm are cured from CLL
- The **FCR suitable** cohort model estimates that risk of CLL progression is maintained for the entire time horizon because background mortality is lower. So arithmetically in the model 0% risk of CLL progression is reached much later for this cohort.

Company

- The age at which PFS is capped by general population mortality is consistent (around 85-86 years) between the cohorts. This shows that the risk of progression reaches zero in both cohorts around the same age in the model (see figure on next slide)
- Clinical opinion suggests that it is possible that people in remission on first line targeted treatment at age 85 are more likely to die than progress
- At TE a scenario was run where the transition probability of progression in FCR unsuitable cohort was capped by (cannot fall below) the FCR suitable cohort. The key conclusions remain the same.

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1L, First line; 2, Second line; FCR, Fludarabine plus cyclophosphamide plus rituximab; PF, progression free; PFS, progression free survival; PP, post progression; I+V ibrutinib plus venetoclax; CLL, chronic lymphocytic leukaemia, TE, Technical engagement

Unresolvable?

Key issue: Inconsistent model outcomes

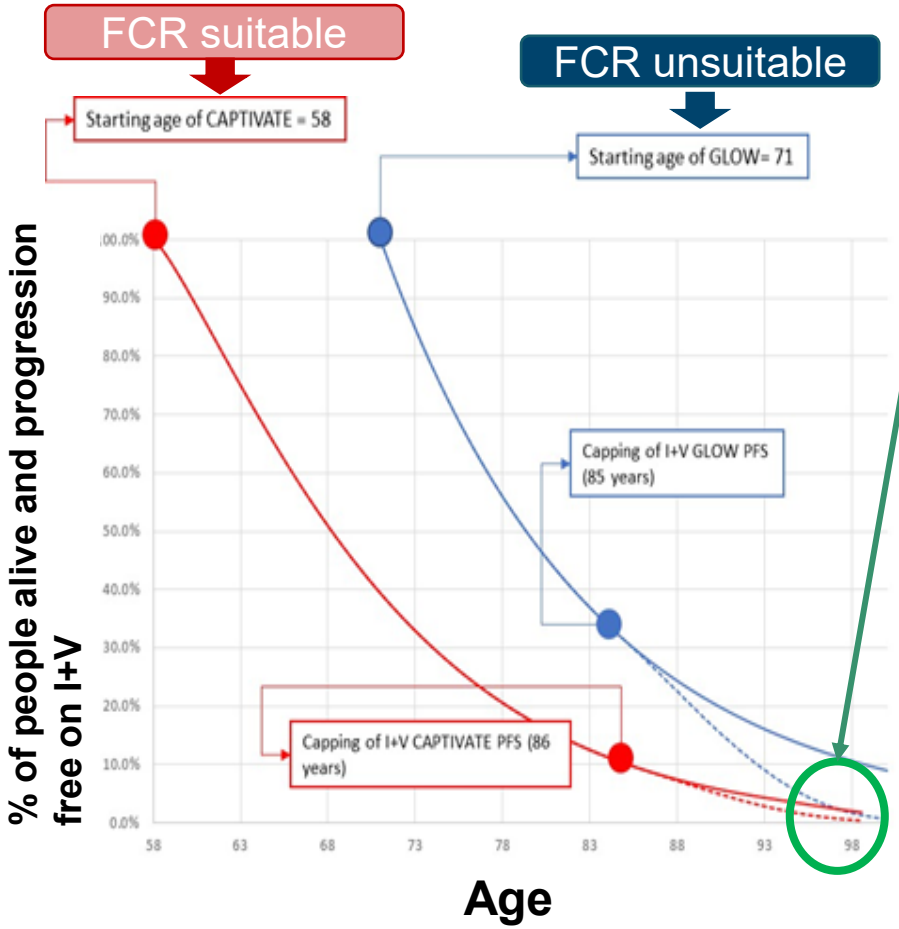

Figure: PFS hazards of I+V in the FCR-suitable and FCR-unsuitable populations capped by general population mortality

EAG comments

- There are concerns with the inconsistency where risk of progression is allowed to fall to 0% in FCR unsuitable arm after a number of years and that happens a lot later in the FCR suitable model arm
- In response the company figure provided at TE shows the risk of progression reaches zero in both cohorts around the same age in the model
- However this happens much later in the time horizon for the younger FCR-suitable cohort (after XX XXXX), when a smaller proportion remain alive and progression free (~XX%) compared with the older FCR-unsuitable cohort (after XX-XX years)
- The EAG acknowledge some people may die before CLL progression
- The company scenario where the transition probability of progression in FCR unsuitable cohort cannot fall below the FCR suitable cohort helps to reduce some uncertainty but limitations of approach remain

Other considerations (clinical experts)

- No data suggesting differential risk of progression between these two subgroups, provided treatment is delivered with adequate intensity

Does the company's scenario of capping risk of progression capture the uncertainty in the absence of no additional data to support this assumptions?

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FCR, Fludarabine plus cyclophosphamide plus rituximab ; CLL, chronic lymphocytic leukaemia; PFS, progression free survival; I+V, ibrutinib plus venetoclax; TE, technical engagement

Summary of company and EAG base case assumptions

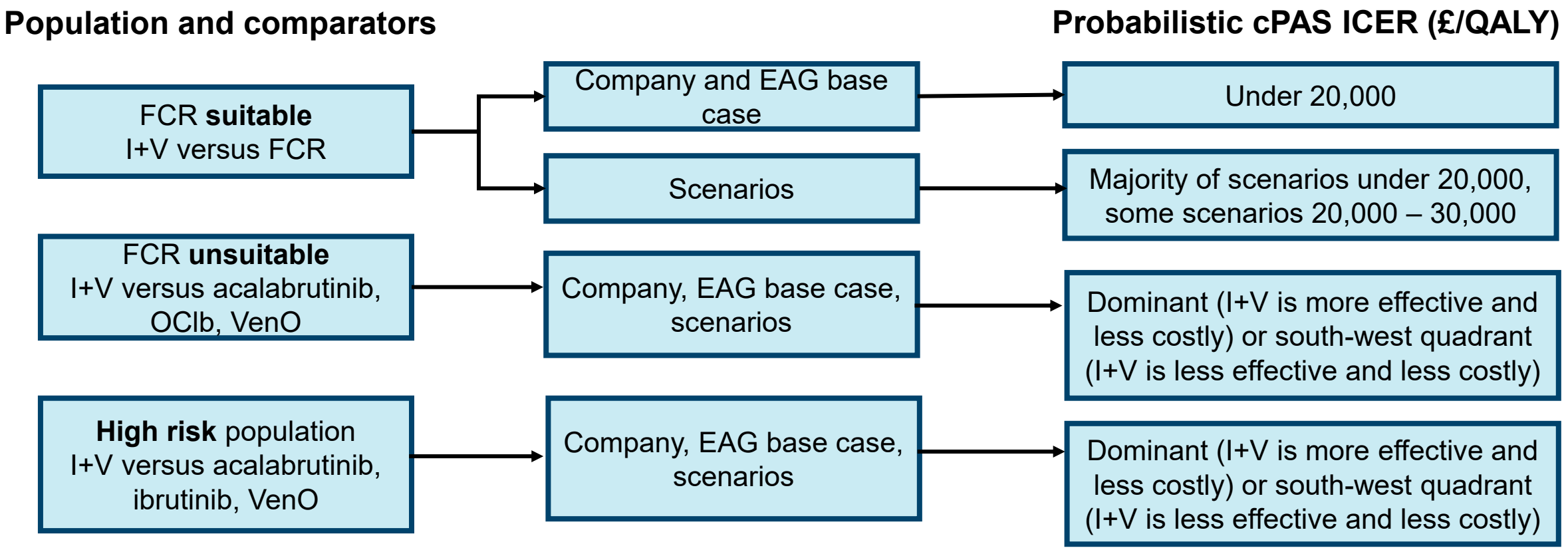
Table: Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Costs and utility decrements, applied from cycle zero in the model rather than cycle one	Not included	Company version corrected and updated
Wastage costs	Intravenous (IV) wastage included; oral wastage excluded	Both IV and oral included. Oral wastage costs included to account for potential incomplete use of unused medicine resulting from dose intensity reductions.
Other issue: Utility values (Please see back up slides for details. Limited impact on ICERs)	Progression free first line (PF 1L): GLOW trial starting utility value not age adjusted to general population: • [redacted] (FCR suitable) • [redacted] (FCR unsuitable/high risk) Progressed disease: Holzner et al. 2004 utility age adjusted to GLOW and E1912 trial populations: • [redacted] (FCR suitable) • [redacted] (FCR unsuitable/high risk)	PF 1L: GLOW trial starting utility value age adjusted to general population: • [redacted] (FCR suitable) • [redacted] (FCR unsuitable) Progression free second line: Multiplier applied: [redacted] • [redacted] (FCR suitable) • [redacted] (FCR unsuitable) Post progression: Holzner et al. 2004 = 0.6

Note: Wastage cost was a minor issue and results in a small increase in ICERs. EAG states excluding it may underestimate costs and would be inconsistent with the preferred approach in TA689 (acalabrutinib)

FCR, Fludarabine plus cyclophosphamide plus rituximab; ICERs, incremental cost-effectiveness ratios; IV, Intravenous PF 1L, Progression free first line

Cost-effectiveness scenarios



All ICERs will be discussed in Part 2 because results include confidential commercial discounts for comparators

cPAS, Comparator patient access scheme; EAG, external assessment group; FCR, Fludarabine plus cyclophosphamide plus rituximab; ICER, incremental cost-effectiveness ratio; I+V, ibrutinib plus venetoclax; OClb, obinutuzumab plus chlorambucil, QALY, Quality adjusted life year; VenO, venetoclax and obinutuzumab,

Other considerations

Equality considerations

- People who are younger and fitter with CLL are offered FCR or VenO (through CDF), both treatment options need intravenous infusion. Clinical experts do not see any equality issues.

Innovation

- Clinical experts explain that combining two novel and effective therapies makes clinical and scientific sense. A fixed duration of treatment is attractive for clinicians and people with CLL.

Severity modifiers

- The company's results of the quality adjusted life year (QALY) shortfall analysis show that the technology does not meet the criteria for a severity weight in the three populations according to proportional shortfall

CDF, Cancer drugs fund; CLL, chronic lymphocytic leukaemia; FCR, Fludarabine plus cyclophosphamide plus rituximab; QALY, quality adjusted life year; VenO, venetoclax and obinutuzumab;

Key issues for discussion

Comparator selection, indirect treatment comparison and model assumptions

	ICER impact
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Uncertain indirect comparison outcomes: • Immature trial data impacts the proportional hazards and treatment effect waning assumptions • FCR unsuitable cohort: The hazard ratio (HR) of I+V versus VenO derived from the indirect comparison remains uncertain and not statistically significant	Treatment effect waning assumptions vary across populations: • ↑ ICER for FCR suitable cohort • Key conclusions remain same for FCR unsuitable cohort HR I+V vs VenO: unknown
Model structure results in inconsistent model outcomes: • Inconsistent risk of progression for the surviving FCR unsuitable cohort compared with the FCR suitable cohort	Small impact/unknown

FCR, Fludarabine plus cyclophosphamide plus rituximab; ICER, Incremental cost-effectiveness ratio; I+V, ibrutinib plus venetoclax; HR, Hazard ratio; VenO, venetoclax plus obinutuzumab

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

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Thank you.

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Back up slides

Table includes issues resolved at technical engagement

Issue	Company technical engagement response	ICER impact
Subgroup analysis for Immunoglobulin heavy chain variable region (IGHV) unmutated CLL should be provided to understand its impact as a treatment effect modifier	IGHV mutation status is not routinely tested in UK and does not impact treatment decisions FCR suitable: No adjustment needed. Indirect treatment comparison (ITC) takes into account IGHV status FCR unsuitable: IGHV mutation status included in matching adjusted indirect comparisons (MAICs). Results slightly favours I+V versus VenO and comparable with acalabrutinib	FCR suitable: No change FCR unsuitable: Minor impact
FCR unsuitable OClb arm accrues higher life years in progressed disease states compared with 1L PFS	Aligned with clinical expert expectations. External assessment group (EAG) accepted rationale	No change
The incidence of treatment-emergent adverse events lower in CAPTIVATE fixed duration (FD) compared with GLOW despite same treatment duration	In line with clinician expectations because FCR unsuitable group (older/unfit) more likely to have co-morbidities, increasing risk of adverse events regardless treatment duration. EAG accepted rationale	No change
Best supportive care (BSC) not offered as an option, most relevant for FCR unsuitable and high risk group	Few people (<5%) would be offered BSC at this stage of the treatment pathway and cost of BSC drugs (such as prednisolone) are inexpensive. Risk of bias by this omission is minimal on the ICER Costs associated with routine care are still being modelled	No change

FCR, Fludarabine plus cyclophosphamide plus rituximab; ICER, Incremental cost-effectiveness ratio; I+V, ibrutinib plus venetoclax; HR, Hazard ratio; OClb, Obinutuzumab plus chlorambucil; OS, Overall survival; PFS 1L, Progression-free survival first line; VenO, venetoclax plus obinutuzumab

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Source: Company technical engagement response, EAG critique of company technical engagement response. Other minor modelling or data issues resolved are included in the back up slides

Issues resolved at technical engagement

Other modelling or data issues

Additional Issue	Company technical engagement response	ICER impact
Adding in third-line treatment costs aligned with RESONATE trial efficacy and clinical practice	RESONATE trial data and clinical opinion used to update cost-effectiveness analysis. People on OClb and FCR spend longer on progressed disease state accruing higher third-line costs compared with I+V	Minor impact in favour of I+V
Incorrect TLS prophylaxis proportion applied to the FCR suitable group	Proportion of people eligible for TLS prophylaxis aligned with CAPTIVATE FD. This was updated in the model from 0% to 17.6%	Minor change
Double counting of disutilities	Justification was provided and EAG accepted the explanation	No change
Scenario with different parametric functions for OClb arm in FCR-unsuitable population	Alternative parametric fits explored in scenarios. Base case conclusions remain unchanged	No change

Source: Company technical engagement response, EAG critique of company technical engagement response

Unresolvable?

Other issue for consideration: Immature trial data

Median PFS and OS not reached for I+V arm resulting in uncertainty

Background

- Company included additional follow up data based on XXXX months from CAPTIVATE and 46 months for GLOW
- Results were consistent with previous data cuts. Median PFS and OS not reached for I+V

Company

- Not reaching median survival times shows lack of events over the follow up period likely implying treatment with I+V is efficacious
- Similar uncertainty was observed in TA663 (VenO) and TA689 (acalabrutinib) where median PFS was not reached

EAG comments

- Consistency of the updated trial results may reduce some concerns about uncertainties in the data
- Lack of events can be because of relatively small sample sizes in the analyses
- A XXXXX follow up cannot be considered as long-term when comparing first line treatments of CLL

Other considerations (clinical experts)

- Longer term outcomes and adverse effects for I+V remain to be established. Ongoing UK FLAIR trial response and minimal residual disease outcomes are consistent with CAPTIVATE. PFS and OS not yet reported because of limited follow-up. No additional trial data available to reduce the uncertainty

Does the limited event numbers and median PFS and OS not being reached for I+V result in considerable uncertainty to the model outcomes?

How company incorporated evidence into model

Table: Input and evidence sources

Input	FCR suitable	FCR unsuitable ★
Baseline characteristics	CAPTIVATE fixed duration (FD), E1912 trial	GLOW intention to treat (ITT)
Intervention efficacy	CAPTIVATE FD, indirect treatment comparison (ITC)	GLOW ITT, ITC
Comparator efficacy	E1912 Fludarabine plus cyclophosphamide plus rituximab (FCR), ITC	GLOW, ITC, matching adjusted indirect comparison (MAIC)
Transition probabilities sources include	E1912 FCR curve, Ibrutinib plus venetoclax (I+V) hazard ratio (HR) vs FCR from ITC, RESONATE trial (1-2 prior lines) ibrutinib arm (see back up slides for details)	GLOW trial extrapolations, I+V HR vs venetoclax + obinutuzumab (VenO) and acalabrutinib from MAIC, RESONATE trial (1-2 prior lines) ibrutinib arm (see back up slides for details)
Utilities	GLOW trial and previous submissions	Same sources as FCR suitable
Costs	MIMS, BNF and NHS reference costs	Same sources as FCR suitable
Resource use	Assumptions aligned with first-line CLL appraisals	Same sources as FCR suitable
Adverse events	Incidence of grade more than or equal to 3 adverse events (AEs) considered from CAPTIVATE FD and E1912	Incidence of grade more than or equal to 3 AEs considered from GLOW, CLL14, ELEVATE-TN

★ Same assumptions used for del17p/TP53 mutated high risk

BNF, British National Formulary; MIMS, Monthly Index of Medical Specialities

Other issue for consideration: Utilities

PF utility value higher than general population age-sex adjusted value

Background

- PF utility values are from the GLOW trial and these are not adjusted for the UK general population utility

Company

- PF utility from GLOW trial is plausible and consistent with previous CLL trials (CLL14 and ELEVATE-TN) and CLL appraisals
- At TE a scenario was provided where PF utility is capped to age-sex adjusted values

Other considerations (clinical experts)

- Quality of life after treatment will be lower than UK general population and even lower with chemoimmunotherapy
- CLL is a chronic disease associated with treatment related morbidities and continuous need for follow-up even during stable remission periods

EAG comments

PF utility is an overestimate because it is higher than UK population age-sex matched utility. GLOW trial patients considered better performing than people in NHS offered treatment for CLL. The utility estimates may not be generalisable.

- PF utility was capped to general population values in previous appraisals (TA689 and TA663)
- EAG's preference is to cap the PF utility at the age-sex adjusted values

Should PF utility be capped by UK age-sex adjusted general population utility?

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TE, Technical engagement; PF, Progression free; Source: TE clinical expert responses, EAG critique of company TE response, Company TE response

Other issue for consideration: Same utilities assumed for PP and PF 2L

Background

- A utility value of 0.6 (from a previous appraisal) is used for the progression free second-line (PF 2L) and post-progression (PP) health states.

Company

- A value of 0.6 was applied to second line and all other progression states for the entire progressed disease state in TA669 and TA663 which was accepted by committee

Other considerations (clinical experts)

- In agreement with modelling lower utility values for PP compared with PF 2L because of more advanced disease in PP health state

EAG comments

- The 0.6 value is from an older source (2004) and may not capture benefit from the newer second line targeted treatments
- The company's granular model and the preferred utilities captures the improved quality of life from 2L CLL treatment. These benefits were not previously captured in other CLL appraisal models (TA669 and TA663)
- Large differences in the mortality rate between PF 2L and PP health states and improved second line treatments mean it is not appropriate to use same utility values for PF 2L and PP
- PF 2L: EAG preference for a utility multiplier based on the progressive disease utility estimate derived from GLOW trial EQ-5D data (=[redacted]).
- PPS: preference for lower value (0.6)

Does committee agree with using different utility values for the PF 2L and PPS health states?

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PF, progression free; PPS, post progression survival; CLL, chronic lymphocytic leukaemia