NICE National Institute for Health and Care Excellence

Acalabrutinib for treating chronic lymphocytic leukaemia

Lead Team Presentation

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Company: AstraZeneca

ACM 1: 5 November 2020

Chronic lymphocytic leukaemia

- Chronic lymphocytic leukaemia (CLL) is a malignant disorder of white blood cells (lymphocytes)
- Symptoms not usually present at time of diagnosis
  - These develop later, including: anaemia, increased infections, swollen glands, spleen enlargement, and weight loss
- CLL is the most common type of leukaemia with 3,157 new cases diagnosed in England in 2017
- Risk of CLL increases with age and is more common in men
- Patients identified with ‘high-risk’ disease if they have:
  - deletion of chromosome 17p (del(17p)), or
  - mutation of the tumour protein p53 (TP53)
- High-risk predicts aggressive disease course & poor prognosis

Patient and carer perspectives

Chronic Lymphocytic Leukaemia Support, Lymphoma Action, Leukaemia Care UK CLL Forum, British Society of Haematology

CLL diagnosis:

- Most common form of leukaemia: the risk increases with age and 70% of cases diagnosed after investigations for other illnesses
- Severe psychological impact: shock at diagnosis, long time living with significant symptoms in "watch and wait" stage, expectations of relapse. *"The reality of the diagnosis dawned on me: slow, unpredictable, incurable"*

Experience of living with the condition:

- Range of debilitating symptoms
- Additional impact on mental state (depression, stress, anxiety, worrying, difficulty sleeping)
- Isolation & reduced social contact due to risk of infections: *"I worry about catching flu as I can't make antibodies myself and so I tend to stay away from people during winter."*
- Increased worry & (sometimes reciprocal) caring responsibilities for family/carers create additional strains. *"The insidious nature of the disease following my diagnosis caused persistent illness and side effects which over time contributed to our eventual break up."*

Patient and carer perspectives

Current treatment experience

- CLL is mostly incurable, with any treatment ending in relapse and response reducing with each treatment cycle
- Toxic chemo-immunotherapy impacts quality of life. *"My husband has been on [this] for a year now and suffers harsh bone pain, difficulty breathing and massive bruising with bleeding on arms. His illness has become our life. His blood counts have improved but the side effects are difficult. We wish there was an alternative therapy."*

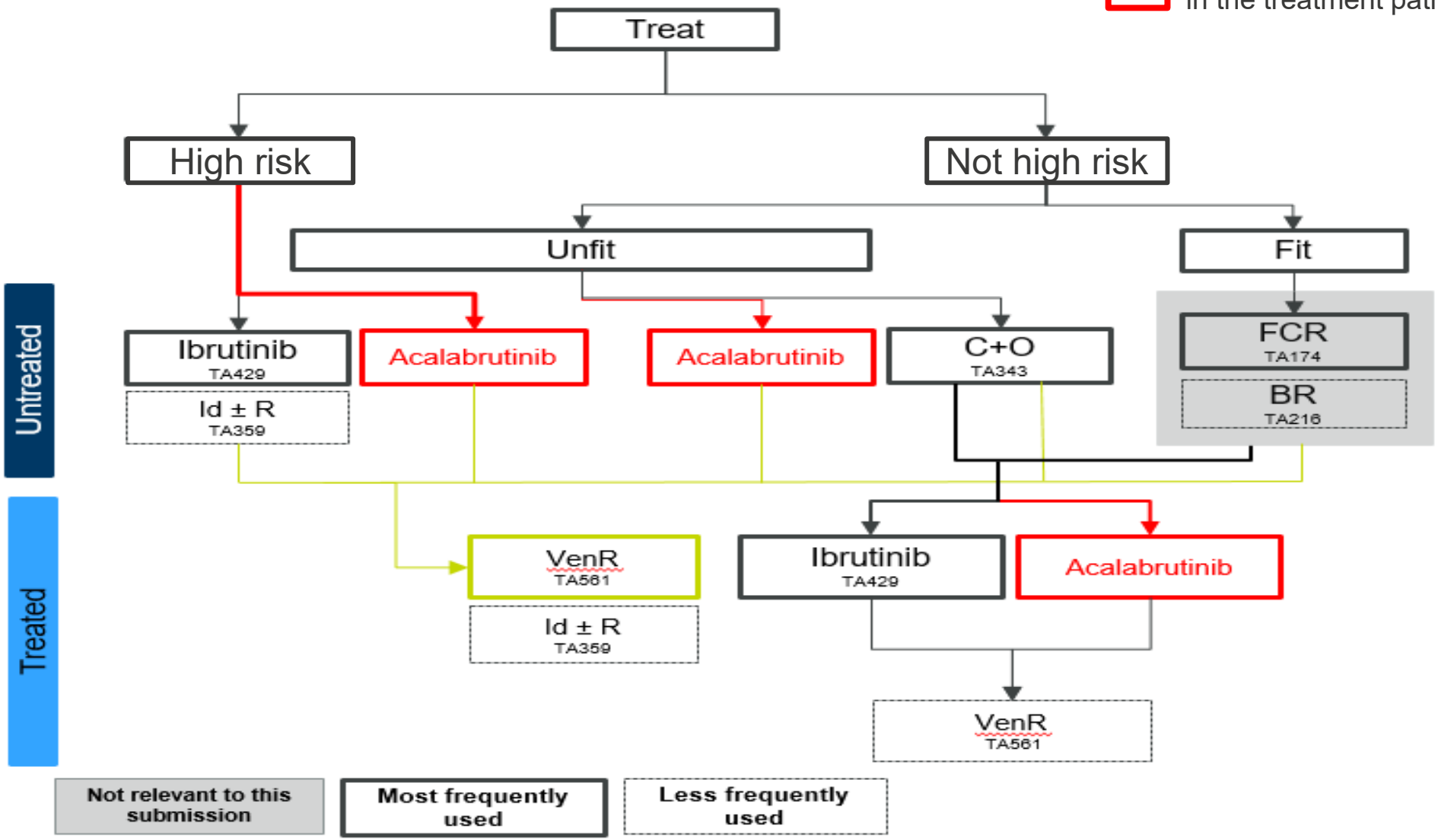
Advantages of acalabrutinib:

- Reduced adverse events compared to ibrutinib (e.g. atrial fibrillation, hypertension)
- Relatively non-toxic treatment option
- Urgent unmet need for first-line treatment in people who are not high-risk
- Survey reports 90% had positive experience of acalabrutinib treatment
- Tablet taken at home reduces hospital attendance

Disadvantages of acalabrutinib:

- Taking the tablet twice a day could be inconvenient
- Treatment needs to be continued long-term

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 (Calquence, AstraZeneca)

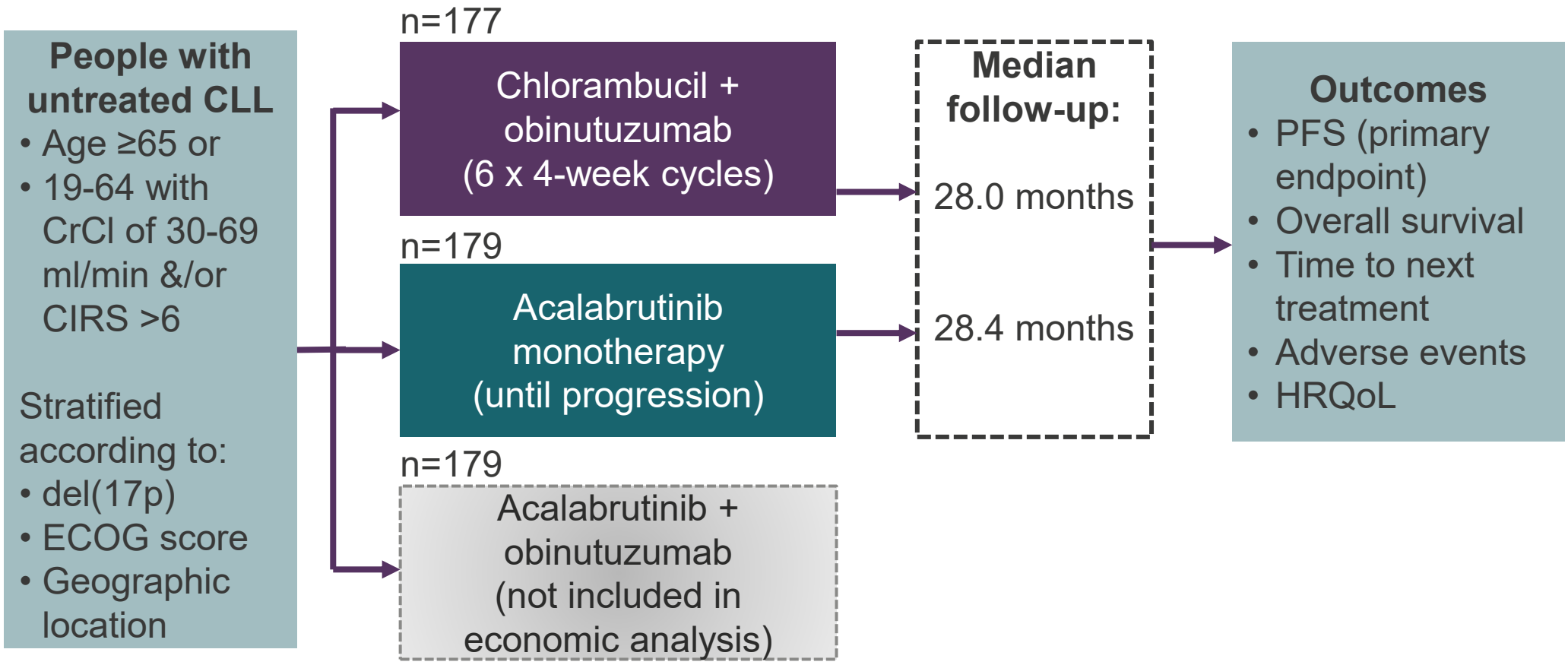
Description of technology	Acalabrutinib is a selective small-molecule inhibitor of Bruton's Tyrosine Kinase (BTK). It forms a bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity.
Marketing authorisation	CHMP positive opinion granted July 2020: • Calquence as monotherapy or in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated CLL. • 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 [redacted] per 30-day pack. A simple PAS discount has been approved for acalabrutinib.

Submission summary – models

Model	Model 1 Cost-utility analysis (semi-Markov model)	Model 2 Cost-minimisation analysis (semi-Markov model)	Model 3 Cost-minimisation analysis (partitioned survival model)
Population	People with previously untreated CLL for whom FCR/BR is unsuitable*	Untreated high-risk (del 17p / TP53 mutation)	Previously treated relapsed/refractory [R/R]
Intervention	Acalabrutinib monotherapy**	Acalabrutinib monotherapy	Acalabrutinib monotherapy
Comparators	chlorambucil plus obinutuzumab	ibrutinib	ibrutinib
Main clinical trials	ELEVATE-TN Post-progression survival estimated from OS of: MURANO & RESONATE	Baseline model: ELEVATE-TN (acalabrutinib arm)	Baseline: RESONATE (ibrutinib arm)
		Equivalence based on MAIC of: ASCEND & RESONATE R/R CLL trials	

- *Company chose not to include people with untreated CLL **for whom FCR/BR is suitable** although its marketing authorisation includes this population.
- **Company also chose not to include acalabrutinib+obinutuzumab as an intervention for the untreated population, although included in its marketing authorisation .

ELEVATE-TN: flow summary



CIRS = Cumulative illness rating scale;
CrCl = Creatinine clearance;
ECOG = Eastern Cooperative Oncology Group;
PFS = Progression-free survival;
HRQoL = Health-related quality of life.

ELEVATE-TN: PFS & OS Kaplan-Meier results

Progression-free survival

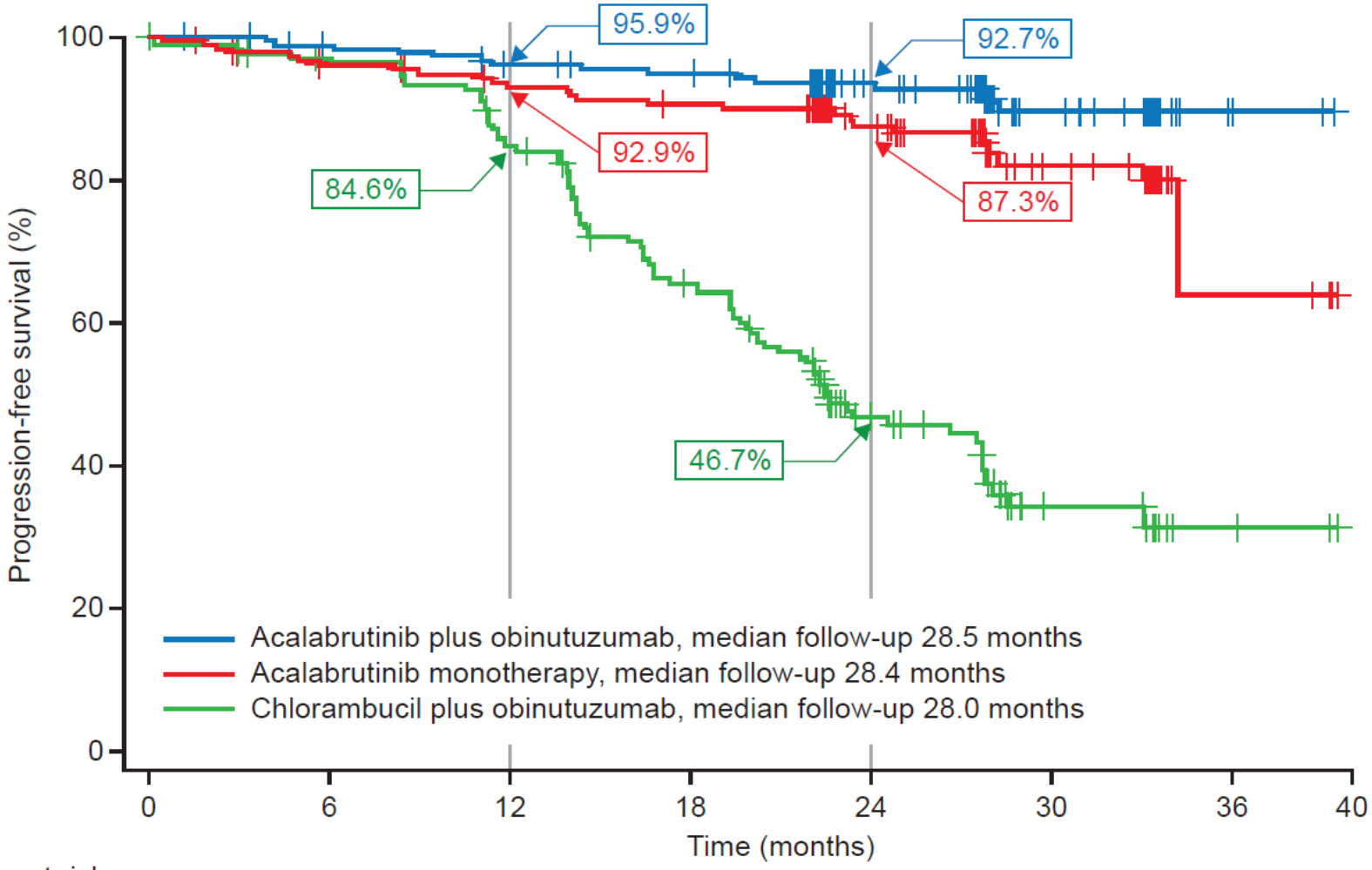
	Acalabrutinib	C+O
Events	26 (14.5%)	93 (52.5%)
Median	Not reached	22.6 months
1-year KM	92.9%	84.6%
2-year KM	87.3%	46.7%
3-year KM	63.9%	31.3%
HR	0.20 (0.13–0.30) p<0.0001	

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	

Time to next treatment HR: [redacted] (95% CI [redacted]) favoured acalabrutinib
Median time to next treatment: not reached in any treatment arm
Adverse event grade ≥3: acalabrutinib = 89 (49.7%), C+O = 118 (69.8%)

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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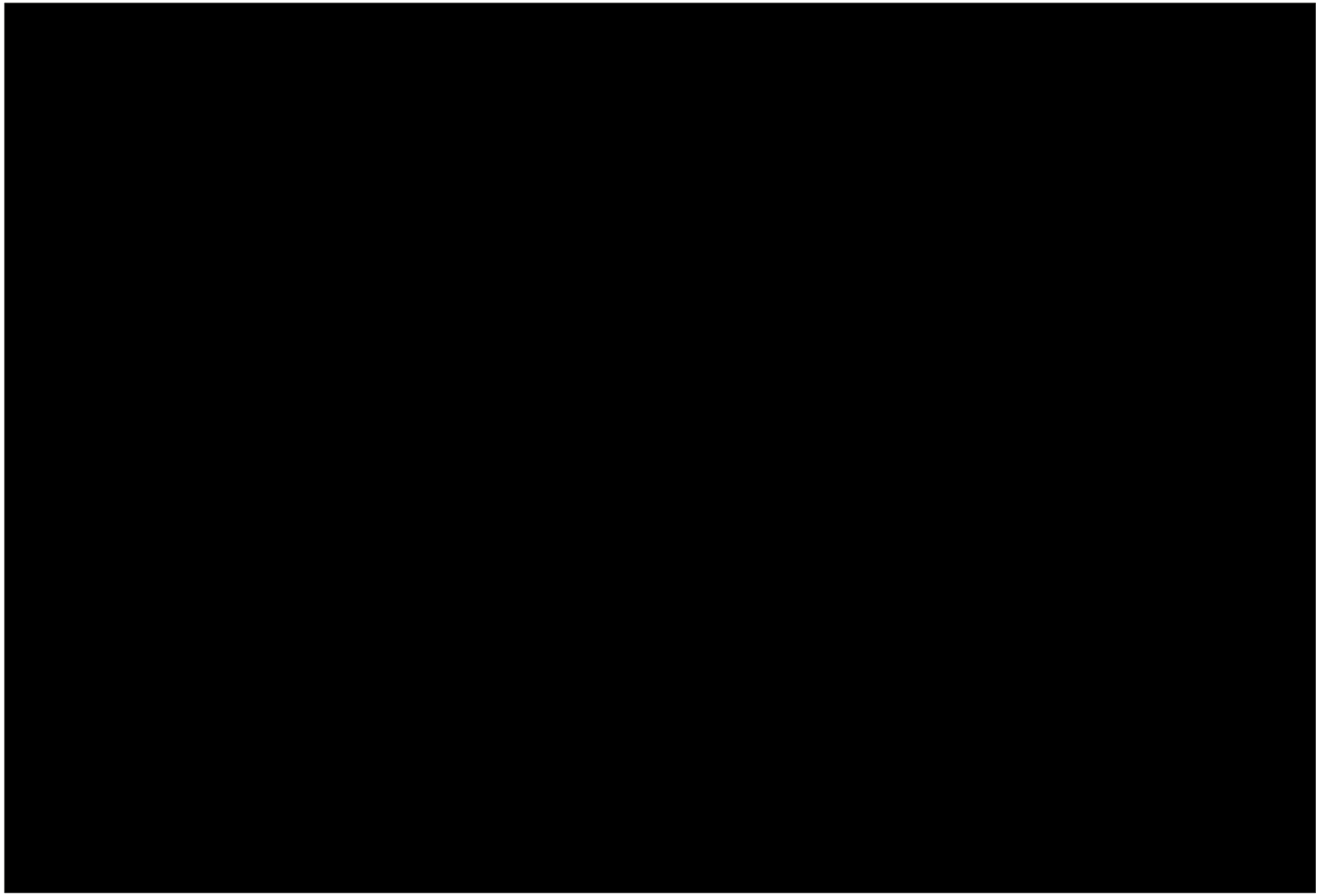
reproduced from CS Figure 2

ELEVATE-TN: OS Kaplan-Meier plot



reproduced from ERG report Figure 14

Health-Related Quality of Life (HRQoL)

- Comparative data on HRQoL presented for the untreated CLL population*
  - Pooled data from EuroQol 5-dimensions questionnaire (EQ-5D-3L)
  - European Organisation for Research and Treatment of Cancer Core Quality of Life (EORTC QLQ-C30) global health status (GHS) domain
  - Functional Assessment of Cancer Therapy-Fatigue (FACIT-F) questionnaire

- No statistically significant differences between treatment groups
- Scores for both treatments improved from baseline
- Across treatments, improvements were greater for people with severe fatigue at baseline

ELEVATE-TN: HRQoL change from baseline over 96 weeks

Instrument	Acalabrutinib monotherapy		Obinutuzumab plus chlorambucil	
	ITT (N=179)	Severe fatigue population [redacted]	ITT (N=177)	Severe fatigue population [redacted]
FACIT-F	4.66	11.79	[redacted]	[redacted]
EORTC QLQ-C30	7.72	12.83	[redacted]	[redacted]

*Not included for the high-risk CLL or R/R CLL populations as cost-minimisation used

Submission summary – treated CLL

Subgroups & comparators	3) Previously treated relapsed/refractory CLL (R/R). **Comparator:** ibrutinib
Clinical trials	**ASCEND:** phase 3, open-label, multicentre RCT in people with R/R CLL. Comparing acalabrutinib monotherapy (n=153) and either idelalisib + rituximab or bendamustine + rituximab* (total comparator n=153). **RESONATE:** phase 3, open-label, multicentre RCT in people with R/R CLL. Comparing ibrutinib (N=195) and ofatumumab (n=196)
Key results (Subgroup 3)	**ASCEND** **PFS HR:** 0.31 (95% CI 0.2-0.49, p<0.0001) favoured acalabrutinib **Median PFS:** not reached in either treatment arm **OS HR:** 0.84 (95% CI 0.42-1.66, p=0.6089) no significant difference **Median OS:** not reached in either treatment arm **TTNT HR:** [redacted] favoured acalabrutinib **RESONATE** **PFS HR:** 0.22 (95% CI 0.15-0.32, p<0.001) favoured ibrutinib **Median PFS:** ibrutinib (not reached), ofatumumab (8.1 months) **OS HR:** 0.43 (95% CI 0.24-0.79, p=0.005) favoured ibrutinib **Median OS:** not reached in either treatment arm

*The idelalisib + rituximab or bendamustine + rituximab arm was not included in economic analysis
**The ofatumumab arm was not included in the economic analysis

Matching adjusted indirect comparison (MAIC)

Methods

- For R/R population, an indirect treatment comparison made using an unanchored MAIC
- Individual patient data (IPD) weighted to allow a comparison of:
  - Acalabrutinib arm of ASCEND (n=132)
  - Ibrutinib arm of RESONATE (n=195)
- IPD weighted to match baseline characteristics between arms
- MAICs require all effect modifiers & prognostic variables to be accounted for

Results

- After weighted adjustments for the R/R population:
  - Kaplan-Meier estimates for PFS & OS appear to be similar for both interventions
  - Company's sensitivity analyses using different covariates found no significant differences between groups
  - Can be reasonably assumed that efficacy of acalabrutinib equivalent to ibrutinib

MAIC – survival

Kaplan Meier survival estimates before and after application of MAIC weights

PFS

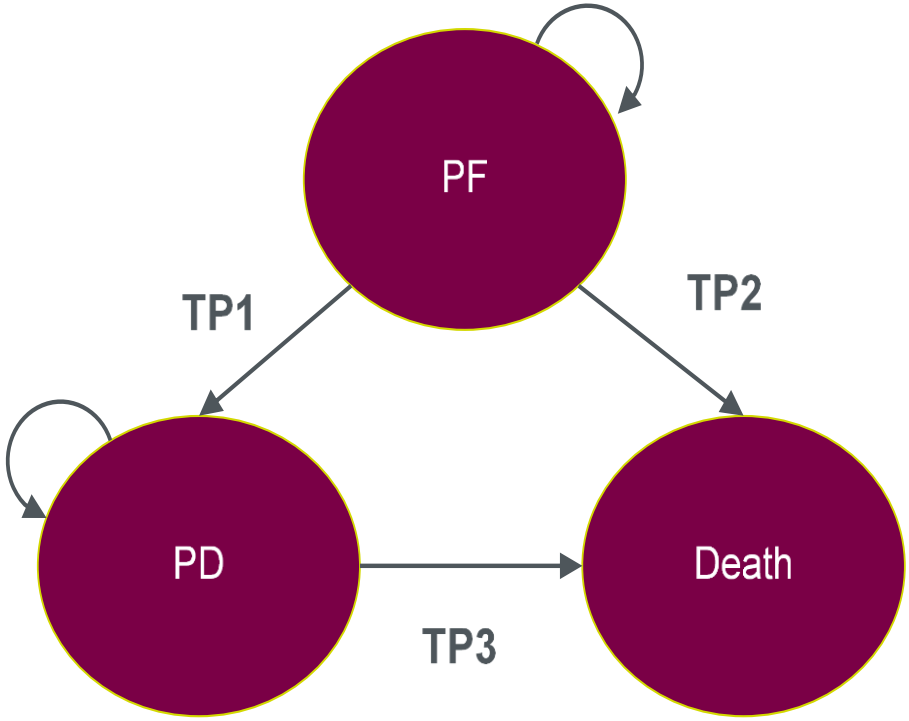
OS

Differences in PFS and OS between treatments not statistically significant before or after matching

Adapted from figures 4 and 5 on pages 67-68 of ERG report

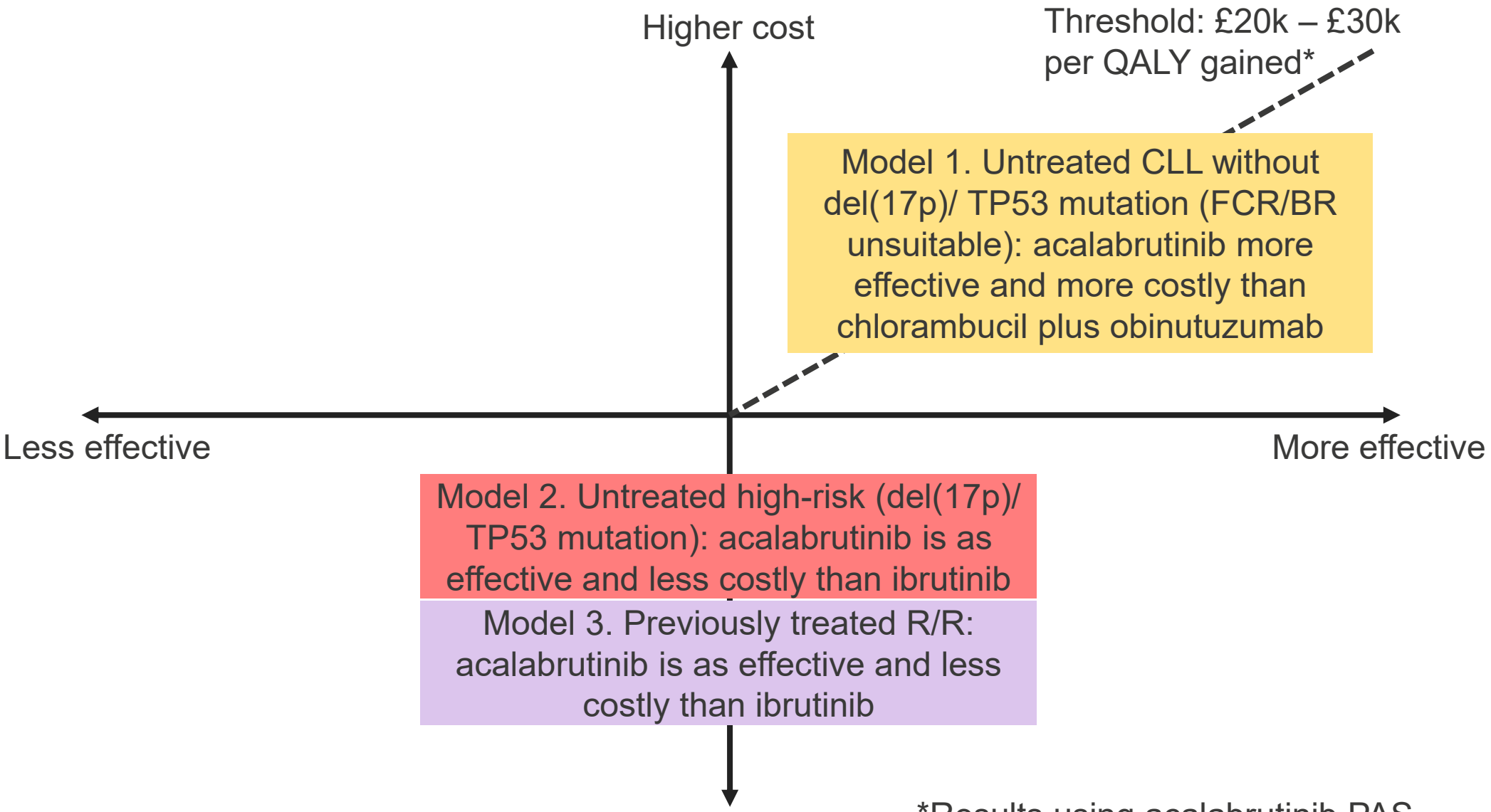
Economic model

- 3 health states: progression-free (PF), progressed disease (PD), & death
- Assessment period at 4-week model cycles over 30-year (lifetime) horizon
- Time dependent transition probabilities (TPs):
  - TP1: Time to progression curve (derived from PFS in ELEVATE-TN)
  - TP2: Time to death curve, pre-progression (derived from PFS in ELEVATE-TN)
  - TP3: Post-progression survival curve (derived from OS data from R/R trials: MURANO & RESONATE)



- High-risk & R/R models consider whether acquisition cost and management of adverse event cost for acalabrutinib are lower than that for ibrutinib
- R/R model uses a different (partitioned survival) model structure without TPs

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



*Results using acalabrutinib PAS & list price for comparators

Key issues

Issue	ERG #	Company base case	Technical team judgement
Population	1	Eligible for FCR/BR excluded	No comparative evidence provided as not part of company value proposition
	3	High-risk CLL population included in model 1	Unknown impact of excluding high-risk from model 1
Subsequent treatment	4	Costs overestimated	Prefer ERG's model to estimate costs
	5	Assume fixed sequences	Discuss 2nd-line VenR in NHS
	7	Optimistic OS benefit	Prefer ERG projection of OS
PFS model	6	Log-normal for PFS in C+O group	Agree with ERG to use generalised gamma for PFS in C+O group
Utilities	8	Progression-free utility [redacted] higher than general population	ERG's utility of 0.78 is more plausible
MAIC	2 & 9	Assume clinical equivalence of acalabrutinib & ibrutinib	No comparative evidence of acalabrutinib vs ibrutinib in high-risk
Comparator	1	2nd line VenR not included	VenR not a comparator in cost-minimisation analysis

Untreated CLL (Model 1)

Untreated high-risk CLL (Model 2)

Treated R/R CLL (Model 3)

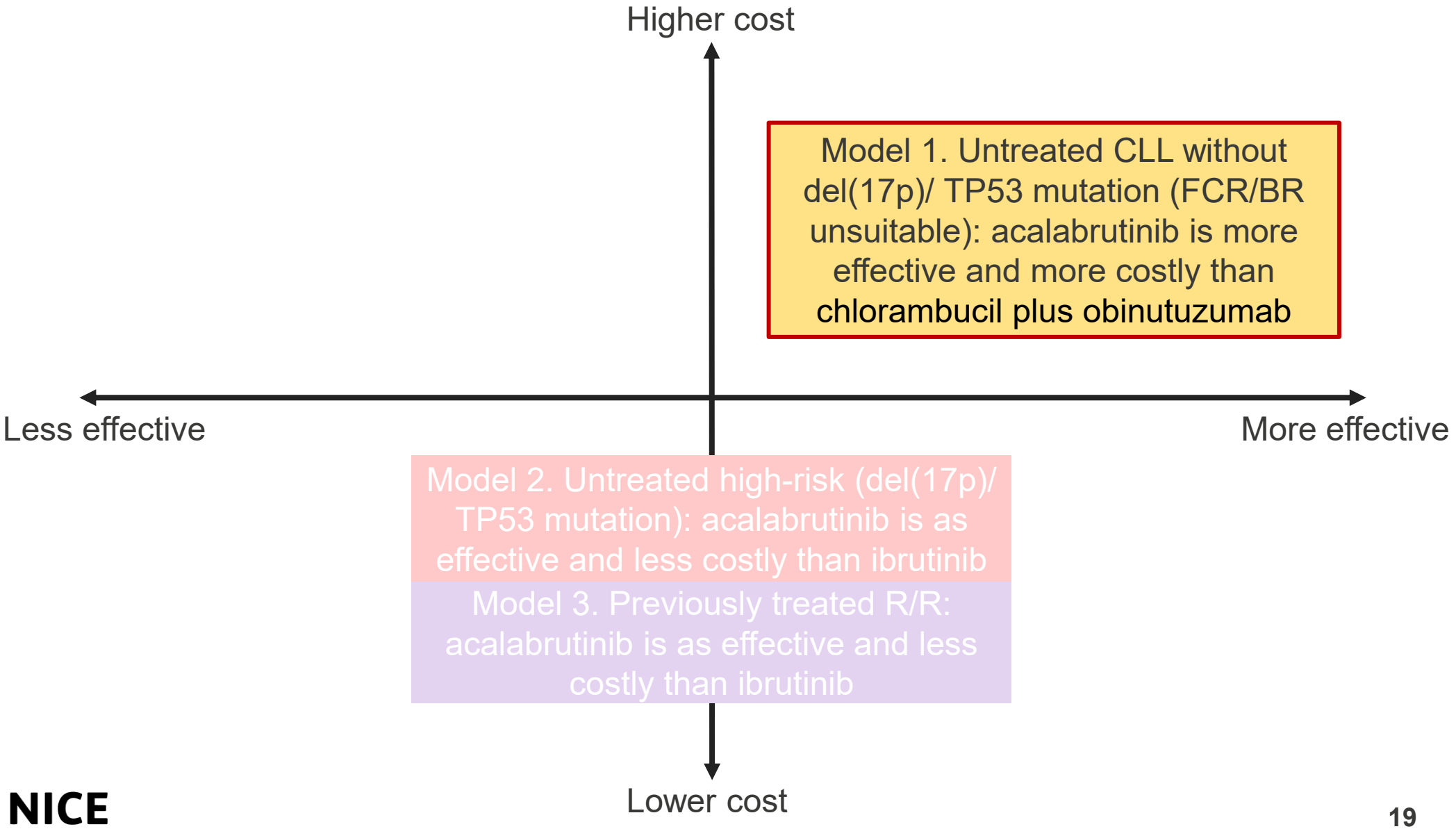
Resolved in updated company base case

For discussion: unknown ICER impact

For discussion: large ICER impact

1. Untreated CLL (FCR/BR unsuitable)

Issues for discussion: Subgroup model 1



Issue 3: high-risk patients included in untreated model

Background

- Company used ELEVATE-TN to inform economic analysis for untreated population
- Around 20% of people in each arm had high-risk del(17p) / TP53 mutations
  - separate analysis is presented for this population as comparator is ibrutinib
- However, analysis for untreated CLL uses full ITT population from ELEVATE-TN
  - same high-risk population is included in 2 models with different comparators
- Company consider treatment effect of acalabrutinib to be consistent across subgroups

ERG comments

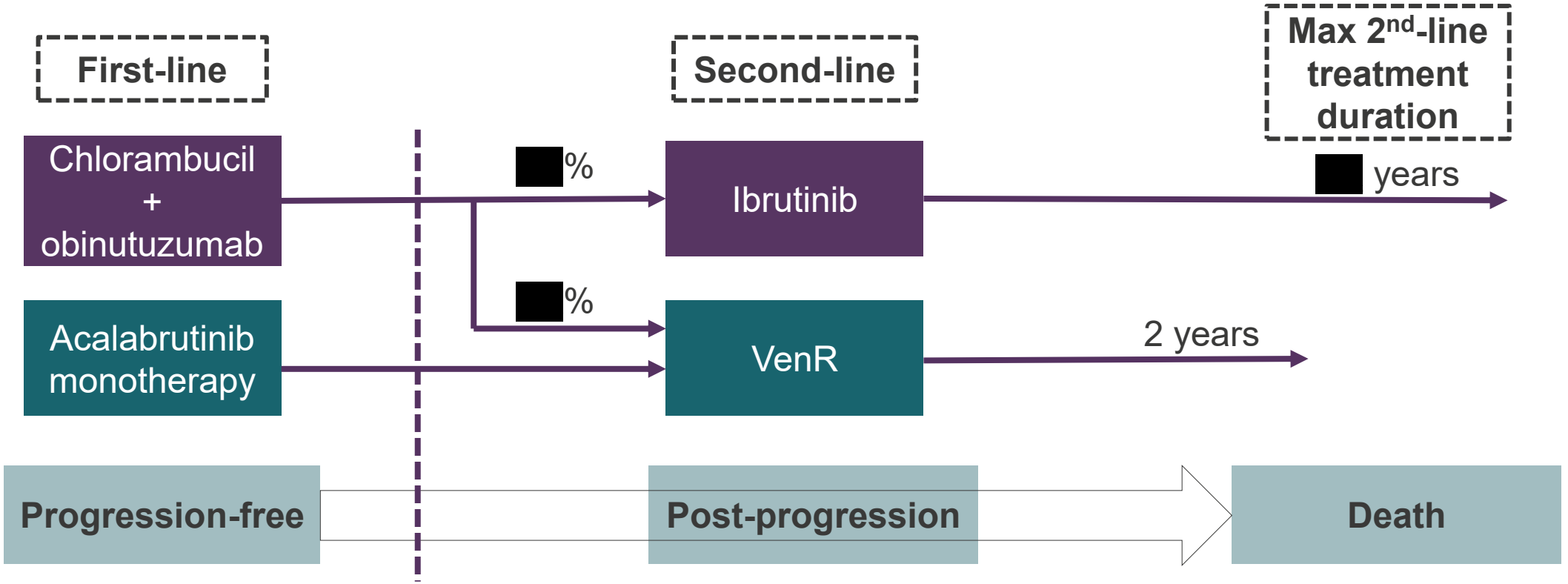
- The same high-risk patients are included in models 1 and 2 but neither model specifically reflects outcomes for high-risk patients
- Using ITT population for untreated CLL analysis preserves randomisation
- Excluding high-risk may lead to confounding - randomisation stratified by del(17p) not TP53

Technical team judgement

- Impact of including the high-risk population in the untreated CLL analysis is unclear

Are the results from the ITT population likely to reflect the cost-effectiveness of acalabrutinib in people with untreated CLL in the NHS?

Issue 4, 5 & 7: Subsequent treatment sequence in model



Delay between progression and initiation of 2nd-line treatment

Costs applied every cycle irrespective of progression status

Model structure does not allow second progression event

Costs applied from start of 2nd-line treatment until death or maximum 2nd-line treatment duration

Ibrutinib assumed to be taken for longer period than VenR

Issue 4, 5 & 7: Subsequent treatment costs

- More than 78% of treatment costs in C+O group attributed to second-line ibrutinib due to:
  - cost of ibrutinib per cycle
  - model assumption that ibrutinib given for long period
  - second-line ibrutinib costs applied to all surviving patients
- Second-line treatment costs in acalabrutinib group are lower due to:
  - comparatively less time alive after progression
  - treatment with VenR is limited to 2 years
- This leads to high second-line costs for the C+O comparator group

Component	Acalabrutinib	C+O
LYGs – progression-free	[redacted]	[redacted]
LYGs – post-progression	[redacted]	[redacted]
LYGs – total	[redacted]	[redacted]
QALYs – progression-free	[redacted]	[redacted]
QALYs – post-progression	[redacted]	[redacted]
QALY loss - AEs	[redacted]	[redacted]
QALYs loss - age decrement	[redacted]	[redacted]
QALYs - total	[redacted]	[redacted]
Costs first-line treatment	[redacted]	[redacted]
Costs second-line treatment	[redacted]	[redacted]
Costs – other	[redacted]	[redacted]
Costs - total	[redacted]	[redacted]

Breakdown of costs* & health outcomes show:

Acalabrutinib group spend longer in the PFS state and more time alive

Majority of C+O costs attributed to second-line ibrutinib treatment

*PAS price for acalabrutinib & list price for C+O

Issue 4: Costs of subsequent treatments overestimated

Company preferences

- Log-normal distribution from RESONATE 1-2 prior lines to estimate duration of 2nd-line ibrutinib
- 14 cycle delay to start of 2nd-line therapy removed and replaced with 1 cycle delay

ERG comments

- SmPCs indicate second-line therapy to be stopped at point of progression
- Prefer model which estimates costs according to PFS rather than OS
  - Weibull model for PFS in ibrutinib-treated patients with 1-2 prior lines from RESONATE
  - Constrained by company's modelled OS and general population mortality risks
  - Costs of 2nd-line treatment dependent on time of disease progression (which affects mortality risk, maximum remaining treatment time and appropriate discounting multipliers)
  - Company assumption of [redacted]-year maximum no longer applied in ERG's preferred analysis
- It is unclear what the delay should be but this could be estimated from ELEVATE-TN

Technical team judgement

- The ERG's preferred model to estimate subsequent treatment costs accounts for progression status
- Appropriate duration of delay to initiate 2nd-line therapy remains unclear

Which parametric model should be preferred and what delay should be assumed?

Issue 5: Assumptions regarding fixed sequences of first- and second-line therapies for CLL

Background

- Company assumes sequence of 2nd-line therapy based on 1st-line therapy (see Issue 4)
- Real world evidence from company suggests [redacted] will have VenR as 2nd-line after C+O

ERG comments

- Sequence of 2nd-line therapy not consistent in model and ELEVATE-TN
- Company assumes 2nd-line ibrutinib is predominantly used in NHS
- But company model disadvantages this sequence as VenR assumed to dominate ibrutinib in 2nd-line
- Some people on 1st-line C+O will have 2nd-line VenR
- Propose to use same post-progression survival distribution for both treatment groups
- And, assume [redacted] 2nd-line VenR after C+O
- Also, 3rd-line treatments not included in company model

Technical team judgement

- Sequences of 1st- and 2nd-line therapies are not fixed
- The proportion of people having 2nd-line VenR after C+O has a large impact on the cost-effectiveness of acalabrutinib

Does [redacted] represent clinical practice for 2nd-line VenR after C+O?

Issue 7: Highly optimistic assumptions regarding overall survival benefit for acalabrutinib

Background

- Current OS data from ELEVATE-TN are immature → highly uncertain survival estimates
- OS is estimated using PFS from ELEVATE-TN & PPS from MURANO & RESONATE
- Evidence to inform OS not related to the subsequent treatment sequences in model

ERG comments

- There is limited evidence demonstrating OS advantage for acalabrutinib
- Data from MURANO & RESONATE may be influenced by confounding
- Company's predicted OS for acalabrutinib is similar to the general population
- The OS hazard converges on the general population OS risk point where 79% of patients are still alive (and the remaining 21% don't lose much survival)
- This implies that a large proportion of people having acalabrutinib are cured
- ERG prefer to project OS using RESONATE for both treatment groups as this leads to less optimistic projections of OS
- But, other sources not presented in the company submission may be more appropriate

Technical team judgement

- Expected OS outcomes are unclear as the data is currently immature

Should RESONATE or another source be used for both treatment groups to project OS?

Issue 7: Highly optimistic assumptions regarding overall survival benefit for acalabrutinib **(continued)**

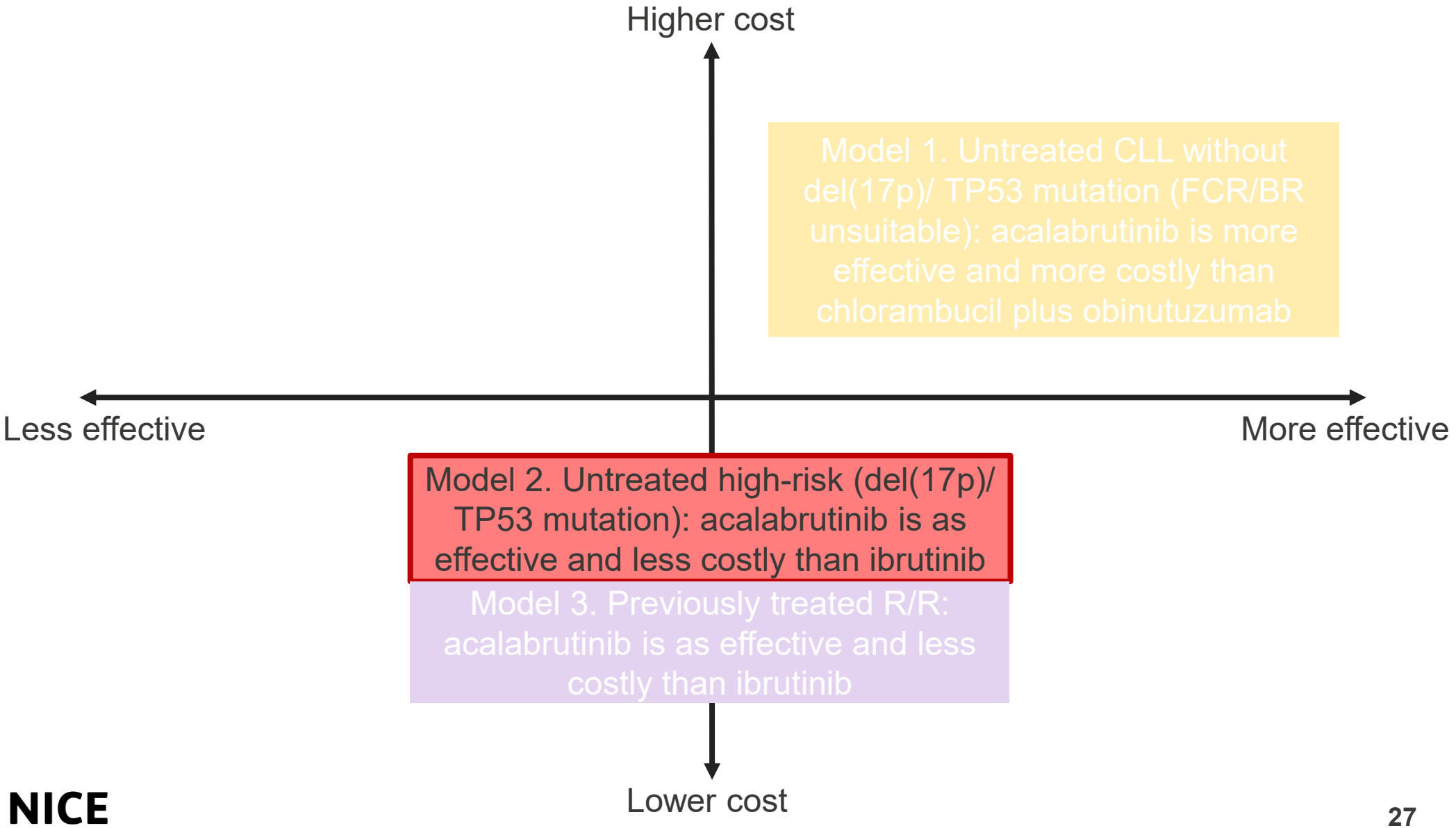
Company's modelled OS compared with general population OS

The same behaviour was exhibited by most of the combinations of parametric survival models for transitions

GClb – obinutuzumab plus chlorambucil; OS – overall survival

Figure 24, ERG report

Issues for discussion: Subgroup model 2



Issue 2 & 9: Absence of comparative evidence for acalabrutinib versus ibrutinib in patients with high-risk CLL

Background

- No direct or indirect comparison of acalabrutinib versus ibrutinib specifically in patients with del(17p) or TP53 mutations (high-risk population)
- The cost minimisation analysis (CMA) is based on MAIC results using R/R CLL patient data
- Results used to justify assumption of clinical equivalence between acalabrutinib & ibrutinib
- CMA used time-to-event data from acalabrutinib arm of ITT population in ELEVATE-TN

ERG comments

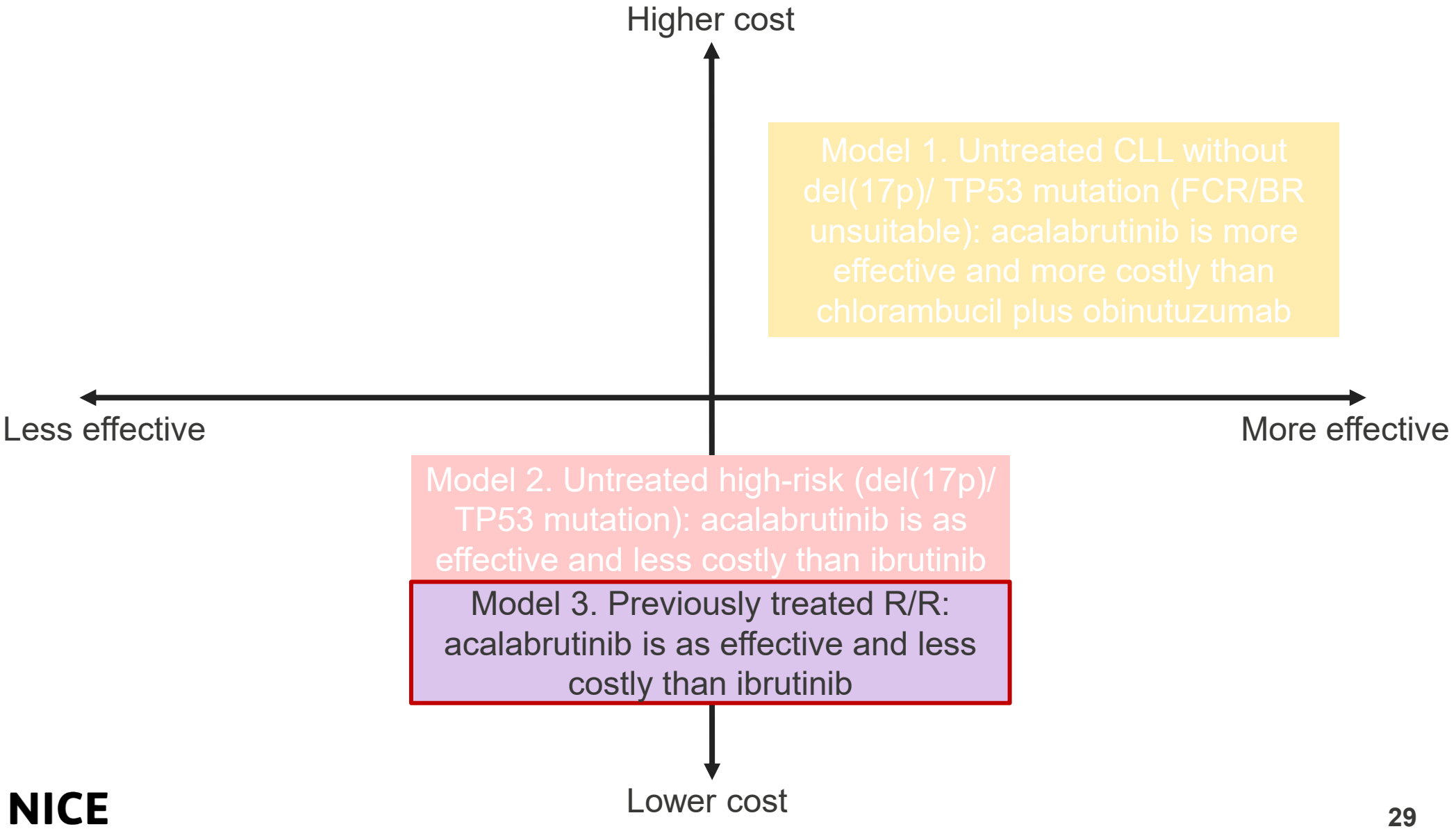
- No comparative evidence for acalabrutinib versus ibrutinib in the high-risk CLL population
- Therefore the CMA in model 2 should be interpreted with caution
- Unclear if meaningful comparison can be made using 35 high-risk patients in ELEVATE-TN
- Unknown if an equivalent dataset is available for high-risk CLL treated with ibrutinib as company only considered RCTs in the systematic literature review

Technical team judgement

- No evidence presented for a comparison of acalabrutinib and ibrutinib in high-risk CLL
- Using the MAIC, clinical equivalence is likely in the R/R population but it is unknown if this can be used as a proxy for the high-risk population

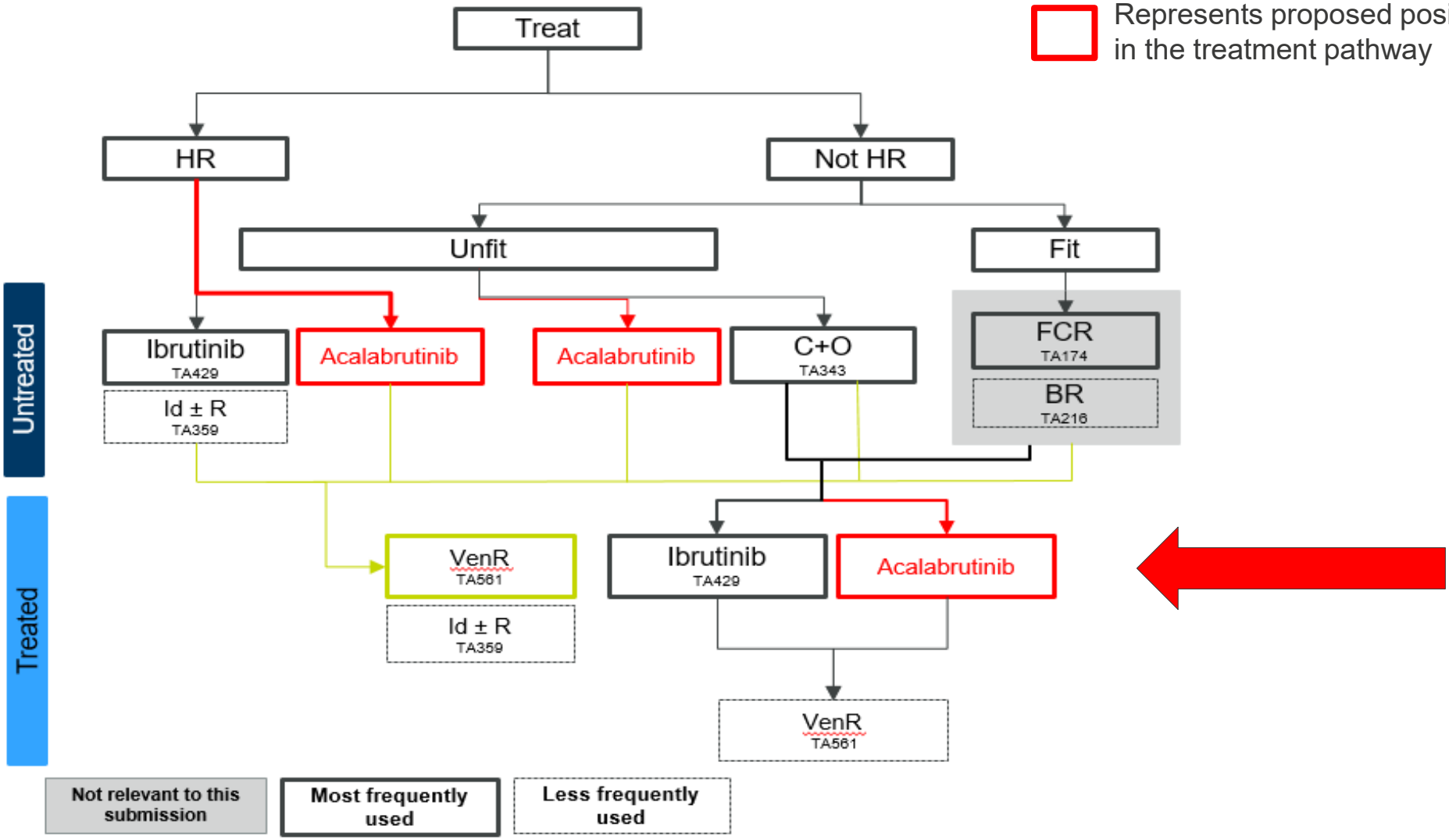
Is it appropriate to assume clinical equivalence in high-risk CLL population?

Issues for discussion: Subgroup model 3



Issue 1: VenR comparator not included

Treated CLL pathway recap



Id ± R - idelalisib ± rituximab; VenR – venetoclax plus rituximab

Issue 1: Restricted comparators

Background

- No comparative evidence presented for acalabrutinib vs VenR in R/R population
- Company does not consider VenR as a commonly used treatment
- And consider ibrutinib as established treatment for R/R CLL

ERG comments

- Clinical and cost effectiveness of acalabrutinib vs VenR for R/R patients is unknown
- Agree that a proportion will receive VenR for R/R
- VenR is likely to cost less than acalabrutinib in the R/R setting
- But, company's cost minimisation analysis for R/R only includes ibrutinib as a comparator

Technical team judgement

- It is likely that VenR is used for some people at 2nd-line
- It is unclear if evidence is available for comparison with VenR for the R/R population
- Costs are not presented in the economic analysis for this comparison
- The results of the analysis are only applicable where you would otherwise use ibrutinib

Is venetoclax plus rituximab a relevant comparator for R/R CLL?

Would any positive recommendation need to be restricted to people for whom ibrutinib would otherwise be used?

Additional areas of uncertainty (1)

Issue	Why issue is important	Impact on ICER
Relative dose intensity (RDI)	• Company originally assumed RDI of 100% for all drug treatments • However, RDI was not 100% in any study • Therefore comparator drug costs overestimated • In updated company base case, agree to use mean RDI from trials	Reduces ICER
Drug wastage	• Company models do not include drug wastage costs • Clinical advisors suggested that, on average, wastage for oral treatments might be around half a pack per patient • In updated company base case, agree with ERG on drug wastage costs	Increases ICER

Additional areas of uncertainty (2)

ERG correction of errors in company's models

Error	Why issue is important	Impact on ICER
Application of half-cycle correction	• Company's approach double-counts QALYs and costs in the first model cycle	Correcting the error reduces ICER
Outdated NHS reference costs	• Company's model uses unit costs sourced from NHS Reference Costs 2017/18. Newer tariff is available	Correcting the error reduces ICER
Estimation of general population mortality risk	• Company's models are based on older UK life tables (2015 to 2017) • Applied a constant proportionate split for men and women	Correcting the error increases ICER
Application of second-line treatment costs	• See issue 4 • Applied to all who progress and survive an additional 14 model cycles	Correcting the error increases ICER

Equalities and innovation

- The company did not identify any equality considerations
- Two patient experts highlighted that acalabrutinib should be available for all groups not just those unsuitable for FCR/BR. However, the company have not presented evidence for a population who are fit and suitable for FCR/BR (see issue 1).

- The company considers the drug to be innovative:
  - significant unmet need in first-line CLL
  - improved safety/tolerability profile
  - step-change in treatment pathway
- However, the technical team considers that all relevant benefits associated with the drug are adequately captured in the model

Key issues

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Utilities	8	Progression-free utility [redacted] higher than general population	ERG's utility of 0.78 is more plausible
MAIC	2 & 9	Assume clinical equivalence of acalabrutinib & ibrutinib	No comparative evidence of acalabrutinib vs ibrutinib in high-risk
Comparator	1	2nd line VenR not included	VenR not a comparator in cost-minimisation analysis

Untreated CLL

Untreated high-risk CLL

Treated R/R CLL

Resolved in updated company base case

For discussion: unknown ICER impact

For discussion: large ICER impact