Supplement

Phase I/II based early economic evaluation of acalabrutinib for relapsed chronic lymphocytic leukemia

Rick A Vreman[1,2], PharmD; Joost W Geenen[1], PharmD; Anke M Hövels[1], PhD; Wim G Goettsch[1,2], PhD; Hubert GM Leufkens[1], PhD; Maiwenn J Al[3], PhD

1. Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands
2. The National Health Care Institute (ZIN), Diemen, The Netherlands
3. Erasmus School of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, the Netherlands.

Corresponding author
Rick Alexander Vreman, PharmD
Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University
Universiteitsweg 99, 3584 CG Utrecht, The Netherlands
T: +31 6 14661403
E: r.a.vreman@uu.nl

Content

Supplement 1. Survival estimation

For the estimation of the OS and PFS survival curves for ibrutinib, the Hoyle & Henley method to recreate individual patient data was used as described in Hoyle *et al* (1). First, we extracted survival data from the Kaplan-Meier curve reported in Byrd *et al* (2). We can input the number at risk and survival at each time point into the Excel file provided by Hoyle & Henley. This Excel file then approximates data on censoring and event times. Via the supplied R code of Hoyle & Henley we can then fit parametric survival models to the recreated data.
These models include an exponential, Weibull, lognormal and a loglogistic curve. Table 1 shows the intercept and ln(scale) for each of these models.

Table 1: Derived parameters for ibrutinib survival curves.

	Parameter		**Exponential**	**Weibull**	**Log normal**	**Log-logistic**
Ibrutinib						
	PFS	Intercept	4.096	4.307	3.929	3.830
		Ln(scale)		0.198	0.619	0.003
	OS	Intercept	4.599	5.032	4.492	4.385
		Ln(scale)		0.263	0.634	0.001

With these data, we can calculate survival at each time point, thus also allowing for extrapolation beyond the observed data. The relative goodness-of-fit for each curve is expressed in the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), where lower values indicate better fit. Table 2 shows the AIC and BIC for the plotted ibrutinib curves, showing that for PFS the lognormal distribution shows the best fit to the KM curve, whereas for OS this is the Weibull distribution.

Table 2: AIC and BIC for extrapolated ibrutinib curves.

		Exponential	**Weibull**	**Lognormal**	**Loglogistic**
PFS	AIC	316.7630	315.0908	313.0206	315.0640
	BIC	321.2884	319.6161	317.5460	319.5893
OS	AIC	217.7135	215.8702	216.0610	217.7807
	BIC	222.1525	220.3092	220.5000	222.2198

For acalabrutinib, survival was extracted from the phase I/II study. It showed a Kaplan-Meier curve for progression free survival (PFS) and the text described overall survival (OS) (one person died during follow-up, at 13 months) (3). According to Hoyle & Henley, survival at different time points was extracted. The data on time points for events and censoring as output of the Hoyle & Henley method were then inputted into SPSS and a Cox regression was performed for acalabrutinib OS and PFS in comparison to ibrutinib OS and PFS.
The outcomes of the Cox regression are presented in table 3 and 4.

Table 3: SPSS results for the Cox regression on PFS between acalabrutinib and ibrutinib.

PFS								
	B	SE	Wald	df	Sig.	Exp(B)	95,0% CI for Exp(B)	
							Lower	Upper
Treatment	-0.735	0.374	3.865	1	0.049	0.479	0.230	0.998

Table 4: SPSS results for the Cox regression on OS between acalabrutinib and ibrutinib.

OS								
	B	SE	Wald	df	Sig.	Exp(B)	95,0% CI for Exp(B)	
							Lower	Upper
Treatment	-0.939	0.519	3.278	1	0.070	0.391	0.141	1.081

Hazard ratios (HR's) of 0.479 (95% confidence interval (CI) 0.230 – 0.998) and 0.391 (95% CI 0.141 – 1.081) were found for PFS and OS, respectively. Note that this is not a valid final measure of PFS and OS, as data are preliminary and incomparable. Therefore, we only use these estimates to define a range, with the maximum benefit representing these HR's and the minimum benefit representing no effect (HR = 1.00).

These hazard ratios were then applied to find the survival for acalabrutinib simply by calculating $S(t)_{acalabrutinib} = S(t)_{ibrutinib}^{\wedge}$(Hazard Ratio)

The survival curves that were derived via these methods are provided in figure 1 and 2.

Figure 1: Plotted survival curves for acalabrutinib and ibrutinib progression-free survival (PFS). The lower curves are for ibrutinib.

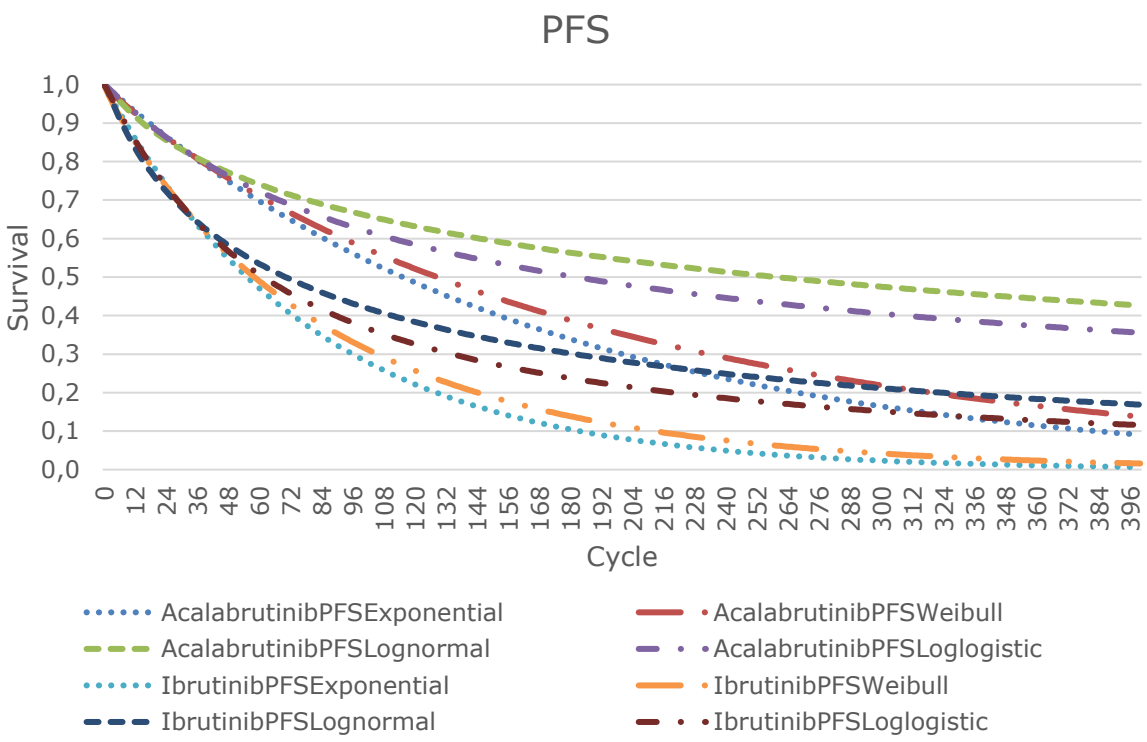
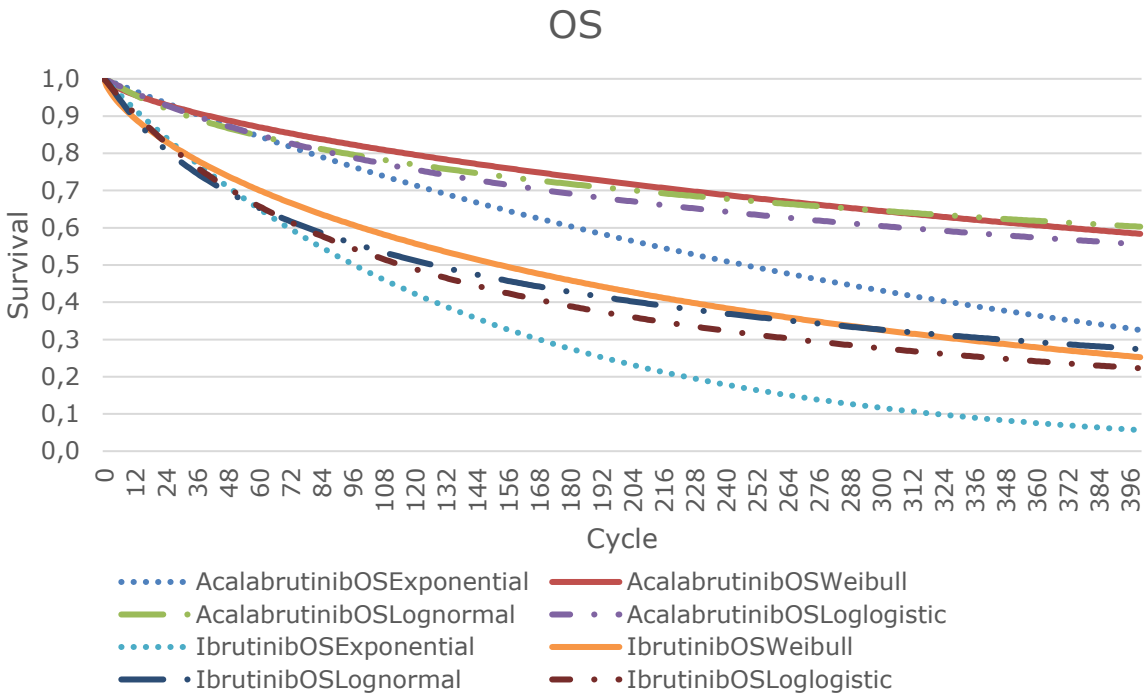


Figure 2: : Plotted survival curves for acalabrutinib and ibrutinib overall survival (OS). The lower curves are for ibrutinib.



To select a curve, AIC and BIC criteria were assessed and physiological plausibility was investigated. Looking at AIC and BIC, for PFS the lognormal distribution shows the best fit while for OS this is the Weibull distribution, though the differences between the goodness-of-fit of the curves is relatively small. When looking at the extrapolated part of the curve, beyond the observed data, the exponential curves show the best fit, because they have the least people surviving after 30 years (400 cycles). This is physiologically the most plausible scenario. Considering that the exponential curves were also used in the ibrutinib submission, we are confident in selecting these for further analysis (4).

For easy sensitivity and scenario analysis, acalabrutinib intercept values were calculated for the exponential curve from the survival found by applying the Hazard Ratio. The found intercept values were 5.045 for PFS and 5.808 for OS.
Figures 3-6 show all the curves, including the published curves, for acalabrutinib and ibrutinib.
It is clear that the tail of the curves for acalabrutinib OS do not match the observed data very well, however, the observed curve is based on very limited data, and hence, the parametric curves may still be reasonable estimates given the overall uncertainty about OS.

Figure 3: Curves for acalabrutinib progression-free survival (PFS), including the published curve.

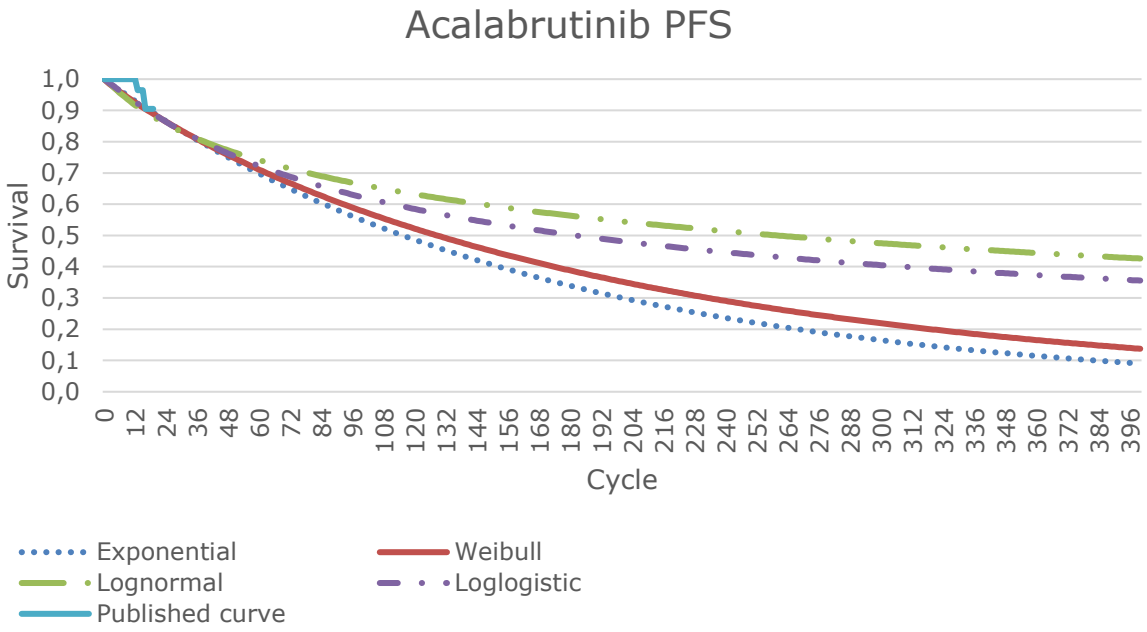


Figure 4: Curves for acalabrutinib overall survival (OS), including a curve based on published data.

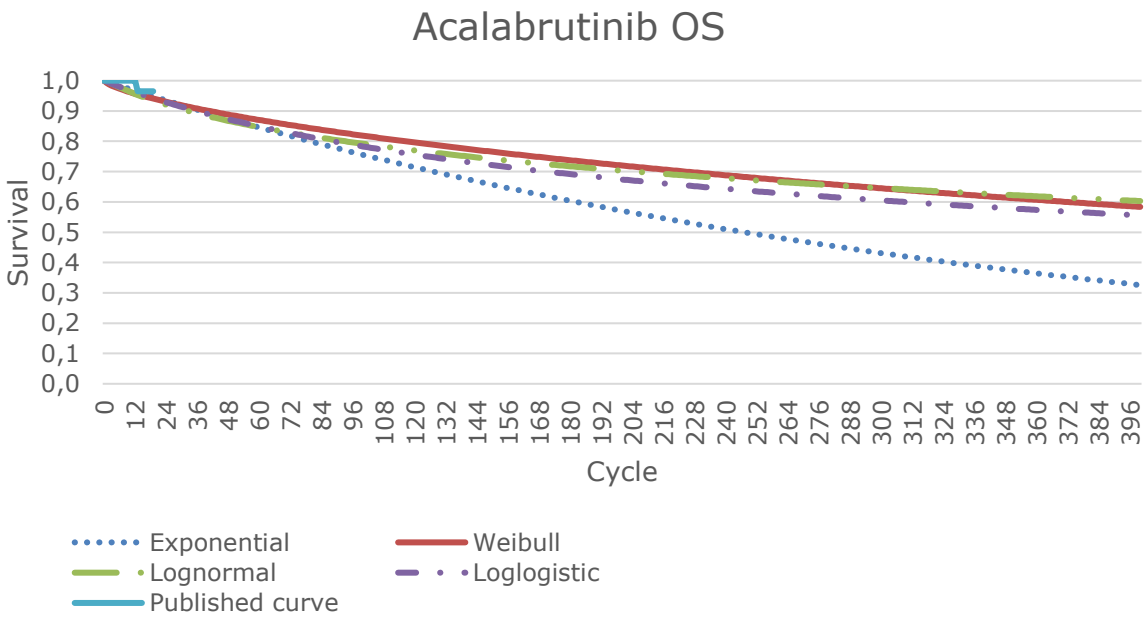


Figure 5: Curves for ibrutinib progression-free survival (PFS), including the published curve.

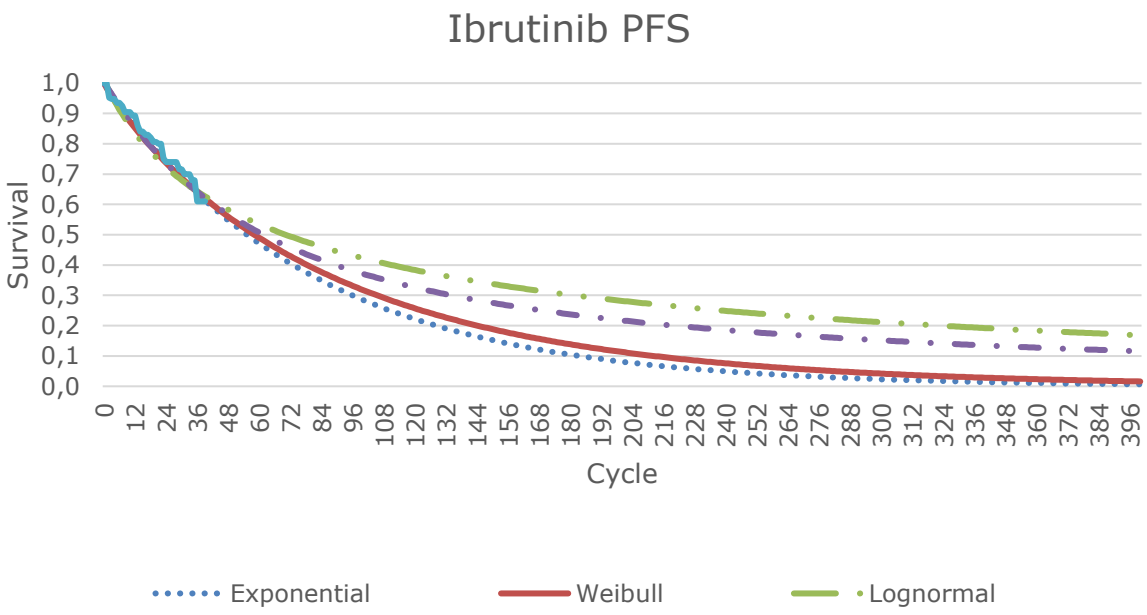
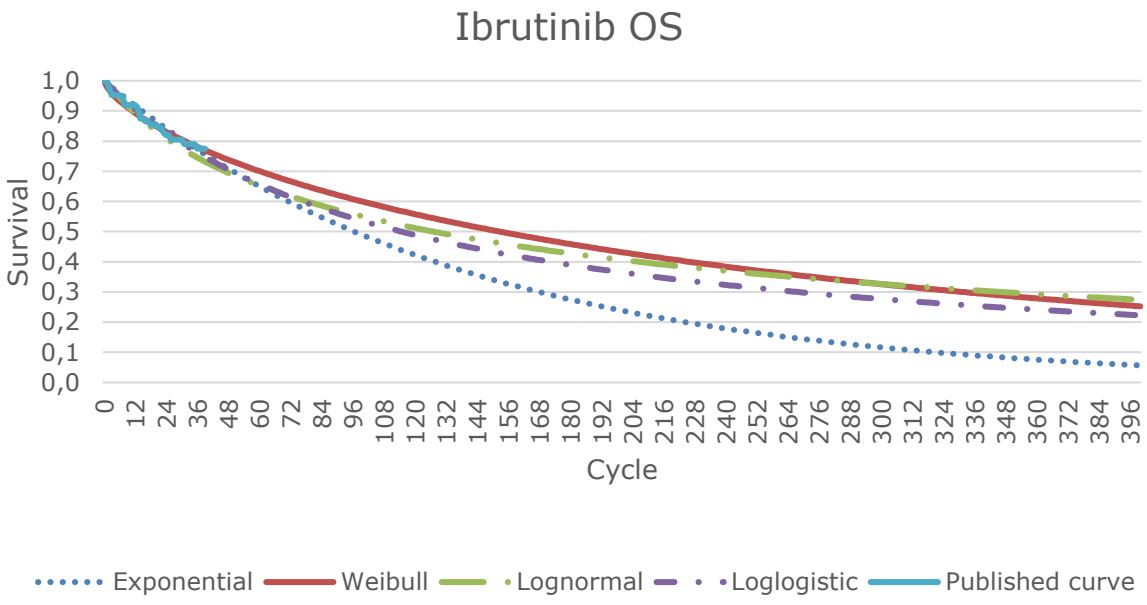


Figure 6: Curves for ibrutinib overall survival (OS), including the published curve.



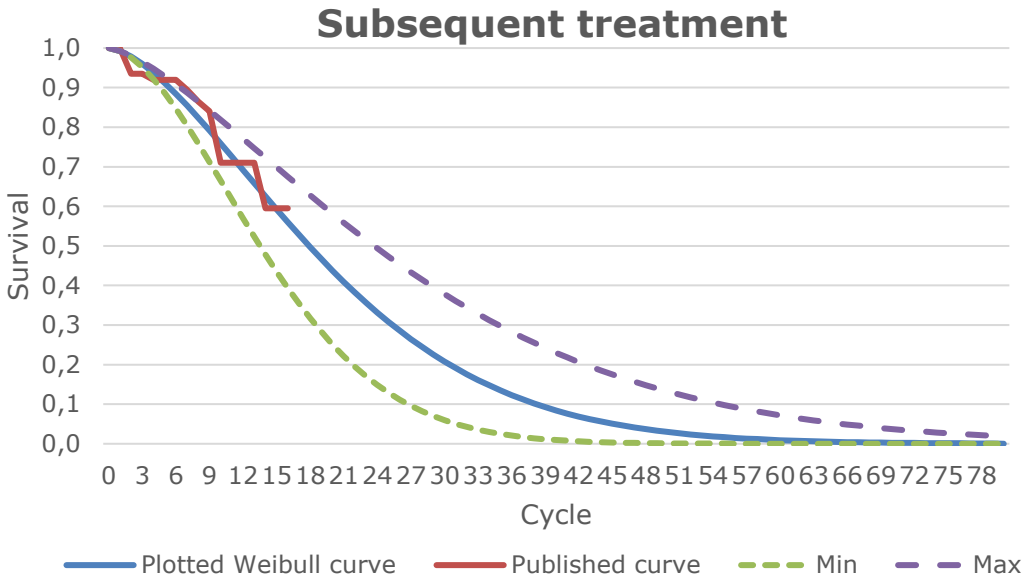
For the subsequent treatment, a similar approach was followed. Via the Hoyle & Henley method, a Weibull curve was estimates from published data for survival on rituximab + idelalisib (5). The parameters for this curve

are presented in table 5 and the curve is presented in figure 7. Figure 7 includes two curves for sensitivity analysis where both the intercept and the scale are varied by 10%.

Table 5: Parameters for the Weibull curve of subsequent treatment.

Subsequent treatment			
	Base Case	Minimum	Maximum
Intercept	3.05	2.74	3.35
Ln(scale)	-0.46	-0.56	-0.36

Figure 7: Base case and minimum and maximum curves for subsequent treatment with rituximab + idelalisib.



Supplement 2. Drug treatment specifications and costs calculations

Ibrutinib is administered as 420mg/day (3 capsules) until disease progression or until no longer tolerated by the patient. Acalabrutinib is given as 200 mg/day (2 capsules). Subsequent treatment exists of rituximab and idelalisib. Rituximab is given during six cycles of four weeks according to the NICE guideline for CLL, with an initial dose of 375 mg/m^2 and subsequent doses of 500 mg/m^2. Idelalisib is administered until disease progression or death in a dose of 150 mg twice daily (6). Dosing intensity for all chronic treatments is assumed equal at 94.8%. No correction was applied for rituximab.

An overview of treatment costs is provided in table 6. Acalabrutinib unit costs are assumed equal to ibrutinib in the base case and calculated by multiplying the unit costs of ibrutinib treatment to the use per day and dividing this by the use of acalabrutinib units per day. Drug costs come from the British National Formulary (4,7).

Table 6: Unit costs and sizes for modeled treatments.

Drug	**Dose/concentration**	**Tablet or vial size**	**Costs per unit**	**Use per day**
Acalabrutinib	100 mg	1	£ 76.65	2
Ibrutinib	140 mg	1	£ 51.10	3
Idelalisib	150 mg	1	£ 51.91	2
Rituximab	10 mg/ml	10	£ 174.63	N/A
Rituximab	50 mg/ml	10	£ 873.15	N/A

Costs per cycle for acalabrutinib and ibrutinib is calculated by multiplying the unit costs with the unit size, the use per day, the dosing intensity and the days per cycle. This gives a treatment cycle costs of £ 4069.20 for both treatments.

For idelalisib and rituximab, the calculations are a bit more complicated. Idelalisib costs per day are calculated by multiplying use per day with costs per unit and the dose intensity, giving a cost of £ 98.43 per day. For the first 6 cycles (one cycle in the model is exactly four weeks, thus this matches the treatment with rituximab), rituximab is added to idelalisib. Rituximab costs are calculated by multiplying the square meters body surface (1.9m^2) with the indicated dose per m^2 (4). This is 375 mg in the first administration and 500 mg in the subsequent five administrations. For each dose, administration costs are added. These are found in the UK National Schedule of Reference costs 2015-2016 and include £ 383.13 for the 'Delivery of Complex Chemotherapy, Including Prolonged Infusional Treatment, at First Attendance and £ 328.10 for the 'Delivery of Subsequent Elements of a Chemotherapy Cycle, for first and subsequent administrations, respectively (8). We assumed no vial sharing.

For example, the first dose includes 375*1.9 = 712.50 mg. This means one vial of 500 mg and 3 vials of 100 mg are needed. The total costs for those vials is £ 1397.04. Including administration costs of £ 383.13 gives a total costs of £ 1780.17.

This was repeated for all six treatment cycles giving a total cost of £ 12,152.17. Including the treatment of idelalisib means that average costs for each cycle during the first six cycles totaled £ 4,781.29. Starting at cycle 7, only costs for idelalisib are included, totaling £2,755.93 per cycle. In sensitivity analyses, the variation of the costs by -80% to +30% was only applied to treatment costs, not administration costs.

Supplement 3. Resource use and state costs

Resource use was derived directly from the ibrutinib submission. The submission included an overview of the use of certain types of resources per disease state and response rate, as specified in table 7. These resources were determined through an expert panel by the manufacturer and were accepted by NICE (4).

Table 7: Resource unit use as defined by an expert panel in the ibrutinib submission. PFS-CR = progression free survival, complete response; PFS-PR = partial response; PFS-SD = stable disease; PPS-ST = post progression state, subsequent treatment; PPS-BSC = best supportive care.

Resources	PFS-CR	PFS-PR	PFS-SD	PPS-ST	PPS-BSC
Full blood count	2	4	4	4	4
LDH	2	2.26	2	2	0
Lymphocyte counts	3.5	7	3.5	3.2	0
Chest X-Ray	0	1	2	2	0
Bone marrow exam	0	1	1	0	0
Hematologist visit	2.26	3	4.5	4	4.9
Inpatient visit	0.66	2	2	2	1
Nurse Home visit	1.5	2.64	3	2	4
Full blood transfusion	0	1	2	2	2
Platelet transfusion	0	1	0	0	0
Biopsy	0	0	2	2	0

Costs per resource unit were informed by the UK National Schedule of Reference Costs 2015-2016 (8). The exact terminology for which the costs were applied is specified in table 8.

Table 8: Overview of costs and their sources within the National Schedule for Reference Costs.

Resources	Code	Source	Costs (£)
Full blood count	DAPS05	Other Currencies Data	3.10
LDH	DAPS04	DIRECTLY ACCESSED PATHOLOGY SERVICES	1.18
Lymphocyte counts	DAPS05	Other Currencies Data	3.10
Chest X-Ray	DAPS02	DIRECTLY ACCESSED PATHOLOGY SERVICES	30.77
Bone marrow exam	SA33Z	OUTPATIENT PROCEDURES	266.83
Hematologist visit	WF01A	Outpatient CL - Clinical Hematologist - Non-Admitted Face to Face Attendance, Follow-Up	166.03
Inpatient visit	WH53B	Follow-Up Examination for Other Conditions, without Interventions	763.42
Nurse Home visit	NURS	COMMUNITY HEALTH SERVICES - District Nurse, Adult, Face to face - Nursing	37.98
Full blood transfusion	SA13A	OUTPATIENT PROCEDURES	225.11
Platelet transfusion	SA13A	OUTPATIENT PROCEDURES	225.11
Biopsy	SA33Z	ELECTIVE INPATIENT	1078.29

To calculate total costs per response and per disease state, the units were multiplied by the price, and then summed. These annual costs were then corrected for cycle duration, as is presented in table 9.

Table 9: Resource costs as calculated by multiplying unit costs with unit use. PFS-CR = progression free survival, complete response; PFS-PR = partial response; PFS-SD = stable disease; PPS-ST = post progression state, subsequent treatment; PPS-BSC = best supportive care.

Resources	PFS-CR (£)	PFS-PR (£)	PFS-SD (£)	PPS-ST (£)	PPS-BSC (£)
Full blood count	6.20	12.41	12.41	12.41	12.41
LDH	2.36	2.67	2.36	2.36	0.00
Lymphocyte counts	10.86	21.72	10.86	9.93	0.00
Chest X-Ray	0.00	30.77	61.55	61.55	0.00
Bone marrow exam	0.00	266.83	266.83	0.00	0.00
Haematologist visit	375.23	498.09	747.13	664.12	813.55
Inpatient visit	503.86	1526.85	1526.85	1526.85	763.42
Nurse Home visit	56.97	100.26	113.93	75.95	151.91
Full blood transfusion	0.00	225.11	450.22	450.22	450.22
Platelet transfusion	0.00	225.11	0.00	0.00	0.00
Biopsy	0.00	0.00	2156.58	2156.58	0.00
Annual costs	955.47	2909.81	5348.71	4959.96	2191.51
Cycle costs	73.25	223.07	410.03	380.23	168.00

To calculate resource costs per cycle per treatment, these costs per disease and response state were multiplied by treatment response known from literature. Treatment response for ibrutinib was reported to be 84% PR, 6% CR and 10% SD. For acalabrutinib, 95% had PR and 5% had SD (2,3,9). Resource costs per disease and response state are presented in table 10.

Table 10: Resource costs per disease state for acalabrutinib and ibrutinib.

Resources	**PFS-CR (£)**	**PFS-PR (£)**	**PFS-SD (£)**	**PFS total (£)**	**PPS-ST (£)**	**PPS-BSC (£)**
Acalabrutinib	0.00	211.91	20.50	232.41	380.23	168.00
Ibrutinib	4.39	187.37	41.00	232.77	380.23	168.00

Other costs included are costs for adverse events and costs for death. Both are inflicted once, in the cycle they happen. For adverse events this is assumed to be the first cycle of the model. Costs for the death state are inflicted once in the cycle (when death happens), and equal the per patient costs of health care utilization (£ 2,900.98) during the last 30 days of life for patients of age 65+ with any cancer reported by Bekelman *et al* (10). Adverse event costs are calculated by multiplying adverse event incidence with their costs. Grade 3 and 4 adverse event incidences are specified in table 11 and were based on clinical trials for ibrutinib and acalabrutinib and on the ibrutinib submission to NICE (2–4,9). Adverse event average costs are specified in table 12. For each adverse event, multiple costs are provided in the National Schedule for Reference Costs (8), depending on disease severity or score. Per adverse event, the average is calculated by multiplying the incidence of each score of the adverse event with the costs for that type, as is shown in table 13. The codes in table 12 indicate all severity types that were included per adverse event.

Table 11: Incidences for adverse events for ibrutinib and acalabrutinib.

Adverse event	**Ibrutinib incidence**	**Acalabrutinib incidence**
Anemia	5.60%	5.60%
Atrial fibrillation	6.00%	0.00%
Diarrhea	4.60%	2.00%
Hypertension	6.20%	7.00%
Neutropenia	18.50%	15.00%
Pneumonia	10.80%	10.80%
Sepsis	1.50%	1.50%
Thrombocytopenia	5.60%	0.00%

Table 12: Overview of costs for adverse events and their sources within the National Schedule for Reference Costs.

Adverse event	**Code**	**Name**	**Average costs (£)**
Anemia	SA03G-H	Hemolytic Anemia	1,129.17
Atrial fibrillation	EB07A-E	Arrhythmia or Conduction Disorders	996.67
Diarrhea	FZ91A-M	Non-Malignant Gastrointestinal Tract Disorders	1,492.69
Hypertension	EB04Z	Hypertension	729.87
Neutropenia	SA01G-K	Acquired Pure Red Cell Aplasia or Other Aplastic Anemia	1,498.86
Pneumonia	DZ11K-V	Lobar, Atypical or Viral Pneumonia, with Multiple Interventions	1,904.86
Sepsis	WJ06A-J	Sepsis	2,163.51
Thrombocytopenia	SA12G-K	Thrombocytopenia	636.19

The costs for adverse events per treatment are then calculated by multiplying the average costs with the incidence and summing those, as is shown in table 13.

Table 13: Total adverse event costs per treatment as is calculated by multiplying the incidence with the costs per adverse event.

Adverse event	Ibru inc	Acal inc	Ibru costs (£)	Acal costs (£)
Anemia	5.60%	5.60%	63.23	63.23
Atrial fibrillation	6.00%	0.00%	59.80	0
Diarrhea	4.60%	2.00%	68.66	29.85
Hypertension	6.20%	7.00%	45.25	51.09
Neutropenia	18.50%	15.00%	277.29	224.83
Pneumonia	10.80%	10.80%	205.72	205.72
Sepsis	1.50%	1.50%	32.45	32.45
Thrombocytopenia	5.60%	0.00%	35.63	0
		Total	788.04	607.18

Supplement 4. Calculations for utility decrement

The utility decrement associated with adverse events is calculated as the utility lost per adverse event as reported in the ibrutinib submission times the incidence of that adverse event, as shown in table 14 (4). Utility decrement for each treatment is inflicted once in the first cycle of the model.

Table 14: Incidences and utility decrements for included adverse events.

Adverse event	Ibru	Acal	Utility decrement	Ibru product	Acal product
Anemia	5.6%	5.6%	0.088	0.0049	0.0049
Atrial fibrillation	6.0%	0.0%	0.195	0.0117	0.0000
Diarrhea	4.6%	2.0%	0.088	0.0040	0.0018
Hypertension	6.2%	7.0%	0.088	0.0055	0.0062
Neutropenia	18.5%	15.0%	0.185	0.0342	0.0278
Pneumonia	10.8%	10.8%	0.195	0.0211	0.0211
Sepsis	1.5%	1.5%	0.195	0.0029	0.0029
Thrombocytopenia	5.6%	0.0%	0.123	0.0069	0.0000
			Total	0.0912	0.0646
				Difference	0.0266

Supplement 5. Calculations for the relative impact of each parameter value.

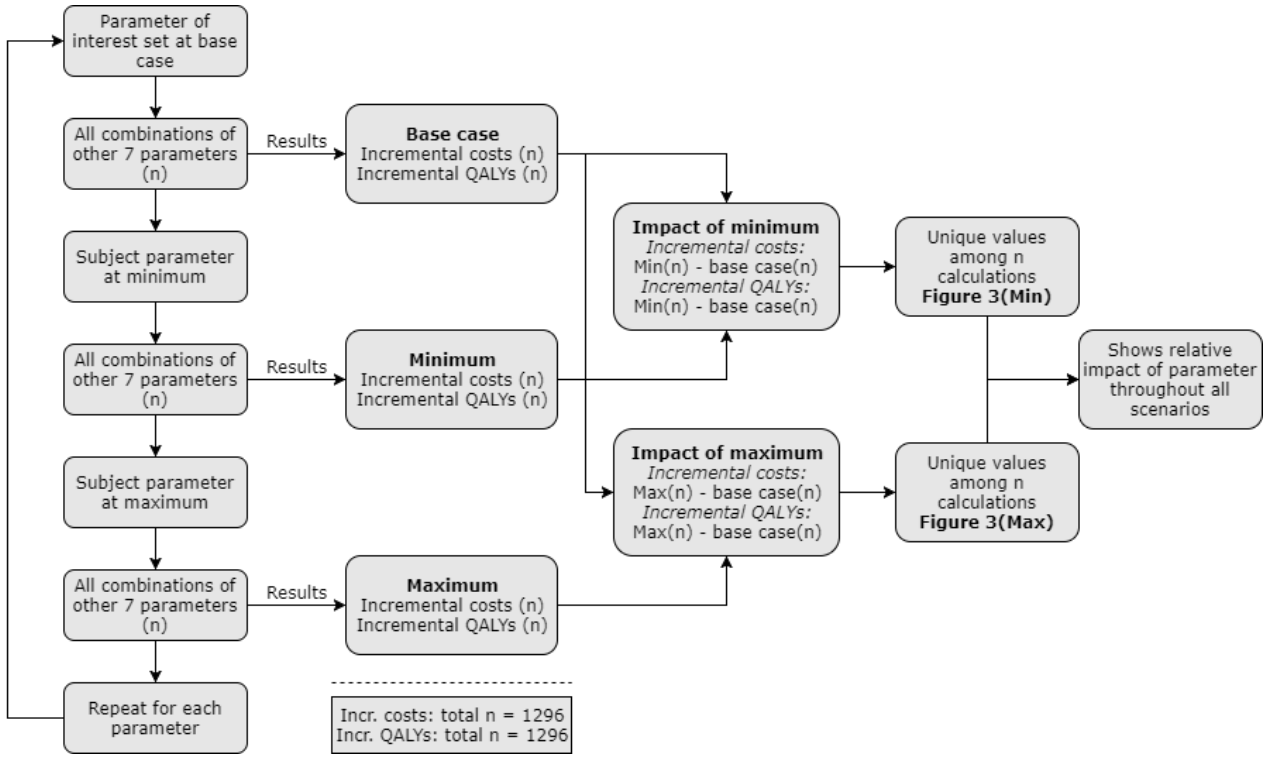


Figure 8: Calculation for relative impact of each parameter value.

References

1. Hoyle MW, Henley W. Improved curve fits to summary survival data: application to economic evaluation of health technologies. BMC Med Res Methodol. 2011 Oct 10;11:139.

2. Byrd JC, Brown JR, O'Brien S, Barrientos JC, Kay NE, Reddy NM, et al. Ibrutinib versus Ofatumumab in Previously Treated Chronic Lymphoid Leukemia. N Engl J Med. 2014 Jul 17;371(3):213–23.

3. Byrd JC, Harrington B, O'Brien S, Jones JA, Schuh A, Devereux S, et al. Acalabrutinib (ACP-196) in Relapsed Chronic Lymphocytic Leukemia. N Engl J Med. 2016 Jan 28;374(4):323–32.

4. National Institute for Health and Care Excellence. Ibrutinib final appraisal determination. Committee papers. United Kingdom. 2017.

5. Furman RR, Sharman JP, Coutre SE, Cheson BD, Pagel JM, Hillmen P, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. N Engl J Med. 2014 Mar 13;370(11):997–1007.

6. National Institute for Health and Care Excellence. Blood and bone marrow cancers pathway. 2017. Accessed at https://pathways.nice.org.uk/pathways/blood-and-bone-marrow-cancers/leukaemia#path=view%3A/pathways/blood-and-bone-marrow-cancers/lymphoid-leukaemia.xml&content=view-node%3Anodes-treatment-for-relapsed-or-refractory-chronic-lymphocytic-leukaemia on Jul 25, 2017.

7. British Medical Association and the Royal Pharmaceutical Society of Great Britain. The British National Formulary (BNF). Accessed at: https://www.medicinescomplete.com/mc/login.htm on Jul 25 2017. London, UK.

8. Department of Health. National Health Service. Reference Cost Collection: National Schedule of Reference Costs - Year 2015-16 - NHS trust and NHS foundation trusts. United Kingdom.

9. Byrd JC, Furman RR, Coutre SE, Burger JA, Blum KA, Coleman M, et al. Three-year follow-up of treatment-naïve and previously treated patients with CLL and SLL receiving single-agent ibrutinib. Blood. 2015 Apr 16;125(16):2497–506.

10. Bekelman JE, Halpern SD, Blankart CR, Bynum JP, Cohen J, Fowler R, et al. Comparison of Site of Death, Health Care Utilization, and Hospital Expenditures for Patients Dying With Cancer in 7 Developed Countries. JAMA. 2016 Jan 19;315(3):272–83.