

SUPPLEMENTARY INFORMATION

Cost-Effectiveness of First-Line Therapies for Treatment-Naïve Chronic Lymphocytic Leukemia in South Africa

Clinical Drug Investigation

Rochelle Woudberg, Edina Sinanovic

Health Economics Unit, School of Public Health, University of Cape Town, Cape Town, South Africa

Correspondence author:

Rochelle Woudberg

Email: SMTROC001@myuct.ac.za

Supplementary Tables and Figures

Supplementary Table S1 Baseline Patient Characteristics from Clinical Trials

Intervention	Clinical Trial (NCT #)	N	Median Age	Males (%)	Advanced disease (% Rai 3/4 / Binet C stage)	% High-Risk Genomic features	Reference
<i>Treatment-naïve CLL patients</i>							
FCR	CLL-8 (NCT00281918)	408	61 years	74%	31%	63%	(1)
BR	ALLIANCE A041202 (NCT01886872)	183	72 years	65%	54%	58%	(2)
ClbO	iLLUMINATE (NCT02264574)	116	63 years	68%	51%	65%	(3)
VenO	CLL14 (NCT02242942)	216	72 years	67.6%	43.1%	60.5%	(4)
Ibrutinib	RESONATE-2 (NCT01722487)	136	73 years	64.7%	34.6%	53%	(5)

*NOTE: High-risk genomic features (i.e., TP53 mutation, del[11q], and/or unmutated IGHV))

Abbreviations: *BR* Bendamustine-plus-rituximab; *ClbO* Chlorambucil-plus-obinutuzumab; *FCR* Fludarabine, cyclophosphamide, and rituximab; *VenO* Venetoclax-plus-obinutuzumab.

Supplementary Table S2 Drug dosing and routes of administration

Regimen	Drug	Admin	Dosing Schedule
FCR	fludarabine	IV	25 mg/m ² D1-D3, C1-C6 for a total of 18 doses
	cyclophosphamide (Endoxan ®)	IV	250 mg/m ² D1-D3, C1-C6 for a total of 18 doses
	rituximab (Ristova ®)	IV	375 mg/m ² D1 C1, 500 mg/m ² D1 C2-C6 for a total of 6 doses
BR	bendamustine (Baximo)	IV	90 mg/ m ² D1-D2, C1-C6 for a total of 12 doses
	rituximab (Ristova ®)	IV	375 mg/ m ² D1 C1, 500 mg/m ² D1 C2-C6 for a total of 6 doses
ClbO	chlorambucil (Leukeran ®)	Oral	0.5 mg/ kg D1 & D15, C1-C6 for a total of 12 doses
	obinutuzumab (Gazyva ®)	IV	100mg D1 C1, 900mg D2 C1, 1000mg D8 & D15 C1, 1000mg D1 & D15 C2-6 for a total of 6 doses
VenO	venetoclax (Venclexta ®)	Oral	Daily dose, 20 mg week 1, 50 mg week 2, 100mg week 3, 200 mg week 4, 400 mg week 5 and 400 mg from week 6 until disease progression or for 12-month treatment duration
	obinutuzumab (Gazyva ®)	IV	100mg D1 C1, 900mg D2 C1, 1000mg D8 & D15 C1, 1000mg D1 & D15 C2-6 for a total of 6 doses
Ibrutinib	ibrutinib (Imbruvica ®)	Oral	Daily dose of 420mg until disease progression

Abbreviations: *BR* Bendamustine-plus-rituximab; *ClbO* Chlorambucil-plus-obinutuzumab; *Cx* cycle; *Dx* day; *FCR* Fludarabine, cyclophosphamide, and rituximab; *IV* intravenous; *VenO* Venetoclax-plus-obinutuzumab.

Supplementary Table S3 Adverse event costs in the cost-effectiveness model

Adverse event	Incidence rate					Cost (\$) per AE event
	ClbO	FCR	BR	VenO	Ibrutinib	
Anaemia	8%	5%	12%	53%	2.2%	597.36
Neutropenia	46%	34%	40%	8%	11%	134.88
Febrile Neutropenia	6%	0%	7%	5.2%	0%	534.14
Pneumonia	4%	0%	0%	4.2%	7%	496.08
Sepsis / Infection	0%	25%	3%	17.5%	3%	495.15
Tumour Lysis Syndrome	3%	1%	0%	3%	0%	285.14

Abbreviations: *AE* Adverse events; *BR* bendamustine and rituximab; *ClbO* chlorambucil in combination with obinutuzumab; *FCR* fludarabine, cyclophosphamide and rituximab; *VenO* Venetoclax in combination with obinutuzumab.

Supplementary Table S4 Comparison of survival models extrapolation

Treatment	Distribution	Progression-free survival		Distribution	Overall survival	
		AIC	BIC		AIC	BIC
FCR	Exponential	228.45	238.90	Exponential	210.62	217.14
	Weibull	226.65	233.51	Weibull	211.95	218.72
	Log-normal	226.56	233.42	Log-normal	210.74	217.69
	Log-logistic	228.14	235.11	Log-logistic	211.79	219.53
	Gompertz	227.69	234.71	Gompertz	211.38	222.58
	Gen Gamma	228.20	238.34	Gen Gamma	212.09	223.26
BR	Exponential	372.92	384.88	Exponential	262.32	275.72
	Weibull	373.80	383.24	Weibull	266.41	273.81
	Log-normal	371.75	382.19	Log-normal	273.02	280.42
	Log-logistic	372.79	383.73	Log-logistic	270.44	276.07
	Gompertz	373.93	384.98	Gompertz	271.33	277.42
	Gen Gamma	374.07	385.27	Gen Gamma	272.48	279.65
ClbO	Exponential	221.07	230.04	Exponential	132.61	144.57
	Weibull	227.91	232.35	Weibull	134.66	145.60
	Log-normal	227.90	231.24	Log-normal	135.61	145.05
	Log-logistic	224.59	232.93	Log-logistic	136.37	149.81
	Gompertz	223.60	232.68	Gompertz	136.06	148.14
	Gen Gamma	226.81	233.36	Gen Gamma	137.42	149.62
VenO	Exponential	459.64	467.60	Exponential	254.61	264.57
	Weibull	458.74	469.30	Weibull	255.73	265.17
	Log-normal	449.25	451.81	Log-normal	254.79	268.14
	Log-logistic	460.86	470.42	Log-logistic	259.46	269.90
	Gompertz	459.23	469.68	Gompertz	258.03	268.42
	Gen Gamma	460.97	470.77	Gen Gamma	260.43	269.94
Ibrutinib	Exponential	438.77	455.65	Exponential	225.29	233.56
	Weibull	440.18	446.20	Weibull	226.84	234.61
	Log-normal	438.15	445.07	Log-normal	226.65	233.59
	Log-logistic	439.23	445.12	Log-logistic	228.14	235.11
	Gompertz	440.19	452.38	Gompertz	227.57	234.69
	Gen Gamma	441.69	455.63	Gen Gamma	228.15	235.06

Abbreviations: *AIC* Akaike information criteria; *BIC* Bayesian information criteria; *BR* bendamustine and rituximab; *ClbO* chlorambucil in combination with obinutuzumab; *FCR* fludarabine, cyclophosphamide and rituximab; *OS* overall survival; *PFS* progression-free survival; *VenO* Venetoclax in combination with obinutuzumab.

References

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