ORIGINAL RESEARCH ARTICLE

Cost Effectiveness of Molecular Diagnostic Testing Algorithms for the Treatment Selection of Frontline Ibrutinib for Patients with Chronic Lymphocytic Leukemia in Australia

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Abstract

Background Clinical indications for ibrutinib reimbursement in Australia should consider the inclusion of patients with chronic lymphocytic leukemia (CLL) harboring prognostically unfavorable *TP53/IGHV* genomic aberrations. This study assessed the cost effectiveness of five first-line treatment strategies in CLL for young (aged ≤ 65 years), fit patients without significant comorbidities: (1) no testing (fludarabine, cyclophosphamide and rituximab [FCR] for all), (2) test for del(17p) only, (3) test for *TP53* gene mutation status, (4) test for *TP53* and *IGHV* gene mutation status and (5) no testing (ibrutinib for all).

Method A decision analytic model (decision tree and partitioned survival model) was developed from the Australian healthcare system perspective with a lifetime horizon. Comparative treatment effects were estimated from indirect treatment comparisons and survival analysis using several studies. Costs, utility and adverse events were derived from public literature sources. Deterministic and probabilistic sensitivity analyses explored the impact of modeling uncertainties on outcomes.

Results Strategy 1 was associated with 5.69 quality-adjusted life-years (QALYs) and cost 458,836 Australian dollars (AUD). All other strategies had greater effectiveness but were more expensive than Strategy 1. At the willingness-to-pay (WTP) threshold of 100,000 AUD per QALY gained, Strategy 1 was most cost effective with an estimated probability of 68.8%. Strategy 4 was cost effective between thresholds 155,000–432,300 AUD per QALY gained, and Strategy 5 >432,300 AUD per QALY gained.

Conclusion Population targeting using mutation testing for *TP53* and *IGHV* when performed with del(17p) testing specifically in the context of frontline ibrutinib choice does not make a cost-ineffective treatment into a cost-effective treatment.

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Key Points for Decision Makers

A health economic model was developed to project clinical and economic outcomes of *TP53* and *IGHV* gene mutation testing for the treatment selection of chronic lymphocytic leukemia (CLL) for young (aged ≤65 years), fit patients without significant comorbidities.

Testing for *TP53* and *IGHV* gene mutation status improved health outcomes for patients with CLL through improved treatment targeting.

Testing for *TP53* and *IGHV* gene mutation status could be cost effective at a WTP threshold of 155,000 AUD per QALY gained or if per-cycle treatment cost of ibrutinib based on list prices was reduced by 41.8%.

1 Introduction

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in Western countries [1]. Global burden from the disease has increased over the past 30 years and in 2019 there were an estimated 103,467 new cases of CLL with 44,613 CLL-related deaths reported [1]. Clinical course of CLL varies extensively between patients; some are asymptomatic and may not need therapy, while others experience rapidly progressive disease and require early intervention. Conventional systemic multi-agent chemoimmunotherapy (CIT) such as the combination of fludarabine, cyclophosphamide and rituximab (FCR) have historically been the standard first-line treatment for CLL in patients with disease requiring treatment [2].

Deletions in chromosome 17p (del(17p)) and/or mutations of the tumor suppressor p53 (*TP53*) gene (herein collectively referred to as *TP53* aberrations) and unmutated immunoglobulin heavy chain (*IGHV*-U) are strong prognostic factors associated with inferior response rates, early progression and development of refractory disease following CIT [3–8]. The *TP53* aberrations and/or *IGHV*-U confer a high-risk CLL disease, and the clinical predictive value for these biomarkers have been recognized by the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) 2018 guidelines and the European Society for Medical Oncology (ESMO) 2021 guidelines [9, 10]. In these guidelines, testing of *TP53* and *IGHV* mutational status is recommended before treatment to establish the presence of high-risk CLL, which, in turn, will inform clinical treatment of the patients using novel agents beyond CIT.

Ibrutinib was among the first novel agents for CLL to be developed and revolutionized treatment options for patients with high-risk CLL. On March 2016, the US Food and Drug Administration (FDA) approved ibrutinib, an oral, once-daily Bruton's tyrosine kinase (BTK) inhibitor, for first-line CLL treatment [11]. The pivotal phase III RESONATE-2 study demonstrated a survival benefit for single-agent ibrutinib compared with chlorambucil in previously untreated patients with CLL, with prolonged progression-free survival (PFS) (hazard ratio (HR) 0.16; 95% confidence interval [CI] 0.09–0.28; $p < 0.001$) and overall survival (OS) (HR 0.16; 95% CI 0.05–0.56; $p = 0.001$) [12]. Importantly, subgroup analyses from the long-term follow-up data of the RESONATE-2 study support superior survival with ibrutinib for patients with the *TP53* aberrations and *IGHV*-U [13, 14]. Subsequent clinical trials have also shown a significant survival advantage for ibrutinib-based regimens compared with CIT in previously untreated patients, particularly in high-risk CLL [15–17]. Furthermore, the ECOG-ACRIN E1912 trial, which compared ibrutinib with rituximab to FCR, showed a reduced rate of grade ≥ 3 treatment-related adverse events (AEs) in the ibrutinib with rituximab group (73.0%) compared with the FCR group (83.5%) (odds ratio (OR) 0.53; 95% CI 0.32–0.88; $p = 0.0097$) [16].

Since ibrutinib, other second-generation BTK agents (e.g., acalabrutinib with or without obinutuzumab) and oral B-cell lymphoma-2 (BCL2) inhibitors (e.g., venetoclax with obinutuzumab) have also been approved for previously untreated CLL. More treatment choice is afforded where patient preferences, concomitant medications and comorbidities may influence decisions between these targeted therapies until there is further evidence to support an optimal first-line treatment regimen beyond CIT. In light of these considerations, for the CLL patient population of young (aged ≤ 65 years), fit patients without significant comorbidities who have a high-risk molecular profile, ibrutinib is recommended as the preferred choice of first-line therapy (unless contraindicated) for many countries owing to extensive follow-up data for this patient group compared with other novel-based agents [18–20]. Conversely, in the same CLL patient population with a low-risk molecular profile (*TP53* wildtype and mutated immunoglobulin heavy chain (*IGHV*-M)), FCR is still an available treatment option.

Despite the current clinical evidence, the definition of who is eligible for treatment reimbursement of first-line ibrutinib is inconsistent with its clinical use. For instance, the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia recommended reimbursement of first-line ibrutinib in CLL for patients with del(17p) only (as opposed to both deletions and mutations of *TP53*) [21]. By contrast, the National Institute for Health and Care Excellence (NICE) in the UK recommended reimbursement for *TP53* aberrations [22] whereas the Canadian Agency for Drugs and Technologies in Health (CADTH) recommended reimbursement for

those in whom fludarabine-based treatment is inappropriate (which may include *TP53* aberrations and/or *IGHV*-U depending on the country's province) [23]. Not only are the funding policies different from the clinical guidelines, but as highlighted, the policies vary depending on the health system and can lead to a subgroup of high-risk patients without access to effective treatment.

Reimbursement policies concerning ibrutinib in Australia require revision to ensure that patients with CLL have appropriate access to the most effective available treatment. Therefore, in accordance with the clinical guidelines, testing for *TP53* aberrations (including deletions and mutations) alongside *IGHV* mutations should be considered before making treatment decisions for patients with CLL. Health economic evidence is a considerable component of reimbursement decisions. In this respect, cost-effectiveness studies to assess the health benefits and costs of molecular testing for *TP53* and *IGHV* to guide first-line treatment decisions with ibrutinib in CLL compared with current standard of care are useful for decision makers. However, these studies are limited. To address this evidence gap, the objective of this study was to evaluate the cost utility of several testing strategies for the molecular characterization of *TP53* and *IGHV* mutations for the frontline treatment of either ibrutinib or CIT in young, fit patients with CLL from the Australian healthcare system perspective.

2 Methods

2.1 Model Overview

The patient population was a hypothetical cohort of young, fit patients with active CLL disease. The perspective was the Australian healthcare system over a lifetime horizon. Both health and economic outcomes were discounted at an annual rate of 5% as per Australian guidelines [24]. The model cycle length was 4 weeks to coincide with a typical CLL treatment cycle. Australia does not have an explicit willingness-to-pay (WTP) threshold, but the analysis assumed a threshold of 100,000 AUD per quality-adjusted life-year (QALY) gained for cancer drugs (two times greater than the commonly used 50,000 AUD per QALY gained) [25]. Outcomes included the incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB). The ICER was the difference in cost in Australia dollars (AUD) divided by the difference in QALY gained between alternative strategies using standard methods for economic evaluations. The NMB was the total QALY multiplied with the WTP threshold subtracted by the total cost for each strategy. The strategy with the highest NMB was considered the most cost effective. Face validity of the model structure was confirmed through ongoing consultations with two clinical hematologists. These experts

were consulted to judge the suitability of the model structure in Australian practice. They were also specifically asked to assess the appropriateness of the identified clinical data sources for populating the model, identify any potential issues of using published clinical trials in the analysis and provide feedback on the sensibility of the model outcomes. The model was developed and analyzed in R Statistical Software version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) following a pre-specified health economic analysis plan (available upon request from author).

2.2 Model Strategies and Structure

A decision analytic model was developed to compare five mutually exclusive strategies consisting of a decision tree for molecular testing and first-line treatment selection, as well as a partitioned survival model (PSM) to assess the health economic consequences of these treatment decisions (Fig. 1).

The decision tree reflected the allocation of first-line treatment following each strategy. These strategies were designed to support policy decision makers to consider a range of potential test-treatment scenarios for patients with CLL, which included the following:

- Strategy 1: no testing (FCR for all). Patients in Strategy 1 all received FCR.
- Strategy 2: test for del(17p) only. Patients in Strategy 2 were tested for del(17p). Patients with del(17p) received ibrutinib, while patients without deletions received FCR. Moreover, health economic outcomes were modeled separately for a subset of patients without deletions but with underlying *TP53* inactivation by mutation (approximately 30–40% of patients with *TP53* aberrations) due to known inferior outcomes with FCR [6, 26].
- Strategy 3: test for *TP53* gene mutation status. Patients in Strategy 3 were tested for *TP53* aberrations (both del(17p) and *TP53* mutations). Patients with *TP53* aberrations received ibrutinib, while patients with *TP53* wildtype received FCR.
- Strategy 4: test for *TP53* and *IGHV* gene mutation status. Patients in Strategy 4 were first tested for *TP53* aberrations (both del(17p) and *TP53* mutations), receiving ibrutinib if *TP53* aberrant. For patients with *TP53* wildtype, there was a second testing for *IGHV* mutations, receiving ibrutinib if *IGHV*-U. Only patients who were *TP53* wildtype and *IGHV*-M received FCR.
- Strategy 5: no testing (ibrutinib for all). Patients in Strategy 5 all received ibrutinib.

Choice of FCR as the CIT regimen is consistent with the clinical management of young, fit patients in Australia outlined by the Australian PBAC [21]. The prevalence of *TP53*

aberrations and *IGHV*-U among treatment-naïve patients for the decision tree was estimated using published literature sources [16, 26].

The PSM estimated the long-term costs and health outcomes of different treatment sequences. The PSM consisted of three mutually exclusive health states common in oncology: progression free (PF), progressive disease (PD) and death (Fig. 1). Two treatment sequences were modeled: (1) first-line ibrutinib in PF followed by venetoclax in combination with rituximab (VR) in PD (PF ibrutinib → PD VR) and (2) first-line FCR in PF followed by ibrutinib in PD (PF FCR → PD ibrutinib). Outcomes for treatment sequences were modeled conditional on the molecular profile of the corresponding patient population. Ibrutinib was an ongoing therapy until PD, whereas FCR was a fixed duration of six cycles and VR was a fixed duration of 26 cycles including

an initial titration cycle. Given the different costs and utility associated with treatment regimens as either ongoing or fixed therapy, two additional substates designated as 'with treatment' and 'without treatment' were modeled for PF and PD. Patients enter the PSM in the PF state beginning 'with treatment' and may remain until 'without treatment', or transition to either the PD or death state over time but cannot revert to a former state. The proportion of patients within each health state over time (i.e., state membership) was calculated by modeling the relative survival of each biomarker-defined treatment group included in the model using an area under the curve approach [27]. The costs and health outcomes accrued over time were calculated based on the proportion of patients in each model state. Due to the limited capacity to monitor the number of treatment cycles that a patient may receive in the PD state, patients entering the PD
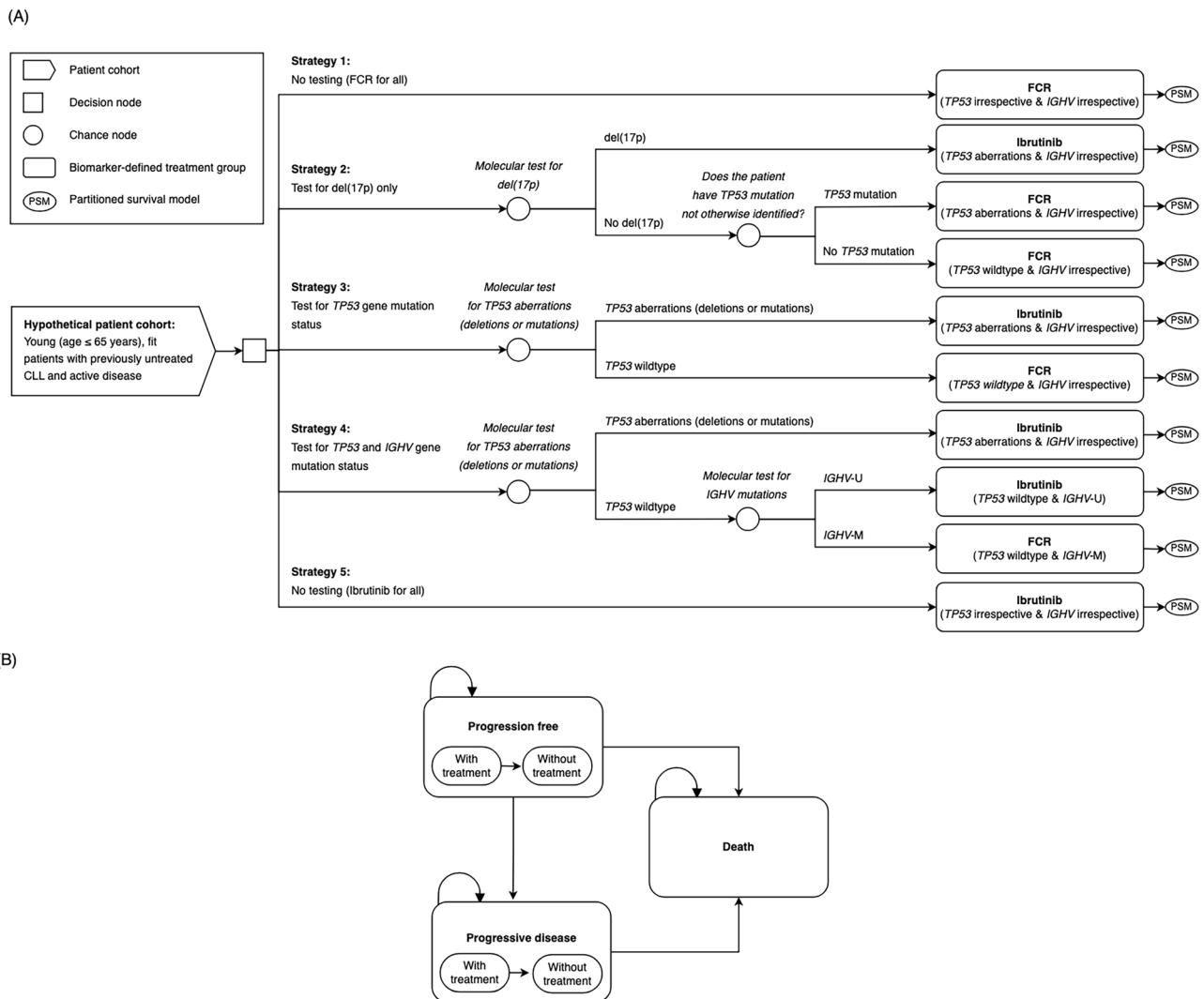

Fig. 1 Graphical diagram of the decision analytic model consisting of a (**A**) decision tree and (**B**) PSM, and the five strategies. *CLL* chronic lymphocytic leukemia, *FCR* fludarabine, cyclophosphamide and rituximab, *IGHV* immunoglobulin heavy chain, *M* mutated, *PSM* partitioned survival model, *TP53* tumor suppressor p53, *U* unmutated

state from the PF state on ibrutinib (i.e., PF ibrutinib → PD VR) incurred a once-off total average expected discounted cost and QALY for VR estimated based on the proportion of patients completing full-course VR treatment reported in the MURANO trial [28]. More specifically, tracking treatment cycles for patients transitioning from PD 'with treatment' to PD 'without treatment' when receiving VR treatment was particularly challenging in cohort models. To address this challenge, we estimated a once-off total average expected discounted cost for VR by aggregating costs across the 26 model cycles (equivalent to 2 years of treatment) considering the proportion of patients with VR treatment across each cycle, assuming 67% of patients completed a full course of treatment. Additionally, we aggregated the discounted utility and disutility of VR treatment over the 26 model cycles, accounting for the proportion of patients receiving VR treatment in each cycle to estimate the once-off total average expected QALY for VR. Further details outlining the transition of patients are outlined in Electronic Supplemental Materials 2 (ESM 2).

2.3 Clinical Data

The PFS and OS curves for each biomarker-defined treatment group were derived from secondary analyses of published literature. Further details are provided in ESM 1 and ESM 2.

Firstly, in the absence of direct head-to-head comparisons of FCR and ibrutinib in patients with either low-risk or high-risk molecular biomarkers, a review of PFS and OS data from phase III or II trials was conducted to estimate the relative HRs with 95% confidence intervals (95% CI) through an indirect treatment comparison (ITC) using the frequentist approach of a fixed effect model. Trials were included if the trial population comprised previously untreated patients with CLL and reported PFS and OS outcomes. From this, several different treatment groups were considered but assumptions were made to enable a connected evidence network (Supplementary Table S1 in the ESM). The evidence network for the ITC of first-line treatment in patients with CLL is presented in Fig. 2. The impact of these assumptions on model outcomes was explored through sensitivity analyses. For the model, FCR in patients with *TP53* wildtype irrespective of *IGHV* mutational status was selected as the reference comparator. This choice reflected the proposed clinical management of first-line CLL treatment by the Australian PBAC [21]. The analyses were conducted using the netmeta package in R [29]. The results of the ITC are presented in Table 1.

Secondly, PFS and OS outcomes for the reference comparator were extrapolated and validated using published clinical trial data from the ECOG-ACRIN E1912 study and CLL8 study, respectively. The ECOG-ACRIN E1912

study was a phase III trial which enrolled 529 previously untreated patients with CLL between March 2014 and June 2016 to receive either a combination of ibrutinib and rituximab or FCR, with a median follow-up of 33.6 months [16]. The FCR trial arm of the study provided the best available evidence to model the reference comparator since patients with del(17p) were excluded from trial participation. Consequently, it was assumed that this would be generalizable to patients with *TP53* wildtype receiving FCR. Although subsequent publications from the ECOG-ACRIN E1912 study reported four patients with *TP53* mutations out of 134 patients with available sequencing results in the FCR trial arm (3.0%), relevant survival outcomes for secondary survival analysis of FCR in a patient cohort of both the del(17p) and *TP53* mutations in literature is limited [30]. Conversely, the ECOG-ACRIN E1912 study published all relevant inputs (i.e., Kaplan–Meier curves and risk table) to replicate survival data.

The published Kaplan–Meier PFS and OS curves of the FCR trial arm in the ECOG-ACRIN E1912 study were digitized using a validated graphical digitizer (WebPlot-Digitizer version 4.5; Ankit Rohatgi, CA, USA). Next, individual patient time-to-event data were reconstructed using an algorithm developed by Guyot et al. [31]. The following parametric distributions were considered for extrapolating PFS and OS: exponential, Gompertz, log-logistic, log-normal and Weibull (in its proportional hazard parameterization) [32]. Candidate distributions were visually assessed for extrapolation plausibility, after which the final selection between plausible distributions was made on likelihood-based goodness-of-fit measures (i.e., Akaike Information Criterion and Bayesian Information Criterion) (Supplemental Table 3 and Supplemental Figs. 1, 2, see ESM). Additional internal validation from a comparison of yearly survival probabilities between the selected distribution and ECOG-ACRIN E1912 trial data, and external validation from the CLL8 study of a similar treatment group, were examined (Supplemental Table 4, see ESM). Although the Gompertz distribution was the best candidate for the PFS data, no distribution appropriately modeled the OS data. To address this issue, PFS and OS were modeled jointly using one Gompertz distribution, with a shared shape parameter but separate rate parameters. Fig. 3 presents the extrapolated survival curve of the reference comparator.

Thirdly, the PFS and OS survival functions for modeled treatments were estimated by multiplying the HRs from the ITC analysis to the hazard function of the reference comparator extrapolated from the ECOG-ACRIN E1912 study, assuming proportional hazards. To ensure that OS of patients in the model could not exceed that of the general population, it was assumed that the treatment effect duration in the PF state was 10 years. After given time $t > 10$ years, the hazard

Fig. 2 Evidence network for the indirect treatment comparison of first-line treatment in patients with chronic lymphocytic leukemia. Each link between modeled biomarker-defined treatment groups represents a direct comparison from a clinical trial study. *FCR* fludarabine, cyclophosphamide and rituximab, *IGHV* immunoglobulin heavy chain, *M* mutated, *TP53* tumor suppressor p53, *U* unmutated
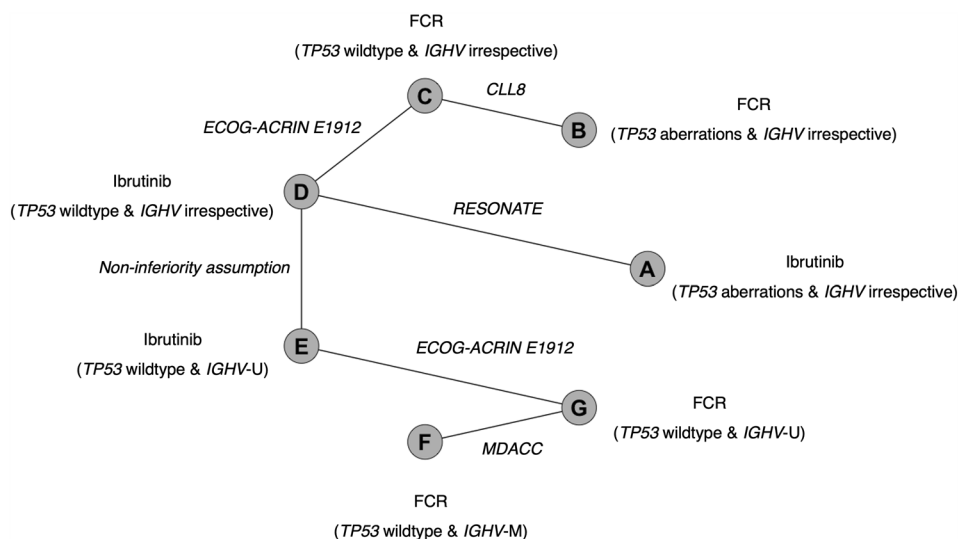

Table 1 Results from the ITC for the modeled biomarker-defined treatment groups

Biomarker-defined treatment group	Reference comparator: FCR (*TP53* wildtype and *IGHV* irrespective)	
	HR PFS (95% CI)	HR OS (95% CI)
FCR (*TP53* aberrations and *IGHV* irrespective)	3.17 (1.60–6.30)	4.45 (1.83–10.78)
FCR (*TP53* wildtype and *IGHV*-M)	0.37 (0.16–0.88)	0.25 (0.06–1.05)
Ibrutinib (*TP53* aberrations and *IGHV* irrespective)	0.21 (0.09–0.48)	0.09 (0.02–0.43)
Ibrutinib (*TP53* wildtype and *IGHV*-U)	0.35 (0.22–0.56)	0.17 (0.05–0.58)

CI confidence interval, *FCR* fludarabine, cyclophosphamide and rituximab, *HR* hazard ratio, *IGHV* immunoglobulin heavy chain, *ITC* indirect treatment comparison, *M* mutated, *OS* overall survival, *PFS* progression-free survival, *TP53* tumor suppressor p53, *U* unmutated

functions were elicited as the maximum value of either the hazard rate of the reference comparator or the hazard rate of the general population mortality derived from the Human Mortality Database [33]. Survival models for each treatment group are presented in Figs S5 and S6 (see ESM).

2.4 Costs

Details of the unit cost inputs are provided in Table 2, and the full itemized cost calculations are provided in ESM 3. All costs were indexed to 2021 AUD. The cost of testing for del(17p) using fluorescence in situ hybridization (FISH) was sourced from the Australian Medical Benefits Schedule (MBS) [34] whereas the cost of testing for *TP53* mutations using targeted amplicon sequencing and cost of testing for *IGHV* mutations using Lymphotrack IGHV Leader Somatic Hypermutation Assay (Invivoscribe) were sourced from the Molecular Haematology Laboratory at the Peter MacCallum Cancer Centre, where testing for *TP53* and *IGHV* mutations are currently performed. Costs of drug therapy were estimated using prices from the Australian Pharmaceutical Benefits Scheme (PBS) [35]

and dosing information from national treatment guidelines developed by eviQ and clinical inputs, assuming an average body surface area of 1.8 m^2 for drug dose calculations [36]. Relevant data sources from the MBS [34] and the Australian Refined Diagnosis Related Group (AR-DRG) [37] were used to estimate the costs of patient administration of chemotherapy. The costs of cancer management and associated laboratory investigations were also considered with the frequency of routine review derived from clinical input and prices from the MBS [34] and PBS [35]. The cost of AE hospitalization was derived from the AR-DRG data [37]. All patients who transitioned to the death state incurred a once-off cost for terminal care [38].

2.5 Utilities

Utility scores for health states were obtained from Kosmas et al. [39], who used a time trade-off methodology to elicit utility values for the different health states associated with the disease and treatment of CLL amongst members of the UK general population. Utility scores were allocated to each health state in the model, with considerations to whether
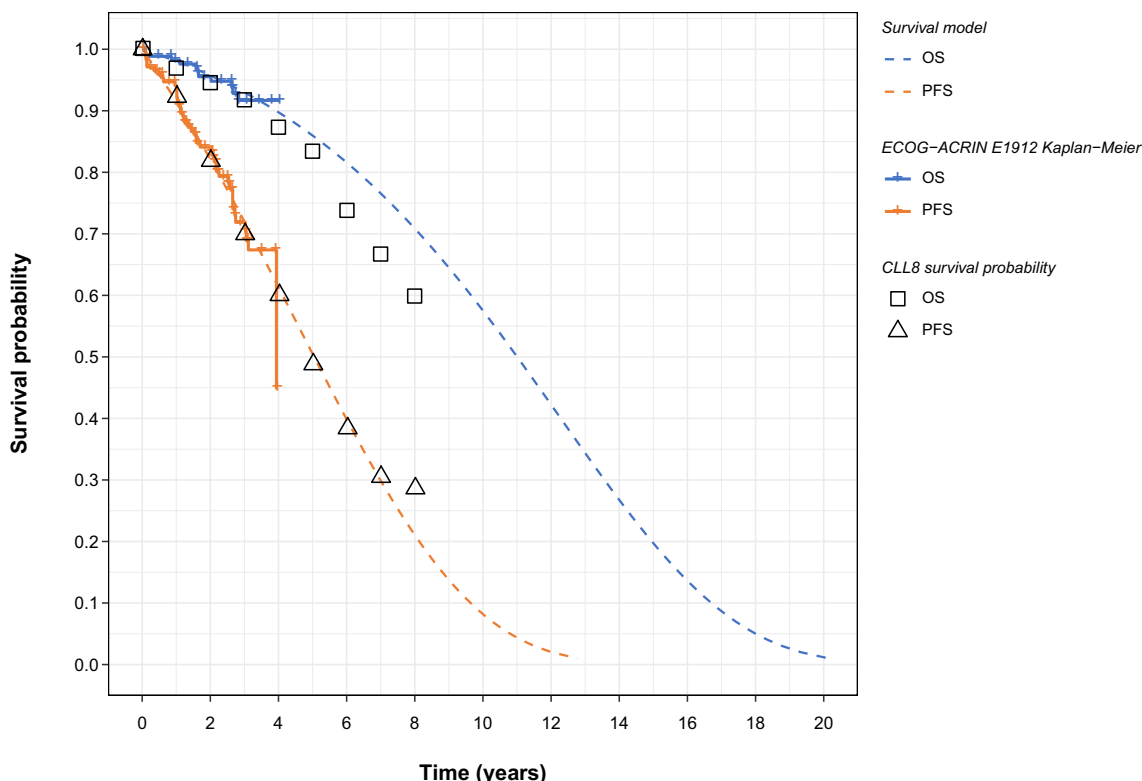
Fig. 3 Modeled PFS and OS curves of the ECOG-ACRIN E1912 study for chronic lymphocytic leukemia patients with *TP53* aberrations irrespective of *IGHV* mutational status receiving first-line FCR therapy, with data from the CLL8 trial presented as external valida-

tion. *FCR* fludarabine, cyclophosphamide and rituximab, *IGHV* immunoglobulin heavy chain, *OS* overall survival, *PFS* progression-free survival, *TP53* tumor suppressor p53

patients are actively receiving treatment and route of treatment administration (Table 2). Disutility associated with AEs were sourced from literature [22, 40].

2.6 Adverse Events

Major grade 3/4 AEs that are likely to result in hospitalization as reported in the ECOG-ACRIN E1912 trial [16] for ibrutinib and FCR, and in the MURANO trial [41] for VR, were considered in the model. A one-off cost and disutility of AE was weighted according to AE incidence rates reported in the trial and the average length of hospitalization for AEs was estimated based on the consensus of two clinical hematologists.

2.7 Model Analyses

Deterministic sensitivity analyses explored the impact of each model parameter on the NMB model output, which is less ambiguous than interpretation of unilateral changes

to ICER. Parameters were varied independently, with HRs and health state utilities tested at the upper and lower of their respective 95% CIs and other parameters using a range of ± 20%. Further, a minimum value of 3% and maximum value of 7% were imposed for the discount rate. A probabilistic analysis quantified the joint impact of parameter uncertainty on the uncertainty in the model outcomes. This was achieved by randomly sampling model parameter values from specified probability distributions for each parameter to generate 5000 cost and effectiveness estimates for each molecular diagnostic testing strategy. The decision to use 5000 iterations in the probabilistic analysis was supported by observing the stability of the mean model outcomes (e.g., ICER and NMB) and CI as a function of the number of runs in the analysis. To incorporate uncertainty in the parameters, standard parametric distributions were used, except for costs (Table 2). The cost estimates were fixed in the analysis because there was limited uncertainty associated with these parameters. Additional sensitivity analyses assessed the uncertainty of ITC assumptions (ESM 1 and ESM 4).

Table 2 Parameters used in the model with their base-case values, ranges considered for the deterministic sensitivity analysis, distribution used in the probabilistic analysis and evidence source

Attribute	Value	Range for DSA	PSA distribution	Source
Prevalence of molecular subgroups				
Del(17p)	0.06	±20% 0.05–0.08	Beta: alpha = 33; beta = 487	[16]
P53 mutations in the absence of del(17p)	0.03	±20% 0.02–0.03	Beta: alpha = 13; beta = 507	[16]
IGHV-U	0.71	±20% 0.60–0.85	Beta: alpha = 281; beta = 114	[16]
Proportion of patients completing full course of VR treatment	0.67	Not varied	Beta: alpha = 130; beta = 64	[28]
PFS HR from ITC analysis compared with FCR (*TP53* wildtype and *IGHV* irrespective)				
FCR (*TP53* aberrations and *IGHV* irrespective)	3.17	95% CI 1.60–6.30	Lognormal: mean-log = 0.50; SD-log = 0.35	
FCR (*TP53* wildtype and *IGHV*-M)	0.37	95% CI 0.16–0.88	Lognormal: mean-log = −0.43; SD-log = 0.45	
Ibrutinib (*TP53* aberrations and *IGHV* irrespective)	0.21	95% CI 0.09–0.48	Lognormal: mean-log = −0.69; SD-log = 0.43	
Ibrutinib (*TP53* wildtype and *IGHV*-U)	0.35	95% CI 0.22–0.56	Lognormal: mean-log = 0.50; SD-log = 0.40	
OS HR from ITC analysis compared with FCR (*TP53* wildtype & *IGHV* irrespective)				
FCR (TP53 aberrations and *IGHV* irrespective)	4.45	95% CI 1.83–10.78	Lognormal: mean-log = 0.65; SD-log = 0.45	
FCR (*TP53* wildtype and *IGHV*-M)	0.25	95% CI 0.06–1.05	Lognormal: mean-log = −0.60; SD-log = 0.71	
Ibrutinib (*TP53* aberrations and *IGHV* irrespective)	0.09	95% CI 0.02–0.43	Lognormal: mean-log = −1.03; SD-log = 0.75	
Ibrutinib (*TP53* wildtype and *IGHV*-U)	0.17	95% CI 0.05–0.58	Lognormal: mean-log = −0.77; SD-log = 0.59	
PFS survival model for FCR (*TP53* wildtype & *IGHV* irrespective)				
Shape	0.20	Not varied	Multivariate normal	
Rate	0.08	Not varied	Multivariate normal	
OS survival model for FCR (*TP53* wildtype & *IGHV* irrespective)				
Shape	0.20	Not varied	Multivariate normal	
Rate	0.02	Not varied	Multivariate normal	
Utility score				
PF, ibrutinib treatment	0.67	95% CI 0.63–0.71	Beta: alpha = 2.39; beta = 1.18	[38]
PF, FCR treatment	0.71	95% CI 0.67–0.75	Beta: alpha = 2.94; beta = 1.20	[38]
PF, not receiving active treatment	0.82	95% CI 0.78–0.85	Beta: alpha = 3.37; beta = 0.74	[38]
PD, all treatment	0.55	95% CI 0.50–0.60	Beta: alpha = 1.63; beta = 1.33	[38]
PD, not receiving active treatment	0.71	95% CI 0.66–0.75	Beta: alpha = 2.05; beta = 0.84	[38]
Cost of ibrutinib (AUD per cycle)	8244	±20% 6595–9893	Fixed	[38]
Cost of FCR (AUD per cycle)				
Treatment cycle 1	11,769	±20% 9415–14,122	Fixed	[35]
Treatment cycle 2–6	9570	±20% 7656–11,484	Fixed	[35]
Cost of VR (AUD per cycle)				
Titration	1881	±20% 1505–2257	Fixed	[35]
Treatment cycle 1	11,721	±20% 9377–14,605	Fixed	[35]
Treatment cycle 2–6	11,473	±20% 9179–13,768	Fixed	[35]
Treatment cycle 7–26	7301	±20% 5841–8763	Fixed	[35]
Cost of ongoing clinical review (no active treatment) (AUD per cycle)	36	±20% 29–43	Fixed	[34]
Cost of end-of-life medical care (AUD)	8495	±20% 6796–10,193	Fixed	[38]

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Table 2 (continued)

Attribute	Value	Range for DSA	PSA distribution	Source
Cost of AE hospitalization (AUD per day)	2060	±20% 1648–2472	Fixed	[37]
Cost of molecular diagnosis (AUD)				
del(17p) FISH test	231	±20% 185–277	Fixed	[34]
TP53 mutation test	250	±20% 200–300	Fixed	Molecular Haematology Laboratory at the Peter MacCallum Cancer Centre
IGHV mutation test	400	±20% 320–480	Fixed	Molecular Haematology Laboratory at the Peter MacCallum Cancer Centre
Incidence of AE ibrutinib				
Anemia	0.03	±20% 0.02–0.03	Beta: alpha = 9; beta = 343	[16]
Febrile neutropenia	0.02	±20% 0.02–0.03	Beta: alpha = 8; beta = 344	[16]
Pneumonia	0.00	Not varied	Not varied	[16]
Sepsis	0.00	±20% 0.00–0.00	Beta: alpha = 1; beta = 351	[16]
Tumor lysis syndrome	0.01	±20% 0.00–0.01	Beta: alpha = 2; beta = 350	[16]
Incidence of AE FCR				
Anemia	0.12	±20% 0.10–0.14	Beta: alpha = 19; beta = 139	[16]
Febrile neutropenia	0.16	±20% 0.13–0.19	Beta: alpha = 25; beta = 134	[16]
Pneumonia	0.01	±20% 0.01–0.02	Beta: alpha = 2; beta = 156	[16]
Sepsis	0.03	±20% 0.02–0.03	Beta: alpha = 4; beta = 154	[16]
Tumor lysis syndrome	0.01	±20% 0.01–0.02	Beta: alpha = 2; beta = 156	[16]
Incidence of AE VR				
Anemia	0.11	±20% 0.09–0.13	Beta: alpha = 21; beta = 173	[41]
Febrile neutropenia	0.04	±20% 0.03–0.04	Beta: alpha = 7; beta = 187	[41]
Pneumonia	0.13	±20% 0.11–0.16	Beta: alpha = 26; beta = 168	[41]
Sepsis	0.01	±20% 0.00–0.01	Beta: alpha = 1; beta = 193	[41]
Tumor lysis syndrome	0.03	±20% 0.02–0.04	Beta: alpha = 6; beta = 188	[41]
Disutility of AE	−0.19	±20% −0.23 to −0.15	Beta: alpha = 35.73; beta = 147.51	[22, 40]
Length of hospitalization for AE (days)				
Anemia	1.0	±20% 0.80–1.20	Fixed	Clinical input
Febrile neutropenia	4.00	±20% 3.20–4.80	Fixed	Clinical input
Pneumonia	4.00	±20% 3.20–4.80	Fixed	Clinical input
Sepsis	4.00	±20% 3.20–4.80	Fixed	Clinical input
Tumor lysis syndrome	2.00	±20% 1.60–2.40	Fixed	Clinical input

AE adverse events, *AUD* Australian dollars, *CI* confidence interval, *DSA* deterministic sensitivity analysis, *FCR* fludarabine, cyclophosphamide and rituximab, *FISH* fluorescence in situ hybridization, *HR* hazard ratio, *IGHV* immunoglobulin heavy chain, *ITC* indirect treatment comparison, *M* mutated, *OS* overall survival, *PD* progressive disease, *PF* progression free, *PFS* progression-free survival, *PSA* probabilistic sensitivity analysis, *SD* standard deviation, *TP53* tumor suppressor p53, *U* unmutated, *VR* venetoclax and rituximab

Subgroup analyses were also performed to explore the health economic impact of ibrutinib versus FCR in the setting of two high-risk treatment groups based on Strategy 4 in Fig. 1 (patients with *TP53* aberrations and *IGHV* irrespective and patients with *TP53* wildtype and *IGHV*-U). The purpose of this was to assess the cost effectiveness if these patients were instead to receive FCR.

3 Results

The cost-effectiveness results comparing the lifetime average discounted costs and QALYs of each strategy for the hypothetical cohort of patients with CLL based on the probabilistic analysis are described in Table 3 and the outcomes illustrated on a cost-effectiveness plane in Fig. 4. The

efficiency frontier in Fig. 3 demonstrates the ICER between alternative strategies. Strategy 1 (no testing (FCR for all)) had the lowest cost per patient (458,836 AUD [95% CI 236,792–786,314]) and was the least effective (5.69 QALY [95% CI 2.85–10.22]). All other strategies were more effective but more expensive than Strategy 1. The ICERs of Strategy 2 (test for del(17p) only), Strategy 3 (test for *TP53* gene mutation status), Strategy 4 (test for *TP53* and *IGHV* gene mutation status) and Strategy 5 (no testing (ibrutinib for all)) were 138,698 AUD, 140,013 AUD, 164,462 AUD and 1,124,983 AUD per QALY gained, respectively, when compared with the next most effective strategy. Despite the health benefits, none of the ICERs were below the 100,000 AUD per QALY gained threshold. Additionally, the 95% confidence ellipsis for the strategies revealed considerable uncertainty of the mean costs and QALYs for each strategy. Strategy 1 had the highest NMB at 110,454 AUD.

The cost-effectiveness acceptability curve summarizing the uncertainty in the model outcomes and probability of cost effectiveness is depicted in Fig. 5. The estimated probability of cost effectiveness for Strategy 1 was 68.8% at the 100,000 AUD per QALY gained threshold. From the cost-effectiveness acceptability frontier in Fig. 4, Strategy 4 was the most cost-effective strategy between a WTP threshold of 155,000 AUD and 432,300 AUD per QALY gained whereas Strategy 5 was the most cost-effective strategy at a WTP threshold > 432,300 AUD per QALY gained.

The tornado diagram illustrating the five single model parameters that had the greatest impact on model outcomes for each strategy is shown in Fig. 6. The parameters with substantial influence for each strategy included the per-cycle treatment cost of ibrutinib and health state utility scores.

In these instances, a lower treatment cost for ibrutinib per cycle or higher utility score was associated with an increase in NMB compared with the base-case outputs. Other model parameters with varying influence on the strategies included per-cycle treatment cost of FCR and VR, relative treatment survival and discount rates.

The additional sensitivity, threshold and subgroup analyses are presented in ESM 4. The additional sensitivity analyses assessed the impact of ITC analysis assumptions, which revealed that there was minimal effect on overall model conclusions (i.e., Strategy 1 as the preferred intervention). The threshold analysis demonstrated that if the cost of ibrutinib was < 4800 AUD per cycle (41.8% decrease from base-case value), the ICERs for Strategy 2, Strategy 3 and Strategy 4 would be below the 100,000 AUD per QALY gained threshold. Ibrutinib is unlikely to be cost effective compared with FCR for patients with *TP53* aberrations and *IGHV* irrespective and patients with *TP53* wildtype and *IGHV*-U.

4 Discussion

This study assessed the health economic impact of targeting first-line treatment with FCR or ibrutinib in young, fit patients with CLL. The results demonstrate that biomarker testing for *TP53* and *IGHV* improved patient's health outcomes but incurred a relatively higher cost than providing FCR treatment for all patients regardless of risk group. At the WTP threshold of 100,000 AUD per QALY gained, this strategy was unlikely to be cost effective, but could be at a higher threshold value (e.g., 155,000 AUD per QALY gained). Although ibrutinib treatment for all patients was the

Table 3 Health and economic outcomes of the alternative strategies

Strategy	Mean discounted cost (AUD) (95% CI)	Mean discounted effectiveness (QALY) (95% CI)	Incremental cost (AUD) (95% CI)	Incremental effectiveness (QALY) (95% CI)	ICER (AUD per QALY gained)	NMB (AUD) at 100,000 AUD per QALY gained
Strategy 1—no testing (FCR for all)	458,836 (236,792–786,314)	5.69 (2.85–10.22)				110,454
Strategy 2—test for del(17p)	496,076 (276,922–812,501)	5.96 (3.14–10.43)	37,240 (12,579–69,118)	0.27 (0.03 to 0.56)	138,698	100,064
Strategy 3—test for *TP53* gene mutation status	510,821 (293,728–823,194)	6.07 (3.24–10.53)	14,745 (4779–29,580)	0.11 (0.01 to 0.24)	140,013	95,850
Strategy 4—test for *TP53* and *IGHV* gene mutation status	742,038 (566,610–1,042,805)	7.47 (4.21–11.83)	231,217 (38,258–430,793)	1.41 (−1.06 to 3.51)	164,462	5224
Strategy 5—no testing (ibrutinib for all)	861,394 (669,429–1,264,748)	7.58 (3.84–12.24)	119,356 (2722–263,980)	0.11 (−1.06 to 1.16)	1,124,983	−103,523

AUD Australian dollars, *CI* confidence interval, *FCR* fludarabine, cyclophosphamide and rituximab, *ICER* incremental cost-effectiveness ratio, *IGHV* immunoglobulin heavy chain, *NMB* net monetary benefit, *QALY* quality-adjusted life-years, *TP53* tumor suppressor p53
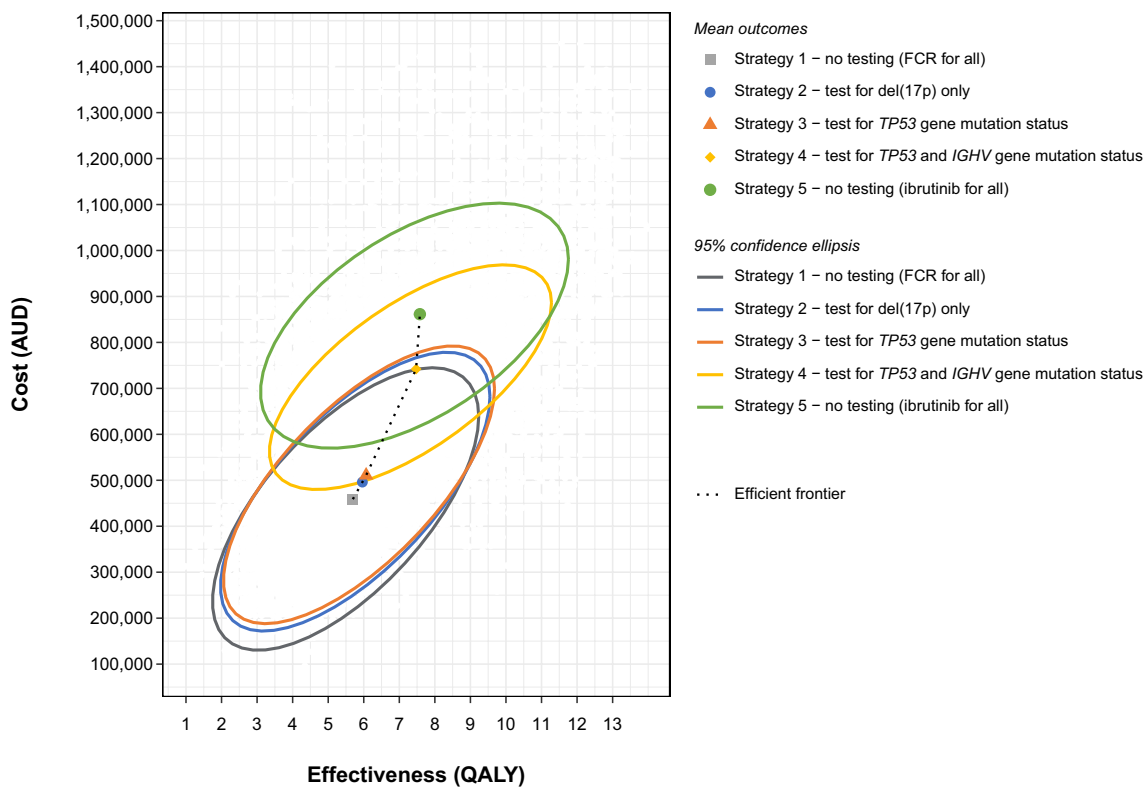
Fig. 4 Incremental cost-effectiveness plane from the probabilistic sensitivity analysis. *AUD* Australian dollars, *FCR* fludarabine, cyclophosphamide and rituximab, *IGHV* immunoglobulin heavy chain, *QALY* quality-adjusted life-years, *TP53* tumor suppressor p53

most effective strategy, a much higher WTP threshold (e.g., > 432,300 AUD per QALY gained) will need to be adopted for it to substantiate value for money. Several factors were identified that could improve the cost effectiveness of *TP53* and *IGHV*, including health state utility scores and relative treatment survival, but notably the per-cycle treatment cost of ibrutinib. The cost of ibrutinib was based on list prices from Australia's national health insurance scheme, but if the cost of ibrutinib was to decrease from 8244 AUD to 4800 AUD per cycle (41.8%), the ICER of molecular testing with *TP53* and *IGHV* would be < 100,000 AUD per QALY gained.

To ensure better access to effective treatments for high-risk patients, it is essential for these health technology assessment (HTA) organizations (e.g., PBAC, NICE and CADTH) to reassess and harmonize their reimbursement policies based on the clinical evidence supporting the inclusion of *TP53* and *IGHV* testing. It is evident that incorporating biomarker testing for *TP53* and *IGHV* improves patient health outcomes but at a higher cost compared with a uniform approach of providing FCR treatment for all patients, regardless of risk group. At the same time, testing for *TP53* and *IGHV* is more cost effective than administering ibrutinib for all patients. Perhaps the most tangible implication for HTA and industry is that reducing the cost of ibrutinib

could potentially enhance the cost effectiveness of *TP53* and *IGHV*. It is important to note that our analysis was conducted using the list price of CLL treatment, and it is possible that the true cost of treatment including ibrutinib may be lower.

The cost effectiveness of upfront ibrutinib (without molecular testing) has been previously investigated amongst several treatment regimens and is unlikely cost effective in CLL despite health benefits gained [42–46]. There are important differences between these studies that limit their direct comparability, such as the choice of comparator, the patient population (i.e., older patients or patients with comorbidities), treatment sequences and the health system under evaluation. Nevertheless, relatively fewer cost-effectiveness studies have assessed molecular diagnostic tools to match high-risk patients (specifically *TP53* aberrations) with targeted treatment. A Markov model published by Buchanan et al. [47] showed that genomic testing to stratify patients with CLL in receiving first-line ibrutinib improved health outcomes, but that this was not cost effective for the UK healthcare system. Of note, similar to our study, the cost of ibrutinib was also identified as a factor that may lead to favorable cost effectiveness of targeted CLL therapies if the cost was lowered. Our study, to our knowledge, is the first to consider *IGHV* gene mutations in view of recent CLL guidelines and although testing for *TP53* and *IGHV* did
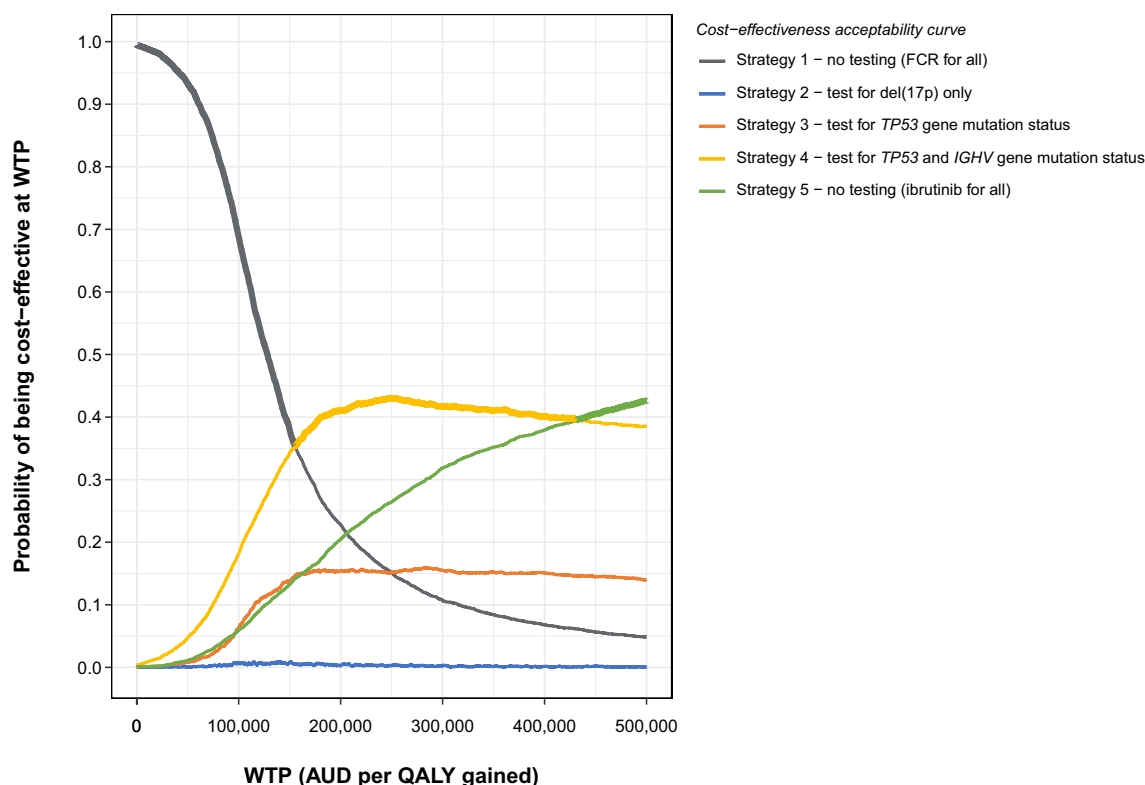
Fig. 5 Cost-effectiveness acceptability curve showing the probability for each strategy of being cost effective as a function of the WTP per QALY gained. Thick border line corresponds to the cost-efficient frontier. *AUD* Australian dollars, *FCR* fludarabine, cyclophosphamide and rituximab, *IGHV* immunoglobulin heavy chain, *QALY* quality-adjusted life-years, *TP53* tumor suppressor p53, *WTP* willingness-to-pay

not necessarily translate to ibrutinib being cost effective, it did at least make such therapies more economical. Specifically, the incremental benefit from providing ibrutinib for all patients compared with the *TP53* and *IGHV* testing strategy as the next best alternative was marginal (0.11 QALY) but the additional cost to deliver treatment was substantial (119,356 AUD). By reason, a greater investment or a higher WTP threshold will need to be adopted to make the uniform ibrutinib treatment worthwhile. This finding could be of particular importance for future studies assessing the health economic impact of second-generation BTK agents, BCL2 inhibitors and other newer therapies as the evidence continues to emerge for young, fit patients with CLL [42, 46].

Still, the question of how to standardize patient access to molecular tests and ibrutinib treatment to ensure clinical evidence for a CLL treatment algorithm is reflected in policy remains. While the role of FCR diminishes to a selected subset of low-risk patients, there are not many alternative therapies in the Australian frontline setting that are also reimbursed [48]. There needs to be a reimbursement pathway driven by the clinical unmet need for effective treatment in high-risk patients, particularly *IGHV*-U. Further, this study emphasizes a cost reduction for ibrutinib

and motivates a price negotiation between funders and manufacturers to assist with achieving cost effectiveness. Alternatively, an outcomes-based payment scheme could be considered, which is a cost-sharing arrangement that establishes the price of drug reimbursement based on the delivery of pre-agreed outcomes in real-world clinical practice [49].

This study has certain limitations. Firstly, there was a lack of direct clinical evidence to inform the comparison of biomarker-defined treatment groups in the model for the ITC analysis, and assumptions were made to form a connected evidence network. This study utilized the best available public literature sources to inform a range of plausible clinical parameters in the model, but further effectiveness evidence may be required to improve the long-term clinical outcome estimates. Yet, such data will remain scarce unless clinical trials are designed to directly investigate the clinical benefit of treatment for predictive groups categorized by *TP53* wildtype/aberrations and *IGHV*-U/*IGHV*-M. These clinical trials are costly to conduct, and it is unlikely future patients with *TP53* aberrations and/or *IGHV*-U enrolled in clinical trials will receive FCR with the shift away from this treatment for these patients [50]. Nonetheless, the trials included in the ITC analysis were comparable based on
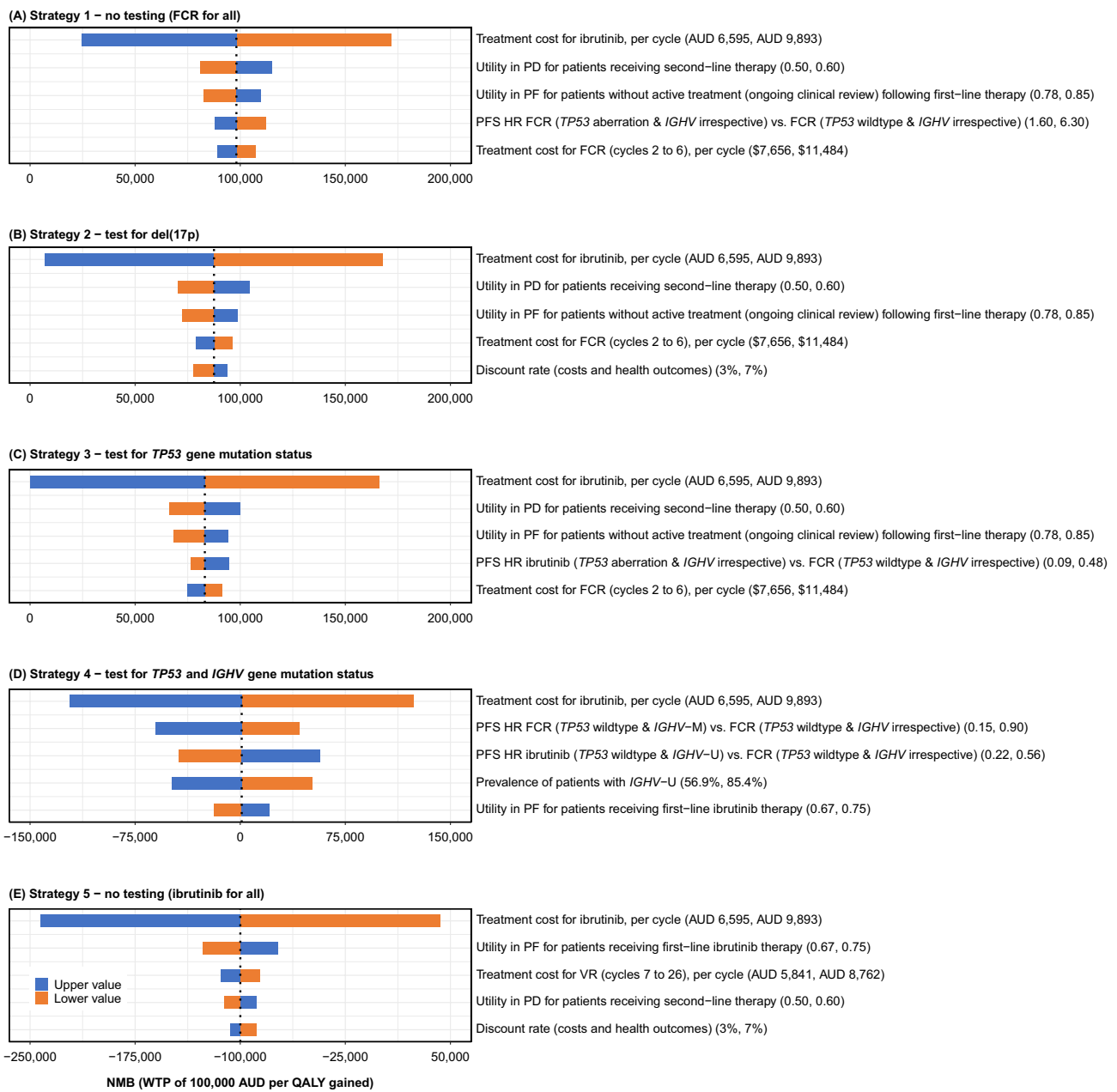
(A) Strategy 1 – no testing (FCR for all)

Treatment cost for ibrutinib, per cycle (AUD 6,595, AUD 9,893)

Utility in PD for patients receiving second-line therapy (0.50, 0.60)

Utility in PF for patients without active treatment (ongoing clinical review) following first-line therapy (0.78, 0.85)

PFS HR FCR (*TP53* aberration & *IGHV* irrespective) vs. FCR (*TP53* wildtype & *IGHV* irrespective) (1.60, 6.30)

Treatment cost for FCR (cycles 2 to 6), per cycle ($7,656, $11,484)

(B) Strategy 2 – test for del(17p)

Treatment cost for ibrutinib, per cycle (AUD 6,595, AUD 9,893)

Utility in PD for patients receiving second-line therapy (0.50, 0.60)

Utility in PF for patients without active treatment (ongoing clinical review) following first-line therapy (0.78, 0.85)

Treatment cost for FCR (cycles 2 to 6), per cycle ($7,656, $11,484)

Discount rate (costs and health outcomes) (3%, 7%)

(C) Strategy 3 – test for *TP53* gene mutation status

Treatment cost for ibrutinib, per cycle (AUD 6,595, AUD 9,893)

Utility in PD for patients receiving second-line therapy (0.50, 0.60)

Utility in PF for patients without active treatment (ongoing clinical review) following first-line therapy (0.78, 0.85)

PFS HR ibrutinib (*TP53* aberration & *IGHV* irrespective) vs. FCR (*TP53* wildtype & *IGHV* irrespective) (0.09, 0.48)

Treatment cost for FCR (cycles 2 to 6), per cycle ($7,656, $11,484)

(D) Strategy 4 – test for *TP53* and *IGHV* gene mutation status

Treatment cost for ibrutinib, per cycle (AUD 6,595, AUD 9,893)

PFS HR FCR (*TP53* wildtype & *IGHV*−M) vs. FCR (*TP53* wildtype & *IGHV* irrespective) (0.15, 0.90)

PFS HR ibrutinib (*TP53* wildtype & *IGHV*−U) vs. FCR (*TP53* wildtype & *IGHV* irrespective) (0.22, 0.56)

Prevalence of patients with *IGHV*−U (56.9%, 85.4%)

Utility in PF for patients receiving first-line ibrutinib therapy (0.67, 0.75)

(E) Strategy 5 – no testing (ibrutinib for all)

Treatment cost for ibrutinib, per cycle (AUD 6,595, AUD 9,893)

Utility in PF for patients receiving first-line ibrutinib therapy (0.67, 0.75)

Treatment cost for VR (cycles 7 to 26), per cycle (AUD 5,841, AUD 8,762)

Utility in PD for patients receiving second-line therapy (0.50, 0.60)

Discount rate (costs and health outcomes) (3%, 7%)

■ Upper value
■ Lower value

NMB (WTP of 100,000 AUD per QALY gained)

Fig. 6 Tornado diagram of the deterministic sensitivity analysis for the five parameters with the greatest impact on NMB across each strategy. *AUD* Australian dollars, *FCR* fludarabine, cyclophosphamide and rituximab, *HR* hazard ratio, *IGHV* immunoglobulin heavy chain, *NMB* net monetary benefit, *PD* progressive disease, *PF* progression free, *PFS* progression-free survival, *QALY* quality-adjusted life-years, *TP53* tumor suppressor p53, *U* unmutated, *VR* venetoclax and rituximab, *WTP* willingness-to-pay

the study design, patient population and outcome measures (Table S2 in the ESM). Assumptions for the ITC analysis were discussed and validated by clinical experts, with justifications provided in Table S1 (see ESM), and their impact was explored in sensitivity analyses. Secondly, uncertainty in extrapolating the long-term OS in the PSM owing to immature long-term follow-up data for the reference comparator in the model could influence outcomes of the cost-effectiveness analysis. However, several efforts ensured the

choice of projecting OS was plausible from the perspective of internal and external validation. Thirdly, utility and disutility scores were from a health state utility study and other public sources in a UK population, which may be different to an Australian population and could limit the generalizability of study findings. Fourthly, only the major grade 3/4 AEs leading to hospitalization were included where all other AEs were excluded from the evaluation. However, findings of the deterministic analysis suggest that the cost

of AEs may not majorly contribute to the cost effectiveness of evaluated strategies. Lastly, upon completion of study conceptualization and analysis, venetoclax in combination with obinutuzumab is now reimbursed for CLL patients in Australia but was not considered in the model [51]. Ibrutinib may still be the preferred treatment option over venetoclax with obinutuzumab depending on the comorbidities profile [52]. Nevertheless, findings of our study are still relevant from a health policy perspective to highlight the potential to enhance eligibility of the current use of ibrutinib through the adoption of a risk-based approach, which includes reducing the cost of ibrutinib treatment.

Declarations

Conflict of interest The authors declare no competing financial interests.

Availability of data and material The model inputs used to inform the decision analytic model and execute the cost-effectiveness analysis are included within the article with appropriate citations.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication from patients/participants Not applicable.

Code availability The custom codes for the model are available from the corresponding author upon reasonable request.

Author contributions All authors contributed to the study conception and design. MV developed the economic model under supervision of KD. The initial draft of the manuscript was written by MV, and critically reviewed for scientific content by all other authors. All authors read and approved the final manuscript.

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