Living Cost-Effectiveness Sequence Analysis (sequence-CEA) for Chronic Lymphocytic Leukemia (CLL): A Payer-Centric Framework for Dynamic Formulary Decision Making

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OBJECTIVES

- To present a methodological framework for a living, sequence-CEA designed to support payer decision making in dynamic CLL treatment landscapes

BACKGROUND

- CLL has evolved into a multi-line, long-duration disease with rapid evidence generation, frequent treatment switching and immature overall survival (OS) data
- While Bruton tyrosine kinase inhibitors (BTKis) are increasingly viewed as comparable in terms of overall survival, they differ meaningfully in tolerability, persistence, pricing dynamics, and downstream economic impact
- In practice, the choice of BTKi depends on comorbidities, concomitant medications, cost and side-effect profiles.[1] Acalabrutinib and zanubrutinib have a more favorable side-effect profile, however, zanubrutinib demonstrated a PFS benefit over ibrutinib in relapsed/refractory setting[1,2]
- Moreover, there is still debate on whether fixed duration combinations of BTKi and venetoclax should be used in favor of venetoclax and obinutuzumab (V+O) or continuous BTKi in first line[3]
- Conventional static CEAs, typically focused on single lines of therapy, fail to capture evolving factors, particularly in the context of Medicare price negotiations[3] and emerging real-world-evidence (RWE)

METHODS

- We constructed a living sequence-CEA framework informed by a Real-time AI-assisted Living Systematic Literature Review (REAL-SLR) able to explicitly represent treatment pathways across multiple lines of therapy
- The framework integrates the most up-to-date information on outcomes (efficacy, safety, discontinuations, etc.) from clinical trials and RWE studies, comparative effectiveness from indirect treatment comparisons, and comparator landscape based on regulatory approvals and guideline recommendations (**Figure 1A**)
- Early treatment attributes are modelled as determinants of downstream sequencing options and cost trajectories (**Figure 1B**)
- Pricing inputs are structured to accommodate evolving policy/contracting environments, including negotiated prices/rebates
- Evidence monitoring is performed daily, via REAL-SLR and the model inputs updates are triggered as relevant new clinical, real-world, and pricing data emerge, without the need for model redevelopment

STRENGTHS

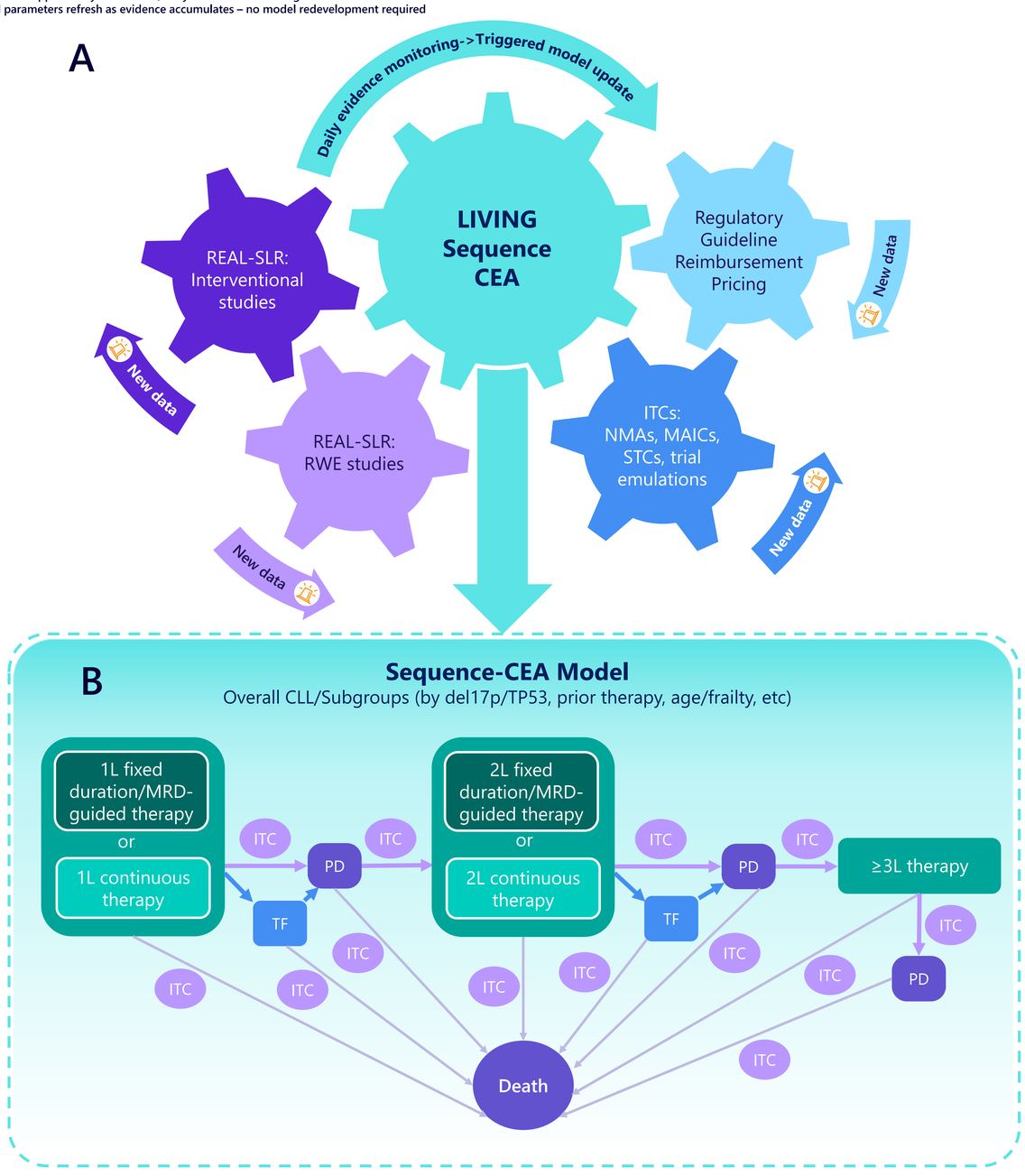
- Our framework aims to closely reflect real-world clinical practice and allows analysis of the different treatment decisions as they propagate across lines of therapy
- By including a treatment-free state, our proposed framework aims towards a more accurate representation of costs and quality of life gains
- Total lifetime costs are more accurately captured in a model that captures multiple lines of therapy

LIMITATIONS

- The model relies heavily on long-term data to accurately estimate progression through health states and from one line of therapy to the another
- Where clinical trial data is missing, RWE can fill in the gaps, however, may introduce bias
- Data on discontinuations, TTNT, and TFI is scarce for patients in third line and beyond. Moreover, as patients progress through multiple lines of therapy, there is less information on the efficacy of different treatment options and if/how prior exposure to an agent affects the outcomes upon re-treatment

Figure 1. Living update mechanism

A. Living CEA supported by continuous, daily evidence monitoring via REAL-SLR
B. Model parameters refresh as evidence accumulates – no model redevelopment required



RESULTS

- The proposed framework shifts evaluative focus from isolated treatment comparisons to sequence-level decisions (**Figure 1B**)
- Recent US studies showed that 33% of patients receive ≥2 lines of therapy and 42% of patients who had second line received a third line of therapy and of those, 42% went on to receive a fourth line[11,12]

Choice of outcomes

- The framework incorporates time to next treatment (TTNT) as an important outcome as longer TTNT with targeted therapies was shown to be associated with lower medical costs during follow-up compared to chemoimmunotherapy[5,10]
- Although more often reported in RWE, differences in TTNT between therapies can significantly impact cost calculations, as drug costs are one of the major drivers in CLL
- RWE studies showed significantly longer time to discontinuation and TTNT with zanubrutinib and acalabrutinib compared to ibrutinib and significantly longer TTNT with V+O compared to second generation BTKis[6,7,8]

Modelling treatment-free interval

- When health states are defined based on time on treatment instead of on progression, the treatment-free interval (TFI) should be considered as an extra health state before the next treatment (**Figure 1B**)[5]
- Treatment-free interval is a value driver for fixed-duration or minimal residual disease-guided venetoclax-based regimens, translating into cost savings compared to continuous therapy strategies
- Even among patients who discontinue therapy due to reasons other than progression (ie, toxicity), TFI is not negligeable. For example, in patients who discontinued ibrutinib due to toxicity, the median time to starting a new therapy was 6.5 months compared to 0.3 months among patients who discontinued due to progression[13]
- A previous analysis comparing various targeted therapies and chemoimmunotherapies, as fixed-duration or continuous regimens, showed the feasibility of including off-treatment intervals and TTNT in the model[9]

Living concept accommodating evolving evidence

- The living structure, informed by a daily-updated REAL-SLR, enables timely reassessment of value as evidence and policy contexts evolve supporting stratified analyses for clinically-relevant subpopulations where safety/tolerability differences are consequential

CONCLUSIONS

- Living sequence-CEAs offer a methodologically coherent alternative for evaluating CLL treatments than static, single-line CEAs
- By aligning modelling structure with living RWE dynamics, this approach provides a decision-relevant basis for strategic formulary evaluation under conditions of uncertainty
- Living CEA models enable better-informed formulary placement and subpopulation-specific coverage strategies in changing CLL treatment landscape

ABBREVIATIONS

1L, first line; 2L, second line; 3L, third line; CEA, cost-effectiveness analysis; CLL, chronic lymphocytic leukemia; ITC, indirect treatment comparison; MAIC, matched-adjusted indirect comparison; MRD, minimal residual disease; PD, progressive disease; RWE, real-world evidence; STC, simulated treatment comparison; TF, treatment-free

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