

**Il punto di vista del «farmaco-
economista»**

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L'OTTIMIZZAZIONE DELLA
**TERAPIA LEUCEMIA
LINFATICA CRONICA:**

UNA CONDIZIONE DINAMICA
ED INNOVATIVA



12-13 APRILE 2022 BOLOGNA ROYAL HOTEL CARLTON

Dichiarazione sul Conflitto di Interessi

Dichiaro di avere ricevuto *research grant* da Abbvie, Amgen, Astrazeneca, Bayer, BMS, Boehringer I, Celgene (BMS), Janssen C, Lundbeck, MSD, Novartis, Roche, Pfizer, Sandoz, Sanofi, Takeda, Teva e Zambon

Dichiaro di avere partecipato come speaker ad Eventi o ad Advisory Board organizzati da Amgen, Astrazeneca, BIP, BMS, Celgene, CSL Behring, Dephaforum, Economia Sanitaria, Fondazione R&S, Gilead, Incyte, MA Provider e 3P Solutions, MSD, Roche, Sanofi, Simon & Kucher, Takeda, Wellmera (ora Alira Health)

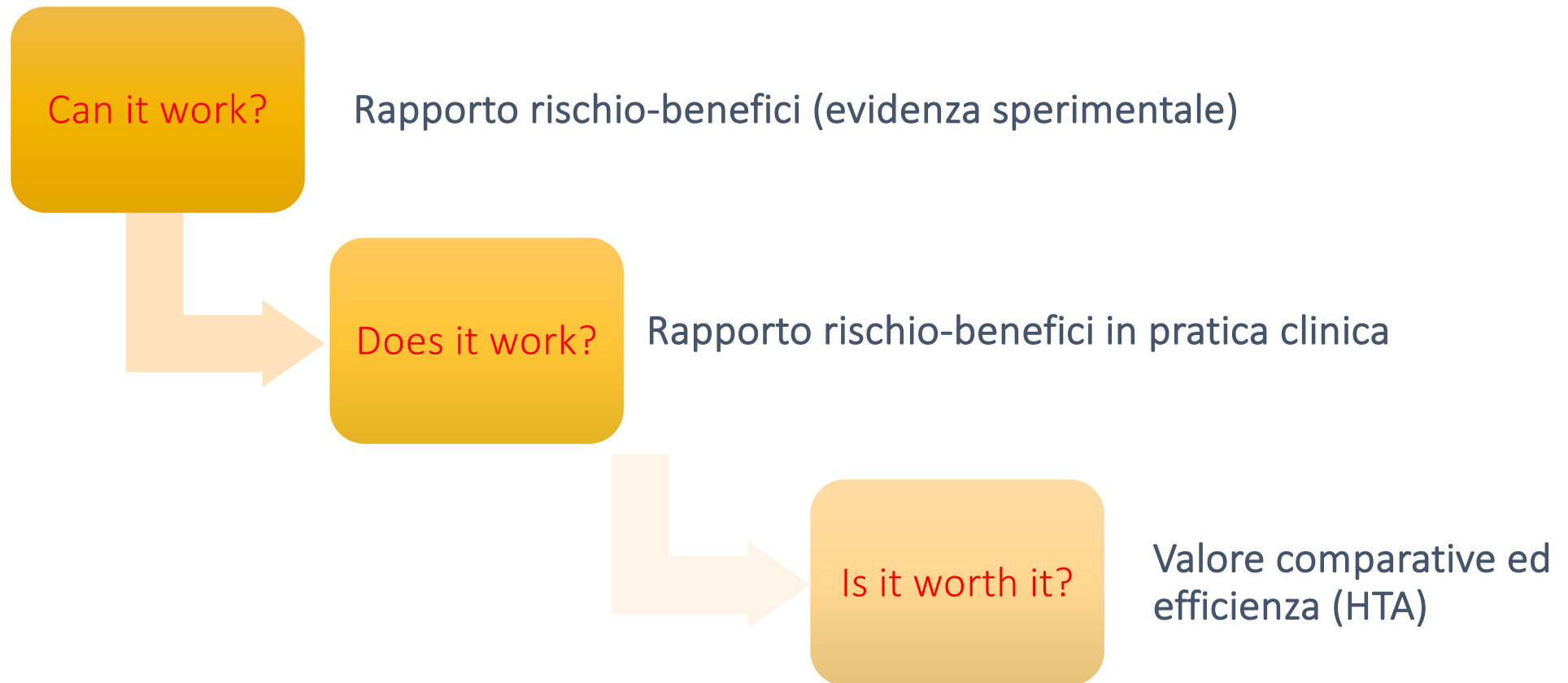


Agenda

- **Le valutazioni di impatto economico dei farmaci**
- Alcune evidenze su Leucemia Linfatica Cronica (LLC)
- Take home message



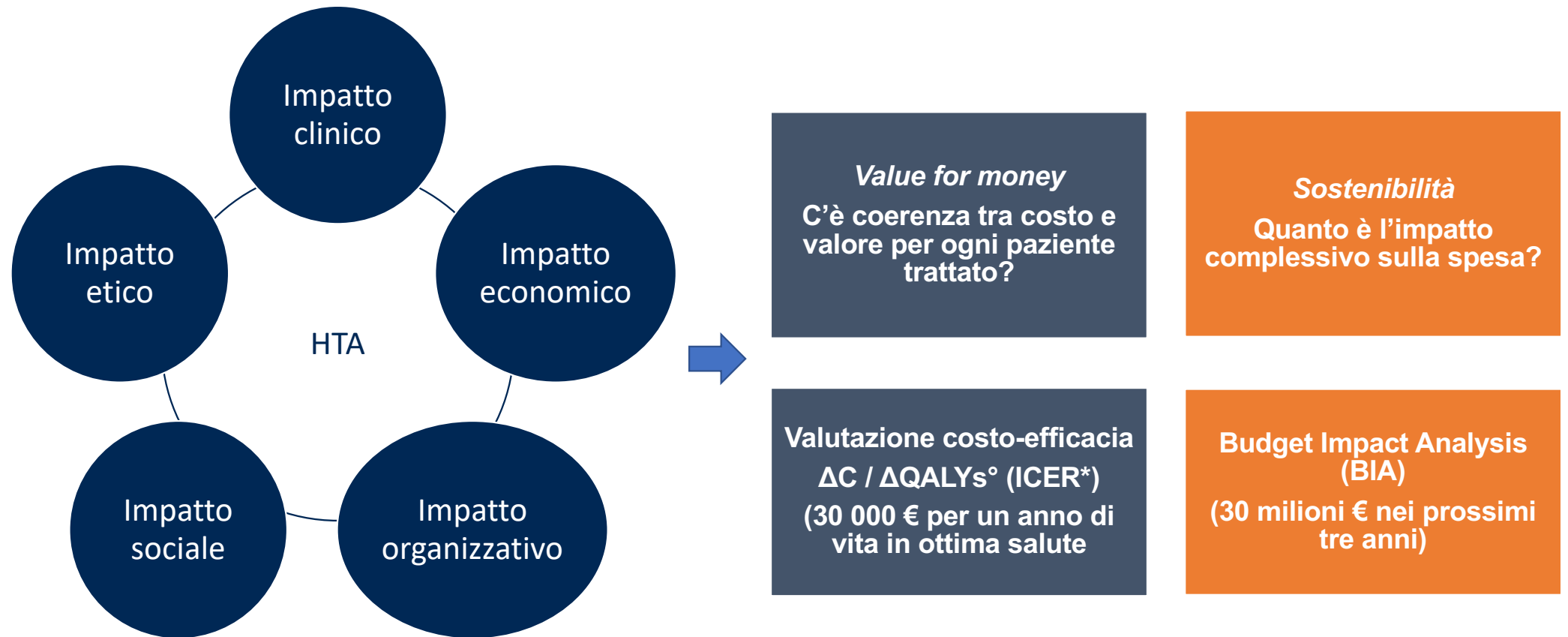
Da evidenze sperimentali a HTA



HTA = Health Technology Assessment



HTA e Valutazioni di Impatto Economico



[°] Quality Adjusted Life Years saved; ^{*} Incremental Cost-Effectiveness Ratio



Confronto tra due alternative: Costi incrementali / costi evitati

**COSTI
INCREMENTALI**



COSTI EVITATI

Δ Costo farmaco (Costo terapia, Costo somministrazione, Costo follow-up pazienti)

Δ Costi associati ad effetti collaterali

Δ Costi associati ad eventi (es. possibile riduzione dei ricoveri; riduzione dei giorni di malattia)

Orizzonte temporale: di norma si dovrebbe considerare un orizzonte temporale oltre il quale le alternative prese in considerazione hanno gli **stessi costi e benefici** (tema molto critico delle sequenze terapeutiche)

= f (...)

Prospettiva adottata



La prospettiva adottata nell'analisi dei costi

Prospettiva SSN
(solo prestazioni rimborsate)

❑ Costi diretti sanitari

- ❑ Terapie farmacologiche
- ❑ Visite specialistiche
- ❑ Esami di laboratorio
- ❑ Diagnostica strumentale
- ❑ Degenza ospedaliera
- ❑ Prestazioni riabilitative
- ❑ Altro

❑ Costi diretti non sanitari

- ❑ Trasporto pazienti
- ❑ Assistenza remunerata
- ❑ Assistenza informale

❑ Costi di produttività persa

- ❑ Assenza dal lavoro
- ❑ Presenteism

Prospettiva Paziente
(solo prestazioni sostenute
direttamente dal paziente)

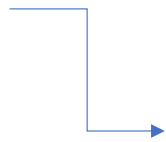
Prospettiva Terzo Pagatore
(solo prestazioni rimborsate)

Prospettiva
della società



La prima sfida: individuazione dei comparatori

- Opzione migliore disponibile per i pazienti
- Corrente pratica clinica
- Alternativa meno costosa
- *Best Supportive Care / Do Nothing (se non ci sono alternative)*



Comparatore in trial? Frequente necessità di confronti indiretti



La seconda sfida: stima dei costi (per paziente)

- Terapia
 - Prezzo
 - Gazzetta Ufficiale
 - Sconto obbligatorio per legge (-5% / -5%) se previsto
 - Eventuale altro sconto negoziato con AIFA (non pubblico, ma noto ai «pagatori»)
 - Dose unitaria (std in caso di dosi associate a peso, BMI, ecc.)
 - Durata trattamento
 - Se durata fissa: dato RCP
 - Se fino a risposta / insorgenza effetti collaterali: Dato studi clinici / RW (se disponibili)
- Somministrazione (se esistente)
- Follow-up (numero prestazioni / tariffe per valorizzazione)

RCP = Riassunto delle Caratteristiche del Prodotto; RW = Real World (data); BMI = Body Mass Index



La seconda sfida: stima dei costi (per paziente)

- Effetti collaterali
 - Gravità (tendenzialmente livello 4)
 - Frequenza desunta da studi clinici o RW
 - Tariffa per valorizzazione dell'episodio di ricovero
- Eventi evitati (es. ospedalizzazioni)
 - Frequenza: studi clinici (se ospedalizzazione è endpoint) o simulati sulla base di modelli
 - Tariffa per valorizzazione dell'episodio di ricovero
- Eventi evitati (es. giorni di malattia)
 - Simulazione / dati di letteratura

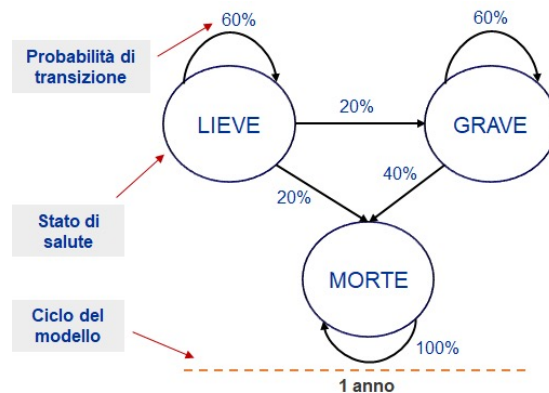


La terza sfida: la stima dei benefici

- Quale beneficio: possibilmente esito finale
 - Anni di vita salvati – LYs
 - Anni di vita salvati corretti (con un peso che va da 0 ad 1) per la qualità di vita – QALYs generata dallo stato di salute
- Due problemi
 - Dal trial non sempre si riesce ad avere il dato di Overall Survival e Quality of Life osservata
 - E' necessario estrapolare i dati nel lungo periodo



Uso di modelli
.... un esempio



Il modello viene fatto girare per «n» cicli fino all'esaurimento della coorte (nessun sopravvissuto). In questo modo possiamo ottenere il dato di OS (Overall Survival) e conseguentemente gli anni di vita guadagnati in seguito all'utilizzo di una terapia



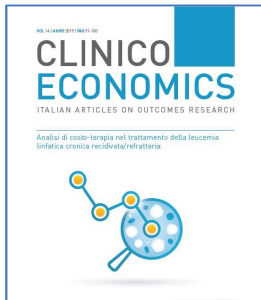
Agenda

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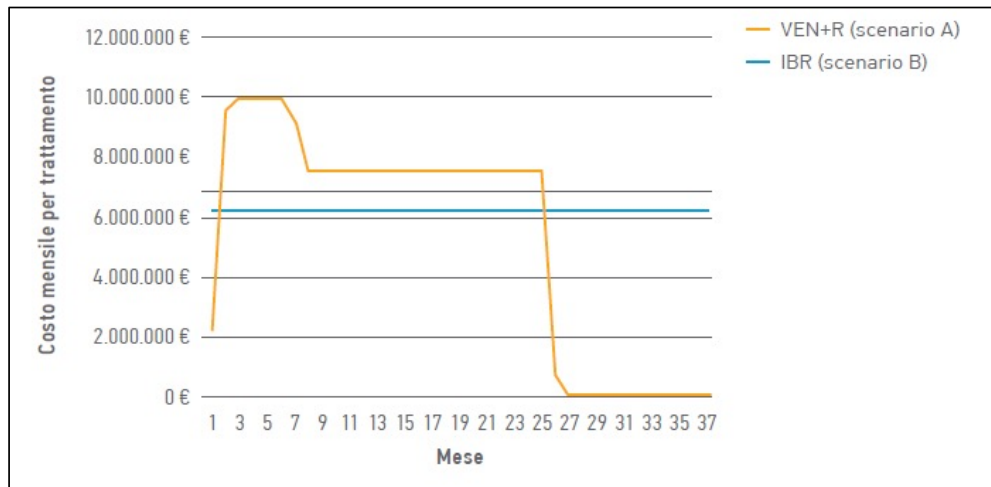
Il confronto tra costi trattamento Ibrutinib vs venetoclax + rituximab (II Linea)



- Prezzo massimo di cessione netto 5+5%
- Dosi da RCP
- Durata massima per venetoclax / DoT – Duration of Treatment (mediana) di studio registrativo per ibrutinib

| | | |
|------------------------|--------------|------------|
| venetoclax + rituximab | 196.546,61 € | } 30,9k €* |
| ibrutinib | 227.440,18 € | |

* Con simulazione ritrattamento post trattamento con venetoclax il differenziale di costo scende da 30,9k€ a 23,2k€



Rigolin GM, Cuneo A, Integlia D, Di Giuseppe F. Analisi di costo-terapia nel trattamento della leucemia linfatica cronica recidivata/refrattaria
Clinico Economics Italian Articles on Outcomes Research 2019. 14, 91-100





Uno studio di costo-efficacia Venetoclax + rituximab (VEN + R) vs altri farmaci (II Linea)



- Dato derivato da adattamento a CH di modello fornito a NICE (England)
- Comparatori individuati
 - Fludarabine + cyclophosphamide + rituximab (FCR)
 - Bendamustine + rituximab (BR)
 - Ibrutinib
 - Ibrutinib + BR
 - Idelalisib + R
 - Venetoclax monoterapia (VEN)
- Prospettiva: Casse Mutue (costi diretti sanitari)
- Orizzonte temporale: 30 anni
- Modello: Three-state partitioned survival model (pre-progressione, post-progressione, morte)
- Fonti dei dati di efficacia: Trial Murano (VEN + R vs BR); Matching adjusted indirect treatment comparison (MAIC) per altri confronti

Barbier M, Durno N, Bennisson C, et al Cost-effectiveness and budget impact of venetoclax in combination with rituximab in relapsed/refractory chronic lymphocytic leukemia in Switzerland. Eur J Health Econ. 2021 Nov 10.



I risultati



| Treatment | Costs (CHF) | QALYs | Comment | Δ Cost (CHF) | Δ QALYs | ICERs (CHF per QALY gained) of non-dominated strategies |
|----------------|-------------|-------|--------------------------|--------------|---------|---|
| BR | 42,004 | 3.981 | | | | Reference |
| FCR | 43,637 | 2.914 | Dominated by BR | | | |
| Idelalisib + R | 114,677 | 2.479 | Dominated by BR, FCR | | | |
| VEN + R | 189,855 | 6.581 | | 147,851 | 2.599 | 56,881 |
| VEN | 275,857 | 4.541 | Dominated by VEN + R | | | |
| Ibrutinib | 375,534 | 4.450 | Dominated by VEN + R, VE | | | |
| Ibrutinib + BR | 504,245 | 5.303 | Dominated by VEN + R | | | |

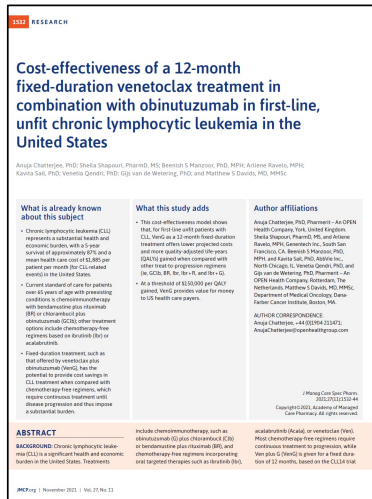
Costo del farmaco rappresenta l'81%-95% dei costi diretti sanitari, eccetto che per rituximab associato a chemioterapie (34-37%).

Risultati più controversi su efficacia comparativa vs ibrutinib in contro-valutazione da parte dell'Evidence Review Group del NICE





Uno secondo studio di costo-efficacia Venetoclax + obinutuzumab (VEN + G) vs altri farmaci (I Linea unfit)



- Comparatori individuati
 - Obinutuzumab + clorambucile (GClb)
 - Bendamustine + rituximab (BR)
 - Ibrutinib (Ibr)
 - Ibrutinib + rituximab (Ibr + R)
 - Acalabrutinib (Acala)
 - Acalabrutinib + obinutuzumab (Acala + G)
- Prospettiva: Pagatore di prestazioni sanitarie (costi diretti sanitari) USA
- Orizzonte temporale: 20 anni
- Modello: Three-state partitioned survival model (pre-progressione, post-progressione, morte)
- Fonti dei dati di efficacia: Trial CLL14 (VEN + G vs GClb); Network metanalisi per altri farmaci
- Fonti dei dati sui trattamenti successivi: expert opinion

Chatterjee A, Shapouri S, Manzoor BS, et al. Cost-effectiveness of a 12-month fixed-duration venetoclax treatment in combination with obinutuzumab in first-line, unfit chronic lymphocytic leukemia in the United States. J Manag Care Spec Pharm. 2021 Nov;27(11):1532-1544.



I risultati

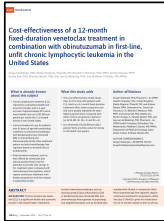


TABLE 2 Cost-Effectiveness of VenG Compared With Other Treatments

| Treatment | Total costs (\$) | Life-years gained | QALYs gained | Incremental costs (\$) | Incremental life-years gained | Incremental QALYs gained | ICER (\$/QALY) |
|-----------|------------------|-------------------|--------------|------------------------|-------------------------------|--------------------------|------------------|
| VenG | \$291,012 | 13.01 | 6.521 | – | – | – | – |
| GClb | \$491,040 | 13.01 | 6.188 | \$200,028 | 0 | –0.333 | VenG is dominant |
| BR | \$595,771 | 12.31 | 5.815 | \$304,759 | –0.70 | –0.706 | VenG is dominant |
| lbr | \$1,045,472 | 12.31 | 6.004 | \$754,460 | –0.70 | –0.517 | VenG is dominant |
| lbr + G | \$1,779,412 | 13.02 | 6.543 | \$1,488,400 | 0.01 | 0.022 | \$67,856,575 |
| lbr + R | \$1,040,860 | 12.22 | 5.946 | \$749,848 | –0.79 | –0.576 | VenG is dominant |
| Acala | \$1,870,749 | 13.55 | 7.194 | \$1,579,737 | 0.54 | 0.672 | \$2,349,304 |
| Acala + G | \$1,947,166 | 13.56 | 7.482 | \$1,656,154 | 0.55 | 0.961 | \$1,724,052 |

Acala = acalabrutinib; B = bendamustine; Clb = chlorambucil; G = obinutuzumab; lbr = ibrutinib; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; R = rituximab; Ven = venetoclax.





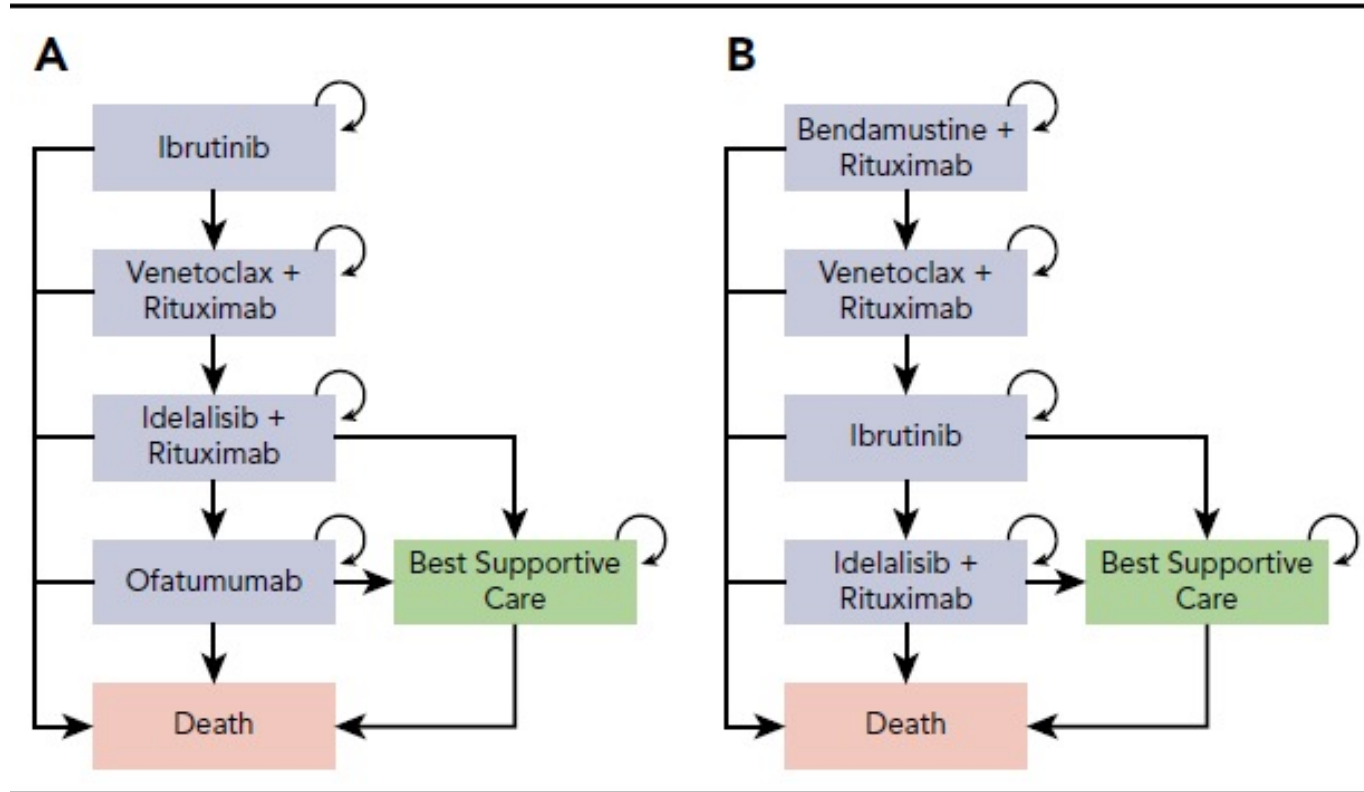
Uno terzo studio di costo-efficacia Valutazione comparativa di due sequenze terapeutiche

Blood Regular Article

UNPUBLISHED MANUSCRIPT
Cost-effectiveness of first-line vs third-line ibrutinib in patients with untreated chronic lymphocytic leukemia
 Barnes JI, Divi V, Begaye A, et al. *Blood* 2018;131:1946-1956. doi:10.1182/blood-2018-07-854444

ABSTRACT
 Ibrutinib is a BTK inhibitor that has been shown to be effective in the treatment of chronic lymphocytic leukemia (CLL). In this study, we assessed the cost-effectiveness of ibrutinib as first-line vs third-line therapy in patients with untreated CLL. We conducted a Markov model analysis comparing the costs and quality-adjusted life expectancy (QALE) of ibrutinib as first-line vs third-line therapy. The model included the costs of ibrutinib, venetoclax, idelalisib, ofatumumab, and best supportive care (BSC). The results showed that ibrutinib as first-line therapy was more cost-effective than ibrutinib as third-line therapy. The incremental cost-effectiveness ratio (ICER) for ibrutinib as first-line therapy was \$100,000 per QALE, which is below the threshold of \$150,000 per QALE. These findings suggest that ibrutinib as first-line therapy is a cost-effective treatment option for patients with untreated CLL.

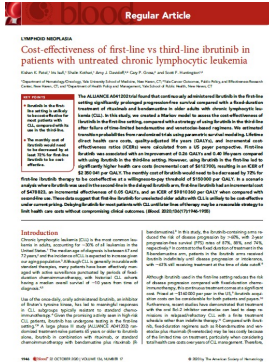
Introduction
 Chronic lymphocytic leukemia (CLL) is a common hematologic malignancy. The standard of care for CLL is ibrutinib, which has been shown to be effective in the treatment of CLL. However, ibrutinib is a costly medication, and its use as first-line therapy may not be cost-effective for all patients. In this study, we assessed the cost-effectiveness of ibrutinib as first-line vs third-line therapy in patients with untreated CLL. We conducted a Markov model analysis comparing the costs and quality-adjusted life expectancy (QALE) of ibrutinib as first-line vs third-line therapy. The model included the costs of ibrutinib, venetoclax, idelalisib, ofatumumab, and best supportive care (BSC). The results showed that ibrutinib as first-line therapy was more cost-effective than ibrutinib as third-line therapy. The incremental cost-effectiveness ratio (ICER) for ibrutinib as first-line therapy was \$100,000 per QALE, which is below the threshold of \$150,000 per QALE. These findings suggest that ibrutinib as first-line therapy is a cost-effective treatment option for patients with untreated CLL.



Barnes JI, Divi V, Begaye A, et al. Cost-effectiveness of ibrutinib as first-line therapy for chronic lymphocytic leukemia in older adults without deletion 17p. *Blood Adv.* 2018 Aug 14;2(15):1946-1956.



La tipologia di studio ed i risultati



- Prospettiva: Pagatore di prestazioni sanitarie (costi diretti sanitari) USA
- Orizzonte temporale: life-time
- Modello: Modello di Markov (a cicli di tre mesi)
- Probabilità di transizione da una terapia all'altra desunta dagli studi clinici di riferimento

| Strategy | Costs (US\$) | Incremental costs (US\$) | Effectiveness (QALY) | Incremental effectiveness (QALY) | ICER (\$ per QALY) |
|----------------------|--------------|--------------------------|----------------------|----------------------------------|--------------------|
| Ibrutinib first-line | \$1 367 275 | \$612 700 | 6.85 | 0.26 | \$2 350 041 |
| Delayed ibrutinib | \$754 575 | — | 6.59 | — | — |

Barnes JJ, Divi V, Begaye A, et al. Cost-effectiveness of ibrutinib as first-line therapy for chronic lymphocytic leukemia in older adults without deletion 17p. *Blood Adv.* 2018 Aug 14;2(15):1946-1956.



Il costo della LLC : una revisione di letteratura

Pharmacoeconomics (2016) 34:479–498
DOI 10.1007/s40273-015-0363-7

SYSTEMATIC REVIEW

Economic Burden and Quality-of-Life Effects of Chronic Lymphocytic Leukemia: A Systematic Review of the Literature

Simon Frey¹ · Carl R. Blankart^{1,2} · Tom Stargardt¹

Published online: 6 January 2016
© Springer International Publishing Switzerland 2015

Abstract
Background Chronic lymphocytic leukemia (CLL) is the most prevalent type of leukemia in the Western hemisphere. The disease affects quality of life (QoL) and poses an economic burden on patients, payers, and society. The objective of this review was to quantify the economic burden and quality-of-life effects and identify the gaps that should be addressed by future research.
Methods Free-text and subject heading searches in MEDLINE, EMBASE, the Cochrane Library, the University of York Centre for Reviews and Dissemination Database, and the Web of Science Core Collection database were conducted to identify observational and interventional studies reporting costs and/or quality-of-life effects published up to 2 October 2015. Studies were included irrespective of whether they were conducted prospectively or retrospectively. The focus population consisted of adult patients aged 18 years or older affected by any stage of CLL. Studies were included regardless of whether the underlying population was treated as baseline or not. Risk of Bias was assessed using a quality checklist developed by the Effective Public Health Practice Project for (randomly) controlled trials, cohort studies, and cross-sectional studies. Economic evaluation were rated using a checklist developed by Stübgen et al. (*Int J Eat Disord* 43:478–91, 2012).
Results From 2451 records identified, 27 studies were found to be eligible for inclusion. Studies were heterogeneous with respect to methodology, perspective, and data used. Annual direct costs per person ranged from US\$491 in Germany to US\$43,913 in the USA. The share of costs attributable to drug treatment varied between 26.2 and 79.9. Indirect costs amounted to US\$208. Severity of disease was a predictor for quality of life, whereas differences by age and sex were mainly present in subdomains. Comparison of treated and untreated populations resulted in an increase of quality of life in favor of treated populations in the long-term perspective. Differences between treatment were small. Consequently, cost effectiveness in decision-analytic models did not depend on whether quality of life or survival are used to describe the benefits of treatment.
Conclusions Although the quantity and the quality of health, economic and quality-of-life evidence have substantially increased, there is still a need for studies that take a patient or societal perspective. Factors that influence costs and the quality of life of patients seem to be well-established, while longitudinal lifetime cost studies at the population level are still scarce.

Electronic supplementary material The online version of this article (doi:10.1007/s40273-015-0363-7) contains supplementary material, which is available to authorized users.

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| | Study | | |
|---|----------------------|--------------------------|------------------|
| | Blankart et al. [22] | Holtzer-Goor et al. [28] | Reis et al. [39] |
| Country | GER | NL | GER |
| Direct costs (US\$) | 6045 | 7736 | 4491 |
| % drug costs | 38.6 | 30.3 | 26.2 |
| % inpatient costs | 53.1 | 43.1 | 58.2 |
| % outpatient costs | 9.8 | 26.6 | 7.0 |
| % other costs | −1.5 ^b | | 8.7 ^d |
| Indirect costs (US\$) | 4208 | | 2496 |
| Burden of disease (population level) (US\$) | 245.94 m | | 364.75 m |

Frey S, Blankart CR, Stargardt T. Economic Burden and Quality-of-Life Effects of Chronic Lymphocytic Leukemia: A Systematic Review of the Literature. *Pharmacoeconomics*. 2016 May;34(5):479-98.





La sostenibilità delle terapie orali continuative per LLC Prospettiva: pagatori di prestazioni sanitarie

Article
Impact of Oral Targeted Therapy on the Economic Burden of Chronic Lymphocytic Leukemia in Canada

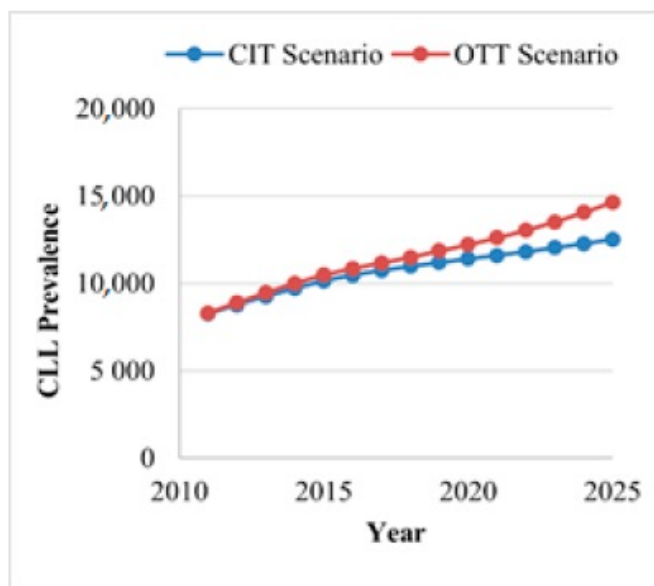
Jean Lachaine ^{1,2,*}, Catherine Beauchemin ^{1,2}, Kimberly Guinan ², Philippe Thebault ², Andrew Aw ³, Versha Banerji ^{4,5}, Isabelle Fleury ⁶ and Carolyn Owen ⁷

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⁶ Maisonneuve-Rosemont Hospital, Montreal, QC H1T 2M4, Canada; ifleury.hmr@ssss.gouv.qc.ca
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* Correspondence: jean.lachaine@peripharm.com

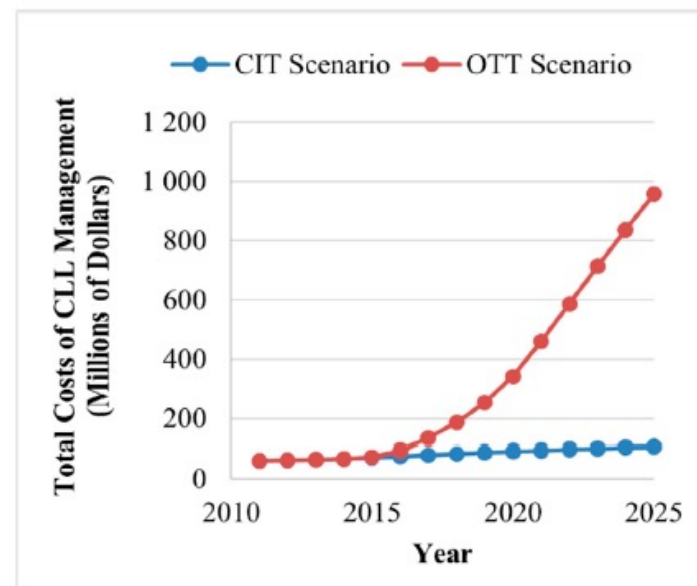
Received: 16 November 2020; Accepted: 30 December 2020; Published: 9 January 2021

Abstract: *Background:* Continuous oral targeted therapy (OTT) for chronic lymphocytic leukemia (CLL) represents an effective therapy but also a major economic burden on the healthcare system. This study aimed to estimate future direct costs, along with the prevalence, of CLL in the era of continuous OTT in Canada. *Methods:* The economic burden of OTT was modelled and compared to chemoimmunotherapy (CIT), for CLL treatment. The burden was assessed/projected from 2011 to 2025. For the OTT scenario, CIT was considered the standard of care before 2015, while OTT was considered standard of care for patients with either unmutated immunoglobulin heavy-chain variable (IGHV) or del(17p)/TP53 mutations starting in 2015 and, from 2020 onwards, for all first-line treatments except for patients with mutated IGHV. A Markov model was developed including four health states: watchful-waiting, first-line treatment, relapse and death. Costs of therapy, follow-up/monitoring and adverse events were included. Key clinical parameters were extracted from pivotal clinical trials. *Results:* As incidence rates and rate of survival are increasing, the prevalence of CLL in Canada is projected to increase 1.8-fold, from 8301 patients in 2011 to 14,654 by 2025. Correspondingly, the total annual costs of CLL management are predicted to increase 15.7-fold, from \$60.8 million to \$957.5 million during that same period. *Conclusions:* Although OTT enhances survival for patients with CLL, it is nonetheless associated with an important economic burden due to the projected vast increase in costs from 2011 to 2025. Changes in clinical strategies, such as implementation of a fixed OTT treatment duration, could help alleviate financial burden.

Keywords: chronic lymphocytic leukemia; oral targeted therapy; economic burden; Markov model



(a)



(b)

CIT = chemoimmunotherapy. OTT = Continuous oral targeted therapy

Lachaine J, Beauchemin C, Guinan K, et al. Impact of Oral Targeted Therapy on the Economic Burden of Chronic Lymphocytic Leukemia in Canada. *Curr Oncol.* 2021 Jan 9;28(1):332-345.



Agenda

- Le valutazioni di impatto economico dei farmaci
- Alcune evidenze su Leucemia Linfatica Cronica (LLC)
- **Take home message**



Take home message

- Le evidenze economiche complete (analisi di costo-efficacia)
 - possono essere di supporto nelle scelte sia per il loro risultato finale (ICER) sia per i dati che generano tale risultato (es. comparazione costo-terapia)
 - risentono della robustezza dei dati clinici (estrapolazione degli effetti nel lungo periodo, confronti indiretti, analisi sequenze)
- La LLC è una patologia caratterizzata da una quota maggiore di costo a carico del sistema sanitario, rispetto al costo complessivo nella prospettiva della società
- La disponibilità di terapie per LLC è sensibilmente aumentata negli ultimi anni
- Le terapie a durata fissa presentano dei vantaggi sotto il profilo dei costi (maggiori incertezze su efficacia comparativa)
- Tali terapie (e le eventuali future terapie *one-shot*) richiedono un approccio di gestione delle risorse con orizzonte temporale medio-lungo
- E' comunque importante rafforzare le evidenze *real-life*



Grazie per l'attenzione

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