# Cost-Utility Analysis in Chronic Lymphocytic Leukemia: Is COVID-19's Impact on National Life Tables Important to Consider?

EE516

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## INTRODUCTION

- The economic value of novel oncology therapies is commonly quantified through a cost-utility analysis (CUA), requiring extrapolation of life-years (LYs) and quality-adjusted LYs (QALYs) over a patient's lifetime.[1] General population survival estimates, stated within national life tables (NLTs), are commonly used to guide long-term predictions of patients' survival, with health authorities requiring the latest available NLTs for CUAs
- The NLTs currently available are based on data from 2020-2021, thus including the initial impact of the COVID-19 pandemic, which led to >6.9 million deaths globally,[2] and decreasing general population life expectancy in 2020-2021 compared with previous years.[3] However, general population life expectancy is expected to increase in the future, despite the short-term impact of the COVID-19 pandemic.[1,4,5] Furthermore, 2022-2023 COVID-19 burden seems reduced vs 2020-2021, likely due to the vaccination program and the SARS-CoV-2 virus evolution
- Therefore, the aim of this study was to conduct a targeted literature review (TLR) to understand whether COVID-19 death burden in the general population during the latest infection waves (2022-2023) has significantly decreased compared with earlier waves (2020-2021). Furthermore, this study aimed to quantify the impact of using 2020-2021 NLTs compared with previous years (with no COVID-19 burden) on CUA outcomes, using a case study in chronic lymphocytic leukemia (CLL)

## METHODS

### Objective 1. TLR of COVID-19 Death Burden

- A TLR was conducted focusing on the change in the risk of severe COVID-19 (hospitalization or death) across COVID-19 waves of infection (ie, ancestral variants vs Alpha vs Delta vs Omicron variants)
  - The Our World in Data (OWID) dashboard was reviewed,[6] which summarizes the daily new confirmed COVID-19 deaths from January 2020 to June 2023 based on the World Health Organization (WHO) COVID-19 dashboard[2]
  - A literature search was then conducted (32 abstracts screened and 15 full text publications reviewed), focusing on publications comparing the change in the risk of severe COVID-19 across COVID-19 waves in the general population or in individuals with hematologic malignancies, with a preference for global studies or studies conducted in the EU-5 (France, Germany, Spain, Italy, and UK)

### Objective 2. Case Study in CLL

- A partitioned survival model with 3 health states (progression free, post progression, and death) was developed to perform a CUA. The analysis compared a hypothetical novel product (HNP) vs the standard of care (SOC); the model inputs are summarized in **Table 1**. The case study inputs were chosen to be representative of the CLL indication but were not specific to a single trial or a single novel product
- The CUA outcomes of interest were incremental LYs between HNP and SOC, incremental QALYs, and monetary impact estimated as willingness-to-pay (WTP) threshold multiplied by incremental QALYs
- The analysis focused on 5 countries (France, Germany, Spain, Italy, and UK) and 5 years (2016-2021) assessing the impact of using NLTs from different years on the CUA outcomes. The base case adopted a lifetime horizon (30 years), with pre-/postprogression utilities scaled for each country using country-specific utilities from the general population
- Scenario analyses were conducted considering (1) the same pre-/postprogression utilities across countries, (2) age-adjusted utilities for each country, (3) a more effective HNP with a 25% lower PFS/OS HR vs SOC compared with the base case, (4) a less effective HNP with a 25% higher PFS/OS HR vs SOC compared with the base case

**Table 1. Summary of Case Study Inputs**

| Parameter | Value and source | | | | |
|---|---|---|---|---|---|
| **Mean age and sex distribution** | 66.9 years and 31.7% women, comparable to ALPINE trial[7] | | | | |
| **SOC PFS and OS efficacy** | Parametric survival analysis (PFS and OS) of the SOC arm of the ALPINE trial,[7] anonymized by adding a random number to the estimated parameters | | | | |
| **HNP efficacy** | PFS HR, 0.4 (95% CI, 0.1[8] to 0.65[7]) and OS HR, 0.75 (95% CI, 0.41[9] to 1.07[10]) vs SOC, selected as plausible midpoints across the values observed in 1L-2L CLL | | | | |
| **Utilities** | Preprogression, 0.748; postprogression, 0.6 (derived from NICE TA 561[11]) | | | | |
| **Countries** | **UK** | **Italy** | **France** | **Germany** | **Spain** |
| **Health outcomes discounting**[a] | 3.5% | 3% | 2.5% | 3% | 3% |
| **NLTs** | Office for National Statistics[12] | Eurostat[13] | | | |
| **General population utilities** | Ara et al 2010[14] | Meregaglia et al 2023[15] | Gautier et al 2023[16] | Marten et al 2021[17] | Hernandez et al 2018[18] |
| **WTP threshold** | £30,000 | €28,396[b] | €34,291[b] | €38,509[b] | €30,000 |

[a]Health outcomes discounting was sourced from local health technology assessment guidelines for CUA modeling. [b]No formal threshold. Estimated as gross domestic product per capita.[19]
1L, first-line; 2L, second-line; CLL, chronic lymphocytic leukemia; HNP, hypothetical novel product; HR, hazard ratio; NICE, National Institute for Health and Care Excellence; NLT, national life table; OS, overall survival; PFS, progression-free survival; SOC, standard of care; TA, technology appraisal; WTP, willingness-to-pay.

## RESULTS

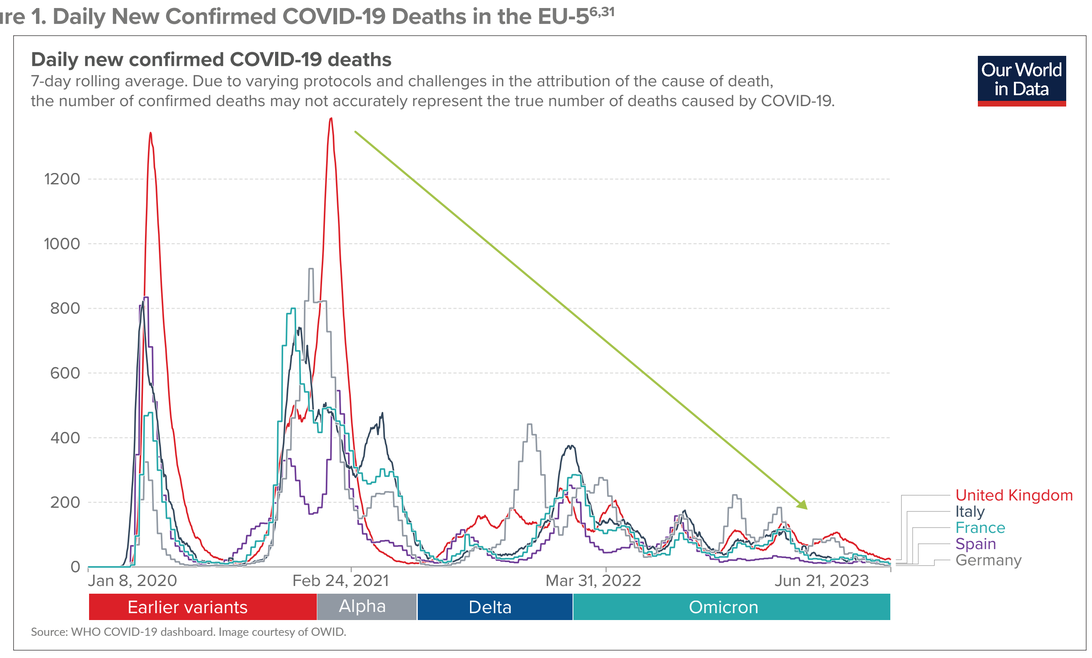
### Objective 1. TLR of COVID-19 Death Burden

- Based on the OWID dashboard review (**Figure 1**), a clear downward trend in COVID-19 deaths was consistently observed across EU-5, from January 2021 onward, despite multiple peaks in cases or hospitalizations across countries in 2022-2023. Therefore, 2022-2023 COVID-19 death burden in the general population was significantly reduced compared with 2020-2021 (years for which the latest NLTs are available and were used in the case study)
- The majority of studies identified in the TLR that focused on comparing the risk of severe COVID-19 during the period when the Delta variant was dominant vs when the Omicron variant was dominant (from the start of 2022 onward) confirmed that the risk of mortality in the general population has decreased during the Omicron waves (adjusted odds ratio [OR],[20] 0.16-0.38; adjusted hazard ratio, 0.31[21]-0.34[22]; log relative risk, 0.59[23]). A similar pattern was observed in the risk of hospital or ICU admission
  - Most of the studies accounted for confounding factors (which differed across studies) and effect modifiers by adjusting for age, sex, and in most cases, vaccination status
  - Qiu et al 2023[23] was the most comprehensive study among the full text publications, with a meta-analysis across 62 studies concluding that the inherent virulence of the Omicron variant is weakened compared with the Delta variant
  - Studies that compared additional COVID-19 waves, such as Florensa et al 2022[24] in Spain, found that rates of admission were halved with the Alpha vs Delta variant, and mortality rates were one-fourth; Varea-Jiménez et al 2023 (Spain)[25] demonstrated further reduction in hospitalization risk with Omicron vs Delta (adjusted OR: 0.28)
- Similarly, most studies focusing on immunocompromised individuals or individuals with hematologic malignancies highlighted a significant decrease in hospitalization and death rates when comparing across COVID-19 waves[26-29]
  - Only one study did not observe significant survival differences following COVID-19 infection when stratifying patients by COVID-19 variant[30]
  - Turtle et al 2023[26] (N=21,954, of whom 5116 were patients with cancer) found that in the fourth COVID-19 wave (nearly a year after the vaccination program was initiated), the OR for death compared with the first wave was 0.38 (95% CI, 0.34-0.42; *P*<.001) for immunocompetent individuals and 0.66 (95% CI, 0.54-0.80; *P*<.001) for immunocompromised patients
  - Willan et al 2023[28] (N=128) observed that, in individuals with hematologic malignancies, the 90-day COVID-19 mortality rate following the ancestral or Alpha variants was 42% vs 9% with the Delta variant and 2% with the Omicron variant
  - Niemann et al 2022 (N=793) observed that the overall CLL patient population had a much milder course of COVID-19 during the Omicron era (especially during BA.2 dominance), with a 30-day fatality rate of 2%[29]
- In summary, the COVID-19 death burden in the general population and in immunocompromised individuals or individuals with hematologic malignancies was highest in 2020-2021 and largely decreased from 2022 onward (Omicron wave)
- The case study then quantifies how the temporary high death burden of COVID-19 in 2020-2021 impacts CUA outcomes in CLL

## CONCLUSIONS

- Using pre-pandemic life tables (ie, 2019) to reflect the current life expectancy seems more appropriate than using 2020-2021 NLTs. This is because 2022-2023 NLTs will likely show an increased life expectancy compared with 2020-2021, given the significantly reduced COVID-19 death burden observed in 2022-2023 vs 2020-2021
  - Using 2020 vs 2019 NLTs for CUA led to an incremental benefit underestimation of novel CLL therapies due to 2020 COVID-19 mortality. This underestimation was more pronounced in Spain, Italy, and the UK and further increased with a more effective HNP. Countries that were least impacted by COVID-19, such as Germany, were also less impacted in this case study

**Figure 1. Daily New Confirmed COVID-19 Deaths in the EU-5[6,31]**

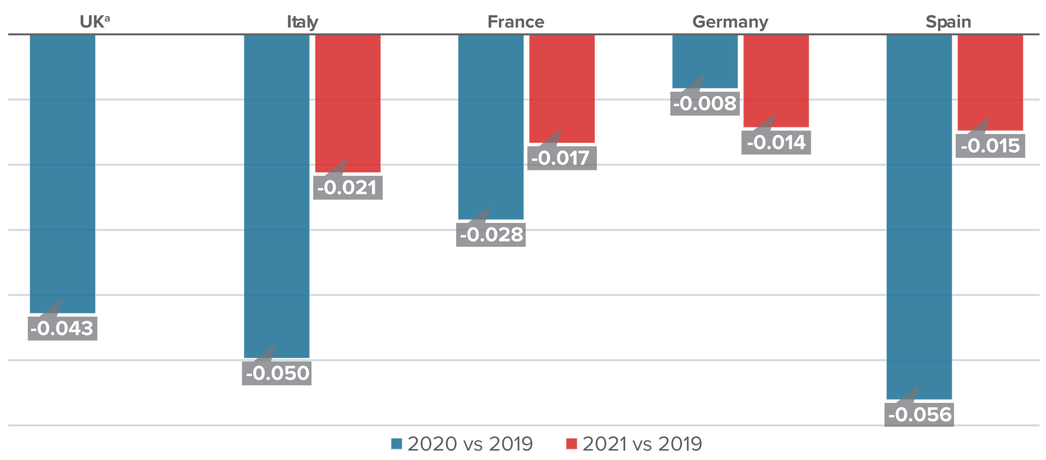



The green arrow highlights the steep decrease observed from Q1 2021 onwards.

### Objective 2. Case Study in CLL

- The incremental QALYs between the SOC and the HNP were either relatively stable or increased across all countries when 2017-2019 vs 2016 NLTs were used. However, a relatively large decrease in incremental QALYs was observed across all countries except Germany when 2020 vs 2019 NLTs were used (**Figure 2**)
  - The decrement in 2020 vs 2019 was far greater than the changes observed for the previous years and was only partially recovered in 2021, with 2021 NLTs providing similar or lower incremental QALYs than 2016 NLTs

**Figure 2. Change in Incremental QALYs (HNP vs SOC) Using 2020 and 2021 vs 2019 NLTs**




[a]No life table data were available for the UK for 2021. HNP, hypothetical novel product; NLT, national life table; QALY, quality-adjusted life-year; SOC, standard of care.

- The incremental QALY results were multiplied by the country-specific WTP threshold to elucidate the monetary impact of using the latest pre–COVID-19 life table (ie, 2019) vs the life tables that included COVID-19 (2020-2021). Using the 2020 vs 2019 NLTs led to a lower economically justifiable price (EJP) of €320–€1681 over the modeled time horizon, as summarized in **Table 2**
  - Using the 2021 NLTs partially reduced the observed 2020 EJP decrement, still leading to a lower EJP than if using the 2019 NLTs
- Scenario analyses demonstrated that the alternative utility approaches that were investigated had a limited impact on the results of the analysis. However, varying the HNP efficacy had a more significant effect on the analysis outcomes
  - A more effective HNP led to a larger impact of 2019 vs 2020 NLTs on the estimated incremental QALYs, and consequently the EJP, over the modeled time horizon (€588-€3301 vs €320-€1681 in the base case)
  - A less effective HNP had a similar impact but in the opposite direction (EJP of €117-€594 vs €320-€1681 in the base case)

**Table 2. Change in Economically Justifiable Price Over the Modeled Time Horizon**

| Change in economically justifiable price (incremental QALYs over the time horizon × WTP) | 2019 | 2020 | 2021 |
|---|---|---|---|
| **United Kingdom** | Reference | −£ 1284.66 | – |
| **Italy** | | −€ 1411.17 | −€ 602.21 |
| **France** | | −€ 975.17 | −€ 572.07 |
| **Germany** | | −€ 320.03 | −€ 549.87 |
| **Spain** | | −€ 1681.58 | −€ 443.74 |

QALY, quality-adjusted life-year; WTP, willingness-to-pay.

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## DISCLOSURES

**SR, AR, BP:** Employment: Evidera, a part of Thermo Fisher Scientific, which received funding from BeiGene to conduct this study. **LM, AP, NB, KY:** Employment: BeiGene.

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