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# Risk of Richter Transformation in Relapsed/Refractory Chronic Lymphocytic Leukemia: Results of Bayesian Network Meta-Analysis

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## INTRODUCTION

### BACKGROUND

- Richter transformation (RT) is a rare but serious complication of chronic lymphocytic leukemia (CLL), in which the disease converts into other aggressive forms of hematological and lymphoid malignancies, like diffuse large B-cell leukemia or Hodgkin's lymphoma[1]
- RT is associated with a poor prognosis, with median overall survival of only a few months in most cases[2]
- The exact cause of RT is poorly understood, but it is thought to be related to genetic mutations that drive the transformation of CLL cells[3]
- The relative risk of developing RT during treatment with various therapeutic options, including novel targeted agents (BCL2 antagonists, BTK inhibitors, and PI3K inhibitors) has not been analyzed yet

### OBJECTIVE

- The study aimed to compare the risk of occurrence of RT between possible therapies for relapsed/refractory CLL using statistical methods of Bayesian network meta-analysis (NMA)
- The analyzed therapies included:
  - Chemotherapy:
    e.g., bendamustine (BEND)
  - Immunotherapy:
    e.g., ofatumumab (OFA), rituximab (RTX)
  - B-cell receptor inhibitors:
    e.g., acalabrutinib (ACA), ibrutinib (IBR), idelalisib (IDE)
  - BCL2 antagonists:
    e.g., venetoclax (VEN)

  which were used as monotherapy or in combination with other agents

## METHODS

### SYSTEMATIC LITERATURE REVIEW

- We performed a systematic search for randomized clinical trials conducted in patients with relapsed/refractory disease who previously received at least one treatment line
- Searched sources included medical databases (MEDLINE, EMBASE, CENTRAL), clinical trials registries (e.g., ClinicalTrials.gov), conference proceedings of hematological and oncological societies (e.g., American Society of Hematology), websites of medicines regulatory authorities (e.g., European Medicines Agency) and health-technology assessment agencies (e.g., National Institute for Health and Care Excellence)
- The last systematic search was performed on August 22, 2022
- The systematic review (CRD42022304330) was performed in agreement with PRISMA guidelines and their extension for network meta-analyses (NMA)[4,5]

### NETWORK META-ANALYSIS

- We performed Bayesian NMAs to synthesize direct and indirect evidence for relapsed/refractory CLL
- Data for the longest follow-up from the identified by systematic search studies were used to compare the RT rates
- All analyses were performed using a fixed model and GeMTC package for R software
- The results of NMA were presented as risk ratios (RR) with 95% credible intervals (CrI)
- SUCRA values were also caluclated for each treatment

## RESULTS

### SEARCH RESULTS

- The systematic search identified 6 randomized clinical trials for relapsed/refractory CLL in which data for RT were reported (ASCEND[6], ELEVATE-RR[7], MURANO[8], RESONATE[9], Study119[10], TUGELA[11]) (Fig. 1)

### RICHTER TRANSFORMATION

- Raw data from identified studies showed that the rate of RT did not exceed 5% for each analyzed therapy
- The relative risk of RT development was comparable between treatments with no statistically significant differences found (Fig. 2)
- The highest value of SUCRA was reported for IDE+BEND+RTX regimen (0.76)

**Figure 1**. Network plot for trials in relapsed/refractory CLL

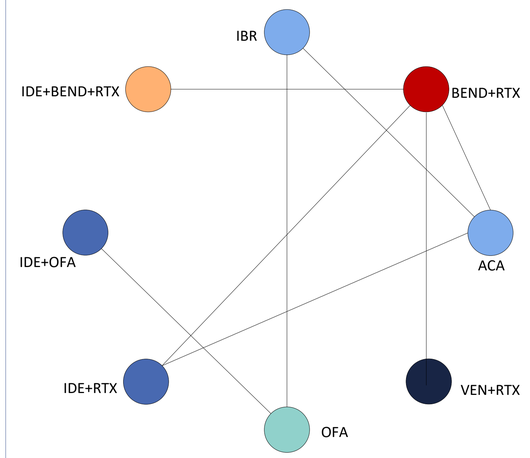


**Figure 2**. Relative safety matrix for RT development
Comparison of the included interventions: risk ratio [95% CrI]. Each cell gives the effect of the column-defining intervention relative to the row-defining intervention

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ACA | 1.32 [0.59; 3.06] | 1.27 [0.12; 12.80] | 0.93 [0.03; 9.62] | 0.81 [0.03; 5,92] | 0.82 [0.05; 11.90] | 1.28 [0.30, 5.47] | 0.43 [0.04; 4.74] |
| | IBR | 0.96 [0.10; 8.32] | 0.69 [0.02; 8.38] | 0.60 [0.02; 5.34] | 0.62 [0.47; 8.09] | 0.97 [0.18; 5.06] | 0.32 [0.01; 4.14] |
| | | OFA | 0.70 [0.01; 20.30] | 0.60 [0.01; 14.40] | 0.64 [0.17; 2.62] | 1.01 [0.07; 16.20] | 0.32 [0.01; 10.00] |
| | | | VEN+RTX | 0.85 [0.28; 2.57] | 0.94 [0.02; 61.90] | 1.37 [0.13; 39.90] | 0.47 [0.08; 2.40] |
| | | | | BEND+RTX | 1.10 [0.03; 62.80] | 1.57 [0.21; 41.20] | 0.56 [0.14; 1.85] |
| | | | | | IDE+OFA | 1.56 [0.38; 5.88] | 0.49 [0.01; 20.00] |
| | | | | | | IDE+RTX | 0.34 [0.01; 3.81] |
| | | | | | | | IDE+BEND+RTX |
| SUCRA | | | | | | | |
| 0.51 | 0.36 | 0.39 | 0.48 | 0.54 | 0.56 | 0.39 | 0.76 |

## CONCLUSIONS

- This study suggests that the choice of treatment regimen has no significant impact on the development of RT.
- The risk of RT is similar between chemoimmunotherapy, immunotherapy, and novel targeted therapies, including BTK and PI3K inhibitors and BCL-2 antagonists

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### FIGURE LEGEND

- BCL2 antagonist + immunotherapy
- Chemoimmunotherapy
- Immunotherapy (anti-CD20)
- PI3K inhibitor + immunotherapy
- PI3K inhibitor + chemoimmunotherapy
- BTK inhibitor + immunotherapy

### ABBREVIATIONS

ACA – acalabrutinib; BEND – bendamustine; CLL – chronic lymphocytic leukemia; CrI – credible interval; IBR – ibrutinib; IDE – idelalisib; NMA – network meta-analysis; OFA – ofatumumab; RT – Richter transformation; RTX – rituximab; RR – risk ratio; VEN – venetoclax

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