Material Suplementar

Quadro 1 – Estratégias de busca e quantitativo de resultados recuperados por base.

	ESTRATÉGIAS DE BUSCA	N
PUBMED	((Leukemia, Lymphocytic, Chronic, B-Cell OR Small-Cell Lymphoma* OR Small Cell Lymphoma* OR Chronic Lymphoblastic Leukemia* OR Lymphocytic Lymphoma* OR Chronic B-Cell Leukemia* OR Low-Grade B-Cell OR Chronic B-Lymphocytic Leukemia* OR Chronic Lymphocytic Leukemia* OR Chronic Lymphatic Leukemia* OR Chronic Lymphocytic Leukaemia* OR CLL) AND (Untreated OR first-line OR first line OR firstline OR näive OR naïve OR Tumor Suppressor Protein p53 OR Genes, p53 OR "Tumor Suppressor p53-Binding Protein 1" OR P53 OR TP53 OR 17p)) AND ("randomized controlled trial"[pt] OR "randomized controlled trials as topic" OR "random allocation" OR "double-blind method" OR "single-blind method" OR random*[tw] OR "Placebos" OR placebo OR Phase 2 OR Phase 3 OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw] OR dumm*[tw])))	**1.495**
EMBASE	('chronic lymphatic leukemia'/exp OR 'chronic lymphatic leukemia':ti,ab OR 'chronic lymphocyte leukaemia':ti,ab OR 'chronic lymphocyte leukemia':ti,ab OR 'chronic lymphocytic leukaemia':ti,ab OR 'chronic lymphocytic leukemia':ti,ab OR 'chronic lymphoid leukaemia':ti,ab OR 'chronic lymphoid leukemia':ti,ab OR 'chronic lymphatic leukaemia':ti,ab OR 'chronic lymphatic leucemia':ti,ab OR 'leukemia, chronic lymphatic':ti,ab OR 'leukemia, lymphocytic, chronic':ti,ab OR 'lymphatic chronic leukaemia':ti,ab OR 'lymphatic chronic leukemia':ti,ab) AND ('Untreated' OR 'first-line' OR 'first line' OR 'firstline' OR 'näive' OR 'naïve' OR 'protein p53'/exp OR 'tp53 protein':ti,ab OR 'p53':ti,ab OR 'p53 protein':ti,ab OR 'phosphoprotein p53':ti,ab OR 'protein tp53':ti,ab OR 'protein p 53':ti,ab OR 'protein p53':ti,ab OR 'tumor suppressor protein p53':ti,ab OR 'tumour suppressor protein p53':ti,ab OR 17p:ti,ab) AND ('randomized controlled trial'/exp OR 'controlled trial, randomized':ti,ab,kw OR 'randomised controlled study':ti,ab,kw OR 'randomised controlled trial':ti,ab,kw OR 'randomized controlled study':ti,ab,kw OR 'randomized controlled trial':ti,ab,kw OR 'trial, randomized controlled':ti,ab,kw OR 'randomized controlled trial'/de) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	**339**
LILACS	("Leukemia Lymphocytic Chronic B-Cell" OR "Small-Cell Lymphoma" OR "Small Cell Lymphomas" OR "Chronic Lymphoblastic Leukemia" OR "Chronic Lymphoblastic Leukemias" OR "Lymphocytic Lymphoma" OR "Lymphocytic Lymphomas" OR "Chronic B-Cell Leukemia" OR "Chronic B-Cell Leukemias" OR "Low-Grade B-Cell" OR "Chronic B-Lymphocytic Leukemia" OR "Chronic B-Lymphocytic Leukemias" OR "Chronic Lymphocytic Leukemia" OR "Chronic Lymphocytic Leukemias" OR cll) AND ("Tumor Suppressor Protein p53" OR "Genes p53" OR "Tumor Suppressor p53-Binding Protein 1" OR p53 OR tp53 OR 17p) AND (type_of_study:("clinical_trials")) AND (db:("WPRIM" OR "LIPECS"))	**06**
COCHRANE	("Leukemia, Lymphocytic, Chronic, B-Cell" OR "Small-Cell Lymphoma" OR "Small Cell Lymphomas" OR "Chronic Lymphoblastic Leukemia" OR "Chronic Lymphoblastic Leukemias" OR "Lymphocytic Lymphoma" OR "Lymphocytic Lymphomas" OR "Chronic B-Cell Leukemia" OR "Chronic B-Cell Leukemias" OR "Low-Grade B-Cell" OR "Chronic B-Lymphocytic Leukemia" OR "Chronic B-Lymphocytic Leukemias" OR "Chronic Lymphocytic Leukemia" OR "Chronic Lymphocytic Leukemias" OR CLL) AND ("Untreated" OR "first-line" OR "first line" OR "firstline" OR "näive" OR "naïve" OR "Tumor Suppressor Protein p53" OR "Genes p53" OR "Tumor Suppressor p53-Binding Protein 1" OR P53 OR TP53 OR 17P) AND ("randomized controlled trial" OR "randomized controlled trials as topic" OR "random allocation" OR "double-blind method" OR "single-blind method" OR Placebo*)	**520**

Quadro 2 – Artigos excluídos após leitura de texto completo.

Nº	Autor (ano)	Título	Motivos para exclusão
1	Allan et al, 2022	Fixed-duration (FD) ibrutinib (Ibr) + venetoclax (Ven) for first-line treatment of chronic lymphocytic leukemia (CLL) in patients (pts) with high-risk features: phase 2 CAPTIVATE study.	Resumo de congresso
2	Al-Sawaf et al, 2020	Fixed-duration venetoclax-obinutuzumab for previously untreated patients with chronic lymphocytic leukemia: Follow-up of efficacy and safety results from the multicentre, open-label, randomized, phase III CLL14 trial.	Resumo de congresso
3	Al-Sawaf et al, 2022	CLL-246 Venetoclax-Obinutuzumab for Previously Untreated Chronic Lymphocytic Leukemia: 5-Year Results of the Randomized CLL14 Study.	Resumo de congresso
4	Al-Sawaf et al, 2021	Health-related quality of life with fixed-duration venetoclax obinutuzumab for previously untreated chronic lymphocytic leukemia: Results from the randomized, phase 3 CLL14 trial.	Outra população
5	Aronson et al, 2016	Ibrutinib increased survival more than chlorambucil in older patients with untreated chronic lymphocytic leukemia.	Outra população
6	Barr et al, 2022	Effective Tumor Debulking with Ibrutinib Before Initiation of Venetoclax: Results from the CAPTIVATE Minimal Residual Disease and Fixed-Duration Cohorts.	Outra população
7	Burger et al, 2022	Up to 6.5 years (median 4 years) of follow-up of first-line ibrutinib in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma and high-risk genomic features: integrated analysis of two phase 3 studies.	Outra população

Nº	Autor (ano)	Título	Motivos para exclusão
8	Burger et al, 2016	International, randomized phase 3 study results: Ibrutinib versus Chlorambucil in patients 65 years and older with treatment-naïve CLL (RESONATE-2™).	Resumo de congresso
9	Burger et al, 2018	Ibrutinib for first-line treatment of older patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): a 4-year experience from the RESONATE-2 Study.	Resumo de congresso
10	Burger et al, 2018	Phase 3 study of ibrutinib as first-line treatment in older patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): a 4-year follow-up from the RESONATE-2 study.	Resumo de congresso
11	Burger et al, 2020	Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study.	Outra população
12	Coutre et al, 2018	Survival adjusting for crossover: phase 3 study of ibrutinib vs. chlorambucil in older patients with untreated chronic lymphocytic leukemia/small lymphocytic lymphoma.	Outra população
13	Davids et al, 2021	Majic: A Phase 3 Prospective, Multicenter, Randomized, Open-Label Trial of Acalabrutinib Plus Venetoclax Versus Venetoclax Plus Obinutuzumab in Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma.	Resumo de congresso
14	Eichhorst et al, 2021	A Randomized Phase III Study of Venetoclax-Based Time-Limited Combination Treatments (RVe, GVe, GIVe) Vs Standard Chemoimmunotherapy (CIT: FCR/BR) in Frontline Chronic Lymphocytic Leukemia (CLL) of Fit Patients: First Co-Primary Endpoint Analysis of the International Intergroup GAIA (CLL13) Trial.	Resumo de congresso

Nº	Autor (ano)	Título	Motivos para exclusão
15	EudraCT, 2014	A clinical study to compare the effect of Ibrutinib or placebo on prolongation of event free survival in patients with early stage Binet A CLL with a high risk for disease progression defined by various clinical and laboratory risk factors.	Outro tipo de publicação
16	Fakhri et al, 2019	CLL14 Trial: Fixed-Duration Chemotherapy-Free Regimen for Frail Patients with Treatment-Naïve CLL.	Outro desenho de estudo
17	Fürstenau et al, 2021	Comparison of Tumor Lysis Syndrome (TLS) Risk Reduction and Incidence in Different Venetoclax-Based Combinations within the Randomized Phase 3 GAIA (CLL13) Trial.	Resumo de congresso
18	Fürstenau et al, 2021	High Resolution Assessment of Minimal Residual Disease (MRD) By Next-Generation Sequencing (NGS) and High-Sensitivity Flow Cytometry (hsFCM) in the Phase 3 GAIA (CLL13) Trial.	Resumo de congresso
19	Gángó et al, 2022	Morphologic and molecular analysis of Richter syndrome in chronic lymphocytic leukaemia patients treated with ibrutinib or venetoclax.	Outro desenho de estudo
20	Gargiulo et al, 2023	SOHO State of the Art Updates and Next Questions. Infections in Chronic Lymphocytic Leukemia Patients: Risks and Management.	Outro desenho de estudo
21	Ghia et al, 2021	First-Line Treatment with Ibrutinib (Ibr) Plus Venetoclax (Ven) for Chronic Lymphocytic Leukemia (CLL): 2-Year Post-Randomization Disease-Free Survival (DFS) Results from the Minimal Residual Disease (MRD) Cohort of the Phase 2 Captivate Study.	Resumo de congresso
22	Ghia et al, 2021	Fixed-duration (FD) first-line treatment (tx) with ibrutinib (I) plus venetoclax (V) for chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL): Primary analysis of the FD cohort of the phase 2 captivate study.	Resumo de congresso

Nº	Autor (ano)	Título	Motivos para exclusão
23	Ghia et al, 2016	Improvement in Quality of Life and well-being in older patients with treatment-naive (TN) CLL: Results from the randomized phase 3 study of Ibrutinib (IBR) versus Chlorambucil (CLB) (RESONATE-2™).	Resumo de congresso
24	Hillmen et al, 2016	Results from the international, randomized phase 3 study of ibrutinib versus chlorambucil in patients 65 Years and older with treatment-naïve (TN) CLL/SLL (RESONATE-2TM).	Resumo de congresso
25	Kipps et al, 2016	Analysis of Quality of Life and Wellbeing from the Randomized Phase 3 Study of Ibrutinib Versus Chlorambucil in Older Patients with Treatment-naïve CLL (RESONATE-2TM).	Resumo de congresso
26	Langerbeins et al, 2021	The CLL12 trial: ibrutinib vs placebo in treatment-naïve, early-stage chronic lymphocytic leukemia.	Resumo de congresso
27	Martens et al, 2021	Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in treatment-naive Chronic Lymphocytic Leukemia: ELEVATE-TN 4-year follow-up.	Resumo de congresso
28	Martens et al, 2022	Acalabrutinib ± Obinutuzumab vs. Obinutuzumab + Chlorambucil bei therapie naiver chronischer lymphatischer Leukämie: ELEVATE-TN 5-Jahres Follow-up	Resumo de congresso
29	Martens et al, 2020	Elevate Tn Phase 3 Study of Acalabrutinib Plus Obinutuzumab or Acalabrutinib Monotherapy vs Chlorambucil Plus Obinutuzumab (ClbO) in Subjects with Previously Untreated Chronic Lymphocytic Leukemia (CLL).	Resumo de congresso
30	Mauro et al, 2022	High rate of durable responses with undetectable minimal residual disease with frontline venetoclax and rituximab in young and fit patients with chronic lymphocytic leukemia and an adverse biologic profile: results of the gimema phase II LLC1518 - 'Veritas' study.	Outro desenho de estudo

Nº	Autor (ano)	Título	Motivos para exclusão
31	Michallet et al, 2021	A fixed-duration, immunochemotherapy approach in CLL: 5.5-year results from the phase 2 ICLL-07 FILO trial.	Outra população
32	Munir et al, 2021	Sudden or Cardiac Deaths on Ibrutinib-Based Therapy Were Associated with a Prior History of Hypertension or Cardiac Disease and the Use of ACE-Inhibitors at Study Entry: Analysis from the Phase III NCRI FLAIR Trial	Resumo de congresso
33	Munir et al, 2020	ELEVATE-TN: A phase 3, multicentre, open-label study of acalabrutinib (Ab) combined with obinutuzumab (O) or Ab alone versus O plus chlorambucil (Clb) in patients (pts) with treatment-naive chronic lymphocytic leukaemia (TN-CLL).	Resumo de congresso
34	Owen et al, 2018	Older patients (pts) with treatment-naïve chronic lymphocytic leukemia (CLL) treated with ibrutinib (IBR): Prolonged improvement in patient-reported outcomes (PROS) and wellbeing in resonate-2.	Resumo de congresso
35	Pophali et al, 2021	Quality of Life in Patients <=70 Years of Age with Chronic Lymphocytic Leukemia Treated Frontline with Ibrutinib-Rituximab Versus Fludarabine Cyclophosphamide Rituximab: Analysis from ECOG-ACRIN E1912.	Resumo de congresso
36	Rawstron et al, 2022	P673: Depletion and recovery of normal B-cells during and after treatment with chemoimmunotherapy, Ibrutinib or Venetoclax.	Resumo de congresso
37	Shanafelt et al, 2022	Long-term outcomes for ibrutinib–rituximab and chemoimmunotherapy in CLL: updated results of the E1912 trial.	Outra população
38	Shanafelt et al, 2019	Ibrutinib–Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia.	Outra população

Nº	Autor (ano)	Título	Motivos para exclusão
39	Sharman et al, 2022	Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in treatment-näive Chronic Lymphocytic Leukemia: ELEVATE-TN 5-year follow-up.	Resumo de congresso
40	Sharman et al, 2021	Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in Treatment-Naïve Chronic Lymphocytic Leukemia: ELEVATE-TN 4-Year Follow-up.	Resumo de congresso
41	Siddiqi et al, 2020	First-line Ibrutinib (IBR) + Venetoclax (VEN) for patients (PTS) with Chronic Lymphocytic Leukemia (CLL)/ Small Lymphocytic Lymphoma (SLL): Efficacy and safety results from CAPTIVATE MRD Cohort.	Resumo de congresso
42	Sivina et al, 2021	Long-Term Outcome of Treatment-Naïve and Relapsed/Refractory Patients with CLL and TP53 Aberrations Treated with Ibrutinib, with or without Rituximab.	Resumo de congresso
43	Wallace et al, 2021	Acalabrutinib and High-Frequency Low-Dose Subcutaneous Rituximab for Initial Therapy of Chronic Lymphocytic Leukemia.	Outro desenho de estudo
44	Wierda et al, 2022	Fixed duration (FD) first line treatment with ibrutinib plus venetoclax for chronic lymphocytic leukemia/small lymphocytic lymphoma: primary analysis of the FD cohort of the phase 2 CAPTIVATE study.	Resumo de congresso
45	Wierda et al, 2018	Phase 2 CAPTIVATE results of ibrutinib (ibr) plus venetoclax (ven) in first-line chronic lymphocytic leukemia (CLL).	Resumo de congresso
46	Wierda et al, 2020	Ibrutinib (Ibr) Plus Venetoclax (Ven) for First-Line Treatment of Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL): 1-Year Disease-Free Survival (DFS) Results from the MRD Cohort of the Phase 2 CAPTIVATE Study.	Resumo de congresso

Nº	Autor (ano)	Título	Motivos para exclusão
47	Wierda et al, 2021	Ibrutinib Plus Venetoclax for First-Line Treatment of Chronic Lymphocytic Leukemia: Primary Analysis Results from the Minimal Residual Disease Cohort of the Randomized Phase II CAPTIVATE Study.	Outro comprador
48	Woyach et al, 2019	Alliance A041702: A Randomized Phase III Study of Ibrutinib Plus Obinutuzumab Versus Ibrutinib Plus Venetoclax and Obinutuzumab in Untreated Older Patients (≥ 70 Years of Age) with Chronic Lymphocytic Leukemia (CLL).	Resumo de congresso
49	Woyach et al, 2021	A041702: A Randomized Phase III Study of Ibrutinib Plus Obinutuzumab Versus Ibrutinib Plus Venetoclax and Obinutuzumab in Untreated Older Patients (≥ 70 Years of Age) with Chronic Lymphocytic Leukemia (CLL)	Resumo de congresso

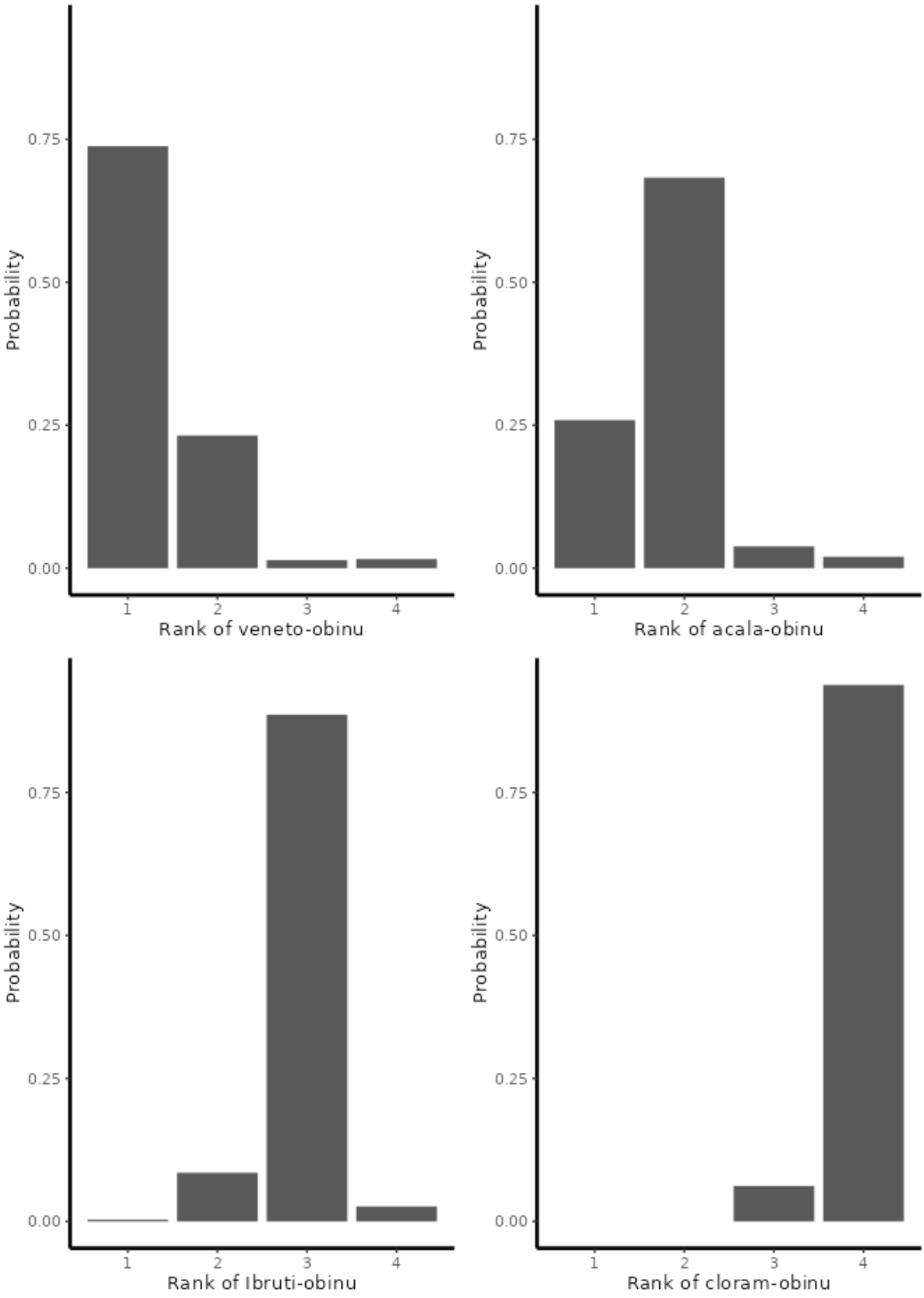

Figura 1 – Classificação de probabilidades (rankogramas) para eficácia das intervenções no tratamento em primeira linha de LLC em indivíduos que apresentavam deleções 11q, 13q, 17p e/ou mutação TP53 e/ou IGHV não mutado.

Quadro 3 – Eventos adversos relacionados ao uso de inibidores BTK e BCL-2*.

Estudo	Intervenções	Suspensão do tratamento por EA (qualquer grau)	Óbitos por EA (todas as causas)	EA mais comuns (graus 3-4)
CLL14 Study (NCT02242942)	Venetoclax + Obinutuzumabe (n=212)	NI	4 (1,89%)	Neutropenia: 112 (52,8%) Trombocitopenia: 30 (14,2%) Segunda malignidade primária: 27 (12,7%) Reação relacionada à infusão: 19 (9%) Anemia: 18 (8,5%) Pneumonia: 14 (6,6%)
	Clorambucil + Obinutuzumabe (n=214)	NI	8 (3,74%)	Neutropenia: 102 (47,7%) Trombocitopenia: 32 (15%) Segunda malignidade primária: 16 (7,5%) Reação relacionada à infusão: 22 (10,3%) Anemia: 14 (6,5%) Pneumonia: 9 (4,2%)
ELEVATE-TN (NCT02475681)	Acalabrutinibe + Obinutuzumabe (n=178)	23 (12,8%)	2 (1,1%)	Neutropenia: 55 (30,9%) Infecções: 42 (23,6%) Eventos cardíacos: 14 (7,9%) Segunda malignidade primária: 13 (7,3%)
	Clorambucil + Obinutuzumabe (n=169)	26 (14,7%)	3 (1,7%)	Neutropenia: 70 (41,4%) Infecções: 14 (8,3%) Eventos cardíacos: 3 (1,8%) Segunda malignidade primária: 3 (1,8%)
iLLUMINATE (NCT02264574)	Ibrutinibe + Obinutuzumabe (n=113)	35 (31%)	13 (12%)	Neutropenia: 41 (36%) Trombocitopenia: 22 (19%) Anemia: 4 (4%) Pneumonia: 9 (8%) Reação relacionada à infusão: 2 (2%)
	Clorambucil + Obinutuzumabe (n=116)	26 (22%)	9 (8%)	Neutropenia: 53 (46%) Trombocitopenia: 12 (10%) Anemia: 9 (8%) Pneumonia: 4 (3%) Reação relacionada à infusão: 9 (8%)

*Os dados de segurança foram apresentados para toda a população com LLC e não apenas para os subgrupos com deleção 17p e mutação TP53.
Legenda: NI: não informado.

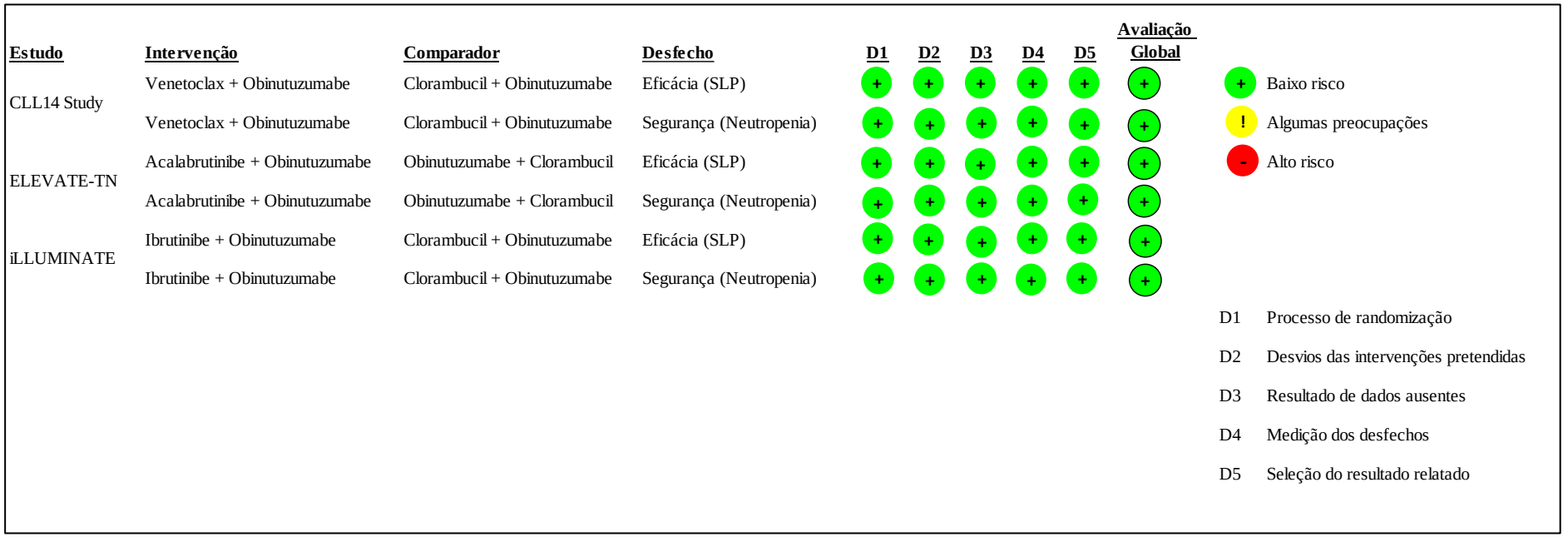

Figura 2 – Avaliação do risco de viés dos ECR por desfecho, a partir da ferramenta RoB 2.0.

Quadro 4 – Avaliação da qualidade da evidência a partir da ferramenta GRADE.

Avaliação da certeza							Impacto	Certeza	Importância
№ dos estudos	**Delineamento do estudo**	**Risco de viés**	**Inconsistência**	**Evidência indireta**	**Imprecisão**	**Outras considerações**			
Sobrevida livre de progressão									
3	ensaios clínicos randomizados	não grave	não grave	não grave	não grave	nenhum	Estudo CLL14: população del 17p e/ou mutação TP53. HR: 0,48 (0,24-0,94) Estudo ELEVATE-TN: população del(17) (p13.1) e/ou TP53 mutado. HR: 0,17 (0,07-0,42); p<0,0001 Estudo iLLUMINATE: população (del[17p]/mutação TP53, del[11q] e/ou IGHV não mutado. HR: 0,17 (0,10-0,28); p<0,0001	⊕⊕⊕⊕ Alta	CRÍTICO
Evento adverso graus 3-4 (Neutropenia)									
3	ensaios clínicos randomizados	não grave	não grave	não grave	não grave	nenhum	Estudo CLL14: venetoclax + obinutuzumabe: 52,8%; clorambucil + obinutuzumabe: 47,7% Estudo ELEVATE-TN: acalabrutinibe + obinutuzumabe: 30,9%; clorambucil + obinutuzumabe: 41,4% Estudo iLLUMINATE: ibrutinibe + obinutuzumabe: 36%; clorambucil + obinutuzumabe: 46%	⊕⊕⊕⊕ Alta	CRÍTICO