CLL and the immune system: Infections, vaccines, and autoimmune disease

Professor Carol Moreno
Hospital de la Santa Creu i Sant Pau, Spain

HOSPITAL DE LA SANTA CREU I SANT PAU
UNIVERSITAT AUTÒNOMA DE BARCELONA

CLL, chronic lymphocytic leukemia.

March 2023 | 0323--MRC-008

Disclosures

- **Advisor/Consultant/Speaker:** Janssen, AbbVie, Pharmacyclics (an AbbVie company), Roche, BeiGene, AstraZeneca, Bristol Myers Squibb, Lilly, Adaptive
- **Research grants:** Janssen, AbbVie, AstraZeneca, Deutsche José Carreras Leukämie-Stiftung, III Carlos Institute

CLL and immune status

BLOOD *The Journal of Hematology*

APRIL, 1967 VOL. XXIX, NO. 4, PART II

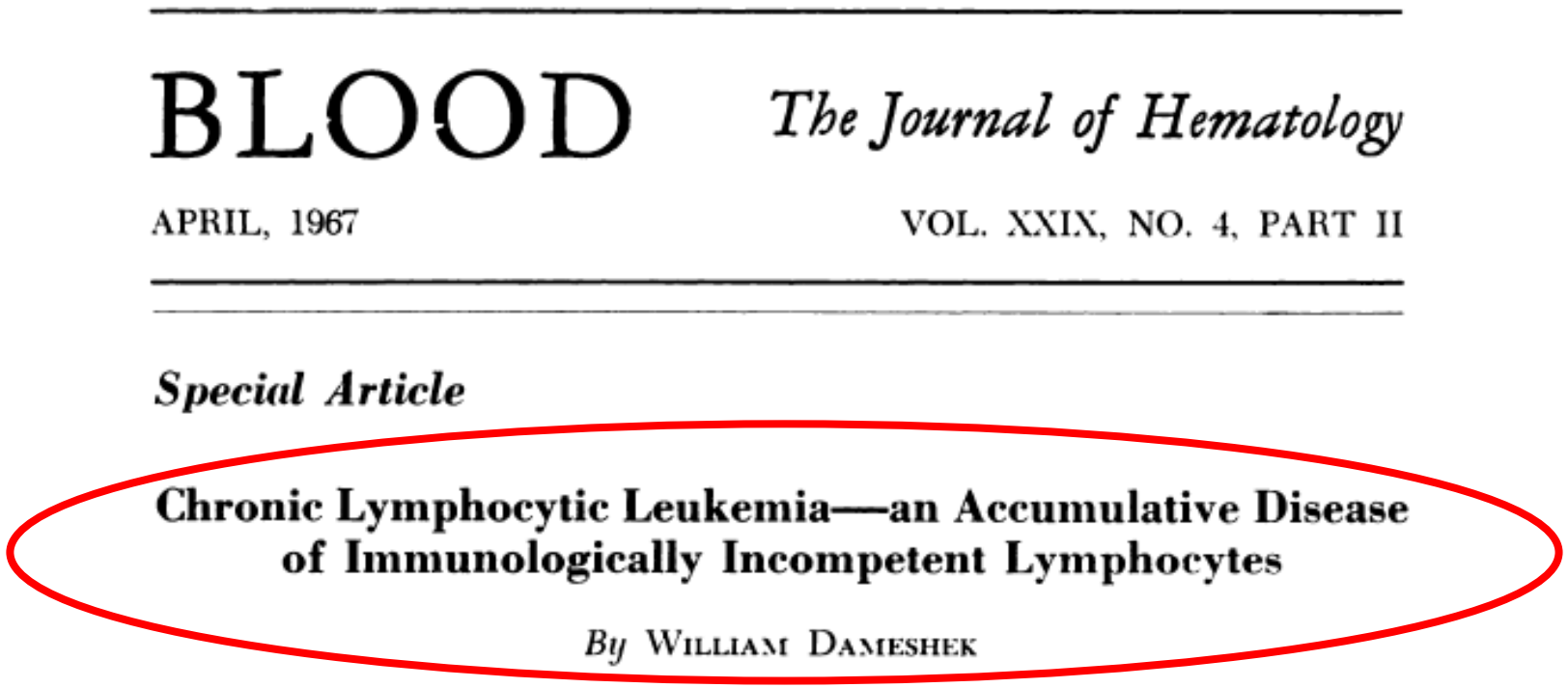
Special Article

Chronic Lymphocytic Leukemia—an Accumulative Disease of Immunologically Incompetent Lymphocytes

By WILLIAM DAMESHEK

CLL, chronic lymphocytic leukemia.
Dameshek W. *Blood* 1967; 29 (4): 566–584.

CLL and immune status



BLOOD The Journal of Hematology

APRIL, 1967 VOL. XXIX, NO. 4, PART II

Special Article

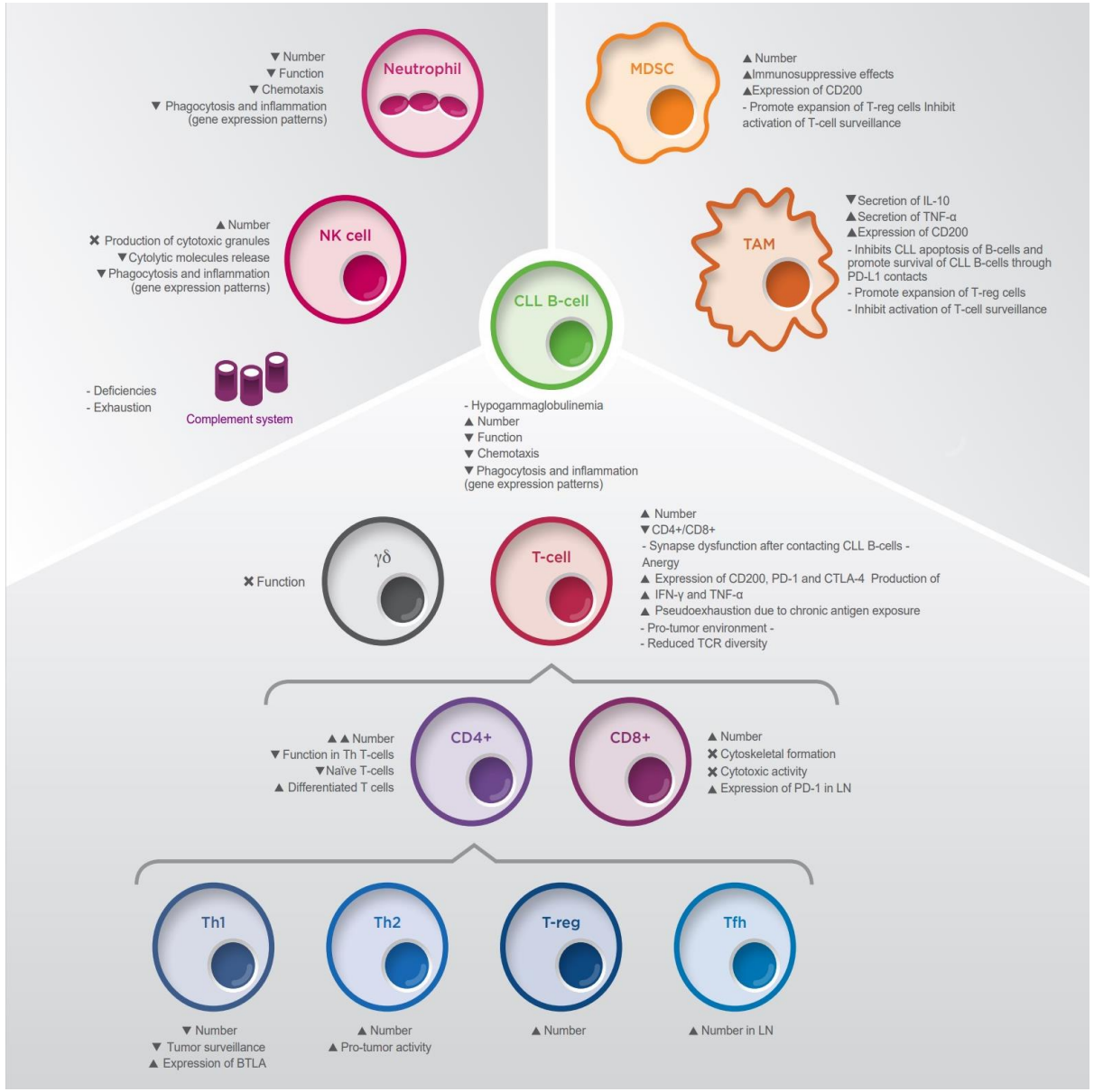
Chronic Lymphocytic Leukemia—an Accumulative Disease of Immunologically Incompetent Lymphocytes

By WILLIAM DAMESHEK

CLL, chronic lymphocytic leukemia.

Dameshek W. *Blood* 1967; 29 (4): 566–584.

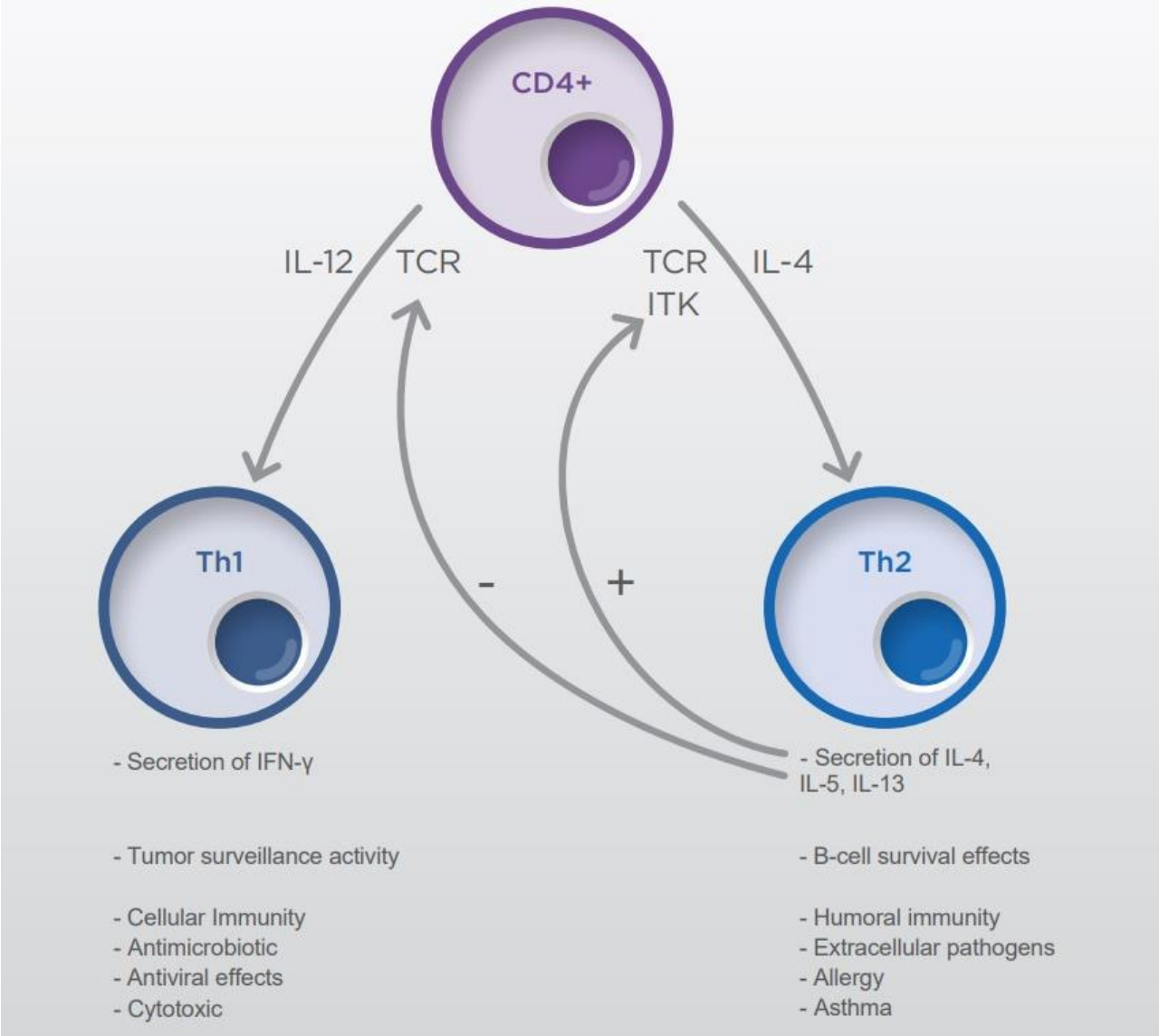
Immune disorders are intrinsic to CLL



BTLA, B and T lymphocyte attenuator; CLL, chronic lymphocytic leukemia; CTLA-4, cytotoxic T lymphocyte–associated antigen 4; IFN-γ, interferon gamma; IL, interleukin; LN, lymph node; MDSC, myeloid-derived suppressor cell; NK, natural killer; PD-1, programmed death receptor-1; PD-L1, programmed death-ligand 1; TAM, tumor-associated macrophage; TCR, T-cell receptor; Tfh, T follicular helper cell; Th, T helper cell; TNF-α, tumor necrosis factor alpha; T-reg, regulatory T cell.

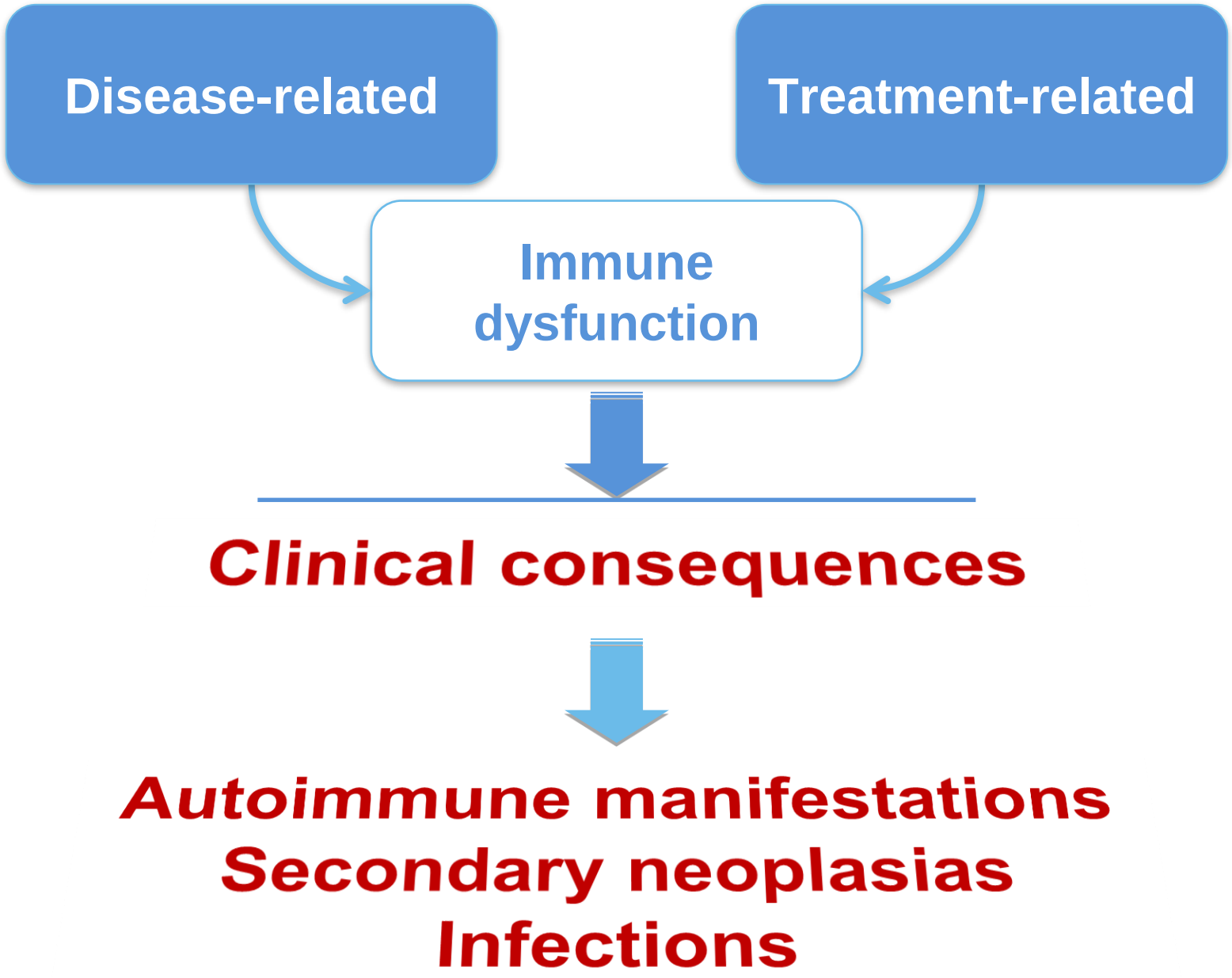
Moreno C *et al. J Exp Clin Cancer Res* 2021; 40 (1): 321.

Equilibrium between Th1 and Th2 subgroup can impact immune tumor surveillance



CLL, chronic lymphocytic leukemia; IFN-γ, interferon gamma; IL, interleukin; ITK, IL2-inducible T-cell kinase; TCR, T-cell receptor; Th, T helper cell.

Moreno C *et al. J Exp Clin Cancer Res* 2021; 40 (1): 321.


Disease-related
Treatment-related
Immune dysfunction
Clinical consequences
Autoimmune manifestations
Secondary neoplasias
Infections

Secondary immunodeficiency associated with chemo(immuno)therapy

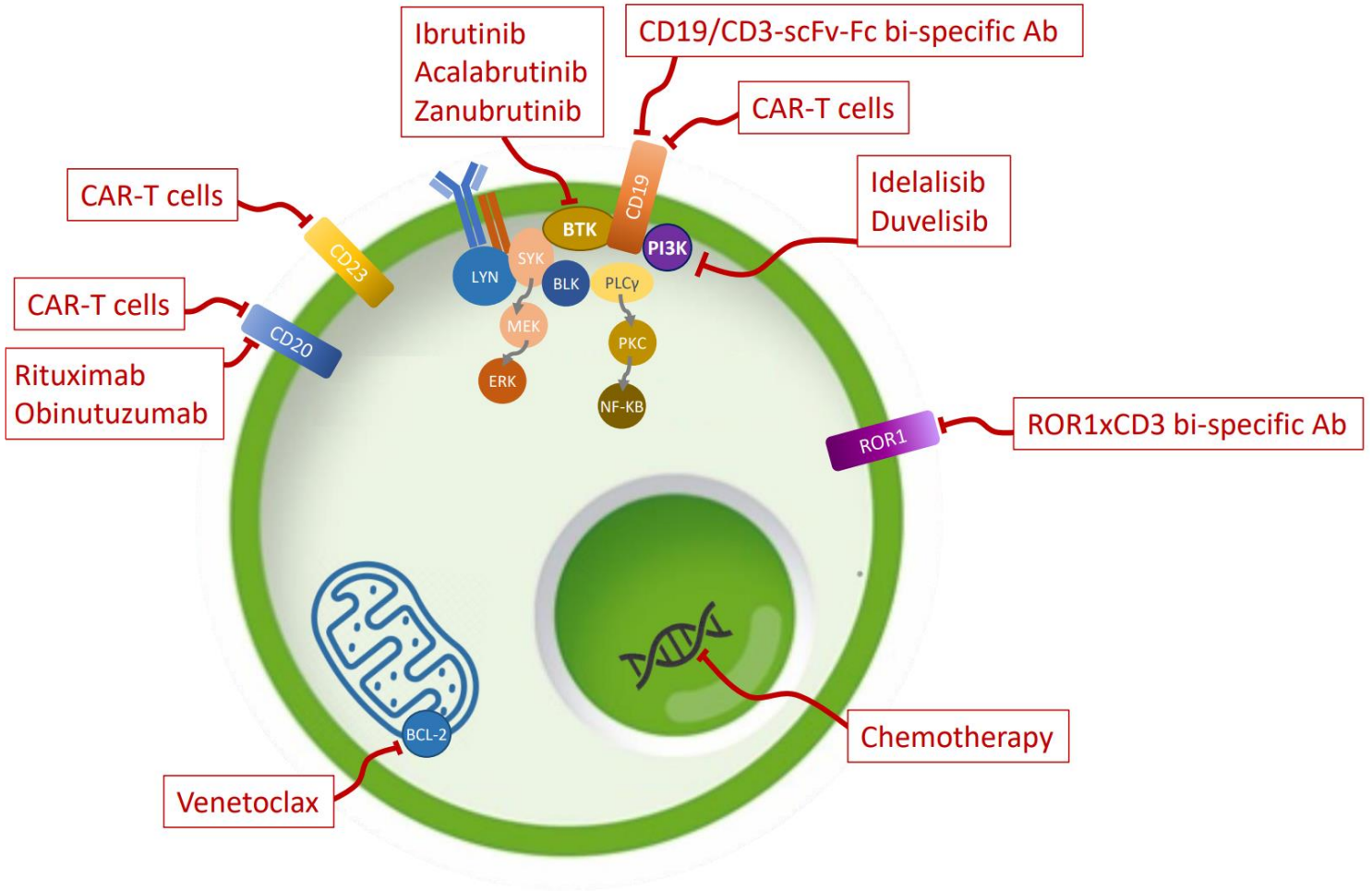
Humoral immunosuppression and defects in T cells

Study	Regimen	Key findings
Beyer *et al*. 2005[1]	Fludarabine	↓ T_{reg} frequency and inhibitory function
Ysebaert *et al*. 2010[2]	FCR	• ↓ CD4+ and CD8+ T cells • Low CD4+ T-cell count post-therapy correlates with MRD
Gassner *et al*. 2011[3]	Fludarabine–cyclophosphamide	• ↓ T cells due to cytotoxicity • Surviving T cells mainly Th1, with high proliferative potential
Martínez-Calle *et al*. 2019[4]	Bendamustine–rituximab	• Delayed CD4+ T cell recovery • ↑ Risk of serious infection

FCR, fludarabine–cyclophosphamide–rituximab; MRD, minimal residual disease; Th1, type 1 T helper cell; T_{reg}, regulatory T cell.

1. Beyer M *et al. Blood* 2005; 106 (6): 2018–2025. 2. Ysebaert L *et al. Leukemia* 2010; 24 (7): 1310–1316. 3. Gassner FJ *et al. Cancer Immunol Immunother* 2011; 60 (1): 75–85.
4. Martínez-Calle N *et al. Br J Haematol* 2019; 184 (6): 957–968.

Therapeutic strategies for CLL



Ab, antibody; BCL-2, B-cell lymphoma 2; BLK, tyrosine-protein kinase; CAR-T, chimeric antigen receptor T; CLL, chronic lymphocytic leukemia; ERK, extracellular signal-regulated kinase; Fc, fragment crystallizable; MEK, mitogen-activated protein kinase kinase; NF-κB, nuclear factor kappa B; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; PLCγ, phospholipase C gamma; ROR1, receptor tyrosine kinase–like orphan receptor 1; scFv, single-chain variable fragment; SYK, spleen tyrosine kinase.

Moreno C *et al. J Exp Clin Cancer Res* 2021; 40 (1): 321.

Infections

- Major cause of morbidity and mortality in CLL
- Multifactorial
  - Patient-related factors (infection history, predisposition [i.e. bronchiectasis])
  - Disease-related immune defects
    - Hypogammaglobulinemia and others (T cells, complement, etc.)
  - Treatment-related immunosuppression*
    - Viral infections (e.g. herpes virus)
    - Opportunistic infections

This slide reflects the speaker's opinion.
*Purine analogs, transplantation.
CLL, chronic lymphocytic leukemia.

Infections associated with BTKis

European label guidance

Agent	Very common (≥1/10); any grade of infection	Additional label information
Ibrutinib[1]	Pneumonia, URTI, skin infections	• Infections (including sepsis, neutropenic sepsis, bacterial, viral, or fungal) reported, some fatal • Invasive fungal infections, including cases of aspergillosis, cryptococcosis, and PJP, some with fatal outcomes • Reactivation of HBV and cases of PML have been reported, some with fatal outcomes
Acalabrutinib[2]	**Monotherapy:** URTI and sinusitis **Combination therapy with obinutuzumab:** URTI, sinusitis, nasopharyngitis, urinary tract infection, and pneumonia	• Serious infections (bacterial, viral, or fungal), including fatal events reported, predominantly in the absence of Grade 3/4 neutropenia • Infections as a result of HBV and HZV reactivation, aspergillosis, and PML have occurred
Zanubrutinib[3]	Pneumonia, URTI, urinary tract infection	• Infections (including sepsis, bacterial, viral, or fungal) reported, some fatal • Reactivation of HBV

HBV, hepatitis B virus; HZV, herpes zoster virus; PJP, *Pneumocystis jirovecii* pneumonia; PML, progressive multifocal leukoencephalopathy; URTI, upper respiratory tract infection.

1. Janssen-Cilag International NV. Imbruvica – summary of product characteristics; November 2022. 2. AstraZeneca AB. Calquence – summary of product characteristics; December 2021.
3. BeiGene Ireland Ltd. Brukinsa – summary of product characteristics; December 2022.

Infections associated with PI3Kis and BCL2is

European label guidance

Agent	Very common (≥1/10); any grade of infection	Additional label information
Idelalisib[1]	• Infections (including PJP and CMV)	• Serious and fatal infections reported, including opportunistic infections such as PJP and CMV • PJP prophylaxis should be administered throughout treatment and up to 6 months after discontinuation
Venetoclax[2]	• Pneumonia and URTI	• Serious infections, including sepsis with fatal outcome, reported

Combining targeted therapies may result in an increase of toxicities including infections

BCL2i, B-cell lymphoma 2 inhibitor; CMV, cytomegalovirus; PI3Ki, phosphoinositide 3-kinase inhibitor; PJP, *Pneumocystis jirovecii* pneumonia; URTI, upper respiratory tract infection.

1. Gilead Sciences Ireland UC. Zydelig – summary of product characteristics; October 2021. 2. AbbVie Deutschland GmbH & Co. KG. Venclyxto – summary of product characteristics; January 2023.

Infection prophylaxis

European label guidance

Prophylaxis*	Ibrutinib	Acalabrutinib	Zanubrutinib	Idelalisib	Venetoclax
Bacterial	–	–	–	–	–
Viral (IVGG)	–	–	–	–	–
Pneumocystis jirovecii	–	–	–	Yes, up to 6 months after treatment is stopped[3]	–
Fungal	–	–	–	–	–

*Consider individual prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Monitor patients for signs and symptoms of infection and treat as medically appropriate.[1–5]

Ig, immunoglobulin; IVGG, intravenous gamma globulin.

1. Janssen-Cilag International NV. Imbruvica – summary of product characteristics; November 2022. 2. AstraZeneca AB. Calquence – summary of product characteristics; December 2021. 3. BeiGene Ireland Ltd. Brukinsa – summary of product characteristics; December 2022. 4. Gilead Sciences Ireland UC. Zydelig – summary of product characteristics; October 2021. 5. AbbVie Deutschland GmbH & Co. KG. Venclyxto – summary of product characteristics; January 2023. 6. Rivera D *et al*. *Curr Oncol Rep* 2022; 24 (8): 1003–1014.

Infection prophylaxis

European label guidance

Prophylaxis*	Ibrutinib	Acalabrutinib	Zanubrutinib	Idelalisib	Venetoclax
Bacterial	–	–	–	–	–
Fungal	–	–	–	–	–

Consider Ig replacement therapy for bacterial prophylaxis only for patients with IgG <400 mg/dL and/or recurrent or severe infections[6]

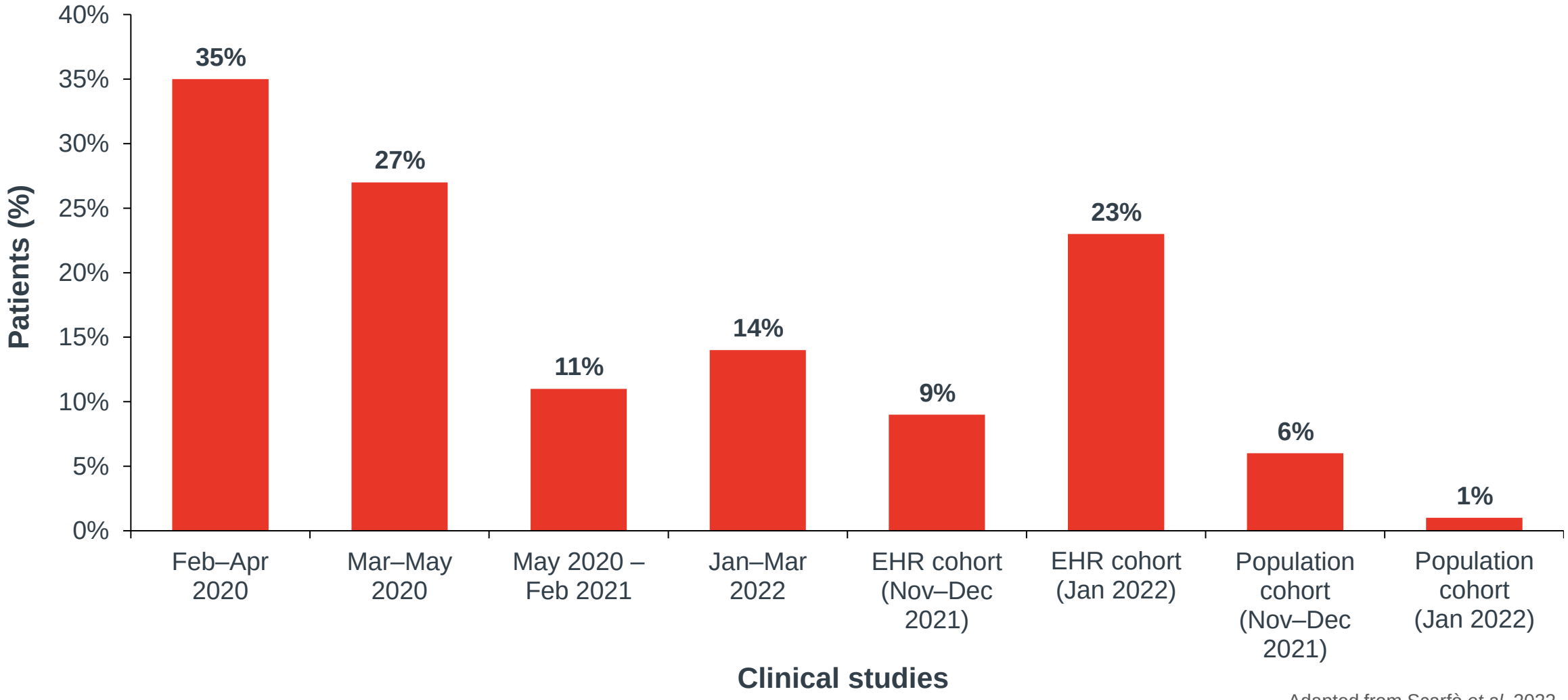
Rivera *et al*. 2022

*Consider individual prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Monitor patients for signs and symptoms of infection and treat as medically appropriate.[1–5]

Ig, immunoglobulin; IVGG, intravenous gamma globulin.

1. Janssen-Cilag International NV. Imbruvica – summary of product characteristics; November 2022. 2. AstraZeneca AB. Calquence – summary of product characteristics; December 2021. 3. BeiGene Ireland Ltd. Brukinsa – summary of product characteristics; December 2022. 4. Gilead Sciences Ireland UC. Zydelig – summary of product characteristics; October 2021. 5. AbbVie Deutschland GmbH & Co. KG. Venclyxto – summary of product characteristics; January 2023. 6. Rivera D *et al*. *Curr Oncol Rep* 2022; 24 (8): 1003–1014.

COVID-19–related mortality in patients with CLL over time



Adapted from Scarfò *et al.* 2022.

CLL, chronic lymphocytic leukemia; EHR, electronic health record.

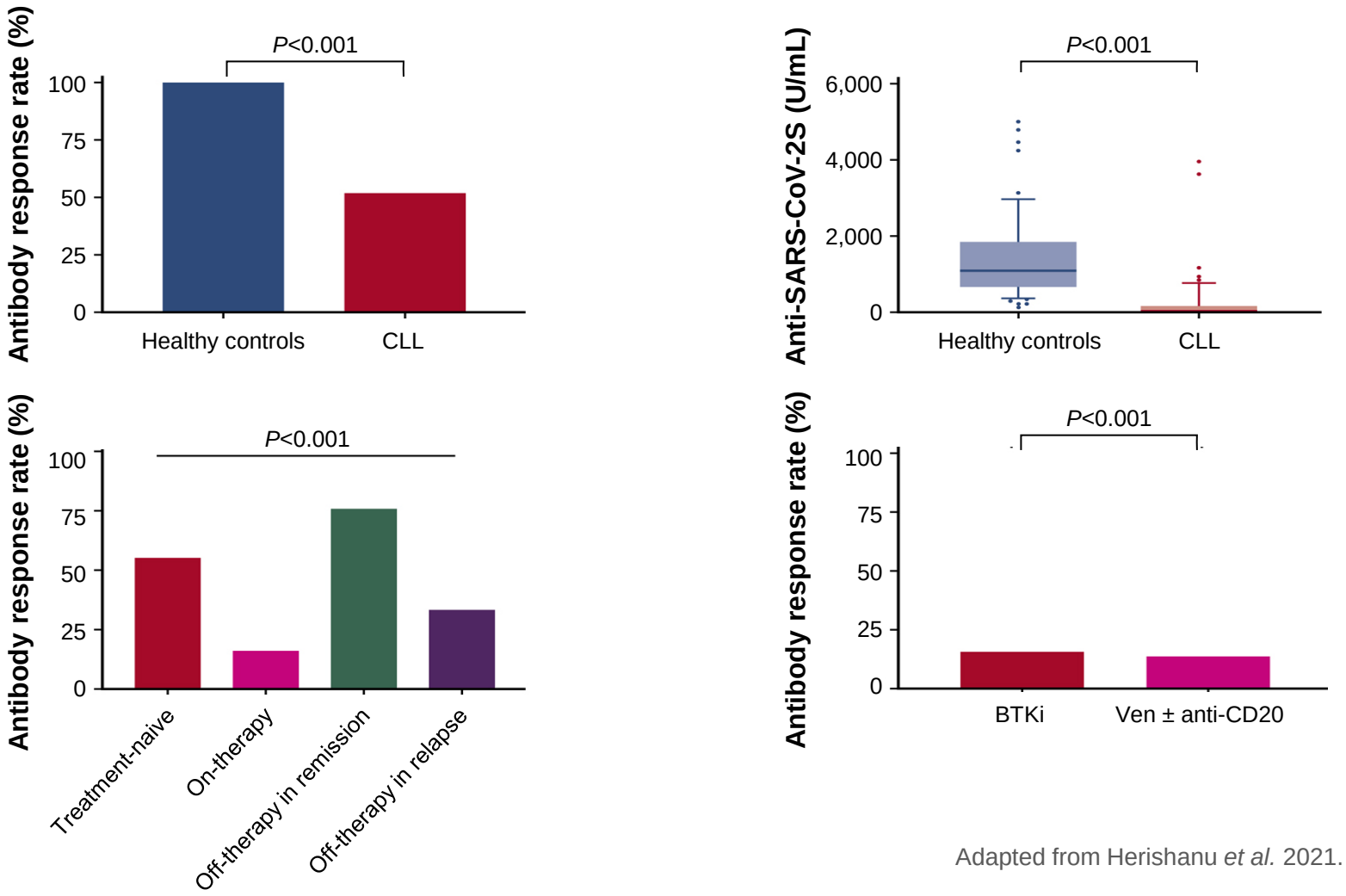
Scarfò L *et al*. *Blood* 2022; 140 (5): 407–409.

Prevention and vaccines for SARS-CoV-2 infection

- Control measures recommended for aerosol-droplet and contact transmission:
  - Hand hygiene
  - Physical distancing
  - Face masks
  - Ventilation of rooms
- Deferral of chemo(immuno)therapy is not advisable in patients with active cancer and asymptomatic COVID-19, but individual risks and benefits should be assessed
- Non-chemotherapy, targeted drugs should not be discontinued, even in patients with COVID-19
- Reduce the number of visits to the hospital (during the pandemic peak)
- Vaccines and vaccination: mRNA-based vectors (BNT162b2 and mRNA-1273)

mRNA, messenger RNA.
Cesaro S *et al. Leukemia* 2022; 36 (6): 1467–1480.

Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with CLL

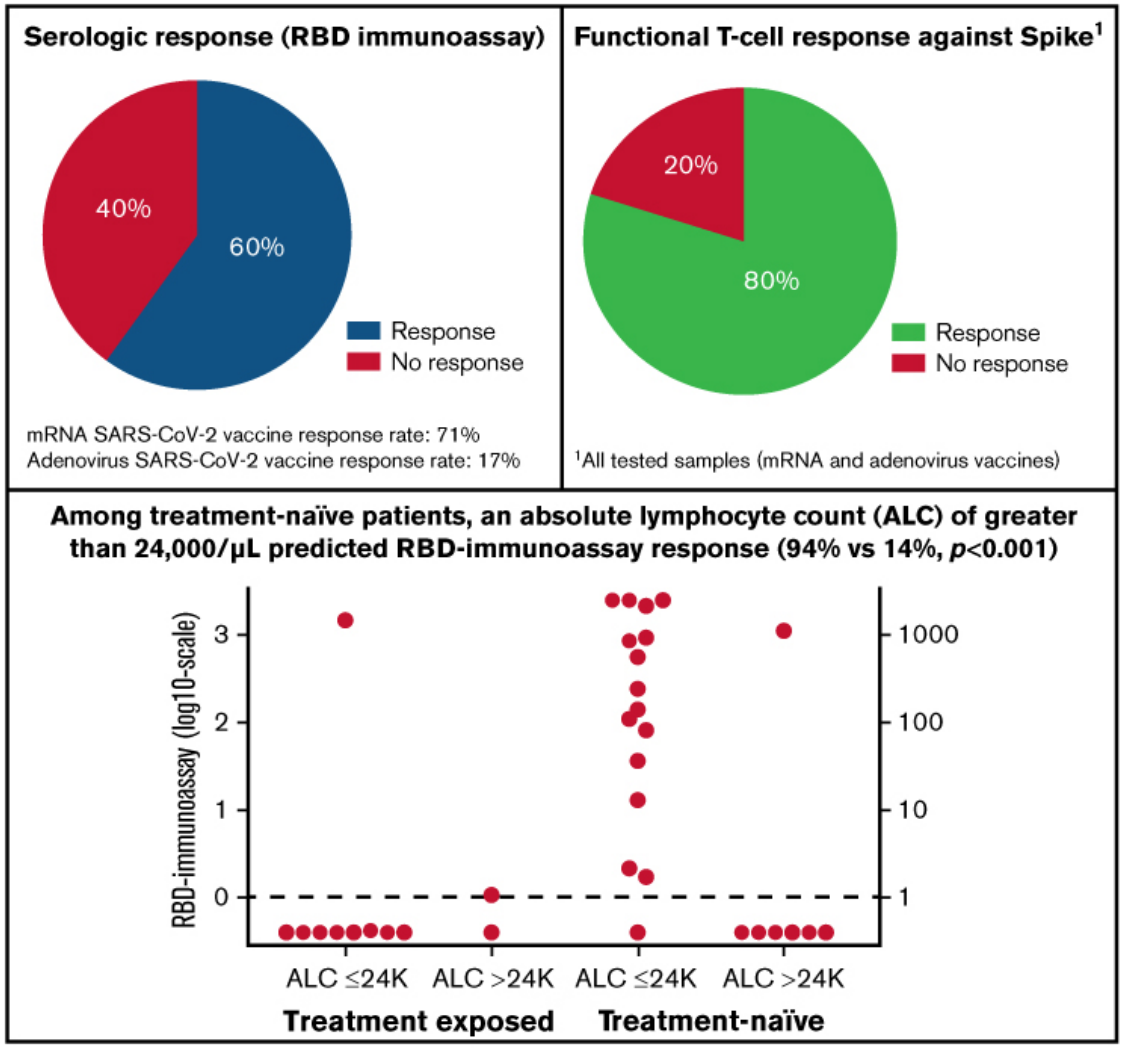


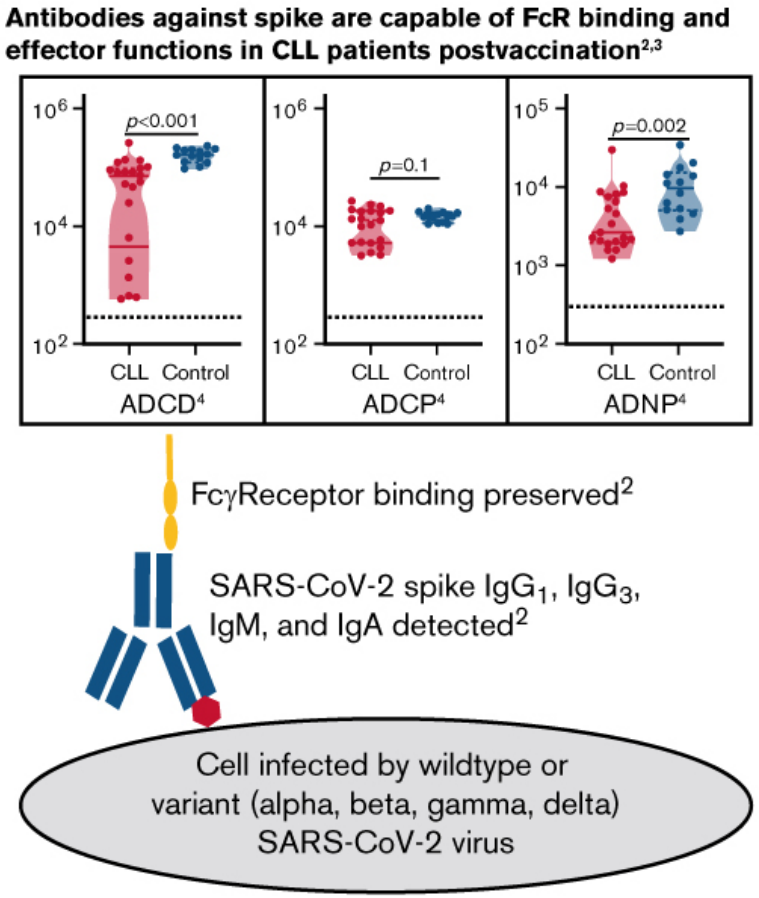
Adapted from Herishanu *et al.* 2021.

CLL, chronic lymphocytic leukemia; Ven, venetoclax.

Herishanu Y *et al. Blood* 2021; 137 (23): 3165–3173.

Humoral and cellular immunogenicity of SARS-CoV-2 vaccines in CLL: A prospective cohort study





[2]All tested samples (mRNA vaccines); [3]Wildtype data shown here; [4]Antibody dependent complement deposition (ADCD), antibody dependent cellular phagocytosis (ADCP), antibody dependent neutrophil phagocytosis (ADNP)

Haydu JE *et al*. *Blood Advances* 2022; 6 (6): 1671–1683.

Possible treatments for SARS-CoV-2 infection

- Monoclonal antibodies (e.g. sotrovimab, etesevimab–bamlanivimab, imdevimab–casirivimab)
- Antiviral treatments (initially remdesivir, then nirmatrelvir–ritonavir and molnupiravir) have been approved to prevent infections from progressing from mild–moderate to severe
- Tixagevimab–cilgavimab has been authorized as pre-exposure prophylaxis for COVID-19 in patients who are moderately to severely immunocompromised

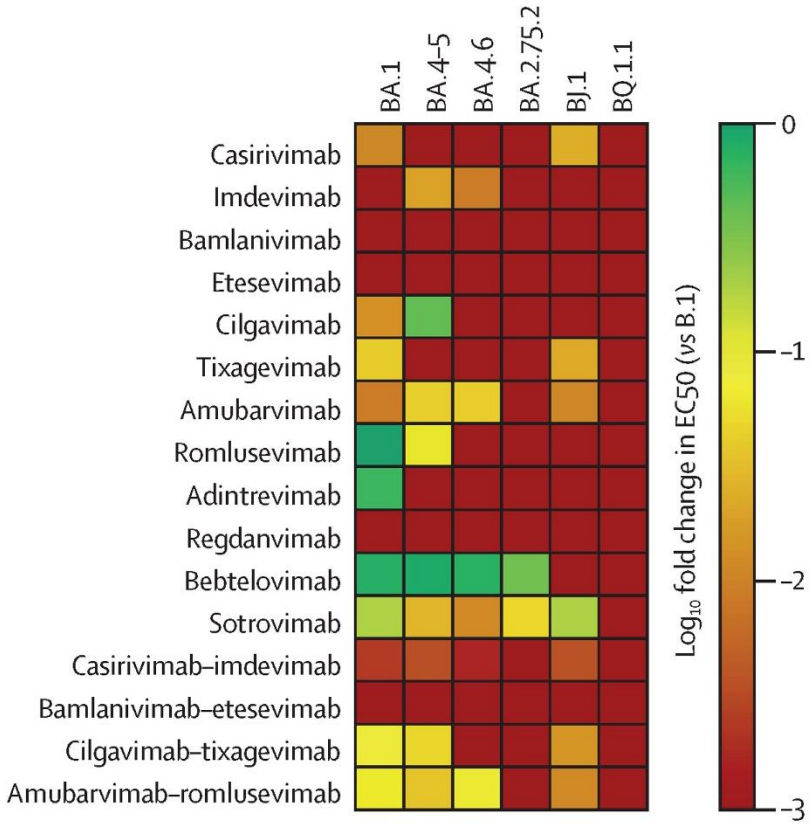
This slide does not include all the possible treatments for SARS-CoV-2 infection.

Coronavirus disease 2019 (COVID-19) treatment guidelines. Available at: https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf. Accessed March 2023.

Omicron BQ.1.1 sublineage shows extensive resistance to anti-SARS-CoV-2 mAbs

		B.1	BA.1	BA.4–5	BA.4.6	BA.2.75.2	BJ.1	BQ.1.1
Single mAbs	Casirivimab	21	1890	>50000	>50000	>50000	880	>50000
	Imdevimab	19	>50000	994	2109	>50000	>50000	>50000
	Bamlanivimab	16	>50000	>50000	>50000	>50000	>50000	>50000
	Etesevimab	53	>50000	>50000	>50000	>50000	>50000	>50000
	Cilgavimab	37	2658	88	24200	>50000	>50000	>50000
	Tixagevimab	7	173	10090	27740	>50000	304	>50000
	Amubarvimab	53	5641	1234	1290	>50000	4762	>50000
	Romlusevimab	852	866	8279	>50000	>50000	>50000	>50000
	Adintrevimab	14	23	>50000	>50000	>50000	>50000	>50000
	Regdanvimab	7	>50000	>50000	>50000	6336	>50000	>50000
	Bebtelovimab	5	7	6	7	14	>50000	>50000
	Sotrovimab	157	833	5554	13000	3239	825	>50000
Cocktails of mAbs	Casirivimab–imdevimab	9	3642	2611	5395	>50000	2456	>50000
	Bamlanivimab–etesevimab	18	>50000	>50000	>50000	>50000	>50000	>50000
	Cilgavimab–tixagevimab	7	97	155	7131	>50000	482	>50000
	Amubarvimab–romlusevimab	64	657	1819	1015	>50000	5359	>50000

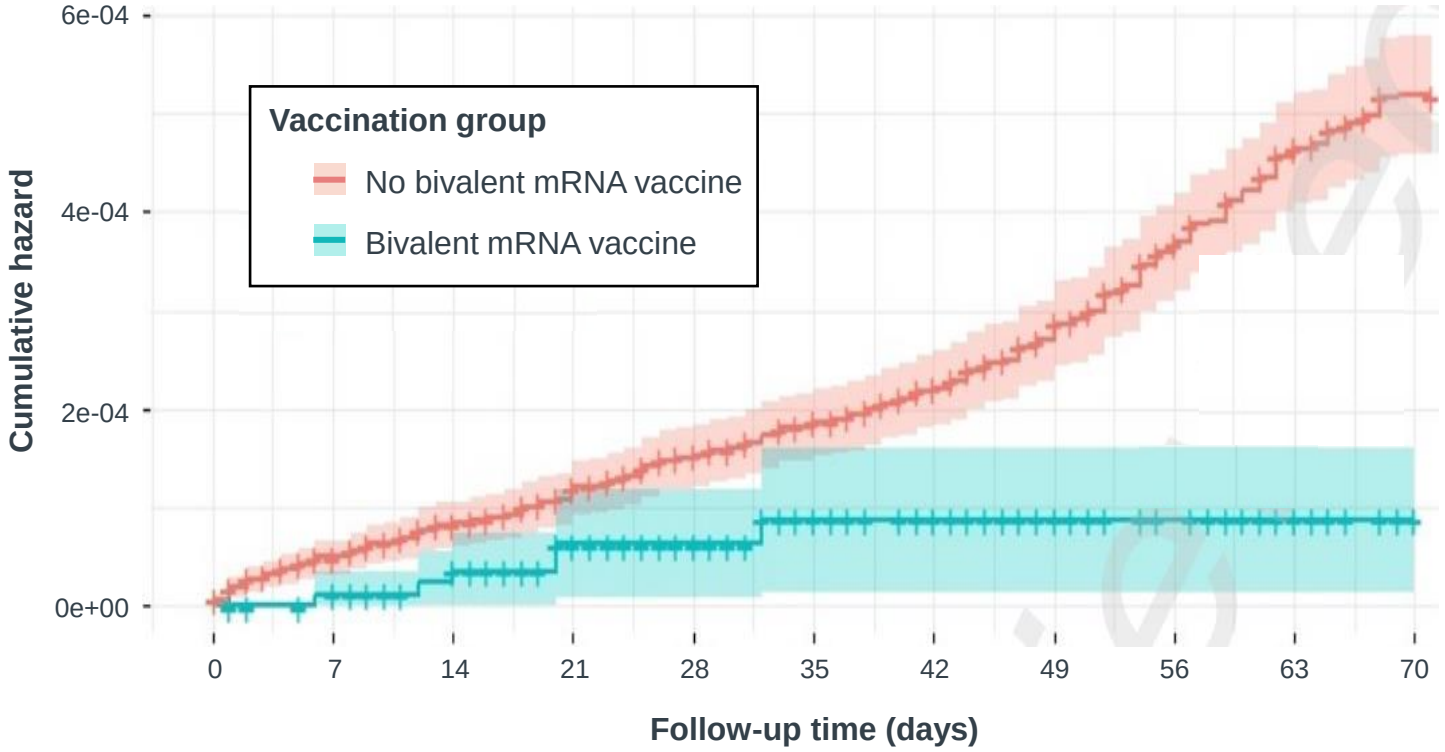
EC50 (ng/ml)



mAb, monoclonal antibody.

Arora P *et al. Lancet Infect Dis* 2023; 23 (1): 22–23.

Efficacy of bivalent mRNA vaccine in preventing severe COVID-19 outcomes

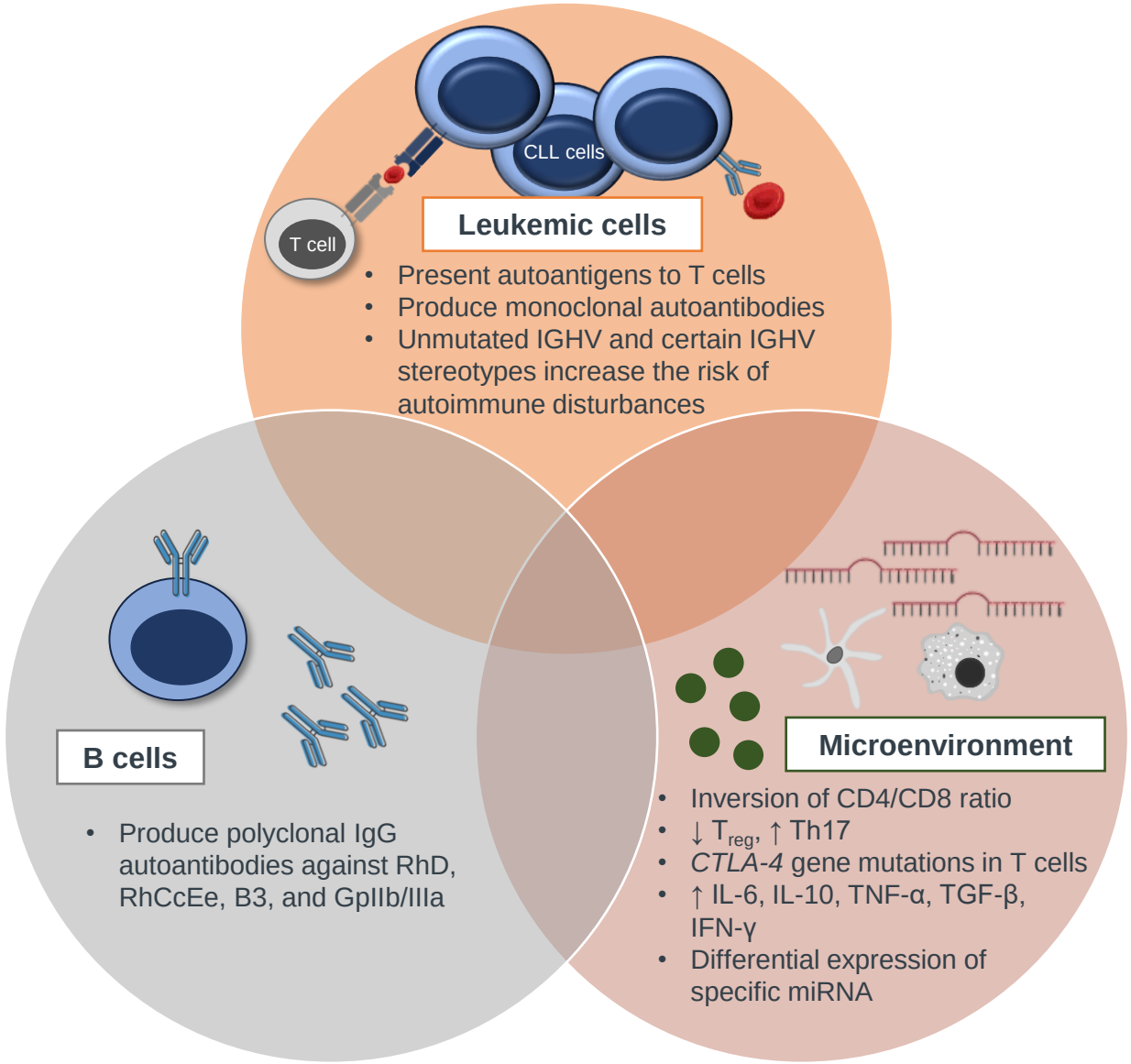


	Bivalent mRNA vaccine	No bivalent mRNA vaccine	HR (95% CI)	Efficacy
Hospitalization	6	297	0.19 (0.08–0.43)	81%
Deaths	1	73	0.14 (0.02–1.04)	86%

CI, confidence interval; HR, hazard ratio; mRNA, messenger RNA.
Arbel R *et al. Lancet* 2023; Preprint (DOI: 10.2139/ssrn.4314067).

Autoimmune phenomena

Autoimmunity in CLL



CLL, chronic lymphocytic leukemia; *CTLA-4*, cytotoxic T lymphocyte–associated antigen 4; Gp, glycoprotein; IFN-γ, interferon gamma; IgG, immunoglobulin G; IGHV, immunoglobulin heavy chain; IL, interleukin; miRNA, microRNA; RhCcEe, Rh blood group CcEe antigens; RhD, Rh blood group D antigen; TGF-β, transforming growth factor beta; Th17, type 17 T helper cell; TNF-α, tumor necrosis factor alpha; T_{reg}, regulatory T cell.
Abiol N *et al*. *Cancer J* 2021; 27 (4): 286–296.

Autoimmune phenomena in CLL

Common[1]

- AIHA (5–9%)
- Immune thrombocytopenia (1%–3%)
- PRCA (<1%)
- Immune neutropenia (?) (LGL)

Infrequent[1,2]

- Autoimmune disorders preceding CLL
  - (e.g. pernicious anemia)
- Concomitant autoimmune disorders / CLL
  - (e.g. cold agglutinin disease, paraneoplastic pemphigus, neuropathies)

AIHA, autoimmune hemolytic anemia; CLL, chronic lymphocytic leukemia; LGL, large granular lymphocytic leukemia; PRCA, pure red cell aplasia.

1. Abiol N *et al*. *Cancer J* 2021; 27 (4): 286–296. 2. Hodgson K *et al. Haematologica* 2011; 96 (5): 752–761.

Anemia/thrombocytopenia: Immune or bone marrow failure?

Some clues

	Immune	Bone marrow failure
Prior history of IC	Yes	No
Ongoing or recent reaction	No	Yes
Onset	Abrupt	Gradual
Plt count / Hb level	Very low	Moderately low
Bone marrow	Not massively infiltrated Glycophorin ++ / Factor VIII	Packed
Indirect signs of hemolysis	Yes, but not always!	No
Spherocytes / large plts	Yes, not striking	No
Laboratory tests	AIHA: DAT(+) ITP: No reliable tests	DAT(−)
Dissociated Hb / plt count	Possible	No
Response to corticosteroids	Yes	No

This slide reflects the speaker's opinion.
AIHA, autoimmune hemolytic anemia; Hb, hemoglobin; DAT, direct antiglobulin test; IC, immunocompromise; ITP, immune thrombocytopenia; Plt, platelet.

Prognostic factors correlated with autoimmune cytopenia

Clinical prognostic factors
Advanced stage
Older age
Male
High white cell count
Short lymphocyte doubling time

Biological prognostic factors
Beta 2 microglobulin
High CD38
High ZAP70
Unmutated IGHV genes
Poor risk cytogenetics

ZAP 70, zeta-chain–associated protein kinase 70.

Hodgson K *et al. Haematologica* 2011; 96 (5): 752–761.

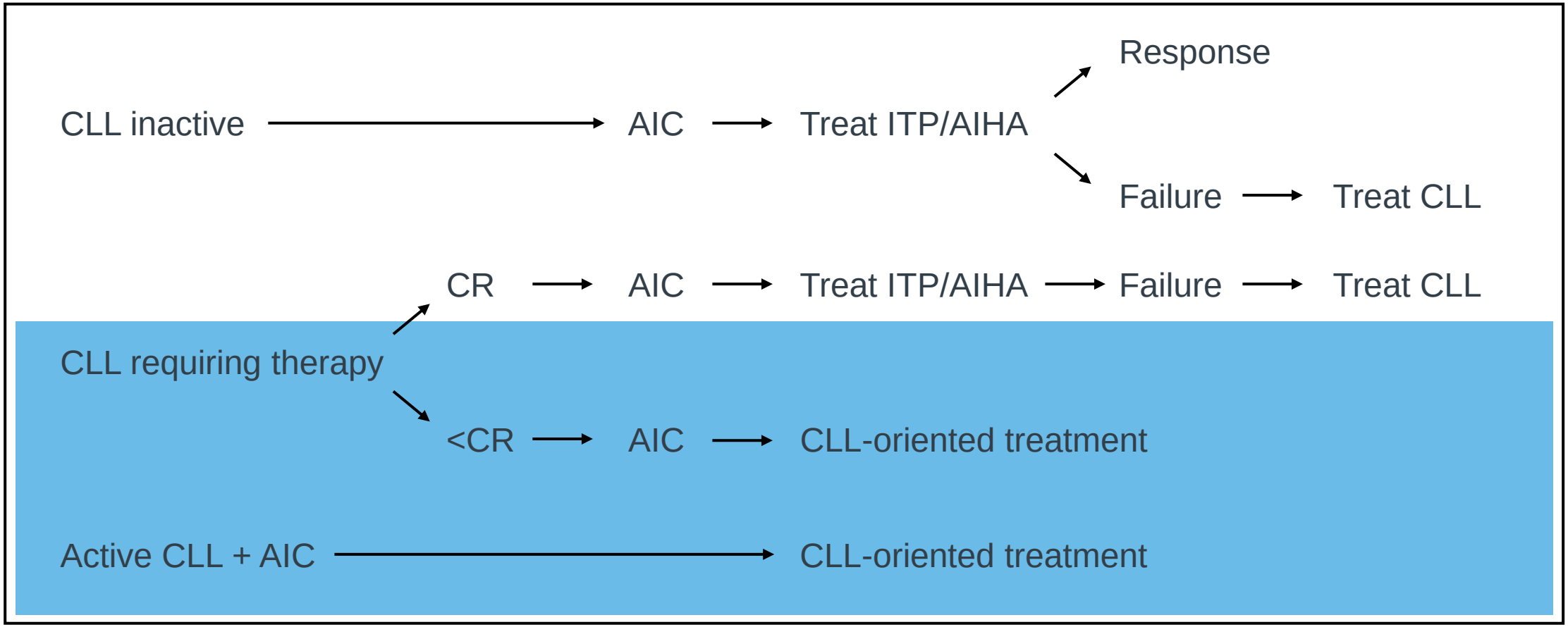
Targeted therapies minimize the risk of developing autoimmune cytopenias

Treatment regimen	AIHA incidence	Remarks
Ibrutinib	0%–3%	Selected patients (trial) Higher in RWD
Acalabrutinib	~3%	Selected patients (trial)
Zanubrutinib	NR	Selected patients (trial) No RWD
Venetoclax	2%–7%	Selected patients (observational study) Heavily pretreated Monotherapy (higher)
PI3Ki	0.9%–3%	Selected patients (trial)

AIHA, autoimmune hemolytic anemia; NR, not reported; PI3Ki, phosphoinositide 3-kinase inhibitor; RWD, real-world data.

Abiol N and Moreno C. *Cancer J* 2021; 27 (4): 286–296.

Treatment for autoimmune cytopenia in CLL



Adapted from Moreno 2021.

AIC, autoimmune complications; AIHA, autoimmune hemolytic anemia; CLL, chronic lymphocytic leukemia; CR, complete response; ITP, immune thrombocytopenia.

Moreno C. *Blood* 2021; 137 (25): 3464–3465.

Summary (1/2)

- Immune disturbances are an intrinsic part of CLL, not an epiphenomenon[1]
- Chemo(immuno)therapy regimens have been shown to be extremely immunosuppressive[2–5]
- Targeted therapies have significantly improved patient outcomes in previously untreated and relapsed/refractory CLL patients[6–8]
- Infections are still the main cause of death in CLL even in the era of targeted therapies[9]
- Patients with CLL show poor serological responses to SARS-CoV-2 vaccination and other viruses[10]

CLL, chronic lymphocytic leukemia.

1. Moreno C *et al. J Exp Clin Cancer Res* 2021; 40 (1): 321. 2. Beyer M *et al. Blood* 2005; 106 (6): 2018–2025. 3. Ysebaert L *et al. Leukemia* 2010; 24 (7): 1310–1316. 4. Gassner FJ *et al. Cancer Immunol Immunother* 2011; 60 (1): 75–85. 5. Martínez-Calle N *et al. Br J Haematol* 2019; 184 (6): 957–968. 6. Janssen-Cilag International NV. Imbruvica – summary of product characteristics; November 2022. 7. AstraZeneca AB. Calquence – summary of product characteristics; December 2021. 8. BeiGene Ireland Ltd. Brukinsa – summary of product characteristics; December 2022. 9. Arzoun H *et al*. *Cureus* 2022; 14 (3): e22927. 10. Arbel R *et al. Lancet* 2023; Preprint (DOI: 10.2139/ssrn.4314067).

Summary (2/2)

- Autoimmune phenomena occur in up to 10% of the CLL population[1]
- Targeted therapies do not increase the risk of autoimmune cytopenias and can be used to treat them[2]
- Further studies are needed to better clarify the role of targeted therapies as immunomodulatory drugs and their potential clinical implications (infections, autoimmunity, and secondary malignancies)

CLL, chronic lymphocytic leukemia.

1. Hodgson K *et al. Haematologica* 2011; 96 (5): 752–761. 2. Abiol N *et al*. *Cancer J* 2021; 27 (4): 286–296.

CLL Group - H. de la Santa Creu i Sant Pau

Carol Moreno
Miguel Arguello
Nil Albiol
Alba Mora
Paola Jara
Esther Moga
Josep Nomdedéu

Other collaborators: Eva Gimeno (H. Mar) / Tomás Roncero (ICO Girona)

Thank you very much!!!