

REAL-WORLD CLL MANAGEMENT

ACCESS, THERAPEUTIC SEQUENCING AND CLINICAL CHALLENGES

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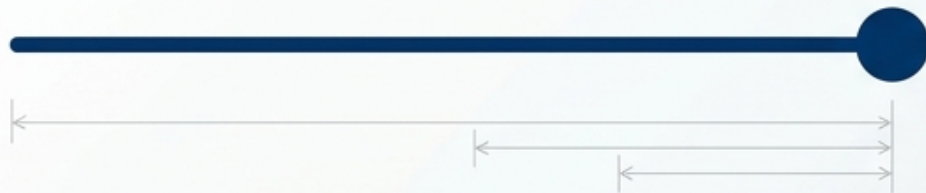


The Paradigm Shift in CLL Management

We have permanently moved away from the “One Best Drug” model.

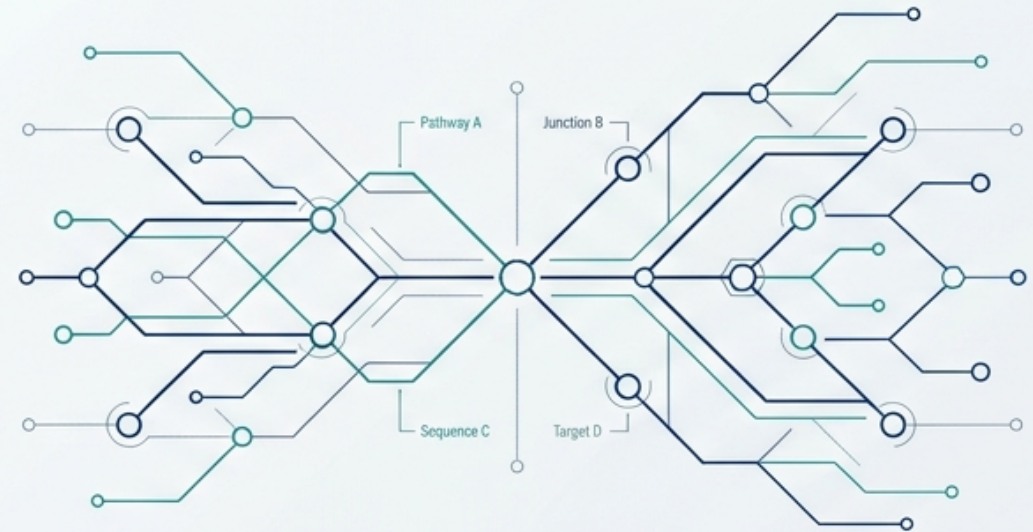
Past Era

Linear focus on finding a single most potent agent.



Current Reality

A multi-dimensional matrix requiring Strategic Navigation.



Multiple highly effective options

Diverse classes and combinations available.



Absolute necessity of therapeutic sequencing

Optimization of treatment lines and timing.



Personalized medicine based on biological markers

Tailored strategies for specific genomic profiles.



Overwhelming importance of logistics and systemic access

Coordination of care and resource availability.





Ideal World vs. The Brazilian Reality

Clinical Trial Utopia



Highly selected patients without interfering comorbidities



Deeply experienced academic centers



Integral, frictionless access



Intensive monitoring capabilities



Elevated patient adherence

Real-World Hematology



Approval does NOT equal access



Deep inequality between Public (SUS) and Private systems



High dependence on judicialization



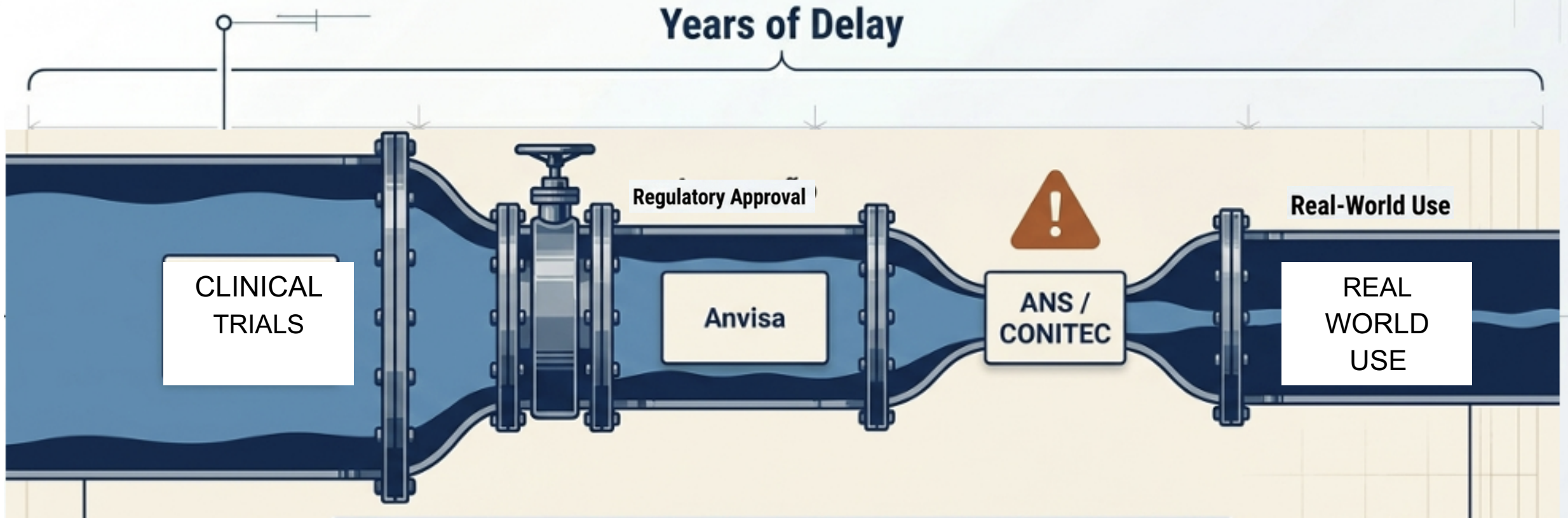
Severe regional heterogeneity and vast geographic distances



Limited access to essential molecular testing

The Translation Lag: From Evidence to the Clinic

The rhythm of incorporation creates severe global and local delays.



1. Scientific Evidence

Global clinical trial success

2. Regulatory Approval

Initial delays in local authorization

3. The Access Bottleneck

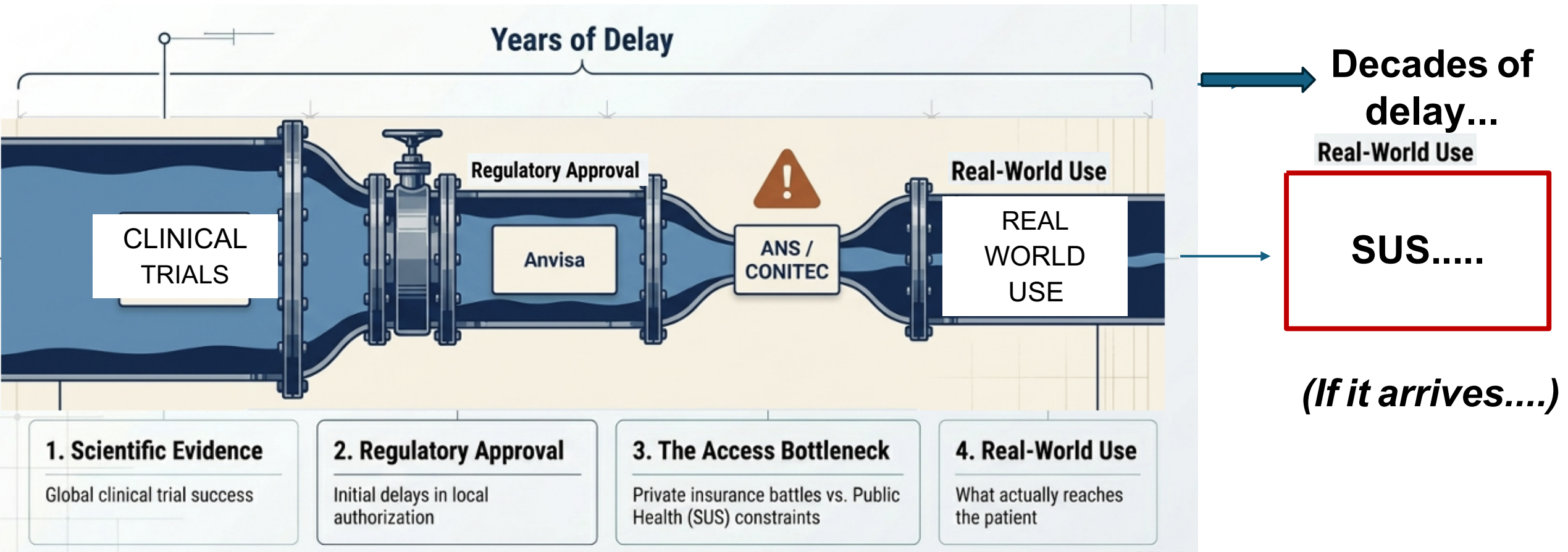
Private insurance battles vs. Public Health (SUS) constraints

4. Real-World Use

What actually reaches the patient

The Translation Lag: From Evidence to the Clinic

The rhythm of incorporation creates severe global and local delays.



Real Access to Targeted Therapies in Brazil

Available Agents

Covalent BTKi

Ibrutinib · Acalabrutinib ·
Zanubrutinib

Non-Covalent BTKi

Pirtobrutinib

BCL-2 Inhibitor

Venetoclax

But Access Remains Unequal

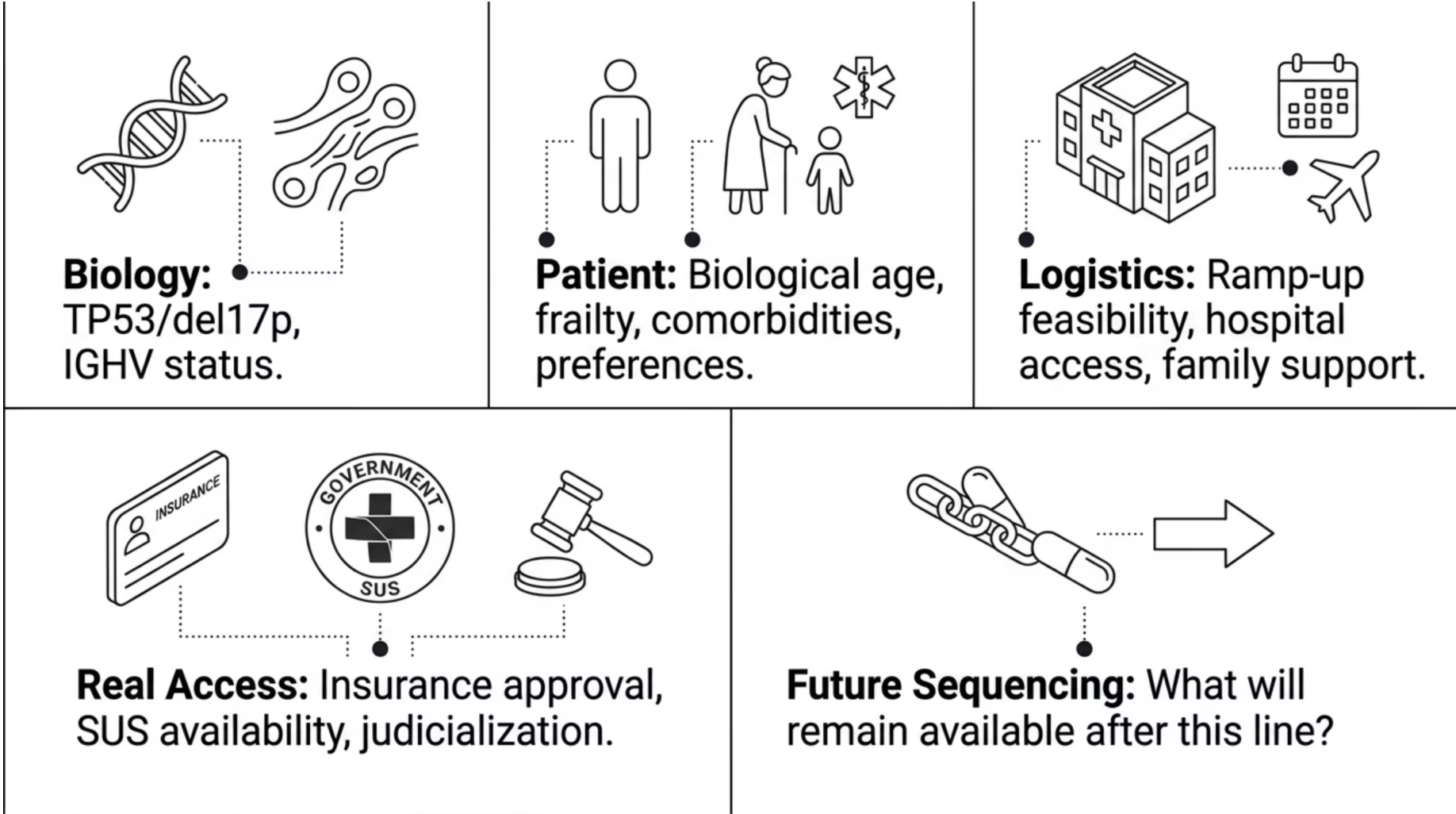
- **Private sector:** gradual incorporation, denials still common, slow approval of combinations
- **SUS:** severe access limitations, dependent on judicialization or clinical trials
- **Academic vs. community centers:** trial access dramatically changes available options

⚠ Access inequality is itself a prognostic factor in Brazilian CLL.



What Really Guides My Decision?

I think through **5 pillars** before any first-line or salvage decision in CLL.



No single pillar overrides the others — the art of CLL management lies in integrating all five simultaneously.

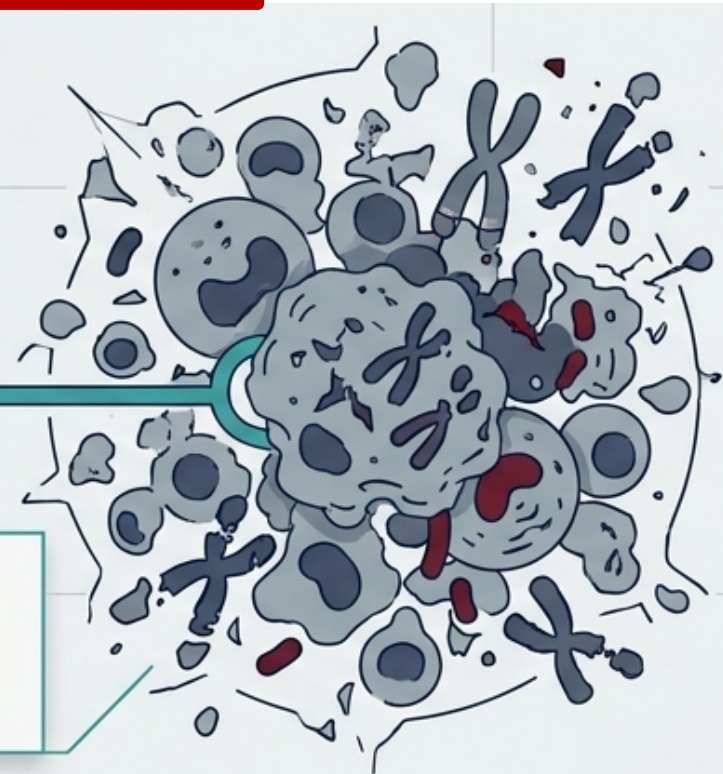
Pillar 1: Genomic Biology & The *TP53* Marker

TP53/del17p remains the principal marker of high biological risk. It is the Guardian of the Genome.

The Strategy: Don't let the dog off the leash.

Continuous BTKi

Without *TP53*: Massive chromosomal instability and rapid clonal evolution.



The Shifting Weight of IGHV

IGHV is now a modulator, not an absolute decider.



FCR Era

Historically: Dictated the use of inte chemoimmunotherapy and served as a massive prognostic baseline.



Targeted Era (2026)

Today: Consistent therapeutic benefit across modern strategies regardless of IGHV status.

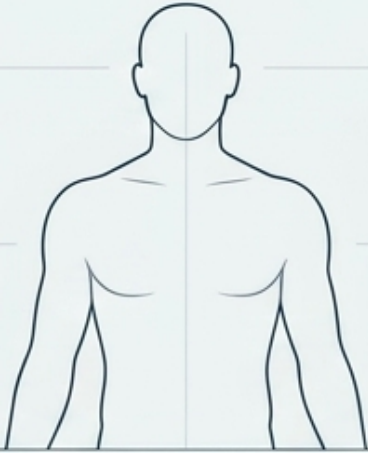


Clinical Caveat:

Unmutated IGHV still shows inferior outcomes when using Venetoclax + anti-CD20 regimens.

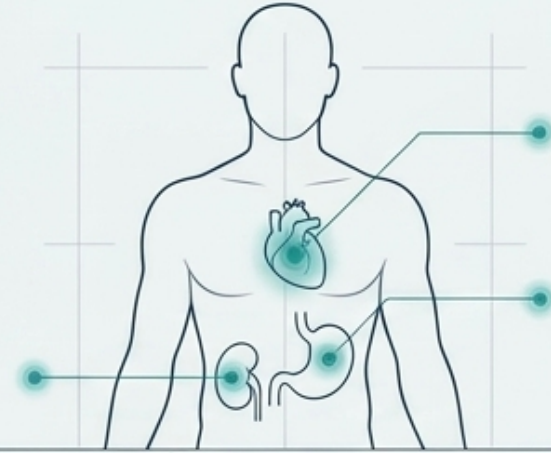
The Frail Patient Reality Check

The Trial Patient



- Isolated CLL
- Robust functional reserve
- Capable of handling intense protocols

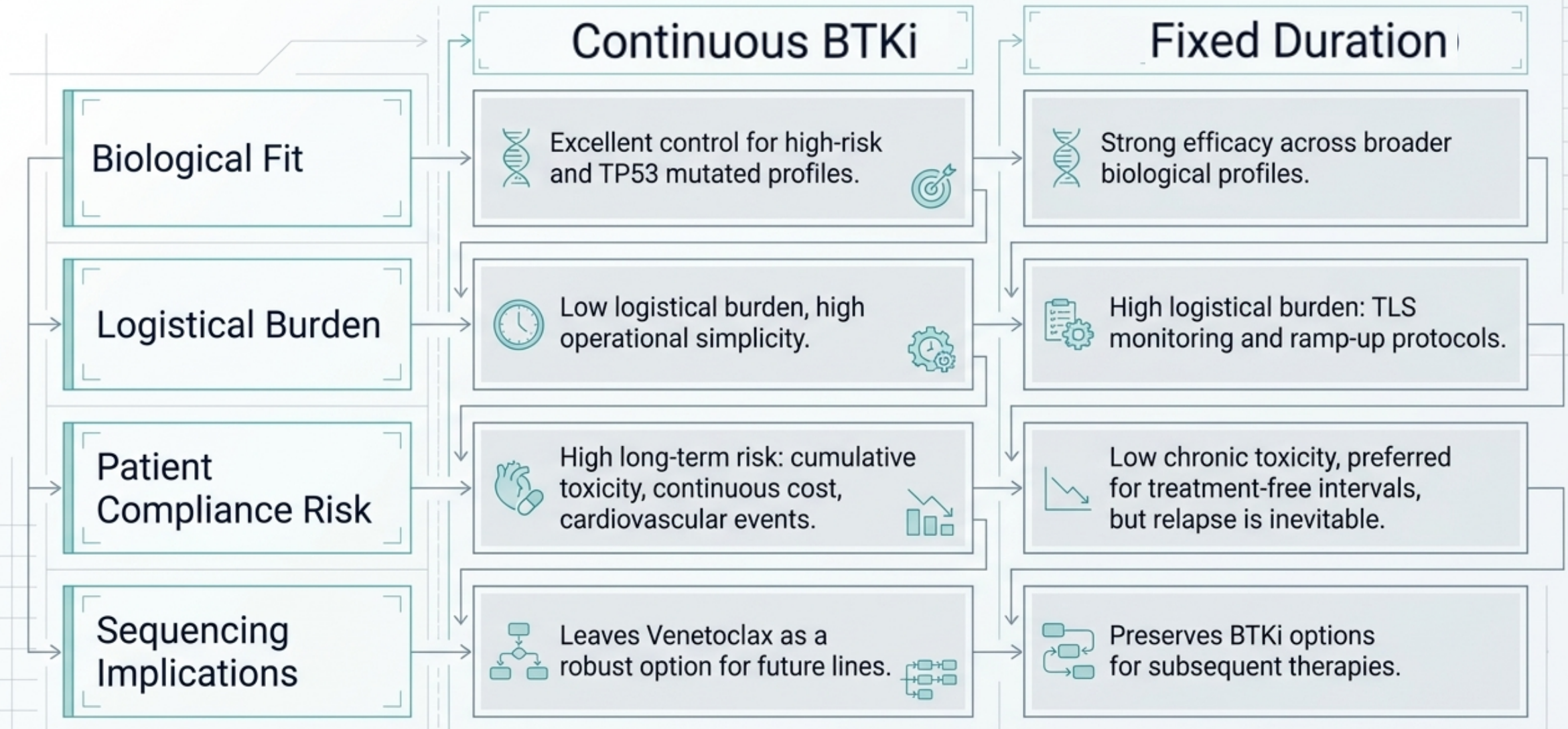
The Clinic Seat



- Atrial Fibrillation (requiring anticoagulation)
- Renal Insufficiency
- Polypharmacy and High Frailty
- Low functional reserve

The “best published regimen” is often incorrect for the real patient. Highly selective BTKis have transformed tolerability, while fixed-duration therapies eliminate chronic toxicity for others.

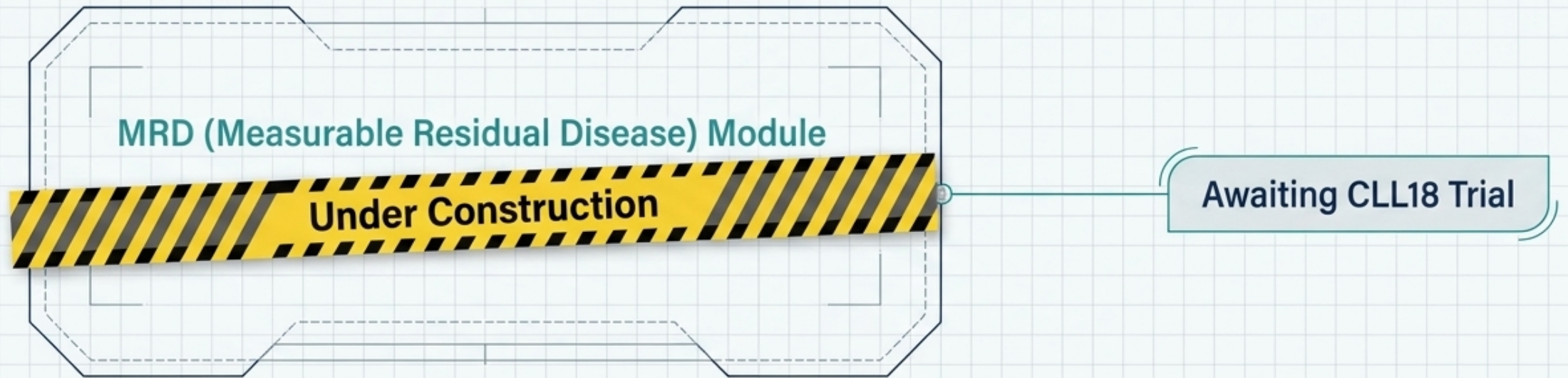
The Therapeutic Strategy Matrix



Future Sequencing & The MRD Reality Check

Is Measurable Residual Disease (MRD) ready to guide real-world targeted practice?

Current Status: No. It remains primarily in the realm of clinical trials.



Real-World Application Today

Strictly limited. Practically utilized only in FCR therapy to safely reduce treatment burden from 6 cycles down to 4.



THE ONLY ONE I USE! PERIPHERAL BLOOD → NEGATIVE → BONE MARROW → NEGATIVE --> STOP!

How I Think about CLLTherapy in 2026

Which therapeutic strategy makes the most sense for **THIS** specific patient, in **THIS** specific healthcare system?



LLC EM 2026: DO RESGATE AO SEQUENCIAMENTO RACIONAL NO BRASIL

A NOVA ERA DO TRATAMENTO

(ONDE ESTAMOS EM 2026)



MUDANÇA DE PARADIGMA: DO RESGATE AO SEQUENCIAMENTO

O modelo evoluiu da quimioimunoterapia seguida de transplante para um sequenciamento de terapias-alvo (BTKi, BCL2 e CAR-T).

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O CENÁRIO BRASILEIRO: O ABISMO DO ACESSO

SETOR SUPLEMENTAR (PRIVADO) EM EXPANSÃO
Inclusão do zanubrutinibe no Rol da ANS em 2024 e aprovação de combinações como acalabrutinibe + venetoclax em 2025.



TESE FINAL: PRESERVAR A PRÓXIMA LINHA

A melhor decisão em 2026 é aquela que evita a resistência cruzada e reduz a toxicidade acumulada para garantir eficácia em tratamentos futuros.



TERAPIAS EMERGENTES E TERCEIRA LINHA

O pirtobrutinibe (BTK não covalente) e o tiso-cel (CAR-T) ganham espaço para pacientes duplamente expostos a BTKi e BCL2.

ESTAGNAÇÃO NO SUS

O PCDT vigente (2023) ainda foca em Flutusimabe + Fludera-bina-Cistofosfamida, com novos alvos dependentes de judicialização.

DISPARIDADE GEGRÁFICA E INSTITUCIONAL

Centros acadêmicos e privados oferecem inovação rapidamente, enquanto hospitais comunitários seguem limitados a esquemas convencionais.

GUIA PRÁTICO DE SEQUENCIAMENTO NA RECAÍDA

RECAÍDA APÓS QUIMIOIMUNOTERAPIA

INICIAR BTKI COVALENTE

COMBINAÇÃO DE VENETOCLAX + ANTI-CD20

PROGRESSÃO EM BTKI COVALENTE

UTILIZAR VENETOCLAX (SE AINDA NÃO USADO)

MIGRAR PARA PIRTOBRUTINIBE (CASO PACIENTE JA TENHA FALHADO A BTKI E BCL2)

PACIENTE DUPLAMENTE EXPOSTO (BTKI + BCL2)

PRIORIZAR PIRTOBRUTINIBE

INCLUSÃO EM ESTUDOS CLINICOS

TERAPIA CAR-T EM CENTROS QUALIFICADOS

CRITÉRIOS PARA ESCOLHA TERAPÊUTICA

TERAPIA CONTÍNUA vs. ESQUEMA FINITO



Regimas de duração fixa (es: Venetoclax combos) oferecem períodos sem tratamento,



enquanto BTKi contínuos são preferíveis em casos de contraindicação ao venetoclax.



IMPACTO DO RISCO MOLECULAR (TP53 E IGHV)

Pacientes com deleção 17p ou mutação TP53 devem evitar quimioterapia, priorizando terapias-alvo desde as primeiras linhas.



ADAPTAÇÃO PARA PACIENTES IDOSOS E FRÁGEIS

Prioriza-se o tolerabilidade, utilizando BTKi mais seletivos (acalabrutinibe) ou ajustes de dose para evitar efeitos como fibrilação atrial e síndrome de lize tumoral.

LLC 1ª LINHA

RESUMO DAS APROVAÇÕES REGULATÓRIAS E DE COBERTURA NO BRASIL

IBRUTINIBE (ANVISA 2013)

✓ ROL ANS
✗ INDISPONÍVEL SUS

VENETOCLAX + OBINUTUZUMABE (ANVISA 2020)

✓ ROL ANS
✗ INDISPONÍVEL SUS

IBRUTINIBE + VENETOCLAX (ANVISA 2023)

✓ ROL ANS
✗ INDISPONÍVEL SUS

ZANUBRUTINIBE (ANVISA 2024)

✓ ROL ANS (2024)
✗ INDISPONÍVEL SUS

ACALABRUTINIBE + VENETOCLAX (ANVISA 2025)

✗ ROL ANS
✗ INDISPONÍVEL SUS

Take-Home Messages

1 Strategy, Not Just Drug Choice

CLL has become a disease of therapeutic sequencing. The order and rationale matter as much as the agent.

2 Access Is a Prognostic Factor

In Brazil, access remains a critical determinant of outcomes — as important as biology.

3 Complementary, Not Competing

Continuous BTKi and fixed-duration strategies each have their place — context defines the choice.

4 TP53 Central; IGHV a Modulator

del(17p)/TP53 remains the dominant high-risk marker. IGHV informs, but no longer decides alone.

5 MRD: Promising, Not Yet Ready

MRD-guided management for novel agents awaits definitive evidence. CLL18 will be pivotal.



Obrigada!


**KEEP
CALM
AND
TRUST A
HEMATOLOGIST**

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