

EVOLUZIONE DELL'ALGORITMO TERAPEUTICO DEL PAZIENTE CON LAL

ESPERIENZA CLINICA NEL PAZIENTE UNFIT CON LLA PH+ «VERSO LA CURA CHEMIO-FREE»

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Ematologia e Trapianti di Cellule Staminali



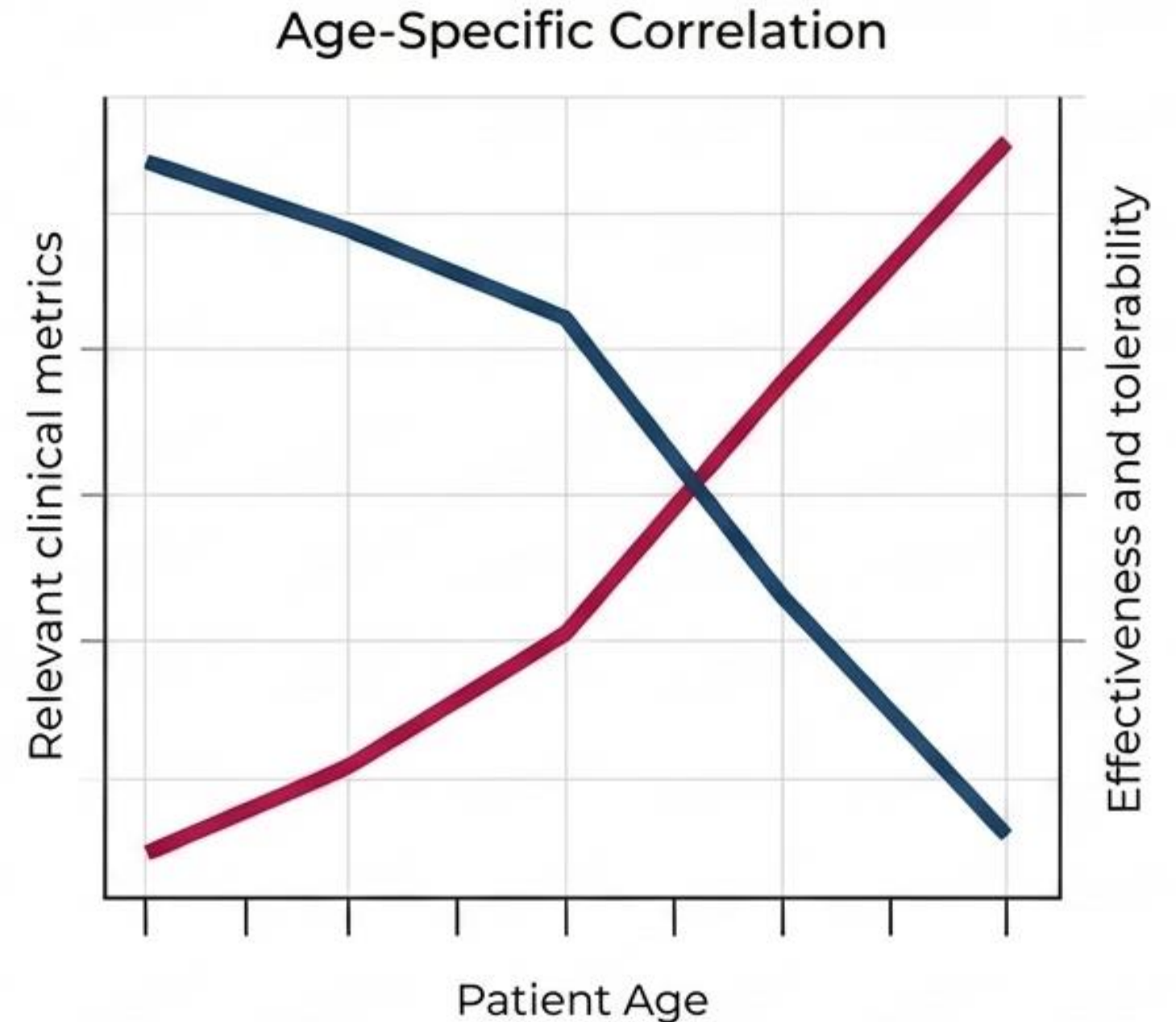
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The Elderly Paradox: High Incidence, Low Tolerability

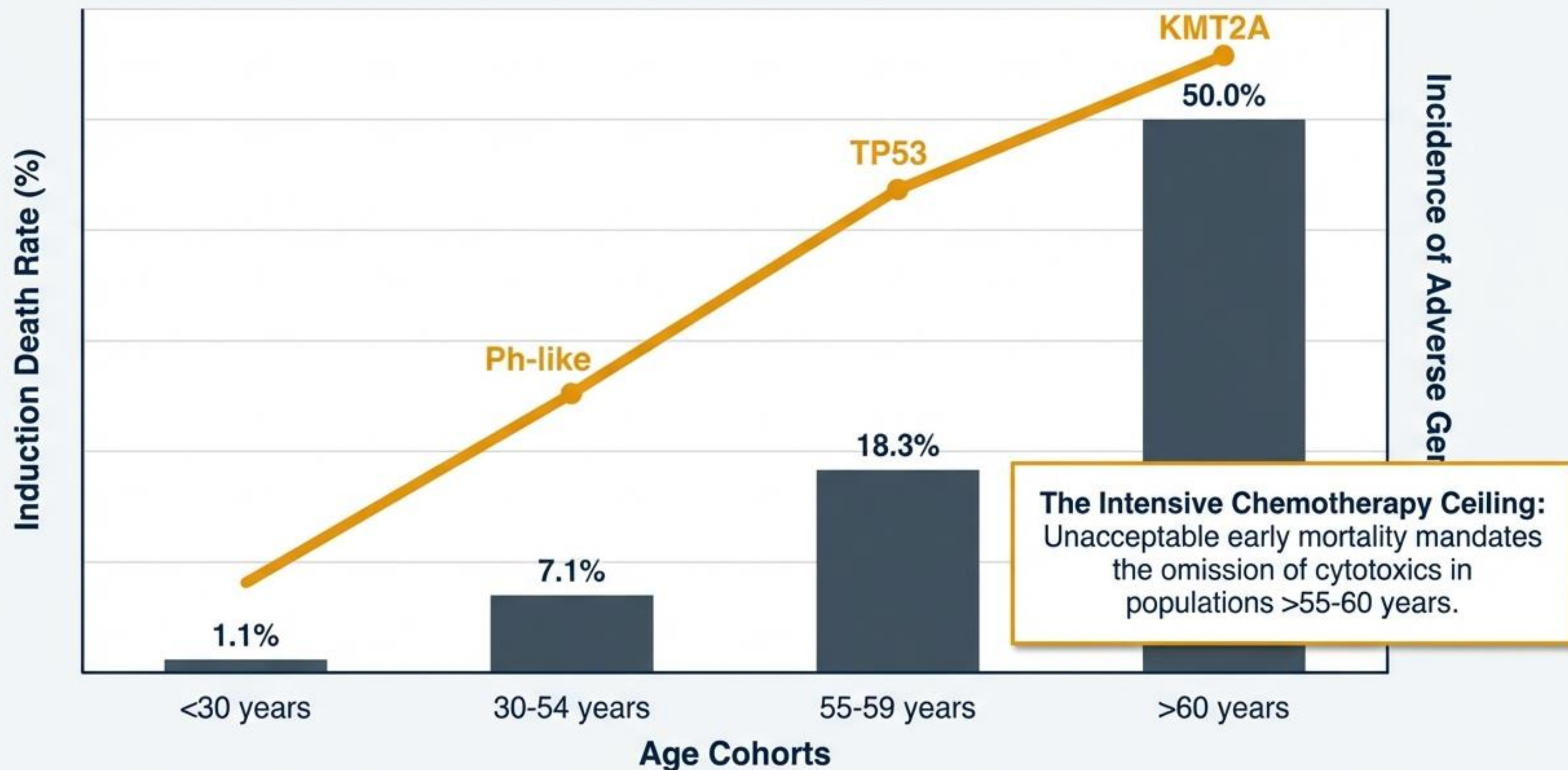
BCR::ABL1 Incidence: >50% in patients over 50.

Historical Therapeutic Nihilism: Before the TKI era, elderly patients were excluded from curative treatments due to unacceptable toxicity (Early Mortality >15-20%).



Absolute necessity to decouple anti-leukemic efficacy from systemic toxicity.

The Clinical Challenge: Age & Toxicity



Paradigm Shift: The Evolution Towards 'Chemo-Free'

PAST

Intensive Chemotherapy

High toxicity, high induction mortality, transient responses.

TRANSITION

TKI + Low-Dose Chemotherapy

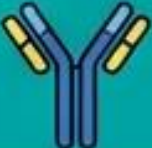
Improvement in remission, but persistence of systemic and infectious toxicity.

PRESENT / FUTURE

TKI + Immunotherapy (Chemo-Free)

Absence of systemic chemotherapy. Long-term survival comparable to young patients.

The Therapeutic Shift in Elderly Ph+ ALL

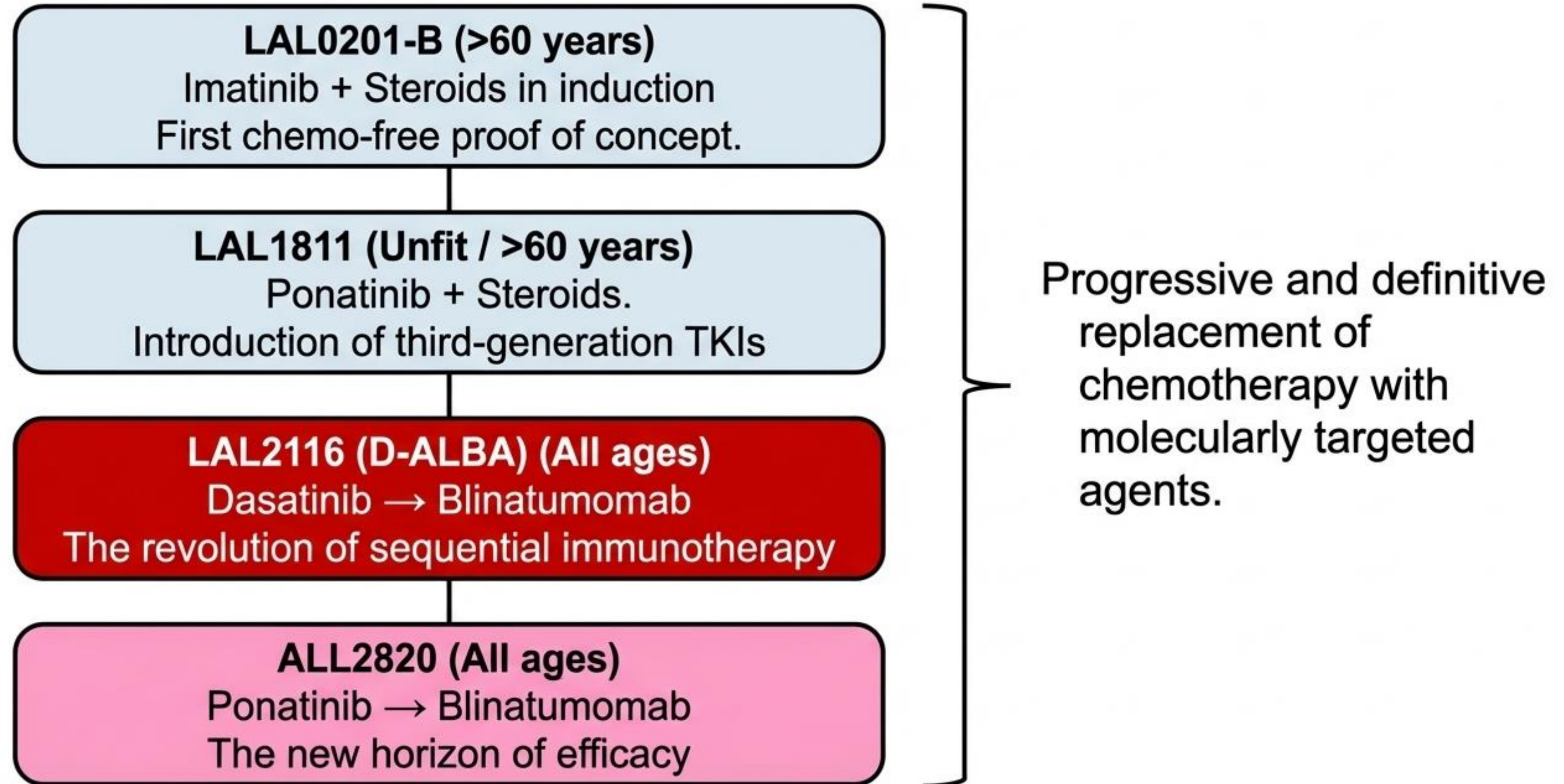
Intensive Chemo + TKI	Low-Dose Chemo + TKI	Chemo-Free (TKI + Steroids/Immuno)
High CHR 	Moderate improvement 	 0-2% Early Death rates 
Unacceptable Early Death (ED) up to 14% 	Persistent toxicity 	 Unprecedented Overall Survival
Poor tolerability in the elderly 	93% grade 3-5 infections with dose-reduced chemo + InO   InO + Chemo	Complete elimination of systemic chemotherapy    

Key Insight: In patients >60 years, the omission of systemic chemotherapy is the primary requisite for survival.

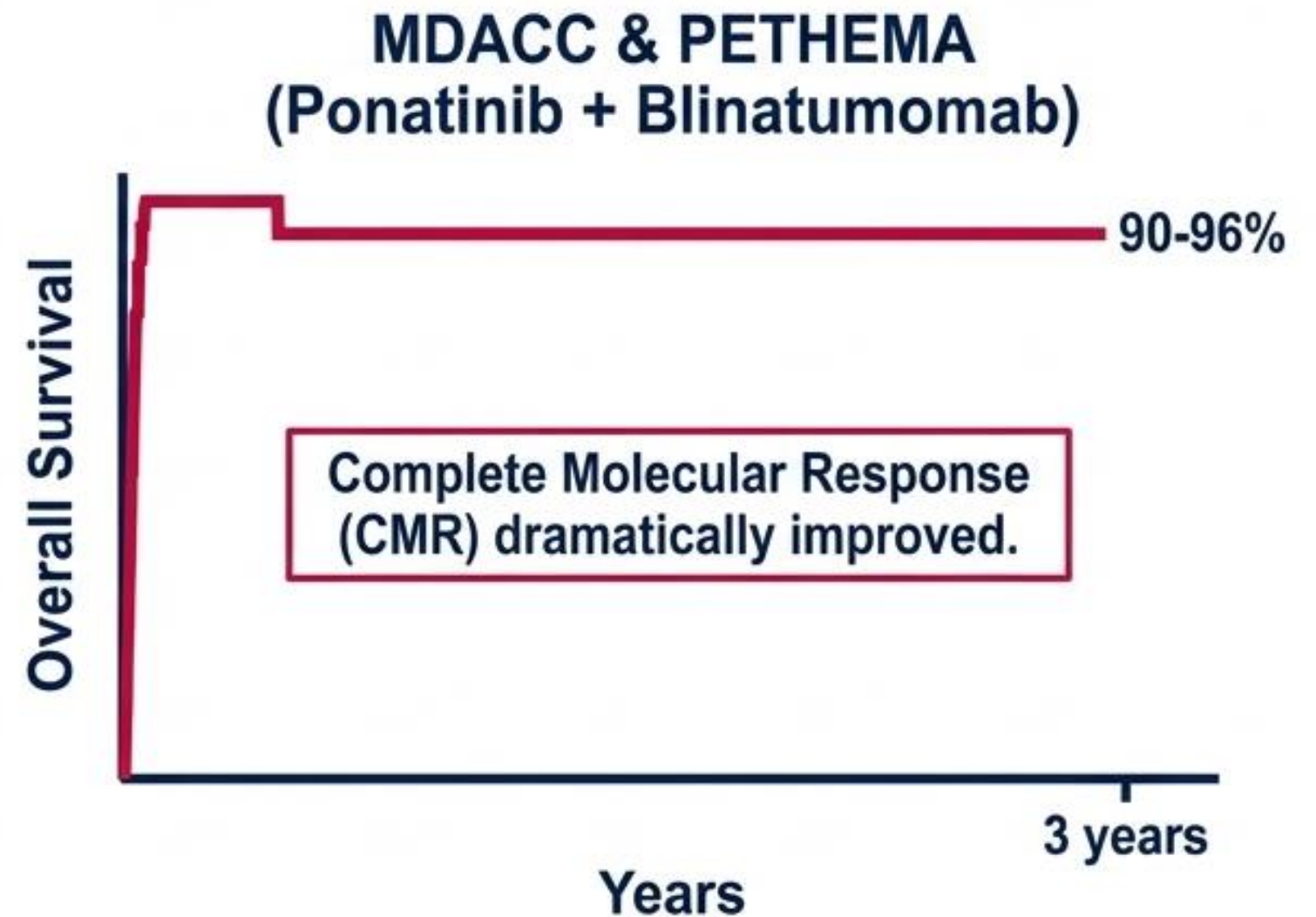
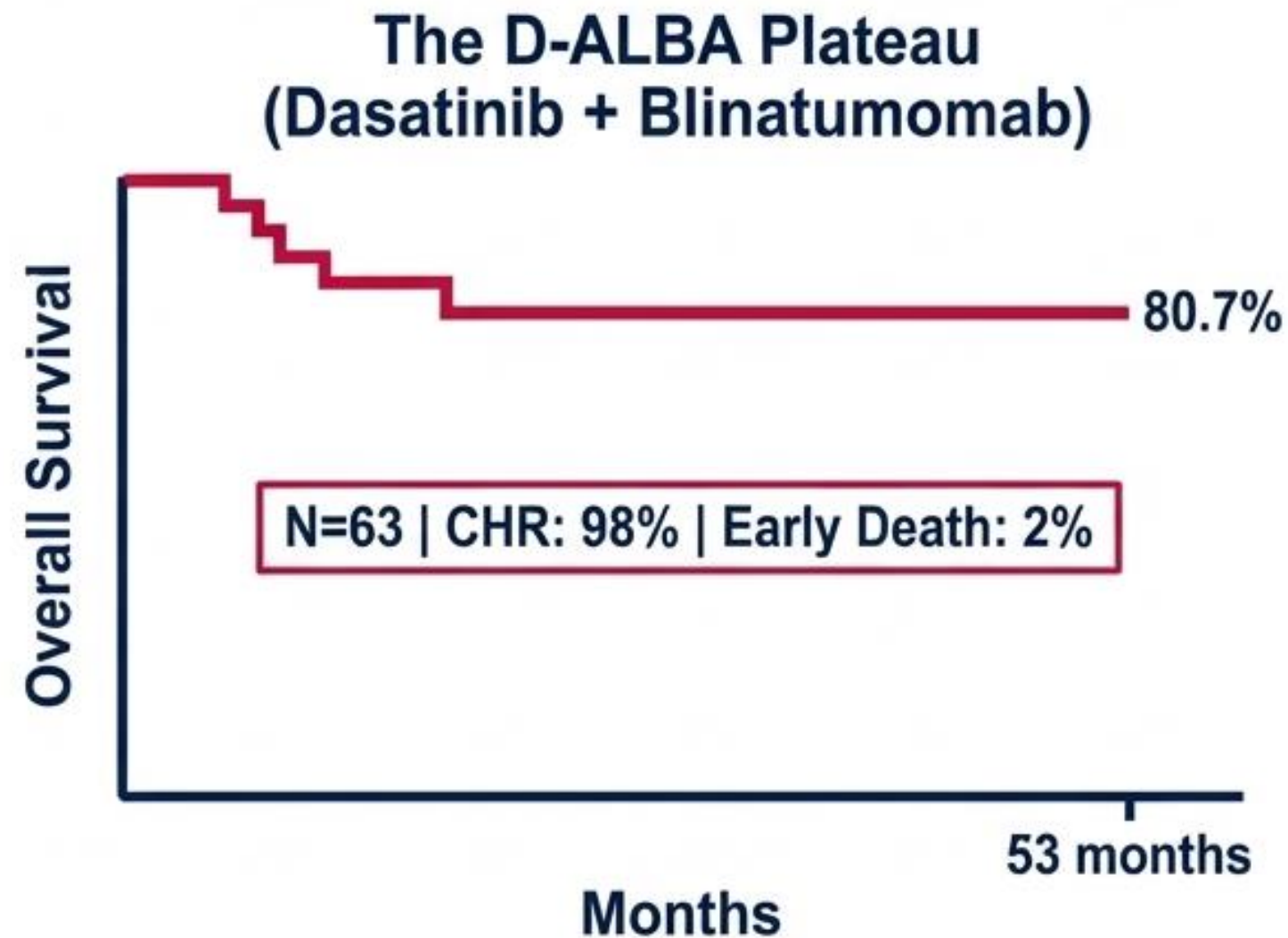
Ph+ ALL: The Evolution of Targeted Regimens

Strategy	Key Trials	CHR %	Early Death %	OS Data
Intensive Chemo + TKI	Bassan 2010 (Imatinib) / Ravandi 2015 (Dasatinib)	92-96%	4%	~46-48% (5y)
Low-Dose Chemo + TKI	Rousselot 2016 / Jabbour 2024	94-97%	1-4%	~36-48%
Chemo-Free Regimens + Blinatumomab	D-ALBA (Dasatinib) MDACC (Ponatinib)	98% 100%	2% 0%	80% (5y) 90% (2y)

The Evolution of GIMEMA Protocols in the Elderly

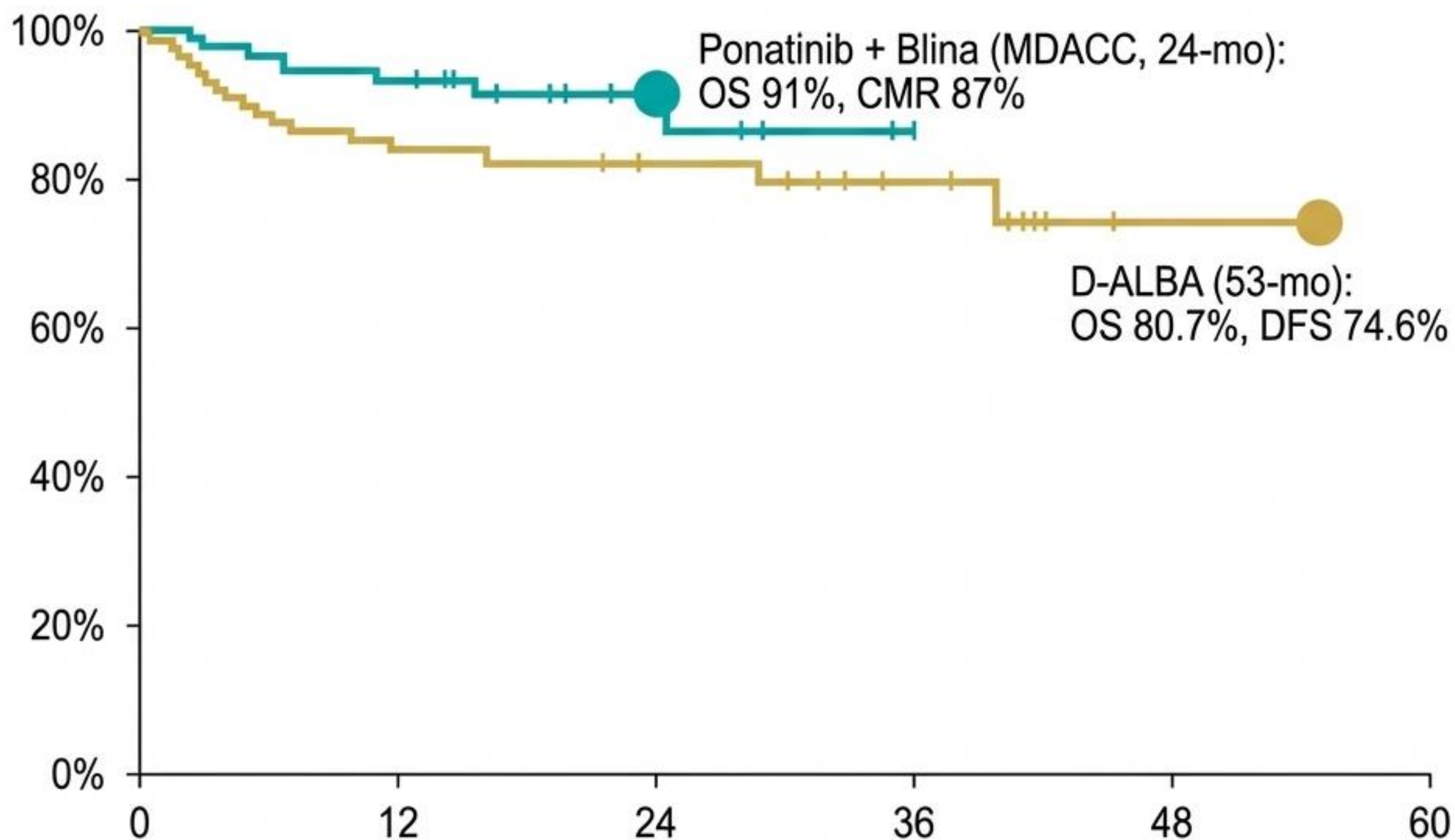


Ph+ ALL: Survival Data (The Chemo-Free Plateau)



Ph+ ALL diagnosed in the 7th-9th decade can achieve long-lived CMR without systemic chemotherapy.

Unprecedented Long-Term Outcomes



In a demographic previously defined by palliative care or rapid toxic death, 4-to-5 year survival rates now exceed 80%.

True chemo-free regimens yield better outcomes than intensive regimens.

Lo Stato dell'Arte: Protocollo GIMEMA ALL2820

Step 1: Pre-fase

Corticosteroidi (riduzione del tumor burden).

Step 2: Induzione

Ponatinib + Prednisone.

**Alta penetranza,
superamento della
resistenza T315I.**

Step 3: Consolidamento

Ponatinib +
Blinatumomab
(fino a 5 cicli)

Insight dalla Letteratura

Efficacia eccezionale documentata in letteratura (Luskin 2024, Jabbour et al.).
Risposte molecolari rapide (CMR >80%), ma con un 'elefante nella stanza':
la tossicità cardiovascolare e pancreatica nel paziente real-world.

The Role of Ponatinib in Elderly/Unfit Patients (GIMEMA LAL1811)



Complete Hematologic Response (CHR) at 24 weeks.



Complete Molecular Response (CMR) at 24 weeks.



Critical need for dose modulation. Early tapering of the starting dose is essential to prevent cardiovascular adverse events while maintaining efficacy in elderly patients.

Caso clinico 1



Uomo, 65 anni

Comorbidità:

- Ipertensione arteriosa
- Dislipidemia
- Storia di pancreatite in età pediatrica
- Trombofilia congenita (mutazione eterozigote Fattore V Leiden)

Caso clinico 1



Uomo, 61 anni

Novembre 2024: giunge in Pronto Soccorso per riscontro, ad esami effettuati esternamente per malessere generale, di leucocitosi.

All'ingresso: WBC: 198.000/mmc Hb: 7.3 g/dl PLT: 78.000/mmc; LDH 1013 U/l;
splenomegalia

Diagnosi

Leucemia Linfoblastica Acuta Ph+

Biologia molecolare: fusione BCR::ABL1 (p190)

Cariotipo complesso: +8, t(9;22), +21

Caso clinico 1



Arruolato nel protocollo:

👉 **GIMEMA ALL2820**

Braccio sperimentale:

Ponatinib + Blinatumomab

Steroid pre-phase

Induzione con:

Ponatinib 45 mg/die

Prednisone

Profilassi SNC con rachicentesi

Dopo 4 giorni:

dolore addominale severo

↑ amilasi/lipasi

Ecografia dell'addome: pancreatite acuta

👉 **Pancreatite acuta G3 da Ponatinib**

Caso clinico 1



Gestione:

- sospensione TKI
- nutrizione parenterale
- antibiotico
- successiva ripresa dopo 10 gg a dose ridotta (30 mg)

Time point 1 (gg+28)

MRD <0.01%

BCR-ABL: 1.6

Time point 2 (gg+70)

MRD <0.01%

BCR-ABL: 0.36

👉 risposta molecolare precoce

Caso clinico 1



Consolidamento

5 cicli di **Blinatumomab** (terminati ad agosto 2025)

Aprile 2026: remissione completa ematologica con BCR-ABL: 0.0000

👉 risposta molecolare profonda

💡 1. Strategia chemo-free nell'anziano

→ TKI + immunoterapia = alta efficacia + minore tossicità

💡 2. Tossicità del Ponatinib

→ pancreatite G3 → necessità di dose reduction

→ gestione senza interrompere il percorso terapeutico

💡 3. MRD-driven approach

→ MRD negativa precoce = forte valore prognostico

💡 4. Ruolo del Blinatumomab

→ consolidamento efficace

Caso clinico 2



Donna, 70 anni

Comorbidità:

- Diabete mellito in terapia insulinica
- Ipertensione arteriosa
- Pregresso carcinoma endometriale (isterectomia 2019, in follow-up)
- Laparocele

Caso clinico 2



Donna, 70 anni

Giugno 2022 alla nostra osservazione per astenia e calo ponderale significativo (~9 kg in 3 mesi).

Esami ematochimici:

- Leucocitosi: 52.000/mmc
- Piastrinopenia: 80.000/mmc
- LDH elevato

Caso clinico 2



Donna, 70 anni

Aspirato midollare:

- Blasti linfoidi > 70%

Immunofenotipo:

- CD19+, CD34+, CD10+, TdT+
→ compatibile con LAL B

Biologia molecolare:

- BCR-ABL p190 positivo

👉 **Diagnosi:**

Leucemia Linfoblastica Acuta

Caso clinico 2



Arruolata nel protocollo GIMEMA ALL2820:

- Ponatinib + Blinatumomab

Fasi:

1. Prefase steroidea
2. Ponatinib 30 mg/die
3. Blinatumomab
4. Profilassi SNC con rachicentesi

Caso clinico 2



Tossicità rilevanti

- Pancreatite (iperlipasemia ricorrente) + 4 gg con sospensione di Ponatinib; riprende terapia dopo 10 gg con dosaggio di 15 mg/die
- Ad agosto 2022 nuovo episodio di iperlipasemia con nuova interruzione per riprendere dopo circa un mese
- Settembre 2023 (MRD negativa) effettua:
 - Angioplastica coronarica (DES su IVA)
- Dosaggio finale di 15 mg a giorni alterni

Caso clinico 2



- Rapida risposta ematologica
- MRD negativa persistente ($<0.01\%$)

Nel follow-up:

- Remissione molecolare mantenuta a lungo termine (>30 mesi)
- BCR-ABL: fino a negativizzazione (0.000)

Gestione della tossicità da Ponatinib

- pancreatite ed eventi cardiovascolari con necessità di:
 - riduzione dose
 - somministrazione a giorni alterni

Strategia “tailored”

- mantenere efficacia anti-leucemica
- ridurre rischio iatrogeno

Matrice Diagnostica e Terapeutica: Caso 1 vs Caso 2

Caso 1

Caso 2

Profilo di Rischio Baseline

Iperleucocitosi estrema, 60M

Fragilità, 70F

Tossicità Primaria

Pancreatite Acuta G3

CV Severa + Pancreatica

Aggiustamento Ponatinib

Step-down a 30mg

Step-down a 15 mg a gg alterni

Partner Immunoterapico

Blinatumomab

Blinatumomab

Outcome Molecolare

CMR / MRD <0.01%

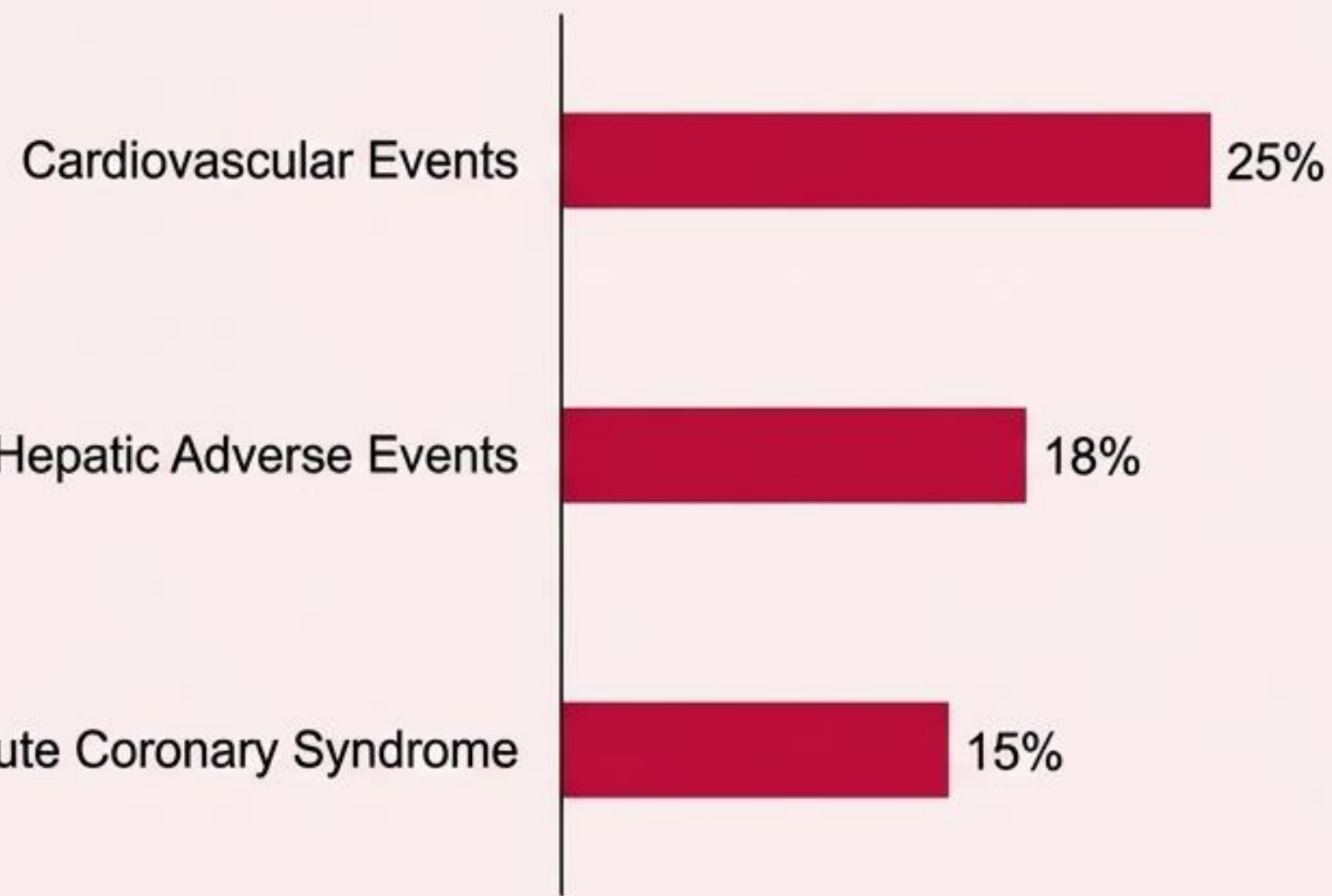
CMR / MRD <0.01%

Percorsi tossicologici divergenti, medesimo eccellente esito molecolare grazie alla modulazione personalizzata della dose.

The Toxicity Challenge: Dynamic Dose Modulation

The Threat

Continuous high-dose TKI drives lethal toxicity.



The Solution

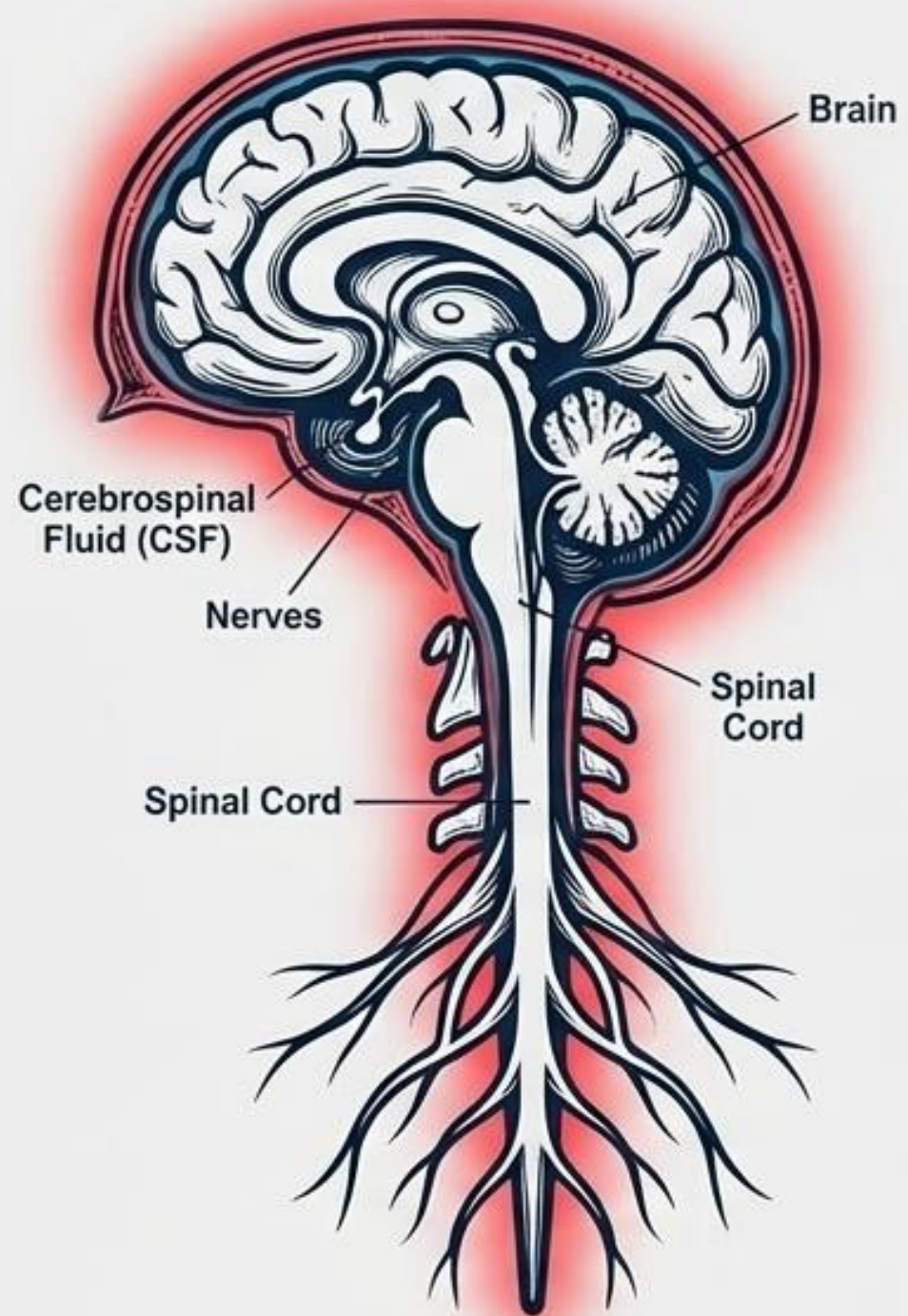
Start: 30 mg/d
(or 45mg if high risk)



Step-Down:
Immediate reduction
to 15 mg/d

Maintains remission
while preventing TEAEs.

The Achilles Heel: CNS Prophylaxis



The Vulnerability

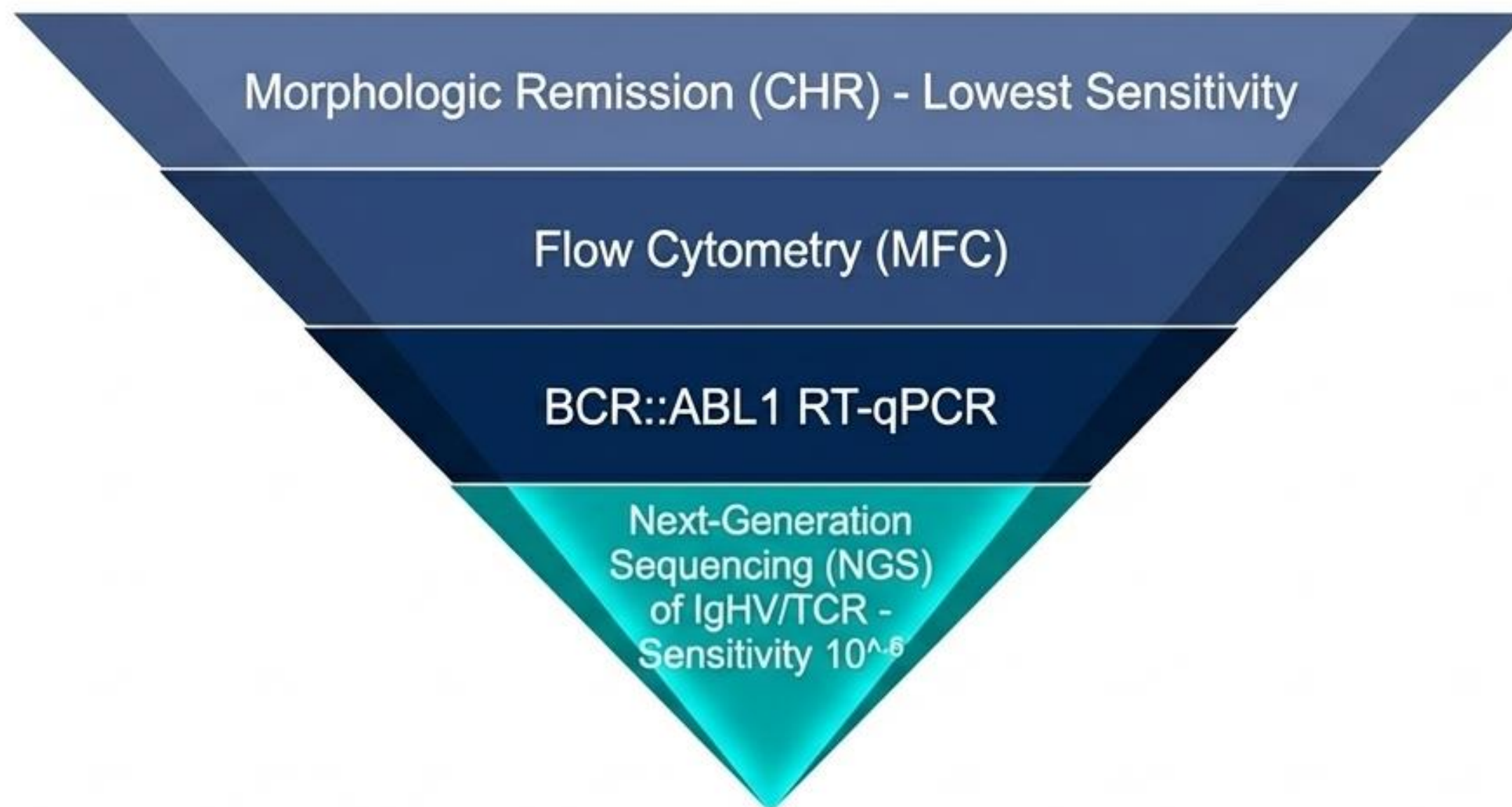
Blinatumomab and specific TKIs exhibit poor CNS penetration.

Omission of high-dose systemic chemotherapy leaves the CNS as a sanctuary site for relapse.

The Clinical Mandate

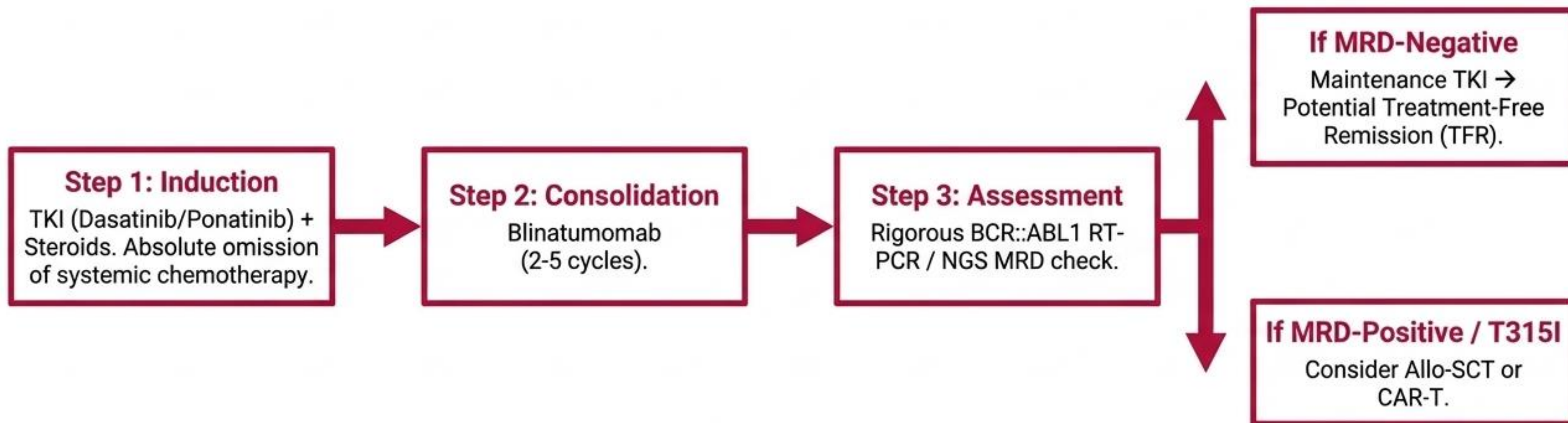
- ✓ **Absolute requirement for 12 to 15 prophylactic lumbar punctures.**
- ✓ **Mandatory use of triple intrathecal therapy (Methotrexate, Cytarabine, Steroids).**
- ✓ **18 lumbar punctures** required if CNS+ at diagnosis.

The Prognostic Engine: MRD Monitoring



Concept Note: Ultra-deep MRD monitoring (NGS) is the absolute prognostic engine that allows clinicians to safely omit allogeneic SCT in elderly patients. Persistent MRD is the sole trigger for altering therapy.

TREATMENT SCHEMA: Adult Ph+ ALL



CAR-T Consolidation: The Frontier

Brexucabtagene autoleucel (ZUMA-3)

Retrospective data in populations
>60 years:

MRD-negative CR: **59%** (Equivalent
to younger cohorts at 66%).

Obecabtagene autoleucel (FELIX)

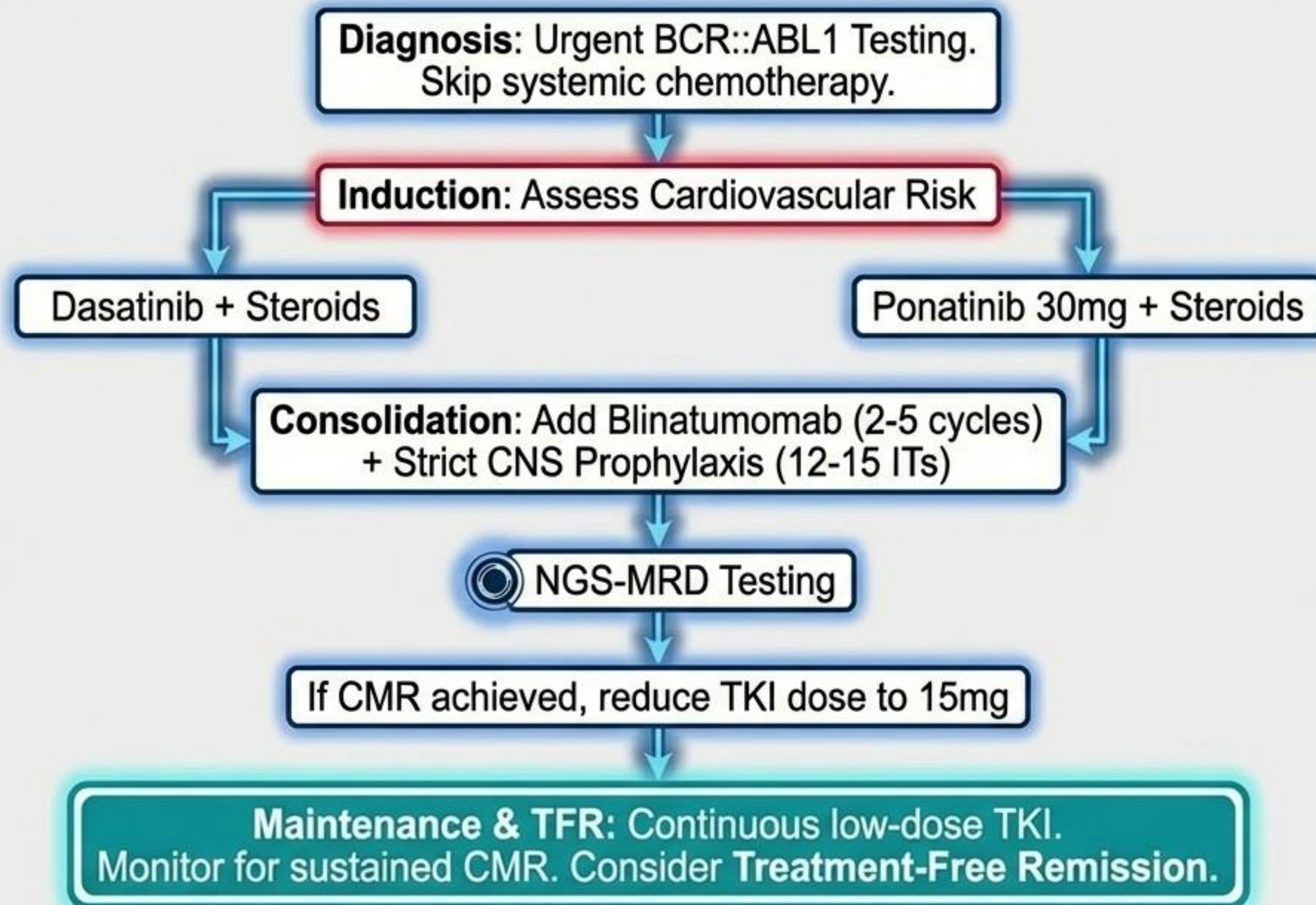
Remarkably low toxicity profile in
older adults:

⚠ Grade 3-4 CRS: **2.4%**

⚠ Grade 3-4 ICANS: **7.1%**

**Low rates of severe CRS/ICANS with obe-cel establish CAR-T as a
highly viable consolidation strategy for older adults unfit for SCT.**

Proposed Master Algorithm for Elderly Ph+ ALL



Treatment-Free Remission (TFR) in the Elderly



Safe TKI suspension after prolonged complete molecular remission (CMR).

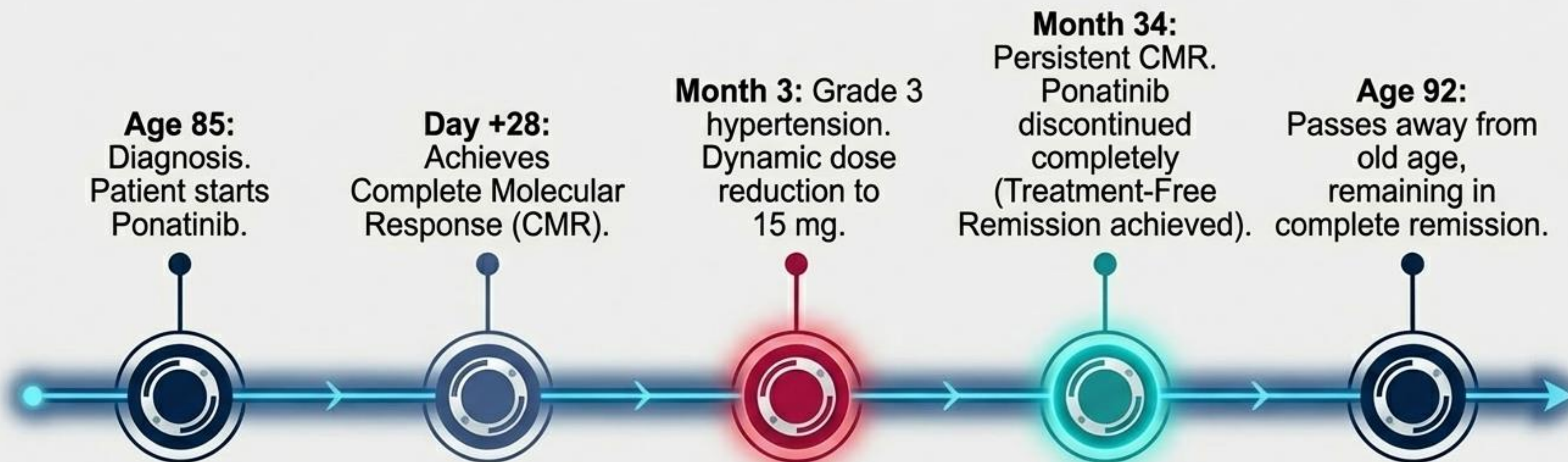
Key Criteria:

- Absence of high-risk mutations.
- Strict post-suspension molecular monitoring.

Biological Rationale:

TKI-induced *in vivo* host immune modulation (drastic reduction of immunosuppressive T-regulatory cells) that helps maintain long-term disease control.

Real-World Proof: TFR in Extreme Old Age



Takeaway: Advanced age is not a barrier to achieving the ultimate goal of precision hematology: curing the disease and stopping all therapy.

Summary of Clinical Mandates



Zero Systemic Chemotherapy

Omission of standard chemo is mandatory; replace entirely with TKI + Steroids/Immunotherapy.



Dynamic Dose Modulation

Actively manage TKI dosing (step down to 15mg upon CMR) to prevent lethal cardiovascular events.



Ultra-Sensitive MRD

NGS monitoring is the sole arbiter of treatment duration and justification for omitting SCT.



Aggressive CNS Prophylaxis

12-15 triple-medicated lumbar punctures are the required defense against sanctuary site relapse.

