

# **CML in 2026:** Optimizing TKI Therapy, Molecular Monitoring, and the Path to Treatment-Free Remission (TFR)

A Tactical Guide to the ELN 2025  
Guidelines and the Brazilian Reality

*Know your weapon. Know your enemy.  
Know when to lay down your arms.*






# The CML Battlefield in Brazil: Strategy Meets Reality




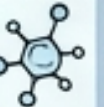

## Public Sector (SUS)



- **Frontline:** Imatinib remains the accessible champion. 
- **Salvage:** Dasatinib/Nilotinib deployed upon failure/intolerance.   


## Private Sector (ANS)



- **Frontline:** Broader initial access to 2G-TKIs. 
- **The 2026 Shift:** Integrating 3rd-gen/STAMP inhibitors (Asciminib) while balancing out-of-pocket costs versus long-term survival value.   


# Reconnaissance: ELN 2025 Molecular Milestones (BCR::ABL1 IS%)



**Quantitative PCR (IS%)** must be executed every 3 months until MMR is achieved, then every 3-6 months.



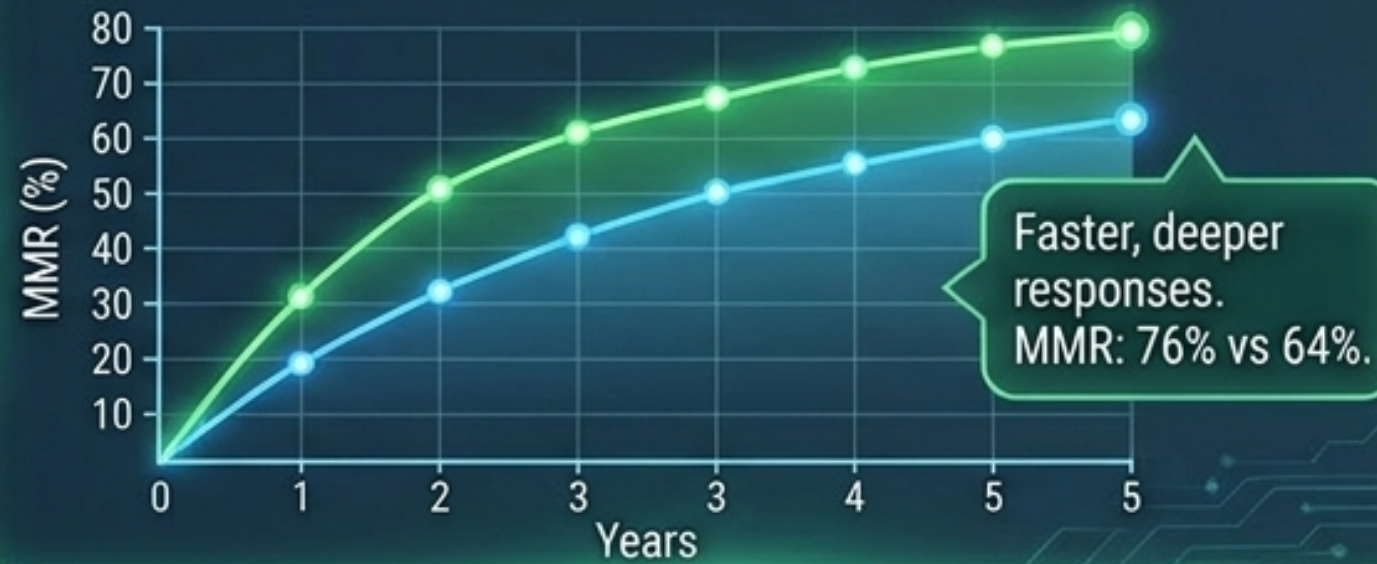
# The TKI Warriors: Selecting Your Frontline Champion

One size does not fit all. Select based on comorbidities, ELTS score, and TFR goals. (ELN 2025)

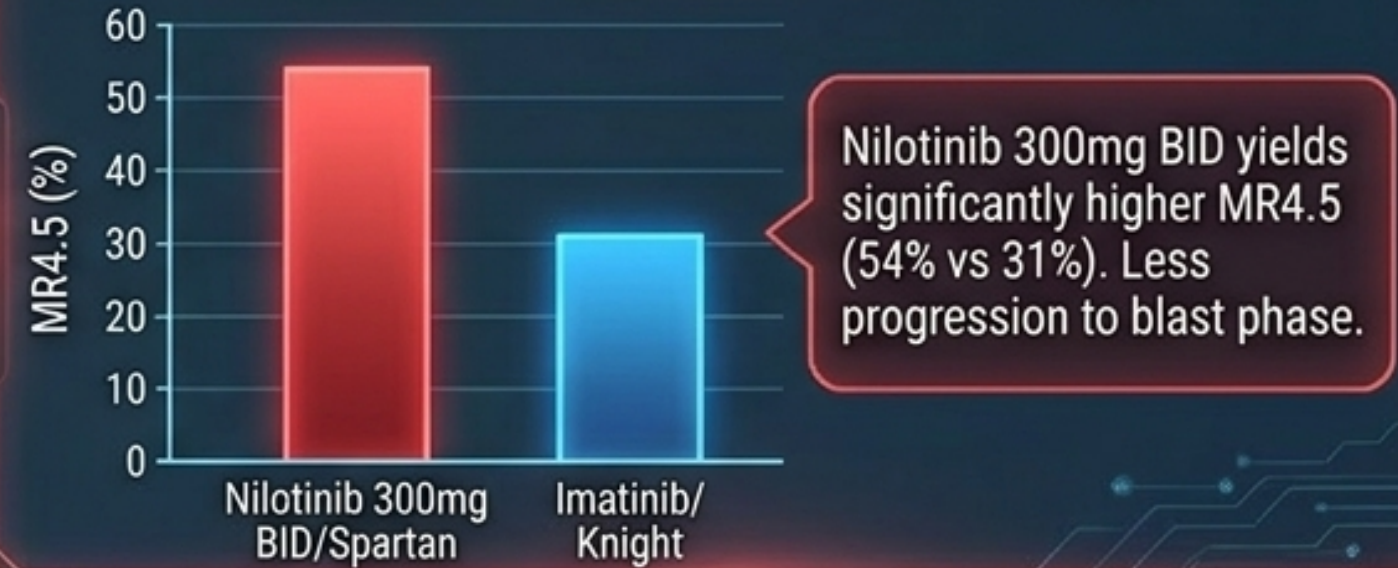
\*Apperley JF, et al. Leukemia (2025).

# Frontline Efficacy Showdown: Deep Molecular Responses (MR4 & MR4.5)

## DASISION (Dasatinib vs Imatinib, 5 yr)



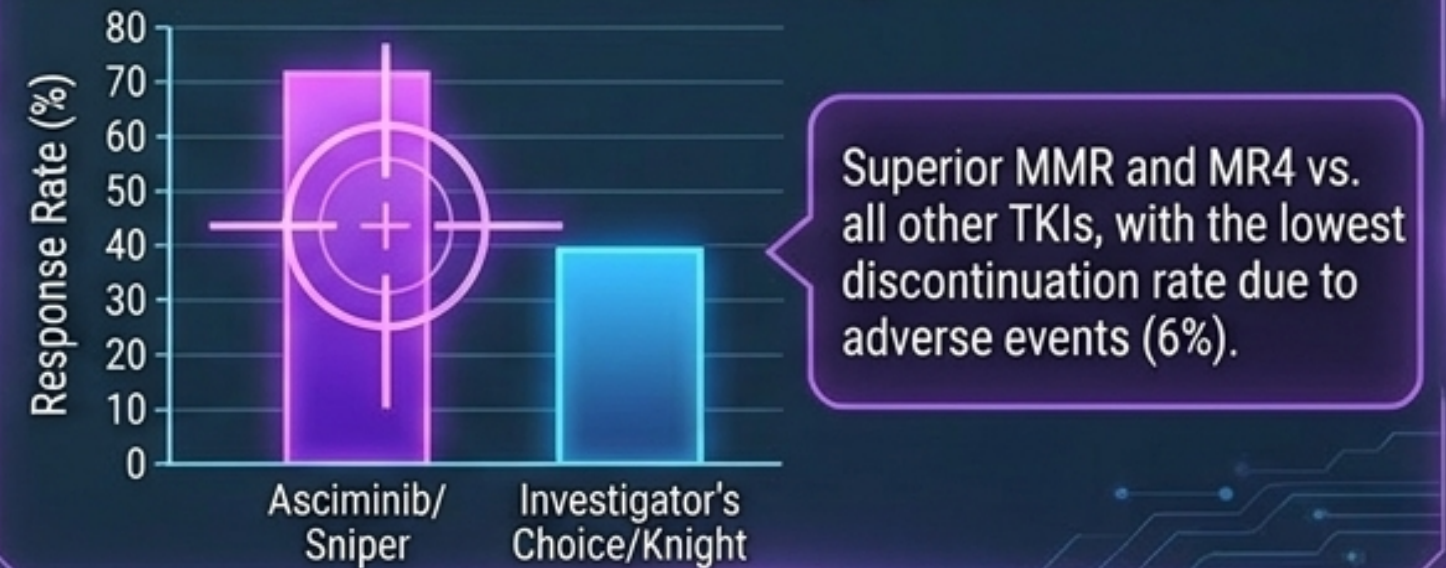
## ENESTnd (Nilotinib vs Imatinib, 10 yr)



## BELA (Bosutinib vs Imatinib)



## ASC4FIRST (Asciminib vs Investigator's Choice, Wk 96)



# Know Your Weapon's Recoil: Toxicity & Individualized Choice

5 TKIs:	 Imatinib	 Dasatinib	 Nilotinib	 Bosutinib	 Asciminib
<b>Organ Systems</b>					
<b>Cardiovascular / AOE</b>	✓	✓	⚠	✓	✓
<b>Pulmonary / Pleural Effusion</b>		⚠	✓	✓	✓
<b>Gastrointestinal / Liver</b>	✓	✓	✓	⚠ (Diarrhea)	✓
<b>Metabolic</b>	✓	✓	⚠ (Hyperglycemia/Cholesterol)	✓	✓
<b>Pancreatic</b>	✓	✓	✓	✓	Monitor Lipase

**Strategy: Match the weapon to the warrior's health. Do not give a heavy shield to an exhausted soldier.**

\*Stegmann JL, et al. Leukemia (2016); ELN 2025 Guidelines (Table 9).



## The Strategic Goal

- ✓ Rapid and deep Major Molecular Response (MMR)
- ✓ Prevention of disease progression
- ✓ Eligibility for Treatment-Free Remission (TFR)

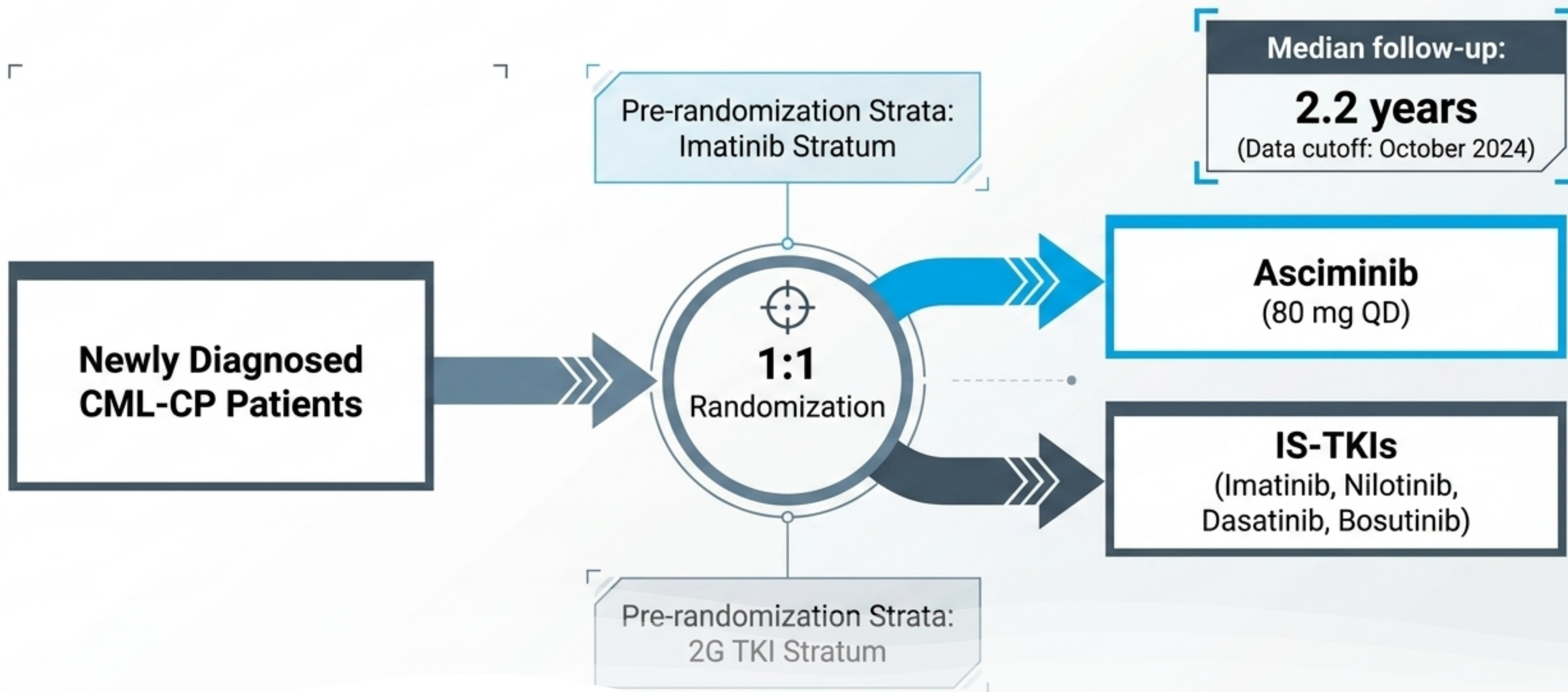
## The Ground Reality

>50% of newly diagnosed patients fail to achieve MMR at 12 months.

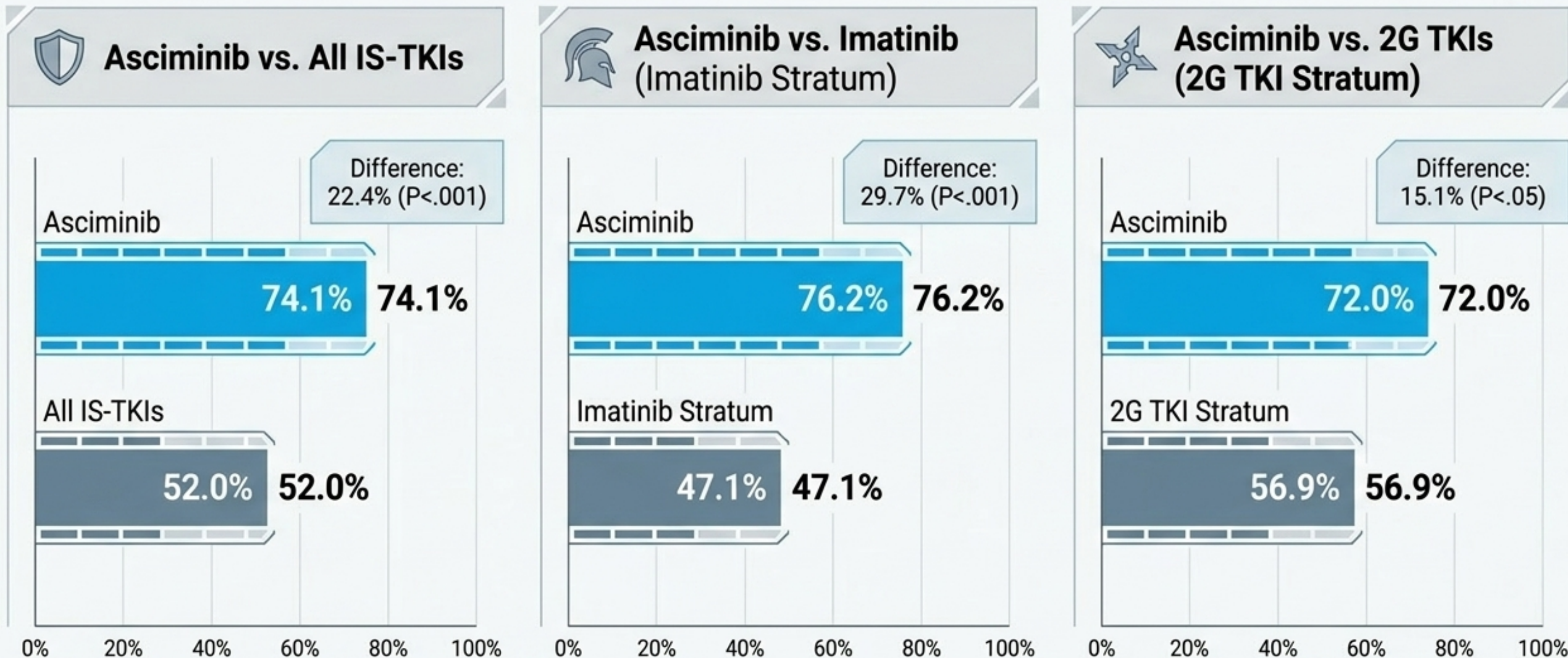
17.8% to 25.0% discontinue treatment in the first year.

Primary causes: Intolerance (Adverse Events) and Primary Resistance.

# The Arena: ASC4FIRST Trial Design



# The Scoreboard: Week 96 MMR Targets



Reference: Cortes JE, et al. ASC4FIRST Week 96 Analysis. Blood 2025.

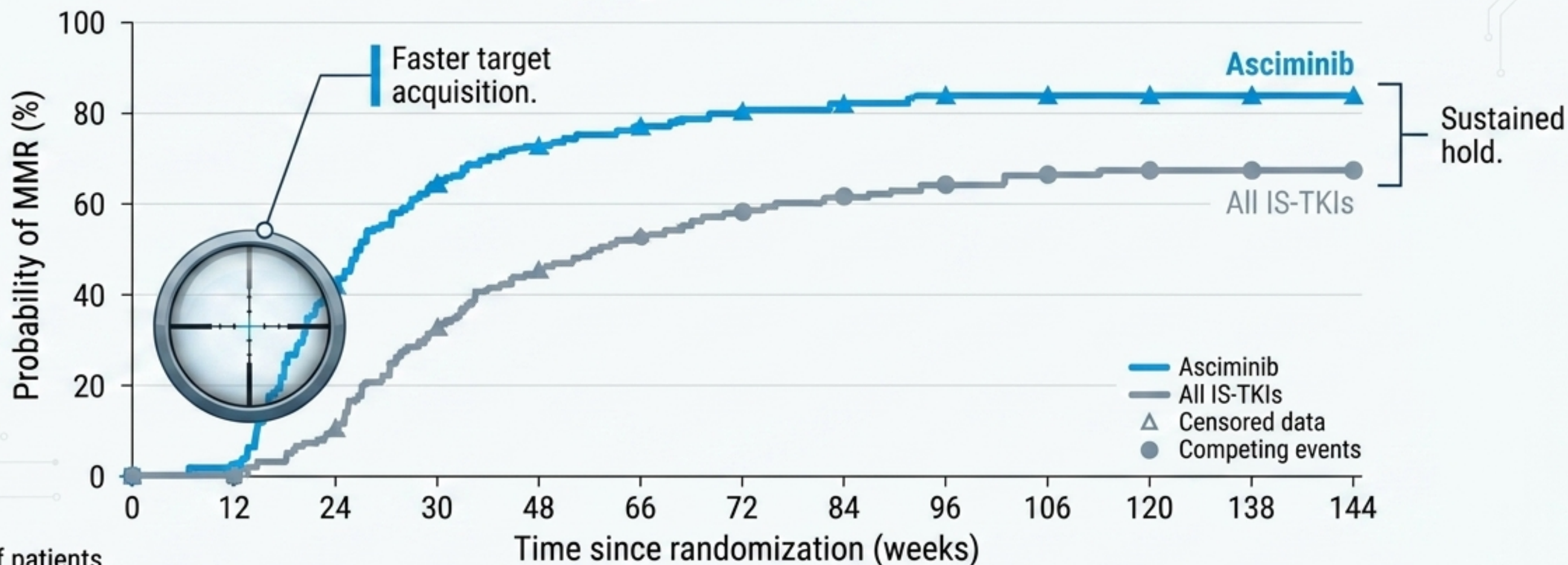
# Precision Striking: Deep Molecular Responses



**The Sniper doesn't just hit the target; it secures the absolute center, achieving deeper molecular responses significantly faster than the combined field.**

# The Tactical Advantage: Sniper vs. The Field

Probability of MMR over time



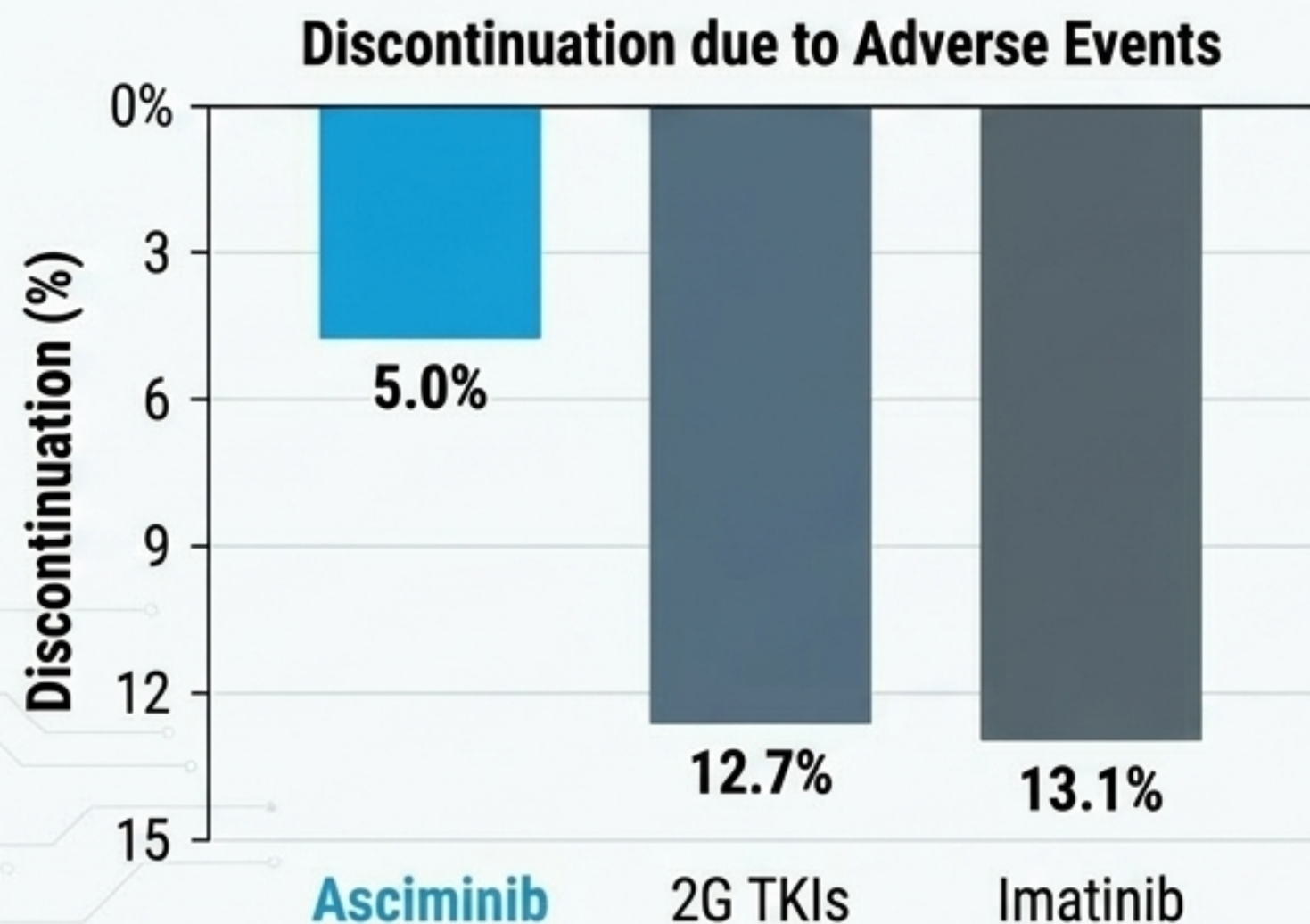
Number of patients still at risk

Asciminib	138	138	133	156	142	120	99	85	84	83	79	77	76
All IS-TKIs	40	13	23	34	36	53	47	49	51	68	13	13	13

Cumulative number of competing events

0	1	2	4	6	8	12	14	15	16	17	18	13
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# Minimizing Collateral Damage: Tolerability



**HR for TTDAE** 0.46  
(Asciminib vs. 2G TKIs)






**HR for TTDAE** 0.38  
(Asciminib vs. Imatinib)



The **Sniper methodology** leaves roughly half the collateral damage of traditional melee combat, keeping patients active in the field longer.

**ARTICLE**

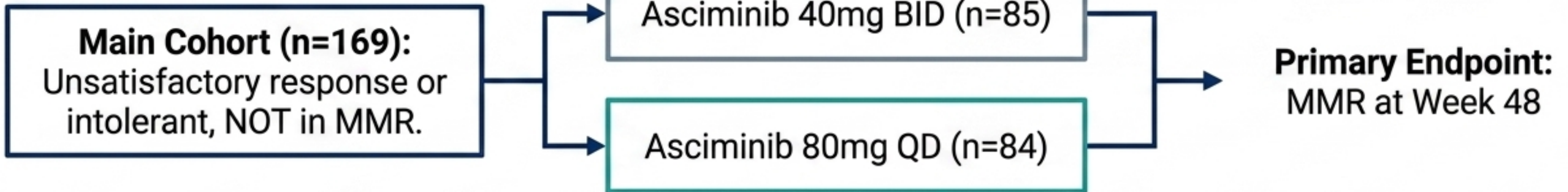
# ASC4OPT: asciminib treatment optimization study in patients with chronic myeloid leukemia in chronic phase previously treated with two or more tyrosine kinase inhibitors

Andreas Hochhaus <sup>1</sup>✉, Philipp le Coutre<sup>2</sup>, Dragana Milojkovic<sup>3</sup>, Dennis Dong Hwan Kim <sup>4</sup>, Soo Min Lim<sup>5</sup>, Carolina Pavlovsky<sup>6</sup>, Thanh Nguyen<sup>7</sup>, Franck Emmanuel Nicolini<sup>8</sup>, Beatriz Moiraghi<sup>9</sup>, Sebastian Grosicki <sup>10</sup>, Chi Dung Phu<sup>11</sup>, Gabriel Etienne<sup>12</sup>, Fernando Marco de Lucas<sup>13</sup>, Rosa Maria Ayala Diaz<sup>14</sup>, Massimo Breccia <sup>15</sup>, Charles Chuah<sup>16</sup>, Roberto Abi Rached<sup>17</sup>, Himanshu Pokhriyal <sup>18</sup>, Aswin IC<sup>18</sup>, Peter Schuld<sup>17</sup>, Virginia Pilipovic<sup>17</sup>, Franz Alisch<sup>17</sup> and Carla Maria Boquimpani<sup>19</sup>

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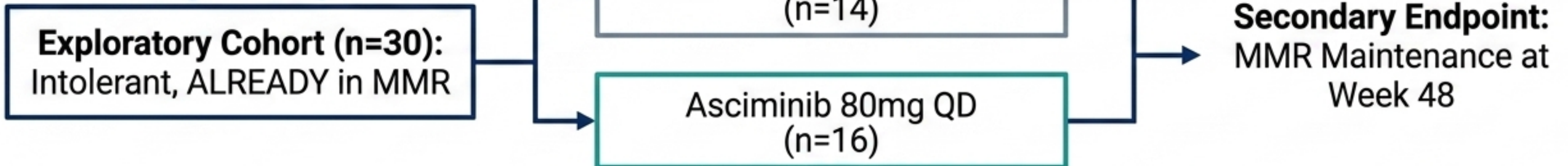
# The ASC4OPT Phase 3b Study Architecture

## Track 1: Main Cohort



**! Dose Escalation Rule:** Patients in the Main Cohort lacking MMR at Week 48 without severe toxicity could escalate to 200mg QD.

## Track 2: Exploratory Cohort



# High Rates of Major Molecular Response Achieved and Sustained

Week 48 Overall MMR

**39.4%**

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**40 mg BID: 43.4%**  
**80 mg QD: 35.4%**

Week 96 Overall MMR

**43.6%**

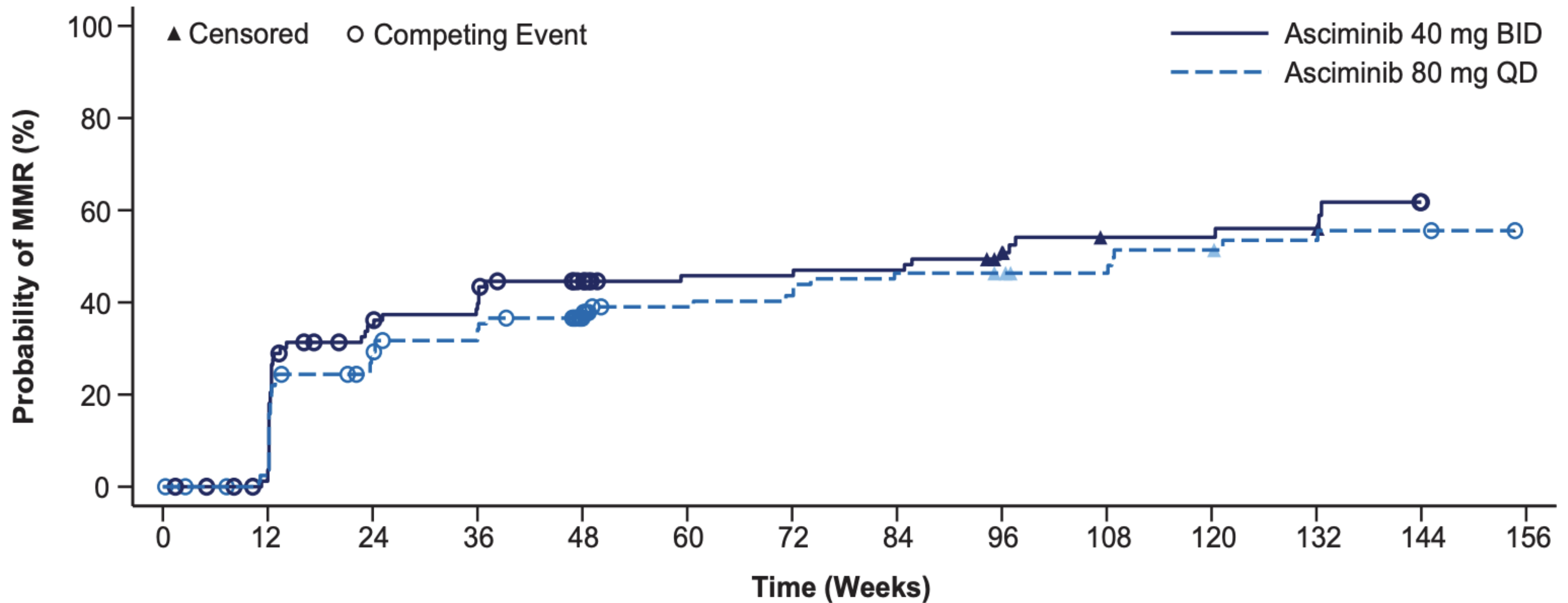
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**40 mg BID: 45.8%**  
**80 mg QD: 41.5%**

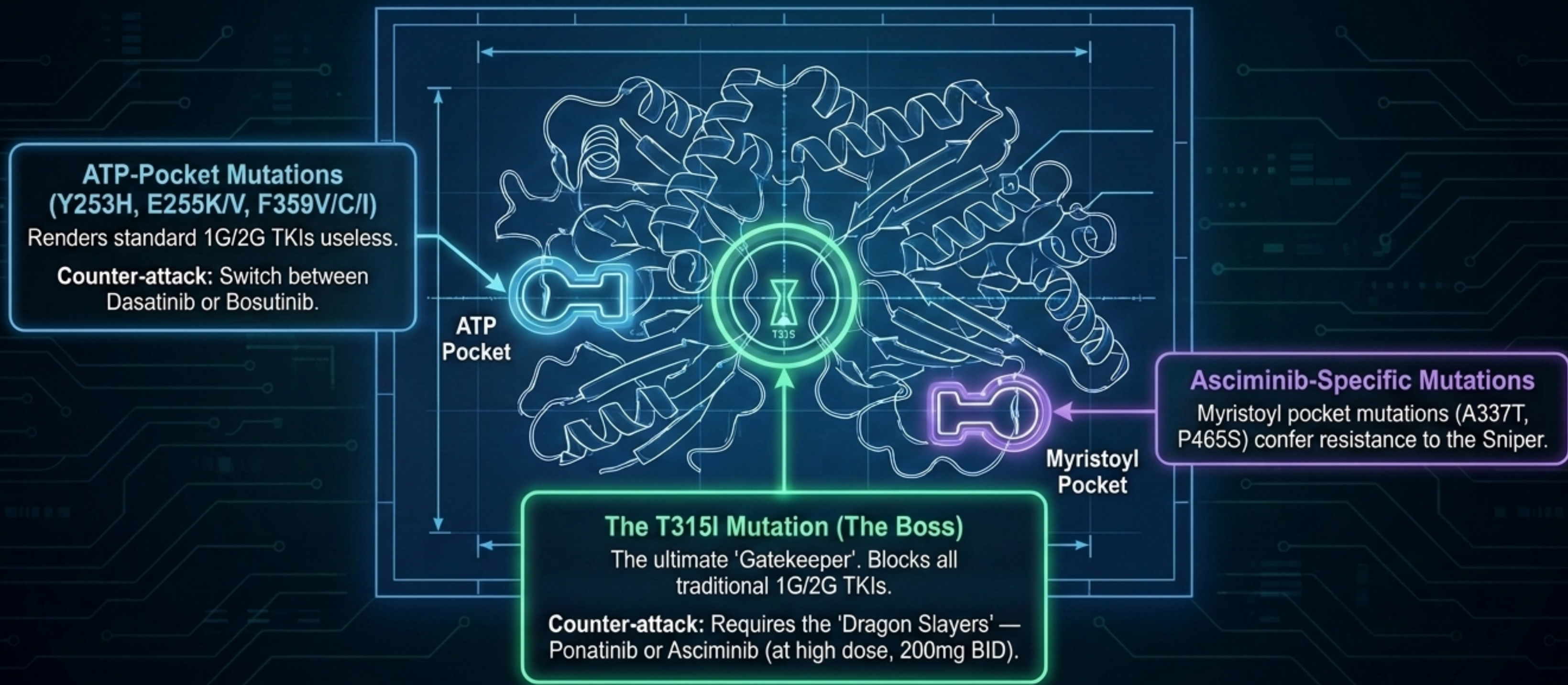
Estimated median time to first MMR was rapid: 22.7 weeks. Nearly two-thirds (~64%) of patients achieved BCR::ABL1  $\leq$  1% by Week 48, a threshold associated with reduced progression risk.

# Longitudinal Efficacy: Sustained and Cumulative Response to Week 96

Cumulative response curve for 'Time to first MMR'



# Mutational Resistance: The T315I Gatekeeper and Beyond



\*Soverini S, et al. *Blood* (2020); Hughes TP, et al. *Haematologica* (2025).

# Salvage Operations: Ponatinib vs. Asciminib in Clinical Practice



## Ponatinib (The Heavy Artillery)

### Points

- **Strengths:** Broadest mutational coverage. Defeats T315I. Deep responses in heavily pre-treated patients (PACE trial).
- **Weaknesses:** Severe cardiovascular risk.
- **Strategy (OPTIC Trial):** Start heavy at 45mg to secure response, rapidly reduce to 15mg upon achieving  $\leq 1\%$  to save the heart.

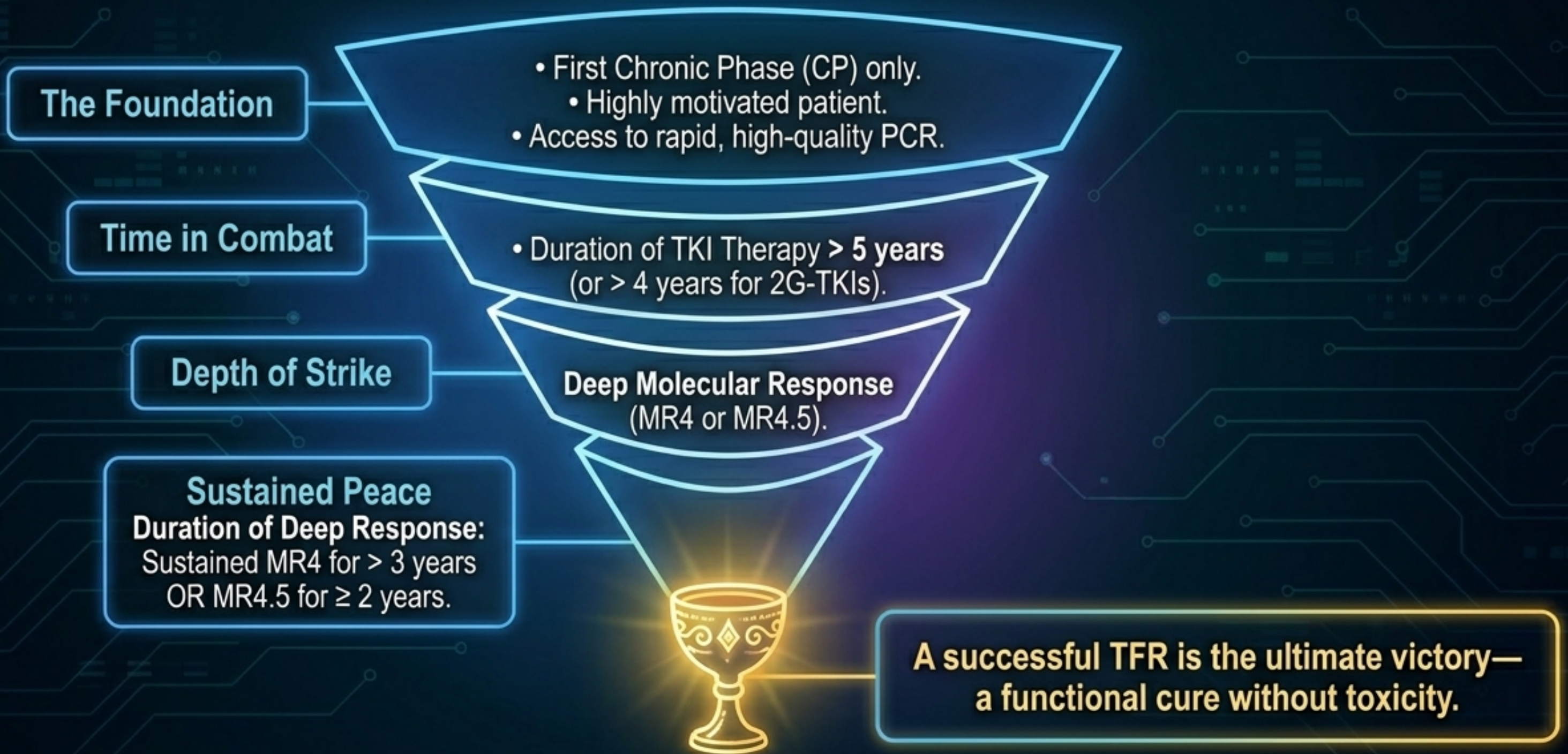


## Asciminib (The Precision Strike)

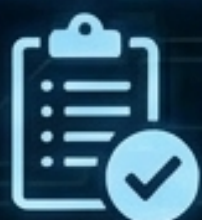
### Points

- **Strengths:** Highly specific, incredibly well-tolerated in 3<sup>rd</sup> line (ASCEMBL trial). Beats Bosutinib in efficacy/safety.
- **Weaknesses:** Cost/Access hurdles in ANS/SUS. Requires different mutation panel.
- **Strategy:** Ideal for pan-intolerant patients or those with high CV risk.

# Laying Down Arms: Eligibility for TFR



# The Discontinuation Protocol: Success Rates and 'Phantom Pain'



## The Protocol

- PCR monthly for 6 months, every 2 months for months 6-12, then every 3 months.
- **Trigger to restart:** Loss of MMR ( $>0.1\%$ ).



## TKI Withdrawal Syndrome (The Phantom Pain)

- Occurs in 30-40% of patients.
- Musculoskeletal pain/joint stiffness starting 1-3 months post-stop.
- Usually resolves and is managed with analgesics/NSAIDs.



# Summary: Mastering CML Therapy in 2026



**Individualize frontline weapons.** Imatinib is the reliable standard, but 2G/STAMP TKIs offer faster DMR for TFR-motivated patients. Match toxicity to comorbidities.



**Monitor relentlessly using ELN 2025 IS% milestones.** Suspect **failure early**, but verify compliance.



**Test for mutations on failure.** Don't fly blind. Use mutational profiles to select salvage therapies.



**Respect the T315I Gatekeeper.** Deploy **Ponatinib** (with dose optimization) or **Asciminib**.



**TFR is the ultimate goal.** Ensure prolonged, deep molecular response ( $MR_{4.5} \geq 2$  yrs) before attempting to lay down arms.

**Victory in CML is no longer just about survival; it is about restoring a normal, treatment-free life.**



Obrigada

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