


# CML: (Other) New Drugs & New Clinical Trials

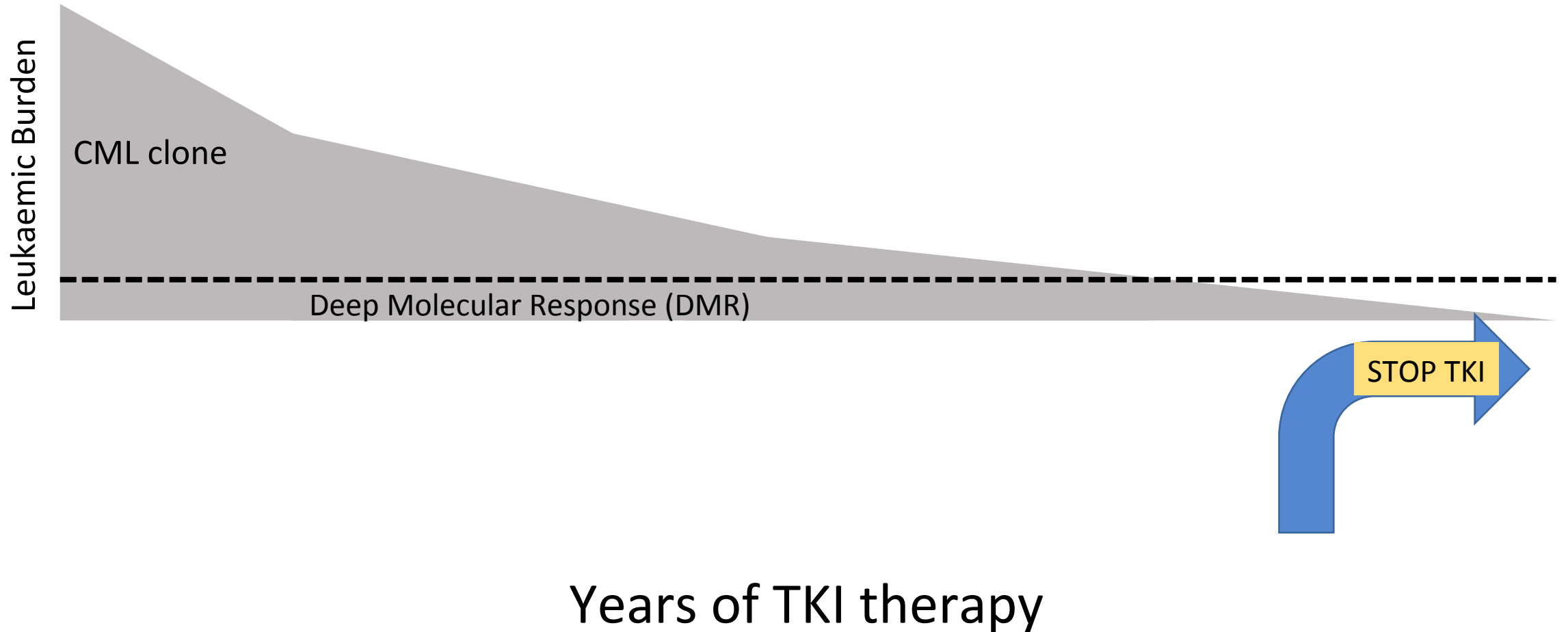


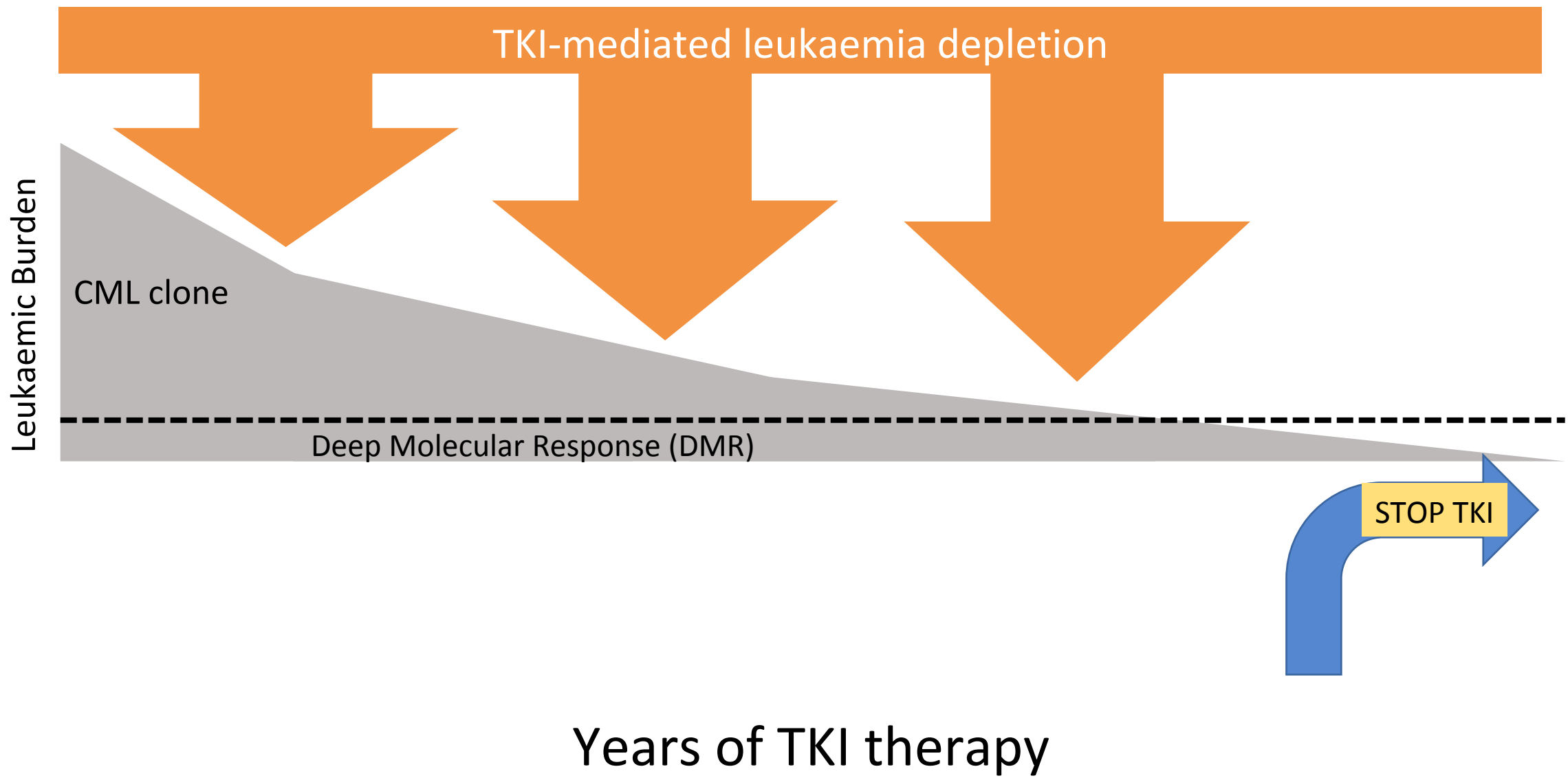
Timothy Hughes, SAHMRI, Adelaide, Australia

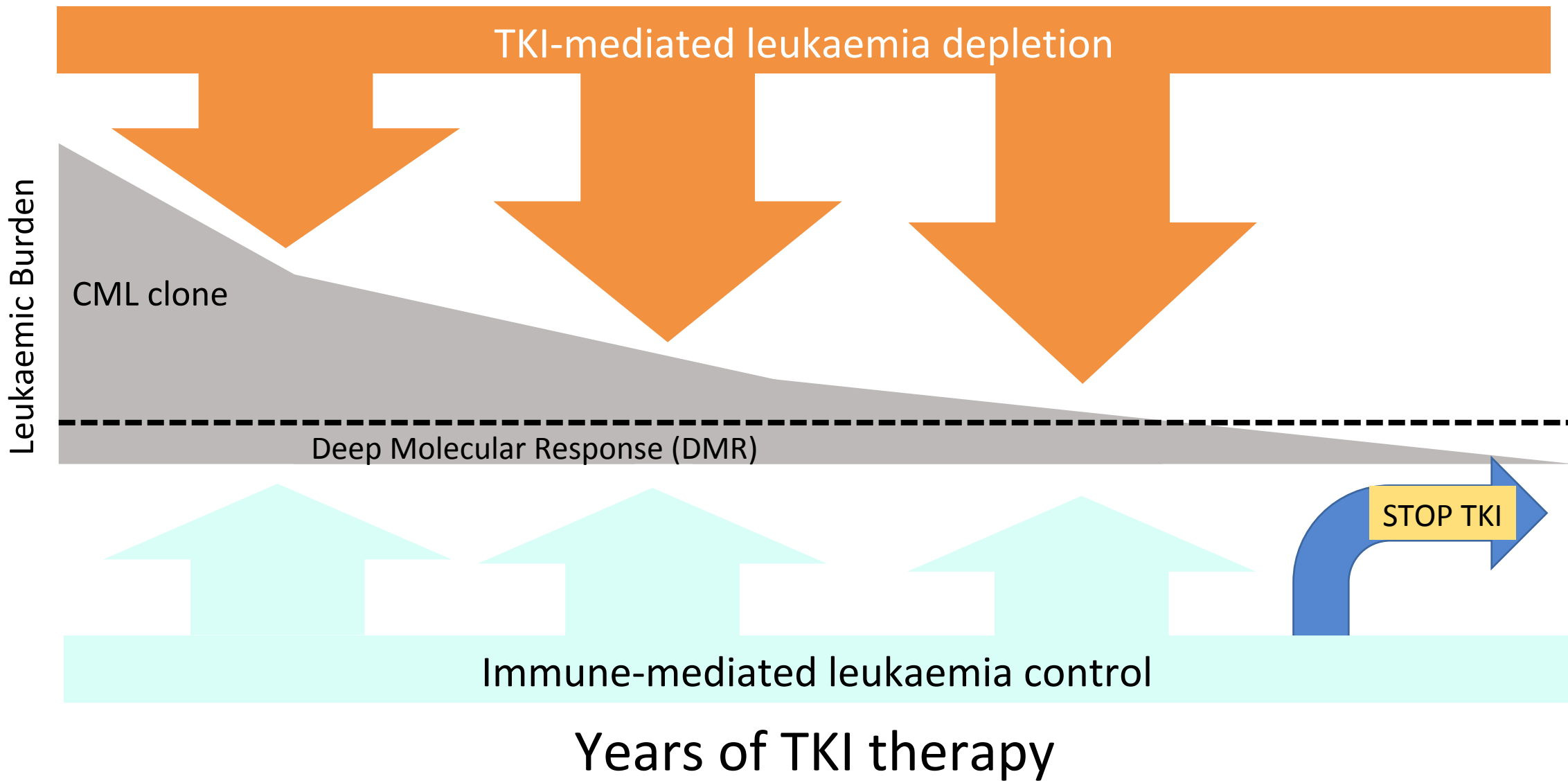


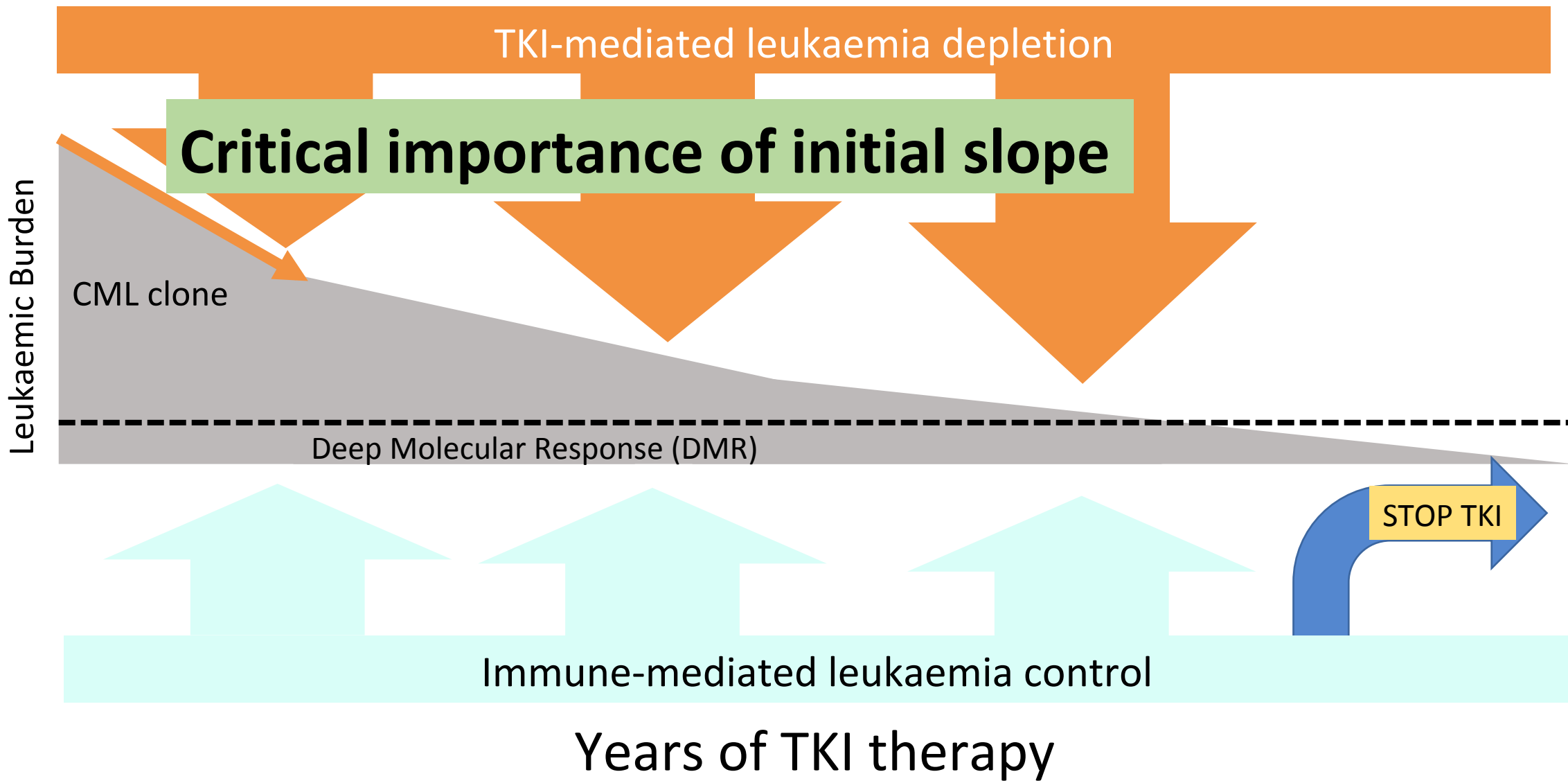
**With 5 approved TKIs and a new STAMP inhibitor- is there a need for more clinical trials for CML?**

# The CML Journey from Diagnosis to Treatment-Free Remission (TFR)









# Are More Drugs Needed in CML?

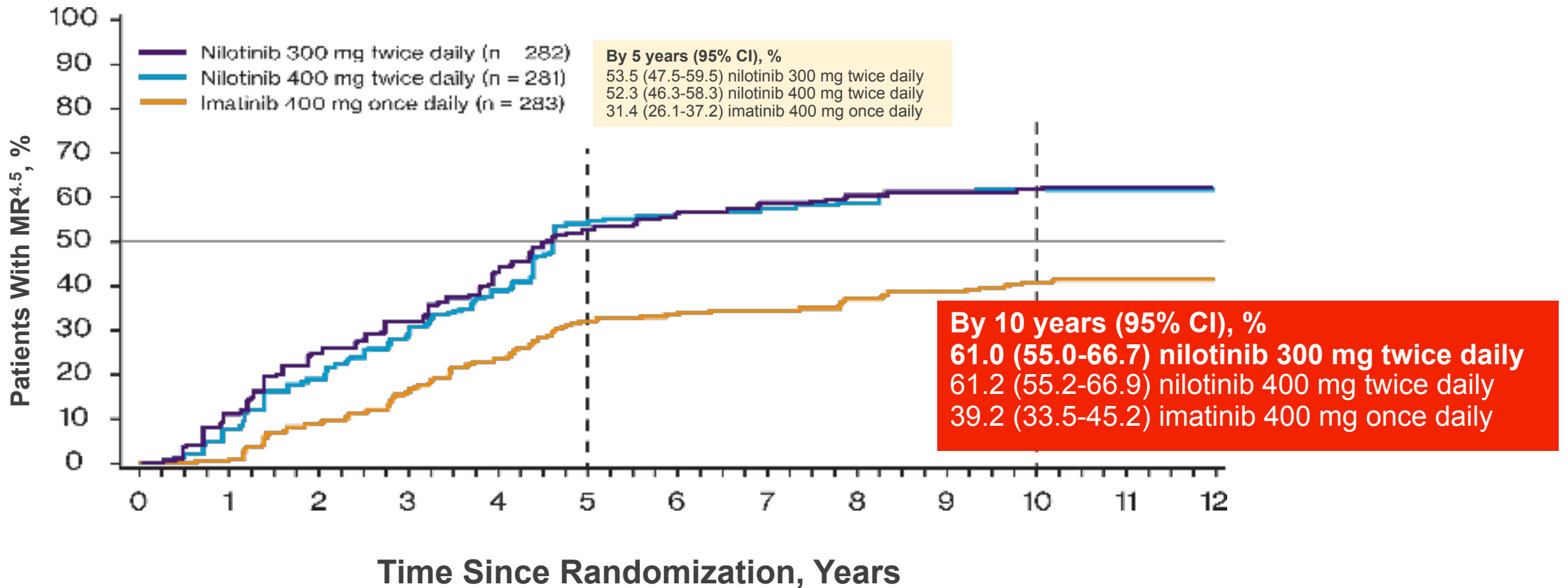
<b>What we have</b>	<b>What could be improved</b>	<b>What is missing</b>
<ul style="list-style-type: none"><li>• <b>Several good choices for frontline therapy</b></li><li>• <b>Effective 2<sup>nd</sup> line therapy post imatinib</b></li><li>• <b>One T315I inhibitor with significant toxicity</b></li></ul>	<ul style="list-style-type: none"><li>• <b>Toxicity profile (chronic low-grade &amp; poor QOL)</b></li><li>• <b>Safety profile of more potent TKIs</b></li><li>• <b>Achievement of Sustained DMR</b></li></ul>	<ul style="list-style-type: none"><li>• <b>Effective options for</b><ul style="list-style-type: none"><li>• <i>2<sup>nd</sup> line post 2G TKI</i></li><li>• <i>≥3<sup>rd</sup> line</i></li><li>• <i>Advanced phase disease</i></li><li>• <i>Compound mutations</i></li></ul></li><li>• <b>Treatment free remission (TFR) for most patients</b></li></ul>

# Update on most interesting ongoing or planned trials for CML

- ENESTnd - long term safety with nilotinib
- OPTIM trial – lower dose dasatinib safer and maintains good molecular responses
- ASCEND – frontline asciminib monotherapy may be the future



# ENESTnd: MR<sup>4.5</sup> GAP PERSISTS AT 10 YEARS



# ENESTnd: CVEs According to Exposure Time Intervals

Patients, n (%)	Nilotinib 300 mg twice daily (n = 279)	Nilotinib 400 mg twice daily (n = 277)	Imatinib 400 mg once daily (n = 280)
<b>CVEs (all)</b>			
<b>0 to &lt; 5 years</b>	<b>20 (7.2)</b>	<b>32 (11.6)</b>	<b>5 (1.8)</b>

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<b>CVEs (all)</b>			
0 to < 5 years	20 (7.2)	32 (11.6)	5 (1.8)
> 5 years	26 (9.3)	33 (11.9)	5 (1.8)

# Framingham Risk Category

High  $\geq 20$  points

Intermediate  $\geq 10$  -  $< 20$  points

Low  $< 10$  points

Risk Factor	Risk Points				Points
	Men		Women		
<b>Age</b>					
30-34	0		0		
35-39	2		2		
40-44	5		4		
45-49	7		5		
50-54	8		7		
55-59	10		8		
60-64	11		9		
65-69	12		10		
70-74	14		11		
75+	15		12		
<b>HDL-C (mmol/L)</b>					
>1.6	-2		-2		
1.3-1.6	-1		-1		
1.2-1.29	0		0		
0.9-1.19	1		1		
<0.9	2		2		
<b>Total Cholesterol</b>					
<4.1	0		0		
4.1-5.19	1		1		
5.2-6.19	2		3		
6.2-7.2	3		4		
>7.2	4		5		
<b>Systolic Blood Pressure (mmHg)</b>	Not Treated	Treated	Not Treated	Treated	
<120	-2	0	-3	-1	
120-129	0	2	0	2	
130-139	1	3	1	3	
140-149	2	4	2	5	
150-159	2	4	4	6	
160+	3	5	5	7	
<b>Smoker</b>	Yes	4		3	
	No	0		0	
<b>Diabetes</b>	Yes	statin-indicated condition			
	No	0		0	
<b>Total Points</b>					

# Framingham Risk Category

High  $\geq 20$  points

Intermediate  $\geq 10$  -  $< 20$  points

Low  $< 10$  points

**At diagnosis**

54 year old male

Mildly elevated BP

Framingham Score: 9

Risk Factor	Risk Points		Points	
	Men	Women		
<b>Age</b>				
30-34	0	0		
35-39	2	2		
40-44	5	4		
45-49	7	5		
50-54	8	7		
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160+	3	5	5	7
<b>Smoker</b>	Yes	4	3	
	No	0	0	
<b>Diabetes</b>	Yes	statin-indicated condition		
	No	0	0	
<b>Total Points</b>				

# FRAMINGHAM RISK SCORE and rates of CVE after 5 years

	Nilotinib 300 mg BID	Imatinib 400 mg BID
<b>Low Framingham Risk (&lt;10%)</b>	<b>n = 178</b>	<b>n = 182</b>
Any CVE, n (%)	3 (1.7)	2 (1.1)
<b>Intermediate Framingham Risk (≥10% to &lt;20%)</b>	<b>n = 41</b>	<b>n = 49</b>
Any CVE, n (%)	5 (12.2)	2 (4.1)
<b>High Framingham Risk (≥20%)</b>	<b>n = 40</b>	<b>n = 33</b>
Any CVE, n (%)	7 (17.5)	1 (3.0)
<b>Cardiovascular Events</b>	<b>n = 279</b>	<b>n = 280</b>
Any Grade, n (%)	21 (7.5)	6 (2.1)

# FRAMINGHAM RISK SCORE and rates of CVE after 10 years

	Nilotinib 300 mg BID	Imatinib 400 mg BID
<b>Low Framingham Risk (&lt;10%)</b>	<b>n = 178</b>	<b>n = 182</b>
Any CVE, n (%)	13 (7.3)	2 (1.1)
<b>Intermediate Framingham Risk (≥10% to &lt;20%)</b>	<b>n = 41</b>	<b>n = 49</b>
Any CVE, n (%)	11 (26.8)	5 (10.2)
<b>High Framingham Risk (≥20%)</b>	<b>n = 40</b>	<b>n = 33</b>
Any CVE, n (%)	13 (32.5)	2 (6.1)
<b>Cardiovascular Events</b>	<b>n = 279</b>	<b>n = 280</b>
Any Grade, n (%)	26 (9.3)	5 (1.8)

## OPTIM DASATINIB

A prospective randomized phase II study evaluating the optimization of the residual plasmatic level of dasatinib (Sprycel®) in patients newly diagnosed with chronic phase Chronic Myelogenous Leukaemia (CP-CML).



Philippe Rousselot, Luigina Molica  
On behalf of the French CML (FiLMC) group  
And the Canadian CML group





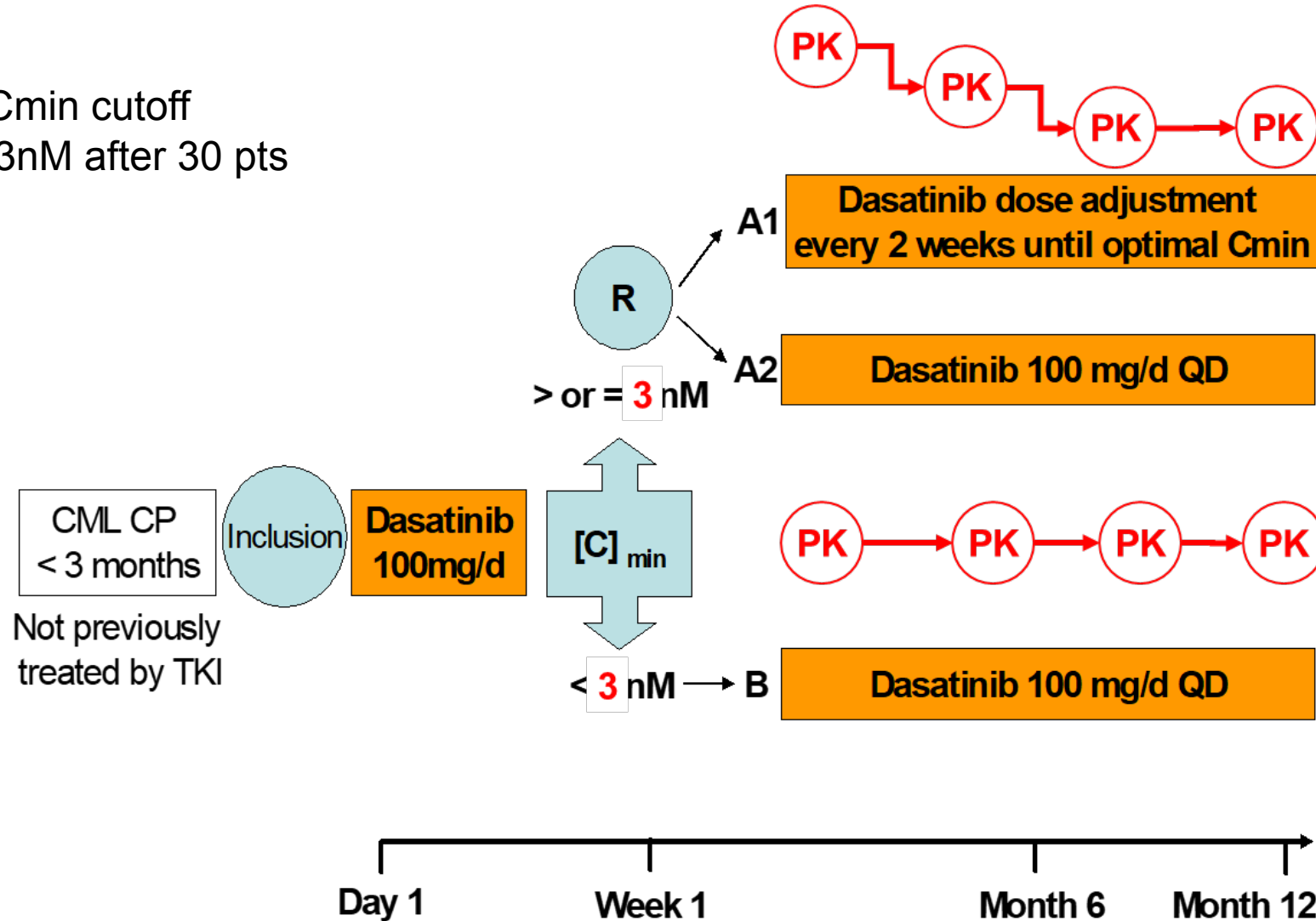


# OPTIM dasatinib trial design

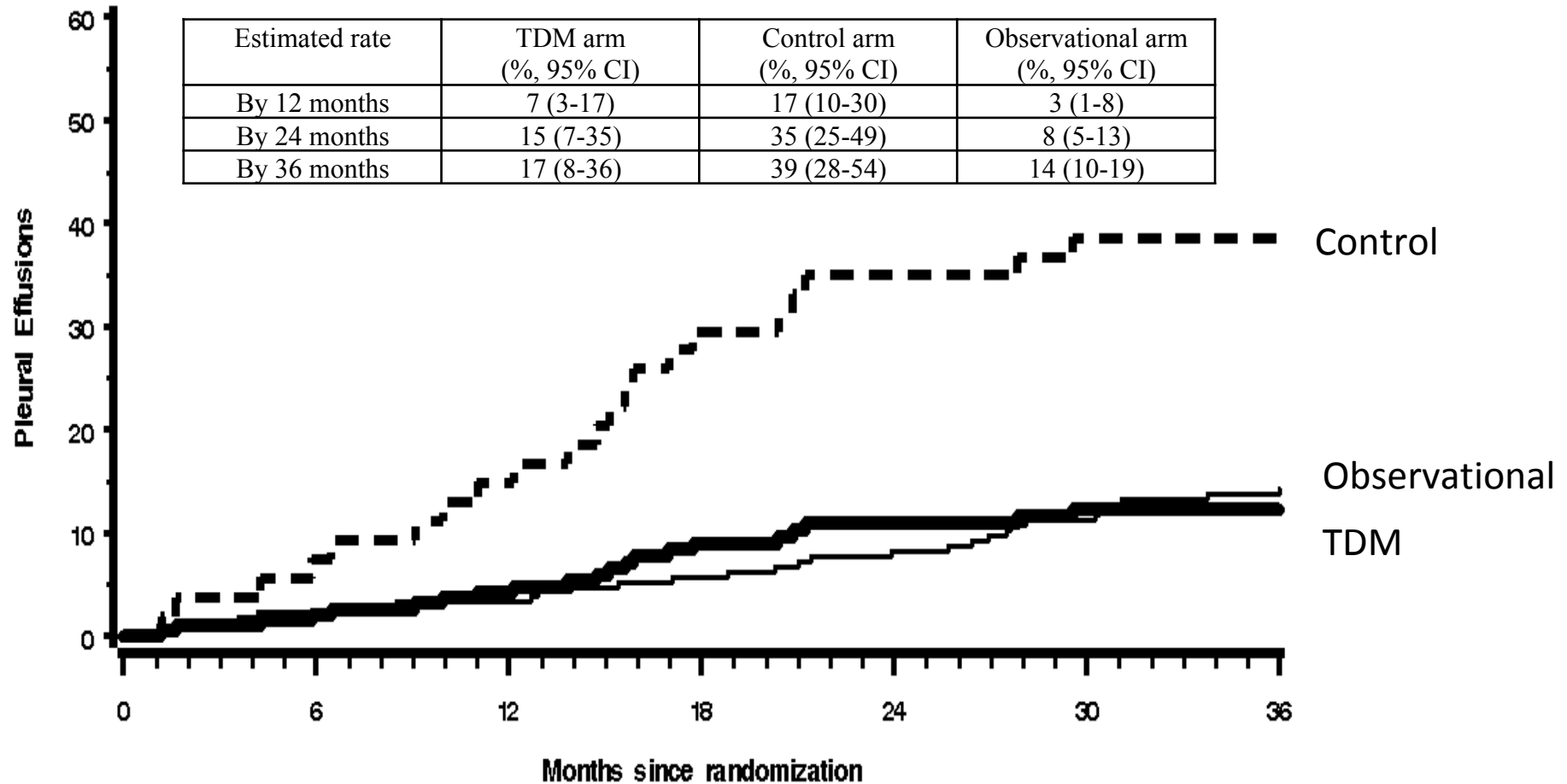


Amendment

Adjustment of the Cmin cutoff value from 5nM to 3nM after 30 pts

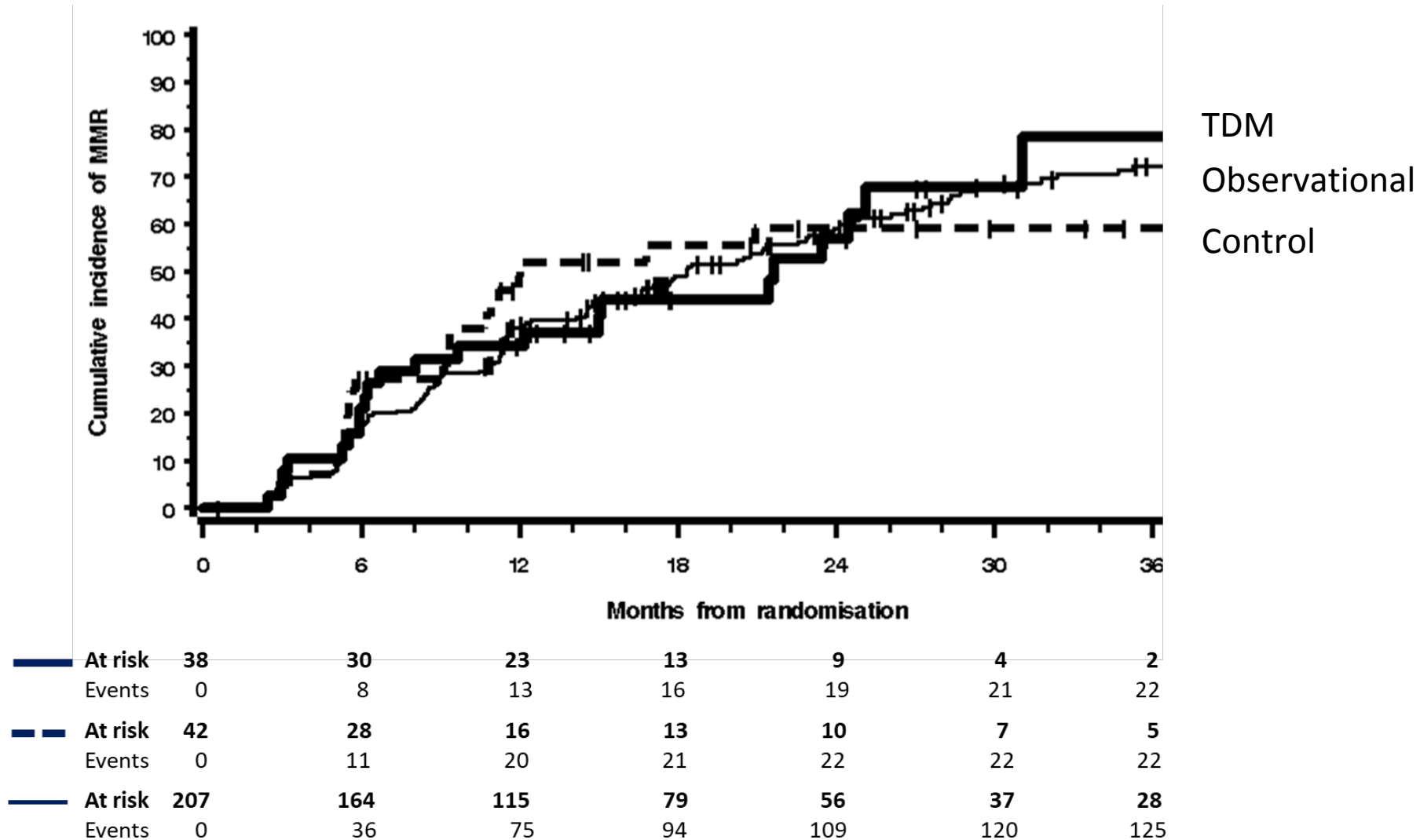


# Impact of TDM on pleural effusions



Cumulative incidence of PE in the TDM arm compared to the control arm.  
The observational arm is indicated for information

# Molecular response (MMR) by 36 months



# Combination trials and new approaches

- Asciminib combination trials logical but lower priority now
- Immunotherapy approaches in TFR

# Are we getting closer to a cure in CML?

CURE: a procedure that ENDS a medical condition

- Risk of disease progression and CML-related death
- Symptoms of disease
- Symptoms of treatment
- Need for ongoing therapy
- Need for ongoing medical care
- Need for ongoing monitoring
- Ideally the “procedure” shouldn’t be prolonged

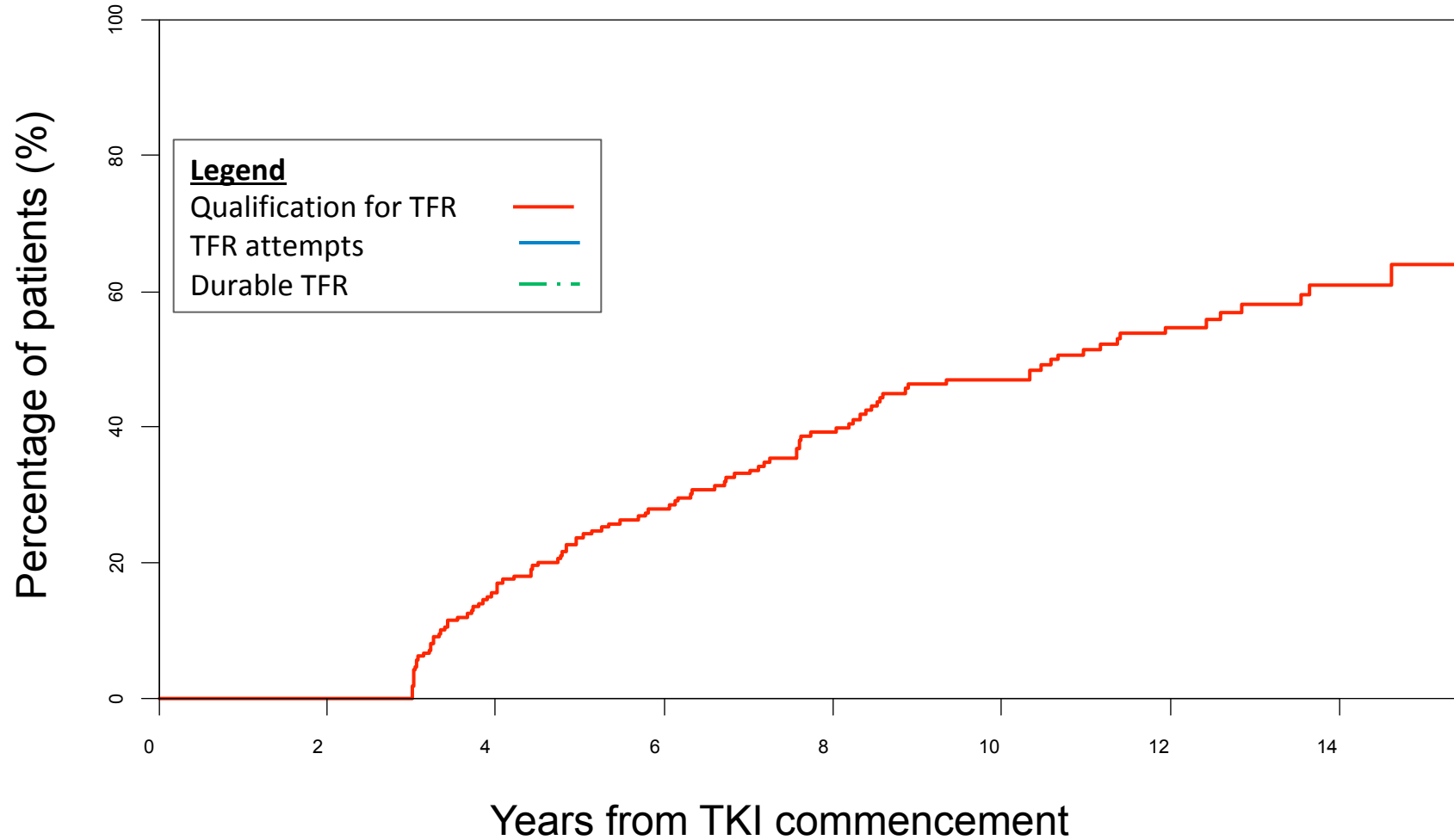
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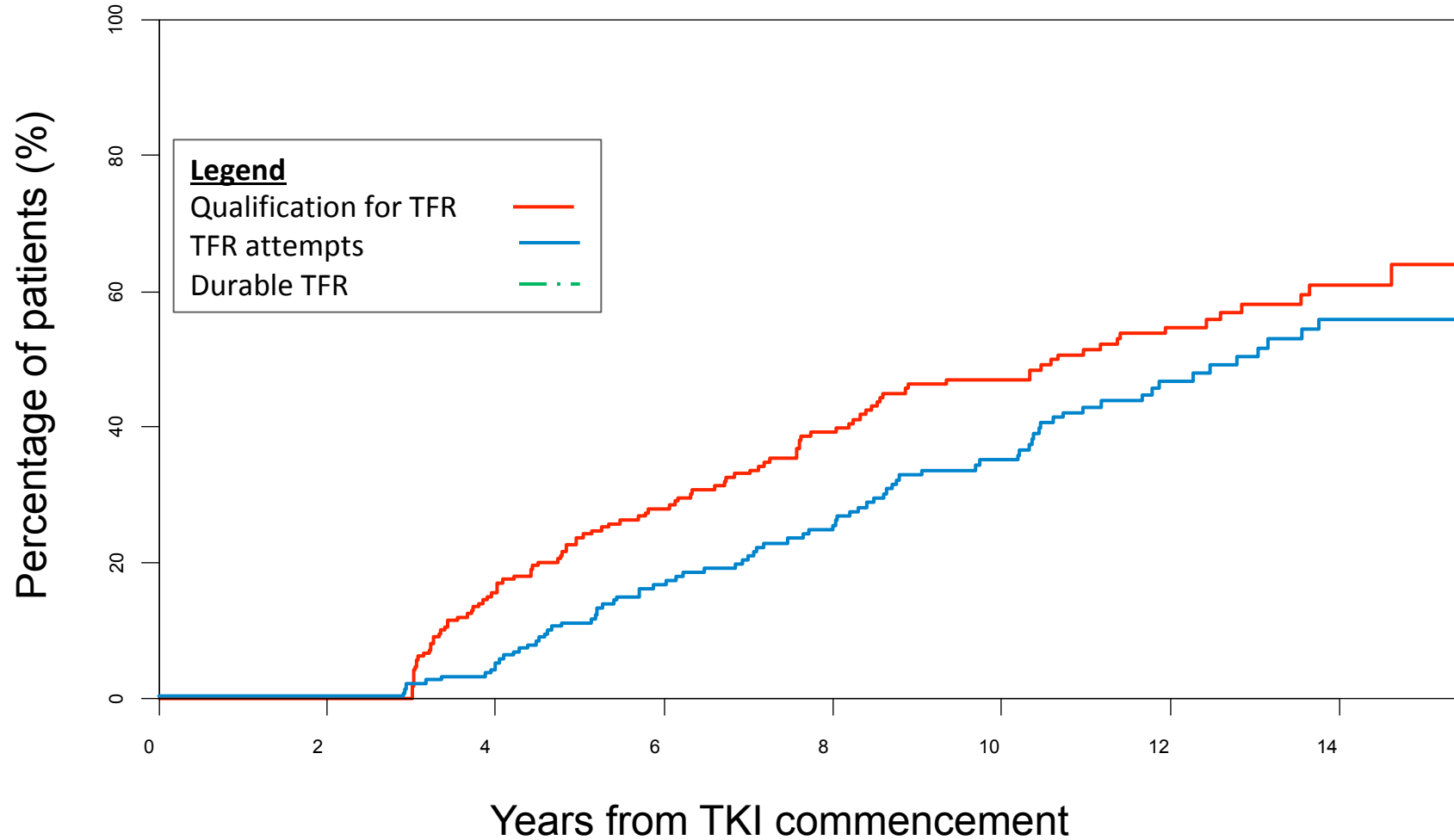
*Does TFR fulfill these requirements?*

- ✓ Risk of disease progression and CML-related death
- ✓ Symptoms of disease
- ✓ Symptoms of treatment
- ✓ Need for ongoing therapy
- ✓ Need for ongoing medical care
- Need for ongoing monitoring
- The “procedure” typically takes 5-10 years!

# Cumulative Incidence of Treatment Free Remission Eligibility, TFR Attempts, and Durable TFR: Adelaide Experience



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