

Optimal Therapy For First Line Treatment of CML:

CURE

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Characteristics of the CML populations in the studied Asian countries compared with US data

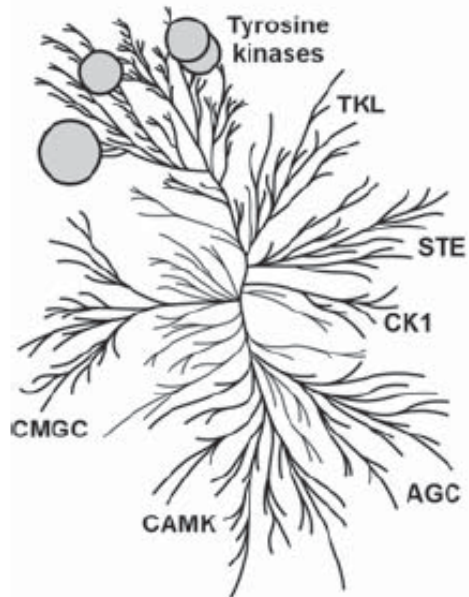
Country/Region	Source	Annual Incidence	Median Age	M:F ratio
China	Local surveys	0.39-0.55	45-50	1.5:1
Hong Kong, China	Cancer Registry (1983-2003)	0.9	49	1.5:1
India	Cancer registries	0.8-2.2 (M) 0.6-1.6 (F)	38-40	NR
Philippines	From IARC data*	0.7-0.9	45-55	1.3:1
Singapore	Singapore Cancer Registry (1998-2002)	0.7	43	1.3:1
South Korea	Government registries	0.8	37	1.6:1
Taiwan	Cancer Registry (1995-2002)	0.60 (M) 0.39 (F)	50 (M) 46 (F)	1.5:1
Thailand	Nine leading university hospitals	0.50	36-38	1.7:1
US	North American Association of Cancer Registries	1.48 1.94 (M)/1.13 (F)	65	1.7:1

Problems of “Nib” For Ever

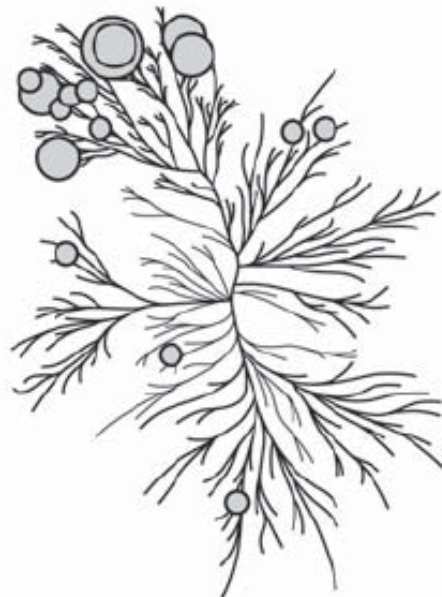
Increased financial burden among patients with CML receiving imatinib in Japan:

- 577 patients completed the questionnaire.
- A financial burden was felt by
 - 41.2 % (28 of 68) of the patients treated with imatinib in 2000
 - 70.8 % (201 of 284) of the patients treated with imatinib in 2005
 - 75.8 % (400 of 528) of the patients treated with imatinib in 2008
- 182 patients (31.7 %) considered its discontinuation because of the financial burden.
- Older patients (OR = 0.96, 95 % CI: 0.95–0.98, $p < 0.0001$), and patients with higher incomes (OR = 0.92, 95 % CI: 0.85–0.99, $p = 0.03$) were less likely to have considered discontinuing imatinib.
- Patients with higher annual co-payments (OR = 2.21, 95 % CI: 1.28–4.28, $p = 0.004$) were more likely to have considered discontinuing imatinib.
- **Conclusions:** Financial support for patients treated with expensive drugs remains a major problem in Japan.

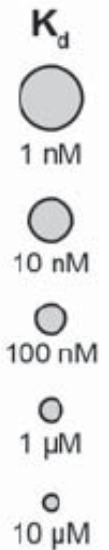
Nilotinib



Imatinib



Dasatinib



Potential Long-term Adverse Effects of TKIs

- Impact of imatinib on skeletal growth and bone health

J Pediatr. 2011;159(4):676-81, Blood. 2010;115(4):766-74.

- Thyroid dysfunction caused by second-generation tyrosine kinase inhibitors in Ph+CML

Thyroid 2010;20(11):1209-14.

- Imatinib and reproduction

- Pregnancy category D

- Oligospermia, gynecomastia in male

Fertil Steril. 2011;95(3):1120.e15-7, Lancet. 2003;361(9373):1954-6.

- Nilotinib-associated vascular events or peripheral arterial occlusive disease (PAOD).

Clin Lymphoma Myeloma Leuk 2012, Am J Hematol 2011;86(7), J Natl Cancer Inst 2011;103:1347-8.

- Precapillary pulmonary arterial hypertension in patients treated by dasatinib

Circulation 2012;125(17):2128-37.

- Platelet dysfunction (dasatinib and imatinib)

Blood 2009;114

Imatinib Adherence in CML

TABLE IV. Summary of Studies of Imatinib Adherence in Chronic Myeloid Leukemia

Study	Method of assessing adherence	Nonadherence rate (%)	Consequence of nonadherence
Noens et al. ³ (ADAGIO study)	Questionnaire and pill counting	32.7 ^b	Increased risk of suboptimal responses
Marin et al. ⁴	Microelectronic monitoring device	26 ^a	Reduced chance of achieving major and complete molecular responses
Darkow et al. ⁵	Electronic refill data	31	Increased health care costs
This study	Patient visits for drug refills	29	Reduced event free survival

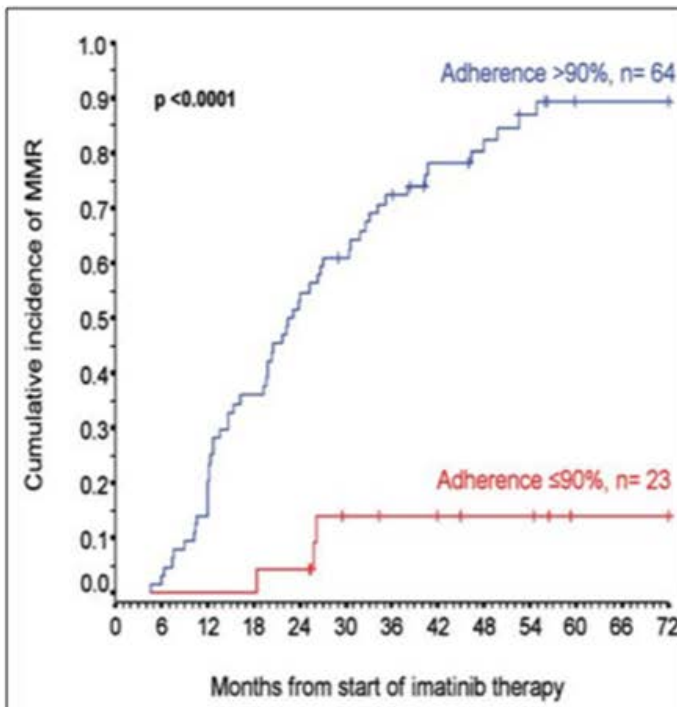
^a Less than 90% adherence rate was 26%.

^b Only 14% were perfectly adherent with 100% imatinib taken.

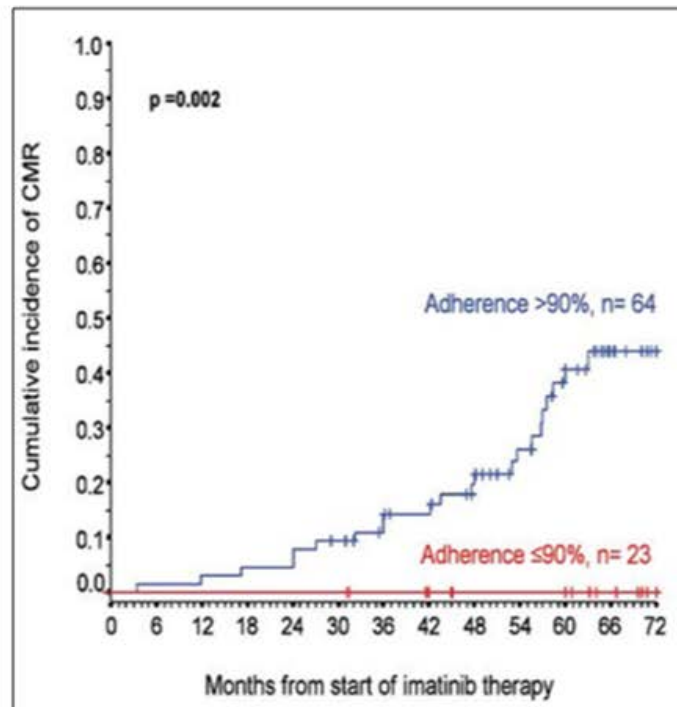
Blood 2009;113,5401–11, J Clin Oncol 2010;28:2381-8,

Pharmacoeconomics 2007;25: 481–96, Am J Hematol. 2011;86:471-4.

MMR



CMR⁴



Association of the *BIM* deletion polymorphism with clinical resistance to imatinib in Asian subjects with CML

	No <i>BIM</i> deletion polymorphism % (<i>n</i>)	<i>BIM</i> deletion polymorphism % (<i>n</i>)	
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Singaporean and Malaysian cohort (*n* = 138)

Sensitive	51 (64)	33 (5)	OR = 2.73 (95% CI 0.87–8.57)
Resistant	49 (59)	67 (10)	<i>P</i> = 0.09

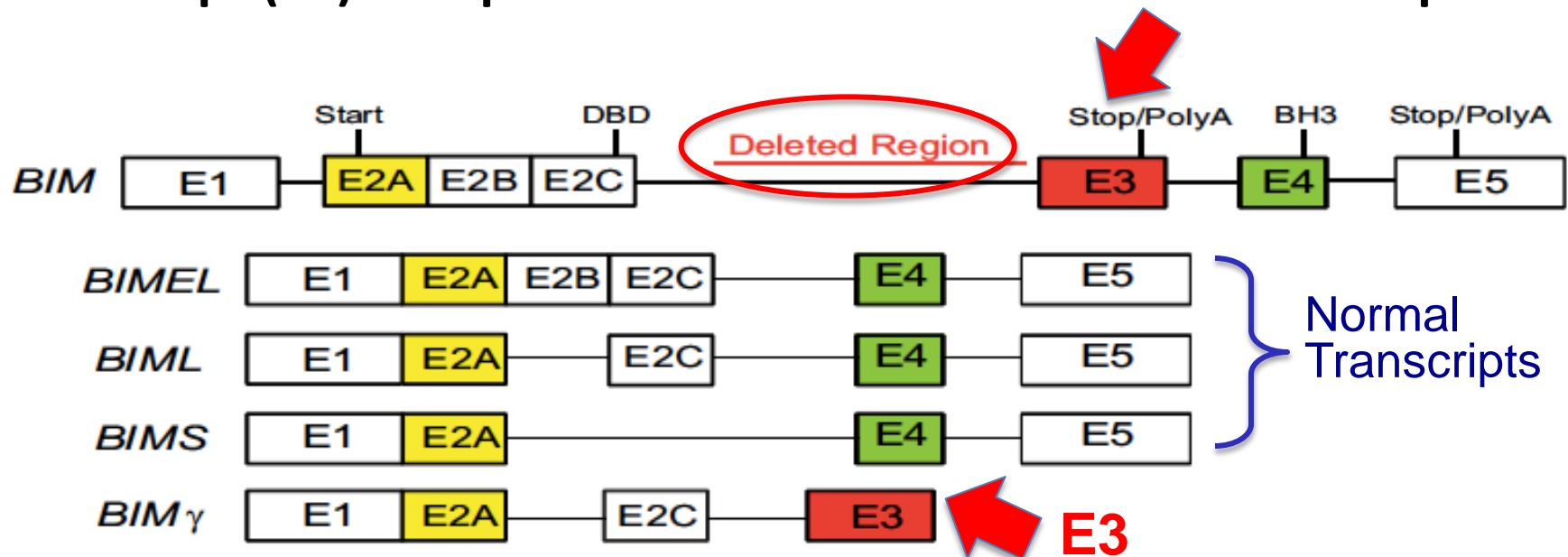
Japanese cohort (*n* = 65)

Sensitive	43 (23)	17 (2)	OR = 3.52 (95% CI 0.69–18.00)
Resistant	57 (30)	83 (10)	<i>P</i> = 0.13

Combined cohorts OR (*n* = 203)

OR = 2.94
(95% CI 1.17–7.43)
***P* = 0.02**

The 2.9kb *BIM* deletion polymorphism results an abnormal transcript (E3) that produces a truncated and inactive BIM protein

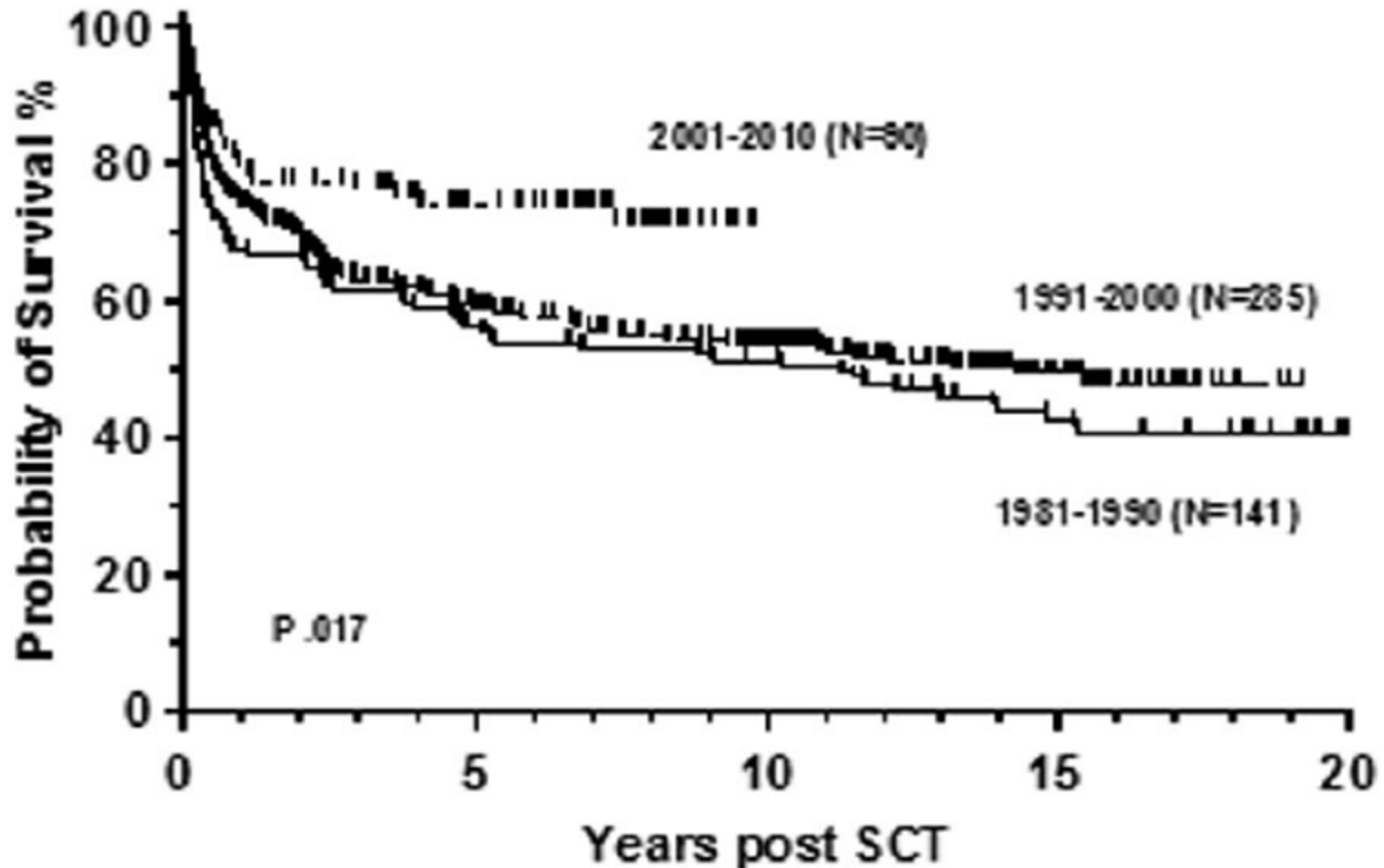


Curative Approach

- Transplant approach
- Non-transplant approach

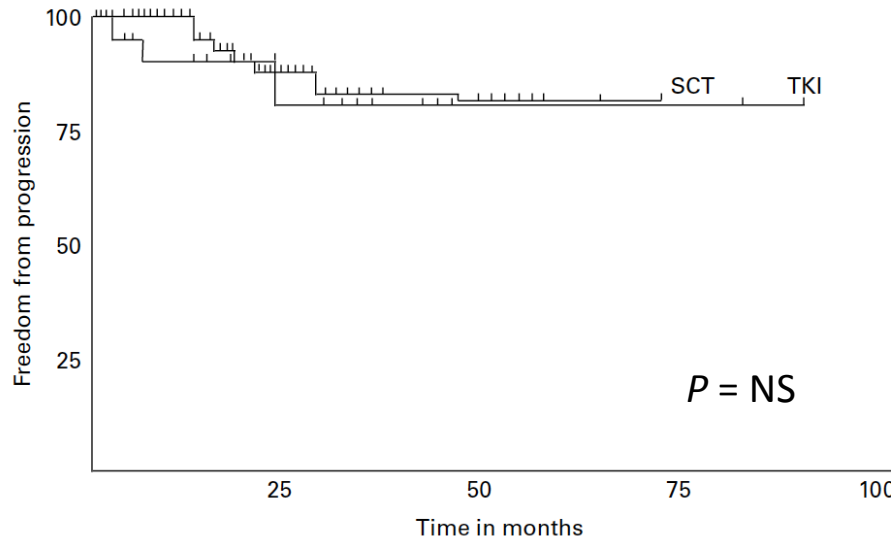
Allo-SCT results have improved over past decade in CML

Survival rates by decade of transplantation

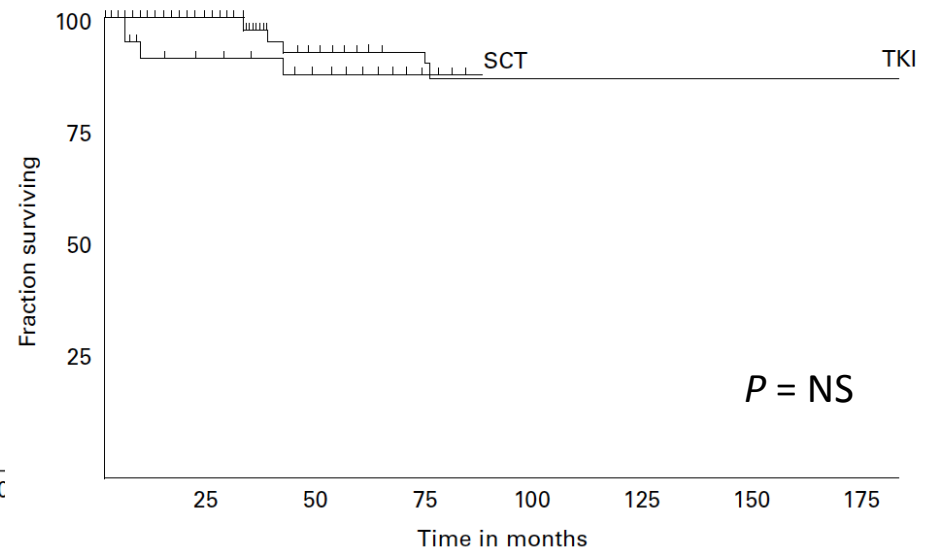


Therapeutic choices in patients with CML living in Mexico in the TKI era: SCT or TKIs?

Freedom from progression



Overall survival

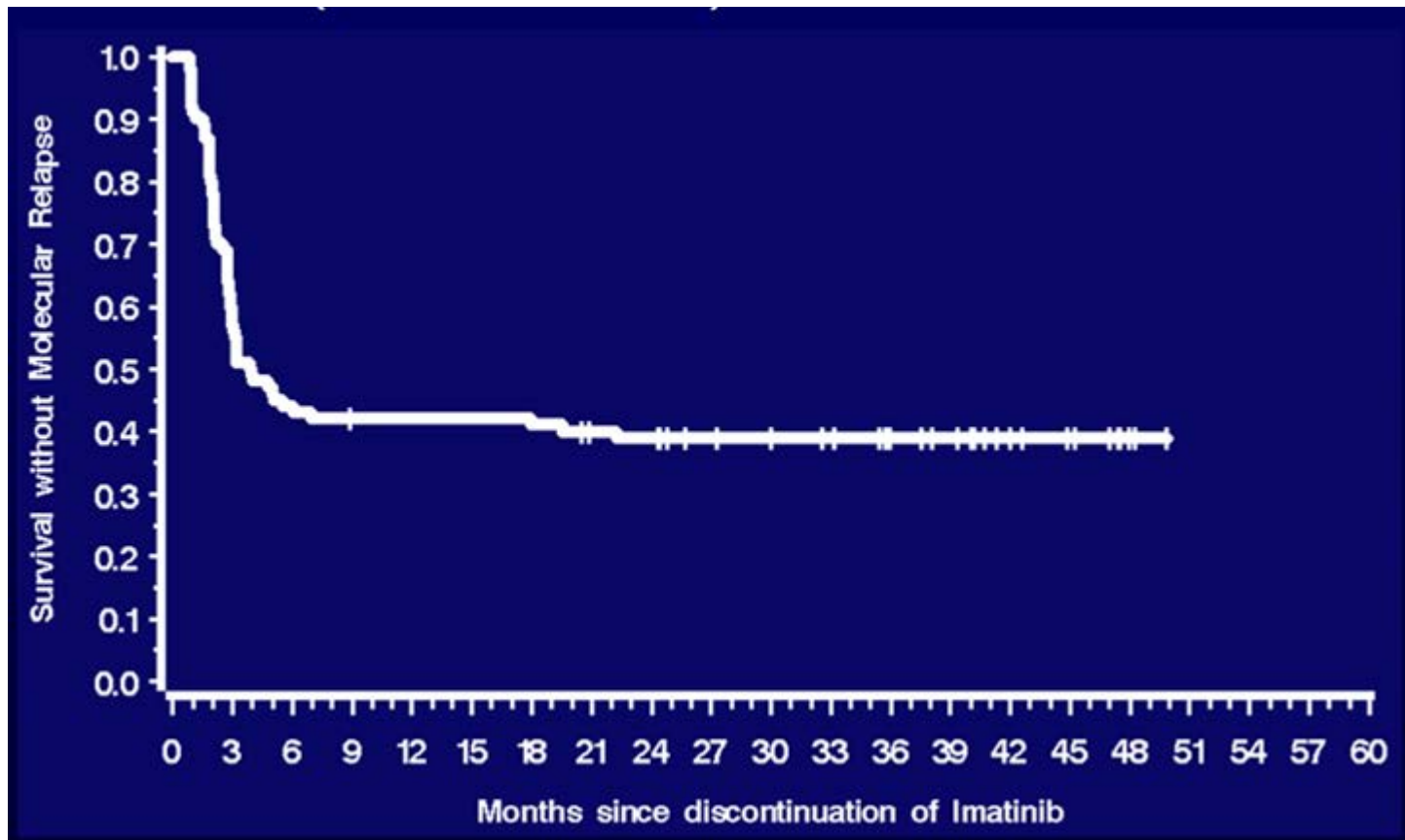


- In Mexico, cost considerations favor allogeneic SCT as a ‘once only’ procedure whereas lifelong treatment with an expensive drug represents an excessive burden on resources.

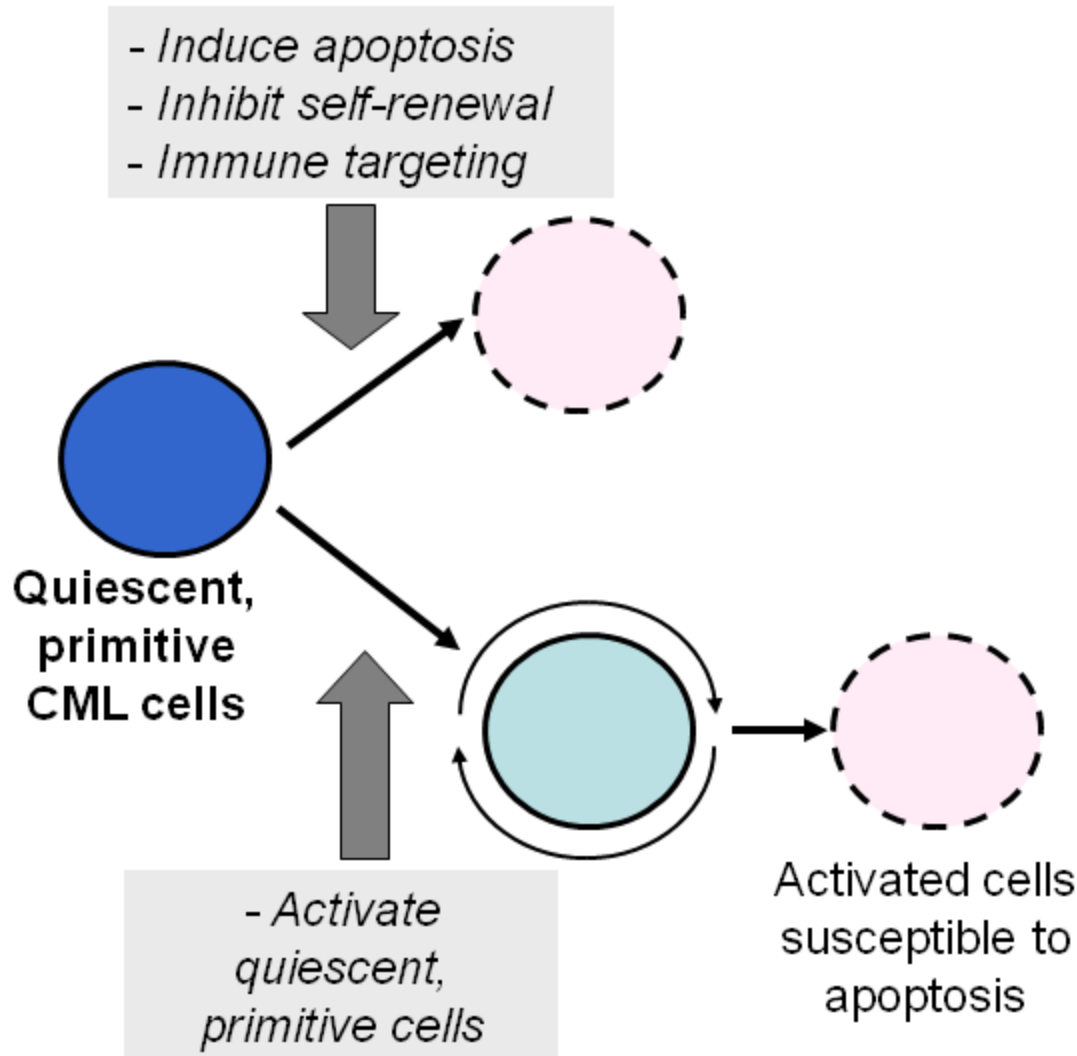
French STIM (Stop Imatinib) Study

Discontinuation of TKI

The overall probability of maintenance of CMR at 24 and 36 months was 39% (95%CI 29-48)



Strategies for targeting leukemia stem cells in CML Patients



- Target LSC survival and/or self-renewal pathways
 - Jak2, PP2A, MCL1, ALOX5, HDAC, SIRT1, autophagy
 - Hedgehog, Wnt-Catenin, CXCR4
- Immune targeting
 - IL1RAP, WT1
- Mobilize primitive cells into cell-cycle
 - Growth factors, interferon

Chronic
Myeloid
Leukemia



Cure
My
Leukemia

Cheer for the **Cure**