I Simpósio Internacional de Onco-Hematologia

8 A 10 DE MARÇO DE 2018

Hotel Pullman São Paulo Vila Olímpia

My patient failed 2 lines TKI. What`s next? HCT point of view

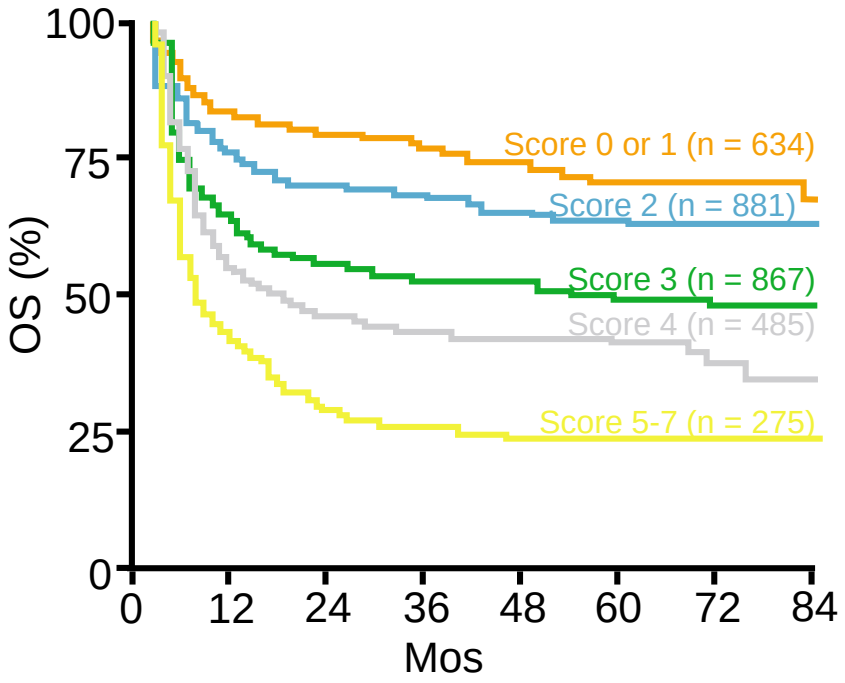
Fábio Kerbauy

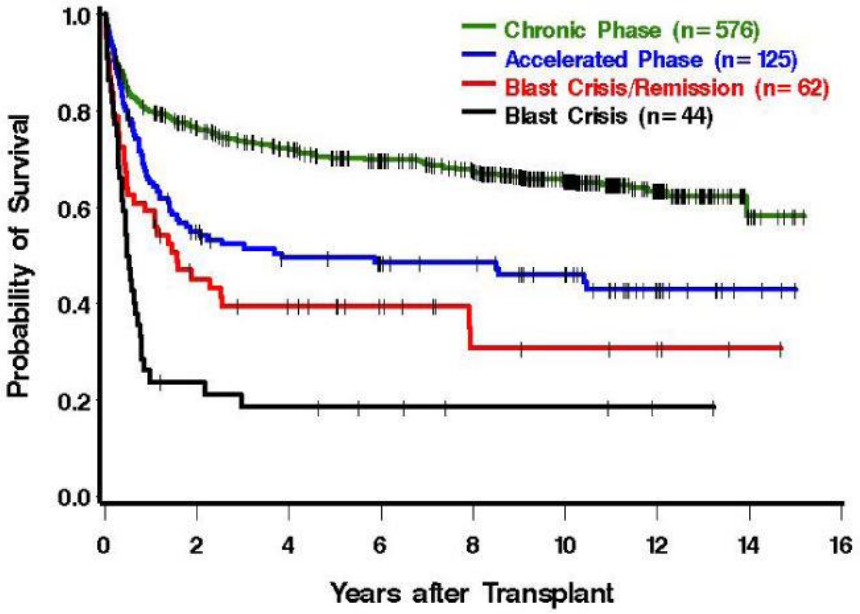
UNIFESP

Universidade Federal de São Paulo

1933

HCT for CML – Pre Imatnib Era

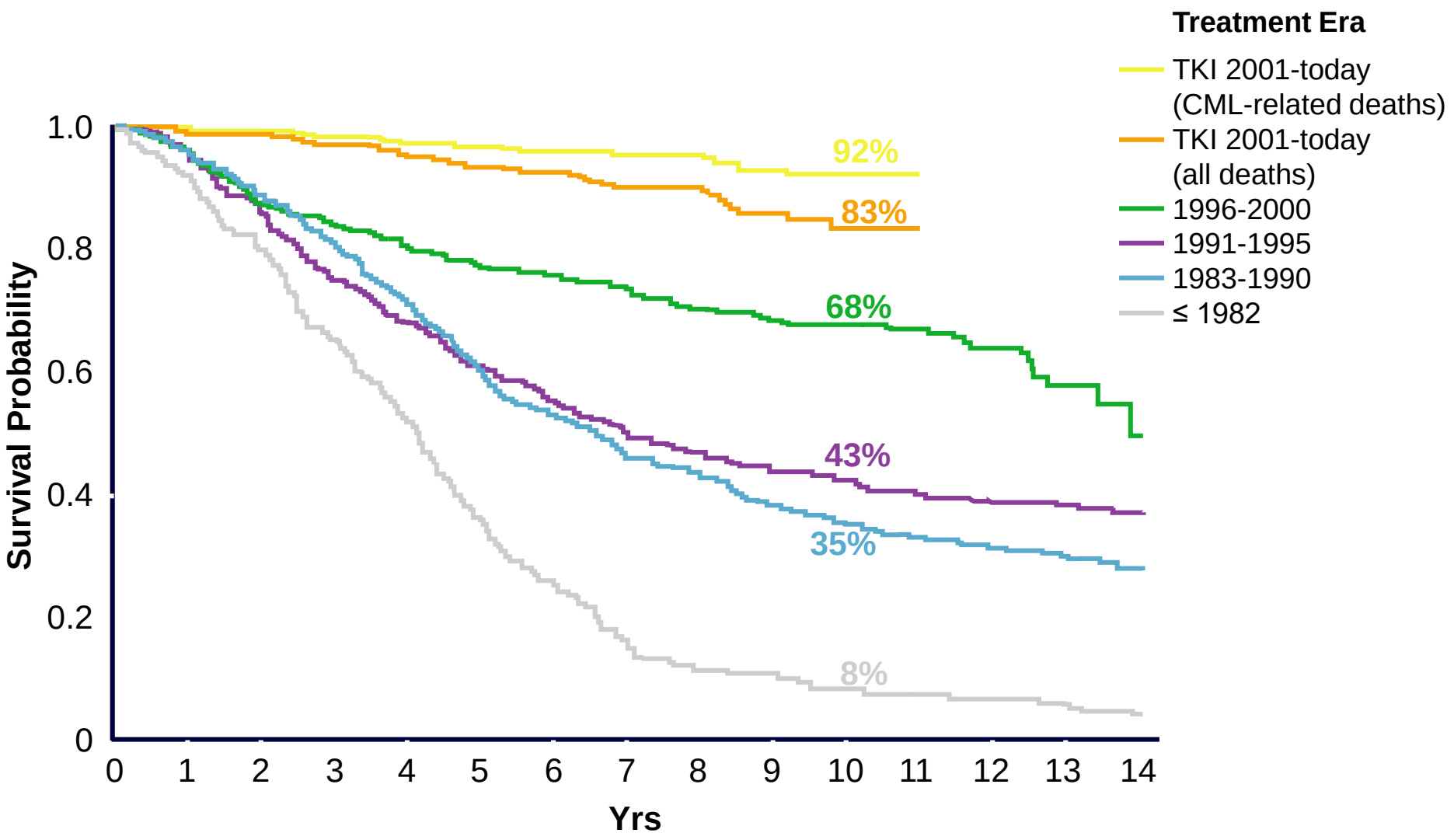




Gratwohl A, et al. Lancet. 1998;352:1087-1092

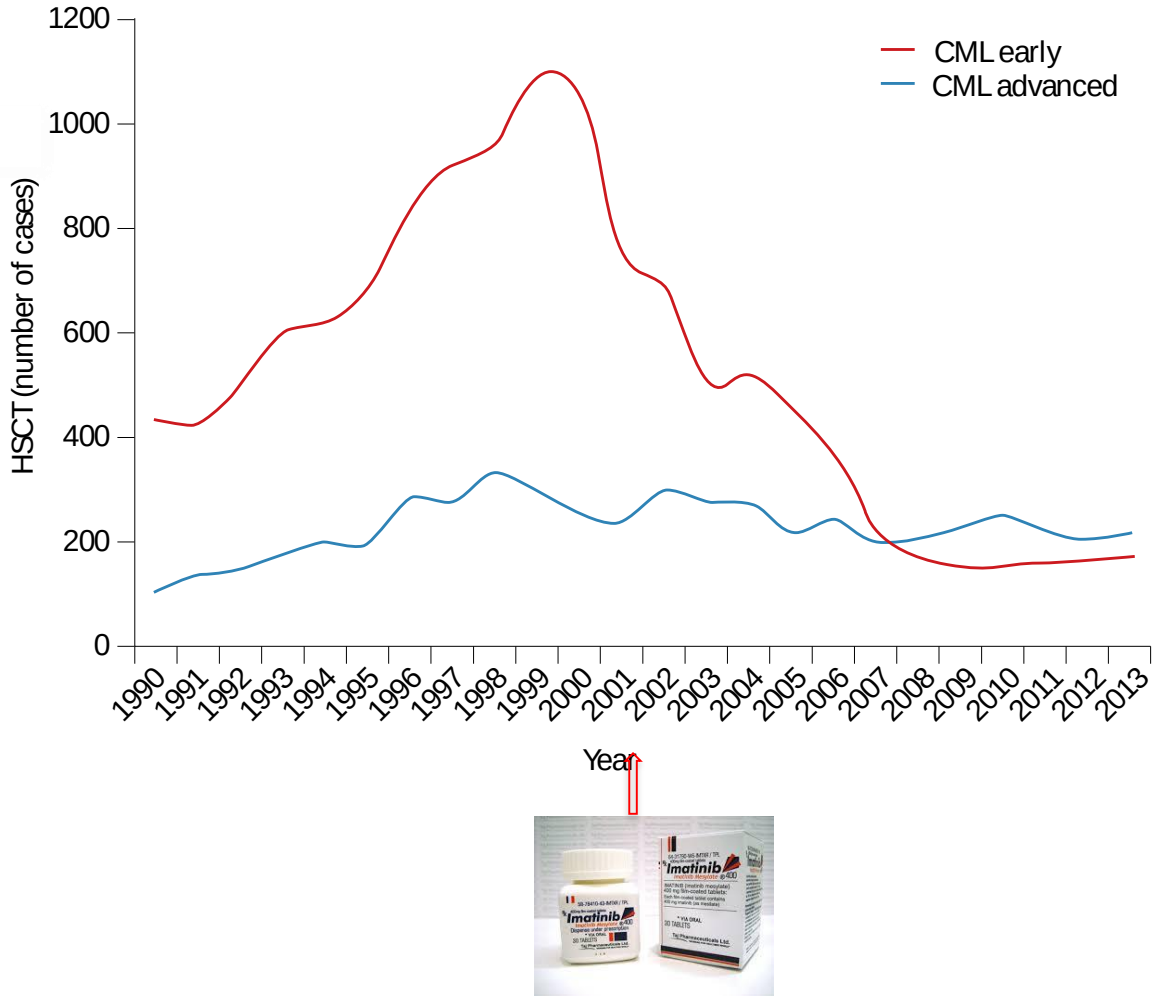
Radich J. Semin Hematol. 2010 Oct;47(4):354-61

CML survival by era



Kantarjian H, et al. Harrison's Principles of Internal Medicine 2014.

Impact of drug development on SCT



EBMT activity survey. Passweg et al. BMT, 2017; 52: 191-196

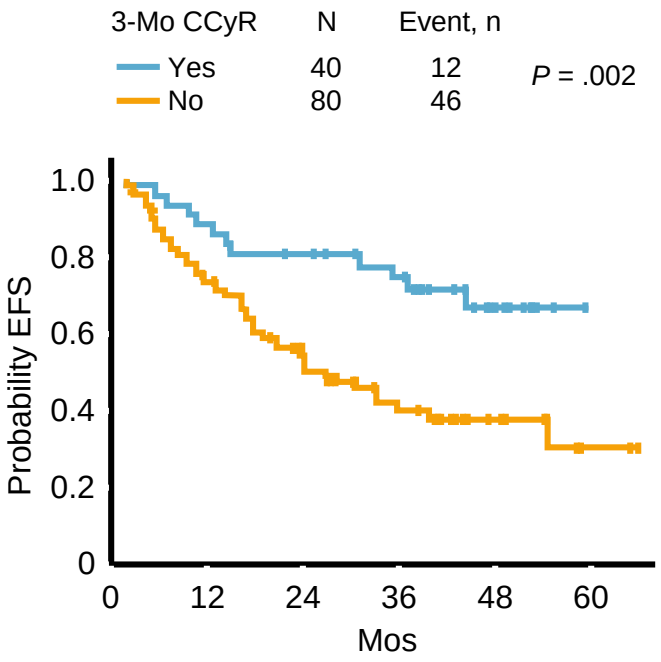
Clinical Discussion

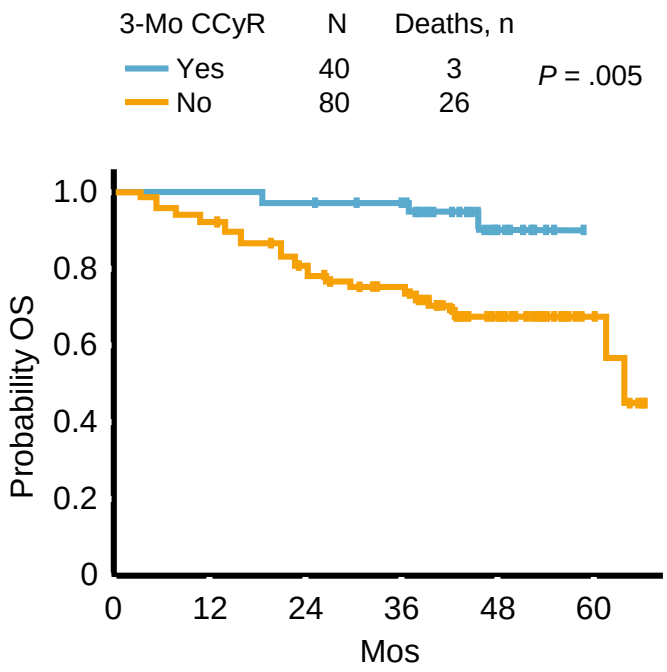
- VSB, 40a, masc
- 2015: CML-CP – SOKAL ato risco; Hasford alto risco
- Imatnib for 6 months: Rash, hematologic toxicity, BCR-ABL 1log/Ph+ 60%
- Nilotnib (nov/2015 a jan/2017): BCR-ABL 1 log – lost response

  T315i: negative

  BCR-ABL KD mutations: NA
- Dasatnibe: fev/2017 till now: Hematologic response
- What's next?
- Ponatnib? MRD (Brother) – HCT?

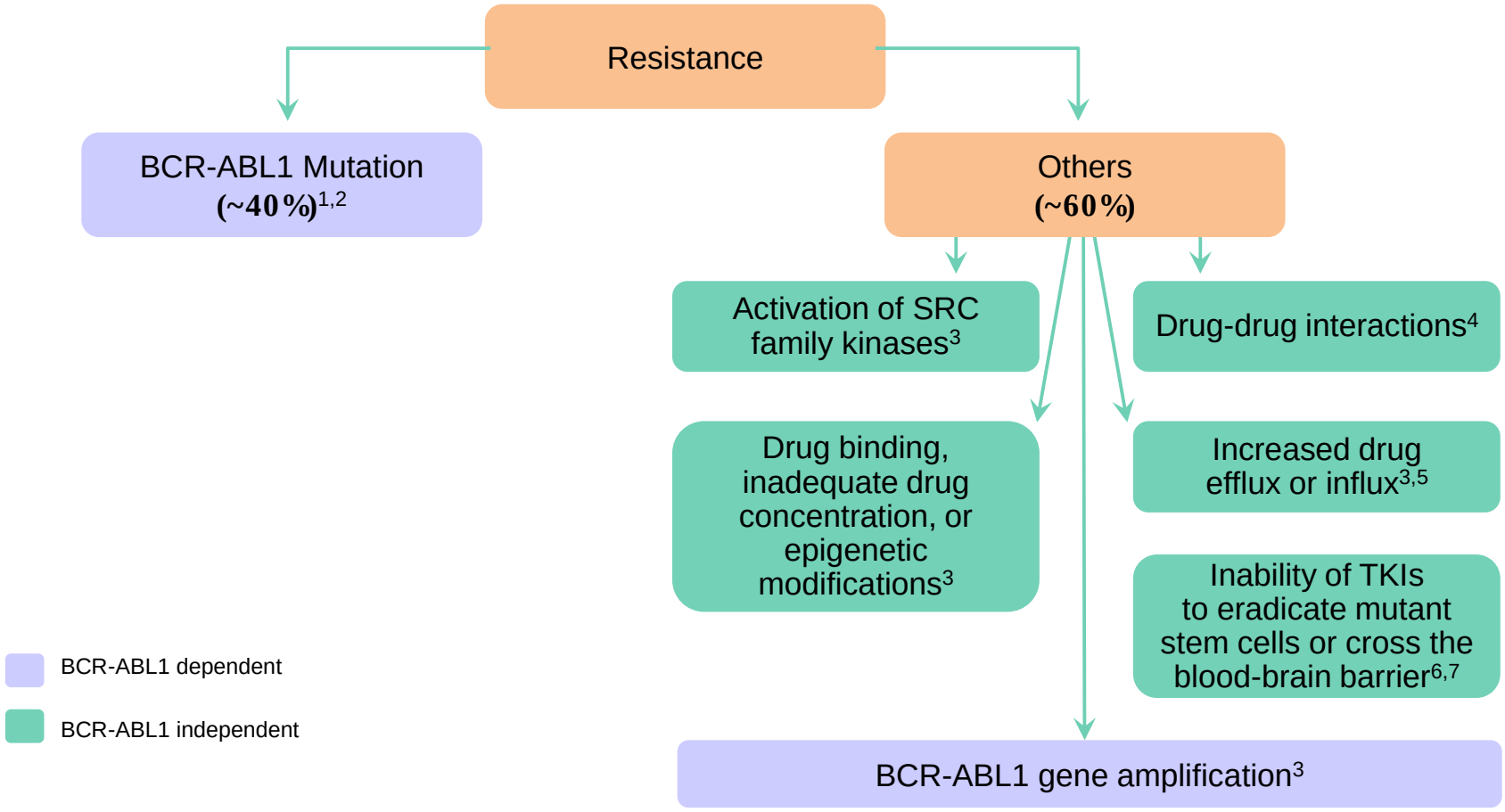
Predictors of Long-term Outcome to Second-line TKIs in Pts With CML





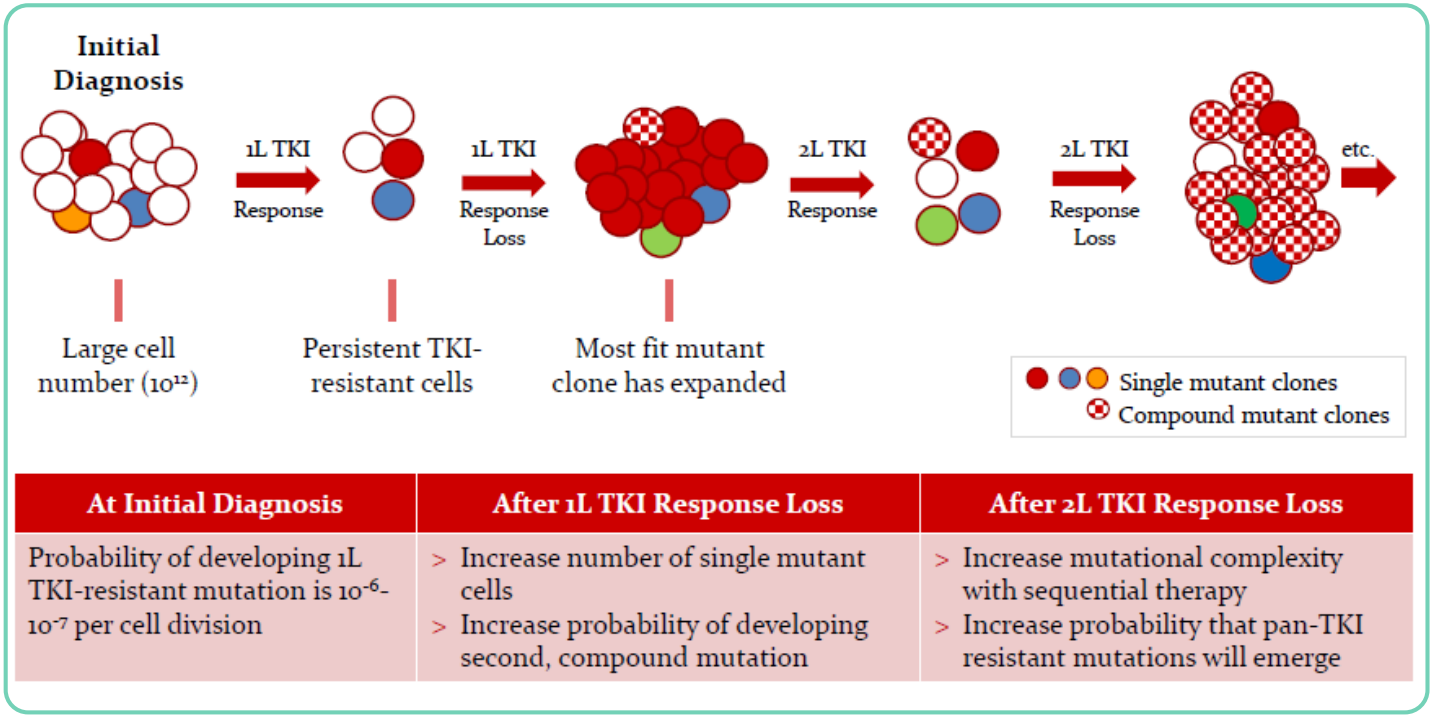
Jabbour E, et al. Clin Lymphoma Myeloma Leuk. 2013;13:302-306.

Mechanisms of treatment failure in CML



1. Soverini S, et al. *Clin Cancer Res*. 2006;12:7374-7379. 2..Cortes J, et al. *Blood*. 2007;109:3207-3213. 3. Bixby D, et al. *Leukemia*. 2011;25:7-22. 4. Bowlin SJ, et al. ASCPT 2012. 5. Quintás-Cardama A, et al. *Cancer Control*. 2009;16:122-131. 6. Valent P. *Biologics*. 2007; 1:433-438. 7. Corbin AS, et al. *J Clin Invest*. 2011;12:396-409.

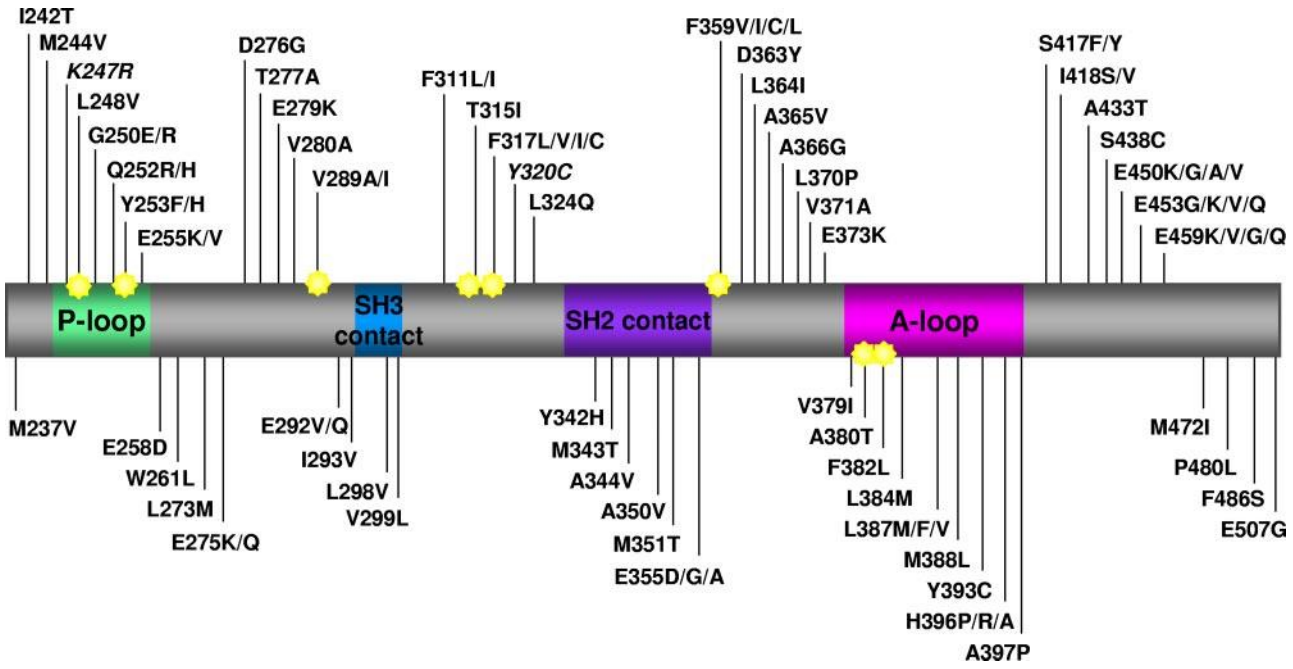
Overall response rate to TKI in CP



At Initial Diagnosis	After 1L TKI Response Loss	After 2L TKI Response Loss
Probability of developing 1L TKI-resistant mutation is 10^{-6}-10^{-7} per cell division	> Increase number of single mutant cells > Increase probability of developing second, compound mutation	> Increase mutational complexity with sequential therapy > Increase probability that pan-TKI resistant mutations will emerge

Shah NP et al. J Clin Invest. 2007 Sep;117(9):2562-9.

BCR-ABL KD mutations in Imatnib resistence



Shah NP et al. Blood 2011 Sep;118(5) :1208-16.

WHEN perform BCR-ABL KD mutations analysis

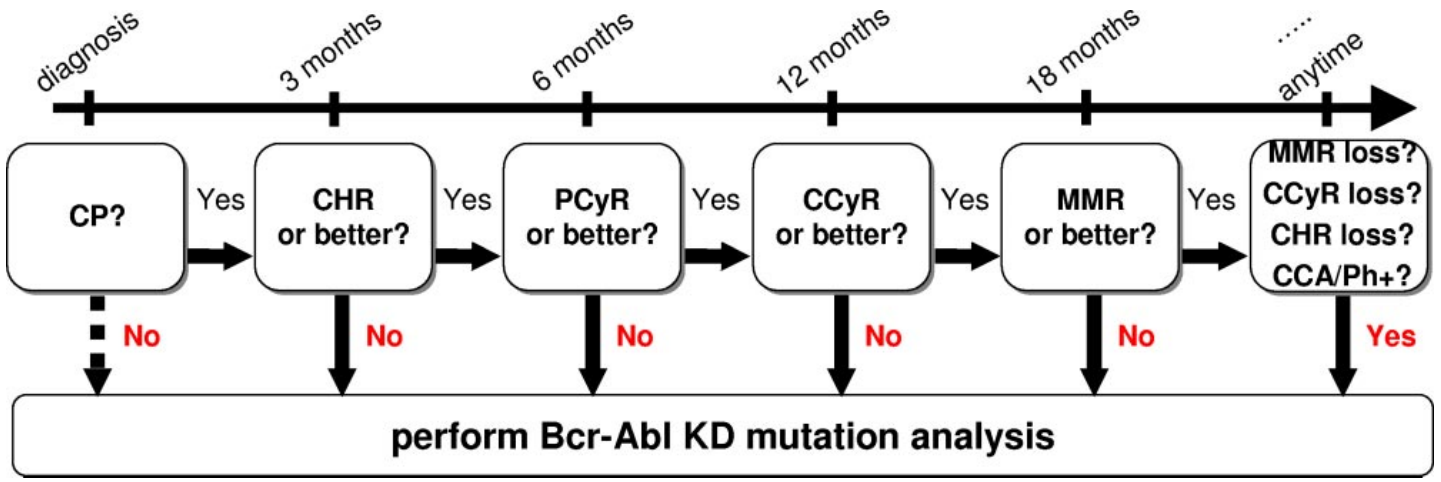


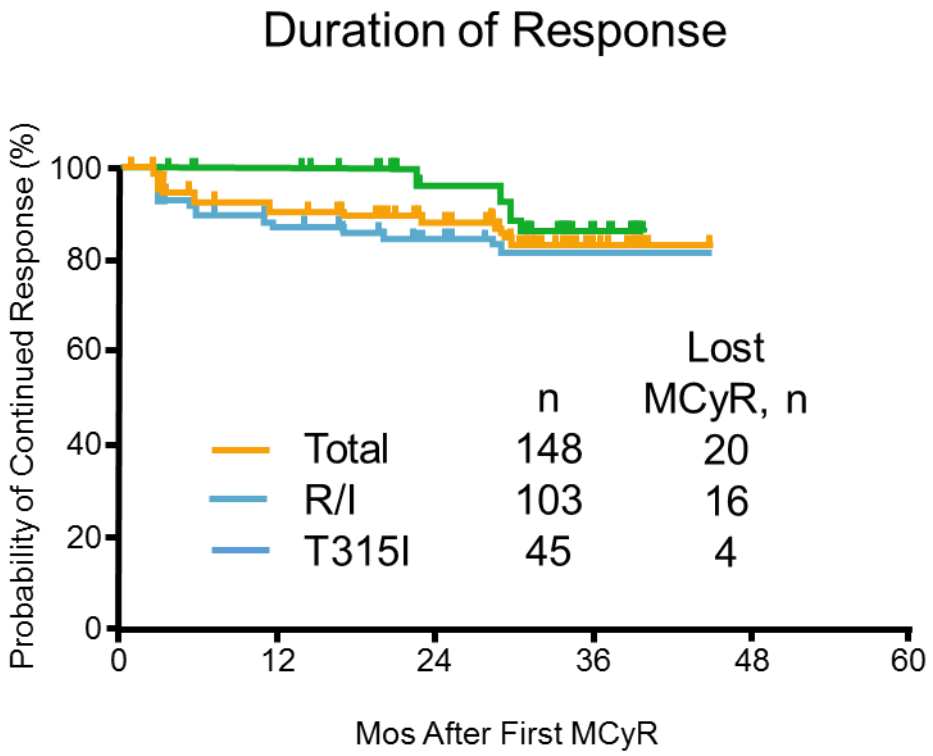
Table 2. Summary of the most appropriate alternative therapeutic options based on the *BCR-ABL* KD mutation status

T315I
HSCT or investigational drugs
V299L, T315A, and F317L/V/I/C
Consider nilotinib rather than dasatinib
Y253H, E255K/V, and F359V/C/I
Consider dasatinib rather than nilotinib
Any other mutation
Consider high-dose imatinib* or dasatinib or nilotinib

HSCT indicates hematopoietic stem cell transplantation.
*No sufficient data on dose escalation available to indicate if mutations with lower IC_{50} values are sensitive to high-dose imatinib.

European LeuknetSoverini S et al. Blood 2011 Sep;118(5) :1208-16.

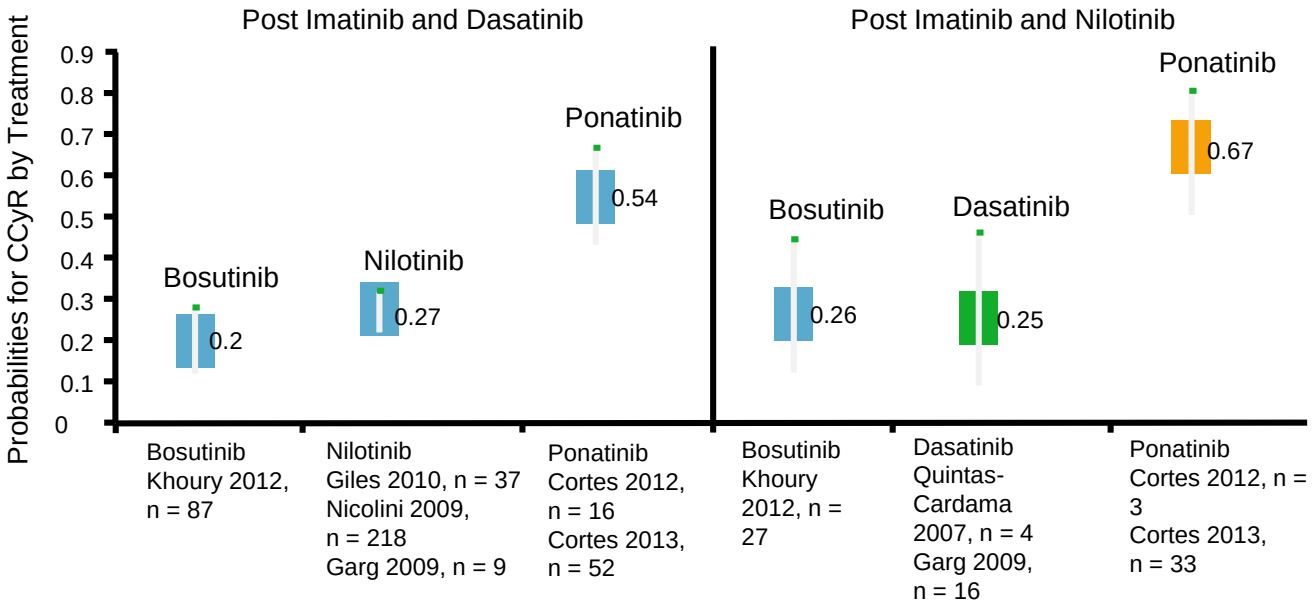
PACE: Efficacy of Ponatinib in CP CML



- 83% estimated to maintain MCyR at 36 mos

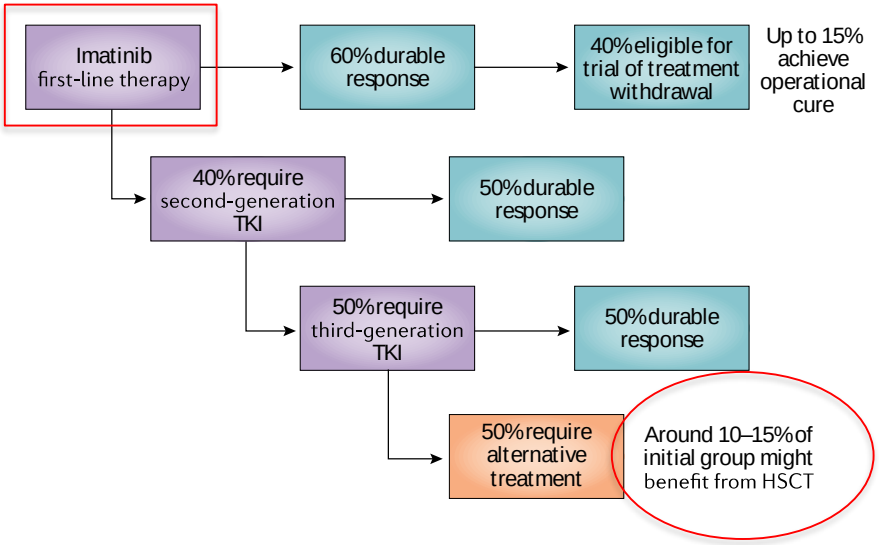
Cortes J, et al. Blood. 2014;124. Abstract 3135.

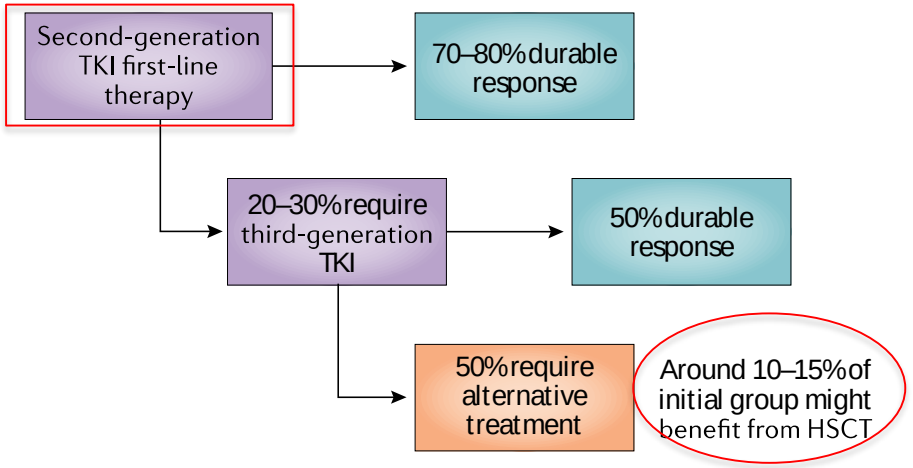
Comparative Efficacy of Third-line TKI Therapy for Achieving CCyR



Lipton JH, et al. Leuk Res. 2015;39:58-64.
Lipton JH, et al. Blood. 2014;124. Abstract 4551.

Overall response rate to TKI in CP

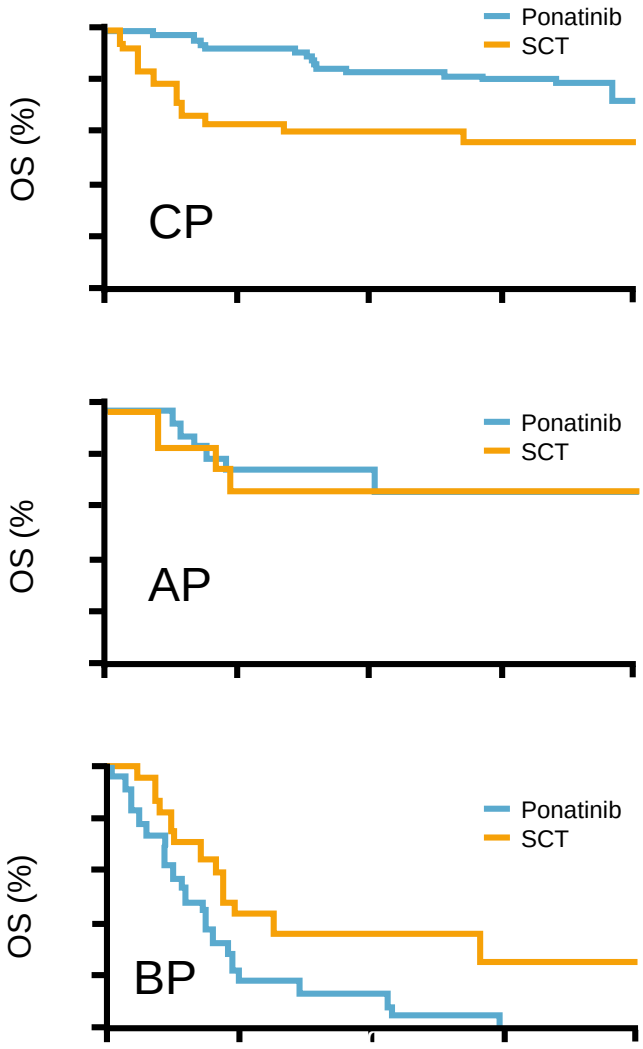




Innes AJ, Milojkovic D & Apperley JA et al. Nature Rev, 2016

Ponatinib vs SCT for CML With T315I Mutation

Disease Group	Ponatinib vs SCT Median OS, Mos		
	Ponatinib	SCT	P Value
CP	NR	103	.013
AP	NR	56	.889
BP	7	11	.026
Ph+ ALL	7	32	.136



Nicolini FE, et al. Blood. 2015;126. Abstract 480.

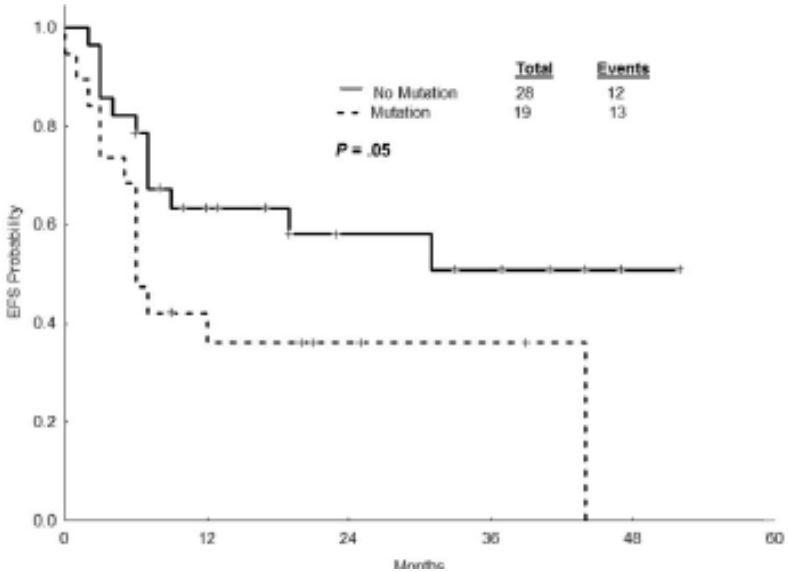
Time for HCT Consultation

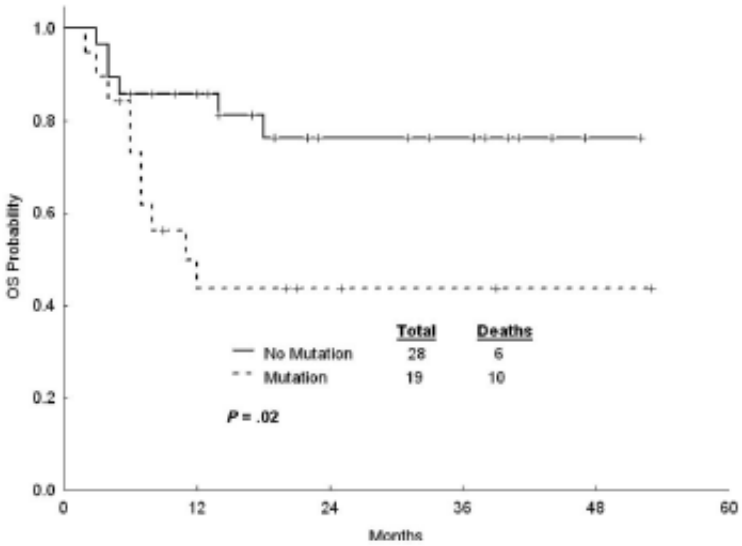
AVOID DISEASE PROGRESSION

- Inadaquete hemat/ Cyt response to TKI
- Intolerance to TKI therapies
- Disease progression
- Accelerated phase
- Blast chrises

Prior treatment with TKI affect HCT?

Not necessarily… but if BCR-ABL KD mutations appear….



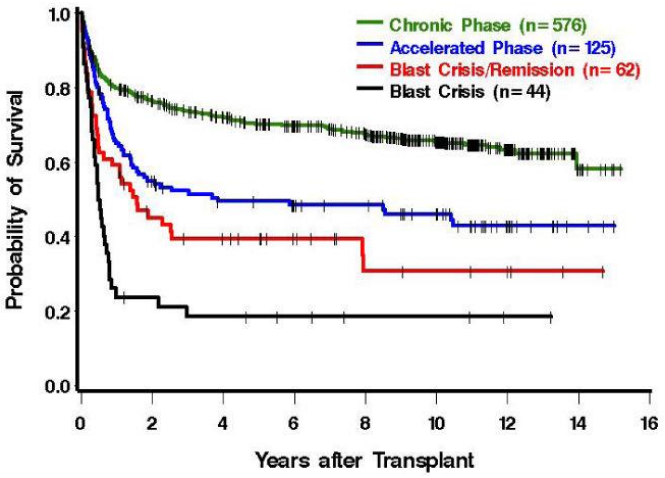


BCR-ABL KD mutations: Independent prognostic marker???

Jabbour E, et al. Blood. 2011;117:3641-3647.

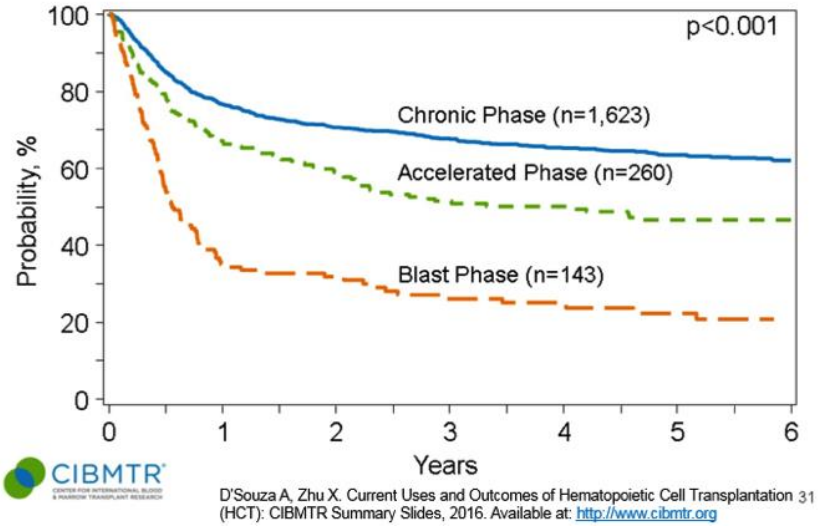
Prior treatment with TKI affect HCT?

Seattle - 1995



Radich J. Semin Hematol. 2010 Oct;47(4):354-61

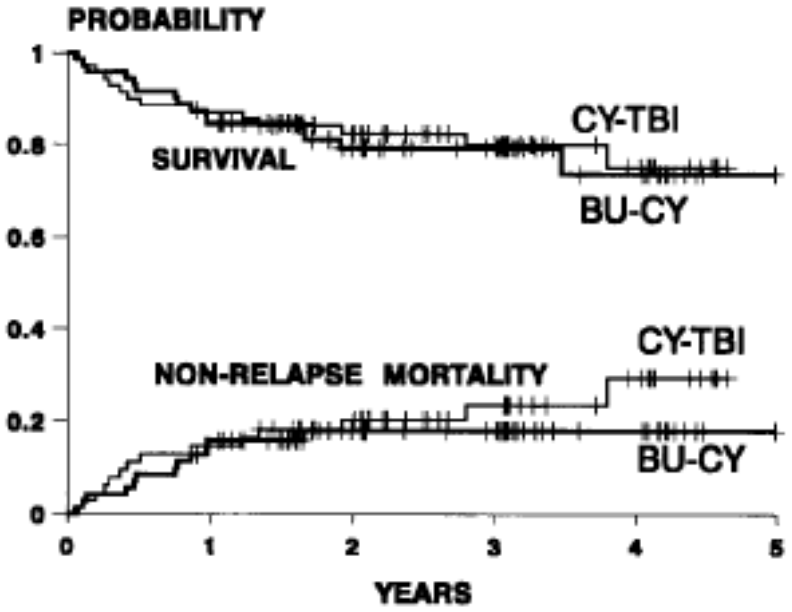
CIBMTR – 2004-2014



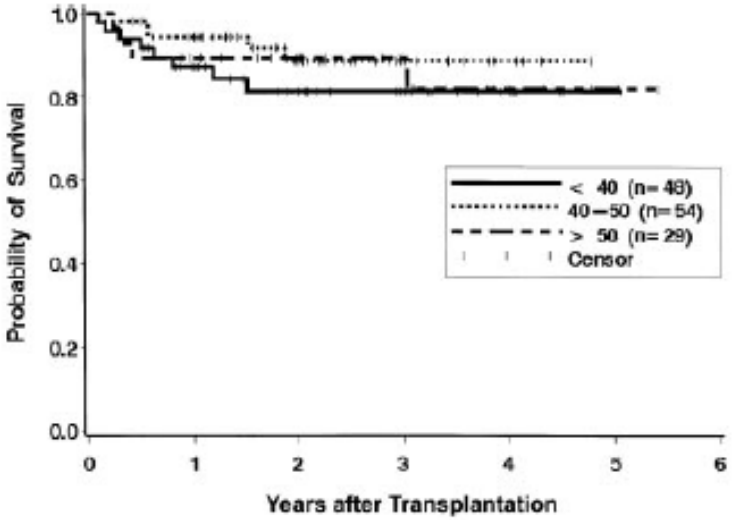
D'Souza A, Zhu X. Current Uses and Outcomes of Hematopoietic Cell Transplantation (HCT): CIBMTR Summary Slides, 2016. Available at: http://www.cibmtr.org

Conditioning regimen – old school

Cy-TBI x BuCy



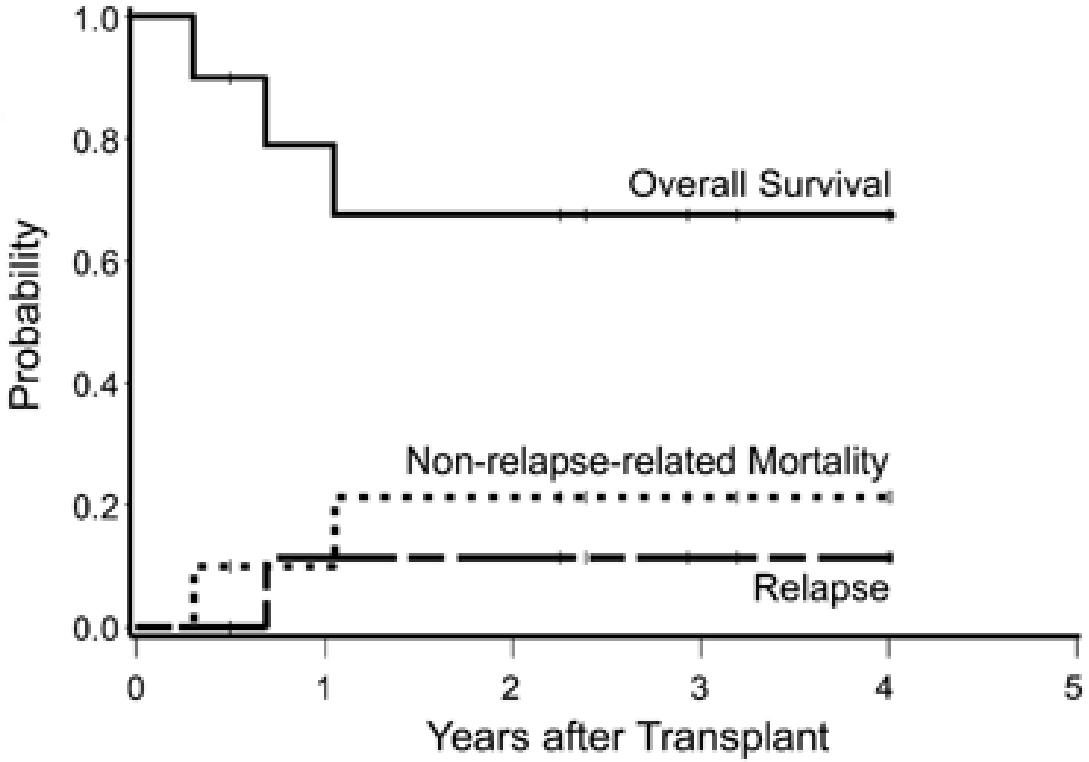
Targeted Busulfan-Cy



Clift et al. Blood 1994; 84(6):2036-2043

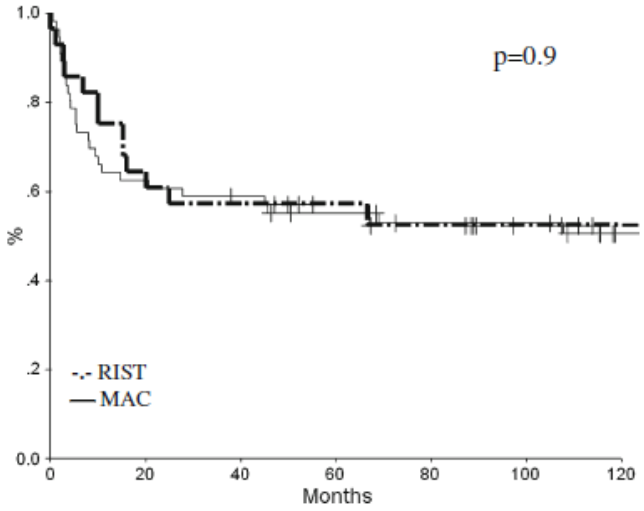
Radich et al, Blood 2003; 102:31-35

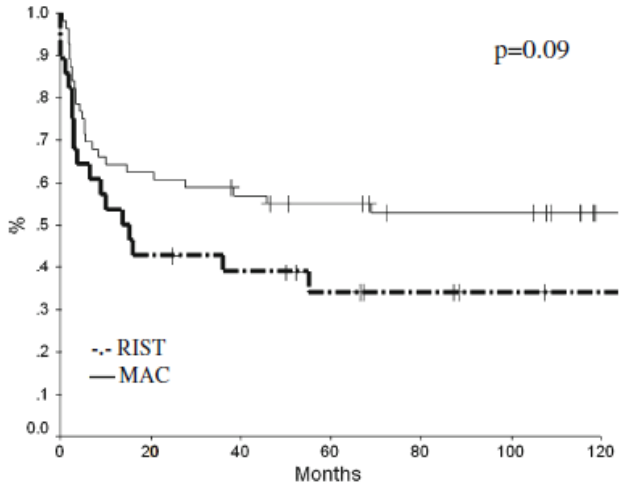
Conditioning regimen – NMA (Flu/TBI200)



Kerbauy FR et al. Leukemia 2005; 19(6):1990-97

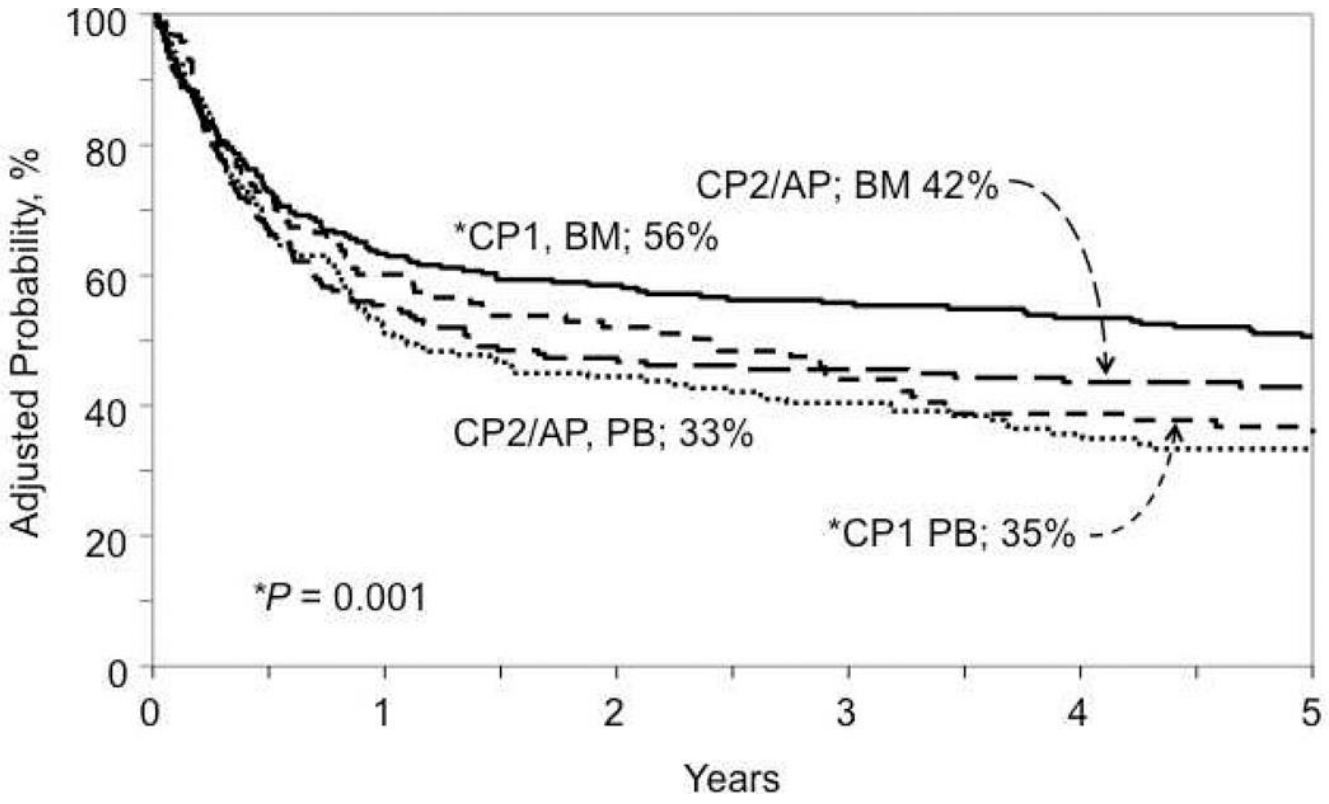
Conditioning regimen – RIC x MA





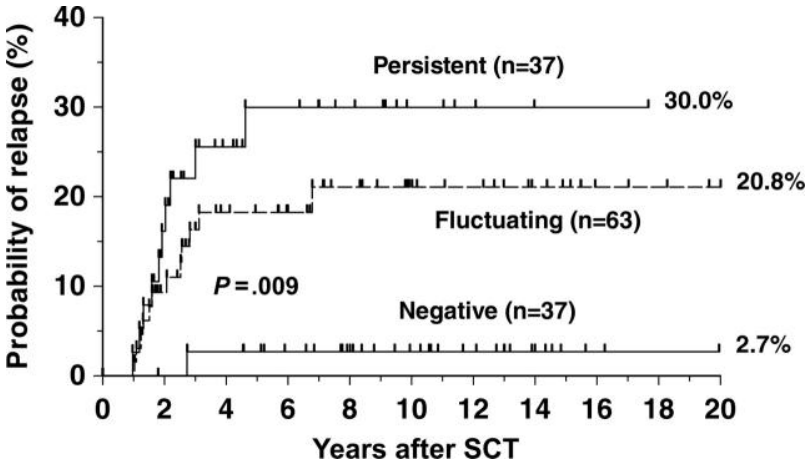
Topcuoglu P et al. Ann Hematol. 2012; 91:577-86

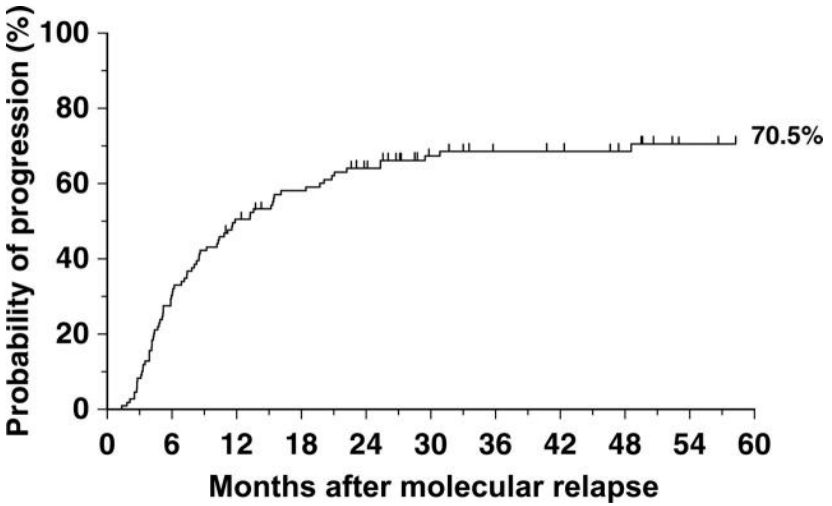
Stem Cells Source



Eapen M et al. BBMT. 2015; 21(1):55-59

Post transplant relapse





Kaeda J et al. Blood. 2006; 107(10):4171-4176

Post transplant relapse - DLI

Donor Leukocyte Transfusions for Treatment of Recurrent Chronic Myelogenous Leukemia in Marrow Transplant Patients

By H.J. Kolb, J. Mittermüller, Ch. Clemm, E. Holler, G. Ledderose, G. Brehm, M. Heim, and W. Wilmanns

Table 3. Percentage of Ph1-Positive Metaphases Before and After Treatment With IFN and Buffy Coat Transfusions

	UPN 105		UPN 132		UPN 169	
	Weeks Posttransplant	% Ph1+ Metaphase (no. evaluated)	Weeks Posttransplant	% Ph1+ Metaphases (no. evaluated)	Weeks Posttransplant	% Ph1+ Metaphases (no. evaluated)
Relapse	166	87 (16)	168	79 (14)	101	45 (11)
IFNα-treatment	169	—	173	—	121	100 (13)
IFNα-treatment	183	100 (19)	181	NE	132	91 (11)
Buffy coat transfusion	184	—	184	—	134	—
	188	100 (15)	—	—	—	—
	191	67 (18)	—	—	—	—
	193	0 (13)	—	—	—	—
	199	0 (16)	200	0 (14)	152	0 (1)
	208	0 (12)	—	—	156	0 (8)
	230	0 (10)	216	0 (12)	169	0 (13)
	236	0 (10)			183	0 (11)
	244	0 (10)				
	275	0 (9)				

Blood, Vol 76, No 12 (December 15), 1990: pp 2462-2465

Post transplant relapse - DLI

Desease Status

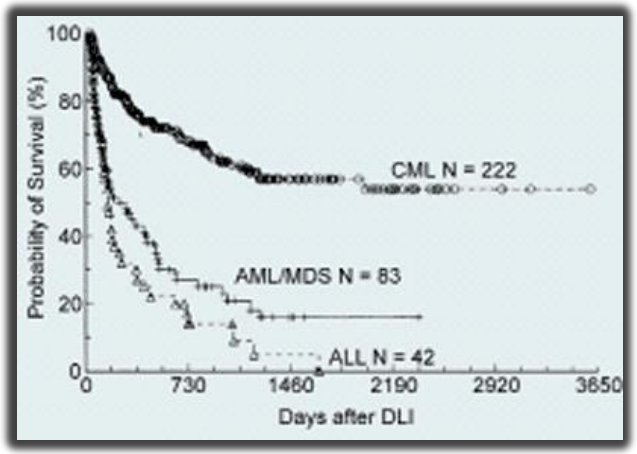
Disease Stage	Europe[28]		North America[14]		Total	
Cytogenetic relapse	40/50	(80%)*	3/3	(100%)	43/53	(81%)
Hematologic relapse	88/114	(77%)	25/34	(74%)	113/148	(76%)
Transformed phase	13/36	(36%)	5/18	(28%)**	18/54	(33%)
All	141/200	(71%)	33/55	(60%)	174/255	(68%)

* Complete responses/total evaluable (%).
** Includes 4 of 12 complete remissions for patients in accelerated phase and 1 of 6 complete remissions for patients in blast crisis.

T Cell dose

Table 4. Relationship Between T-Cell Dose, Leukemia Remissions, and GVHD

T-Cell Dose/kg	No. of Patients Treated With This Cell Dose	GVL Effect	GVHD
1×10^5	10	0	0
5×10^5	10	0	0
1×10^6	9	0	0
5×10^6	8	0	0
1×10^7	21	8	1
5×10^7	14	4	3
$\geq 1 \times 10^8$	17	7	5

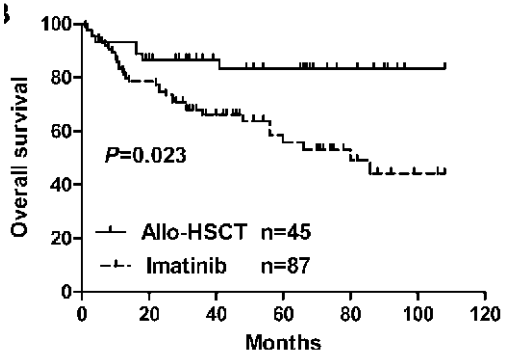


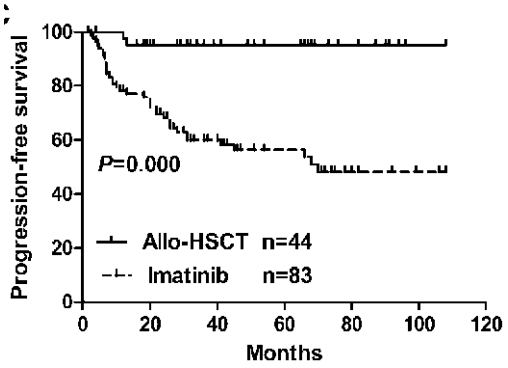
Luznik L and Fuchs E. Cancer Control; 2002: 9; 123
Mackinnon S, et al. Blood;1995: 86:1261

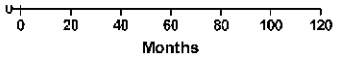
Post transplant relapse - TKI

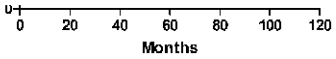
- EC, 36a, fem
- CML-CP, EBMT score:2 (2003)
- Bu16/Cy120 – CSA/MTX (2003)
- Source: MRD, BM (5 x 10e8 TNC)
- No major complication, remain CR (Citogenetic)
- 2015: Hematologic relapse 12y post HCT – CML CP
- DLI? Imatnib?

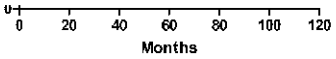
Accelerated phase – Imatnib x SCT











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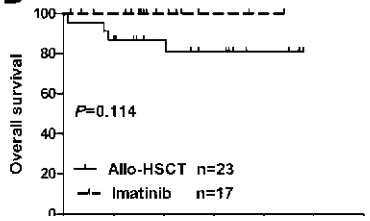
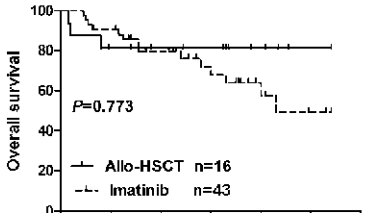
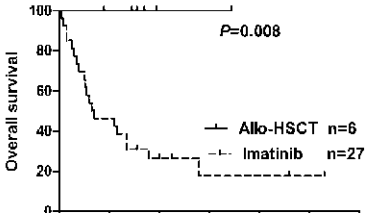


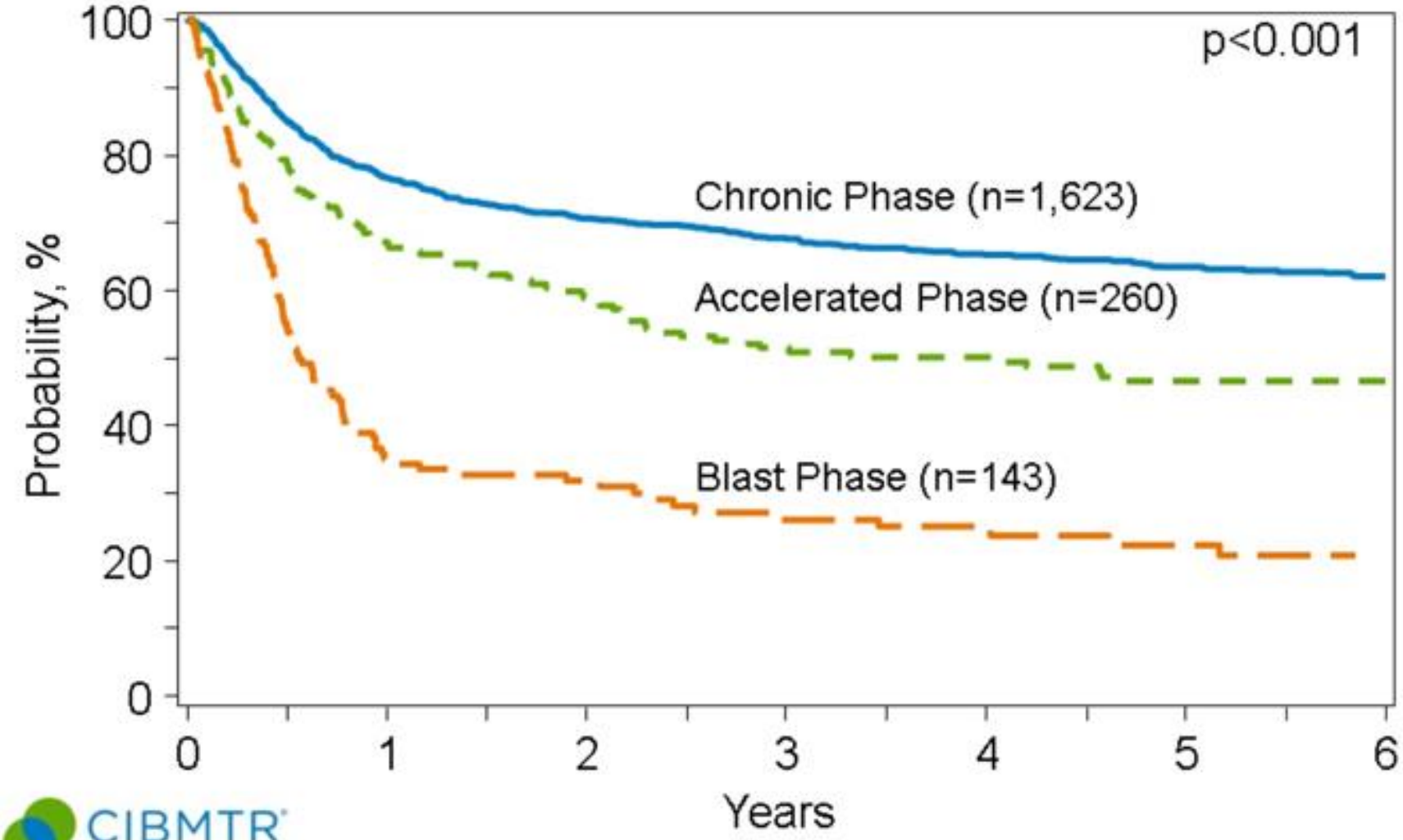




Risk factors	Risk category
CML duration ≥12 months	High risk: at least two risk factors
Haemoglobin <100 g/l	Intermediate risk: any risk factor
Peripheral blood blasts ≥5%	Low risk: no risk factors

Jiang Q et al. Blood. 2000: 117(11); 3032-40

Survival after HLA Matched Sibling HCT for CML, 2004-2014



CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

D'Souza A, Zhu X. Current Uses and Outcomes of Hematopoietic Cell Transplantation (HCT): CIBMTR Summary Slides, 2016. Available at: http://www.cibmtr.org

Conclusions

- Failed 2 lines TKI: Ponatnib x HCT
- 10-15% patients – Allog HCT feasible strategy
- Early strategy to define candidates
- Myeloablative (RIC?) is the conditioning regiment of choice.
  - NMA for unfitted patients
- BM over PBSC – AVOID GVHD
- Haploidentical donors – Why not?
- Molecular relapse: DLI x TKI

Conclusions

- No Ponatinib, bosutinib, omacetaxine, etc
- More HCT candidates

TKI drug interactions

Drugs	Efects
Agents inhibiting CYP3A Metabolism	Increase in exposure to ITKs
Warfarin and heparin	Increase the levels/effects of Warfarin and Heparin. Decreased levels /effects of ITKs
Agents inducers (strong) CYP3A Metabolism	Decreased levels/effects of ITKs
Tramadol	ITKs may decrease the levels/effects of Tramadol
Vaccines (inactived; live)	ITKs may decrease the levels/effects of Vaccines (inactived; live)
Acetominophen	Decreased levels/effects of imatinib
Fentanyl	Imatinib may increase the levels/effects of Fentanyl
Cyclosporine	Imatinib may increase the levels/effects of Cyclosporine
Antiacids, H2Antagonist, Proton Pump Inhibitors	Deacresed levels/Effects of Dasatinib and Nilotinib

Agents inhibiting CYP3A Metabolism: Ketoconazole, Itraconazole, Clarithomycin, voriconazole

Agents inducers CYP3A Metabolism:Rifampin; Pioglitazone; phenytoin; phenobarbital

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Obrigado!!

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