# Management of Advanced Phase Chronic Myelogenous Leukemia

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National Comprehensive Cancer Network®

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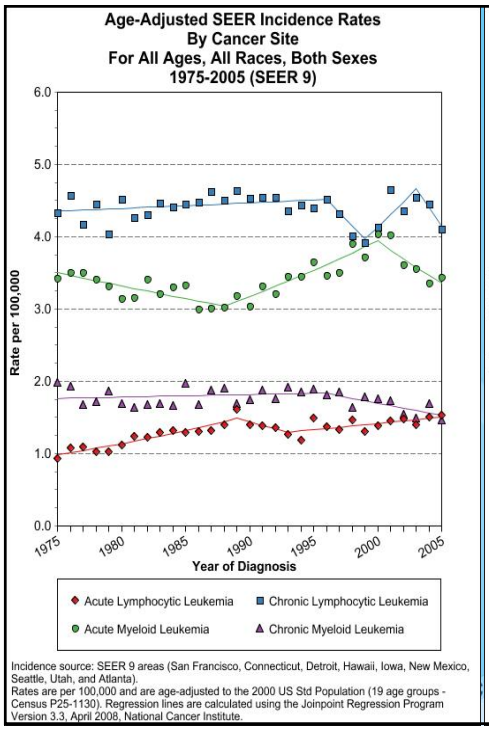
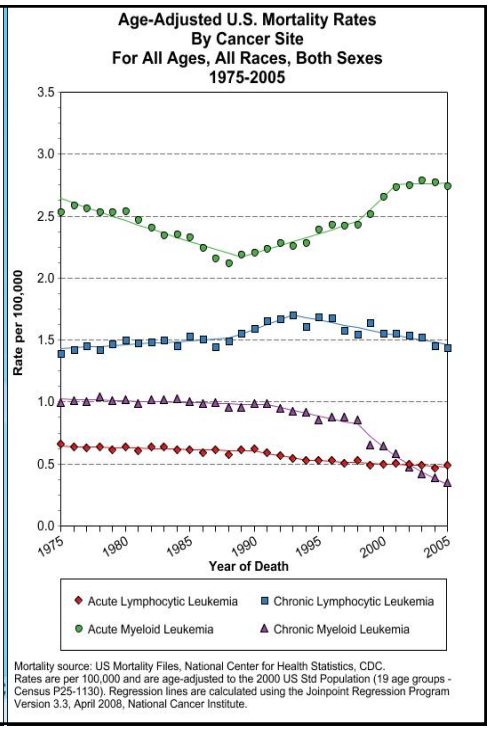
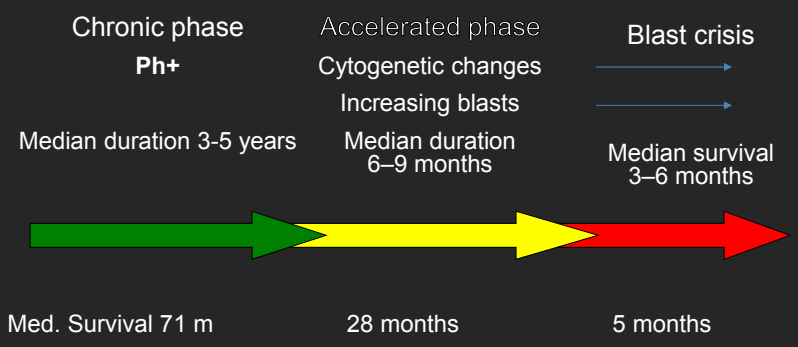


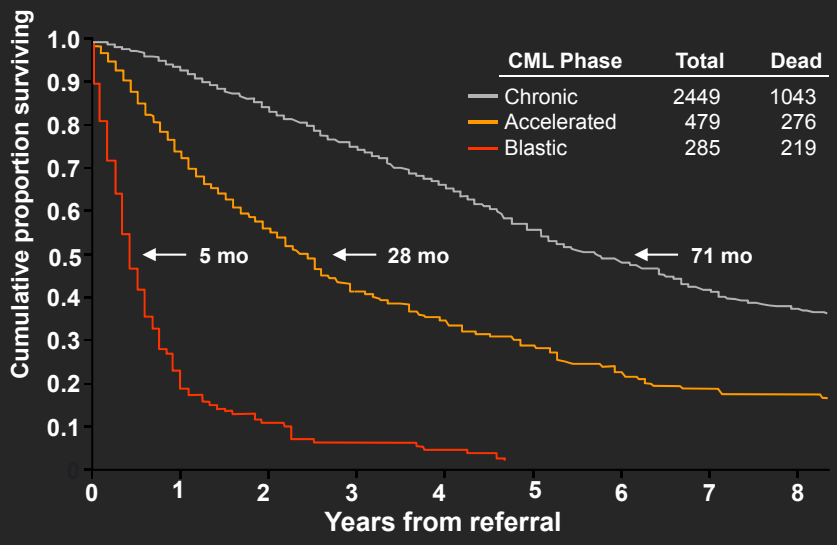
# Natural history of CML



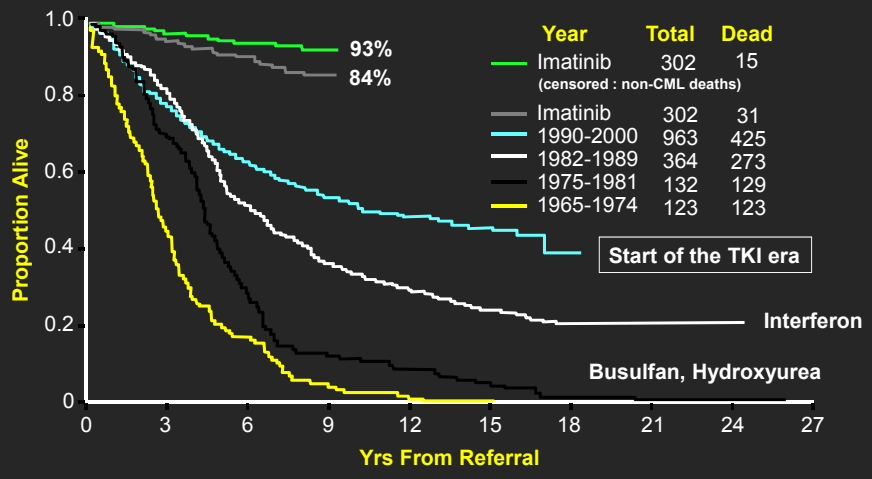

Med. Survival 71 m | 28 months | 5 months

# Survival by phase of CML

20 years B.I. (Before imatinib)



# Survival in Early CP-CML




The University of Texas MD Anderson Cancer Center Database.

# Therapy of CML in 2016

- **Frontline**
  - Imatinib 400 mg daily
  - Nilotinib 300 mg twice daily
  - Dasatinib 100 mg daily
- **Second/third line**
  - Nilotinib, dasatinib, bosutinib, ponatinib
  - Omacetaxine
  - Allogeneic SCT
- **Other**
  - Decitabine, interferon
  - Hydroxyurea, cytarabine, combos of TKIs
  - Investigational agents, clinical trials

# Definition of AP and BC

- **AP**[1]
  - 15 – 29% blasts in blood or marrow (WHO 10 – 19%)
  - More than 20% basophils in blood
  - Persistent thrombocytopenia unrelated to therapy
  - Unresponsiveness to therapy
- **BC**[2]
  - More than 30% blasts in blood or marrow (WHO 20%)
  - Extramedullary blastic infiltrates
  - Varying degrees of fever, anemia, splenomegaly, leukocytosis

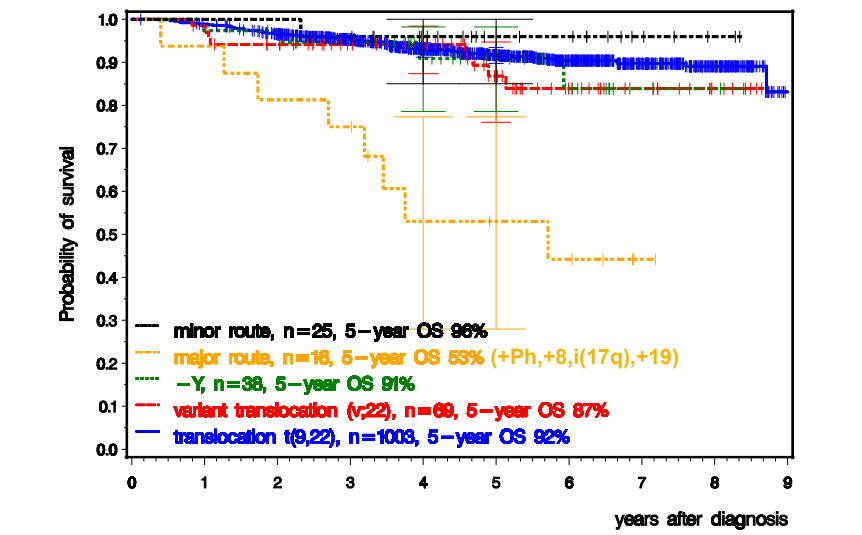
1. Talpaz M, et al.. Blood 2002;99:1928-1937. 2. Druker BJ. Chronic Myelogenous Leukemia In: DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology. Vol. 2 (ed 8); 2007:2267-2304.

# Additional cytogenetic aberrations (ACA) in advanced phase (AP and BC) CML

- "Major route" aberrations
  - +8 (30%)
  - +der(22)t(9;22) (30%)
  - +19 (10%)
  - i(17)(q10) (20%)
- "Minor route" aberrations
  - Gains of chromosomes 17 and 21
  - Losses of chromosomes Y, 7, 17
  - t(3;21)(q26;q22)

Mitelman F. Leuk Lymphoma. 1993;11 Suppl 1:11-5. Johnson et al., Acta Haematol 2002; 107: 76 – 94.

## Impact of major route aberrations at diagnosis on progression and survival

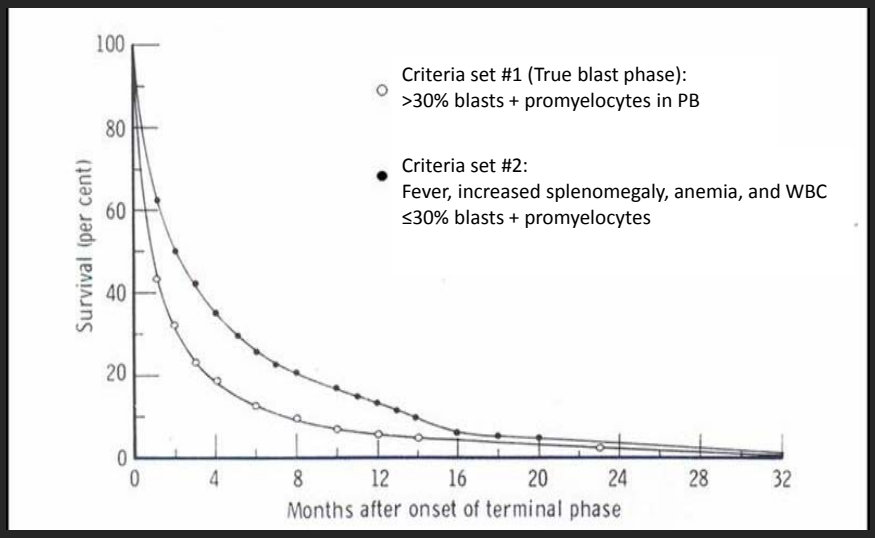



Fabarius A. et al., Blood 2011; 118: 6760 - 6768.

## Blast crisis

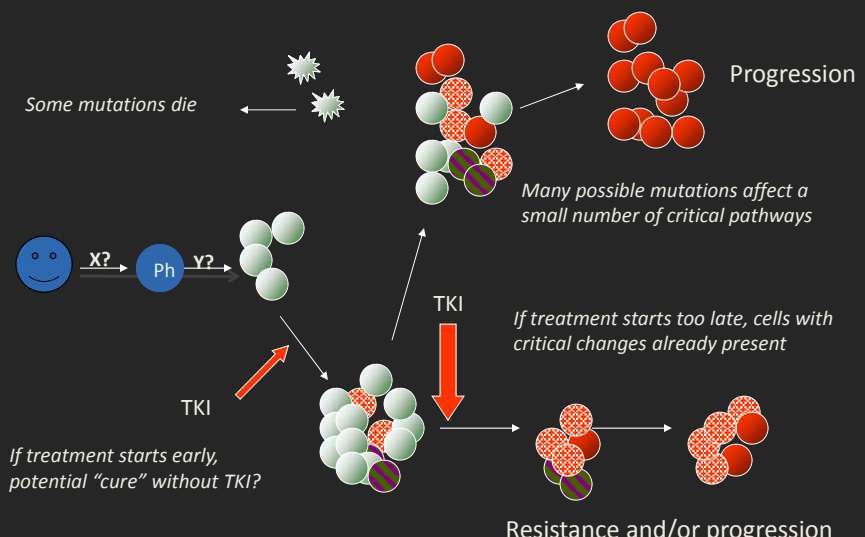
- Progression to blast crisis is still a phenomenon that is only incompletely understood.
- In up to 80% of BC patients, additional chromosomal aberrations are reported.
- In up to 77% mutations are detected.
- In gene expression profiles blast crisis appears as a disease distinct from CML.
- Treatment continues to be mostly unsuccessful unless allo SCT is offered.

## WHO vs. traditional classification: Does blast count at diagnosis make a difference in outcome?

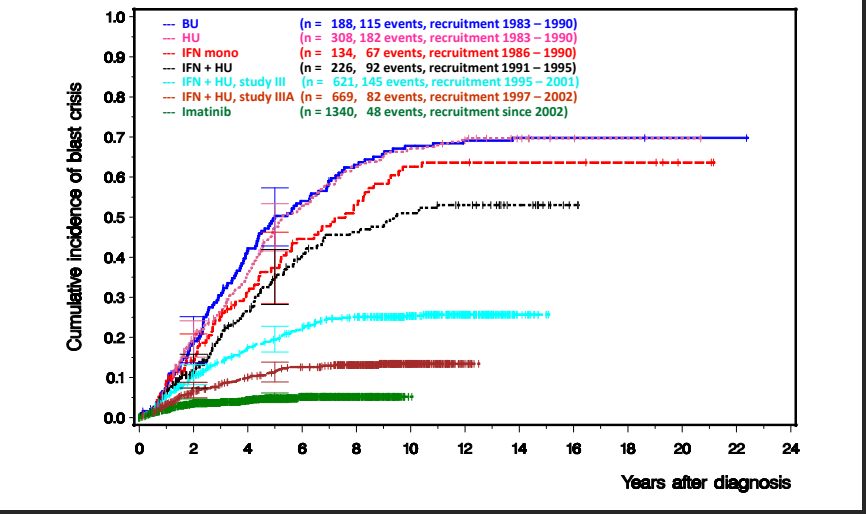



Karanas A, Silver RT. Blood. 1968 Sep;32(3):445-459.

## A simple model of CML progression/resistance

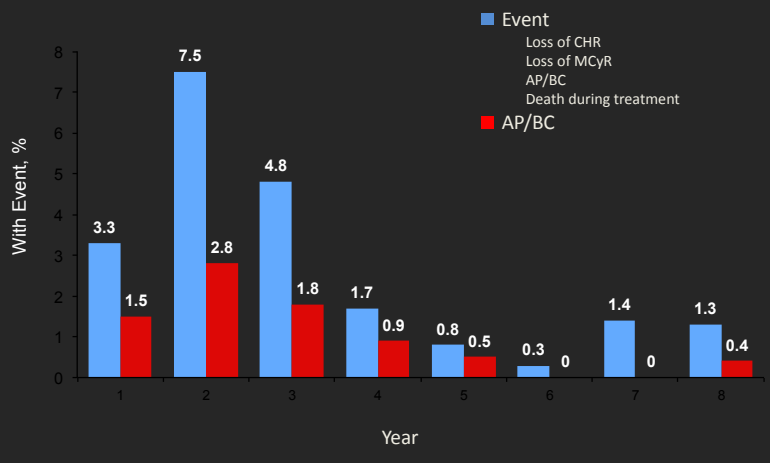


# Prevention of blast crisis
## Cumulative Incidences 1983 – 2013



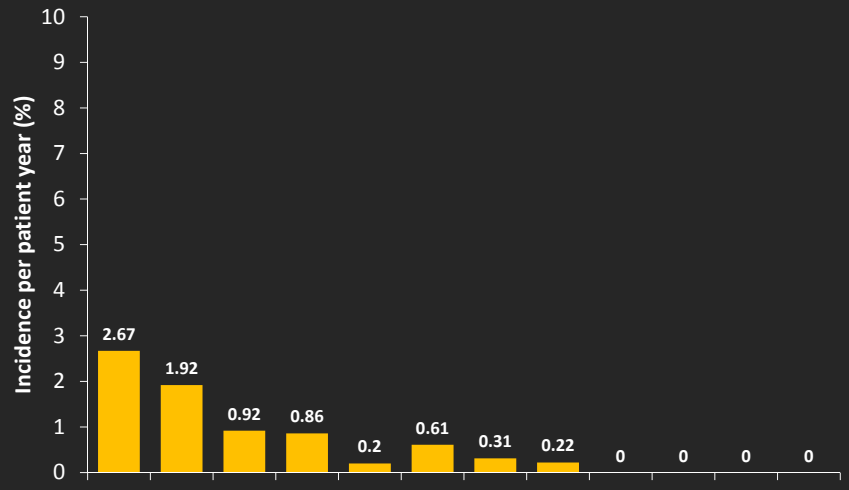

German CML Study group, unpublished

# Progression on IRIS trial declines over time




Derived from Druker BJ, et al. *N Engl J Med*. 2006;355(23):2408-2417; Deininger M, et al. *Blood*. 2009;114:Abstract 1126.

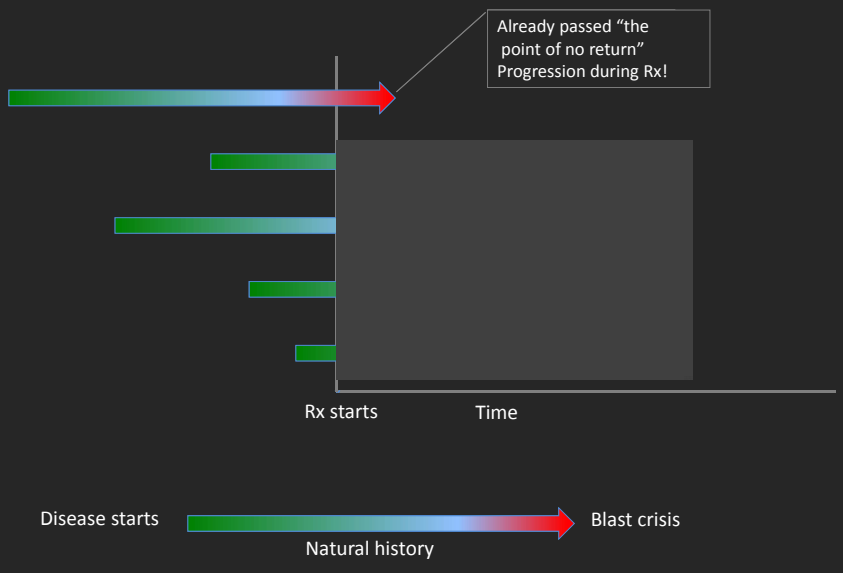
## Incidence of blast crisis under TKI (CML study IV)




| Years | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient years | 1500 | 1410 | 1305 | 1157 | 991 | 824 | 645 | 457 | 292 | 152 | 31 | 0.5 |

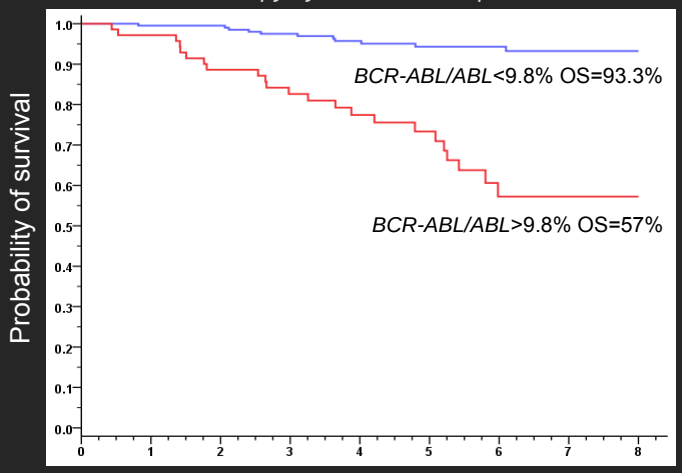
German CML Study Group, unpublished

## Lead time bias and progression



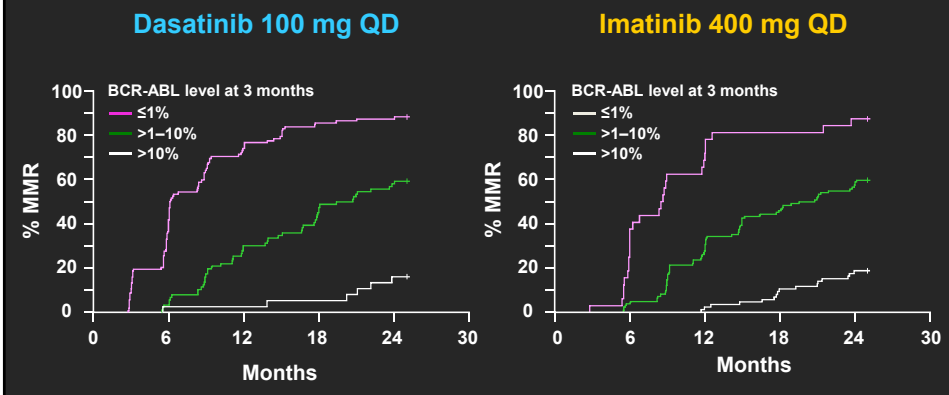
# Survival Based on 3 Months of Molecular Response

*Survival After Imatinib Therapy by Molecular Response Achieved at 3 Months*



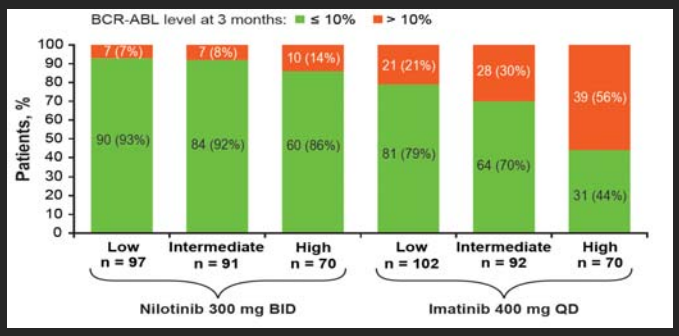

Marin D, et al. *J Clin Oncol*. 2012;30(3):232-238.

# Cumulative Incidence of MMR According to BCR-ABL level at 3 Months



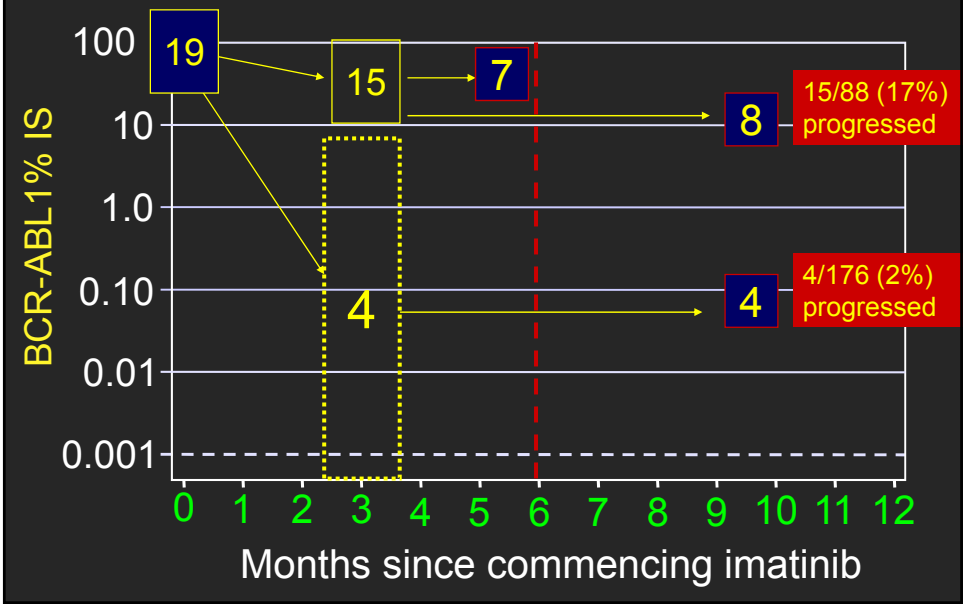

Hochhaus A, et al. Blood. 2011;118(21):[abstract 2767].

# EMR according to Sokal score




Hochhaus A, et al. *Haematologica*. 2012;97(s1):237 [abstract 0584].

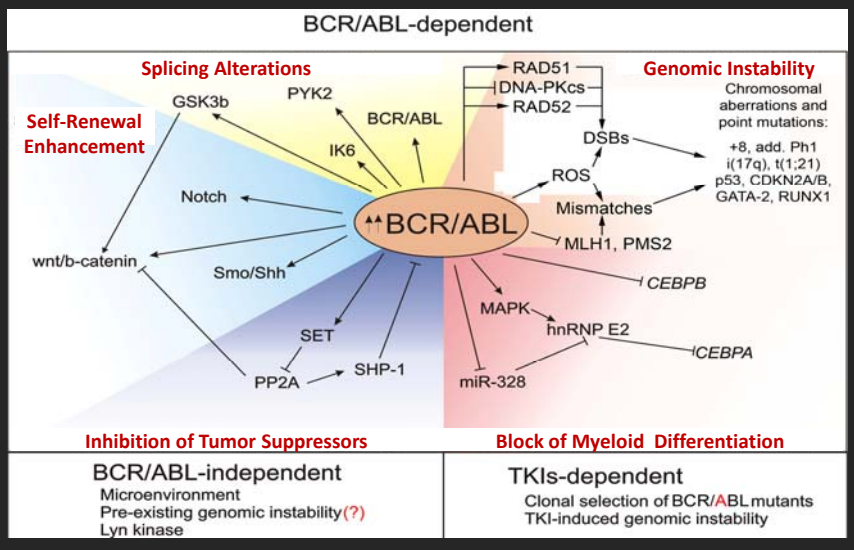
# Molecular response in patients who progressed on imatinib arm of ENESTnd



## EMR Failure: What is at stake?

- Risk of transformation >10%
- Risk of death >10%
- Risk of failing to achieve MR4.5 >90%

## Pathways to progression




Skorski et al. Leuk Lymphoma. 2011 Feb; 52 Suppl 1: 23 –29

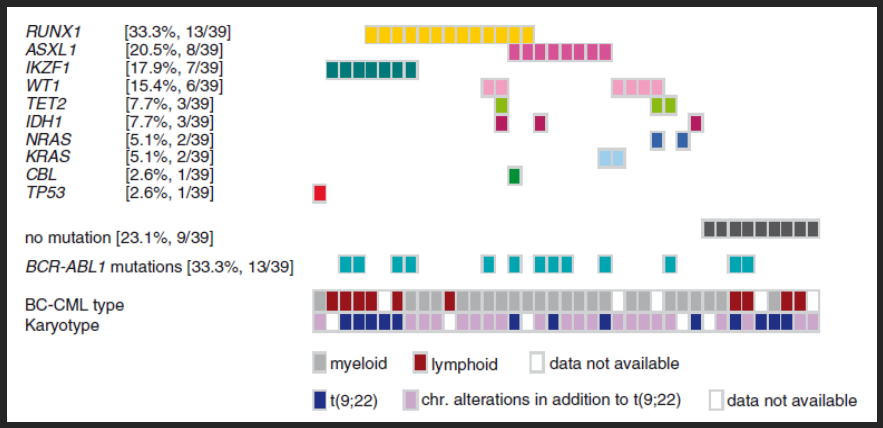
# Molecular findings in progression

- Mutations / deletions,
  p53 in ~24% of myeloid BC
  p16 in ~50% of lymphoid BC
  RUNX-1, IKZF1 (Ikaros), ASXL1, WT1, TET1, IDH1, NRAS, KRAS, CBL, in ~77% of all BC
- Alteration of gene expression (progression genes)

Calabretta and Perrotti, Blood 2004; 103: 4010 – 4022.
Grossmann et al., Leukemia 2011; 25: 557 – 560
Zheng et al., Leukemia 2006; 20: 1028 – 1034.

# Cytologic, cytogenetic and molecular findings in blast crisis (n = 39)

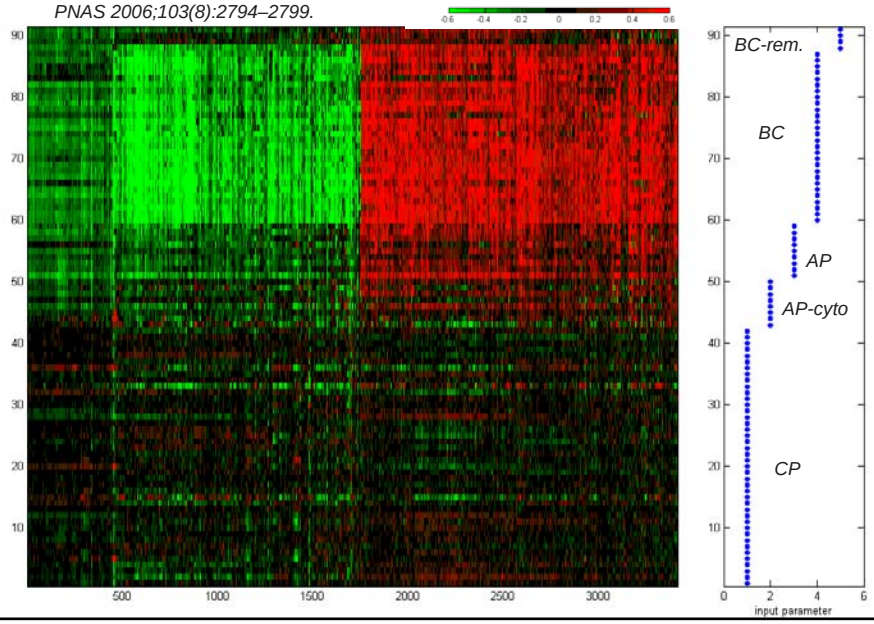
Mutations in 77% by deep-sequencing




Grossmann et al., Leukemia 2011; 25: 557 – 560

## Genes associated with CML phase ($p < 10^{-12}$)

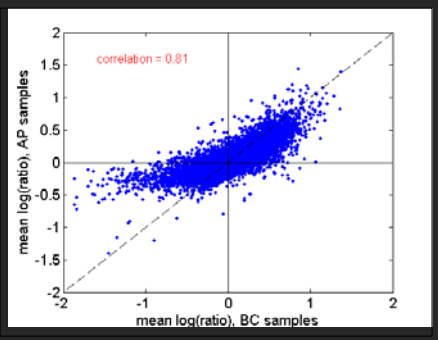
*PNAS 2006;103(8):2794–2799.*

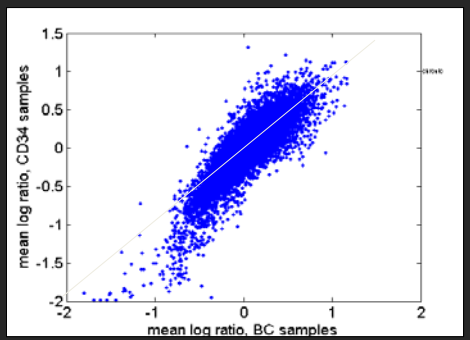



## Two lessons from gene expression arrays

1. AP is similar to BC
   *Thus, progression more like a two-step process*

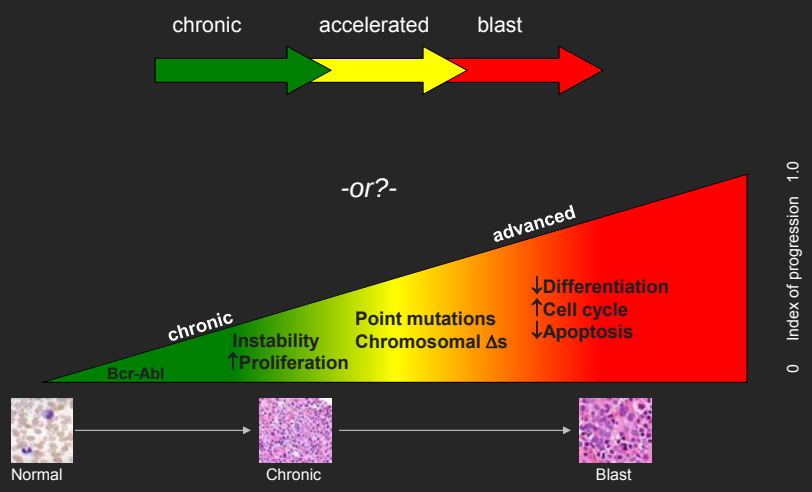
2. BC is pretty similar to normal CD34+ cells




*PNAS 2006;103(8):2794–2799.*

# Conceptual models of CML progression

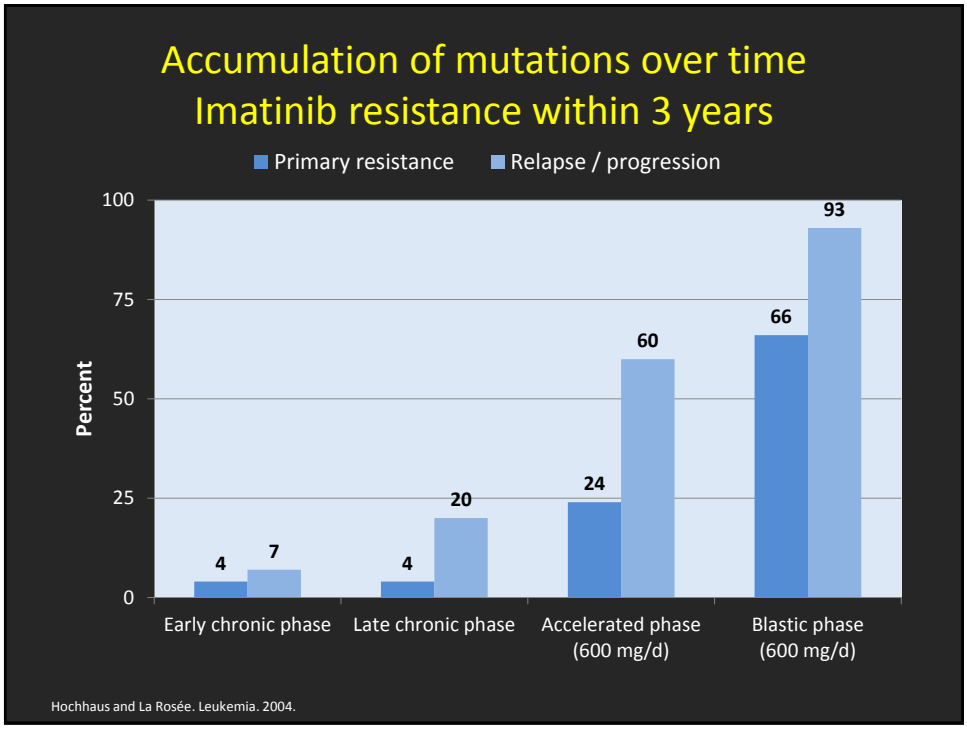


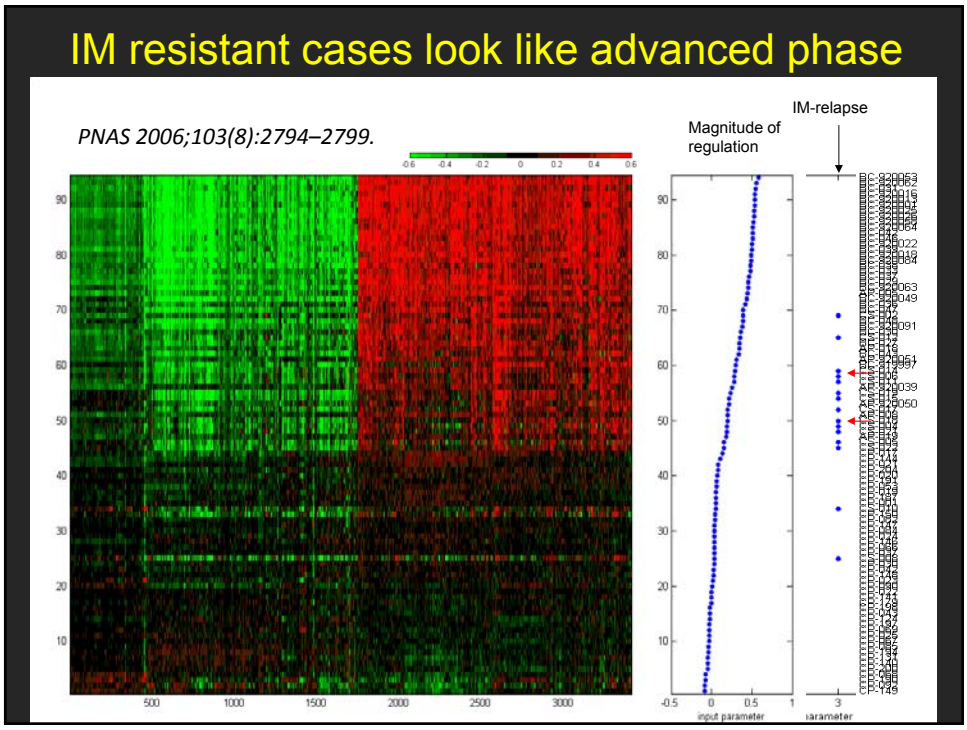

# "Targetable" pathways in CML progression

| | Keyword | Number (%)@ | Examples | p-value |
|---|---|---|---|---|
| | Ribosome | 18 (21) | ROK13A* | $9 \times 10^{-11}$ |
| → | Wnt signaling | 16 (11) | Cadherin, MDI1, Prickle 1, FZD2 | $2 \times 10^{-5}$ |
| | Nucleosome | 22 (22) | BSZ1A, HIST1H2AE* | $3 \times 10^{-11}$ |
| | Sugar metabolism | 45 (26) | RP1A, ALDOC, G6PD | $4 \times 10^{-9}$ |
| → | Myeloid differentiation | 27 (14) | CEBPA, CEBPE, FOXO3A | $3 \times 10^{-8}$ |
| → | Apoptosis | 42 (10) | GADD45G, BCL2, FOXO3A | $2 \times 10^{-7}$ |
| | DNA damage response | 36 (10) | GASDD45G, FANCG, XRN2 | $2 \times 10^{-7}$ |

New drugs and trials of advanced phase CML

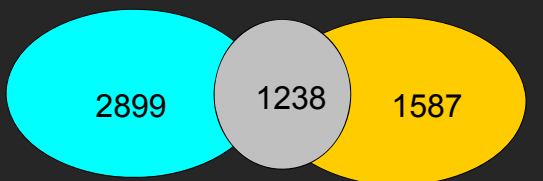
1. Wnt/SHH: B-catenein co-factor inhibitors (CBP, p300), SMO inhibitors
2. Differentiation: PRAME
3. Apoptosis: histone deacetylase inhibitors
4. Proliferation: PP2A inhibitors (SET overexpression)



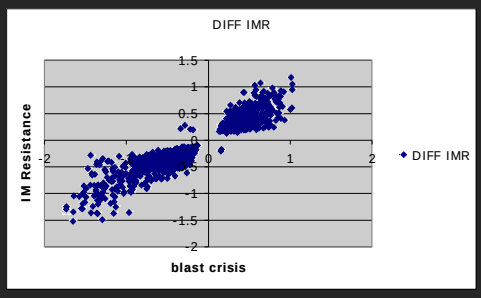



## CML progression and IM resistance are similar

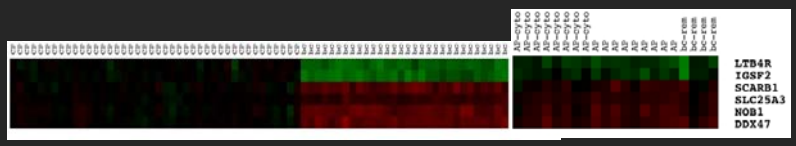
CP
AP
BC




CP (unRx)
v.
IMR CP

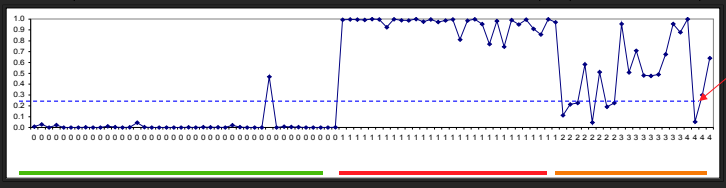



## 6 genes predict advanced phase and outcome?




Training Set- 72 samples: average over 100 CV runs

Test Set – 21 samples

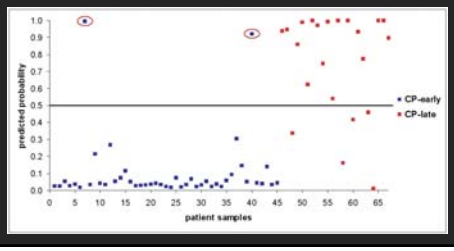


At probability score cut-off of 0.3:

(< 0.3) 1/6 died

(> or = 0.3) 7/11 died (OR =9)

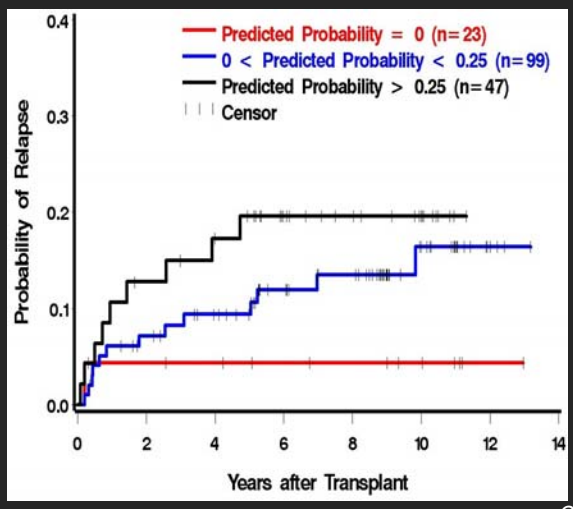
CP BC AP, BC-rem




Samples from:
Early = RIGHT trial
Late = AMN trial
2 early cases misclassified:
both relapsed
5 late cases misclassified:
3 relapsed, two responded

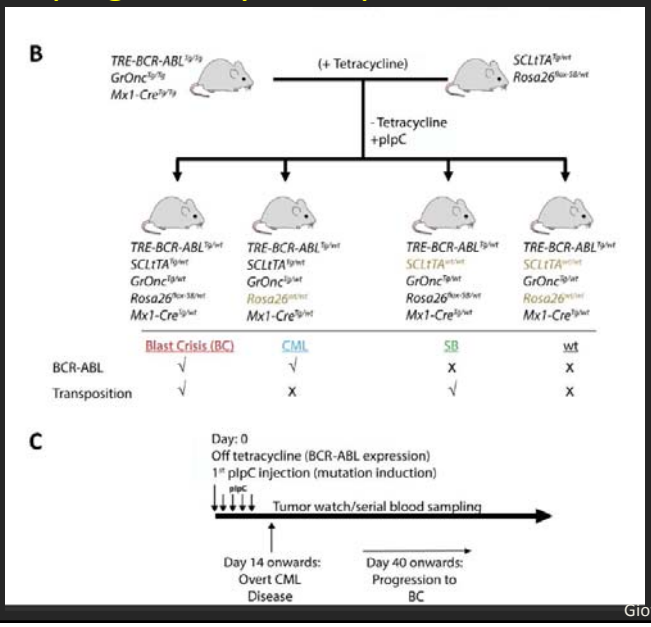
*Oehler, Blood 2009*

## Super 6 predicts outcome in CP transplants




*Oehler, Blood 2009*

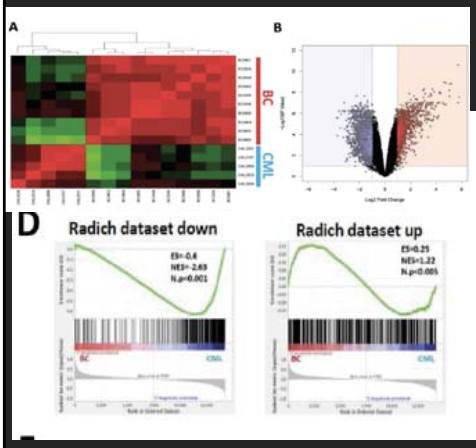
## Mouse model of CML: Induction of BCR-ABL and "Sleeping Beauty" recapitulates human CML BC



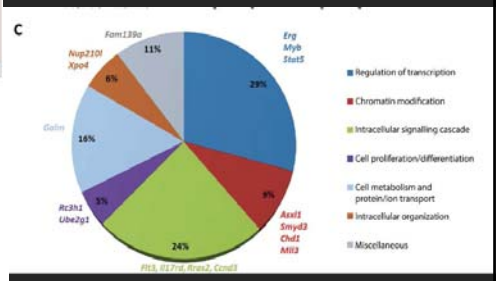

Giotopoulos et al, JEM 2015

# A murine model that mimics human progression

**Gene expression CP->BC**

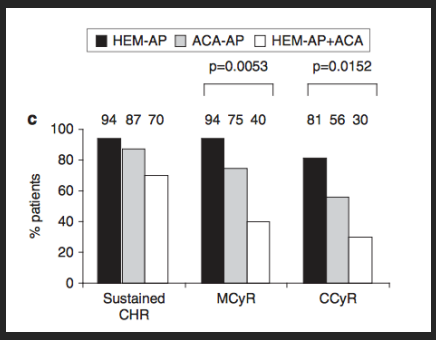


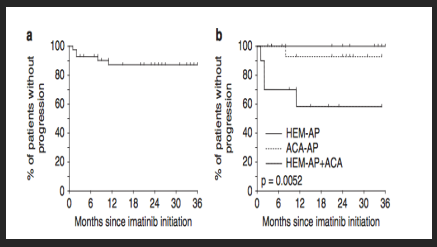

**Pathways CP->BC**




Giotopoulos et al, JEM 2015

# Newly diagnosed AP do *surprisingly* well on TKIs

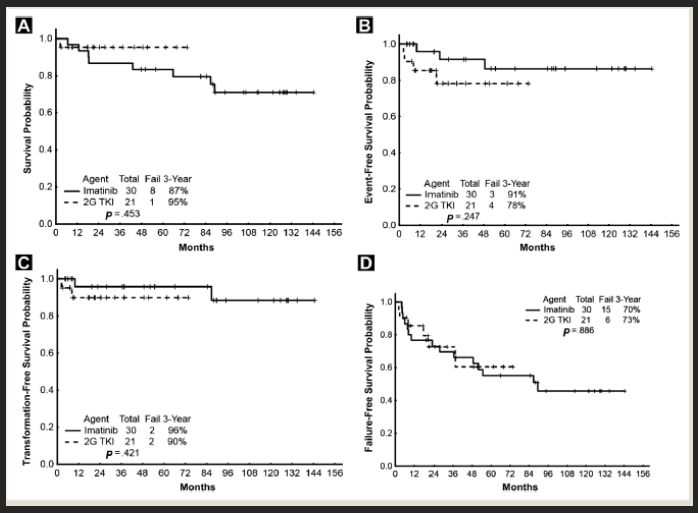



N= 42 new AP cases
- 16 heme AP (15-30% blasts)
- 16 new cyto (AC)
- 10 both

Rea et al Leukemia, 2012

## *Newly diagnosed* AP CML do well with TKIs




Ohanian, et al. Clin Lymphoma, Myeloma, and Leukemia, 2014

## Treatment of BC in the 80s and 90s

- Acute leukemia type induction therapies
- Various combinations of
  5-azacytidine, etoposide, mitoxantrone,
  carboplatin, ara-C, fludarabine, decitabine etc.
- No benefit, ↑ toxicity
- Return to CP ~9%
- No cures in absence of SCT

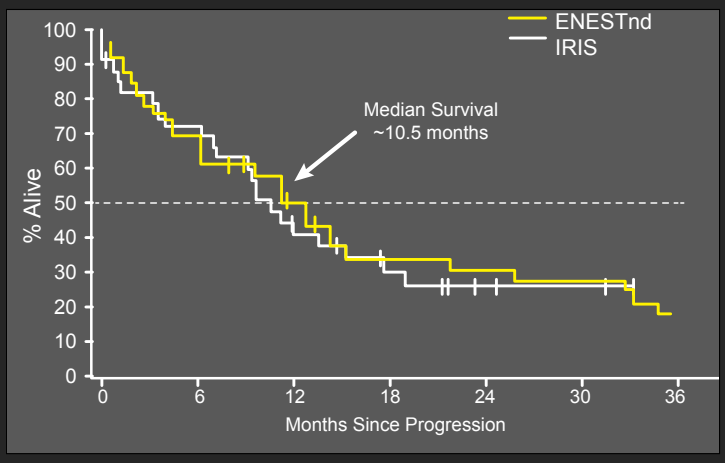
Hehlmann, CML and IFN, Springer 1988; Sacchi et al., Cancer 1999; 86: 2632 – 2641;
Kantarjian et al, Cancer 1988; 62: 672 – 676; Jacoboni et al., JCO 1986; 4: 1079 – 1088.

## Treatment of BC: resistance is apparently not so futile

| | Response | Med. Surv. |
|---|---|---|
| • Chemotherapy | 30-50% | 6 m. |
| • AML like | | |
| • ALL like | | |
| • Others (Flag-IDA, MEA) | | |
| • TKI | 40-50% | 6 m. |
| • Imatinib | | |
| • Second generation (Dasatinib) | | |
| • Chemo and TKI | ~50% | 6 m. |
| • IM, Ara-c, IDA | | |
| • IM, MEA | | |

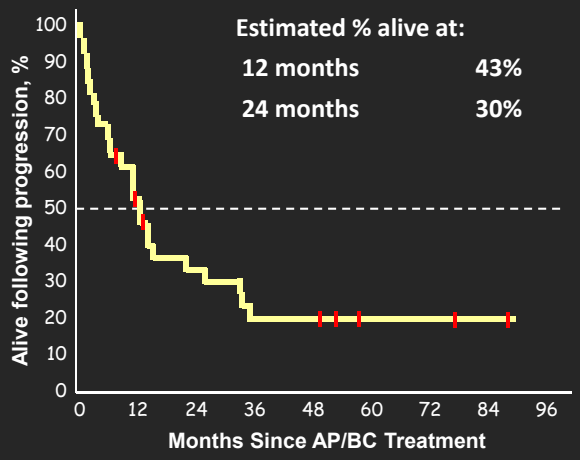
## OS After Progression to AP/BC in the ENESTnd and IRIS Trials

*Progression during TKI therapy is not good*




Larson RA, et al. *Leukemia*. 2012;26(10):2197-2203.

# Survival of BC on Imatinib (IRIS)




- At 12 months, 57% of patients who progressed on imatinib died

IRIS data on file.

# Imatinib in BC

*(5 studies, 484 patients, 50 with Lymphoid BC)*

| | |
|---|---|
| • HR | 50% – 70%<br>(70% with LBC) |
| • CR<br>(all responses) | 12% – 17% |
| • Survival at 1 year | 22% – 36% |
| • Median survival | 6.5 – 10 months |

Druker et al., NEJM 2001; Sawyers et al., Blood 2002; Kantarjian et al., Blood 2002; Sureda et al., Haematologica 2003; Palandri et al., Haematologica 2008

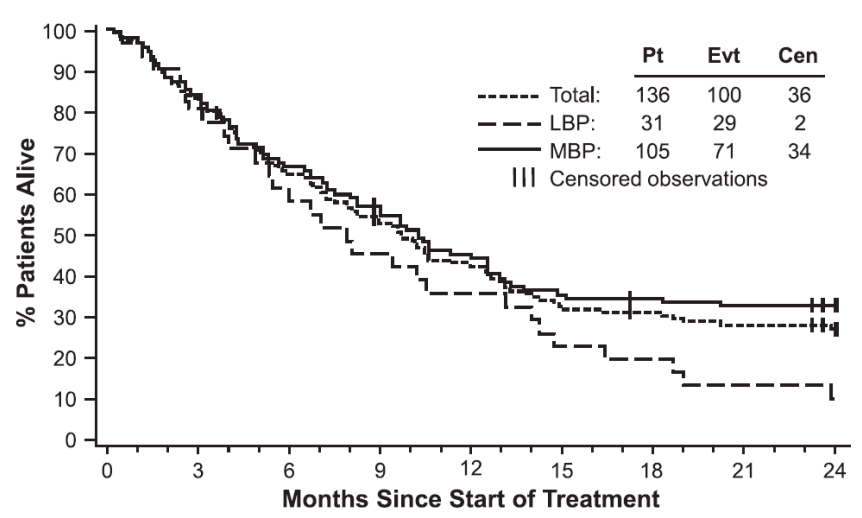
## How can you treat AP? Nilotinib in AP-CML

| Response | N (%) |
|---|---|
| Hematologic response | 38 (59) |
| CHR | 15 (23) |
| NEL | 8 (13) |
| RTC | 15 (23) |
| Cytogenetic | |
| Major CG response | 23 (36) |
| Complete CG response | 14 (22) |

CHR = complete hematologic response; NEL = no evidence of leukemia; RTC = return to chronic phase.

Kantarjian H et al. ASH 2006. Abstract 2169.

## Survival of myeloid and lymphoid BC with nilotinib 400 – 600 mg bid



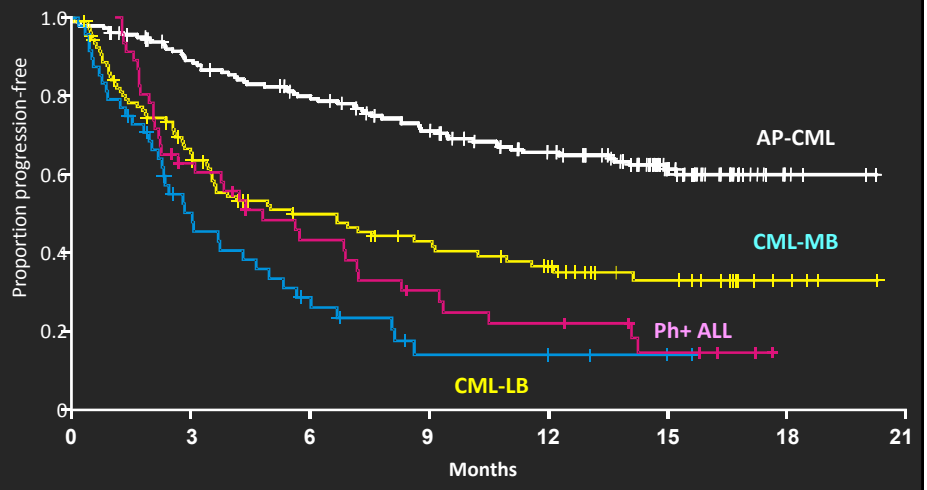

Giles et al., Leukemia 2012

# Dasatinib in Advanced Phase CML/ Ph+ ALL

| | Response Rate |
|---|---|
| Accelerated Phase CML[1] | |
| Major Hematologic Response (CHR + NEL) | 64% |
| Major Cytogenetic Response | 45% |
| Complete Cytogenetic Response | 32% |
| Myeloid Blast Phase CML [2] | |
| Major Hematologic Response (CHR + NEL) | 33% |
| Major Cytogenetic Response | 33% |
| Complete Cytogenetic Response | 26% |
| Lymphoid Blast Phase CML [2] | |
| Major Hematologic Response (CHR + NEL) | 35% |
| Major Cytogenetic Response | 52% |
| Complete Cytogenetic Response | 46% |
| Ph+ ALL[2] | |
| Major Hematologic Response (CHR + NEL) | 41% |
| Major Cytogenetic Response | 56% |
| Complete Cytogenetic Response | 54% |

1. Apperley JF et al. J Clin Oncol 2009; 27: 3472- 3479; 2. Cortes J et al. Leukemia 2008;22:2176-2183.

# Dasatinib in advanced CML and Ph+ ALL progression-free survival



# Dasatinib in BC

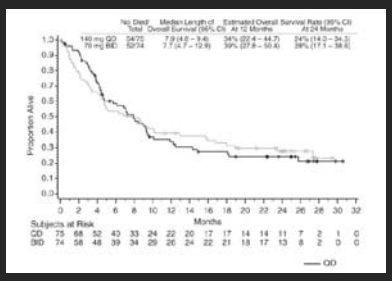
*(3 studies, 400 patients, 119 with Lymphoid BC)*

| | |
|---|---|
| • HR | 33% – 61%<br>(LBC 36% – 80%) |
| • CR (major) | 35% – 56% |
| • Survival at 1 year | 40% – 50% |
| at 2 years | 20% – 30% |
| • Median survival | 8 – 11 months |

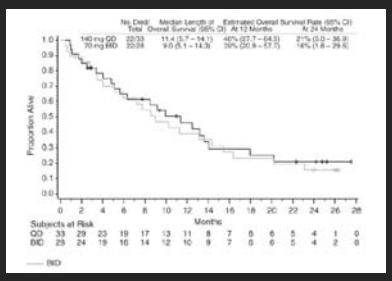
Talpaz et al., NEJM 2006; Cortes et al., Leukemia 2008; Gambacorti et al., ASH 2007; Saglio et al., Cancer 2010; 116: 3852 – 3861

# Survival of myeloid and lymphoid BC with dasatinib 140 mg qd vs. 70 mg bid

**A. Myeloid**



**B. Lymphoid**



Saglio et al., Cancer 2010; 116: 3852 – 3861

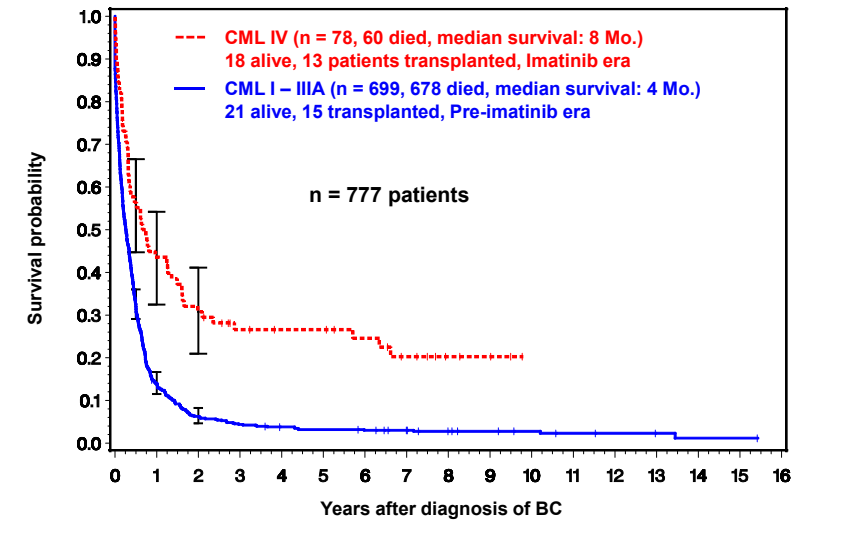
# Treatment of BC by BCR-ABL TKI

| Drug | Reference | Patients | CR | Survival | |
|---|---|---|---|---|---|
| | | | MBC / LBC | 12 months | Median, months |
| **Imatinib** | | | | | |
| 300 – 600 mg | Druker et al., 2001 | 58 (20 LBC) | 12% | NA | NA |
| 400 – 600 mg | Sawyers et al., 2002 | 229 (MBC only) | 16% | 30% | 6.9 |
| 300 – 1000 mg | Kantarjian et al., 2002 | 75 (10 LBC) | 16% | 22% | 6.5 |
| 600 mg | Sureda et al., 2003 | 30 | 13% | 36% | 10 |
| 600 mg | Palandri et al., 2008 | 92 (20 LBC) | 17% | 29% | 7 |
| **Dasatinib** | | | | | |
| 50 – 100 mg bid | Talpaz et al., 2006 | 33 (10 LBC) | 52% / 90% | ~22% [a] | ~6 |
| 70 – 100 mg bid | Cortes et al., 2008 | 157 (48 LBC) | 35% / 56% [b] | 49% / 30% | 11.8 (5.3) |
| 70 bid vs. 140 mg qd | Saglio et al., 2010 | 210 (61 LBC) | 25 – 28% / 40 – 50% | 34 – 39% / 39 – 46% | 8 (10) |
| **Nilotinib** | | | | | |
| up to 1200 mg | Kantarjian et al., 2006 | 33 (9 LBC) | 18% | NA | NA |
| 400 – 600 mg bid | Giles et al., 2012 | 136 (31 LBC) | 40% | 42% | 10 |

LBC: lymphoid blast crisis; MBC: myeloid blast crisis; HR: hematologic remission, includes complete HR, return to CP and no evidence of leukemia; CR: cytogenetic response, includes complete, partial, minimal and minor response when available; NA: not available; TKI: tyrosine kinase inhibitors
[a] at 18 months; [b] only complete and major cytogenetic response listed. Updated from Hehlmann and Saußele., Haematologica. 2008; 93 (12): 1765 –1769.

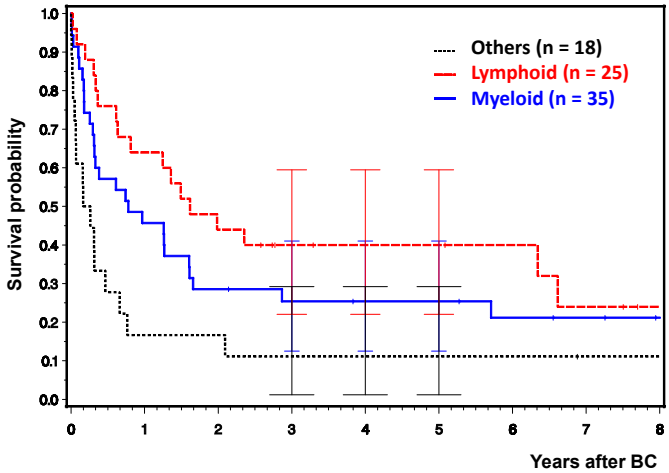
# Survival after blast crisis 1983 – 2013

## *Still bad, but better*




German CML Study group, unpublished

## Comparison myeloid vs. lymphoid BC
*German CML IV, n= 78*




Lymphoid BC [median survival: 1.62 (0.01 – 9.8+)]
Myeloid BC [median survival: 0.74 (0.02 – 9.6+)]

## TKI in blast crisis

| TKI | Studies / Patients | Median Survival |
|---|---|---|
| Imatinib[1–5] | 5 / 484 pts, 50 with LBC | 6.5 – 10 months |
| Dasatinib[6–8] | 3 / 400 pts, 119 with LBC | 8 – 11 months |
| Nilotinib[9–10] | 2 / 169 pts, 40 with LBC | 10 (LBC 7.9) months |

[1] Druker et al., 2001; [2] Sawyers et al., 2002; [3] Kantarjian et al., 2002; [4] Sureda et al., 2003; [5] Palandri et al., 2008; [6] Talpaz et al., 2005; [7] Cortes et al., 2008; [8] Saglio et al., 2010; [9] Kantarjian et al., 2006; [10] Giles et al., 2012.

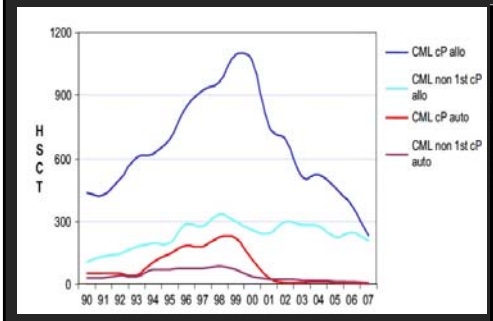
# Investigational approaches

| Mode of action | Agent(s) |
|---|---|
| PP2A activation | Fingolimod (FTY720) |
| | SET antagonist OP449 |
| | CIP2A inhibitor |
| Self renewal of LSC | BCL6 + TK inhibitors |
| | HIF1α inhibitor |
| | IL1 RAP antibodies |
| | Smoothened inhibitors (in combination with TKI) |
| | Jak2 inhibitor (in combination with TKI) |
| Activation of apoptosis | BCL2-inhibitor ABT-737 |
| | Triptolide |
| | Dual-kinase inhibitor ON044580 |
| | MEK inhibitor PD184352 + farnesyltransferase inhibitor BMS-214662 |
| Others | Peg-IFN, HDAC inhibitor, Hsp90 inhibitors |

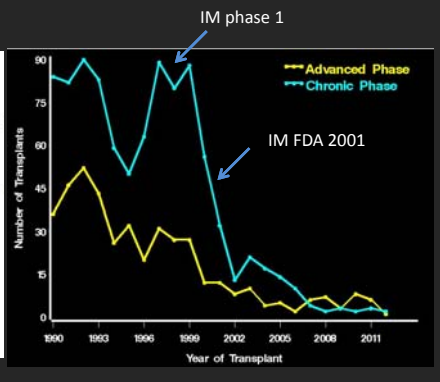
TKI: tyrosine kinase inhibitor; PP2A: protein phosphatase 2A; LSC: leukemia stem cells; MEK: mitogen-activated protein kinase; HIF: hypoxia; HDAC: histone deacetylase; Hsp: heat shock protein.

# The demise of allogeneic HCT in CML

EBMTR

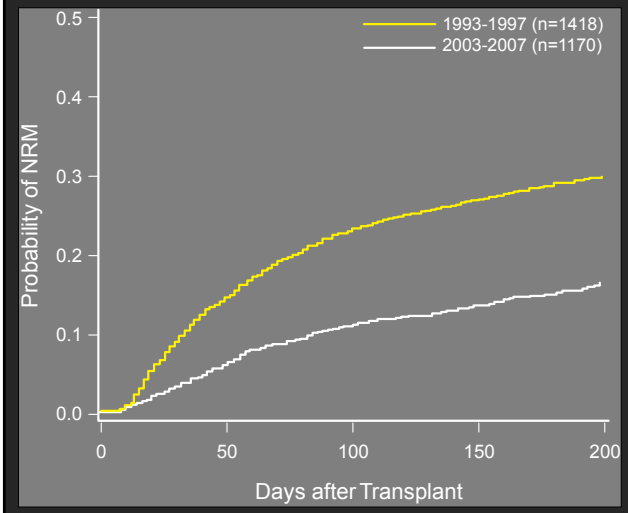



FHCRC, CP and AP/BP



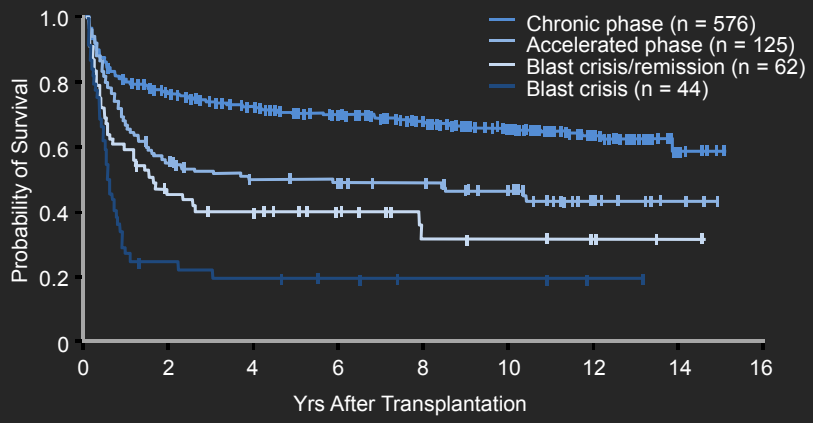
# Allogeneic HCT is getting better

## Non-relapse mortality




1. Pharmacologic (Bu,Cy,Flu)
2. Treatment of GVHD (beclo+↓pred)
3. Ursodiol
4. Hardwired management of CNI dosing, CMV rx
5. Fungal treatment

# CML Survival After Allogeneic HCT (FHCRC)

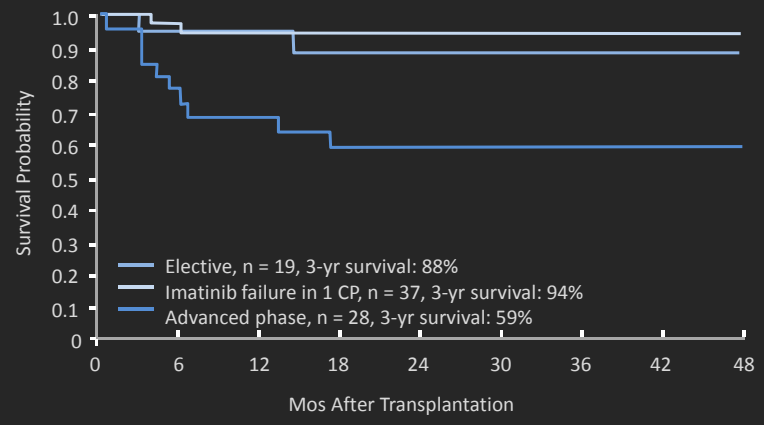



*Includes both matched related and unrelated donors.

Patients receiving allografts at the Fred Hutchinson Cancer Research Center from 1995 to the present.
Figure is courtesy of Dr. Ted Gooley.

# Allogeneic HCT for CML in the Imatinib Era

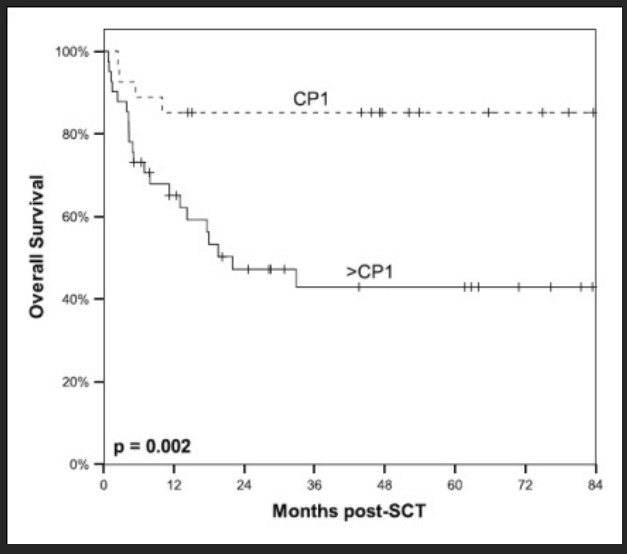
## *CML Study IV (n = 84)*




Saussele S, et al. *Blood.* 2010;115:1880-1885.

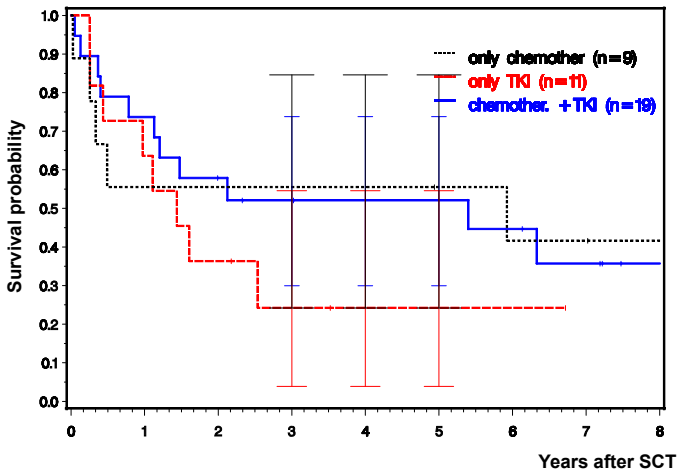
# Allogeneic HCT as 2nd line therapy in CML BC

## *Hamburg (n = 68)*




Oyekunle et al., Ann Hematol (2013) 92: 487 – 496.

# Survival after transplantation




# HCT in BC

- Successful in only a minority of patients,
- Mostly after return to CP
- 10 year survival ~16 – 25%, but
- Best chance of a cure in BC
- Most long term BC survivors have received transplant in 2nd CP

Saußele et al., Blood 2010; 115: 1880 – 1885

## What's in a name? STI571

- Then: "Stop transplantation now!"
- Now: "Some transplants indicated."

## Success of TKI might increase BMT

*(assumption: 1 or 10% AP/BC, resistance, intolerance)*

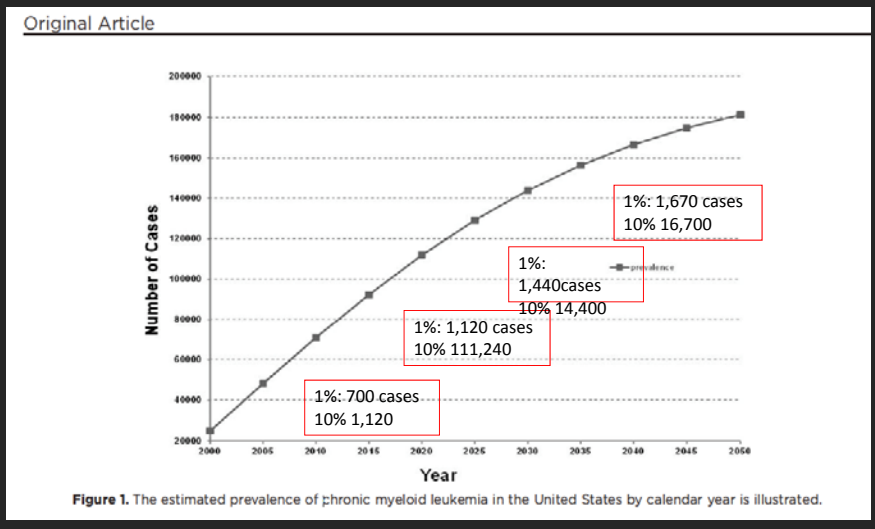
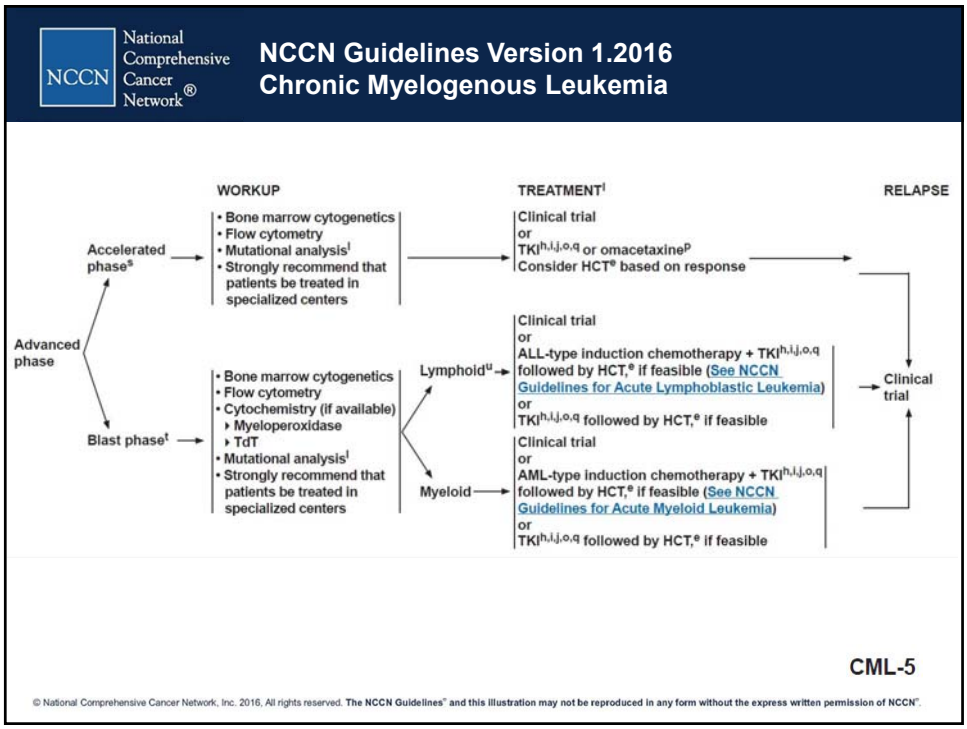



**Figure 1.** The estimated prevalence of chronic myeloid leukemia in the United States by calendar year is illustrated.

Kantarjian, Cancer 2012

# NCCN and ELN recommendations for allogeneic HCT in CML

- Baseline: Never
- Second-line: "Always" in blast phase irrespective of the response to TKIs
  "Always" in accelerated phase, if the response to TKI is less than optimal
- Third-line: "Always" if the response to second-line TKI is less than optimal
- The value and the meaning of "Always" depend on transplant risk (age, comorbidities, performance status, donor, etc.).



## Summary-progression in the TKI era

- Incidence of BC greatly decreased with TKI!
- Survival in BC not clearly improved with TKI since 1970s
- No recommendation of a specific drug treatment possible
- Transplantation carries the best long term prognosis in BC
- Allogeneic HCT recommended in BC by NCCN and ELN