LMC, perché rinviare il trapianto

Gianantonio Rosti, MD
Scientific Direction
IRCCS/SIRHHC Scientific Institute for Research, Hospitalization and Health Care
«Dino Amadori» – Meldola (FC), Italy

Leukemia www.nature.com/leu

PERSPECTIVE OPEN

Check for updates

Questions concerning tyrosine kinase-inhibitor therapy and transplants in chronic phase chronic myeloid leukaemia

Michele Baccarani[1,2,7], Francesca Bonifazi[1✉], Simona Soverini[2], Fausto Castagnetti[1,2], Gabriele Gugliotta[1], Wael Saber[3,4], Noel Estrada-Merly[3], Gianantonio Rosti[5] and Robert Peter Gale[6]

«We suggest transplants should be more often considered in the metric when counseling people with CML»

«The question of who should receive a transplant in CP is complex and controversial.»

Leukemia (2022) 36:1227–1236; https://doi.org/10.1038/s41375-022-01522-3

G. Rosti

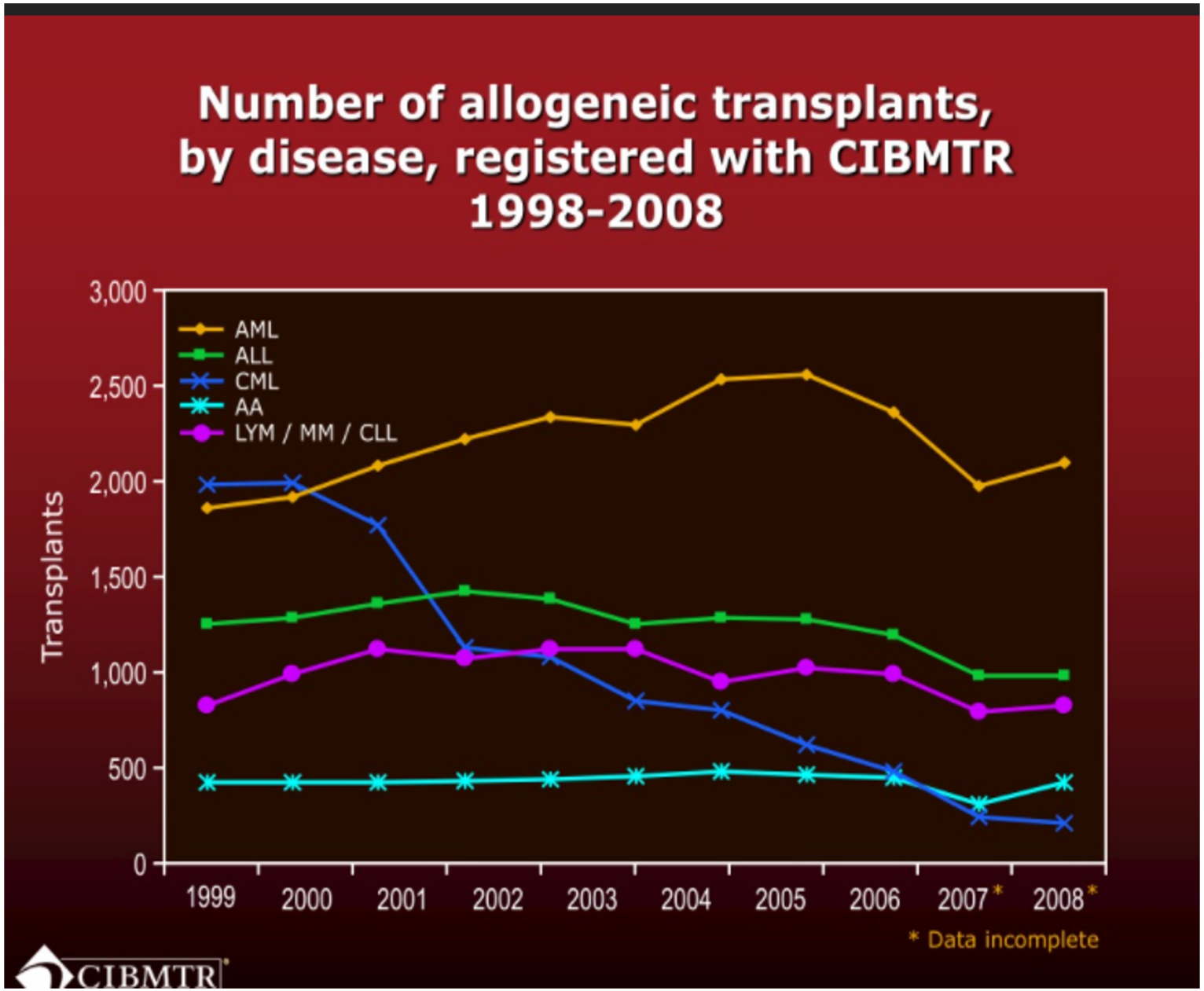
Marrow Transplantation for the Treatment of Chronic Myelogenous Leukemia, ED Thomas et al , Annals of Internal Medicine 1986; Vol 104, Number 2

OS & Disease phase (50% OS in CP) and age (increased TRM in older)

CML main indication for AlloSCT until ….

1999 STI571 Signal Transductor Inhibitor

STI571 Stop Transplant Immediately


Number of allogeneic transplants, by disease, registered with CIBMTR 1998-2008
Transplants
3,000
2,500
2,000
1,500
1,000
500
0
AML
ALL
CML
AA
LYM / MM / CLL
1999
2000
2001
2002
2003
2004
2005
2006
2007*
2008*
* Data incomplete
CIBMTR

2024 STI571 Some Transplants Indicated

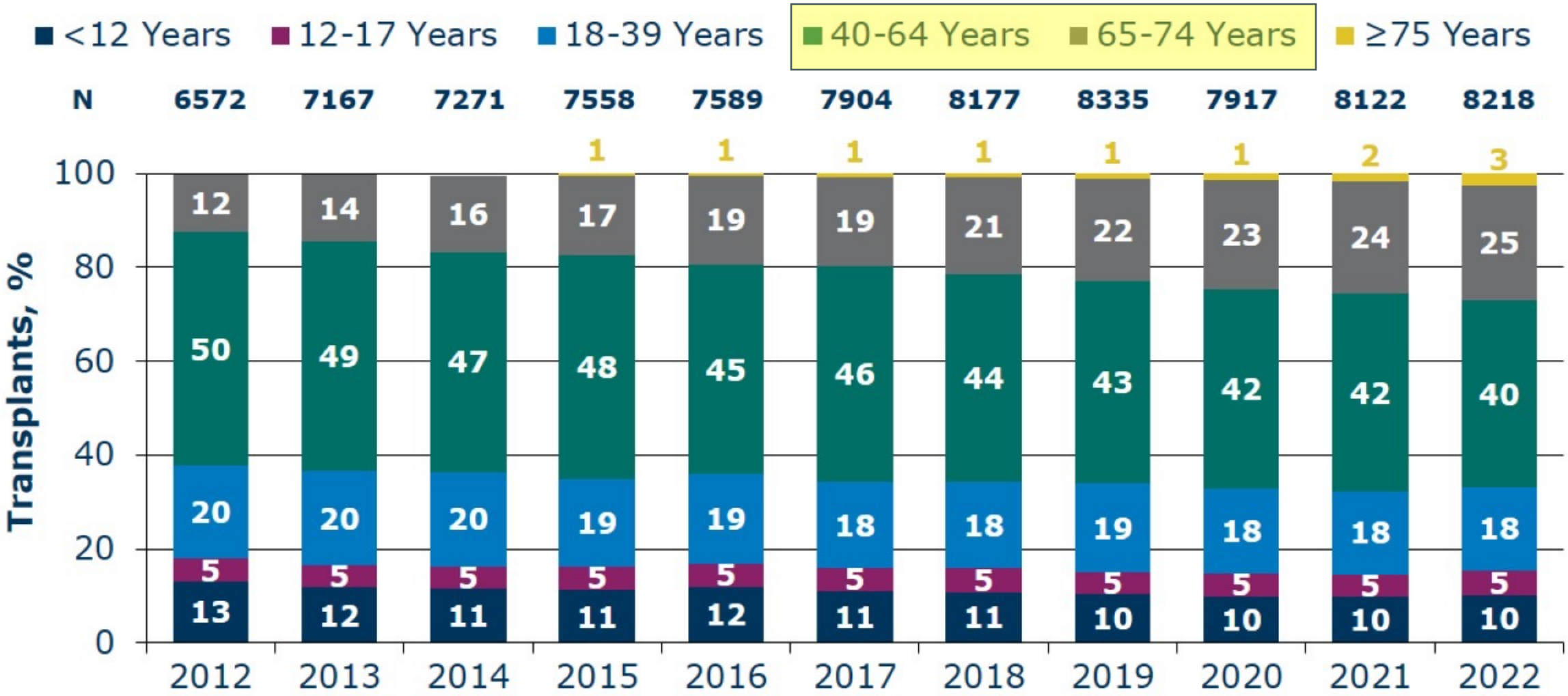
*« Today, we are on the opposite side of the spectrum, and physicians and **patients often wait too long to transplant…** hoping that the "N +1"h TKI will magically eliminate resistance and/or intolerance where other TKIs have persistently failed.*

*However, **hope is not a plan**.*

Thus, it is reasonable to at least begin preparing for the possibility of transplant «

J. Radich, Am J Hematol 2023; 98:4-5

Recipient Age of Allogeneic HCTs in the US



CIBMTR
A RESEARCH COLLABORATION BETWEEN THE MEDICAL COLLEGE OF WISCONSIN AND NMDP

G. Rosti

CML 1st CP, allo-SCT outcomes

Study[1]	Registry	interval	N	Median age	Conditioning	Donor	1-year survival	5-year survival	10-year survival
Millot et al.[2]	SGFMTC	1982–1998	42	14	MA	REL	87%	73%	73%
Cwynarski et al.[3]	EBMT	1985–2001	156	14	NR	REL	78%	72%	70%
Arora et al.[4]	CIBMTR	1988–2003	3514	36	MA	REL	74%	63%	60%
Arora et al.[4]	CIBMTR	1988–2003	531	37	MA	UNR	70%	55%	50%
Radich et al.[5]	Seattle	1995–2000	131	43	MA	REL	91%	NA	NA
Gratwohl et al.[6]	German Study III	1997–2004	151	38	MA	REL	90%	78%	76%
Gratwohl et al.[6]	German Study III	1997–2004	148	41	MA	UNR	97%	76%	76%
Bacher et al.[7]	German Registry	1998–2004	1084	40	MA 62%	REL 61%	67%	64%	64%
Ohashi et al.[8]	Japanese Registry	2000–2009	531	40	MA 89%	UNR 51%	87%	85%	78%
Chaudury et al.[9]	CIBMTR	2001–2010	224	24	MA	REL	90%	83%	NA
Chaudury et al.[9]	CIBMTR	2001–2010	225	24	MA	UNR	80%	68%	NA
Lee et al.[10]	Korean	2001–2012	47	32	MA 77%	UNR 43%	88%	NA	NA
Lee et al.[10]	Korean	2001–2012	50	33	MA 48%	UNR 42%	90%	NA	NA
Koenecke et al.[11]	EBMT	2002–2005	193	31	MA	REL	90%	85%	84%
Saussele et al.[12]	German Study IV	2003–2008	19	35	MA 79%	REL 53%	95%	NA	NA
Saussele et al.[12]	German Study IV	2003–2008	37	38	MA 65%	UNR 70%	95%	NA	NA

CIBMTR, Center for International Blood and Marrow Transplantation; EBMT, European Group for Marrow and Blood Transplantation; MA, myeloablative; NA, not reported; REL, related donor; SGFMTC, Société Française de Greffe de Moelle et de Thérapie Cellulaire; UNR, unrelated donor; .

1.Baccarani, M, et al. *Leukemia* 2022; 2. Millot F, et al. *Bone Marrow Transplantation* 2003;32:993-999; 3. Cwynarski K, et al. *Blood* 2003;102:1224-1231; 4. Arora M, et al. *Journal of Clinical Oncology* 2009;27:1644-1652; 5. Radich J, et al. *Blood* 2003;102:31-35; 6. Gratwohl A, et al. *Leukemia*, 2015;30:562-569; 7. Bacher U, et al. *Annals of Hematology* 2009;88:1237-1247; 8. Ohashi K, et al. *International Journal of Hematology* 2014;100:296-306; 9. Chaudhury S, et al. *Biology of Blood and Marrow Transplantation* 2016;22:1056-1064; 10. Lee S, et al. *Hematology* 2013;19:63-72; 11. Koenecke C, et al. *Bone Marrow Transplantation* 2016 51;1259-61; 12. Saussele, S, et al. *Blood* 2010;115:1880-1885.

CML 1st CP, allo-SCT outcomes

Study[1]	Registry	interval	N	Median age	Conditioning	Donor	1-year survival	5-year survival	10-year survival
Millot et al.[2]	SGFMTC	1982–1998	42	14	MA	REL	87%	73%	73%
Cwynarski et al.[3]	EBMT	1985–2001	156	14	NR	REL	78%	72%	70%
Arora et al.[4]	CIBMTR	1988–2003	3514	36	MA	REL	74%	63%	60%
Arora et al.[4]	CIBMTR	1988–2003	531	37	MA	UNR	70%	55%	50%
Radich et al.[5]	Seattle	1995–2000	131	43	MA	REL	91%	NA	NA
Gratwohl et al.[6]	German Study III	1997–2004	151	38	MA	REL	90%	78%	76%
Gratwohl et al.[6]	German Study III	1997–2004	148	41	MA	UNR	97%	76%	76%
Bacher et al.[7]	German Registry	1998–2004	1084	40	MA 62%	REL 61%	67%	64%	64%
Ohashi et al.[8]	Japanese Registry	2000–2009	531	40	MA 89%	UNR 51%	87%	85%	78%
Chaudury et al.[9]	CIBMTR	2001–2010	224	24	MA	REL	90%	83%	NA
Chaudury et al.[9]	CIBMTR	2001–2010	225	24	MA	UNR	80%	68%	NA
Lee et al.[10]	Korean	2001–2012	47	32	MA 77%	UNR 43%	88%	NA	NA
Lee et al.[10]	Korean	2001–2012	50	33	MA 48%	UNR 42%	90%	NA	NA
Koenecke et al.[11]	EBMT	2002–2005	193	31	MA	REL	90%	85%	84%
Saussele et al.[12]	German Study IV	2003–2008	19	35	MA 79%	REL 53%	95%	NA	NA
Saussele et al.[12]	German Study IV	2003–2008	37	38	MA 65%	UNR 70%	95%	NA	NA

CIBMTR, Center for International Blood and Marrow Transplantation; EBMT, European Group for Marrow and Blood Transplantation; MA, myeloablative; NA, not reported; REL, related donor; SGFMTC, Société Française de Greffe de Moelle et de Thérapie Cellulaire; UNR, unrelated donor; .

1.Baccarani, M, et al. *Leukemia* 2022; 2. Millot F, et al. *Bone Marrow Transplantation* 2003;32:993-999; 3. Cwynarski K, et al. *Blood* 2003;102:1224-1231; 4. Arora M, et al. *Journal of Clinical Oncology* 2009;27:1644-1652; 5. Radich J, et al. *Blood* 2003;102:31-35; 6. Gratwohl A, et al. *Leukemia*, 2015;30:562-569; 7. Bacher U, et al. *Annals of Hematology* 2009;88:1237-1247; 8. Ohashi K, et al. *International Journal of Hematology* 2014;100:296-306; 9. Chaudhury S, et al. *Biology of Blood and Marrow Transplantation* 2016;22:1056-1064; 10. Lee S, et al. *Hematology* 2013;19:63-72; 11. Koenecke C, et al. *Bone Marrow Transplantation* 2016 51;1259-61; 12. Saussele, S, et al. *Blood* 2010;115:1880-1885.

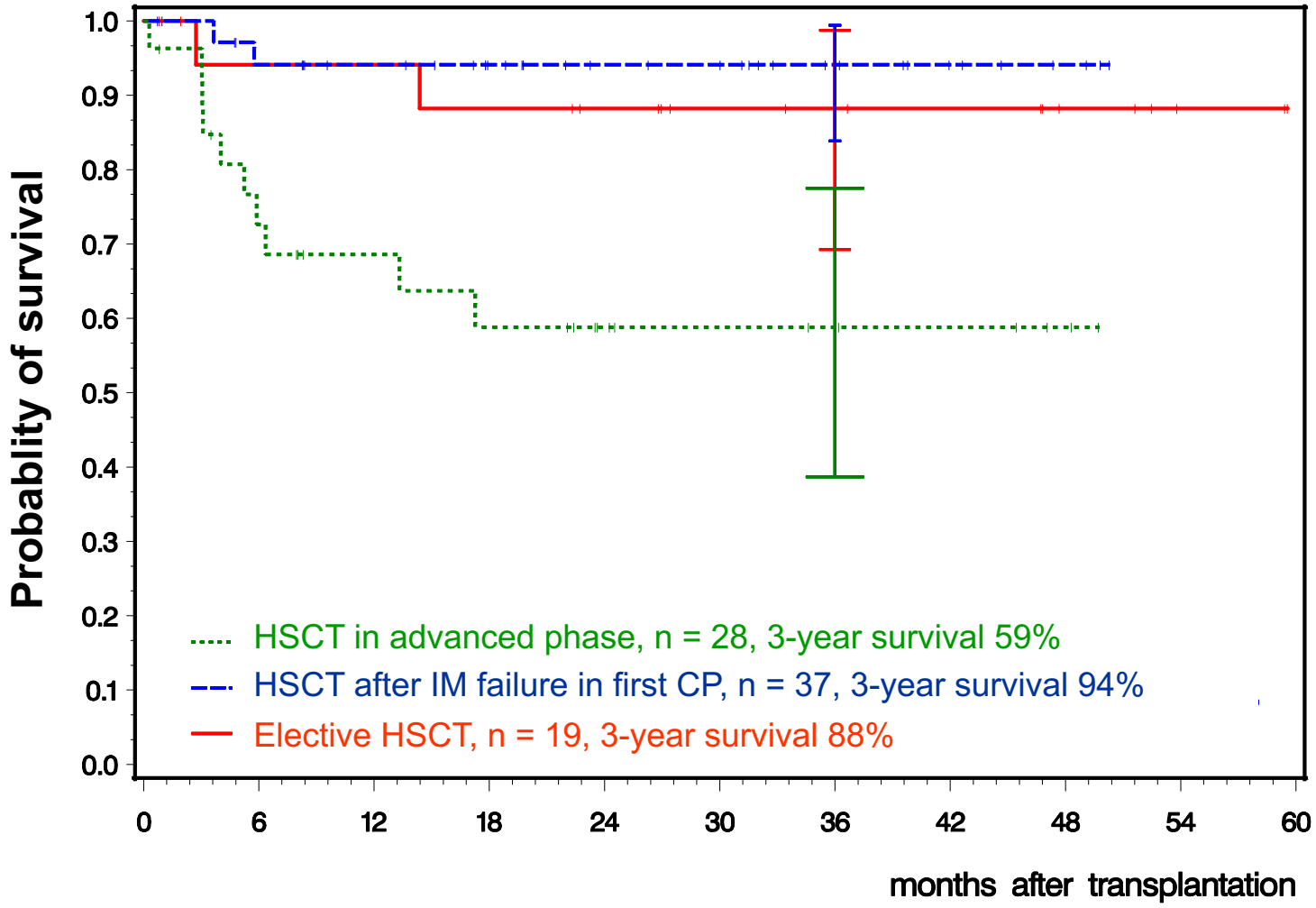
ALLOGENEIC STEM CELL TRANSPLANTATION, AGE, AND TRANSPLANT RELATED MORTALITY (TRM)

3033 HLA-MATCHED PATIENTS

AGE	RELATIVE RISK OF TRM	P-value
< 20 y	1.00	
20-39 y	1.21	0.29
40-49 y	1.48	0.04
50-59 y	1.75	0.004
≥ 60 y	1.84	0.005

Sorror ML et al, JCO 2014;32:3249-3256

CML study IV: outcome of alloSCT patients (n = 84)

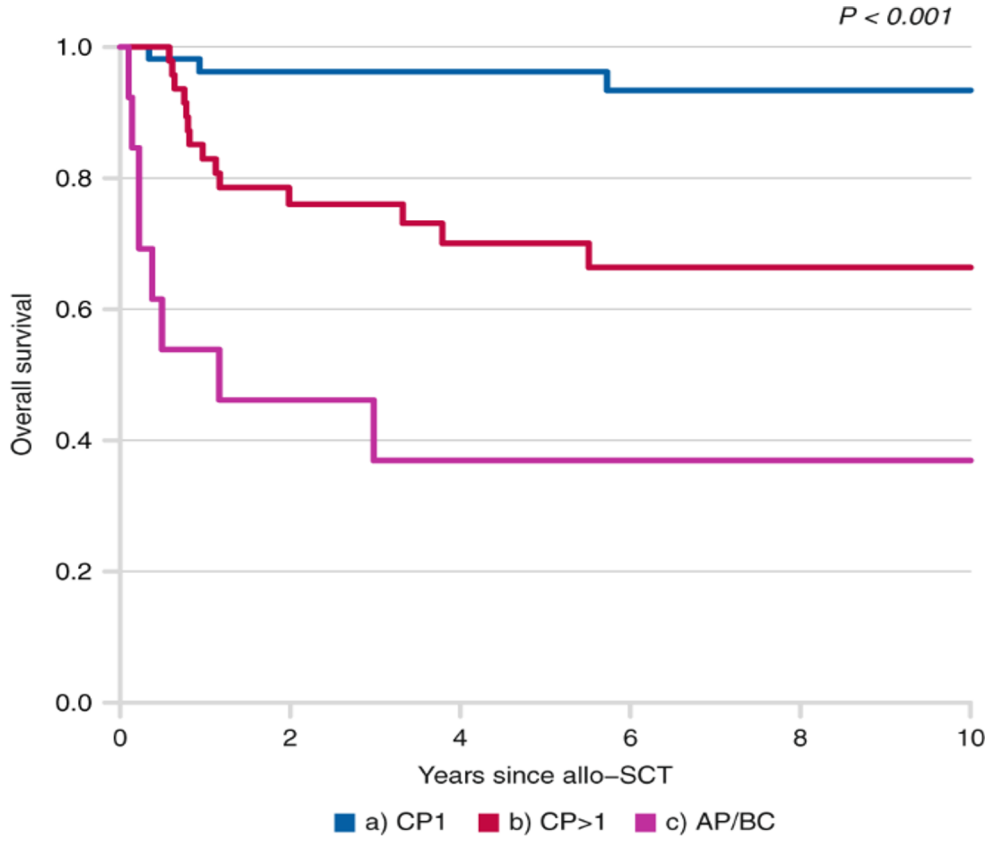


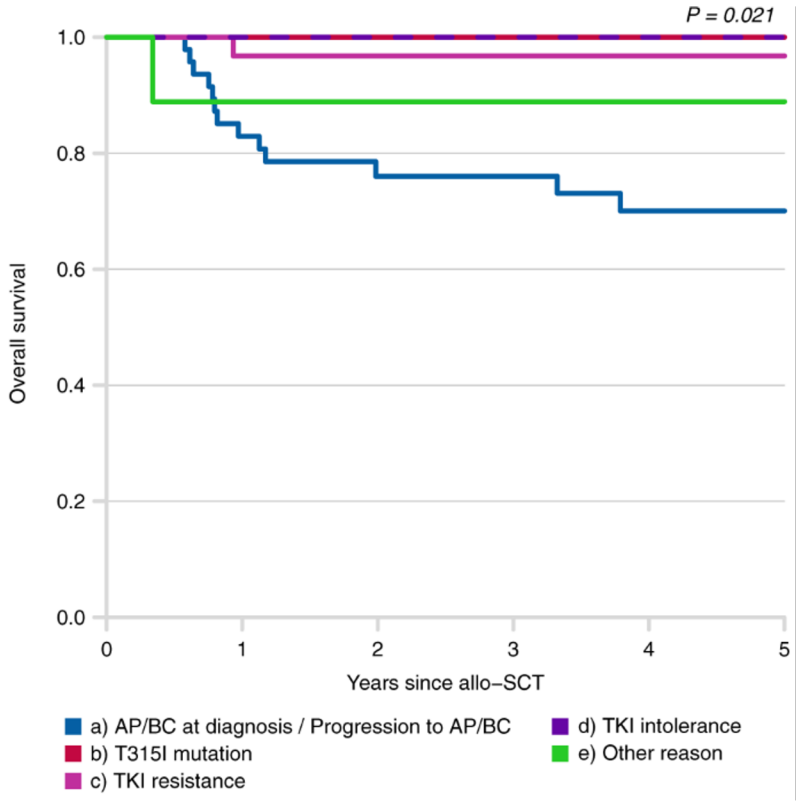
Age at diagnosis
37 (16-56)

Saussele et al., Blood 2010

Population-based data from the Swedish cancer registry

CP1 n. 56, age 43 (21–65)

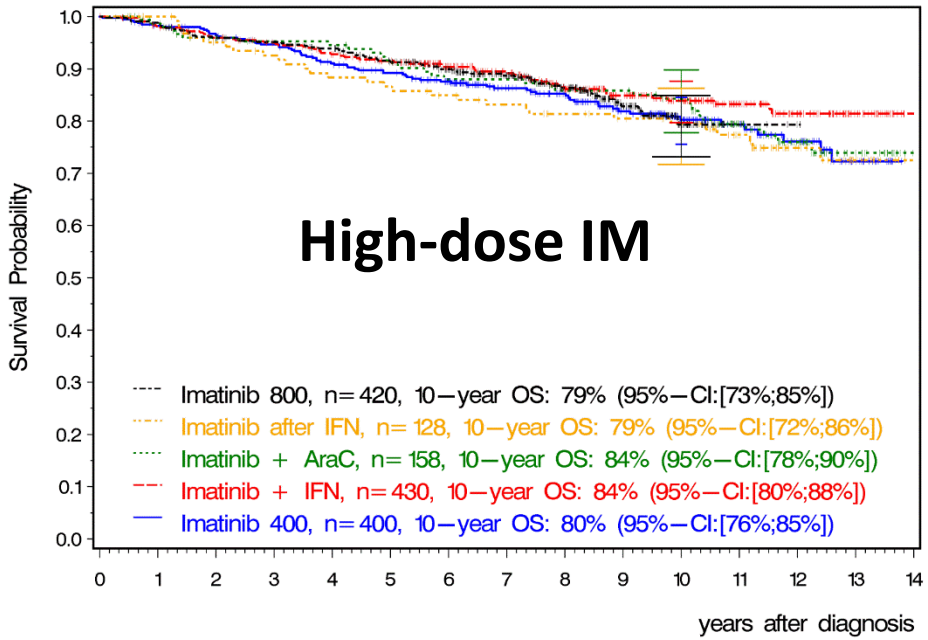


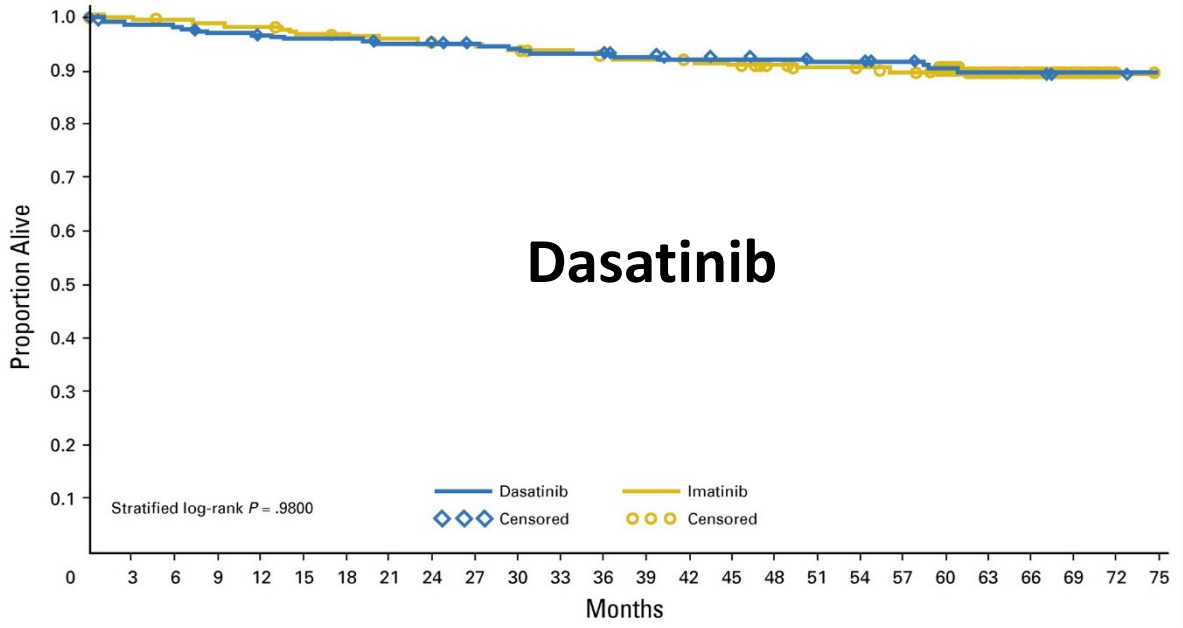


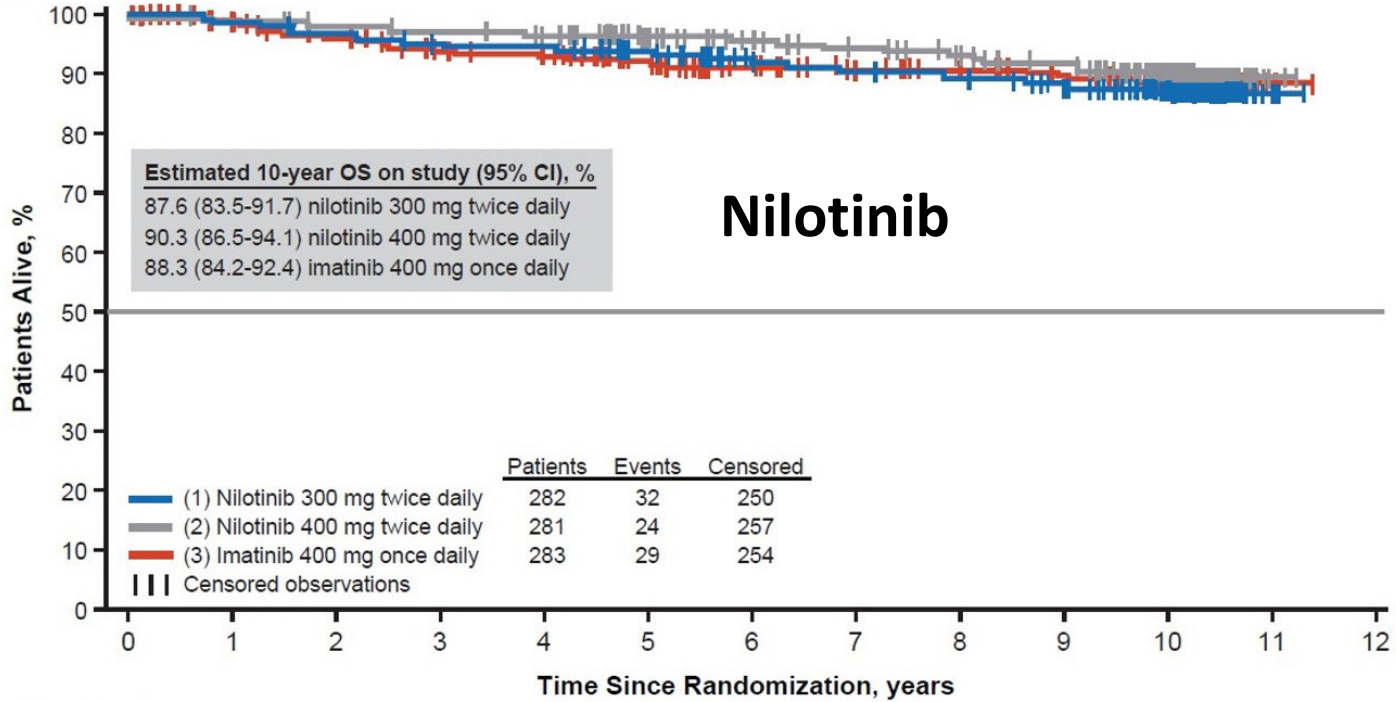
ASCT, allogeneic stem cell transplantation; AP, accelerated phase; BC, blast crisis; CP, chronic phase, TKI; tyrosine kinase inhibitor.

1. Lübking A, et al. *Bone Marrow Transplantation* 2019;54:1764-74.

OS with high-dose IM, dasatinib and nilotinib vs IM 400mg





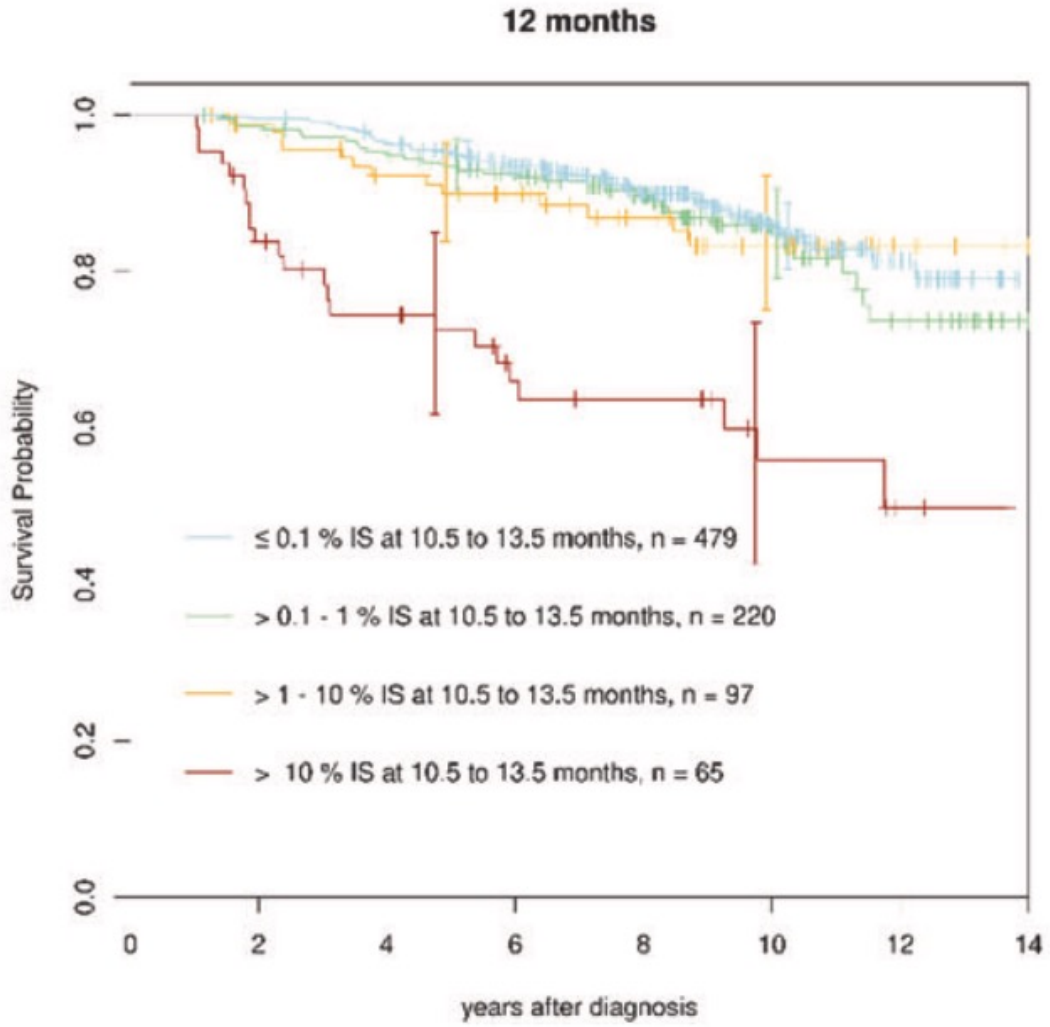


Hehlmann et al, Leukemia 2017
Cortes et al, JCO 2016
Kantarjian et al, Leukemia 2021

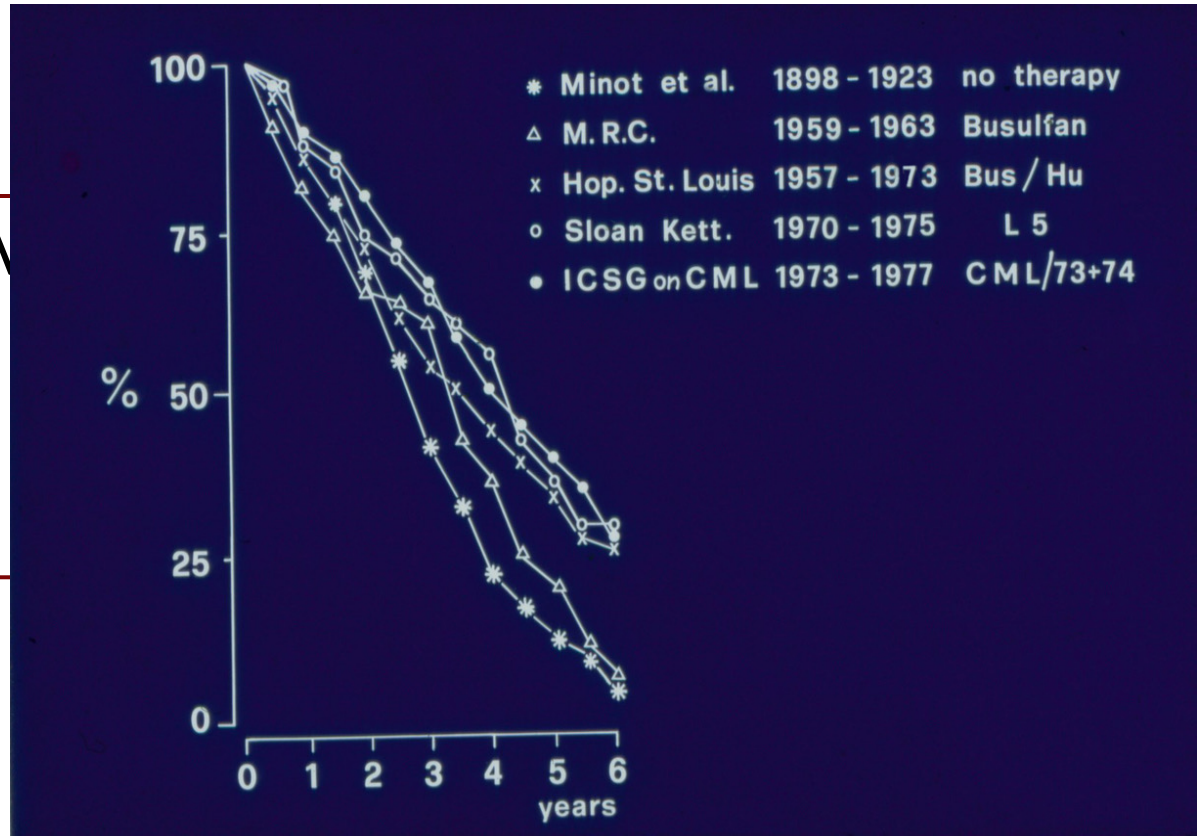
G. Rosti

Spostiamo l’attenzione sui pazienti che falliscono la terapia con TKIs

Survival with chronic myeloid leukaemia after failing milestones



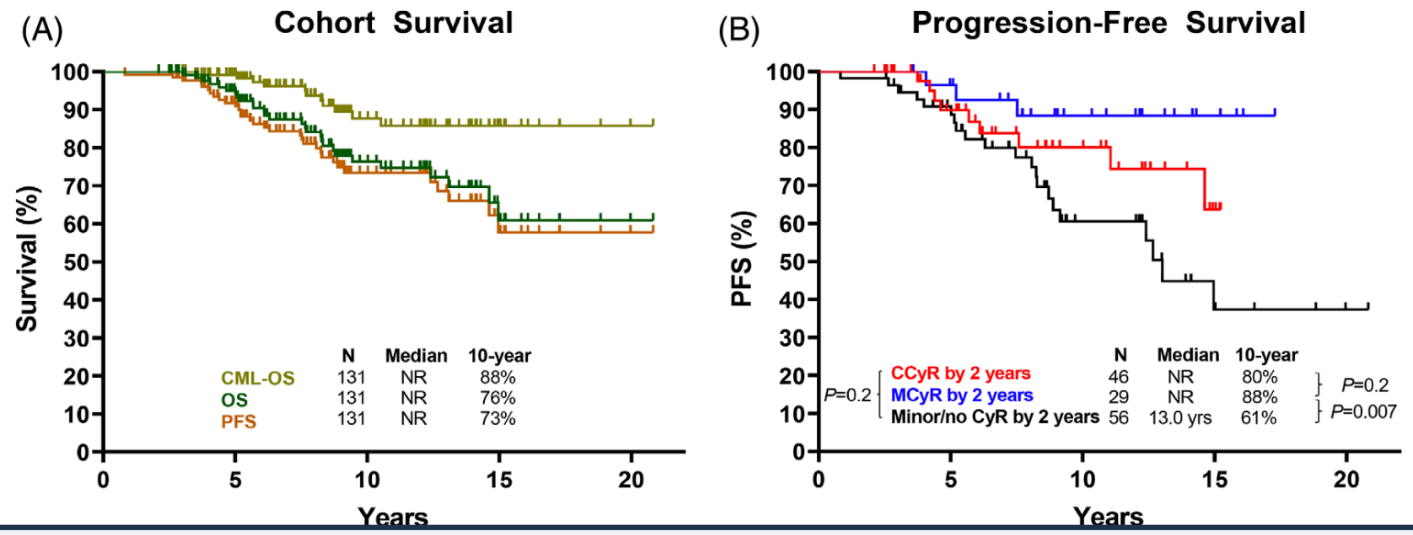
CM



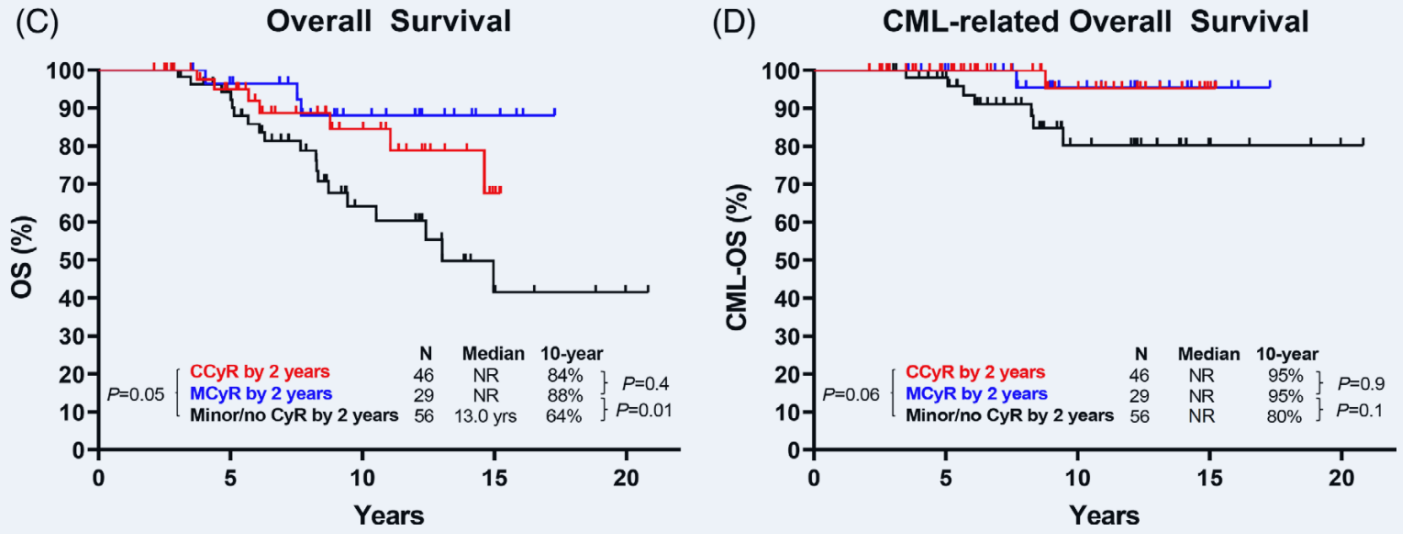
Lauseker, M *et al. Leukemia* **37**, 2231–2236 (2023).

G. Rosti

Chronic myeloid leukemia without major molecular response after 2 years of treatment with tyrosine kinase inhibitor



131 CP patients

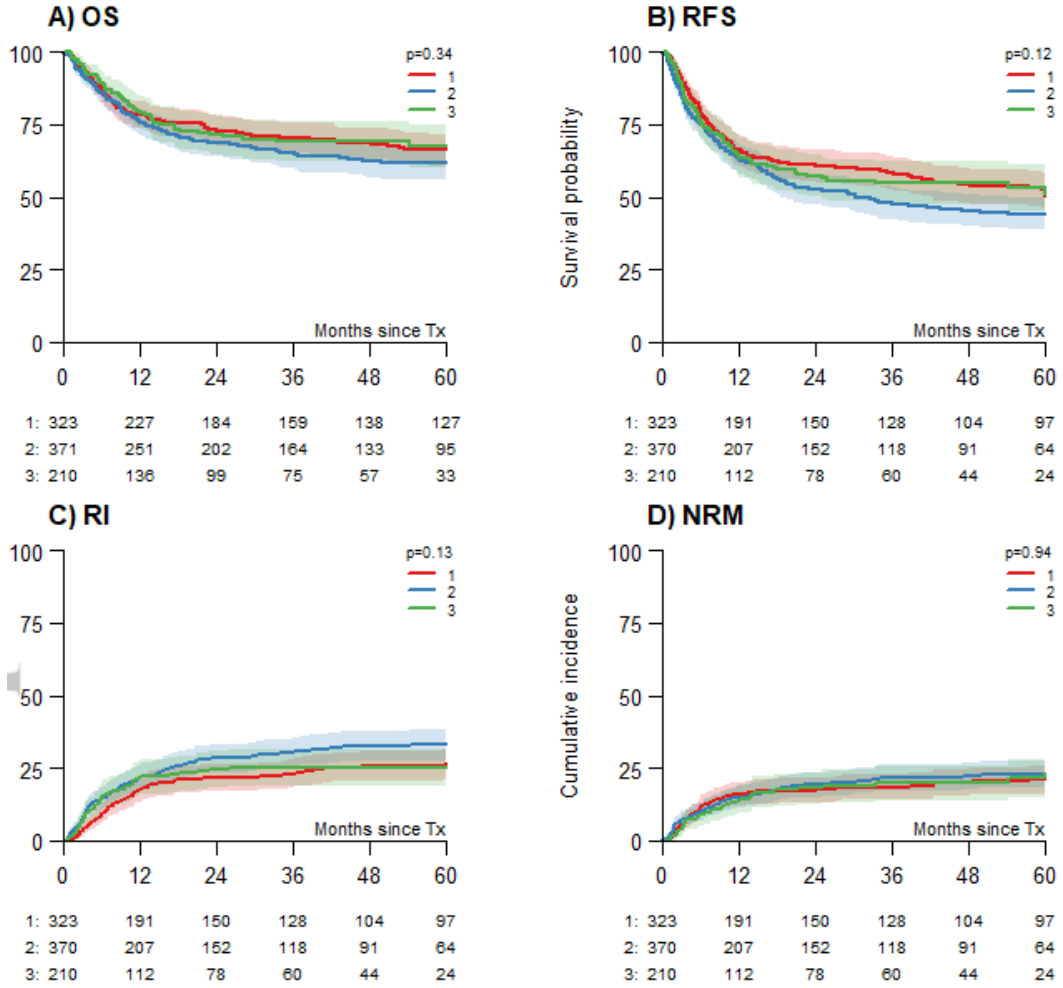


> 60 yrs

A Bidikian et al Am J Hematol. 2023;98:639–644.

G. Rosti

No impact of the use of multiple TKIs prior to SCT



n. 904, alloSCT 2006-2016

Y Chalandon et al, AJH 2023;98:112–121

Transplantation in CML in the TKI era: who, when, and how ?

Accelerated phase (AP)

ELN 2020[25]

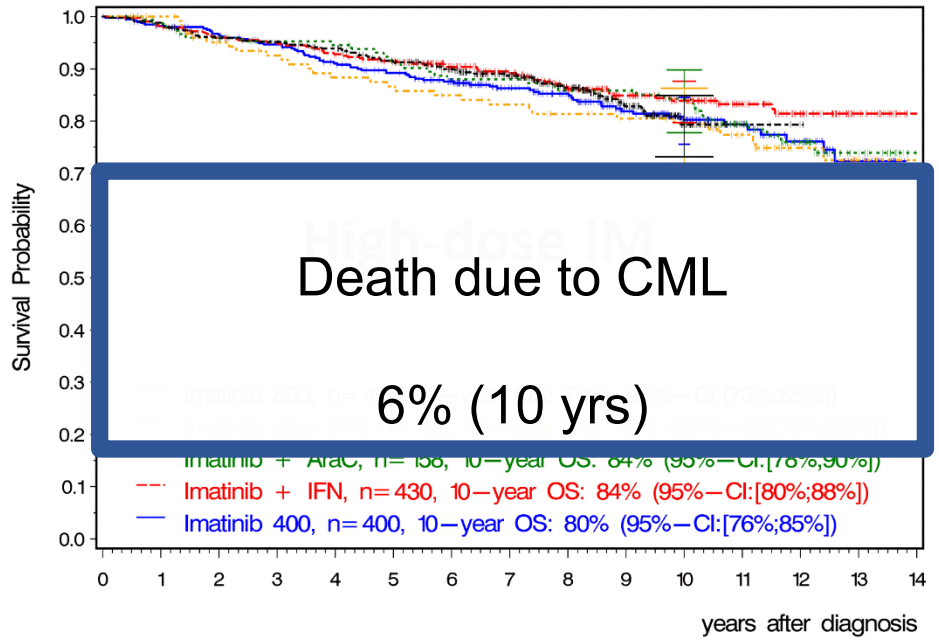
- A patient **presenting** in AP should be treated as a high-risk patient, becoming eligible for HSCT if the response is not optimal
- A patient **progressing** to AP during treatment should immediately be considered for HSCT

NCCN guidelines[26]

- Disease progression to AP while on TKI therapy should be considered for HSCT
- Patients who **present** with AP at diagnosis should be treated with a TKI, followed by evaluation for allogeneic HSCT based on response to therapy after 3, 6, or 12 months

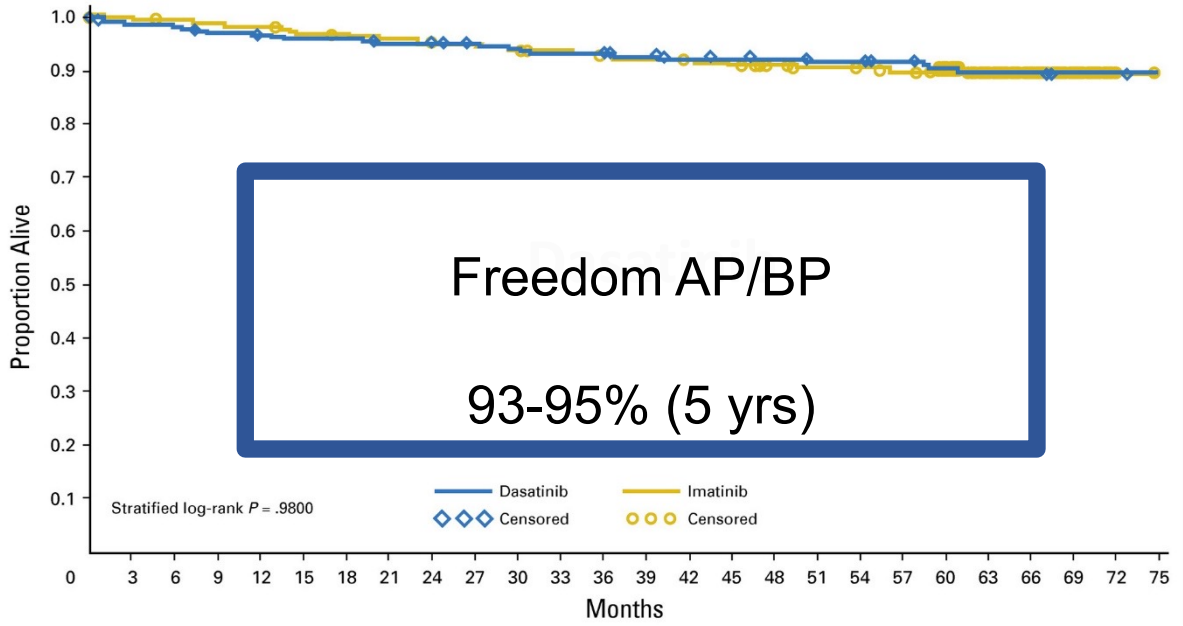
Christian Niederwieser and Nicolaus Kröger, ASH 2022, Educational Program

OS with high-dose IM, dasatinib and nilotinib vs IM 400mg



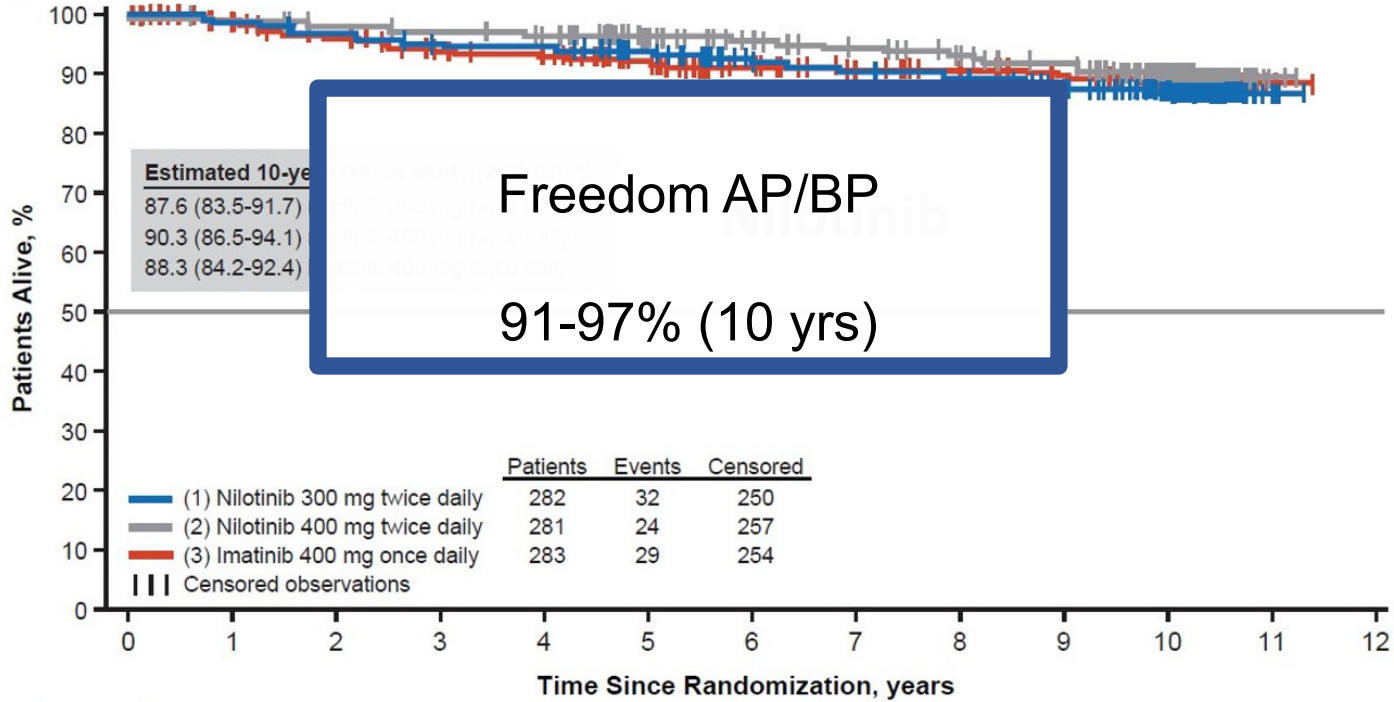
Death due to CML

6% (10 yrs)



Freedom AP/BP

93-95% (5 yrs)



Freedom AP/BP

91-97% (10 yrs)

Hehlmann et al, Leukemia 2017
Cortes et al, JCO 2016
Kantarjian et al, Leukemia 2021

G. Rosti

Transplantation in CML in the TKI era: who, when, and how ?

Accelerated phase (AP)
ELN 2020[25] - A patient **presenting** in AP should be treated as a high-risk patient, becoming eligible for HSCT if the response is not optimal - A patient **progressing** to AP during treatment should immediately be considered for HSCT
NCCN guidelines[26] - Disease progression to AP while on TKI therapy should be considered for HSCT - Patients who **present** with AP at diagnosis should be treated with a TKI, followed by evaluation for allogeneic HSCT based on response to therapy after 3, 6, or 12 months

Christian Niederwieser and Nicolaus Kröger, ASH 2022, Educational Program

CML Risk factors

At diagnosis

- High ELTS score
- 10–19% blasts in the peripheral blood and/or bone marrow[ab]
- ≥20% basophils in the peripheral blood
- Additional chromosomal abnormalities in Ph+ cells, including 3q26.2 rearrangements, monosomy 7, isochromosome 17q and complex karyotype
- Additional chromosomal abnormalities in Ph+ cells, including trisomy 8, 11q23 rearrangements, trisomy 19, trisomy 21, additional Ph+ (evidence of association with disease progression less clear)
- Clusters of small megakaryocytes (including true micromegakaryocytes similar to those seen in myelodysplastic syndromes), associated with significant reticulin and/or collagen fibrosis, which is best assessed in biopsy sections.

a. The finding of bona fide lymphoblasts in the peripheral blood or bone marrow (even if <10%) is consistent with the diagnosis of blast phase

b. ≥20% blasts in the peripheral blood or bone marrow, or an infiltrative proliferation of blasts in an extramedullary site, is diagnostic of blast phase

ELTS score	0.0025 × (**age**/10)^3 + 0.0615 × **spleen size** + 0.1052 × **peripheral blood blasts** + 0.4104 × (**platelet count**/1000)$^{-0.5}$	Low-risk: < 1.5680 Intermediate-risk: 1.5680- 2.2185 High-risk: > 2.2185

Emerging on treatment

Resistance to TKI as defined by ELN 2020, including loss of prior responses, emergence of ACA and BCR::ABL1 kinase domain mutations.

Khoury et al., Leukemia. 2022;36:1703-19

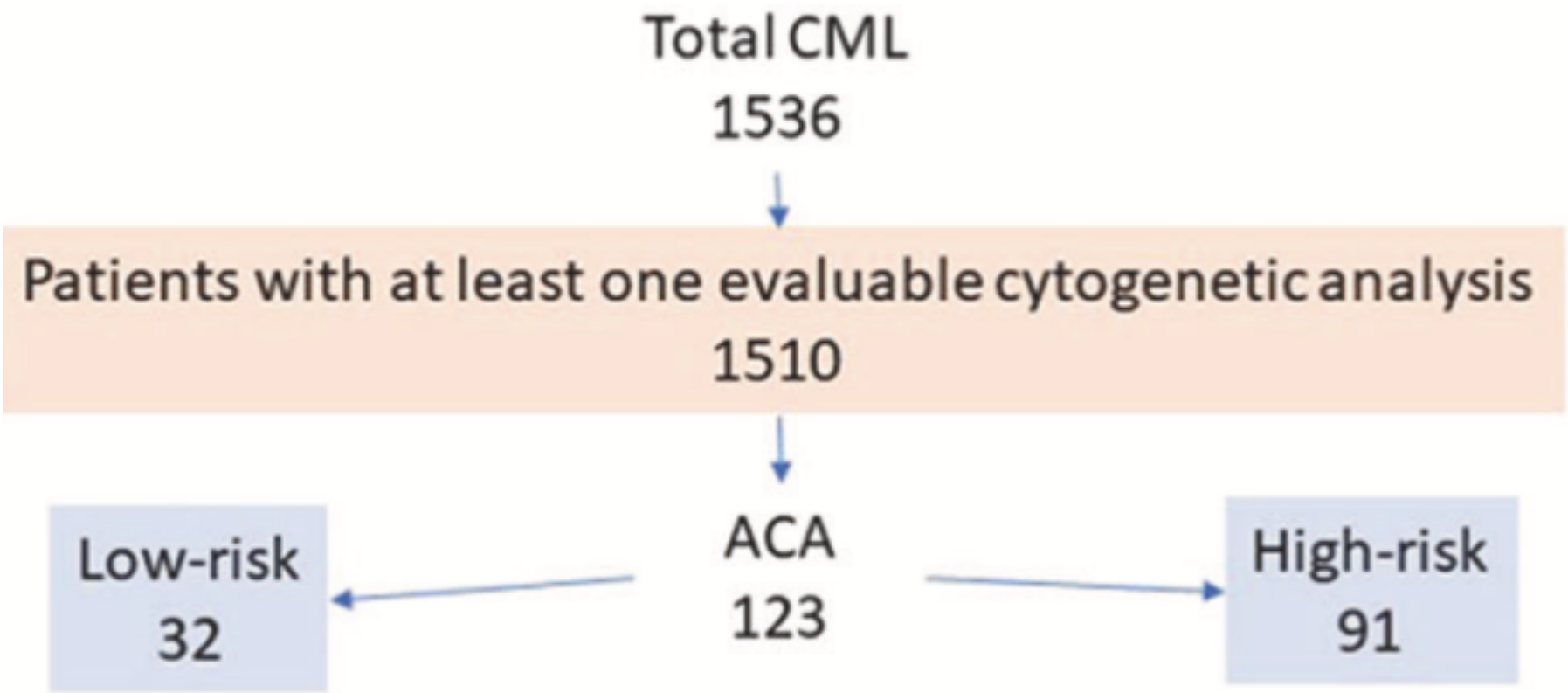
G. Rosti

Transplantation in CML in the TKI era: who, when, and how ?

Chronic phase (chP)
ELN 2020[25] - Disease resistant or intolerant (suboptimal response to 2 or more TKIs) - For the very rare patient with inadequate recovery of normal hematopoiesis - Resistance to 2G-TKIs (first or second line) ponatinib or experimental agent - Failure to respond to ponatinib after 3 months' treatment - Emergence of high-risk cytogenetics: observe closely, consider intensification of treatment (ponatinib, early allo-SCT)
NCCN guidelines[26] - If TKI-resistant disease *BCR-ABL1* (IS) >10% at >3 months, switch to alternate TKI and evaluate for HSCT

Christian Niederwieser and Nicolaus Kröger, ASH 2022, Educational Program

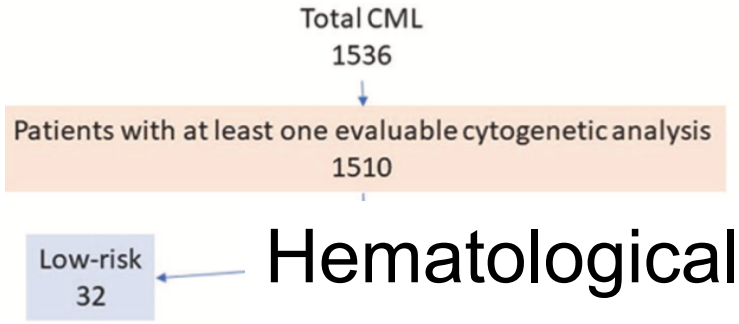
High risk additional chromosomal aberrations herald advanced disease and predict survival probability: CML IV cohort



Hehlmann R, et al. Leukemia. 2020;34:2074-86

G. Rosti

High risk additional chromosomal aberrations herald advanced disease and predict survival probability: CML IV cohort



25/123 at diagnosis
66/123 during the course of the disease

Hematological and clinical abnormalities at ACA appearance

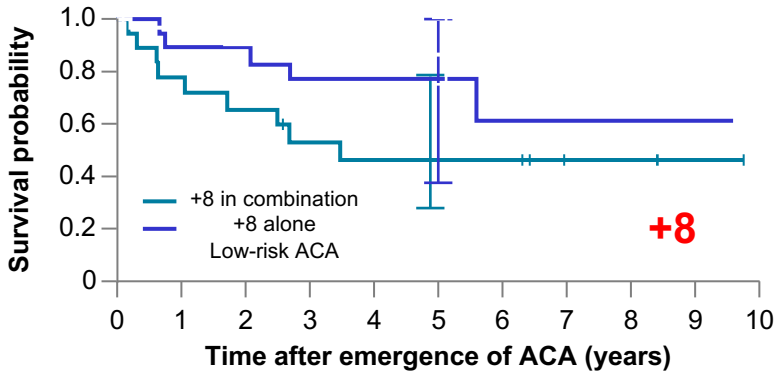
42/138 (30%) of alloSCT@ CML IV for the 6% ACA patients:

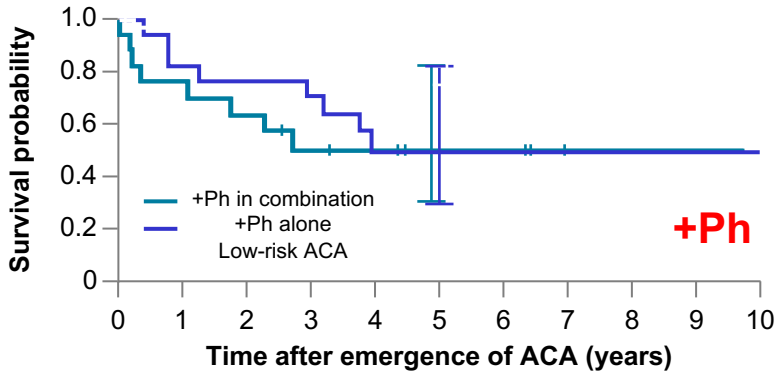
26/42 in AP/BP 2 yrs OS 44%
13/42 in CP 2 yrs OS 77%

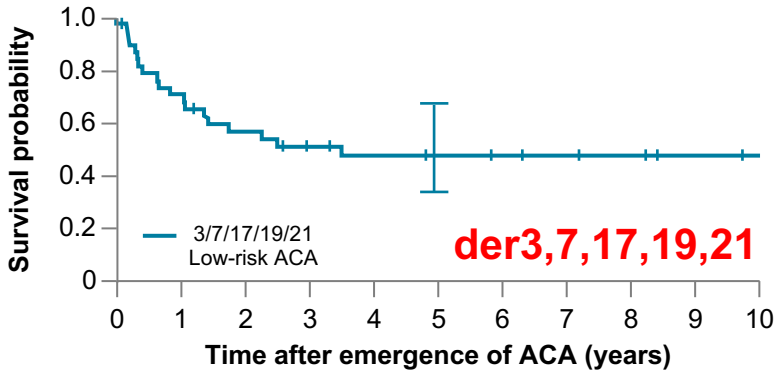
Hehlmann R, et al. Leukemia. 2020;34:2074-86

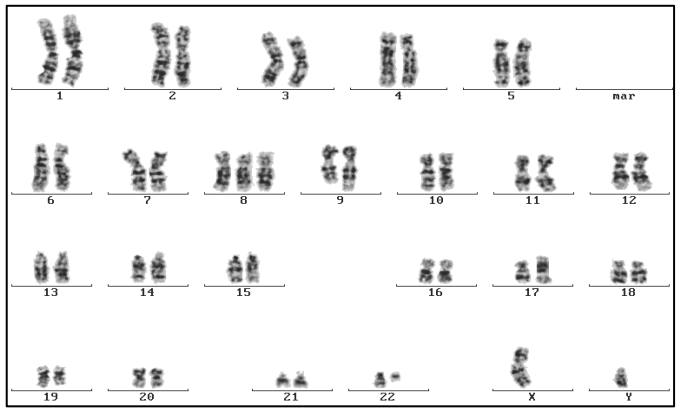
G. Rosti

High risk additional chromosomal aberrations herald advanced disease and predict survival probability: CML IV cohort









ACA, Additional cytogenetic abnormalities.

Hehlmann R, et al. Leukemia. 2020;34:2074-86

G. Rosti

Transplantation in CML in the TKI era: who, when, and how ?

Chronic phase (chP)
ELN 2020[25] - Disease resistant or intolerant (suboptimal response to 2 or more TKIs) - For the very rare patient with inadequate recovery of normal hematopoiesis - Resistance to 2G-TKIs (first or second line) ponatinib or experimental agent - Failure to respond to ponatinib after 3 months' treatment - Emergence of high-risk cytogenetics: observe closely, consider intensification of treatment (ponatinib, early allo-SCT)
NCCN guidelines[26] - If TKI-resistant disease *BCR-ABL1* (IS) >10% at >3 months, switch to alternate TKI and evaluate for HSCT

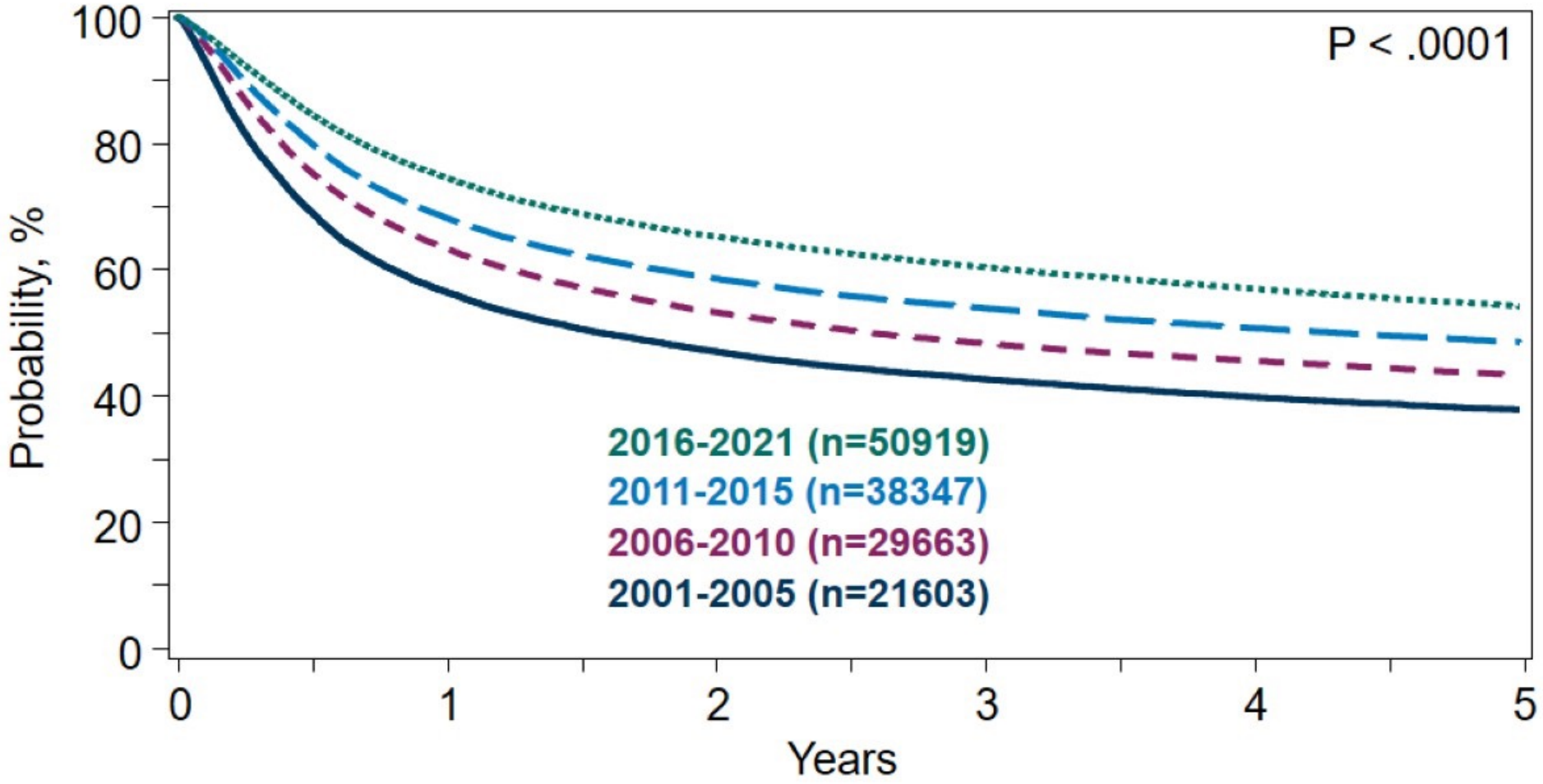
Christian Niederwieser and Nicolaus Kröger, ASH 2022, Educational Program

Transplantation in CML in the TKI era: who, when, and how ?

Chronic phase (chP)
ELN 2020[25] - Disease resistant or intolerant (suboptimal response to 2 or more TKIs) - For the very rare patient with inadequate recovery of normal hematopoiesis - Resistance to 2G-TKIs (first or second line) ponatinib or experimental agent - Failure to respond to ponatinib after 3 months' treatment - Emergence of high-risk cytogenetics: observe closely, consider intensification of treatment (ponatinib, early allo-SCT)
NCCN guidelines[26] - If TKI-resistant disease *BCR-ABL1* (IS) >10% at >3 months, switch to alternate TKI and evaluate for HSCT

Christian Niederwieser and Nicolaus Kröger, ASH 2022, Educational Program

Trends in Survival after Allogeneic HCTs, in the US, 2001-2021



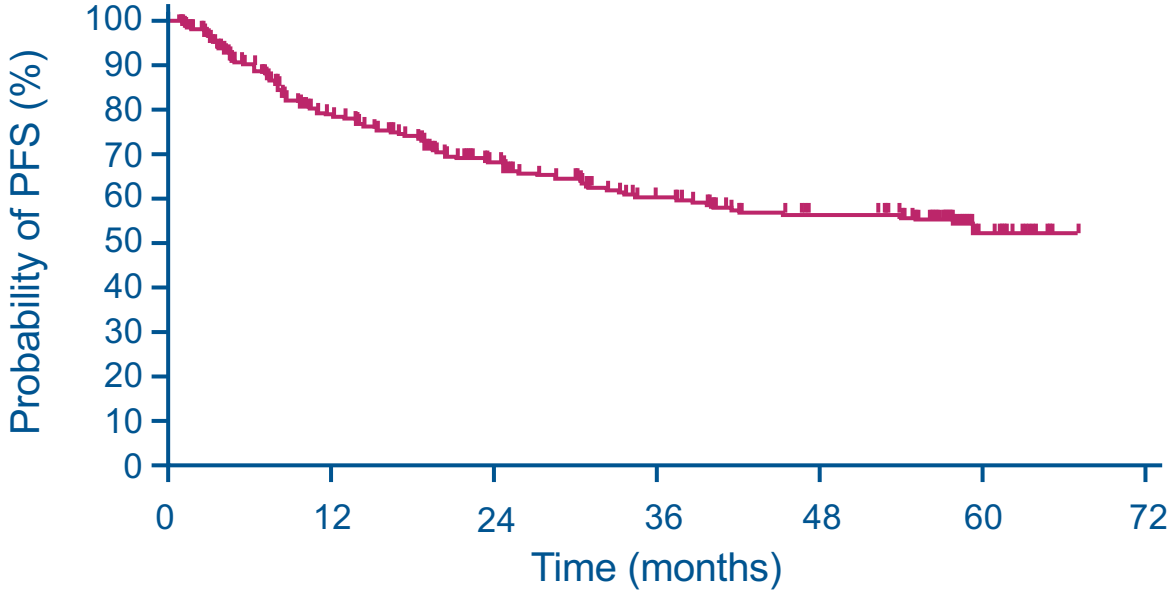
CIBMTR
A RESEARCH COLLABORATION BETWEEN THE MEDICAL COLLEGE OF WISCONSIN AND NMDP

CIBMTR.org

G. Rosti

PACE (Ponatinib in multiresistant CML)
PFS and OS in the Overall Population

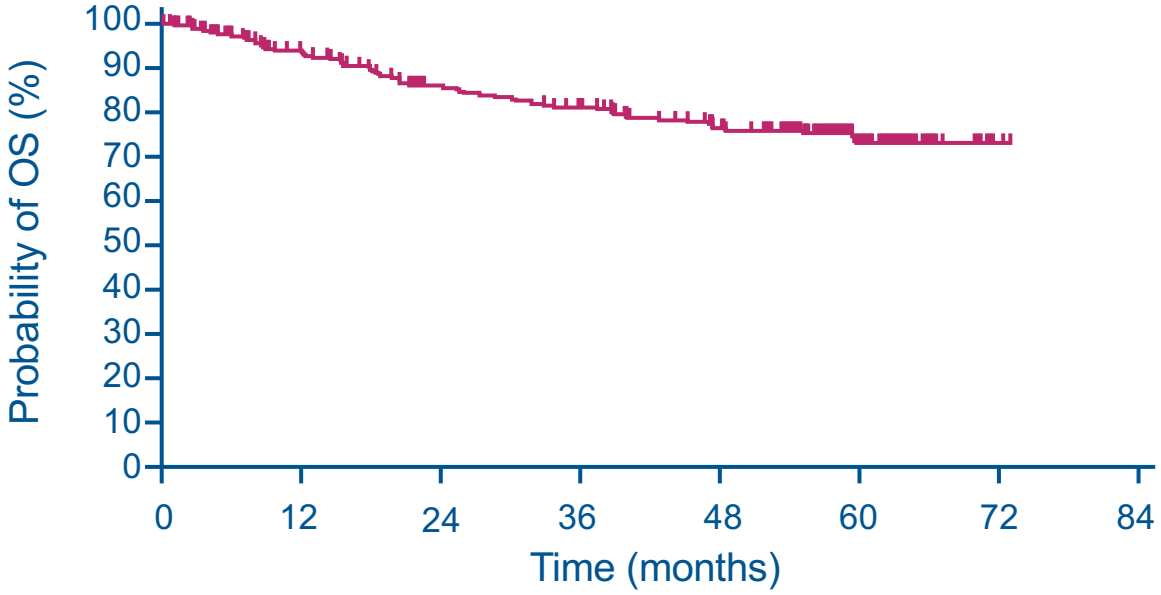
PFS



Patients at risk, n

267	178	143	112	97	22	0

OS



Patients at risk, n

267	226	199	176	161	54	3	0

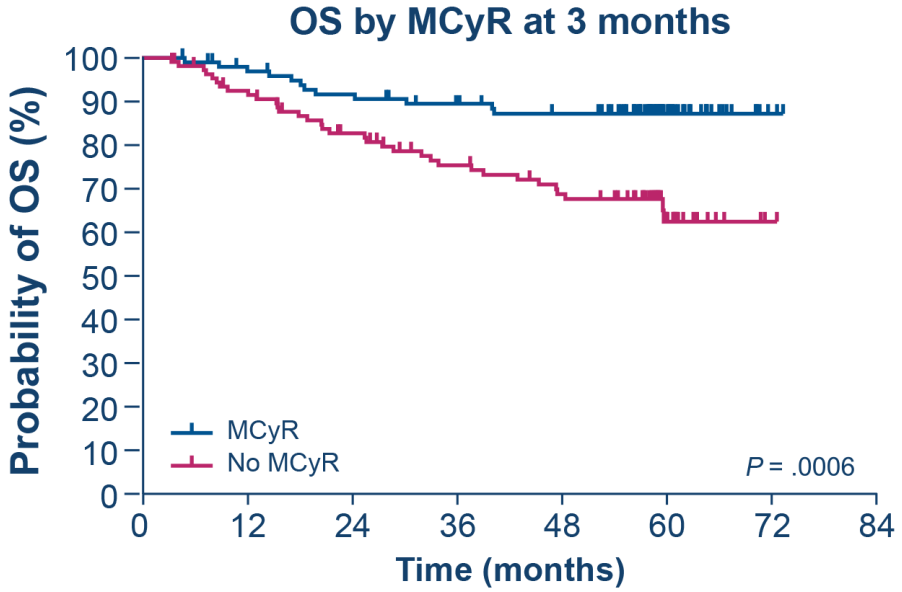
n. 233, 61% res/int ≧3 TKIs

PFS, progression-free survival; OS, overall survival.
Cortes JE, et al. Blood. 2018;132(4):393-404.

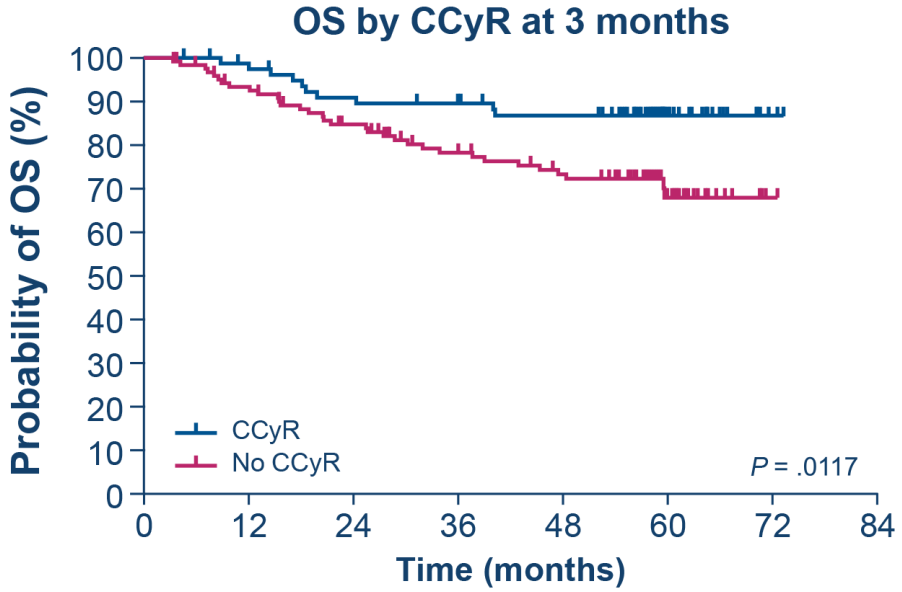
G. Rosti

PACE (Ponatinib in multiresistant CML)
OS[a] by cytogenetic response at 3 months

- Patients with cytogenetic responses of MCyR or CCyR were significantly more likely to have improved OS at 4 years compared with patients who did not achieve a cytogenetic response



Patients at risk, n								
MCyR	100	94	87	80	75	28	2	0
No MCyR	109	97	82	70	62	19	1	0



Patients at risk, n								
CCyR	80	76	69	66	62	20	2	0
No CCyR	123	110	95	80	72	26	1	0

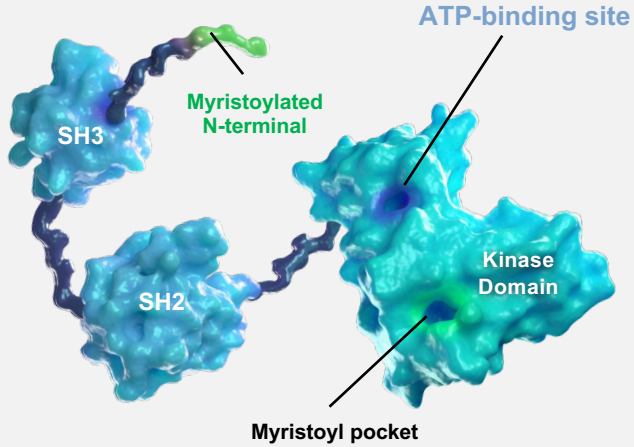
[a] Patients who discontinued were followed approximately every 12 weeks for survival; patients without an event at the time of the analysis were censored at last contact
CCyR, complete cytogenetic response; MCyR, major cytogenetic response

G. Rosti

Autoregulation of ABL1 kinase occurs when a myristoyl group at the N-terminus of ABL1 binds to the myristoyl-binding pocket

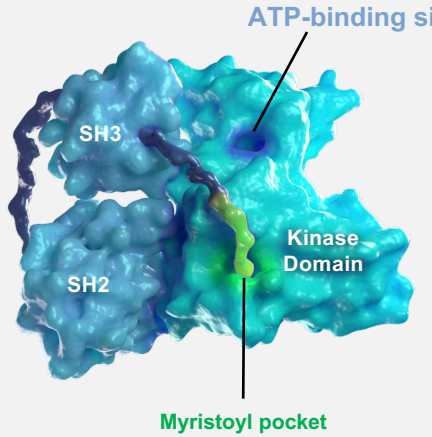
close (inactive) and open (active) conformation

Active ABL1 (open)



- ABL1 is in an **open/active conformation** when the **myristoylated N-terminus is displaced** from its **binding pocket**[2,3]

Inactive ABL1 (close)



- When the **myristoyl group** docks, it **locks ABL1 in a closed/inactive conformation**[2,3]

ABL1, Abelson tyrosine kinase 1; ATP, adenosine triphosphate.

1. Colicelli J. *Sci Signal*. 2010;3(139)re6; 2. Hughes TP, et al. *N Engl J Med.* 2019;381:2315-2326; 3. Hantschel O. *Genes Cancer*. 2012;3: 436-446.

G. Rosti

Preliminary safety and efficacy of ELVN-001, a selective active site inhibitor of BCR::ABL1 in CML

ELVN-001:

- Selectively inhibits ABL with low off target activity against other kinases
- Maintains activity against T315I and other BCR::ABL1 mutations known to confer resistance to asciminib

Patient population:

- ≥18 years (≥19 years in Korea) with BCR::ABL1-positive CP-CML, ± T315I mutation
- Intolerant to, failed, or not a candidate for available therapies for CML
- ECOG PS 0-2
- Bone marrow transplantation allowed only if ≥6 months prior

Study design:

- **Ph. 1a (N=50 max.):** Dose escalation 10/20/40/80/120 mg QD; **Ph. 1b (N=60):** Dose expansion, stratified by *T315I* status
- **Primary endpoint:** Dose-limiting toxicities, AEs, clinically significant lab and ECG abnormalities
- **Secondary endpoints (Ph. Ia):** PK parameters, molecular response

.

Lang F, et al. Presented at: ESH-iCMLf 2024, Prague, Czech Republic, 27–29 September. Oral presentation.

Leukemia

www.nature.com/leu

PERSPECTIVE OPEN

Check for updates

Questions concerning tyrosine kinase-inhibitor therapy and transplants in chronic phase chronic myeloid leukaemia

Michele Baccarani[1,2,7], Francesca Bonifazi[1]✉, Simona Soverini[2], Fausto Castagnetti[1,2], Gabriele Gugliotta[1], Wael Saber[3,4], Noel Estrada-Merly[3], Gianantonio Rosti[5] and Robert Peter Gale[6]

«We suggest transplants should be more often considered in the metric when counseling people with CML»

«The question of who should receive a transplant in CP is complex and controversial.»

Leukemia (2022) 36:1227–1236; https://doi.org/10.1038/s41375-022-01522-3

LMC, perché rinviare il trapianto

Gianantonio Rosti, MD
Scientific Direction
IRCCS/SIRHHC Scientific Institute for Research, Hospitalization and Health Care
«Dino Amadori» – Meldola (FC), Italy

DO WE NEED TO RECONSIDER USE OF TRANSPLANT IN CHRONIC PHASE CML?

Rates of ***cure*** are higher in persons receiving a transplant vs. TKIs (few patients will reach TFR)

HOWEVER:

(1) **few transplants** have been done for CML recently, limiting the certainty of estimating outcomes;
(2) selection **biases favoring transplants** including younger **age, better performance score and fewer comorbidities** in transplant recipients compared with persons receiving TKIs;
(3) selection **biases against transplant** recipients who are more likely to have had a **worse prognosis at diagnosis or soon thereafter** compared with those receiving only TKI therapy;
(4) the almost **20% 1-year mortality** associated with transplants and risk of transplant-related complications such as **chronic GvHD**

Baccarani M et al, Leukemia 2022

WHO 2022 CML

2 phase disease

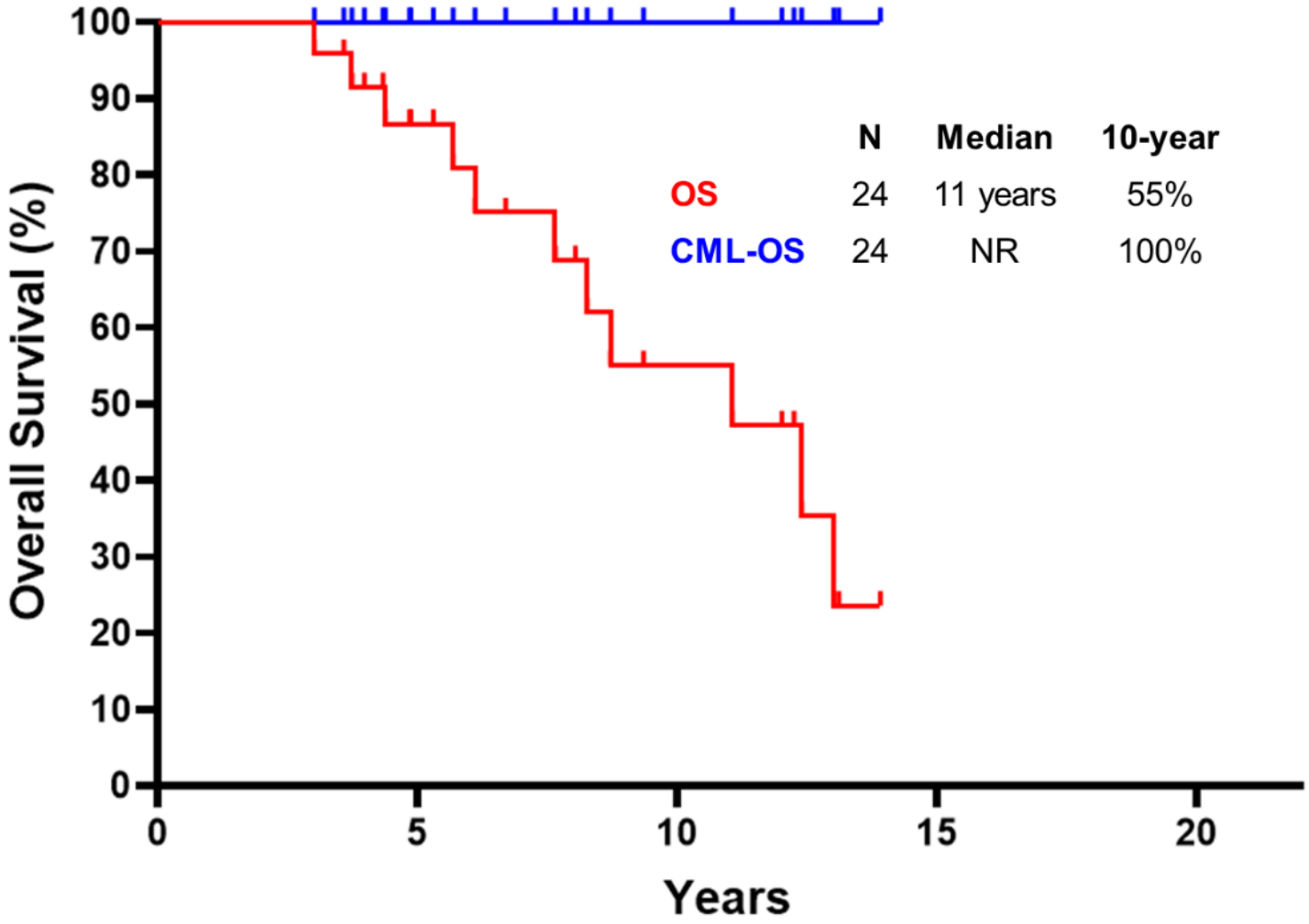
Diagnosis: CP (with clinical and biological risk factors)
BP (≥20% blasts)

On therapy: CP (Remission status according to ELN)
BP (≥20% blasts)

AP definition in TKI era less important.

Khoury et al., Leukemia. 2022;36:1703-19

Chronic myeloid leukemia without major molecular response after 2 years of treatment with tyrosine kinase inhibitor

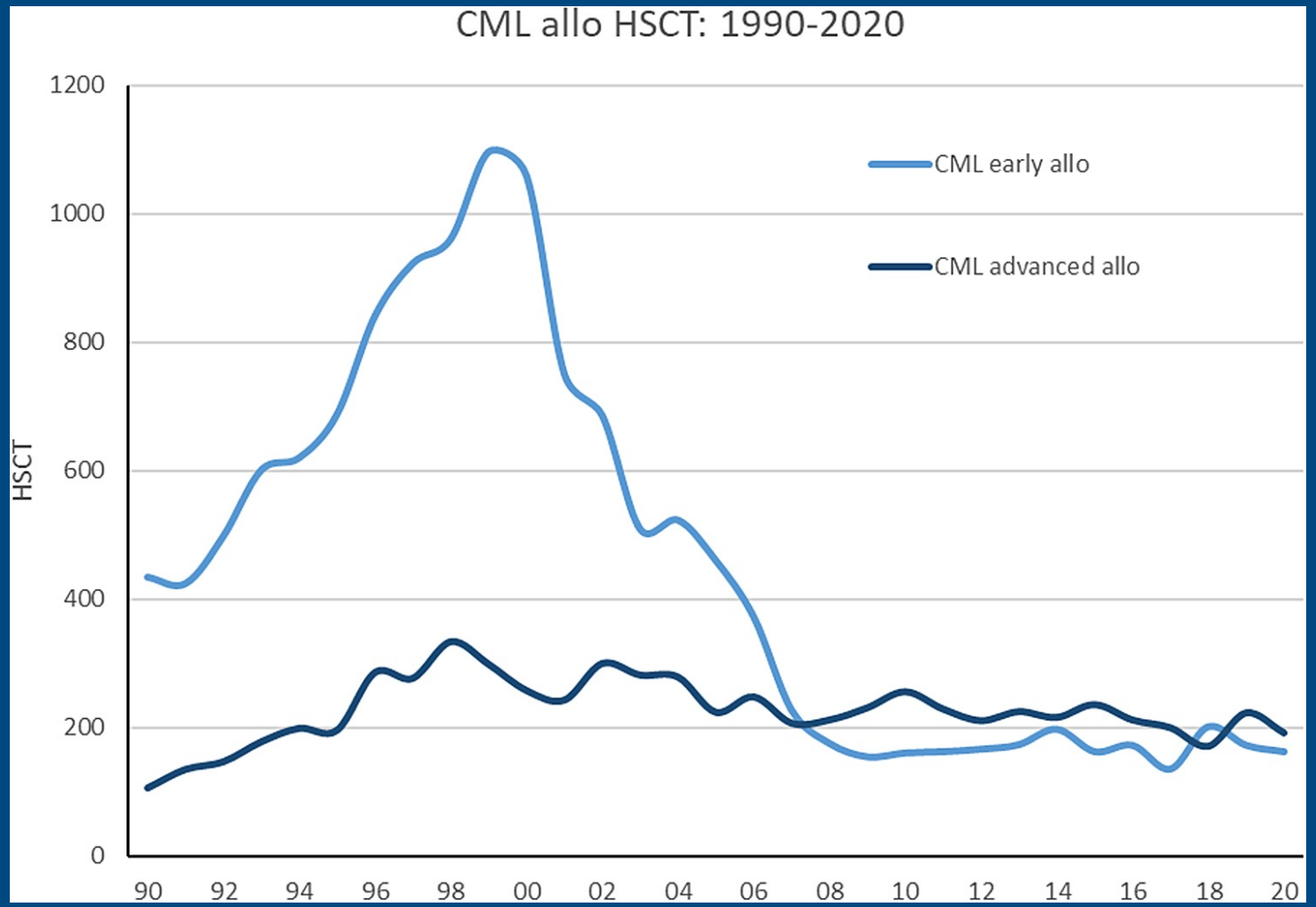


Overall survival (OS) and CML-related overall survival (CML-OS) of patients aged ≥60 years at diagnosis without MMR after two years of TKIs

A Bidikian et al Am J Hematol. 2023;98:639–644.

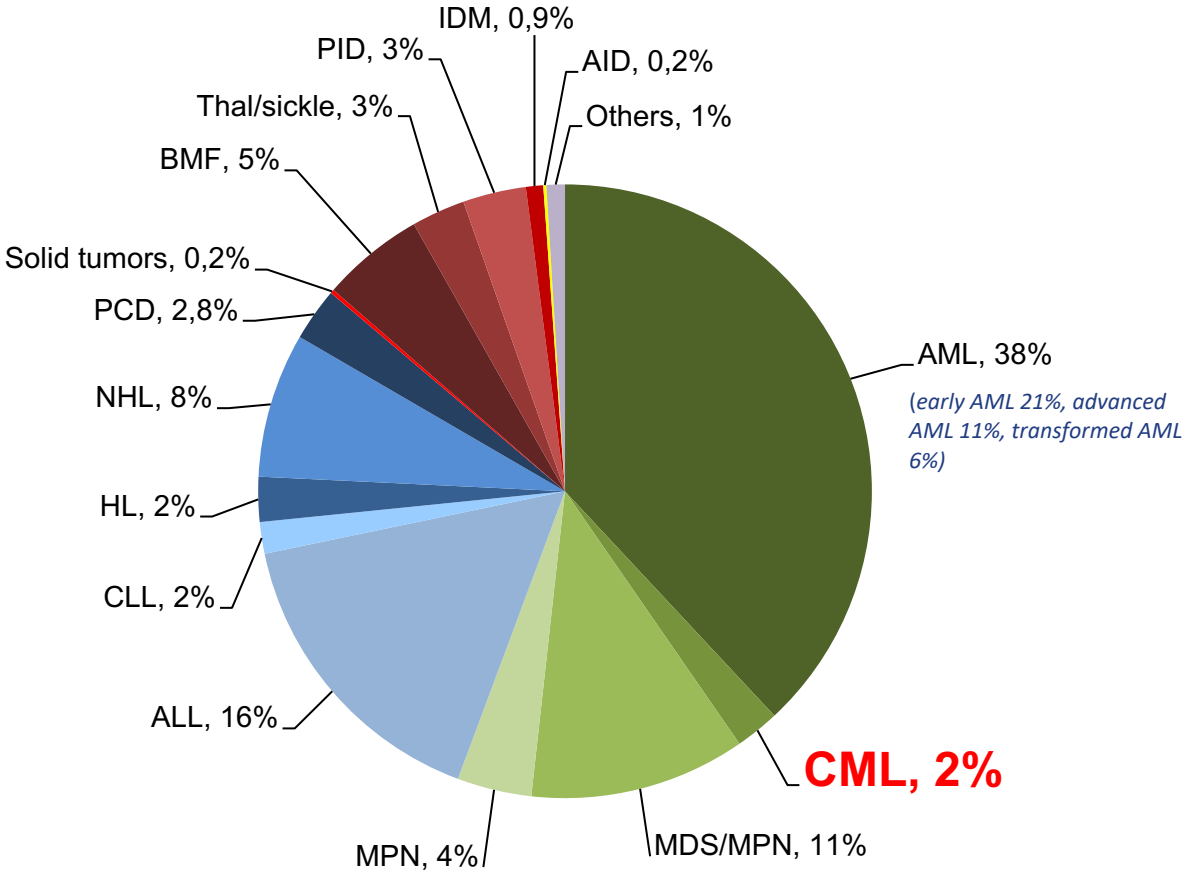
G. Rosti

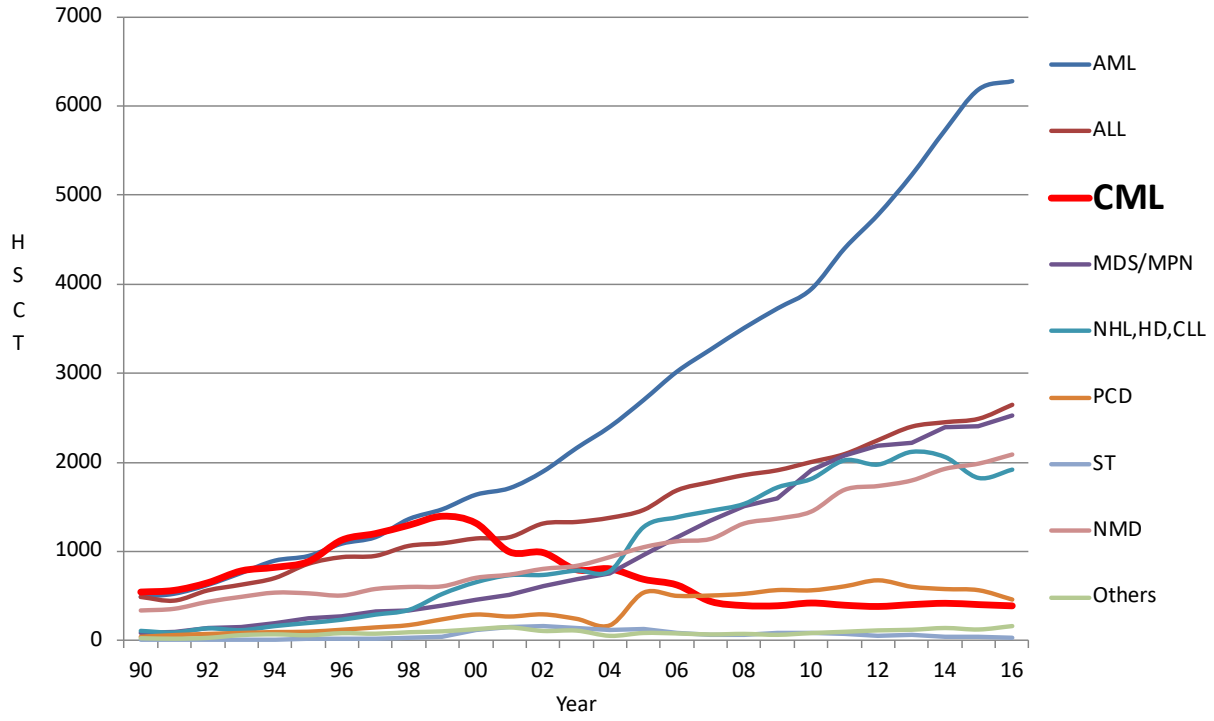
SCT for CML in Europe



EBMT registry

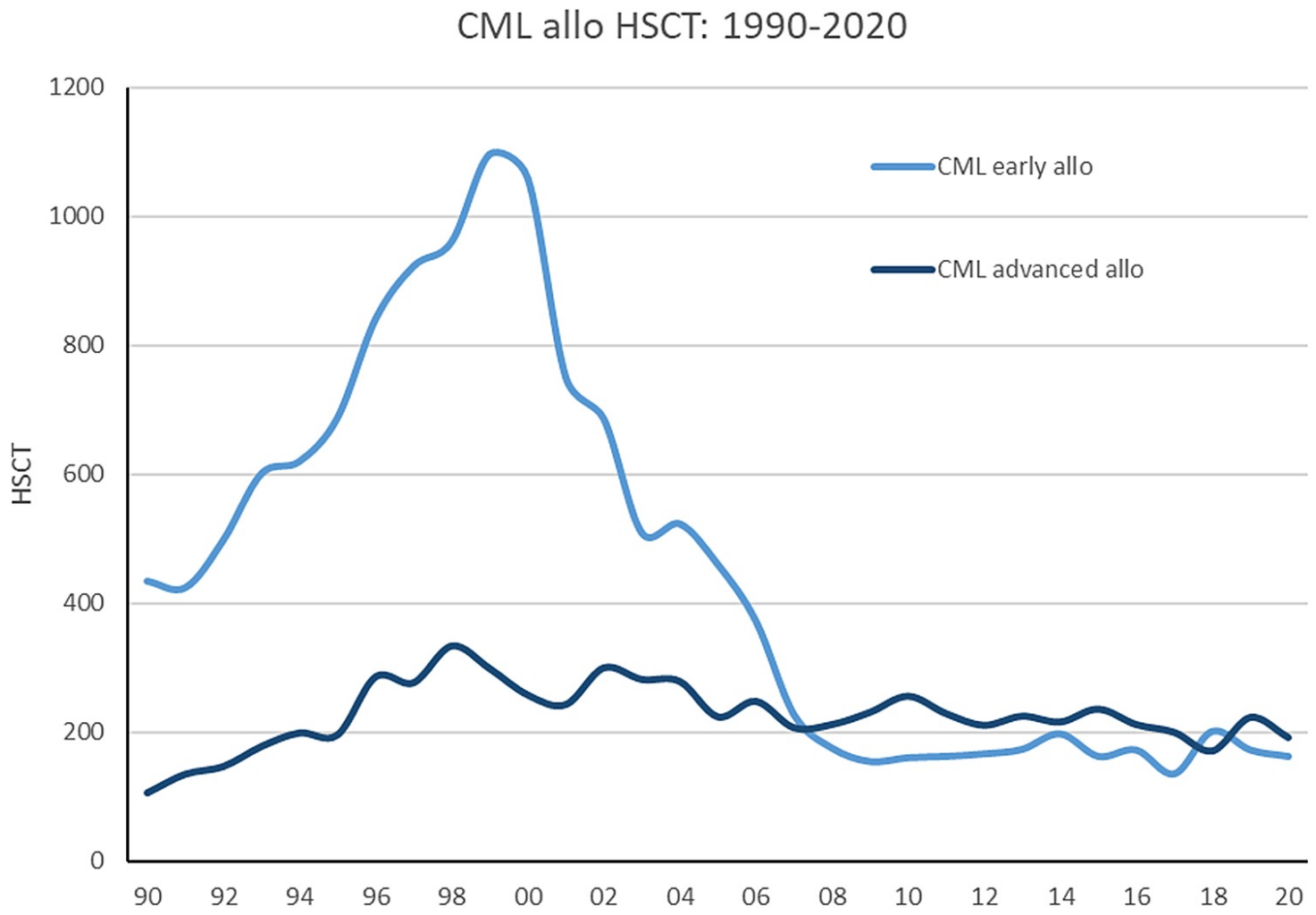
Allogeneic HSCT in Europe 2016
1st HSCT





J.R. Passweg et al, Bone Marrow Transplantation, Jan 2018

SCT for CML in Europe



More patients in advanced phase than in CP are transplanted world wide, underlying the importance of optimizing outcome by improving the **timing** of HSCT

EBMT registry

DO WE NEED TO RECONSIDER USE OF TRANSPLANT IN CHRONIC PHASE CML?

- There are several time- dependent predictive and prognostic models and scores which enable physicians to estimate the **likelihood of success of TKI therapy in achieving TFR** reasonably early after starting TKI therapy.

- In potential transplant candidates, physicians and patients must choose between probable lifetime TKI therapy with attendant medical, physical and psychological costs versus likelihood of success and risks of a transplant.

The issue is not whether one or the other therapy is better, but which therapy is more appropriate for different persons at different times after CML diagnosis and after observing response to TKI therapy

Baccarani M et al, Leukemia 2022

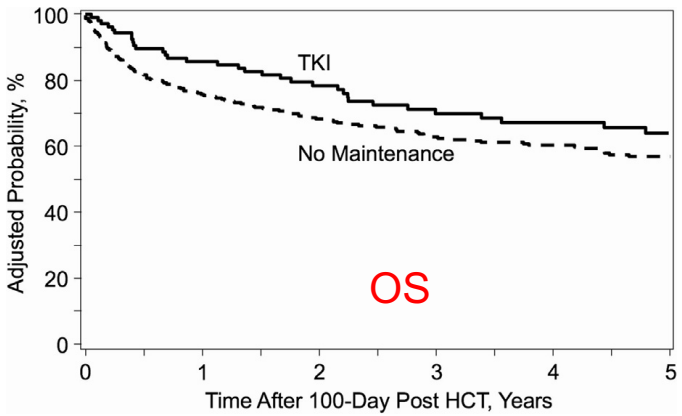
Biology of Blood and Marrow Transplantation

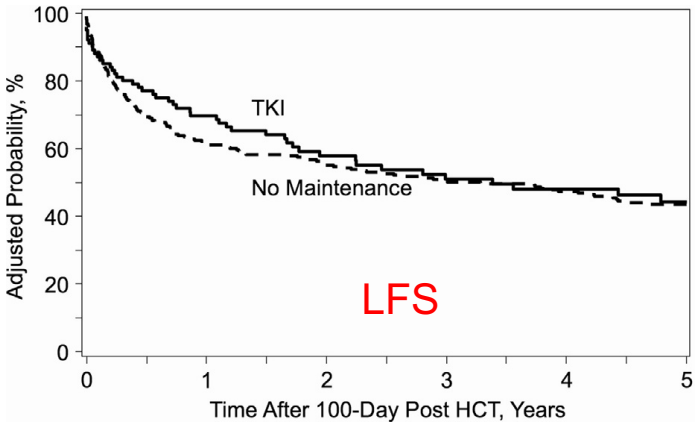
journal homepage: www.bbmt.org

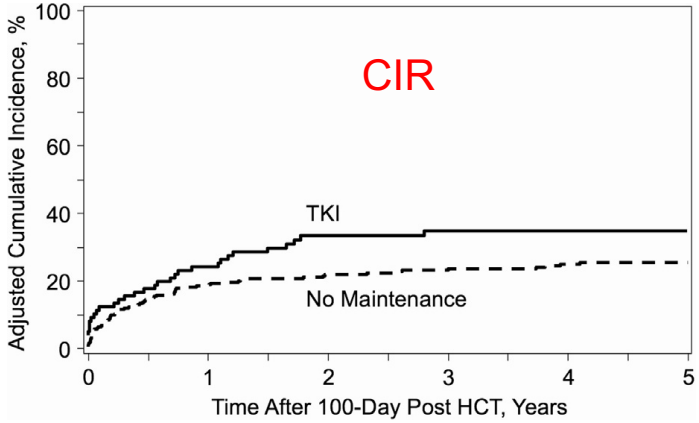
Post-SCT maintenance

Maintenance Tyrosine Kinase Inhibitors Following Allogeneic Hematopoietic Stem Cell Transplantation for Chronic Myelogenous Leukemia: A Center for International Blood and Marrow Transplant Research Study

390 adult patients with CML who underwent transplantation between 2007 and 2014 and received maintenance TKI following HCT (n = 89) compared with no TKI maintenance (n = 301)







- Results unchanged in multivariate analysis and were not modified by disease status before transplantation.
- In conclusion, **NO significant impact of maintenance TKI therapy on clinical outcomes.**
- **The optimal approach to TKI administration in the post-transplantation setting in patients with CML remains undetermined.**

DeFilipp Z et al. 2020

Incidence of GVHD after DLI (n=500)

		GVHD post DLI	
		No	Yes
Response (CCyR/CMR)	No	**24%**	**8%**
	Yes	**32%**	**36%**

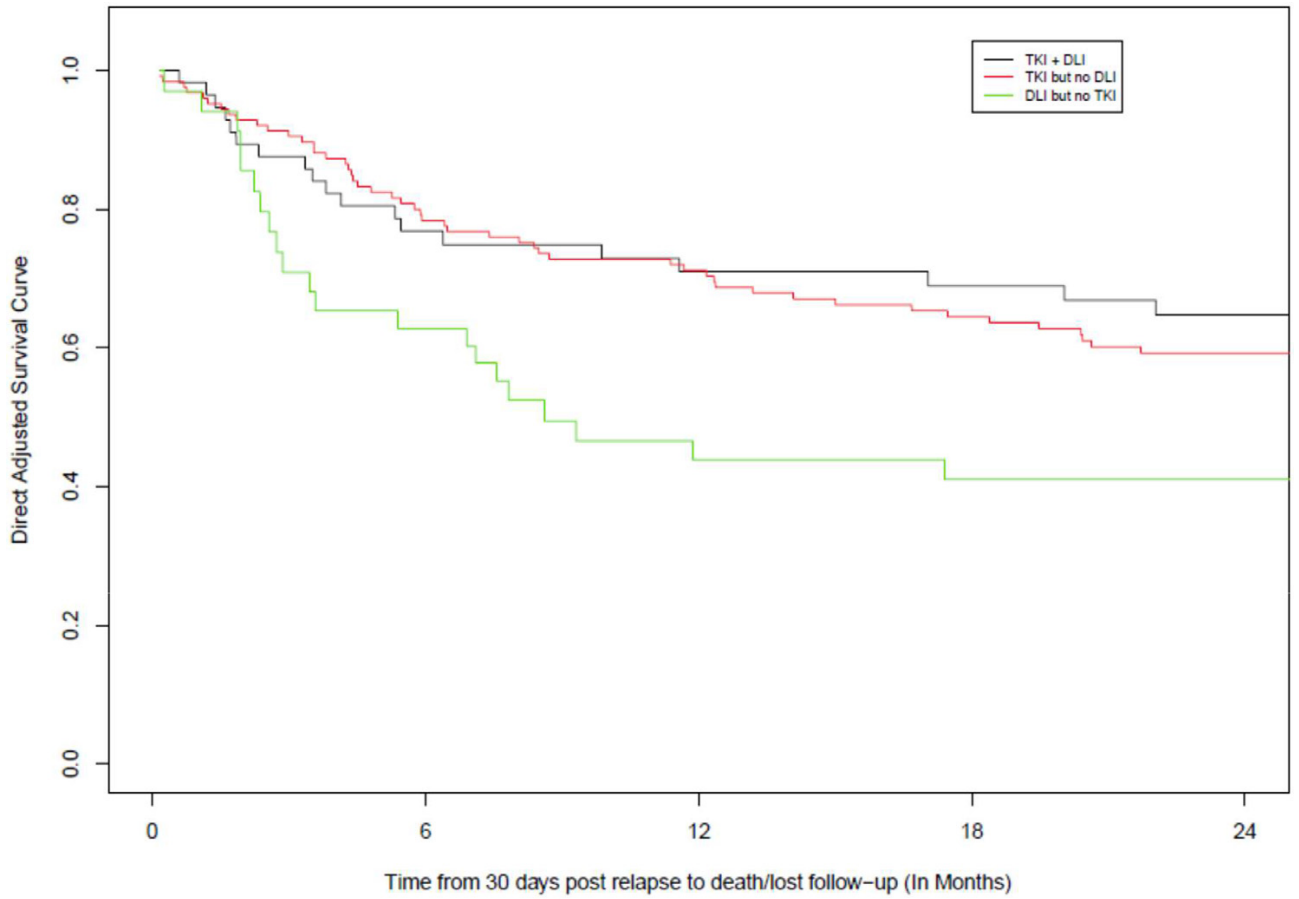
The Role of Donor Lymphocyte Infusion (DLI) in Post-Hematopoietic Cell Transplant (HCT) Relapse for Chronic Myeloid Leukemia (CML) in the Tyrosine Kinase Inhibitor (TKI) Era

A total of 215 HCT recipients relapsed and were analyzed in the following groups:

(1) TKI alone (n = 128)

(2) TKI with DLI (n = 48)

(3) DLI without TKI (n = 39)



Biol Blood Marrow Transplant 26 (2020) 1137–1143

Take home-messages

WHO and WHEN?

- ELN RECOMMENDATIONS / EBMT and HCI SCORE

WHICH DONOR / SOURCE?

- Any, but HLA-id sib better / Marrow better than blood

WHICH CONDITIONING?

- Myeloablative first option

TKI MAINTENANCE AFTER TRANSPLANT?

- Benefit undetermined

RELAPSE AFTER SCT?

- preferably TKI alone (+/- DLI)

PERSPECTIVE: TRANSPLANT IN 1ST CP IN PATIENTS NOT CANDIDATE FOR TFR?

DOI: 10.1002/ajh.24793

RESEARCH ARTICLE Am J Hematol. 2017;92:902–908. WILEY AJH

Clinical impact of pretransplant use of multiple tyrosine kinase inhibitors on the outcome of allogeneic hematopoietic stem cell transplantation for chronic myelogenous leukemia

237 pts diagnosed in CP between 2001 and 2012 in Japan, which received allo-SCT

TABLE 3 Multivariate analysis of variables affecting RI and NRM

Outcome	Factors		HR	95% CI	*P*-value
RI	Disease status at SCT	CP1	1		
		CP2	2.163	0.858–5.455	.100
		CP3-	1.110	0.158–7.784	.920
		AP	2.378	0.902–6.269	.080
		BC	5.299	2.385–11.770	<.001
NRM	Pretransplant TKI Number	TKI=1/2	1		
		TKI=3	2.554	1.185–5.504	.017
	Male recipient/Female donor	no	1		
		yes	2.107	1.022–4.346	.044
	Age at SCT	-49	1		
		50-	3.016	1.520–5.984	.002

"TKI = 3 is a significant factor for survival after allo-HSCT besides disease progression and patient's age. Allo-HSCT could be considered for young patients with CML showing resistance to second-line TKI therapy who did not have disease progression and who have an appropriate donor"

DOI: 10.1002/ajh.24793

RESEARCH ARTICLE

Am J Hematol. 2017;92:902–908.

WILEY AJH

Clinical impact of pretransplant use of multiple tyrosine kinase inhibitors on the outcome of allogeneic hematopoietic stem cell transplantation for chronic myelogenous leukemia