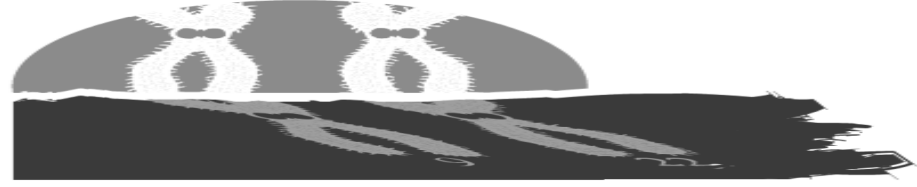




Prague, 3-5May, 2013



**CML
HORIZONS**



**What do the treatment guidelines say?
Update of the new ELN, NCCN
recommendations.**

Gianantonio Rosti, MD

Institute "Seràgnoli", Bologna

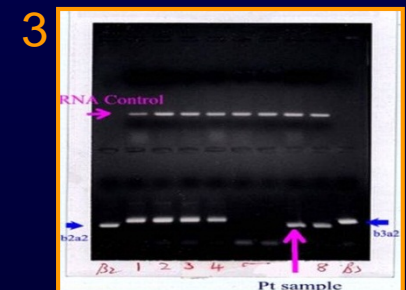
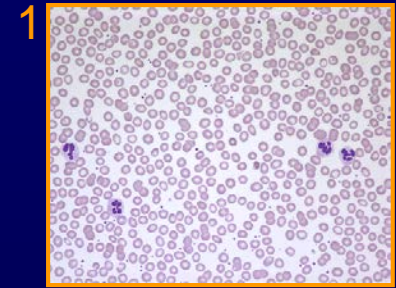
GIMEMA CML WP

Guidelines are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment.

Any clinician seeking to apply or consult guidelines is expected to use independent medical judgment in the context of **individual clinical circumstances** to determine any patient's care or treatment

Monitoring Ph+ CML Disease

- Hematologic response (HR)
 - Measure of blood counts and differentials
- Cytogenetic response (CyR)
 - Chromosome banding analysis of marrow cell metaphases
- Molecular response (MR)
 - Measurement of BCR-ABL transcript levels relative to a control gene
 - Most sensitive measure of Ph+ CML disease burden



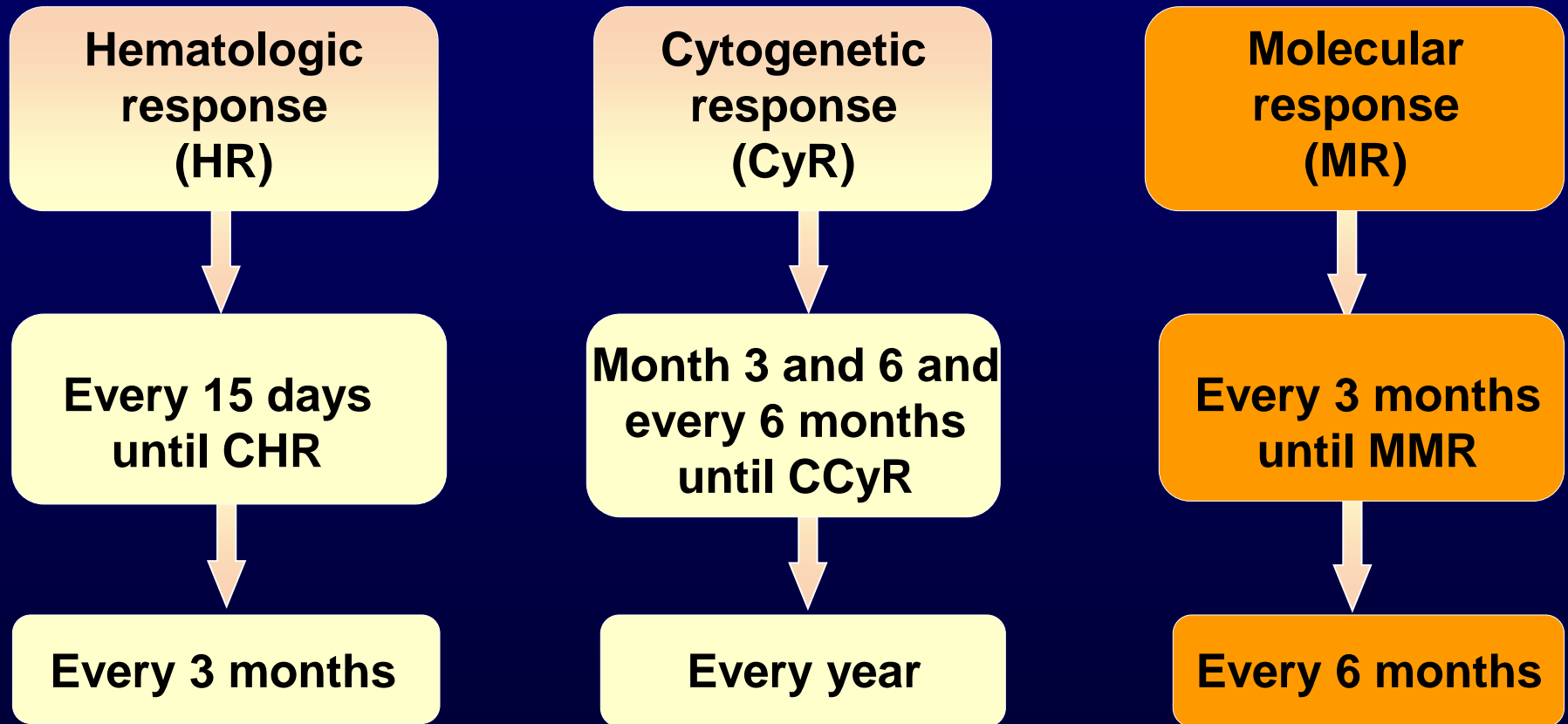
CML, chronic myeloid leukemia; Ph+, Philadelphia chromosome-positive.

1. Maslak P. ASH Image Bank. Oct 2008. **8-00067**. <http://ashimagebank.hematologylibrary.org/>. Copyright American Society of Hematology 2008.

2. Quintás-Cardama A, et al. *Leukemia*. 2007; 21(11): 2394-2396. Reprinted by permission from Macmillan Publishers Ltd: *Leukemia*. 2007;21: 2394-2396, copyright 2007.

3. Maslak P. ASH Image Bank. Dec 2001. **100202**. <http://ashimagebank.hematologylibrary.org/>. Copyright American Society of Hematology 2001.

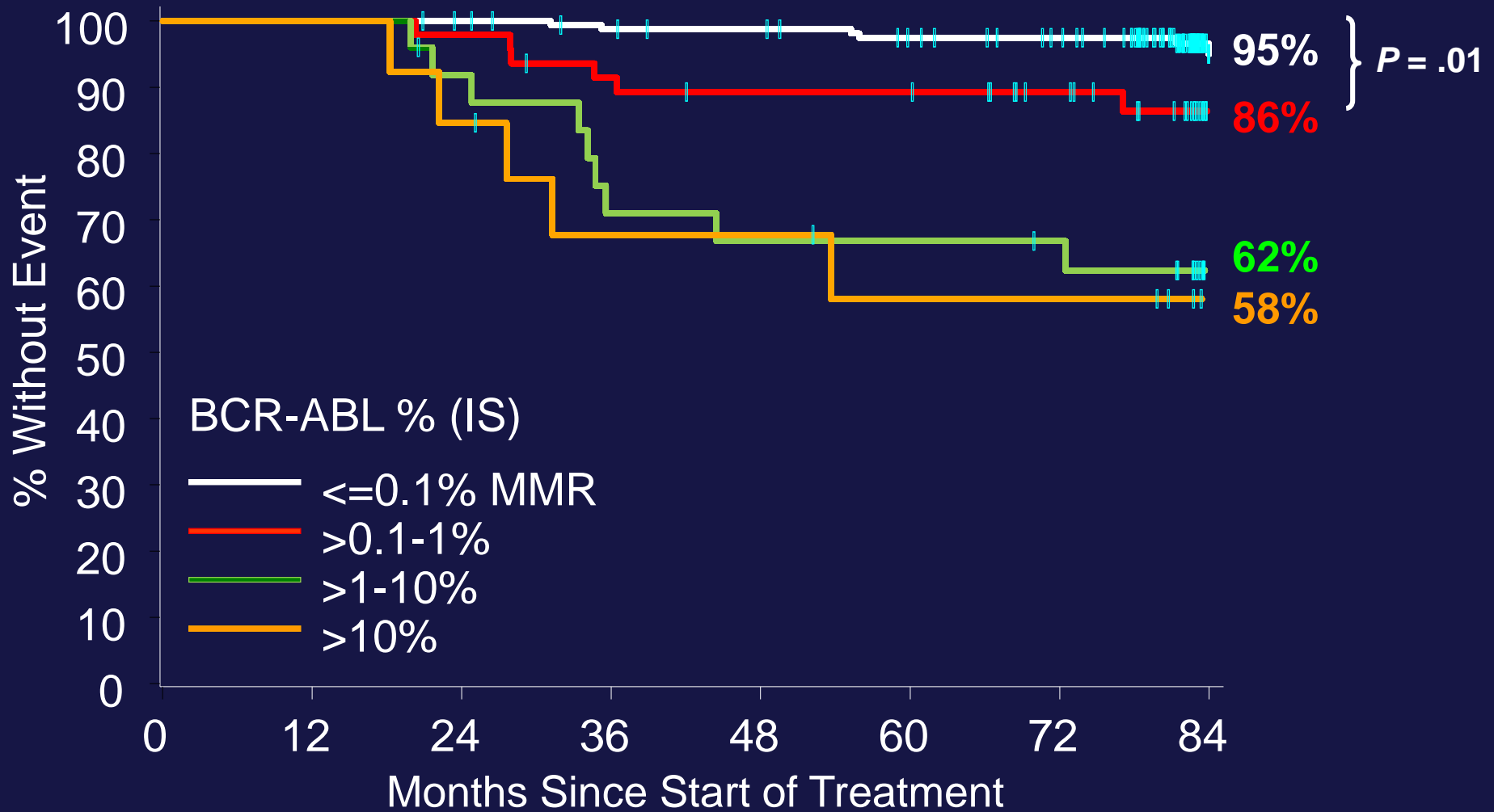
Molecular Monitoring: European LeukemiaNet Recommendations



CHR, complete hematologic response; CCyR, complete cytogenetic response; MMR, major molecular response.

- **The outcomes of the patients are evaluated based on the level of responses achieved at given time points:**
- **Example: which is the probability of patients achieving an MMR within 18 months from starting imatinib treatment of being “alive and well” 6 years later?**

Importance of Response at 18 Months



European LeukemiaNet: Definitions of Response to Imatinib

Overall Response Definitions for Patients With CML-CP
Treated With Frontline Imatinib (First 18 Months)

Time	Optimal	Suboptimal	Failure	Warnings
Diagnosis	–	–	–	High risk CCA in Ph+
3 months	CHR, > minor CyR	No CyR	No CHR	N/A
6 months	PCyR	< PCyR	No CyR	N/A
12 months	CCyR	< CCyR (PCyR)	< PCyR	< MMR
18 months	MMR	< MMR	< CCyR	N/A

European LeukemiaNet: Definitions of Response to Imatinib

Overall Response Definitions for Patients With CML-CP
Treated With Frontline Imatinib (First 18 Months)

Time	Optimal	Suboptimal	Failure	Warnings
Diagnosis	–	–	–	High risk CCA in Ph+
3 months	Complete Hematological Response, > minor Cytogenetic Response	Absence of cytogenetic response	Absence of complete hematological response	N/A
6 months	PCyR	< PCyR	No CyR	N/A
12 months	CCyR	< CCyR (PCyR)	< PCyR	< MMR
18 months	MMR	< MMR	< CCyR	N/A

ELN RECOMMENDATIONS

WARNING > Be Careful, monitor closely

FAILURE > Change treatment

SUBOPTIMAL > “in the middle – Grey zone”,
monitor closely, treatment change may be necessary
in part of the patients

OPTIMAL > Go on, same treatment, better not
possible...

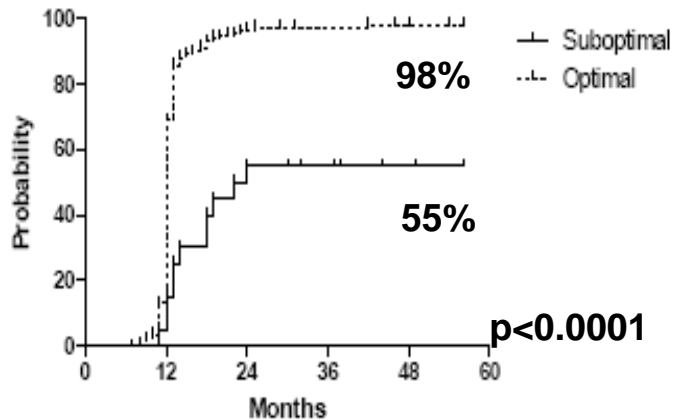
Suboptimal Responders are Relatively Few

GIMEMA Experience

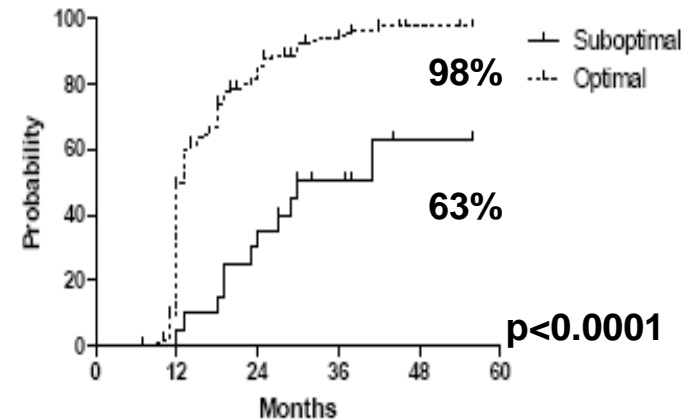
Time	Optimal Response	Suboptimal Response	Failure	Other events	NE
6 M	81%	5%	3%	3%	9%
12 M	79%	8%	6%	4%	3%
18 M	62%	10%	10%	6%	12%

Suboptimal responders at 6 months had significantly lower CCgR, MMR and FFS

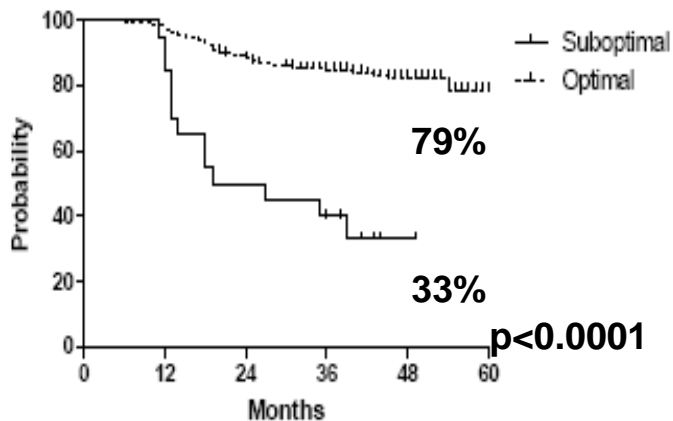
Estimated Probability of CCgR by Response at 6 months



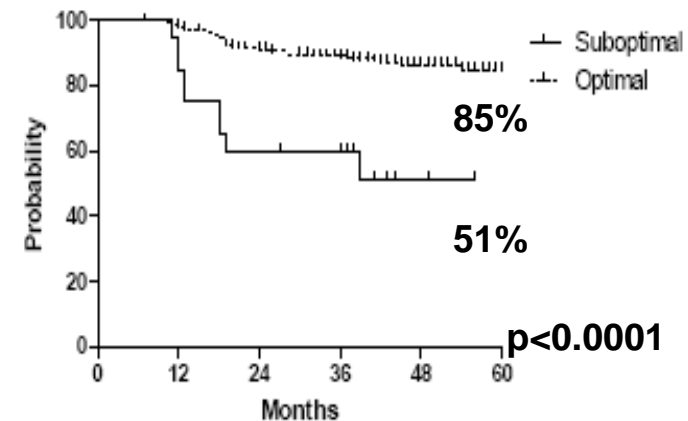
Estimated Probability of MMR by Response at 6 months



Event-Free Survival by Response at 6 months



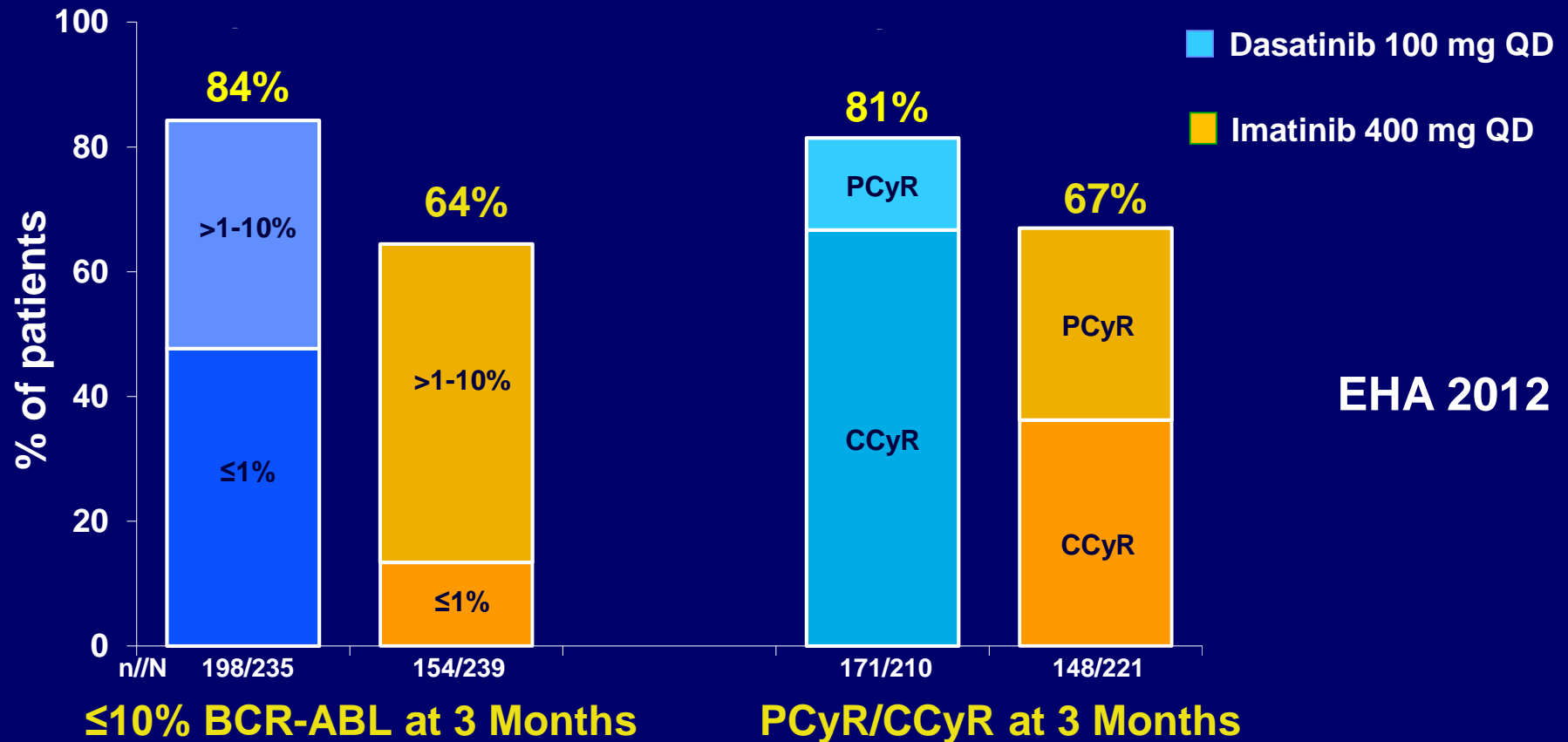
Failure-Free Survival by Response at 6 months



Newest Data: Importance of Response at 3 Months

	Ref. (Study)	Title	TKI
ASH 2011	Marin et al., abstract 785 (SPIRIT 2)	The Predictive Value of Early Molecular Response in Chronic Phase CML Patients Treated with Dasatinib First Line Therapy	Dasatinib
	Hochhaus et al., abstract 2767 (DASISION)	Patients with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP): Analysis of Molecular Response Kinetics in the DASISION Trial	Imatinib and dasatinib
	Hanfstein et al., abstract 783 (CML IV)	Molecular and Cytogenetic Response After 3 Months of Imatinib Treatment Is Predictive for the Risk of Disease Progression and Death in Newly Diagnosed Chronic Myeloid Leukemia Patients – a Follow-up Analysis of the German CML Study IV	Imatinib (with and without interferon)
	Nicolini et al., abstract 1684	The Month Three Major Molecular Response in Chronic Phase Chronic Myeloid Leukemia on imatinib400, Nilotinib and Dasatinib Is a Major Prognostic Factor for Failure-Free and Progression-Free Survival	Imatinib, nilotinib, and dasatinib
JCO 2012	Marin et al., JCO 2012	Assessment of BCR-ABL1 transcript levels at 3 months is the only requirement for predicting outcome for patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors.	Imatinib and dasatinib
EHA 2012	Hochhaus et al., EHA 2012	Early BCR-ABL Transcript Levels Predict Future Molecular Response And Long-term Outcomes In Newly-diagnosed Patients With CML-CP: Analysis Of ENESTnd 3-year Data	Imatinib and nilotinib
	Jabbour et al., EHA 2012	An exploratory analysis from 3 year DASISION follow-up examining the impact on patient outcomes of early complete cytogenetic responses at 3 months and major molecular responses at 12 months	Imatinib and dasatinib
ASH 2012	Hochhaus et al., ASH 2012	Outcome of Patients with CML-CP Based on Early Molecular Response and Factors Associated with Early Response: 4-Year Follow-up Data from ENESTnd	Imatinib and nilotinib

Molecular and Cytogenetic Response at 3 Months^a



EHA 2012

- BCR-ABL of $<10\%$ and $\le 1\%$ are not fully concordant with $\ge \text{PCyR}$ and CCyR , respectively
 - 96% and 83% of dasatinib and imatinib pts with $\ge \text{PCyR}$ had $<10\%$ BCR-ABL, respectively
 - 68% and 26% of dasatinib and imatinib pts with CCyR had $\le 1\%$ BCR-ABL, respectively

^a Calculated from total number of evaluable patients with PCR assessments at 3 months; restricted to subjects with B2A2 and B3A2 transcripts

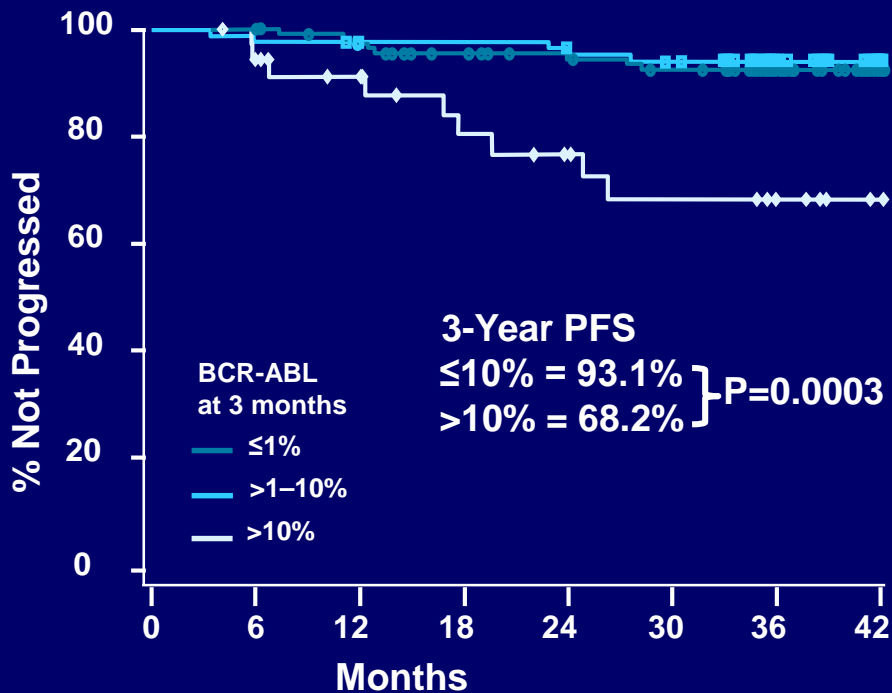
Survival without progression to accelerated and blastic phase according to BCR-ABL Level at 3 Months^a

Dasatinib 100 mg QD

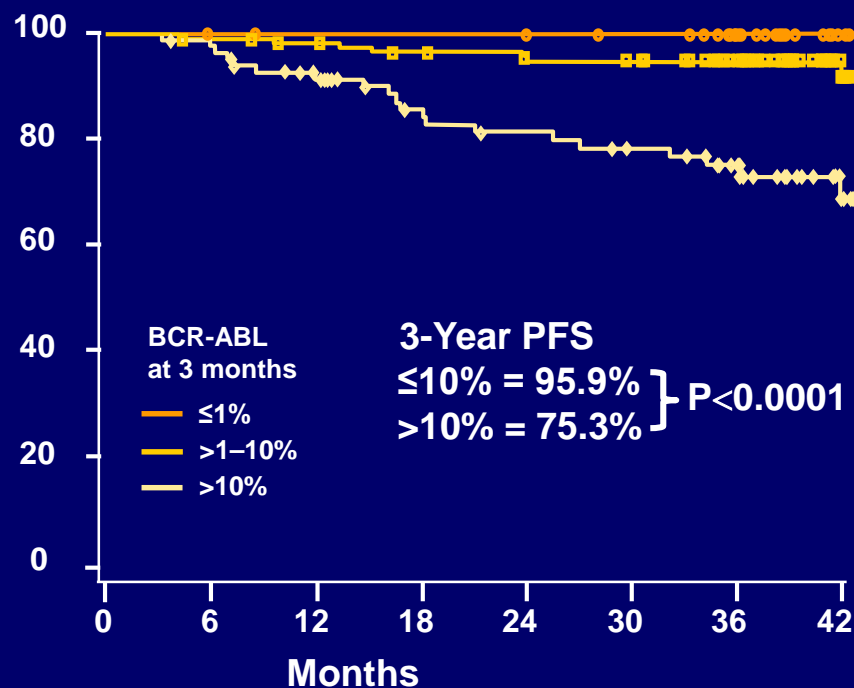
84% had $\leq 10\%$ BCR-ABL

Imatinib 400 mg QD

64% had $\leq 10\%$ BCR-ABL



Subjects at risk



Subjects at risk

European LeukemiaNet: Definitions of Response to TKIs Frontline

Time	Optimal	Warning	Failure
Diagnosis	–	High risk CCA in Ph+	–
3 months	PCgR And/or < 10%	minorCgR to 95% Ph+ And/or > 10%	No CHR and/or 95% Ph+
6 months	CCyR and/or < 1%	< CCgR to minor CgR and/or 1-10%	< minor CgR and/or > 10%
12 months	MMR	<0.1-1%	> 1% Ph+ and/or > 1%

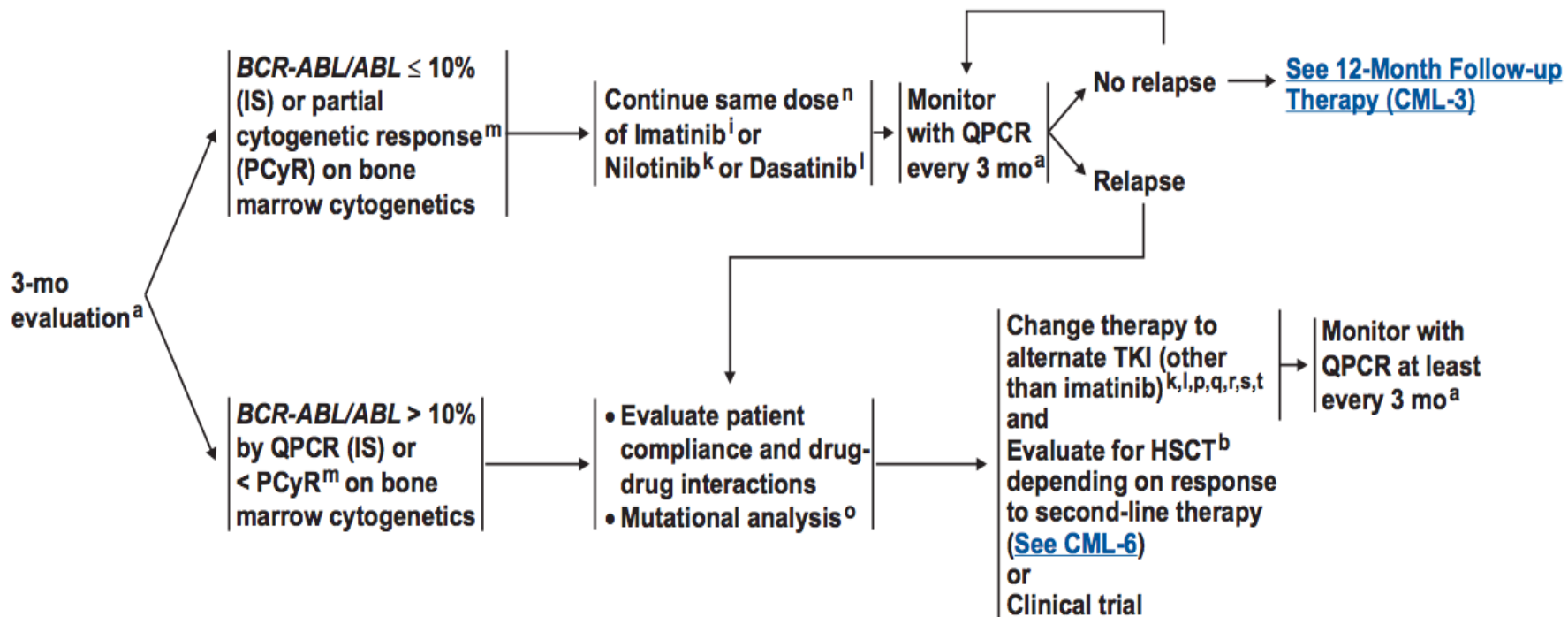
European LeukemiaNet: Definitions of Response to TKIs Frontline

Time	Optimal	Warning	Failure
Diagnosis	–	High risk CCA in Ph+	–
3 months	PCgR And/or < 10%	minorCgR to 95% Ph+ And/or > 10%	No CHR and/or 95% Ph+ And/or > 10%*
6 months	CCyR and/or < 1%	< CCgR to minor CgR and/or 1-10%	< minor CgR and/or > 10%
12 months	MMR	<0.1-1%	> 1% Ph+ and/or > 1%

* As clinically largely accepted

NCCN Guidelines V. 4/13, 3-months milestone

3 MONTH FOLLOW-UP THERAPY^a



2013 - PROVISIONAL TREATMENT CONSIDERATIONS

1st LINE

IMATINIB 400 mg (600-800 ?)
NILOTINIB 300 mg twice daily
DASATINIB 100 mg once daily

2nd LINE

- INTOLERANCE
- SUBOPTIMAL RESPONSE
- FAILURE

Change to “ANOTHER TKI”

/////

- ✓ IMA > nilotinib or dasatinib
- ✓ NILOTINIB > dasatinib
- ✓ DASATINIB > nilotinib
- ✓ ALLOGENEIC SCT
- ✓ Experimental Treatment
- ✓ Allogeneic SCT
- ✓ Experimental Treatment
- ✓ Change to “another TKI”

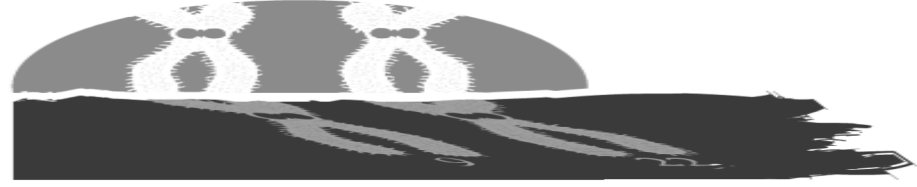
3rd LINE



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