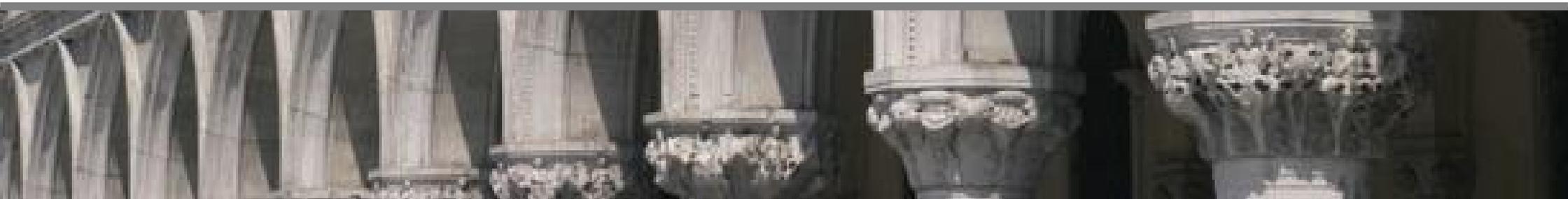




# Response Definition, Evaluation and Monitoring

**Michele Baccharani**





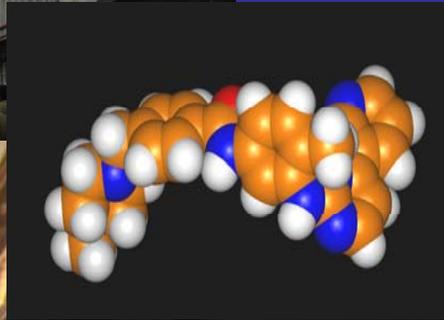
# European LeukemiaNet

## EVOLVING CONCEPTS IN THE MANAGEMENT OF CHRONIC MYELOID LEUKEMIA

VENICE 8 – 9 MAY 2006

Response definition, evaluation and  
monitoring

Michele Baccarani



# COMPLETE HEMATOLOGIC RESPONSE

- PLATELET COUNT <math>< 450 \times 10^9/L</math>
- WBCC <math>< 10 \times 10^9/L</math>
- DIFFERENTIAL WITHOUT IMMATURE GRANULOCYTES (MC,PMC,MB) AND WITH LESS THAN 5% BASOPHILS
- NON-PALPABLE SPLEEN

CHECK EVERY 2 WEEKS UNTIL ACHIEVED AND CONFIRMED, HENCE EVERY 3 MONTHS UNLESS OTHERWISE REQUIRED

# **CYTOGENETIC RESPONSE**

## **BY CONVENTIONAL CYTOGENETICS**

**COMPLETE**

**Ph+ 0**

**PARTIAL**

**Ph+ 1-35%**

**MINOR**

**Ph+ 36-65%**

**MINIMAL**

**Ph+ 66-95%**

**NONE**

**Ph+ >95%**

**CHECK EVERY 6 MONTHS UNTIL A CC<sub>g</sub>R HAS BEEN ACHIEVED AND CONFIRMED, HENCE EVERY 12 MONTHS**

**FISH AT BASELINE, HENCE IF MARROW CANNOT BE OBTAINED OR METAPHASES CANNOT BE ANALYZED**

# MOLECULAR RESPONSE

**COMPLETE = BCR-ABL TRANSCRIPTS NON  
QUANTIFIABLE AND NON  
DETECTABLE**

**MAJOR = BCR-ABL<sup>IS</sup> ≤ 0.10\***

\*BCR-ABL to control gene ratio according to the international scale (IS)

**CHECK EVERY 3 MONTHS**

**BLOOD 5 - 20 ml**

# MUTATIONAL ANALYSIS

**PRIOR TO TREATMENT ? NO – WE SHOULD STORE THE CELLS FOR INVESTIGATIONAL PURPOSES**

**DURING TREATMENT ?** IN CASE OF FAILURE  
IN CASE OF SUBOPTIMAL RESPONSE  
IN CASE OF SUSTAINED /  
CONFIRMED INCREASE OF BCR-ABL TRANSCRIPTS LEVEL

**SCIENTIFIC VALUE ?** OUTSTANDING

**CLINICAL VALUE ?** IT IS REQUIRED TO PLAN TREATMENT CHANGES

<b>TIME</b>	<b>FAILURE</b>	<b>SUBOPTIMAL RESPONSE</b>	<b>WARNINGS</b>
<b>DIAGNOSIS</b>	<b>NA</b>	<b>NA</b>	- <b>HIGH RISK</b> - <b>Del 9q+</b> - <b>ACA IN Ph+ CELLS</b>
<b>3 MONTHS</b>	- <b>NO HR</b>	- <b>LESS THAN CHR</b>	
<b>6 MONTHS</b>	- <b>LESS THAN CHR</b> - <b>Ph+ &gt; 95%</b>	- <b>Ph+ &gt; 35%</b>	
<b>12 MONTHS</b>	- <b>Ph+ &gt; 35%</b>	- <b>Ph+ 1 - 35%</b>	- <b>MMoLR<sup>IS</sup> &gt; 0.10</b>
<b>18 MONTHS</b>	- <b>Ph+ 1 - 35%</b>	- <b>MMoLR<sup>IS</sup> &gt; 0.10</b>	
<b>ANY TIME</b>	- <b>LOSS OF CHR</b> - <b>LOSS OF CCgR</b> - <b>MUTATIONS*</b>	- <b>LOSS OF MMoLR</b> - <b>ACA IN Ph+CELLS</b> - <b>MUTATIONS**</b>	- <b>ANY RISE IN TRANSCRIPT LEVEL</b> - <b>ACA IN Ph+ CELLS</b>

**\* HIGH / \*\*LOW LEVEL OF INSENSIVITY TO IMATINIB**

# **CML - DEFINITION OF THE RESPONSE TO IMATINIB**

**FAILURE** - MEANS THAT CONTINUING IMATINIB TREATMENT AT THE CURRENT DOSE IS NO LONGER APPROPRIATE FOR THE PATIENT, WHO WOULD LIKELY BENEFIT MORE FROM OTHER TREATMENTS.

# **CML - DEFINITION OF THE RESPONSE TO IMATINIB**

**SUBOPTIMAL RESPONSE - MEANS THAT THE PATIENT MAY STILL HAVE A SUBSTANTIAL BENEFIT FROM CONTINUING IMATINIB AT THE CURRENT DOSE, BUT THAT THE LONG-TERM OUTCOME OF THE TREATMENT WOULD NOT LIKELY BE FAVORABLE. THE PATIENT IS ELIGIBLE FOR OTHER TREATMENTS.**

# **CML - DEFINITION OF THE RESPONSE TO IMATINIB**

**WARNINGS** - STANDARD DOSE IMATINIB MAY NOT BE THE BEST CHOICE. THE CASE REQUIRES MORE CAREFUL MONITORING. THE PATIENT MAY BECOME ELIGIBLE FOR OTHER TREATMENTS

# **FAILURE**

**3 MONTHS** - **NO HR (Stable disease / disease progression)**

**6 MONTHS** - **NO COMPLETE HR, or**  
- **NO CgR (Ph POS > 95%)**

**12 MONTHS** - **LESS THAN PARTIAL CgR (Ph POS > 35%)**

**18 MONTHS** - **LESS THAN COMPLETE**  
**CgR (Ph POS  $\geq$  1 %)**

# SUBOPTIMAL RESPONSE

- 3 MONTHS** - LESS THAN COMPLETE HR
- 6 MONTHS** - LESS THAN PARTIAL CgR (Ph POS > 35%)
- 12 MONTHS** - LESS THAN COMPLETE CgR  
(Ph POS  $\geq$  1%)
- 18 MONTHS** - LESS THAN MAJOR MOL RESPONSE  
(BCR-ABL<sup>IS</sup> > 0.10)

# WARNINGS

**DIAGNOSIS** - **HIGH RISK**  
- **DEL 9q +**  
- **ADDITIONAL CHROMOSOME**  
**ABNORMALITIES IN Ph POS CELLS**

**12 MONTHS** - **LESS THAN MAJOR MOL RESPONSE**  
(**BCR-ABL<sup>IS</sup> > 0.10**)

**ANY TIMES** - **ANY RISE IN BCR-ABL TRANSCRIPTS**  
**LEVEL**  
- **other chromosome abnormalities in Ph neg cells**

	<b>Phase II and Iris Study (2003)</b>	<b>Italian Studies (2004)</b>	<b>Houston Studies (2003/2004)</b>	<b>German Studies (2003)</b>
Symptoms			none	none
Extramedullary Involvement	none	*	*	*
Spleen	(non spec)	non palp	non palp	non palp
Platelet	< 450	< 450	< 450	140-450
WBCC	< 10	< 10	< 10	< 10
Myeloblasts/ Promyelocytes	none	none	none	none
Myelocytes/ Metamyelocytes	< 5%	none	none	none
Basophils	< 20%	(normal)	(normal)	(normal)

\*Defining accelerated phase or blast crisis

Kantarjian et al, NEJM 2002; 346: 645-652 – O'Brien et al, NEJM 2003; 348: 994-1004 – Rosti et al, Blood 2004: 103; 2284-2290 – Baccarani et al, Blood 2004; 104: 4245-4251 – Cortes et al, Blood 2003; 102: 83-86 – Kantarjian et al, Blood 2004; 103: 2873-2878 – Hehlmann et al, Leukemia 2003; 17: 1529-1537

# CYTOGENETIC RESPONSE

<b>6 MONTHS</b>	<b>- NONE (Ph+ &gt; 95%)</b> <b>- LESS THAN</b> <b>PARTIAL (Ph+ &gt; 35%)</b>	<b>FAILURE</b> <b>SUBOPTIMAL RESPONSE</b>
<b>12 MONTHS</b>	<b>- LESS THAN</b> <b>PARTIAL (Ph+ &gt; 35%)</b> <b>- LESS THAN</b> <b>COMPLETE</b> <b>(Ph + 1-34 %)</b>	<b>FAILURE</b> <b>SUBOPTIMAL RESPONSE</b>
<b>18 MONTHS</b>	<b>- LESS THAN</b> <b>COMPLETE</b> <b>(Ph+ 1 - 34%)</b>	<b>FAILURE</b>
<b>ANY TIMES</b>	<b>- LOSS OF CCgR</b>	<b>FAILURE</b>

# MOLECULAR RESPONSE

<b>12 MONTHS</b>	<b>- LESS THAN MAJOR (&gt; 0.10)</b>	<b>WARNING</b>
<b>18 MONTHS</b>	<b>- LESS THAN MAJOR (&gt; 0.10)</b>	<b>SUBOPTIMAL RESPONSE</b>
<b>ANY TIMES</b>	<b>- LOSS OF MM<sub>0</sub>IR</b>	<b>SUBOPTIMAL RESPONSE</b>
	<b>- ANY RISE IN TRANSCRIPT LEVEL</b>	<b>WARNING</b>
	<b>- MUTATION</b>	<b>FAILURE/SUBOPTIMAL RESPONSE</b>

**LOSS OF CHR**

**FAILURE**

**LOSS OF CCgR**

**FAILURE**

**MUTATION**

**FAILURE/SUBOPTIMAL RESPONSE**

**ADD. CHROMOSOME  
ABNORMALITIES  
IN Ph+ CELLS**

**SUBOPTIMAL RESPONSE**

**LOSS OF MMoIR**

**SUBOPTIMAL RESPONSE**

**ANY RISE IN BCR-ABL  
TRANSCRIPTS LEVEL**

**WARNING**

**CHROMOSOME  
ABNORMALITIES  
IN Ph NEG CELLS**

**WARNING**

<b>TIME</b>	<b>FAILURE</b>	<b>SUBOPTIMAL RESPONSE</b>	<b>WARNINGS</b>
<b>DIAGNOSIS</b>	<b>NA</b>	<b>NA</b>	- <b>HIGH RISK</b> - <b>Del 9q+</b> - <b>ACA IN Ph+ CELLS</b>
<b>3 MONTHS</b>	- <b>NO HR</b>	- <b>LESS THAN CHR</b>	
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**\* HIGH / \*\*LOW LEVEL OF INSENSIVITY TO IMATINIB**

# MONITORING THE RESPONSE

	3	6	9	12	
<b>*CYTOGENETICS (MARROW)</b>	<b>(X)</b>	<b>X</b>		<b>X</b>	<b>q 6-12 MO</b>
<b>RT-Q-PCR</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>q 3 MO</b>
<b>MUTATIONAL ANALYSIS</b>	<b>ONLY IN CASE OF FAILURE, SUBOPTIMAL RESPONSE, OR SUSTAINED – CONFIRMED INCREASE OF BCR-ABL TRANSCRIPTS LEVEL</b>				

**\*FISH SHOULD BE DONE BEFORE TREATMENT (Del9 q+) AND CAN BE USED DURING TREATMENT IF CONVENTIONAL CYTOGENETICS FAILS OR CANNOT BE OBTAINED**

EVOLVING CONCEPTS IN THE MANAGEMENT OF CHRONIC MYELOID LEUKEMIA



RECOMMENDATIONS FROM AN EXPERT PANEL ON BEHALF OF THE EUROPEAN LEUKEMIANET