Presentation on

Monitoring patients with CML on tyrosine kinase inhibitors(TKIs)

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Summery

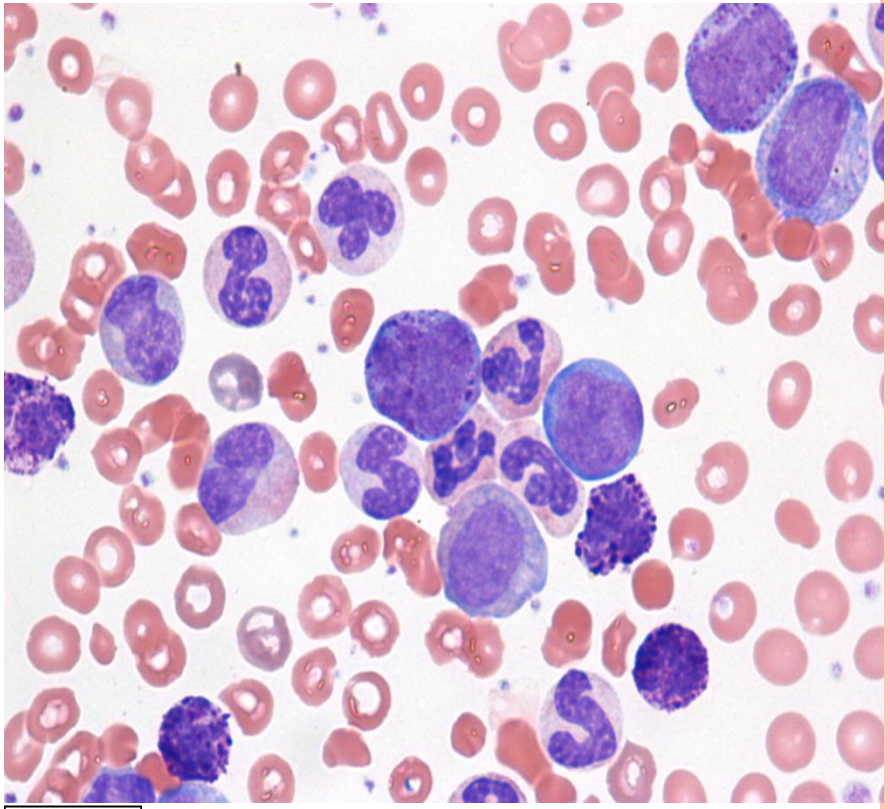
- Brief introduction on CML
- Discussion on TKI therapy
- Current goals of monitoring chronic phase (CP) CML patients
- Prevention of CML progression and monitoring for intolerance and resistance.
- The rationale for long-term monitoring is also reviewed

Brief introduction on CML

CML – Peripheral Blood and BM Findings

Peripheral smear can only give a presumptive diagnosis of CML [to confirm the t(9;22)]:

1) leukocytosis with a 'left shift'
2) normocytic anemia
3) thrombocytosis in 50% of pts
4) absolute eosinophilia
5) absolute and relative increase in basophils
6) LAP score is low.



Brief introduction on CML

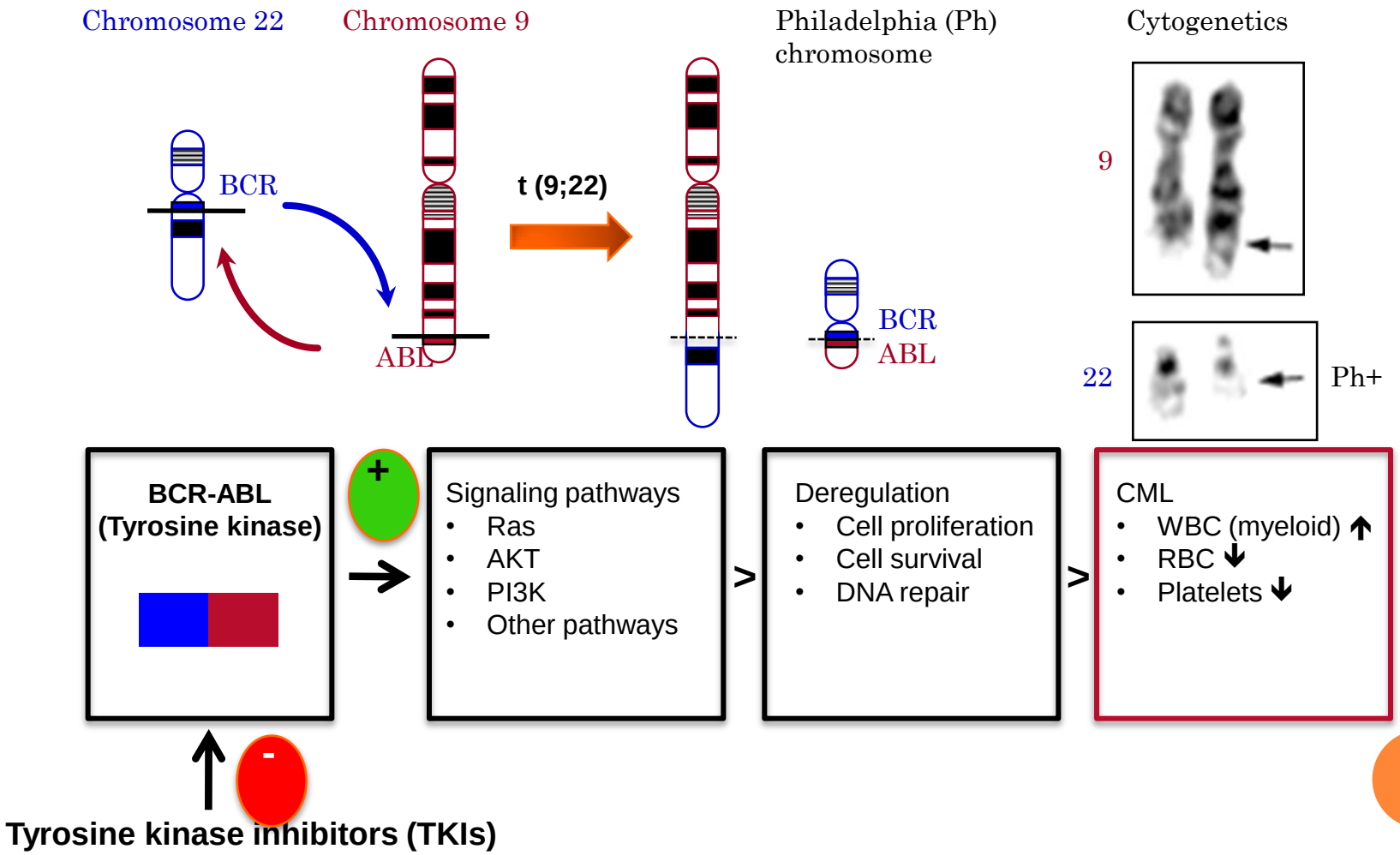
- The presence of *BCR/ABL* rearrangement is the hallmark of CML, and responsible for accelerated cell growth and decelerated cell death

Brief introduction on CML

CML is unique

- Single chromosomal abnormality, the (Ph), as the aetiology of the disease.
- Best success stories for allogeneic transplantation,
- First successful molecular targeted therapy
- Molecular monitoring of so-called “minimal residual disease” by (RT-PCR) techniques predictive of future relapse.

Biology of CML



Brief introduction on CML

- **History of CML**

History of CML

- First described in early nineteenth century(1845 Rudolph virchow)
- In 1960, Nowell and Hungerford detected the Philadelphia chromosome (22q-).
- In 1973, Rowley identified the reciprocal translocation involving chromosome 9 : t(9;22)(q34;q11).
- In 1980s, the unique fusion gene termed BCR-ABL was discovered.

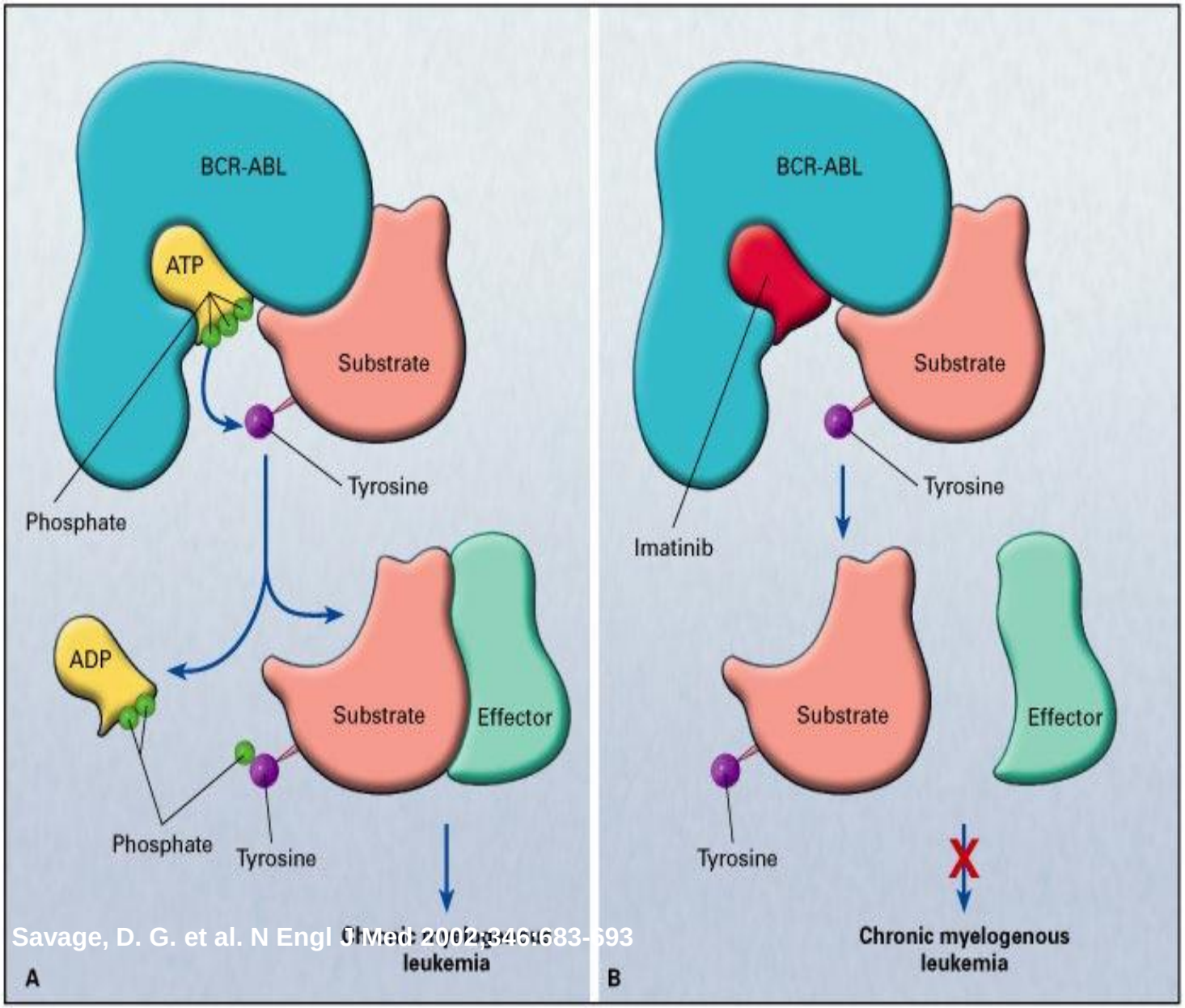
Treatment History

- Treatment in the nineteenth century was unsatisfactory
- Busulphan started in 1950
- Hydroxycarbamide replaced busulphan
- First successful allotransplant in CML-1975
- Interferon alfa first agent to induce philadelphia negetivity-1980

Treatment History

Revolutionary introduction of Tyrosine kinase inhibitor(TKI)-Imatinib msylate

- First targted therapy in cancer
- FDA approved as first line treatment for CML in the year 2001.



Savage, D. G. et al. N Engl J Med 2002;346:683-693

Imatinib Mesylate

- Imatnb was discovered 20 years back
- Highly effective in the treatment of CML
- Revolutionized the treatment of CML
- Served as a paradigm of success for targeted drug therapy in cancer treament
- Several new TKIs approved over the last 2 decades

TKI Treatment recommendation

As of 2017, 5 TKIs are available in the United States,

- 3 as first-line
- imatinib mesylate (IM),
- dasatinib (DAS), and nilotinib (NIL),
- and 5 as second-line (IM, DAS, NIL, bosutinib, and ponatinib).

Second-generation TKIs are increasingly used as first-line therapy.

TKI Treatment recommendation

Chronic phase	
First line	Imatinib 400 mg, or nilotinib 300 mg × 2, or dasatinib 100 mg
Second line	In case of intolerance, switch to another TKI, taking into consideration the side effects of the first TKI, and comorbidities
	In case of failure of imatinib, switch to nilotinib, or dasatinib, taking into consideration the presence and the type of BCR-ABL KD mutation
	In case of failure of nilotinib or dasatinib, switch to dasatinib or nilotinib, taking into consideration the presence and the type of BCR-ABL KD mutation. Consider alloHSCT
Third line	In case of failure of two or three TKI, consider alloHSC
Accelerated/blastic phase	
TKI naïve	Imatinib 600 or 800 mg, or nilotinib 400 mg × 2 or dasatinib 140 mg, and consider alloHSCT
TKI pretreated	Switch to another TKI, consider chemotherapy and alloHS

Adverse effects of Imatinib

- Myelosupression (single lineage or pancytopenia),cause unknown
- Neutropenia can be managed by granulocyte colony-stimulating factor (G-CSF) 300 µg/kg (daily, alternate daily, or once weekly),- and
- Anemia usually responds to erythropoietin.
- Severe thrombocytopenia may necessitate temporary interruption of IM.

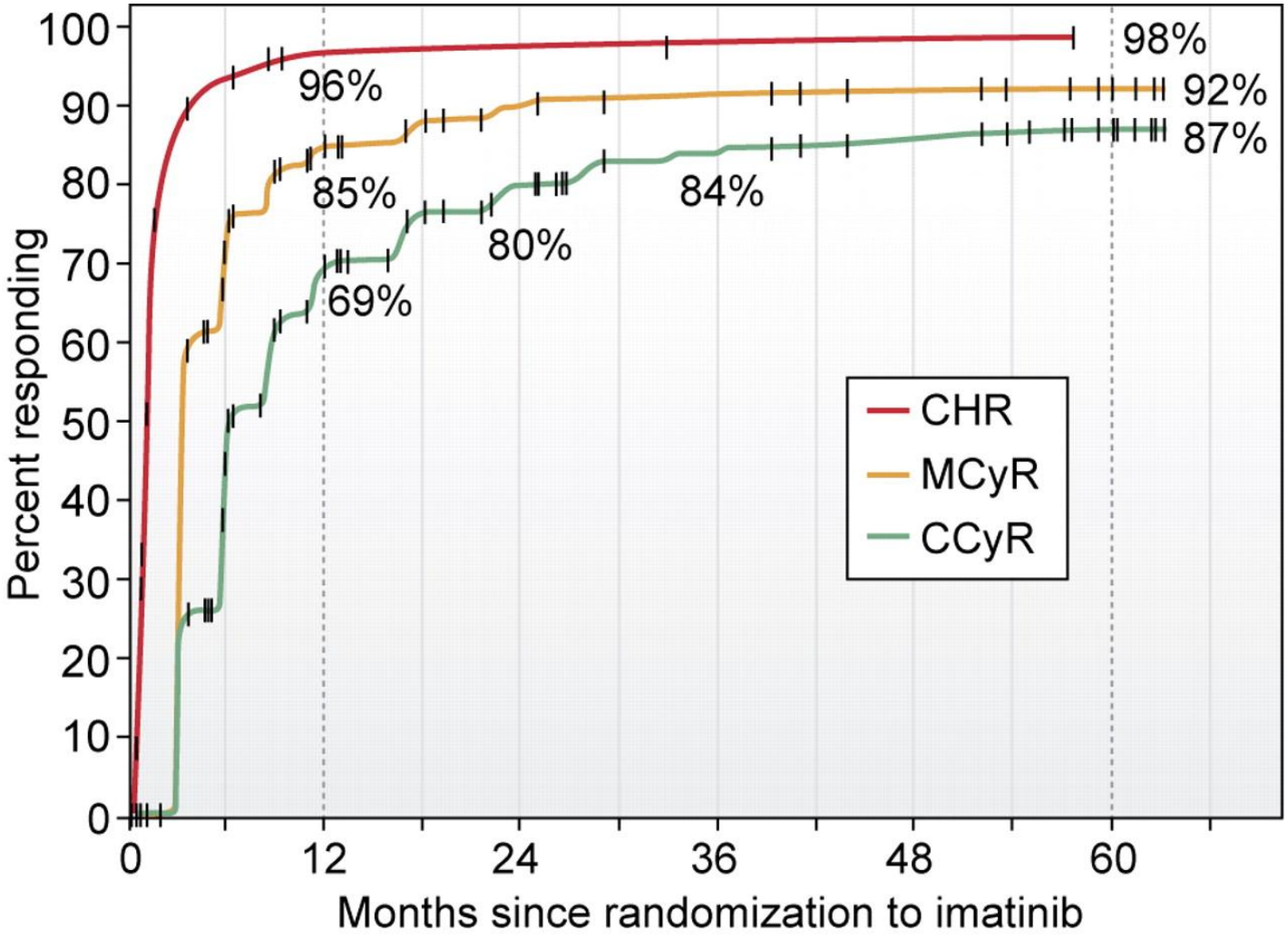
It is recommended that the drug should be stopped entirely and then resumed when the cytopenia has resolved rather than reducing the dosage lower than 300 mg/day.

Adverse effects of Imatinib

Adverse effects of Imatinib (Nonhematologic toxic effects**)**

- Infraorbital **edema** or rarely more generalized edema.
- **Pains** in bones and joints may occur.
- A variety of **rashes**
- Abnormalities of **liver enzymes** that necessitate interrupting treatment. Occasional patients have proceeded to hepatic failure.
- Hypo-phosphatemia associated with decreased levels of calcium AND vitamin D,
- Adverse effects do not usually recur with other TKIs.

Survival for previously untreated chronic-phase patients who received imatinib 400 mg daily as initial therapy for newly diagnosed CML in chronic phase.



Goldman J M Blood 2007;110:2828-2837

Monitoring of CML

- Molecular monitoring was used in the TKI trials as a measure of disease response
- Monitoring is now advocated for the routine clinical care of CML.

Monitoring of CML in the imatinib era

Monitoring of CML on Imatinib

- Why?
- How?
- When?

Monitoring of CML in the imatinib era

Monitoring of CML

- Why?
  - To see ***desired response*** to treatment
  - To asses serial achievement of treatment milestone
- Assessment of adherence to treatment are essential for successful outcomes
- Identify patients at risk for failing therapy.

Response to treatment with Imatinib

Monitoring of CML on Imatinib

- How?

Summery of monitoring

Monitoring Includes assessment of

- Hematologic response
- Cytogenetic response
- Molecular response

Monitoring of CML in the imatinib era

Response to treatment with Imatinib

Response occurs in an orderly manner, first with the

- Restoration of spleen size to normal
- Normalization of the blood count
- Reversion of bone marrow Ph negativity
- Reduction in the number of BCR-ABL transcripts in the blood and bone marrow to very low or undectable levels

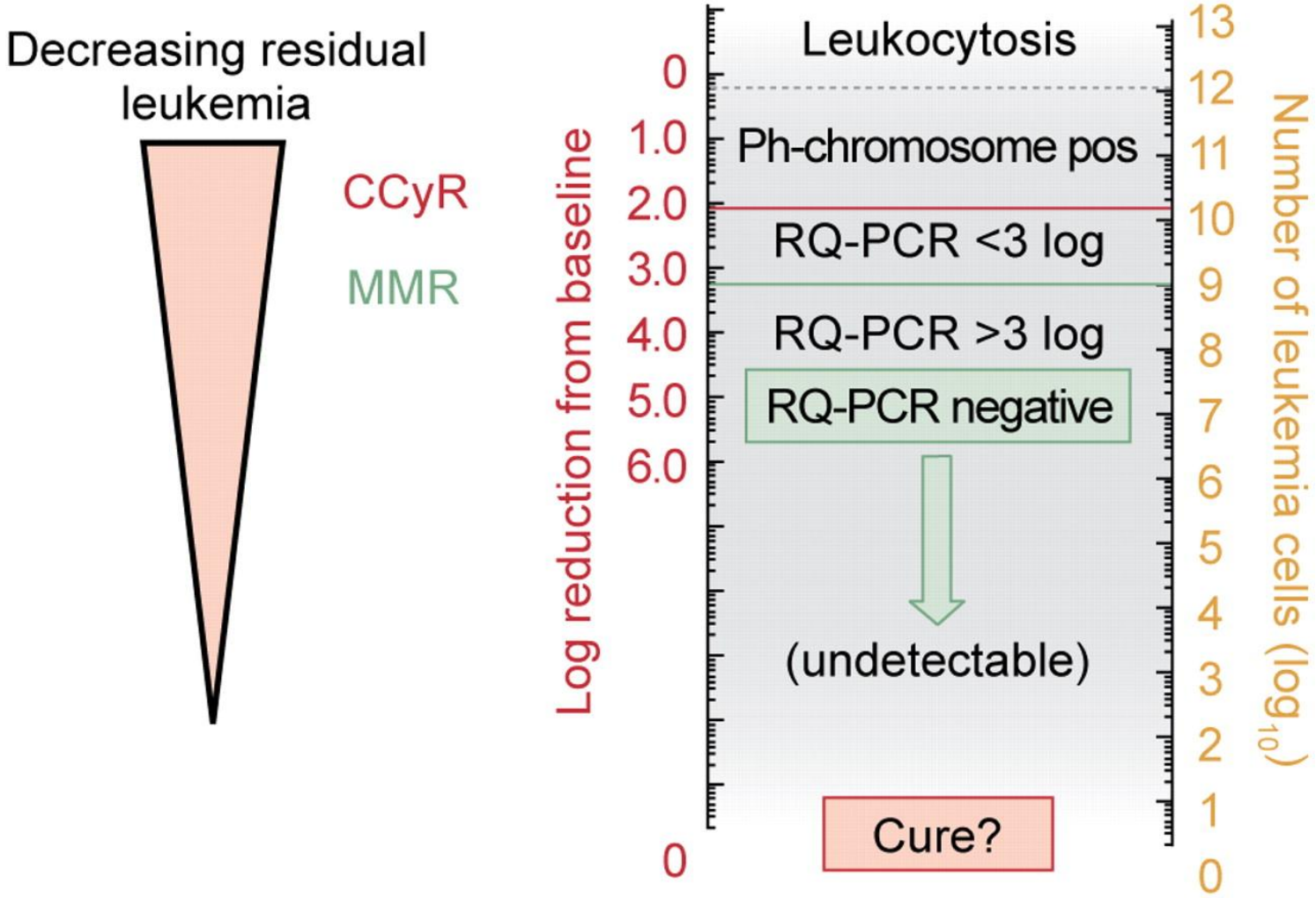
These criteria can be used sequentially to monitor the response.

Monitoring of CML in the imatinib era

Molecular monitoring

- Molecular monitoring of BCR-ABL transcripts (RQ-PCR) has become an integral component for management of patients with chronic myeloid leukaemia (CML) on TKIs
- An important assessment is molecular analysis using ***RQ-PCR at diagnosis.***

Schematic representation of decreasing residual disease related to numbers of BCR-ABL transcripts in the peripheral blood (left scale) and estimated number of residual leukemia cells in a patient's body (right scale)



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Monitoring of CML in the imatinib era

The definitions of molecular response

Major molecular response (MMR).

- The absolute BCR-ABL value representing MMR is standardized at 0.1%.

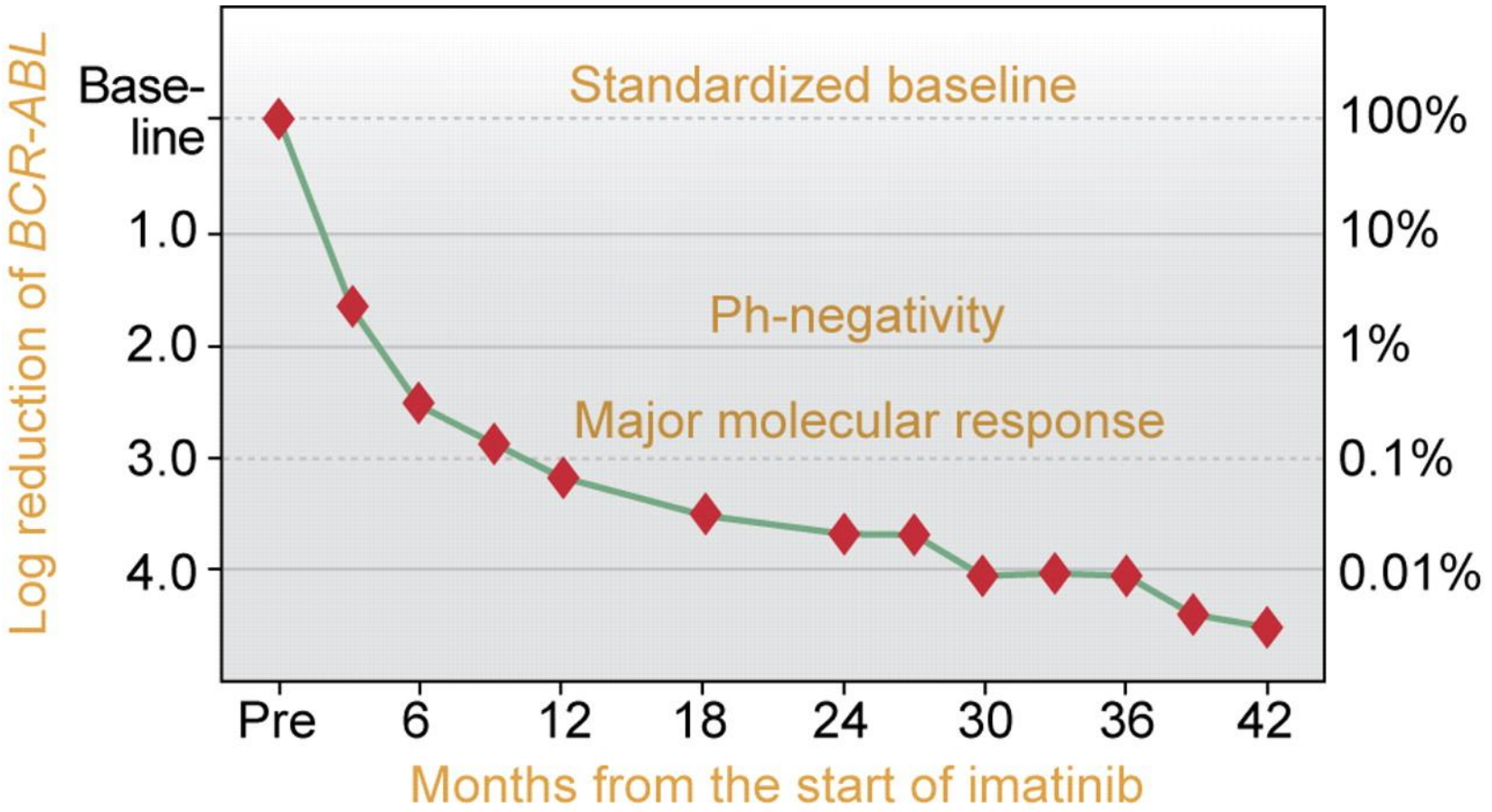
Monitoring of CML in the imatinib era

The definitions of molecular response

- Deep molecular response **(MR)**
- Unlike MMR, there are various definitions of deep molecular response (MR)
  - MR 4.0 (*BCR-ABL1*), ≤ 0.01%
  - MR 4.5 (*BCR-ABL1* ≤ 0.0032%),
  - MR 5.0 (*BCR-ABL1* ≤ 0.001)

even with the most sensitive assay, complete molecular remission is consistent with the persistence in the patient's body of up to 10^6 or 10^7 leukemia cells.

Schematic representation of the reduction in BCR-ABL transcript numbers after start of imatinib for CML in chronic phase.



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Monitoring of CML in the imatinib era

Summry of goal of response

- <10% IS by 3months (lack of MCyR)
- <1% IS at 6months (CCyR)
- <0.1% at 12 months (MMR)

- Failure to achieve major cytogenetic response or reduce *BCR-ABL1* below 10% IS level by 3 and 6 months is predictive of poorer outcome.
- High-risk patients were also those in whom *BCR-ABL1* remained above 1% IS at 6 months.

Monitoring of CML in the imatinib era

Why molecular monitoring is important?

Monitoring is fundamental for achieving optimal patient outcomes.

- degree of reduction of BCR-ABL correlates with progression-free survival.
- It will allow the initiation of timely therapeutic intervention for patients with a
  - **suboptimal response**
  - **kinase inhibitor therapy failure.**
  - **non adherence**
  - To asses eligibility for a discontinuation trial **(TFR)**

Definitions of failure or suboptimal response to imatinib

Time	Failure	Suboptimal response	Warnings
Diagnosis	NA	NA	High risk; del(9q$^+$); ACA in Ph-positive cells
3 mo	No HR; stable disease or disease progression	Less than CHR	NA
6 mo	Less than CHR; no cytogenetic response: Ph$^+$ more than 95%	Less than PCyR: Ph$^+$ more than 35%	NA
12 mo	Less than PCyR: Ph$^+$ more than 35%	Less than CCyR	Less than MMR
18 mo	Less than CCyR	Less than MMR	NA
Any time	Loss of CHR; loss of CCyR; mutation (eg, T315I)	ACA in Ph$^+$ cells; loss of MMR; mutation	Any rise in transcript level; ACA in Ph-negative cells

Monitoring of CML in the imatinib era

Management of suboptimal response

- Category **"failure"** should be changed to alternative therapy and
- Category **"suboptimal response"** should be considered for a change in therapeutic strategy.
- Category, **"warnings,"** patient who expected to respond less well to IM. Such patients should presumably continue IM but should be monitored more closely than average.

Monitoring of response to therapy

- For how long should the drug be continued in patients who have achieved and maintain a complete molecular response?
  - Life long
  - **TFR** can be tried in clinical trial by confirming sustained undetectable BCR-ABL
  - Documentation of sustained MR4.5 over 2 years can be a candidate for a discontinuation

THANK YOU