مؤسسة مستشفى سرطان الأطفال-مصر
Children's Cancer Hospital Foundation - Egypt
57357

Tyrosine kinase inhibitor

Prepared by Dispense team

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Agenda

- Clinical case
- Philadelphia chromosome
- Imatinib
- Dasatinib
- Nilotinib
- Sorfinib

A known case of 7 years old, digonsed as ALL Ph + start on dasatinib, with poor response.

1. Ph + .
2. Response monitoring
3. Dasatinib

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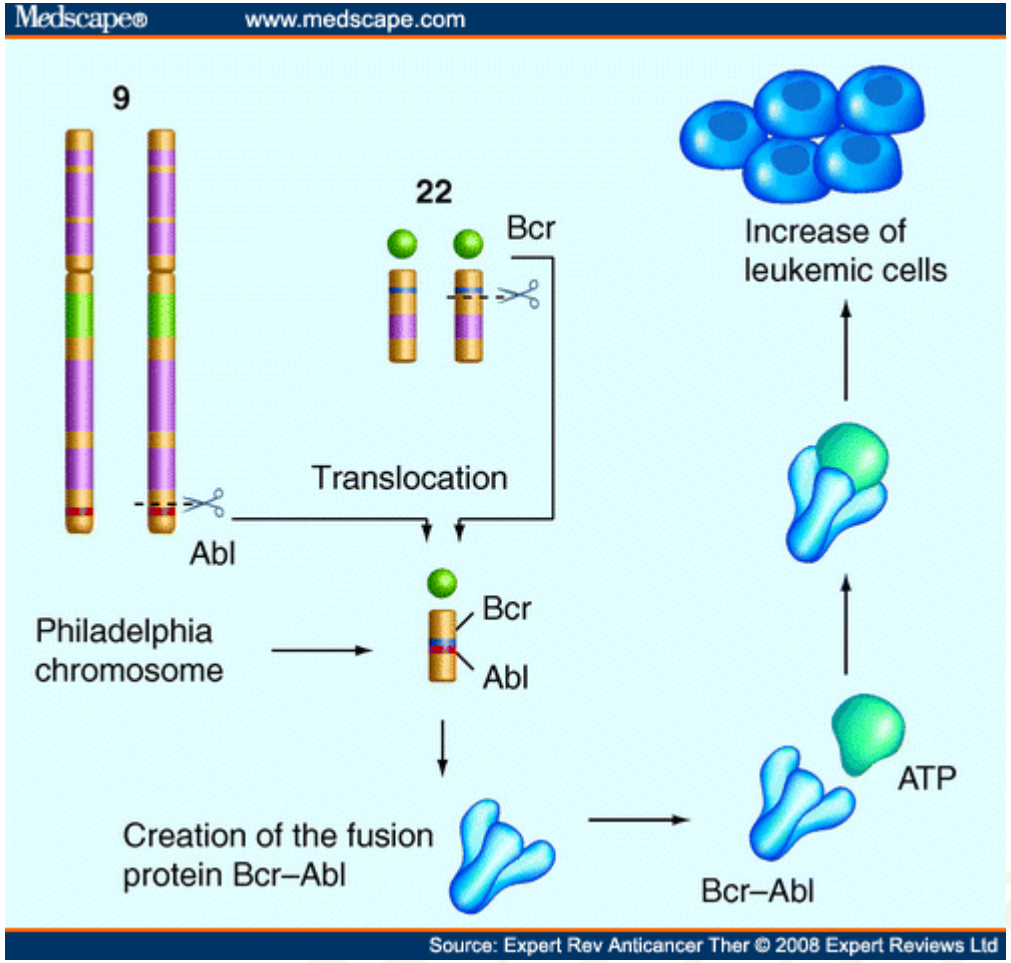
Philadelphia chromosome

The Philadelphia (Ph) chromosome is an abnormal chromosome that is made when pieces of chromosomes 9 and 22 break off and trade places. The ABL gene from chromosome 9 joins to the BCR gene on chromosome 22 to form the BCR::ABL fusion gene. The changed chromosome 22 with the fusion gene on it is called the Ph chromosome. BCR-ABL1 can promote cell proliferation and block apoptosis



Cytogenetics Report									
FISH for t(9;22), BCR/ABL									
Chromsomal Analysis								CG-20-00279C	

* Final Report *

CG-20-002790

Chromosome Analysis Report

Accession Number: CG-20-002790
Collected Date/Time: 08/07/2020 13:37
Sample Type: Bone Marrow

Culture type:
16

Karyotype
46, XX, t(9;22)(q34;q11)[10]

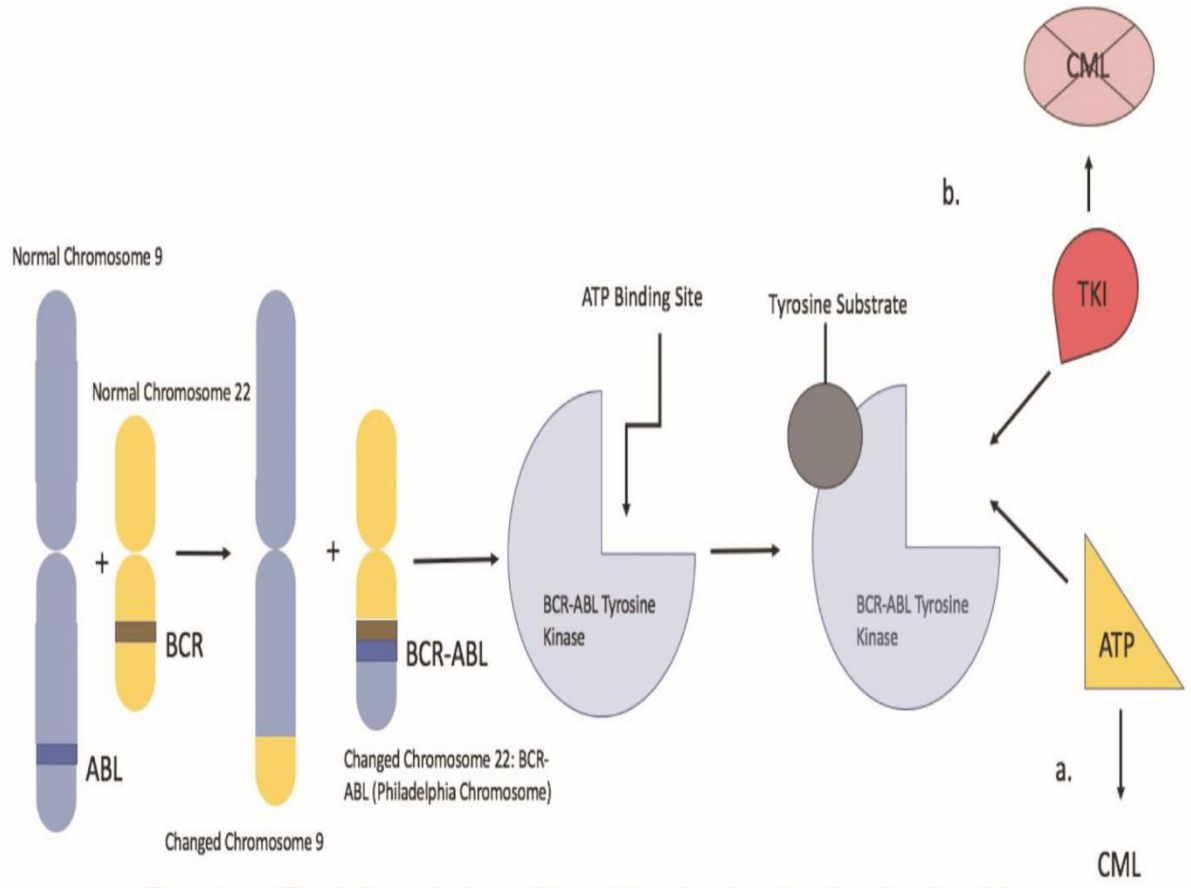
Comment:
Karyotype showing Philadelphia chromosome

950-20

Tyrosine kinase inhibitor

Tyrosine kinase inhibitors (TKIs) are a type of targeted therapy. A targeted therapy identifies and attacks specific types of cancer cells while causing less damage to normal cells. In CML, TKIs target the abnormal BCR::ABL1 protein that causes uncontrolled CML cell growth and block its function, causing the CML cells to die ,induces hematologic and molecular remission in 80–90% of CML patients, with a survival rate comparable to that of age-matched healthy individuals:

- Imatinib mesylate (Gleevec®)
- Dasatinib (Sprycel®)
- Nilotinib (Tasigna®)



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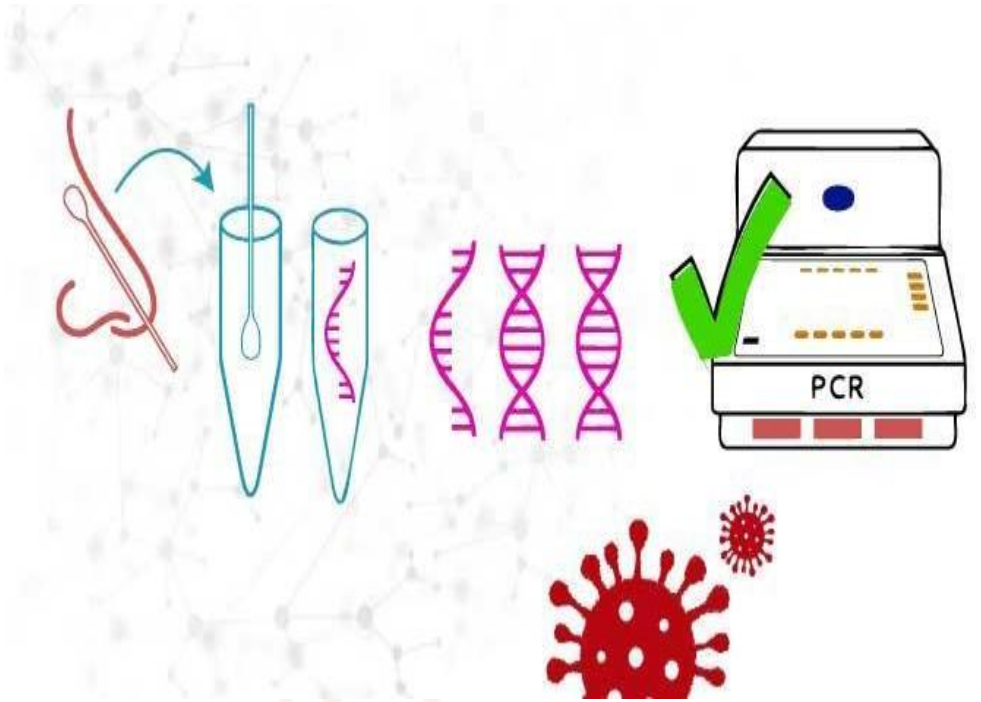
Molecular diagnostic test



Detection of the BCR-ABL1 transcript level by quantitative reverse-transcriptase polymerase chain reaction (RQ-PCR) is the gold standard method for monitoring CML **minimal residual disease (MRD)** and the optimal CML patient management. To detect response **to treatment and choosing the best therapeutic strategy**.

- General Hematology
- Routine Chem
- Molecular Hematology Report

Quick View	12:17 Etc/GMT-2	11:37 Etc/GMT-2	09:21 Etc/GMT-2	12:15 Etc/GMT-2	12:23 Etc/GMT-2	11:22 Etc/GMT-2	11:35 Etc/GMT-2	12:14 Etc/GMT-2	09:34 Etc/GMT-2	10:38 Etc/GMT
Molecular Hematology Report										
MRD CML By Molecualr		MH-23-000786								
Measurements										

Document Viewer - AZEZ, SHENODA ADEL BEBAWY - 20143383

Accession Number: MH-23-000786
Collected Date/Time: 20/03/2023 11:37
Sample Type: Blood
Lab Number: 6976/2719.
Method: RT-qPCR

MRD By Molecular For CML
(By Xpert BCR-ABL Ultra (Gene expert)

FGcn/HKcn Ratio:

Log Reduction :

Previous Results:

Date	Result
19/12/2022	MR: > 4.52
19/09/2022	MR: 4.17

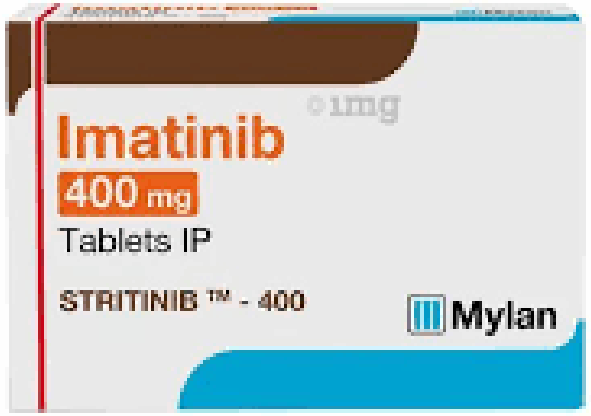
Comment:

The sample was inadequate to perform the test, another sample is required.

Comment:
MRD Detection was performed by RT-qPCR and not by (By Xpert BCR-ABL Ultra (Gene expert) due to shortage of reagents at the supplying company.

Imatinib

- Dose : 260 mg/m^2 to 360 mg/m^2 administrated **once per day**
- Max **: 600 mg /day**
- Oral: **Administer with a meal** and a large glass of water, antiemetic may be recommended to prevent nausea and vomiting.
- Toxicity:
- Bone marrow suppression: May cause bone marrow suppression (**anemia, neutropenia**, and **thrombocytopenia)**, usually occurring within the first several months of treatment. Median duration of neutropenia is 2 to 3 weeks; median duration of thrombocytopenia.



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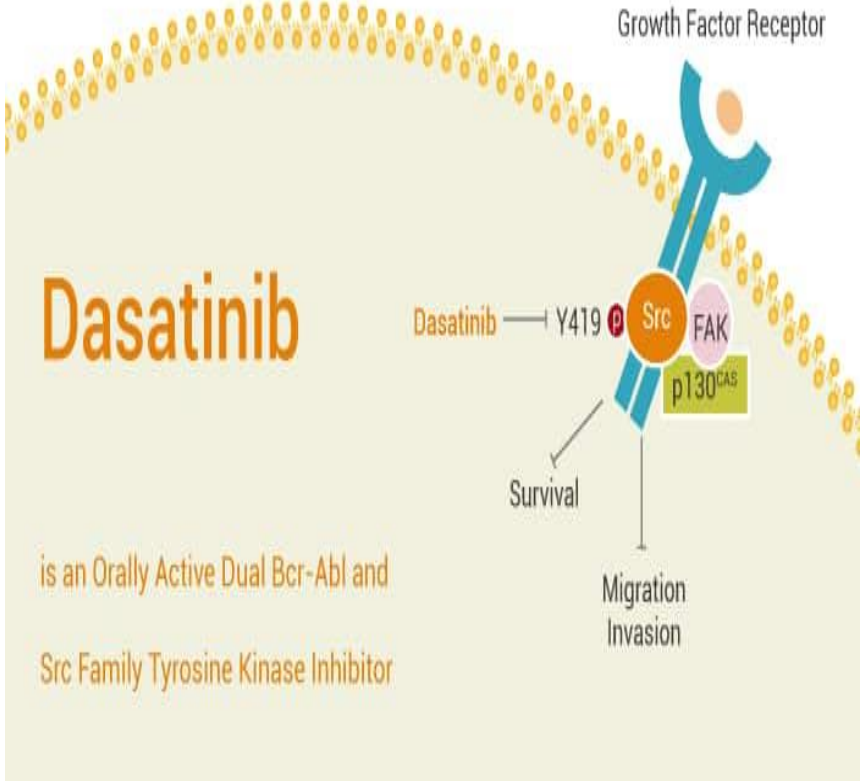
Dasatinib

•Dasatinib is 325 times as potent as imatinib in inhibiting unmutated BCR-ABL kinase in vitro. Since increased inhibition of BCR-ABL kinase correlates with a better clinical response , **dasatinib induced a complete cytogenetic** response by 12 months in 98% of the patients and had an **acceptable side-effect profile.** Dasatinib acts as a potent **Src/Abl kinase inhibitor** with excellent antiproliferative activity against hematological and solid tumor cell lines.



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Dasatinib

- Dose :Dasatinib **80mg/m²/day** (max 140 mg) on The dose will be given as 40 mg/m2 **q 12hr**
- May be **taken without regard to food**. Swallow whole; do not break, crush, or chew tablets.
- **Do not administer proton pump inhibitors** concomitantly with dasatinib. If needed, may consider antacid administration, separated by at least **2 hours before or 2 hours after the dasatinib dose**
- **Drug interaction:**
- **CYP3A4 Inhibitors** (e.g. voriconazole, posaconazole, erythromycin**) Avoid co administration.**
- If concomitant administration with a strong CYP3A inhibitor cannot be avoided, dose reduction and monitoring for toxicity is required. Dasatinib dose will be reduced from 80 mg/m2 once daily (max 140mg) **to 20 mg/m2 once daily (max 40mg).**

Dasatinib

Toxicity

• Bone marrow suppression: Severe dose-related bone marrow suppression thrombocytopenia, neutropenia, anemia.((**holding** dasatinib during periods of myelosuppression, **until ANC > 300/mm3** and **platelet count > 50 x 109 /L))**

•QT Prolongation : Correct hypokalemia and hypomagnesemia during dasatinib therapy.

•Dasatinib may cause fluid retention, including pleural and pericardial effusions

(Utilizing **once-daily dosing** is associated with a decreased frequency of fluid retention)

Nilotinib

- Chronic myeloid leukemia, Philadelphia chromosome-positive, resistant or intolerant in chronic phase and accelerated phase .
- **Mutational analysis: M244V**(imatinib-resistant CML.)
- Children and Adolescents: Oral: **230 mg/m²/dose twice daily**; maximum dose**: 400 mg/dose**
- Administer on **an empty stomach**; no food should be consumed for at least 2 hours before and for at least 1 hour after a dose.

•Capsules should be swallowed whole with water.
•If unable to swallow whole, may empty contents into 5 mL applesauce (puréed apple) and administer **within 15 minutes** (do not save for later use).
•. Toxicity : Hematological **(ANC < 1000/mm3, PLT < 50)** , Non Hematological **QT prolongation,(**Withhold nilotinib and monitor and correct potassium and magnesium levels; review concurrent medications.) **pancreatitis**

Sorafinib

•oral **multiple tyrosine kinase inhibitor**. Main targets are receptor tyrosine kinase pathways frequently deregulated in cancer such as the Raf-Ras pathway, **vascular endothelial growth factor (VEGF) pathway**, and FMS-like tyrosine kinase 3 (FLT3).

- AML dose **200 mg/m2/dose/day**, the maximum dose will be **400 mg** During Maintenance (100 mg/m2/dose/day, rounded to accommodate tablet size), the maximum dose will be 200 mg.
- Fibromatosis : 200mg q12.
- Administer **without food** (at least 1 hour before or 2 hours after a meal).

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Hand-foot skin reaction

Hold Sorafinib until Grade I skin rash then continue on 100m/m2/day

Topical steroids and antihistamines

Topical pain relievers are used as a cream or a patch over painful areas in the palms and soles.

Topical moisturizing exfoliate creams

Pain relievers, such as ibuprofen

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Reference

• Lombardo LJ, Lee FY, Chen P, et al. Discovery of N-(2-chloro-6-methyl-phenyl)-2-(6-(4-(2-hydroxyethyl)-piperazin-1-yl)-2-methylpyrimidin-4-ylamino)thiazole-5-carboxamide (BMS-354825), a dual Src/Abl kinase inhibitor with potent antitumor activity in preclinical assays. J Med Chem 2004;47:6658-6661.

•Cortes JE, Jones D, O'Brien S, et al. Results of dasatinib therapy in patients with early chronic-phase chronic myeloid leukemia. J Clin Oncol 2010;28:398-404

• Jabbour E, Branford S, Saglio G, et al. Practical advice for determining the role of BCR-ABL mutations in guiding tyrosine kinase inhibitor therapy in patients with chronic myeloid leukemia. *Cancer.* 2011;117:1800–1811. doi: 10.1002/cncr.25717.

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