HLS

MODIFIED NO. 8

PHARMACOLOGY

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Color code

- Slides
- Doctor
- Additional info
- Important

Previously, we talked about acute lymphocytic leukaemia, in this lecture we will be talking about AML (Acute Myelocytic Leukaemia) which is similar to ALL to some degree, but the difference is that AML is a more aggressive disease thus, the approach is going to be different, the main cause for using different approach is:
-AML cell can synthesize asparagine, so there is no place for asparaginase here, for that reason we don't have the luxury of using asparaginase as the main therapy for AML instead, we'll be using an aggressive way which depends on something called (3+7).

An explanation for the (3+7) method (all the mentioned drugs are going to be explained in the next few slides):
3+7 refers to using daunorubicin (not a cell cycle specific) for 3 days followed by 7 days of using cytosine arabinosides (antimetabolite) as the two drugs cause bone marrow suppression, so we don't give them together.

AML: INDUCTION THERAPY

The idea of the (3+7) method is that we induce remission by using:

- Two cycles of cytosine arabinoside + daunorubicin +/-thioguanine and other agents gives remissions in 70-90%
- **Chemotherapy alone has given 30-50 % cure rates.**
- **Cure is higher after timed-sequential induction therapy (42% if we do timed sequential vs. 27% if we do it once).**

There is an idea here but it's not that important though ☺ (just for better understanding): We usually do a sequential induction, we found that if we do the induction phase more than once (time sequential induction) it'll produce better activity and that is measured by the cureness.

- **Short (4-12 months) of post-induction therapy is adequate**
- **CNS leukemia is less common than in ALL; 'prophylaxis' may be accomplished with high dose Ara-C +/- intrathecal Ara-C**

CNS leukaemia is less common however, we still do prophylaxis which depends on cytosine arabinoside (Ara-C). We either give the patient a high dose within the blood or sometimes we need to inject it within the brain of our patient (intrathecal Ara-C).

- Cytosine arabinoside: A drug that will be used as antimetabolite which will enter the nucleotide and act as a false nucleotide and stop DNA polymerase from replicating, it is a cell cycle specific that's why it will stop the cell in the S phase, most cells will undergo apoptosis or stay without division by that, we have stopped the division of AML.

- Daunorubicin: A drug like doxorubicin but the difference is the presence of an OH group within the structure, these two drugs are considered topoisomerase poisons as they capture topoisomerase while it cuts DNA; when topoisomerase cuts the DNA in the process of unwinding DNA coiling, daunorubicin and doxorubicin then capture it performing what is called "trapping on a cleavable complex". Daunorubicin is considered another anthracycline, as we said, it is similar to doxorubicin, but we found that daunorubicin has better activity and better response toward AML.

Sometimes we add thioguanine,
- Thioguanine: Is an antimetabolite that looks like guanine, it incorporates within the DNA and stops DNA polymerase.

- After giving these drugs, we wait for 12 months (when we see induction) then we induce again, we usually do this twice or 3 times to make sure that the remission stayed there and that the induction is working.

AML Treatment: Consolidation

Following induction into Complete Remission

Here we have two choices:

- 3-4 cycles of high dose cytosine arabinoside (HiDAC) administered approximately every 5-6 weeks

Our consolidation therapy for AML

OR

- Bone marrow (peripheral blood stem cell) transplant

(Depends on degree of risk)

- Why some people go toward this option? In case of AML, there is a high recurrence rate and the cureness rate is low (max= 42%).
- Also, some studies state that we shouldn't consolidate with the main drug.

Common side effects

More than 10 in every 100 people have one or more of the side effects listed below.

- Fatigue (tiredness) during and after treatment – most people find their energy levels are back to normal after 6 months to a year

  Fatigue due to anemia, bone marrow suppression, decreased energy level.

- Soreness at the injection site (if you are having injections under the skin)
- Women may stop having periods (amenorrhoea) but this may only be temporary

Occasional side effects

- Dizziness (Trademark side effect for cytosine arabinoside).

Remember:
- Vincristine causes constipation
- Doxorubicin and daunorubicin cause cardiotoxicity.

CLL – treatment

⚠️ Not required for the exam, although it's important, we don't need to go that far on it as it's not very easy, so just enjoy reading unrequired drugs ☺

But the only 2 important points here in CLL:

The way of treatment is different.

The type of treatment is different.

- **Watch and wait**
- **Monotherapy**
  - glucocorticoids
  - alkylating agents (Chlorambucil, Cyclophosphamide)
  - purine analogues (Fludarabine, Cladribine, Pentostatin)
- **Combination chemotherapy**
  - Chlorambucil/ Cyclophosphamide + Prednisone
  - Fludarabine + Cyclophosphamide +/- Mitoxantrone
  - CVP, CHOP
- **Monoclonal antibodies (monotherapy and in combination)**
  - Alemtuzumab (anti-CD52)
  - Rituximab (anti-CD20)

⚠ **Remember, this is NOT REQUIRED for the exam.**

We will consider CLL cell is a CD20+

Treatment of CLL

We depend on:
-Chemotherapy (حوارق)
Mostly fludarabine alone or combined
-Targeted therapy

Categorize According to Risk

(FISH, CD38, ZAP-70, Ig mutational status)

Low Risk

Will give 1 type of drugs

Minimally toxic therapy

- Rituximab
- Chlorambucil
- Fludarabine

Intermediate Risk

Nucleoside analog combination regimens

- Fludarabine and cyclophosphamide (Another type of antimetabolites; DNA alkylating agent.)
- Fludarabine and rituximab

This depends on the risk of the disease

- Fludarabine, cyclophosphamide, and rituximab +/- (It's an anti-CD20)

High Risk

- Clinical trial
- BMT, In most cases myeloablative or non-myeloablative

Rituximab as part of first-line therapy for CLL: Rationale

⚠ **Remember: All of this isn't required ☺**

- Rituximab monotherapy is moderately active in CLL
  - Activity is dose dependent (between 500–2250 mg/m^2)[1]
- Rituximab acts synergistically with other cytotoxic agents *in vitro*
  - Increases fludarabine activity in NHL cell lines
  - Increases activity of bendamustine, mitoxantrone and other chemotherapeutic agents in CLL cells

-Anti CD20
-We will also use it in non-Hodgkin lymphoma
(as CD-20 is positive in this disease).

CLL

The only thing the doctor would like you to know:
It's a watch and see (we don't always treat!)

Determining when to start treatment and by what means is often difficult; studies have shown there is no survival advantage to treating the disease too early.

الدواء الذي أحدث ثورة هائلة في عالم السرطان

Imatinib

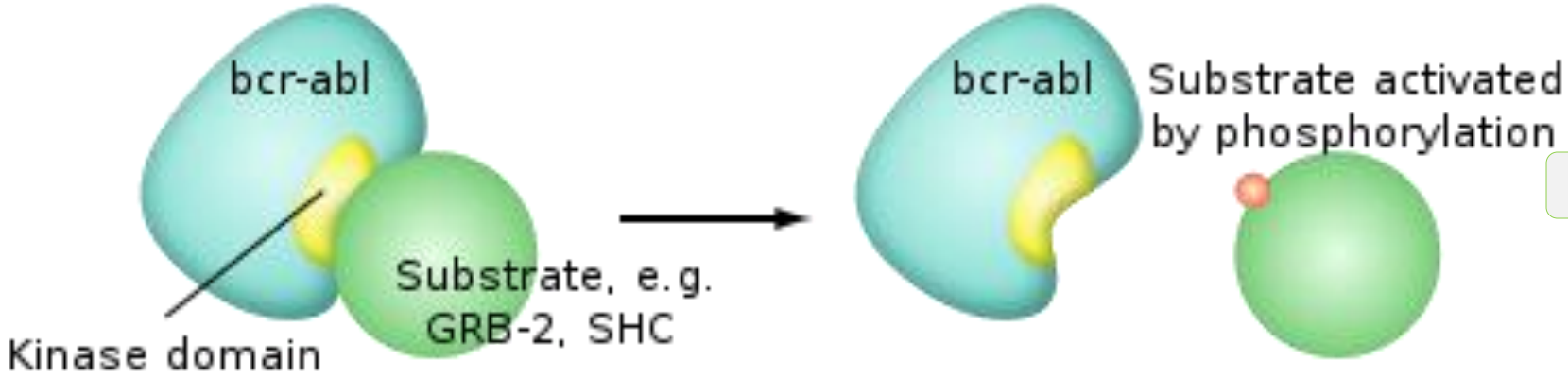
The last leukemia type is CML.
In this topic we'll learn about something called Pharmacogenetics of cancer and how we treat cancer.
All new drugs depend mainly on the genetic makeup of the disease itself but sometimes we look for the patient's.

- **Philadelphia chromosome** or **Philadelphia translocation** is a specific chromosomal abnormality that is associated with chronic myelogenous leukemia (CML).

If we stop this driver with imatinib that's going to stop the whole story and change the CML from a deadly disease to a benign nice disease that the patient can live with.

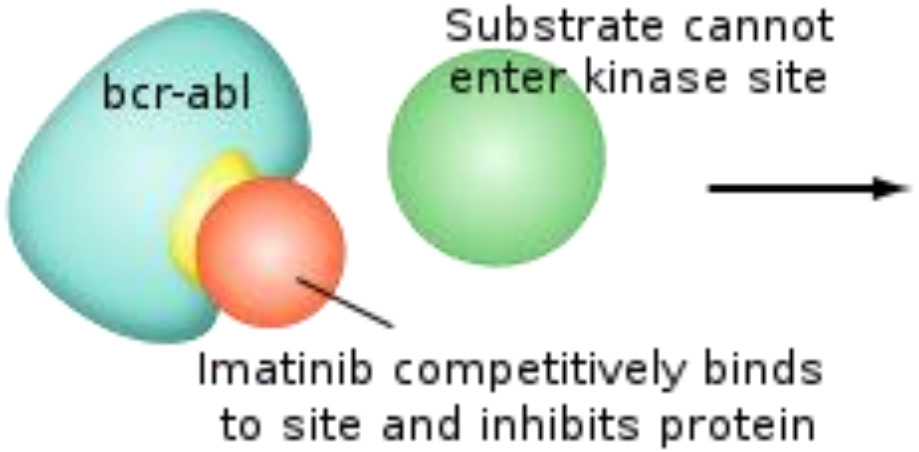
- **This translocation** in Philadelphia chromosome **results in the Bcr-Abl** (the only driver for CML) **fusion protein, the causative agent in CML, and is present in up to 95% of patients with this disease.**
- **Imatinib is an inhibitor of the tyrosine kinase domain of the Bcr-Abl oncoprotein and prevents the phosphorylation of the kinase substrate by ATP.**

Bcr-abl is a protein that phosphorylates another protein (in cell signalling), which leads to the stimulation of multiple functions within the cell, producing more tumorgenicity and more malignancy.



No imatinib

Imatinib inhibits reversable binding toward ATP side of this bcr-abl that phosphorylate the SHC and GRB-2, this will stop the tumor progression.



Tumor cell cannot proliferate

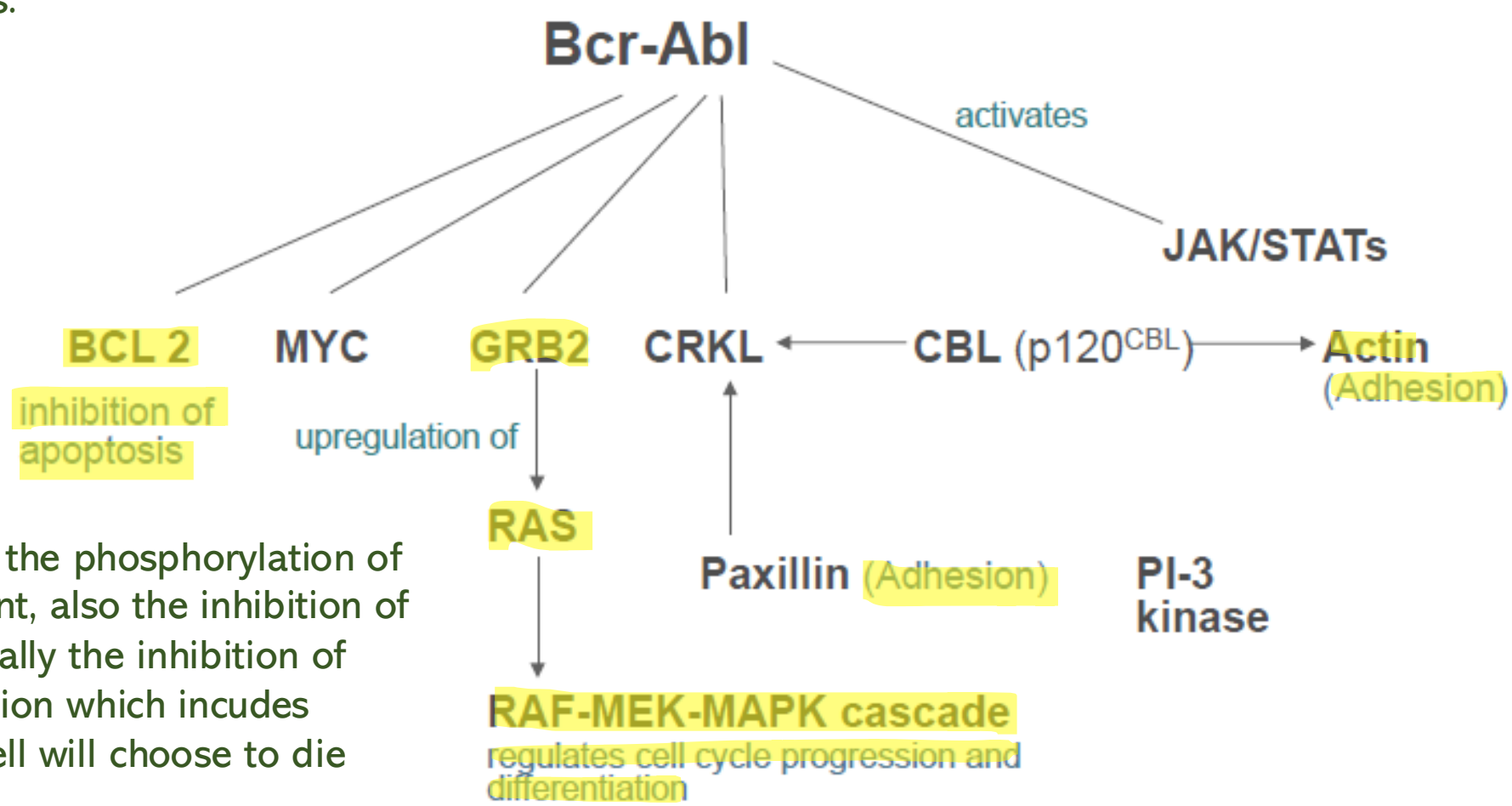
With imatinib

-Imatinib is the drug of choice for long time (about 25 years)
-people live with it
-the patient must take daily doses of this drug

Gleevec is one of the most effective modern medications for cancer treatment,.

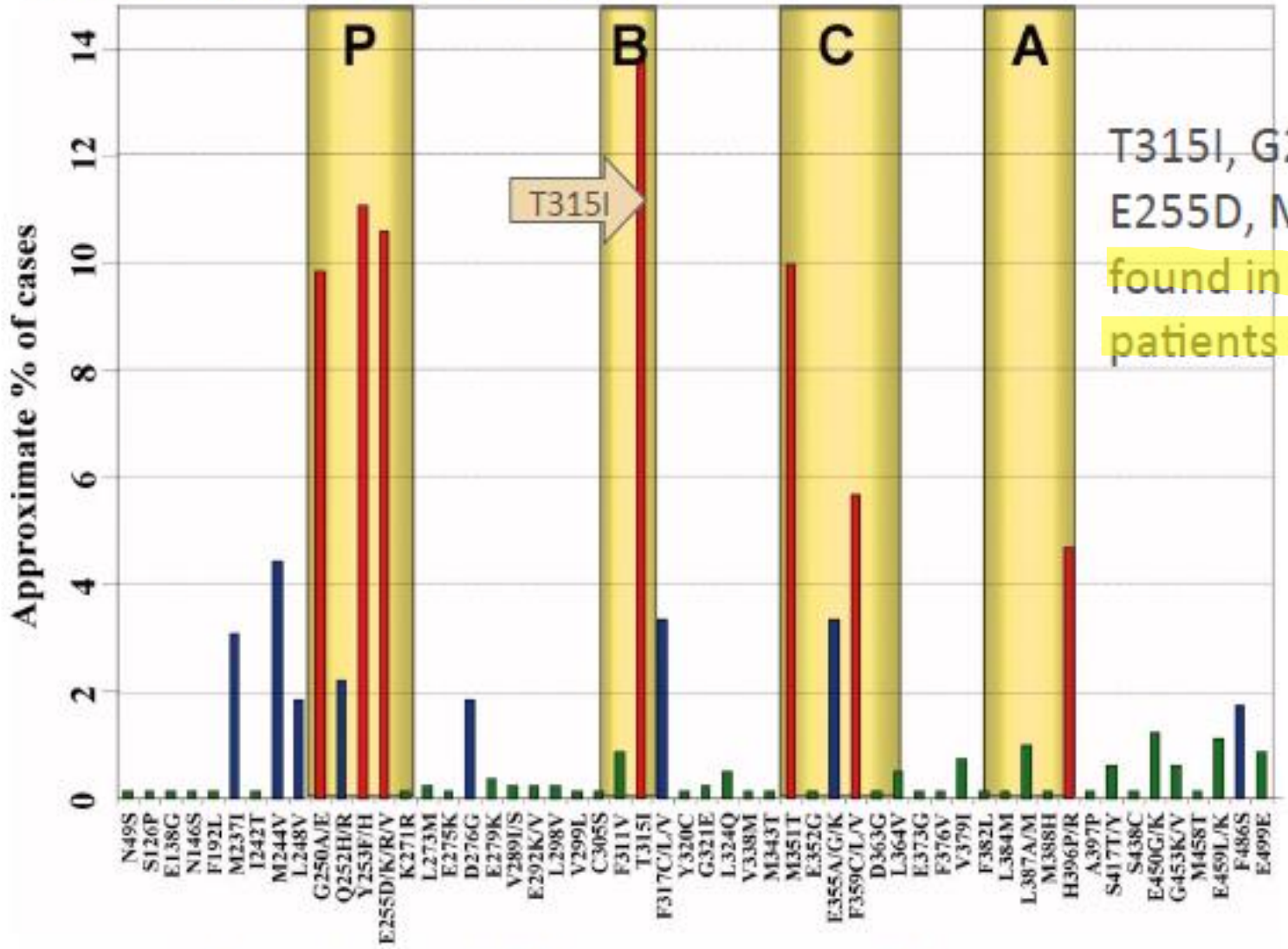
Bcr-Abl Signal Transduction Pathways

Stopping the bcr-abl means deactivating all these oncogenes.



The inhibition of the phosphorylation of GRB2 is important, also the inhibition of adhesion and finally the inhibition of apoptosis inhibition which incudes apoptosis, the cell will choose to die (apoptosis).

Incidence of BCR-ABL Mutations After Imatinib Failure



T315I, G250A, Y253F, E255D, M351T are found in >10% of patients with mutations

p = P-loop, b = imatinib binding, c = catalytic domain, a = activation loop.

Is it going to end here?
No😮👊. As the cancer will produce multiple sites of mutation, here we are talking about all mutations that might happen on the gene level (it is a fusion gene and contains 2 DNA sections, from chromosome 9 and chromosome 22 which resulted in a fusion protein).

- One of the worst mutations that would happen is T315I; when the mutation happens on the DNA level, the produced protein (bcr-abl) have a pocket where the imatinib will enter and bind, but in case of T315I mutation, this pocket will be closed.

- Some patients already have this mutation before the treatment, but here we will consider that we treated the patient and with time (after treatment) we lost the response to imatinib because of the mutation.

- That explains the importance of performing a follow up to your patient as some drugs should be changed according to the genetic makeup (pharmacogenetics).

- If the patient has any type of mutations rather than the bad mutation (T315I), then we will have the luxury to give the patient either Nilotinib or Dasatinib (choosing between of them depends on the side effects).
But why we don't start with these drugs? Because they both have a wide profile of side effects. (will be discussed in the next slides)

Nilotinib and Dasatinib

They are more potent than imatinib!

- Nilotinib (AMN107)
  - Developed from imatinib
  - Structure similar; altered to allow for greater ABL potency and selectivity
  - 20-50x more potent *in vitro*
  - Active against some imatinib resistant Abl kinase mutants except T315I
  - FDA approved Nov 2007
- Dasatinib (BMS 354825)
  - Developed as an inhibitor of Src kinase
  - Structure different than imatinib; greater potency; able to bind different conformations
  - ~300x more potent *in vitro*
  - Active against some imatinib resistant Abl kinase mutants except T315I
  - FDA approved June 2006

ENESTnd: Cardiovascular Events by Year of Treatment

First Cardiovascular Event by Year, n (%)[a]	Nilotinib 300 mg BID (n = 279)	Nilotinib 400 mg BID (n = 277)	Imatinib 400 mg QD (n = 280)
< 1 y	4 (1.4)	10 (3.6)	2 (0.7)
≥ 1 y to < 2 y	4 (1.4)	6 (2.2)	0
≥ 2 y to < 3 y	7 (2.5)	6 (2.2)	1 (0.4)
≥ 3 y to < 4 y	4 (1.4)	4 (1.4)	1 (0.4)
≥ 4 y to < 5 y	1 (0.4)	6 (2.2)	1 (0.4)
≥ 5 y to < 6 y	5 (1.8)	9 (3.2)	1 (0.4)
≥ 6 y to < 7 y	3 (1.1)	2 (0.7)	1 (0.4)
≥ 7 y to < 8 y	0	1 (0.4)	0

Year of first cardiovascular event was assigned based on the start date of the first cardiovascular event reported in each patient. Patients with multiple events were counted only once under the year during which their first cardiovascular event was reported.

-If we look at nilotinib with the dose of 300 mg or 400 mg BID (BID means twice daily), the people who will develop a cardiovascular events (the main side effect from these drugs) are going to be 10 (for 400 mg) and 4 for (300 mg), while in imatinib only 2 patients.

-It increases with time and we are producing more people suffering from cardiovascular disease, so stay on Imatinib as the side effect profile for nilotinib is really bad!

	Recorded in CML Patients treated with* Dasatinib*	Nilotinib*
Pleural effusion	+++	+/-
Pulmonary hypertension	+	+/-
Pericardial effusion	+	+/-
Viral reactivation	+	+/-
Increase in NK cells	++	+/-
Peripheral edema	++	++
Skin rash	+++	+++
Major bleeding	+	+
Diarrhea	+++	+++
Increase in fasting glucose	+/-	+++
Increase in pancreatic enzymes	+/-	+++
Progressive peripheral arterial occlusive disease	- (n.r.)**	++**

*+++, reported in >15% of all patients; ++, reported in 5-14% of all patients; +, reported in 1-4% of all patients; +/-, recorded in less than 1% of patients. *Data refer to previous studies performed in CML patients given dasatinib (100-140 mg daily) or nilotinib (2x300 or 2x400 mg daily). **Peripheral arterial occlusive disease has not been examined for or reported (n.r.) in dasatinib-treated patients so far, and was examined for in nilotinib-treated patients in only one recent multicenter investigation.[16]*

- Doctor mentioned the highlighted side effects especially pleural effusion and peripheral edema as more common with Dasanitib except for progressive peripheral arterial occlusive disease which is more common with Nilotinib (it also causes clotting).

Ponatinib:
A Pan-BCR-ABL Inhibitor

Rationally designed inhibitor of BCR-ABL

Active against T315I mutant

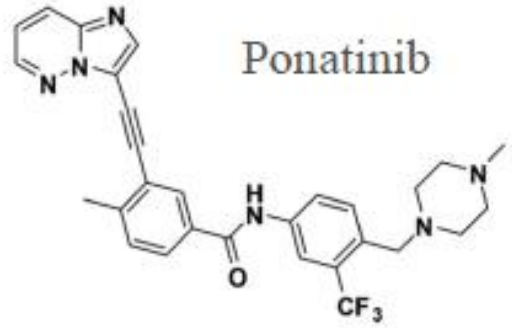
- Unique approach to accommodating gatekeeper residue
- Binds inactive (closed) ABL conformation

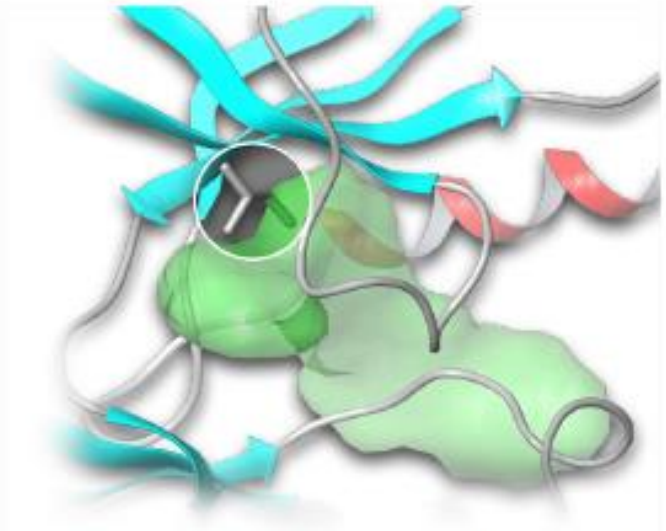
Broad spectrum of activity against an array of BCR-ABL variants

Multi-targeted kinase inhibitor

- Tyrosine kinases, including VEGF, FGF, and PDGF receptors, c-KIT and SRC kinase

Once-daily oral activity in murine models





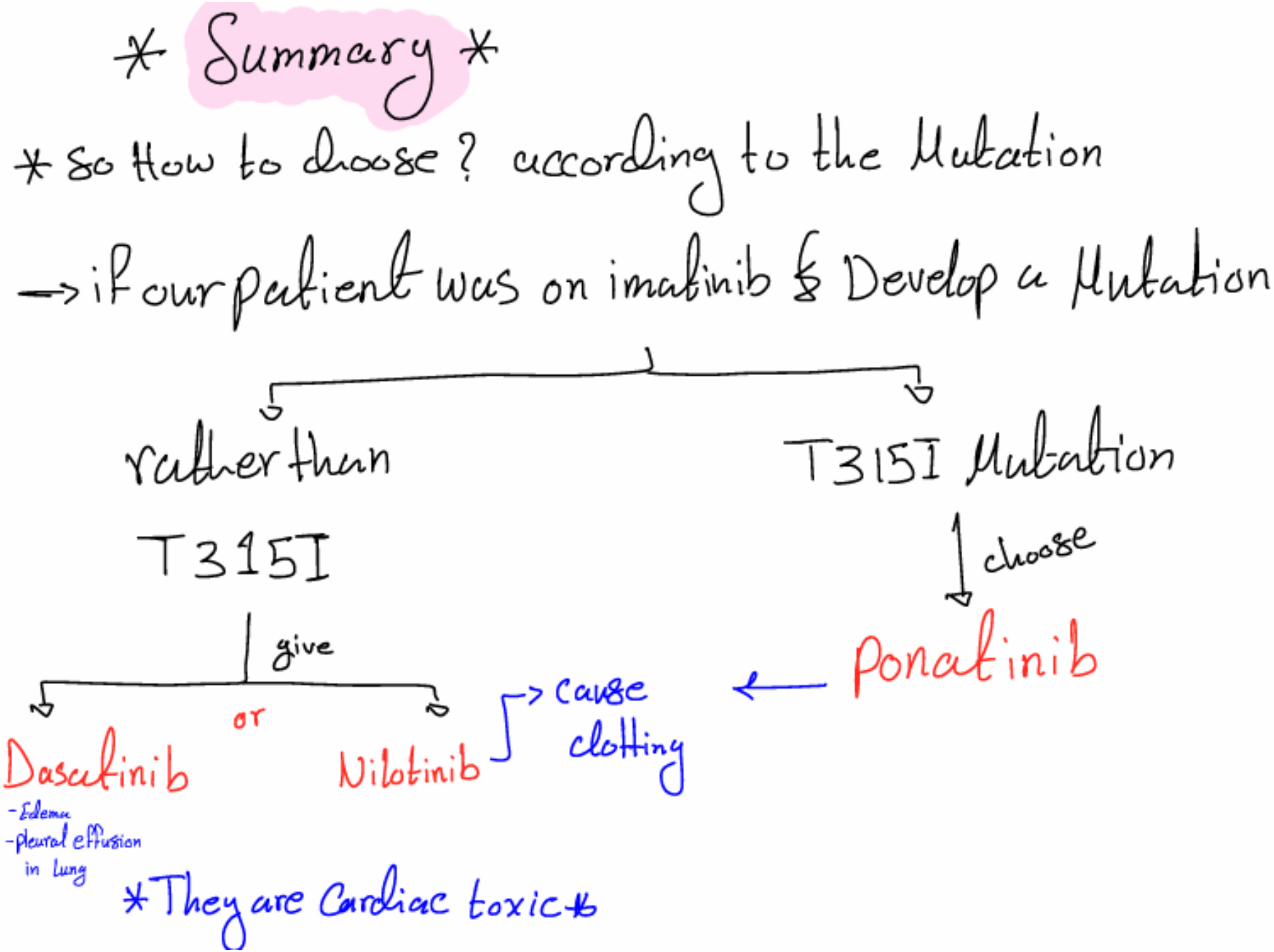
Ponatinib cocrystal structure with ABL^{T315I}

- So, what is the solution if the patient has (T315I) mutation?

- We found a drug that can always enter this closed pocket called Ponatinib which can enter the pocket whatever the mutation or the situation is, as it is way more efficient and potent comparing to the other drugs.

- But the bad news is that it has bad side effects like:
-Liver problem
-Heart problems
-Blockage in arteries and veins
-Blood clots

At the end of the lecture, doctor summarized how to choose between drugs, so we recommend you to look at this summary as it helps a lot :)



قال رسول الله -صلى الله عليه وسلم-: (ما يُصِيبُ المُؤْمِنَ مِن وصَبٍ، ولا نَصَبٍ، ولا سَقَمٍ، ولا حَزَنٍ حتَّى الهَمِّ يُهَمُّهُ، إلَّا كُفِّرَ به مِن سَيِّئَاتِهِ)

اللهم اشفِ مرضى السرطان وأنزل عليهم العافية اللهم احفظ صحتهم وقوتهم وخفف عنهم كل ألم يشعرون به وأبعد عنهم كل ضرر يا رب العالمين 🤲🤲

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2			
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!