# CML HORIZONS 101 AND CML 101

by

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# Goals of this Session

*"Everything you ever wanted to know and were afraid of asking"*

- ✓ Help you navigate the conference
- ✓ Help you set goals for yourself at the conference
- ✓ Provide you with background to help you follow the medical sessions

# CML Horizons
## Historical overview

- First meeting organized by Novartis in 2003
  - 25 CML and GIST advocates in Switzerland
- Subsequently Novartis organized New Horizons yearly, CML and GIST together, until 2010
- 2011 onwards, conference organized by the patient community, with multi-sponsorship; CML and GIST split
- Renamed CML Horizons. Supported by Novartis, BMS, Pfizer, Ariad, Leukemia & Lymphoma Society, iCMLf

# CML Advocates Network

## 87 organizations from 67 countries

- Started by 4 advocates
  - Central idea initiated at 2005 New Horizons conference
  - Initial goal: continue the networking in between New Horizons conferences, increase collaboration

- CML Advocates Network today
  - Hosted by the Leukemia Patient Advocates Foundation, Registered global organization in Switzerland since 2011

- Today: 87 organizations, 3 founders, 5 regional representatives, 1 coordinator

# CML Advocates Network
## Goals

Provide a worldwide web directory of CML organizations

Stimulate collaboration and best practice sharing

CML Advocates Network

Grow capacity in CML patient advocacy organisations

Provide educational materials on CML

# Who is here?

93 delegates
(23 newcomers)

22 pharma representatives

11 speakers

# Why are we here?

## AUDIENCE GOAL SETTING

# Why are we here?

| **Goals** | |
|---|---|
| Learn about advances in the treatment of CML | Medical sessions |
| Learn from others' experiences | Posters and networking |
| Learn about advocacy | Advocacy sessions |
| Meet industry representatives and speakers | Networking |
| Produce a report for my group | Note-taking |

# How is the conference structured?

## 4 medical sessions

- CML Updates
- CML in Real Life
- The New Realities: generics and copy drugs in CML
- Treatment free remission, or eradicating CML?

## 4 advocacy sessions

- Presentation of each region, challenges and priorities in the region, what can CML advocates do for the region
- Hands on use of social media
- Developing and implementing an advocacy strategy
- Supporting people living with CML

# To whom can I address my questions?

- Logistics: anyone at Liberty
- Other: Nicole (CML Advocates  Network coordinator)
- Any of the Steering Committee representatives!

**This is your meeting!**

Speak out, ask questions!

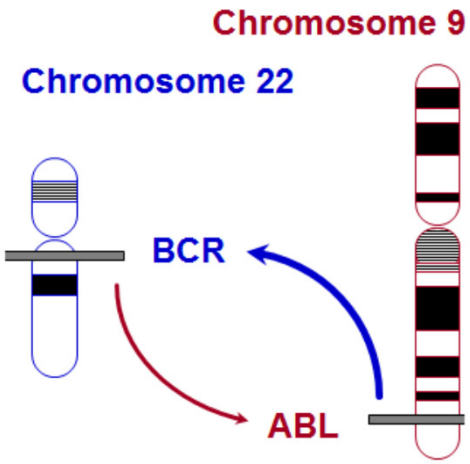
Make your participation count!

# CML 101

## UNDERSTANDING THE DISCUSSION IN THE MEDICAL SESSIONS

# What is BCR-ABL?

- CML is a type of cancer that begins in the cells in the bone marrow
- A piece of the chromosome 22 and a piece of chromosome 9 break off and swap places




- BCR-ABL cancer gene:
  - The break on chromosome 9 = ABL
  - The break on chromosome 22 = BCR
- People living with CML carry the BCR-ABL gene

**BCR-ABL gene = type of protein known as tyrosine kinase**

# Causes of CML = Unknown

- However…

  - ✓ We know it is **not hereditary** (children of people with CML do not have a higher chance to get it)
  - ✓ We know it is **not contagious** (it doesn't pass from one person to the next)
  - ✓ The **average age of diagnosis in western countries is 65**. It is rare in children (although in developing countries it seems more likely to occur in children and young adults)
  - ✓ It more often occurs in men than women

# Tyrosine Kinase Inhibitors (TKIs)

**BCR-ABL gene = type of protein known as <u>tyrosine kinase</u>**

(Inhibit = prevent, impede, stop)

- TKIs target BCR-ABL and don't target normal cells (targeted therapies)
- Currently 5 TKIs for CML available, plus a number of generics/copies

| Drug | Market Name | Manufacturer |
|---|---|---|
| 1. Imatinib | Glivec/Gleevec | Novartis |
| Imatinib | (Various) | Generics companies |
| 2. Dasatinib | Srpycel | BMS |
| 3. Nilotinib | Tasigna | Novartis |
| 4. Bosutinib | Bosulif | Pfizer |
| 5. Ponatinib | Iclusig | Ariad |

# First Generation TKI, Second Generation TKI

- Imatinib (Glivec) if often referred to as **First Generation** TKI because it was the first one to be developed
- Dasatinib and nilotinib (Sprycel and Tasigna) are sometimes referred to as **Second Generation** TKI because their came out later that imatinib
- Ponatinib is sometimes referred to **Third Generation** TKI

***Second generation* TKI is not the same as *second line* treatment**

# What is an approved label?

- After drugs are developed and tested, they get approved by each country's Health Authority for use by everyone
- Depending on how good are the results of the treatment (**EFFICACY**), they are approved very specifically (**LABEL INDICATION**)
- Generally, when a drug is first approved in CML, it is often approved for use in adults and not children; and it is approved only for those who are resistant, or cannot tolerate, the drugs already in the market (**SECOND LINE TREATMENT**)
- After it is proven to be safe, drugs may be approved for patients that are newly diagnosed (**FIRST LINE TREATMENT**)

# What if a drug is not approved in my country?

- If a drug is not approved, it means the Health Authority has not given permission to use by patients in that country
  - It can only be used in special circumstances which require special permission from Health Authorities
    - **Clinical trial** (usually sponsored by pharma companies)
    - **Compassionate Use** (some companies agree to supply clinical drug approved for individual cases, for indications where the drug has shown efficacy)
    - **Humanitarian aid** (health authorities might approve importation and use of a drug that is not locally approved, as humanitarian aid)

**Advocacy note: Running trials and offering compassionate use programs are very expensive to companies. Companies decide where they will seek approval for their drugs**

# Treating CML in 2014

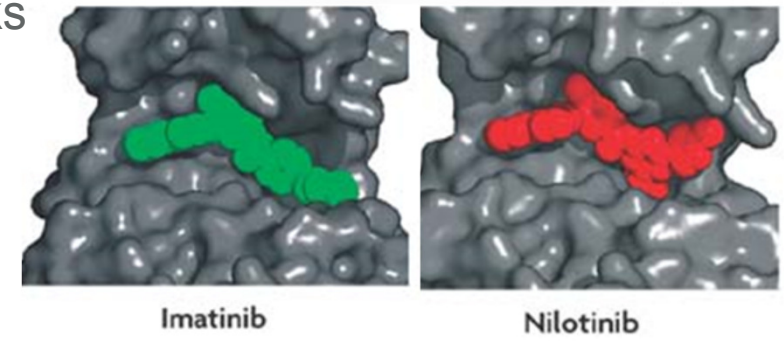
- General consensus is to start with one of the TKIs approved for first line treatment
- Glivec (imatinib) is approved for first line treatment in most countries
- Labels vary from country to country. Example: Tasigna (nilotinib) and Sprycel (dasatinib) are approved for first line in some countries and second line in some others, and not approved at all in other countries

**Advocacy Note:**

- **Need to know which drugs are approved in our country and how this compares to other countries**
- **Need to know the regulatory process in our country for approval and reimbursement of drugs**

# What is Drug Resistance?

- The cells become resistant to the drug (TKI cannot inhibit the BCR-ABL any more)
- The TKI stops working for some reason
  - Look for other changes in the chromosomes or genes (mutations), so “the key” (TKI) does no longer fit into “the lock” (BCR-ABL)
  - Doctors know which TKI works best for which mutation
    - Example: mutation T 315i = ponatinib works and the others don’t
- A LOT ABOUT THIS IS STILL UNKNOWN



# What is Drug Intolerance?

- The drug causes side effects that the patient cannot tolerate
- Caused by drugs also interfering with other body functions and not just BCR-ABL
- Some patients have more side effects than others
  - Always talk to your doctor about side effects
  - Intolerance is one reason identified in a label, where it is allowed to change treatment to a second line TKI

- A LOT ABOUT THIS IS STILL UNKNOWN

# Monitoring CML Treatment

- Monitoring = checking how the treatment is working
  - Is the TKI still inhibiting the BCR-ABL or are the cells becoming resistant?
  - Need to check how deep is the response

- Monitoring CML, different methods:
  - **CBC / Blood counts**
    = measures hematological response = most superficial response
  - **Cytogenetics and FISH** = measures cytogenetic response = number of cells carrying the “Philadelphia Chromosome”
  - **PCR** = measures molecular response = amount of BCR-ABL present
    (also called ‘residual disease’)

# Monitoring CML

- Types of response to treatment

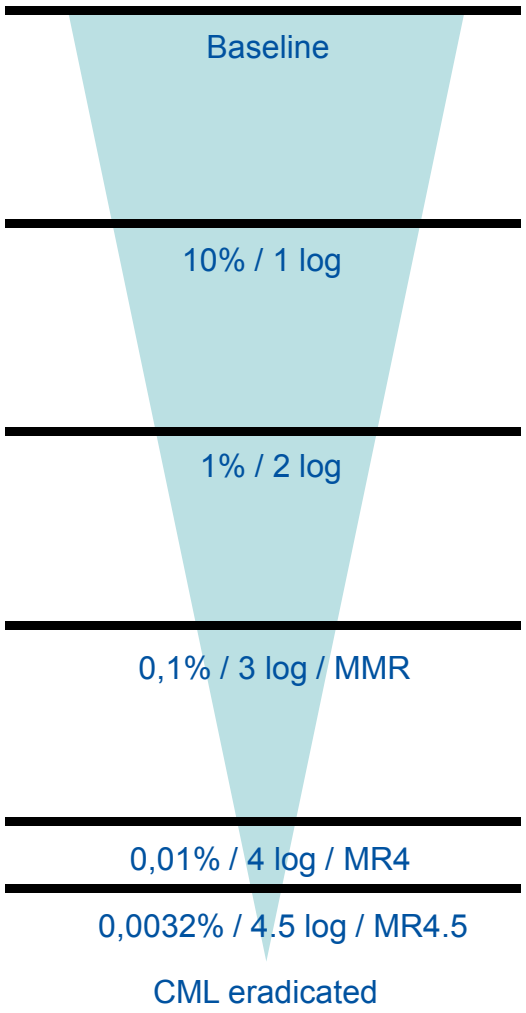
| Response type | Partial | Major | Complete/Deep |
|---|---|---|---|
| Hematological (H) | PHR | MHR | CHR |
| Cytogenetic (Cy) | PCyR | MCR | CCyR (2 log reduction) |
| Molecular (M) | PMR | MMR (3 log reduction) | MR4.5 (4.5 log reduction) |
| | | | "Undetectable" |

- ELN & NCCN = 2 entities that produce guidelines for physicians on
  - When should they switch from one treatment to another
  - How often tests should be performed
- CML Advocates Network, patient summary, www.cmladvocates.net/cmlsummary

# Log Reduction

- "Log reduction" is a mathematical term (as is "log increase") used to show the relative number of BCR-ABL eliminated from the sample
  - It is another way to express how deep is the response

- Log reduction:
- 1 log reduction means the number of cells with BCR-ABL is 10 times smaller
- 2 log reduction means the number is 100 times smaller
- 3 log reduction means the number is 1000 times smaller (MMR)
- 4 log reduction means the number is 10,000 times smaller (MR4)
- 4.5 log reduction means the number is 32,000 times smaller (MR4.5)



# PCR, what is all the fuss about?

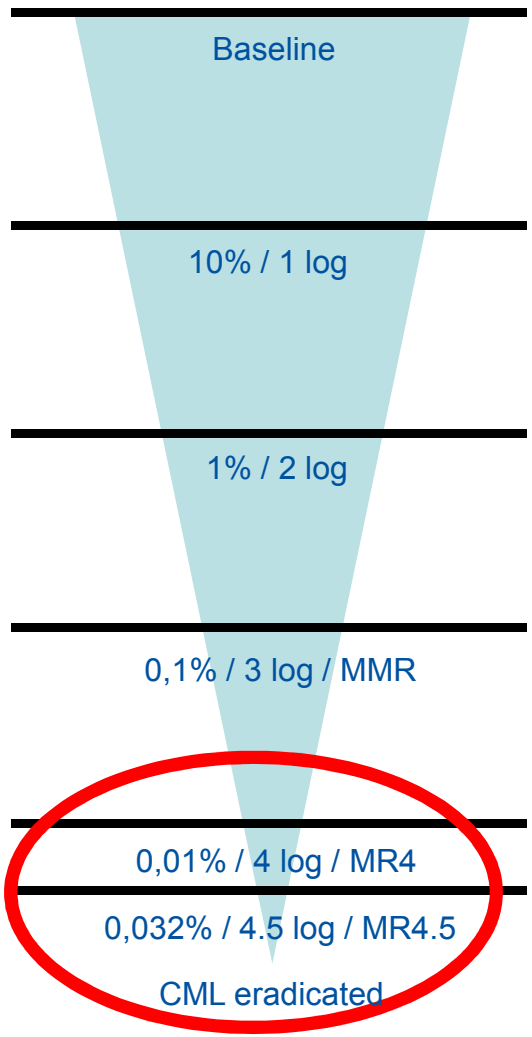
- **Prognosis** (ability to predict if a patient will continue to do well for a long time) depends on **how fast** patients achieve response, and on **how deep** is a patient's response, and whether they **meet certain milestones** within a certain time
  - Therapy recommendations (e.g. ELN, NCCN) help to understand the goals of treatment
  - PCR technology helps doctors know how deep is the response
  - Current research focusses on the consequences of **not having an early, fast response**, on what to do after a **long period of very deep remission**, and **how to eradicate CML** altogether.
- Traditional PCR technology is not easy to do well, and not available everywhere
  - Complicated, very dependent on technology and staff
  - Needs to be standardized (in the international scale) to be comparable between labs

**IF NOT ON THE INTERNATIONAL SCALE, IT IS DIFFICULT TO INTERPRET THE RESULTS**

# Treatment Free Remission vs Eradicating CML

- **Treatment Free Remission**: describes the status of patients who stop taking TKI and still maintain their PCR undetectable or very low
  - Used instead of the word cure, because the disease might still be there, however not progressing even without therapy

- **Eradicating CML**: refers to the potential of treatment to actually cure CML
  - Some new drugs (not TKIs) are being tested to see if they eradicate also the last residual CML stem cell



# Current Research for CML

- Current research assumes that all treatments are available, all patients have access to standardized PCR, and focuses on how to use them optimally
  - When is the best time to switch TKI (ELN, NCCN guidelines, milestones)
  - What dose gives best efficacy
  - When and who can stop treatment (treatment free remission)

- Quality of life, use of existing therapies, new types of therapies
  - The interactions of **additional diseases** (“co-morbidities”) on CML therapy
  - How to **optimize quality of life** given specific, also low-grade side effects of TKIs
  - New therapies that can **eradicate CML**
  - Does the **immune system and/or interferon** have a role in controlling CML

# Key Clinical Trials focused on response and efficacy

- Current research assumes that all treatments are available, all patients have access to standardized PCR, and focuses on how to use them optimally

| | |
|---|---|
| IRIS | Original trial that compared imatinib to interferon, and let to Glivec approval - run by Novartis |
| CML-IV | German study (12 years, still ongoing) comparing Imatinib 400, Imatinib 800, Imatinib+Interferon |
| ENEST | Original nilotinib trial by Novartis<br>ENESTnd, ENEST1st, efficacy of nilotinib first line |
| DASISION | Compared dasatinib and imatinib first line - BMS |
| PACE | Original ponatinib trial - ARIAD |
| BELA | Original bosutinib trial - Pfizer |

# Current key Clinical Trials assessing Therapy-Free Remission (STOP)

Ongoing, but no longer recruiting:

- STIM, A-STIM: French trials stopping Imatinib, academic trials
- STIM2: Stopping 2nd generation TKI, academic trials
- Nordic STIM (Imatinib stop, academic trial)
- TIGER (Nilotinib vs. Nilotinib+Interferon, with potential to stop therapy)
- Korean, Japanese STOP trials (imatinib stop)

New trials:

- DECLINE (Imatinib to nilotinib escalation in case of non-optimal response, with potential to stop therapy)
- EUROSKI (stopping any TKI, academic trial in 9 European countries)
- ENESTpath, ENESTop, ENESTfreedom (Novartis Tasigna Stop Trials)
- DASFREE (BMS Sprycel stop study)

# Helpful resources that help you and patients to understand CML

**Many are available in multiple languages, your organisation can use them!**


- **Patient-friendly summary of ELN Recommendations**
  http://www.cmladvocates.net/cmlsummary
  (2009 version, 2013 version will be published soon)
- **ASH Reports** (in many languages, thanks for translations!)
  http://www.cmladvocates.net/ashreports
- **Educational videos on adherence, side effects, testing and monitoring**
  http://www.cmladvocates.net/education/educational-videos
- **Inofficial CML trial registry**, also linking to patient information on trials
  http://www.cmladvocates.net/cmltrials
- **CML Glossary** with all common terms used in CML
  http://www.cmladvocates.net/glossary

# Not discussed topics, questions

- Phases of CML
- Other treatments: Hydrea, Interferon, Transplant, Synribo (omacetaxine), chemotherapy
- Understanding PCR results

**ANYTHING ELSE? THIS IS YOUR CHANCE TO ASK QUESTIONS!**