

CML HORIZONS 101 AND CML 201

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Slovenia

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
- ✓ Refresh medical CML concepts to help you follow the medical sessions

CML Horizons

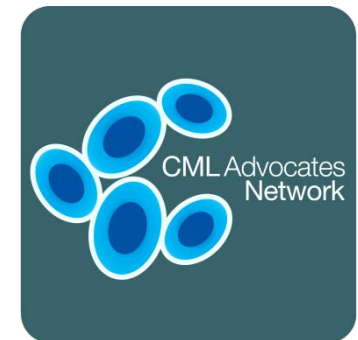
Historical overview

- 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

106 organizations from 81 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: 106 organizations, 3 founders, 6 regional representatives, 1 coordinator



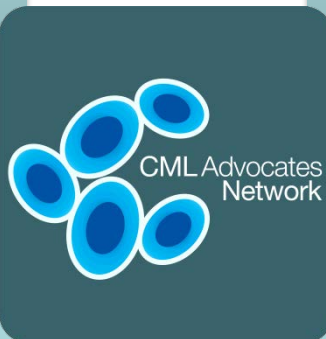
CML Advocates Network Goals

Provide a
worldwide web
directory of CML
organizations

Stimulate
collaboration
and best
practice sharing

Grow capacity in
CML patient
advocacy
organisations

Provide
educational
materials on
CML



Who is here?



93 delegates



25 pharma
representatives



13 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

- Patient Advocacy in Research
- CML State of Play and Future
- Stopping Treatment
- CML at both ends of Life

5 advocacy sessions (1 more in 2016)

- Patient Advocacy in Research
- Best Practice in Advocacy (Generics, Access)
- Financial Management
- World CML Day -- Training and Best Practices
- Psychosocial issues

To whom can I address my questions?

- Logistics: anyone at Liberty
- Any of the Steering Committee representatives!
- Twitter wall using #CMLHZ16

This is your meeting!

Speak out, ask questions!

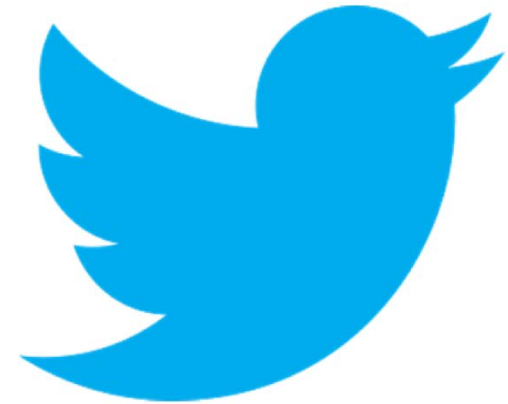
Make your participation count!

To send your Twitter messages
to our “Social Media wall”, include

#CMLHZ16

in the text of your message.

It will appear in the room, and at walls.io/cmlnet



CML 201

TESTING AND REFRESHING OUR KNOWLEDGE
ABOUT CHRONIC MYELOID LEUKEMIA



Practice question



What is the name of the city where
CML Horizons 2015 was held?



What is the name of the city where CML Horizons 2015 was held?

- CML Horizons 2015 was held in Barcelona, Spain





What is CML?



What is CML?

- Chronic Myeloid Leukemia (CML), also known as *chronic myelogenous leukemia*, is a type of cancer that starts in certain blood-forming cells of the bone marrow.
- In CML, a genetic change takes place in an early (immature) version of myeloid cells - the cells that make red blood cells, platelets, and most types of white blood cells (except lymphocytes).
- (Definition from American Cancer Society website)



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 and in developing countries is 38**. 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

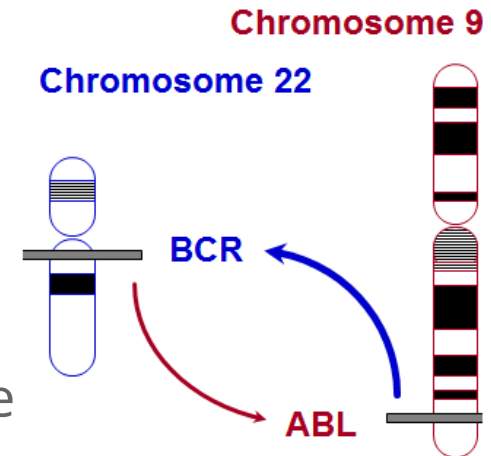


What is BCR-ABL?



What is BCR-ABL?

- In CML 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



What does TKI stand for?



Tyrosine Kinase Inhibitors (TKIs)

BCR-ABL gene = type of protein known as tyrosine kinase (Inhibit = prevent, impede, stop)

- TKIs target BCR-ABL and mostly 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) is often referred to as **First Generation** TKI because it was the first one to be developed
- Dasatinib and nilotinib (Sprycel and Tasisign) are sometimes referred to as **Second Generation** TKI because they came out later than imatinib
- Ponatinib is sometimes referred to **Third Generation** TKI

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

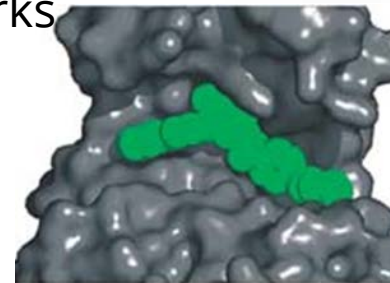


What is resistance and what is intolerance?

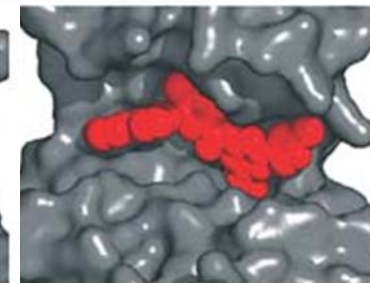


What is Drug Resistance?

- 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 T315i = ponatinib works and the others don't
- A LOT ABOUT THIS IS STILL UNKNOWN



Imatinib



Nilotinib

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





What does PCR stand for?



PCR = Polymerase Chain Reaction

A very sensitive diagnostic test that allows the detection of certain genes (DNA) on a very sensitive level

PCR can detect up to one single gene in about 1 million genes

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 treatment goals
 - 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 INTERNATIONAL SCALE, IT IS DIFFICULT TO COMPARE THE RESULTS



Name two methods of
monitoring CML



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

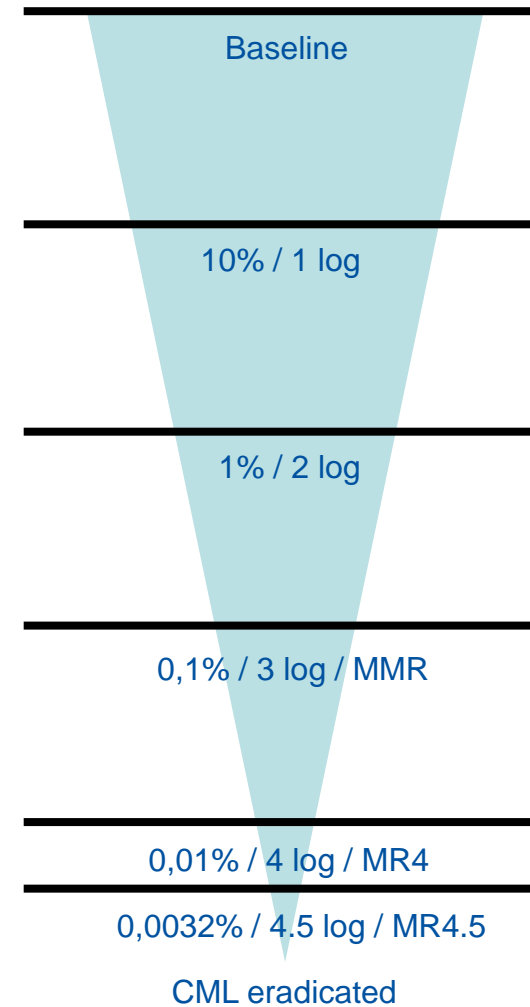


Log Reduction – what is that?



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)



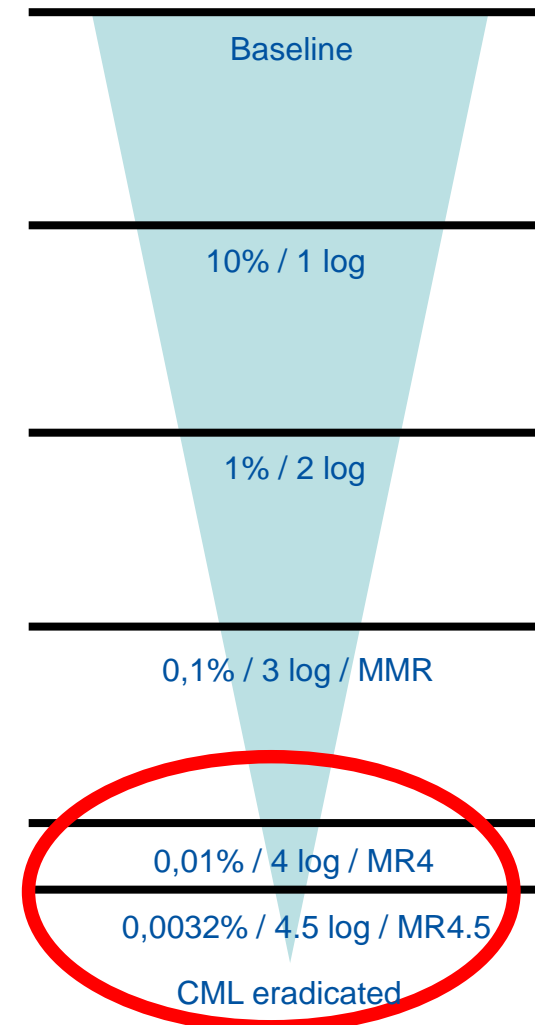


What is Treatment Free Remission?



Treatment Free Remission (TFR) 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





What is the 'approved label'
of a drug?



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**)

Advocacy note: every advocate should know what drugs are approved in their country and for what specific use (label). Pharma representatives can provide information about their own drug's situation in your country.

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



What is a 'Generic Drug'?



What is a generic drug?

- After drugs are developed and tested, they get approved by each country's Health Authority for use by everyone.
- The country gives the manufacturer a patent (exclusive marketing rights) for a number of years (10 – 15) to be the only ones that can market the drug, so they can recuperate the investment in development.
- After the patent expires, other companies can copy the drug. These copies are called generics. Usually much cheaper (90%)
- Some countries don't protect the patent and allow others to make cheap copies during patent time.
- It is hard to know if the generics are exactly the same as the original.

Treating CML in 2015

- 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 the regulatory process in our country for approval and reimbursement of drugs

Winner Group is...



Current Research for CML

1. New drugs:

Phase I/II trials for new compounds, e.g. ABL001, Ruxolitinib, Nivolumab in combination with existing TKIs

2. What is the optimal way to treat CML given the current drugs in the market:

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, TFR)?

Does the **immune system and/or interferon** have a role in controlling CML?

3. Quality of life:

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

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 led 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 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 (TFR, STOP)

Ongoing, but non-recruiting STOP trials:

- **STIM, A-STIM:** French trials stopping Imatinib, academic trials
- **STIM2:** Stopping 2nd generation TKI, academic trials
- **Nordic STIM** (Imatinib, academic trial)
- Korean, Japanese STOP trials (imatinib)
- **EUROSKI** (largest STOP study with >700 participants, stopping any TKI, academic trial in 9 European countries)
- **ENESTpath, ENESTfreedom ENESTop,** (Novartis Tasigna Stop Trials)

Ongoing, recruiting STOP trials:

- **TIGER** (Nilotinib vs. Nilotinib+Interferon, with potential to stop therapy)
- **DECLINE** (Imatinib to nilotinib escalation in case of non-optimal response, with potential to stop therapy)
- **DASFREE** (BMS Sprycel stop study)
- **DESTINY** = De-Escalation and Stopping of Imatinib, Nilotinib or Dasatinib in CML (UK)
- **LAST** Stopping Tyrosine kinase inhibitors (any TKI, USA)
- **MSIT** = Malaysia Stop Tyrosine Kinase Inhibitor Trial

See CML Advocates Network Study Database:

<http://www.cmladvocates.net/cmltrials>

Helpful resources that help you and patients to understand CML

Your organisation can use them to support patients!

- **Patient-friendly summary of Treatment Recommendations of the European LeukemiaNET in 17 languages**
<http://www.cmladvocates.net/cmlsummary>
- **Reports from the ASH congress in multiple languages**
<http://www.cmladvocates.net/ashreports>
- **Summary of the CML Adherence Study in 79 countries**
<http://www.cmladvocates.net/adherence>
- **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 Generics Knowledge Base**
<http://www.cmladvocates.net/generics>
- **CML Glossary** with all common terms used in CML
<http://www.cmladvocates.net/glossary>



World CML Day, 9/22

TODAY WE LIVE, TOGETHER WE FIGHT



Around 22 Sept 2008, the CML Society of Canada announced the creation of the first CML Awareness Day in Canada

Around 22 Sept 2011, CML patient organisations across collaborated on “International CML Awareness Day”, with 2.100 signatures of the Baveno Declaration, 140 photos of “Faces of CML” collected, 15 countries participating

Around 22 Sept 2012, 34 organisations held events. World CML Day posters provided.

Around 22 Sept 2013, it became “World CML Day”, using the slogan “All United, All Unique”. 30 countries participated. 8.500 World CML Day pins distributed.

Around 22 Sept 2014, 32 countries. 35.000 pins were distributed. Book “Faces of Courage and Hope” in 50 countries.

Around 22 Sept 2015, 24 countries participated. World CML Day Toolkit first used. Training at this CML Horizons Meeting!

