

IINFORMING PATIENTS ABOUT TFR

Giora Sharf
CML Horizons 2018
Warsaw

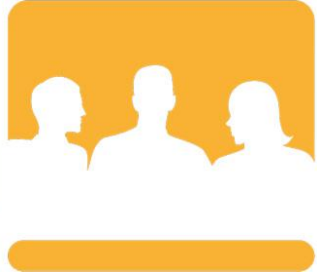


TFR PHASES



CML Patient Environment- 2017

- Lack of “patient-friendly” TFR information- you cant decide stopping if you do not have the data
- Different standards at different TFR trials
- TFR done in and out of clinical trials
- Companies are pushing second-generation TKIs as better option for future TFR – not really proven in real life yet
- Bottom line: TFR not well understood, much confusion as well as hope, excitement



WHAT HAS CHANGED IN THE LAST YEAR

- Lack of “patient-friendly” TFR information- you cant decide stopping if you do not have the data

Changes:

- TFR leaflet by the “What If What Now” Team
- TFR Video Interview of Prof Saglio by Giora
- TFR Position Paper to be published soon in the journal *Clinical Lymphoma, Myeloma and Leukemia*



WHAT IS “WHAT IF WHAT NOW”?

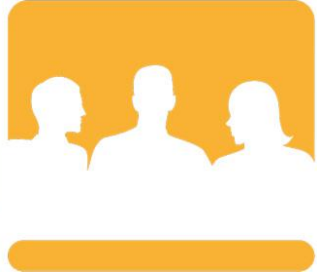
- Working group consisting from 7 CML Advocates: Mina Daban, Jan De Jong, Nigel Deekes, Felice Bombaci, Jelena Cugurovic, Sarunas Narbutas and Giora Sharf
- 5 CML experts- Prof Saglio, Dr Andrija Bogdanovic, Dr Antonio Medina Almeida, Dr Valentine Garcia Gutierrez and Dr Daniela Zackova.
- Organized and sponsored by Novartis region Europe

WHAT IS “WHAT IF WHAT NOW”?

Team Work parallelly on 6 CML educational topics :

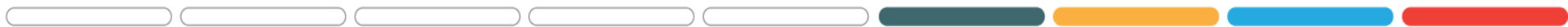
- Treatment-free remission
- Generic tyrosine kinase inhibitors
- CML: understanding your diagnosis
- TKIs: managing side effects
- CML, fertility and the young adult
- Information for caregivers

There is a video on each of these topics done by one of the advocates and one of the experts.



WHAT IS “WHAT IF WHAT NOW”?

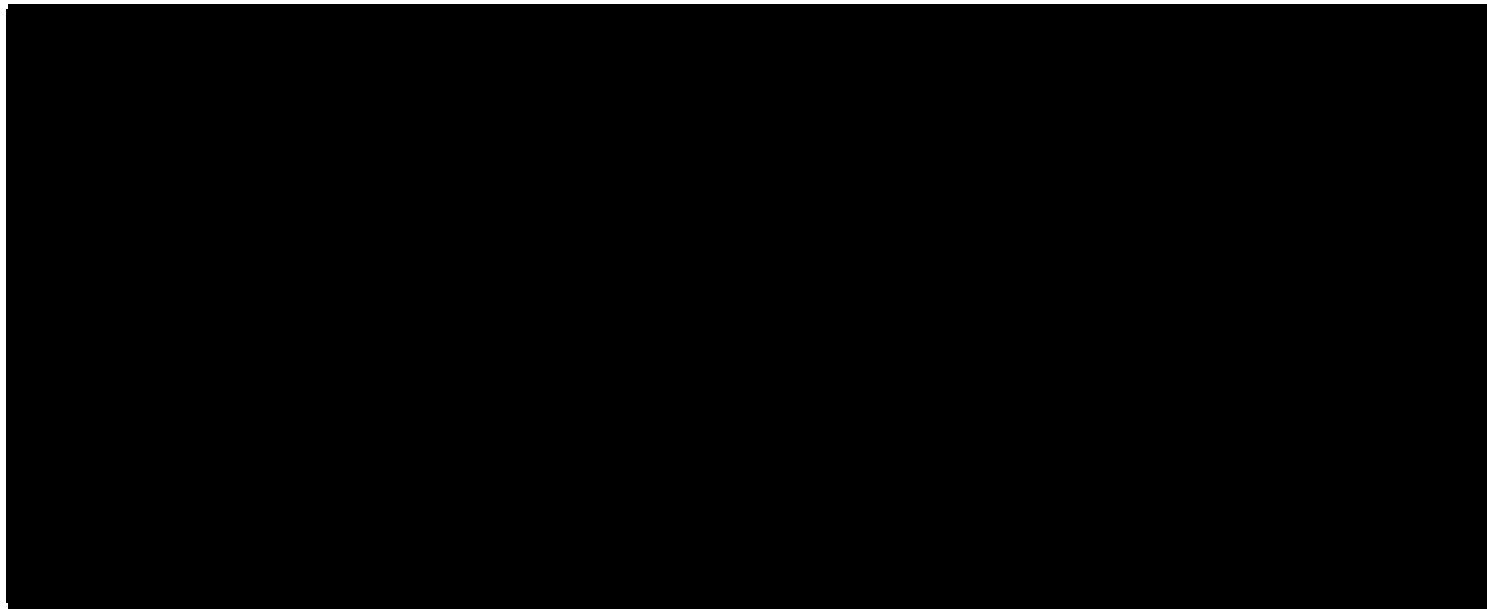
- All Materials are now available without any branding
- It will be soon available in 7 languages and we can add more if needed
- We are now exploring taking over the responsibility to continue to develop educational material for CML patients that all our members will be able to use freely.



WHAT IS “WHAT IF WHAT NOW”?

Treatment Free Remission:

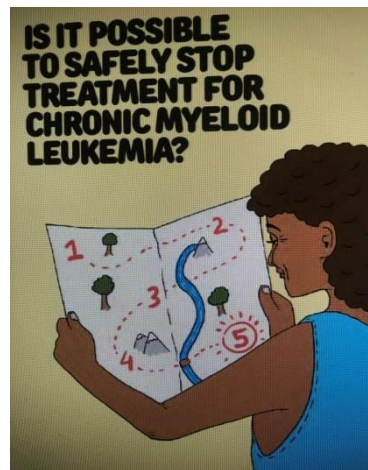
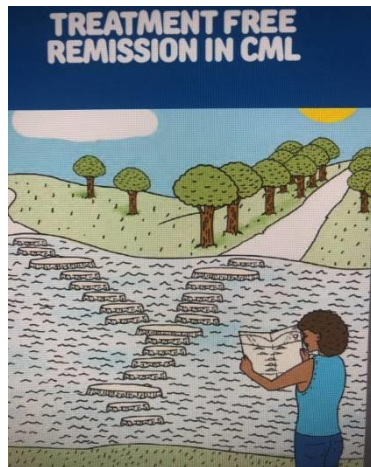
- Video Interview of Prof Saglio by Giora
- Available on CML Advocates Website





WHAT IS “WHAT IF WHAT NOW”?

TFR Leaflet



WHAT IS TFR?

TFR is the long-term maintenance of Major Molecular Response (MR3: <math><0.1\%</math> BCR-ABL), a sign of disease remission, in CML patients after discontinuing their TKI therapy.

Clinical studies have shown that some patients who have achieved a stable, deep molecular response are able to stop taking tyrosine kinase inhibitors (TKIs) without recurrence of their disease.^{1,2} A deep molecular response is when there are only tiny amounts of BCR-ABL gene transcripts detectable in the blood, or when these are no longer detectable at the limit of sensitivity allowed by currently available technologies.²

AM I ELIGIBLE TO STOP TKI TREATMENT?

Important factors in deciding if stopping treatment is a suitable option for you could include³

- The state of your CML
- Which phase of the disease you were in when you started initial TKI therapy, for example, chronic or accelerated phase
- The level of your molecular response to the disease, as measured in a laboratory using the International Scale (IS) of reporting
- How long you have been on TKI therapy
- The length of time for which you have maintained a deep molecular response
- You can find more information about the eligibility criteria for TFR on the CML Advocate Network's website (www.cmladvocates.net)

WILL MONITORING CONTINUE INTO LONG-TERM TFR?

It is very important that PCR monitoring continues long after you have stopped taking medication. Even though the risk of relapse is highest during the first 6 months after stopping, late recurrences, even if rare, are possible and it is important to detect them as soon as possible so that TKI treatment can be restarted.

HOW CONCERNED SHOULD I BE ABOUT MY PCR RESULTS?

A system to standardize PCR results has been introduced to make monitoring as accurate as possible and to ensure a correct assessment of response. As long as your PCR is done in a standardized lab, there is no need to worry. Results may sometimes fluctuate a little but you only need to restart treatment if there is loss of MR3.

Many patients feel worried before PCR tests as fluctuations in results can be confusing. It can be worrying if your PCR result rises but you should remember that longer term trends are more important than the outcomes of individual tests. You should discuss any concerns you may have with your doctor.

IS THERE ANY RISK IN DISCONTINUING TREATMENT?

As long as you are eligible to stop treatment and are monitored adequately, there are no risks from attempting TFR.^{1,2}

Even if the BCR-ABL level is rising above the MR3 threshold, studies have shown that practically all patients are able to regain a deep molecular response after restarting their TKI. According to current knowledge, there are no reports of progressions or developing resistance to TKI therapy while off treatment.

ARE THERE ANY SIDE EFFECTS TO STOPPING TREATMENT?

After discontinuation, some patients may experience a withdrawal syndrome, characterized by pain in their muscles, joints or bones. In most cases it is mild and can be managed with simple painkillers. Symptoms can last for weeks, or, more rarely, a few months, and generally get better on their own.⁴

IS THERE ANYTHING I CAN DO IF I FEEL WORRIED ABOUT STOPPING TREATMENT?

Stopping treatment will understandably cause some concerns. If you feel isolated, you may find it helpful to talk to other people going through TFR. It is normal to be apprehensive about stopping treatment. Seek guidance from your doctor to ensure you receive the best support.

HAVE I FAILED IF I AM NOT ELIGIBLE FOR TFR OR NEED TO START TREATMENT AGAIN?

You should never feel as though you have failed if TFR does not work for you. It does not matter if you are unable to stop taking medication, or if you need to start taking it again. Regardless of the decision you and your doctor make about your care, the aims of treatment are always to prevent disease progression, to achieve a deep molecular response and to improve your quality of life.

COULD I STILL BE OFFERED THE CHANCE TO STOP TREATMENT EVEN IF I DON'T MEET ALL OF THE CRITERIA?

It can be risky to attempt TFR if you are not clinically eligible. Unfortunately, not all patients will be eligible, even with long-term treatment. Talk to your doctor who will be able to discuss your

GLOSSARY

BCR-ABL GENE
The BCR-ABL gene is a unique fusion of CML cells. It is formed through fusion of two other genes, BCR and ABL, which normally exist as separate units within the genetic code. When these genes combine, the instructions they contain are changed. In CML, cells with the BCR-ABL gene behave differently from how they should.

BLOOD COUNT
A blood count is a test requested which gives information about the number of cells of each type.

BONE MARROW
Bone marrow is the soft tissue found inside bones. It contains stem cells which produce new blood cells.

CHRONIC MYELOID LEUKEMIA (CML)
Chronic myeloid leukemia, or CML, is a cancer of the bone marrow that causes too many white blood cells to be produced. These cells multiply more than they should. Eventually, these leukemia cells acquire other errors and stop normal cells from doing their jobs properly. This creates disease progression. There are three stages to the disease, the chronic, accelerated and blast phase.

GENES
Genes are the individual units of the genetic code. Each gene provides a code to tell a cell what to do. There are many ways to read these genetic instructions, leading to different types of cells.

GENETIC CODE
The genetic code, also known as DNA, is the instruction set genes provide every cell.

MOLECULAR RESPONSE
Molecular response is a measure of the reduction in the number of cells with the BCR-ABL gene. It is sometimes assessed by using sensitive tests which measure residual amounts of the gene.

STEM CELL
Stem cells produce other types of cell.

TYROSINE KINASE INHIBITOR (TKI)
Tyrosine kinase inhibitors, or TKIs, are a type of drug used to treat CML. They work by blocking the effect of the BCR-ABL gene in leukemia cells.

TREATMENT-FREE REMISSION (TFR)
It is possible for some CML patients to stop taking medication if they have a deep molecular response that has been stable for some time. This pause in taking medication is known as treatment-free remission (TFR), and is a state where a CML patient who has discontinued TKI therapy does not lose MR3/ABL.

WHITE BLOOD CELLS
This group of cells is a part of the immune system known as lymphocytes and other elements. They are produced by stem cells in the bone marrow.

PCR
The polymerase chain reaction, or PCR, is a test which measures the amount of a specific gene. Doctors use PCR to monitor your molecular response by measuring the amount of the BCR-ABL gene present.

PCR RESULTS
There are different levels of molecular response:

- Major molecular response, or MR3.0, is when the amount of BCR-ABL is very low and the number of cells with the gene is around 1 in 1000.¹
- MR4.0, is when fewer than 1 in 10,000 cells with the BCR-ABL gene are found.⁴
- MR4.5, is when fewer than 1 in 32,000 cells with the BCR-ABL gene are found.⁴

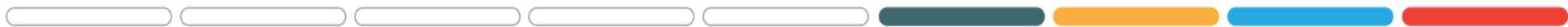


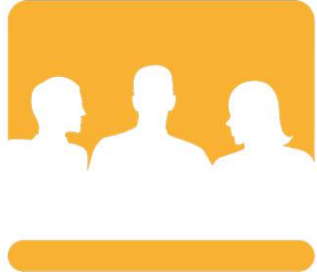
WHAT HAS CHANGED IN THE LAST YEAR

TFR done in and out of clinical trials

Change-

- Very few open trials for stopping. Only 2 trials are currently recruiting: One in Malaysia and one in Germany for a 2 ed stop.
- Most stopping occur in clinical practice.





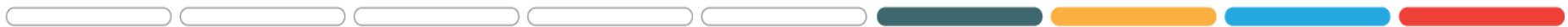
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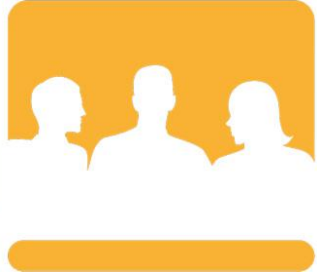
Companies are pushing second-generation TKIs as better option for future TFR – not really proven in real life yet

Change

- Nilotinib received an EHA and FDA label for TFR drug.
- Similar label is being requested for Dasatinib (Probably)

Has this changed the perspective of Drs and patients in regards to using 2 ed generation out-front for possible future TFR???



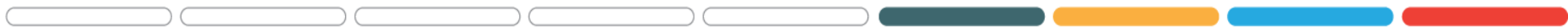


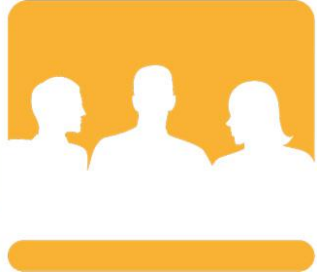
What Has changed in the last year

TFR not well understood, much confusion as well as hope, excitement

Change-

No Change Yet. Hopefully the data from our global TFR study will give some answers to clarify the topic, in addition to the planned HCP and Patients educational TFR material





GLOBAL TFR SURVEY

Organized by CML Advocates network

- TFR Workgroup of 10 CML patients on TFR
- Team work Led by Giora and Celia



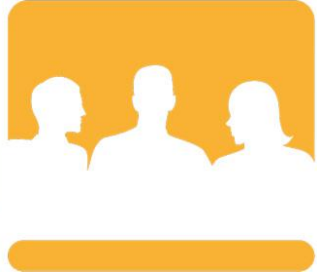
TFR WORKGROUP

- ▣ Giora Sharf
- ▣ Jan Geissler
- ▣ Pat Elliot
- ▣ Rita O. Christensen
- ▣ Bernhard Schwarzer
- ▣ Felice Bombaci
- ▣ Nigel Deekes
- ▣ Bahija Gouimi
- ▣ Mina daban
- ▣ Tamie Kimmelman
- ▣ Sriram Ranganathan

TREATMENT-FREE REMISSION FOR CML PATIENTS

-Interim results from the global online
survey of TFR patients -

#TFR4CML



**55 countries
+500 responses
6 weeks...**

**Have you already taken
the #TFR4CML
survey?**

CML Advocates Network

bit.ly/tfr4cml



Introduction

- The “**TFR 4 CML PATIENTS**” project consists of a global online survey of **TFR** patients to collect the viewpoints, needs and experiences of **CML** patients that are considering or have already started **Treatment Free Remission (TFR)**
- The aim is to provide **CML** patients and healthcare providers with more evidence when considering or managing **TFR**
- Fieldwork is underway at: www.cmladvocates.net/tfr-cml-patients

Questionnaire Design

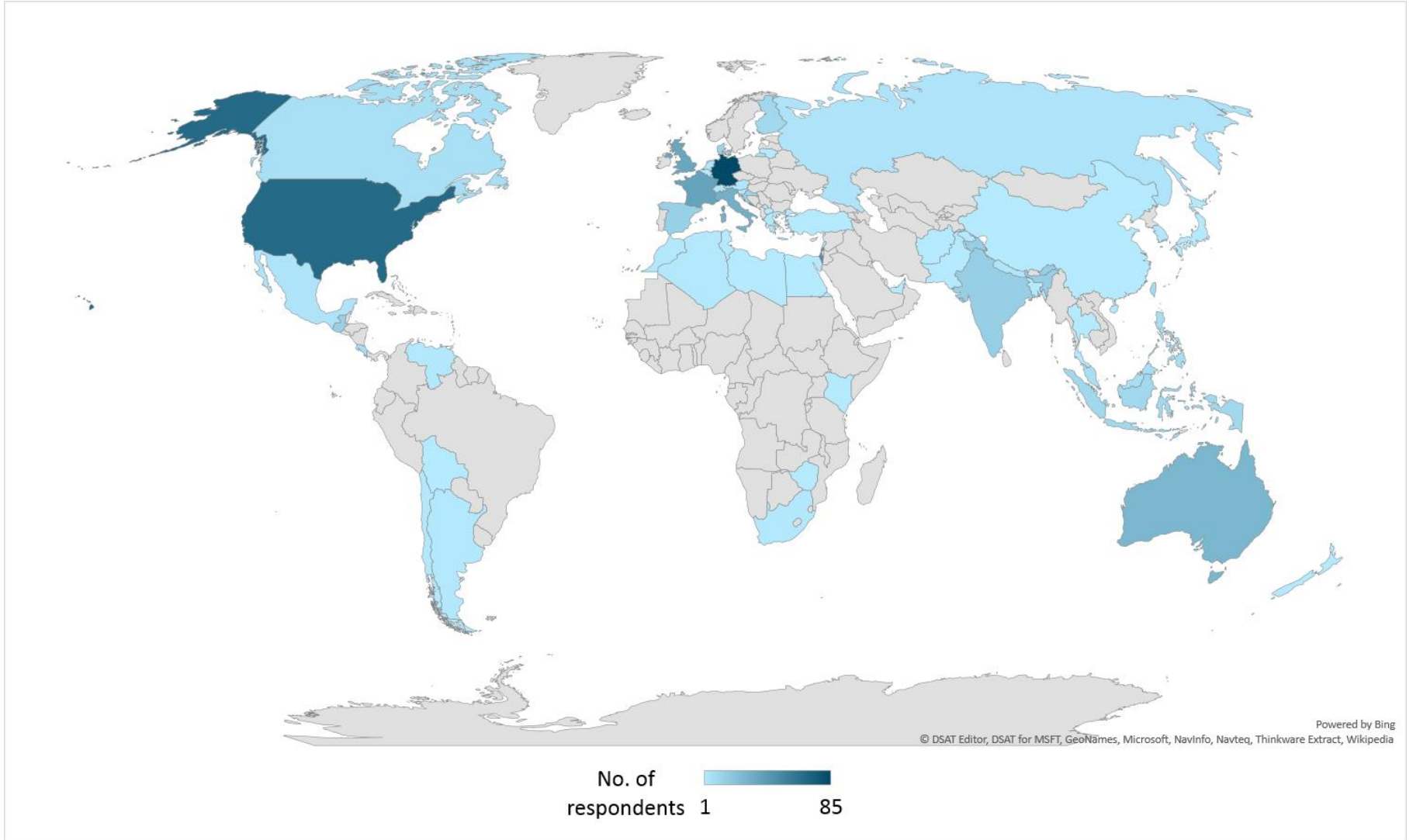
- The questionnaire was developed and designed over a number of months in 2017/18, following detailed discussion between CML Advocates and the survey provider, Quality Health
- The questionnaire has been tested by patient volunteers and reviewed by a number of stakeholders. This exercise contributed towards refining the questionnaire into a finished version
- The survey was originally available in seven languages: English, Spanish, German, Italian, French, Finnish and Hebrew. Additional languages, including Danish and Arabic are currently available online.

Response Rates

- The number of respondents at the time the interim results were analysed was 546

Country	No. of respondents	Country	No. of respondents	Country	No. of respondents
Afghanistan	1	Greece	2	New Zealand	1
Algeria	2	Guatemala	14	Pakistan	1
Argentina	2	India	15	Philippines	7
Australia	28	Indonesia	10	Russia	5
Austria	3	Israel	50	Slovenia	1
Bangladesh	1	Italy	32	South Africa	2
Belgium	1	Japan	1	South Korea	3
Bolivia	1	Kenya	1	Spain	14
Cabo Verde	1	Kosovo	1	Switzerland	3
Canada	6	Lebanon	2	Taiwan	17
Chile	2	Libya	1	Thailand	1
China	1	Lithuania	1	Tunisia	1
Costa Rica	7	Luxembourg	1	Turkey	1
Croatia	12	Macedonia	1	United Arab Emirates	1
Denmark	13	Malaysia	7	United Kingdom	37
Egypt	1	Mexico	4	United States of America	68
Finland	10	Morocco	2	Venezuela	2
France	39	Nepal	3	Zimbabwe	1
Germany	88	Netherlands	3	Blank	10

Response Rates



TFR for CML Patients Survey Impact

14th March- 30 April 2018

+12.200 on TFR website:

<http://www.cmladvocates.net/tfr-cml-patients>

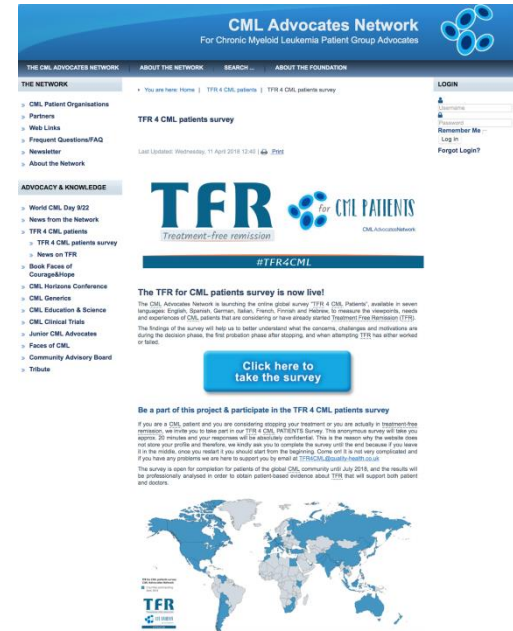
+35.000 impressions in Twitter with #TFR4CML and @cmlnet

+1100 views TFR video Youtube

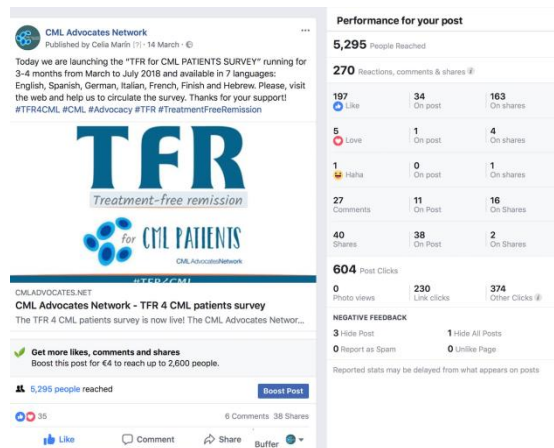
+20.000 organic reach of #TFR4CML publications

in Facebook

Instagram, Google+, LinkedIn, other channels

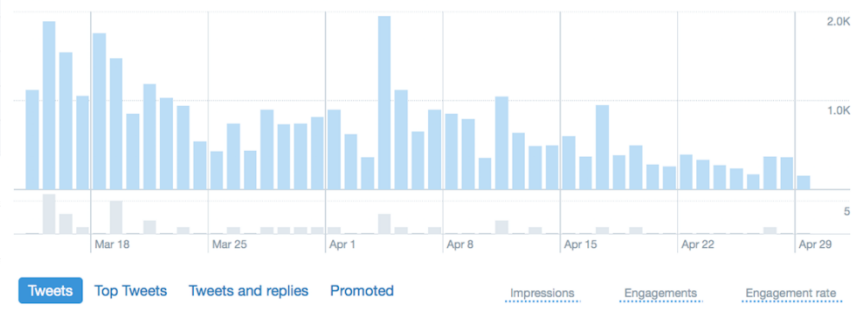


The screenshot shows the CML Advocates Network website with a prominent banner for the 'TFR 4 CML patients survey'. The banner includes the TFR logo and the text 'The TFR for CML patients survey is now live!'. Below the banner, there is a call to action button that says 'Click here to take the survey'. The website also features a navigation menu and a sidebar with various links and information.



The screenshot shows a Facebook post from CML Advocates Network. The post text reads: 'Today we are launching the "TFR for CML PATIENTS SURVEY" running for 3-4 months from March to July 2018 and available in 7 languages: English, Spanish, German, Italian, French, Finnish and Hebrew. Please, visit the web and help us to circulate the survey. Thanks for your support! #TFR4CML #CML #Advocacy #TFR #TreatmentFreeRemission'. The post includes the TFR logo and a link to the survey. The performance statistics for the post are: 5,295 people reached, 270 reactions, comments & shares, 197 likes, 34 on post, 163 on shares, 5 love, 1 on post, 4 on shares, 1 haha, 0 on post, 1 on shares, 27 comments, 11 on post, 16 on shares, 40 shares, 38 on post, 2 on shares, 604 post clicks, 0 photo views, 230 link clicks, 374 other clicks, 3 hide post, 1 report as spam, 0 unlike page, and 0 unlike page.

Your Tweets earned 34.9K impressions over this 47 day period



#TFR4CML

Topic One:

Reasons to consider TFR (Phase I)

- Respondents could tick all the reasons that made them consider stopping treatment:

16. What are the main reasons that made you consider stopping treatment?

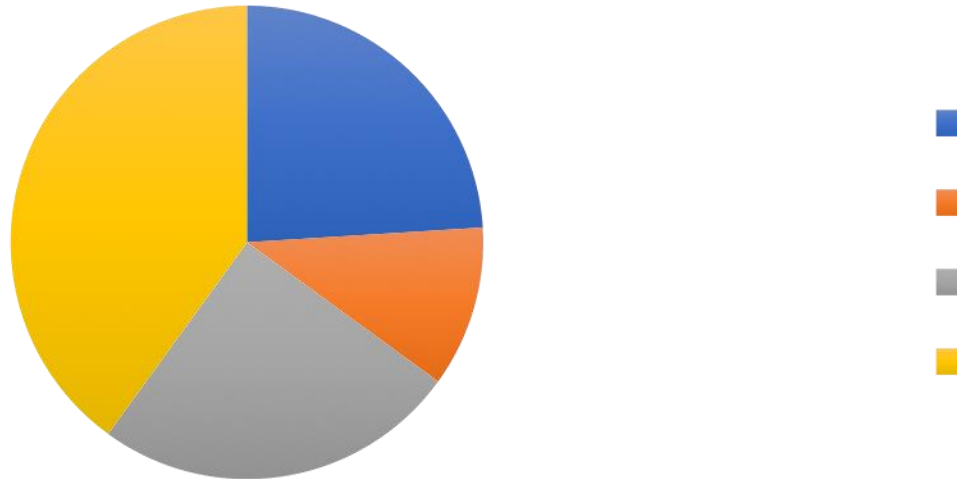
Please tick all that apply

- | | |
|--------------------------|---|
| <input type="checkbox"/> | To get rid of current treatment side effects |
| <input type="checkbox"/> | The fear of side effects caused by long-term treatment |
| <input type="checkbox"/> | Not needing to take medication everyday |
| <input type="checkbox"/> | To see if I can be free of CML without therapy |
| <input type="checkbox"/> | My doctor proposed I join a 'stopping treatment' clinical trial |
| <input type="checkbox"/> | Financial reasons - reduction of costs |
| <input type="checkbox"/> | Planned or unplanned pregnancy |
| <input type="checkbox"/> | Other, please specify below |

Topic Two: Time living with CML (Phase II)

Q25. How many years were you on medication for CML before stopping?

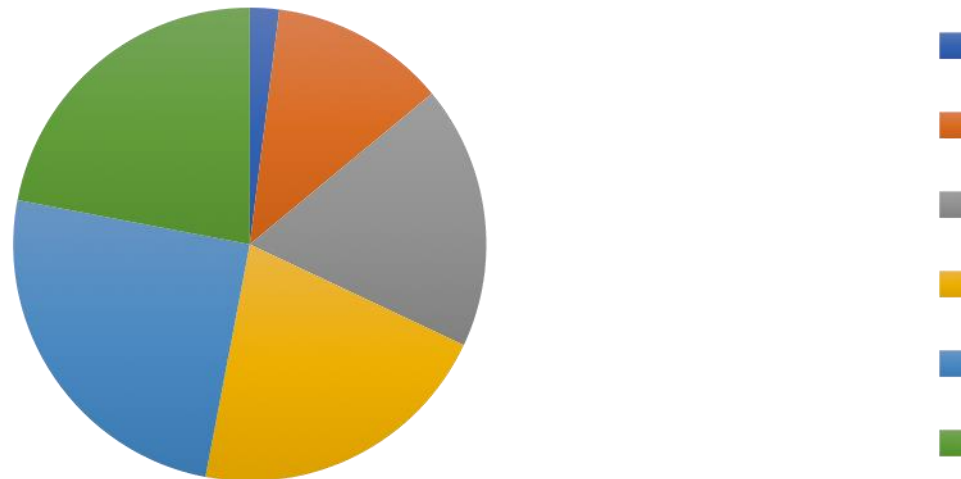
Answers



Topic Two: Time living with CML (Phase II)

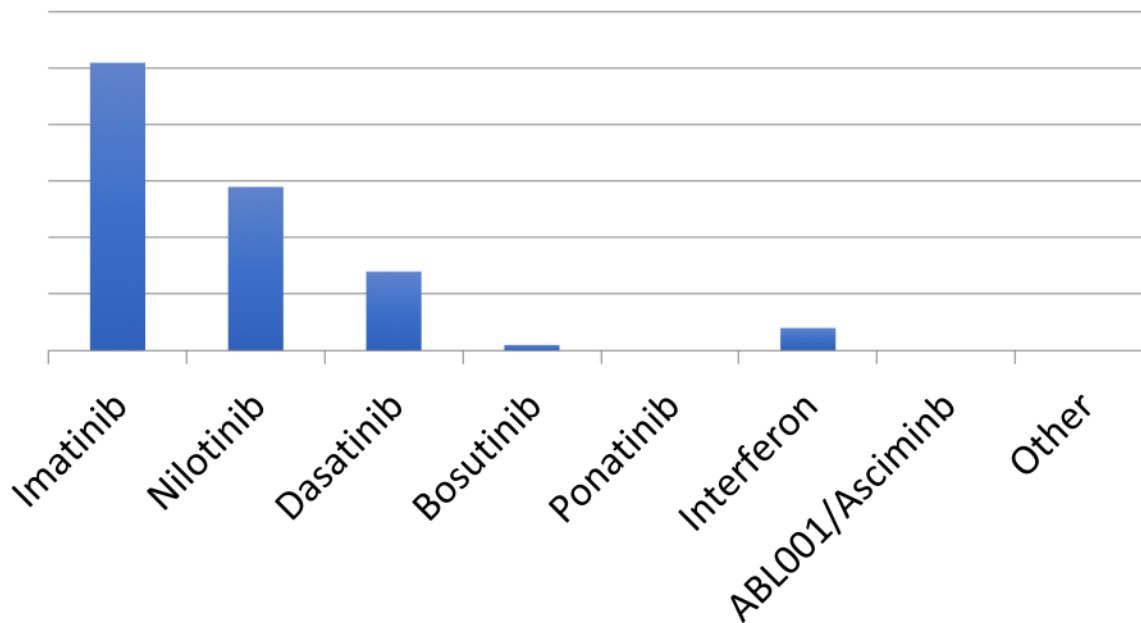
Q26. How long were you in deep molecular response (at least MR4, or BCR-ABL below 0.01%) before you stopped CML treatment?

Answers



Topic Three: Which medication were you on before stopping treatment (Phase I)

Q10. What CML medication were you taking just before you stopped?



Topic Four:

Reasons to worry about stopping (Phase I)

- Respondents could tick all the reasons that made them worry about stopping treatment

17. What are the main reasons that made you worry about stopping treatment?

Please tick all that apply

- I didn't have enough information about stopping treatment
- I wouldn't feel safe going off treatment
- There is a lack of proper quality PCR monitoring
- The fear of withdrawal symptoms
- Recurrence of disease (stopping treatment unsuccessful)
- I wasn't worried about stopping treatment
- Other please specify below

Topic Five:

Withdrawal symptoms (Phase II)

- Respondents could tick all the withdrawal effects they experienced when treatment stopped *

31. What withdrawal effects did you experience when treatment was stopped?

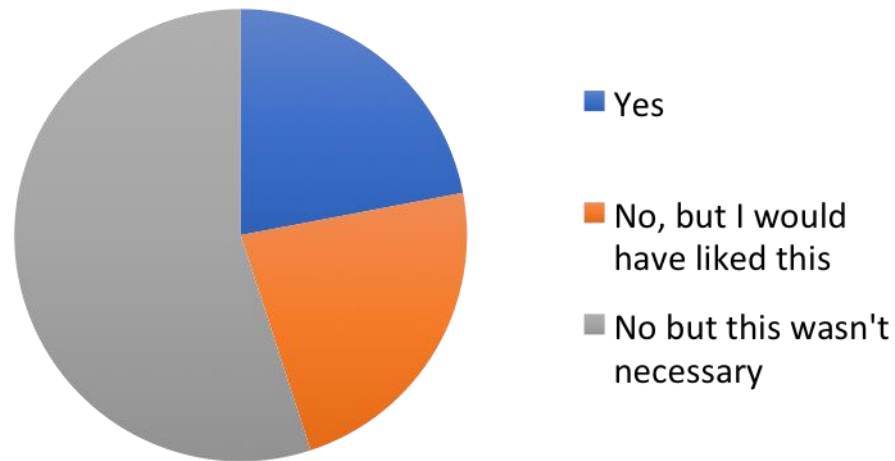
Please tick all that apply

- | | |
|--------------------------|---|
| <input type="checkbox"/> | Pain in muscles, joints or bones |
| <input type="checkbox"/> | Sweating or skin problems |
| <input type="checkbox"/> | Depressive episodes or fear or bad mood |
| <input type="checkbox"/> | Tiredness |
| <input type="checkbox"/> | Weight loss |
| <input type="checkbox"/> | Other, please specify below |

Topic Six: Psychological support (Phase II)

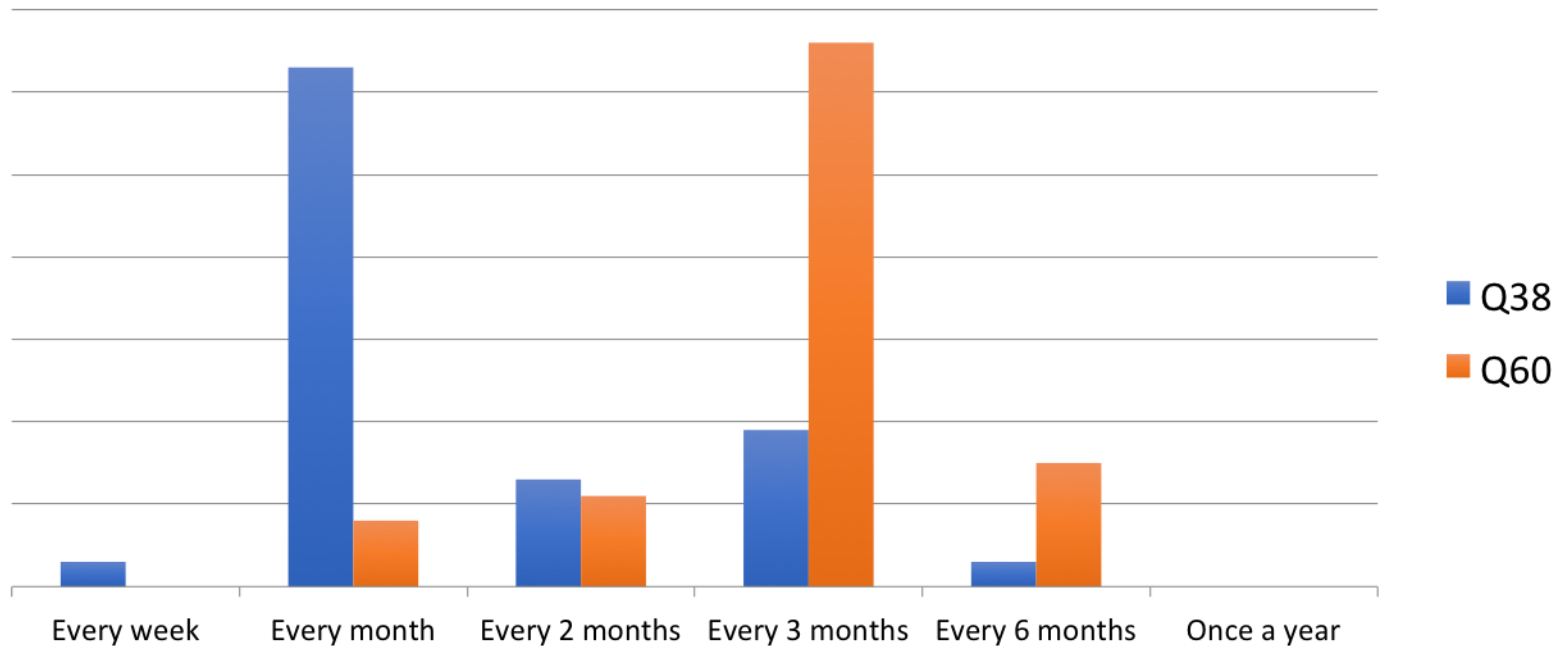
Q35. Did you receive psychological and/or emotional support during the stopping of treatment?

Answers



Topic Seven: Monitoring(Phase II)

- The chart below compares the frequency of monitoring of respondents in the 6 month probationary period (Q38) to those in long term remission (Q60)



Conclusions

- Looking at the participating countries it is clear that TFR is currently implemented mainly in developed western countries.
- We need better monitoring in other countries to let patients stop safely.
- We need clear and agreed guideline for stopping treatment, so patients can do it safely.
- More information is needed for both patients and Healthcare providers.