

## **Response to Tyrosine Kinase Inhibitors in patients with BCR-ABL1 Positive Chronic Myeloid Leukemia; 13.5 years' experience at Patan Hospital, Nepal**

Abstract:

Background:

Since the advent of Tyrosine Kinase Inhibitor (TKI), well controlled studies in developed world have shown that the life expectancy of patients with CML is comparable to normal people without the disease. But long-term follow up studies are lacking in resource poor setting.

Method:

This is a retrospective follow up study looking at the molecular response and resistance to Tyrosine Kinase Inhibitors (TKI) in patients enrolled in the Max Access Program since February 2003 till March 2017. Patients with two or more BCR-ABL1 levels by Karyotyping/ fluorescent in situ hybridization (FISH) / reverse transcriptase polymerase chain reaction (RT-PCR) were included. At baseline, complete blood count (CBC), renal function test (RFT), and liver function test (LFT) were evaluated. Bone marrow aspiration and biopsy for morphology, cytogenetic analysis by Karyotyping/FISH and/or molecular analysis by RT-PCR were also done if these tests were not performed earlier. FISH or RT-PCR was done on peripheral blood every 3–12 months as necessary if the patient could afford. Patients with warning response/failure underwent BCR-ABL1 Resistance Mutation Analysis (IRMA).

Result:

Three hundred and forty six (346) patients had two or more BCR-ABL1 monitoring tests done. Optimal response was seen in 49.42%. Similarly, suboptimal response and failure were seen in 16.5% and 34% respectively. Overall Survival is 89.6% (at 1.8 -165 months, mean 62 months) . If only CML related events is considered survival is 95.9%. Seventy seven (77) patients with a total of 80 BCR-ABL1 domain Imatinib Resistance Mutation Analyses (IRMA) showed 19 different types of mutations with the most common being T315I mutation (8 and 19.5%). About 22.25% of the total patients showed resistance to Glivec out of which 10.98% showed mutations. Nine patients underwent trial for treatment free response (TFR) and 5 of them relapsed between 2-8 months.

Conclusions:

Despite all the odds of having financial problem, accessibility problem due to distances, transportation, etc. and difficulty monitoring with routine BCR-ABL1 and IRMA, our findings

show that the outcome of TKI therapy in our CML patients is comparable to well controlled studies done elsewhere. Overall survival, molecular and cytogenetic responses and mutations in our patients who developed resistance as well as TFR are also similar to other studies. The resistance rate of 22.25% is slightly higher compared to other studies in developed world. This is mainly because of poor monitoring due to unavailability of the test including IRMA in our country and affordability until 2012. It proves that TKI is very effective in CML even in a resource-poor, developing country.

Key words: Chronic Myeloid Leukemia, CML in Nepal, Tyrosine Kinase Inhibitors, TKI in Nepal, BCR-ABL1, Nilotinib, Dasatinib, Ponatinib, Response to TKI in CML patients, Resistance to TKI, IRMA

#### Introduction:

Chronic Myeloid Leukemia (CML) is a form of blood cancer. Among all the forms of blood cancers, CML is relatively good in terms of prognosis due to the availability of targeted therapy. In 1973 Janet Rowley made the discovery of Philadelphia chromosome which was BCR-ABL1 translocation between chromosomes 9 and 22.<sup>1</sup> Philadelphia Chromosome is the translocation of Abelson gene (ABL1) from Chromosome 9 to Breakpoint cluster region gene (BCR) on chromosome 22 leading to t(9;22) fusion oncogene BCR-ABL1. This oncogene leads to translation of constitutively active BCR-ABL1 tyrosine kinase consequently leading to uncontrolled proliferation of white blood cells. Ph negative but BCR-ABL1 positive at molecular level can also occur in 5-10% of CML cases. These cases have sub-microscopic rearrangements of BCR-ABL1.<sup>2</sup> Sokal and Hasford scores used to be the prognostic indicators. Additional chromosomal abnormalities (ACA) generally bear poorer prognosis compare to the patients without ACA.<sup>3</sup> More and more genetic factors are also known which determine the prognosis. Genetic abnormalities such as trisomy 8, 2Y and extra Ph chromosome bear relatively good prognosis compared to i(17)(q10), 27/del7q, and 3q26.2 rearrangements.<sup>4-7</sup>

Patients with CML, nowadays, can virtually expect the life expectancy of a normal person. Prof. Francois-Xavier Mahon, a French hematologist, found that targeted therapy with Glivec not only controls the disease process but also cures the disease in some lucky 40% of the patients who have had Glivec for at least 50 months and a deep molecular response for at least two years.<sup>8-11</sup> What determines which patients are lucky 40% is also interesting! Increased proportion of mature NK cells is associated with successful Imatinib discontinuation in chronic myeloid leukemia.<sup>12</sup>

Patan Hospital is one of the GIPAP (Glivec International Patient Assistance Program - The Max Access) centers of the Max Foundation. It, in collaboration with Novartis Pharmaceuticals, is

helping patients with CML to access Imatinib free of cost since February 2003. It was first introduced by Prof. Mark Zimmerman who was the then director of this hospital. Nilotinib, and Dasatinib; the second generation tyrosine kinase inhibitors (TKIs) and Ponatinib, the only third generation TKI are available for switch over therapy. At present, we have more than 600 patients with CML, Gastrointestinal stromal cell tumor (GIST), Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL), dermatofibrosarcoma (DFSP), hypereosinophilic syndrome (HES) receiving Glivec on a compassionate basis.

Since 2012, the Government of Nepal started giving financial assistance of Rs. 100,000 (US\$ 900.00) to each patient with cancer. This enabled us to monitor our patients with CML closely with fluorescent in situ hybridization (FISH) initially and subsequently with Reverse transcriptase polymerase chain reaction (RT-PCR). We performed these molecular tests at least twice a year. Patients who developed resistance to Imatinib underwent BCR-ABL domain Imatinib resistance Mutation Analysis (IRMA) and were switched over to appropriate second or third generation TKIs as necessary, when available or referred for hematopoietic stem cell transplantation.

Although there are many controlled studies in the developed world, there are no reports of studies with long follow up in resource poor setting. We have published 4 articles with regard to response and resistance in our patients with CML.<sup>13-16</sup> We hypothesize that the survival in our set up is similar to well controlled studies elsewhere. About 18% of the patients with CML develop resistance to Imatinib at 5 years.<sup>17-18</sup>

#### Study design:

This is a retrospective study mainly looking at the molecular response and resistance to Glivec in patients enrolled between February 2003 and March 2017. All patients with CML diagnosed at, or referred to, Patan Hospital were included. Patients with two or more BCR-ABL1 levels by Karyotyping/FISH/RTPCR were included. A written informed consent was taken from the patient or from the parents of patients for children under 15 before starting the treatment. At baseline, complete blood count (CBC), renal function test (RFT), and liver function test (LFT) were evaluated. Bone marrow aspiration and biopsy for morphology, cytogenetic analysis by Karyotyping/FISH and/or molecular analysis by RT-PCR were also done if these tests were not performed earlier. Patients with tests performed outside our institution were also included. After treatment was started, the patients were evaluated with CBC and ALT every week during the first month, then every 2 weeks for the next 2 months and then every 6 weeks. FISH or RTPCR was done on peripheral blood every 3–12 months as necessary if the patient can afford. Patients with warning response/failure underwent IRMA. The dose of Glivec was adjusted as necessary immediately followed by switch over to second or third generation TKI as guided by IRMA report.

#### Results:

The study period was from February 2003 till March 2017. Altogether 464 patients were registered in the pharmacy, 346 patients were eligible for analysis. 118 patients were excluded. Medical records of 70 patients' were not available and 48 patients had incomplete records. Follow up ranged from a minimum of 53 days to a maximum of 4952 days (1.8 – 165 months). Mean and median follow up were 1854 days (62 months) and 1656 days (55 months) respectively.

Although, there were a total of 464 patients registered in the pharmacy, only 444 patients were found registered in the GIPAP computer record. Twenty patients were not found to be registered although they were taking medications on a regular basis. Among the registered patients, there were 273 males and 171 females (Ratio: M:F=1.59). Of the total 444 cases of CML; 419 cases were CP, 17 cases were AP and 8 were BC at the time of presentation. At the time of analysis, out of 444 cases registered, 362 cases were active and 82 cases have been already closed.

There were 70 patients with 2 tests, 51 patients with 3 tests, and 225 patients with more than 3 tests. Among the patients with 2 tests; 10 patients had optimal response with major molecular response (MMR) or complete molecular response (CMR), 14 patients had minimal molecular response (mMR) (<1%), 13 patients had early molecular response (EMR) (<10%) and 15 patients had failure (>10%). Four (4) patients had complete cytogenetic response (CCyR) and 14 patients had poor cytogenetic response.

Among patients with 3 tests (51 patients), 13 patients had optimal response (MMR/CMR), 12 patients had minimal response (<1%), 7 patients had early molecular response (<10%), and 7 patients had failure (>10%). Four (4) patients showed CCyR and 8 patients had poor cytogenetic response.

Among the patients with more than 3 tests (225 patients), 139 patients had optimal results (CMR/MMR). 31 patients had minimal molecular response (<1%) and 20 patients had early molecular response (<10%). Thirty-one (31) patients had failure (>10%). One patient had CCyR and 3 patients had poor cytogenetic response. **(Figure 1)**

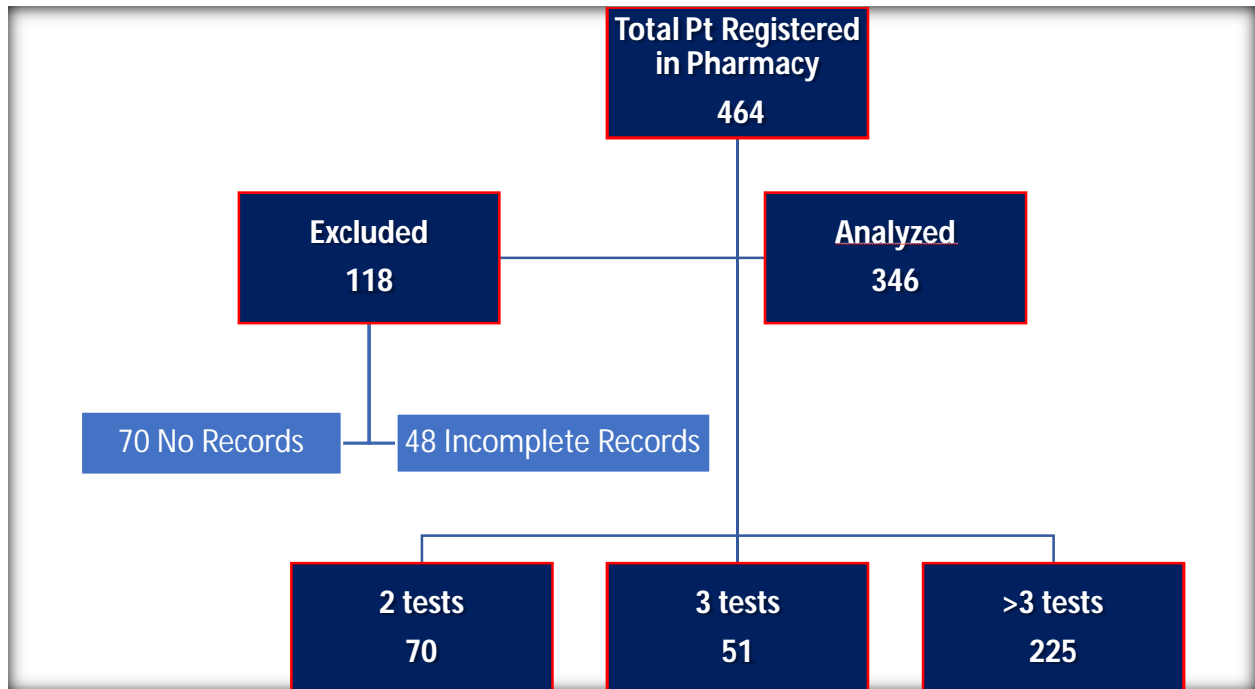


Figure 1: Flow chart of the total patients under study

Overall, out of 346 patients, 312 (90.2%) had two or more RT-PCR tests and 34 (9.8%) had cytogenetic tests done. Among the patients with RT-PCR, 162 (46.8%) had optimal response with MMR/CCR and 57 (16.5%) had minimal molecular response (mMR<1%). 40 patients (11.6%) had early molecular response (EMR<10%) and 53 (15.3%) patients had failure (>10%). Among the 34 (9.8%) patients who underwent only cytogenetic tests, 9 (2.6%) had CCyR and 25 (7.2%) had poor cytogenetic response. Altogether 49.422% has optimal response and 16.5 % has suboptimal response and 34.1% have failure by definition.

**(Figure 2): Flow chart of the molecular and cytogenetic analyses**

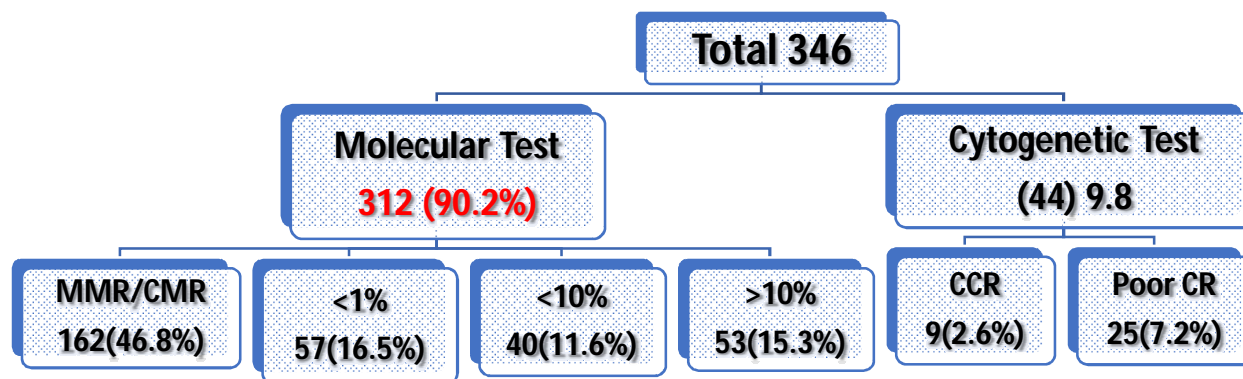
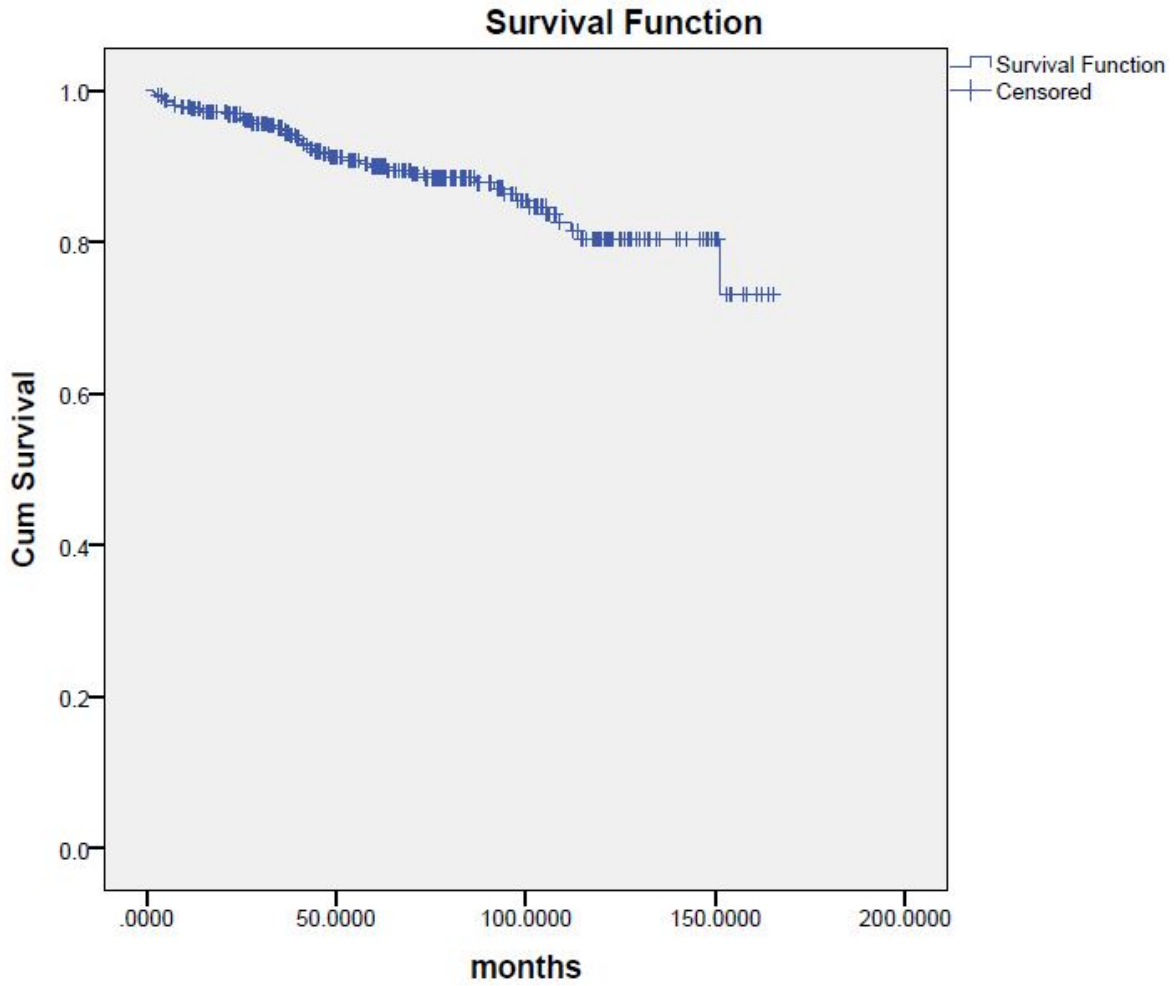


Figure 2: Flow chart of overall molecular/cytogenetic responses in all patients under study

Among the 82 patients closed from GIPAP for Imatinib, 21 patients were switched over to Nilotinib. Similarly, 4 patients were switched over to Dasatinib, and 3 patients were switched to Ponatinib. 3 patients had been referred to India. Twenty-seven (27) patients were lost to follow up, and 19 patients expired. Five patients stopped taking Imatinib. Altogether, 9 patients with deep molecular responses for more than 2 years were followed for TFR. Five of them relapsed within 3-5 months. But 4 of them maintained MR4 to MR4.5 without relapse and they are being closely monitored with regular RT-PCR for BCR-ABL1 transcript. Imatinib was restarted on the patients who relapsed after discontinuation of Imatinib. They responded well with MMR to DMR again.

**Figure 3+Table 1 (Kaplan Meier Curve Showing Overall Survival)**



**Table 1: Kaplan Meier Curve Showing Overall Survival**

**Case Processing Summary**

Total N	N of Events	Censored	
		N	Percent
444	46	398	89.6%

**Figure 4+Table 2 (Kaplan Meier Curve Showing Survival Function in Male vs. Female)**

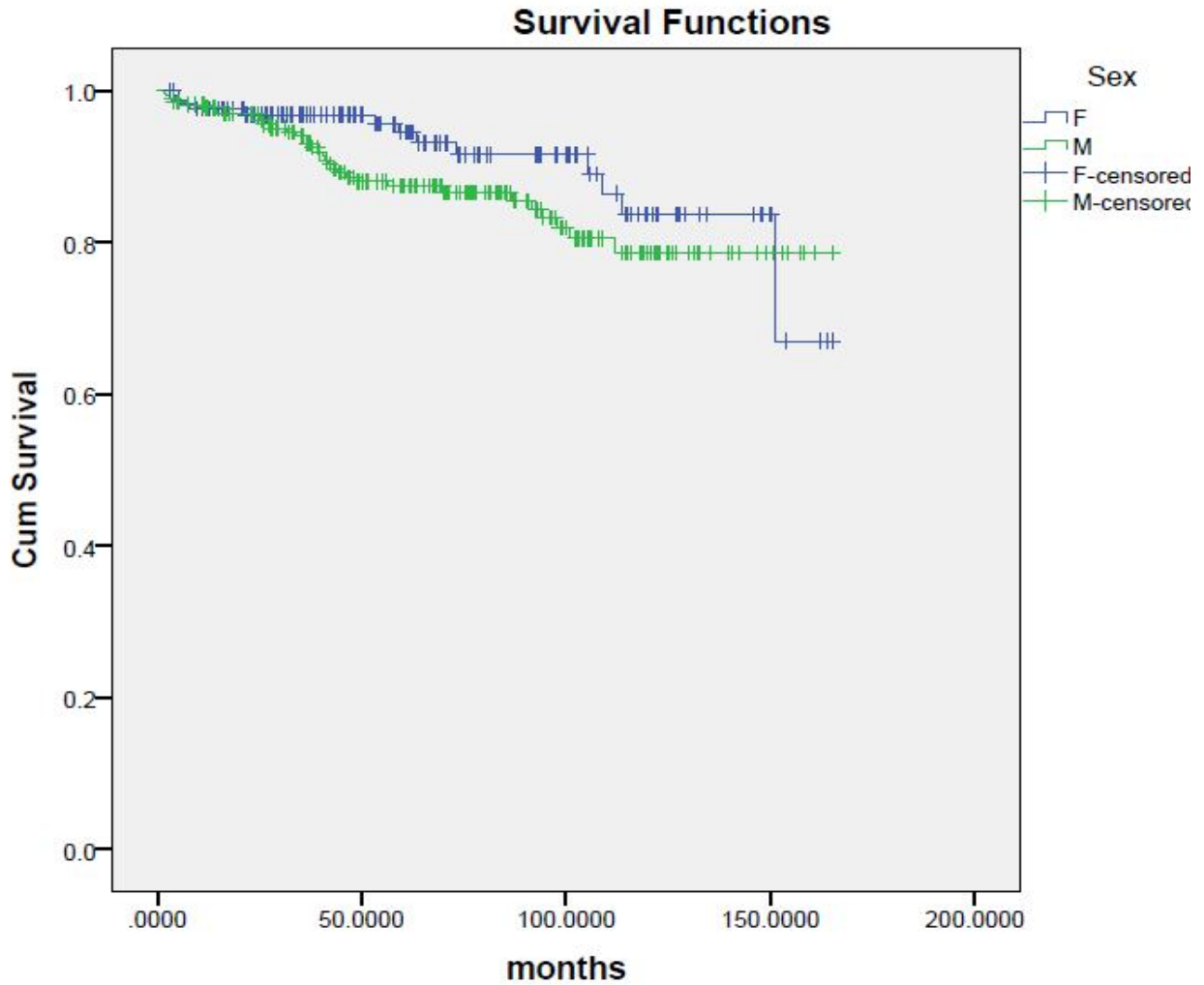


Figure 4: Kaplan Meier Curve Showing Survival Function in Male vs. Female

Table 2: Kaplan Meier Curve Showing Survival Function in Male vs. Female

**Case Processing Summary**

Sex	Total N	N of Events	Censored	
			N	Percent
F	171	13	158	92.4%
M	273	33	240	87.9%
Overall	444	46	398	89.6%

Figure 5+ Table 3 (Kaplan Meier Curve Showing Survival Function in CML related events)

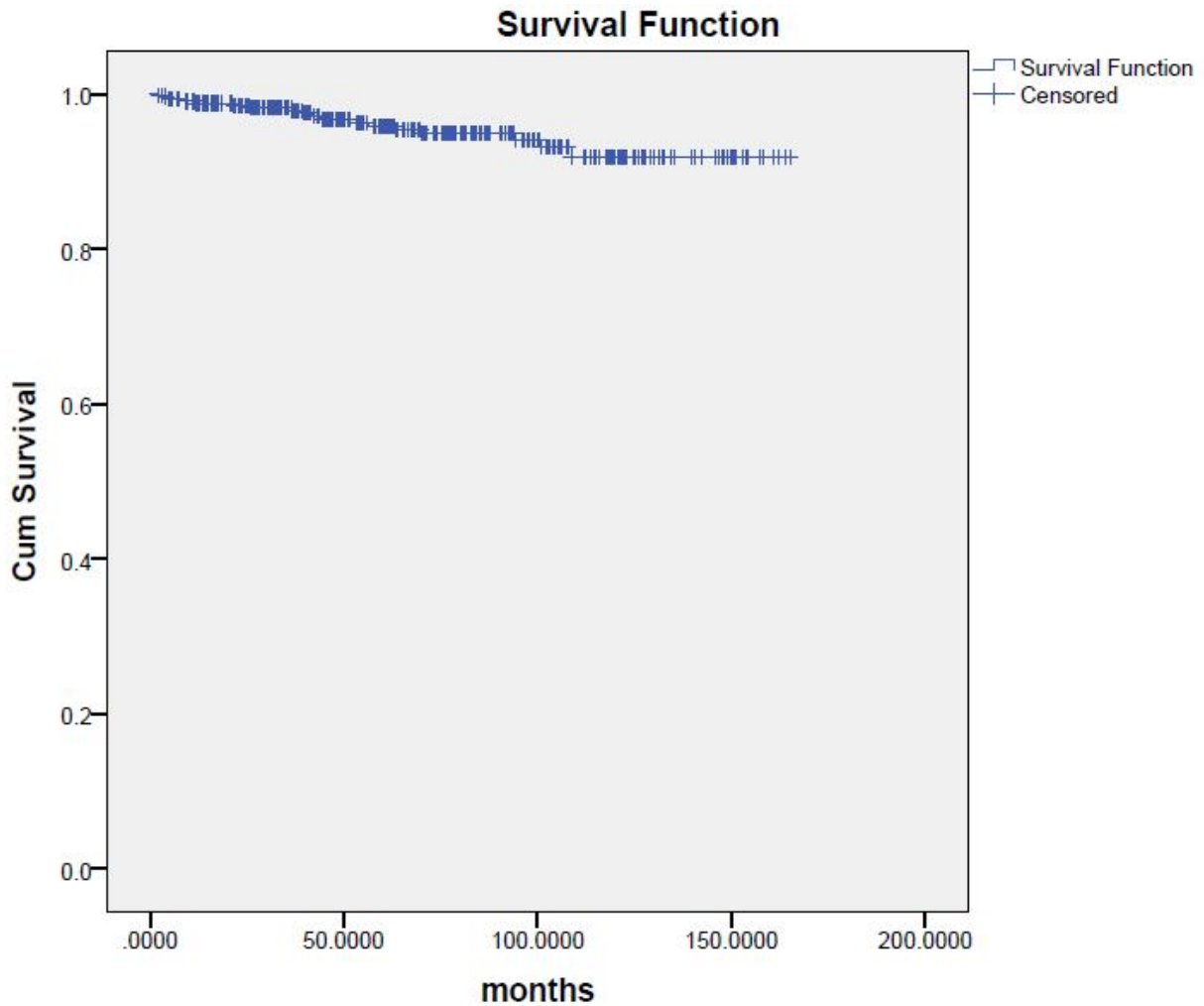


Figure 5: Kaplan Meier Curve Showing Survival Function in CML related events

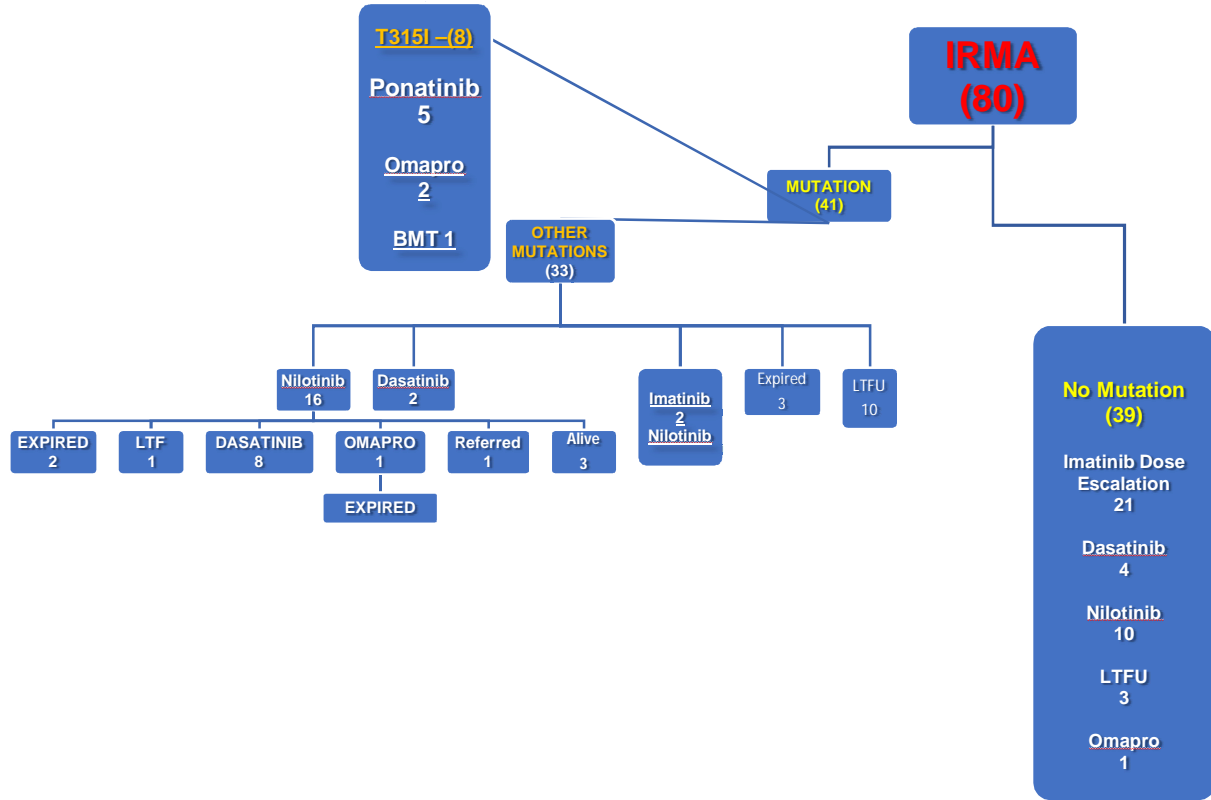
Table 3: Kaplan Meier Curve Showing Survival Function in CML related events

**Case Processing Summary**

Total N	N of Events	Censored	
		N	Percent
444	18	426	95.9%

At the time of analysis there were 46 events occurred among 444 patients registered; showing overall survival of 89.6% with survival in female little better than that of male (92.4% vs. 87.9%). But if we consider only CML related events it was only 18 out of 444 showing 95.9% survival.

**Figure 6: Flow chart of status of patients following IRMA result.**



**Figure 6: Flow chart of patients receiving specific TKI after IRMA**

At the time of analysis 77 patients underwent a total of 80 IRMA. Forty-one (41) mutations were observed in 38 patients and rest 39 patients were negative for mutation. Altogether 19 different types of mutations were noted. T315I mutation was the most frequent one with a total of 8 (20%) followed by M244V and F359V mutations in 4 patients each respectively.

**Table 4: 19 types of mutations (Total 41)**

Type	Number	Type	Number
T315I	8	F359C	1
M244V	4	V379I	1
F359V	4	E279K	1

Y253H	3	E459K	1
E355G	3	Splice Variant	1
E255V	2	M351T	1
F317L	2	M388I	1
L287M	2	Q252H	1
H396R	2	L248V	1
G250E	2	Total Mutations	41

Patients who had T315I positive (8) mutations; five of them were switched to Ponatinib, two patients were switched to Omacetaxine and one patient was referred for Hematopoietic Stem Cell Transplantation (HSCT). Unfortunately, the two patients who received Omapro died. In the remaining 33 patients with positive mutations, 16 patients receive Nilotinib, 2 patients received Dasatinib. Two patients on Glivec were ultimately switched to Nilotinib, and 3 patients expired and the rest 10 patients were lost to follow up.

Among the 39 patients who underwent IRMA but did not show mutation, 21 patients were managed with Imatinib dose escalation initially because second generation TKIs were not available then in Nepal. Later on, some of them were switched over to second generation. Twelve patients received Nilotinib and 6 patients were switched over to Dasatinib. There were 3 patients lost to follow up. One patient who received Omacetaxine died.

**Table 5 Status of TFR trial result of individual patients**

TFR trial patient status at the time of this analysis:

Number	Patients	Status of Molecular Response
1.	31F:	Maintaining MMR >3 years
2.	58M:	Maintaining CMR even at 20 <sup>th</sup> month

3.	57M:	Maintaining CMR at 20 <sup>th</sup> month
4.	42M	Maintained MMR at 20 <sup>th</sup> month
5.	30F:	Lost CMR at 8 <sup>th</sup> month
6.	30F:	Lost CMR at 2 <sup>nd</sup> month
7.	59F:	Lost CMR at 3 <sup>rd</sup> month
8.	70M:	Lost CMR at 3 <sup>rd</sup> month
9.	50F:	Lost MMR in 3 <sup>rd</sup> month

Nine (9) patients with DMR/CMR who voluntarily stopped taking Imatinib were observed for treatment free response (TFR). Five of them relapsed; 4 of them within 2-3 months and one pregnant lady relapsed at 8<sup>th</sup> month. Rest 4 out of 9 has been maintaining TFR beyond 20 months at the time of analysis.

### **Discussion and Conclusions**

**Molecular test and response:** Our analysis showed that overall, out of 346 patients 312 (90.2%) had performed RT-PCR and 34 (9.8%) had cytogenetic tests. Among the patients with molecular tests 162 (46.8%) had optimal response with MMR to CCR and 57 (16.5%) had minimal molecular response (<1%). Forty (40) patients (11.6%) had early molecular response and 53 (15.3%) patients had failure (>10%). Among the 34 (9.8%) patients who underwent only cytogenetic tests, 9 (2.6%) had CCyR and 25 (7.2%) had poor cytogenetic response. Overall 49.4% of our patients had optimal response and 16.5 % had suboptimal response and 34.1% had failure by definition. Our failure rate is also similar.

**Response and Survival:** International Randomized Study of Interferon Vs STI571 (IRIS) at 5 year and 8 year follow up showed overall survival of 90% and 85% respectively of the patients with CML on Imatinib.<sup>18-20</sup> When only CML related deaths were considered it was 93% at 8 years. Overall survival in our patients with CML is 89.6%. If only CML related death are considered survival is 95.9%. The increase survival in our patients probably is due to good response and lack of choices among the patients who were on Imatinib.

**Mutations:** Altogether 77 patients underwent 80 IRMA that showed 19 types of common mutations in 38 patients. Rest of the 39 patients had no mutation. The most common mutation was T315I followed by M244V and F359V mutations. Though the mutation findings are very much similar to the European and American studies<sup>21</sup>, our resistance rate of 22.25% is slightly higher. This is partly because of unavailability of IRMA in Nepal and many patients could not afford the cost. It was only after Nepalese Government started providing an assistance of Rs.

100,000.00 (US\$ 900.00) per patient with cancer since 2012, we have been able to routinely monitor the response at least twice a year with BCR-ABL1 through RT-PCR. We also performed IRMA in resistant cases and switched over to appropriate second or third generation TKI. Patients with T315I mutation were all doing well on Ponatinib (Ponatinib). Response to Ponatinib is better as seen in the study by JE Cortes et al.<sup>22</sup> In chronic phase CML with T315I mutation, treatment with ponatinib yielded better overall survival compare to HSCT.<sup>23</sup> All our 5 patients receiving Ponatinib have molecular responses ranging from MR 3.0 to MR 4.0.

Treatment Free Remission (TFR) Trials mostly showed relapses within first six months after stopping Imatinib and about 40% have sustained TFR beyond two years.<sup>8,9,24,25</sup> Although, we had good number of patients eligible for TFR trial, due to financial reason and difficulty monitoring closely with BCR-ABL1 tests, only nine patients with DMR/CMR for two or more years underwent with discontinuation of imatinib. Four out of nine patients have been maintaining TFR beyond 20 months which is very much similar to Prof. Mahon's study that revealed about 40% of the patients with CML who have achieved DMR/CMR for more than two years continued to maintain TFR. In our center, one pregnant lady relapsed at eight months during pregnancy and other four patients who relapsed at 2-5 months but responded well after restarting Imatinib. The pregnant lady was also restarted on Imatinib after delivery of her baby. All five of them responded well with MMR or better response after restarting Imatinib.

#### Limitations:

We were not able to do the recommended standard 3 monthly molecular tests due to financial reason in most of our patients. This might have skewed the findings with more people having failure. Had there been regular timely molecular monitoring, suboptimal responses would have been noticed earlier and timely switch over to appropriate TKI would have been done early. It was only after Nepal government's one-time financial assistance of Rs. 100,000.00 (US \$900.00) per patient since 2012; we have been able to do regular monitoring by RT-PCR 3-6 monthly and IRMA if necessary. Most of our patients are from outside the Kathmandu valley. It costs additional financial burden for transportation in order to come to Kathmandu, and for lodging and food while in Kathmandu. Besides, many of them are illiterate and do not have access to telephone or internet. It is difficult to ascertain compliance. Quite often, we were not able to switch over to appropriate TKI because IRMA report was not available. We are sending samples to the laboratories in India for IRMA. It is very expensive and costs NPR16000.00 per test (US \$140.00/IRMA test). It often took several weeks before the reports were available.

Despite all the odds of having financial and accessibility problems due to distances, transportation, etc. and difficulty in monitoring with routine RT-PCR and IRMA, our findings show that the outcome of TKI therapy in our CML patients is comparable to the well-controlled studies elsewhere. Overall survival, molecular and cytogenetic responses are similar to other studies. Mutations in our patients who developed resistance as well as TFR are also similar to other studies.

## References:

1. Janet Davison Rowley. [Geoff Watts](https://doi.org/10.1016/S0140-6736(14)60142-2), February 01,14 DOI: [https://doi.org/10.1016/S0140-6736\(14\)60142-2](https://doi.org/10.1016/S0140-6736(14)60142-2)
2. [Seong D](#) et al. Analysis of Philadelphia chromosome-negative BCR-ABL1-positive chronic myelogenous leukemia by hypermetaphase fluorescence in situ hybridization. [Ann Oncol](#). 1999 Aug;10(8):955-9.
3. Richard E. Clark, Jane F. Apperley, Mhairi Copland, and Silvia Cicconi. Additional chromosomal abnormalities at chronic myeloid leukemia diagnosis predict an increased risk of progression. Submitted 9 October 2020; accepted 28 December 2020; published online 22 February 2021. DOI 10.1182/bloodadvances.2020003570 (Blood Advances 23 FEBRUARY 2021 x VOLUME 5, NUMBER 4)
4. Wei Wang et al. Risk stratification of chromosomal abnormalities in chronic myelogenous leukemia in the era of tyrosine kinase inhibitor therapy *Blood*. 2016 Jun 2;127(22):2742-50. doi: 10.1182/blood-2016-01-690230. Epub 2016 Mar 22
5. [Hasford J<sup>1</sup>](#), [Pffirmann M](#), [Hehlmann R](#), [Allan NC](#), [Baccarani M](#), [Kluin-Nelemans JC](#), [Alimena G](#), [Stegmann JL](#), [Ansari H](#). A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. Writing Committee for the Collaborative CML Prognostic Factors Project Group. [J Natl Cancer Inst](#). 1998 Jun 3;90(11):850-8
6. Shafaq Maqsood, Fatima Ali, Abdul Hameed, Neelam Siddiqui. Chromosomal Aberrations in Chronic Myeloid Leukemia: Response to Conventional TKIs and Risk of Blastic Transformation. DOI:10.31557/APJCC.2021.6.1.35 Asian Pac J Cancer Care, 6 (1), 35-39.
7. Mariam IS et al. Differential prognostic impact of stratified additional chromosome abnormalities on disease progression among Malaysian chronic myeloid leukemia patients undergoing treatment with imatinib mesylate *Front. Oncol.*, 08 August 2022, Sec. Cancer Genetics. Volume 12 - 2022 <https://doi.org/10.3389/fonc.2022.720845>
8. [Mahon FX](#) et al. Discontinuation of imatinib in patients with chronic myeloid leukemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. [Lancet Oncol](#). 2010 Nov;11(11):1029-35. doi: 10.1016/S1470-2045(10)70233-3. Epub 2010 Oct 19.
9. Mahon FX. Treatment-free remission in CML: who, how, and why? *Hematology Am Soc Hematol Educ Program*. 2017;2017:102-9.
10. Hughes TP et al. Moving treatment-free remission into mainstream clinical practice in CML. *Blood*. 2016;128:17-23.
11. Saussele S et al. The concept of treatment-free remission in chronic myeloid leukemia. *Leukemia*. 2016;30:1638-47.
12. [Ilander M](#) et al. NK cells is associated with successful imatinib discontinuation in chronic myeloid leukemia. [Leukemia](#). 2017 May;31(5):1108-1116. doi: 10.1038/leu.2016.360. Epub 2016 Nov 28.
13. [Kayastha GK](#) et al. Patan hospital experience in treating Philadelphia chromosome/BCR-ABL1 positive chronic myeloid leukemia patients with gleevec (imatinib mesylate); the first generation specific tyrosine kinase inhibitor. [BMC Blood Disord](#). 2010 Dec 7;10:8. doi: 10.1186/1471-2326-10-8.

14. Gyan K. Kayastha et al. Treating Philadelphia chromosome/BCR-ABL1 positive patients with Glivec (imatinib mesylate): 10 years' experience at Patan Hospital, Nepal doi: 10.1111/bjh.14645 British Journal of Haematology, 2017,177,991–999
15. Gyan K. Kayastha et al. The use of imatinib resistance mutation analysis to direct therapy in Philadelphia chromosome/BCR-ABL1 positive chronic myeloid leukemia patients failing BCR-ABL1 treatment, in Patan Hospital, Nepal DOI:[10.1111/bjh.14683](https://doi.org/10.1111/bjh.14683) Corpus ID: 24907138 British Journal of Haematology, 2017,177,1000–1007
16. Nora Ranjitkar Manandhar et al. Dasatinib tyrosine kinase inhibitor as second and third line therapy in chronic myeloid leukemia: outcome of a Nepalese study. Journal of Patan Academy of Health Sciences. 2018 Jun;5(1):47-56.
17. [Michael J. Mauro](#), Defining and Managing Imatinib Resistance, doi: 10.1182/asheducation-2006.1.219 (ASH Education Book January 1, 2006 vol. 2006 no. 1 219-225)
18. Druker BJ, Guilhot F, O'Brien S, et al. Long-term benefits of imatinib (IM) for patients newly diagnosed with chronic myelogenous leukemia in chronic phase (CML-CP): the 5-year update from the IRIS study [abstract]. *J Clin Oncol*; 2006;24:338s
19. Druker BJ, Guilhot F, O'Brien SG, et al. IRIS Investigators Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med*. 2006;355:2408–17.
20. Deininger M, O'Brien SG, Guilhot F, et al. International randomized study of interferon vs. STI571 (IRIS) 8-year follow up: sustained survival and low risk for progression or events in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) treated with imatinib. *51st ASH Annual Meeting and Exposition. Oral and Poster Abstracts. Poster Session: Chronic Myeloid Leukemia - Therapy Poster*
21. Julian Borrow, Guidelines for mutation analysis of BCR/ABL kinase domain: Interpreting TKI-Resistance Mutations in CML Patients West Midlands Regional Genetics Laboratory March 2007; Revised December 2007 WMRGL, December 2007
22. [Franck E Nicolini](#) et al. Overall survival with ponatinib versus allogeneic stem cell transplantation in Philadelphia chromosome-positive leukemias with the T315I mutation DOI: [10.1002/cncr.30558](https://doi.org/10.1002/cncr.30558)
23. J.E. Cortes et al. A Phase 2 Trial of Ponatinib in Philadelphia Chromosome-Positive Leukemias. [November 7, 2013](#) N Engl J Med 2013; 369:1783-1796
24. [Susanne Saussele](#) et al. Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukemia (EURO-SKI): a prespecified interim analysis of a prospective, multicentre, non-randomised, trial Lancet Oncol 2018 Jun;19(6):747-757. doi: 10.1016/S1470-2045(18)30192-X.Epub 2018 May 4.
25. Sheena Bhalla et. al. Discontinuing Tyrosine Kinase Inhibitor Therapy in Chronic Myelogenous Leukemia: Current Understanding and Future Directions. Clin Lymphoma Myeloma Leuk: 2016 Sep;16(9):488-494. doi: 10.1016/j.clml.2016.06.012. Epub 2016 Jun 16.