Graduate thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Clinical and Molecular Medicine

Oda Victoria Tafjord

Chronic myeloid leukemia & TKI-discontinuation at St. Olavs hospital

Graduate thesis in Programme of Professional Study, Medicine
Supervisor: Henrik Hjorth-Hansen
June 2021

NTNU
Norwegian University of Science and Technology

Oda Victoria Tafjord

Chronic myeloid leukemia & TKI-discontinuation at St. Olavs hospital

Graduate thesis in Programme of Professional Study, Medicine
Supervisor: Henrik Hjorth-Hansen
June 2021

Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Clinical and Molecular Medicine

NTNU
Norwegian University of
Science and Technology

Abstract

Chronic myeloid leukemia (CML) is a clonal stem cell disease and was originally fatal until the introduction of tyrosine kinase inhibitor (TKI) in the early 2000s. In 2010 the STIM-study established treatment free remission (TFR), which means remission of disease without ongoing treatment. Since 2016, discontinuation of TKI has been included in the Norwegian national guidelines for CML. The purpose of this research paper is to maintain the database of CML-patients and to quality assure the TKI-discontinuation attempts at St. Olavs hospital. Survival and allogeneic hematopoietic stem cell transplantation (aHSCT) after the introduction of TKI, and differences between second- and first-generation TKIs regarding molecular response and treatment-free survival (TFS), are also addressed. The study is an anonymized retrospective systematization of follow-up and treatment results of CML-patients at the Dept of Hematology at St. Olavs hospital. The data collection was done by viewing 77 patients' medical records diagnosed with CML 1996-2015, the analyses were done by IBM SPSS.

The eight-year overall survival was 50.0% and 79.6%, and the eight-year CML-specific survival was 62.9% and 93.5%, for the pre-TKI and TKI era respectively. Only three of 14 deceased in the TKI era died due to CML, and none received aHSCT. Within 12 months a cumulative proportion of 22.0% with first-generation TKI, and 50.0% with second-generation TKI, had achieved MR4. After TKI-discontinuation, the TFS was 65.4% at 6 months and plateaued on 48.5% at 12.0 months. The TFS plateaued at 60.6% at 6.2 months for second-generation TKIs, and 39.0% at 12.0 months for first-generation TKI. 13 of 27 patients relapsed, all within 12 months. All regained $\geqslant$ MMR after relapse.

There was a large and significant improvement in overall- and CML-specific survival, and a reduction in aHSCT after the introduction of TKI. The results support the theory that second-generation TKIs generates deeper molecular response faster, than first generation TKI. We can conclude with that the use of second- instead of first-generation TKI, can possibly lead to TKI-discontinuation and TFR in more patients, however further research is needed to investigate if it leads to higher TFS. Based on the results we can advocate that TKI-discontinuation at St. Olavs hospital had a similar success rate as international studies. The majority of the discontinuation attempts in this study followed current guidelines, if not, there were valid reasons to deviate in most cases.

Table of Contents

Introduction

Topic

Chronic myeloid leukemia (CML) is a clonal stem cell disease with proliferation of granulocytes and immature cells in the granulocytic lineage, in blood and bone marrow. There are about 45 new cases of CML yearly in Norway (1). The treatment of CML has been through a revolution, CML was originally a fatal disease, but is now mainly a chronic disease due to the development of tyrosine kinase inhibitors (TKI)(2). Most CML-patients in chronic phase have a normal life expectancy if the treatment response is monitored, and you change treatment based on the ELN-algorithm(3). Allogeneic stem cell transplantation is the only treatment option that is documented potentially curative, but discontinuation of TKI in patients with a specified good response is now included in guidelines for CML (1, 3). TKI can therefore also be a potential «curative» treatment option(1). Curation in this context means remission of disease without ongoing treatment, treatment free remission (TFR). The patients still have leukemic stem cells, and it is necessary to monitor the patients in case of late recurrence.

Background

Chronic myeloid leukemia

The diagnosis CML is relevant in cases of leukocytosis, thrombocytosis, splenomegaly or reduced general condition. The symptoms can be absent or pronounced, with weight loss, night sweat, bleeding tendency, bone pain and abdominal swelling due to enlarged spleen. Untreated CML goes through three phases: chronic, accelerated and blast phase. Accelerated phase and blast crisis are also known as advanced phase. In the chronic phase, there is slow progression of disease, with reduced general condition, splenomegaly and left-shifted granulocytopoiesis. The disease is often discovered accidentally through blood sampling for other reasons due to conspicuous leukocytosis. In accelerated phase the patients get a rising amount of blasts and basophilia, together with splenomegaly and signs of bone marrow failure. CML transforms clinically and morphologically into an acute leukemia in the blast phase, both myeloid and lymphoid differentiation is observed.

CML is by and large a monocausal cancer disease, one change in the genome is necessary and sufficient for development of the disease. Translocation between chromosome 9 and 22, creates the fusion gene BCR-ABL, which codes for a constitutional active tyrosine kinase

that stimulates proliferation and inhibits apoptosis. The Philadelphia chromosome is an abnormally small chromosome 22, it is created when there is a balanced translocation between chromosome 9 and 22 t(9:22). More than 90% of CML patients have the Ph-chromosome. The remaining still have a BCR-ABL translocation present in the leukemic cells, but the small Ph-chromosome cannot be detected by karyotyping (1). CML is defined by detection of ABL-BCR as t(9:22) or with PCR (1).

CML is diagnosed through disease history, clinical examination of the spleen size and hematologic diagnostic work-up. Cytogenetic and molecular pathological examinations of the blood and bone marrow is performed to detect Ph-chromosome and BCR-ABL fusion. The Ph-chromosome may be detected with karyotyping, and the BCR-ABL fusion gene by PCR or FISH. Quantitative PCR-analysis (qPCR) is used to monitor treatment effect (3).

Treatment and TKI

Evolution in treatment of CML

The treatment of CML has been through a revolution, CML was originally a fatal disease, but is now mainly a chronic disease because of the development of tyrosine kinase inhibitors (TKI)(2). The early treatment options were spleen x-radiation and conventional chemotherapy, mainly busulfan and hydroxyurea. This treatment improved the quality of life in patients in the chronic phase, though did not stop progression of the disease. The first big treatment breakthrough was the introduction of allogeneic stem cell transplantation, which was the first curative treatment option. The next breakthrough was the introduction of interferon. Interferon used as monotherapy or combined with chemotherapy, gave better survival compared with conventional chemotherapy. From the early 2000s, these treatment strategies were replaced with TKI, which is the standard first line treatment today(4). The first approved TKI, Imatinib, was approved for clinical use for CML in 2001(5).

Effect mechanism of TKI

The BCR-ABL gene codes for an tyrosine kinase which is a constitutional active enzyme. The enzyme binds ATP and phosphorylates proteins which further on affects proliferation, apoptosis and differentiation of CML-cells. The normal ABL-protein is predominantly proapoptopic and is located in the cytoplasm and cell nucleus. While the BCR-ABL protein is primarily antiapoptopic and is only located in the cytoplasm.

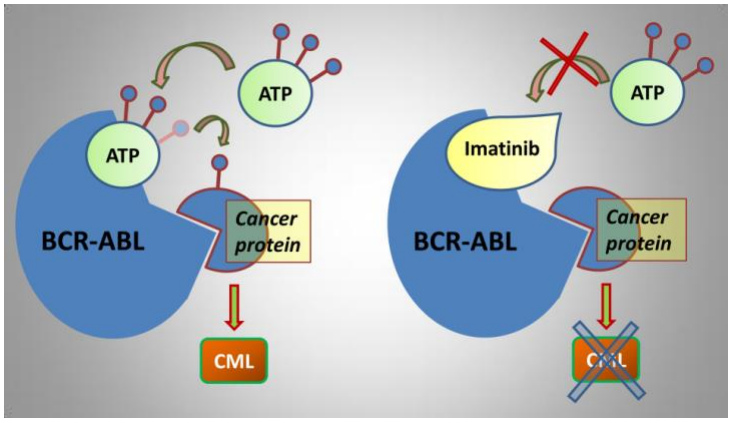


Figure 1: Imatinib blocks the ATP-binding seat, which inhibits BCR-ABL´s phosphorylation activity (6).

TKIs have high affinity for the ATP-binding site in the tyrosine kinase. The TKI therefore binds this site and blocks the interaction with ATP, which then inhibits downstream reactions and transmission of oncogenic signals. In addition, TKI leads to transport and trapping of the BCR-ABL oncoprotein in the nucleus. Through these mechanisms, TKI inhibits the oncogene signal by inhibiting proliferation and inducing apoptosis in the CML-cells(7).

Treatment goals and strategies

When the CML diagnosis is certain the patient should start with TKI. There are two main strategies for TKI-treatment. One strategy is to start with first-generation TKI (Imatinib), and then switch to a second-generation TKI (Dasatinib, Nilotinib or Bosutinib), if inadequate effect or intolerance. The other strategy is to start with a second-generation TKI. The third-generation TKI, ponatinib, is indicated with certain point mutations or TKI-resistance. The main treatment goal is to stop progression of the disease and achieve good quality of life, however for some patients, "curation" can and should be the goal, particularly for the younger CML patients. In the current treatment programme, TKI-treatment may be discontinued if the response is of sufficient duration and depth, but most patients need lifelong treatment. If one starts with a second-generation TKI, the patients respond faster and deeper, which again may lead to discontinuation of treatment and treatment free remission in more patients(1, 8).

Monitoring of treatment effect

To monitor treatment effect it is important with regular monitoring mainly by qPCR, but initially also by hematological response.

Complete hematologic response (CHR) is defined as Hb >11 g/dl, leukocytes within the reference range with < 5 % metamyelocytes and band granulocytes, no blasts in blood, normal thrombocyte counts and non-palpable spleen(1).

Cytogenetic response (CgR) can be complete (0 % Ph positive metaphases, CCgR), partial (1-35 % Ph positive metaphases, PCgR) or minor (36-65 % Ph positive metaphases, MCgR). The term ”major” cytogenetic response (MCgR) include both complete and partial response(1). In the most recent ELN guideline of 2020, monitoring by karyotyping has been omitted(9). At diagnosis karyotyping must be performed to exclude other karyotypic abnormalities than Ph, of which some bear negative prognostic value and represent signs of “warning” (9, 10).

Molecular response (MR) is evaluated by measuring quantitative PCR (qPCR) for the BCR-ABL transcript. This is the most sensitive measurement of disease activity and displays the percentage of BCR-ABL transcript in the sample. The term ”major molecular remission” (MMR/MR3) is when the amount of transcript is reduced by 3 log (equivalent >1000 times reduction)) with origin in the reference population in the pivotal IRIS study of imatinib-treated CML-patients at the time of diagnosis (equivalent < 0,10 %). The term complete molecular remission (CMR) means that you cannot detect any transcript. Today it is more common to use MR4/DMR, MR4.5 and MR5 instead of CMR. These are better defined concepts, taking the quality of the RNA sample and consequently the sensitivity of the assay into consideration(1).

Table 1: Definitions of the different MR-categories.

Molecular response	**% IS**
MR0	>10%
MR1	≤ 10.0 %
MR2	≤ 1.0 %
MR3/MMR	≤ 0.1 %
MR3.5	≤ 0.032 %
MR4/DMR	≤ 0.01 %
MR4.5	≤ 0.0032 %
MR5	≤ 0.001 %

Discontinuation of TKI and treatment-free remission.

In 2010 the STIM-study established TFR, which is maintaining MMR without restarting treatment after TKI-discontinuation(11, 12). Later more than 10 studies on TKI-discontinuation in patients with deep response (DMR) have been performed, and all of them show a long time TFR on 40-50%(1). EURO-SKI, the largest study of TKI-discontinuation, presented a treatment-free survival on 60% at 6 months, and 49% at 24 months(13). The studies EURO-SKI and aSTIM have demonstrated that relapse defined as loss of MR3 is safe, because the patients will regain their response when they restart TKI-treatment(14). Some patients can have detectable disease down to MR3 over a long time period without relapsing, called "fluctuators"(1). DASTOP-2 is now an ongoing trial where patients who relapsed in their first discontinuation of TKI, stop TKI a second time(1).

It is difficult to decide minimum criteria for TKI-discontinuation (15). EURO-SKI observed that longer duration of treatment and DMR, increased the probability for persistent MMR at 6 months, with duration of DMR being more important than duration of treatment (16). A Swedish study from 2020, revealed that patients stopping outside trials had a 61% probability of staying in TFR at 22 months(17). The reason for higher TFR-rates outside studies may be longer duration of therapy and/or more frequent use of second generation TKI(17).

Table 2: Criteria for TKI-discontinuation in the Norwegian national guidelines from 2018(1).

Resistance against any TKI?	No
Duration of TKI-treatment	5 years tentatively
Duration of MR4	2 years
Good monitorization	PCR monthly for 6 months, then every 6.-7. week until month 12, then every 3. month.

According to Norwegian guidelines, CML patients with MR4 for two or more years and minimal TKI-treatment duration of five years may attempt discontinuation with frequent guideline-mandated monitoring (1). Studies show that this gives a TFR rate of approximately 50%(15).

Benefits of TFR

There are many advantages with TFR, both for the patients and the society. TFR can spare the patient from treatment-induced side effects and reduce health expenditure for the patient

and the health care system(13). In addition, this can especially benefit women with pregnancy wishes, and need for treatment-free periods to have babies.

Purpose

The purpose with this research paper is to maintain the database of CML-patients, and to quality assure the TKI-discontinuation attempts, at St. Olavs hospital. I will do this by viewing the patients' medical records, and will try to answer following questions:

- How has the introduction of TKI affected survival and the use of allogeneic stem cell transplantation in CML-patients?
- Is there any difference between first- and second-generation TKI, regarding molecular response and TFS?
- Are the TKI-discontinuation attempts at St. Olavs hospital on level with international results?
- Are the national guidelines for TKI-discontinuation being followed?

Method

The study is an observation study, an anonymized retrospective systematization of follow-up and treatment results of CML-patients at the hematologic section at St. Olavs hospital. The study is approved by the head of department and fulfills the criteria for information security. The study can be divided in two parts; quality assurance of the TKI-discontinuation attempts, and to maintain the CML-database at St. Olavs hospital, that Kristin Rønning og Elisabeth Wendelbo started on in «Kronisk myelogen leukemi ved St. Olavs Hospital 1996-2009» (18). The collection of data is done by reviewing medical records of patients included in the study. The data were written into Microsoft Excel and transferred to SPSS. Analyses of the data were done in SPSS and Microsoft Excel.

Material

To maintain the database, I reviewed patients diagnosed with CML in the period 1996 -2015 at St. Olavs hospital, and followed them for five years. The majority of patients diagnosed from 1996 to 2009 were already registered in the database from the earlier done observation study(18). I recorded date of diagnosis, phase at diagnosis, cytogenetic results, qPCR-results, treatment and start of treatment date, switch of treatment, reason for switch, switch date,

interferon-treatment, allogeneic stem cell transplantation, disease-progression, cause and date of death, and date of last observation.

To quality assure the TKI-discontinuation attempts, I registered patients who intentionally discontinued TKI within 2020 from the updated database and followed them from date of diagnosis to March 2021. I recorded the same factors mentioned above, and in addition recorded date of discontinuation (first and second attempt), date of relapse, TKI after relapse, date of TKI resumption and remission.

Statistical analysis

"Overall survival (OS)", "CML-specific survival", "Five-year progression free survival (PFS)", "Achieved MR4 within 5 years" and "Treatment-free survival" were calculated by the Kaplan-Meier method and compared by the log rank test in SPSS. OS, CML-specific-survival and PFS were calculated from date of diagnosis to first event, "Achieved MR4 within 5 years" from date of TKI-start to first event, and "Treatment-free survival" from date of TKI-discontinuation to date of first event.

Table 3: Definitions of "event" and "censored" in the different Kaplan-Meier Plots.

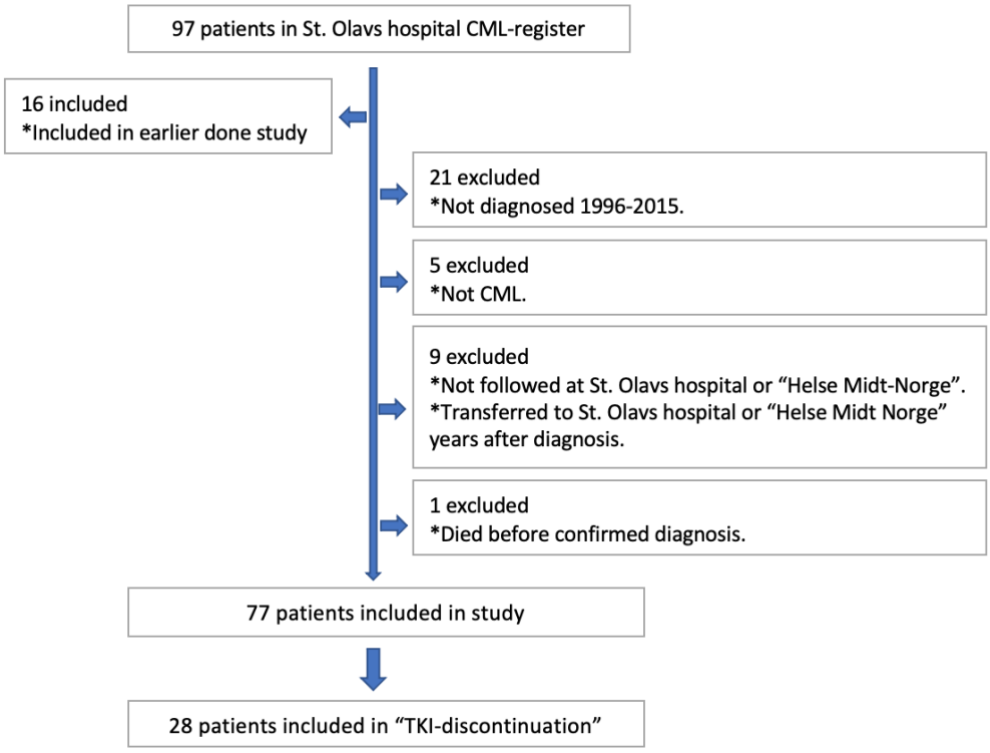
Kaplan-Meier Plot	**Event**	**Censored**
Overall survival	Death	Date of last observation.
CML-specific survival	Death due to progression of disease or SCT-complications	Date of last observation or death (unrelated to CML or its treatment).
Five-year PFS	Progression of disease or CML-related death.	Date of last observation or death (unrelated to CML or its treatment).
Achieved MR4 within 5 years	MR4 within 5 years	Date 5 years after start of treatment or date of last qPCR-result.
Treatment-free survival	Loss of MMR or restarting TKI	Date of last qPCR-result.

Line chart in Microsoft Excel was used to make a graphical presentation of molecular responses. Frequency analysis was done to make tables of how many patients reached the different molecular response categories at different times in their treatment, treatment, switch of treatment, switch drugs, and duration of treatment and MR4 before discontinuation.

Inclusion and exclusion criteria

Patients who were diagnosed with CML from 1996 to 2015, who has been followed up and treated at St. Olavs hospital. Some of the patients have been treated by other hospitals, mainly in “Helse Midt-Norge”, but with guidance/collaboration with St. Olavs hospital. Some patients have been diagnosed before they came to St. Olavs, and if a short period of < 1 year they have been included. It depends on access to medical history from time of diagnosis. Inclusion criteria for “TKI-discontinuation” are the criteria mentioned above, in addition to intentional TKI-discontinuation within 2020.

Consort diagram 1: Inclusion and exclusion criteria.



Results

Patients diagnosed with CML from 1996-2015

77 patients, diagnosed in the time period 1996-2015, were included. At diagnosis, 74 patients were in chronic phase, two in accelerated phase and one in blast phase.

Treatment and switch of treatment

57 had TKI as first drug, and the remaining 20 had hydroxyurea (HU). 17 patients received interferon-treatment (IFN-α). Nine patients underwent allogeneic hematopoietic stem cell transplantation (aHSCT), all of them had hydroxyurea as first drug.

Table 4: Start drug, IFN-α and aHSCT in patients diagnosed in 1996-November 2002 and December 2002-2015.

		Start drug				IFN-α		aHSCT	
		Imatinib	Dasatinib	Nilotinib	HU	No	Yes	No	Yes
		N	N	N	N	N	N	N	N
Date of diagnosis	1996 - Nov 2002	0	0	0	20	11	9	11	9
	Dec 2002 -2015	45	5	7	0	49	8	57	0
	Total	45	5	7	20	60	17	68	9

All patients diagnosed in the time period December 2002 to 2015, had TKI as start drug and none received aHSCT. The first patient who received Imatinib as start drug, was diagnosed December 2002, and started Imatinib February 2003. The period from 1996 to November 2002 is therefore defined as the pre-TKI era at St. Olavs hospital, and the TKI-era from December 2002.

Table 5: Number of patients who switched treatment (1-4 switches) within 5 years from diagnosis and the switch drugs.

		Switch within 5 years		Switch x 1						Switch x 2				S x 3	S x 4
		No	Yes	Im	Da	Ni	Po	My	HU	Im	Da	Ni	HU	Bo	Po
		N	N	N	N	N	N	N	N	N	N	N	N	N	N
Start drug	Im	26	19	0	10	7	1	0	1	1	4	2	0	2	1
	Da	4	1	1	0	0	0	0	0	0	0	0	0	0	0
	Ni	5	2	2	0	0	0	0	0	0	0	0	0	0	0
	HU	13	7	6	0	0	0	1	0	0	0	0	2	0	0
	Total	48	29	9	10	7	1	1	1	1	4	2	2	2	1

** Imatinib (Im), Dasatinib (Da), Nilotinib (Ni), Ponatinib (Po), Bosutinib (Bo), Myleran (My) and hydroxyurea (HU).*

29 of the 77 patients, 37.7 %, switched treatment one time in the five-year follow-up period, nine patients switched treatment two times, two patients switched three times and one patient switched treatment four times. 38.6% of the patients with any TKI and 42.2 % of the patients with Imatinib, as start drug, switched treatment. 30.0% of the patients with hydroxyurea as start drug switched to a TKI.

41 switches in total for the 77 patients during the five-year follow-up period. Reason for switch in order from most to less common: Intolerance (N=18), treatment failure (N=13), change of study (N=6), intolerance + treatment failure (N=3), other (N=1).

Molecular response

Table 6: Molecular milestones for the 57 patients in the TKI-era (diagnosed Des 2002-2015). N% = column% of number of patients.

	Time in months																			
Molecular response	0		3		6		9		12		18		24		36		48		60	
	N	N %	N	N %	N	N %	N	N %	N	N %	N	N %	N	N %	N	N %	N	N %	N	N %
MR 0	44	77.2	12	21.1	2	3.5	4	7.0	1	1.8	2	3.5	2	3.5	2	3.5	0	.0	0	.0
MR 1	2	3.5	21	36.8	12	21.1	6	10.5	5	8.8	3	5.3	2	3.5	3	5.3	1	1.8	2	3.5
MR 2	1	1.8	8	14.0	16	28.1	18	31.6	18	31.6	9	15.8	3	5.3	8	14.0	3	5.3	4	7.0
MR 3	0	.0	3	5.3	9	15.8	8	14.0	7	12.3	10	17.5	10	17.5	4	7.0	12	21.1	8	14.0
MR 3.5	0	.0	1	1.8	5	8.8	6	10.5	5	8.8	6	10.5	6	10.5	3	5.3	4	7.0	2	3.5
MR 4	0	.0	3	5.3	4	7.0	6	10.5	13	22.8	14	24.6	21	36.8	24	42.1	17	29.8	18	31.6
MR 4.5	0	.0	0	.0	0	.0	1	1.8	2	3.5	5	8.8	2	3.5	4	7.0	9	15.8	10	17.5
MR 5	0	.0	0	.0	1	1.8	0	.0	0	.0	2	3.5	1	1.8	2	3.5	3	5.3	4	7.0
Missing	10	17.5	9	15.8	8	14.0	8	14.0	6	10.5	6	10.5	10	17.5	7	12.3	8	14.0	9	15.8

Patients treated with hydroxyurea are not expected to achieve molecular response and were not followed with qPCR. In addition, qPCR was not introduced in clinical practice before 2003-2004. It is therefore more relevant to look at molecular milestones in the TKI era. "Missing" includes lack of documentation, unsuccessful qPCR-analysis, and lack of sampling for any cause (including death and loss to follow-up). E.g., one of the patients had a special type of transcript that qPCR did not detect and one patient quickly progressed to blast phase, and were consequently not followed with qPCR.

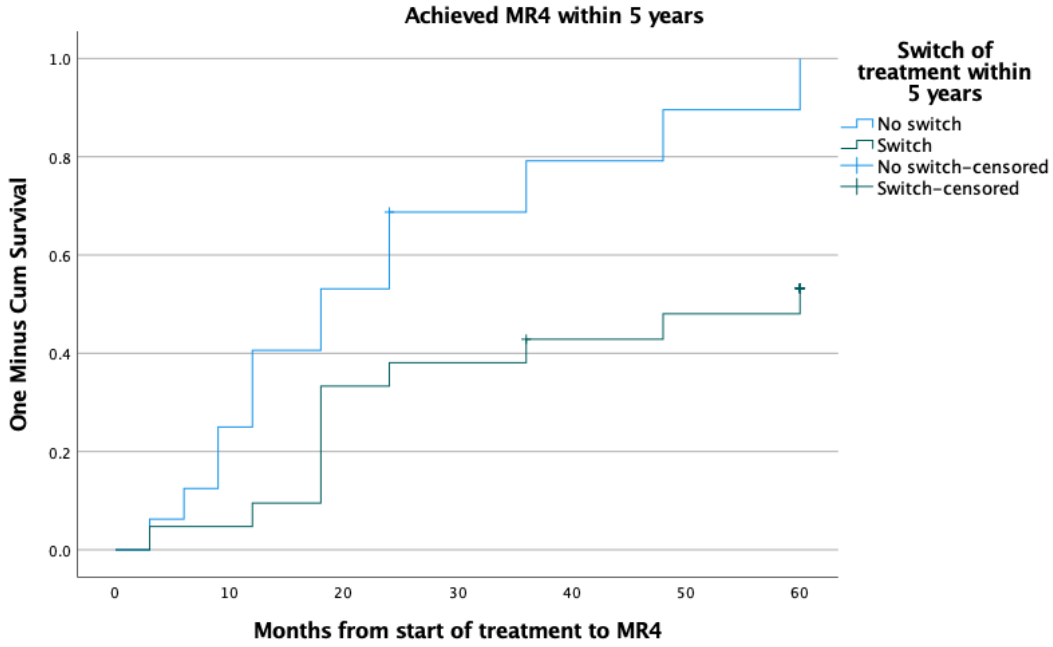
MR4 within 5 years and variables

46 of 59 valid patients, 78.0%, achieved MR4 within five years (missing 18 patients due to missing qPCR-results). 53 of the 59 valid patients had TKI as first drug, 72.9% of them achieved MR4 within 5 years. The following analyses in this chapter will be based on those 53 patients.

Switch of treatment within five years

96.9% of the 32 patients that did not switch treatment achieved MR4 in 5 years, but only 52.4% of the 21 patients that switched did the same, probably reflecting resistance as a reason for switching TKI. Allogeneic stem cell transplantation is not considered as switch of treatment.

Figure 2: Kaplan-Meier plot of months from start of treatment to achieved MR4(within 5 years), comparing switch vs. no switch of treatment. 53 valid patients. Based on table 3.

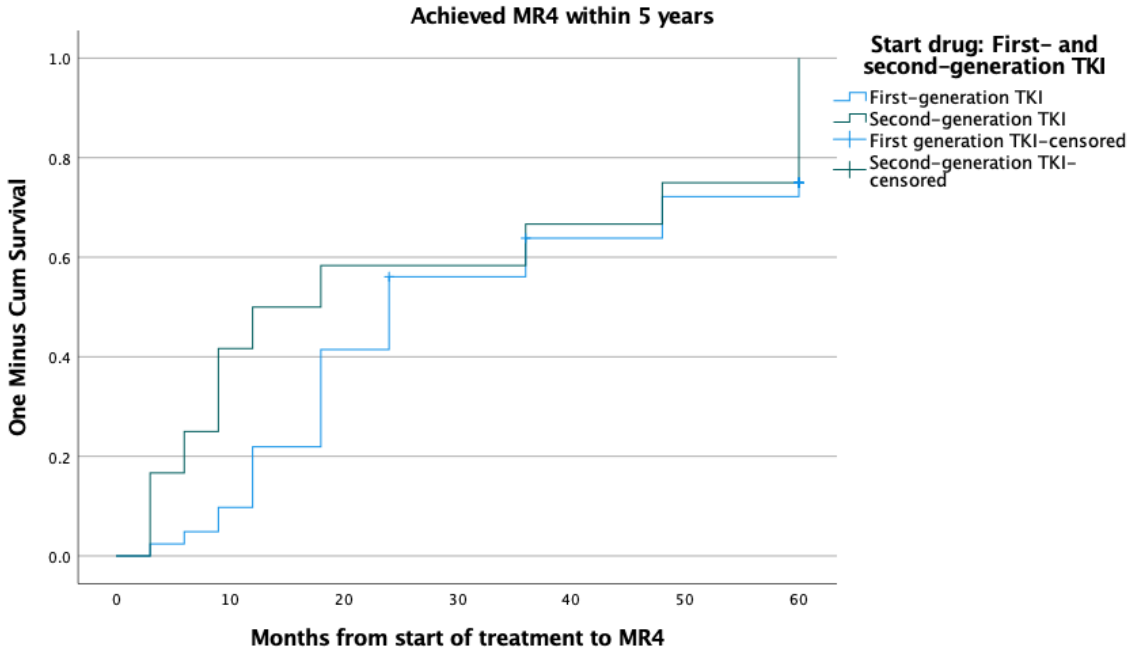


At 24 and 60 months, a cumulative proportion of 56.6% and 81.2%, had reached MR4. No switch: 68.7% and 100%, and switch: 38.1% and 53.3%. Log Rank $p < 0.001$, the difference is significant. Mean duration of follow-up was 57.2 months (95% CI 54.6-59.8). Two of the patients who did not reach MR4 within 5 years, were followed for less than 60 months (24 and 36 months), one of them switched treatment and both had Imatinib as start drug.

First- vs. second-generation TKI

73.2% of the 41 patients who had Imatinib as start drug, and 100% of the 12 patients who had Nilotinib or Dasatinib as start drug, reached MR4 within 5 years.

Figure 3: Kaplan-Meier plot of months from start of treatment to achieved MR4 (within 5 years), comparing first- and second-generation TKI as start drug. 53 valid patients. Based on table 3.



At 12 months a cumulative proportion of 22.0% with first-generation TKI, and 50.0% with second-generation TKI, had achieved MR4. The difference between the groups decreases at 24 months, with 56.1% for the first- and 58.3% for the second-generation TKI. Log rank p= 0.088, the difference is not significant.

Table 7: Start drug and MR4 within 5 years, compared to switch of treatment within 5 years and the switch drugs (x 1-4), in 53 valid patients.

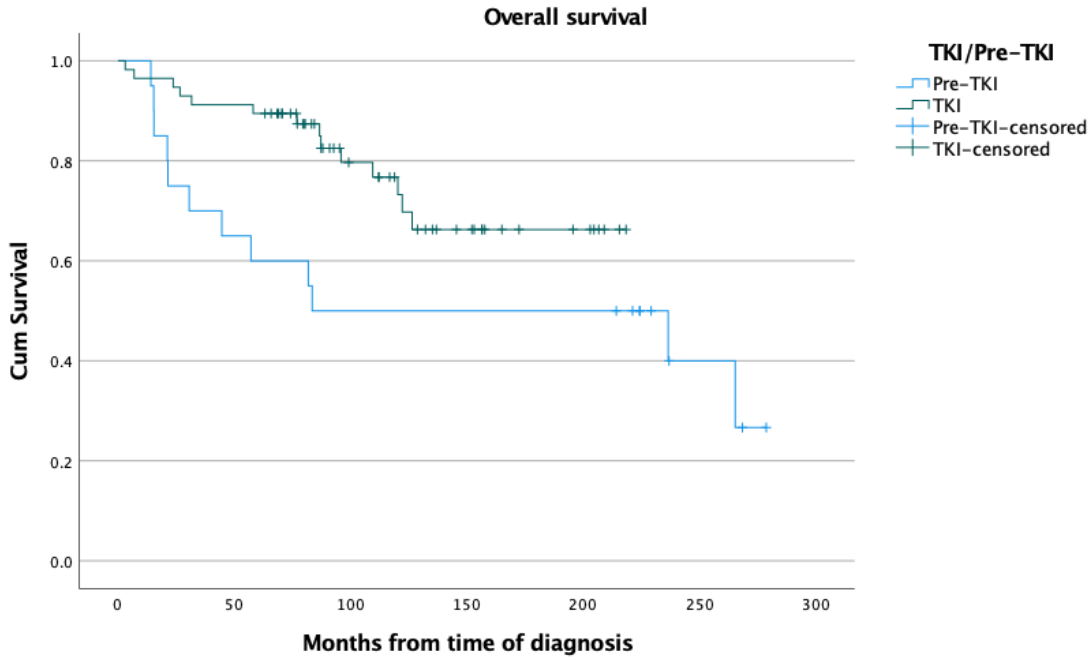
			Switch within 5 years			Switch x 1					Switch x 2			S x 3	S x 4
			No	Yes	Total	Im	Da	Ni	HU	Po	Im	Da	Ni	Bo	Po
			N	N	N	N	N	N	N	N	N	N	N	N	N
Start drug	Im	No MR4	1	10	11	0	5	4	1	0	1	3	1	2	1
		MR4	22	8	30	0	4	3	0	1	0	1	1	0	0
	Da	No MR4	0	0	0	0	0	0	0	0	0	0	0	0	0
		MR4	4	1	5	1	0	0	0	0	0	0	0	0	0
	Ni	No MR4	0	0	0	0	0	0	0	0	0	0	0	0	0
		MR4	5	2	7	2	0	0	0	0	0	0	0	0	0
	Total	No MR4	1	10	11	0	5	4	1	0	1	3	1	2	1
		MR4	31	11	42	3	4	3	0	1	0	1	1	0	0

Three of the 12 patients who had a second-generation TKI as start drug, switched to Imatinib due to intolerance, but one of them switched after MR4 was achieved. Eight of the patients who had Imatinib as start drug and achieved MR4 within five years, switched treatment. Seven of the patients switched to a second generation (two of them later switched to another

second-generation TKI), and one to a third-generation TKI, due to intolerance or failure. Three of the eight patients switched treatment after MR4 was achieved. In total, two patients with a second-generation TKI as start drug switched to Imatinib, and five patients with Imatinib as start drug switched to a second- or third-generation TKI, before MR4 was achieved.

Survival and progression of disease

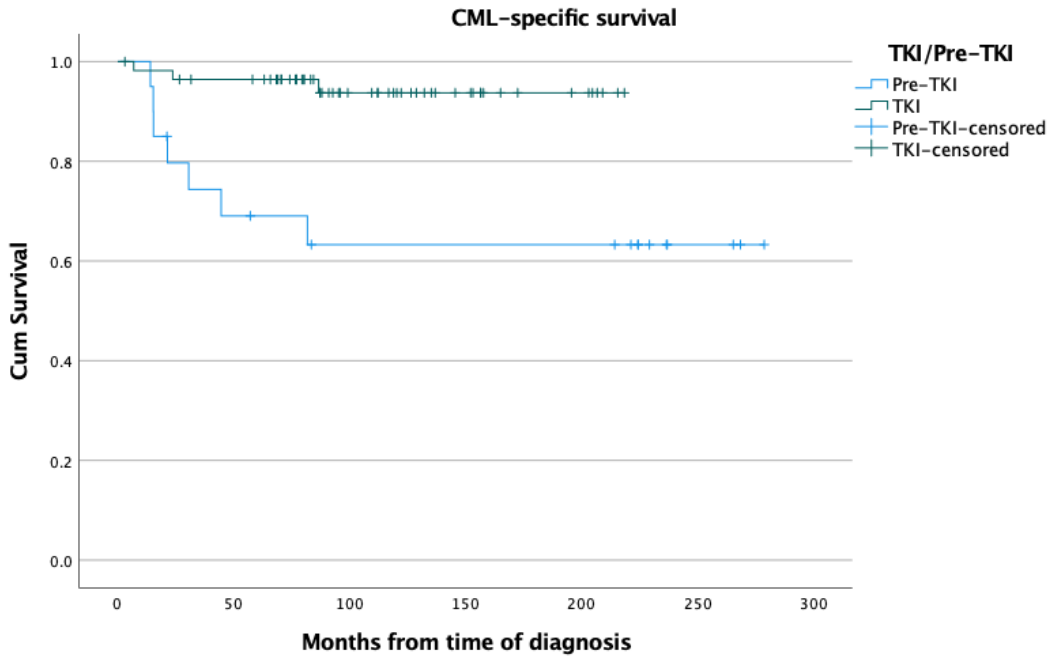
Figure 4: Kaplan-Meier plot of overall survival in the TKI vs. pre-TKI era. 77 valid patients.



At five and eight years, OS (cumulative proportion surviving) is 81.8 % and 72.0%, TKI: 89.5% and 79.6%, and pre-TKI: 60.0% and 50.0%. Log rank= 0.047, the difference is significant. In the TKI era, the survival plateaued at 66.3% at 126.5 months. Duration of follow-up (date of diagnosis to date of death/last observation): pre-TKI: mean 139.2 months (95% CI 89.6-188.9), median 148.9 months (95% CI 30.7-229.2), TKI: mean 110.1 months (95% 96.1-124.1), median 95.9 months (95% CI 86.6-122.1).

26 of 77 patients died, 10 CML-related. 14 of the deceased were from the TKI-era. Cause of death in the TKI-era from most to less common: Cancer (N=6), CML (N=3), unknown (N=3), old age (N=1) and sepsis (N=1).

Figure 5: Kaplan-Meier plot of CML-specific survival in the TKI vs. pre-TKI era. 77 valid patients.



The CML-specific survival plateaued at 93.7% at 86.6 months and 63.3% at 81.8 months for the TKI and pre-TKI era respectively. The five and eight year CML-specific survival (cumulative proportion surviving) is 89.3% and 85.6%, pre-TKI era: 68.9% and 62.9%, and TKI era: 96.4 % and 93.5%. Log Rank $p < 0.001$, the difference is significant. The duration of follow-up is the same as for OS.

10 of the 77 patients died of CML: Blast crisis (N=7), SCT-complications (N=2) and treatment resistance (N=1). Three of these 10 patients were treated in the TKI-era, of whom two died of blast crisis and one of treatment resistance.

Five patients from the pre-TKI era and three from the TKI era, had progression of disease within 5 years from diagnosis, six to blast phase and two to accelerated phase. The 5-year PFS mean time is 54.8 months (95 % CI 51.6-58.0), and 46.5 months (95 % CI 37.8-55.2) and 57.8 months (95 % CI 55.2-60.3) for the pre-TKI and TKI-era respectively. Log Rank $p<0.001$, the difference is significant.

TKI-discontinuation

28 of the patients discontinued TKI-treatment, within and outside studies, one or more times within 2020. The different studies include EURO-SKI, NordCML-studies and DASTOP2. Three of the patients transferred to other hospitals before the discontinuation. All debuted in chronic phase, and all patients had TKI as start drug, except for one patient (hydroxyurea) who was diagnosed in pre-TKI era. 20 patients had Imatinib as start-TKI, five Nilotinib and three Dasatinib. One patient was partial resistant against Dasatinib. Six patients received interferon-treatment, and none of the patients underwent allogeneic stem cell transplantation. All patients reached MR4 within 5 years (one missing, too early to perform qPCR). One of the patients discontinued TKI-treatment for three short periods < 5 months, due to pregnancy planning, before the attempts that are included in this study.

Duration of treatment and MR4 before TKI-discontinuation

Table 8: Duration of treatment and persistent ≥MR4 in months before TKI-discontinuation

	N	Mean	95% CI (mean)	Median	Max	Min	SD
Treatment	28	86.0	73.3–98.6	78.9	161.4	39.7	32.7
MR4	28	51.1	39.7–62.4	42.7	109.2	10.2	29.3

Six patients discontinued before they were TKI-treated five years (39.7-57.9 months), all of them had a duration of ≥MR4 for ≥30.7 months. Four patients discontinued treatment before they had ≥MR4 for 2 years (10.2-22.1 months), all of them were TKI-treated > 60.7 months. The patient who discontinued at only 10.2 months in MR4 (minimum months of MR4) was due to pregnancy planning.

Molecular response

Table 9: Molecular milestones after TKI-discontinuation in the 28 discontinuation-patients.

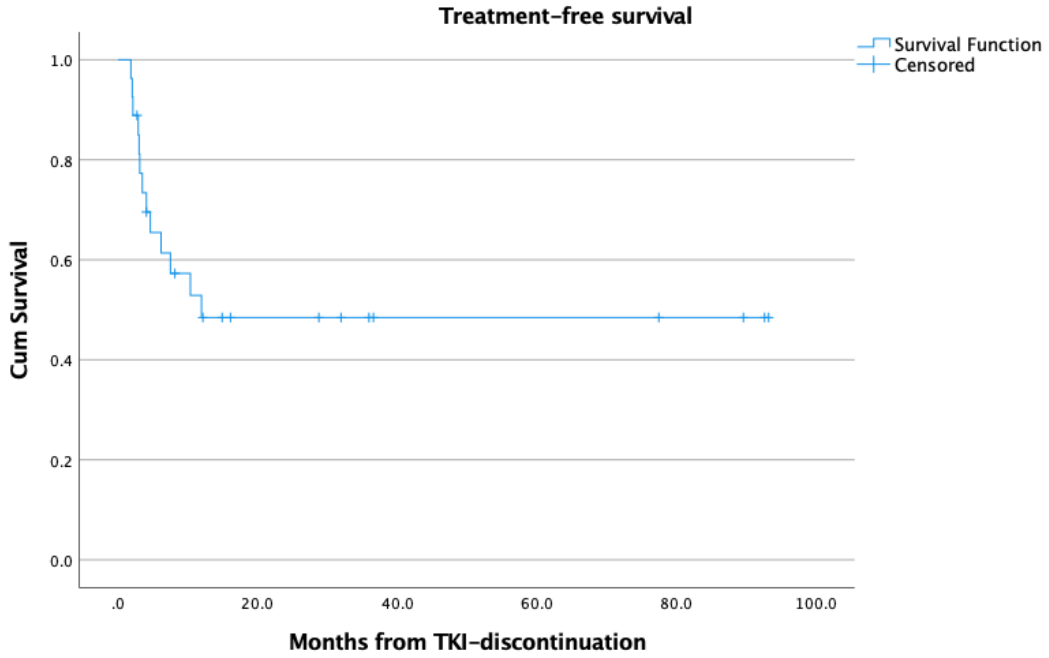
	Months from time of TKI-discontinuation																							
	0		3		6		9		12		18		24		36		48		60		72		84		96	
MR	N	N %	N	N %	N	N %	N	N %	N	N %	N	N %	N	N %	N	N %	N	N %	N	N %	N	N %	N	N %	N	N %
MR 0	0	.0	1	3.7	0	.0	0	.0	0	.0	0	.0	0	.0	0	.0	0	.0	0	.0	0	.0	0	.0	0	.0
MR 1	0	.0	1	3.7	1	4.0	0	.0	0	.0	0	.0	0	.0	0	.0	0	.0	0	.0	0	.0	0	.0	0	.0
MR 2	0	.0	4	14.8	4	16.0	1	4.0	2	9.1	1	5.0	0	.0	0	.0	1	9.1	0	.0	0	.0	0	.0	0	.0
MR 3	0	.0	1	3.7	1	4.0	3	12.0	0	.0	1	5.0	0	.0	1	7.1	0	.0	1	9.1	1	10.0	0	.0	1	20.0
MR 3.5	0	.0	2	7.4	4	16.0	3	12.0	1	4.5	0	.0	1	5.9	0	.0	0	.0	0	.0	1	10.0	2	25.0	0	.0
MR 4	9	32.1	5	18.5	5	20.0	7	28.0	6	27.3	4	20.0	3	17.6	2	14.3	2	18.2	3	27.3	1	10.0	0	.0	0	.0
MR 4.5	16	57.1	13	48.1	10	40.0	8	32.0	11	50.0	13	65.0	9	52.9	8	57.1	7	63.6	7	63.6	5	50.0	5	62.5	2	40.0
MR 5	3	10.7	0	.0	0	.0	1	4.0	0	.0	1	5.0	2	11.8	3	21.4	0	.0	0	.0	2	20.0	1	12.5	2	40.0
Missing	0	.0	0	.0	0	.0	2	8.0	2	9.1	0	.0	2	11.8	0	.0	1	9.1	0	.0	0	.0	0	.0	0	.0

Duration of follow-up is 0 to 97.3 months (date of discontinuation to last qPCR-analysis).

One patient lost MR3 at 48 months, but regained MR3 spontaneously without restarting TKI.

Treatment-free survival

Figure 6: Kaplan-Meier plot of TFS in 27 valid patients. One patient died 7 weeks after discontinuation for reason unrelated to CML and its treatment and is therefore missing.



The TFS (cumulative proportion surviving) is 65.4% at 6 months and plateaued at 48.5% at 12.0 months. Follow-up time after discontinuation is 2.7-97.3 months, mean 47.6 months (95% CI 33.6-61.7), median: 35.4 months (95% CI 27.6-80.9). St. Deviation 35.6 months.

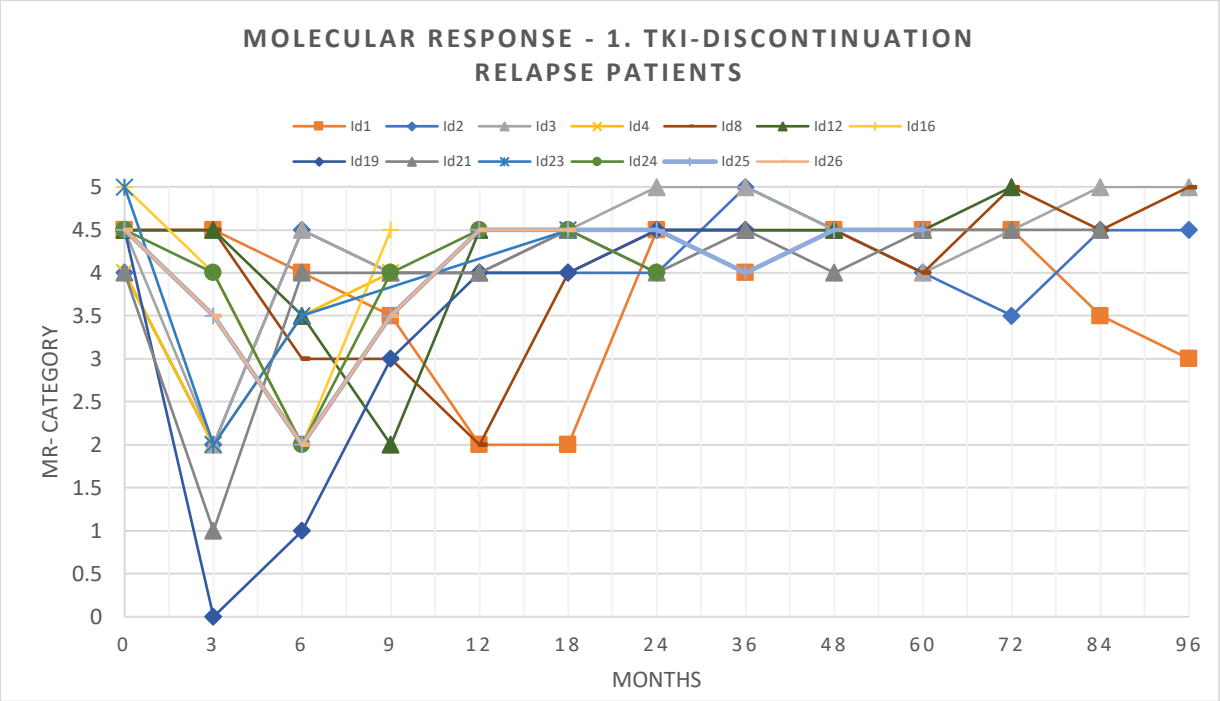
Table 10: Number of patients entering, with last observation date and relapsing in different time intervals.

Interval in months	N entering interval	N last observation	N relapse	Cumulative N last observation	Cumulative N relapse
0-3	27	1	4	1	4
3-6	22	1	5	2	9
6-9	16	1	2	3	11
9-12	13	0	2	3	13
12-15	11	2	0	5	13
15-18	9	1	0	6	13
18-27	8	0	0	6	13
27-30	8	1	0	7	13
30-33	7	1	0	8	13
33-36	6	1	0	9	13
36-39	5	1	0	10	13
39-75	4	0	0	10	13
75-78	4	1	0	11	13
78-87	3	0	0	11	13
87-90	3	1	0	12	13
90-93	2	1	0	13	13
93-94	1	1	0	14	13

Within six months, five of 27 patients relapsed (two patients with < six months of follow-up). There were 13 relapses in total, all occurred within 12 months (three patients with < 12 months of follow-up). The patient who lost MMR and regained it without restarting TKI, is not defined as a “relapse patient” in this study.

Relapse and remission

Chart 1: Graphic presentation of molecular response to the 13 patients who relapsed and restarted TKI. Missing values: Excel has generated a line between the closest qPCR-results.



All the patients achieved ≥ MMR within 4.8 months after TKI resumption. Mean time from start of treatment to remission is 2.6 months (95% CI 1.9-3.3) and median time is 2.4 months (95% CI 1.9-3.4). Standard deviation 1.2 months.

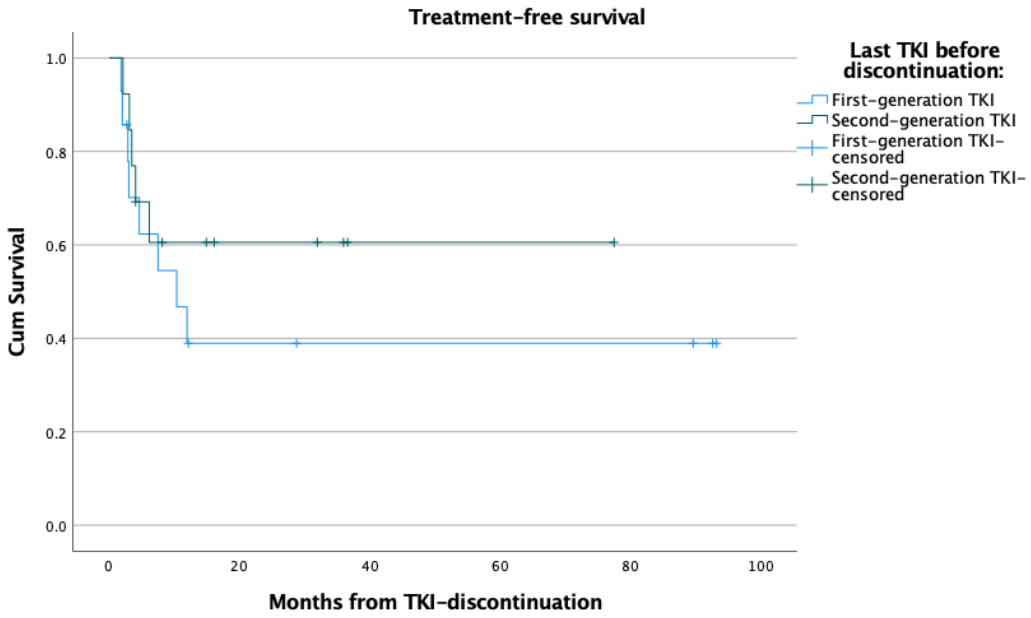
Mean time from loss of MR3 to start of treatment is 1.6 months (95% CI 0.2-2.9), median 0.8 months (95% CI 0.7-1.1). Minimum time 0.2 months, maximum time 8.3 months. Standard deviation 2.2 months.

Variables

First- and second-generation TKI before discontinuation

During the follow-up time after discontinuation (2.7-97.3 months), eight of 14 patients, 57.1%, who discontinued first-generation TKI relapsed. While five of 13 patients, 38.5%, who discontinued second-generation TKI did the same. In total 13 of 27 patients, 48.1%, relapsed.

Figure 7: Kaplan-Meier plot of TFS in the 27 discontinue-patients (missing one), comparing discontinuation of first- and second-generation TKI. The "last TKI before discontinuation" varies between being first- to third-line TKI.



The TFS plateaued at 60.6% at 6.2 months for second-generation TKI, and 39.0% at 12.0 months for first-generation TKI. Log rank p=0.369, the difference is not significant. The follow-up time after discontinuation is higher for the first-generation with a mean time of 64.3 months (95% CI 42.3-86.4), compared to 29.7 months (95% CI 16.3-43.0) in the second-generation.

Duration of treatment and MR4 before discontinuation

Table 11: Duration of treatment and MR4 before TKI-discontinuation in the 27 valid patients, relapse vs. no relapse.

	Months of treatment before TKI-discontinuation				Months of MR4 before TKI-discontinuation			
	Mean	95% CI (Mean)	Median	95% CI (Median)	Mean	95% CI (Mean)	Median	95% CI (Median)
No relapse	88.0	66.4-109.6	75.2	63.3-114.2	50.5	34.1-66.9	41.4	32.3-53.0
Relapse	83.8	65.9-101.8	75.2	60.7-112.0	51.4	31.8-71.1	40.0	28.3-98.0

Mean time of treatment in no-relapse patients is 4.2 months longer than in relapse patients. Mean duration of MR4 is 0.9 months longer in relapse patients than in no-relapse patients. The differences in duration of treatment and MR4 in the relapse vs. no relapse group are not significant.

Survival

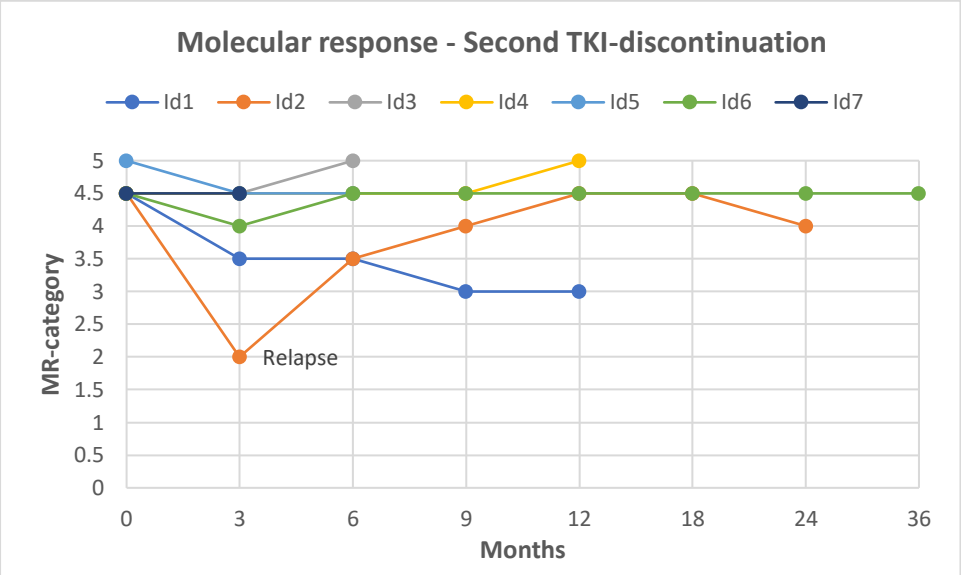
The CML-specific survival in this group is 100%. Four of the patients died for reasons unrelated to CML. None had progression of disease.

TKI-discontinuation – second attempt

There are seven patients who have discontinued TKI for the second time, in the time period from December 2017- to July 2020. Four patients were included in the stop-trial "DASTOP2", the remaining three discontinued outside trials.

Molecular response

Chart 2: Graphic presentation of molecular response in the second TKI-discontinuation attempt to the seven patients in a line chart. There are no missing qPCR-results.



Second stop attempts are still subject of research and not part of clinical practice. Most of these patients have been included in the DASTOP2 study. Many of these have short follow-up time. Only one of the seven patients (Id2), relapsed after 2.7 months, and regained ⩾MR3 again 2.6 months after start of treatment. The remaining six patients have a TFR-range on 4.1-37.6 months, three of them still in TFR after 12.0, 12.3 and 36.7 months.

Duration of treatment and MR4 before the second TKI-discontinuation.

Table 12: Duration of treatment and persistent ⩾MR4 in months before the second TKI-discontinuation

	N	Mean	95%CI (mean)	Median	Max	Min	SD
Treatment	7	63.7	51.0–76.4	63.0	87.6	43.1	13.7
MR4	7	56.4	41.8–71.0	58.3	84.5	36.1	15.8

All seven patients had persistent ⩾ MR4 over three years, and were TKI-treated over 3.5 years before the second discontinuation. Even though not all of the patients in the second discontinuation attempt were included in the DASTOP2 study, all seven patients followed the inclusion criteria for the clinical trial, which is MR4 for ≥ 1 year, and TKI-treatment for ≥3 years from the first relapse (1).

Discussion

Survival and aHSCT before and after the introduction of TKI

The eight year OS was 50.0% and 79.6%, and the eight year CML-specific survival was 62.9% and 93.5%, for the pre-TKI and TKI era respectively. Only three of 14 deceased in the TKI era died due to CML, and none received aHSCT. These results build on existing evidence of that there has been a large and significant improvement in OS and CML-specific survival, and a reduction in aHSCT, after the introduction of TKI.

The large and significant difference in OS and CML-specific survival after the introduction TKI is not surprising, because other studies have shown that TKI has improved the 10-year survival rate from approximately 20% to 80%-90%(19). Today, the OS of CML-patients treated with TKIs is very close to that of the healthy population(20). However the higher follow-up time in the pre-TKI era than in the TKI era, could lead to a bigger difference in survival than it really is. Contrarily, it is possible that patients diagnosed in the late 90s are alive due to TKIs being available later in the course of the disease. The majority of the deceased in the TKI era died of reasons unrelated to CML or its treatment, which correlates with findings in a study of 2290 CML patients in chronic phase with first line imatinib treatment, where 44% of the 208 deceased patients died of CML (21). The same study showed an eight year OS at 89%, and an eight-year relative survival probability with CML at

96% (21). The OS and CML-specific survival in the TKI era in this group is lower, this could be due to difference in demography and/or different inclusion criteria.

After the introduction of TKI, the number of patients in need of aHSCT has been reduced internationally and in this group of patients(19). Almost 50% of the patients in the pre-TKI era, and none from the TKI era, received aHSCT. Allogeneic HSCT is curative, but also carries risks of morbidities and mortality. It has therefore also been a reduction in CML-specific death due to aHSCT-complications. However aHSCT still remains as an important therapeutic alternative for patients with TKI-resistance and CML in advanced phase(19).

First- vs. second-generation TKIs regarding molecular response

Second-generation TKIs appeared to have a more favorable outcome regarding molecular response, than Imatinib. Within 12 months a cumulative proportion of 22.0% with first-generation TKI, and 50.0% with second-generation TKI, had achieved MR4. This analysis support the theory that second-generation TKIs generates a deeper molecular response faster, than first-generation TKI(8).

The patients who had second-generation TKIs as start drug, had a relative increase of more than 100% in the proportion of patients that achieved MR4 within 12 months, compared to the patients with Imatinib as start drug. The result is not statistically significant, this could be due to low number of patients. The reliability of this data is impacted by the small patient sample with switch of treatment as a source of error (table 7). Nevertheless the results implies the same as the studies ENESTfreedom and ENESTnd, which showed higher rates of DMR and sustained DMR with nilotinib vs. imatinib(8, 22). The use of second-generation instead of first-generation TKI, can therefore increase the proportion of patients that are eligible for TKI-discontinuation(23).

TKI-discontinuation at St. Olavs hospital

After TKI-discontinuation, the treatment-free survival was 65.4% at six months and plateaued on 48.5% at 12.0 months. 13 of 27 patients relapsed, nine within six months and all within 12 months. All regained ⩾ MMR after relapse. These results indicate that TKI-discontinuation at St. Olavs had a similar success rate as international studies. Second-generation TKIs appeared to have a more favorable outcome regarding TFS. After discontinuation the TFS plateaued at 60.6% at 6.2 months for second-generation TKIs, and

39.0% at 12.0 months for Imatinib, which suggest that discontinuation of second generation TKIs can lead to higher TFS.

The treatment-free survival is comparable with the TFS in EURO-SKI, which was 60% and 49%, at six and 24 months (13). The reliability of the data is impacted by the small patient sample and wide range in duration of follow-up (2.7-97.2 months). Both short duration of follow-up and delayed qPCR-analysis are possible sources to higher TFR-rates. The relapse-pattern correlates to EURO-SKI and STIM, where loss of MMR occurred most frequently within the first six months (12, 13, 17). All the patients who relapsed regained MMR within 4.8 months from start of treatment, median time 2.4 months. This is a higher and faster remission-rate than in EURO-SKI, where 86% regained MMR after relapse, and the median time from TKI-resumption to remission was 2.8 months (13). The small patient sample impairs the result. In addition, there are differences in the inclusion criteria in EURO-SKI and this study, which makes comparisons less significant. With origin in the fact that all patients that relapsed regained MMR, our results support the findings from STIM-trial and EURO-SKI, that it is safe to discontinue TKI if the guidelines are being followed (12, 13).

Discontinuation of second-generation TKIs, lead to a higher TFS, than discontinuation of Imatinib. After TKI-discontinuation 57.1% of patients who discontinued Imatinib and 38.5% of patients who discontinued second-generation TKIs, relapsed. The result is not statistically significant. If the result is generalizable, it could affect the current treatment strategy for CML-patients. There has not been a unambiguously proof in literature that second-generation TKIs induces higher rates of TFR than first-generation TKI(20). The French 2 STOP 2G-study showed similar results regarding TFR as the A-STIM study, where Imatinib was discontinued under comparable circumstances(24). In an observational study of 293 Italian CML patients in chronic phase, who discontinued in DMR, estimated TFR was 68% for imatinib and 73% for second-generation TKIs at 12 months, which can support our findings(25). EURO-SKI found that the duration of DMR before discontinuation was the most important factor regarding remaining in MMR or better at six months(13). Type of TKI may therefore be of less or no importance, as long as the duration of DMR is sufficient. The statistical analysis is not adjusted for confounding factors, the difference between first- and second-generation TKI regarding TFS may therefore not be real. The follow-up time is higher for the patients with Imatinib (mean time 64.3 vs. 29.7 months), which can lead to lower relapse-rates and a better outcome for second-generation TKIs. In addition the TKI before

discontinuation varies between being the first- to third-line TKI. The generalizability of the results is limited, and further research is needed. There is now an ongoing randomized study, SUSTRENIM, that will investigate TFR-rates after four years of treatment with either Imatinib or Nilotinib(9).

Guideline compliance

There were some deviations from the guidelines. Three of the patients discontinued "early", one patient was partial resistant against a TKI, and two patients restarted treatment "late". In addition there were a few discrepancies regarding monitorization. The majority of the discontinuation attempts in this study, followed current guidelines, if not, there were valid reasons to deviate in most cases.

The national guidelines for CML has changed over the years, which complicates the quality assurance. The first guidelines who mentioned TKI-discontinuation (besides in relation to pregnancy) was published in October 2016(26). The guidelines from 2016 is similar to the current guidelines, with exception of the duration of treatment and MR4, which were not specified in the stopping criteria until the guidelines from September 2018 (26, 27). In table 14 there is an overview of current criteria's/recommendations and the year they were published. Nevertheless the patients subjective side-effects and wishes are important in the decision of TKI-discontinuation.

Table 13: Criteria and recommendations for TKI-discontinuation in the current Norwegian national CML-guidelines, and the date they were originally published(1, 26, 27).

Criteria/recommendations	**Valid from**
No resistance against any TKI.	October 2016
Restart TKI-treatment when/if MR3 is lost.	
Good monitorization: PCR monthly for 6 months, then every 2. month (*every 6-7 weeks from September 2018) until month 12, then every 3. month. Every 3. month after relapse.	
Duration of TKI-treatment: 5 years tentatively	September 2018
Duration of MR4: 2 years	

Six patients discontinued before they were TKI-treated five years (39.7-57.9 months), all of them had a duration of ≥MR4 for ≥30.7 months. Four patients discontinued treatment before they had ≥MR4 for 2 years (10.2-22.1 months), all of them were TKI-treated > 60.7 months.

Three of the 10 patients who discontinued “early”, discontinued after September 2018. One discontinued after 46.3 months of treatment with ≥MR4 for over three years, due to side-effects. The other patient discontinued after 20.0 months of ≥ MR4 in the NordCML013 study, and would have had ≥ MR4 for over 64 months, if it wasn’t for one qPCR-result on MR3.5. The third patient discontinued after 17.4 months with ≥MR4, after being TKI-treated for 112.0 months. This patient was followed at another hospital at the time, the cause for the “early” discontinuation is therefore not known.

One patient discontinued despite partial resistance against Dasatinib. However, the mutation analysis showed normal conditions, and the patient had been TKI-treated for 119.4 months and had persistent MR4 for 69.8 months before discontinuation. All patients who relapsed, restarted TKI-treatment within 1.1 months after loss of MR3, excepts for two patients with valid causes. One restarted after 4.0 months due to pregnancy. The other patient restarted 8.3 months after first loss of MR3, due to months of fluctuation right around MR3.

Since October 2016, 14 patients have discontinued. Regarding these 14 patients, the test-intervals in the guidelines have not been followed rigorously. There a some missing test-results, causes include lack of documentation and lack of sampling for any cause. One patient had the first qPCR-analysis ca. 3.5 months after discontinuation, which revealed a relapse. In general the qPCR-analyses have been taken at the right intervals with a few weeks leeway. It has to be acknowledged that there are logistical challenges of sampling at exact intervals. If the patients have had a good molecular response over time, the test-intervals have been increased intentionally to 4-6 months instead of three months in some patients. The benefits by increasing the test-intervals have to be compared to the risk of later discovery of relapse, and a delay in TKI-resumption. The defined test-intervals are only recommendations, and it is questionable if it is necessary to take tests at so close intervals in all patients. An analysis of the patients included in EURO-SKI, AFTER-SKI, discovered that the kinetics in later relapses was slower than in relapses within the first six months after discontinuation(28). Molecular status at 36 months was highly predictive of molecular relapse, AFTER-SKI therefore raised the question that it could be possible do decrease the intensity of monitoring in those with MR4 at 36 months(28). All patients regained ≥MMR after TKI-resumption, it can therefore be argued that even though the increased test-intervals had a possible therapeutic consequence, it did not have a prognostic consequence.

Weaknesses in the study

Small sample

The study has included patients who got diagnosed with CML from 1996 to 2015, who has been followed up and treated at St. Olavs hospital. Because of low incidence and a small recruiting area there are few patients. The sample for "TKI-discontinuation" is even smaller.

Selection- and loss to follow-up bias

Some patients have been transferred to St. Olavs hospital after time of diagnosis, most of these patients are not included, but if it is a short time and the data is available, they have been included. There are also some patients who have transferred to other hospitals after time of diagnosis.

Molecular responses and missing data

In the review of medical records there were incidents where I couldn't find qPCR analysis. "Missing data" include lack of documentation and lack of sampling for any cause. Some patients are not followed with qPCR, due to undetectable mutations, blast crisis or hydroxyurea-treatment.

Furthermore the sensitivity of qPCR has improved over the last years, the molecular category in patients who got their diagnosis early is therefore less accurate than the patients who got their diagnosis later. The controls is not always taken at the exact times, I have therefore chosen the qPCR-result closest to the control month.

"Achieved MR4 within five years" analyses

The Kaplan Meyer plots are based on results from table 3 and not exact dates. Missing/delayed qPCR- results can lead to extended time to achieved MR4.

Survival analyses

The survival analyses look at the patients all together, not adjusted for risk score or specific treatment, it is therefore difficult to compare survival and treatment results with international studies, who often look at the effect of each individual treatment. In addition there is a higher

duration of follow-up in the pre-TKI era, than in the TKI era, which can lead to a higher survival-rate in the TKI-era.

Treatment-free survival analyses

Many of the patients have a short follow-up time, which makes the treatment free survival less significant. In addition the follow-up time is higher for the patients with first-generation TKI, which can lead to lower relapse-rates and higher TFS for second-generation TKIs. Missing/delayed qPCR-results can lead to a delay in discovering relapse, and can therefore give improved TFR-rates.

Summary/conclusion

The introduction of TKI has significantly improved the OS and CML-specific survival, and reduced the need for aHSCT, for CML patients at St. Olavs hospital. Most of the CML-patients in the TKI-era died of reasons unrelated to CML or its treatment.

There appeared to be a more favorable outcome in patients using second-generation TKIs than first-generation TKI, regarding molecular response and TFS. The results support the theory that second-generation TKI generates deeper molecular response faster. We can conclude with that the use of second- instead of first-generation TKI, can possibly lead to TKI-discontinuation and TFR in more patients, however further research is needed to investigate if it leads to higher TFR-rates. We will know more after the SUSTRENIM-study.

The decision to discontinue TKI-treatment was substantiated in all patients who discontinued at St. Olavs hospital. The majority of the discontinuation attempts in this study, followed current guidelines, if not, there were valid reasons to deviate in most cases. The results from the TKI-discontinuation attempts regarding relapse-pattern, regaining MMR and treatment-free survival are similar to results from EURO-SKI. Based on the results we can advocate that TKI-discontinuation at St. Olavs hospital had a similar success rate as international studies. In addition it is worth to mention that the results for the second TKI-discontinuation attempt looks promising.

These results are of importance for the hematological department at St. Olavs hospital and patients who are treated there. It has contributed to maintaining the CML-database at St.

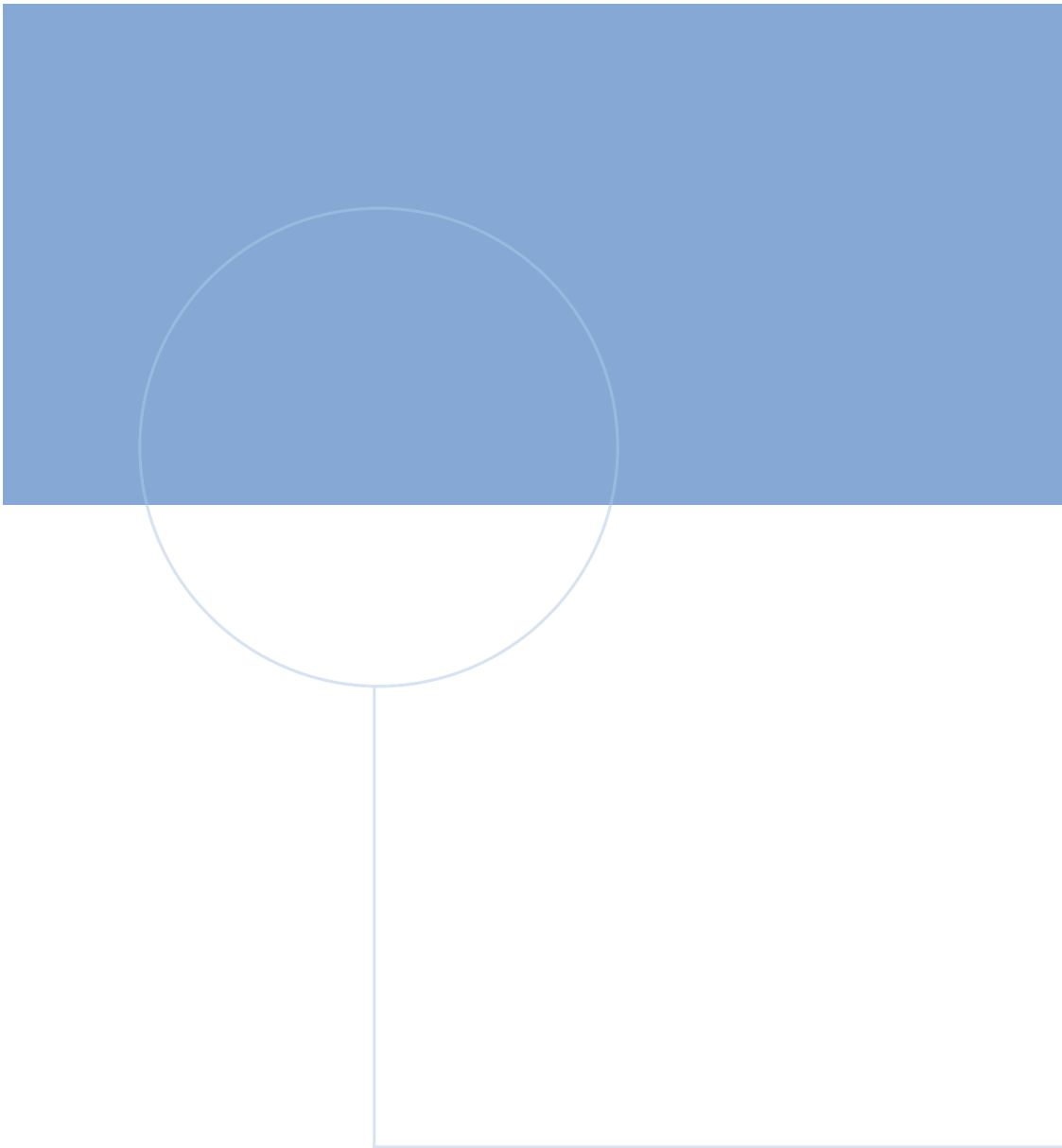
Olavs hospital. In addition this is the first quality assurance of TKI-discontinuation at St. Olavs hospital, and it could be the basis for later reviews.

Acknowledgments
I would like to thank my supervisor Henrik Hjorth-Hansen for guidance and constructive feedback. I also want to thank the Medicine and Health Library at NTNU for informative courses in PubMed and EndNote.

References

1. Hjorth-Hansen H, Gedde-Dahl T, Ghanima W. Kronisk myelogen leukemi (KML). 2020. In: Maligne blodsykdommer – Nasjonalt handlingsprogram med retningslinjer for diagnostikk, behandling og oppfølging [Internet]. Oslo: Helsedirektoratet. 7. [100-14]. Available from: https://www.helsedirektoratet.no/retningslinjer/maligne-blodsykdommer-handlingsprogram.
2. Santos FP, Kantarjian H, Quintás-Cardama A, Cortes J. Evolution of therapies for chronic myelogenous leukemia. Cancer J. 2011;17(6):465-76.
3. Gedde-Dahl T. Leukemi: Kronisk myelogen leukemi. In: Birkeland KI, Gullestad L, Aabakken L, editors. Indremedisin 1. 1 ed. Oslo: Vett & Viten; 2017. p. 426-8.
4. Baccarani M, Castagnetti F, Gugliotta G, Palandri F, Rosti G. Treatment recommendations for chronic myeloid leukemia. Mediterr J Hematol Infect Dis. 2014;6(1):e2014005.
5. Roskoski R, Jr. A historical overview of protein kinases and their targeted small molecule inhibitors. Pharmacol Res. 2015;100:1-23.
6. Zaharieva MM, Amudov G, Konstantinov SM, Guenova ML. Leukemia. intechopen.com: IntechOpen; 2013. p. 231.
7. Goldman JM, Melo JV. Chronic myeloid leukemia--advances in biology and new approaches to treatment. N Engl J Med. 2003;349(15):1451-64.
8. Kantarjian HM, Hughes TP, Larson RA, Kim DW, Issaragrisil S, le Coutre P, et al. Long-term outcomes with frontline nilotinib versus imatinib in newly diagnosed chronic myeloid leukemia in chronic phase: ENESTnd 10-year analysis. Leukemia. 2021;35(2):440-53.
9. Hochhaus A, Baccarani M, Silver RT, Schiffer C, Apperley JF, Cervantes F, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia. 2020;34(4):966-84.
10. Fabarius A, Kalmanti L, Dietz CT, Lauseker M, Rinaldetti S, Haferlach C, et al. Impact of unbalanced minor route versus major route karyotypes at diagnosis on prognosis of CML. Ann Hematol. 2015;94(12):2015-24.
11. Mahon F-X, Réa D, Guilhot J, Guilhot F, Huguet F, Nicolini F, et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. The Lancet Oncology. 2010;11(11):1029-35.
12. Mahon FX, Réa D, Guilhot J, Guilhot F, Huguet F, Nicolini F, et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. Lancet Oncol. 2010;11(11):1029-35.
13. Saussele S, Richter J, Guilhot J, Gruber FX, Hjorth-Hansen H, Almeida A, et al. Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukaemia (EURO-SKI): a prespecified interim analysis of a prospective, multicentre, non-randomised, trial. Lancet Oncol. 2018;19(6):747-57.
14. Rousselot P, Charbonnier A, Cony-Makhoul P, Agape P, Nicolini FE, Varet B, et al. Loss of major molecular response as a trigger for restarting tyrosine kinase inhibitor therapy in patients with chronic-phase chronic myelogenous leukemia who have stopped imatinib after durable undetectable disease. J Clin Oncol. 2014;32(5):424-30.
15. Laneuville P. When to Stop Tyrosine Kinase Inhibitors for the Treatment of Chronic Myeloid Leukemia. Curr Treat Options Oncol. 2018;19(3):15.
16. Saussele S, Richter J, Guilhot J, Gruber FX, Hjorth-Hansen H, Almeida A, et al. Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukaemia (EURO-

SKI): a prespecified interim analysis of a prospective, multicentre, non-randomised, trial. The Lancet Oncology. 2018;19(6):747-57.
17. Flygt H, Sandin F, Dreimane A, Markevärn B, Olsson K, Wadenvik H, et al. HIGH LEVEL OF SUCCESSFUL TKI DISCONTINUATION OUTSIDE CLINICAL TRIALS - A POPULATION-BASED STUDY FROM THE SWEDISH CML REGISTRY. European Hematology Association. 2020.
18. Rønning K, Wendelbo E. Kronisk myelogen leukemi ved St. Olavs Hospital 1996-2009 [Master thesis]. Trondheim: NTNU; 2016.
19. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2020 update on diagnosis, therapy and monitoring. Am J Hematol. 2020;95(6):691-709.
20. Mahon FX. Treatment-free remission in CML: who, how, and why? Hematology Am Soc Hematol Educ Program. 2017;2017(1):102-9.
21. Pfirrmann M, Baccarani M, Saussele S, Guilhot J, Cervantes F, Ossenkoppele G, et al. Prognosis of long-term survival considering disease-specific death in patients with chronic myeloid leukemia. Leukemia. 2016;30(1):48-56.
22. Hochhaus A, Masszi T, Giles FJ, Radich JP, Ross DM, Gómez Casares MT, et al. Treatment-free remission following frontline nilotinib in patients with chronic myeloid leukemia in chronic phase: results from the ENESTfreedom study. Leukemia. 2017;31(7):1525-31.
23. Cortes J, Rea D, Lipton JH. Treatment-free remission with first- and second-generation tyrosine kinase inhibitors. Am J Hematol. 2019;94(3):346-57.
24. Rea D, Nicolini FE, Tulliez M, Guilhot F, Guilhot J, Guerci-Bresler A, et al. Discontinuation of dasatinib or nilotinib in chronic myeloid leukemia: interim analysis of the STOP 2G-TKI study. Blood. 2017;129(7):846-54.
25. Fava C, Rege-Cambrin G, Dogliotti I, Cerrano M, Berchialla P, Dragani M, et al. Observational study of chronic myeloid leukemia Italian patients who discontinued tyrosine kinase inhibitors in clinical practice. Haematologica. 2019;104(8):1589-96.
26. Helsedirektoratet. Kronisk myelogen leukemi (KML). 2016. In: Nasjonalt handlingsprogram med retningslinjer for diagnostikk, behandling og oppfølging av maligne blodsykdommer [Internet]. Oslo: Helsedirektoratet. 5.
27. Hjorth-Hansen H, Gedde-Dahl T, Ghanima W. Kronisk myelogen leukemi (KML). 2018. In: Nasjonalt handlingsprogram med retningslinjer for diagnostikk, behandling og oppfølging av maligne blodsykdommer [Internet]. Oslo: Helsedirektoratet. 6. [27].
28. Richter J, Lübking A, Söderlund S, Lotfi K, Markevärn B, Själander A, et al. Molecular status 36 months after TKI discontinuation in CML is highly predictive for subsequent loss of MMR-final report from AFTER-SKI. Leukemia. 2021.



NTNU

Norwegian University of
Science and Technology