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Flygt, Hjalmar

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Long-term tolerability and efficacy after initial PegIFN- α addition to dasatinib in CML-CP: Five-year follow-up of the NordCML007 study

Hjalmar Flygt¹  | Stina Söderlund¹ | Jesper Stentoft² | Johan Richter³ |
Perttu Koskenvesa⁴ | Satu Mustjoki^{4,5} | Waleed Majeed⁶ | Anna Lübking³ |
Arta Dreimane⁷ | Berit Markevörn⁸ | Leif Stenke⁹ | Kristina Myhr Eriksson¹⁰ |
Bjørn Tore Gjertsen¹¹ | Tobias Gedde-Dahl¹² | Andreja Dimitrijevic¹³ | Lene Udby¹⁴ |
Ulla Olsson-Strömberg¹ | Henrik Hjorth-Hansen^{15,16}

¹Department of Medical Science and Division of Hematology, Uppsala University Hospital, Uppsala, Sweden

²Department of Hematology, Aarhus University Hospital, Aarhus, Denmark

³Department of Hematology, Oncology and Radiation Physics, Skåne University Hospital, Lund, Sweden

⁴Hematology Research Unit Helsinki, and Department of Hematology, Helsinki University Hospital Comprehensive Cancer Center, University of Helsinki, Helsinki, Finland

⁵Translational Immunology Research Program and Department of Clinical Chemistry and Hematology, University of Helsinki, Helsinki, Finland

⁶Department of Hemato-Oncology, Stavanger University Hospital, Stavanger, Norway

⁷Department of Hematology, Linköping University Hospital, Linköping, Sweden

⁸Department of Hematology, Umeå University Hospital, Umeå, Sweden

⁹Department of Medicine Solna, Karolinska Institutet and Division of Hematology, Karolinska University Hospital, Stockholm, Sweden

¹⁰Department of Internal Medicine and Hematology, Sunderby Hospital, Luleå, Sweden

¹¹Department of Internal Medicine, Hematology Section, Haukeland University Hospital, Bergen, Norway

¹²Department of Hematology, Oslo University Hospital, Rikshospitalet, Oslo, Norway

¹³Department of Hematology, Odense University Hospital, Odense, Denmark

¹⁴Department of Hematology, Zealand University Hospital, Roskilde, Denmark

¹⁵Department of Hematology, St Olavs Hospital Trondheim, Trondheim, Norway

¹⁶Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway

Correspondence

Hjalmar Flygt, Department of Medical Science and Division of Hematology, Uppsala University Hospital, Internmedicin, Ing 40 Akademiska Sjukhuset, 75185 Uppsala, Sweden.
Email: hjalmar.flygt@medsci.uu.se

Abstract

Objectives: Treatment-free remission (TFR) has emerged as a treatment goal in chronic myeloid leukemia in the chronic phase (CML-CP). Attempts to increase proportion of patients achieving TFR include combination of tyrosine kinase inhibitors (TKI) and other drugs. Interferon- α in addition to TKI has shown promising efficacy but with dose-dependent toxicity and discontinuations. NordCML007 was initiated

Novelty Statement: To our knowledge this is the first long-term follow-up of patients with chronic-phase chronic myeloid leukemia initially treated with a low dose of PegIFN- α in addition to dasatinib. Our findings show that the treatment was well tolerated and did not give rise to any unexpected late adverse events. Molecular response rates remained high throughout the study, and further randomized controlled trials are warranted to determine if low-dose PegIFN- α may add to the efficacy of TKI treatment.

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to study the efficacy and safety of low dose pegylated IFN- α (PegIFN- α) in combination with dasatinib (DAS) in CML-CP.

Methods: Forty patients with newly diagnosed CML-CP were given DAS upfront. After month 3 (M3) 15 $\mu\text{g}/\text{wk}$ of PegIFN- α was added and increased to 25 $\mu\text{g}/\text{wk}$ from M7 until M15. DAS treatment was continued and adverse events and BCR-ABL1 qRT-PCR values were reported yearly after M24. Results from M1 to M18 have previously been published, and here we present long-term data.

Results: After 5 years of follow-up, there were no suspected unexpected serious adverse reactions, no increase in serosal effusions, no disease progressions and no CML-related deaths. Rates of MR^{3.0} (MMR), MR^{4.0} and MR^{4.5} were 84.6%, 64.1% and 51.3% respectively at M60, and 95% of patients reached MMR at some point during the study.

Conclusion: Initial addition of PegIFN- α to DAS shows good long-term efficacy without increased toxicity.

KEYWORDS

BCR-ABL Positive, chronic myelogenous leukemia, clinical trial, dasatinib, interferon-alpha

1 | INTRODUCTION

The first TKI imatinib (IMA) was introduced in 2001, and second-generation TKI dasatinib (DAS), nilotinib (NIL), bosutinib and third-generation TKI ponatinib have since been developed. With TKI treatment, the survival rate in chronic myeloid leukemia (CML) in the chronic phase (CP) has improved dramatically and is approaching that of the comparable general population.^{1,2} TKI treatment is generally well tolerated but long-term follow-up shows that approximately one quarter of patients become resistant or intolerant to first line IMA.³ Second-generation TKI have shown faster and deeper response rates than IMA, but may lead to potentially irreversible toxicity such as cardiovascular adverse events.⁴ In recent years, several TKI discontinuation studies have shown that a large proportion of CML-CP patients in a durable deep molecular response (DMR, MR^{4.0} or better for ≥ 1 year) could successfully stop treatment without relapse, the largest being the EURO-SKI study.⁵⁻⁷ TKI discontinuation has been implemented into clinical routine, and it is of interest to find ways to increase the proportion of patients that achieve a durable TFR. There are currently no randomized controlled trials comparing second generation TKI to IMA with regards to discontinuation, and there is no compelling evidence that treatment with second generation TKI alone results in a higher proportion of stop patients achieving TFR.⁷⁻¹⁰ Before the introduction of TKI, IFN- α was standard treatment for patients not eligible for allogeneic stem cell transplantation, in rare instances leading to DMR, and even TFR.¹¹ The exact anti-leukemic mechanism of IFN- α is still not completely understood but differs from that of TKI. Because of different mechanism of action, and synergistic effects in vitro, the combination of PegIFN- α and TKI has been investigated as a way to improve response rates.¹²⁻¹⁷ Due to the short half-life of IFN- α , pegylated

IFN- α 2a or b with prolonged half-life was developed allowing for administration once weekly. Previous studies of the combination of IMA and PegIFN- α have shown promising efficacy compared to IMA alone, but with high rates of PegIFN- α discontinuation due to toxicity, most commonly hematological adverse events (AE) and constitutional symptoms (fatigue, fever, flu-like syndrome etc).¹³⁻¹⁶ In addition, a post-hoc analysis has shown that previous treatment with IFN- α for more than 1.5 years significantly increased the chance of successful TFR in EURO-SKI.⁶ Lower-dose regimens have been explored to improve tolerability in a population who, treated with TKI alone, enjoy a good quality of life.

The NordCML007 trial was set up by the Nordic CML study group (NCMLSG) to determine the safety and efficacy of adding a low dose of PegIFN- α 2b (PegIntron) to DAS for 12 months in CML-CP patients. In previous studies DAS has been associated with a higher rate of hematological toxicity than IMA, but the vast majority of AE occur early in the treatment. DAS-related serosal effusion is an exception, with cases presenting years after treatment onset, often leading to treatment discontinuation.^{18,19} However, serosal effusion is also associated with immunomodulation and a better prognosis.^{20,21} Results from the first 18 months of NordCML007 have previously been published. No increase in serosal effusions and no suspected unexpected serious adverse reactions (SUSAR) were seen on the combination treatment.²² To determine long-term safety and efficacy, patients were followed for 5 years, and here we present long-term data.

2 | METHOD

NordCML007 was initiated by the Nordic CML Study Group (NCMLSG) and sponsored by The Norwegian University of Science



and Technology (NTNU). Study drugs were provided by Bristol-Myers Squibb, New York, NY, USA (BMS) and Merck Sharp & Dohme, Kenilworth, NJ, USA (MSD). The trial was registered in www.clinicaltrials.gov with study ID NCT01725204. It was conducted according to the Declaration of Helsinki and Good Clinical Practice. Ethical approval was obtained from ethical committees in all participating countries, and all patients provided written informed consent.

2.1 | Study protocol

The NordCML007 trial was an open-label, single-arm phase II study of the combination of DAS and PegIFN- α 2b.²² For the full inclusion and exclusion criteria, see supplementary material. In short, patients between 18 and 70 years of age with newly diagnosed CML-CP were eligible for inclusion. No other antileukemic drug was allowed prior to inclusion except for hydroxyurea for up to 30 days. Patients with significant heart disease, other primary malignant diseases or severe liver or gastrointestinal disease were also excluded. Patients were included at 14 university or regional hospitals in Norway, Sweden, Finland, and Denmark. According to protocol, a standard dose of 100 mg DAS was given up front and maintained until month 24 (M24). At the start of M4, a low dose of 15 μ g PegIFN- α 2b per week was added as subcutaneous injections and if well tolerated a dose escalation to 25 μ g was attempted and maintained until the end of M15 when PegIFN- α 2b was discontinued. After 24 months, DAS was continuously provided within the trial, but all treatment decisions were made at the discretion of the treating physician. BCR-ABL1 copies measured by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR), current treatment and adverse events were reported yearly after M24 until M60. Figure 1 shows a summarized outline.

2.2 | Monitoring

Standard laboratory testing, bone marrow karyotyping, and peripheral blood qRT-PCR of BCR-ABL1 were performed every third month until M18 according to protocol. Starting at M24 BCR-ABL1, monitoring was done according to clinical practice, and values at 36, 48 and 60 months from inclusion were reported in a web-based case report form. Samples were analyzed at 10 university hospital laboratories standardized to the international scale. All labs were certified

for MR⁴ measurement within EUTOS. MMR, MR^{4.0} and MR^{4.5} were defined according to Cross et al²³ In cases of undetectable BCR-ABL1 levels, $\geq 10\ 000$ ABL or $\geq 24\ 000$ GUS and $\geq 32\ 000$ ABL and $\geq 77\ 000$ GUS transcripts, were used as minimal criteria for the definition of MR^{4.0} and MR^{4.5} respectively. Clinical assessments beyond M24 were done according to clinical routine at the treating hospitals.

2.3 | Adverse event reporting

Adverse events were graded and reported according to common terminology criteria for adverse events v 3.0 (CTCAE v3.0). Only clinically significant grade 2 AE and all grade 3-4 AE were reported according to protocol. Reported AE were divided into hematological, non-hematological, and biochemical adverse events. Only AE occurring on the study drug or within 1 month of discontinuation were included in the AE summation.

2.4 | Endpoints

The primary efficacy endpoint of the trial was rate of MMR at 12 months. There was also a primary safety criterion that if reached would terminate the trial prematurely. Results regarding primary and secondary endpoints within the first 18 months have previously been published and will not be further described in detail.²² Follow-up of patients after M24 was to determine long-term safety and efficacy, and there were no pre-specified endpoints beyond M24 in the protocol. The proportion of patients still on study treatment; proportion of patients with different AE; proportion of patients with, number and description of serious adverse events (SAE); SUSAR and progressions to accelerated phase (AP) or blast crisis (BC) were evaluated. Efficacy was measured as proportion of patients in MMR, MR^{4.0}, and MR^{4.5} at 24, 36, 48, and 60 months. In addition, the cumulative incidences of MMR, MR^{4.0}, and MR^{4.5} were calculated for comparison with historical cohorts.

2.5 | Statistical analysis

Response variables were binomial and presented as percentage of patients according to an intention-to-treat principle, ie including patients on second line treatment. When presenting proportions,

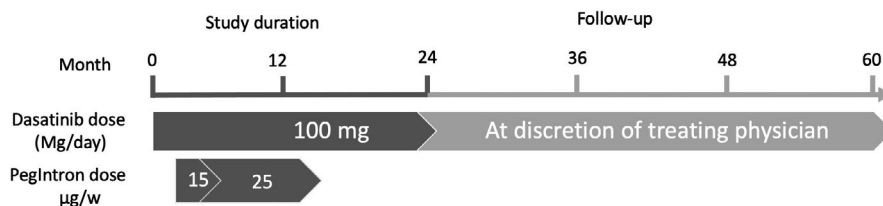


FIGURE 1 General outline of the trial. Dasatinib 100 mg was given up-front and maintained until the end of month 24 (M24), after which treatment decisions were made at discretion of treating physician. PegIFN- α 2b was given from beginning of M4 to the end of M15. Past M24 qRT-PCR values of BCR-ABL1, current treatment and adverse events were reported yearly



patients lost to follow-up were not included in analysis after time of last follow-up, ie the denominator was decreased. Patients who died were continuously included in the denominator and considered as loss of response. Confidence intervals of 95% were calculated using the Clopper-Pearson exact method. Cumulative incidences were calculated using the Kaplan-Meier method to facilitate comparison to historical cohorts. Patient death and allogeneic stem cell transplantation were considered competing events, and patients lost to follow were censored at last follow-up. Cumulative rates at each time-point are presented after all evaluable patients had completed the respective yearly follow-up.

3 | RESULTS

3.1 | Patients

Forty-two patients were assessed for eligibility, and 40 were included in the trial between February 2013 and May 2014. Complete patient characteristics have been described in the original publication.²² Proportion of patients in high-, intermediate-, and low-risk groups according to ELTS score were 10%, 42%, and 48% respectively. Mean and median age was 47.5 years (Range: 19-71) and 78% were male. One patient was lost to follow-up after M6 due to moving to another country. One patient that died of lung cancer between the M36 and M48 follow-up was treated as a loss of response in subsequent follow-ups. At 5 years, 38 patients were alive and evaluable.

3.2 | Efficacy of the treatment

In short, early results showed that 10.0% ($n = 4$) of patients reached MMR by 3 months, ie prior to addition of PegIFN. By 12 months, 82.1% reached MMR.²² Proportion in MMR were 87.2% (34/39, 95% CI: 72.6%, 95.7%), 89.7% (35/39, 95% CI: 75.8%, 97.1%), 89.7% (35/39, 95% CI: 75.8%, 97.1%) 87.2% (34/39, 95% CI: 72.6%, 95.7%), and 84.6% (33/39, 95% CI: 69.5%, 94.1%) at M18, M24, M36, M48, and M60 respectively. The proportion of patients in MR^{4.0} and MR^{4.5} at 5 years were 64.1% (25/39) and 51.3% (20/39) respectively. Cumulative rates of MMR, MR^{4.0}, and MR^{4.5} are presented in Figure 2.

Of all patients reaching MMR at any point during follow-up, five patients had lost MMR by M60. Reasons for loss of MMR for these patients were TKI interruption and later change of therapy due to pleural effusion (PE) in two patients, discontinuation attempt in one patient, dosing misconduct and protocol violation in one patient and loss of MMR despite stable TKI treatment in one patient. All but two patients reached MMR on at least one follow-up. Of the two patients failing to reach MMR, one was lost to follow-up after 6 months, and one had consistent poor response to DAS and NIL and successfully underwent allogeneic stem cell transplantation in chronic phase in M18. No transformations to AP- or BC- or CML-related deaths were observed.

3.3 | Safety

The incidence of hematological and non-hematological toxicity during the first year of the study and SAE during M1-M24 has previously been published.²² No additional grade ≥ 2 hematological adverse events were seen after M12. Percentage of patients with non-hematological adverse events from inclusion to M60 are presented in Table 1. Clinically significant adverse events after M24 were generally uncommon, but 10% ($N = 4$) had PE diagnosed between M24-M60. From inclusion to M60 eight patients (20.0%) had PE, 1 in year one, 3 in year two, 1 in year three, 2 in year four, and 1 in year five. Two of the patients with PE had dose interruptions and corticosteroid treatment but could later continue with DAS 50 mg, the remaining six patients discontinued due to PE. In addition, one patient had grade 2 pericardial fluid at M60. Other significant non-serious AE were limited to one case each of erysipelas, skin discoloration, hemorrhagic colitis, Graves' disease, pancreatitis, anxiety/depression, and breathing difficulty with CT scan showing ground glass changes. After M24 one patient with PE was hospitalized four times between M47-M54, and later developed an empyema secondary to pleural drainage. Another patient who discontinued treatment due to PE was later found to have a lung tumor and died two months after discontinuation. The patient had a long history of smoking. Other SAE after M24 included one patient diagnosed with pulmonary arterial hypertension (probable relation to DAS) at M29 which subsided after DAS discontinuation, one patient with erysipelas on the back (unlikely relation to DAS) at M42 and one patient with rectal bleeding (unlikely relation to DAS) at M41. No SUSAR were seen.

3.4 | Tolerability and discontinuations

As previously reported, the combination treatment had an acceptable toxicity profile and 83.8% of patients who started PegIFN were still on combination treatment by 12 months.²² By M24 92% of patients were still on DAS. From M24, all treatment decisions were made at the discretion of the treating physician, and at 5 years 65.8% of evaluable patients were still on DAS. Other treatments were IMA, NIL and no TKI in 21.0%, 5.3% and 7.9% respectively. DAS discontinuations and subsequent treatments are described in Figure 3. Reasons for discontinuation were PE ($N = 6$), poor response ($N = 2$), stable MR^{4.5} with discontinuation attempt ($N = 2$), headache ($N = 1$), pulmonary hypertension ($N = 1$), breathing difficulty with ground glass changes ($N = 1$; symptoms disappeared, and repeated CT was normal one month after discontinuation), protocol violation ($N = 1$) and lost to follow-up due to moving abroad ($N = 1$). Of the two patients attempting to discontinue due to stable MR^{4.5} one discontinued at M43 and relapsed at M47, was restarted on IMA and reached MMR within two months. The other patient gradually lowered the DAS dose to 20 mg, and subsequently discontinued in M57 and had lost MMR at the M60 follow-up. In addition, a patient who switched to NIL due to headache in M3 later discontinued treatment in M43



due to stable MR^{4.5} and was still without TKI and in MR^{4.5} at M60. Throughout the study, the whole cohort received 75% of scheduled DAS dose, and 42% of patients still on DAS treatment had a reduced dose by M60.

Forty-one percent (16/39) of patients were still on TKI treatment and had MR^{4.0} or better at both the M48 and M60 follow-up, ie, had sustained MR^{4.0} or better for 1 year. Based on the assumption that a third BCR-ABL1 measurement between these time points

would also have shown MR^{4.0}, these patients would be eligible for discontinuation according to EURO-SKI criteria. In addition, three patients underwent discontinuation attempts during the M24-M60 time frame. Consequently, forty-nine percent (19/39) of the cohort was eligible for or had already attempted TKI discontinuation.

4 | DISCUSSION

To our knowledge, this is the first long-term follow-up of patients initially treated with a low dose of PegIFN- α 2b in addition to DAS. The combination was safe, well tolerated and the addition of PegIFN- α 2b induced a rapid increase in the proportion of patients reaching MMR by M12 as compared to DASISION.^{19,22} Rates of MMR and deeper molecular responses remain high after 5 years of follow-up. In addition, no excessive incidence of late PE and no SUSAR with progressions to AP- or BC- or CML-related deaths were seen.

The most common late (after M24) AE reported was PE in 10% of patients occurring as late as M50, resulting in 20% of patients having PE in total. This is similar to the SPIRIT2 trial (22%, median follow-up 37 months), but less than DASISION (28% after 5 years). Hence, the early addition of PegIFN- α 2b does not appear to adversely influence the occurrence of serosal effusion.

The proportion of patients who attained MMR, MR⁴, and MR^{4.5} remained high until M60. For efficacy comparison, cumulative response rates in DASISION showed that 46% reached MMR

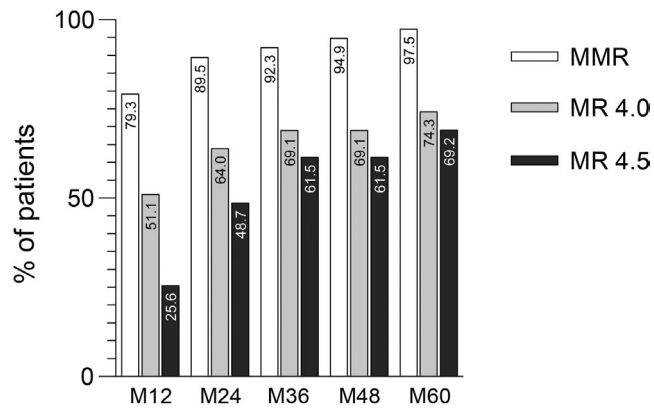


FIGURE 2 Response rates in NordCML007 illustrated as cumulative incidence of MMR, MR4.0 and MR4.5 after all patients had completed the M12, M24, M36, M48, and M60 follow-up in NordCML007, presented according to an intention-to-treat principle

TABLE 1 Non-hematological adverse events (AE). Percentage and number of patients with non-hematological AE from inclusion to 5-year follow-up and percentage and number of patients with late non-hematological AE per year between year three to five. Adverse events were reported yearly after year 2

Non-hematological AE	Year 1-5		Year 3		Year 4		Year 5	
	Gr II	Gr III-IV	Gr II	Gr III-IV	Gr II	Gr III-IV	Gr II	Gr III-IV
	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)
Gastrointestinal	25 (10)	3 (1)	0 (0)	0 (0)	5 (2)	0 (0)	3 (1)	0 (0)
Fatigue	30 (12)	0 (0)	0 (0)	0 (0)	3 (1)	0 (0)	0 (0)	0 (0)
Dermatological/Rash	30 (12)	3 (1)	0 (0)	0 (0)	3 (1)	0 (0)	0 (0)	0 (0)
Cardiac	8 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Infections	20 (8)	8 (3)	5 (2)	0 (0)	0 (0)	3 (1)	0 (0)	3 (1)
Depression/anxiety	13 (5)	3 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Flu-like symptoms	8 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Musculoskeletal	18 (7)	5 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Headache	5 (2)	3 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Superficial edema	5 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Pleural/pericardial effusion	18 (7)	5 (2)	5 (2)	0 (0)	10 (4)	3 (1)	5 (2)	0 (0)
Anaphylaxis	0 (0)	3 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Pulmonary arterial hypertension	0 (0)	3 (1)	0 (0)	3 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Thyroid	5 (2)	0 (0)	3 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Miscellaneous	20 (8)	5 (2)	5 (2)	0 (0)	3 (1)	0 (0)	3 (1)	0 (0)

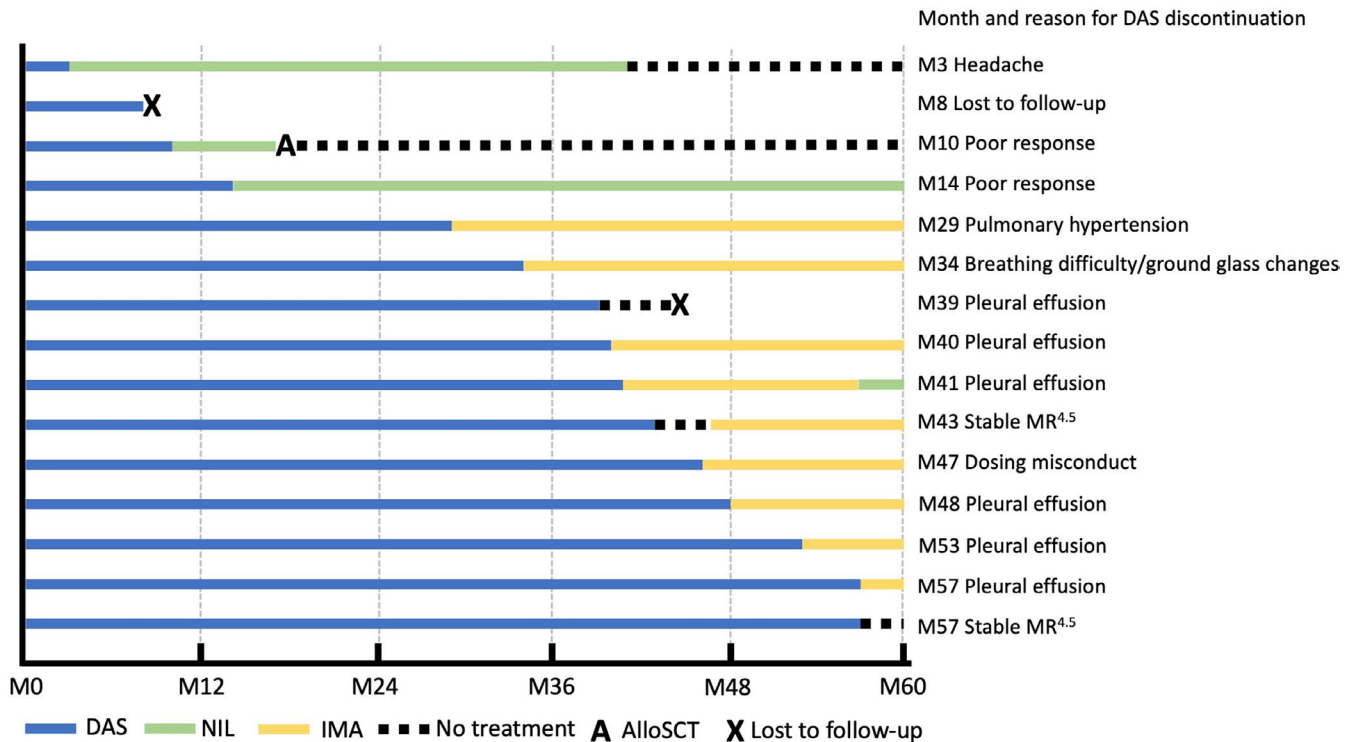


FIGURE 3 Dasatinib discontinuations and subsequent treatments. Month (M) and reason for discontinuation

by 12 months, and 76% and 42% reached MMR and MR^{4.5} respectively at 5 years.¹⁹ Correspondingly, cumulative rates of MMR and MR^{4.5} were 97.5% and 69.2% in the NordCML007 cohort at 5 years (Figure 2). Missing values in DASISION were considered lack-of-response, and there were almost no missing data from the NordCML007 patients, which may exaggerate responses relative to DASISION. Moreover, long-term follow-up of DAS-treated patients by Maiti et al recently showed a 12-month MMR rate of 74% and 5-year cumulative MMR and MR^{4.0} rates of 89% and 79% respectively.¹⁸ Moreover, in previous DAS study NordCML006 and studies of DAS by Radich et al and Naqvi et al, the reported 12-month MMR rates were 81%, 59% and 80% respectively, all significantly better than the DASISION cohort.²⁴⁻²⁶ In these studies, however, 3-month MMR rates were 30%, 37%, 18% and 33% respectively^{18,24-26} while the MMR rate at 3 months (prior to the addition of PegIFN) was 10% in NordCML007 similar to 8% in DASISION.^{19,22} In our study, treatment decisions beyond M24 were at discretion of the treating physicians. Subsequent treatments after DAS discontinuation were IMA in 9 (22.5%) patients and NIL in 3 (7.5%) patients, also similar to DASISION with 19% and 9%, respectively.

The small number of patients in NordCML007 makes differences attributable to chance more likely. Other limitations in this study include data being reported yearly beyond M24, which might increase the risk of underreporting of adverse events. Yearly reporting also means that exact proportion of patients eligible for discontinuation cannot be accurately determined (three qRT-PCR IS values within 12 months are required according to most discontinuation protocols) and is estimated based on the available data. Of patients still on DAS

at M60, 42% were treated with a reduced dose but with maintained excellent efficacy, indicating that the standard dose of 100 mg is difficult to maintain and not necessary for many patients. In the recent study from MD Anderson Cancer Center by Naqvi et al, patients with CML-CP were given 50 mg DAS once daily upfront. The reported 12 month rates of MMR, MR^{4.0}, and MR^{4.5} were 81%, 55%, and 49% respectively, and only 6% had pleural effusions, supporting the idea that DAS dose can be lowered with maintained efficacy.²⁴

In summary, addition of a low dose of PegIFN- α 2b to DAS 3 months after TKI-start was well tolerated and did not give rise to unexpected late adverse events. The incidence of late toxicity of DAS such as PE and PAH were in accordance with data from other studies. Promisingly, approximately 70% of patients attained MR^{4.5} within 5 years. Randomized controlled trials are warranted to determine if addition of low-dose PegIFN- α can add to the efficacy of TKI treatment and increase the proportion of patients achieving TFR.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.



ORCID

Hjalmar Flygt  <https://orcid.org/0000-0002-8912-2324>

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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