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The Long-term Efficacy and Safety of Nilotinib in Pediatric Patients With CML: a 5-Year Update of the DIALOG Study

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Abstract:
The efficacy and safety of nilotinib in pediatric patients with imatinib/dasatinib resistant/intolerant (R/I) or newly diagnosed (ND) Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia in chronic phase (CML-CP) was demonstrated in the phase II, open-label DIALOG study. In this final analysis, long-term efficacy and safety are presented for patients who completed 66 cycles (of 28 days) of treatment with nilotinib (230 mg/m2 twice daily) or discontinued early. Fifty-nine patients were enrolled and 58 were treated (R/I, n=33; ND n=25; median time on treatment: 60.5 and 51.9 months, respectively). In the R/I cohort, the cumulative major molecular response (MMR) rate was 60.6% and no patients had a confirmed loss of MMR. Among ND patients, the best overall MMR rate was 76.0%; three patients had a confirmed loss of MMR. The cumulative molecular response MR4 and MR4.5 (BCR::ABL1IS {less than or equal to}0.01% and {less than or equal to}0.0032%, respectively) rates by 66 cycles were 27.3% and 12.1% in the R/I cohort, and 56.0% and 44.0% in the ND cohort, respectively. The safety profile of nilotinib was consistent with earlier reports. No on-treatment deaths occurred. These long-term (up to approximately 5 years) data support the efficacy and safety of nilotinib in pediatric patients with Ph+ CML-CP. www.clinicaltrials.gov.uk #NCT01844765.

Conflict of interest: COI declared - see note

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Clinical trial registration information (if any): www.clinicaltrials.gov.uk #NCT01844765

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The Long-term Efficacy and Safety of Nilotinib in Pediatric Patients With CML: a 5-Year Update of the DIALOG Study

Running title: Nilotinib in pediatric CML: long-term efficacy

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Key points

- Nilotinib treatment demonstrated sustained long-term efficacy in pediatric patients with CML-CP
- The overall benefit-risk assessment of nilotinib in pediatric patients with CML remains favorable making it a valuable treatment option

Abstract (197/250 words)

The efficacy and safety of nilotinib in pediatric patients with imatinib/dasatinib resistant/intolerant (R/I) or newly diagnosed (ND) Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia in chronic phase (CML-CP) was demonstrated in the phase II, open-label DIALOG study. In this final analysis, long-term efficacy and safety are presented for patients who completed 66 cycles (of 28 days) of treatment with nilotinib (230 mg/m^2 twice daily) or discontinued early. Fifty-nine patients were enrolled and 58 were treated (R/I, n=33; ND n=25; median time on treatment: 60.5 and 51.9 months, respectively). In the R/I cohort, the cumulative major molecular response (MMR) rate was 60.6% and no patients had a confirmed loss of MMR. Among ND patients, the best overall MMR rate was 76.0%; three patients had a confirmed loss of MMR. The cumulative molecular response MR^4 and MR$^{4.5}$ (*BCR*::*ABL1*^{IS} ≤0.01% and ≤0.0032%, respectively) rates by 66 cycles were 27.3% and 12.1% in the R/I cohort, and 56.0% and 44.0% in the ND cohort, respectively. The safety profile of nilotinib was consistent with earlier reports. No on-treatment deaths occurred. These long-term (up to approximately 5 years) data support the efficacy and safety of nilotinib in pediatric patients with Ph+ CML-CP. www.clinicaltrials.gov.uk #NCT01844765.

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INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm associated with the activity of the BCR::ABL1 fusion oncoprotein, a product of the Philadelphia chromosome which is formed by a reciprocal translocation between the long arms of chromosomes 9 and 22.[1] Incidence of CML among children and adolescents is low, accounting for approximately 2–3% of all leukemias in children <15 years of age and 9% in adolescents aged 15–19 years.[2]

Multiple tyrosine kinase inhibitors (TKI), including imatinib,[3,4] dasatinib,[5,6] and nilotinib,[7,8] have been approved for the treatment of pediatric patients with Philadelphia chromosome-positive (Ph+) CML. Currently, bosutinib,[9] ponatinib,[10] and asciminib[11] (a BCR::ABL1 inhibitor that works by specifically targeting the ABL myristoyl pocket [STAMP])[12] are under clinical investigation for children.

Nilotinib (Tasigna®, AMN107), a second-generation TKI considered a more potent inhibitor of BCR::ABL1 than imatinib,[13] has been approved for the treatment of pediatric patients with newly diagnosed (ND) Ph+ CML in chronic phase (CML-CP) and Ph+ CML-CP that is resistant or intolerant (R/I) to prior therapy.[7,8] In the US, nilotinib has also been approved for patients ≥1 year old with Ph+ CML in accelerated phase (AP) that is R/I to prior TKI therapy.[14]

Clinical outcomes in pediatric patients with CML have been improved with TKI treatment. However, similar to adults, not all pediatric patients will respond to imatinib or dasatinib, and some may become resistant to these therapies. In a phase III pediatric study, imatinib failure was observed in 27% of patients[15] and in a phase IV study, 30% of patients discontinued imatinib mainly due to an unsatisfactory response.[16] Prior to nilotinib, there were no approved therapies for pediatric patients with imatinib or dasatinib R/I CML-CP. Children may receive TKI therapy

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for many years, including during times of active growth and onset of puberty and, therefore face potential unique side effects of receiving treatment whilst actively growing.[17-20]

DIALOG is a phase II, open-label study (NCT01844765) of nilotinib in pediatric patients with Ph+ CML-CP. The primary efficacy endpoints from the DIALOG study have been previously reported and the efficacy and safety of nilotinib in this patient population was demonstrated[21]. Analysis of long-term safety data from DIALOG revealed a trend towards growth deceleration over time after ≥36 and ≥48 cycles of treatment.[22,23]

We present the final analysis of efficacy and safety data from the DIALOG study after the completion of 66 cycles of treatment or until study treatment discontinuation. To our knowledge this is the longest follow-up of TKI treatment in pediatric patients with Ph+ CML-CP.

MATERIALS AND METHODS

Study design and patient population

DIALOG was a multicenter, open-label, non-controlled phase II study of nilotinib in pediatric patients with Ph+ CML conducted at 36 centers across 13 countries; methods have previously been published.[21,23] In brief, eligible patients aged 1 to <18 years were enrolled into one of three cohorts: (1) patients with Ph+ CML-CP R/I to either imatinib or dasatinib (R/I Cohort), (2) patients with Ph+ CML-AP R/I to either imatinib or dasatinib, and (3) patients with ND Ph+ CML-CP (ND Cohort).

Nilotinib was administered orally at a dose of 230 mg/m^2 twice daily (BID; rounded to the nearest 50 mg to a maximum of 400 mg BID)[24] in capsule form for a total of 66 cycles of 28 days unless the patient discontinued early. The same nilotinib dose was selected for both ND and

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R/I pediatric patients based on pharmacokinetic (PK) data from adult studies which demonstrated an overlap of PK parameters for 300 mg and 400 mg doses, and the acceptable safety profile of a 400 mg dose. Prior pediatric data have demonstrated the 230 mg/m^2 dose to have a safety profile consistent with that observed in adults with PK exposure coverage of both the 300 mg and 400 mg doses.[24]

All patients completed a safety follow-up of 30 days following the last dose of study treatment and were followed for survival every 6 months until study completion (defined as the completion of last patient safety visit). At the end of the planned 66 cycles, patients could continue to receive nilotinib if they continued to demonstrate a clinical benefit by enrollment into a roll over study or via a managed access program, if nilotinib was not available commercially in their country of residence.[25] The final analysis was based on a last patient last visit of 28th August 2020.

Ethics

This study was conducted in accordance with the principles of the Declaration of Helsinki and local laws and regulations. The study protocol and all amendments were approved by the independent ethics committee and/or institutional review board for each study center. Prior written informed consent was provided by the patients' parents or caregivers and from patients able to provide a signature.

Endpoints and assessments

The objective of this analysis was to evaluate the long-term efficacy and safety (including growth assessments) of nilotinib in study participants. The primary efficacy and safety analysis was reported when all patients had completed 24 cycles of treatment or discontinued earlier,[21] and later safety analyses were reported when all patients had completed 36 and 48 cycles of

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treatment or discontinued earlier.[22,23] Secondary efficacy endpoints included the rate of molecular, cytogenetic, and hematologic response, time to response, duration of response, time to disease progression, event free survival (EFS) and overall survival (OS) (**Supplementary Methods**).

Safety assessments included adverse events (AE) which were recorded by preferred term according to Medical Dictionary for Regulatory Activities (MedDRA) version 23.0; severity was assessed according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Serious adverse events (SAE) were defined as AEs that were fatal or life threatening, resulted in persistent or significant disability/incapacity, or required inpatient hospitalization or prolonged existing hospitalization. AEs of special interest (AESI) were defined based on groups of preferred terms. Routine clinical laboratory evaluations and thyroid function tests were performed. Assessment of growth, development and sexual maturation were performed as previously reported (**Supplementary Methods**).[21,23]

Statistical analysis

All analyses were conducted descriptively using the full analysis set (FAS; all patients who received ≥1 dose of study treatment). Efficacy results were based on the final analysis with cumulative data after the last patient last visit took place. Response rates by time points were reported; these were cumulative and indicate the total number of patients who achieved that response level at any time. Confidence intervals (CI) for response rates were calculated using the Pearson-Clopper method by cohort.[26] The time to first major molecular response (MMR), first complete cytogenetic response (CCyR), first major cytogenetic response (MCyR) and first complete hematological response (CHR) were summarized for responders. EFS was defined as

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time from first study drug intake to the first occurrence of loss of CHR or MCyR, progression to AP or blast crisis (BC), or death from any cause, during treatment [27]. Time of EFS was censored at the date of last on-treatment assessment for patients without an event. Disease progression was defined as progression to AP/BC or CML-related death. Any value of AP or BC within the first 4 weeks of study treatment was not defined as progression to AP/BC within the study unless the patient discontinued study treatment due to progression or the treating physician determined there was unsatisfactory therapeutic effect with the first 8 weeks. Duration of response and disease progression was estimated by Kaplan Meier (K-M) methodology. OS was defined as the time from first study drug intake to the date of death due to any cause during the study, including the follow-up period after discontinuation of treatment.

Height and body mass index (BMI) were summarized at 6-month intervals, using standard deviation scores (SDS, also known as Z-score). Height deceleration was quantified based on the number of main percentile lines crossed by patients falling off the growth curve compared with baseline. Growth data analysis was completed using the FAS and for the prepubescent/pubescent subpopulation at study entry (FAS excluding patients who had completed puberty [defined as Tanner stage 5 attained for both testis and pubic hair for boys, breast development, and pubic hair for girls][28,29]). As previously described, height was evaluated in a linear mixed-effects model, to assess changes in the slope parameter (FAS only; **Supplementary Methods**).[23]

RESULTS

Patient disposition

Fifty-nine patients were enrolled, of which 58 were treated (33/34 and 25/25 patients in the R/I and ND cohorts, respectively; **Figure 1**). No patients with Ph+ CML-AP were enrolled. Nineteen

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(55.9%) patients in the R/I cohort and 10 (40%) patients in the ND cohort completed 66 cycles of treatment as per protocol; AE was the most common reason for treatment discontinuation (6/34 [17.6%] R/I cohort; 8/25 [32.0%] ND cohort).

Patient characteristics

In both cohorts, the median age was 13 years, and most patients were male (**Table 1**). In the R/I cohort, 31 (93.9%) patients had previously received imatinib and two (6.1%) patients had previously received dasatinib; three (9.1%) patients were intolerant of imatinib, 25 (75.8%) were resistant to imatinib, three (9.1%) patients were intolerant of and resistant to imatinib, and two (6.1%) were resistant to dasatinib. Of the 29 R/I cohort patients with evaluable mutational analyses at baseline, three had *BCR*::*ABL1* baseline mutations and none of the 25 ND patients had *BCR*::*ABL1* baseline mutations. At baseline, two patients in the R/I cohort and three ND patients had additional chromosomal abnormalities in Ph+ metaphases, and two R/I cohort patients had additional chromosomal abnormalities in Ph- metaphases.

Baseline median height SDS were -0.56 and 0.06 in the R/I and ND cohorts, respectively. At baseline, 24.2% (8/33) and 16.0% (4/25) of patients in the R/I and ND cohorts, respectively had completed pubertal development.

Nilotinib exposure

Median (range) time on treatment was 60.5 months (0.7 to 63.5 months) and 51.9 months (1.4 to 61.2 months) in the R/I and ND cohorts, respectively. The median (range) actual dose intensity in the R/I cohort was 436.9 mg/m^2/day (196.0 to 493.0 mg/m^2/day) representing a median (range) relative dose intensity of 95% (43 to 107%) compared to the planned dose of 230 mg/m^2 BID; actual and relative dose intensity in the ND cohort were 377.0 mg/m^2/day (149.0 to 468.0

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mg/m^2/day) and 82% (32 to 102%), respectively. Fifteen (45.5%) and eight (32.0%) patients in the R/I and ND cohorts, respectively, were exposed to nilotinib for ≥60 months.

Efficacy

At study conclusion, 20 (60.6%) R/I cohort patients were in MMR at least once (including seven patients who were in MMR at baseline), with a median time to first MMR of 2.8 months (95% CI: 0.0, 5.8); with the exclusion of patients in MMR at baseline the median time to first MMR was 5.6 months (95% CI: 2.8, 10.9). Similarly, 19 (76.0%) ND cohort patients achieved MMR, with a median time for first MMR of 5.6 months (95% CI: 5.5, 10.8). None of the 20 R/I cohort patients who achieved MMR had a confirmed loss of MMR by study completion; 3/19 (15.8%) ND cohort patients had a confirmed loss of MMR. Cumulative MMR rates are shown in **Figure 2**. In a post-hoc analysis, the cumulative molecular response MR^4 and MR$^{4.5}$ (*BCR*::*ABL1*^{IS} ≤0.01% and ≤0.0032%, respectively) rates by 66 cycles were 27.3% (9/33) and 12.1% (4/33; two patients were in MR^4 [one of which was in MR$^{4.5}$] at baseline) in the R/I cohort, respectively, and 56.0% (14/25) and 44.0% (11/25) in the ND cohort, respectively (**Figure 2**).

At baseline, 21 (63.6%) and 14 (42.4%) R/I cohort patients were in MCyR and CCyR, respectively. Twenty-eight (84.8%) patients were in MCyR by cycle 36 and 27 (81.8%) patients were in CCyR by cycle 48; rates remained the same until study conclusion. One R/I cohort patient progressed to BC after 10.1 months on treatment [21], after which no additional events of loss of CHR or CCyR, progression to AP/BC, or on-treatment death occurred. The K-M estimated rate of EFS was 96.3% (95% CI: 76.5, 99.5) at 12 months and remained unchanged until study completion.

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In the ND cohort, 21 (84.0%) patients were in CCyR by cycle 12 and until study completion; median time to first CCyR was 5.6 months (95% CI: 5.5, 5.6). One ND cohort patient had a confirmed loss of CCyR. One patient had confirmed loss of MCyR, and one patient temporarily matched the technical definition criteria for progression to AP/BC (i.e., the progression was not considered to be clinically notable based on clinical review due to temporary interruption of nilotinib treatment for 13 days during the first 28-day cycle owing to a prolonged QT event) solely on account of increased basophil cell count one month after the start of nilotinib, but continued treatment and was in CCyR by cycle 6. This patient discontinued nilotinib treatment due to hyperbilirubinemia after 13.8 months on treatment without losing CCyR. The K-M estimated rates of EFS at 12 months was 91.2% (95% CI: 69.0, 97.7) for the ND cohort, and remained unchanged until study completion.

While on treatment, no patients had emerging *BCR*::*ABL1* mutations. The median time to disease progression was not reached in either of the cohorts. The K-M estimated rates of disease progression on nilotinib at 12 months for the R/I and ND cohorts were 3.7% (95% CI: 0.5, 23.5) and 8.4% (95% CI: 2.2, 29.6), respectively, and remained so until the study completion. The median OS was not estimable. The K-M estimated rate of OS at 24 months was 96.9% (95% CI: 79.8, 99.6) for patients in the R/I cohort and remained unchanged until study completion. The K-M estimated rate of OS for patients in the ND cohort up to 24 months was 100% (95% CI: 100, 100), 95.5% (95% CI: 71.9, 99.3) at 48 months and 81.6% (95% CI: 50.4, 94.2) at 66 months.

Safety

All patients in both cohorts experienced at least one AE (any grade). Grade 3/4 AEs were observed in 60.6% (20/33) and 72.0% (18/25) of patients in the R/I and ND cohorts, respectively

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(**Table 2**). The most common AEs were increased blood bilirubin (R/I cohort: 48.5% [16/33]; ND cohort: 64.0% [16/25]) and headache (R/I cohort: 39.4% [13/33]; ND cohort: 60.0% [15/25]; **Table S1**). The most frequently reported (≥5%) grade 3/4 non-hematologic AEs were increased blood bilirubin (R/I cohort: 9.1%; ND cohort: 16.0%), increased alanine aminotransferase (ALT; R/I cohort: 12.1%; ND cohort: 12.0%), and rash (R/I cohort: 9.1%; ND cohort: 8.0%; **Table S1**). The most common grade 3/4 hematologic AEs reported in ≥5% of patients included anemia (6.1%) in the R/I cohort, and decreased neutrophil count (12.0%), decreased platelet count (8.0%) and neutropenia (8.0%) in the ND cohort.

AEs suspected to be related to study drug occurred in 87.9% (29/33) and 96.0% (24/25) of patients in the R/I and ND cohorts, respectively. The most frequently reported AEs suspected to be treatment related were increased blood bilirubin (48.5% [9.1% were grade 3/4] and 60.0% [16.0% were grade 3/4] in the R/I and ND cohorts, respectively) and increased ALT (30.3% [12.1% were grade 3/4] and 40.0% [12.0% were grade 3/4] in the R/I and ND cohorts, respectively; **Table S2**).

Serious AEs (SAEs) were reported in 11 (33.3%) R/I cohort patients and four (16.0%) ND cohort patients. One R/I cohort patient (grade 1 growth hormone deficiency) and two ND cohort patients (one patient experienced diarrhoea, abdominal pain, and rash [all grade 1], and one patient experienced QT prolongation [grade 1] and hyperbilirubinemia [grade 3]) had SAEs suspected to be study drug-related.

AESI are presented in **Table 3** and MedDRA preferred terms reported in ≥1 patient within each group term are shown in **Table S3**. Details of AESIs which occurred up to 48 cycles have previously been reported including three growth-related AEs [23]. Following the 48-cycle analysis,

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three additional ND cohort patients reported AESIs of increased blood cholesterol, increased blood glucose and fluid retention (one patient each).

No patient died during the study while on treatment. Four patients died during the survival follow-up phase of the study. One R/I cohort patient discontinued the study because of progression to BC and subsequently died of lymphoid blast crisis 8 months after the end of nilotinib treatment. Three ND cohort patients died; causes of deaths were due to CML, respiratory failure, and post-transplantation lymphoproliferative disorder (one patient each); all deaths occurred ≥1 year following the discontinuation of nilotinib, and all had subsequently received other antineoplastic therapy.

Nilotinib dose reductions and discontinuations

Twenty-one (63.6%) R/I cohort patients and 16 (64.0%) ND cohort patients required ≥1 dose reduction, and 21 (63.6%) R/I cohort patients and 20 (80.0%) ND cohort patients required ≥1 dose interruption. Twenty-two (66.7%) R/I cohort patients and 18 (72.0%) ND cohort patients required a dose reduction or interruption due to an AE. The most frequent (≥10% of patients) AEs requiring dose adjustment or interruption were increased blood bilirubin (24.2%), increased ALT (12.1%) and rash (12.1%) in the R/I cohort, and increased blood bilirubin (44.0%), increased aspartate aminotransferase (AST; 16%), increased ALT (16%), and vomiting (12.0%) in the ND cohort.

AEs led to treatment discontinuation in six (18.2%) R/I cohort patients, of which two patients had grade 3/4 AEs. Since the 48-cycle analysis, one additional patient in the R/I cohort had a treatment-related AE that led to study discontinuation (grade 1 bone pain). AEs led to treatment discontinuation in eight (32.0%) ND cohort patients (four had grade 3/4 treatment-related AEs);

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all occurred before cycle 48. Increased blood bilirubin was the most common AE associated with discontinuation (**Table S4)**.

Effect on growth and development

In both cohorts, there was a negative slope of height SDS indicating a deceleration of growth over time compared with baseline (**Figure 3A**); the same trend was observed in the prepubescent/pubescent subpopulation (**Figure S1**). At baseline, R/I cohort patients were relatively shorter than ND cohort patients and remained so throughout the study period. Median (range) height SDS at baseline and 66 cycles were -0.56 (-4.3, 1.2) and -1.8 (-5.2, 0.2), respectively in the R/I cohort, and 0.06 (-0.9, 1.7) and -1.0 (-2.0, 0.7), respectively in the ND cohort. Overall median (range) change from baseline in height SDS at 66 cycles was -0.7 SDS (-2.0, 0.4) and -0.7 SDS (-1.7, -0.6) in the R/I and ND cohorts, respectively. The estimated average loss of height SDS for each subsequent visit was 6% (6% of height SDS per 6 months) for patients in the R/I cohort and 9% for patients in the ND cohort ($P<0.0001$ for both); corresponding values for the prepubescent/pubescent subpopulation were 7% and 9%. Height velocity SDS was relatively constant until end of treatment (cycle 66) and the median was always below the 50th percentile of the reference population (SDS 0) for both cohorts (**Figure 3B**); the same trend was observed for the prepubescent/pubescent subpopulation (**Figure S1**).

Eight prepubescent/pubescent patients had a height SDS drop crossing ≥2 main percentile lines (**Table S5**). Three patients had growth deceleration AEs suspected to be related to nilotinib exposure, all of which were reported at the cycle 48 analysis [23]. Two patients with height decreases of ≥1 main percentile line experienced AEs which were ongoing at the last assessment date; one ND cohort patient had a grade 2 AE of growth retardation and one R/I cohort patient

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had grade 1 AEs of growth hormone deficiency and body height below normal. One R/I cohort patient who did not have a height decrease crossing a main percentile line had an AE of grade 1 growth retardation; height SDS had improved by the end of the study compared with baseline.

In a model-based analysis, changes in height were evaluated considering the covariates of age, pubertal status (as a baseline and time-dependent variable) and gender (**Table S6**). In both cohorts, the estimated average loss of height SDS was statistically significantly higher in younger patients (<12 years vs ≥12 years). There was no difference in estimated average loss of height SDS by baseline pubertal status (prepubertal vs post-pubertal) but as a time-dependent variable, the loss of height SDS was higher during the prepubertal vs post-pubertal period in the ND cohort, but not in the R/I cohort. This finding should be interpreted with caution considering that only four patients in the ND cohort were prepubertal at baseline. The estimated average loss of height SDS was statistically significantly higher in female patients of the R/I cohort, but not in the ND cohort.

No clear trend was observed for BMI SDS (**Figure S2**), bone age SDS (**Table S7**), bone density (**Figure S3**) or thyroid function. Among patients at risk of delayed puberty at treatment initiation, no patients experienced delayed puberty.

DISCUSSION

The final analysis of the DIALOG study demonstrated long-term (up to 66 cycles) efficacy and safety of nilotinib in pediatric patients with R/I or ND Ph+ CML-CP. The clinical activity and safety of nilotinib 230 mg/m^2 BID in pediatric patients with R/I or ND Ph+ CML-CP has previously been reported up to cycle 24,[21] and further safety data were reported after ≥36 and

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≥48 cycles.[22,23] To our knowledge, this final analysis is the longest follow-up of pediatric patients with CML-CP receiving treatment with a TKI.

Previous efficacy analyses reported that MMR was achieved by 39.4% of R/I patients at cycle 6 (R/I cohort primary endpoint) and the cumulative MMR rate by cycle 24 was 57.6%; among ND patients, the cumulative MMR rates were 64.0% and 68.0% by cycles 12 (ND cohort primary endpoint) and 24, respectively.[21] In this final analysis with a median treatment duration of approximately 5 years, the MMR rate was sustained with best MMR rates of 60.6% and 76.0% in the R/I and ND cohorts, respectively; no patients in the R/I cohort and only three patients in the ND cohort lost MMR during the study, confirming the sustained efficacy of nilotinib in these patient populations. In addition, by study conclusion, MR^4 and $MR^{4.5}$ had been achieved by 27.3% and 12.1% of patients in the R/I cohort, and 56.0% and 44.0% of patients in the ND cohorts. Furthermore, secondary endpoints of MCyR, CCyR and EFS remained consistent from the previous analysis[21] supporting the sustained efficacious benefit of nilotinib. Furthermore, the efficacy of nilotinib observed in pediatric patients with ND CML-CP after approximately 5 years of treatment is similar to what has been observed in adult patients.[30]

The DIALOG study's outcomes for patients receiving first-line nilotinib are comparable to those of pediatric patients receiving first-line imatinib and dasatinib. The ND cohort in this study had a CCyR rate of 84% by month 12 and an MMR rate of 76% by month 36; both rates were maintained until the end of the study. CCyR and MMR rates at 12 months in a French National phase IV trial of imatinib-treated pediatric patients with ND CML-CP were 61% and 31%, respectively, with an estimated MMR rate at 36 months of 71%.[16] Between 25% and 29% of pediatric patients with CML treated with imatinib will discontinue therapy due to a poor response or toxicity[16,31] and current alternative TKI therapy for these patients include dasatinib

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and nilotinib. In a phase II, open-label, nonrandomized prospective trial of pediatric patients receiving dasatinib, CCyR and MMR rates by 12 months in the ND cohort were 92% and 52%, respectively.[32] In the R/I cohort of the DIALOG study, the cumulative MMR rate by 12 months was 57.6% and 60.6% of patients were in MMR at least once during the study. These rates are comparable to those observed in a phase II prospective trial evaluating dasatinib treatment in pediatric patients in which 41% and 55% of patients with imatinib resistant/intolerant CML treated with dasatinib achieved MMR by 12 and 24 months, respectively.[32] Compared with previous studies of TKI treatment in pediatric patients with CML-CP, the DIALOG data presented are from a longer observation period; it is important to note that there were no patients with emergent mutations.

In this final analysis, the safety profile of nilotinib was consistent with previous reports.[21,23] No new safety signals were reported. Adult patients treated with nilotinib have a higher risk of elevated glucose and cardiovascular events compared with imatinib-treated patients.[33] In this pediatric study, no cardiovascular events were observed, and no grade 3/4 events of increased blood glucose were reported. The DIALOG study protocol included a glucose/HbA1c increase and cardiovascular events risk management plan for whilst the study was ongoing, however, no risk management plan for after study completion was provided. As noted in the previous safety analysis,[23] AESIs of elevated bilirubin and liver enzymes were more common among pediatric patients compared with adults. Overall, in the DIALOG study, 14 patients discontinued treatment due to an AE, of which 11 had discontinued by 24-cycles[21] and three patients discontinued after, suggesting that the majority of AEs leading to treatment discontinuation appear early during treatment with nilotinib.

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Previously, a growth deceleration trend was noted in the DIALOG study[22,23] and although the proportion of patients with reported growth retardation AEs was low, data continue to show a negative slope in height SDS in both cohorts. Similar studies of imatinib- and dasatinib-treated pediatric patients support this observation.[18,20] Earlier pediatric studies of patients with CML treated with a TKI have reported the impact of pubertal age on growth impairment with conflicting results.[17-19] In a subpopulation analysis of patients considered to be at increased risk of growth impact (prepubescent or pubescent patients) in the DIALOG study, height velocity SDS was relatively constant until the end of the study and eight patients experienced a decrease in growth of two main percentile lines. As noted previously, growth deceleration may have already occurred in R/I cohort patients prior to enrollment in the study and a high proportion of ND cohort patients were pubertal.[23]

In conclusion, this final analysis of the DIALOG study of nilotinib treatment up to 66 cycles demonstrated sustained long-term efficacy in pediatric patients with CML-CP in both the R/I and ND patient cohorts. The safety profile in both cohorts was consistent with previously reported safety results for nilotinib in pediatric patients. The trend towards growth deceleration, that was first observed during the 36-cycle analysis[22] and confirmed at the 48-cycle analysis,[23] is further supported by this long-term analysis. The overall benefit-risk assessment of nilotinib use in pediatric patients with ND Ph+ CML-CP or with Ph+ CML-CP R/I to either imatinib or dasatinib remains favorable and nilotinib is an additional valuable treatment option for pediatric patients with CML-CP.

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AUTHORSHIP

Contributions

Nobuko Hijiya designed the study and all authors contributed to data acquisition and interpretation, writing the manuscript, and review and approval of the final manuscript.

Data sharing statement

Novartis is committed to sharing with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. Trial data availability is according to the criteria and process described on www.clinicalstudydatarequest.com.

Conflict of interest disclosure

N.H. has received research funding from Novartis and Pfizer, served on the data monitoring committee for Incyte and Novartis, participated on an advisory board for Stemline Therapeutics and has been a consultant for Novartis. A.M. reports receiving lecture fees from Novartis.

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Hiroaki Goto reports receiving lecture fees from Novartis. Z.K. reports receiving grants from Novartis. C.M.Z. reports serving as a consultant to Novartis and has obtained institutional funding from Bristol Myers Squibb and Pfizer for the development of other CML therapies. J.S. reports serving as a consultant to Novartis, Bristol-Meyers-Squibb and Tolmar Pharmaceuticals and has received speaker fees from Tolmar Pharmaceuticals. M.I. and S.L. report employment at and ownership of stock in Novartis. K.T. reports employment at Novartis. C.R., H.S., C.D., H.J.K., T.G., F.B., S.D., K.H.Y., F.M., B.P., and D.S. have no conflicts of interest to disclose.

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TABLES

Table 1. Baseline characteristics

	R/I cohort* N=33	ND cohort N=25
Median age (range), years	13 (2–17)	13 (10–16)
Patients aged 1 to <12 years, n (%)	12 (36.4)	6 (24.0)
Patients aged 12 to <18 years, n (%)	21 (63.6)	19 (76.0)
Female, n (%)	12 (36.4)	12 (48.0)
Male, n (%)	21 (63.6)	13 (52.0)
Median BMI SDS, (range)	-0.57 (-3.4–3.4)	-0.09 (-2.8–2.1)
Median Height SDS, (range)	-0.56 (-4.3–1.2)	0.06 (-0.9–1.7)
Pubertal status, n (%)		
Tanner stage 1 (Prepubertal)	9 (27.3)	4 (16.0)
Tanner stage 2–4	15 (45.5)	17 (68.0)
Tanner stage 5†	8 (24.2)	4 (16.0)
Missing, n (%)	1 (3.0)	0
Prior antineoplastic TKI therapies, n (%)		
Imatinib	31 (93.9)	N/A
Dasatinib	2 (6.1)	N/A
Intolerant of imatinib/dasatinib, n (%)‡	6 (18.2)/0	N/A
Resistant to imatinib/dasatinib, n (%)‡	28 (84.8)/2 (6.1)	N/A
BCR::ABL1^{IS}, n (%)		
≤0.0032	1 (3.0)	0
>0.0032 to ≤0.01	1 (3.0)	0
>0.01 to ≤0.1	5 (15.2)	0
CCyR at baseline, n (%)	14 (42.4)	0
Known *BCR::ABL1* mutation at baseline, n/m§	3/29	0/25

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Presence of other chromosomal abnormalities in Ph+ metaphases, n (%)	2 (6.1)‖	3 (12.0)¶
Presence of chromosomal abnormalities in Ph- metaphases, n (%)	2 (6.1)#	0

BMI, Body mass index; CML, chronic myeloid leukemia; CP, chronic phase; IS, international scale; ND, newly diagnosed CML-CP; N/A, not applicable; Ph, Philadelphia chromosome; R/I, imatinib/dasatinib resistant/intolerant CML-CP; TKI, tyrosine kinase inhibitor.

*Patients were resistant to and/or intolerant of one prior TKI, either imatinib or dasatinib.

†Patients had completed puberty before study enrollment.

‡Three patients were both intolerant of and resistant to imatinib and are counted once as resistant and once as intolerant.

§Numerator (n) is the number of patients with known baseline mutations. Denominator (m) is the number of patients with an evaluable baseline mutational assessment. Mutations detected at baseline were E255K and E255V in 1 patient, G250E and E255K in 1 patient, and L387M in 1 patient.

‖Data were available for 30 R/I patients. The abnormalities in Ph+ metaphases were 47,XX, t(9,22)(Q34;Q11.2), +der(22)t(9;22)[18]/46, XX[2] in 1 patient and a 3-way translocation between chromosome 4, 9 and 22 in 1 patient.

¶The abnormalities in Ph+ metaphases were chromosome 3 abnormality in 1 patient, 46,IDEM,add(14)(Q22) OR inv(14)(Q22Q32)[14] in 1 patient, and trisomy 19 in 1 patient.

#Data were available for 30 R/I patients. The abnormalities in Ph- metaphases were 46, XX, del(17)(p?) and t(11;17) (1 patient each).

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Table 2. Safety Summary

AE, n (%)	R/I cohort N=33		ND cohort N=25		All patients N=58	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Any AE	33 (100)	20 (60.6)	25 (100)	18 (72.0)	58 (100)	38 (65.5)
AEs suspected to be treatment-related	29 (87.9)	16 (48.5)	24 (96.0)	17 (68.0)	53 (91.4)	33 (56.9)
AEs leading to discontinuation	6 (18.2)	2 (6.1)	8 (32.0)	4 (16.0)	14 (24.1)	6 (10.3)
AEs leading to dose adjustment or interruption[*]	22 (66.7)	15 (45.5)	18 (72.0)	16 (64.0)	40 (69.0)	31 (53.4)
SAEs	11 (33.3)	7 (21.2)	4 (16.0)	3 (12.0)	15 (25.9)	10 (17.2)
SAEs suspected to be treatment-related	1 (3.0)[†]	0	2 (8.0)[‡]	1 (4.0)	3 (5.2)	1 (1.7)
All deaths[§]	1 (3.0)[‖]	-	3 (12.0)[¶]	-	4 (6.9)	-

AE, adverse event; CML, chronic myeloid leukemia; CP, chronic phase; ND, newly diagnosed CML-CP; R/I, imatinib/dasatinib resistant/intolerant CML-CP; SAE, serious AE.

[*]A patient with multiple reasons for dose reduction or interruption is only counted once; [†]One patient had an SAE of grade 1 growth hormone deficiency; [‡]One patient had diarrhea, abdominal pain, and rash (all grade 1) and one patient had grade 1 QT prolongation and grade 3 hyperbilirubinemia; [§]Includes deaths which occurred during the treatment and survival follow-up periods. No deaths occurred during nilotinib treatment; [‖]Reason for death was study indication which occurred during the follow-up period; [¶]Reasons for death were study indication, respiratory failure, and post transplantation of lymphoproliferative disorder (one patient each) all of which occurred during the follow-up period.

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Table 3. AESIs

AE, n (%)	R/I cohort N=33		ND cohort N=25		All patients N=58	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Increased blood cholesterol	3 (9.1)	0	3 (12.0)	1 (4.0)	6 (10.3)	1 (1.7)
Increased blood glucose	2 (6.1)	0	1 (4.0)	0	3 (5.2)	0
Fluid retention	2 (6.1)	0	5 (20.0)	1 (4.0)	7 (12.1)	1 (1.7)
Oedema and other fluid retention	2 (6.1)	0	5 (20.0)	1 (4.0)	7 (12.1)	1 (1.7)
Growth retardation	2 (6.1)	0	1 (4.0)	0	3 (5.2)	0
Hepatotoxicity	19 (57.6)	9 (27.3)	17 (68.0)	7 (28.0)	36 (62.1)	16 (27.6)
Drug induced liver injury	1 (3.0)	1 (3.0)	0	0	1 (1.7)	1 (1.7)
Hepatic transamine and bilirubin elevations	19 (57.6)	8 (24.2)	17 (68.0)	7 (28.0)	36 (62.1)	15 (25.9)
Myelosuppression (Thrombocytopenia)	1 (3.0)	0	8 (32.0)	3 (12.0)	9 (15.5)	3 (5.2)
QT prolongation*	5 (15.2)	0	3 (12.0)	0	8 (13.8)	0
Rash	16 (48.5)	5 (15.2)	15 (60.0)	3 (12.0)	31 (53.4)	8 (13.8)

AE, adverse event; AESI, AEs of special interest CML, chronic myeloid leukemia; CP, chronic phase; ND, newly diagnosed CML-CP; PT, preferred term; R/I, imatinib/dasatinib resistant/intolerant CML-CP.

A patient with multiple severity grades for an AE was counted only under the maximum grade. No events were reported for the following AESI group terms: "cardiovascular event" (including ischemic cerebrovascular events, ischemic heart disease, peripheral arterial occlusive disease, and other cardiovascular events); "cardiac failure"; "pancreatitis, lipase, and amylase elevations"; "renal events"; or "significant bleeding" (including central nervous system or gastrointestinal hemorrhage).

*MedDRA PT included syncope for 1 patient and QT prolonged for 7 patients (reported in Hijiya et al[21]).

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FIGURE LEGENDS

Figure 1. Study design and patient disposition

AE, adverse event; AP, accelerated phase BID, twice daily; CML, chronic myeloid leukemia; CP, chronic phase; CRF, case report form; Ph+, Philadelphia chromosome positive.

[a]The study design includes a third cohort to recruit patients with CML-AP resistant or intolerant to imatinib or dasatinib. No patients were enrolled in this cohort; [b]Nilotinib was administered at a dose of 230 mg/m^2 twice daily (rounded to the nearest 50 mg, to a maximum dose of 400 mg) based on the recommended dose for adults of 400 mg twice daily, scaled to body surface area. At any time, discontinuation was allowed due to patient/investigator decision or due to unacceptable toxicities, disease progression, protocol deviations resulting in a significant risk to the patient's safety, use of prohibited treatments, or pregnancy. Patients who discontinued the treatment early were contacted for study evaluation completion and survival status; [c]One enrolled patient did not receive any study medication; [d]Administrative problems were 4 cases of "lack of efficacy" (2 in each cohort), 1 case of "lack of study compliance by patient" (resistant/intolerant imatinib/dasatinib Ph+ CML-CP cohort) and 2 cases of "new cancer therapy" (1 in each cohort) (the CRF does not have separate reasons for discontinuation for such cases, the information was thus voluntarily stored under the category "administrative problem"); [e]Protocol deviations were two cases of non-compliance.

Figure 2. Cumulative incidence of (A) MMR, (B) MR^4 and (C) MR$^{4.5}$ by cohort

CML, chronic myeloid leukemia; CP, chronic phase; K-M, Kaplan-Meier; MMR, major molecular response (*BCR::ABL1*^{IS} ≤0.1%); MR^4, molecular response 4 (*BCR::ABL1*^{IS} ≤0.01%); MR$^{4.5}$, molecular response 4.5 (*BCR::ABL1*^{IS} ≤0.0032%); ND, newly diagnosed; R/I, resistant or intolerant.

In the R/I cohort at baseline, 7 patients were in already in MMR, 2 patients were were already in MR^4 and one patient was already in MR$^{4.5}$ hence the K-M curves start at 21%, 6% and 3% from day 0, respectively.

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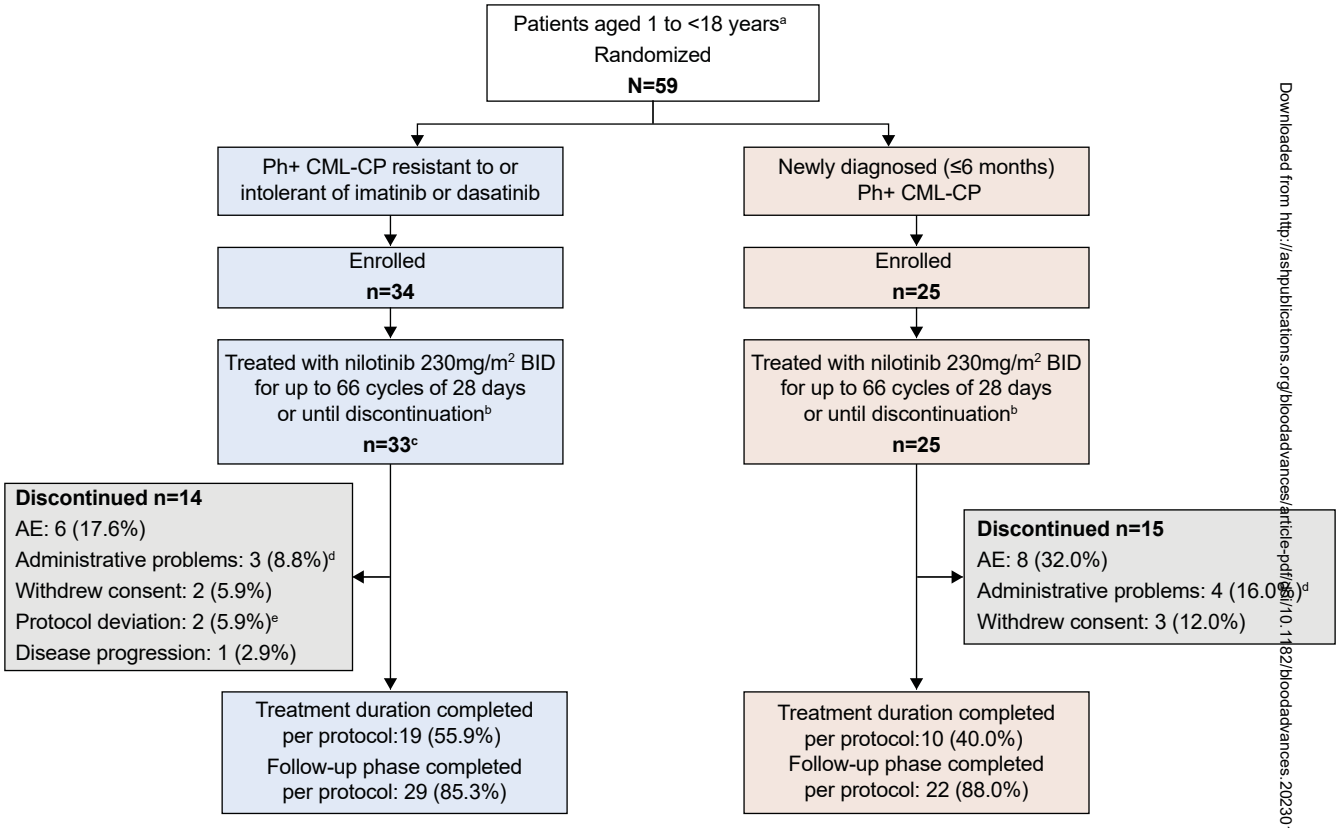
Figure 3. Height SDS (A) and height velocity SDS (B) over time by cohort (FAS)

CML, chronic myeloid leukemia; CP, chronic phase; FAS, full analysis set; ND, newly diagnosed; Ph+, Philadelphia chromosome-positive; R/I, resistant or intolerant; SD, standard deviation; SDS, standard deviation scores.

Plot shows boxes (25^{th}–75^{th} percentiles) with median as horizontal line. The dots in the boxes and joining lines represent mean values. Whiskers extend to 10^{th} and 90^{th} percentiles. Values outside this range are not displayed.

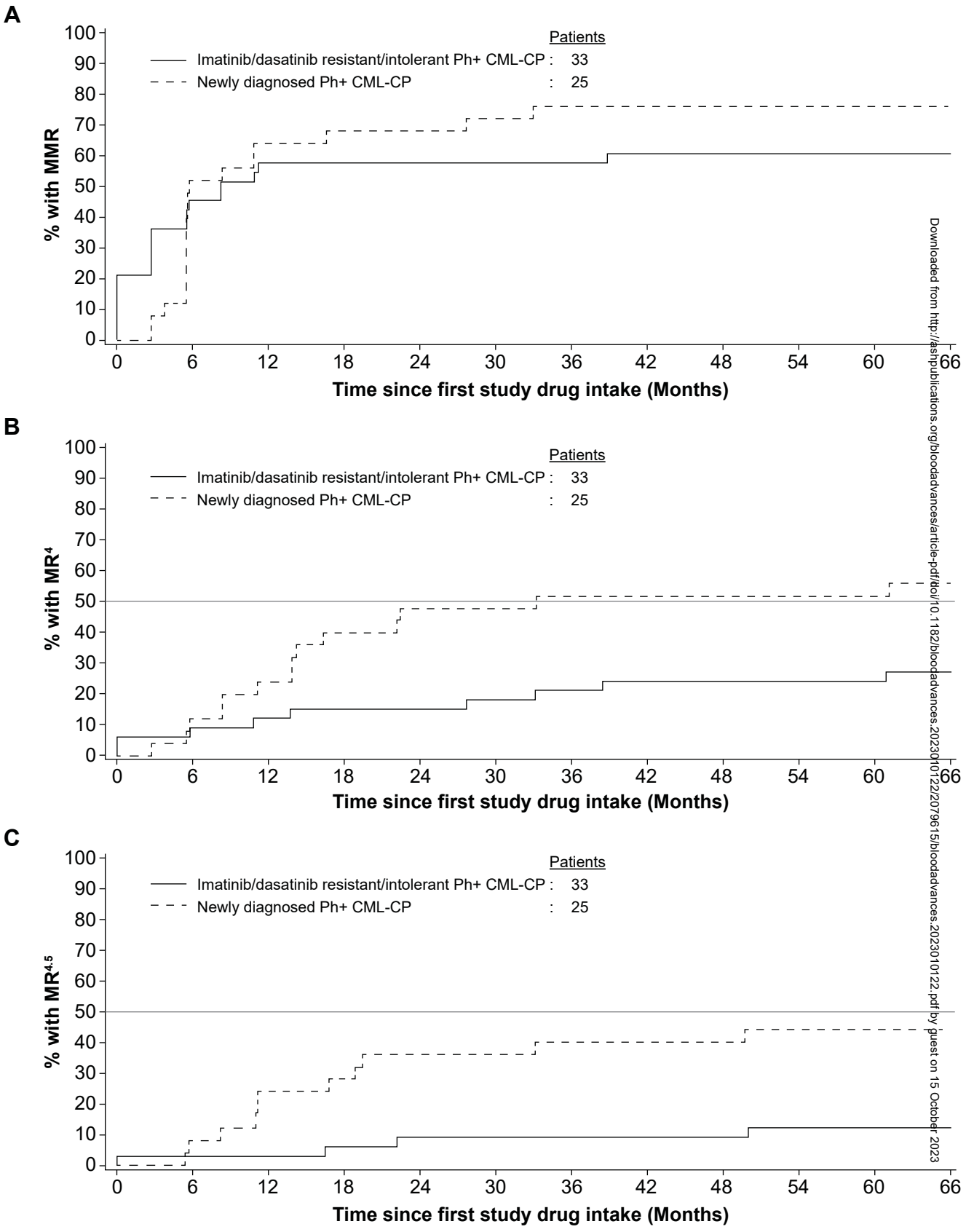
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Figure 1



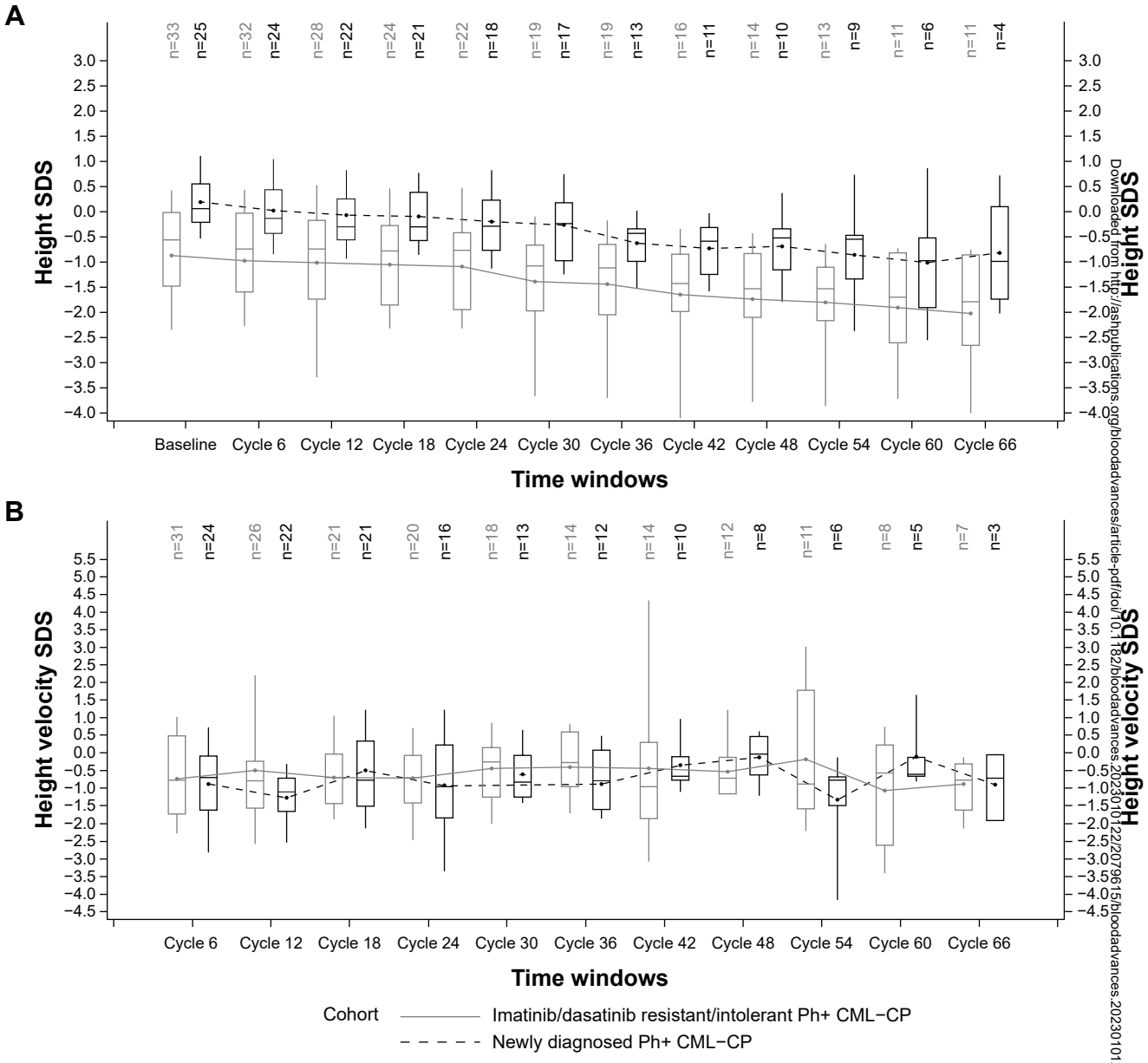
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Figure 2



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Figure 3



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