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Treatment-Free Remission in Chronic Phase Chronic Myeloid Leukemia After Nilotinib De-Escalation: 96-Week Update of the DANTE Study

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ABSTRACT

Treatment-free remission (TFR) in chronic myeloid leukemia (CML) can be considered for patients in sustained deep molecular response (DMR) who can discontinue tyrosine kinase inhibitors (TKIs) while maintaining responses. Studies suggest that TKI de-escalation before TFR is feasible. This phase II study evaluated nilotinib de-escalation outcomes in adults with CML in chronic phase (CP) treated with first-line nilotinib for ≥ 3 years and in sustained DMR for ≥ 1 year. The study had four phases: screening, de-escalation (week 0–48), TFR (week 48–144) and follow-up. During de-escalation, patients received nilotinib 300 mg once daily, and those with sustained DMR entered TFR and discontinued nilotinib. Patients with major molecular response (MMR) but without sustained DMR continued nilotinib. At the data cut-off, 107 patients entered, and 98 (91.6%) completed de-escalation. TFR was entered by 90 patients (84.1%) with sustained DMR. At 96 weeks, 71/107 patients (66.4%) were in full TFR; 64/90 patients (71.1%) who entered TFR remained in ≥ MMR, and the median time-to-loss of MMR was not reached. During TFR, adverse events occurred in 64 patients (71.1%), including one serious event (pneumonia). Our data suggest that the de-escalation of nilotinib before a TFR attempt in CML-CP patients with sustained DMR can be a successful dose optimization strategy.

1 | Introduction

Chronic myeloid leukemia (CML) is characterized by the presence of the *BCR::ABL1* fusion gene on the Philadelphia chromosome [1]. This gene produces the BCR::ABL1 tyrosine kinase, which results in leukemia cell proliferation [2]. CML usually presents in chronic phase (CP), in which the clonal expansion of mature myeloid cells leads to an elevated white blood cell count [3]. The annual incidence of CML ranges from 0.4 to 1.75/100,000, and the median age at diagnosis is 57–60 years [4]. The prevalence of CML is estimated to be 10–12/100,000 and is increasing due to considerable improvements in patient survival [4].

The optimal front-line treatment for patients with CML-CP is the subject of active clinical evaluation but involves *BCR::ABL1* tyrosine kinase inhibitors (TKIs), namely imatinib, nilotinib, dasatinib, and bosutinib [5]. Outcomes for patients with CML have vastly improved with the introduction of TKIs, with life expectancy reaching that of healthy age-matched individuals [6]. However, the adverse effects and costs associated with lifelong TKI treatment considerably affect patients' quality of life, ultimately impacting treatment adherence and response [7–10].

This has led to a focus on whether it is possible to discontinue treatment in certain patients to mitigate adverse effects and financial burdens [11]. Furthermore, female patients who are pregnant or planning to become pregnant may benefit from stopping TKIs to reduce the risk of teratogenic effects [12]. Because of the success of TKIs, treatment discontinuation became a new goal of therapeutic projects: indeed, many studies have shown that 40%–70% of patients with sustained deep molecular response (DMR) can safely discontinue TKIs without hematological relapse [13–19]. The 2020 European LeukemiaNet recommendations state that discontinuation of TKIs may be considered in CML patients with durable DMR with the goal of achieving treatment-free remission (TFR) [20]. However, there is a need to make both patients and clinicians more confident about TKI discontinuation, and this may be achieved by adopting a step-by-step approach in which patients are treated with a lower dose of a TKI during a DMR de-escalation period before the TFR phase. A study investigating imatinib de-escalation before TFR in patients with CML-CP suggests that this stepwise approach is feasible [17]. Reduced-dose TKI and TFR might also reduce the risk of cardiovascular events, which is higher with second- and third-generation TKIs compared with imatinib [21].

Nilotinib is a second-generation TKI that has been designed to be more selective against the *BCR::ABL1* tyrosine kinase than imatinib [22]. Although nilotinib is the first and only TKI approved for stopping therapy in patients with CML-CP [23], nilotinib-based TFR optimization strategy has not been formally studied.

Our phase II study (DANTE) aimed to assess the effect of reduced-dose nilotinib (to half the standard dose) for 12 months in patients in TFR in patients with CML-CP treated with first-line nilotinib who reached a sustained DMR before entering the study. An interim analysis involving 40 patients with sustained DMR who entered the TFR phase showed that 67.5% of patients remained in major molecular response (MMR) or better 1 year after stopping nilotinib [24]. Here we present the final results from 90 patients who successfully completed nilotinib de-escalation and ≥ 1 year of TFR.

2 | Materials and Methods

2.1 | Study Design and Patients

This prospective, single-arm, phase II study (NCT03874858) enrolled patients with CML-CP at 27 centers in Italy. Key eligibility criteria included patients aged ≥ 18 years with a diagnosis of CML-CP according to World Health Organization criteria treated with first-line nilotinib 300 mg twice daily (bid) for ≥ 3 years who achieved sustained DMR for ≥ 1 year (Supporting Information S1: Table S1). Sustained DMR was defined as a molecular response ≥ 4.0 logs ($MR^{4.0}$; i.e., *BCR::ABL1/ABL1* international scale [IS] ≤ 0.01%) in all of the last four *BCR::ABL1* real-time quantitative reverse transcription polymerase chain reaction (qRT-PCR) assessments with an interval between each assessment of 3–6 months. Inclusion criteria also included Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2. Key exclusion criteria included having a known atypical transcript, previous treatment resistance dose reductions/interruptions due to neutropenia or thrombocytopenia in the past 6 months, or impaired cardiac function (Supporting Information S1: Table S1).

The study consisted of four phases: screening (week −4 to week 0), nilotinib de-escalation (week 0–48), TFR (week 48–144), and follow-up (until week 144; Figure 1). Ongoing treatment with nilotinib ≥ 400 mg/day was allowed at study entry. During nilotinib de-escalation, patients were treated with nilotinib 300 mg once daily orally. At the end of the nilotinib de-escalation phase, patients with sustained DMR entered the TFR phase and nilotinib was discontinued. Patients with a major molecular response (MMR; defined as *BCR::ABL1/ABL1* ≤ 0.1% IS) but without sustained DMR continued nilotinib 300 mg once daily. At any time, patients with loss of MMR returned to nilotinib 300 mg bid. During the TFR phase, *BCR::ABL1* levels were monitored monthly from week 52–96 and then every 3 months thereafter. During the follow-up phase, patients who remained on a half-dose of nilotinib after week 48 and patients with loss of MMR at any time during the study were monitored every 3 months until week 144.

The DANTE trial was designed, implemented, and reported in accordance with the International Council for Harmonization Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki. The protocol and proposed informed consent form were reviewed and approved by a properly constituted

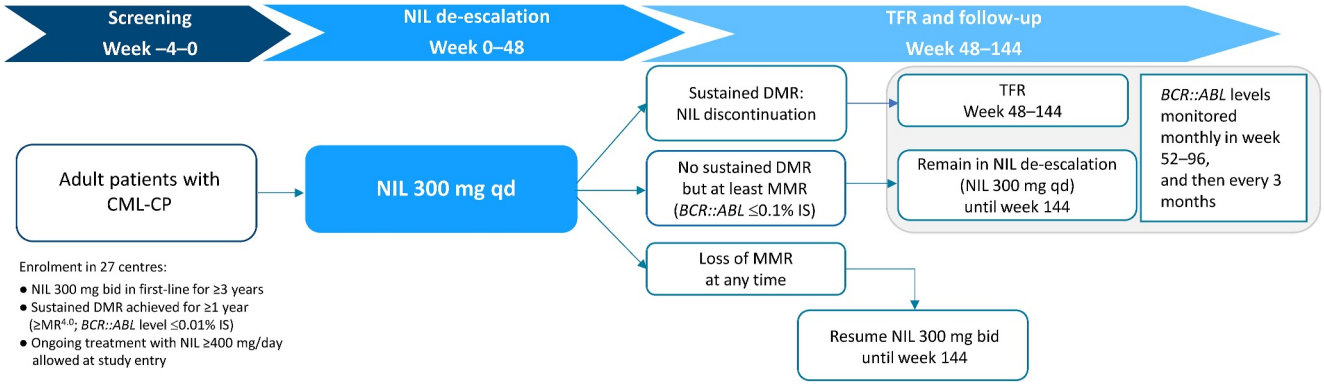

FIGURE 1 | Study design. Bid, twice daily; CML-CP, chronic myeloid leukemia in chronic phase; DMR, deep molecular response; IS, international scale; MMR, major molecular response; MR, molecular response; NIL, nilotinib; TFR, treatment-free remission; qd, once daily.

Independent Ethics Committee before the start of the study. Written informed consent was obtained from each patient.

2.2 | Outcomes

The primary objective was to determine the percentage of patients in full TFR (FTFR) 96 weeks after the start of the de-escalation phase. FTFR was defined as patients with MMR or better who remained in discontinuation during the TFR phase or were treated with half the standard dose of nilotinib. The study also explored whether suspending nilotinib or maintaining nilotinib at half the standard dose for those patients not eligible for TFR does not cause short- or long-term harm. The transcription levels of *BCR::ABL1* were evaluated using standardized qRT-PCR.

Secondary objectives included: the proportion of patients who remained in sustained DMR at the end of the de-escalation phase (week 48); the proportion of patients who remained in DMR at the end of the de-escalation phase (week 48) and at 96 weeks after the start of the de-escalation phase; the proportion of patients with MMR or better at the end of the de-escalation phase (week 48) and at 96 weeks after the start of the de-escalation phase, regardless of whether they required reinitiation of treatment. Finally, safety was also investigated during the nilotinib de-escalation phase, TFR phase, and reinitiation of treatment with nilotinib.

Adverse events (AEs) were assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. Severe AEs were defined as CTCAE grade 3–4. Serious AEs were defined as those that were fatal or life-threatening, resulted in persistent or significant disability/incapacity, resulted in congenital anomaly, or required inpatient hospitalization. AEs of special interest (AESI) were defined as events (serious or non-serious) that were of scientific and medical concern specific to the sponsor's product or program. These events were blood cholesterol increased, blood glucose increased, fluid retention, hepatic transaminase/bilirubin elevations, musculoskeletal pain, rash, and thrombocytopenia (Supporting Information S1: Table S2).

2.3 | Statistical Analysis

Demonstration of successful FTFR of nilotinib was evaluated using the following hypotheses: H0: $p \leq 0.50$, and H1: $p > 0.50$, where P is the proportion of patients in successful FTFR 96 weeks after the start of the consolidation phase, computed as defined above. The null hypothesis was rejected, and successful FTFR was demonstrated if the lower limit of the 95% confidence interval (CI) was greater than 0.50. The study was designed with 80% power to test the null hypothesis that the rate of MMR or better at 96 weeks after the start of the study was $p \leq 0.50$. The sample size was based on the one-sided exact binomial test. If the true rate was $p \geq 0.65$, a minimum of 93 patients would be required to test the null hypothesis H0: $p \leq 0.5$, with a one-sided alpha level of 2.5% and a power of 80%. Considering a dropout rate of 10% during the study, approximately 103 patients would have to be enrolled into the trial.

For patients with loss of MMR during TFR, the time to loss of MMR was computed in months as follows: date of *BCR::ABL1* qRT-PCR assessments with loss of MMR minus baseline date of TFR (i.e. end date of previous period plus one day) plus one day. Patients without loss of MMR during TFR were censored at the end date of TFR or at the cut-off date, whichever occurred first. The median time to event/censor and its corresponding two-sided 95% CI was estimated using the Kaplan–Meier product-limit method and presented as a Kaplan–Meier plot.

The primary efficacy analysis was performed on the full analysis set (FAS), defined as all patients who received at least one dose of study treatment. The safety set included all patients who received at least one dose of study treatment. Demographic and other baseline data are summarized descriptively for the FAS. Categorical data are presented as numerical frequencies and proportions of patients. For continuous data, mean, standard deviation, median, interquartile range (IQR), and range are presented.

Here, we report updated results collected until the cut-off date of 8 February 2023, when all patients who entered the TFR phase had completed ≥ 1 year (48 weeks) of TFR, switched to full dose nilotinib, entered in follow-up, or discontinued the study.

3 | Results

3.1 | Patient Disposition

Overall, 113 patients were screened and 107 entered the nilotinib de-escalation phase and were included in the FAS (Figure 2). Among these 107 patients, the median age was 52 years, 57% were male, and 104 (97.2%) had an ECOG PS score of 0 (Table 1). The nilotinib de-escalation phase was completed by 98 patients (91.6%), while 9 patients (8.4%) discontinued permanently due to patient decision ($n = 4$), AEs ($n = 3$) or loss of MMR ($n = 2$). A total of 90 patients (84.1%) with sustained DMR at week 48 entered the TFR phase, while 8 patients (7.5%) maintained MMR but did not sustain DMR and entered the nilotinib half-dose period (7 of these patients were in FTFR at 96 weeks).

3.2 | Efficacy

Of the 90 patients who entered the TFR phase, 64 (71.1%) remained in MMR or better after a median duration of 20.4 months (IQR 1.9–32.4). Of the remaining 26 patients (28.9%) who discontinued the TFR phase, 22 had a loss of MMR (which mostly occurred during the first 5 months), 3 did so by choice (patient decision), and 1 did so due to AEs. The median time-to-loss of MMR in the TFR phase was not reached (Figure 3); in the TFR phase, the median time until loss of MMR was 3.6 months (IQR 2–19). At the 1-year data cut-off (8 February 2023), 71 patients (66.4%) were in FTFR at 96 weeks after the start of the nilotinib de-escalation phase (the 64 patients who entered the TFR phase and remained in MMR or better plus the 7 patients who entered the nilotinib half-dose period mentioned above); the 66.4% FTFR achieved the primary endpoint because the threshold of 50% was exceeded.

Of the 24 patients who restarted nilotinib after MMR loss (2 patients from the de-escalation phase and 22 from the TFR phase), 23 (95.8%) regained MMR after a median (IQR) of 11.0 (4.1–22.7) weeks and achieved $MR^{4.0}$ after a median (IQR) of 16.4 (4.7–40.1) weeks. The 24th patient did not achieve MMR or better. $MR^{4.5}$ was regained by 20 patients (83.3%) after a median of 25.8 weeks (IQR 8.1–67.7).

Fifty-two of the 107 patients who entered the nilotinib de-escalation phase (48.6%) remained in sustained DMR from the de-escalation phase until week 96. No deaths or cases of disease progression were observed.

3.3 | Safety

AEs of any grade that occurred at any time point during the study were observed in 81/107 patients (75.7%; Table 2). 20 patients (18.7%) had Grade 3 or 4 (severe) AEs, AEs, 6 (5.6%) had serious AEs, 46 (43.0%) had AESI, 27 (25.2%) had study drug-related AEs, 12 (11.2%) had AEs leading to dose adjustment/temporary interruption, and 7 (6.5%) had AEs leading to permanent discontinuation of therapy.

During the nilotinib de-escalation phase, AEs of any grade were observed in 44 of 107 patients (41.1%; Table 2). The most common AEs by system organ class during de-escalation were autoimmune musculoskeletal and connective tissue disorders (12.2%). 10 patients (9.4%) had severe AEs, and 5 patients (4.7%) had serious AEs (unstable angina, myocardial ischemia, COVID-19 pneumonia, skin ulcer, acetabulum fracture, femur fracture and separation of the pubic symphysis [some patients had more than one event]). Two serious AEs (grade 3 myocardial ischemia and grade 4 unstable angina) were considered related to nilotinib treatment; both events were resolved with no intervention and permanent nilotinib discontinuation, respectively. Eighteen patients (16.8%) had AESI, 16 (15.0%) had study

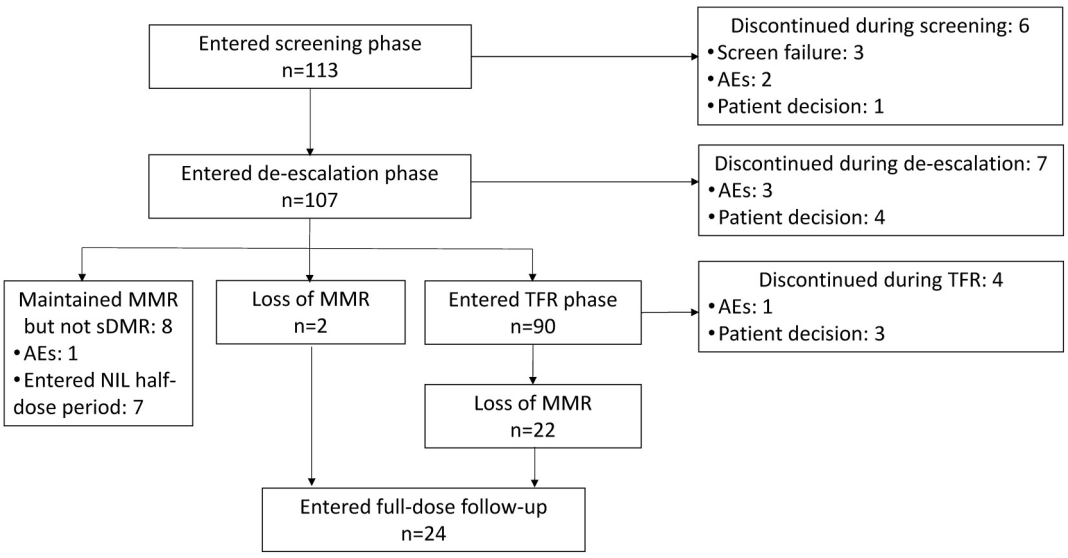

FIGURE 2 | Patient disposition at data cut-off (8 February 2023). AEs, adverse events; MMR, major molecular response; sDMR, sustained deep molecular response; TFR, treatment-free remission.

TABLE 1 | Baseline characteristics of patients entered in the nilotinib de-escalation phase.

	Total (n = 107)
Age, years, median (range)	52 (21–75)
Sex	
Male	61 (57.0)
Female	46 (43.0)
ECOG PS	
Grade 0	104 (97.2)
Grade 1	3 (2.8)
Time from diagnosis to informed consent, years, median (range)	5.5 (3–13)
Type of transcript at diagnosis	
e13a2	29 (27.1)
e14a2	53 (49.5)
Both/other	9 (8.4)
Unknown	16 (15.0)
Sokal risk score at diagnosis	
Low (RR < 0.8)	46 (43.0)
Intermediate (RR 0.8–1.2)	41 (38.3)
High (RR > 1.2)	17 (15.9)
Unknown/not evaluated	3 (2.8)
Duration of last sustained $MR^{4.5}$ until screening, months, median (range)	12.5 (0–94)
Nilotinib exposure time before de-escalation phase, years, median (range)	5.5 (3–13)
Last nilotinib dose before de-escalation phase	
< 300 mg bid	8 (7.5)
300 mg bid	98 (91.6)
None reported	1 (0.9)

Note: Values are n (%) unless otherwise stated.
Abbreviations: bid, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; MR, molecular response; RR, relative risk.

drug-related AEs, 7 (6.5%) had AEs leading to dose adjustment/temporary interruption, and four (3.7%) had AEs leading to permanent discontinuation of therapy.

During the TFR phase, AEs of any grade were reported in 64 of 90 patients (71.1%; Table 2). The most common AEs of any grade by system organ class were musculoskeletal and connective tissue disorders (38.9%; Table 3).

Twelve patients (13.3%) had severe AEs, and one patient (1.1%) had a serious AE (pneumonia). Forty patients (44.4%) had AESI, the most common of which were musculoskeletal pain (31.1%), blood cholesterol increase (6.7%) and high blood glucose levels (5.6%). During the half-dose follow-up, 6 patients (75%) had AEs, but only three of these experienced a study drug-related AE (Table 2). During the full-dose follow-up phase, AEs were observed in 17 patients (70.8%; Table 2), none of which were serious; 6 patients (25%) experienced a study drug-related AE.

4 | Discussion

The 96-week results of the DANTE study demonstrate that de-escalation of nilotinib can be a successful dose-optimization strategy for patients with CML-CP and sustained DMR. Two-thirds of patients were in FTFR at 96 weeks after the start of the nilotinib de-escalation phase, meeting the primary endpoint of the study. Furthermore, 71% of patients remained in MMR or better after a median treatment duration of 20 months, and loss of MMR during de-escalation occurred in only 2 of 107 patients who entered the nilotinib de-escalation phase. Nilotinib de-escalation also appeared to be safe, with serious AEs occurring in five patients during the de-escalation phase and in only one patient during the TFR phase.

The majority of previous TFR studies in patients with CML discontinued TKI treatment abruptly [13, 16, 25], whereas nilotinib treatment was de-escalated in our study. In these previous studies, relapse-free survival rates were 38.0%–51.6% at 11–60 months after discontinuation [13, 16, 25]. In comparison, 71.1% of patients in our study who entered TFR remained in ≥ MMR after a median duration of 20.4 months. The Stop Imatinib trial (STIM1) was the first to demonstrate the potential for patients who achieve DMR to remain in remission after stopping TKI therapy [13]. In that trial, stopping criteria were imatinib treatment for ≥ 2 years and undetectable minimal residual disease for ≥ 2 years. In the European Stop Kinase Inhibitor (EURO-SKI) trial, patients received imatinib, nilotinib or dasatinib [25, 26]. The duration of TKI treatment before enrollment in EURO-SKI was required to be ≥ 3 years and no PCR results > 0.01% (corresponding to $MR^{4.0}$) in the last year before TKI discontinuation was allowed. Finally, the ENESTfreedom trial enrolled patients with $MR^{4.5}$ and ≥ 2 years of front-line nilotinib therapy [16]. Patients with sustained DMR during the full-dose 1-year consolidation phase were eligible to stop treatment and enter the TFR phase.

Despite these previous study data supporting TKI discontinuation in patients with CML-CP, both patients and clinicians appear to have concerns about attempting TFR [27, 28]. Sharf and colleagues reported that 56%–59% of patients experienced fear, anxiety or depression during TFR or when they reinitiated TKI therapy [29]. Therefore, de-escalation of nilotinib therapy may present a more feasible and reassuring option for these patients.

The findings of our study are consistent with those of the De-Escalation and Stopping Treatment with Imatinib, Nilotinib or Dasatinib (DESTINY) study, where treatment was de-escalated to half the standard dose for 12 months, then stopped for a further 24 months [17]. In the final analysis of DESTINY, recurrence-free survival at 36 months was 72% in $MR^{4.0}$ patients and 36% in MMR patients [17].

Data from three real-world studies also report de-escalation of TKI therapy in patients with CML-CP [30–32]. In a retrospective analysis of 77 patients who discontinued TKIs, 26 were managed with a low-dose TKI before stopping treatment [30]. After a median follow-up of 61.5 months, the 60-month TFR rate was 58.8%. In a real-world study of 52 patients on low-dose ponatinib, one of 15 patients who obtained DMR also achieved

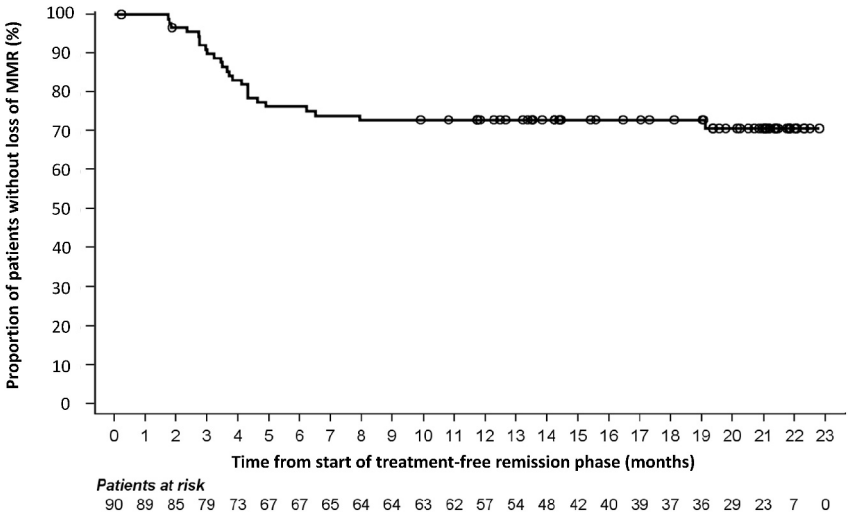

FIGURE 3 | Kaplan–Meier plot of loss of major molecular response (MMR) in the treatment-free remission phase. Circles represent censors. Patients at risk are those who had no censored observations and did not have loss of MMR at the considered timepoint.

TABLE 2 | Summary of patients with adverse events.

	Safety set (n = 107)	De-escalation (n = 107)	TFR[a] (n = 90)	Half-dose follow-up (n = 8)	Full-dose follow-up (n = 24)
AEs	81 (75.7)	44 (41.1)	64 (71.1)	6 (75.0)	17 (70.8)
Grade 3 or 4 (severe) AEs	20 (18.7)	10 (9.4)	12 (13.3)	2 (25.0)	2 (8.3)
Serious AEs	6 (5.6)	5 (4.7)	1 (1.1)	0	0
AESI	46 (43.0)	18 (16.8)	40 (44.4)	2 (25.0)	9 (37.5)
Drug-related AEs	27 (25.2)	16 (15.0)	17 (18.9)[b]	3 (37.5)	6 (25.0)
AEs leading to treatment dosage adjustment/temporary interruption	12 (11.2)	7 (6.5)	1 (1.1)	1 (12.5)	5 (20.8)
AEs leading to permanent discontinuation of the study therapy	7 (6.5)	4 (3.7)	1 (1.1)	1 (12.5)	2 (8.3)
Fatal AEs	0	0	0	0	0

Note: Values are n (%). Only AEs that started or worsened after the start of the de-escalation phase (i.e. first nilotinib dose 300 mg qd) were considered. Severity of AEs was evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
Abbreviations: AEs, adverse events; AESI, adverse events of special interest; TKI, tyrosine kinase inhibitor; TRF, treatment-free remission; qd, once daily.
[a]Includes patients who restarted treatment after TFR failure.
[b]8 patients had musculoskeletal and connective tissue disorders related to TKI withdrawal syndrome.

TFR [31]. In another real-world study of 248 patients who discontinued low-dose TKI treatment, 172 patients (69.4%) were still in TFR after a median follow-up of 24.9 months [32].

Recent studies have shown that a significant proportion of patients can achieve a DMR with TKIs, and that treatment discontinuation can be successfully achieved in approximately 50% of these patients. However, the remaining 50% require the reintroduction of TKI therapy. Although around 90%–95% of patients who experience molecular recurrence regain their initial molecular level after restarting TKI therapy, success rates of a second attempt at TFR tend to be lower than those of the first, with reports of 35% at 12 months [33], 44.3%, 38.5%, and 33.2% at 24, 36, and 48 months, respectively [34], and 21.5% at 6 months [35].

The DANTE trial consists of two stages, a Treatment-Free Remission 1 (TFR1) stage, reported here, and a Treatment-Free Remission 2 (TFR2) stage. The purpose of the TFR2 stage is to evaluate whether the use of asciminib in combination with full-dose nilotinib after failure of a first attempt at TFR can lead to higher and more durable TFR rates after a second attempt at TKI discontinuation than those reported in other studies. Asciminib is a first-in-class STAMP (Specifically Targeting the ABL Myristoyl Pocket) inhibitor, with demonstrated clinical efficacy in patients who have received more than two TKIs [36]. The TFR2 stage will enroll two cohorts of patients: an internal cohort comprising patients who failed a first attempt at TFR during the TFR1 stage of the present study, and an external cohort of patients who failed their first attempt following discontinuation of nilotinib outside of this study. The study is ongoing, and the results of TFR2 are eagerly anticipated.

Nilotinib de-escalation was well tolerated in our study. The most common AEs by system organ class during the de-escalation and TFR phase were autoimmune musculoskeletal and

TABLE 3 | Most common adverse events occurring in > 5% of patients at treatment-free remission by system organ class.

	Total (n = 90)				
	Overall	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Total AEs	64 (71.1)	56 (62.2)	30 (33.3)	12 (13.3)	0
Musculoskeletal and connective tissue disorders	35 (38.9)	28 (31.1)	15 (16.7)	1 (1.1)	0
Arthralgia	14 (15.6)	12 (13.3)	4 (4.4)	1 (1.1)	0
Myalgia	12 (13.3)	10 (11.1)	4 (4.4)	0	0
Laboratory investigations	20 (22.2)	15 (16.7)	5 (5.6)	8 (8.9)	0
Lipase increased	9 (10.0)	2 (2.2)	3 (3.3)	6 (6.7)	0
Amylase increased	6 (6.7)	4 (4.4)	2 (2.2)	0	0
Infections and infestations	19 (21.1)	15 (16.7)	5 (5.6)	0	0
COVID-19	13 (14.4)	11 (12.2)	2 (2.2)	0	0
Metabolism and nutrition disorders	13 (14.4)	12 (13.3)	4 (4.4)	0	0
Nervous system disorders	10 (11.1)	8 (8.9)	3 (3.3)	0	0
Headache	5 (5.6)	5 (5.6)	0	0	0
Cardiac disorders	5 (5.6)	3 (3.3)	2 (2.2)	0	0

Note: Values are n (%).
Abbreviation: AEs, adverse events.

connective tissue disorders (12.2% and 38.9%, respectively). During the TFR phase, autoimmune musculoskeletal and connective tissue disorders were grade 1–2 in all but one patient, who had grade 3 arthralgia, which was managed with corticosteroid treatment. This safety profile is also consistent with that reported in DESTINY, in which 39.7% of patients reported musculoskeletal symptoms during the first 12 months of stopping therapy [17]. Musculoskeletal and/or joint pain occurring after TKI discontinuation, known as TKI withdrawal syndrome, is thought to be an off-target effect of TKIs [20]. In most patients, such symptoms are mild and self-limiting; however, some patients may require treatment with acetaminophen (paracetamol), nonsteroidal anti-inflammatory drugs, or oral corticosteroids. Progressive de-escalation of the TKI dose, rather than abruptly interrupting therapy, may be useful for avoiding withdrawal syndrome symptoms without jeopardizing the possibility of maintaining a good response and achieving TFR [32]. Potential benefits of a longer treatment period with a reduced dosage, such as leukemic stem cell exhaustion and reduced AEs, could further support this strategy [17].

The main limitations of our study are the small sample size and the lack of a comparator group.

5 | Conclusions

The phase II DANTE study is the first to prospectively investigate the use of TKI dose de-escalation before stopping treatment. The final results showed that two-thirds of patients who entered the de-escalation phase achieved FTFR at 96 weeks after the start of the de-escalation period, with 71% of patients remaining disease-free at 1 year. These findings suggest that de-escalation of nilotinib before attempting TFR in CML-CP patients with sustained DMR can be a successful dose-optimization strategy. Based on the results of this trial and previous real-world evidence, this treatment optimization strategy may be applied safely in clinical practice.

Author Contributions

A.I., M.B., F.S., G.S., G.R. are members of the DANTE protocol steering committee, enrolled patients, contributed to the preparation of the manuscript and study design, and read and approved drafts and the final manuscript. E.A., F.P., I.A., P.S., M.C., S.G., B.S., M.M., S.S., I.C., enrolled patients, read and approved drafts and final manuscript. D.V., A.P.N., A.M., P.C. as employees of Novartis Farma Italy designed and conducted the study, as well as collected, analyzed, and interpreted the data, contributed to the preparation of the manuscript, and read and approved drafts and the final manuscript.

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Conflicts of Interest

During the last 2 years, A.I. received honoraria for lectures from Incyte, Novartis, Bristol Myers Squibb, GSK, Pfizer and AOP Health, and for advisory boards from Incyte, Novartis, Bristol Myers Squibb and AOP Health. M.B. has received honoraria from Novartis, Incyte, Bristol Myers Squibb, GSK, Pfizer and AOP, and advisory board honoraria from Novartis, Incyte, Bristol Myers Squibb, AOP and GSK. F.S. has received honoraria from Incyte, Novartis and Pfizer. E.A. has participated in consultancies and/or advisory boards with Ascentage, Bristol Myers

Squibb, Incyte, Pfizer and Takeda. F.P. received honoraria during the last 2 years for lectures from Incyte, Novartis, Bristol Myers Squibb, and for advisory boards from Incyte, Novartis. PS received honoraria from Novartis, Abbvie, J and J and Beigene. M.C. has received honoraria from Novartis, Incyte, Amgen, Otsuka, Astellas, Servier, Italfarmaco, Abbvie, Janssen and Jazz. S.G. received honoraria from Novartis, Incyte, Abbvie, Janssen, Pfizer, Astra Zeneca, Beigene, Lilly, Roche, and Jazz. B.S. received honoraria from Novartis, Incyte, Amgen, Sanofi, Pfizer. IC received honoraria from Novartis, Incyte, Bristol Myers Squibb, Pfizer. G.S. is on a speakers' bureau for Novartis. D.V., A.P.N., A.M. and P.C. are employees of Novartis. G.R. has received honoraria from Novartis, Incyte, Bristol Myers Squibb, Pfizer, Angelini and Sun Pharma. I.A., M. M., and S.S. have no competing financial interests.

Data Availability Statement

Deidentified data that support the findings of this study can be made available on request to the corresponding author, Alessandra Iurlo (alessandra.iurlo@policlinico.mi.it).

Peer Review

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1002/hon.70126.

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Supporting Information

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

Supporting Information S1: hon70126-sup-0001-suppl-data.pdf.