Original Study

The Italian Multicentric Randomized OPTkIMA Trial on Fixed vs Progressive Intermittent TKI Therapy in CML Elderly Patients: 3-Years of Molecular Response and Quality of Life Monitoring After Completing the Treatment Plan

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Abstract

- **Both FIXED and PROGRESSIVE intermittent tyrosine kinase inhibitor therapy are feasible and safe schedules in elderly patients with sustained major or deep molecular response.**
- **The PROGRESSIVE intermittent schedule is associated with a higher incidence of molecular remission$^{3.0}$ loss.**
- **The Health-Related Quality of Life improved during both intermittent schedules.**
- **The PROGRESSIVE schedule was considered by Clinicians as a valid tool to select patients eligible for tyrosine kinase inhibitor discontinuation.**

Background: Intermittent treatment with tyrosine kinase inhibitors (TKIs) is an option for elderly chronic myeloid leukemia (CML) patients who are often candidates for life-long treatment. **Materials and Methods:** The Italian phase

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III multicentric randomized Optimize TKIs Multiple Approaches (OPTkIMA) study aimed to evaluate if a progressive de-escalation of TKIs is able to maintain the molecular remission ($MR^{3.0}$) and to improve Health-Related Quality of Life (HRQoL) in CML elderly patients. **Results:** A total of 215 patients in stable $MR^{3.0}$/$MR^{4.0}$ were randomized to receive an intermittent TKI schedule 1 month ON-1 month OFF for 3 years (FIXED arm; n = 111) vs. a progressive de-escalation TKI dose up to one-third of the starting dose at the 3rd year (PROGRESSIVE arm; n = 104). Two hundred three patients completed the 3rd year of OPTkIMA study. At the last follow-up, $MR^{3.0}$ loss was 27% vs. 46% ($P = .005$) in the FIXED vs PROGRESSIVE arm, respectively. None of these patients experienced disease progression. The 3-year probability of maintaining the $MR^{3.0}$ was 59% vs. 53%, respectively ($P = .13$). HRQoL globally improved from the baseline to the 3rd year, without any significant difference between the 2 arms. After the 3rd year, the proportion of patients who was address to TKI discontinuation in the 2 arms was 36% (FIXED) vs. 58% (PROGRESSIVE) ($P = .03$). **Conclusions:** The intensification of intermittent TKI therapy is associated with a higher incidence of $MR^{3.0}$ loss, but those patients who maintain the $MR^{3.0}$ molecular response at the end of the study have been frequently considered eligible for TFR. The HRQoL generally improved during the de-escalation therapy in both randomization arms.

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Introduction

Currently, the prognosis of elderly patients (> 60 years) with Philadelphia positive chronic myeloid leukemia (Ph+ - CML) treated with TKIs is superimposable to that observed in younger patients.[1] Data from multicentric, prospective trials show that the probability to achieve a major molecular remission (MMR – $MR^{3.0}$) at 5 years from TKI start is not less than 80%.[2,3] Moreover, the probability of long-term overall survival is around 75% and the main causes of death in these patients are represented by other conditions related to senectus and not by CML progression.[2,3]

Thus, similarly to what is observed in younger patients, elderly patients are planned to receive tyrosine kinase inhibitor (TKI) lifelong, if they don't reach the criteria for TKI discontinuation, with the aim to enter treatment free remission (TFR).[4] As a consequence, the issue of management of elderly patients who achieve $MR^{3.0}$ or a deeper MR (namely ≥ $MR^{4.0}$) is an unmet clinical need, and strategies alternative to TKI discontinuation could be proposed. These strategies mainly focus on the de-escalation of TKI dose, with the aim to maintain at least the $MR^{3.0}$, which is known to be the surrogate marker of long-term survival.[5-11]

Overall, the percentage of patients eligible for treatment discontinuation is approximately 50% to 60% and the TFR rate is approximately 50%. This means that the benefit of the TFR strategy is restricted to no more than 25% to 30% of the entire CML population, and the great majority of older patients will never enter the TFR. Thus, elderly patients are destined to maintain a continuous TKI treatment for many years, and this raises concerns in regard to tolerability, adherence, and side effects of TKI therapy and, last but not least, to Health-Related quality of life (HRQoL), which is often compromised by concomitant comorbidities and poli-pharmacy.[12]

Clark and Colleagues investigated a strategy based on the de-escalation and then the stop of TKI with the aim to get the TFR (DESTINY)[10,11] and they showed that recurrence-free survival was 36% in the $MR^{3.0}$ group and 72% n the ≥ $MR^{4.0}$ group.

Another strategy addressed to the identification of the minimal effective dose (MED) to maintain at least the $MR^{3.0}$ in the elderly was investigated by our Group in the phase II multicentric prospective INTERIM trial, in which imatinib (IM) was administered 1 month ON and 1 month OFF in patients in stable Complete Cytogenetic Response (CcyR) .[5,6] After 6 years of follow-up, 16/76 patients (21%) have lost CCyR and $MR^{3.0}$, and 16 patients (21%) have lost MMR only. Neither progression to the blastic phase nor CML-related deaths were recorded. All the patients who had lost the CCyR re-gained the CCyR after resuming continuous therapy.[5,6] The treatment strategy explored in the INTERIM trial was used as control arm in the ongoing multicentric randomized Optimize TKIs Multiple ApproachesMR means: molecular response (OPTkIMA) trial, in which the experimental arm was represented by a progressive de-escalation of TKI dose, with the aim to reach one-third of the baseline dose during the third year after enrollment. Among elderly patients with stable and confirmed $MR^{3.0}$ at baseline, the probability of $MR^{3.0}$ maintenance after the first year (1 month ON and 1 month OFF) of OPTkIMA trial was 81%, thus superimposable to that observed in the INTERIM trial.[5-7]

The aim of this work is to present an update on the OPTkIMA trial, focusing on the rate of $MR^{3.0}$ loss in the 2 randomization arms during the second and third year of treatment, and including data on patients' reported HRQoL. Moreover, we report some results on the transition from study to real-life management of the 2 cohorts of CML patients beyond the third year.

Patients and Methods

OPTkIMA study includes patients with chronic-phase (CP) Ph+ CML older than 60 years and in $MR^{3.0}$ or $MR^{4.0}$ after at least 2 years of daily treatment with TKIs [either imatinib (IM), nilotinib (NIL), or dasatinib (DAS)] (NCT02326311) who were randomized 1:1 to receive the same daily dose of ongoing TKI, at a "FIXED" intermittent schedule (1 month ON/OFF) of TKI (control arm) or at a "PROGRESSIVE" intermittent schedule (1 month ON–1 month OFF for the 1st year; 1 month ON–2 months OFF for the 2nd year; and 1 month ON–3 months OFF for the 3rd year) (experimental arm).[8]

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The study started in July 2015 and aimed to evaluate if a progressive increase in the intermittent schedule until the 3rd year can maintain the $MR^{3.0}$ or $MR^{4.0}$ molecular response and improve the HRQoL.[8] For this latter purpose, as previously reported,[8] HRQoL was assessed at baseline, and then at 3, 6, 12, 18, 24, 30, and 36 months with the following questionnaires: EORTC Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and its QLQ-CML24 and QLQ-ELD-14 modules.[8]

During the study, the patients had to discontinue the intermittent treatment, fixed or progressive, and resume continuous treatment, in case of $MR^{3.0}$ loss. In the meantime, mutational analysis was recommended. At the end of the third year, Clinicians were free to choose between 3 options for each patient: i) resume daily TKI treatment; ii) maintain the intermittent schedule; iii) discontinue the TKI and enter a TFR phase.

Statistical Analysis

Dichotomous variables were summarized as numbers and percentages and compared using the χ^2 text. Continuous variables were summarized as median and range and compared using the Wilcoxon rank-sum test. Probability of survival without $MR^{3.0}$ loss while on OPTkIMA was calculated according to the Kaplan-Meier method from the date of randomization to the date of death or $MR^{3.0}$ loss or last follow-up[13]; the log-rank test was used to detect significant differences among subgroups. Cox proportional hazard regressions were used for univariate and multivariate analyses on the probability to maintain the $MR^{3.0}$. The following variables were included in the regression models: age (as a continuous variable), sex, Sokal risk, fusion transcript, TKI type, and mean duration (113 months), randomization arm (FIXED vs. PROGRESSIVE), and depth of molecular response. All resulting variables associated with the probability of maintaining the $MR^{3.0}$ with $P < .05$ in univariate analysis were subjected to multivariate analysis. All $P < .05$ were considered statistically significant. Statistical analysis was performed with EZR version 1.54).[14]

For analysis purposes, we grouped the HRQoL questions included in the 3 questionnaires (EORTC QLQ-C30, EORTC QLQ-CML24, EORTC QLQ-ELD14) into 4 clusters: i) autonomy (QLQ-ELD14, items 31-35: difficulty with stairs, joints stiffness and pain, need help with household chores); ii) anxiety/psychological status (QLQ-ELD14, items 36-44 and QLQ-CML24, items 45-54: uncertainty and worries about future health, mood swings, disease burden, motivation, satisfaction with the cure, need of social support, depression); iii) fatigue (QLQ-C30, items 1-13: troubles doing strenuous activities, walking, eating, dressing, washing himself, short breath, asthenia, pain, insomnia, lack of appetite); iv) organ toxicity and side effects (QLQ-CML24, items 31-44 and QLQ-C30, items 14-28: nausea and vomiting, constipation and diarrhea, weight loss, headache, abdominal pain, muscle cramps, edema, irritability, difficulty in concentrating and remembering things, interference of physical conditions and/or medical treatment with family life and socio-economic activities). To draw trajectories in the change of HRQoL during OPTkIMA in each cluster, we considered the mean value of all the questions included at baseline, 12th, 24th, and 36th month.

Results

From July 2015 (enrollment of the first patient) to June 2023 (data cut-off for the present analysis) a total of 215 patients have been randomized (111 in the FIXED arm and 104 in the PROGRESSIVE arm). The patients who have completed the 3-years of follow-up and have been included in this analysis are 203: 104/203 (51%) and 99/203 (49%) in the FIXED and PROGRESSIVE arm, respectively.

Table 1 reports the clinical and biological characteristics of these patients. As expected, the great majority of the patients were on IM at enrollment (74% of the cases), had a low/intermediate Sokal-risk score (84% of the cases), and were in deep molecular response at the enrollment (80% of the cases), after a median duration of TKI treatment of 108 months. No differences were observed in the 2 randomization arms in the different variables analyzed, with the exception of a slight increase in patients' age in the PROGRESSIVE arm (median 70 vs. 72 years; $P = .02$), a higher percentage of Sokal high-risk patients in the FIXED arm (22% vs. 11%; $P = .03$), and a higher percentage of patients with at least 2 comorbidities in the progressive arm (55% vs. 71%; $P = .02$).

OPTkIMA Discontinuation During the 3 Years of the Study

Table 2 reports the rate and causes of OPTkIMA discontinuation towards the study time (3 years). At last follow up, 101/104 (97%) and 98/99 patients (99%) discontinued OPTkIMA in the FIXED and PROGRESSIVE arm, respectively ($P = .33$). The main reasons for OPTkIMA discontinuation in the FIXED vs PROGRESSIVE arm were: end of the study protocol (59% vs. 36%; $P = .001$), and $MR^{3.0}$ loss (27% vs. 46%; $P = .005$). Other reasons for OPTkIMA discontinuation included death not related to CML or withdrawn of informed consent (11% vs. 17%; $P = .25$).

Looking closer to the outcome per year, the rate of $MR^{3.0}$ loss after the first year, was 24% in both randomization arms. On the other hand, at the end of the second and the third year the rate of $MR^{3.0}$ loss was significantly lower in the FIXED arm: 1% vs. 22% ($P = .001$) in second year, and 3% vs. 15% ($P = .01$) at the third year, respectively.

All the patients who discontinued OPTkIMA for $MR^{3.0}$ loss (n = 73), resumed the same TKI continuously, and all but one obtained at least the $MR^{3.0}$ response (71/73-97% within 6 months). The mutational analysis was performed by denaturing high-performance liquid chromatography (DHPLC) in all the cases and in 2/73 patients (3%) and ABL mutation was detected (D363Y and Y320C).[8] The 2 patients who developed mutations were both in the fixed arm and were both assuming IM at the time of mutation detection. The mutations were developed at the 6th month from enrollment in 1 case and at 9th month in the other. The first one shifted to NIL, re-achieved a deep molecular response after 6 months, and is currently in $MR^{4.5}$ with continuous NIL therapy. The second one died of progressive rheumatologic disease not in $MR^{3.0}$.

As reported in Figure 1, the 1-, 2-, 3-years probability of maintaining the $MR^{3.0}$ while on OPTkIMA in the FIXED vs. PROGRESSIVE arm was 81%, 69%, and 66% vs. 81%, 59%, and 53% ($P = .13$).

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Table 1 Clinical and Biological Characteristics of the 215 Patients Enrolled in OPTkIMA Trial

Variable	Total (n = 215)	FIXED (n = 111%-52%)	PROGRESSIVE (n = 104%-48%)	*P*
M/F	123/92	58/53	65/39	.13
	(57% / 43%)	(52% / 48%)	(63% / 37%)	
Median age (range)	71	70	72	**.02**
	(60-89)	(60-89)	(60-88)	
Type of transcript	212 available	111	101	.43
b3a2	137 (65%)	69 (62%)	68 (67%)	
b2a2	75 (35%)	42 (38%)	33 (33%)	
Sokal	214 available	110	104	.06
Low	79 (37%)	41 (37%)	38 (36%)	.91
Int	100 (47%)	45 (41%)	55 (53%)	.08
High	35 (16%)	24 (22%)	11 (11%)	**.03**
TKI				.64
- IMA	159 (74%)	80 (72%)	79 (76%)	.52
- NILO	32 (15%)	19 (17%)	13 (12%)	.34
- DAS	24 (11%)	12 (11%)	12 (12%)	.87
Median duration of TKI (mo)	108 (24-372)	116 (31-372)	106 (24-328)	.79
Molecular response at enrollment				.87
- $MR^{3.0}$	39 (18%)	19 (17%)	20 (19%)	.69
- $MR^{4.0}$	171 (80%)	89 (80%)	82 (79%)	.81
- $\geq MR^{4.0}$	5 (2%)	3 (3%)	2 (2%)	.70
Pts with at least 2 comorbidities	131/209 (63%)	60/109 (55%)	71/100 (71%)	**.02**
Pts with at least 2 drugs other than TKI	127/209 (61%)	62/109 (57%)	65/100 (65%)	.23

Abbreviations: DAS = dasatinib; F = female; IMA= imatinib; M = male; NILO = nilotinib; pts = patients.
The bold values cited in the tables are those with statistically significance (p value < .05).

Table 2 Distribution of OPTkIMA Discontinuation Causes During the 3 Years of the Trial Duration

OUT	FIXED (n = 104)	%	PROGRESSIVE (n = 99)	%	*P*
1st year OUT	32/104	31	30/99	30	.94
- OUT for $MR^{3.0}$ loss	25/104	24	24/99	24	.97
- OUT for other reasons	7/104	7	6/99	6	.84
On OPTkIMA	72/104	69	69/99	70	
2nd year OUT	6/72	8	23/69	33	**.002**
- OUT for $MR^{3.0}$ loss	1/72	1	15/69	22	**.001**
- OUT for other reasons	5/72	7	8/69	12	.34
On OPTkIMA	66/72	92	46/69	67	
3rd year OUT	63/66	95	45/46	98	.5
- OUT for $MR^{3.0}$ loss	2/66	3	7/46	15	**.01**
- OUT for other reasons	61/66	92	38/46	83	.11
Total OUT	101/104	97	98/99	99	.33
- OUT for study completion	61/104	59	36/99	36	**.001**
- OUT for $MR^{3.0}$ loss	28/104	27	45/99	46	**.005**
- OUT for other reasons	12/104	11	17/99	17	.25

The bold values cited in the tables are those with statistically significance (p value < .05).

Univariate and Multivariate Analysis

Table 3 reports the results of the univariate and multivariate analysis on the probability of $MR^{3.0}$ loss. By univariate analysis, factors that were significantly associated with an increased risk of $MR^{3.0}$ loss were: b2a2 fusion transcript (HR 1.936; $P = .01$), and PROGRESSIVE arm (HR 1.891; $P = .02$). On the other hand, considering the mean duration of TKI at enrollment as cut-off, TKI duration > 113 months (HR 0.433; $P = .004$), FIXED randomization arm (HR 0.529; $P = .02$), and molecular response at enrollment deeper than $MR^{3.0}$ (HR 0.385; $P = .0005$)

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Figure 1 Probability of survival without MR$^{3.0}$ loss (FIXED vs. PROGRESSIVE arm at 1-, 2-, 3-years: 81%, 69%, and 66% vs. 81%, 59%, and 53%; $P = 0.13$).

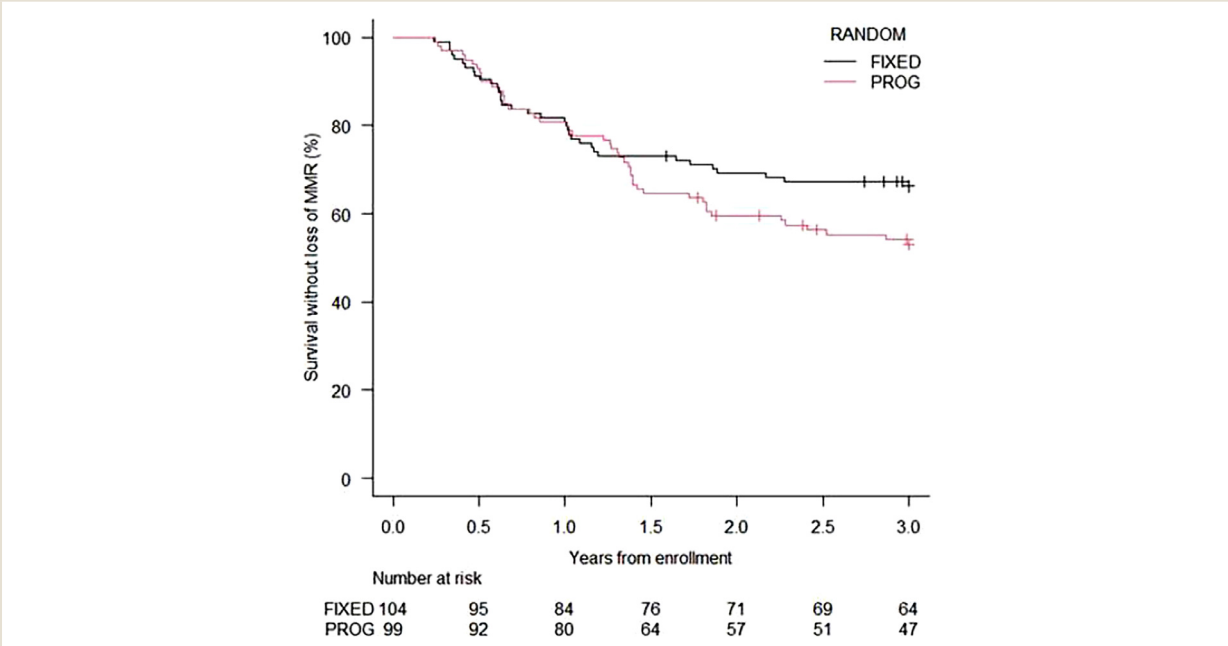

Table 3 Univariate and Multivariate Analysis on the Probability of MR$^{3.0}$ Loss

Univariate Analysis				
Variables	**HR**	**Lower 95% CI**	**Upper 95% CI**	***P***
Age (y)	1.019	0.984	1.056	.298
Being male	0.798	0.483	1.318	.379
Sokal	0.980	0.759	1.266	.879
b2a2 transcript	1.936	1.139	3.292	**.01**
Dasatinib	0.761	0.346	1.674	.497
Imatinib	1.381	0.761	2.508	.288
Nilotinib	0.755	0.342	1.665	.486
TKI duration ≥ 113 mo	0.433	0.245	0.764	**.004**
Fixed	0.529	0.314	0.891	**.02**
Progressive	1.891	1.122	3.186	**.02**
Molecular response deeper than MR$^{3.0}$	0.385	0.2254	0.6586	**.0005**
Multivariate Analysis				
Variables	HR	Lower 95% CI	Upper 95% CI	*P*
b2a2 transcript	2.255	1.2820	3.9670	**.005**
TKI duration ≥ 113 mo	0.446	0.2491	0.7994	**.007**
Fixed	0.516	0.3016	0.8835	**.02**
Molecular response deeper than MR$^{3.0}$	0.555	0.3144	0.9807	**.04**

The bold values cited in the tables are those with statistically significance (p value < .05).

significantly protected from MR$^{3.0}$ loss. Moving to multivariate analysis the factor that resulted independently associated with an increased risk of MR$^{3.0}$ loss was b2a2 fusion transcript (HR 2.255; $P = .005$), whereas a TKI duration > 113 months (HR 0.446; $P = .007$), the randomization to a FIXED intermittent schedule (HR 0.516; $P = .02$) and a deep molecular response (HR 0.555; $P = .04$) were significantly associated with a reduced risk of MR$^{3.0}$ loss.

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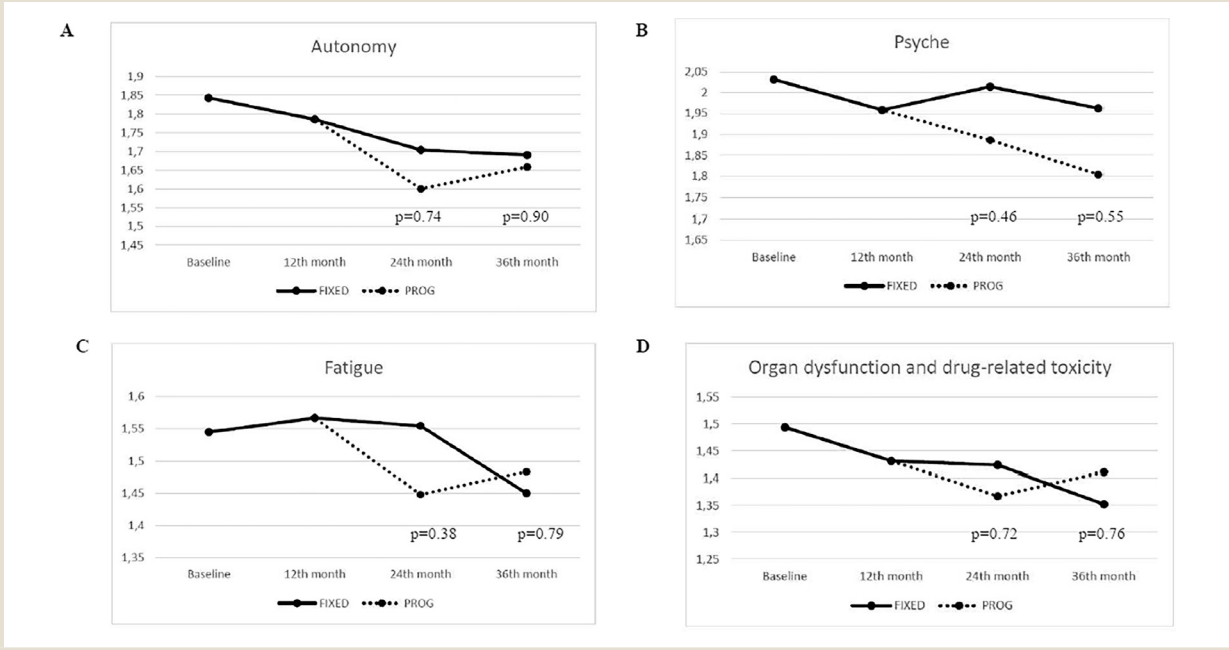
Figure 2 Trajectories in the HRQoL clusters from the 1st to the 3rd year after randomization (A = Automomy; B = Psyche; C = Fatigue; D = Organ disfunction and drug-related toxicities).



Real-Life Treatment Transition After OPTkIMA Study Completion

As previously reported, the rate of OPTkIMA discontinuation for study completion was 59% (61/104) vs. 36% (36/99) in the FIXED vs. PROGRESSIVE arm, respectively ($P = .001$) (Table 2). All these patients did not lose the $MR^{3.0}$ while on OPTkIMA and Clinicians were free to resume TKI continuously, maintain the intermittent schedule outside the clinical trial, or discontinue the TKI and enter the TFR. The results of this real-life treatment transition are reported in Table 3. A minority of these patients resumed the same TKI daily (11/61-18% vs. 5/36-14% in the FIXED vs. PROGRESSIVE arm, respectively; $P = .59$). On the other hand, a significantly higher proportion of patients in the FIXED vs. PROGRESSIVE arm maintained the intermittent schedule beyond the 3rd year (28/61-46% vs. 10/36-28%; $P = .01$). In contrast, according to Clinicians' choice, a significantly higher proportion of patients in the PROGRESSIVE vs. FIXED arm was addressed to TKI discontinuation, and, thus, entered treatment-free remission (21/36-58% vs. 22/61-36%; $P = .03$).

Trajectories of HRQoL Assessment During OPTkIMA Trial

The results of the first year HRQoL have been already reported.[8] As a consequence, we report here the results of the trajectories of changes in HRQoL during the second and the third year of OPtkIMA, that is when the schedule of TKI treatment in the fixed and progressive arm changes (Figure 2). The median value of the different scores for each item of each cluster is reported. The lower the value is, the better the patients feel.

The successful HRQoL questionnaires collection at 24 and 36 months of OPTkIMA were 70% and 52%, respectively. It is worth note that the median value of all the analyzed clusters reduced during the transition from the baseline to the first, second, and third year in both randomization arms (Figure 2A – autonomy; Figure 2B – psyche; Figure 2C – fatigue; Figure 2C - organ disfunction and drug-related toxicity). Although between the first and second year this reduction was more pronounced in the PROGRESSIVE arm for all the clusters, this difference never reached significance.

Discussion

This manuscript is an update of the previously published OPTkIMA trial,[8] in which we observed that, among elderly patients in $MR^{3.0}$/$MR^{4.0}$ who completed the first year of any TKI intermittent schedule 1 month ON and 1 month OFF, the first year probability of maintaining the $MR^{3.0}$ was 81%. Of note these results are well comparable to the ones obtained by Luo and Colleagues who registered a molecular recurrence-free survival of 88% at 1 year among 62 patients aged 18-70 years in $MR^{4.5}$, who reduced TKI dose to 50% of the baseline one.[15]

Moving to a longer follow-up of the OPTkIMA trial, we observed that the rate of $MR^{3.0}$ loss significantly increases when the dose of TKI is progressively reduced. In particular, by comparing the FIXED and the PROGRESSIVE arms we observed that the percentages of patients who discontinued OPTkIMA and resumed daily

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Table 4 Real-Life Treatment Transition After OPTkIMA Study Completion

	FIXED (n = 104)	%	PROGRESSIVE (n = 99)	%	*P*
OUT for study completion	61/104	59	36/99	36	**.001**
Maintain the intermittent schedule	28/61	46	10/36	28	**.01**
TKI discontinuation	22/61	36	21/36	58	**.03**
Resume TKI daily	11/61	18	5/36	14	0.59

The bold values cited in the tables are those with statistically significance (p value < .05).

TKI for molecular relapse at 24 and 36 months were 1% vs. 22% ($P = .001$) and 3% vs 15% ($P = .01$), respectively (Table 2). However, this did not translate into impairment in the probability of being alive and in $MR^{3.0}$ at 1-, 2- and 3 years (81%, 69%, and 66% vs 81%, 59%, and 53%; $P = 0.13$; Figure 1). This may be partially influenced by the relatively small number of patients randomized in each arm. Moreover, the impact of the TKI schedule on the probability of $MR^{3.0}$ maintenance is confirmed by the multivariate analysis, according to which the FIXED randomization arm, together with a duration of TKI treatment longer than 113 months, a deep molecular response, and b2a2 fusion transcript are the factors independently associated with higher probability to maintain the $MR^{3.0}$ (Table 3). Finally, no patient progressed to the accelerated/blastic phase, and all but 1 patient re-achieved the $MR^{3.0}$ after daily TKI resumption.

A second interesting piece of information regards the data on real-life treatment transition after OPTkIMA study completion (36th month). It is worth note that, beyond the third year, the choice to maintain the intermittent schedule, definitively stop the TKI, or resume TKI daily was remitted to the Physicians in charge of each patient. As shown in Table 4, the proportion of patients who, by Clinicians' choice, were addressed to TKI discontinuation with the aim of TFR, was significantly higher in the PROGRESSIVE vs. FIXED arm (58% vs. 36%; $P = .03$). On the other hand, Clinicians maintained on the intermittent schedule 46% of the patients in the FIXED arm vs. 28% of the patients in the PROGRESSIVE arm ($P = .01$). These findings suggest that the maintenance of $MR^{3.0}$ after 3 years of progressive de-escalation of TKI dose up to one-third of the baseline dose was considered predictive of high probability to maintain the TFR. In other words, we can speculate that, although patients in the PROGRESSIVE arm lost the $MR^{3.0}$ more frequently, the maintenance of an MMR while on a progressive TKI de-escalation was considered as a selection tool for identifying patients able to maintain the TFR. Indeed, we cannot conclude that the patients in the PROGRESSIVE arm who maintained the $MR^{3.0}$ up to the end of the study are cured, because we don't have biological information in this regard (eg, leukemic stem cell track, dPCR,….).[16] Considering both the FIXED and the PROGRESSIVE arm, by intention to treat, the overall rate of molecular relapse observed while on the intermittent schedule was 36% (73/203 evaluable patients). In the optic view of treatment optimization, our intermittent schedule, independently from the FIXED or the PROGRESSIVE form, favorably compares to the one proposed in the DESTINY trial,[9,10] in which the de-escalation phase was followed by TKI discontinuation. In the $MR^{3.0}$ group, Clark and Colleagues reported a failure-free survival of 36%. Overall, our rate of molecular recurrence is lower than that observed in the case of TKI discontinuation in patients in deep molecular response (approximately 50%) and that observed with other strategies of TKI reduction and discontinuation. The aim of these considerations is not to "pick a winner" schedule for any patient, but, more importantly, to stress the importance of adopting different treatment strategies in different subsets of patients.

To our knowledge, this is the first time that a policy of de-escalation of TKI treatment in the elderly is explored and evaluated within a randomized multicentric trial. This is a key point, because the treatment paradigm of CML in the most recent years has significantly changed, particularly in the elderly, who represent more than two-thirds of CML patients. Considering that 70% to 80% of CML patients will never achieve a deep molecular response which will make them eligible for treatment discontinuation and TFR, we can consider the intermittent schedule as a safe alternative strategy. The aim of this strategy is firstly the identification the minimal effective dose to maintain the $MR^{3.0}$ that is a well-known surrogate marker of long-term OS.[4] Moreover, towards a reduction of TKI dose in elderly patients with comorbidities and receiving other drugs for underlying diseases (eg, hypertension, dyslipidemia, diabetes,…), we can reach the goal of reducing the side-effects, and, thus, improve the HRQoL. Indeed, this was the primary end-point of the OPTkIMA trial. As reported in Figure 2, in all the different clusters grouping the items of the 3 EORTC questionnaires (QLQ-C30, QLQ-CML24, QLQ-ELD14), we recorded a progressive improvement of the HRQoL moving from baseline to the 3rd year after randomization. Nevertheless, no significant differences between the FIXED and the PROGRESSIVE arm were observed in neither autonomy (Figure 2A), nor psyche (Figure 2B), fatigue (Figure 2C), and organ dysfunction/drug-related toxicity (Figure 2D). Unfortunately, the low number of patients randomized in the trial clearly confirms a well-known problem with un-sponsored, spontaneous clinical research: the issue of patients' recruitment. This is why we have not been able to meet the primary endpoint of the study (is the PROGRESIVE schedule able to significantly improve HRQoL with respect to the FIXED one?).

In summary, both the FIXED and the PROGRESSIVE intermittent TKI schedule explored in the randomized, multicentric OPTkIMA trial were feasible and safe in elderly patients. In particular no progression to accelerated/blastic phase was recorded. We thus agree with the observation from Fassoni and Colleagues that TKI dose reduction could be considered as a long-term treatment option for CML patients with good response, thanks to its safety profile, as well as for treatment-related side-effects and treatment costs reduction.[17] The intensification of intermittent therapy, leading to a reduction to one-third of the TKI dose by the 3rd year, is associated with a higher incidence of $MR^{3.0}$ loss. Moreover, by multivariate

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analysis, being randomized to a fixed schedule is protective against molecular relapse. Overall these results shed a light on the topic of TKI-dose optimization in long-term treatment of optimal responders, which is still a matter of debate.[18]

Interestingly, those patients who maintained the $MR^{3.0}$ molecular response at the end of the study were considered cured enough to be eligible for TKI discontinuation. Follow up data on this cohort of patients will be collected systematically. Patients' HRQoL generally improved during the de-escalation therapy, and, in the PROGRESSIVE arm, improvements were slightly more evident, but without any significance with respect to the FIXED arm. In conclusion, while waiting to better identify (eg, with dPCR) those patients who are cured and, thus, eligible for TKI discontinuation, the intermittent schedule seems a valid option, particularly in elderly patients with at least a $MR^{3.0}$ molecular response.

Conclusions

Although the intensification of the intermittent TKI schedule in the PROGRESSIVE arm of the OPTkIMA trial was associated to a higher rate of $MR^{3.0}$ loss, this did not translate into an increased incidence of disease progression. The percentage of patients who, by the end of the trial and by Clinicians' choice, were addressed to TKI discontinuation were significantly higher in the PROGRESSIVE vs. FIXED arm. This suggests that the PROGRESSIVE intermittent schedule was considered a sort of "patients' selection tool" for TKI discontinuation. HRQoL gradually improved with both the intermittent schedules.

Clinical Practice Points

- Less than 25% of the whole CML patients population is eligible for TKI discontinuation with the aim of treatment free remission (TFR). Thus, the great majority of elderly patients are destined to maintain a continuous TKI treatment lifelong, leading to an expected impairment of the Health-Related quality of life (HRQoL), which is often compromised by concomitant comorbidities and poli-pharmacy. As a consequence, strategies alternative to TKI discontinuation has been explored, and mainly focus on the de-escalation of TKI dose, with the aim to maintain at least the MR3.0.
- We report here an update on the OPTkIMA trial, in which CML elderly patients in stable MR3.0/MR4.0 were randomized to receive an intermittent TKI schedule 1 month ON-1 month OFF for 3 years (FIXED arm) vs. a progressive de-escalation TKI dose up to one-third of the starting dose at the third year (PROGRESSIVE arm).
- The PROGRESSIVE TKI de-escalation schedule is associated with a higher incidence of $MR^{3.0}$ loss, without any evidence of disease progression. In the transition from the clinical trial to the real-life management, those patients who maintained the MR3.0 molecular response during the trial have been frequently considered eligible for TFR. The HRQoL generally improved during the de-escalation therapy in both randomization arms.

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CRediT authorship contribution statement

Michele Malagola: Writing – original draft, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Alessandra Iurlo:** Writing – review & editing, Data curation. **Cristina Bucelli:** Writing – review & editing, Data curation. **Massimiliano Bonifacio:** Writing – review & editing, Data curation. **Fabio Stagno:** Writing – review & editing, Data curation. **Gianni Binotto:** Writing – review & editing, Data curation. **Monia Lunghi:** Writing – review & editing, Data curation. **Monica Crugnola:** Writing – review & editing, Data curation. **Maria Luisa Ferrari:** Writing – review & editing, Data curation. **Fausto Castagnetti:** Writing – review & editing, Data curation. **Gianantonio Rosti:** Writing – review & editing, Data curation. **Roberto Massimo Lemoli:** Writing – review & editing, Data curation. **Maria Rosaria Coppi:** Writing – review & editing, Data curation. **Maria Teresa Corsetti:** Writing – review & editing, Data curation. **Marco De Gobbi:** Writing – review & editing, Data curation. **Atelda Romano:** Writing – review & editing, Data curation. **Mario Tiribelli:** Writing – review & editing, Data curation. **Antonella Russo Rossi:** Writing – review & editing, Data curation. **Sabina Russo:** Writing – review & editing, Data curation. **Marzia Defina:** Writing – review & editing, Data curation. **Mirko Farina:** Writing – review & editing, Data curation. **Simona Bernardi:** Writing – review & editing, Data curation. **Giulia Butturini:** Writing – review & editing, Data curation. **Simone Pellizzeri:** Writing – review & editing, Formal analysis, Data curation. **Aldo Maria Roccaro:** Writing – review & editing. **Domenico Russo:** Writing – original draft, Validation, Methodology, Formal analysis, Conceptualization.

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