A phase 2 trial of decreasing tyrosine kinase inhibitor dose in chronic myeloid leukaemia patients with stable major molecular response: data from the British DESTINY study

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ABSTRACT

BACKGROUND: Discontinuation of tyrosine kinase inhibitor (TKI) therapy is feasible for some patients with chronic myeloid leukaemia (CML) with deep molecular responses, defined as stable MR4 (*BCR-ABL1/ABL1* ratio <0.01%). However, patients in stable major molecular response (MMR; MR3; *BCR-ABL1/ABL1* ratio consistently < 0.1%) but not MR4 have not hitherto been studied. In addition, the effect of treatment de-escalation rather than outright stopping has not been investigated so far.

PATIENTS and METHODS: This study recruited 174 British adult CML patients in first chronic phase who had received TKI for ≥3 years and were either in stable MR4 (the 'MR4 cohort' n=125) or in stable MMR but not MR4 (the 'MMR cohort'; n=49) for ≥12 months. Participants received half their standard TKI dose for 12 months. Molecular recurrence was defined as loss of MMR (>0.1%) on two consecutive samples. The study endpoint is the proportion of patients who lose their MMR on de-escalation and regain MMR on TKI resumption. The trial was registered at https://clinicaltrials.gov/ as NCT 01804985.

FINDINGS: During the 12 months of half-dose therapy, 12 patients had molecular recurrence, all of whom regained MMR within 4 months of full dose TKI resumption. Recurrence was lower in the MR4 cohort (3 of 121 evaluable patients; 2.5%, 90% CI: 0.2-4.8%) than in the MMR cohort (9 of 48 evaluable patients; 18.8%, 90% CI: 9.5-28%) (p = 0.0007), but was unrelated to prior TKI or TKI therapy duration. Many adverse events improved during the first 3 months of de-escalation, though not thereafter. Overall, de-escalation saved 46.7% from an expected TKI budget (without de-escalation) of £4,156,969.

INTERPRETATION: TKI de-escalation is safe for the vast majority of patients with excellent responses to TKI therapy, and is associated with improvement in symptoms and significant financial savings. The data imply that lower TKI doses may maintain responses in these patients.

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INTRODUCTION

The advent of daily tyrosine kinase inhibitor (TKI) therapy for chronic myeloid leukaemia (CML) has transformed the outlook for CML to a disease where the majority of patients can expect a normal life span.[1] However, TKI therapy is not without adverse effects[2] and is expensive[3]. This has led to CML specialists and patients asking whether after a few years of TKI therapy, the disease may be sufficiently suppressed to permit treatment discontinuation. Several studies have established that some patients with enduring deep molecular responses to TKI therapy can discontinue treatment (reviewed in[4,5]). Early studies were confined to patients with undetectable *BCR-ABL1* transcripts by standard reverse transcriptase polymerase chain reaction (RT-PCR), and defined molecular recurrence as the reappearance of *BCR-ABL1* transcript positivity[6,7]. More recent studies have specified recurrence as the loss of major molecular response (MMR, defined as *BCR-ABL1/ABL1* transcript ratio of >0.1%, also called MR3 [molecular response of 3 logs below an arbitrary standard baseline]). Using this definition of recurrence, at 24 months after TKI cessation the A-STIM and KIDS studies reported that 58-64% of patients are recurrence-free[8, 9] and the large EUROSKI study of 868 patients similarly recently reported a rate of 52% at the same time point[10].

However, these studies were confined to patients in stable MR4 at entry, i.e. whose *BCR-ABL1/ABL1* ratio is consistently below 0.01% (molecular response 4 logs below the standard arbitrary baseline). Although there are anecdotal reports of successful treatment cessation for a few months in patients in stable MMR but not MR4, e.g. during pregnancy[11], such patients have not hitherto been formally studied in a stopping trial. In addition, TKI dose reduction in patients with good responses to TKI therapy but also troublesome adverse events can

ameliorate these yet maintain deep molecular response[2]. We therefore questioned whether some patients who might experience molecular recurrence on stopping TKI might nevertheless have been able to safely decrease TKI treatment without an increase in tumour burden.

The present De-Escalation and Stopping Therapy with Imatinib, Nilotinib or sprYcel (DESTINY) study was designed to examine the effects of treatment de-escalation as a prelude to complete cessation, in patients not only with deep molecular responses of MR4 or greater, but also to include patients with MMR but not MR4. The cessation phase is ongoing; here we report that de-escalation is safe for the vast majority of patients and that it is associated with a decrease in the severity of adverse events and significant savings in TKI costs.

PATIENTS and METHODS

Entry/exclusion criteria

Trial entry was restricted to *BCR-ABL1* transcript positive patients with either an e13a2, e14a2 or e19a2 fusion transcript, aged 18 or over in first chronic phase of CML, who had either received the same TKI (imatinib, dasatinib or nilotinib) since diagnosis or had switched only once for intolerance to the initial drug. Patients who showed resistance to prior TKIs and switched to another TKI were excluded. Prior interferon treatment was not an exclusion criterion as long as it had finished at least 12 months before entry; Philadelphia chromosome positivity was not mandatory. Participants must have received TKI for at least 3 years, and all PCR tests (minimum of 3) in the 12 months before trial entry must have been $\leq$0.1% (i.e. MMR), each with $\geq$ 10,000 *ABL1* control transcripts. Patients who had previously received more than 400mg daily of imatinib or 100mg daily of dasatinib or 400mg twice daily of

nilotinib were ineligible unless their high dose arose from participation in an earlier clinical trial in which higher doses were being compared with standard doses. Recipients of bosutinib or ponatinib at any point were ineligible. All entrants provided informed consent, and the trial was carried out in line with the Declaration of Helsinki, sponsored jointly by the University of Liverpool and Royal Liverpool & Broadgreen University Hospitals Trust, and they and the funding sources had no role in study design, or collection, analysis, or interpretation of the data or in the writing of this manuscript. Ethical approval was granted by the North West - Liverpool East Committee of the UK National Research Ethics Service. The trial was registered at https://clinicaltrials.gov/ as NCT 01804985.

Trial design

Participants decreased their entry TKI to half the standard dose for 12 months, as follows: imatinib 200mg daily, dasatinib 50mg daily or nilotinib 200mg twice daily. Central monitoring was carried out monthly in a central laboratory at Imperial Molecular Pathology at Hammersmith Hospital, London, and all *BCR-ABL1* ratios were expressed according to International Scale. Any result > 0.1% prompted an urgent 'alert' to the site to request a further confirmatory sample, typically carried out within 2 weeks of the alerting sample. Molecular recurrence was defined as loss of MR3 (>0.1%) on these two consecutive samples and timed as the date of the first of these samples. In the event of recurrence, all patients were required to resume the standard dose of their entry TKI. Molecular monitoring continued monthly until MMR was reached again. The study endpoint is the proportion of patients who lose their MMR on de-escalation and regain MMR on TKI resumption.

Formal adverse event reporting was not attempted, though the presence and severity of TKI related symptoms were recorded at each monthly visit, both by verbal reporting and by the

formal quality of life instruments EQ-5D[12] and FACT-BRM[13]. In addition each patient was asked to complete a diary of symptoms arising between scheduled visits.

Sample size and statistical analysis

The trial was originally structured as 2 parallel cohorts, one comprising patients who were in MR4 for all assessments in the 12 months prior to entry, and the other for patients who were partially or wholly in MMR but not stable MR4 during this time. Since the latter cohort could be regarded as more experimental, this arrangement provided a mechanism for the independent Data Monitoring Committee to close that arm if its recurrence rate was unacceptably high, without prejudicing the MR4 cohort. The minimum required sample size (168) was calculated on the basis of the maximum width of the 90% confidence interval for a wide range of values of the proportion of relapsing patients; we required the maximum width for the smallest group to be smaller than 0.28.

Authors REC (corresponding author), FP and TC had full access to all of the data, and LF had access to the molecular data. Authors REC and FP had the final responsibility to submit for publication. All statistical analyses were performed on an intention to treat basis using the R Programming Language for Statistical Analyses, version 3.3.1. No adjustment for multiple testing or missing data was incorporated. The proportions of patients relapsing were estimated together with 90% confidence intervals. Survival distribution curves were estimated by the method of Kaplan and Meier. Five patients (3 imatinib, 1 each for nilotinib and dasatinib) were already on the half-dose at trial entry because of toxicity at standard/intermediate doses (their entry was not excluded in the protocol). These patients all continued on half-dose treatment and are included in all the analyses.

In the calculation of TKI drug costs, the UK National Health Service list price for each TKI dose was used, without any local discounts and without Value Added Tax (20% currently in the UK).

RESULTS

Between 16th December 2013 and 10th April 2015, 174 patients (male 98; female 76) were recruited after giving informed consent from 20 UK centres. Their flow through the trial is summarised in the CONSORT diagram in Figure 1. Of these, 125 fulfilled the definition for the MR4 cohort and 49 fell into the definition of 'MMR but not MR4' (hereafter referred to as 'the MMR cohort') as defined above. At entry, 148 patients were receiving imatinib, 16 nilotinib and 10 dasatinib. Details for the study population are given in Table 1. The median duration of TKI therapy was 7.7 and 6.5 years for the MMR and MR4 cohorts respectively though this was not significantly different; otherwise the MMR and MR4 cohorts were broadly comparable.

Effect of de-escalation on molecular recurrence

During the 12 months of half-dose therapy, 12 patients had molecular recurrence (loss of MMR), all of whom were receiving imatinib. Molecular recurrence was significantly lower in the MR4 cohort (3 of 121 evaluable patients; 2.5%, 90% CI: 0.2-4.8%) than in the MMR cohort (9 of 48 evaluable patients; 18.8%, 90% CI: 9.5-28%) ($p = 0.0007$). The median time to relapse was shorter in the MMR cohort than in the MR4 cohort (4.4 months vs. 8.7 months), as shown in Figure 2 panel A. As shown in Table 2, the probability of molecular recurrence on de-escalation was not related to age, gender, weight, performance status, *BCR-ABL1* transcript type, or the duration of TKI therapy (median 6.9 years overall). In this

regard, no recurrences were observed in the quartile with the shortest prior TKI treatment (< 4.8 years), compared with 5/43 in the 2nd quartile (4.8-6.9 years), 4/43 in the 3rd quartile (6.9-10.2 years) and 3/44 in the 4th quartile (10.2-14.1 years). Too few data were available from diagnosis on the components (especially spleen size) of the Sokal, EURO/Hasford or more recent scoring systems to investigate whether these might predict molecular recurrence. Too few patients were receiving dasatinib or nilotinib to allow comparison of recurrence rates between imatinib and second generation TKI recipients. In addition, the probability of molecular recurrence was not related to simple blood count parameters (data not shown). Five patients (1 MMR and 4 MR4) did not complete 12 months of de-escalation for various reasons (poor protocol adherence (2 patients), relocation, pregnancy and intercurrent illness). Table 4 shows that 22 patients entered the trial on lower than usual TKI doses. Two recurrences occurred among the 18 patients taking less than imatinib 400mg daily (11.1%), which is comparable to the 10 recurrences among 130 patients (7.7%) entering on 400mg daily. We cannot comment on the effect of lower entrance doses for dasatinib (2 cases) or nilotinib (2 cases) as no 2G TKI recipient had molecular recurrence.

No progression to advanced phase or loss of cytogenetic response was seen. No tyrosine kinase domain mutation was detected at the time of molecular relapse in any of 7 patients analysed to date by next generation sequencing. As shown in Figure 2 panel B, all 12 patients with molecular recurrence regained MMR within 4 months of resumption of full dose TKI (median time to recovery = 77 days). As shown in the CONSORT diagram of Figure 1, 36 (73%) patients in the MMR cohort and 117 (94%) in the MR4 cohort have proceeded to the currently ongoing stopping phase of the trial.

Effect of de-escalation on adverse events

Many patients described symptoms present at trial entry, either in verbal reporting at scheduled visits or in their diaries. In the first 3 months of de-escalation, many of these improved as shown in Figure 3. However, little further improvement was seen in the subsequent ~9 months. Details of symptoms that were not present at trial entry that arose during de-escalation are given in the Supplementary Table. Fifty-three new musculoskeletal symptoms were reported by 36 patients (21%), of which 43 were assessed as grade 1 (not interfering with the patient's usual function), and 10 as grade 2 (enough discomfort to interfere with usual activity). The episodes were described as cramps, arthritis or musculoskeletal pain. No grade 3 or 4 episodes were recorded. A similar pattern, albeit at lower frequency, was also observed for other common TKI adverse events, summarised in the Supplementary Table. Interestingly, all 12 recurrences occurred in the 138 patients that did not report any musculoskeletal withdrawal symptoms (i.e. recurrence rate of 8.7%). During the course of the trial, 15 serious adverse events were reported, summarised in Table 3. All were assessed by sites as unrelated to the TKI or the underlying CML. They included one fatality due to worsening pre-existing peripheral arterial occlusive disease in a patient who had received only imatinib.

Formal quality of life assessments by EQ-5D and FACT-BRM were of marginal use as the mean scores for each instrument were similar to that of a healthy control population at trial entry and did not appreciably change during de-escalation (data not shown).

Financial effect of de-escalation

Table 4 gives details of the savings in drug costs during the 12 months of de-escalation. Figures are in UK pounds sterling throughout. In the UK, although the cost of imatinib is directly proportional to the dose used, this is not the case for nilotinib (400mg twice daily and 300mg twice daily cost the same) or dasatinib (100mg daily and 80mg daily cost the same).

Among the 12 patients undergoing molecular recurrence, the timing of relapse and of the subsequent resumption of standard TKI dose was variable, resulting in saved TKI costs varying from £3,038 to £12,311 per relapsing patient. Overall, 46.7% (£1,943,364) was saved from an expected TKI budget (without de-escalation) of £4,156,969. If considering the MR4 cohort alone, the saving was 47.7% (£1,429,330 from an expected budget of £2,993,854). Similarly, in the MMR cohort alone, the saving was 44.2% (£514,034 from an expected budget of £1,163,115).

DISCUSSION

Although several studies of TKI cessation have been reported, almost nothing is known about the feasibility of treatment de-escalation in patients with stable molecular responses. A single-arm study commenced in 2008 of 76 patients aged 65 years or older who had received imatinib for at least 2 years and in stable complete cytogenetic response (for at least 1 year) examined intermittent imatinib (1 month on alternating with 1 month off). Almost all entrants were in fact also in MMR. With a minimum follow-up of 4 years, 27 patients (35%) lost MMR (and 13 (17%) lost cytogenetic remission)[14], though all patients with adequate follow up regained MMR within 7 months. In the present study, we demonstrate 3 principal findings. Firstly, with a molecular recurrence rate of 2.5% after 12 months, de-escalation is clearly safe for patients in stable MR4 or deeper remission. Similarly, since 81% of patients in stable MR3 though not MR4 remain recurrence-free at 12 months, it is also clinically reasonable to offer de-escalation to such patients. It has been suggested that the absence of stable MR4 should be a 'red light' warning against treatment cessation[4]. The present report is confined to treatment de-escalation so does not allow comment on this, but does suggest that as long as the patient is in stable MMR, de-escalation may be a reasonable option. Also, our findings cannot be generalised to patients with excellent responses to a TKI given as second

line after initial resistance, since these patients were excluded here. It is of interest that all 12 patients experiencing molecular recurrence were among the 148 receiving imatinib, while no recurrences were seen in the recipients of second generation TKI; this difference was not statistically significant. Since all relapsing patients promptly returned to MMR or better within 4 months of resumption of full TKI dose, it is plausible that de-escalation should become the standard of care for such patients.

Secondly, this practice-changing view is reinforced by the demonstration of general improvement of adverse events in both the MMR and MR4 cohorts, with only mild (none > grade 2 severity) and transient evidence of the musculoskeletal symptoms that have recently been described on complete TKI withdrawal[9,15]. Although these and other symptoms generally improved during de-escalation as shown in Figure 3, this trend was not of sufficient strength to be detectable by the quality of life assessment tools used here, emphasising their inappropriateness for well controlled CML patients in the TKI era[16,17]. Quality of life data using a symptom assessment tool more dedicated to TKI-treated CML patients[18,19] would be of interest in future studies of TKI de-escalation/discontinuation. Although the trial protocol required patients with molecular recurrence to resume their TKI at full dose until MMR was re-attained, it would be interesting to formally study whether it is possible to subsequently resume reduced-dose treatment without molecular recurrence.

Thirdly, de-escalation in the MR4 cohort alone, the MMR cohort alone or the combined population is associated with a saving of almost half their expected TKI costs. The exact magnitude of these savings is dependent on local base prices, including any taxes, and for imatinib these are currently falling as generic alternatives are introduced. Although we have used individual patient TKI consumption data, it does not take account of the increased PCR monitoring and associated clinical visits that are advisable in patients undergoing de-escalation (or complete cessation). These appear very unlikely to significantly impact on the

impressive savings on TKI costs, though require further study in trials incorporating detailed pharmaco-economic evaluation of TKI de-escalation/cessation.

In summary, in CML patients with stable MR3 or better, decreasing TKI treatment to half the standard dose appears safe, and is associated with improvement in TKI related side effects, implying that many patients with stable responses may be able to maintain their responses on lower TKI doses. De-escalation is also associated with substantial financial savings. Studies of more ambitious de-escalation are warranted.

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AUTHOR CONTRIBUTIONS

REC is the Chief Investigator. He has contributed to the study design, data collection and data interpretation, and wrote the manuscript.

FP is the study's statistician and has contributed generally but focussed on data analysis and has co-written the manuscript.

TC is the study co-ordinator, in charge of site set up, sponsor liaison and administrative aspects of study administration, and contributing to central data collection.

LF has been responsible for all the PCR laboratory studies.

The study management group comprised REC, MC, SO'B and LF, together with TC and FP.

All authors contributed to study design and commented on and approved the manuscript. REC, JFA, DM, CP, GS, JLB, HdL, SO'B, and MC were all Principal Investigators at their various sites and recruited patients.

DECLARATION of INTERESTS

REC reports other grants from Bloodwise during the conduct of the study; grants and personal fees from Novartis, Bristol Myers Squibb and Pfizer, and personal fees from Ariad/Incyte, outside the submitted work. JFA reports grants and personal fees from Ariad/Incyte and Pfizer, and personal fees from Bristol Myers Squibb and Novartis, outside the submitted work. DM reports personal fees from Novartis, Bristol Myers Squibb, Pfizer and Ariad/Incyte, outside the submitted work. GS reports personal fees from Pfizer, Bristol Myers Squibb and Novartis, outside the submitted work. JLB reports personal fees from Novartis pharmaceuticals, Pfizer, Ariad / Incyte and Bristol Myers Squibb, outside the submitted work. HdL reports grants and personal fees from Ariad/Incyte, grants from Bristol Myers Squibb and personal fees from Novartis and Pfizer, outside the submitted work. SGO'B reports grants from Ariad during the conduct of the study; grants and personal fees from Bristol Myers Squibb and personal fees from Pfizer, outside the submitted work. MC reports grants from Bloodwise during the conduct of the study; personal fees from Ariad/Incyte and Pfizer, personal fees and non-financial support from Novartis Pharma and Bristol-Myers Squibb, outside the submitted work. FP, CP, TC and LF declare no conflict of interests.

TABLE and FIGURE LEGENDS

Table 1. Patient characteristics at trial entry. IQR = interquartile range. *BCR-ABL1* data are the centralised results at trial entry.

Table 2. Effect of various parameters on molecular recurrence. Data are frequency (proportion) for categorical variables, and median (IQR) for continuous variables. Statistical tests are Fisher's exact test for categorical variables and the Mann-Whitney U-test for continuous variables.

Table 3. Serious adverse events during de-escalation. SAE = serious adverse event. Data are the number of SAEs (number of patients). Grading is according to the National Cancer Institute Common Toxicity criteria. * denotes the single fatality.

Table 4. Financial implications of de-escalation. All costs are in pounds sterling using the UK National Health Service list price, exclusive of Value Added Tax. Costs for imatinib are for commercial Glivec®. UPN = unique patient number.

Figure 1. CONSORT diagram of patient disposition during de-escalation.

Figure 2. Molecular recurrence-free survival (panel A) and time to re-attaining MMR (panel B), for the MMR and the MR4 cohorts. Numbers at risk are as stated. The hazard ratio for the difference in recurrence free survival between the two groups is 0.12 (90% Confidence Interval = 0.04 – 0.37).

Figure 3. Evolution of patient-reported symptoms by month, for the MMR (left panel) and MR4 (right panel) cohorts.

Table 1. Patient characteristics at trial entry.

	MMR N = 49	**MR4 N = 125**	**Overall N = 174**
Demographic Characteristics			
Age median (IQR)	57 (45, 66)	61 (51, 68)	59 (50, 68)
Gender Male [n (%)]	25 (51%)	73 (58%)	98 (56%)
Physical findings			
Weight median (IQR) *Missing*	79 (70, 89) *1*	81 (72, 94) -	81 (72, 92) *1*
ECOG performance status [n, (%)]			
0 - Fully Active	42 (86%)	113 (90%)	155 (89%)
1 - Work Able	7 (14%)	10 (8%)	17 (9%)
2 - Not Work Able	-	1 (1%)	1 (1%)
3 - Limited Self Care	-	1 (1%)	1 (1%)
4 - Completely Disabled	-	-	-
Clinical characteristics			
BCR-ABL1/ABL1 transcript ratio (%) median (IQR, range)	0.0047 (0.002, 0.009)	0.001 (0.0003, 0.002)	0.001 (0.0006, 0.003)
Medical History			
Total time on TKI (years) median (IQR) *Missing*	7.7 (5.1, 10.7) -	6.5 (4.8, 10.2) *1*	6.9 (4.8, 10.2) *1*
Medication			
Imatinib [n (%)]	43 (88%)	105 (84%)	148 (85%)
Nilotinib [n (%)]	2 (4%)	14 (11%)	16 (9%)
Dasatinib [n (%)]	4 (8%)	6 (5%)	10 (6%)

Table 2. Effect of various parameters on molecular recurrence.

Characteristic	Molecular Recurrence		p-value
	Yes (n = 12)	No (n = 162)	
Molecular cohort			
MMR	9 (75%)	40 (25%)	0.0007
MR4	3 (25%)	122 (75%)	
Gender			
Male	6 (50%)	92 (57%)	0.77
Female	6 (50%)	70 (43%)	
ECOG performance status			
0	12 (100%)	143 (88%)	0.37
1+	0 (0%)	19 (12%)	
Age	60 (46, 69)	59 (50, 68)	0.84
Weight (kg)	84 (74, 90)	80 (71, 92)	0.90
Time on TKI (years)	7.6 (6.4, 9.1)	6.8 (4.8, 10.2)	0.36
Time in MMR (years)	5.1 (4.4, 6.6)	5.5 (3.8, 8.4)	0.68
Missing	-	*1*	
BCR-ABL1 transcript type			
e13a2	5 (42%)	29 (22%)	0.28
e14a2	5 (42%)	72 (55%)	
Other/both	2 (16%)	31 (24%)	
Unknown	-	30	

Table 3. Serious adverse events during de-escalation.

		Grade				
Name (number) of SAE	Treatment cohort	1	2	3	4	5
Myocardial infarction (2), Syncope (1)	MMR	-	-	-	-	-
	MR4	-	1 (1)	2 (2)	-	-
Abdominal pain (1)	MMR	-	-	-	-	-
	MR4	-	-	-	1 (1)	-
Pain in lower limbs* (1)	MMR	-	-	-	-	-
	MR4	-	-	1 (1)	-	-
Gallbladder pain (1)	MMR	-	-	-	-	-
	MR4	-	-	1 (1)	-	-
Allergic reaction (1)	MMR	-	-	-	-	-
	MR4	-	1 (1)	-	-	-
Sepsis (3), Urinary tract infection (1), Skin Infection (1)	MMR	-	-	1 (1)	-	-
	MR4	-	2 (1)	2 (2)	-	-
Bone pain (1), Other (1)	MMR	-	-	-	-	-
	MR4	-	-	2 (2)	-	-
Urinary retention (1)	MMR	-	-	-	-	-
	MR4	-	1 (1)	-	-	-
Total	MMR	-	-	1 (1)	-	-
	MR4	-	5 (4)	8 (7)	1 (1)	-

Table 4. Financial implications of de-escalation.

Patients with molecular recurrence:

UPN	At trial entry:		Cohort	TKI cost without de-escalation	Months to recurrence	Total months at half dose	Actual TKI cost (£)	TKI cost saved (£)
	TKI	Dose						
8	Imatinib	400mg daily	MMR	23700	10.2	10.4	13596	10104
22	Imatinib	300mg daily	MMR	17775	12.0	13.8	11076	6699
23	Imatinib	400mg daily	MMR	23700	8.0	8.3	15643	8058
44	Imatinib	400mg daily	MMR	23700	4.1	4.1	19736	3965
51	Imatinib	400mg daily	MMR	23700	4.8	5.3	18521	5180
76	Imatinib	300mg daily	MMR	17775	4.3	4.3	15697	2078
79	Imatinib	400mg daily	MMR	23700	2.5	3.1	20663	3038
107	Imatinib	400mg daily	MMR	23700	3.2	3.2	20599	3102
138	Imatinib	400mg daily	MMR	23700	5.9	5.9	17913	5788
28	Imatinib	400mg daily	MR4	23700	8.6	8.9	15003	8697
89	Imatinib	400mg daily	MR4	23700	8.0	8.1	15771	7930
99	Imatinib	400mg daily	MR4	23700	12.0	12.6	11390	12311

Patients completing 12 months of de-escalation without molecular recurrence:

No. of patients	At trial entry:		TKI cost without de-escalation (£)	Total TKI cost saved (£)
	TKI	Dose		
120	Imatinib	400mg daily	2844085	1422064
1	Imatinib	350mg daily	20738	8888
11	Imatinib	300mg daily	195528	65176
1	Imatinib	250mg daily	14813	2962
3	Imatinib	200mg daily	35551	0
10	Nilotinib	400mg twice daily	317356	158678
4	Nilotinib	300mg twice daily	126942	63471
1	Nilotinib	225mg twice daily	23802	7934
1	Nilotinib	200mg twice daily	15868	0
8	Dasatinib	100mg daily	243983	121992
1	Dasatinib	80mg daily	30498	15249
1	Dasatinib	50mg daily	15249	0

Figure 1. CONSORT diagram of patient disposition during de-escalation.

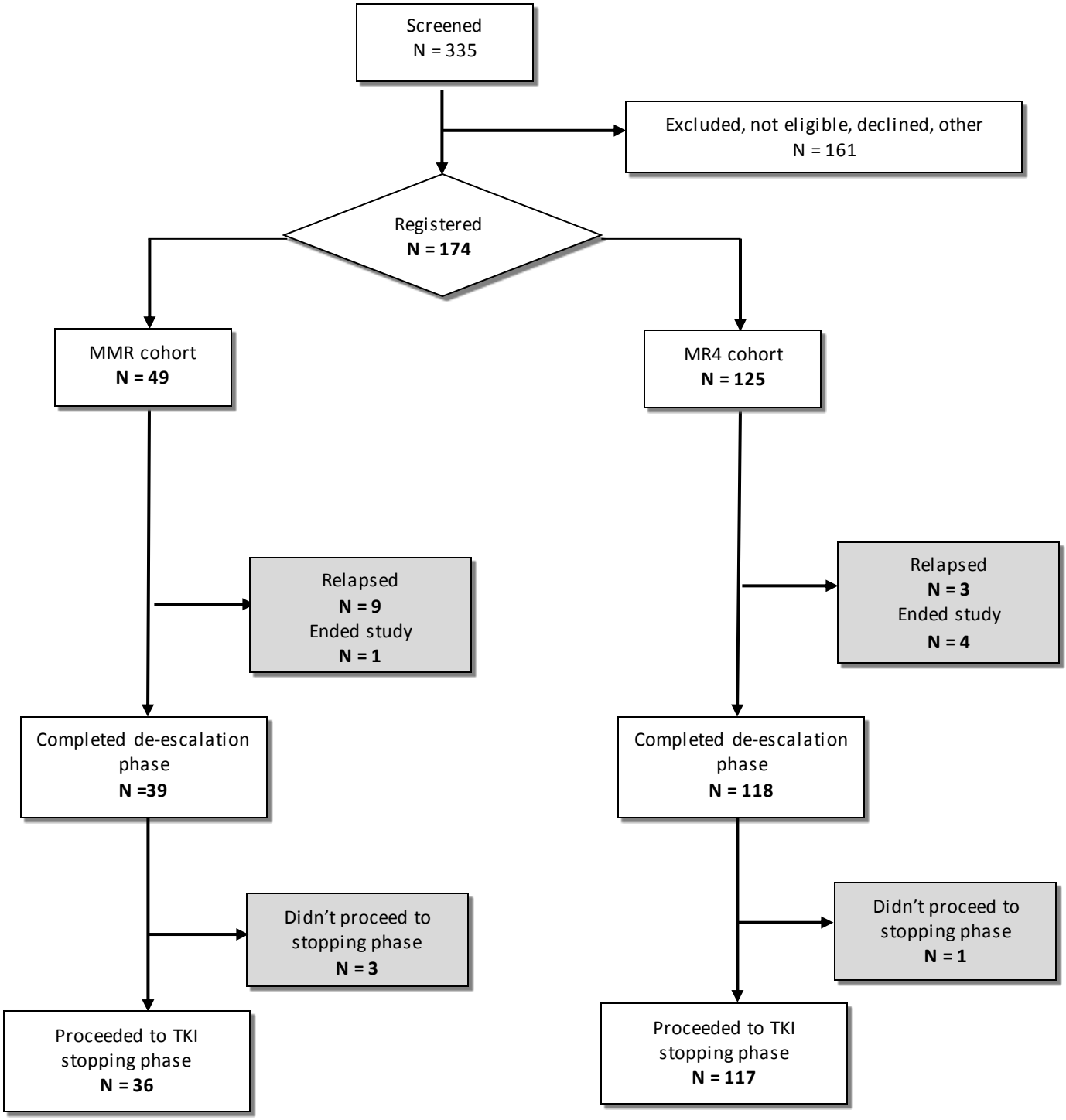
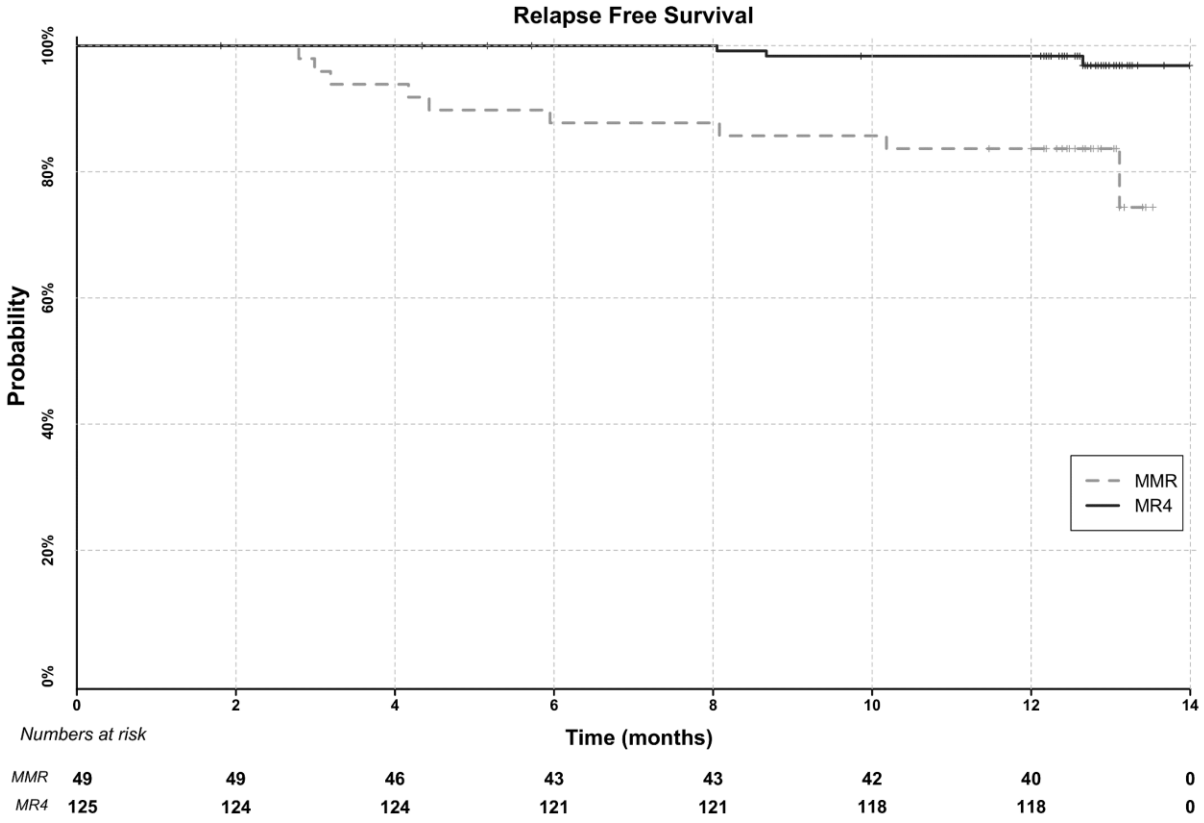


Figure 2.

A


Relapse Free Survival
Probability
100%
80%
60%
40%
20%
0%
MMR
MR4
0
2
4
6
8
10
12
14
Time (months)
Numbers at risk
MMR 49 49 46 43 43 42 40 0
MR4 125 124 124 121 121 118 118 0

B

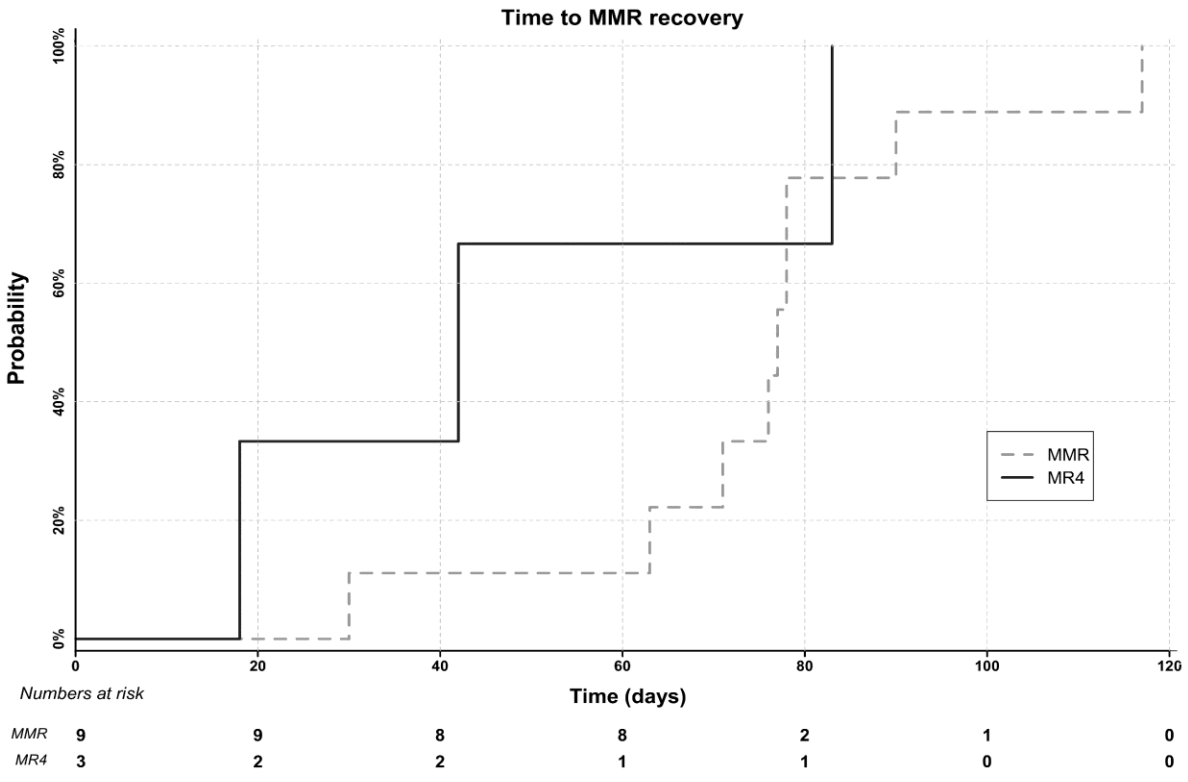
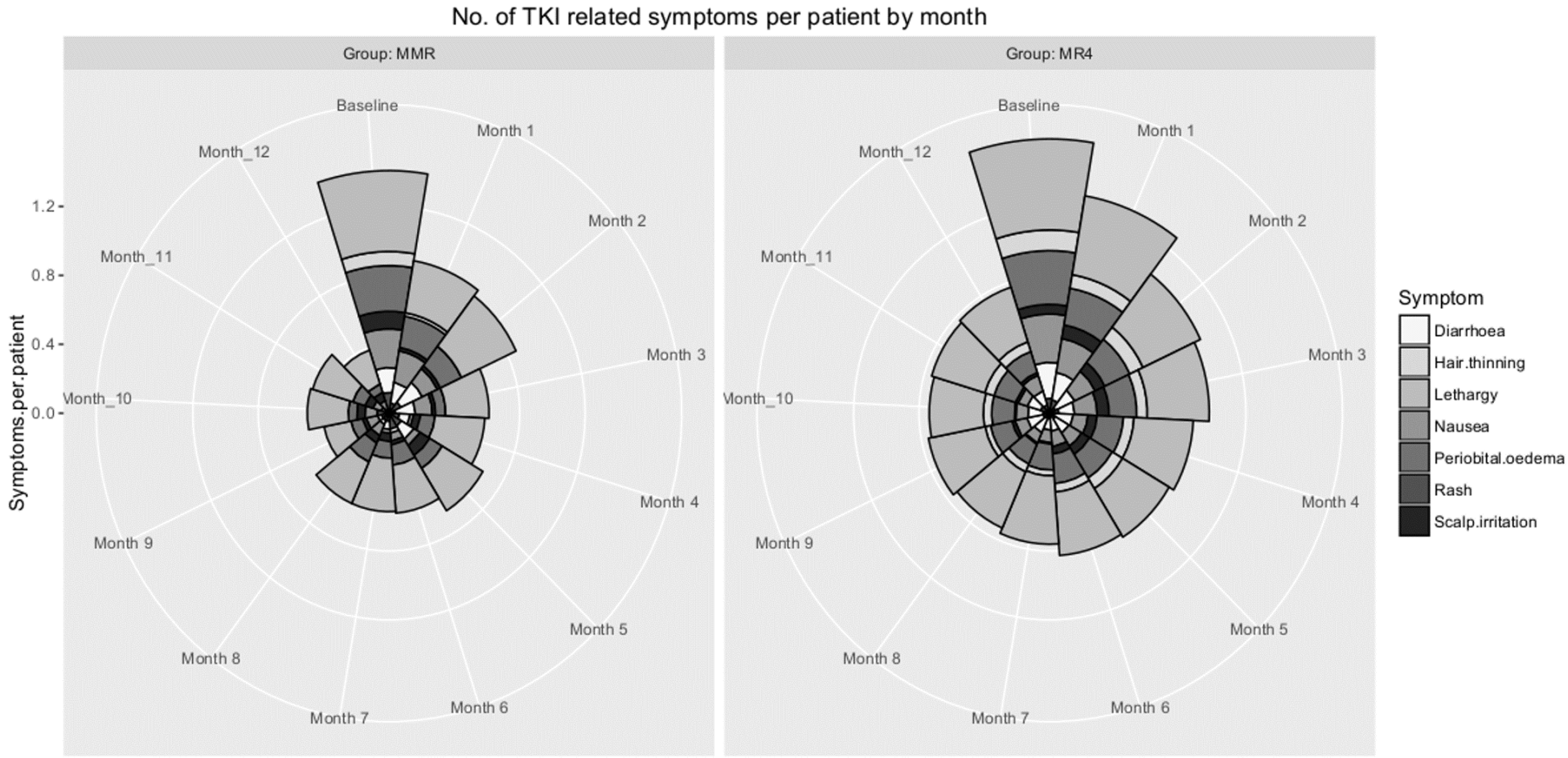

Time to MMR recovery
Probability
100%
80%
60%
40%
20%
0%
MMR
MR4
0
20
40
60
80
100
120
Time (days)
Numbers at risk
MMR 9 9 8 8 2 1 0
MR4 3 2 2 1 1 0 0

Figure 3


No. of TKI related symptoms per patient by month
Group: MMR
Group: MR4
Symptoms.per.patient
0.0
0.4
0.8
1.2
Baseline
Month 1
Month 2
Month 3
Month 4
Month 5
Month 6
Month 7
Month 8
Month 9
Month_10
Month_11
Month_12
Symptom
Diarrhoea
Hair.thinning
Lethargy
Nausea
Periobital.oedema
Rash
Scalp.irritation

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