(De- Escalation and Stopping Treatment of Imatinib, Nilotinib or sprYcel in chronic myeloid leukaemia) (DESTINY)

NCT01804985

ISRCTN Number: 74084226

EudraCT number: 2012-004025-24

Final Statistical Analysis Report Plan

Version 1

17th July 2019

A trial of de-escalation and stopping treatment in chronic myeloid leukaemia patients with excellent responses to tyrosine kinase inhibitor therapy

(**D**e- **E**scalation and **S**topping **T**reatment of **I**matinib, **N**ilotinib or spr**Y**cel in chronic myeloid leukaemia)
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Prepared by: Silvia Cicconi - Trial Statistician

Contents

1. INTRODUCTION

This document details the rules proposed and the presentation that will be followed, as closely as possible, when analysing and reporting the main results from the trial of de-escalation and stopping treatment in chronic myeloid leukaemia funded by the Leukaemia and Lymphoma Research Clinical Trials Committee.

The purpose of the plan is to:

a. Ensure that the analysis is appropriate for the aims of the trial, reflects good statistical practice in general, and minimises bias by preventing inappropriate post hoc analyses;
b. Explain in detail how the data will be handled and analysed to enable others to perform the actual analysis in the event of sickness or other absence;
c. Protect the project by helping it keep to timelines and within scope.

Additional exploratory or auxiliary analyses of data not specified in the protocol are permitted but fall outside the scope of this analysis plan (although such analyses would be expected to follow Good Statistical Practice).

The analysis strategy will be made available if required by journal editors or referees when the main papers are submitted for publication. Additional analyses suggested by reviewers or editors will, if considered appropriate, be performed in accordance with the Analysis Plan, but if reported the source of such a post-hoc analysis will be declared.

Amendments to the statistical analysis plan will be described and justified in the final report of the trial.

2. TRIAL DESIGN

2.1. Configuration

A multi-centre, single arm, Phase II, prevalence study.

2.2. Interventions

De-escalation to half the standard TKI dose for up to 13 months, followed by 2 years treatment cessation. If on imatinib, the dose should be decreased to 200mg daily; if on nilotinib to 200mg twice daily and if on dasatinib to 50 mg daily.

2.3. Objectives

To determine the safety and efficacy of initially de-escalating and then stopping TKI treatment, in CML patients with either undetectable disease or with stable MMR.

2.4. Eligibility Criteria

Inclusion Criteria

1. CML in first chronic phase.
2. Demonstration of BCR-ABL1 positivity at or shortly after original diagnosis*.
3. Written Informed Consent
4. Must have received TKI treatment for at least 3 years.
5. At least 3 molecular results over the preceding 12 months that fit either of the following groups (results from any UK lab are acceptable):
    - (MR^4 group) all the available BCR-ABL1 molecular results over the preceding 12 months are in MR^4 (MR^4 is defined as a BCR-ABL1/ABL1 ratio of zero, (reported to international standard (IS) where possible); with at least 10,000 ABL1 control transcripts).
    - (MMR group) some or all BCR-ABL1 molecular results are in MMR (BCR-ABL1/ABL1 ratio of 0.1% or less, (reported to International Standard (IS) where possible), but not zero, with at least 10,000 ABL1 control transcripts). If the results over the preceding 12 months are a mix of MMR and undetectable BCR-ABL1, then the patient is eligible for the MMR but not the MR^4 group.

** Patients who are Philadelphia chromosome (Ph) negative (or whose Ph status is not known) are eligible. Patients who do not have a standard BCR-ABL1 fusion transcript (i.e. other than e13a2 or e14a2, also known as b2a2 and b3a2) may be eligible, but before screening the patient, contact should be made with Prof Foroni at Hammersmith Hospital (see contacts in the Protocol) since specialised quantitative molecular assessment will be required.*

Exclusion Criteria

1. Age under 18
2. Life expectancy is predicted to be less than 37 months because of intercurrent illness
3. Presence of serious concomitant illness (e.g. heart, renal, respiratory or active malignant disease) that might preclude completion of the trial
4. CML in accelerated phase or blast crisis at any time
5. Any molecular result during the preceding 12 months that is not in either MMR or MR^4.

6. Patients who switched previous licensed TKI treatment (imatinib, nilotinib or dasatinib) twice or more because of intolerance.
7. Treatment with higher than standard TKI doses ('standard' is defined as imatinib 400mg daily, nilotinib 400mg twice daily or dasatinib 100mg daily). However, an exception is made for patients who at original diagnosis commenced on either 800mg of imatinib on the SPIRIT1 study, or 140mg (or 70mg b.d.) of dasatinib in the Bristol-Myers Squibb 034 study. In each case these latter patients ARE eligible provided they fulfil other molecular criteria, since they do not demonstrate resistant disease.
8. Patients who switched previous licensed TKI treatment (imatinib, nilotinib or dasatinib) because of resistance. Patients treated with lower (but at least 50%) than standard TKI doses (as defined in the previous criterion) for tolerance reasons may be included, but will de-escalate to the same doses as for standard dose patients and will be analysed separately, as they could be seen as undertreated.
9. Previous treatment with ponatinib or bosutinib. Patients who received interferon prior to commencing TKI (even if resistant to their interferon) are eligible, provided their response to TKI fits the entry criteria and the use of interferon ceased at least 12 months prior to study entry.
10. Pregnant or lactating women
11. Women of childbearing potential, including women whose last menstrual period was less than one year prior to screening, unable or unwilling to use adequate contraception from trial start to one year after the last dose of protocol therapy. Adequate contraception is defined as hormonal birth control, intrauterine device, double barrier method or total abstinence.

2.5. Sample size

Seventy cases will give a 90% confidence interval of maximum width 0.2, for a wide range (0.3 to 0.7) of values of the proportion, p, of relapsing patients. The width will be smaller the closer the estimate is to 0 (or 1). Assuming a dropout rate of 17% and an anticipated equal group allocation, 168 patients are needed.

The accrual of patients within each group largely depends on factors that cannot be controlled or specified a-priori. Hence, to avoid early closing of recruitment in one group which could potentially have a negative effect in overall recruitment and would require substantial extension in the recruitment period we are willing to allow for unequal group allocation and some variation in the maximum confidence interval width. Assuming that we recruit 168 patients in total, under the worst case scenario (p=0.5, group allocation 1:3) the 90% confidence intervals for the two groups ("larger" and "smaller") will have a maximum width of 0.16 and 0.28 respectively.

2.6. Randomisation procedure

None – this is a single arm trial.

2.7. Blinding

None - open label

2.8. Endpoints

Primary outcome

The proportion of patients who can first de-escalate their treatment (to half the standard dose of their TKI) for 12 months, and then stop treatment completely for a further 2 years, without losing MMR. This will be calculated separately for each of the two groups (MR^4 and MMR).

Secondary outcomes

- Proportion of patients who can successfully de-escalate their treatment (to half the standard dose of their TKI), but who then lose MMR on complete TKI cessation.
- Proportion of patients who lose their MMR on de-escalation/stopping and regain MMR on resumption of their TKI.
- Molecular relapse-free survival (RFS); RFS is defined as the time from the first day of de-escalation to the date of confirmed loss of MMR (two consecutive BCR-ABL >0.1% IS).
- Progression-free survival (PFS); PFS is defined as the time from the first day of de-escalation to the date of progression to accelerated phase/ blast crisis or death from any cause (earliest occurrence).
- Overall survival (OS); OS is defined as the time from the first day of de-escalation to the date of death from any cause.
- Event-free survival (EFS); EFS is defined as the time from the first day of de-escalation to the date of confirmed loss of MMR, progression to AP/BC or death from any cause.
- Time to MMR recovery (TTR); TTR is defined as the time from the date of confirmed loss of MMR to the date of MMR recovery.
- Proportion of registered MMR and MR^4 patients in confirmed $MR^{4.5}$ (BCR-ABL ≤ 0.0032% IS with at least 31,623 ABL1 control transcripts) prior to being enrolled in the study (screening phase).
- Quality of Life
- Health Economic Assessment
- Lab studies to define subsets of patients who are more likely to relapse on de-escalation / cessation.

The last two secondary outcomes are not part of this statistical analysis plan.

2.9. Interim Monitoring and Analyses

The proportion of relapsing patients will be assessed at 3 planned interim analyses: when 60 patients relapse or complete 12 months de-escalation, when 60 relapse or complete 12 months of cessation, and when 60 relapse or complete 24 months cessation. There are no formal stopping rules but the Independent Data Monitoring and Safety Committee (ISDMC) will review the interim analyses and give advice on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients or further follow-up.

A decision to discontinue recruitment will be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community. The entire trial (or the MMR or MR^4 elements alone) may be stopped if de-escalation or

stopping are producing an unacceptable rate of molecular relapse. For this purpose, the MMR and MR^4 groups will be treated separately, since the former may well have a higher relapse rate. Unacceptable relapse for this purpose is at the discretion of the Data Monitoring Committee, bearing in mind that the relapse rate in the STIM trial was 61% overall and 59% (48% - 71%) after 12 months of cessation.

Regardless of the reason(s) for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented. In terminating the trial, the sponsor and the Investigators will ensure that adequate consideration is given to the protection of the patient's interest.

All interim analysis results of the primary and secondary outcome measures will be confidential to the ISDMC members and will not be for review by the trial management group (except the trial statistician preparing the ISDMC report), Trial Steering Committee, investigators or collaborators.

3. TRIAL HISTORY

3.1. Quality control and data validation procedures

Randomisation checks
Not applicable – there is no randomisation in this trial.

Derivation of primary outcome
The code for derivation of the primary outcome will be validated by an independent statistician on a risk approach basis. The same will apply to secondary outcomes code.

Automated checks
The MACRO database includes validation features which to alert the user to certain inconsistent or missing data on data entry and automatically raise a query which is emailed to the research site. Automated email reminders are also generated by the database if follow up data from a scheduled patient visit is overdue.

Other checks
Eligibility criteria, informed consent and registration dates/numbers are checked by the trial team at the time of registration.

3.2. Protocol Amendments

This will include a short summary of all protocol amendments.

3.3. Trial Milestones

First patient was recruited on:	
Latest patient was recruited on:	
Cut-off date (data freeze) for this report:	
Date of final data extraction for this report:	
Total number screened to data freeze:	
Total number recruited to data freeze:	
Target number of patients:	
Proportion of target number recruited:	

4. PROPOSED METHODOLOGY

The trigger for the final analysis will be the date when the last relapse-free patient completes 37 months of follow-up or the date when the last relapsed patient regains MMR (latest occurrence) unless the TSC decides to terminate the trial prematurely.

As this is a prevalence study, analyses of the two cohorts (MMR and MR^4) will be carried out separately, using the same methods for each. For any statistical analysis MR^4 patients will be re-classified to either MMR or MR^4 group based on the following criterion:

- MR^4: At least complete molecular remission MR^4 (either (i) detectable disease **≤0.01%** BCR-ABL IS or (ii) undetectable disease in cDNA with ≥ 10,000 ABL or ≥ 24,000 GUS transcripts) for at least one year; at least three PCR-results with MR^4 within the last year (+- 2 months) before study entry and no PCR-results > 0.01% during the same period.

4.1. Patient Groups for Analysis

Full Analysis set: In order to follow the Intention to Treat (ITT) principle this consists of all registered patients excepting for:

a) Patients withdrawing consent between registration and starting therapy
b) Patients withdrawn from the study after registration because of irregularities with the consent process and
c) Patients whose information determining ineligibility existed before registration but was not read until after registration.

Per protocol set: This consists of those patients in the Full Analysis set without any major protocol deviations, following review by the Trial Management Group.

Safety set: All patients who received any trial treatment.

4.2. Handling of dropouts

Dropouts, that is unevaluable patients, will be censored at last visit date in survival analyses or treated as non-responders for the purpose of clinical response.

4.3. Identification and handling of Outliers

For continuous variables potential outliers will be defined as follows (Tukey, 1977)[1] after testing for symmetry and if non-symmetric, transforming to approximate symmetry using a "ladder of powers" approach using the Stata command *ladder*:

"Mild" outliers: UQ+1.5×IQR to UQ+3×IQR **or** LQ-1.5×IQ to LQ-3×IQR
"Severe" outliers: values more extreme than the above

(Note: UQ=Upper Quartile, LQ=Lower Quartile, IQR=Inter Quartile Range)

If after transformation no outliers are apparent then no action will be taken even if values appear as outliers on the original scale, apart from use of the transformation if normality is

[1] Tukey, J.W. (1977), Exploratory Data Analysis, Reading, MA: Addison-Wesley

required for a particular statistical procedure, or to remove the leverage effect of the outlying values.

Otherwise outliers in quantitative data will be queried but no action taken if the result is not amended.

4.4. Study centre effects

There will be limited capacity to investigate these formally and such centre effects are to be expected by chance.

4.5. Adjustment for covariates

No appropriate adjustment for covariates has been identified.

4.6. Multiplicity adjustments

No adjustment will be made.

4.7. Missing data

This problem is not expected to arise for the primary outcome analysis; the primary outcome is relapse rate which is easily ascertained. If >20% of patients have missing/unacceptable values on any of the variables of interest (e.g., secondary outcomes), then multiple imputation should be attempted, performing at least 10 separate sets of multiple imputations using chained equations using separate imputations for MMR and MR^4 groups.

4.8. Sensitivity analyses

These will consist of:

- Per-protocol analysis for primary endpoint

4.9. Pre-specified subgroup analyses

The final analysis of primary and secondary outcomes will be analysed in the following subgroups:

- MMR
- MR^4

The primary outcome and time to molecular relapse will also be analysed according to $MR^{4.5}$ status prior entering the study within each subgroup:

- MMR - $MR^{4.5}$
- MMR - not $MR^{4.5}$
- MR^4 - $MR^{4.5}$
- MR^4 - not $MR^{4.5}$

4.10. Derived variables & Definitions

Definitions

Cut-off date: this is the date after which all events, readings etc. are ignored, in order to provide a defined reference point for calculating survival time, etc. For the final analysis the cut-off date will be the date of completion of minimum follow-up on last patient.

Exit date: this is the date assigned to the event of interest (progression, death, etc.) provided this is earlier than the cut-off date. If date of event is known to be later than the cut-off date then the exit date = cut-off date. If date of event is not recorded then the exit date will be the most recent visit date.

Visit date: this is the date of patient attendance for assessment, treatment etc.

Exit status: this is coded as "1" if the event of interest has occurred, "0" otherwise (censoring indicator).

Primary Outcome

- **Proportion of patients who can first de-escalate their treatment (to half the standard dose of their TKI) for 12 months, and then stop treatment completely for a further 2 years, without losing MMR.**

  Event of interest = Molecular Relapse by the end of month 37 - defined as loss of MMR on 2 consecutive occasions (BCT-ABL > 0.1% IS)
  Relapse date = the date that the confirmation sample was collected

Secondary outcomes

- **Proportion of patients who can successfully de-escalate their treatment (to half the standard dose of their TKI), but who then lose MMR on complete TKI cessation.**

  Event of interest = Molecular Relapse after 12 months of de-escalation
  Relapse date = the date that the confirmation sample was collected
  Exit date = Relapse date if Relapse date < cut-off date, last visit date otherwise

- **Proportion of patients who lose their MMR on de-escalation/stopping and regain MMR on resumption of their TKI.**

  Event of interest = Regaining MMR after relapse
  Regaining MMR date = the date that the confirmation sample was collected
  Exit date = Regain MMR date if Regain MMR date < cut-off date, last visit date otherwise

- **Molecular relapse-free survival (RFS).**

  RFS is defined as the time from the first day of de-escalation to the date of confirmed loss of MMR (two consecutive BCR-ABL > 0.1% IS).
  Date of event = Date of confirmed loss of MMR
  Exit date = Date of confirmed loss of MMR if date < cut-off date, last visit date otherwise
  Relapse-free Survival (months) = {exit date – date of first day of de-escalation}/30.4

Exit status = 1 if molecular relapse occurred before cut-off date, 0 otherwise

- **Progression-free survival**

  PFS is defined as the time from the first day of de-escalation to the date of progression to accelerated phase/blast crisis or death from any cause (first occurrence).
  Event of interest = progression to accelerated phase/blast crisis
  Progression date = min(date of death, Progression date)
  Exit date = Progression date if Progression date < cut-off date, last visit date otherwise
  Progression-free Survival (months) = (exit date – date of first day of de-escalation)/30.4
  Exit status = 1 if disease progression or dead from any cause before cut-off date, 0 otherwise.

- ***Overall survival***
  OS is defined as the time from the first day of de-escalation to the date of death from any cause.
  Event of interest = death from any cause
  Date of event = Date of death
  Exit date = Date of death if date < cut-off date, last visit date otherwise
  Overall Survival (months) = {exit date – date of first day of de-escalation}/30.4
  Exit status = 1 if dead before cut-off date, 0 otherwise

- **Event-free survival (EFS)**
  EFS is defined as the time from the first day of de-escalation to the date of confirmed loss of MMR, progression to AP/BC or death from any cause.
  Date of event = Date of EFS event
  Exit date = Date of EFS event if date < cut-off date, last visit date otherwise
  Event-free Survival (months) = {exit date – date of first day of de-escalation}/30.4
  Exit status = 1 if event occurred before cut-off date, 0 otherwise

- **Time to MMR recovery (TTR)**
  TTR is defined as the time from the date of confirmed loss of MMR to the date of MMR recovery.
  Date of event = Date of MMR recovery
  Exit date = Date of MMR recovery if date < cut-off date, last visit date otherwise
  TTR (months) = {exit date – date of confirmed loss of MMR}/30.4
  Exit status = 1 if MMR recovery occurred before cut-off date, 0 otherwise

- **Proportion of registered MMR and MR^4 patients in confirmed $MR^{4.5}$ (BCR-ABL ≤ 0.0032% IS with at least 31,623 ABL1 control transcripts) prior to being enrolled in the study (screening phase).**
  $MR^{4.5}$ is defined as MMR or MA^4 patients with BCR-ABL ≤ 0.0032% IS and at least 31,623 ABL1 control transcripts prior to entering the study.

- ***Quality of life***

  Quality of life will be assessed using the EQ-5D, EQ-VAS and FACT-BRM questionnaires. Additional information collected regarding TKI related symptoms will also be assessed.

4.11. Null hypothesis, levels of significance

Since this is a prevalence study the aim is to provide estimates of the efficacy parameters with a certain level of confidence. The primary efficacy parameter of relapse rate will be estimated on an Intention-to-Treat basis and reported together with a 90% confidence interval. All secondary parameter estimates will also be reported with 90% confidence intervals.

4.12. Specification and estimation of efficacy parameters

Table 1: Summary of outcome variables and corresponding efficacy parameters.

Outcome variable	*Efficacy parameter*	*Comment*	*Method*
Relapse rate	*Proportion of patients with molecular relapse at any time point during the 37 months*	*Estimated separately for each cohort (MMR, MR^4) and for the $MR^{4.5}$ subgroups (MMR-$MR^{4.5}$, MMR-not$MR^{4.5}$, MR^4-$MR^{4.5}$, MR^4-not$MR^{4.5}$)*	*Binomial proportion with normal approximation confidence interval*
Relapse rate after successful de-escalation	*Proportion of patients with molecular relapse after successful de-escalation*	*Estimated separately for each cohort (MMR, MR^4)*	*Binomial proportion with normal approximation confidence interval*
Regain MMR rate	*Proportion of patients who regain MMR after molecular relapse at any time point*	*Estimated separately for each cohort (MMR, MR^4)*	*Binomial proportion with normal approximation confidence interval*
Molecular Relapse-free survival (RFS)	*Median RFS time*	*Supported by* • *12-36 months RFS* *Estimated separately for each cohort (MMR, MR^4) and for the $MR^{4.5}$ subgroups (MMR-$MR^{4.5}$, MMR-not$MR^{4.5}$, MR^4-$MR^{4.5}$, MR^4-not$MR^{4.5}$)*	*Kaplan-Meier estimator with pointwise bounds*
Progression-free Survival (PFS)	*Median PFS time*	*Supported by* • *12-36 month PFS* *Estimated separately for each cohort (MMR, MR^4)*	*Kaplan-Meier estimator with pointwise bounds*
Overall survival (OS)	*Median OS time*	*Supported by* • *12-36 month OS* *Estimated separately for each cohort (MMR, MR^4)*	*Kaplan-Meier estimator with pointwise bounds*

Event-free survival (EFS)	*Median EFS time*	*Supported by* • *12-36 month EFS* *Estimated separately for each cohort (MMR, MR^4)*	*Kaplan-Meier estimator with pointwise bounds*
Time to MMR recovery (TTR)	*Median TTR time*	*Supported by* • *12-36 month TTR* *Estimated separately for each cohort (MMR, MR^4)*	*Cumulative incidence estimate adjusting for the competing risks of progression/death*
$MR^{4.5}$ rate	*Proportion of MMR and MR^4 patients in confirmed $MR^{4.5}$ prior to entering the study*	*Estimated separately for each cohort (MMR, MR^4)*	*Binomial proportion with normal approximation confidence interval*
Quality of Life	*Mean scores at baseline and each time point questionnaires were completed*	*Estimated separately for each cohort (MMR, MR^4)*	*Graphs showing measurements overtime. Further QoL assessments will be performed using joint longitudinal and survival analysis to assess the difference between relapsing and not relapsing patients*

5. RESULTS

5.1. Recruitment and disposition

Table 2: Recruitment by centre

Site Name	Date of green light*	Date of first recruitment	Date of last recruitment	MMR	MR[4]	Total
			Total			

Figure 1: Recruitment graph (example)

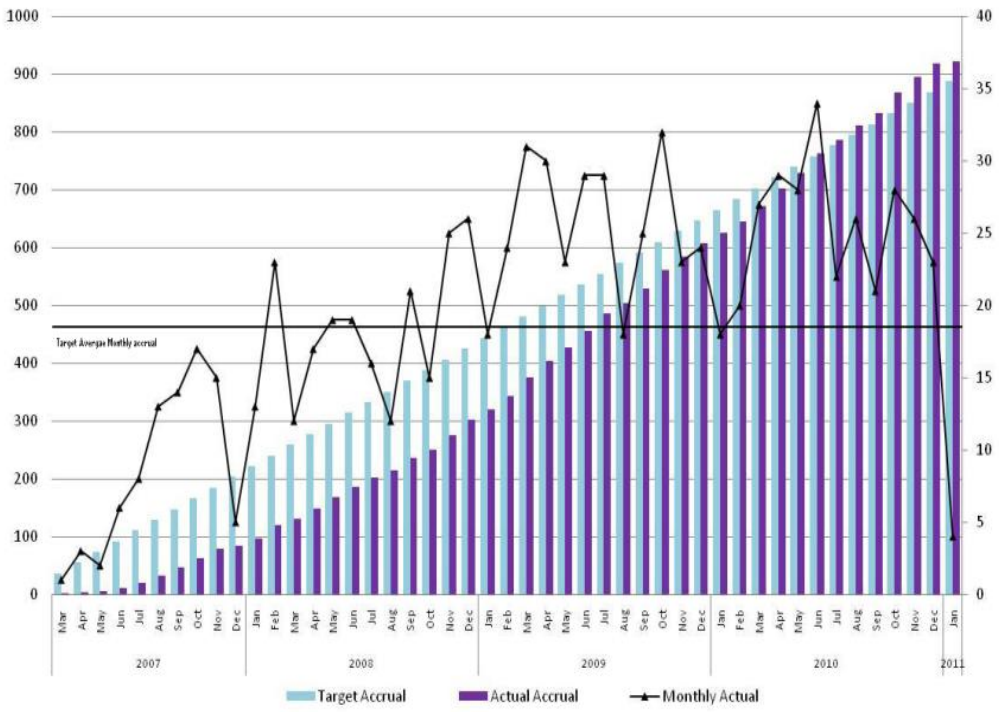
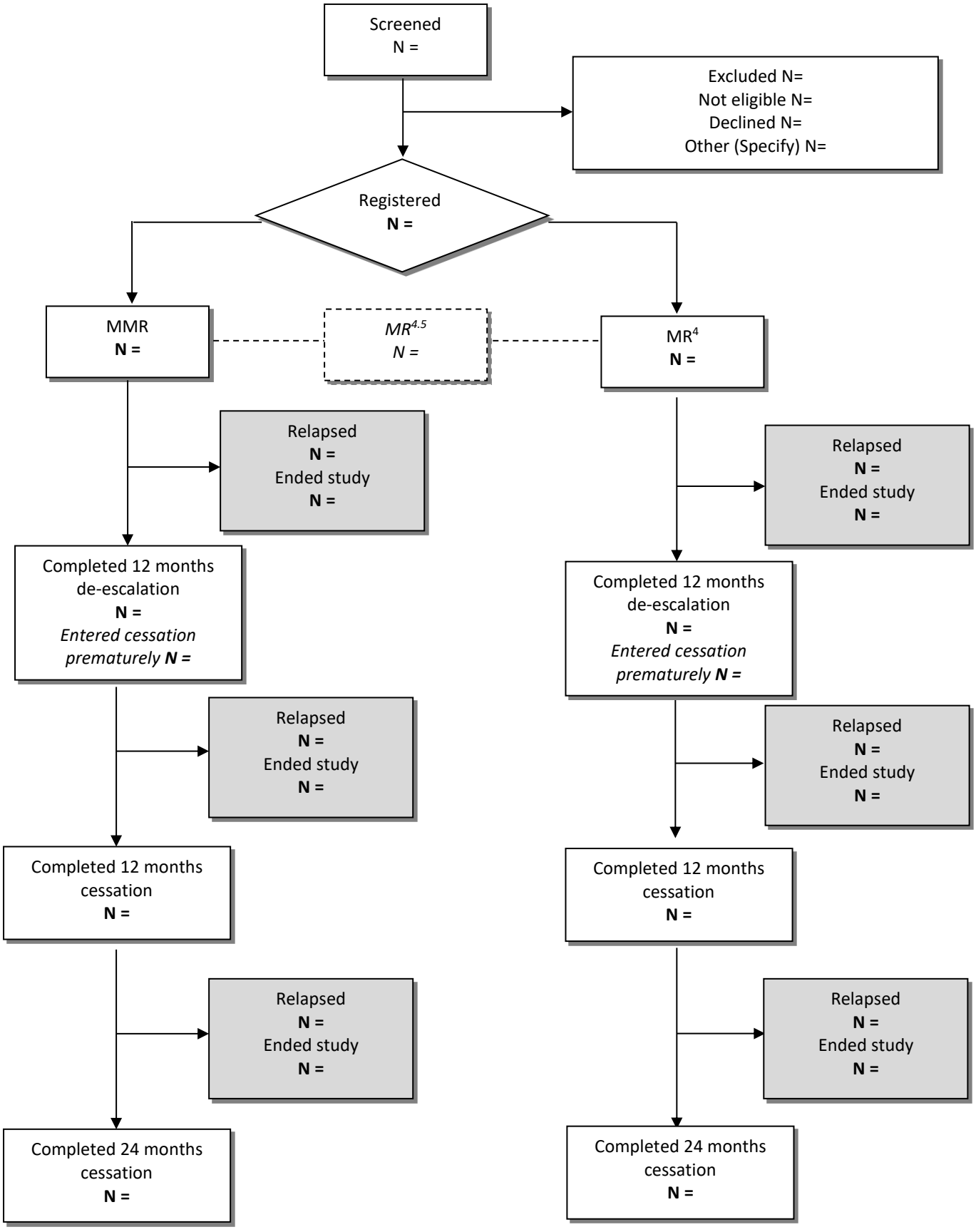


Figure 2: Patient disposition



5.2. Assessment of data quality

Table 3: Protocol treatment & Trial dropouts

Characteristic	MMR N =	MR[4] N =	Overall N =
Total discontinued protocol treatment *[n, (%)]*			
Serious Adverse Event/ Toxicity			
Death			
Patient / Clinical decision (not SAE, not trial related)			
Serious violation of study protocol			
Withdrawal of consent			
Disease progression/ Molecular Relapse			
Intercurrent illness			
Other			
Reason missing			
Days from recruitment to discontinuation of protocol treatment *Median* *IQR* *Range*			
Total discontinued trial *[n, (%)]*			
Consent withdrawn			
Lost to follow up			
Death			
Other			
Days from recruitment to discontinuation of trial *Median* *IQR* *Range*			

Protocol deviations: Protocol Deviations are accidental or unintentional change to or non-compliance with the trial protocol.

Table 4a: Summary of Deviations

Type	Description of Deviation	Category	Total No.
Major	Entered but subsequently found not to satisfy the entry criteria	1	
	Developed withdrawal criteria but not withdrawn	2	
	Received an excluded concomitant treatment	3	
	Received the wrong treatment or incorrect dose	4	
	Deviation from patient management/assessment	5	
	Other	6	

Minor	Protocol Deviations not expected to have an impact on defined endpoints of the trial	7	

Review for Major Deviations will be performed by the Trial Management Group on a regular basis (hence before any per-protocol analysis).

Table 4b: Details of Major Deviations by site

Site Name	Date	Category	Details

Table 5: Available Data Description

Patients missing values on:	MMR	MR[4]
Primary outcome *Relapse Rate*		
Secondary outcomes *Relapse rate after 12 months* *Regain MMR rate* *Relapse-free Survival* *Progression-free Survival* *Overall Survival* *Event-free Survival* *Time to MMR recovery*		

5.3. Description of baseline subject characteristics

Categorical variables are summarised as N (%); continuous variables by mean (SD) and lower and upper quartiles.

Table 6: Baseline characteristics

	MMR N =	MR[4] N =	Overall N =
Demographic Characteristics			
Age median (IQR)			
Gender [n (%)] Male Female			
Physical findings			
Weight median (IQR)			
ECOG performance status [n, (%)] Fully Active Work Able Not Work Able Limited Self Care Completely Disabled			
Clinical characteristics			
BCR-ABL % (Hammersmith results) median (IQR, range)			
Medical History			
Medical history or baseline symptoms [n (%)] None Current Previous			
Medication			
Current CML Medication [n (%)] Imatinib Nilotinib Dasatinib			
Haematology results			
Haemoglobin g/L median (IQR)			
WBC $\times 10^9$ median (IQR)			
TKI related symptoms			
Symptom [n, (%)] Rash Diarrhoea Nausea Scalp irritation Periobital oedema Hair thinning Lethargy Other			

Grade CTCAE [n, (%)] 3+ <3			

5.4. Exposure to treatment and compliance

Table 7: Details of treatment doses administered

Group	No. of patients administered at least one day of protocol treatment	No. of patients with at least one dose missed	No. of patients with at least one dose increase	No. of patients with premature TKI cessation
MMR				
MR[4]				

5.5. Analysis of Primary Outcome

Table 8: Relapse rate at 37 months

Group	Total no. of patients	No. of evaluable patients *	Completeness of follow up (C)[2]	No. of relapsed patients	% of evaluable patients who completed 37 months without relapse	90% Confidence Interval
MMR						
MR[4]						

**Subtracting losses to follow-up & complete withdrawals (prior to experiencing any event) from the total.*

[2] Clark TG, Altman DG, De Stavola BL (2002) "Quantification of the completeness of follow-up" Lancet 359: 1309-1310

Table 9: Results of Sensitivity analyses for relapse rate at 37 months

Sensitivity Analysis - allowance for	Group	No. of patients	No. of evaluable patients	No. of relapsed patients	% of evaluable patients who completed 37 months without relapse	90 % Confidence Interval
Per-protocol analysis	MMR					
	MR^4					

Table 10: Results of subgroup analysis based on $MR^{4.5}$ status for relapse rate at 37 months

Group	No. of patients	No. of evaluable patients	No. of relapsed patients	% of evaluable patients who completed 37 months without relapse	90 % Confidence Interval
MMR – $MR^{4.5}$					
MMR – not $MR^{4.5}$					
MR^4 – $MR^{4.5}$					
MR^4 – not $MR^{4.5}$					

5.6. Analyses of secondary outcomes

Relapse on cessation

Table 11: Results for patients who relapse on cessation

Group	No. of patients	No. of patients who completed de-escalation without relapsing	No. of relapsed patients after de-escalation	% of patients who relapse on cessation	90% Confidence Interval
MMR					
MR^4					

Regained MMR

Table 12: Results for relapsed patients who regained MMR

Group	No. of relapsed patients	No. of patients who regained MMR on resumption	% of patients who regained MMR on resumption	90% Confidence Interval
MMR				
MR[4]				

Molecular relapse-free survival

Table 13: Results for molecular relapse-free survival

	MMR N =	MR[4] N =	Total N =
Molecular relapses, n(%) Median time to molecular relapse in months (IQR) - "if estimable"			

Figure 3: Kaplan-Meier plot for molecular relapse-free survival (Example)

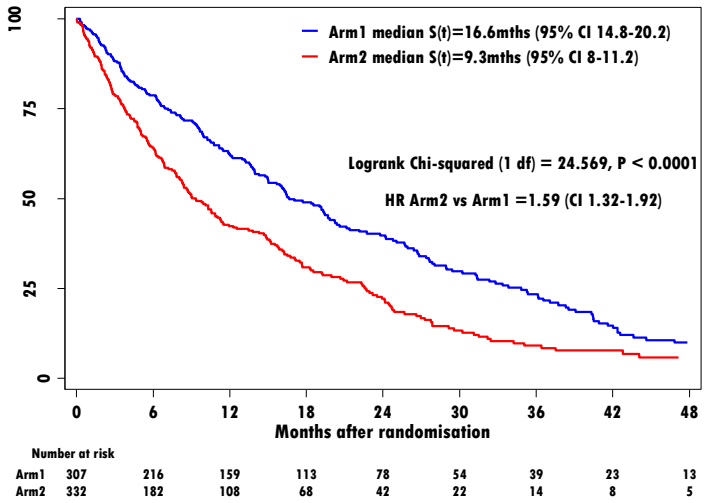
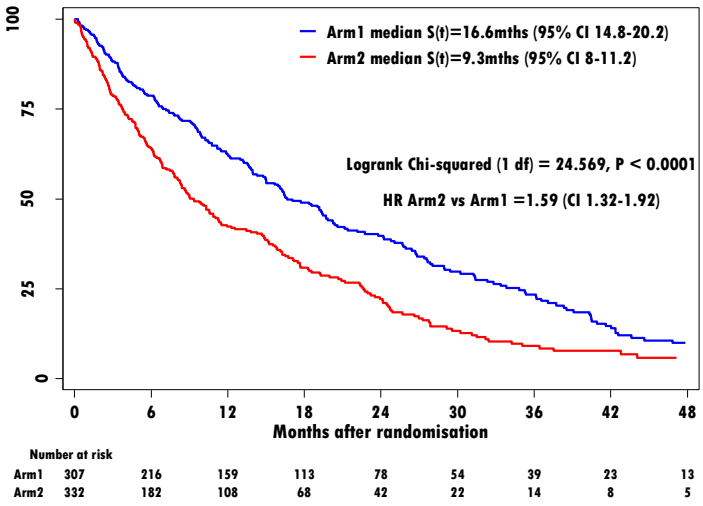


Table 14: Results for molecular relapse-free survival according to $MR^{4.5}$ status

	MMR – $MR^{4.5}$ N =	MMR – not $MR^{4.5}$ N =	MR^4 - $MR^{4.5}$ N=	MR^4 – not $MR^{4.5}$ N=
Molecular relapses, n(%) Median time to molecular relapse in months (IQR) - "if estimable"				

Figure 4: Kaplan-Meier plot for molecular relapse-free survival according to $MR^{4.5}$ status (Example)

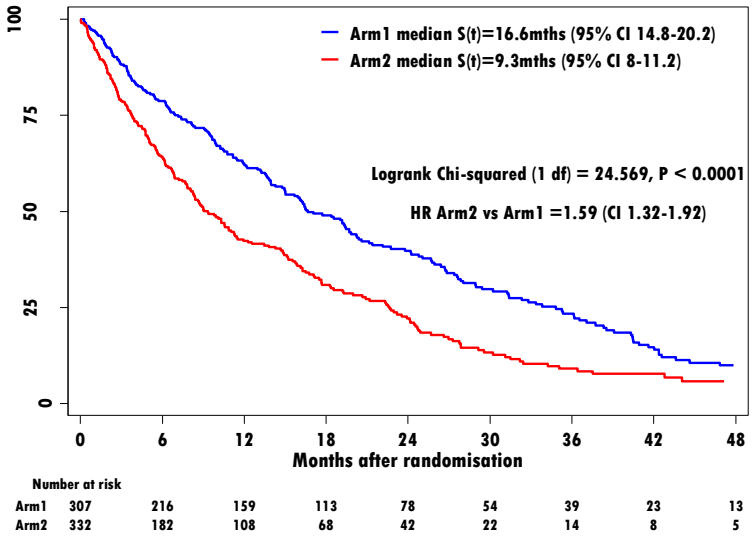


Progression-free Survival

Table 15: Results for progression-free survival

	MMR N =	MR[4] N =	Total N =
Progressions/deaths (first occurrence), n(%) Median time to progression/death in months (IQR) - "if estimable"			

Figure 6: Kaplan-Meier plot for progression-free survival (Example)

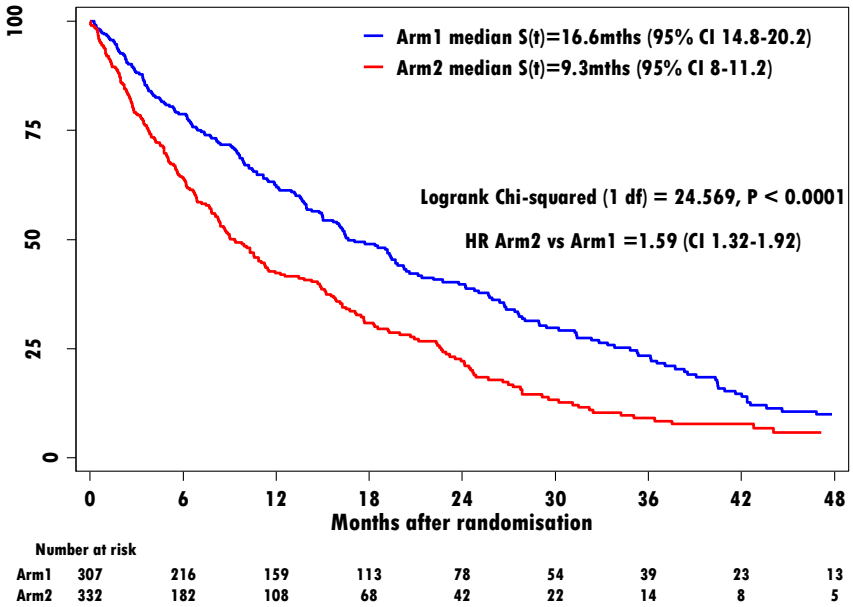


Overall Survival

Table 16: Results for overall survival

	MMR N =	MR[4] N =	Total N =
Deaths from any cause, n(%) Median time to death in months (IQR) "if estimable"			

Figure 6: Kaplan-Meier plot for overall survival (Example)

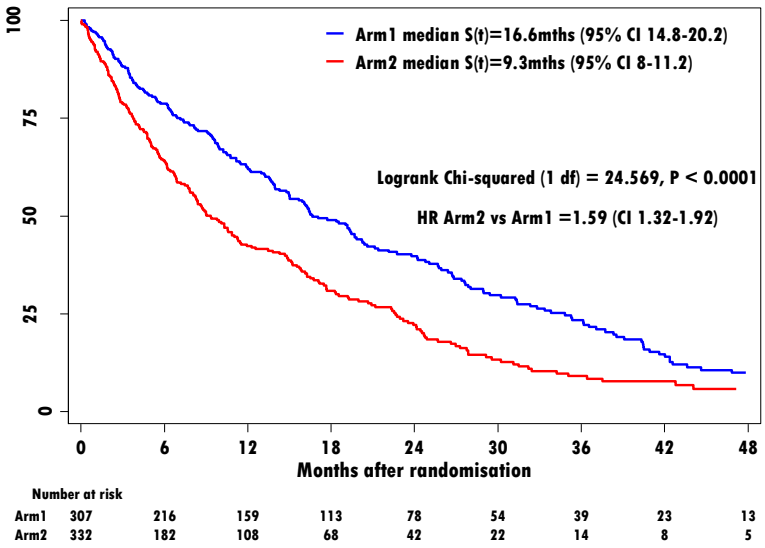


Event-free survival

Table 17: Results for event-free survival

	MMR N =	MR[4] N =	Total N =
Losses of MMR / progressions to AP/BC / deaths (first occurrence), n(%) Median time to death in months (IQR) "if estimable"			

Figure 7: Kaplan-Meier plot for event-free survival (Example)



Time to MMR recovery

Table 18: Results for time to MMR recovery

	MMR N =	MR[4] N =	Total N =
MMR recoveries, n(%) Median time to MMR recovery in months (IQR) "if estimable"			

Figure 8: Cumulative incidence plot for time to MMR recovery

$MR^{4.5}$ prior study entry

Table 19: Proportion of MMR and MR^4 in confirmed $MR^{4.5}$ prior entering the study

Group	No. of patients $MR^{4.5}$ prior study entry	% of patients $MR^{4.5}$ prior study entry	90% Confidence Interval
MMR			
MR^4			

Quality of Life and TKI related symptoms

Figure 9: EQ-index score profile over time (example)

EQ-index Score range: 0 – 100 (0: worst possible score, 100: best possible score)

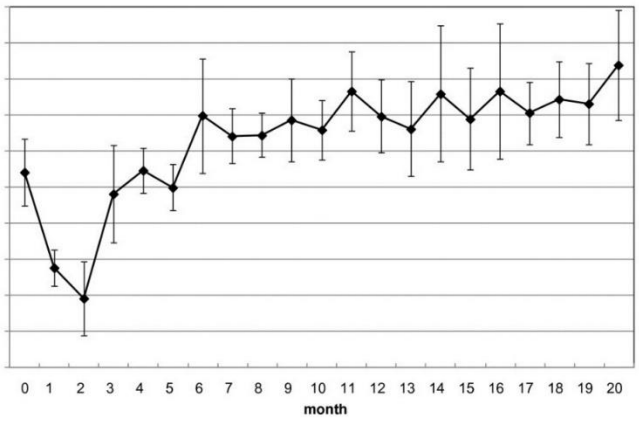


Figure 9: EQ-VAS score profile over time (example)

EQ-VAS Score range: 0 – 100 (0: worst possible score, 100: best possible score)

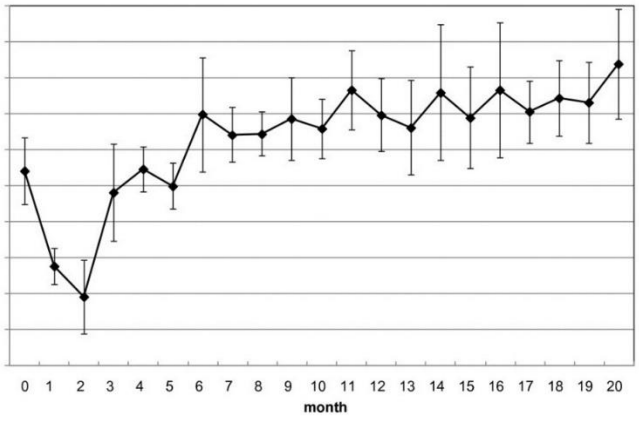


Figure 11: Mean FACT-BRMTOI score profile over time (example)

FACT-BRMTOI Score range: 0 – 106 (0: worst possible score, 106: best possible score)

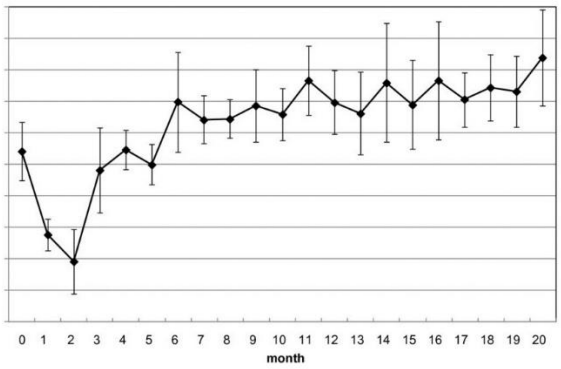


Figure 12: Mean FACT-G score profile over time (example)

FACT-G Score range: 0 – 106 (0: worst possible score, 106: best possible score)

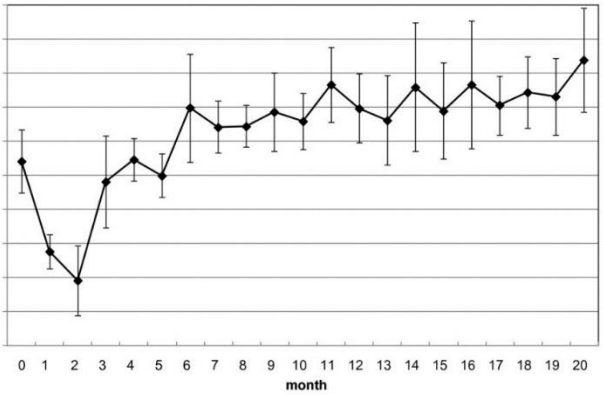


Figure 13: FACT-BRM total score profile over time (example)

FACT –BRM Total Score range: 0 – 160 (0: worst possible score, 160: best possible score)

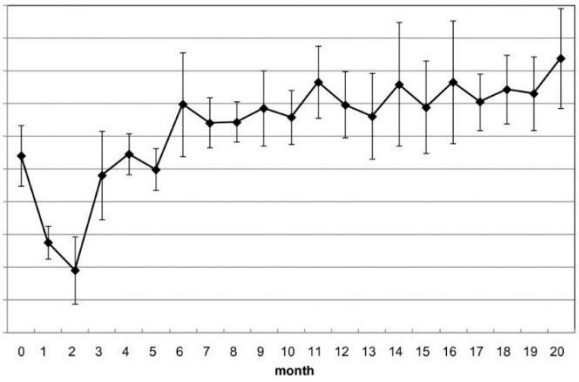


Table 20: Joint longitudinal and survival modelling of QoL data.

Component	Parameter	Estimate	SE	90% Confidence interval
Longitudinal Model	Factor 1			
	Factor 2			
	Factor 3			
	…			
Failure Model	Factor 1			
	Factor 2			
	Factor 3			
	…			
Association	…			
Variance Parameters	…			
	…			

Figure 14: Kaplan Meier plot to show overall survival and integrated QoL utility over time.

Table 21: Number of Patient with TKI related symptoms.

Time point (month)	Group	Rash	Diarrhoea	Nausea	Scalp irritation	Periobital oedema	Hair thinning	Lethargy	Other	3+ CTCAE Grade
Baseline	MMR									
	MR4									
1	MMR									
	MR4									
2	MMR									
	MR4									
3	MMR									
	MR4									
6	MMR									
	MR4									
9	MMR									
	MR4									
…	…									

Figure 12: Number of Patient with TKI related symptoms over time (radar plot).

5.9. Analysis of safety & tolerability

The number and percentage of patients reporting a Serious Adverse Event (SAE) lead to study discontinuation will be summarised by group.

Table 21: N (%) Patients withdrawing due to SAE

	MMR	MR[4]
N (%)		
Mean SAEs/patient		

The number of patients reporting a serious adverse event will be summarised by group and CTCAE preferred term.

Table 22: Aggregated Serious Adverse Event

CTCAE category	CTCAE short name	MMR	MR[4]
YYYY	aaaaa		
	bbbbb		
	ccccc		
XXXX	aaaaa		
	bbbbb		
	ccccc		

Table 23: Line Listing of Grade 3+ Serious Adverse Events

Patient No	Group	CTCAE Event Name	CTCAE Grade	Onset Date	Offset Date	Outcome

FINAL REPORT PLAN SIGN-OFF SHEET

This confirms approval of the Final report plan version 2 for DESTINY

Trial statistician:

Signature .....

Date 17/07/2019

Reviewing statistician:

Signature .....

Date 17/07/2019

Chief Investigator:

Signature .....

Date 17/07/2019.

Chair of Trial Steering Committee:

Signature .....

Date 17/07/2019

Add: Retain Original Copy of Final Report Plan & Sign-off sheet in appropriate sections of Statistics File
Keep a scanned copy of each in corresponding electronic folder

FINAL STATISTICAL REPORT SIGN-OFF SHEET

Programming and Reporting Checklist for DESTINY Final statistical report	TS	RS
Programming		
Has the relevant analysis plan been written and signed off		
Timescales agreed for database lock, data download into R/Stata/SAS etc, analysis and dissemination		
Have MACRO Queries been created to supply data needed for each table /figure in Report		
Have you checked that the data have been read into SAS/Stata correctly		
Have all SAS/Stata/etc analysis programs been listed in the relevant index?		
Have all SAS/Stata/etc analysis programs been risk-assessed, with appropriate review & sign-off in the validation log		
Have the numbers in the tables been checked against the relevant SAS/Stata output		
Report		
Pagination correct		
Open meeting section clearly distinct from closed section (DMC Report)		
All tables/graphs stipulated in Report Plan/subsequent amendments are present/accounted for		
Layout & formatting acceptable (percentages as a whole number, means to 1 d.p. more than unit of measurement)		
Table rows/columns labelled clearly, with units		
Graph axes labelled clearly, with units		
All accompanying text consistent with presented results		
Has report been reviewed and signed off by statistical lead?		

This confirms approval of the Final Statistical Report for DESTINY

Signed (TS)
Date

Signed (RS)
Date

Retain Original Copy of Report & Sign-off sheet in appropriate sections of Statistics File
Keep a scanned copy of each in corresponding electronic folder