Statistical Analysis Plan for

Official Title of Study

A PHASE 1B DOSE ESCALATION STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY AND PRELIMINARY EFFICACY FOR THE COMBINATION OF DASATINIB (BMS-354825) PLUS NIVOLUMAB (BMS-936558) IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA (CML)

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STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

A PHASE 1B DOSE ESCALATION STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY AND PRELIMINARY EFFICACY FOR THE COMBINATION OF DASATINIB (BMS-354825) PLUS NIVOLUMAB (BMS-936558) IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA (CML)

PROTOCOL(S) CA180373

VERSION # 1.0

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2 STUDY DESCRIPTION

2.1 Study Design

This is an open-label non-randomized Phase Ib trial investigating the combination of dasatinib and nivolumab in CML subjects with chronic phase (CML-CP) or accelerated phase (CML-AP), who are progressing on, resistant to, sub-optimally responding to, or intolerant to prior treatment with any TKI (except dasatinib in case of prior intolerance).

The study consists of an escalation and an expansion phase. Dose levels are defined by the nivolumab dose (see Table Table 2.1-1). All subjects are treated until progression/treatment failure or intolerance for a maximum of up to 2 years with dasatinib and nivolumab combination and up to 1 additional year with dasatinib alone.

In the escalation phase, safety and tolerability will be assessed in cohorts of up to 12 subjects using a modified toxicity probability interval (mTPI) design[1]. This method is expected to more accurately estimate the maximum tolerated dose (MTD) among a set of proposed doses than designs like 3 + 3 or 6 + 6 (when the same cohort size is used). The mTPI method uses a set of decision rules guided by posterior inference and requires the definition of a target toxicity rate and an equivalence interval (EI), in which any dose is considered sufficiently close to the true MTD as to be selected as the estimated MTD. Dose-limiting toxicity (DLT) will be assessed for CML-CP and CML-AP in a pooled fashion. Approximately 24 - 48 subjects will be required for the escalation phase (see Section 5). Subjects who do not complete the DLT period for reasons other than dose-limiting toxicities will be replaced.

The Study Team (Principal Investigators and Sponsor representatives) will determine accrual schedule and timing of cohort escalation and dose for expansion based on all available information. Refer to protocol Section 3.1.3 for the criteria for dose escalation. Decisions will be based primarily on safety data for the first 6 weeks of combined treatment (Weeks 3 - 8 inclusive) in subjects with both CML-CP and AP but all relevant experience, including interruption or discontinuation for toxicity after the DLT period and AEs during subsequent treatment, will be considered. Refer to protocol Section 3.1.3.1 for the definition of DLT. At completion of the escalation phase, the MTD will be assessed based on the estimate derived from the mTPI method (the dose for which the difference between the estimated toxicity and the target toxicity is smallest among the doses tested).

Subsequently, 21 - 33 additional subjects will be treated in an expansion phase at a dose selected during the escalation phase (recommended Phase 2 dose), in order to achieve a total of 45 - 68 subjects (see Section 5). If the overall safety profile of the study drugs is less favorable than that initially observed in the escalation phase, then further enrollment to the expansion cohort will be interrupted and a decision whether or not to continue dosing will be based on discussions of the observed aggregate (acute and chronic) toxicities between the study Investigators and the Sponsor.

Dasatinib is administered once-daily (QD) starting in Week 1 (Day 1) at 100mg po QD in subjects with CML-CP and at 140mg po QD in those with CML-AP. In selected cases, a lower starting dose of dasatinib could be allowed. Subjects will receive dasatinib alone during

Weeks 1 - 2 of this study. Nivolumab will be administered as an IV infusion beginning on treatment Day 15 (Week 3) and then every two weeks (± 3 days). In the escalation phase, DLT assessment will occur during the first 6 weeks of combination therapy (Weeks 3-8, inclusive). Dose levels are defined as in Table Table 2.1-1 below.

Table 2.1-1: Dose Levels for Dose-escalation of Nivolumab in Combination with Dasatinib

Dose Level	Nivolumab (mg/kg)	Dasatinib (mg)
-1	0.3	100/140
1	1	100/140
2	3	100/140

Initially, subjects will be treated at DL 1. DL -1 is provided in case DL 1 is not tolerated and dose reduction would be needed for subsequent subjects.

2.2 Treatment Assignment

Not applicable (open label study).

2.3 Blinding and Unblinding

There are currently 6 approved amendments. The history of protocol amendments including the dates and changes to the protocol are summarized below.

- Amendment 1 (11-Jul-2013, all sites): The objective of this amendment was to permit the collection and storage of blood samples for use in future exploratory pharmacogenetic research.
- Amendment 2 (12-Sep-2013, all German sites): This amendment was written in response to a request from the German Health Authorities to ensure that HIV positive subjects are excluded from the study in Germany.
- Amendment 3 (23-Oct-2013, all sites): The main objective of this amendment was to implement recommendations received from the United State Food and Drug Administration (FDA). These recommendations were mainly to have ≥ 2 prior TKI therapies for CML prior to entering the trial and to include all non-hematologic Grade 3 or greater adverse events (AE) irrespective of duration in the definition of DLT. The pharmacokinetic and anti-drug antibody sampling schedules were amended as well as the analysis section (to add report of immunogenicity and neutralizing antibodies analyses). In addition, the method to assess the selected dose for the expansion phase, the MTD, as well as some inclusion or exclusion criteria, and the time and event schedule were corrected or clarified.
- Amendment 4 (07-Feb-2014, all French sites): The main objective of this amendment was to implement recommendations received from the French Health Authorities. The major changes resulting from this amendment were the exclusion of subjects with suboptimal response during or intolerance to the last prior TKI, to consider possible pulmonary arterial

hypertension (PAH) at cardiac evaluations and to change slightly the QTcF (Fridericia correction) level at which dasatinib must be discontinued.

- Amendment 5 (01-Oct-2014, all sites): The main objectives of this amendment were to clarify some eligibility criteria, to update the DLT definition (by excluding Grade 4 hematologic AEs attributable to disease and dasatinib, as cytopenia is very common in TKI-pretreated CML patients with hematologic progression who are starting dasatinib), to remove most dasatinib PK sampling, and to allow a starting dose of dasatinib lower than 100mg/140mg daily for CML-CP/AP in select cases. In addition, edits to provide consistency, clarification, correction, simplification of time and events schedules or fix typographical errors were made.
- Amendment 6 (15-Apr-2015, all sites): Escalation to nivolumab 3mg/kg will be permitted for subjects receiving a nivolumab dose of 1mg/kg (n = 9, at time of this Amendment) after ≥ 9 months on study.

  Now that Dose Level 2, nivolumab 3mg/kg, is open to enrollment, this option becomes appropriate. The minimum of 9 months treatment at 1mg/kg will assure that safety data is adequate at this dose. This change will permit subjects to escalate under the following conditions:

  – Only subjects with clear evidence that their disease is not responding at 1mg/kg nivolumab could be escalated. There is evidence that nivolumab efficacy is dose-dependent, with different thresholds for different tumors.
  – Only subjects with very good tolerance of 1mg/kg (i.e., have no clinically-significant nivolumab-related AEs of any grade) after > 9 months on study could be escalated. No DLTs were observed among the 12 evaluable subjects treated at nivolumab dose of 1mg/kg. Subjects who have tolerated 1mg/kg are expected to tolerate 3mg/kg equally well.

3 OBJECTIVES

3.1 Primary

The primary objective is to assess the safety and tolerability for the combination of dasatinib and nivolumab in subjects with CP or AP CML, in order to select a Phase 2 dose. The assessment of safety and tolerability will be based on:

- Dose limiting toxicities (DLTs) as defined in Section 3.1.3.1 of the protocol,
- Incidences of adverse events (AEs) and serious adverse events (SAEs), during the DLT period, the full treatment period of the subjects with the combination therapy, and during the expansion phase,
- Frequencies of abnormal clinical laboratory tests (summarized by worst toxicity grade).

3.2 Secondary

The secondary objectives are based on Major Molecular Response (MMR) and Molecular Response 4.5 (MR4.5):

- MMR and MR4.5 at 6, 12, 24, and 36 months
- To evaluate time to and duration of MMR and MR4.5.

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[redacted]).

[redacted]
[redacted]

4 ENDPOINTS

The primary endpoint is to assess the safety and tolerability for the combination of dasatinib and nivolumab in subjects with CML-CP or CML-AP, in order to select a Phase 2 dose. The assessment of safety and tolerability will be based on:

- Dose limiting toxicities
- Incidences of adverse events
- Incidences of serious adverse events
- Frequencies of clinical laboratory tests by worst toxicity grade.

Timing of evaluation of the efficacy and safety endpoints is detailed in Tables 5.1-1, 5.1-2 and 5.1-3 of the protocol.

4.1 Efficacy Endpoints

Efficacy will be assessed by molecular assessment, cytogenetic assessment, and hematological assessment.

4.1.1 Molecular Response

Molecular response will be assessed using BCR-ABL transcript levels measurement by real-time quantitative polymerase chain reaction (RQ-PCR). The assay will be run in a centralized laboratory and data will be expressed on the international scale (IS)[2].

- A major molecular response (MMR) is defined as a ratio BCR-ABL/ABL ≤ 0.1% on the international scale (i.e., at least 3 log reduction from a standardized baseline value).
- A molecular response 4.5 (MR4.5 or complete molecular response, CMR) will be defined as a ratio BCR-ABL/ABL ≤ $10^{-4.5}$%, which equals to approximately 0.0032% on the international scale (i.e. at least 4.5 log reduction from a standardized baseline value).

Time to MMR (or to MR4.5): It will be measured from the date of first dosing until measurement criteria are first met for MMR (or for MR4.5) response. The subjects who do not respond will be censored on the date of their last molecular assessment. It is defined for all treated subjects.

Duration of MMR (or of MR4.5): will be computed for subjects who have achieved MMR (or MR4.5). It will be defined as the time from the first assessment in which MMR (or MR4.5), is documented until the first assessment at which disease progression (or confirmed loss of MMR) is documented (see Section 4.1.2). Subjects who neither progress nor die will be censored on the date of their last molecular assessment.

[redacted]

4.2 Safety Endpoints

Beside the evaluations used to address the primary endpoint (see Section 4), safety endpoints include deaths, SAEs and AEs, laboratory evaluations, electrocardiograms (ECG), echocardiograms, and reasons off treatment.

[redacted]

5 SAMPLE SIZE AND POWER

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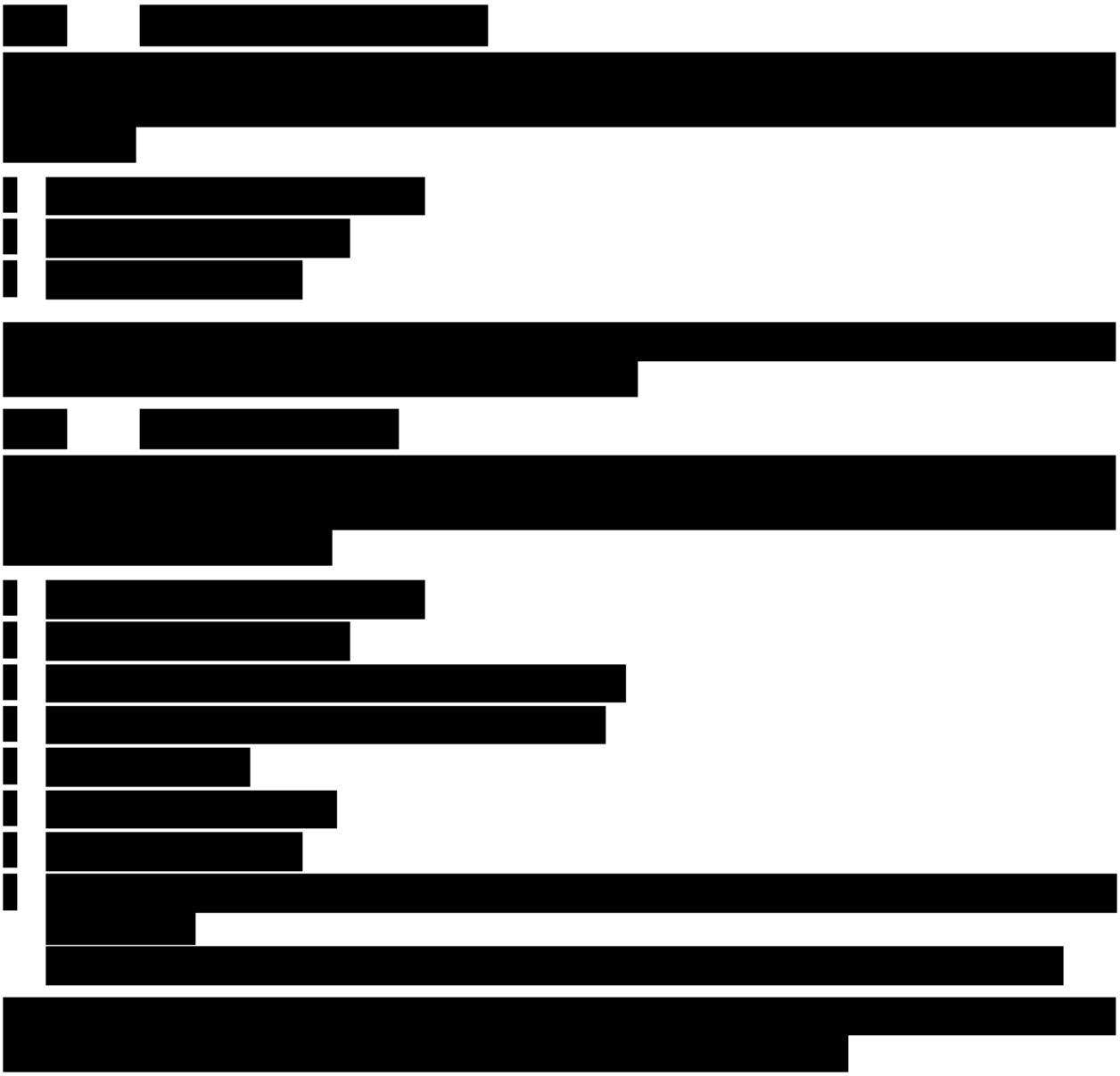

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Beside the evaluations used to address the primary endpoint (see Section 4), safety endpoints include deaths, SAEs and AEs, laboratory evaluations, electrocardiograms (ECG), echocardiograms, and reasons off treatment.

[redacted]

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

6.1.1 Baseline

- Baseline AEs will be defined as AEs with an onset date prior to but not including the first day of dasatinib treatment in study CA180373.
- For all other evaluations (ECOG, laboratory evaluations, extramedullary assessments, ECGs, pulse oximetry, vital signs, etc.) baseline will be defined as evaluations with an onset date on or prior to the first day of dasatinib treatment in study CA180373.

6.1.2 On-study

- On-study AEs will be defined as AEs with an onset date on or after the first day of treatment. For subjects off treatment, AEs will be counted as on-study if the event occurred within 100 days of the last dose of nivolumab or within 30 days of the last dose of dasatinib, whichever is later.
- For all other evaluations (ECOG, laboratory evaluations, extramedullary assessments, ECGs, pulse oximetry, vital signs, etc.) on-study will be defined as evaluations taken after the first day of treatment. For subjects off treatment, on-study evaluations will also be within 100 days of the last dose of nivolumab or within 30 days of the last dose of dasatinib, whichever is later.

6.2 Treatment Regimens

Treatment regimen will be represented by the assigned starting dose level defined by the nivolumab dose (Table Table 2.1-1) or reported as DAS if subject did not start nivolumab dosing.

6.3 Populations for Analyses

The following populations will be used in this study:

- All Enrolled Subjects: All subjects who signed an informed consent form and were registered into the Interactive Voice Response System (IVRS).
- All Treated Subjects: All enrolled subjects who received at least one dose of dasatinib.
- Molecular Response-evaluable Subjects: All treated subjects without a MMR at study entry.
- DLT-evaluable Subjects: All treated subjects who completed the DLT phase (i.e., received study treatment for at least 8 weeks, to Day 57) or experienced DLT.

Determination of an MTD, if any, will be based on AEs in DLT-evaluable subjects. Except where indicated, all other analyses will be based on All Treated Subjects population.

7 STATISTICAL ANALYSES

7.1 General Methods

Descriptive summaries of continuous and other numeric variables will at least consist of the following summary statistics: median, minimum and maximum values. Categorical variables will be summarized by frequencies and percentages. Unless otherwise indicated, percentages in tables will be column percentages, using the total number of observations in the population as the denominator. Percentages will be rounded to one decimal place, and thus may not always add up to exactly 100%.

AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) system organ classes and preferred terms. AEs and laboratory tests will be graded using the National Cancer Institute - Common Toxicity Criteria for Adverse Event (NCI-CTCAE) Version 4.03 dated 14-Jun-2010 criteria. Laboratory results will be presented using the United States standard units.

Subjects in 1mg/kg nivolumab cohort who will escalate to 3mg/kg nivolumab will be reported in the 1mg/kg nivolumab dose level cohort.

7.2 Interim Analysis

An interim analysis will be performed at the time the last subject in the escalation phase completes the DLT period, i.e. when that subject has been observed for a minimum of 8 weeks. The interim analysis will provide preliminary safety and efficacy information on the treatment combination; the list of outputs to be produced for the interim analysis will be specified in the Data Presentation Plan.

7.3 Study Population

Unless otherwise indicated, analyses in this section will be tabulated or listed by disease state at study entry (CML-CP without prior dasatinib, CML-CP with prior dasatinib, CML-AP), by dose level and overall (for the tables, only) using the All Treated Subjects population.

7.3.1 Subject Disposition

The number of subjects enrolled (by disease state and overall only) and treated or not treated (with reasons, by disease state and overall only) will be tabulated. Subjects who were treated will further be categorized by off treatment reasons. Reasons for discontinuing the treatment will be listed.

7.3.2 Demographics and Subject Characteristics

The following subject characteristics will be tabulated:

- Demographics: (age [year, as summary statistics and by group of < 65, ≥ 65 years], gender, race, and ethnicity),
- Medical history: abnormal medical history (body system),

7.3.3 Subject Disease Characteristics

The following baseline disease characteristics will be tabulated and listed:

- ECOG performance status: 0, 1, or 2,
- Time from initial cancer diagnosis to start of study therapy (months): summary statistics,
- Current disease state: CML-CP or CML-AP by prior dasatinib use (yes or no).

[redacted]

[redacted]

7.3.6 *Baseline Examinations*

Baseline laboratory data needed for the CSR will be extracted from the on-study shift tables in toxicity grading from baseline. Baseline values without any post baseline values will be reported in the shift tables.

7.4 Extent of Exposure

Extent of exposure will be presented separately for dasatinib and for nivolumab using the All Treated Subjects population. Dasatinib data will be reported by disease phase (CML-CP without prior dasatinib, CML-CP with prior dasatinib, CML-AP) and nivolumab data will be reported by assigned starting dose level. A total column will be provided for each table.

[redacted]

[redacted]

[redacted]

7.5 Efficacy

All efficacy tables and listings will be displayed by disease state at study entry (CML-CP without prior dasatinib, CML-CP with prior dasatinib, CML-AP) and dose level.

The exact two-sided 95% confidence intervals (CI) around a rate will be computed using the method of Clopper and Pearson[3]. For variables summarized with the Kaplan-Meier product limit method[4], the CI around the median time or duration will be computed using the method of Brookmeyer-Crowley[5].

7.5.1 Molecular Response

MMR and MR4.5 rates as well as 95% exact CI at 6, 12, 24, and 36 months will be tabulated using the All Treated Subjects population. As some subjects may have entered the study with a MMR, the analysis on MMR rates will be repeated using the Molecular Response-evaluable Subjects population.

Time to MMR and to MR4.5 will be estimated using the Kaplan-Meier product limit method and median time will be reported along with 95% CI using the All Treated Subjects population.

Duration of MMR and of MR4.5 will be estimated using the Kaplan-Meier product limit method and median time will be reported along with 95% CI using the Treated Subjects with a MMR (or a MR4.5) population.

Response variables will be listed using the All Treated Subjects population.

[redacted]

7.5.5 Other Efficacy

A listing with peripheral hematology (WBC, ANC, platelets, blasts, promyelocytes, myelocytes, metamyelocytes, and basophils, bone marrow (number of metaphases, metaphase positive values, and blast) and extramedullary disease (any and spleen or liver) by subject and assessment date will be provided using the All Treated Subjects population.

7.6 Safety

Analyses of safety (tables and listings) will be based on the All Treated Subjects population (All Enrolled Subjects for the SAE and death listings), and will be displayed by disease state at study entry (CML-CP without prior dasatinib, CML-CP with prior dasatinib, CML-AP), dose level and overall.

[redacted]

7.6.2 Adverse Events

The following summaries will be provided by worst toxicity grade on-study (0, 1, 2, 3, 4, and 5):

- On-study AEs,
- On-study drug-related AEs,
- On-study SAEs,
- On-study drug-related SAEs,
- On-study AEs leading to discontinuation,
- On-study drug-related AEs leading to discontinuation.

Listing of AEs, SAEs and AEs leading to discontinuation will be provided.

The following will be provided by dose level (disease state pooled):

- On-study non-serious AEs reported for at least 5% subjects within any dose level,
- Standard analyses on multiple AEs:
  - Exposure adjusted adverse event summary,
  - Frequency of unique adverse events summary, and
  - Listing of unique events.

7.6.3 Clinical laboratory Evaluations

Summary of laboratory tests consisting of shift tables in CTC toxicity grading from baseline to worst grade on-study (0, 1, 2, 3, and 4) will be provided.

The following laboratory tests will be considered for tabulation:

- Hematology: WBC, neutrophil (ANC), platelets, hemoglobin
- Serum chemistry for liver function: alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin

- Serum chemistry for renal function: creatinine
- Other serum chemistry: calcium (low and high), magnesium (low and high), phosphorus, potassium (low and high), sodium (low and high), amylase and lipase.

Listing of all laboratory data will be provided.

Because of the combination with nivolumab, the following laboratory abnormalities (vs. lower limit of normal, LLN or upper limit of normal, ULN) will be tabulated and listed by dose level (disease state pooled):

- Liver specific tests in relation to potential drug induced liver injury (DILI):
  - ALT or AST > 3xULN, > 5xULN, > 10xULN or > 20xULN;
  - Total bilirubin > 2xULN;
  - Concurrent (within one day) ALT or AST elevation > 3xULN and total bilirubin > 2xULN;
  - Concurrent (within 30 days) ALT or AST elevation > 3xULN and total bilirubin > 2xULN..
- Thyroid specific test (TSH) > ULN:
  - Any,
  - With TSH ≤ ULN at baseline,
  - With at least one FT3/FT4 test value < LLN,
  - With all other FT3/FT4 test values ≥ LLN,
  - With FT3/FT4 test missing.
- Thyroid specific test (TSH) > 2*ULN:
  - Same categories as above.
- Thyroid specific test (TSH) < LLN:
  - Any,
  - With TSH ≥ LLN at baseline,
  - With at least one FT3/FT4 test value > ULN,
  - With all other FT3/FT4 test values ≤ ULN,
  - With FT3/FT4 test missing.

7.6.4 Electrocardiogram

Frequency distribution of maximal QTc(F) intervals and QTc(F) changes from baseline (> 30msec, > 60msec, etc.) will be tabulated. A listing of ECG parameters (e.g., HR, QTc(F)) will be provided.

7.6.5 Echocardiogram

A listing of echocardiogram parameters will be provided.

7.6.6 Deaths

All deaths and deaths within 30 days of last treatment of dasatinib or within 100 days of last treatment of nivolumab (whichever comes later), will be tabulated. A listing of deaths will also be provided.

7.6.7 Vital Signs

Vital signs (including respiration rate) and pulse oximetry will be listed.

[redacted]