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Clinical Protocol CA180373

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)

Revised Protocol Number: 05

Incorporates Amendment(s) 08

Central Medical Monitor

Daniela Buglio, MD, PhD

[redacted]

Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 05	13-Oct-2016	Incorporates Amendment 08
Amendment 08	13-Oct-2016	To update the adverse event management algorithms, and to update contraception language based on updates made in Nivolumab Investigator Brochure Version Number 15. This amendment also updates the medical monitor contact information and provides for clarification of various typographical errors.
Revised Protocol 04	13-Apr-2016	Incorporates Amendment 07& Administrative Letters 03 & 04
Amendment 07	13-Apr-2016	[redacted]
Administrative Letter 04	09-Nov-2015	Change in the Medical Monitor
Administrative Letter 03	24-Aug-2015	[redacted]
Revised Protocol 03	17-Apr-2015	Incorporates Amendment 06 & Administrative Letter 02
Amendment 06	17-Apr-2015	[redacted]

Document	Date of Issue	Summary of Change
Administrative Letter 02	30-Jan-2015	The objective of the administrative letter is to provide clarification regarding a recent change made to the protocol section 4.3.1.1 through Amendment 5 and Revised Protocol 02. In the section 4.3.1.1, the clause requiring interruption for dasatinib-related DLT was deleted but the intent of this deletion was not to remove the requirement to interrupt dasatinib for DLT.
Revised Protocol 02	01-Oct-2014	Incorporates Amendment 05
Amendment 05	01-Oct-2014	[redacted]
Administrative Letter 01	22-Jan-2014	The objective of the administrative letter is to correct a typo in the pharmacogenetics blood sample amendment number 01.
Revised Protocol 01	23-Oct-2013	Incorporates Amendment 03

Document	Date of Issue	Summary of Change
Amendment 03	23-Oct-2013	[redacted]
Original Protocol	11-Jul-2013	Not applicable

SYNOPSIS

Clinical Protocol CA180373

Protocol Title: 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)

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):

Dasatinib Dose and Schedule:

Dasatinib will be administered at standard doses appropriate for the phase of CML. The dasatinib (starting) dose will be as per the current dasatinib prescribing information for these patient populations: 100 mg daily for CML-CP and 140 mg for CML-AP.

Nivolumab Dose and Schedule:

The starting dose for this trial of 1 mg/kg every 2 weeks is tolerable as a single agent and is within the range that has shown anti-tumor activity in solid tumors. The maximum nivolumab dose in this trial is 3 mg/kg every 2 weeks. A dose de-escalation of nivolumab to 0.3 mg/kg maybe investigated, depending on the safety profile at 1 mg/kg.

Study Duration:

Study duration per subject is defined as a maximum of 3 years. Subjects will receive a maximum 2 years of treatment with dasatinib and nivolumab or until treatment failure or intolerance- whichever comes first. In the absence of disease progression or intolerance, subjects may receive up to a maximum of one additional year of dasatinib alone following cessation of nivolumab.

At the end of the study duration, BMS will not continue to supply study drug to subjects/investigators unless BMS chooses to extend the study. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

Study Phase: Phase 1B

Research Hypothesis: The combination of dasatinib and nivolumab will be safe, well tolerated and provide preliminary evidence of efficacy in subjects with previously treated CML-CP and CML-AP.

Objectives:

Primary Objective:

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

- Dose limiting toxicities (DLTs)
- 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).

Secondary Objectives:

- To evaluate the rate of Major Molecular Response (MMR) and Molecular Response 4.5 (MR4.5) at 6, 12, 24, and 36 months
- To evaluate time to and duration of MMR and MR4.5.

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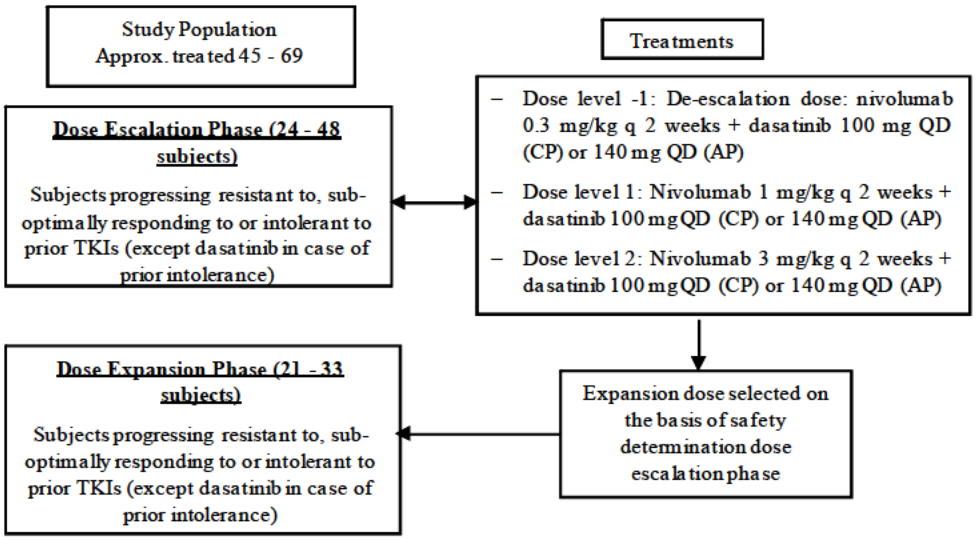
Study Design:



This is a phase 1B trial with an escalation and expansion cohort investigating the combination of dasatinib and nivolumab in subjects with CML-CP and CML-AP, who are progressing on, resistant to, suboptimally responding to, or intolerant of prior treatment with any Tyrone Kinase Inhibitors (TKI) (except dasatinib in case of prior intolerance).

Adult patients, both male and female with a confirmed diagnosis of CML will be enrolled. Two or more prior TKI therapies for CML are allowed, therefore, patients with resistance or suboptimal response per inclusion criteria remain eligible regardless of other intervening treatments.

To further characterize safety and efficacy an expansion cohort will be enrolled. Between 21 and 33 treated subjects will be enrolled at the dose selected for expansion (ie, 0.3 mg/kg, 1.0mg/kg or 3.0 mg/kg nivolumab), in combination with dasatinib 100 mg QD /140 mg QD, (as applicable for CP and AP-CML, respectively), based on the safety profile observed in the escalation phase.

Study Population:

Key Inclusion Criteria:

- Confirmed diagnosis of chronic myeloid leukemia (CML), in chronic phase (CP) or accelerated phase (AP):
  a) With historically documented either cytogenetic Ph+ cells on BMA or molecular results from peripheral blood
  b) ≥ 2 prior TKI therapies for CML
  c) Meeting one of the following criteria:
    i) Progression, resistance or suboptimal response to most recent prior Abl-kinase inhibitor (imatinib, nilotinib ponatinib, bosutinib or dasatinib)
    ii) Intolerance to most recent prior TKI (other than dasatinib) at the lowest possible effective dose
- ECOG Performance Status (PS) Score 0 - 1
- Toxicity of any prior therapy must have returned to Grade 0 - 1 (Grade 2 for hematologic) or be considered irreversible.

Key Exclusion Criteria:

- Known dasatinib-resistant Abl-kinase mutations (eg, T315I or T315A) (test results not required)
- Blast phase CML: Subjects cannot be (or have been within prior 6 months) in blast phase defined as ≥ 30% blasts in peripheral blood (PB) or in Bone Marrow Aspirates (BMA) and/or extramedullary disease other than hepatosplenomegaly
- Prior intolerance to dasatinib, defined as Grade ≥ 2 adverse event requiring discontinuation
- Any serious or uncontrolled medical disorder or active infection that would impair the ability of the subject to receive protocol therapy, including:
  a) Known pleural or pericardial (s) effusion at baseline
  b) Clinically-significant gastrointestinal disease, digestive dysfunction or surgery that would compromise absorption of dasatinib or the administration of dasatinib by mouth (eg, uncontrolled nausea or malabsorption syndrome)
  c) Thromboembolic disease requiring ongoing anticoagulation or deep vein thrombosis that is not adequately controlled
  d) Clinically-significant coagulation or platelet function disorder (other than related to thrombocytopenia), eg, von Willebrand's disease
  e) A history of pulmonary arterial hypertension
- Uncontrolled or significant cardiovascular disease, including any of the following:
  a) Myocardial infarction within 6 months of enrollment date
  b) Uncontrolled angina or congestive heart failure within 3 months of enrollment date

c) Left ventricular ejection fraction (LVEF) < 40%
d) Significant cardiac conduction abnormality, including
   i) History of clinically-significant ventricular arrhythmia (such as ventricular tachycardia, ventricular fibrillation, or Torsades de Pointe)
   ii) History of second or third degree heart block (except for second degree type 1 is not excluded)
   iii) Prolonged QTc/f interval > 450 msec on baseline ECG (unless a cardiac pacemaker is present).

Study Assessments:

The safety and tolerability of the combination dasatinib and nivolumab will be assessed continuously during the study and for 100 days post last dose of nivolumab and for 30 days post last dose of dasatinib.

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

Pharmacokinetics, anti-drug antibody and biomarkers samples will be collected at several timepoints.

Statistical Considerations:

Sample Size:

Dose Escalation Phase

The sample size at each of the 3 dose levels in the dose escalation phase of this study depends on observed toxicity and posterior inference. Twenty-four (24) subjects are expected to be treated during the dose escalation phase. There may be more than 24 subjects treated due to replacement, or less than 24 subjects treated due to toxicity at the lowest dose level. The number of subjects was derived by simulation. The simulation results from mTPI with totals of 24 and 36 subjects suggest that a sample size of 24 subjects is appropriate for the dose escalation phase. Additional subjects however, may be enrolled to dose level 2 if 24 subjects were treated at dose level 1 and escalation to dose level 2 is suggested either by decision rule or by investigators following careful review of study data. In that case the dose escalation phase may include 36 or 48 subjects.

Dose Expansion Phase

The total number of subjects treated in this study depends on the number of subjects treated in the escalation phase, but is expected to be at least 45 and to be below 70. In the dose expansion phase subjects will initiate treatment with the dose assessed to be the maximum tolerated dose among the three proposed doses. In the dose escalation phase and the dose expansion phase combined approximately 45 subjects will be treated at that dose. Administration of nivolumab in combination with dasatinib in 45 subjects will provide 90% probability of observing at least one occurrence of any adverse event that would occur with a 5% incidence in the population from which the sample is drawn.

Endpoints:

Primary Endpoint(s)

The primary objective is to assess the safety and tolerability for the combination of dasatinib and nivolumab in patients with chronic phase or accelerated phase CML, 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.

Secondary Endpoint(s)

The secondary endpoints are based on MMR and MR4.5:

- MMR and MR4.5 rates at 6, 12, 24, and 36 month
- Time to, and duration of, MMR and MR4.5

[redacted]

Analyses:

Efficacy Analyses

MMR and MR4.5 rates at 6, 12, 24, and 36 months will be provided by dose level and disease state at study entry with their corresponding 2-sided 95% exact (Clopper and Pearson) confidence intervals. Time to event and duration of event analyses will be analyzed using Kaplan-Meier methodology. Median time to event and median duration will be presented with their 95% confidence intervals derived with the method of Brookmeyer and Crowley.

Safety Analyses

All recorded adverse events will be listed and tabulated by system organ class, preferred term, treatment arm, dose level and disease state at study entry and coded according to the most current version of MedDRA. Vital signs and clinical laboratory test results will be listed and summarized by dose level and disease state at study entry. Any significant physical examination findings and results of clinical laboratory test will be listed.

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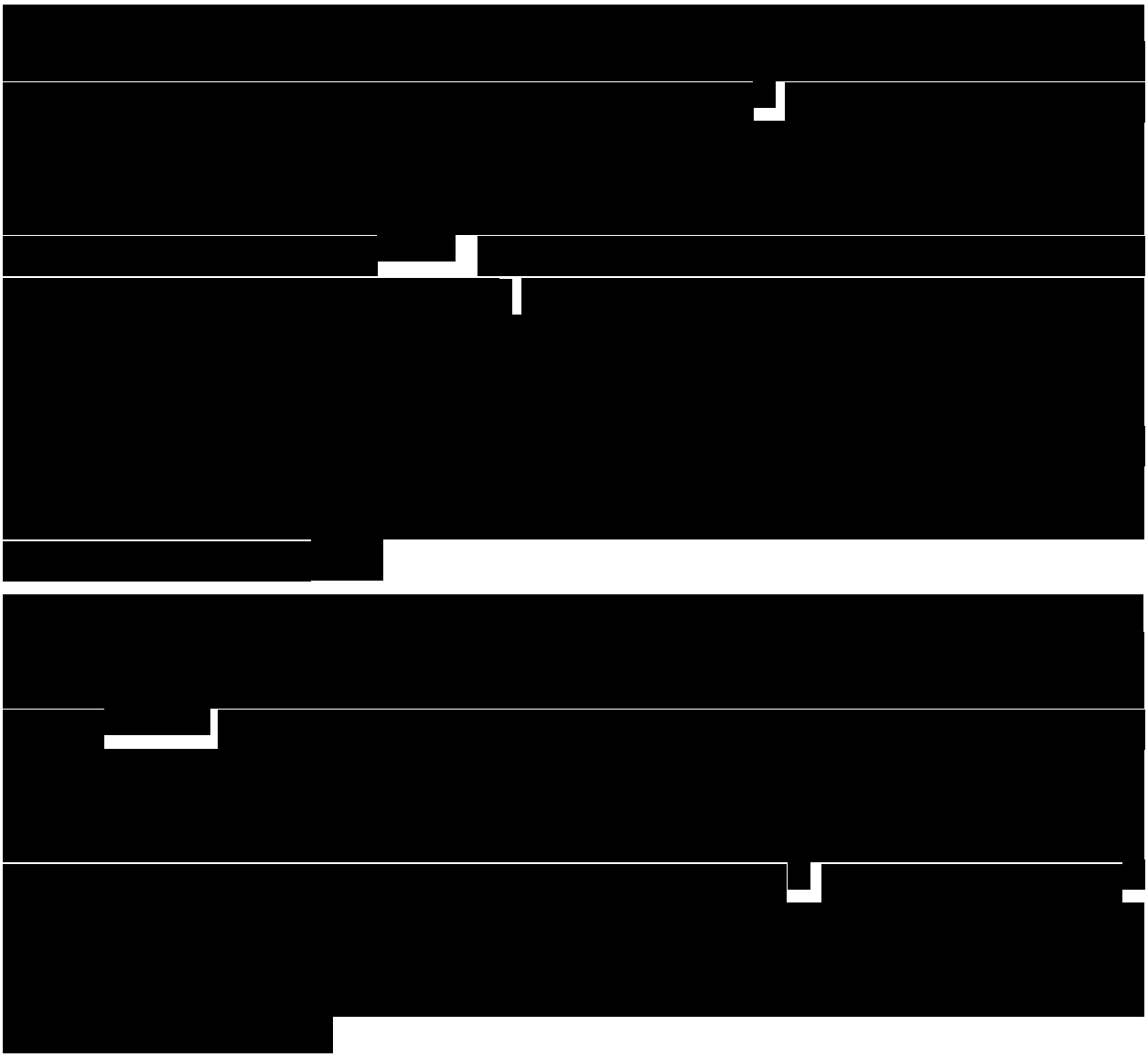

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1.3 Objectives(s)

1.3.1 Primary Objectives

The primary objective is to assess the safety and tolerability for the combination of dasatinib and nivolumab in subjects with chronic phase (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,
- 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).

1.3.2 Secondary Objectives

- To evaluate the rate of Major Molecular Response (MMR) and Molecular Response 4.5 (MR4.5) at 6, 12, 24, and 36 months
- To evaluate time to and duration of MMR and MR4.5.

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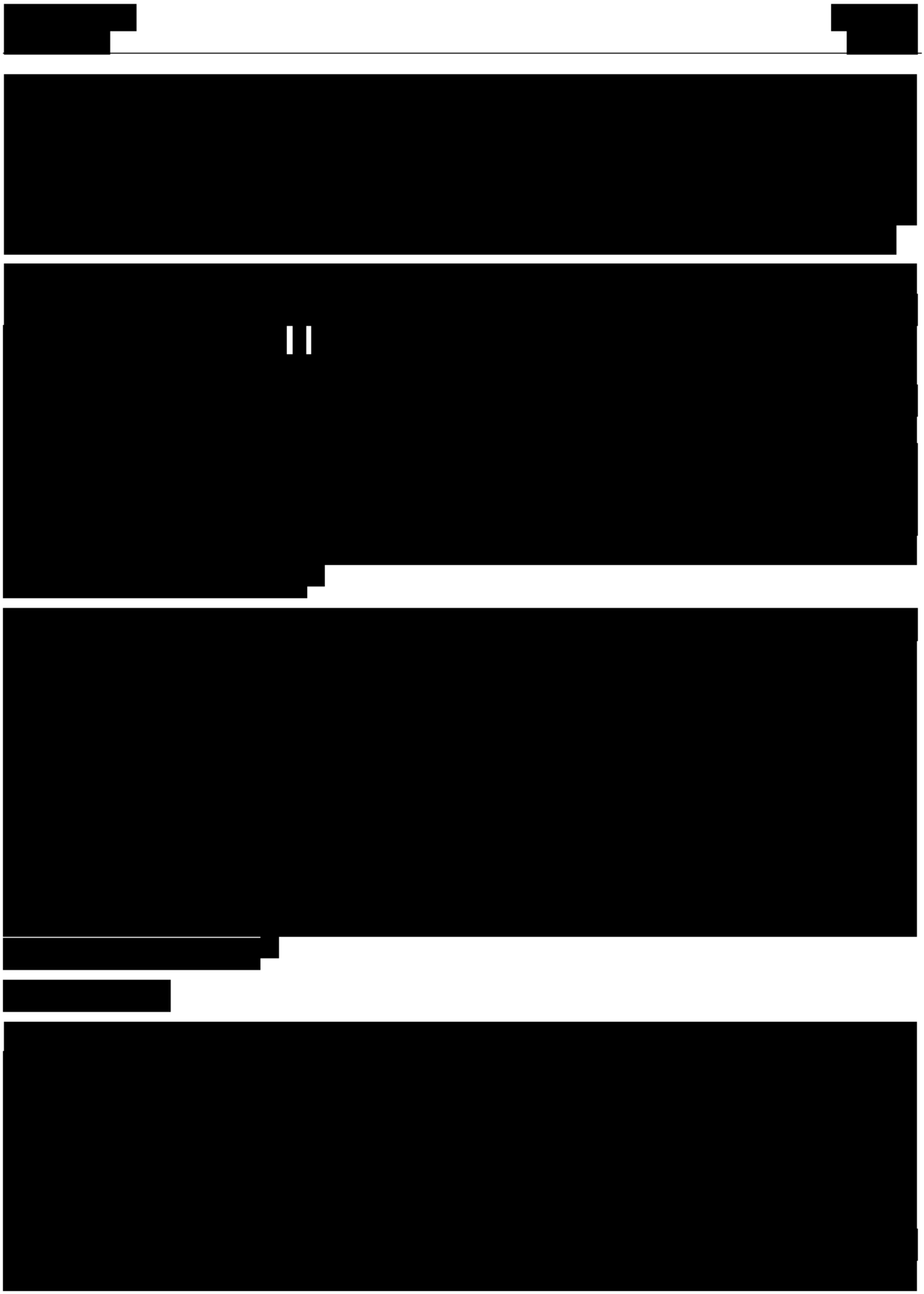

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1.5 Overall Risk/Benefit Assessment

Dasatinib has proven therapeutic value in CML and is considered to be a standard of care. Dasatinib will be administered at the approved doses and schedule for CML-CP and CML-AP. The safety profile of dasatinib is mostly characterized by fluid retention, GI toxicities (nausea & diarrhea), fatigue and myelosuppression. The fluid retention seen was most commonly: pleural or pericardial effusions, superficial edema, pulmonary hypertension, and congestive heart failure. As referred to earlier, results of a Phase 3 (dose-optimization) study led to the approval of 100 mg QD dasatinib in patients with CML-CP with resistance, intolerance, or suboptimal response to imatinib. A four-year follow-up (between 24 and 48 months) of these patients confirmed 100 mg QD as the best-tolerated dose, with few Grade 3/4 side effects. In a Phase 3 dose-optimization study in patients with advanced phase CML and Ph+ ALL (median duration of treatment of 14 months for CML-AP, 3 months for myeloid blast CML, 4 months for lymphoid blast CML and 3 months for Ph+ ALL), fluid retention (pleural effusion and pericardial effusion) was reported less frequently in patients treated with dasatinib 140 mg once daily than in those treated with 70 mg twice daily. Based on these collective data, 100 mg QD and 140 mg QD have been selected as the most appropriate doses in this study for CML-CP and CML-AP patients respectively; these dasatinib doses are used in this trial, but if a lower dasatinib dose is clinically indicated in an otherwise-eligible patient, then it may be allowed with agreement of BMS monitor. Dasatinib at both doses has a well described safety profile with most subjects experiencing Grade 1 - 2 AE that can be managed with dose interruptions and/or reductions. Myelosuppression is common at initiation of dasatinib treatment in patients with resistant CML (see Section 1.4.2), attributable to control of the Abl-driven clone; it will therefore not be considered a DLT. In light of potential benefit from dasatinib, furthermore, a DLT will not require discontinuation from study therapy.

In CA180323, a previous Phase I study of dasatinib in a similar population, most patients with CML-BP at study entry were not able to complete the DLT period; for this reason, they are excluded from this trial. However, patients with prior history of CML-BP (> 6 months prior to enrollment) may be DLT-evaluable and are eligible.

Dasatinib is potentially harmful to the developing fetus, and pregnancy must be avoided during treatment periods. In this study, investigators will counsel women of childbearing potential and male subjects who are sexually active with women of child bearing potential on the importance

of pregnancy prevention and the implications of an unexpected pregnancy during treatment with dasatinib.

Nivolumab has documented efficacy in a variety of solid tumors and will be administered at doses within the known tolerable range using a q2 week schedule. In multiple nivolumab trials, treatment-related AEs were reported for most subjects including treatment-related AEs of Grade 3 or 4. Some of the most frequently reported AEs, regardless of causality, included: fatigue, nausea, proteinuria, constipation, back pain, dry mouth, vomiting, rash and dyspnea. Additional events of interest include diarrhea and increase in thyroid stimulating hormone. Treatment-related SAEs of hypothyroidism, colitis, anemia and pneumonitis (including fatal) have been reported, however there was no dose-related pattern with regard to the incidence, severity, or relationship of AEs. Common laboratory abnormalities that were considered related to nivolumab that have been reported include decreases in CD4 counts, lymphopenia, increases in C-reactive protein and decrease in lymphocyte counts.

AEs reported in a trial of metastatic RCC subjects treated with nivolumab 2 mg/kg in combination with sunitinib (n = 6) or pazopanib (n = 10)[42] are of particular interest since this is a combination study with a TKI. A review of the data at the last interim analysis (03-Jul-2012) indicated that the AEs/SAEs were comparable to that reported in RCC subjects treated with nivolumab monotherapy. Although a Grade 3 SAEs of abdominal pain and syncope was reported in one subject treated with nivolumab + pazopanib and one additional ungraded SAE was reported as “early bowel obstruction” for a second subject in the same treatment group, neither were considered related to study treatment.

Drug-related AEOSIs with potential immune-related etiologies, that were reported in nivolumab trials include: pneumonitis, vitiligo, colitis, hepatitis, hypophysitis, and thyroiditis, among others. AEOSIs including hepatic, gastrointestinal and respiratory were managed with treatment interruption and administration of corticosteroids, and were generally completely reversible. Endocrine AEOSIs were managed with replacement therapy. Several subjects in these categories successfully reinitiated treatment with nivolumab. Drug-related pneumonitis has been shown to occurred in less than 3% of all subjects treated with nivolumab with Grade 3~4 pneumonitis reported in < 1%, most of who presented with NSCLC No clear relationship between the occurrence of pneumonitis and tumor type, dose level, or the number of doses received was noted. Early grade pneumonitis was generally reversible with treatment discontinuation and corticosteroid administration. In 3 subjects, infliximab and/or mycophenolate were utilized for additional immunosuppression, with unclear effectiveness. There were 3 (1%) drug-related deaths, due to pneumonitis.

Because of the potential for the development of nivolumab-related AEs including AEOSI, management algorithms have been developed to assist investigators in assessing and managing the following groups of AEs: **Endocrinopathy, Gastrointestinal, Hepatic, Neurological**. **Pulmonary, Renal, and Skin.** These algorithms are found in the Nivolumab IB and in Appendix 2 of this protocol.

The combination of dasatinib and nivolumab has not been previously studied. Due to the possible overlap in toxicities between dasatinib and nivolumab, as outlined above, several safety precautions to mitigate risk have been implemented in this trial which, are outlined below:

- Several doses of nivolumab will be investigated however; the first subjects will be treated with a dose of 1 mg/kg, which is 1/10th the maximal dose studied in other nivolumab trials.
- Enrollment will initially be limited to 6 subjects in dose level 1 and potentially for other dose levels as appropriate. Data from these 6 subjects will be evaluated and all 6 subjects must have completed the DLT evaluation period (described in Section 3.1.3.1) before initiating combination treatment of subsequent subjects into the cohort. This will limit the number of subjects exposed to the combination prior to understanding potential overlapping toxicities.
- An mTPI design is used in this trial, using a low predefined target DLT rate (~ 11%) that will allow for nivolumab dose escalation only if acceptable tolerability is observed.
- Algorithms are provided for the management of nivolumab AEs, and dose modification guidelines are provide for dasatinib for management of AEs with recommendations on study drug interruption, dose reduction and discontinuation.

Finally, there is a low potential risk of pharmacokinetic interactions between the drugs given their different elimination pathways (liver vs kidney). Dasatinib is primarily metabolized by liver enzyme CYP3A4, whereas nivolumab as an IgG antibody, the majority of its elimination occurs via intracellular catabolism, following fluid-phase or receptor mediated endocytosis. PK data for nivolumab are needed in this study population, but (as dasatinib PK is well-characterized) intensive dasatinib PK sampling is not warranted.

The potential benefits of nivolumab with or without dasatinib in subjects with CML is unknown as to date no trials in Ph+ leukemias have been conducted. However, responses to nivolumab monotherapy have been observed in both solid tumors and subjects with other hematological malignancies such as non-Hodgkin's lymphoma and multiple myeloma (Nivolumab IB version 12 and data on file).In addition (and as previously mentioned), other *immunomodulatory-like* therapies (SCT and DLI) have a known curative potential in CML which points to CML's responsiveness to T-Cell mediated immunity. Hence there is potential for a novel immune-targeted therapy such as nivolumab to add to the benefit of dasatinib in CML patients previously treated with a TKI by helping to overcoming TKI resistance, deepening responses and potentially prolonging a treatment free-interval.

In conclusion, in subjects with CML-CP and CML-AP with relapsed, refractory or suboptimal-responding disease there is an acceptable risk/benefit profile and appropriate safeguards to initiate a Phase 1 trial with the combination of dasatinib and nivolumab.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles

underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

The investigator or BMS should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.

2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4) Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is a phase 1B trial with an escalation and expansion cohort investigating the combination of dasatinib and nivolumab in subjects with CML-CP and CML-AP, who are progressing on, resistant to, sub-optimally responding to, or intolerant of prior treatment with any TKI (except dasatinib in case of prior intolerance).

Adult subjects, both male and female with a confirmed diagnosis of CML will be enrolled. Two or more prior TKI therapies for CML are allowed; therefore, subjects with resistance or suboptimal response per inclusion criteria remain eligible regardless of other intervening treatments.

Cohorts of subjects will be treated with escalating doses of nivolumab as described in the treatment plan below. All subjects are treated until progression/treatment failure (see Section 5.4.2) or intolerance for a maximum of up to 2 years with dasatinib and nivolumab combination and up to 1 additional year with dasatinib alone. Subjects stopping nivolumab prior

to two years will be able to receive one additional year with dasatinib alone, from the date of nivolumab cessation.

The proportion of subjects with CML-CP and CML-AP is not known in advance. However it is not the intention to separate these subjects into different cohorts for the purposes of a safety evaluation. 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. 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. Approximately 24 - 48 subjects will be required for escalation phase. Subsequently, 21 - 33 additional subjects will be treated in an expansion phase at the selected dose.

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Figure 3.1.2-1: Study Design Schematic

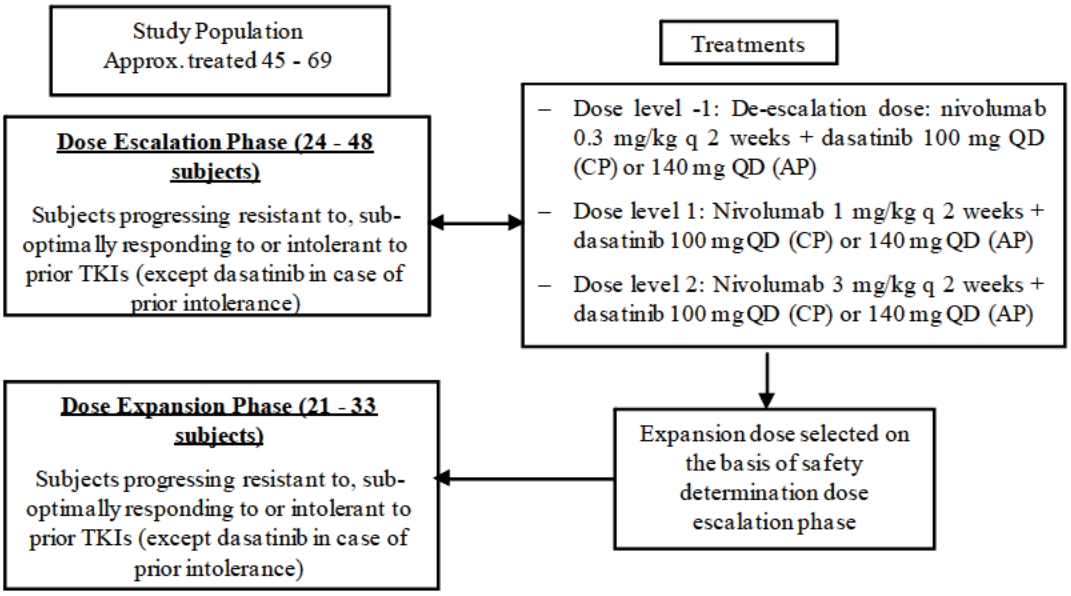
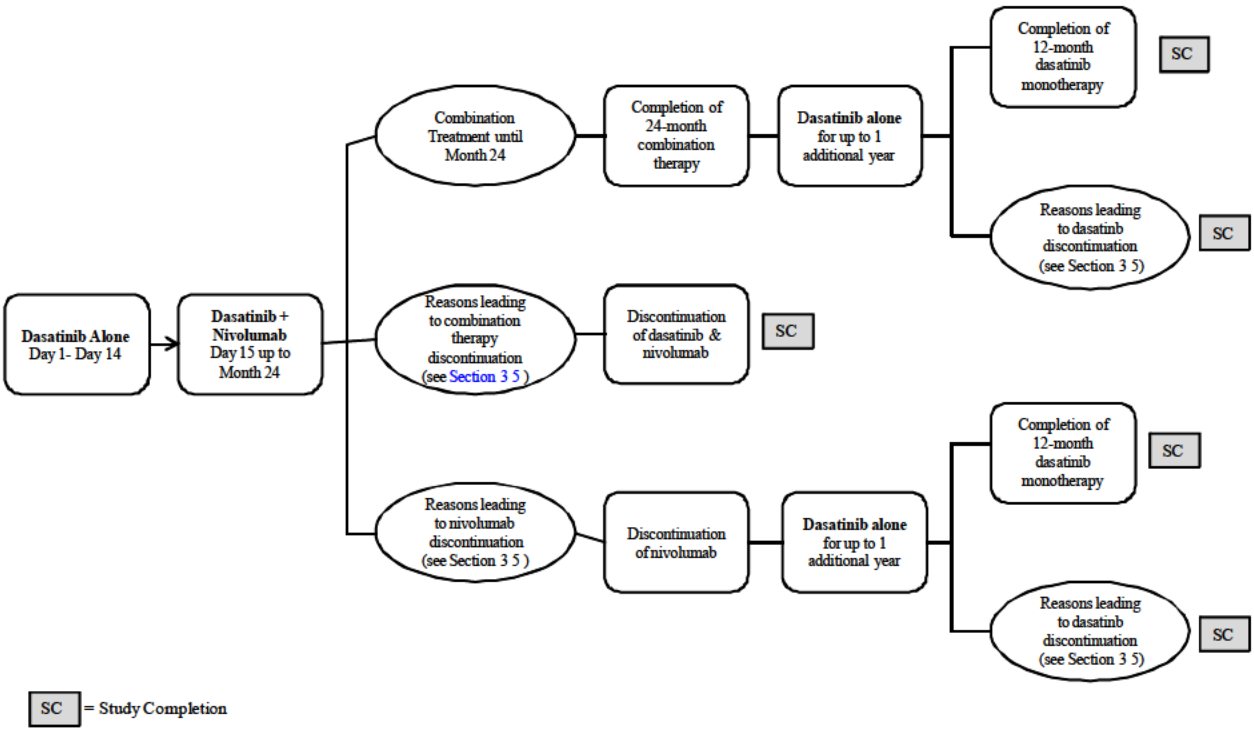


Figure 3.1.2-2: Study Treatment Schematic



3.1.3 Dose Escalation

A modified toxicity probability interval (mTPI) design with dose cohorts of 12 will be used in this Phase 1B study. The nivolumab dose in the first cohort will be 1 mg/kg (dose level 1).

Additional cohorts will be enrolled either at the same dose, at 3 mg/kg (dose level 2), or at 0.3 mg/kg (dose level -1) as per mTPI decision rules (see Table 3.1.3-2).

Dose levels are defined as in Table 3.1.3-1 below.

Table 3.1.3-1: Dose Levels for Dose-escalation of Nivolumab in Combination with Dasatinib

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

[a] Subjects will only be enrolled at dose level -1 if de-escalation is required from dose level 1.

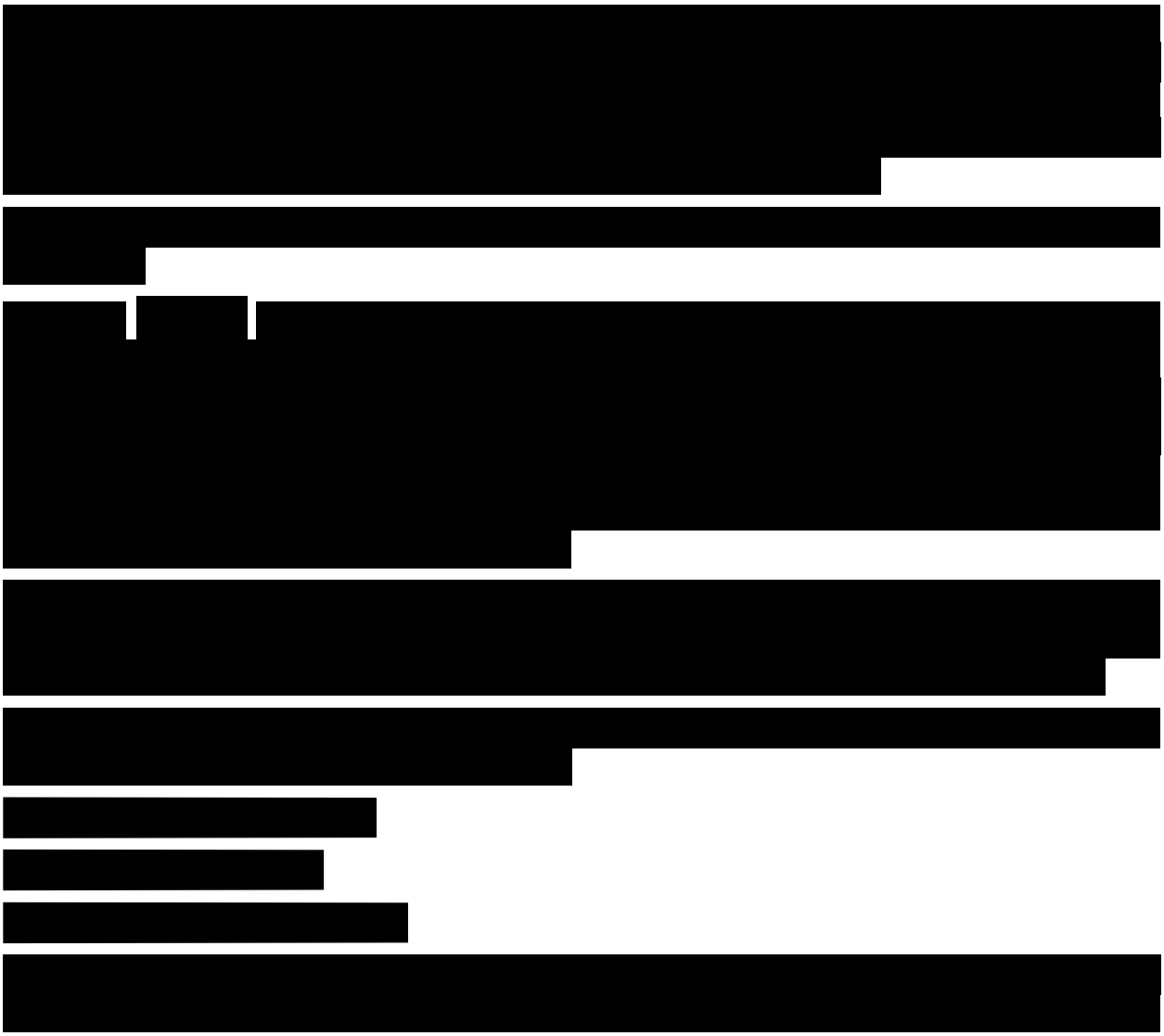


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Table 3.1.3-2: Dose Assignment Decision Rules Based on Observed Dose Limiting Toxicities and the mTPI Method

Number of DLTs	Number of Subjects Treated at Current Dose	
	12	24
0	E	E
1	S	E
2	S	S
3	D(U)	S
4	D(U)	S
5	D(U)	D(U)
6	D(U)	D(U)

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). The toxicity probabilities needed for the above comparison to the target toxicity probability will be estimated based on toxicity outcomes during the DLT period observed on all patients evaluated in the dose escalation phase, utilizing an isotonic regression procedure.[43] The MTD is the maximum tolerated dose among the doses tested.

3.1.3.1 Dose Limiting Toxicity

DLT will be determined based on the incidence and intensity of drug related adverse events (AEs). The following **drug-related** AEs (whether related to one or both agents) occurring during the first 6 weeks of combined treatment with both dasatinib plus nivolumab (ie, Weeks 3 to 8, inclusive) would be considered DLTs:

- Grade 4 hematologic AE lasting > 7 days despite appropriate medical intervention, except as noted below;
- Grade 3 or Grade 4 nonhematologic AE irrespective of duration;
- Grade 2 nonhematologic AE lasting > 7 days despite appropriate medical intervention (exception: asymptomatic laboratory values of Grade 2 which do not require medical intervention);
- Any toxicity managed by discontinuation of nivolumab;

- Grade ≥ 2 AE not controlled by medical intervention and requiring dasatinib treatment interruption for > 28 consecutive days;
- Grade ≥ 2 AE not controlled by medical intervention and requiring missing 2 consecutive doses of nivolumab.

Cytopenias (especially absolute neutrophil count [ANC] and platelets) are common and expected when patients with TKI-pretreated resistant CML begin dasatinib treatment. These are related to rapid control of Abl-driven myeloproliferation in the setting of reduced normal hematopoietic progenitors. Therefore Grade 4 hematologic AEs attributable to disease and dasatinib are not considered DLT.

Criteria for dose delay during the DLT period are outlined in Section 4.3.1.

3.1.4 Expansion Cohorts

To further characterize safety and efficacy an expansion cohort will be enrolled. Between 21 and 33 treated subjects will be enrolled at the dose selected for expansion (ie, 0.3 mg/kg, 1.0 mg/kg or 3.0 mg/kg nivolumab), in combination with dasatinib 100 mg QD /140 mg QD, (as applicable for CP and AP-CML, respectively), based on the safety profile observed in the escalation phase.

In the dose expansion phase, subjects will initiate treatment with the dose selected in the escalation phase of the trial based on the totality of the data, including AEs during subsequent treatment or related to dose escalation. The dose in the expansion phase will be no higher than the MTD, or Dose Level 2 if no MTD is identified. In the dose escalation phase and the dose expansion phase combined approximately 45 subjects will be treated. Clinical safety monitoring of subjects enrolled during this additional cohort expansion portion of the study will be similar to that conducted during the dose-escalation portion of the study. 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. An expanded mTPI toxicity monitoring table provided in Appendix 3 of the protocol may also be used as an additional resource to facilitate decisions related to subject accrual during cohort expansion. An agreement will be reached as to whether a lower dose should be examined, or whether any additional treatment guidelines should be implemented prior to enrollment of additional subjects.

3.2 Post Study Access to Therapy

Study duration per subject is defined as a maximum of 3 years. Subjects will receive a maximum 2 years of treatment with dasatinib and nivolumab or until treatment failure or intolerance-whichever comes first. In the absence of disease progression or intolerance, subjects may receive up to a maximum of one additional year of dasatinib alone following cessation of nivolumab.

At the end of the study duration, BMS will not continue to supply study drug to subjects/investigators unless BMS chooses to extend the study. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

3.3 Study Population

For entry into the study, the following criteria MUST be met.

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

a) Subjects must have signed and dated an IRB/EC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal subject care

b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study

2. Target Population

a) Confirmed diagnosis of CML, in chronic phase (CP) or accelerated phase (AP):

i) With historically documented either cytogenetic Ph+ cells on Bone Marrow Aspirates (BMA) or molecular results from peripheral blood

ii) ≥ 2prior TKI therapies for CML

iii) Meeting one of the following criteria:

(1) Progression, resistance or suboptimal response to most recent prior Abl-kinase inhibitor (imatinib, nilotinib, ponatinib, bosutinib or dasatinib)-(see Appendix 4)

(2) Intolerance to most recent prior TKI (other than dasatinib) at the lowest possible effective dose.

A subject is defined as being intolerant to prior TKI (other than dasatinib) if he or she had a Grade ≥ 3 toxicity considered at least possibly related to that TKI at the dose which led to discontinuation of therapy. Subjects intolerant to prior dasatinib (experiencing a grade ≥ 2 adverse event requiring discontinuation) are excluded.

b) Subject Re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, subject has not been treated) after obtaining agreement from the BMS Central Medical Monitor prior to re-enrolling a subject. If re-enrolled, the subject must be re-consented.

c) ECOG Performance Status (PS) Score 0 - 1 (see Appendix 5)

d) Toxicity of any prior therapy must have returned to Grade 0 - 1 (Grade 2 for hematologic) or be considered irreversible.

3. Age and Reproductive Status

a) Males and Females, ages 18 years and older

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug

c) Women must not be breastfeeding

d) WOCBP must agree to follow instructions for method(s) of contraception from the time of enrollment for the duration of treatment with study drug dasatinib plus time required for the study drug nivolumab to undergo approximately five half lives plus 30 days (duration of ovulatory cycle) for a total of 5 months post-treatment completion of nivolumab and 30 days post treatment completion of dasatinib.

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug dasatinib plus time required for the investigational drug nivolumab to undergo approximately five half-lives plus 90 days (duration of sperm turnover) for a total of 7 months post-treatment completion of nivolumab and 90 days post treatment completion of dasatinib.

f) Male subjects whose partners are WOCBP must use condoms, including male subjects who are azoospermic. WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements but still must undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% per year when used consistently and correctly.

At a minimum, subjects must agree to the use of two methods of contraception, with one method being highly effective and the other method being either highly effective or less effective as listed in appendix 9.

3.3.2 Exclusion Criteria

1. Target Disease Exclusions

a) Known dasatinib-resistant Abl-kinase mutations (eg, T315I or T315A) (test results not required to start therapy)

b) Blast phase CML: Subjects cannot be (or have been within prior 6 months) in blast phase defined as ≥ 30% blasts in peripheral blood (PB) or in BMA and/or extramedullary disease other than hepatosplenomegaly

2. Medical History and Concurrent Diseases

a) Prior intolerance to dasatinib, defined as Grade ≥ 2 adverse event requiring discontinuation

b) Any serious or uncontrolled medical disorder or active infection that would impair the ability of the subject to receive protocol therapy, including:

i) Known pleural or pericardial (s) effusion at baseline

ii) Clinically-significant gastrointestinal disease, digestive dysfunction or surgery that would compromise absorption of dasatinib or the administration of dasatinib by mouth (eg, uncontrolled nausea or malabsorption syndrome)

iii) Thromboembolic disease requiring ongoing anticoagulation or deep vein thrombosis that is not adequately controlled

iv) A history of pulmonary arterial hypertension

c) Uncontrolled or significant cardiovascular disease, including any of the following:

i) Myocardial infarction within 6 months of enrollment date

ii) Uncontrolled angina or congestive heart failure within 3 months of enrollment date

iii) Left ventricular ejection fraction (LVEF) < 40%

iv) Significant cardiac conduction abnormality, including

(1) History of clinically-significant ventricular arrhythmia (such as ventricular tachycardia, ventricular fibrillation, or Torsades de Pointe)

(2) History of second or third degree heart block (except for second degree type 1 is not excluded)

(3) Prolonged QTc/f interval > 450 msec on baseline ECG (unless a cardiac pacemaker is present)

d) History of significant bleeding disorder unrelated to CML, including:

i) Diagnosed congenital bleeding disorders (eg, von Willebrand's disease)

ii) Diagnosed acquired bleeding disorder within one year (eg, acquired anti-factor VIII antibodies).

e) Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast

f) Subjects with active, known or suspected autoimmune disease. (Note: Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.)

g) A serious uncontrolled medical disorder or active infection which would impair the ability of the subject to receive protocol therapy or whose control may be jeopardized by the complications of this therapy.

i) Although subjects with acute hepatitis B virus (HBV) infection or who are HBsAg positive are excluded, subjects who are positive for anti-HBc only may be enrolled if they meet all other eligibility criteria. See section 5.3 for recommendations regarding subjects with positive HBV serology.

3. Physical and Laboratory Test Findings

a) Positive test for hepatitis B virus (HBV) or hepatitis C virus (HCV) indicating acute or chronic infection

b) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)

c) Grade ≥ 3 peripheral blood count deficiency, ie:

i) ANC < 1,000 cells/mm^3

ii) Platelet count < 50,000 cells/mm^3

iii) Hemoglobin < 8 g/dL (transfusion-support permitted)

d) Laboratory abnormalities (per CTCAE v 4.03):

i) Serum sodium, potassium or calcium (ionized or corrected for albumin) or phosphate below ILLN (Institutional lower limit of normal)

ii) Baseline magnesium Grade ≥ 2

iii) Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 2.5 X institutional upper limit of normal (IULN). Total bilirubin > 2.0 X ULN (unless Gilbert syndrome has been diagnosed)

iv) Creatinine clearance < 40 mL/min (measured or calculated by Cockroft-Gault formula).

e) Oxygen saturation < 92% (by pulse oximetry).

4. Allergies and Adverse Drug Reaction

a) History of allergy to dasatinib

b) History of grade 4 anaphylactic reaction to monoclonal antibody therapy or known hypersensitivity reactions to drugs formulated with polysorbate 90)

5. Sex and Reproductive Status

a) Subjects who are pregnant or breastfeeding or likely to become pregnant.

b) Men whose partner is unwilling or unable to avoid pregnancy

6. Prohibited Treatments and/or Therapies

a) Prior therapies for CML are permitted with the following restrictions

i) Investigational agent must be ≥ 28 days before first dasatinib dose (Note: regardless of approval status, imatinib, nilotinib, ponatinib, bosutinib and dasatinib are not considered investigational)

ii) Standard chemotherapy or TKI treatment except dasatinib must be discontinued ≥ 7 days before first dasatinib dose (no interruption for ongoing dasatinib)

b) Subjects currently taking QT prolonging agents strongly associated with Torsades de Pointes (see Section 3.4.1.2)

c) Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137 or anti CTLA-4 antibody (or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways)

d) Prior organ allograft or allogeneic bone marrow transplantation must have been > 1 year before enrollment, and **only** if there is no history of Grade ≥ 3 rejection or GVHD at any time, there have been no signs of rejection nor GVHD for > 6 months before enrollment, and there is no ongoing therapy for GVHD.

e) Concomitant use of strong inhibitors of the CYP3A4 isoenzyme, unless appropriate wash-out period (5 times half-live compound) before first dasatinib dosing

f) Non-oncology vaccine therapies for prevention of infectious diseases (eg HPV vaccine-within 28 days of first nivolumab dose (see Section 3.4.2.5).

7. Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated

b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

3.3.3 Women of Childbearing Potential

A Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, women under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.*

*Women treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels. If the serum FSH level is > 40 mIU/mL at any time during the washout period, the woman can be considered postmenopausal:

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months.

[redacted]

[redacted]

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3.4.1.2 Medications that Prolong QT Interval

Medications associated with QT interval prolongation **are prohibited** while subjects are on therapy with dasatinib, including:

- Anti-arrhythmics: quinidine, procainamide, disopyramide, amiodarone, sotalol, ibutilide, dofetilide, bepridil
- CNS agents: propofol, chlorpromazine, droperidol, haloperidol, thioridazine, pimozide, citalopram, escalitopram, haloperidol, methadone, levomethadyl
- Antibiotics: fluconazole, chloroquine, halofantrine, ciprofloxacin, erythromycin, clarithromycin, azithromycin, levofloxacin, sparfloxacin, pentamidine
- Other: cocaine (topical), cisapride, domperidone, astemizole, terfenadine

Ideally, subjects enrolled in this study should not begin taking other medications known to prolong the QT interval. A website and further information on medications known to prolong the QT interval is found in Appendix 6. However, should the investigator believe that beginning therapy with a potentially QT prolonging medication (other than the ones listed above which are explicitly prohibited) is vital to an individual subject's care, then additional ECG(s) will be done at the investigator's discretion to ensure the subject's safety.

3.4.1.3 Use of Growth Factors during the DLT Evaluation Period

Growth factors such as G-CSF/GM-CSF or epo-compounds (eg, erythropoietin or darbepoetin) are **not permitted** during the 6-week DLT evaluation period for subjects enrolled in the escalation phase as these may mask potential DLT. There are no restrictions on growth factors outside this period (see Section 3.4.3.2 for further guidance).

3.4.2 Other Restrictions and Precautions

Restricted therapies are not prohibited, but are not recommended; therefore, the following are permitted **with caution if clearly medically indicated**.

[redacted]

[redacted]

[redacted]

[redacted]

3.5 Discontinuation of Subjects from Treatment

3.5.1 During Combination Therapy Period (During Escalation or Expansion Phase)

Subjects MUST discontinue both dasatinib and nivolumab for any of the following reasons:

- Subject's request to stop study treatment

- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- QTc Fridericia value > 500 msec, if confirmed on repeat ECG
- Treatment Failure while receiving active study therapies (see Section 5.4.2).

Outside of the DLT period, subjects MUST discontinue nivolumab only for any of the following reasons:

- Subject's request to stop nivolumab
- Any drug-related adverse event requiring nivolumab discontinuation as described in Appendix 2 including the following, if related to nivolumab:
  - Grade 4 hematologic AE lasting > 7 days despite appropriate medical intervention
  - Grade 4 nonhematologic AE irrespective of duration
  - Grade 3 nonhematologic AE lasting > 7 days despite appropriate medical intervention (exception: asymptomatic laboratory values of Grade 3 which do not require medical intervention, and alopecia will not require discontinuation), unless requiring immediate discontinuation per Appendix 2.
  - Grade 3-4 hypersensitivity reaction

Please see Table 5.1-3 for procedures on continuing dasatinib monotherapy after discontinuation from nivolumab therapy.

3.5.2 During Dasatinib Monotherapy Phase

Subjects MUST discontinue dasatinib for any of the following reasons:

- Subject's request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- QTc Fridericia value > 500 msec, if confirmed on repeat ECG
- Treatment Failure while receiving active study therapies (see Section 5.4.2).

All subjects who discontinue investigational product should comply with protocol specified follow-up procedures as outlined in Section 5.

The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study treatment is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

3.6 Post Treatment Study Follow up

Subjects who discontinue study treatment should continue to be followed for safety assessments as described in Table 5.1-2 and Table 5.1-3.

Subjects who discontinue dasatinib from Day 1 to Day 14 must perform the dasatinib alone Follow-up visit within 30 days (± 7 days) from the last dose of dasatinib.

Combination Period

During the combination period, subjects who discontinue both dasatinib and nivolumab must perform the Follow-up visits 1 & 2 for nivolumab toxicities. The Follow-up visit 1 should be performed 35 days (± 7 days) from the last dose of nivolumab. The Follow-up visit 2 must be performed 80 days (± 7 days) from the Follow-up visit 1.

Dasatinib Monotherapy Period

Subjects who discontinue nivolumab but continue on dasatinib alone beyond Month 4 visit should not perform the follow-up visits 1 & 2 for nivolumab toxicities. The assessments performed during these visits are identical to those performed during the dasatinib alone Month 1 and Month 4 visits.

However, subjects who discontinue dasatinib alone before Month 1 visit must perform two follow-up visits for assessment of nivolumab toxicities: Follow-up visit 1 approximately 35 days (± 7 days) from the last dose of nivolumab and a Follow-up visit 2 approximately 80 days (± 7 days) from the first follow-up visit.

Subjects who discontinue dasatinib alone after Month 1 and prior to Month 4 visits must also have a follow-up visit for nivolumab toxicities assessment approximately 100 days (± 7 days) from the last dose of nivolumab.

Finally, subjects that discontinue dasatinib alone treatment after Month 4 visit must have a follow-up visit for dasatinib toxicities assessment performed 30 days (± 7 days) from the last dose of dasatinib.

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 TREATMENTS

Study drugs include both Non-investigational (NIMP) and Investigational Medicinal Products (IMP) and can consist of the following:

- All products, active or placebo, being tested or used as a comparator in a clinical trial.
- Study required premedication, and
- Other drugs administered as part of the study that are critical to claims of efficacy (eg, background therapy, rescue medications)
- Diagnostic agents: (such as glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection.

4.1 Study Treatments

Table 4.1-1: Product Description: Open Label Period

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
Dasatinib Tablet	20 mg	30 tablets per bottle / open label	NA	Film coated tablets, biconvex, round, white to off-white in appearance with "20" or "BMS" debossed on one side and "527" on the other side	15° - 25°C (59° - 77°F)
Dasatinib Tablet	50 mg	30 tablets per bottle / open label	NA	Film coated tablets, biconvex, round, white to off-white in appearance with "50" or "BMS" debossed on one side and "528" on the other side	15° - 25°C (59° - 77°F)
Nivolumab Injection	10 mg/mL	10 mL (100 mg/vial) Booklet label	6 vials per carton Booklet label	Clear to opalescent, colorless to pale yellow liquid, light (few) particulates may be present	2°- 8° C (36° - 46°F) Protect from light Protect from freezing

Medications used to treat infusion-related reactions should be sourced by the investigative sites if available and permitted by local regulations.

4.1.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational product(s) is/are:

- nivolumab 10 mg/mL
- dasatinib tablets, 20 mg and 50 mg.

[redacted]

4.1.3 Handling and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets). Study medication should be stored in a secure area according to local regulations. Storage facilities for investigational agents must be substantially constructed, securely locked and access restricted to prevent theft or diversion, and as applicable by local regulations.

For supportive care therapies product, if marketed product is utilized, it should be stored in accordance with the package insert, summary of product characteristics (SmPC), or similar.

Storage facilities for controlled substances must be securely locked and substantially constructed, with restricted access to prevent theft or diversion, as applicable by local regulations.

Please refer to Section 9.2 for investigational product record retention and Section 4.6 for return and destruction instructions.

Dasatinib

Dasatinib should be stored at 59°F to 77°F (15°C to 25°C). The investigator (or assigned designee, eg, study pharmacist) will dispense the proper number of each strength tablet to the subject to satisfy dosing requirements for 4 weeks, or longer if appropriate (eg, during dasatinib monotherapy). The label ID number or batch number, date and amount dispensed for each dosage strength must be recorded on the drug accountability pages. The subject must be instructed to return all unused study medications in the provided packaging at each subsequent visit.

Please refer to the current version of the dasatinib Investigator Brochure and/or pharmacy reference sheets for complete storage, handling, and dispensing information for dasatinib.

Nivolumab

Nivolumab vials must be stored at a temperature of 2°C to 8°C and should be protected from light and freezing. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

For details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the BMS-936558 (nivolumab) Investigator Brochure section for "Recommended Storage and Use Conditions" and/or pharmacy reference sheets.

Nivolumab is to be administered as a 60-minute IV infusion. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

Infusion-related supplies (eg, IV bags, in-line filters, 0.9% NaCl, or 5% dextrose solution) will not be supplied by the sponsor and should be purchased locally if permitted by local regulations.

Please refer to the current version of the BMS-936558 (nivolumab) Investigator Brochure and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information.

[redacted]

4.3 Selection and Timing of Dose for Each Subject

Dasatinib

Dasatinib is administered from Day 1 for 2 weeks (14 days) prior to starting of nivolumab dosing (see below).

The starting dose of dasatinib is 100 mg QD for subject with CML-CP and 140 mg QD for subjects with CML-AP. In selected cases, a starting dose of dasatinib lower than 100 mg QD for CML-CP and 140 mg QD for CML-AP can be allowed with written agreement from the BMS Central Medical Monitor.

Dasatinib dosing must be held on the day of PK trough determinations for dasatinib until after PK predose samples for dasatinib have been drawn, as appropriate.

On the Day 29, when both dasatinib and nivolumab samples are drawn, dasatinib dosing must be immediately before nivolumab infusion is begun in order to accurately evaluate PK.

Dasatinib 50 mg and/or 20 mg tablets should be administered as two/four tablets taken once per day at the same time with or without food. Dose modifications are permitted and are outlined below in Section 4.3.2.

In the event of adverse event or intolerance, subjects may adjust the time of the day they take dasatinib as long as they take the drug approximately every 24 hours, except the days where PK samples are drawn for dasatinib.

Nivolumab

Nivolumab will be administered as an IV infusion beginning on treatment Day 15 and then every two weeks (± 3 days) for up to 2 years. Subjects may be dosed no less than 11 days from the previous dose of drug.

Nivolumab infusion should begin right after administration of dasatinib, as described above, whenever possible.

In the escalation phase, multiple dose levels of nivolumab will potentially be explored (see Table 4.3-1).

Table 4.3-1: Nivolumab Dose Level

Dose Levels	Dose of Nivolumab Intravenous, q2 wks
-1	0.3 mg/kg
1	1 mg/kg
2	3 mg/kg

Dosing calculations should be based on body weight. Dose should be recalculated if weight has changed more than 5%. All doses should be rounded to the nearest milligram. However, nivolumab doses may be rounded down to the nearest 100 mg (vial size) if the difference is ≤ 10 mg; at 3 mg/kg, this applies to subjects 67 - 70 kg or 100 - 103 kg.

There will be no dose modifications allowed, except as specified in Section 4.3.3.

4.3.1 Dose Interruption or Delay

4.3.1.1 Dasatinib Interruption

Interruption of dasatinib administration is at investigator discretion. Depending on the nature of the AE, dasatinib should be interrupted for drug-related AE of Grade ≥ 2 or laboratory abnormality of Grade ≥ 4. Omitted/skipped doses should not be made up. Please refer to Section 4.3.2.

Dasatinib interruption is required for a dasatinib-related DLT (see Section 3.1.3.1, Dose Limiting Toxicity) and must follow the same instructions under Section 4.3.2, Dose Modifications.

Subjects must be re-treated within 28 days from the previous dose during the DLT period. Following the DLT period subjects may be allowed to remain on therapy following delays > 28 days after discussion and agreement with the BMS Central Medical Monitor.

Please refer to Table 5.1-3 for procedures on continuing dasatinib monotherapy after discontinuation from combination study therapy.

4.3.1.2 Nivolumab Dose Delay

Nivolumab administration should be delayed for the following drug-related AEs:

- Any Grade ≥ 2 non-skin AE, except that
  - Grade 2 fatigue or laboratory abnormalities do not require delay, however
    - For a subject with baseline AST, ALT, or total bilirubin within normal limits, delay dosing for drug-related Grade ≥ 2 values
- Any Grade 3 skin AE, or Grade 3 laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or leukopenia does not require dose delay.
  - If a subject has Grade 1 baseline AST, ALT, or total bilirubin, delay dosing for drug-related Grade 3 toxicity
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Please refer to Appendix 2 for algorithms pertaining to nivolumab concerning the management of drug related adverse events. If the criterion to resume treatment is met, the subject should restart treatment at the next scheduled timepoint per protocol.

Consultation between the Investigator of record and the BMS Central Medical Monitor is mandatory prior to resuming nivolumab dosing after nivolumab delay. The BMS Central Medical Monitor may decide on nivolumab delay that supercedes the guidance in Appendix 2.

Subjects must be re-treated within 28 days from the previous dose during the DLT period. Following the DLT period subjects may be allowed to remain on therapy following delays > 28 days after discussion and agreement with the BMS Central Medical Monitor.

Important note: For clarity, the term "delay" is used to mean withholding of nivolumab dosing. "Interruption" of nivolumab refers to infusion reactions. Please refer to Section 4.3.4.2 for infusion interruption.

[redacted]

[redacted]

[redacted]

[redacted]

4.4 Blinding/Unblinding

Not applicable: this is an open-label trial.

4.5 Treatment Compliance

Treatment compliance will be monitored by drug accountability as well as the subject's medical record and eCRF

4.6 Destruction and Return of Study Drug

4.6.1 Destruction of Study Drug

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the BMS Study Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met the responsible BMS Study Monitor will make arrangements for return of study drug.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.6.2 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible BMS Study Monitor.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

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5 STUDY ASSESSMENTS AND PROCEDURES

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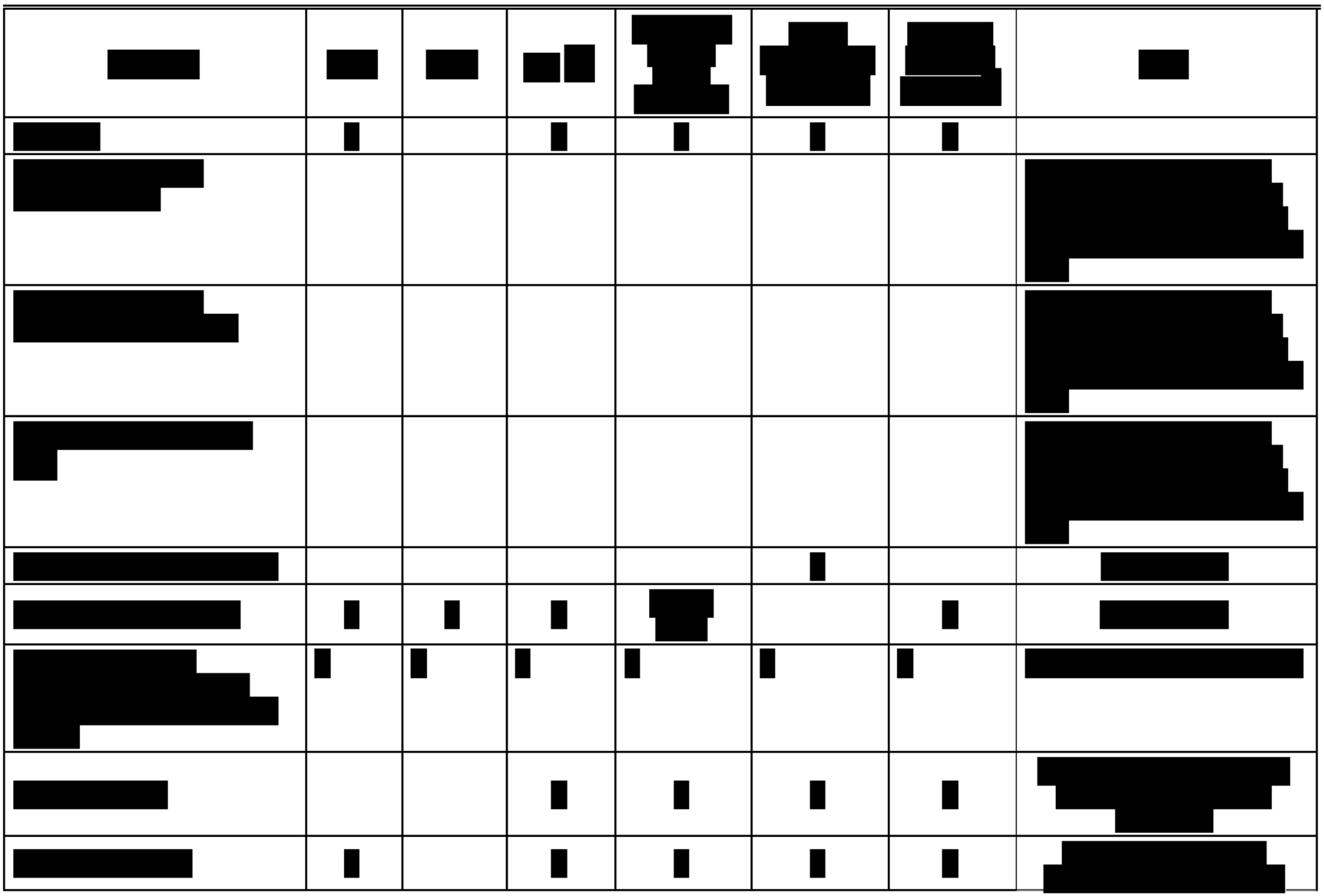

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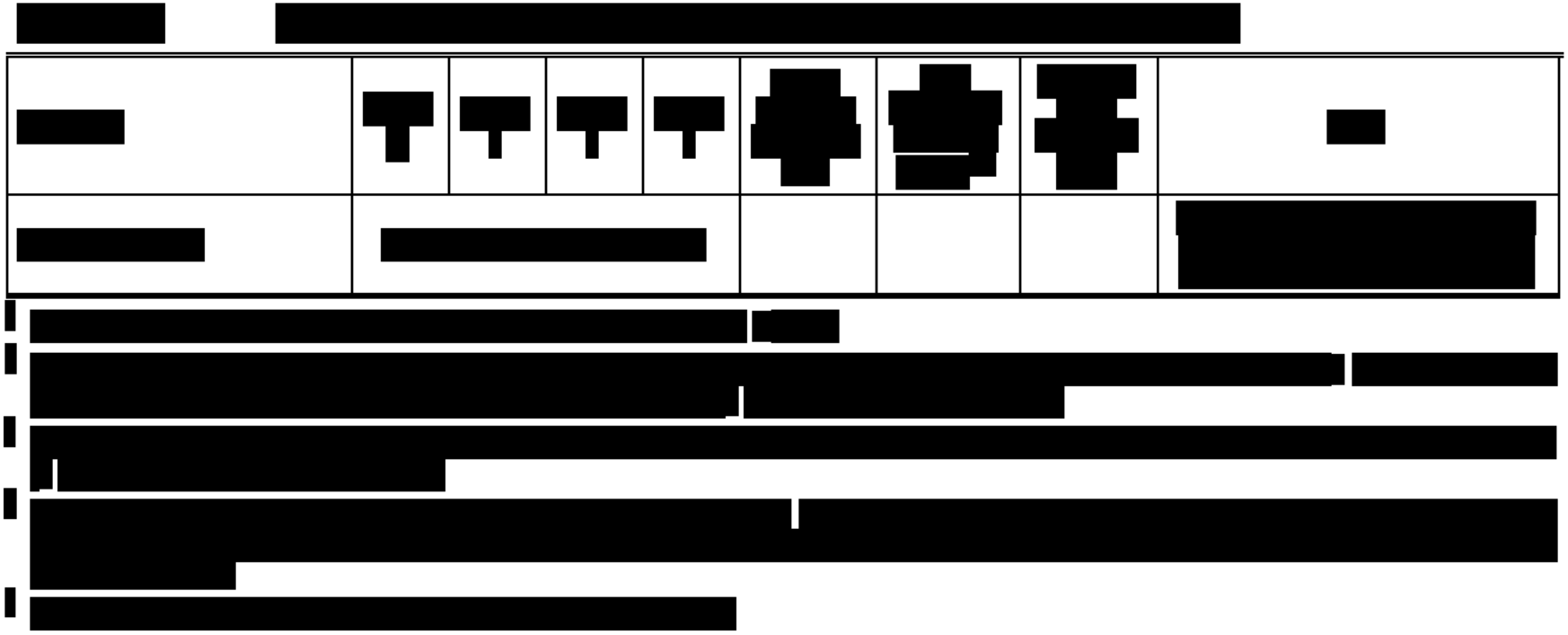

5.2 Study Materials

- NCI CTCAE version 4.03
- Dasatinib Investigator Brochure
- Nivolumab Investigator Brochure
- Pharmacy Binder
- Laboratory manuals for collection and handling of blood (including biomarkers, PK and ADA) and tissue specimens
- Site manual for operation of Interactive Voice Response System
- Manual for entry of local laboratory data
- Pregnancy Surveillance Forms
- Pregnancy Log.

5.3 Safety Assessments

At screening, a medical history will be obtained to capture relevant underlying conditions. The baseline examinations should include weight, height, ECOG Performance Status, vital signs, chest x-ray, 12-lead ECG, echocardiogram, pregnancy testing for WOCBP, and oxygen saturation by pulse oximetry at rest and after exertion and should be performed within 28 days of first dasatinib dose. Pre-treatment medications will be collected from within 14 days prior to first treatment through the study treatment period (see Table 5.1-1).

Screening local laboratory assessments should be done within 14 days of first dose of dasatinib include: CBC with differential and platelets, AST, ALT, direct bilirubin (reflex only), alkaline phosphatase, creatinine, BUN, uric acid, glucose, albumin, sodium, potassium, chloride, calcium, magnesium, phosphorus, lipase, amylase, TSH, urinalysis, HBV surface Ag, anti-HBc and HCV Ab or HCV RNA.

During the combination treatment period, pregnancy testing for WOCBP must be performed within 24 hours prior to the first dose of dasatinib, within 24 hours prior to first nivolumab infusion, at Day 15, Day 29, and every 4 weeks thereafter, at the combination EOT visit and at the Follow-Up visits 1 & 2 for nivolumab toxicities. During the dasatinib monotherapy period, pregnancy testing for WOCBP must be performed monthly and at the Dasatinib Alone EOT Visit.

During the combination treatment period, vital signs and weight should be assessed at Day 1 and every 2 weeks thereafter. During the dasatinib monotherapy period, vital signs and weight should be assessed at Month 1, 4, 6, and at the Dasatinib Alone EOT visit. Vital signs should also be taken as per institutional standard of care prior to, during and after dosing. ECOG Performance status should be assessed as described in the Table 5.1-2 and Table 5.1-3.

On study local laboratory assessments should be done as described in the Table 5.1-2 and Table 5.1-3, and should include the same hematology and chemistry laboratory tests done at screening. Additional measures including non-study required laboratory tests should be performed as

clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme elevations) will be monitored during the follow-up phase via on site/local labs until all study drug related toxicities resolve, return to baseline or are deemed irreversible. Screening for anti-HBc should be done for subjects not previously tested.

Vital signs include BP, HR, respiratory rate, and temperature. A complete physical exam includes observation of general appearance and examination of HEENT, neck, cardiovascular, lungs, abdomen, lymph nodes, genitourinary, extremities, neurological, skin, and musculoskeletal. A brief physical includes heart and lung and other body systems as indicated.

Oxygen saturation by pulse oximetry should be obtained prior to each dosing and at any time a subject has any new or worsening respiratory symptoms. The start and stop time of the nivolumab infusion should be documented. A reading at rest and on exertion should be obtained at each time point. The extent of the exertion should be based on the judgment of the investigator, but should remain consistent for each individual subject throughout the study. If the subject's status changes, the investigator can alter the extent of exertion based on their medical judgment. If a subject shows changes on pulse oximetry or other pulmonary related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, fever) consistent with possible pulmonary adverse events, the subject should be immediately evaluated to rule out pulmonary toxicity. An algorithm for the management of suspected pulmonary toxicity can be found in Appendix 2.

Adverse events will be assessed continuously during the study and for at least 100 days post last dose of nivolumab and for 30 days post last dose of dasatinib. Adverse events will be coded using the most current version of MedDRA and reviewed for potential significance and clinical importance. Adverse events will be evaluated according to the NCI CTCAE Version 4.03 dated 14-Jun-2010. Subjects should be followed until all treatment-related adverse events have recovered to baseline or are deemed irreversible by the investigator.

Some of the previously referred to assessments may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

HBV Serology

Although subjects with acute hepatitis B virus (HBV) infection or who are HBsAg positive are excluded, subjects who are positive for anti-HBc only may be enrolled as long as they meet all other eligibility criteria. Consultation with a physician with expertise in the treatment of HBV is recommended for subjects who test positive for HBV serology. Subjects who are carriers of HBV should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In subjects who develop reactivation of HBV while receiving dasatinib, prompt consultation with a physician with expertise in the treatment of HBV is recommended. Subjects not previously tested for anti-HBc should be tested while on study. They may remain on study regardless of the result but follow guidance above if they test positive.

5.3.1 Imaging Assessment for the Study

Not applicable

5.4 Efficacy Assessments

Efficacy will be assessed by hematological assessment, cytogenetic assessment and molecular assessment See Table 5.1-2 and Table 5.1-3 for the schedule of assessments. Detailed instructions for processing and shipment of blood samples will be provided in a separate Procedure Manual at the time of study initiation.

Mutation analysis will be performed as applicable in case of loss of response or treatment failure and at the end of treatment visit.

The definitions of response and treatment failure provided below should be used when determining an individual subject's response and treatment failure to treatment and in making treatment decisions. Response and treatment failure definitions are provided below as they may require one or more actions on the part of the investigator and/or site staff.

These assessments can be performed with visit a window of ± 7 days.

5.4.1 Molecular Response Assessment

Molecular response will be assessed by BCR-ABL transcript levels measurement using qPCR.

5.4.1.1 Definition of Major Molecular Response (MMR)

MMR is defined as ≥ 3-log reduction in BCR-ABL transcripts or a ratio of ≤ 0.1% on the International Scale (IS).

5.4.1.2 Definition of Molecular Response4.5 (MR4.5)

A molecular response 4.5 (MR4.5) is defined as ≥ 4.5-log reduction in BCR-ABL transcripts or a ratio of ≤ 0.00316% on the International Scale (IS).

5.4.2 Definitions of Treatment Failure Requiring Discontinuation of Study Treatment

Any of the following events occurring while a subject is continuously on study therapy would define treatment failure and would require withdrawal of the subject from treatment. **Subjects should be on the maximum tolerated dose (as determined by the investigator) before criteria for treatment failure is considered**. Please refer to the dose escalation section (Section 4.3.3) for more details.

The date of treatment failure will be defined and documented as the date any of the below criteria is first met.

Table 5.4.2-1: Definitions of Treatment Failure Requiring Discontinuation of Study Treatment

Type of Treatment Failure	Definition		Confirmation
Loss of Cytogenetic Response [a]	Loss of Complete Cytogenetic Response (CCyR) or Partial Cytogenetic Response (PCyR)	An increase in the Ph+ bone marrow cells by at least 30% from the subject's nadir	
Loss of Hematologic Response	Increasing WBC:	Doubling of WBC to > 20.0 x 10^9/L [> 20,000/mm^3]	Confirmed at least 28 days apart in a subject who never achieved a confirmed Complete Hematologic Response (CHR).
	Loss of CHR:	Defined as any one of the following: WBC count that rises to > 20.0 x 10^9/L (> 20,000/mm^3) Platelet count that rises to > 600 x 10^9/L (> 600,000/mm^3) Appearance of extramedullary disease not present at baseline including hepatosplenomegaly by palpation or other extramedullary involvement proven by biopsy Appearance of > 5% myelocytes + metamyelocytes in the peripheral blood Appearance of blasts or promyelocytes in the peripheral blood.	Confirmed at least 28 days apart, unless associated with progression to accelerated or blast phase CML.
Progression	Criteria for accelerated phase are met for subject enrolled in CP or who attain CP during the study	As per Investigator decision	NA
	Criteria for blast phase are met at any time	≥ 30% blasts in peripheral blood or in bone marrow aspirates and/or extramedullary disease other than hepatosplenomegaly	NA

[a] Cytogenetic evaluation except at baseline and EOT is not mandatory, but may be performed if deemed necessary.

5.4.3 Definition of Loss of Response or Other Definitions of Treatment Failure Not Requiring Discontinuation from Therapy

The definitions listed below indicate that the subject has had a loss of response or a treatment failure but may not require discontinuation of study medication. Discontinuation is at the discretion of the Investigator.

5.4.3.1 Loss of Molecular Response

For the loss of either MMR and/or MR4.5 as defined above in Section 5.4.1, confirmation is recommended at least 28 days later but does not require discontinuation of study medication. At the discretion of the Investigator, subjects may stay on treatment, possibly at an increased dose of dasatinib as noted in Section 4.3.3.

5.4.3.2 Treatment Failure

Additional forms of treatment failure, not listed above in Table 5.4.2-1, are defined by the ELN guidelines based on poor response at various time points (see Appendix 4). At the discretion of the Investigator, subjects experiencing treatment failure NOT specifically defined in Table 5.4.2-1 may stay on treatment, possibly at an increased dose of dasatinib as noted in Section 4.3.3.

5.4.4 Mutation Analysis

Blood for mutation analysis will be collected and send to the specialty lab per laboratory manual.

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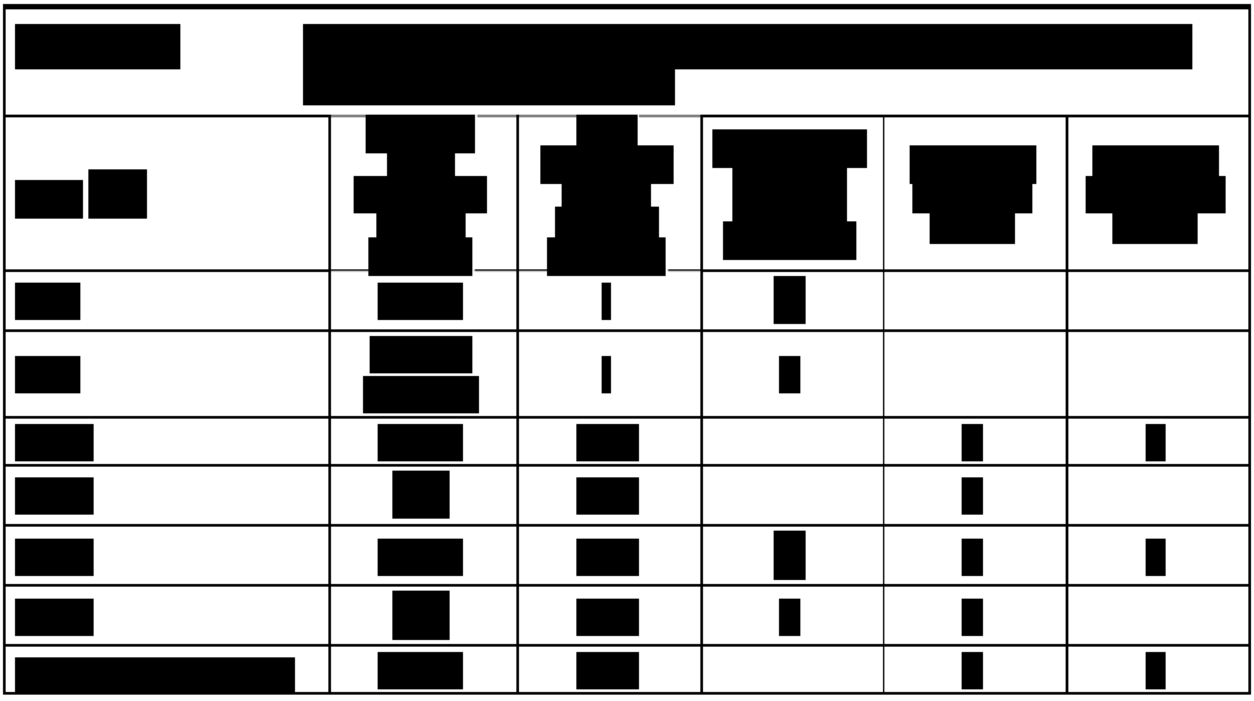

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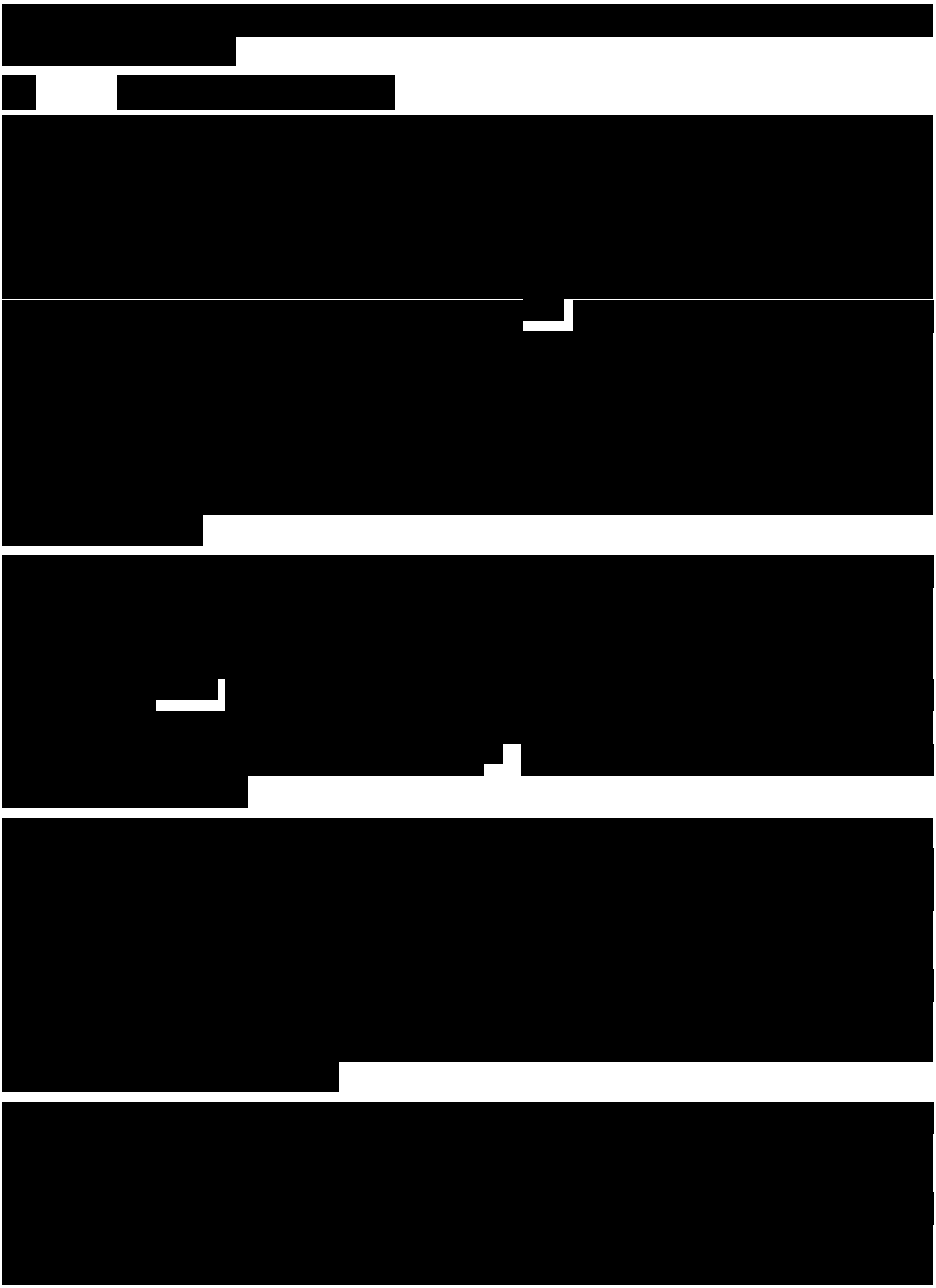

CP CML subjects in hematological remission, this population will be evaluated prior to treatment

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[redacted]

5.7 Outcomes Research Assessments

Not applicable

5.8 Results of Central Assessments

Not applicable

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

> Related: There is a reasonable causal relationship between study drug administration and the AE.
>
> Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

6.1 Serious Adverse Events

A S***erious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (see Section 6.1.1 for reporting details).

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
- admission for administration of anticancer therapy in the absence of any other SAEs

6.1.1 Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of nivolumab dosing and 30 days of dasatinib dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

The investigator should report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

SAE Telephone Contact (required for SAE and pregnancy reporting): Refer also to Contact Information list.

Contact Information for SAEs:

Name: Daniela Buglio, MD, PhD

[redacted]

[redacted]

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

6.4 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half lives after product administration, the investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours of awareness of the event and in accordance with the SAE reporting procedures described in Section 6.1.1.

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS, the pregnant subject may continue study drug, after a thorough discussion of benefits and risk with the subject.

Protocol required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and where applicable, offspring information must be reported on the Pregnancy Surveillance form

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

All occurrences of overdose must be reported as SAEs (see Section 6.1.1 for reporting details).

6.6 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

Potential drug induced liver injury is defined as:

1) ALT (ALT or AST) elevation > 3 times upper limit of normal (ULN)
   AND
2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),
   AND
3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

Not applicable

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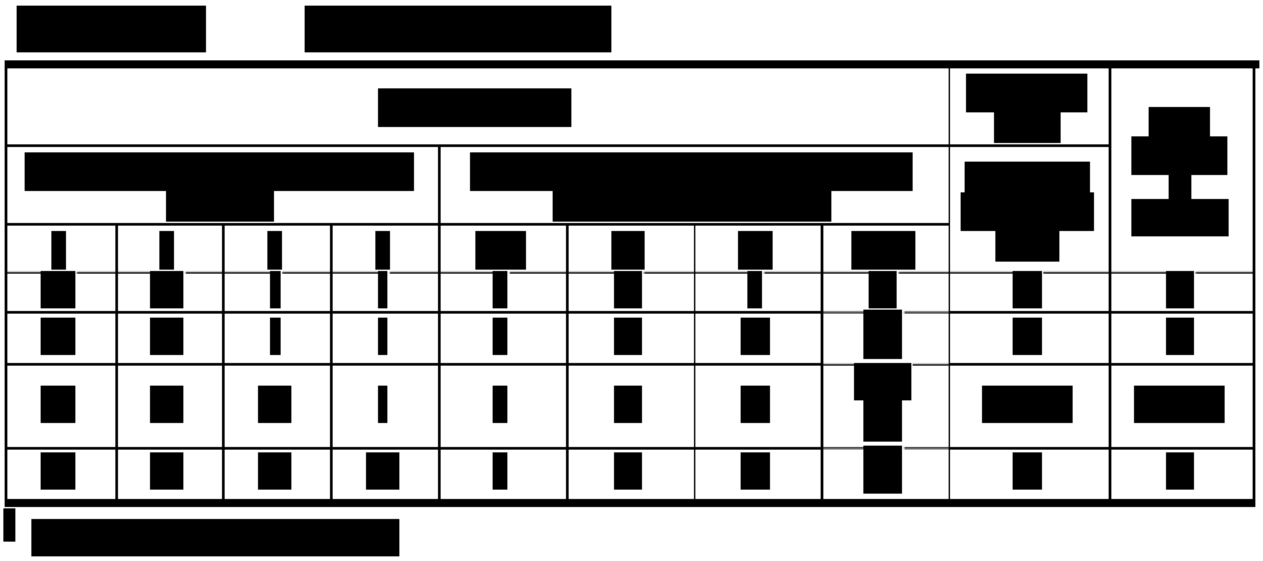

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8.2 Populations for Analyses

- All Enrolled Subjects: All subjects who signed the informed consent form.
- All Treated Subjects: All subjects who received at least 1 dose of dasatinib.
- Escalation Phase Evaluable Subjects: All subjects who completed the escalation phase or experienced DLTs.
- Pharmacokinetic Data Set: All available PK data from subjects who received dasatinib and nivolumab.
- ADA Data Set: All available ADA data from subjects with CML who received dasatinib and nivolumab and have at least 1 post-treatment ADA measurement.
- Biomarker Data Set: All available biomarker data from the subjects who received dasatinib.

Analyses of safety, extent of exposure, pharmacokinetics, biomarkers, efficacy, and ADA will be based on all treated subjects. Determination of the MTD among the 3 candidate dose levels at completion of the escalation phase will be based on the Escalation Phase evaluable subjects.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The primary is to assess the safety and tolerability for the combination of dasatinib and nivolumab in subjects with chronic phase or accelerated phase CML, 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.

8.3.2 Secondary Endpoint(s)

The secondary endpoints are based on MMR and MR4.5:

- MMR and MR4.5 rates at 6, 12, 24, and 36 months
- Time to, and duration of, MMR and MR4.5.

[redacted]

[redacted]

8.4 Analysis

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.

Subjects escalated from 1 mg/kg to 3 mg/kg nivolumab will be reported as per dose level at study entry (1 mg/kg dose level).

8.4.1 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by dose level and disease state at study entry (CP/AP CML) using descriptive statistics.

8.4.2 Efficacy Analyses

MMR and MR4.5 rates at 6, 12, 24, and 36 months will be provided by dose level and disease state at study entry with their corresponding 2-sided 95% exact (Clopper and Pearson) confidence intervals. Time to event and duration of event will be analyzed using Kaplan-Meier methodology. Median time to event and median duration will be presented with their 95% confidence intervals derived with the method of Brookmeyer and Crowley.[48]

8.4.3 Safety Analyses

All recorded adverse events will be listed and tabulated by system organ class, preferred term, treatment arm, dose level and disease state at study entry and coded according to the most current version of MedDRA. Vital signs and clinical laboratory test results will be listed and summarized by dose level and disease state at study entry. Any significant physical examination findings and results of clinical laboratory test will be listed.

[redacted]

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare

them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by BMS) is maintained at each study site where study drug are inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- nonstudy disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS

- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

BMS will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form .For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected considering the following criteria:

- External Principal Investigator designated at protocol development
- Study Steering Committee chair or their designee

- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to BMS at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

10 GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or BMS as related to the investigational product
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for an unapproved investigational product)
Serious Adverse Event	Serious adverse event defined as any untoward medical occurrence that at any dose: results in death; is life threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe), requires inpatient hospitalization or causes prolongation of existing hospitalization; results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect; is an important medical event (defined as a medical event(s) that may not be immediately life threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.). For reporting purposes only, BMS also considers the occurrence of pregnancy, overdose (regardless of association with an AE), and cancer as important medical events.

11 LIST OF ABBREVIATIONS

Term	Definition
ADA	Anti-drug antibody
ADL	Activities of Daily Living
AE	adverse event
AEOSIs	Drug-related adverse events of special interests
AIDS	Acquired immunodeficiency syndrome
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AP	accelerated phase
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
β-HCG	beta-human chorionic gonadotrophin
BID, bid	bis in die, twice daily
[redacted]	[redacted]
BMS	Bristol-Myers Squibb
BP	Blastic Phase
BP	blood pressure
BSA	Body Surface Area
BUN	blood urea nitrogen
C	Celsius
C12	concentration at 12 hours
C24	concentration at 24 hours
Ca++	calcium
CBC	complete blood count

Term	Definition
CCyR	Complete Cytogenetic Response
Cexpected-tau	expected concentration in a dosing interval
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CHR	Complete Hematologic Response
CI	confidence interval
C1-	chloride
CL	clearance
cm	centimeter
Cmax, CMAX	maximum observed concentration
Cmin, CMIN	trough observed concentration
CML	Chronic myeloid leukemia
CP	chronic phase
CRF	Case Report Form, paper or electronic
Ct	Expected concentration at a certain time, usually at the end of an expected future dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
Ctau	Concentration in a dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
CTCAE	Common Toxicity Criteria
Ctrough	Trough observed plasma concentration
CV	coefficient of variation
CYP	cytochrome p-450
D	day
DEHP	di(2-ethylhexyl)phthalate
DILI	drug induced liver injury
dL	deciliter
DLI	donor lymphocyte infusion
DLT	Dose limiting toxicity
ECG	electrocardiogram
ECHO	
ECOG	Eastern Cooperative Oncology Group

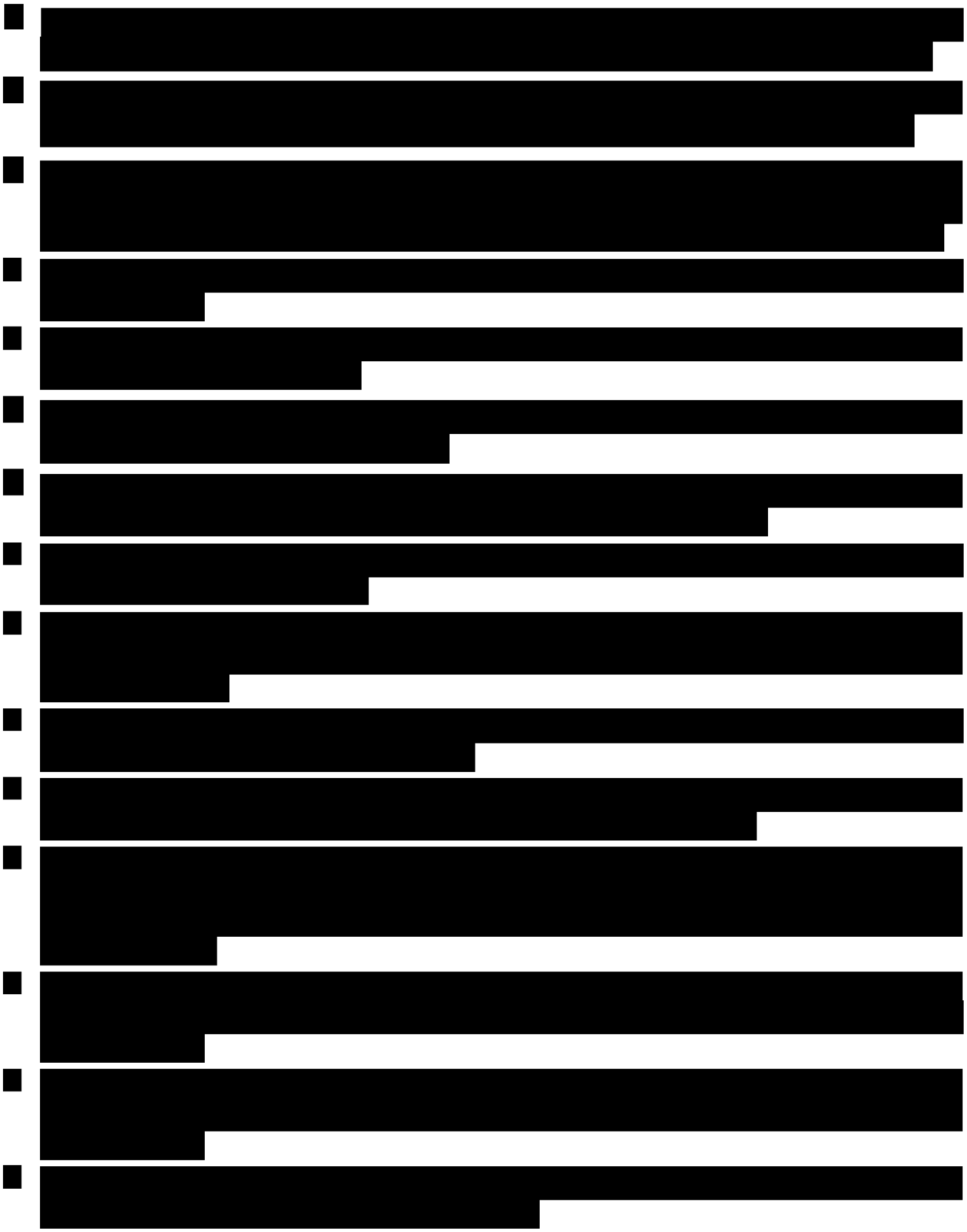
Term	Definition
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EFS	event free survival
eg	exempli gratia (for example)
ELISA	Enzyme-linked immunosorbent assay
EOI	End Of Infusion
EOT	End of Treatment
EPH	ephrin
F	bioavailability
F	Fahrenheit
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
FU	Follow-up
g	gram
GCP	Good Clinical Practice
h	hour
HBV	hepatitis B virus
HCG	human chorionic gonadotrophin
HCV	hepatitis C virus
HEENT	Hear, ears, eyes, nose and throat
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy
HU	hydroxyurea
IB	Investigator brochure
ICF	Informed Consent
ICH	International Conference on Harmonisation
ID	number
ie	id est (that is)

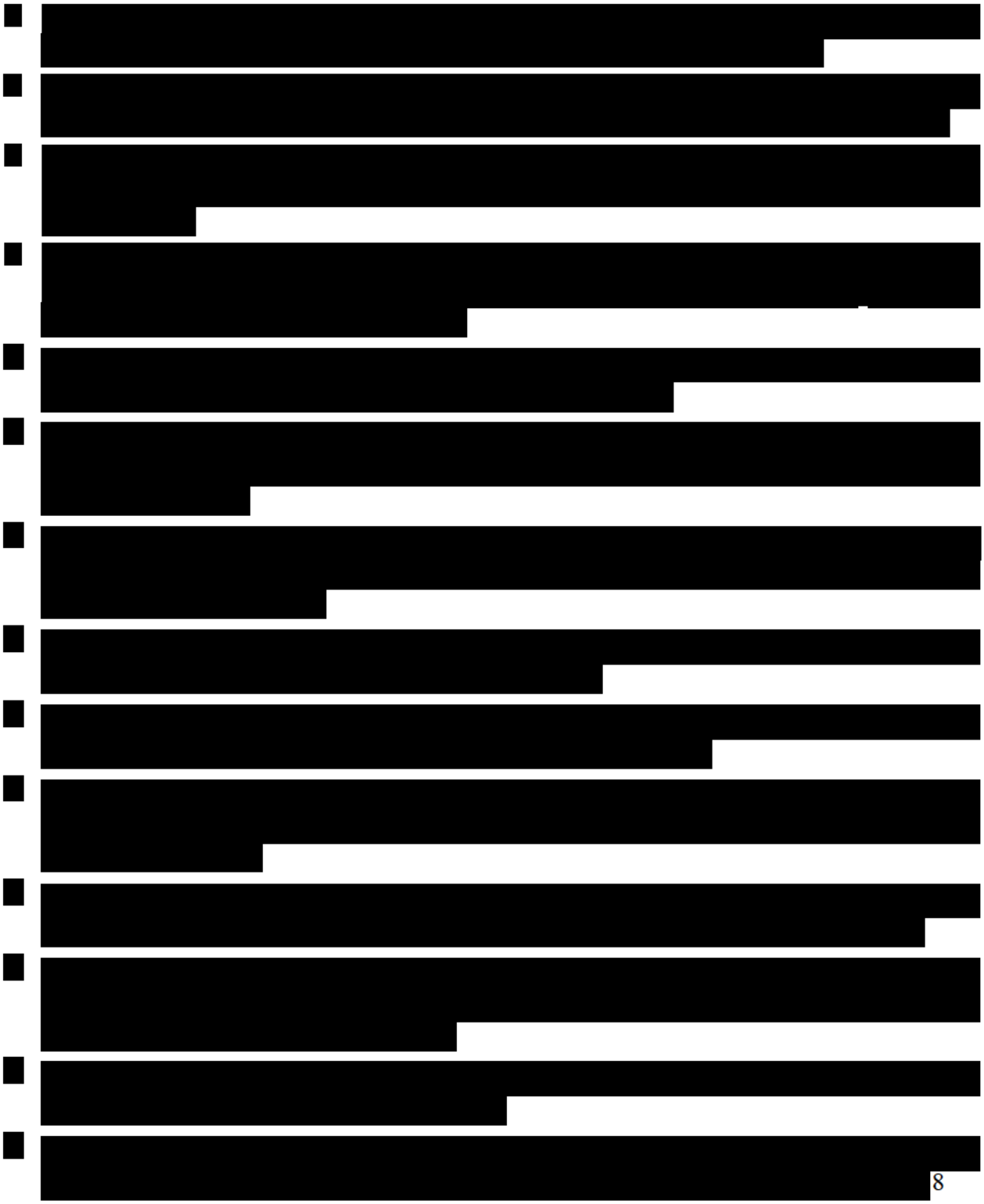
Term	Definition
IEC	Independent Ethics Committee
IFNα	Interferon alpha
IL	interleukin
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
I-O	Immuno Oncology
IRB	Institutional Review Board
ITIM	immunoreceptor tyrosine inhibitory motif
ITSM	immunoreceptor tyrosine based switch motif
IU	International Unit
IUD	intrauterine devices
IULN	institutional upper limit of normal
IV	intravenous
IVIG	intravenous immuno globulin
IVRS	Interactive Voice Response System
K	slope of the terminal phase of the log concentration-time curve
K3EDTA	potassium ethylenediaminetetraacetic acid
K+	potassium
kg	kilogram
L	liter
LFT	Liver function test
LGL	Large granular lymphocyte
LVEF	Left ventricular ejection fraction
Mg	magnesium
mg	milligram
min	minute
mL	milliliter
MLR	mixed lymphocyte reaction
mmHg	millimeters of mercury
MMR	major molecular response

Term	Definition
MR	molecular response
MRD	minimal residual disease
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
µg	microgram
N	number of subjects or observations
Na+	sodium
N/A	not applicable
ng	nanogram
NIMP	non-investigational medicinal products
NSCLC	Non-small cell lung cancer
ORR	Overall Response Rate
OS	overall survival
PCyR	Partial Cytogenetic Response
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamics
PDGFβ	Platelet-derived growth factor beta
PD-L1	Programmed cell death 1 ligand 1
PFS	Progression-free survival
PH	Philadelphia chromosome
PK	pharmacokinetics
PO	Per os, by mouth
PPI	Proton pump inhibitor
PPK	preliminary population PK
PS	Performance Status
PVC	polyvinyl chloride
QC	quality control
QD, qd	quaque die, once daily
qPCR	Real-time polymerase chain reaction
RCC	renal cell carcinoma

Term	Definition
RECIST	Response Evaluation Criteria In Solid Tumors
RR	respiratory rate
SAE	serious adverse event
SCT	stem cell transplant
SD	standard deviation
SHP	src homology phosphatase
SmPC	Summary of product characteristics
SOP	Standard Operating Procedures
sp.	species
t	temperature
T	time
TAO	Trial Access Online, the BMS implementation of an EDC capability
TCR	T-cell receptor
TGF-beta	Transforming growth factor beta
T-HALF	Half life
TID, tid	ter in die, three times a day
TKIs	tyrosine kinase inhibitors
Tmax, TMAX	time of maximum observed concentration
T3	triiodotyronine
TR_Cmax	Cmax treatment ratio
TSH	Thyroid-stimulating hormone
ULN	Upper Limit Normal
W	washout
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

[redacted]





APPENDIX 1 ADDITIONAL ETHICAL CONSIDERATIONS

1 INFORMED CONSENT PROCEDURES

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records. Prior to the beginning of the study, the investigator must have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects.

The investigator must provide the subject, or, in those situations where consent cannot be given by subjects, their legally acceptable representative with a copy of the consent form and written information about the study in the language in which the subject is most proficient. The language must be non-technical and easily understood. The investigator should allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study, then informed consent must be signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion. The subject or legally acceptable representative should receive a copy of the signed informed consent and any other written information provided to study subjects prior to subject's participation in the study.

1.1 Subjects Unable to Give Written Informed Consent

1.1.1 Minors

For minors, according to local legislation, one or both parents or a legally acceptable representative must be informed of the study procedures and must sign the informed consent form approved for the study prior to clinical study participation. (In the event that the parents or legal guardians are unable to read, then an impartial witness should be present during the entire informed consent discussion). Whenever feasible, minors who are judged to be of an age of reason must also give their written assent by signing and dating the completed informed consent. All local laws, rules and regulations regarding informed consent of minors must be followed.

1.1.2 Subjects Experiencing Acute Events or Emergencies

A legally acceptable representative or legal guardian must provide informed consent when consent of the subject is not possible prior to clinical study participation, eg, for subjects experiencing an acute medical event such as myocardial infarction or stroke. Informed consent of the subject must additionally be obtained if they become capable of making and communicating their informed consent during the clinical study. All local laws, rules and regulations regarding informed consent of adult subjects incapable of giving informed consent must be followed.

1.1.3 Mentally Impaired or Incapacitated Subjects

Investigators (or whoever required by local regulations) should determine whether or not a mentally impaired or incapacitated subject is capable of giving informed consent and should sign a statement to that effect. If the subject is deemed mentally competent to give informed consent, the investigator should follow standard procedures. If the subject is deemed not to be mentally competent to give informed consent, a fully informed legal guardian or legally acceptable representative can be asked to give consent for, or on behalf of, the subject. All local laws, rules and regulations regarding informed consent of mentally impaired or incapacitated subjects must be followed.

Patients who are involuntarily hospitalized because of mental illness must not be enrolled in clinical studies

1.1.4 Other Circumstances

Subjects who are imprisoned or involuntarily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness must not be enrolled in clinical studies.

In circumstances where a subject's only access to treatment is through enrollment in a clinical study, eg, for subjects in developing countries with limited resources or for subjects with no marketed treatment options, the investigator must take special care to explain the potential risks and benefits associated with the study and ensure that the subject is giving informed consent.

When a subject may be in a dependent relationship with the investigator, a well-informed physician who is not engaged in the clinical study and is completely independent of the relationship between the subject and investigator should obtain the subject's informed consent.

1.1.5 Illiterate Subjects

If the subject, or, in those situations where consent cannot be given by the subject, their legally acceptable representative is unable to read, a reliable and independent witness should be present during the entire informed consent discussion. The choice of the witness must not breach the subject's rights to confidentiality. A reliable independent witness is defined as one not affiliated with the institution or engaged in the investigation. A family member or acquaintance is an appropriate independent witness. After the subject or legally acceptable representative orally consents and has signed, if capable, the witness should sign and personally date the consent form attesting that the information is accurate and that the subject, or, in those situations where consent cannot be given by subjects, their legally acceptable representative has fully understood the content of the informed consent agreement and is giving true informed consent.

1.2 Update of Informed Consent

The informed consent and any other information provided to subjects, or, in those situations where consent cannot be given by subjects, the subject's legally acceptable representative, should be revised whenever important new information becomes available that is relevant to the subject's consent, and should receive IRB/IEC approval/favorable opinion prior to use. The investigator, or a person designated by the investigator should fully inform the subject or the

subject's legally acceptable representative of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

During a subject's participation in the study, any updates to the consent form and any updates to the written information will be provided to the subject.

[redacted]