# STATISTICAL ANALYSIS PLAN

## Protocol: BT-CL-PGG-MEL/BCA-1621/MK3475 PN-545

## A Multicenter, Open-label, Phase 2 Study of Imprime PGG and Pembrolizumab in Subjects with Advanced Melanoma Failing Front-line Treatment with Checkpoint Inhibitors (CPI) or Triple Negative Breast Cancer (TNBC) Failing Front-line Chemotherapy for Metastatic Disease

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# 1 INTRODUCTION

This Statistical Analysis Plan (SAP) is to describe in detail the statistical analyses to be conducted for the protocol BT-CL-PGG-MEL/BCA-1621/MK3475 PN-545. This is a Phase 2 study of Imprime PGG and pembrolizumab in subjects with advanced melanoma failing front-line treatment with checkpoint inhibitors or triple negative breast cancer failing front-line chemotherapy for metastatic disease. All decisions regarding the interim, primary and final analyses will be made prior to the database freeze of the study data.

For further information on the study design, see Protocol BT-CL-PGG-MEL/BCA- 1621/MK3475 PN-545 version 2.0, dated 10August 2017.

# 2 STUDY OBJECTIVES

## 2.1 Primary Objective

- **Objective:** To determine the Overall Response Rate (ORR) to Imprime PGG + pembrolizumab in subjects with advanced melanoma or metastatic triple negative breast cancer (TNBC)
- **Safety:** To characterize the safety of Imprime PGG + pembrolizumab given in combination

**Hypothesis:** Restore (for melanoma) or enhance (for TNBC) sensitivity to checkpoint inhibitors (CPI) by appropriate and effective stimulation of the subject's innate and adaptive immune systems in those subjects who have failed front line therapy

**Melanoma Subjects:**

- $H_0$: ORR $\leq$ 5%
- $H_A$: ORR $\geq$ 23%

**TNBC Subjects:**

- $H_0$: ORR $\leq$ 5%
- $H_A$: ORR $\geq$ 21%

Rejection of the null hypothesis will require documenting at least 4 objective responses among the total of up to 29 subjects with melanoma (Stage 1 + Stage 2), and 5 objective responses among the total of up to 41 subjects with TNBC (Stage 1 + Stage 2).

RECIST v1.1 criteria will be used for all applicable primary and secondary endpoints. Immune related response criteria (irRECIST) will be used for exploratory efficacy endpoints.

## 2.2 Secondary Objectives

1. To determine the time to response (TTR), complete response rate (CRR), and duration of overall response (DoR) in subjects with advanced melanoma or metastatic TNBC when treated with Imprime PGG in combination with pembrolizumab
2. To measure the Progression-Free Survival (PFS) and PFS rate at 6 months and 1 year in subjects with advanced melanoma or metastatic TNBC when treated with Imprime PGG in combination with pembrolizumab
3. To measure overall survival (OS) and OS rate at 1 year in subjects with advanced melanoma or metastatic TNBC when treated with Imprime PGG in combination with pembrolizumab

4. To profile pharmacokinetic (PK) data in subjects with advanced melanoma or metastatic TNBC when treated with Imprime PGG in combination with pembrolizumab

### 2.3 Exploratory Objectives

1. Determine ORR and PFS based on irRECIST in subjects with advanced melanoma or metastatic TNBC when treated with Imprime PGG in combination with pembrolizumab
2. Correlate levels of baseline serum anti-β-glucan antibody (ABA) with objective response and treatment outcomes
3. Correlate changes in immune cell activation markers, such as CD86 expression in tumor biopsy samples and in peripheral blood immune cells with objective response and treatment outcome
4. In tumor biopsies, correlate changes in the tumor immune microenvironment including TILs (Tumor-infiltrating Lymphocytes) and tumor-infiltrating myeloid cells with objective response and treatment outcome
5. Correlate PD-L1 expression in tumor biopsy samples (in tumor cells and myeloid cells) with objective response and treatment outcome

## 3 END POINTS

### 3.1 Primary

The primary efficacy endpoint is ORR, which is defined as the proportion of subjects demonstrating complete response (CR) or partial response (PR) based on RECIST v1.1 criteria.

Safety endpoints include the incidence of adverse events, serious adverse events, laboratory safety tests (hematology, clinical chemistry, and urinalysis), and ECOG performance.

### 3.2 Secondary

Measurement of the secondary endpoints is based on RECIST v1.1 criteria.

- Time to response (TTR) is defined as time from first dose of study treatment (Study Day1) to first response (CR or PR)
- Complete response rate (CRR) is defined as the proportion of subjects demonstrating CR
- Duration of response (DoR) is defined as the time from the first documented evidence of CR or PR until time of documented disease progression (PD) or death due to any cause, whichever is first
    - For responders who are lost to follow-up or who discontinue study before PD or death, DoR will be censored at the date of last radiological assessment
- Progression-free survival (PFS) is defined as:
    - Time from Study Day 1 until PD or death due to any cause, whichever occurs first
    - For subjects who are lost to follow-up or who discontinue study before PD or death, PFS will be censored at the date of the last radiological assessment
- Overall survival (OS) is defined as:
    - Time from Study Day 1 until date of death due to any cause
    - For subjects who have not died or who are lost to follow-up or withdrew consent, OS will be censored at the date of last contact
- Pharmacokinetic profile

### 3.3 Exploratory

- ORR, as defined by irRECIST
- PFS, with date of PD as defined by irRECIST

The following exploratory analyses will be conducted to examine the relationship between biomarker data and endpoints if the data warrants:

- Analysis of ABA and endpoints
- Analysis of change in the immune cell activation markers and endpoints
- Analysis of change in the tumor immune microenvironment and endpoints

## 4 STUDY DESIGN

This is a Phase 2 study of Imprime PGG and pembrolizumab in subjects with advanced melanoma failing front-line treatment with checkpoint inhibitors or TNBC failing front-line chemotherapy for metastatic disease.

The study design is based on hypothesis testing of the ORR for pembrolizumab + Imprime PGG. For melanoma subjects, the null hypothesis is ORR $\leq$ 5%, versus the alternative hypothesis of ORR $\geq$ 23%; for the TNBC subjects, the null hypothesis is ORR $\leq$ 5% (ORR=5% in KEYNOTE-086), and the alternative hypothesis is ORR $\geq$ 21%. Hypotheses testing will be conducted using a one-sided type I error of 0.05.

The study will incorporate Simon's optimal 2-stage design with sample size fixed at 12 subjects each in Stage 1 for advanced melanoma and for TNBC subjects. The safety criterion of $\leq$ 4 (or $\leq$ 33%) subjects with Grade 3/4 adverse events in Cycle 1 within either tumor type must be met in order to proceed to Stage 2 (Grade 3/4 infusion reactions which occur during Cycle 1 that either resolve or decrease to Grade 1/ 2 and recur in Cycle 2, will not be counted towards the total of $\geq$ 4). The starting dose is 4 mg/kg for Imprime PGG. In the event there are a total of > 4 (or > 33%) of subjects with Grade 3/4 adverse events in Cycle 1, the dose of Imprime PGG will be reduced to 2 mg/kg, and Stage 1 will be repeated at a dose of 2 mg/kg with an additional cohort of n=12 subjects. For the dose that meets the safety criterion in Stage 1, at least 1 response in melanoma subjects and 1 response in TNBC subjects amongst the 12 subjects within each tumor type must be observed in order to proceed to Stage 2. Stage 2 will enroll an additional 17 subjects with melanoma, and 29 subjects with TNBC. For the dose that meets the Stage 1 safety criterion, success will be declared if at least 4 amongst the total of up to 29 subjects with melanoma, and 5 amongst the total of up to 41 subjects with TNBC achieve an objective response. The above design corresponds to a type I error 0.05 and power of 90% for both melanoma and TNBC.

The dosing schedule and the study assessments are presented in the schedule of assessment in the protocol.

All subjects will receive Imprime PGG and pembrolizumab. Imprime PGG will be administered IV at a dose of 4 mg/kg over a 2-hour infusion time period on Day 1, Day 8, and Day 15 of each 3-week cycle for subjects at stage 1. If Stage 1 proceeds without safety concerns necessitating a second cohort at 2 mg/kg, Imprime PGG will be administered to the Stage 2 subjects at a dose of 4 mg/kg IV over a 2-hour infusion time period on Day 1, Day 8, and Day 15 of each 3-week cycle. If enrollment into an additional cohort for 2 mg/kg in Stage 1 is required and dosing proceeds to Stage 2, Imprime PGG will be administered in Stage 2 at a dose of 2 mg/kg IV over a 2-hour infusion time period on Day 1, Day 8, and Day 15 of each 3-week cycle. The pembrolizumab fixed dose of 200 mg will be administered IV over 30 minutes on Day 1 of each 3-week treatment.

Subjects will be dosed until disease progression, death, 2 years of treatment or study completion, whichever occurs first. After treatment discontinuation, subjects will be monitored every 2 months for survival until death or study completion. Study completion is defined as the death of at least 70% of subjects or 3 years after the last subject's first dose, whichever occurs earlier.

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR, who have been treated for at least 24 weeks, and who had at least 2 treatments with study medications beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to 1 year of additional treatment with Imprime PGG + pembrolizumab at the discretion of the Investigator if:

- No cancer treatment was administered since the last dose of pembrolizumab
- The subject meets the safety parameters listed in the Inclusion/Exclusion criteria
- The trial is open

Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Response or progression in this resumed course of therapy will not count towards the ORR of the primary endpoint in this trial.

# 5 PLANNED ANALYSES

## 5.1 Interim Analyses

An informal interim analysis was conducted at the end of Stage 1 to assess the safety criterion for each tumor type and confirm the dose of Imprime PGG before continuing enrollment in Stage 2. Overall response rate based on RECIST 1.1 and adverse events including Grade 3/4 adverse events were considered for decision-making. Safety data will be summarized periodically throughout the study as part of ongoing safety review.

## 5.2 Primary Analyses

The primary analyses for the melanoma and TNBC subjects will be conducted when all subjects have completed the treatment phase of the study. All data will be included in the primary analyses and each tumor type will be analyzed separately.

## 5.3 Final Analysis

The final analysis will be conducted after study completion. Study completion is defined as the death of at least 70% of subjects or 3 years after the last subject's first dose, whichever occurs earlier. Overall survival data will be included in the final analysis.

# 6 ANALYSIS POPULATIONS

The **ABA pre-screening** population will comprise all subjects who have been pre-screened for ABA test only (who have signed the ABA informed consent form but not the full informed consent form).

The **Screening** population will comprise all subjects who have been screened for the study (who have signed the full informed consent form).

The **All Treated** population will comprise all subjects in the Screening population who receive at least one dose of study treatment. The All Treated population will be the primary population for the baseline characteristics and safety analysis and the secondary population for the efficacy analysis.

The **Evaluable** population will comprise all subjects in the All Treated population who 1) have measurable disease at baseline per RECIST 1.1, AND 2) have at least one post-baseline radiological disease assessment, or discontinue study treatment as a result of progressive disease, death, or a treatment-related adverse event before the first post-baseline radiological disease assessment. The Evaluable population will be the primary population for the efficacy analysis.

The **Per-Protocol** population will comprise all subjects in the All Treated population who do not have any important protocol deviations (IPD) as defined in the study IPD list. The Per- Protocol population will be the tertiary population for the efficacy analysis.

In the Screening population, subjects who do not meet eligibility criteria will be defined as screen failures, and subjects who meet all eligibility criteria but do not receive any study treatment will be defined as non-treated subjects. The Screening population will comprise of All Treated subjects, non-treated subjects, and screen failure subjects.

Limited data will be collected for the ABA pre-screening population and the non-treated subjects and screen failure subjects in the Screening population. Summaries of these data may be produced:

- ABA Pre-screening population: ABA level at screening, demography, inclusion/exclusion, adverse event (if any), concomitant medication (if any) and death data will be collected;
- Screen failure subjects: ABA level at screening, demography, inclusion/exclusion, adverse event (if any), concomitant medication (if any) and death data will be collected;
- Non-treated subjects: ABA level at screening, all other data that are planned to be collected at screening for All Treated subjects, adverse event (if any), concomitant medication (if any), death (if any) and end of study record will be collected.

## 7 TREATMENT COMPARISONS

As this is a single arm study for each tumor type, the primary endpoint ORR is compared against the historical control ORR as defined in the null hypothesis. The primary objective will be achieved through a test of the hypotheses evaluating ORR in the Evaluable population using a one-sided alpha level of 0.05.

## 8 GENERAL CONSIDERATIONS FOR DATA ANALYSES

Clinical Data Interchange Standard Consortium (CDISC) Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) will be used for the primary and final data analyses.

**Data analysis will be conducted separately for the melanoma and the TNBC tumor types**. Summary tables/figures will be provided separately for the melanoma and the TNBC tumor type, and all summary tables will be produced by dose level (if there are >1 dose levels for a tumor type). Listings will be provided with both tumor types being included in one listing, and all listings will be sorted by cancer type (melanoma then TNBC), site ID, subject ID, and then by visit date and time.

All analyses will be performed using SAS® Version 9.4 or higher. Continuous variables will be summarized with number of subjects (n), mean, median, standard deviation, minimum and maximum, and categorical variables will be summarized with frequency counts and percentages.

In the event that the study is prematurely discontinued, all available data will be listed and a review will be carried out by the study team to assess which statistical analyses are still considered appropriate.

Deviations from the planned analyses in the SAP will be identified in the study report.

## 8.1 Multicenter Study

It is anticipated that subject accrual will be spread thinly across sites and summaries of data by site would be unlikely to be informative, therefore the data from all participating sites will be pooled prior to the analysis.

## 8.2 Examination of Subgroups

The following subgroups may be explored in the efficacy analysis for the melanoma subjects if the subgroups are large enough to result in meaningful analyses:

- IgG anti-β-glucan antibody (higher vs lower at baseline)
- Previous anti-CTLA-4 inhibitor (ipilimumab) treatment (Yes vs No)
- PD-L1 expression (if sample analyses are run)
- Number of prior systemic regimens for metastatic disease
- ECOG performance (0 vs 1)
- BRAF V600 mutation
- Prior BRAF or MEK inhibitor
- LDH level (normal vs elevated at baseline)
- Liver metastasis (Yes vs No at baseline)

The following subgroups may be explored in the efficacy analysis for the TNBC subjects if the subgroups are large enough to result in meaningful analyses:

- IgG anti-β-glucan antibody (higher vs lower at baseline)
- PD-L1 expression (if sample analyses are run)
- Number of prior systemic regimens for metastatic disease
- Prior hormone therapy (Yes vs No; number of regimens)
- ECOG performance status (0 vs 1)
- LDH level (Normal vs elevated at baseline)
- Liver metastasis (Yes vs No at baseline)

Additional subgroups may be explored for efficacy data analysis if needed.

# 9 DATA HANDLING CONVENTIONS

## 9.1 Premature Withdrawal and Missing Data

For all subjects, all data up to the time of completion of study participation will be included in the analysis, regardless of duration of treatment or follow-up.

Missing data occurs when any requested data is not provided leading to blank field on the collection instrument. These data will be indicated by a dash in the subject listing displays. Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.

### 9.1.1 Missing Data in Objective Response

When determining the percentage of responders (CR or PR), subjects with unknown or not evaluable or missing best overall response will be assumed to be non-responders, and will be included in the denominator when calculating the percentage.

### 9.1.2 Missing Data in Adverse Event

Subjects with missing data with regard to the designation of treatment relationship for adverse events and serious adverse events will have the worst-case assumed to impute the relationship: if relationship to study treatment is missing it will be assumed to be “Yes”.

## 9.2 Derived and Transformed Data

The following sections provide a general description of the derived and transformed variables that are used to describe and analyze the data.

### 9.2.1 Reference Dates

The reference date for age is the date of informed consent form signed.

The efficacy and safety reference date are the date of the first dose of study treatment, and will be used to calculate the study day for study measurements/assessments and baseline characteristics (such as time since the most recent recurrence or progression). If the date of interest occurs on or after the reference date, then the study day will be calculated as (date of interest - reference date

+ 1). If the date of interest occurs before the reference date, then the study days will be calculated as (date of interest – reference date).

### 9.2.2 Duration and Elapsed Time

Durations (e.g., the duration of an adverse event, duration on study treatment, etc.) are calculated as the stop date minus the start date plus one.

For elapsed time (e.g., the time since most recent recurrence or progression), if the reference date is on or after the event date, then the elapsed time is calculated as the reference date minus the event date + 1.

When reporting OS and PFS in months, divide the number of days by 30.4375; to report in weeks divide the number of days by 7; to report in years divide the number of days by 365.25. The "year" used in these algorithms is 365.25 days long, and the "month" is one-twelfth of that year.

## 9.3 Imputation of Partial Dates

Partial dates in selected datasets as specified below will be imputed. Imputed partial dates will not be used to derive the study day, duration (e.g., duration of adverse events), or elapsed time variables. However, imputed dates may be used as temporary variables for the purpose of sorting data in the listings. In addition, partial dates may be imputed for 'slotting' data to specific study time periods. Imputed dates will not be displayed in the listings.

The partial date will be included in the dataset with the imputed date and a flag variable to indicate the level of imputation. The flag variable can contain the values: blank and 'D'.

Blank: indicates that no imputation is done

D='Day': indicates that the day portion of the date is imputed

Start dates for the new anti-cancer therapy after the study treatment discontinuation will be temporarily imputed in order to define the event and censoring rules for PFS and duration of response. Dates will only be imputed when a month and year are available but the day is missing. The following rules will be used to impute the date when partial start dates are present on the post-treatment new anti-cancer therapy dataset:

*Table 1: Rules for Imputation of Partial Dates*

| Dataset | Date | Missing Element | Rule |
|---|---|---|---|
| Anti-Cancer Therapy | Start Date | day, month, and year | No Imputation for completely missing dates |
| | | day, month | No imputation for missing day and month |
| | | day | If the partial date falls in the same month as the last dose of the study treatment, then assign to earlier of (date of last dose of study treatment+1, last day of month).<br><br>If the partial date falls in the same month as the subject's last radiological disease assessment and the subject's last assessment is PD, then assign to earlier of (date of PD+1, last day of month).<br><br>If both rules above apply, then assign to the later of the 2 dates.<br><br>If the partial date falls in the months after the month of last dose of study treatment or last radiological assessment of PD, impute the missing day to the first day of the month. |

## 9.4 Baseline Definition

Baseline will be defined as the most recent, non-missing value prior to or on the day of the first dose of study treatment (prior to first dose).

## 9.5 Multiple Assessments

For any summary by visit, all data will be reported according to the scheduled visit date for which it is reported (that is, no visit windows will be applied during dataset creation). Data from the unscheduled visit will only be included in the summary that report worst-case or best-case post-baseline. All data from the scheduled visits and the unscheduled visits will be included in the listings.

# 10 STUDY POPULATION

Unless stated otherwise, all tables and listings in this section will be produced using the All Treated population. Summary tables for study population data will be provided separately for the melanoma and the TNBC tumor subjects, and all summary tables will be produced by dose level (if there are >1 dose levels). Listings will be provided with both tumor types being included in the listing, and all listings will be sorted by tumor type (melanoma then TNBC), center, subject ID, and then by visit date and time.

The list of displays for the study population data is shown in Section 15.1.

## 10.1 Disposition of Subjects

A summary of the number of subjects in the All Treated, Evaluable and Per-Protocol populations as well as the subgroups of subjects as defined in Section 8.2 will be provided. A listing of subjects excluded from the Evaluable and Per-Protocol population will be provided.

Using the ALL Treated population, summary of study treatment status will be provided for each drug. This display will show the number and percentage of subjects who are still receiving study treatment or who have discontinued study treatment, and a summary of reasons for study treatment discontinuation. A listing of study drug discontinuation will be generated for each study drug. The listing will include the date of last dose for each study drug, and reasons for study drug discontinuation.

A summary of subject end of study status will be provided. This display will show the number and percentage of subjects who have died or are alive at time of study discontinuation, and reason for study discontinuation. A listing of subject end of study status will be provided for the ALL Treated population.

If there are subjects who have discontinued study treatment after complete response and then re-entered the study to continue study treatment after meeting protocol specified criteria, a listing of disease characteristics at time of re-entry will be provided for these subjects.

## 10.2 Protocol Deviations

All important protocol deviations including inclusion/exclusion criteria deviations and other deviations will be summarized and listed. A separate summary and listing will be provided for the inclusion/exclusion criteria deviations.

For the efficacy and safety analysis based on the All Treated population, deviations will not impact analyses nor result in subject exclusion from the All Treated population.

## 10.3 Demographic and Baseline Characteristics

The demographic characteristics (e.g., age, race, ethnicity, sex, and baseline weight) will be summarized for the All Treated, Evaluable and Per-Protocol populations. Age and weight will be summarized using the mean, standard deviation, minimum, median, and maximum. The count and percentage will be computed for sex, race and ethnicity. Listing of demographic characteristics will be provided for the melanoma and TNBC subjects in the ALL Treated population. Listing of demography data also will be provided for the screen failure and non- treated subjects in the Screening population and the ABA Pre-screening population.

Cancer history and characteristics including date of initial diagnosis, date of the first presentation with distant metastatic disease, date of the most recent disease progression, stage at enrollment, M stage, N stage and overall staging, and BRAF V600 mutation status and C-kit mutation status for melanoma subjects and inflammatory breast cancer status for TNBC subjects will be listed. Summary of cancer history and disease characteristics will be provided for the All Treated, Evaluable and Per-protocol population.

Prior cancer therapy will be listed for each subject. A summary of the number of prior anti- cancer therapy regimens for advanced or metastatic disease will be produced for the All Treated, Evaluable and Per-protocol population. Prior therapy regimens with intent as palliative or maintenance will be reviewed by clinical team to determine if these regimes are for metastatic disease.

Medical history will be listed.

### 10.4 Concomitant Medications

Prior and concomitant medications including pre-medication will be coded using the WHO Drug dictionary. Prior medications include medications that were taken prior to the first dose of the study drug. Any medication used on or after the first dose of study drug during the course of the study will be considered a concomitant medication. Pre-medications include medications that are taken prior to study drug infusion such as standard anti-histamine medications. Concomitant medications will be summarized by anatomic therapeutic chemical classification (ATC) level 1 and preferred term. Pre-medication will be summarized by preferred term.

Listing of prior and concomitant medications will be provided for the melanoma and TNBC subjects in the All Treated population. A separate listing of pre-medications will be provided for the All Treated population.

### 10.5 Post Study Treatment Cancer Therapies

Post study treatment cancer therapy along with start date will be listed.

## 11 EFFICACY ANALYSIS

The primary efficacy population will be the Evaluable population, the secondary efficacy populations will be the All Treated, and the tertiary efficacy population will be the PP population.

Efficacy data will be summarized separately for each tumor type. Listings of efficacy data will include both tumor types. Unless stated otherwise, all listings in this section will be produced using the All Treated population.

The definition efficacy endpoints are based on US Food and Drug Administration Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007.

The list of displays for efficacy analysis is shown in Section 15.2.

### 11.1 Primary Efficacy Analysis

The primary efficacy endpoint is the overall response rate (ORR), which is defined as the proportion of subjects demonstrating complete response (CR) or partial response (PR) based on RECIST1.1.

The evaluation of response based on RECIST 1.1 will be performed at baseline and then at 6- week intervals beginning at week 6. The best response is the best response recorded from the start of study treatment until the first disease progression based on RECIST1.1 or start of new cancer therapy, whichever occurs earlier. The best response will be determined programmatically based on the investigator's assessment of response at each time point, using the following rules:

*Table 1 Best Overall Response When Confirmation of Complete Response and Partial Response is Required*

| Overall Response First Timepoint | Overall Response Subsequent Timepoint | Best Overall Response |
|---|---|---|
| CR | CR | CR |
| CR | PR | SD, PD or PR[a] |
| CR | SD | SD provided minimum criteria for SD duration was met, otherwise, PD |
| CR | PD | SD provided minimum criteria for SD duration was met, otherwise, PD |
| CR | NE | SD provided minimum criteria for SD duration was met, otherwise, NE |
| PR | CR | PR |
| PR | PR | PR |
| PR | SD | SD |
| PR | PD | SD provided minimum criteria for SD duration was met, otherwise, PD |
| PR | NE | SD provided minimum criteria for SD duration was met, otherwise, NE |
| NE | NE | NE |

a: If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

CR=complete response; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease.

Note: the minimum criteria for SD is the interval of 5 weeks (35 days).

As further clarification:

- To be assigned CR or PR as the best response, it must be confirmed no less than 4 weeks (28 days) from the time of the initial CR or PR;
- If a best response of CR or PR cannot be established, stable disease (SD) can be assigned as a best response if the SD assessment is at least 5 weeks [35 days] after the first dose of study treatment (Note: a minimum interval of 5 weeks was chosen because tumor imaging is scheduled every 6 weeks +/- 1 week).
- If the CR is not confirmed, and a best response of PR can not be established, then the best response will be SD if the CR, PR, or SD assessment is at least 5 weeks after the first dose of study treatment.
- If the PR is not confirmed, and a best response of CR can not be established, then the best response will be SD if the CR, PR or SD assessment is at least 5 weeks after the first dose of study treatment.

- If the CR or PR is not confirmed, and the assessment date does not meet SD criteria (a minimum interval of 5 weeks after the first dose of study treatment), then the best response will depend on the subsequent assessments: if an assessment of PD follows CR or PR, then the best response will be PD; if subjects are lost to follow up after only one CR or PR assessment, then the best response will be considered as NE.
- If the SD assessment is less than 5 weeks after the first dose of study treatment and a best response of CR and PR could not be established, the best response will depend on the subsequent assessments: if an assessment of PD follows the SD, then the best response will be PD; if subjects are lost to follow up after the SD assessment, then the best response will be considered as NE.
- PD is considered the best response when PD is documented and a best response of CR, PR, or SD could not be established. Clinical progression alone in the absence of radiological confirmation is not a progression event in this analysis.
- NE is considered the best response when PD has not been documented and a best response of CR, PR, or SD could not be established.

Specifically, overall response rate = (number of subjects with a best response of confirmed CR or PR) divided by the total number of subjects in the corresponding analysis population; complete response rate (CRR) = (number of subjects with a best response of confirmed CR) divided by the total number of subjects in the corresponding analysis population; and disease control rate (DCR) = (number of subjects with a best response of confirmed CR, confirmed PR or SD) divided by the total number of subjects in the corresponding analysis population. Subjects with not evaluable, unknown or missing best response will be treated as non-responders, i.e. they will be included in the denominator when calculating the percentage.

For all assessments after the baseline visit, if tumor imaging for the target lesion, non-target lesion and new lesion are done in different dates for a scan visit, the date of response will be assigned as following:

- If the overall response is CR/PR, the date of CR/PR response will be the latest date;
- If the overall response is SD, the date of SD response will be the latest date;
- If the overall response is PD, the date of PD response will be the earliest date among the new lesion, PD for target lesion or PD for non-target lesion;

The best response will be summarized for the Evaluable, All Treated and Per-Protocol populations. In the summary, the ORR, CRR and DCR along with the number (%) of subjects with the best overall response of CR, PR, SD, PD, and NE will be included, and an exact 95% confidence interval will be computed for the ORR, CRR, and DCR. Summary of ORR will also be provided for each subgroup as defined in Section 8.2. A summary of DCR at ≥24 weeks may also be presented.

For target lesions, sum of lesion diameters (SLD) will be calculated as the sum of shortest axes for lymph node target lesions and longest diameters for solid tumor target lesions at each visit. For target lesions lesion for which lesion diameter is missing and reported as too small to be measured, the lesion diameter will be set as 5mm for the SLD calculation. New lesions will NOT be included in the target lesion SLD calculation.

A summary of disease burden at baseline will be produced for the Evaluable, All Treated and Per-Protocol population, which will include measurable disease status, SLD for target lesions, and location of disease at specific sites.

The maximum percent reduction from the baseline SLD will be plotted for the Evaluable and All Treated population. The maximum percent reduction is defined as the maximum reduction from the baseline SLD until the first disease progression or start of new anti-cancer therapy, whichever occurs earlier. In the plot of maximum reduction from baseline SLD, horizontal lines at 30% and 20% will be provided.

Listings of assessment based on RECIST 1.1 will be provided for the ALL Treated population. Listing of response will include the target lesion response along with SLD percent change from baseline and SLD percent change from nadir, non-target lesion response, new lesion and overall response at each visit, and the best overall response for each subject. For each post-baseline visits, the nadir SLD for target lesions is defined as the smallest SLD among all prior visits (this includes baseline visit).

Target lesion assessments and non-target lesion assessments will be listed separately. Clinical progression based on investigator assessment will also be listed.

## 11.2 Secondary Efficacy Analysis

Secondary efficacy endpoints include the time to response, CRR, DoR, PFS and OS.

### 11.2.1 Time to Response

For the subset of subjects who show a confirmed CR or PR (RECIST 1.1), time to response is defined as time from the date of the first dose to the first response (the CR/PR prior to the confirmation). The Kaplan-Meier method will be used to summarize time to response descriptively and graphically. The median and the first and third quartiles will be presented, along with approximate 95% confidence intervals. Brookmeyer-Crowley method will be used for the confidence interval calculation. Time to response will also be summarized descriptively by planned assessment times (week 6, week 12, etc.). Time to response will be summarized for the Evaluable, All Treated and PP population, respectively. The Kaplan-Meier Plot of time to response will be provided for the Evaluable population.

### 11.2.2 Complete Response Rate

Complete response rate analysis is described in section 11.1.

### 11.2.3 Duration of Response

For the subset of subjects who show a confirmed CR or PR (RECIST 1.1), DoR is defined as the time from the first documented evidence of CR or PR (the response prior to the confirmation) until the time of documented disease progression or death due to any cause, whichever occurs earlier. Disease progression will be based on radiological assessments RECIST 1.1. Subjects who do not meet the RECIST 1.1 criteria for progression or die will be censored. Censoring rules for this analysis will follow those of the PFS based on radiological assessment as defined in Section 11.2.4.

The Kaplan-Meier method will be used to summarize DoR descriptively and graphically. The Kaplan-Meier estimate for the median, first and third quartiles will be determined along with 95% confidence intervals (CI). The Brookmeyer-Crowley method will be used for confidence interval calculation. Summary of DoR will be provided for the Evaluable, All Treated and PP population, respectively. The Kaplan-Meier Plot of DoR will be provided for the Evaluable and All Treated population. Listing of DoR will be provided for the All Treated population.

### 11.2.4 Progression Free Survival

Progression-free survival is defined as the time from the date of the first dose until the first progressive disease or death due to any causes whichever occurs first. PFS based on radiological assessment RECIST 1.1 is defined as the time from the first dose until the earlier date of radiological PD based on investigator radiological assessment (RECIST 1.1) or death; and PFS based on radiological RECIST 1.1 and clinical assessment is defined as the time from the first dose until the earliest date of PD based on radiological assessment (RECIST 1.1), PD based on clinical assessment, or death. For subjects who have neither progressed nor died, PFS will be censored at the date of the last adequate assessment of CR, PR or SD before the start of new anti-cancer therapy.

PFS will be analyzed with censoring for the extended loss to follow-up to account for two or more missed radiological assessments before PFS events (PD or death). Specifically, if there are two or more scheduled assessments that are missing or not evaluable followed by PD or death, PFS will be censored at the last adequate assessment of CR, PR or SD prior to the PD or death. In this study, the radiological assessment scheduled is every 6 weeks. If the time difference between the PD or death and the last adequate assessment of CR, PR or SD is more than 2 times scheduled time plus 14-day window, the PFS will be censored at the last adequate assessment prior to the PD or death. For example, a window of 98 days (12 weeks + 14 days window) will be used to determine whether there is an extended loss to follow-up.

For subjects who receive post-treatment new anti-cancer therapy, the following rules will apply:

- If an anti-cancer therapy is started without documented disease progression or is started prior to documented disease progression, then PFS will be censored at the date of the last adequate assessment of CR, PR or SD that is no later than the date of initiation of anti-cancer therapy (i.e. if an assessment occurs on the same day as the start of new anti-cancer therapy, the assessment will be used as it will be assumed that the assessment occurred prior to the administration of new anti-cancer therapy).
- If a subject has only a baseline visit or does not have any adequate assessment of CR, PR, SD or PD that is no later than the date of initiation of anti-cancer therapy, PFS will be censored at the date of the first dose.

A summary of the assignments for event and censoring dates for PFS are specified in the following Table 3.

*Table 2: Assignments for Event and Censoring Dates for PFS Analysis*

| Situation | Date of Event (PD/Death) or Censoring | Outcome |
|---|---|---|
| No (or inadequate) baseline tumor assessments and the subject has not died (if the subject has died follow the rules for death indicted at the bottom of the table) | Date of the first dose | Censored |

| Situation | Date of Event (PD/Death) or Censoring | Outcome |
|---|---|---|
| No adequate post-baseline assessments of CR, PR, SD or PD, and the subject has not died (if the subject has died follow the rules for death indicted at the bottom of the table) | Date of the first dose | Censored |
| Progression documented before death or without death | Date of assessment of progression | Event |
| No progression (or death) | Date of last adequate assessment of CR, PR or SD (on or prior to starting new anti-cancer therapy) | Censored |
| New anti-cancer treatment starting prior to documented disease progression | Date of last adequate assessment of CR, PR or SD (on or prior to starting new anti-cancer therapy) | Censored |
| Death before assessment of PD or before any adequate assessment of response | Date of death | Event |
| PD or death after missing one scheduled assessment | Date of PD or death | Event |
| PD or death after missing two or more scheduled assessments | Date of last adequate assessment of response of CR, PR or SD (prior to the missed assessments) | Censored |

The primary analysis of PFS will be based on the radiological assessment, and the sensitivity analysis of PFS will be based on the radiological and clinical assessment. The PFS based on radiological assessment and PFS based on the radiological and clinical assessment will be summarized descriptively using the Kaplan-Meier method for the Evaluable, All Treated and PP populations. The Kaplan-Meier estimate for the median, first and third quartiles will be determined along with 95% confidence intervals (CI). The Brookmeyer-Crowley method will be used for the conference interval calculation. The Kaplan-Meier estimate of PFS rate at landmark times including but not limited to 3, 6, 9 and 12 months will be summarized. The Kaplan-Meier Plot of PFS will be provided for the Evaluable and All Treated population. Listing of PFS will be provided for the All Treated population.

### 11.2.5 Overall Survival

The overall survival is defined as the time from the date of the first dose until the date of death due to any causes. For subjects who have not died or who are lost to follow-up or withdraw consent, OS will be censored at the date of the last contact.

The overall survival will be summarized descriptively using the Kaplan-Meier method for the Evaluable, All Treated and PP populations. The Kaplan-Meier estimate for the median, first and third quartiles will be determined along with 95% confidence intervals (CI). The Brookmeyer-Crowley method will be used for the confidence interval calculation. The Kaplan-Meier estimate of OS rate at landmark times including but not limited to 3, 6, 9, 12, 18, and 24 months will be summarized. The overall survival will also be summarized by status of post study treatment new anti-cancer therapy (Yes or No) for the All Treated population. The Kaplan-Meier Plot of OS will be provided for the Evaluable and All Treated population. Listing of OS will be provided using the All Treated population.

## 11.3 Exploratory Efficacy Analysis Based on irRECIST

Exploratory efficacy analysis based on irRECIST may be run, including but not limited to analysis of ORR and PFS based on irRECIST. The irRECIST will be performed to confirm PD once PD is determined based on the RECIST 1.1. The following are scenarios where PD is confirmed based on irRECIST:

- Target lesions resulting in initial PD remains ≥ 20% and at least 5 mm absolute increase compared to nadir sum of lesion diameters
- New PD due to target lesions sum of lesion diameters ≥ 20% and at least 5 mm absolute increase compared to nadir
- Non-target lesions resulting in initial PD is worse (qualitative)
- New unequivocal PD of non-target lesions
- New lesion resulting in initial PD is worse (qualitative)
- Additional new lesion(s) since last evaluation

The PD confirmation status based on irRECIST will be collected in the CRF.

### 11.3.1 ORR Based on irRECIST

The best response based on irRECIST is the best response recorded from the start of study treatment until the disease progression (the PD per RECIST1.1 or the PD confirmed by irRECIST, whichever is later) or start of new anti-cancer therapy, whichever occurs earlier. The best response will be determined programmatically in the same way as the best response based on RECIST 1.1 (Section 11.1) except the following:

- Confirmed PD is considered the best response when PD is documented and confirmed by irRECIST and a best response of CR, PR, or SD could not be established before documentation of PD. Clinical progression alone in the absence of radiological confirmation is not a progression event in this analysis.

- Unconfirmed PD is considered the best response when PD is documented but not confirmed and a best response of CR, PR, or SD could not be established before documentation of PD. Unconfirmed PD will be further categorized as PD with further assessment but not confirmed by irRECIST vs PD without further assessment to confirm.

The best response based on irRECIST will be summarized for the Evaluable, All Treated and Per-Protocol populations. Calculation of ORR and CRR based on irRECIST are the same as those based on RECIST 1.1 in Section 11.1. In the summary, ORR, CRR, DCR, the number (%) of subjects with the best overall response of CR, PR, SD, confirmation PD, unconfirmed PD, and NE will be included, and an exact 95% confidence interval will be computed for the rates of ORR, CRR and DCR.

Listing of PD based on RECIST 1.1 and whether PD is confirmed by irRECIST at next visit will be provided.

### 11.3.2. PFS Based on irRECIST

Progression-free survival based on irRECIST is defined as the time from the date of the first dose until the PD or death due to any cause, whichever occurs first. The determination of PD as PFS event will be as following:

- For subjects with confirmed PD, the first PD (prior to the confirmation) that is confirmed by irRECIST will be the PFS event;
- For subjects with PD but not confirmed by irRECIST and no further disease assessment after the last unconfirmed PD, the last unconfirmed PD will be the PFS event.

For subjects who have neither progressed nor died, PFS will be censored at the date of the last adequate assessment of CR, PR or SD on/prior to the start of new anti-cancer systemic therapy and before missed visits (if 2 or more scheduled assessments are missed). Assignment of event and censoring date is similar with those of the PFS based on radiological assessment RECIST 1.1 (as defined in Section 11.2.4) with the exception that PD is determined differently for subjects with confirmed PD and subjects with unconfirmed PD as stated above.

The PFS based on irRECIST will be summarized descriptively and graphically using the Kaplan-Meier method for the Evaluable, All Treated and PP populations. The Kaplan-Meier estimate for the median, first and third quartiles will be determined along with 95% confidence intervals. The Brookmeyer-Crowley method will be used for the conference interval calculation. The Kaplan-Meier estimate of PFS rate at landmark times including but not limited to 3, 6 and 12 months will be summarized. The Kaplan-Meier Plot of PFS will be provided for the Evaluable and All Treated population. Listing of PFS based on irRECIST will be provided for the All Treated population.

### 11.4 Exploratory Efficacy Analysis Based on Biomarker Data

Exploratory efficacy analysis will be conducted with the biomarker data including, but not limited to the following:

- Correlate levels of baseline serum anti-β-glucan antibody (ABA) with objective response and treatment outcomes;
- Correlate changes in immune cell activation markers with objective response and treatment outcome;
- In tumor biopsies, correlate changes in the tumor immune microenvironment including TILs (Tumor-infiltrating Lymphocytes) and tumor-infiltrating myeloid cells with objective response and treatment outcome; and/or
- Correlate PD-L1 expression in tumor biopsy samples (in tumor cells and myeloid cells) with objective response and treatment outcome.

Due to the exploratory nature of the analysis, the list of tables and figures for the efficacy analysis with biomarker data will be determined after conducting the analysis.

## 12 SAFETY ANALYSIS

Safety measurements include adverse events, serious adverse events, death, ECOG performance status, laboratory tests (hematology, clinical chemistry, coagulation, and urinalysis), vital signs, physical examination, and ECG measurements. Unless stated otherwise, all safety analyses will be based on the All Treated population, and will be conducted separately for each tumor type. Listings of safety data will include both tumor types.

## 12.1 Study Treatment Administration

A listing of the individual Imprime PGG infusion data will be provided. The individual Imprime infusion data will include the date of administration, start and end time of infusion, total infusion time, actual dose (2 mg/kg or 4 mg/kg), total dose based on weight (actual dose times body weight), total dose received, total infusion volume, infusion rate (volume infused per minute), pre-medication status, details about infusion interruption (including interrupted time, restarted time, total interrupted time, and reason for infusion not restarted after interruption), any dose modifications including dose delayed/interrupted, and dose reduced, and reasons for dose modifications.

A listing of the individual pembrolizumab infusion data will be provided. The individual pembrolizumab data will include the date of administration, actual dose (200mg), actual dose received, total infusion volume, start and end time of administration, total infusion time, pre-medication status, details about infusion interruption (including interrupted time, restarted time, total interrupted time, and reason for infusion not restarted after interruption), and dose delay/interruption along with reasons.

Summary of cycles/days on study treatment and number of doses received will be provided for Imprime PGG and pembrolizumab infusion. Cycles and days on study treatment are defined as the number of cycles or days from the first dose of any study drugs until the last dose of any study drugs. As subjects may discontinue study treatment at any day of last cycle, receiving at least one dose of any study drug in the last cycle will be counted as one cycle for the calculation of cycles on study treatment.

Dose modifications including dose delayed/interrupted, dose reduced (Imprime PGG only), infusion rate reduced (Imprime PGG only) will be summarized. For each type of dose modification, the number of subjects with dose modification, total number of dose modifications and reasons for dose modifications will be summarized, in which the total number of dose modifications is calculated across all subjects with dose modifications. For example, if a subject has two dose delay/interruptions for Imprime PGG, then this subject will be counted 2 times while calculating the total number of dose delay/interruptions. For reasons of dose modifications, the total number of dose modification events will be used as denominator for the percent calculation.

## 12.2 Adverse Events

All subjects will be assessed regularly for the potential occurrence of adverse events (AEs) from the date of informed consent to 30 days after the last dose of study drug. The incidence of treatment-emergent AEs (TEAEs) will be summarized and tabulated using MedDRA (version 18.1), by System Organ Class (SOC) and Preferred Term (PT). A TEAE is defined as an AE that first occurs or worsens in severity on or after the first dose of any study drug and within 30 days after the last dose of any study drug.

The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) (Version 4.03) will be used to grade both clinical and laboratory AEs. A subject with several occurrences of the same AE will be counted once and classified by the most severe occurrence. AEs with missing severity ratings will be classified as having unknown severity.

An overview summary of AEs will be produced, which will include counts and percentages of subjects with any AEs and Grade III/IV AEs, AEs and Grade III/IV AEs related to study treatment, SAEs, SAEs related to study treatment, fatal SAEs, infusion reactions, AEs leading to dose delayed, dose reduced, and dose withdrawn for Imprime PGG, AEs leading to dose delayed and dose withdrawn for pembrolizumab, and AEs leading to study treatment discontinuation. AEs related to study treatment will be further categorized as AEs related to Imprime PGG and/or pembrolizumab, Imprime PGG only, pembrolizumab only, and both Imprime PGG and pembrolizumab.

A treatment-related AE is defined as an AE for which the investigator classifies the relationship to study treatment as "Yes". A worst-case scenario approach will be taken to handle missing data, i.e. AEs related to study treatment will include events with the relationship to study treatment as 'YES' or missing. Adverse event data will be reviewed periodically to identify infusion reactions, new cancers, and events related to pembrolizumab overdose (>=1000mg).

The AE summary tables will use the following algorithms for counting subjects:

- **Preferred term rows:** each subject is counted once within each unique preferred term at the maximum grade. For example, if a subject has two headaches, the subject is counted only once under the preferred term "Headache". Subjects experiencing the same AE preferred term several times with different grades will only be counted once with the maximum grade.
- **System Organ Class (SOC) rows:** each subject is counted only once at the maximum grade at each SOC level although they may have several different preferred term events within the same SOC.
- **Any event row**: each subject with at least one AE will be counted only once at the maximum grade of all AEs he/she experiences.

All AEs and study treatment related AEs will be summarized by maximum toxicity grade, SOC and preferred term. Infusion reactions will be summarized similarly. In addition, AEs will be summarized by SOC and preferred term for the following time periods: 0-3, 3-6, 6-12 and >12 months.

A summary of non-serious AEs that occurred in strictly 5% of subjects or above will be provided (no rounding for the percentage will be used in terms of 5% threshold, e.g., event with 4.9% incidence rate will not be included in this table).

The listing of all AEs and Grade III/IV will be provided. Separate listing of infusion reaction, adverse events of new cancer (that is not a condition of the study) and adverse event associated with pembrolizumab overdose as determined by clinical team review will also be provided.

Listing of AEs (if any) may be provided for the screen failure or non-treated subjects in the Screening population and the subjects in the ABA Pre-screening population.

### 12.3 Serious Adverse Events

Serious adverse events will be summarized similarly as AEs. A treatment related SAE is defined as an AE for which the investigator classifies the relationship to study drug as "Yes". A worst- case scenario approach will be taken to handle missing data, i.e. SAEs related to study treatment will include events with the relationship to study treatment as 'YES' or missing.

For serious adverse events, the treatment-emergent time period begins at treatment enrollment through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier.

Supportive listings with subject-level details will be generated for fatal and all SAEs separately.

### 12.4 Adverse Events Leading to Study Discontinuation and Dose Modification

Adverse events leading to study discontinuation, Imprime PGG dose modification (dose withdrawn, dose reduced and dose interrupted), and pembrolizumab dose modification (dose withdrawn and dose interrupted) will be summarized.

Listing of AEs leading to study discontinuation, Imprime PGG dose modifications and pembrolizumab dose modifications will be provided.

### 12.5 Deaths

All deaths will be summarized based on the number and percentage of subjects. This summary will classify subjects by time of death relative to the last dose of study treatment (>30 days or ≤ 30 days) and primary cause of death. A supportive listing will be generated to provide subject- specific details for subjects who died and the reason for death.

### 12.6 Pregnancies

A listing of pregnancy test results will be provided.

### 12.7 Clinical Laboratory Evaluations

The assessment of laboratory toxicities includes hematology safety, timed completed blood count (CBC) with differential, clinical chemistry, coagulation and urinalysis. Laboratory toxicity grades will be reported using the CTCAE v4.03.

- **Hematology safety**: Hemoglobin (HGB), hematocrit (HCT), platelet count, erythrocytes, and leukocytes, with differential including absolute neutrophils, monocytes, lymphocytes, eosinophils, and basophils. Hematology sample will be collected at pre-Imprime infusion. Hematocrit, red blood cell count, monocytes, eosinophils, and basophils are not graded by CTCAE v4.03. Lymphocyte count and hemoglobin are graded by CTCAE 4.03 for both increase and decrease directions.
- **Timed CBC with differential** is the same set of tests as for hematology safety but collected pre-Imprime PGG infusion and 4 hours post start of Imprime infusion on the selected visit days.
- **Clinical Chemistry:** Albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, direct bilirubin (if total bilirubin is elevated above ULN), lactate dehydrogenase (LDH), carbon dioxide (if considered standard of care in the region), uric acid (urate), calcium, chloride, creatinine, glucose, phosphorus, potassium, sodium, magnesium, total protein, blood urea nitrogen, and thyroid function including total triiodothyronine (T3), free triiodothyronine (FT3), free thyroxine (FT4), thyroid stimulating hormone (TSH), and creatinine clearance. For sodium, potassium, calcium, glucose, and magnesium there will be bi- directional parameters (hyper and hypo) created, and the tests will be graded by CTCAE v4.03 in both directions. Chloride, direct bilirubin, LDH, carbon dioxide, blood urea nitrogen, T3, FT3, FT4, TSH, and total protein are not graded by CTCAE v4.03.

- **Coagulation**: Prothrombin time (PT), international normalized ratio (INR), and activated partial prothrombin time (aPTT) at screening.
- **Urinalysis:** Blood, glucose, protein, specific gravity, and microscopic exam including bacteria, RBC and WBC (if abnormal results noted)

The individual subject level data will be listed for hematology safety, timed CBC with differential, clinical chemistry, coagulation, and urinalysis/microscopic data. The listing of hematology tests will include the data from hematology safety and timed CBC data with differential. For the listing of hematology and clinical chemistry, the baseline value will be specified for each subject.

The normal ranges from each site will be used to identify values that are out of normal range. Standard units will be used to report lab test results for hematology safety, timed CBC and clinical chemistry. The list of standard units for each lab test will be determined by the study team.

A separate listing of liver function tests (ALP, AST, ALT, total and direct bilirubin) will be provided for subjects who have the following clinical event of interest:

- Elevated AST or ALT value that is ≥ 3 x upper limit of normal range (ULN) and elevated total bilirubin value being ≥ 2 x ULN, and at the same time, alkaline phosphatase <2 x ULN.

For each test of timed CBC with differential, the following will be summarized using mean, median, standard deviation, minimum and maximum:

- Assessment value at the pre-Imprime infusion and 4-hour post start of Imprime infusion for each visit;
- The 4-hour post start of Imprime infusion change from pre-Imprime infusion for each visit;
- Change from baseline at pre-Imprime infusion and 4-hour post start of Imprime infusion for each visit, and baseline is defined as pre-infusion on Cycle 1 Day 1.

Summaries of hematology (including hematology safety and timed CBC) and clinical chemistry toxicity grade shift from baseline will be provided for all graded laboratory tests for the worst- case post-baseline. The determination of the worst-case post-baseline will take into account both the planned and unscheduled assessments.

### 12.8 Vital Signs

Vital signs data (blood pressure, heart rate, respiration rate and temperature) will be listed for each subject. Body weight and change from baseline will be listed.

### 12.9 Electrocardiograms

The 12-lead Electrocardiogram (ECG) measurement will be listed for each subject.

### 12.10 ECOG Performance Status

The ECOG performance score shift from baseline will be produced for the worst-case post-baseline. The ECOG performance status values will be listed. Baseline value for each subject will be specified in the listing.

### 12.11 Physical Examination

Physical examination data will be listed.

## 13 PHARMACOKINETICS

The PK concentration data analysis will be described in a separate PK analysis plan and data will be analyzed separately, independent of the data analysis conducted under this SAP.

## 14 BIOMARKER ANALYSIS

The ABA values assessed at screening will be summarized for the All Treated, Screening, and possibly the ABA Pre-screening population. Listing of ABA will be provided separately for the All Treated subjects and possibly for the screen failure and non-treated subjects in the Screening population and subjects in the ABA Pre-screening population.

Data analysis for all other biomarker data will be described in a separate biomarker analysis plan(s) and data will be analyzed separately, independent of the data analysis conducted under this SAP.

## 15 DATA DISPLAY SPECIFICATIONS

All analyses will be performed using SAS® Version 9.2 or higher. Continuous variables will be summarized with the number of subjects (n), mean, median, standard deviation, minimum and maximum; and categorical variables will be summarized with frequency counts and percentages. For summary statistics, mean and median will be displayed to one more decimal place than the original value and dispersion statistics (e.g. standard deviation) will have two more decimal places than the original value. P-values will be reported to four (4) decimal places and those less than 0.0001 will be reported as <.0001. When no data are available for a listing, summary table, or graph, the text "No Data to Report" will be printed in the body of the statistical reporting display.