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Statistical Analysis Plan

A Multi-Center Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, in combination with Durvalumab (MEDI4736), in Subjects with Relapsed or Refractory Solid Tumors

PCYC-1135-CA

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Confidentiality Statement

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ANC	Absolute neutrophil counts
ATC	Anatomical Therapeutic Chemical
BOR	best overall response
CBC	complete blood count
CIT	Chemoimmunotherapy
CR	complete response
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DOR	Duration of response
DLT	Dose limiting toxicity
EOT	End of treatment
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EU	European Union
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
Hgb	hemoglobin
IPD	important protocol deviation
ITT	intent-to-treat
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NE	not evaluable
ORR	overall response rate
OS	overall survival
PCYC	Pharmacyclics LLC
PD	progressive disease
PFS	Progression free survival

Abbreviation	Definition
PK	Pharmacokinetic
PLT	platelets
PR	partial response
RP2D	Recommended Phase 2 dose
SAP	statistical analysis plan
SD	stable disease
SOC	system organ class
TEAE	Treatment-emergent adverse events
TNM	Tumor node metastases staging
TTP	time to progression
TTR	time to response
UNK	unknown
WBC	white blood count
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) lays out key elements including definitions and statistical methods for analysis of data in evaluation of efficacy and safety for the PCYC-1135-CA study. Analyses of pharmacokinetics data and biomarkers will be addressed in separate documents.

1.1. Stud y Design

This is a non-randomized, open-label, multi-center, Phase 1b/2 study to evaluate the efficacy and safety of ibrutinib in combination with durvalumab in subjects with relapsed or refractory solid tumor types (Stage III/IV per TNM staging):

- Non-small Cell Lung cancer (NSCLC): adenocarcinoma or squamous-cell carcinoma
- Breast cancer: HER2 positive or triple negative
- Pancreatic cancer: adenocarcinoma

RECIST 1.1 criteria will be used to evaluate response and document objective disease progression.

Phase 1b:

Phase 1b will follow a 6+3 dose de-escalation design to evaluate dose limiting toxicity (DLT) and determine the recommended phase 2 dose (RP2D) or maximum tolerated dose (MTD) for this study. In cohort 1 (consisting 6 subjects regardless of tumor type), ibrutinib will be administered PO at a dose of 560 mg daily in combination with durvalumab at a dose of 10 mg/kg IV every 2 weeks in 28-day cycles until DLT or disease progression occurs. The DLT observation period includes Cycle 1 and laboratory assessments on Day 1 of Cycle 2 which will occur before the durvalumab infusion on Day 1 of Cycle 2. If 2 subjects within the initial cohort of 6 subjects experience a DLT, an additional 3 subjects will be enrolled at the same dose level. If 3 or more of 6 subjects experience a DLT, dose de-escalation will occur. If the subject incidence of DLTs during the first 28 days (Cycle 1=28 days and including laboratory assessments on Day 1 Cycle 2) of study treatment is <33.3% (ie, ≤1 of 6 or ≤2 of 9), this dose level will be considered safe to proceed to Phase 2, and will be defined as the RP2D. A DLT is defined as any Grade 3 or higher non-hematologic or Grade 4 hematologic AE possibly related to study treatment(s) occurring during the DLT observation period.

A similar 6+3 cohort design will be utilized in the dose de-escalation cohorts (see Table 1). De-escalation cohorts -1A and -1B will be opened simultaneously to determine which dosing schedule is most appropriate for the phase 2 portion of the study. Determination of the RP2D will be based on the safety profile of the 2 treatment regimens. If necessary, the dose de-escalation cohort -2 will be enrolled thereafter.

Table 1: Phase 1b Dosing Levels

28-Day Dosing Cycle	Ibrutinib	MEDI4736
Cohort 1	560 mg once daily PO	10 mg/kg IV
Cohort -1A*	420 mg once daily PO	10 mg/kg IV
Cohort -1B*	560 mg once daily PO	3 mg/kg IV
Cohort -2	420 mg once daily PO	3 mg/kg IV

*: Cohorts -1A and -1B are 2 parallel cohorts and will be enrolled concurrently in the sequence of -1A followed by -1B.

After the RP2D is determined, enrollment in Phase 2 will commence. Subjects who were not treated at the RP2D in Phase 1b will continue to be treated at the assigned dose. All subjects enrolled under Phase 1b will be followed for response evaluation and overall survival.

Phase 2:

Subjects with one of three solid tumor types (Stage III/IV) will be enrolled per the specifications below.

- NSCLC (adenocarcinoma and squamous-cell carcinoma at an approximate 2:1 ratio) (ie, at least 15 subjects with squamous-cell carcinoma will be enrolled)
- Breast cancer (triple-negative and HER2-positive cancer at an approximate 2:1 ratio) (ie, 15 subjects with triple-negative breast cancer will be enrolled)
- Pancreatic Cancer Cohort: (adenocarcinoma)

For each of the above three cohorts, the statistical framework of Simon's optimal 2-stage design will be implemented to enroll subjects (an interim analysis for futility in the first stage and the final analysis in the second stage). The interim analysis for futility will be performed to evaluate the response and safety profile. Enrollment will continue while the interim analysis is performed. A cohort may be discontinued based on the interim efficacy and/or safety results. The decisions based on the results of the interim analysis are independent in the 3 individual disease cohorts. At the time of the interim safety assessment, Investigators that enrolled subjects and the Sponsor (at a minimum: a Medical Monitor, a Drug Safety representative, and a Biostatistician) will review safety data and make recommendations for the conduct of the study: continue the trial unchanged, consider modifying in part or in whole, or stop the trial due to safety concerns.

NSCLC and breast cancer cohorts (n=43 per cohort):

The breast and NSCLC cohorts will each enroll 43 evaluable subjects. Subjects who discontinue prior to the first tumor response assessment for reasons other than progressive disease will not be considered evaluable for response. An interim analysis for futility will be performed for each cohort independently after first 18 subjects in a cohort are evaluable for tumor response. If 2 or fewer responders are observed among the 18 evaluable subjects, the Sponsor may consider discontinuation of this cohort; however, assessment of biomarkers (that may aid in prospective

enrichment for responders) or tumor measurements (showing clinically relevant tumor reductions, ie, <30%, that fit the criteria for SD) may support continued enrollment.

Pancreatic cancer cohort (n=44):

This cohort will enroll 44 evaluable subjects. An interim analysis for futility will be performed after 17 subjects are evaluable for tumor response. If 1 or no responder is observed among the first 17 evaluable subjects, the Sponsor may consider discontinuation of this cohort. Same as in the other two cohorts, the assessment of biomarkers or tumor measurements may support continued enrollment.

1.2. Endpoints

Primary Endpoints

Phase 1b:

- Recommended Phase 2 Dose (RP2D) or Maximum Tolerated Dose (MTD)
- Safety and tolerability of ibrutinib in combination with durvalumab

Phase 2:

- Overall Response Rate (ORR)

Secondary Endpoints

Phase 1b:

- ORR
- Disease control rate (DCR) at Week 20 (end of Cycle 5)
- Duration of response (DOR)

Phase 2:

- DCR at Week 20 (end of Cycle 5)
- DOR
- Progression-free survival (PFS)
- Overall survival (OS)

Safety Assessments

Safety and tolerability assessments include adverse events, clinical laboratory tests, and vital signs.

1.3. Statistical Hypotheses

There is no hypothesis testing for Phase1b. The primary objective of Phase 2 is to evaluate overall response rate (ORR) for the combination therapy at RP2D. Hypothesis testing will be conducted to address this objective as follows:

Null hypothesis (H_0): P <= x%; where P denotes overall response rate.
Alternative hypothesis (H_a): P >= y%; where P denotes overall response rate.

For NSCLC cohort and breast cancer cohort, a true response rate of 10% (H_0) versus 25% (H_a) will be tested. For pancreatic cancer cohort, a true response rate of 5% (H_0) versus 18% (H_a) will be tested.

1.4. Sample Size Determination

The study is not powered for comparison of dose cohorts or tumor type cohorts.

Phase 1b: Dose de-escalation will follow the 6+3 design and up to four dose cohorts will be enrolled for the DLT to determine the RP2D for the combination therapy. Therefore, Phase 1b will enroll a minimum of 6 and a maximum of 36 evaluable subjects.

Phase 2: Hypothesis for the true response rate will be tested as described below independently for each tumor type cohort based on the statistical framework of Simon's optimal 2-stage design. With a 1-sided error rate of 0.05, each tumor type cohort would have 80% power based on the true response rate in the alternative hypothesis. Approximately 130 subjects (including the subjects treated at the RP2D in Phase 1b and with the tumor type) across the three tumor type cohorts will be included in the Phase 2 analyses.

NSCLC cohort and breast cancer cohort (n=18 for interim and n=43 for final per cohort):

For each of the two tumor type cohorts, a true response rate of 10% (H_0) versus 25% (H_a) will be tested and the probability of early stopping is at least 73.4% if the true response rate is ≤10% (H_0), and no greater than 13.5% if the true response rate is ≥25% (H_a).

An interim analysis (for futility) will be performed based on the first 18 evaluable subjects for each cohort independently. If 2 or fewer responders are observed among the 18 evaluable subjects in a cohort, the enrollment may be stopped. Otherwise, the cohort will continue to enroll an additional 25 evaluable subjects for a total of 43 evaluable subjects for the final analysis. The null hypothesis will be rejected if 8 or more responders are observed among the 43 evaluable subjects.

Each cohort will enroll subjects according to the histology ratio described in Section 1.1.

Pancreatic cancer cohort (n=17 for interim and n=44 for final):

A true response rate of 5% (H_0) versus 18% (H_a) will be tested and the probability of early stopping is at least 79.2% if the true response rate is ≤5% (H_0), and no greater than 16.2% if the true response rate is ≥18% (H_a).

An interim analysis (for futility) will be performed based on the first 17 evaluable subjects. If 1 or no responder is observed among the 17 evaluable subjects, the enrollment may be stopped. Otherwise, this cohort will continue to enroll an additional 27 evaluable subjects for a total of 44 evaluable subjects for the final analysis. The null hypothesis will be rejected if 5 or more responders are observed among the 44 evaluable subjects.

1.5. Planned Analyses

1.5.1. Phase 1b Analyses

The primary objective of Phase 1b is to determine the RP2D or MTD and to evaluate safety and tolerability of ibrutinib in combination with durvalumab. The secondary objectives are to evaluate efficacy and PK and PD in subjects receiving the combination regimen.

1.5.2. Phase 2 Analyses

Interim Analysis for Futility: For each tumor type cohort, the interim analysis will be performed after the first 18 evaluable subjects (for the NSCLC and breast cancer cohorts) /17 evaluable subjects (for the pancreatic cancer cohort) completed at least one tumor response assessment or at least 3 responders (in the NSCLC and breast cancer cohorts) / 2 responders (in the pancreatic cancer cohort) were observed, whichever occurs first. Confirmation of response is not required for those responders for the interim analysis.

Final Analysis: The final analysis for both safety and efficacy will be performed at the end of the study based on all subjects treated for this study. A Clinical Study Report (CSR) will be produced when the analysis has been performed for all three cohorts.

1.6. Testing Procedure and Level of Significance

The 2-sided significance level for the final analysis of primary endpoint (ORR) will be 0.05. Analyses of secondary endpoints will be performed using the same significance level.

2. GENERAL ANALYSIS CONSIDERATION

Time to event or duration of event endpoints will be based on the actual event date (or censoring date) rather than visit number or visit label. Missing efficacy or safety data will not be imputed unless otherwise specified.

In general, the baseline value is defined as the last valid measurement on or prior to the first dose of study treatment. For by-visit analysis, visit windows will be used to associate assessment with a scheduled visit and will be created in reference to the date of first dose of study treatment to assign visit number based on assessment date.

2.1. Analysis Sets

Enrolled Population

This population includes all subjects who were enrolled in Phase 1b and Phase 2 (signed the informed consent and met all eligibility criteria).

Response-evaluable Population

The Response-evaluable Population is defined as all enrolled subjects who received at least one dose of study treatment (ibrutinib or durvalumab) and provided at least one post-baseline response assessment. This population includes all the qualified subjects from both Phase 1b and Phase 2. The Response-evaluable Population will be used as the primary population for analyses based on overall response rate and disease control rate at Week 20 (end of Cycle 5).

Safety Population (Treated Population)

Safety population (Treated Population) includes all subjects who received at least 1 dose of study treatment (ibrutinib or durvalumab). Subjects in this population will be analyzed as randomized for the randomized subjects. The safety population will be used to summarize the safety (including dosing) data.

DLT Evaluable Population for Phase 1b

DLT evaluable population includes Phase 1b subjects who received study treatment and did not meet the criteria for subject replacement (in Section 1.4.1) during the DLT observation period.

2.2. Definition of Subgroups

Subgroup	Definition of subgroup	Type of Analysis
PD-L1 Expression	High versus Low/None	D, E (ORR)
Histology for NSCLC cohort	adenocarcinoma versus squamous-cell carcinoma	D, E (ORR)
Histology for Breast Cancer cohort	HER2-positive versus triple-negative	D, E (ORR)

D: Demographics and baseline disease characteristics. E: Efficacy. ORR: Overall response rate.

3. SUBJECT INFORMATION

3.1. Subject Disposition

Subject disposition will be summarized by each tumor type cohort. Subject enrollment will be summarized by region, country, and investigator.

Time on study is defined in the same way as overall survival with reversed censoring, i.e., subjects who died will be censored at death date. The Kaplan-Meier method will be used to estimate the median time on study.

3.2. Demographics and Baseline Characteristics

Baseline characteristics and demographic information at baseline will be summarized with descriptive statistics by tumor type cohort.

3.3. Prior and Concomitant Medications

Medications will be coded to a generic name and an Anatomical Therapeutic Chemical (ATC) class per the World Health Organization (WHO) drug dictionary. Concomitant medications will be summarized by therapeutic class and preferred term and by tumor type cohort. Concomitant medications are defined as medications that were taken at any time on treatment (i.e. from the date of the first dose of study treatment through the date of the last dose of study treatment). The following concomitant medications will be summarized separately: growth factors, blood supportive products and immunoglobulin, CYP3A inhibitors/inducers, anticoagulants and/or antiplatelets.

3.4. Extent of Exposure to Study Treatment

Exposure to study treatment will be summarized by tumor type cohort. Descriptive statistics will be provided for treatment duration and dosing information (e.g. total cumulative dose administered, relative dose intensity, dose reduction due to adverse events) for all study treatments.

3.5. Previous Treatment History and Subsequent Antineoplastic Therapies

Previous treatment history and subsequent antineoplastic agents will be summarized separately.

4. EFFICACY AND SAFETY ANALYSES

4.1. Efficacy Analyses

Efficacy endpoints and analysis methods are summarized in Table 2.

Table 2: Summary of Efficacy Analyses

Endpoint	Definition	Analysis Methods
Primary Endpoint		
Overall Response Rate (ORR)	Proportion of subjects achieving the best overall responses of CR or PR with confirmation	Primary (Response-evaluable population) • Proportion and 2-sided 95% CI based on exact Binomial distribution (Clopper-Pearson) • Waterfall plot on tumor load from target lesion Sensitivity (Treated population) Proportion and 2-sided 95% CI based on exact Binomial distribution (Clopper-Pearson Subgroup (Response-evaluable population) • PD-L1: High vs. Low/None (all cohorts) • Histology (Breast Ca: HER2 positive vs. Triple negative; NSCLC: Adenocarcinoma vs. Squamous-cell Carcinoma)
Secondary Endpoints		
Disease Control Rate (DCR) at Cycle 5	Proportion of response-evaluable subjects who maintain disease control (CR, PR or SD) at Week 20 (Cycle 5)	Primary (Response-evaluable population) Proportion and 2-sided 95% CI based on exact Binomial distribution (Clopper-Pearson) Sensitivity (Treated population) Proportion and 2-sided 95% CI based on exact Binomial distribution (Clopper-Pearson)
Duration of Response (DOR)	Duration of time from the date of initial response to the date of disease progression or the date of death due to any cause, whichever occurs first	Primary (Response-evaluable population) Proportion and Kaplan-Meier estimate Sensitivity (Response-evaluable population) Proportion and Kaplan-Meier estimate for confirmed and unconfirmed response
Progression Free Survival (PFS)	Duration of time from the first dose date of study treatment (ibrutinib or durvalumab) to the first documentation of disease	Primary (Treated population) • All PD and death considered events regardless any anticancer therapy prior to PD • Kaplan-Meier curve

Endpoint	Definition	Analysis Methods
	progression or the date of death due to any cause, whichever occurs first	Sensitivity (Treated population) • Subjects are censored for use of subsequent anticancer therapy prior to PD or death; subjects are censored after missing two or more consecutive assessment prior to PD or death • Kaplan-Meier curve
Overall Survival (OS)	Duration of time from the first dose date of study treatment (ibrutinib or durvalumab) to the date of death due to any cause	Primary (Treated population) • All death considered events regardless of any anticancer therapy prior to death • Kaplan-Meier curve

4.2. Safety Analyses

Safety data will be summarized by tumor type cohorts. Table 3 summarizes the safety analyses to be performed for all tumor type cohorts.

Adverse events (AEs) will be coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA). Severity of AEs will be graded by the investigator according the NCI-CTCAE v4.03.

All laboratory values will be converted to and reported as international standard (SI) units. In general, only data from the central laboratory will be summarized and analyzed. Laboratory parameters will be graded using the NCI CTCAE v4.03.

Unless otherwise specified, only baseline and post-baseline values collected during the treatment-emergent period will be included in the safety analysis. In general, the treatment-emergent period is defined as the period from the date of the first dose of study treatment up to 30 days after last dose of ibrutinib or 90 days after last dose of durvalumab, whichever occurs later, or the day before initiation of subsequent antineoplastic therapy.

The treatment-emergent adverse events (TEAEs) are those events that occur or worsen during the treatment-emergent period or that are related to the study treatment. Safety data include subject disposition/ study status, demographics, baseline characteristics and baseline disease characteristics, study drug and treatment exposure, treatment discontinuation and study exit including primary reason, duration of treatment, TEAEs of grade 3 and above, serious TEAEs, TEAEs of major hemorrhage, TEAEs leading to any study treatment discontinuation, survival status, and death listings.

Table 3: Summary of Safety Analyses

Safety Assessment	Definition	Analysis Methods
Safety and tolerability	AE: TEAEs, SAEs, grade 3 or worse TEAEs, related TEAEs, TEAEs leading to treatment discontinuation, TEAEs leading to dose reduction, TEAEs leading to death, protocol- defined events of special interest, and other safety observations Worst post-baseline toxicity grade for selected lab tests: Worst post-baseline toxicity grade, Hgb, creatinine clearance, abnormal uric acid, liver function abnormalities Vital signs, blood pressure, heart rate, temperature, respiratory rate, weight	Descriptive summary statistics and/or listings

AE: adverse event; SAE: serious adverse event; TEAE: treatment-emergent adverse event

5. MODIFICATION OF ANALYSIS TO THE PROTOCOL

Below is the major change made to the analyses in the protocol:

- Data from all three tumor type cohorts will be pooled together to perform a total analysis in the final analysis. This analysis is not specified in the protocol.
- The terminology 'Safety Assessments' instead of 'Safety Endpoints' is used in Section 1.2 safety analysis part

6. REFERENCES

Simon R, "Optimal Two-Stage Designs for Phase II Clinical Trials" Controlled Clinical Trials 10:1-10 (1989)

Rubinstein L and Simon R, "Phase I Clinical Trial Design" Biometric Research Branch, National Cancer Institute, Handbook of Anticancer Drug Development (2004)

Eisenhauer EA et al, "New Response Evaluation Criteria in Solid Tumors; Revised RECIST Guideline (version 1.1). European Journal of Cancer 45:228-247 (2009)

US Food and Drug Administration, "Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" (May 2007)

US Food and Drug Administration, "Guidance for Industry: Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics" (April 2015)

EMA, Appendix1 to the Guideline on the Evaluation of Anticancer Medicinal Products in Man: Methodological Considerations for Using Progression-free Survival (PFS) or Disease-free Survival in Confirmatory Trials (2011)

Fleming TR, Rothmann MD, and Lu HL, "Issues in using progression-free survival when evaluating oncology products" J Clin Oncol 27:2874-2880 (2009)