

Statistical Analysis Plan

Phase 1/2 Dose-Escalation and Expansion Study of FLX475 Alone and in Combination with
Pembrolizumab in Advanced Cancer

Protocol Number: FLX475-02

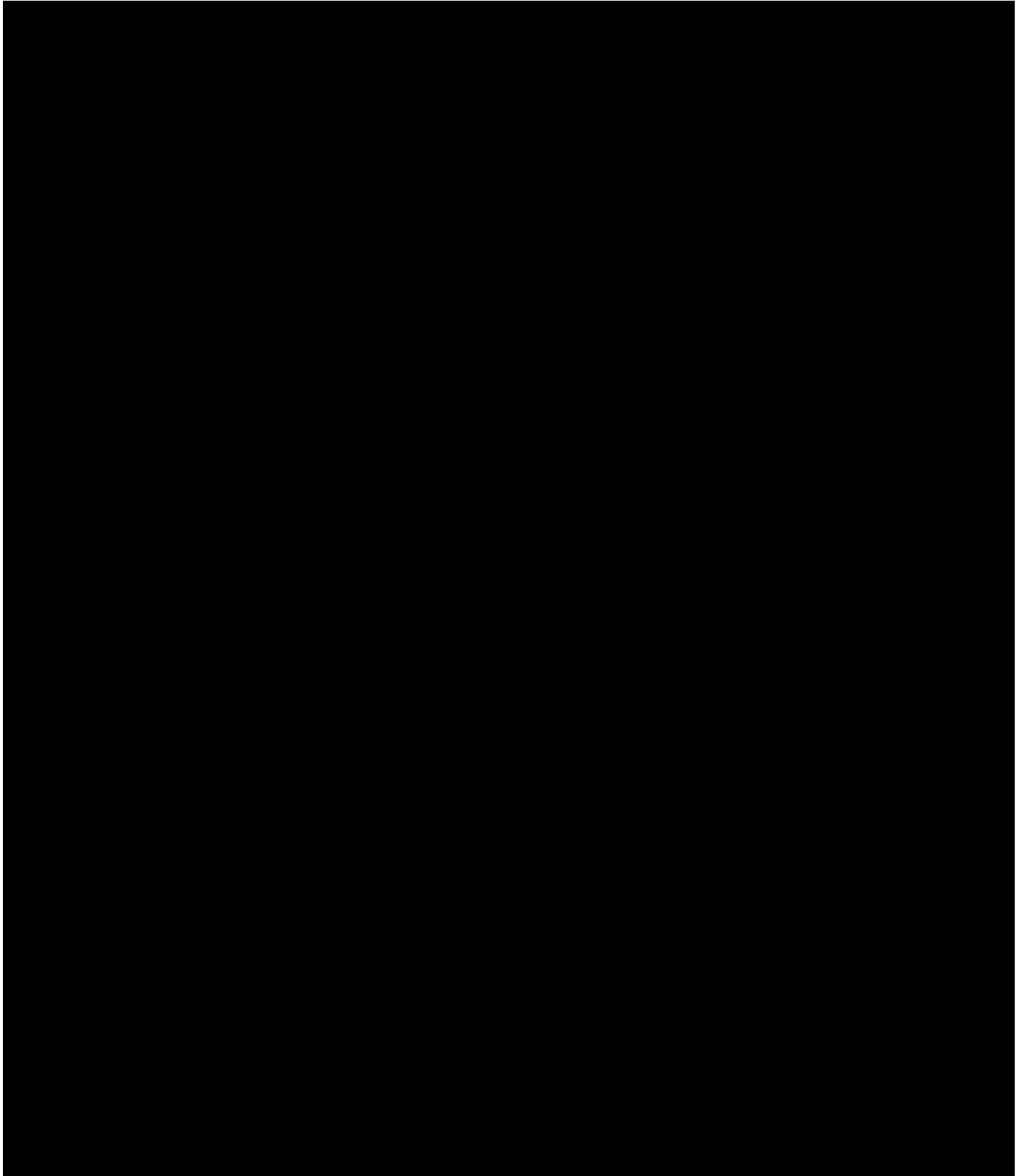


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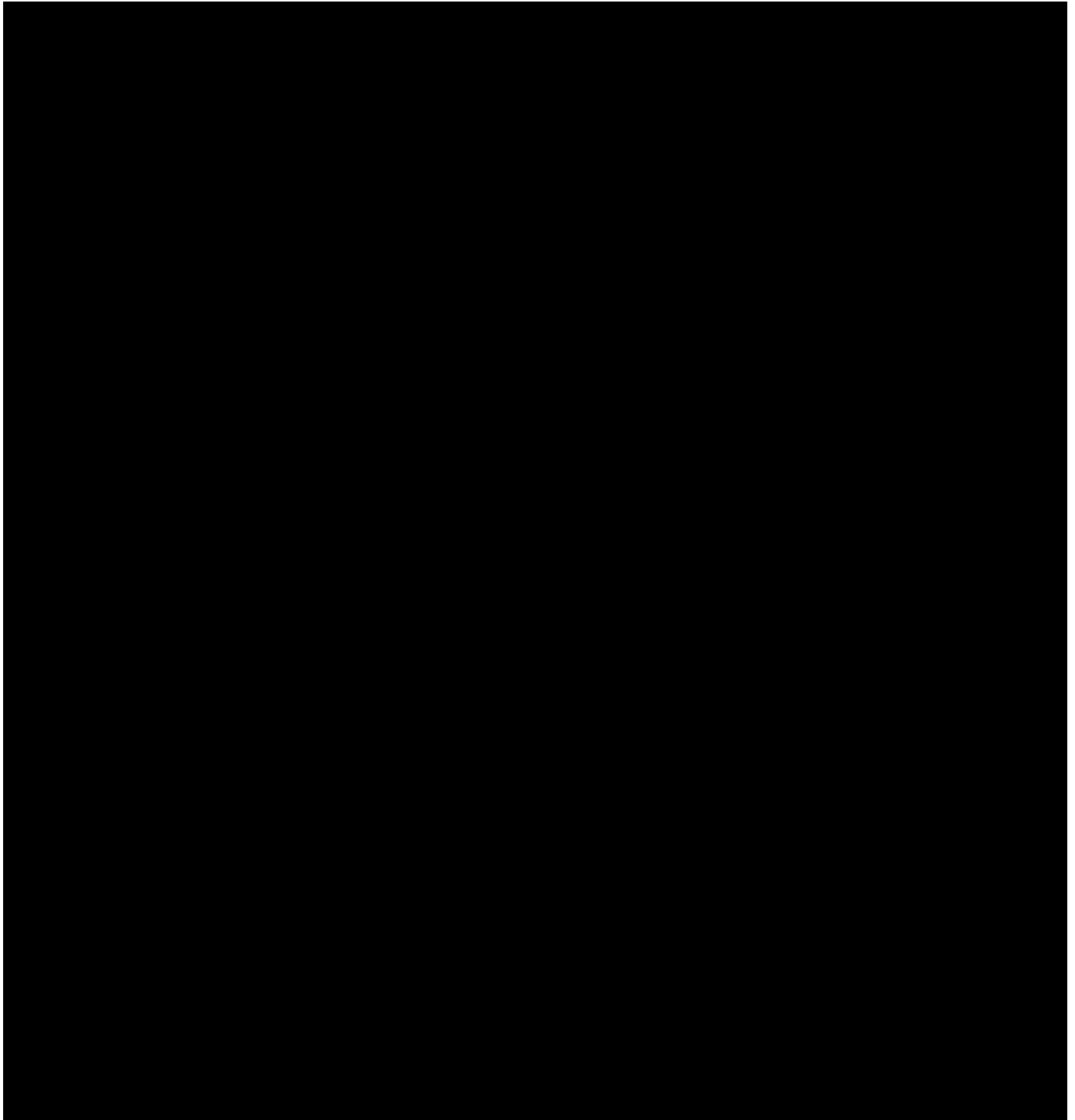


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List of Abbreviations

Abbreviations/Acronyms

AE	adverse event
ATC	anatomical therapeutic chemical
BOR	best overall response
CBR	clinical benefit rate
CI	confidence interval
CPI	checkpoint inhibitor
CR	complete response
CRO	contract research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	cutaneous T cell lymphoma
CTM	clinical trial manager
DLT	dose-limiting toxicity
DOR	duration of response
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report forms
HNSCC	head and neck squamous cell carcinoma
ICH	international conference on harmonization
iCPD	immune-based confirmed progressive disease
iCR	immune-based complete response

Abbreviations/Acronyms

iPR	immune-based partial response
iRECIST	modified RECIST 1.1 for immune-based therapeutics
iSD	immune-based stable disease
ITT	Intent-to-Treat
iUPD	immune-based unconfirmed progressive disease
KM	Kaplan-Meier
Max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum
MTD	maximum tolerated dose
NSCLC	non-small-cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death receptor 1
PD-L1	programmed cell death-ligand 1
PFS	progression-free survival
PR	partial response
PS	performance status
PT	preferred term
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1

Abbreviations/Acronyms

RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
Std Dev	standard deviation
SOC	system organ class
SRC	safety review committee
TEAE	treatment-emergent adverse event
TLF	tables, data listings, figures
TNBC	triple-negative breast cancer
TTR	time to response
US	United States
WHO	World Health Organization

1 INTRODUCTION

This Statistical Analysis Plan (SAP) has been developed after review of Protocol FLX475-02 (Amendment 6, dated 01 September 2022), along with the corresponding electronic case report forms (eCRF). This SAP describes the analysis sets, data-handling rules, and statistical methods to be used for the analysis and reporting of all efficacy and clinical safety data collected during the conduct of Protocol FLX475-02. The planned analysis of pharmacokinetic (PK) and pharmacodynamics (PD) data will be described in a separate document.

If the protocol is amended during the course of the study, the SAP will not require an amendment unless the protocol revisions have an impact on the statistical methodology or data presentations. This SAP has been developed and finalized prior to database lock of the clinical database for Protocol FLX475-02. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the Clinical Study Report (CSR).

This SAP is being written with consideration of the recommendations outlined in the International Conference on Harmonization (ICH) E9 Guideline entitled “Guidance for Industry: Statistical Principles for Clinical Trials” and the most recent ICH E3 Guideline, entitled “Guidance for Industry: Structure and Content of Clinical Study Reports.”

2 OBJECTIVES

The objectives of this study are as follows:

2.1 Primary Objective

The primary objectives of the study are:

- To evaluate the safety and tolerability of FLX475 as a single agent and in combination with pembrolizumab in subjects with advanced cancer
- To evaluate the anti-tumor activity of FLX475 as a single agent and in combination with pembrolizumab in subjects with advanced solid tumors

2.2 Secondary Objectives

The secondary objectives of this study are:

- To define the maximum tolerated dose (MTD) and/or Recommended Phase 2 dose (RP2D) of FLX475, both as a single agent and in combination with pembrolizumab
- To evaluate the PK profile of FLX475 alone and in combination with pembrolizumab
- To assess the effects of FLX475 alone or in combination with pembrolizumab on PD markers relating to drug mechanism of action
- To explore the relationships of PK and PD parameters to clinical drug activity

- To characterize the onset, magnitude, and duration of tumor control in subjects receiving FLX475 alone or in combination with pembrolizumab

3 OVERALL STUDY DESIGN AND TREATMENT PLAN

This is a Phase 1/2, open-label, sequential-group, dose-escalation and cohort expansion study to determine the safety (MTD and/or RP2D) and preliminary antitumor activity of FLX475 as monotherapy and in combination with pembrolizumab.

Potentially, a total of up to 442 subjects or more, depending on the observed MTD, may be enrolled in the United States (US) and internationally.

For each subject, the study consists of the following: screening period, treatment phase, and long-term follow-up:

- Screening visit within 21 days of enrollment into the Treatment Phase
- Treatment Phase comprising up to 35 treatment cycles for FLX475 and a maximum of 2 years' treatment (35 doses) for pembrolizumab and FLX475, unless another intervening reason for discontinuation occurs. Each treatment cycle is 3 weeks in duration.
- End-of-treatment visit within 90 days after the final dose of study treatment
- Posttreatment survival follow-up phase

The definition of the end of the study is the date of the data cutoff for the final analysis or last subject/last visit, including discontinuation from the study for any reason, whichever occurs later.

The study will be conducted in 2 parts, a dose-escalation phase (Part 1) and a cohort expansion phase (Part 2). In Part 1 of the study, at least 3 to 6 eligible subjects will be enrolled in sequential cohorts treated with successively higher doses of FLX475 as monotherapy (Part 1a) or up to 10 in combination with pembrolizumab (Part 1b).

In Part 2 of the study, at least 10 eligible subjects will be initially enrolled in Stage 1 of parallel expansion cohorts of FLX475 as monotherapy (Part 2a) or in combination with pembrolizumab (Part 2b); additional subjects may be enrolled per cohort in Stage 2 to a cumulative total of at least 29. Enrollment may also be expanded in Part 2 to ensure at least 10 (or 29 in Stage 2) subjects of a specific subset of patients within a particular cohort (e.g. CPI-naïve vs experienced EBV⁺ NPC or lymphoma, HPV⁺ HNSCC, squamous vs non-squamous NSCLC, CPI-experienced without or in combination with chemotherapy) are evaluable (For details, see Protocol Section 8.1).

Subjects will undergo safety and efficacy evaluations as specified in the protocol (Schedule of Procedures/Assessments, Tables 8 through 11, for each part of the study).

Response Evaluation Criteria in Solid Tumors (RECIST 1.1) will be used for assessment of tumor response and progression, date of progressive disease, and as a basis for all protocol

guidelines related to disease status (e.g., discontinuation of study treatment), based on the 2009 article by Eisenhauer, et al., entitled *New Response Evaluation Criteria in Solid Tumors: revised RECIST guideline* (version 1.1). See Protocol Appendix 4 for details. Investigator-determined response assessments will be performed at each assessment time point and recorded on the CRF.

For subjects with radiological PD based on RECIST 1.1, the investigator may choose to keep the subject on study treatment and continue performing tumor assessments until repeat, confirmatory imaging is obtained using modified RECIST 1.1 for immune-based therapeutics (iRECIST) based on the 2017 article by Seymour et al, entitled *iRECIST: Guidelines for response criteria for use in trials testing immunotherapeutics*. These guidelines are an adaptation of RECIST 1.1. (See [Protocol Appendix 5 for details](#).) Lugano criteria (Cheson et al, 2014) will be used for subjects with lymphoma (See [Protocol Appendix 6](#)) other than those with cutaneous T cell lymphoma (CTCL), for which alternative criteria should be used (Olsen, 2011).

3.1 Part 1 (Dose Escalation)

The Dose Escalation phase (Part 1) is designed primarily to determine the MTD and/or RP2D of FLX475 alone (Part 1a) or in combination with pembrolizumab (Part 1b) in subjects with several types of advanced cancer:

- Part 1a: Monotherapy Dose Escalation
- Part 1b: Combination Dose Escalation

Dose escalation in Part 1 will be performed with cohort sizes of at least 3 to 6 subjects using a 3+3 design.

3.2 Part 2 (Cohort Expansion)

The Cohort Expansion phase (Part 2) is designed to assess the potential anti-tumor activity of FLX475 alone (Part 2a) or in combination with pembrolizumab (Part 2b) when administered at the RP2D to subjects with selected advanced cancers. Once the MTDs and/or RP2Ds for the monotherapy and combination cohorts are established in Parts 1a and 1b, subjects with advanced cancer will be enrolled in Part 2 based on tumor type.

Cohorts in Part 2 will be enrolled using the optimal Simon 2-stage design, starting with at least 10 subjects per cohort in the first stage. Continued enrollment in a specific cohort in the second stage, up to a total of at least 29 subjects, will only occur if evidence of clinical activity (including, but not limited to, at least 2 partial responses (PR) or complete response (CR) in the first 10 subjects) is observed in the first stage of enrollment.

3.2.1 Part 2a: Monotherapy Cohort Expansion

Cohorts M1-M2 (FLX475 Monotherapy): Subjects with a documented Epstein-Barr virus positive (EBV⁺) malignancy who are ineligible for standard therapy

M1: EBV⁺ Nasopharyngeal cancer (N = 10 Stage 1)

M2: EBV⁺ Hodgkin or non-Hodgkin lymphoma (N = 10 Stage 1)

Any EBV⁺ indications that pass Stage 1 may be combined into a single Stage 2 EBV⁺ basket expansion of up to 19 additional subjects for monotherapy, if emerging data suggest similar clinical activity across EBV⁺ NPC and lymphoma.

Cohorts M3-M4 (FLX475 Monotherapy): Subjects with any of the following tumor types whose disease progressed during treatment with standard available therapies, or who are not eligible for such therapy, and who are also able to and consent to providing tumor biopsies at screening and during study treatment:

M3: Recurrent or metastatic Head and neck squamous cell carcinoma (HNSCC) (specifically of the oral cavity, oropharynx, hypopharynx, or larynx) with no prior treatment with anti-PD-1 or anti-PD-L1 therapy (N = 10–29)

M4: Recurrent or metastatic cervical squamous cell carcinoma with no prior treatment with anti-PD-1 or anti-PD-L1 therapy (N = 10–29)

Cohort M5 (FLX475 Monotherapy): Subjects with EBV-negative lymphoma who are ineligible for standard therapy (specific subtypes permitted will be communicated by the Sponsor based upon available data) (N = 10–29)

3.2.2 Part 2b: Combination Cohort Expansion

Cohort C1 (FLX475/Pembrolizumab Combination Therapy): Subjects with recurrent/metastatic HNSCC (specifically of the oral cavity, oropharynx, hypopharynx, or larynx) with no prior treatment with anti-PD-1 or anti-PD-L1 therapy (N = 10–29)

Cohort C2 (FLX475/Pembrolizumab Combination Therapy): Subjects with recurrent/metastatic HNSCC (specifically of the oral cavity, oropharynx, hypopharynx, or larynx) and documented disease progression or relapse more than 3 months after initiation of prior anti-PD-1 or anti-PD-L1 therapy (N = 10–29)

Cohort C3 (FLX475/Pembrolizumab Combination Therapy): Subjects with Stage IIIB/IV squamous or nonsquamous non-small cell lung carcinoma (NSCLC) and documented disease progression or relapse more than 3 months after initiation of prior anti-PD-1 or anti-PD-L1 therapy (N = 10–29)

Cohort C4 (FLX475/Pembrolizumab Combination Therapy): Subjects with metastatic triple-negative breast cancer (TNBC) with disease progression after treatment with available

therapies known to confer clinical benefit and with no prior treatment with anti-PD-1 or anti-PD-L1 therapy (N = 10–29).

Cohort C6 (FLX475/Pembrolizumab Combination Therapy): Subjects with a documented EBV+ lymphoma (as determined by standard methods, e.g., EBER ISH or LMP-1 IHC) who are ineligible for standard therapy. (N = 10–29).

Cohort C7 (FLX475/Pembrolizumab Combination Therapy): Subjects with an EBV-negative lymphoma (specific subtypes permitted to be communicated by Sponsor based upon available data) who are ineligible for standard therapy (N = 10–29).

Cohort C8 (FLX475/Pembrolizumab Combination Therapy): Subjects with documented EBV+ nasopharyngeal carcinoma (as determined by standard methods, e.g., EBER ISH or LMP-1 IHC) who are ineligible for standard therapy (N = 10–29).

Cohort C9 (FLX475/Pembrolizumab Combination Therapy): Subjects with Stage IIIB/IV squamous or nonsquamous NSCLC with no prior treatment with anti-PD-1 or anti PD-L1 therapy (N = 10–29).

Cohort C10 (Lead-In FLX475/Pembrolizumab Combination Therapy with pembrolizumab starting on Cycle 2 Day 1): Subjects with documented EBV+ nasopharyngeal carcinoma (as determined by standard methods, e.g. EBER ISH or LMP-1 IHC) with no prior treatment with anti-PD-1 or anti PD-L1 therapy who are ineligible for standard therapy (N = 10–29)

Cohort C11 (Lead-In FLX475/Pembrolizumab Combination Therapy with pembrolizumab starting on Cycle 2 Day 1): Subjects with recurrent/metastatic HNSCC (specifically of the oral cavity, oropharynx, hypopharynx, or larynx) with no prior treatment with anti-PD-1 or anti PD-L1 therapy (N = 10-29)

Cohort C12 (Lead-In FLX475/Pembrolizumab Combination Therapy with pembrolizumab starting on Cycle 2 Day 1): Subjects with recurrent/metastatic HNSCC (specifically of the oral cavity, oropharynx, hypopharynx, or larynx) and documented disease progression or relapse more than 3 months after initiation of prior anti-PD-1 or anti-PD-L1 therapy (N = 10-29) [Optional Cohort pending results from C10 and C11]

Cohort C13 (Lead-In FLX475/Pembrolizumab Combination Therapy with pembrolizumab starting on Cycle 2 Day 1): Subjects with Stage IIIB/IV squamous or nonsquamous NSCLC with no prior treatment with anti-PD-1 or anti PD-L1 therapy (N = 10–29) [Optional Cohort pending results from C10 and C11]

3.2.3 Intrасubject Dose Escalation and Crossover

Subjects treated with FLX475 monotherapy in Parts 1a and 2a may be eligible to crossover and be treated with combination therapy in Parts 1b or 2b (respectively). Subjects crossing over to a combination dose escalation cohort may only do so to the highest combination dose

escalation cohort that has already been completed and cleared and will not be included as part of the primary cohort of subjects used for combination dose escalation decisions. Subjects from Part 2a monotherapy expansion cohorts M1-M5 eligible to crossover to combination therapy would do so to the basket combination crossover cohort C5.

3.3 Planned Dose Levels and Treatment Cohorts

The following table summarizes the anticipated set of FLX475 dose levels and the size of treatment cohorts to be evaluated in each part of the study.

Table 1 Anticipated FLX475 Dose Levels and Treatment Cohorts

Dose Level/ Cohort	FLX475 Dosage	Number of Subjects	Intergroup Increase
Part 1a: Monotherapy Dose Escalation			
1a	25 mg QD	3-6	NA
2a	50 mg QD	3-6	2.00-fold
3a	75 mg QD	3-6	1.50-fold
4a	100 mg QD	3-6	1.33-fold
5a	300/100 mg QD*	3-6	NA
6a	300/150 mg QD*	3-6	1.50-fold
7a	300/200 mg QD*	3-6	1.33-fold
Part 1b: Combination Dose Escalation			
1b	50 mg QD	3-6	NA
2b	75 mg QD	3-6	1.50-fold
3b	100 mg QD	3-6	1.33-fold
4b	300/100 mg QD*	3-6	NA
Part 2a: Monotherapy Cohort Expansion			
Cohorts			
M1-M5	RP2D	10-29 ea.	NA
Part 2b: Combination Cohort Expansion			
CI-C13 [†]	RP2D (combo)	10-29 ea.	NA

NA =Not applicable, QD = daily; RP2D =recommended phase 2 dose, TBD =to be determined.

*: Loading doses of FLX475 are planned for these dose levels. The loading (first) dose will be given on Cycle 1 Day 1, followed by lower maintenance (second) doses given once daily (QD) thereafter.

[†]: Note that as C5 is a basket cohort for crossover subjects, it does not have a 2-stage design.

Note that actual dose levels used in a cohort may be lower than stated above if a smaller dose increment is chosen due to DLTs or toxicity observed during dose escalation and will be determined by the Sponsor medical monitor in consultation with the investigators. In addition, dose escalation in Part 1a and/or Part 1b may continue in additional cohorts beyond those listed if an MID has not been reached and cumulative safety and PK/PD data support doing so.

4 STATISTICAL METHODOLOGY

This plan describes methods planned for the analysis and display of efficacy and safety endpoints. The specific endpoints are as follows.

4.1 Primary Endpoints

The primary endpoint in [Part 1](#) of the study is safety and tolerability by the determination of adverse events (AEs), including DLTs and the MTD. The following safety parameters will be characterized and summarized:

- Treatment-emergent adverse events (TEAEs) and SAEs together with all other safety Parameters
- Number (%) of subjects who discontinue treatment due to TEAEs
- Time to treatment failure due to toxicity, defined as the time from the date of start of treatment to the date that a subject discontinues study treatment due to TEAEs
- Dose-limiting toxicity
- Laboratory abnormalities
- Vital sign abnormalities
- Adverse ECG findings

The primary endpoint in [Part 2](#) of the study is objective response rate (ORR), defined as the proportion of subjects who have best overall response of CR or PR as determined using RECIST 1.1 (or iRECIST) for subjects with solid tumors (Eisenhauer, et al, 2009; Seymour, et al., 2017) [See Protocol Appendices 4 and 5 for details]. Lugano criteria (Cheson et al, 2014) will be used for subjects with lymphoma (See [Protocol Appendix 6 for details](#)) other than those with CTCL, for which alternative criteria should be used (Olsen, 2011).

4.2 Secondary Endpoints

Secondary efficacy endpoints are as follows:

- Overall Survival (OS), defined as the time from the date of start of treatment to the date of death from any cause. Subjects who are lost to follow-up and those who are alive at the date of data cutoff will be censored at the date the subject was last known alive, or date of data cutoff, whichever occurs first.
- Clinical Benefit Rate (CBR), defined as the proportion of subjects who achieve a CR, a PR, or durable SD duration of at least 6 months from start of study treatment.
- Time to Response (TTR), defined as the interval from start of study treatment to the first documentation of CR or PR.
- Duration of Response (DOR), defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of PD or death from any cause.

- Progression-free Survival (PFS), defined as the interval from the start of study treatment to the earlier of the first documentation of PD or death from any cause.

4.3 General Statistical Considerations

All data collected for the dose finding phase (Part 1) and the cohort-expansion phase (Part 2) will be listed. Data from Part 1 will be summarized for all subjects and separately for individual dose-escalation cohorts with mono- or combination therapy. Part 2 data will be summarized for all subjects, for monotherapy and combination therapy (across tumor types) and separately for monotherapy and combination therapy cohorts, if appropriate. All subjects will be summarized according to the dose-level and treatment type they were initially assigned to (i.e., if there is intra-subject dose-escalation or a subject crosses over from monotherapy to combination therapy, the subject will still be summarized according to the initially assigned dose level or as part of the monotherapy cohort, respectively). For subjects who cross over from monotherapy to combination therapy, data collected during the crossover period (after adding pembrolizumab) will not be summarized under monotherapy cohorts. Data listings will identify crossover subjects and flag assessments of efficacy and safety obtained after the start of combination therapy. Tables for selected endpoints will identify crossover subjects as a separate cohort in order to describe their status and summarize their experience during combination therapy (following the start of pembrolizumab). Details are described in sections below.

Descriptive statistics (mean, standard deviation [Std Dev], median, minimum [Min], and maximum [Max]) will be used for continuous variables; number and percentage of subjects will be used for discrete variables. For change-from-baseline calculations, the last measurement prior to the first dose of any study treatment will be used as the baseline value.

For summary statistics, the mean and median will be displayed to one decimal place greater than the original values; the standard deviation will be displayed to two decimal places greater than the original values.

All tabulations of summary statistics, graphical presentations, and statistical analyses will be performed using SAS® Version 9.4 or higher.

4.4 Determination of Sample Size

Part 1 (dose escalation):

The planned 3+3 dose-escalation scheme will result in 3 to 6 subjects being evaluated at each of the proposed dose levels. Table 2 shows the probability of escalating to the next dose level based on the true rate of DLT at the current dose level.

Table 2 Incidence of Dose-Limiting Toxicity and the Probability of Dose Escalation

True Incidence of DLT	Probability of Escalation
-----------------------	---------------------------

10%	0.91
20%	0.71
30%	0.49
40%	0.31
50%	0.17
60%	0.08

Thus, if the true underlying proportion of DLT is low (e.g., $\leq 10\%$ at the current dose level), there is a high probability (≥ 0.91) of dose escalation to the next dose level. Conversely, if the true underlying proportion of DLT is high (e.g., $\geq 60\%$) at the current dose level, there is a low probability (≤ 0.08) of escalation to the next dose level.

Part 2 (cohort expansion):

The primary efficacy endpoint in the expansion cohorts will be the overall response rate (ORR). Simon's 2-stage design will be used for evaluating ORR in each expansion cohort. A cohort will be considered for termination due to lack of efficacy if too few tumor responses (either confirmed or unconfirmed) are observed in Stage 1. An initial evaluation of efficacy will be performed after 10 treated subjects in each cohort have evaluable tumor response data. If no more than 1 response is observed, the cohort may be terminated. Otherwise, at least 19 additional subjects will be enrolled in the cohort to obtain a total of 29 efficacy evaluable subjects. In the example of a 30% overall response rate being the target for a specific cohort, if 5 or fewer responses are observed in 29 subjects, no further investigation of the drug may be warranted in the tumor type represented by this cohort. This design yields a type I error rate of 5% and power of 80% when the true response rate is 30%.

To ensure that data are available for the pre-planned number of evaluable subjects in each cohort, a slightly larger number might be enrolled in Part 2. Enrollment may also be expanded in Part 2 to ensure at least 10 (or 29 in Stage 2) subjects of a specific subset of patients within a particular cohort (e.g. CPI-naïve vs experienced EBV⁺ NPC or lymphoma, HPV⁺ HNSCC, squamous vs non-squamous NSCLC, CPI-experienced without or in combination with chemotherapy) are evaluable. However, at each stage, the primary analysis will be based on the specific number of subjects required by the sample size calculation, per cohort, in the order of first treatment received.

The decision to terminate the cohort or to allow it to continue will be made after taking into consideration other relevant observations such as duration and extent of response, clinical characteristics of the subjects enrolled and treated, and risk/benefit profile. The number of subjects receiving treatment at the time of the Stage 1 efficacy evaluation may exceed the specified Stage 1 sample size depending on accrual rate, response lag, and other factors.

After Stage 1 enrollment is complete for a given cohort, the Safety Review Committee (SRC) will review available efficacy and safety data and determine whether enrollment into Stage 2 may continue, even if not all response data are yet available to determine whether the Stage 1 stopping criteria have been met. The SRC may decide that enrollment may continue if the benefit risk assessment is perceived to be positive.

Starting with 10 subjects per Expansion Cohort, a minimum of 50 subjects will participate in Stage 1 Expansion Cohorts M1 through M5 to evaluate FLX475 monotherapy in Stage 1. A minimum of 100 subjects will be enrolled into Stage 1 Expansion Cohorts C1-C4 and C6-C11 (FLX475 + pembrolizumab). Total sample size will depend on the final number of cohorts and whether or not responses exceed cohort-specific stopping boundaries, and if it is decided to increase the minimum number of a particular subset of subjects within a particular expansion cohort. A maximum of 377 subjects are planned to be enrolled in Part 2 of the study if 13 cohorts are fully enrolled.

4.5 Disposition of Subjects

The numbers of subjects enrolled, treated, discontinued from treatment (by reason), and discontinued from study (by reason), will be presented by therapy type (monotherapy and combination therapy), and by dose cohort. For crossover subjects, similar information will be provided for the crossover period. Adverse events that caused discontinuation of treatment will be listed according to time of onset in relation to start of study treatment.

4.6 Data Sets Analyzed

The following analysis sets will be used in the study:

Full Analysis Set: All subjects enrolled in the study, also known as the “Intent-to-Treat” (ITT) population. To be enrolled, a subject must have signed the informed consent form and met study eligibility criteria.

Safety Analysis Set: All subjects who receive at least one dose of the investigational product, FLX475 (even a partial dose).

Efficacy Eligible Set: All subjects who receive at least one dose of study treatment, have measurable disease at baseline per RECIST 1.1 (or appropriate lymphoma criteria), and have at least one post-baseline scan or discontinue study treatment as a result of progressive disease, death, or a treatment-related adverse event before the first post-baseline scan.

Efficacy Evaluable Set: All subjects in the Cohort Expansion phase (Part 2) of the study who complete at least one cycle of FLX475 and have a baseline and at least one post baseline on-study assessment of tumor response.

The number and percentage of subjects in each analysis set will be summarized, with percentages based on the number of subjects in the Full Analysis Set.

4.7 Protocol Violation/Deviations

Protocol deviations (PDs) will be identified, logged, and reviewed during the course of the study. A determination of major versus minor PDs will be made according to the criteria outlined in the study protocol deviation review plan. A listing of all PDs will be provided. For purposes of CSR reporting, all important/major protocol deviations will be identified based on the following minimum criteria:

- Subjects who entered the study even though they did not satisfy the entry criteria
- Subjects who developed withdrawal criteria during the study but were not withdrawn
- Subjects who received the wrong treatment or incorrect dose
- Subjects who received an excluded concomitant treatment.

As warranted by the data, efficacy may also be assessed in a Per-Protocol Population comprising all Efficacy Evaluable subjects who have no major protocol violations, as defined by the Sponsor prior to database lock.

4.8 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively for the Safety analysis set, Efficacy eligible set, and the Efficacy evaluable set. Gender, race, ethnicity, and baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) will be summarized with number and percentage presented for each category. Age, height, and weight at baseline will be described with summary statistics (n, mean, Std Dev, median, minimum, and maximum).

In addition, subject cancer history will be summarized descriptively. The characteristics include:

- Primary tumor type;
- Time from initial diagnosis of tumor to first dose day (in months);
- Time from first recurrence/advancement to first dose day (in months);
- Stage at enrollment (locally advanced, metastatic);
- Time from most recent progression/recurrence to first dose day (in months);
- Prior radiation therapy (yes, no)
- Prior Check Point Inhibitor (CPI) use (yes, no).

The above demographic and baseline characteristics, and cancer history will be summarized for crossover subjects as a separate cohort.

4.8.1 Medical History

Medical history data will be presented in data listings for individual subjects.

4.9 Prior/Concomitant Cancer and Non-Cancer Therapies/Procedures

4.9.1 Prior Cancer Therapy

The number of cancer therapy regimens that subjects received prior to enrollment will be summarized by frequency counts. The best response to the most recent line of therapy will be provided. This will be performed on the Safety analysis set, and Efficacy evaluable set.

4.9.2 Post Treatment Cancer Therapy

The number and percentage of subjects who received any post-treatment cancer therapy will be summarized for the Safety analysis set, and Efficacy evaluable set. For crossover subjects, post treatment cancer therapy is therapy post crossover combination therapy, and will be summarized separately.

4.9.3 Other Prior/Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (WHODrug Global). Prior medications include medications that were stopped before the first dose of study treatment. Concomitant medications include medications that (1) started before the first dose of study treatment and are continuing at the time of the first dose of study treatment, or (2) started on or after the date of the first dose of study treatment up to 30 days after the subject's final dose. Medications started during the crossover period will be summarized separately for the crossover cohort. All medications will be presented in subject data listings.

The number and percentage of subjects taking prior medications or concomitant medications will be summarized by anatomical therapeutic chemical (ATC) and preferred term (PT) for the Safety analysis set. If a subject takes more than one medication in the same ATC class, the subject will be counted only once within that classification. The same subject may contribute to two or more preferred terms within the same ATC classification.

4.10 Study Drug Exposure and Compliance

Three weeks of treatment is considered as one cycle. The maximum number of cycles initiated, cycles that a subject initiated, and extent of exposure (defined as Last Dose Date – First Dose Date + 1) will be summarized for FLX475 for each therapy and cohort. For pembrolizumab, total number of infusions will also be presented. In addition, the number and percentage of subjects with any dose reduction, or dose interruptions, of FLX475 anytime during the study will be summarized. The number and percentage of subjects who cross over from monotherapy to combination therapy will also be summarized. For the crossover cohort, treatment exposure during the combination crossover period will also be

summarized as described above. These parameters will be summarized for the Safety analysis set.

4.11 Efficacy Analysis

The efficacy analysis is based on disease response assessments. Assessment of disease response will be performed by investigators using RECIST 1.1 (or iRECIST 1.1) or appropriate lymphoma criteria (for lymphoma only). Responses for each disease evaluation assessment will be recorded in eCRFs.

Minor modifications to RECIST 1.1 will be implemented in this study. One is that chest x-rays may not be used to follow disease; only CT scans may be used to follow chest disease. Second, as required by RECIST 1.1, the protocol states that the minimum duration of SD is 7 weeks. Third, although RECIST 1.1 allows the site to select up to 5 target lesions at baseline, 2 per organ, if clinically relevant via CT/MRI scans or by electronic calipers for skin lesions, this protocol will follow 10 target lesions with 2 per organ to maintain consistency in target lesion selection across tumor types.

Tumor response is determined by the investigator at each timepoint when tumor imaging is performed. All response-related endpoints (ORR, CBR, TTR, DOR, and PFS) will be based on RECIST 1.1 (or iRECIST) and derived programmatically using the investigator's assessments of tumor response at each timepoint. The date of response is based on the image dates. In the event that there are images taken on different days, the latest date among all images taken will be used for the response date if the overall response is non-PD. If the overall response is PD, then the earliest date of all images taken will be used for the progression date.

All analyses described below will be conducted for the Efficacy Evaluable Set.

4.11.1 Best Overall Response (BOR)

Overall response will be evaluated using RECIST 1.1 for subjects with solid tumors and Lugano criteria for subjects with lymphoma. A subject's best overall response (BOR) is the most favorable response recorded any time after the start of study medication until the date when any new anticancer therapy is initiated or crossover combination therapy started, whichever is earlier. A BOR of either complete response (CR) or partial response (PR) requires confirmation of the assessment at least 4 weeks later. A BOR of stable disease (SD) requires the assessment to be recorded no less than 7 weeks after the start of study medication. For crossover subjects, response assessments during the crossover period will be separately summarized.

For this study, the investigator may use iRECIST to assess progressive disease (PD). This requires confirmation of PD 4-8 weeks after the first radiologic evidence of PD. As a result,

BOR can be any of the following: CR, PR, SD, PD (including either immune-based unconfirmed progressive disease [iUPD] or immune-based confirmed progressive disease [iCPD]), and not evaluable. Note that tumor assessments obtained after a subject starts the crossover period will not be used to confirm progressive disease. The number and percentage of subjects in each BOR category will be summarized.

Table 3 below describes the derivation of BOR from overall response assessments at each visit. Note that BOR categories referenced in this table can be based on overall response evaluated by either RECIST 1.1 or iRECIST. The assessment of iUPD is considered a subcategory of PD. In the situation where a confirmatory PD assessment resolves iUPD to be immune-based stable disease (iSD), immune-based partial response (iPR), or immune-based complete response (iCR), the initial iUPD will be reset to not evaluable (i.e., ‘reset’ progression).

Table 3 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.

PD: includes either iUPD or iCPD. SD: requires a minimum duration of 7 weeks from the start of treatment.

4.11.1.1 Best Response When Confirmation of CR and PR are Not Required

With the objective of detection of early treatment effect signals, a BOR of CR or PR will be assessed without the requirement of a confirmatory response measure.

4.11.2 Objective Response Rate (ORR)

The number and percentage of subjects with BORs of either CR or PR, taking into account any requirement for confirmation, will be calculated. The rates will be presented along with two-sided 95% exact confidence intervals. The 95% CIs will be derived using the Clopper-Pearson (Hollander, 1973) exact binomial confidence interval method.

The analysis of ORR will be performed for the Efficacy Evaluable Set, the Efficacy Eligible Set, and for the subset of subjects who are anti-PD-(L)1 refractory, as defined below. ORR assessments during combination crossover treatment will be summarized separately for the crossover cohort as well.

[REDACTED]

4.11.3 Clinical Benefit Rate (CBR)

The number and percentage of subjects with a confirmed CR or PR, or an SD of at least 6 months duration, will be summarized. To be counted in the calculation of CBR, the CR or PR must be confirmed by a second assessment at least 4 weeks later; otherwise, the SD must be observed at least 6 months from the start of study treatment. The rates will be presented along with two-sided 95% exact confidence intervals; 95% CIs will be derived using the Clopper-Pearson method. Similarly, the CBR assessments during the crossover period will be summarized separately for the crossover cohort.

4.11.4 Time to Response (TTR)

Time to response, defined as the time from the first dose of study treatment to the first assessment of PR or CR, will be summarized descriptively for responders (i.e., subjects with a confirmed CR or PR). Note that, tumor assessments obtained after a subject starts the crossover period will not be used. However, TTR for the crossover cohort will be defined from the first dose of combination crossover therapy to the first assessment of PR or CR after the start of the crossover.

4.11.5 Duration of Response (DOR)

Duration of response will be calculated from the first date of confirmed CR/PR to the date of death or the date of first documented tumor progression (PD), whichever is earlier, using RECIST 1.1 (or iRECIST). Subjects who remain alive without evidence of disease progression will be censored on the date of their last tumor assessment. Subjects who start a new anticancer therapy or initiate crossover combination therapy without a prior PD will be censored on the date of their last tumor assessment prior to initiating the new or crossover anticancer therapy. Response duration will only be evaluated in subjects who have an objective response of CR or PR.

The median DOR, along with its two-sided 95% CI (Brookmeyer, 1982), will be estimated using the Kaplan-Meier (KM) method.

This analysis will also be provided for the crossover cohort, with DOR calculated from the first date of confirmed CR/PR after the start of combination crossover treatment to the date of death or the date of first documented PD, whichever is earlier, using RECIST 1.1 (or iRECIST). Similar censoring rules will be applied. That is, subjects who remain alive without evidence of disease progression will be censored on the date of their last tumor assessment prior to the start of any new anticancer therapy.

4.11.6 Progression-Free Survival (PFS)

PFS will be calculated as the number of days from the first dose of study treatment to the date of death or PD (including iUPD or iCPD), whichever is earlier. Subjects who remain alive and do not progress will be censored on the last tumor assessment date. Subjects who start subsequent therapy without a prior reported progression will be censored on the date of last tumor assessment prior to initiation of subsequent anticancer therapy. Subjects who cross over from monotherapy to combination therapy without a prior PD will be censored on the date of their last tumor assessment before crossing over. Subjects who have no post-baseline tumor assessments and do not die will be censored on Day 1.

The median PFS time, along with its two-sided 95% CI, will be estimated using the KM method. In addition, two-sided 95% CIs for the PFS rate will be constructed at pre-specified

time intervals (such as 3 months, 6 months, ..., etc.), using the log-log transformation methodology of Kalbfleisch and Prentice (Kalbfleisch, 1980) where the estimated variance of $\log(-\log(\hat{S}(t)))$ is:

$$\tau^2(t) = \sigma^2[\hat{S}(t)\log(\hat{S}(t))]^2$$

The 100 x (1-α)% CI for S(t) is given by:

$$\left[\hat{S}(t)\right]^{\exp(-Z_{\alpha/2}\tau(t))} \leq S(t) \leq \left[\hat{S}(t)\right]^{\exp(-Z_{\alpha/2}\tau(t))}$$

This analysis will also be performed for the crossover cohort, with PFS calculated from the start of combination crossover treatment to the date of death or PD (including iUPD or iCPD), whichever is earlier. Subjects who remain alive and do not progress will be censored on the date of last tumor assessment prior to the start of any new anticancer therapy.

4.11.7 Overall Survival (OS)

Overall survival is defined as the time from the first dose of study treatment to the date of death due to any cause. For subjects who do not die, the OS time will be censored on the date when the subject was last known to be alive. The date “last known to be alive” will be defined as the latest date of contact with the subject based on the following: non-imputed AE start and stop dates, visit/collection dates (including unscheduled visits) of pharmacokinetic/pharmacodynamic assessments, serum/urine pregnancy tests, safety laboratory collection (e.g., hematology, serum chemistry, coagulation profiles, thyroid function, and urinalysis), vital signs, physical exams, ECG assessments, tumor biopsy or tumor assessments, concomitant medication/post treatment cancer therapy, and extended survival follow-up contact dates where the subject’s status is “alive”. The analysis methodology for OS will be similar to that used for PFS, with the exception that all data collected after the start of treatment, including the crossover period, will be used for analyses. Subjects who crossover to combination therapy will be summarized under their initial monotherapy cohort; no separate crossover cohort will be applicable to this endpoint.

4.11.8 Sensitivity Analyses

Sensitivity analyses will be performed on TTR, DOR, and PFS where the subjects with CTCL are excluded.

4.11.9 Statistical / Analytical Issues

4.11.9.1 Handling of Dropouts or Missing Data

Missing values will not be substituted by estimated values, but treated as missing in the statistical evaluation. All data from all subjects dosed in the study will be included in all listings, plots, summary tables, and statistical analyses when appropriate.

4.11.9.2 Interim Analyses and Data Monitoring

Safety monitoring will be conducted throughout the study. A Safety Review Committee (SRC) will meet periodically to review accumulating safety information for each cohort and make recommendations to continue or curtail enrollment. The SRC will comprise appropriate Sponsor and Contract Research Organization (CRO) representatives, including the Sponsor's medical monitor or designee(s), safety officer or designee, and clinical trial managers (CTMs). Additional members may be added as needed (e.g. PK scientist and/or biostatistician). For Part 2 of the study, an interim efficacy analysis will be conducted at the end of Stage 1 for each tumor type in order to evaluate whether the number of responders is sufficient to justify cohort expansion in Stage 2.

4.11.9.3 Frequency of On-Treatment Imaging for CTCL Subjects

On-treatment imaging studies for response assessment in subjects with CTCL should only be obtained at time of PR or CR in the skin, at any time there is a question of new or PD in the lymph nodes or viscera, and at end of study.

4.12 Safety Analysis

The safety and tolerability of the investigational products will be determined by reported AEs, physical examinations, ECGs, vital signs, and laboratory test results.

All safety summaries will be based on the Safety Analysis Set.

4.12.1 Adverse Events

All subjects will be assessed regularly for the potential occurrence of adverse events (AEs) from the date of informed consent to 90 days after the last dose of study treatment. For subjects who crossover to a combination therapy, data included in summaries described below are data collected prior to crossover. Crossover period AEs (i.e., AEs with onset after the start of crossover combination therapy) will be summarized separately. The incidence of treatment-emergent AEs (TEAEs) will be summarized and tabulated using MedDRA (Version 21.0), 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 treatment. Furthermore, an AE is not considered treatment emergent if it is not treatment

related and its onset is more than 30 days after the last dose of study drug. All adverse events recorded in the eCRF will be presented in data listings.

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, but will be assigned Grade 3 severity for analysis and summarization.

The relationship of each AE to the study treatment will be classified as related or unrelated; an AE that is possibly, probably or definitely related to study treatment will be considered related. Any AE with an eCRF description of related will be considered related. A subject with several occurrences of the same AE will be counted once and classified as related if at least one of them is classified as related. An AE with a missing relationship to study treatment will be assumed to be related to study treatment for the purpose of analysis and summarization. Relationship of AEs to FLX475 and pembrolizumab will be separately recorded and analyzed.

An overview of adverse events for the Safety Analysis Set will be provided, summarizing the incidence of the following:

- Any DLT;
- Any TEAEs; FLX475-related TEAEs; pembrolizumab-related TEAEs;
- Any NCI/CTCAE Grade ≥ 3 TEAEs; FLX475-related NCI/CTCAE Grade ≥ 3 TEAEs; pembrolizumab-related NCI/CTCAE Grade ≥ 3 TEAEs;
- Any serious TEAEs; FLX475-related serious TEAEs; pembrolizumab-related serious TEAEs;
- Any discontinuation of study treatment due to TEAEs; discontinuation of FLX475 due to FLX475-related TEAEs; discontinuation of pembrolizumab due to pembrolizumab-related TEAEs;
- Any NCI/CTCAE Grade 5 TEAEs; FLX475-related NCI/CTCAE Grade 5 TEAEs; pembrolizumab-related NCI/CTCAE Grade 5 TEAEs;

TEAE summaries by SOC and PT will be provided for the following:

- TEAEs (overall and any treatment-related, FLX475-related, pembrolizumab-related);
- Grade ≥ 3 TEAEs (overall and any treatment-related, FLX475-related, pembrolizumab-related);
- Serious TEAEs (overall and any Serious treatment-related, Serious FLX475-related, Serious pembrolizumab-related);
- TEAEs leading to discontinuation of study treatment (TEAEs leading to any treatment discontinuation, TEAEs leading to FLX475 discontinuation, TEAEs leading to pembrolizumab discontinuation);

- Related TEAEs leading to discontinuation (overall and treatment-related TEAEs leading to any treatment discontinuation, FLX475-related TEAEs leading to FLX475 discontinuation, pembrolizumab-related TEAEs leading to pembrolizumab discontinuation);
- TE Fatal AEs (overall and any treatment-related, FLX475-related, pembrolizumab-related)

In addition, a summary will be provided for the number and percentage of subjects with TEAEs by the highest NCI CTCAE grade. For this summary, subjects with multiple adverse events will be counted only once by the highest NCI CTCAE grade within an SOC and preferred term.

For crossover period AEs, separate summaries as listed below will be provided for the crossover cohort.

- An overview of crossover period AEs including:
 - Any TEAEs; FLX475-related TEAEs; pembrolizumab-related TEAEs;
 - Any NCI/CTCAE Grade ≥ 3 TEAEs; FLX475-related NCI/CTCAE Grade ≥ 3 TEAEs; pembrolizumab-related NCI/CTCAE Grade ≥ 3 TEAEs;
 - Any serious TEAEs; FLX475-related serious TEAEs; pembrolizumab-related serious TEAEs;
 - Any discontinuation of study treatment due to TEAEs; discontinuation of FLX475 due to FLX475-related TEAEs; discontinuation of pembrolizumab due to pembrolizumab-related TEAEs;
 - Any NCI/CTCAE Grade 5 TEAEs; FLX475-related NCI/CTCAE Grade 5 TEAEs; pembrolizumab-related NCI/CTCAE Grade 5 TEAEs;
- Overall TEAEs
- Overall Serious TEAEs
- TEAEs leading to discontinuation of study treatment (TEAEs leading to any treatment discontinuation, TEAEs leading to FLX475 discontinuation, TEAEs leading to pembrolizumab discontinuation)
- Overall TE Fatal AEs

4.12.2 Clinical Laboratory Evaluation

For chemistry, coagulation, thyroid function, and hematology parameters, laboratory measurements (including actual values collected pre-dose of each cycle, last value post baseline, and their changes from baseline) will be summarized. Only scheduled visit values will be included in this summary. In addition, the maximum and minimum post-baseline values with their changes from baseline will be presented.

Shift tables from baseline to the worst post-baseline values during the treatment period will be provided for chemistry parameters and hematology parameters that have NCI-CTCAE

toxicity grades. Both scheduled and unscheduled post baseline values during the treatment period will be considered. Additionally, the number and percentage of subjects with Grade ≥ 3 will be presented for each CTCAE gradable laboratory test. For non-CTCAE gradable laboratory tests, the shift table based on the laboratory normal range will be presented.

The above summaries are based on data collected prior to the crossover period (if applicable).

All clinical laboratory data will be listed by subject. Values outside the normal ranges will be flagged and toxicity grades will be displayed for relevant parameters.

4.12.3 Vital Signs and Weight Measurement

Vital signs measurements include heart rate, respiratory rate, temperature, systolic blood pressure, and diastolic blood pressure. Vital sign measurements and weight measurement at baseline, changes from baseline to the measurement at pre-dose of each cycle, and the last visit value post baseline with its change from baseline will be summarized. Only scheduled visit values will be included in this summary.

In addition, the maximum and minimum post-baseline values and their changes from baseline will be summarized.

The above summaries are based on data collected prior to the crossover period (if applicable).

4.12.4 12-Lead Electrocardiogram (ECG)

ECG measurements include heart rate, PR interval, RR interval, QRS interval, QT interval, QTcF and QTcB intervals. ECG measurements at baseline, changes from baseline to the measurements at pre-dose and 2 hours post dose of each cycle, and the last visit value post baseline with its change from baseline will be summarized. Only scheduled visit values will be included in this summary. In addition, the maximum and minimum post-baseline values will be summarized. The mean of triplicate values at each timepoint will be used for these summaries.

The number and percentage of subjects with elevated QTcF or QTcB values (≥ 450 msec, > 480 msec, and > 500 msec) at baseline and any time post baseline will be presented. In addition, the number and percentage of subjects with QTcF or QTcB values that increase by > 30 msec and > 60 msec from baseline to any time post baseline will be presented.

A shift table from baseline (defined as average QTcF value from C1D1 triplicate ECGs at 0.75 hours, 0.5 hours, and 0.25 hours pre-dose timepoints (9 values)) to the worst post-baseline values during the treatment period will be provided for QTcF and QTcB intervals. The following categories will be used: < 450 msec, ≥ 450 and ≤ 480 msec, > 480 and ≤ 500 msec, and > 500 msec.

The above summaries are based on data collected prior to the crossover period (if applicable).

4.12.5 ECOG Performance Status

A frequency table will present the number and percentage of subjects classified by their highest (worst) grade for ECOG performance status observed during the treatment period (excluding crossover period).

5 REFERENCES

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6 PROGRAMMING CONSIDERATIONS

All tables, data listings, figures (TLFs), and statistical analyses will be generated using SAS[®] Version 9.4 (or higher). Generated outputs will adhere to the following specifications.

6.1 Table, Listing, and Figure Format

6.1.1 General

- 1) All TLFs will be produced in landscape format.

- 2) All TLFs will be produced using the Times New Roman font, size 9.
- 3) The data displays for all TLFs will have a 1.5-inch binding margin on top of a landscape-oriented page and a minimum 1-inch margin on the other 3 sides.
- 4) Headers and footers for figures will be in Times New Roman font, size 9.
- 5) Legends will be used for all figures with more than 1 variable, group, or item displayed.
- 6) TLFs will be in black and white (no color).
- 7) Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- 8) Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain superscripts (e.g., cm^2) will be employed on a case-by-case basis.
- 9) Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats.

6.1.2 Headers

All output will have the following header at the top of the page:

RAPT Therapeutics

Page n of N

Study: FLX475-02

All output will have page numbers. TLFs will be internally paginated in relation to the total length (i.e., the page number will appear sequentially as page n of N, where N is the total number of pages in the table).

6.1.3 Display Titles

Each TLF will be identified by a numeral, and the designation (i.e., Table 1) will be centered above the title. A decimal system (14.x-y.z, 14.x.y-z, and 16.2.x-y) will be used to identify TLFs with related contents. The title will be centered in initial capital characters. The analysis set will be identified on the line immediately following the title. The title and table designation will be single spaced. A solid line spanning the margins will separate the titles from the column headers. There will be 1 blank line between the last title line and the solid line.

Table 14.x.y-z

First Line of Title

Second Line of Title if Needed

Safety Analysis Set

6.1.4 Column Headers

- 1) Column headings will be displayed immediately below the solid line described above, in initial upper-case characters.
- 2) For numeric variables, units will be included in column or row heading when appropriate.
- 3) Analysis set sizes will be provided for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of subjects in the analysis set.
- 4) The treatment in the tables and listings will be:
 - a) Part 1a/2a: FLX475 25 mg QD, FLX475 50 mg QD, FLX475 75 mg QD, FLX475 100 mg QD, FLX475 300/100 mg QD, FLX475 300/150 mg QD, FLX475 300/200 mg QD;
 - b) Part 1b/2b: FLX475 50 mg QD + Pembrolizumab 200 mg Q3W, FLX475 75 mg QD + Pembrolizumab 200 mg Q3W, FLX475 100 mg QD + Pembrolizumab 200 mg Q3W, FLX475 300/100 mg QD + Pembrolizumab 200 mg Q3W.

6.1.5 Body of the Data Display

- 1) Listings will be sorted for presentation in order of cohort (Part 1a: [FLX doses], Part 1b: [FLX doses + Pembrolizumab], Part 2a: [M1-M5], Part 2b: [C1-C4 and C6-C9, C5]), subject ID, collection day, and collection time.
- 2) If the categories of a parameter are ordered, then all categories between the maximum and minimum category will be provided in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	n
severe	0
moderate	8

mild	3
------	---

Where percentages are provided in these tables, any counts of 0 will appear as 0, not as 0 (0%).

- 3) If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups will be included.
- 4) An Unknown or Missing category will be added to the summary of any categorical parameter for which information is not available for 1 or more subjects.
- 5) Unless otherwise specified, the estimated mean and median for a set of values will be presented to 1 more significant digit than the original values, and standard deviations will be presented to 2 more significant digits than the original values. The minimum and maximum will be presented with the same number of significant digits as the original values. For example, for systolic blood pressure:

n	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- 6) Data in columns of a table will be formatted as follows:
 - alphanumeric values left-justified;
 - whole numbers (e.g., counts) right-justified; and
 - numbers containing fractional portions decimal-aligned.
- 7) Percentage values will be formatted with 1 digit to the right of the decimal point in parentheses, 1 space after the count (e.g., 7 (12.8%), 13 (5.4%)). Less-than signs (e.g., “< 0.1%”) will appear when values are >0.0% and <0.1% (but not equal to 0.0%). Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator.
- 8) Tabular displays of data for prior/concomitant medications and all tabular displays of adverse event data will be provided by the body system, drug class, or SOC with the highest occurrence in the overall total group, in decreasing order. Within the body system, drug class and SOC, medical history (by PT), drugs (by ATC code), and adverse events (by PT) will be displayed in decreasing order. If the incidences for multiple terms are identical, they will be sorted alphabetically.

- 9) Missing data will be represented on subject listings as either a hyphen (“-”) with a corresponding footnote (“ - = unknown or not evaluated”), or as “N/A” (footnote “N/A = not applicable”), whichever is appropriate. Missing descriptive statistics or p-values due to non-estimability will be reported as “-”.
- 10) Dates will be formatted in SAS[®] ISO date format yyyy-mm-dd (e.g., “2000-07-01”). Missing portions of dates will be represented on subject listings as blank (e.g., “2000-07”). Dates that are missing because they are not applicable for the particular subject will be presented as “N/A”, unless otherwise specified.
- 11) All observed time values will be presented using a 24-hour clock in hh:mm:ss format (e.g., “01:35:45”, “21:26”). Time values will be reported only if they were measured as part of the study.

6.1.6 Footnotes

- 1) A solid line spanning the margins will separate the body of the data display from the footnotes.
- 2) All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- 3) Informational footnote will begin with “Note:”. Annotation footnotes will begin with an asterisk and other non-numeric symbol. Each new footnote will start on a new line.
- 4) Footnotes will appear on each page. Subject specific footnotes will be avoided.
- 5) Footnotes will be used sparingly, and only if they add value to the table, figure, or data listing. If a data display has more than 4 footnotes and made the number of records showing on each page decreased in fair amount, they will all appear on a cover page for the data display; only those footnotes essential to comprehension of the data will be repeated on each page. Footnotes will not repeat definitions already provided in the SAP.
- 6) The last line of the footnote section will be a standard source line, indicating the data source used by the SAS program that produced the data display, the name of the SAS program, and the listing source (e.g., “Data source: xyzabc.sas7bdat Program source: myprogram.sas Listing source: 16.x.y.z”).

6.2 Data-Handling Rules

This section describes naming conventions and rules for calculations common to all applicable tables. Some rules specific to a table can be found in the relevant mock-ups.

6.2.1 Unit Conversion to Months

If months are calculated for a duration, the following conversion is used.

- 1) Duration (months): {Duration (days)} / 30.4375

6.2.2 Visits

- 1) Relative Study Day: The first day of any study treatment is Day 1. A minus (-) sign indicates days prior to the start of study treatment (e.g., Day -5 represents 5 days before start of therapy. There is no Day 0.). The relative study day for a specific visit is calculated as (Visit Date – Date of First Dose +1).
- 2) Baseline: For all study variables, baseline is defined as the last measurement obtained prior to the first dose of the study treatment.

6.2.3 Demographics and Baseline Characteristics

- 1) Age = (Date of informed consent–Date of birth + 1) / 365.25 and truncated to complete years.
- 2) Conversion factors and calculations for height and weight:
 - Height (in cm) = height (in inches) * 2.54
 - Weight (in kg) = weight (in lbs) * 0.4536

6.2.4 Prior and Concomitant Medications

- 1) Prior and concomitant medications will be coded and classified using the World Health Organization (WHO) Drug Dictionary (WHODrug Global). The specific dictionary version will appear in the actual tables/listings.
- 2) Counting rules for prior/concomitant medications: Prior medications include medications that were taken prior to first dose of study treatment and ended before the first dose. Concomitant medications during the treatment period include medications that started at any time and were taken at any time after the start of study treatment until 90 days after the last dose of the study treatment.
- 3) Medications missing both start and stop dates, or having a start date within 30 days after the last dose of study treatment and missing the stop date, or having a stop date after the start of study treatment and missing the start date, will be counted as concomitant. When partial dates are present in the data, both a partial start date and/or a partial stop date will be evaluated to determine whether it can be conclusively established that the medication either ended prior to the start of study

treatment or started more than 30 days after the last dose of study treatment. If the above cannot be conclusively established based on the partial and/or present dates, then the medication will be counted as concomitant.

6.2.5 Safety

- 1) Adverse events will be coded and classified using MedDRA 21.0. The specific dictionary version will appear in the actual tables/listings.
- 2) Counting rules for AEs: AEs with missing start dates, but with stop dates either overlapping the treatment period or missing, will be counted as treatment-emergent, taking the worst-case approach. Special care will be taken regarding partial dates, applying similar logic to that of the prior/concomitant medications.
- 3) For purposes of flagging individual subject data, laboratory test result abnormalities are defined as values above or below the normal range.

6.2.6 SAS® Procedures

This section provides sample SAS® code to illustrate statistical analyses specified in the statistical methods section. All computer output from SAS® statistical procedures serving as a basis for extracted results (e.g., LIFETEST) will be retained for quality control procedures and will be included in CSR appendices.

- 1) Exact 95% confidence interval on BOR (CR/PR):

```
proc freq;  
    by trt;  
    table resp / binomial;  
  
run;
```

- 2) Median survival time with 95% confidence interval:

```
proc lifetest outsurv=surv;  
    time tte*censor(0);  
    strata trt;  
  
run;
```

Note: 95% confidence intervals for time intervals (e.g., 3 months, 6 months, etc.) will be extracted from data set *SURV*.