

CLINICAL STUDY PROTOCOL

Study Protocol Number: FLX475-02

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

Investigational Product Name: FLX475 (F003475) and pembrolizumab

Indication: Advanced solid tumors

Phase: 1/2

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Amendment 2: July 25, 2018
Amendment 3: January 29, 2019
Amendment 4: February 7, 2020
Amendment 5: December 27, 2020
Amendment 6: September 01, 2022

GCP Statement: This study is to be performed in full compliance with International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use guidances and all applicable local Good Clinical Practices (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.

CONFIDENTIALITY STATEMENT

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1 CLINICAL PROTOCOL SYNOPSIS

Investigational Product Name(s): FLX475, pembrolizumab
Study Protocol Title Phase 1/2 Dose-Escalation and Expansion Study of FLX475 Alone and in Combination with Pembrolizumab in Advanced Cancer
Sites Approximately 30 sites in the United States (US) and internationally
Study Period and Phase of Development Phase 1/2
Objectives Primary Objectives • 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 Secondary Objectives • To define the maximum tolerated dose (MTD) and/or 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
Number of Subjects Approximately 190 subjects (through Stage 1 of Part 2); up to 442 subjects (if 13 Stage 2 cohorts fully enroll)
Study Design: This clinical trial 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 anti-tumor activity of FLX475 as monotherapy and in combination with pembrolizumab. The study will be conducted in 2 parts, a dose-escalation phase (Part 1) and a cohort expansion phase (Part 2) as described in detail below. 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 or in combination with pembrolizumab (Part 1b). In Part 2 of the study, up to 10 eligible subjects will be enrolled per cohort in Stage 1 of parallel expansion cohorts of FLX475 as monotherapy (Part 2a) or in combination with pembrolizumab (Part 2b); up to 19 additional subjects may be enrolled per cohort in Stage 2.

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

This portion of the study will evaluate the safety and pharmacology of a range of FLX475 doses in subjects with designated types of advanced cancer. The MTD will be based on the occurrence of dose-limiting toxicity (DLT). The RP2D will be selected based on safety, PK, PD and efficacy findings, and may be determined prior to establishing an MTD.

In Part 1a, cohorts of subjects will be sequentially enrolled at progressively higher dose levels of FLX475 given as a single agent. Dose escalation will be performed with cohort sizes of at least 3 to 6 subjects using a standard 3+3 design.

In Part 1b, cohorts of subjects will be sequentially enrolled at progressively higher dose levels of FLX475 in combination with standard doses of pembrolizumab (200 mg Q3W). Once a full cohort of at least 3 subjects in the designated Part 1a monotherapy dose-escalation cohort (e.g. 100 mg) has completed 3 weeks of treatment (Cycle 1 in the DLT Observation Period) with no more than 0/3 or 1/6 DLTs, dose escalation in the combination-therapy cohort will begin with the previously-cleared dose of FLX475 (e.g., 50 mg). Combination dose escalation will proceed in parallel with, but staggered behind, dose escalation of FLX475 alone in Part 1a, and will also be performed with cohort sizes of at least 3 to 6 subjects using a standard 3+3 design.

In both Parts 1a and 1b, dose escalation will proceed to the MTD (unless a RP2D is selected prior to establishing an MTD), defined as the highest tested dose level at which ≥ 6 subjects have been treated and which is associated with DLT during the first 3 weeks of treatment (the DLT Observation Period) in fewer than 33% of the subjects at that dose level. For Part 1b, at least 10 subjects should be evaluated at a dose level of FLX475 used in combination with pembrolizumab in order to designate it as the RP2D prior to initiation of Part 2b expansion cohorts. The RP2D for Parts 2a and 2b of the study will be selected based on safety, PK, PD and efficacy findings established in Parts 1a and 1b, respectively. The RP2D for single-agent FLX475 in Part 2a or combination therapy with FLX475-pembrolizumab in Part 2b will be a dose level at or below any MTD determined in Part 1a and Part 1b, respectively.

In addition, at least one dose escalation cohort in Parts 1a and 1b may test a loading dose of FLX475 to be given on Cycle 1 Day 1 followed by a lower daily maintenance dose. The goal of using a loading dose will be to achieve steady-state drug levels earlier than if a loading dose is not used.

If 6 subjects at 9 dose levels are evaluated, as many as 54 subjects could be enrolled. To allow for the possibility that some subjects may not be fully evaluable for DLT, approximately 65 subjects may be enrolled. In addition, more than 3 to 6 subjects per cohort may be enrolled to collect additional safety data or to enroll subjects able to provide tumor biopsies before and during/after study treatment.

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 a 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 responses (CR) in the first 10 subjects) is observed in the first stage of enrollment. Note that either of the EBV⁺ indications that pass Stage 1 may be combined into a single Stage 2 EBV⁺ basket expansion.

If 13 expansion cohorts are fully accrued, as many as 377 subjects could be enrolled in Part 2 of the study: 130 in Stage 1 [10 x 13 cohorts] and 247 in Stage 2 [19 x 13 cohorts]. In addition, more than 29 subjects per cohort may be enrolled to collect additional safety data or to enroll subjects able to provide tumor biopsies before and during/after study treatment. 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. checkpoint inhibitor (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 response. Accrual to specific expansion cohorts may also be discontinued prior to completing either Stage 1 or Stage 2 of enrollment, for reasons including, but not limited to, unacceptable safety, slow/insufficient enrollment, or changes in standard clinical practice.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible to receive study treatment:

1. All subjects must have histologically or cytologically confirmed, advanced or metastatic tumors and (1) have disease progression after treatment with other available therapies for advanced or metastatic disease that are known to confer clinical benefit or (2) do not tolerate or refuse standard treatment(s). (Cohort C9 may include previously untreated subjects if recommended by the treating physician and agreed to by Sponsor.)
2. Subject must have one of the following diagnoses to be eligible for enrollment into a dose escalation cohort (Parts 1a and 1b), or otherwise have pre-approval from the Sponsor medical monitor for any diagnoses not listed below:
 - a. Stage IIIB/IV squamous or non-squamous non-small cell lung carcinoma (NSCLC)
 - b. Recurrent or metastatic head and neck squamous cell carcinoma (HNSCC; specifically of the oral cavity, oropharynx, hypopharynx, or larynx; and nasopharyngeal carcinoma)
 - c. Metastatic triple-negative breast cancer
 - d. Locally advanced or metastatic urothelial carcinoma (UC)
 - e. Locally advanced, recurrent, or metastatic gastric cancer (GC)
 - f. Locally advanced, recurrent, or metastatic esophageal or esophagogastric junction cancer
 - g. Recurrent or metastatic cervical squamous cell carcinoma or endocervical adenocarcinoma
 - h. Metastatic melanoma
 - i. Recurrent EBV⁺ classical Hodgkin lymphoma
3. Subject must have one of the following diagnoses to be eligible for enrollment into a corresponding expansion cohort (Parts 2a and 2b):

Part 2a

 - Cohorts M1-M2 (FLX475 Monotherapy): Subjects with a documented Epstein-Barr virus positive (EBV⁺) malignancy (as determined by standard methods, e.g. EBER ISH or LMP-1 IHC) who are ineligible for standard therapy
 - M1: 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, 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 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)

Part 2b

- 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 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].
4. Men and women ≥ 18 years of age on day of signing informed consent.
 5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 or 1 (Subjects with stable ECOG PS of 2 due to a non-cancer-related condition may be permitted with the approval of the medical monitor.)
 6. Evaluable disease (i.e., by imaging and/or tumor markers) at baseline for dose escalation (Parts 1a and 1b). For expansion cohorts (Parts 2a and 2b), subjects must have at least one measurable lesion at baseline by computed tomography (CT) or magnetic resonance imaging (MRI) per Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions. Liver metastases of eligible tumor types are permitted.
Note: Subjects with lymphoma in the expansion cohorts should have measurable disease, defined as at least 1 lesion that can be accurately measured in at least 2 dimensions with spiral CT scan (Cheson, et al., 2014). The minimum measurement must be > 15 mm in the longest diameter.
 7. Subjects with brain metastases that improve or are stable upon repeat MRI after at least 4 weeks after radiation therapy (and who are not receiving steroids) are permitted.
 8. Subjects who enroll and are treated in Parts 1a or 2a of this study (FLX475 monotherapy dose escalation or expansion cohorts), and who complete at least three 3 week cycles of study treatment including the first response assessment, but who have documented PD and discontinue study treatment without significant treatment-related toxicity, may be eligible to crossover to receive combination therapy, provided an appropriate combination-therapy cohort is open to enrollment, they otherwise meet selection criteria, and it is determined by the investigator, in consultation with the Sponsor's medical monitor, to be in the subjects' best interest to receive combination therapy. Subjects in Part 1a (monotherapy dose escalation) could potentially crossover to an available Part 1b (combination dose escalation) cohort, while subjects in Part 2a (monotherapy expansion) could potentially crossover to a basket combination therapy cohort (C5).
 9. Considered by the investigator to be an appropriate candidate for a Phase 1 clinical study, with a life expectancy of ≥ 12 weeks
 10. All acute toxic effects of any prior therapy have resolved to Grade 0 or 1 or to baseline level before the start of study treatment (except that up to Grade 2 alopecia, neurotoxicity, and bone marrow abnormalities, as well as endocrine insufficiency managed with replacement therapy, may be permitted with Sponsor agreement).
 11. Adequate organ function as defined in [Table 1](#). Specimens must be collected within 21 days

prior to the start of study treatment.

12. Subjects enrolled must be willing and able to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion not previously irradiated (unless subsequent progression demonstrated; minimum of 3 cores). Subjects in Phase 1 dose escalation for whom newly obtained pretreatment samples (i.e. tumor biopsies obtained at baseline screening, prior to initiation of study treatment) cannot be provided (e.g., inaccessible or subject safety concern) may submit an archived specimen only upon agreement from the Sponsor (not applicable for Part 2 expansion cohorts). Formalin-fixed, paraffin-embedded tissue blocks are preferred to slides for those escalation subjects who have been given prior approval by Sponsor (not applicable to for Part 2 expansion cohorts). In addition, subjects must be willing to provide a tumor biopsy (minimum of 3 cores) while on treatment at Cycle 3 Day 1 (± 7 days) (or Cycle 2 Day 1 ± 3 days for subjects in lead-in cohorts such as C10-13) and may be asked to provide additional biopsies at other timepoints such as the time of discontinuation due to progression.

Notes: If submitting unstained cut slides (only after prior approval by Sponsor), newly cut slides should be submitted to the testing laboratory within 14 days from the date that slides are cut. Details pertaining to tumor tissue submission can be found in the Laboratory Manual.

Subjects with lymphoma should be able to provide a core or excisional lymph node biopsy for biomarker analysis at screening as above.

13. For women of childbearing potential, negative results on a serum pregnancy test prior to starting study treatment.
14. For women of childbearing potential, willingness to use an effective method of contraception (e.g., oral contraceptives, double-barrier methods such as a condom and a diaphragm, intrauterine device) during the study and for 120 days following the final dose of study treatment or to abstain from sexual intercourse for this period of time.
- Note: A female subject is considered to be of childbearing potential unless she has had a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy; has medically documented ovarian failure (with serum estradiol and follicle-stimulating hormone levels within the institutional postmenopausal range and a negative result on serum or urine beta-human chorionic gonadotropin [β -HCG]) pregnancy test, or is postmenopausal (age ≥ 55 years with amenorrhea for ≥ 6 months).**

15. For male subjects of childbearing potential having intercourse with females of childbearing potential, willingness to abstain from heterosexual intercourse or use of a protocol-recommended method of contraception (e.g., partner use of oral contraceptives or an intrauterine device, or double-barrier methods such as a condom and a diaphragm) from the start of study treatment to 120 days following the final dose of study treatment and to refrain from sperm donation from the start of study treatment to 120 days following the final dose of study treatment.

Note: A male subject is considered able to father a child unless he has had a bilateral vasectomy or a bilateral orchiectomy with confirmed azoospermia or has ongoing medical testicular suppression.

16. Ability to swallow tablets without difficulty.
17. Willingness to comply with scheduled visits, drug administration plan, protocol specified tumor biopsies, laboratory tests, other study procedures, and study restrictions.
- Note: Psychological, social, familial, or geographical factors that might preclude adequate study participation should be considered.

18. Signed Informed Consent Form by the subject or his/her legal guardian indicating that the subject is aware of the neoplastic nature of the disease and has been informed of and understands the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, possible side effects, potential risks and discomforts, and other pertinent aspects of study participation.

Exclusion Criteria

Subjects who meet any of the following exclusion criteria will not be eligible to receive study treatment:

1. History of known antidrug antibodies or severe allergic, anaphylactic, or other infusion related reaction to a previous biologic agent (for subjects to be treated with pembrolizumab).
2. History of severe hypersensitivity ($\geq$ Grade 3) to pembrolizumab and/or any of its excipients (for subjects to be treated with pembrolizumab)
3. In subjects who received prior therapy with an anti-PD-1, anti-PD-L1, or anti PD-L2 agent or an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX-40, CD137), any history of discontinuing prior treatment due to Grade 3–4 immune-related adverse events (irAEs).
4. Has received prior systemic anticancer therapy including investigational agents within 4 weeks (or < 5 half-lives for investigational/noncytotoxic agents, whichever is shorter) prior to first dose of study treatment.
5. Any active autoimmune disease or documented history of serious autoimmune disease within the past 2 years requiring systemic therapy (i.e., with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
6. History of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, idiopathic pneumonitis, (non-infectious) pneumonitis that required steroids, or clinical symptoms of active pneumonitis.
7. Known carcinomatous meningitis and/or active central nervous system (CNS) metastasis. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e., without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable, and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.
8. History of another malignancy that has progressed or has required active treatment within the past 2 years except for the following: adequately treated local basal cell or squamous cell carcinoma of the skin; in situ cervical carcinoma; adequately treated papillary, noninvasive bladder cancer; asymptomatic prostate cancer without known metastatic disease and not requiring therapy or requiring only hormonal therapy, and with normal prostate specific antigen for ≥ 1 year prior to start of study treatment; other adequately treated Stage 1 or 2 cancers currently in complete remission, or any other cancer that has been in complete remission for ≥ 2 years.

9. Significant cardiovascular disease, including myocardial infarction, arterial thromboembolism, or cerebrovascular thromboembolism within 6 months prior to start of study treatment, symptomatic dysrhythmias or unstable dysrhythmias requiring medical therapy, angina requiring therapy, symptomatic peripheral vascular disease, clinically significant history of syncope, New York Heart Association (NYHA) Class 3 or 4 congestive heart failure ([Appendix 3](#)), or chronic Grade 3 hypertension (diastolic blood pressure ≥ 100 mmHg or systolic blood pressure ≥ 160 mmHg).
10. Significant screening electrocardiogram (ECG) abnormalities including atrial fibrillation (unstable or newly diagnosed), double (left and right) bundle branch block, second degree atrioventricular block type II, third-degree atrioventricular block, Grade ≥ 2 bradycardia, QTcF interval ≥ 450 msec, or unstable cardiac arrhythmia requiring medication. Chronic asymptomatic atrial fibrillation stably controlled with medications is permitted.
11. Known family history of sudden cardiac death.
12. Ongoing risk for bleeding due to active peptic ulcer disease or bleeding diathesis.
13. Significant active gastrointestinal disease (e.g., malabsorption syndrome, resection of the stomach or small bowel, symptomatic inflammatory bowel disease, gastrointestinal perforation, or partial or complete bowel obstruction) that might impair absorption of study treatment.
14. Evidence of an ongoing, uncontrolled systemic bacterial, fungal, or viral infection or an uncontrolled local infection requiring therapy at the time of start of study treatment.
Note: Subjects with localized fungal infections of skin or nails are eligible.
15. Subjects with human immunodeficiency virus (HIV) infection who do not meet the following criteria are excluded: HIV-infected subjects must be on anti-retroviral therapy (ART) and have well-controlled HIV infection/disease defined as: (a) CD4⁺ T cell count > 350 cells/mm³ at time of screening, (b) achieved and maintained virologic suppression defined as confirmed HIV RNA level < 50 copies/mL or the lower limit of qualification (below the limit of detection) using the locally available assay at the time of screening and for at least 12 weeks prior to screening, (c) must have been on a stable anti-retroviral regimen, without changes in drugs or dose modification, for at least 4 weeks prior to start of study treatment (C1D1), and (d) the combination ART regimen must not contain any retroviral medications OTHER THAN abacavir, dolutegravir, emtricitabine, lamivudine, raltegravir, or tenofovir (due to potential CYP interactions, exceptions permitted only with prior Sponsor clearance). Subjects with a history of Kaposi Sarcoma and/or Multicentric Castleman Disease are excluded.
16. Known history of Hepatitis B (defined as Hepatitis B surface antigen reactive) or known active Hepatitis C virus (defined as detection of HCV RNA [qualitative]) infection.
17. Diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (at doses exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 14 days prior to the first dose of study treatment.
18. Prior allogeneic organ transplant.
19. Receipt of live vaccine within 30 days prior to study entry or within 30 days of receiving study treatment. Examples of live vaccines include, but are not limited to, measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.
20. Has undergone prior allogeneic hematopoietic stem cell transplantation within the last 5 years. (Subjects who have had a transplant more than 5 years before the start of study treatment are eligible as long as there are no symptoms of graft-versus-host-disease.)

21. Females who are pregnant, breastfeeding, or expect to become pregnant within the projected duration of the study, starting with the screening visit through 120 days after the final dose of study treatment. Males who plan to father children within the projected duration of the study, starting with the screening visit through 120 days after the final dose of study treatment.
22. Major surgery within 28 days (or inadequate recovery from the toxicity or complications of the intervention) before the start of study treatment.
23. Radiotherapy within 14 days of start of study treatment. (NSCLC subjects who have received radiation therapy to the lung that is >30Gy within 6 months of start of study treatment are also excluded.) Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 7-day washout is permitted for palliative radiation (i.e., $\leq$ 14-day course of radiotherapy) to non-CNS lesions.
24. Subjects currently receiving treatment with any medications that have the potential to prolong the QT interval and that cannot be either discontinued or substituted with a different medication prior to starting study treatment.
Note: See [Appendix 8](#) for a list of proscribed drugs.
25. Subjects currently receiving treatment with strong cytochrome P450 (CYP)3A4 inhibitors or inducers should discontinue such treatment or be switched to a different medication prior to starting study treatment.
Note: See [Appendix 8](#) for a list of proscribed drugs.
26. Current participation in another study of an investigational agent or device.
27. Any illness, medical condition, organ system dysfunction, or social situation, including mental illness or substance abuse, deemed by the investigator to be likely to interfere with a subject's ability to sign informed consent, adversely affect the subject's ability to cooperate and participate in the study, or compromise the interpretation of study results.

Test Product, Dose, and Mode of Administration:

FLX475 for oral administration is provided as tablets. All subjects will take FLX475 with water orally once daily at approximately the same time each day at their assigned dose on a continual basis. On days when pembrolizumab is also administered (i.e., Day 1 of each cycle, unless for “lead-in” cohorts when pembrolizumab starts on Day 1 of cycles 2 and beyond), FLX475 should be taken approximately 1 hour before the pembrolizumab infusion.

Pembrolizumab 200 mg will be administered as an IV infusion over 30 minutes on Day 1 of every 3-week treatment cycle (i.e., every 21 days [± 3 days]), and approximately 1 hour after the Day 1 dose of FLX475. (For “lead-in” dosing cohorts (e.g. C10 and C11) pembrolizumab will start on Day 1 of Cycle 2. Note that in the event that lead-in dosing is determined to potentially provide added clinical benefit over concurrent dosing, lead-in dosing may be implemented across additional/all combination cohorts within the study.)

Planned Dose Levels:

Sequential cohorts of 3 to 6 evaluable subjects will be enrolled at progressively higher dose levels as illustrated in the table below.

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	100 mg QD	3–6	2.00-fold
4a	300/100 mg QD*	3–6	NA
5a	300/150 mg QD*	3–6	1.50-fold
6a	300/200 mg QD*	3–6	1.33-fold
Part 1b: Combination Dose Escalation			
1b	50 mg QD	3–6	NA
2b	100 mg QD	3–6	2.00-fold
3b	300/100 mg QD*	3–6	NA
Part 2a: Monotherapy Cohort Expansion			
Cohorts			
M1-M5	RP2D	10-29	NA
Part 2b: Combination Cohort Expansion			
C1-C13 [†]	RP2D (combo)	10-29	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 MTD has not been reached and cumulative safety and PK/PD data support doing so.

Dose-Escalation Rules:

The following dose-escalation rules will be employed:

- The first subject to be enrolled at the starting dose level (25 mg/dose QD) of FLX475 in Part 1a will be observed for ≥ 1 week after initiation of treatment before any subsequent subjects are treated at the same dose level.
- Each dose level cohort will initially enroll at least 3 subjects.
- If none (0) of the first 3 subjects in a cohort has a DLT, the next cohort of subjects will be treated at the next higher dose level of FLX475.
- If 1 subject in the first set of subjects experiences a DLT, additional subjects up to a cumulative total of 6 will be enrolled at that dose level. If none (0) of the additional subjects experience a DLT, the next cohort of subjects will be treated at the next higher dose level.
- If ≥ 2 of 3 to 6 subjects experience a DLT at a particular dose level, the Sponsor will consider the MTD to have been exceeded and additional subjects will be treated at the previous lower dose level, to a cumulative total of 6 if < 6 subjects were previously treated at that prior dose level. If none (0) of the additional subjects experience a DLT, that dose level will be considered the MTD. If 6 subjects were previously treated at the prior dose level, that prior dose level will be considered the MTD.
- With the concurrence of the principal investigators and the Sponsor's medical monitor, intermediate dose levels between 2 planned dose levels may be added to the dose escalation scheme in order to further refine the estimation of the MTD.
- Each group of 3 to 6 subjects within a cohort must be observed for a minimum period of 3 weeks during Cycle 1 for the occurrence of DLTs (the DLT Observation Period) before subsequent subjects are enrolled to expand the cohort at the current dose level or before any subjects are enrolled at the next higher dose level.
- Escalation to the next higher dose level or progression to the expansion portion of the study can occur upon review of the safety data from all ongoing and previous subjects and with the concurrence of the principal investigators and the Sponsor's medical monitor.
- To maximize the collection of information at relevant doses and to minimize the exposure of subjects to potentially suboptimal doses, intrasubject dose escalation may be permitted in subjects enrolled in Parts 1a and 1b of the study under the following conditions:
 - Subjects must complete at least three 3-week (21-day) cycles at their originally assigned dose level prior to the dose escalation
 - Subjects may only escalate their dose to the highest dose level cohort in which at least 3 subjects have successfully completed at least one 3-week (21 day) cycle of FLX475 (i.e., the DLT Observation Period) with no more than 0/3 or 1/6 DLTs
 - All intrasubject dose escalation decisions will be made in coordination with the Sponsor's medical monitor based on an investigator's judgment of whether such an escalation is in the best interest of the subject.

After all subjects in a cohort have completed the 3-week safety observation period, a Safety Review Committee (SRC) will be convened. The SRC members will comprise appropriate Sponsor and 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). The SRC will carefully consider all available safety, laboratory, and PK information in consultation with the study investigators. Safety data from all enrolled subjects in preceding cohorts and dose levels will also be considered. After review of all available data, the SRC may recommend escalation to the next planned dose; escalation to an intermediate dose (a dose lower than the next planned dose); de-escalation to a lower dose; continuation, delay, or termination of dosing; or repetition or expansion of a cohort. Beyond Phase 1 dose escalation, the SRC will continue to meet at least quarterly during the Phase 2 expansion phase of the study to

review accumulating safety data and may also recommend an amendment to the protocol to evaluate alternate study drug administration schedules or other changes in study design as may be appropriate based on emerging clinical data.

Definition of DLT:

Reference should be made to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 ([Appendix 1](#)) for grading of the severity of AEs and laboratory abnormalities. A DLT is defined as an AE or abnormal laboratory value observed in a Phase 1 dose escalation subject assessed by the investigator as possibly, probably, or definitely related to study treatment, excluding toxicities clearly not related to study treatment, such as disease progression, environmental factors, unrelated trauma, etc. occurring during Days 1–21 of Cycle 1 (“DLT Observation Period”), that meets any of the following criteria:

- Grade 4 hematological laboratory abnormality lasting ≥ 7 days, except thrombocytopenia, or:
 - Grade 4 thrombocytopenia of any duration; or
 - Grade 3 thrombocytopenia associated with clinically significant bleeding
- Nonhematological Grade 3 or 4 laboratory abnormalities:
 - Grade 3 or 4 liver enzyme elevation, including aspartate aminotransferase (AST)/gamma glutamyl transferase and alanine aminotransferase (ALT), that does not return to baseline level within 7 days and requires systemic immunosuppression
 - Hepatocellular injury caused by drug ingestion consistent with Hy’s Law with the following acute changes:
 - ALT or AST $> 3X$ ULN
 - Total bilirubin $> 2X$ ULN
 - No signs of cholestasis (ALP $< 2X$ ULN)
 - No other assignable cause such as liver metastases, pre-existing hepatic disease, viral hepatitis, alcohol abuse, ischemia, etc.
 - Grade 3 or 4 serum electrolyte or mineral abnormalities (i.e., hypermagnesemia, hyperkalemia, hypernatremia, hypomagnesemia, hypokalemia, hyponatremia, or hypophosphatemia) unresponsive to supplementation within 72 hours
 - Grade 3 or 4 amylase or lipase abnormalities that are not associated with diabetes mellitus, associated liver or gall bladder inflammation, clinical manifestations of pancreatitis, and which did not decrease to Grade ≤ 2 within 7 days (isolated asymptomatic Grade 3 amylase abnormalities or lipase abnormalities are excluded)
- Any Grade 4 non-hematologic AE of any duration, with the following exception:
 - Grade 4 diarrhea lasting 48–72 hours in subjects who have received suboptimal anti-diarrheal therapy
- Grade 3 rash that does not resolve to Grade 1 or baseline level (whichever is higher) within 7 days
- Grade 3 fever that does not resolve to Grade 1 or baseline level (whichever is higher) within 7 days
- Grade 3 fatigue that does not resolve to Grade 2 or baseline level (whichever is higher) within 7 days
- Grade ≥ 3 creatinine
- Grade 3 nausea, vomiting, colitis, or diarrhea requiring total parenteral nutrition or hospitalization (e.g., duration > 48 hours despite optimal management) that does not resolve to Grade 1 or baseline level (whichever is higher) within 7 days
- Grade 2–3 uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 0 or 1 within 7 days

- Grade ≥ 2 nonhematological toxicity requiring systemic immunosuppressive therapy. This includes, but is not limited to, autoimmune diseases of the lung, heart, kidney, bowel, CNS, pituitary, or eye
- Grade ≥ 2 endocrine toxicity requiring hormone replacement, with the exception of Grade 2 thyroiditis and thyroid dysfunction
- Grade ≥ 3 adrenal insufficiency
- Grade ≥ 3 febrile neutropenia:
 - Grade 3 is defined as absolute neutrophil count (ANC) $< 1000/\text{mm}^3$ with a single temperature of $> 38.3^\circ\text{C}$ (101°F) or a sustained temperature of $\geq 38^\circ\text{C}$ (100.4°F) for more than 1 hour
 - Grade 4 is defined as ANC $< 1000/\text{mm}^3$ with a single temperature of $> 38.3^\circ\text{C}$ (101°F) or a sustained temperature of $\geq 38^\circ\text{C}$ (100.4°F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated
- QTcF interval ≥ 501 msec and > 60 msec prolongation from baseline (defined as average QTcF value from C1D1 pre-dose ECGs), or associated with Torsades de pointes, polymorphic ventricular tachycardia, or serious arrhythmia
- Prolonged delay (> 2 weeks) in initiating Cycle 2 due to treatment-related toxicity;
- Any treatment-related toxicity that causes the subject to discontinue treatment during Cycle 1.
- Missing $> 20\%$ of FLX475 doses as a result of drug-related AE(s) during the first cycle.
- Any Grade 5 toxicity.

Definition of MTD and RP2D:

The MTD is defined as the highest tested dose level at which ≥ 6 subjects have been treated and which is associated with DLT during the first 3 weeks of treatment (the DLT Observation Period) in fewer than 33% of the subjects at that dose level.

The RP2D for Parts 2a and 2b of the study will be selected based on safety, PK, PD and efficacy findings established in Parts 1a and 1b, respectively. The RP2D for single-agent FLX475 in Part 2a or combination therapy with FLX475-pembrolizumab in Part 2b will be a dose level at or below any MTD determined in Part 1a and Part 1b, respectively. For Part 1b, at least 10 subjects should be evaluated at a dose level of FLX475 used in combination with pembrolizumab in order to designate it as the RP2D prior to initiation of Part 2b expansion cohorts. Safety findings to be considered in selecting the MTD and/or RP2D will also include AEs observed to date beyond the DLT Observation Period, including any late immune-related AEs observed during the 90-day evaluation period following the last dose of study treatment.

Duration of Treatment

Subjects may continue to receive study therapy until the earliest of the following: subject withdrawal from study, confirmed progression of cancer, intolerable study-drug-related toxicity despite appropriate dose modification, the development of intercurrent illness that precludes continued study therapy, pregnancy or breastfeeding, substantial noncompliance with study procedures, completion of Treatment Phase comprising up to 35 treatment cycles for FLX475 and a maximum of 2 years' treatment (35 doses) for pembrolizumab, or study discontinuation.

Study Endpoints:

Safety:

The primary endpoint in Part 1 of the study is safety and tolerability by the determination of 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 (defined in [Section 10.4](#))
- Laboratory abnormalities
- Vital sign abnormalities
- Adverse ECG findings

Pharmacokinetics:

The following PK parameters for FLX475 will be analyzed:

- $AUC_{(0-t)}$: Area under the plasma concentration-time curve (AUC) calculated using linear trapezoidal summation from time 0 to time t, where t is the time of the last measurable concentration (Ct)
- $AUC_{(0-24)}$: Area under the plasma concentration-time curve from 0 to 24 hours, calculated using linear trapezoidal summation
- $AUC_{(0-\infty)}$: Area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: $AUC_{(0-\infty)} = AUC_{(0-t)} + C_t / \lambda_z$, where λ_z is the apparent terminal elimination rate constant (whenever possible)
- C_{max} : Maximum observed plasma concentration
- T_{max} : Time of the maximum plasma concentration (obtained without interpolation)
- $t_{1/2}$: Terminal half-life (whenever possible)
- λ_z : Terminal elimination rate constant (whenever possible)
- CL/F: Oral clearance of FLX475
- Vz/F: Oral volume of distribution of FLX475

Pharmacodynamics:

- Changes in CCR4 receptor occupancy on peripheral blood cells
- Changes in immune parameters, e.g., lymphocyte subpopulations and plasma cytokines or chemokines in peripheral blood or in tumor

Efficacy:

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 ([Appendix 4](#)) for subjects with solid tumors. Lugano criteria ([Cheson et al., 2014](#)) will be used for subjects with lymphoma (see [Appendix 6](#) for details) other than those with cutaneous T cell lymphoma (CTCL), for which alternative criteria should be used ([Olsen et al., 2011](#)).

Other 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, defined as the interval from start of study treatment to the first documentation of CR or PR
- Duration of Response, 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

Statistical Methods:

Analysis Sets

The following sets of data will be defined for this study:

Full Analysis Set (FAS): All subjects enrolled in the study. The FAS will be used to summarize subject disposition, demographics and baseline data, cancer history, and exposure to study treatment.

Safety Analysis Set: All subjects who receive at least one dose of the investigational product, FLX475 (even a partial dose). This set will be used for the analysis of all safety data, including adverse events, vital signs, and clinical laboratory data. Separate analyses will be performed using safety data from the FLX475 monotherapy and combination therapy phases of the study.

Efficacy Eligible Set: All subjects who receive at least one dose of study treatment, have measurable disease at baseline per RECIST v1.1 (or 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. This set will be used for sensitivity analysis of the primary efficacy endpoint, ORR.

Efficacy Evaluable Set: All subjects in the Cohort Expansion phase (Stage 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. This set will serve as the primary basis for analysis of all efficacy endpoints, including ORR, DOR, PFS, and OS.

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.

Pharmacokinetic (PK) Analysis Set: All subjects who receive at least 1 dose of FLX475 as monotherapy or in combination with pembrolizumab, and have measurable plasma concentrations of FLX475.

Pharmacodynamic (PD) Analysis Set: All subjects who receive at least 1 dose of investigational product and have sufficient PD data to derive at least 1 PD measurement.

Analysis Methods

Evaluation of data will consist primarily of descriptive statistics, summary displays, and data listings. In Part 1 (dose escalation), safety data will be tabulated by treatment (monotherapy and combination therapy) and by dose cohort. In Part 2, efficacy and safety data will be presented by treatment, cohort, and tumor type.

The number of subjects enrolled and discontinued from the study (by reason) will be presented separately for Part 1 (Dose Escalation) and Part 2 (Cohort Expansion) by cohort and tumor type. Demographic and baseline characteristics will be summarized for both the Safety Analysis Set and Efficacy Evaluable Set.

The incidence of adverse events will be presented by system organ class, preferred term, and maximum toxicity grade for subjects in each treatment cohort. Separate summaries will be provided for all adverse events, drug-related adverse events, serious adverse events, and adverse events leading to discontinuation of study treatment. Hematology and clinical chemistry data will be summarized by worst-case toxicity grade shift relative to baseline. Deaths will be listed by primary cause and date relative to last dose of study medication.

Efficacy endpoints will be summarized using descriptive statistics, including mean, standard deviation, median, and range for continuous endpoints and frequency tables for categorical data. Estimates of ORR and other response proportions will be presented together with 95% confidence intervals calculated using the Clopper-Pearson method. Kaplan-Meier estimation will be used for the analysis of time-to-event endpoints, including DOR, PFS, and OS.

Statistical Basis for 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. This design will ensure a high probability (≥ 0.91) of dose escalation if the true DLT rate is less than 10%, and a low probability (≤ 0.08) of dose escalation if the true DLT rate is high ($\geq 60\%$).

Statistical Basis for Sample Sizes in Part 2 (Cohort Expansion)

The primary efficacy endpoint in the expansion cohorts will be the ORR. Simon's two-stage design will be used for sample size estimation in Part 2. The null hypothesis that the true response rate is 10% will be tested against a one-sided alternative. An initial evaluation of efficacy will be performed after the first 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, 19 additional subjects will be enrolled for a total of 29 efficacy evaluable subjects. If 5 or fewer responses are observed in 29 subjects, then no further investigation of the drug may be warranted for the cancer 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 be considered evaluable, subjects must meet criteria for the Efficacy Evaluable Set (defined above), be evaluable as per RECIST v1.1 at 9 weeks, and should have no major protocol deviations. Evaluability for tumor response will be based on the following:

- Subjects who remain on study until the first evaluation (at 9 weeks) and are evaluated.
- Subjects who withdraw from the study due to disease progression before the first evaluation (at 9 weeks) will be considered as subjects with early progression
- Subjects who died from malignant disease before the first evaluation (at 9 weeks) will be considered as subjects with early death
- Subjects with measurable disease, for whom all baseline target lesions have been assessed at least once after 9 weeks, with the same method of measurement used at baseline.
- Subjects with only non-measurable disease, for whom non-target lesions have been assessed at least once after 9 weeks.

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.

A Safety Review Committee will evaluate response rates in each cohort after Stage 1 enrollment is complete to assess futility and make recommendations about continued enrollment. Up to 213 subjects will participate in the Dose Expansion phase.

2 TABLE OF CONTENTS

CLINICAL STUDY PROTOCOL	1
1 CLINICAL PROTOCOL SYNOPSIS	2
2 TABLE OF CONTENTS	20
LIST OF IN-TEXT TABLES	25
LIST OF IN-TEXT FIGURES	25
LIST OF APPENDICES	25
3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS	26
4 ETHICS	29
4.1 Institutional Review Boards/Independent Ethics Committees	29
4.2 Ethical Conduct of the Study	30
4.3 Subject Information and Informed Consent	30
5 INVESTIGATORS AND STUDY PERSONNEL	32
6 INTRODUCTION	33
6.1 Background	33
6.1.1 Immunotherapy for Cancer	33
6.1.1.1 Pharmaceutical and Therapeutic Background	33
6.1.1.1.1 Pre-clinical and Clinical Trials	34
6.1.2 Pembrolizumab	34
6.1.3 FLX475	35
6.1.3.1 Preclinical Experience with FLX475	35
6.1.3.1.1 Non-clinical Pharmacology	35
6.1.3.1.2 Preclinical Pharmacokinetics	35
6.1.3.1.3 Preclinical Toxicology	36
6.1.3.2 Clinical Experience with FLX475	37
6.1.3.2.1 Phase 1 Healthy Volunteer Study	37
6.1.4 Dose Rationale for Combination Therapy	37
6.1.4.1 FLX475	37
6.1.4.2 Pembrolizumab	38
6.2 Risk-Benefit Assessment	39
6.3 Study Rationale	40
7 STUDY OBJECTIVES	42
7.1 Primary Objective	42
7.2 Secondary Objectives	42
8 INVESTIGATIONAL PLAN	43
8.1 Overall Study Design and Plan	43
8.2 Study Phases	49
8.2.1 Pretreatment Phase	49
8.2.2 Treatment Phase	49

8.2.3	Follow-Up Phase.....	50
8.3	Discussion of Study Design.....	51
9	STUDY POPULATION	53
9.1	Inclusion Criteria	53
9.2	Exclusion Criteria	59
9.3	Replacement of Subjects.....	61
9.4	Removal of Subjects from Therapy or Assessment.....	62
10	TREATMENTS	63
10.1	Overview of Treatments Administered.....	63
10.2	FLX475 Administration.....	63
10.2.1	Dose Escalation Plan.....	63
10.2.1.1	Planned Dose Levels.....	63
10.2.1.2	Dose Escalation.....	65
10.3	Pembrolizumab Administration.....	66
10.4	Dose-Limiting Toxicity and Stopping Criteria.....	67
10.5	Dose Modifications for Toxicity.....	69
10.5.1	FLX475	69
10.5.2	Dose Modification for Pembrolizumab	71
10.6	Identity of Investigational Products	78
10.6.1	FLX475	78
10.6.2	Pembrolizumab	78
10.6.3	Supply, Packaging, and Labeling of Study Drug.....	78
10.6.4	Storage Conditions.....	78
10.7	Method of Assigning Subjects to Treatment Arms.....	79
10.8	Selection of Doses in the Study	79
10.9	Selection of Dose and Timing for Each Subject.....	80
10.10	Blinding.....	80
10.11	Prior and Concomitant Therapy	80
10.11.1	Recording of Prior and Concomitant Treatments and Procedures.....	80
10.11.2	Drug-Drug Interactions.....	81
10.11.3	Permitted Concomitant Therapies.....	81
10.11.4	Prohibited Concomitant Therapies and Drugs	81
10.11.5	Rescue Medication and Supportive Care	83
10.12	FLX475 Treatment Compliance	83
10.13	Drug Accountability.....	84
11	STUDY PROCEDURES AND ASSESSMENTS.....	86
11.1	Screening Assessments	86
11.2	Baseline Assessments	88
11.3	Efficacy Assessments.....	88

11.3.1	Tumor Imaging and Disease Assessment	88
11.3.1.1	Timing of Tumor Imaging	90
11.3.1.2	Disease Assessment by iRECIST	91
11.4	Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments	92
11.4.1	Pharmacokinetic Assessments	92
11.4.2	Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments	92
11.5	Safety Assessments	94
11.5.1	Adverse Events and Events of Clinical Interest.....	94
11.5.2	Serious Adverse Events, Events of Clinical Interest, and Events Associated with Special Situations	97
11.5.3	Overdose	99
11.5.4	Pregnancy, Contraception, and Breastfeeding	99
11.5.5	Laboratory Measurements	99
11.5.6	Vital Signs and Weight Measurements	100
11.5.7	Physical Examinations	101
11.5.8	Electrocardiograms	101
11.6	Schedule of Procedures/Assessments	101
11.6.1	Appropriateness of Measurements.....	118
11.6.2	Completion/Discontinuation of Subjects	118
11.7	Reporting of Adverse Events	118
11.7.1	Reporting of Serious Adverse Events	118
11.7.2	Reporting of Pregnancy and Breastfeeding	119
11.7.3	Reporting of Events Associated with Special Situations.....	120
11.7.3.1	Reporting of Adverse Events Associated with Study Drug Overdose, Misuse, Abuse, or Medication Error	120
11.7.4	Expedited Reporting	120
11.7.5	Regulatory Reporting of Adverse Events	121
11.8	Confirmation of Medical Care by Another Physician	121
11.9	Data Quality Assurance	121
11.9.1	Data Collection	121
11.9.2	Clinical Data Management	122
12	STATISTICAL METHODS.....	123
12.1	General Statistical Considerations	123
12.1.1	Statistical Design and Sample Size Determination.....	123
12.1.1.1	Part 1 (Dose Escalation).....	123
12.1.1.2	Statistical Basis for Study Design of Part 2 (Cohort Expansion)	124
12.1.2	Statistical and Analytical Plans.....	125

12.1.2.1	Study Endpoints	125
12.1.2.1.1	Safety Endpoints	125
12.1.2.1.2	Efficacy Endpoints	126
12.1.2.2	Pharmacokinetic and Pharmacodynamic Endpoints	126
12.1.2.3	Analysis Sets	127
12.1.3	Subject Disposition	128
12.1.4	Demographic and Other Baseline Characteristics	128
12.1.5	Prior and Concomitant Therapy	128
12.1.6	Efficacy Analyses	128
12.1.7	Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses	130
12.1.7.1	Pharmacokinetic Analyses	130
12.1.7.2	Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses	130
12.1.8	Safety Analyses	131
12.1.8.1	Extent of Exposure	131
12.1.8.2	Adverse Events	131
12.1.8.3	Laboratory Values	132
12.1.8.4	Vital Signs	132
12.1.8.5	Electrocardiograms	132
12.1.9	Interim Analysis	133
13	REFERENCE LIST	134
14	PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)	138
14.1	Changes to the Protocol	138
14.2	Adherence to the Protocol	138
14.3	Monitoring Procedures	138
14.4	Recording of Data	139
14.5	Retention of Records	140
14.6	Auditing Procedures and Inspection	140
14.7	Handling of Study Drug	140
14.8	Publication of Results	141
14.9	Disclosure and Confidentiality	141
14.10	Termination of the Study	141
14.11	Subject Insurance and Indemnity	142
15	APPENDICES	143
Appendix 1	Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03	143
Appendix 2	Eastern Cooperative Oncology Group Performance Status Scale	144
Appendix 3	New York Heart Association (NYHA) Cardiac Disease Classification	145

Appendix 4	Response Evaluation Criteria in Solid Tumors (RECIST)	146
Appendix 5	Description of the Modified Response Evaluation Criteria in Solid Tumors 1.1 for Immune-based Therapeutics (iRECIST) Process for Assessment of Disease Progression	147
Appendix 6	Lugano Criteria for Response Assessment in Malignant Lymphoma (Based on Cheson, 2014).....	152
Appendix 7	Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research	155
Appendix 8	Prohibited Medications and Therapies.....	158
Appendix 9	Anti-PD-(L)1 Refractory Definition.....	161
Appendix 10	Summary of Changes	162

LIST OF IN-TEXT TABLES

Table 1	Laboratory Values that Define Adequate Organ Function for Eligibility	57
Table 2	Study Treatments	63
Table 3	Anticipated Dose Levels of FLX475	64
Table 4	Dose Modification Guidelines for FLX475-Related Toxicity*	71
Table 5	Infusion Reaction Treatment Guidelines for Pembrolizumab	73
Table 6	Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab	74
Table 7	Clinical Laboratory Tests.....	100
Table 8	Schedule of Procedures/Assessments in Study FLX475-02: Part 1a: FLX475 Monotherapy Dose Escalation.....	102
Table 9	Schedule of Visits and Procedures in Study FLX475-02: Part 1b: FLX475/Pembrolizumab Combination Dose Escalation.....	106
Table 10	Schedule of Visits and Procedures in Study FLX475-02 – Part 2a: FLX475 Monotherapy Expansion Cohorts.....	110
Table 11	Schedule of Visits and Procedures in Study FLX475-02: Part 2b: FLX475/Pembrolizumab Combination Expansion Cohorts	114
Table 12	Incidence of Dose-Limiting Toxicity and the Probability of Dose Escalation.....	123
Table 13	Imaging and Treatment after First Radiologic Evidence of Progressive Disease in Subjects Receiving FLX475 and Pembrolizumab.....	151

LIST OF IN-TEXT FIGURES

Figure 1	Study Schema.....	44
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LIST OF APPENDICES

Appendix 1	Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.....	143
Appendix 2	Eastern Cooperative Oncology Group Performance Status Scale	144
Appendix 3	New York Heart Association (NYHA) Cardiac Disease Classification ..	145
Appendix 4	Response Evaluation Criteria in Solid Tumors (RECIST)	146
Appendix 5	Description of the Modified Response Evaluation Criteria in Solid Tumors 1.1 for Immune-based Therapeutics (iRECIST) Process for Assessment of Disease Progression	147
Appendix 6	Lugano Criteria for Response Assessment in Malignant Lymphoma (Based on Cheson, 2014)	152
Appendix 7	Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research	155
Appendix 8	Prohibited Medications and Therapies.....	158
Appendix 9	Anti-PD-(L)1 Refractory Definition	161
Appendix 10	Summary of Changes	162

3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADL	Activities of daily living
AEs	Adverse events
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the plasma time-concentration curve
BCG	Bacillus Calmette–Guérin
β-hCG	Beta-human chorionic gonadotropin
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CBC	Complete blood count
CBR	Clinical benefit rate (CR + PR + durable SD ≥23 weeks)
CI	Confidence interval
Cl	Clearance
CL/F	Oral clearance
CLIA	Clinical Laboratory Improvement Amendment
C _{max}	Maximum concentration
CNS	Central nervous system
CPI	Checkpoint inhibitor
CR	Complete response
CRA	Clinical research associate
CRC	Colorectal adenocarcinoma
CrCl	Creatinine clearance
CRF	Case report form
CRO	Contract research organization
CRPC	Castration-resistant prostate cancer
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Curriculum vitae
DLT	Dose-limiting toxicity
DM	Diabetes mellitus
DOR	Duration of response
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECI	Events of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EU	European Union

FDA	Food and Drug Administration
GC	Gastric cancer
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GI	Gastrointestinal
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HNSCC	Head and neck squamous cell carcinoma
ICF	Informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
iCPD	Confirmed radiographic progression
iCR	Immune-based complete response
IEC	Independent Ethics Committee
INR	International normalized ratio
iPR	Immune-based partial response
irAE	Immune-related adverse event
IRB	Institutional Review Board
iRECIST	Modified RECIST for immunotherapies
iSD	Immune-based stable disease
ITT	Intent-to-treat data set
iUPD	Immune-based unconfirmed progressive disease
IV	Intravenous
K-M	Kaplan-Meier
LDH	Lactase dehydrogenase
mAb	Monoclonal antibody(ies)
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mRECIST	Modified Response Evaluation Criteria In Solid Tumors
MRI	Magnetic resonance imaging
MRSD	Maximum recommended starting dose
MTD	Maximum tolerated dose
NA	Not applicable
NCI	National Cancer Institute
NSAID	Nonsteroidal anti-inflammatory drug
NSCLC	Non-small-cell lung cancer
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PBPK	Physiologically-based pharmacokinetics
PD	Progressive disease; pharmacodynamics
PFS	Progression-free survival

PG	Pharmacogenomics
PI	Principal investigator
PO	By mouth
PR	Partial response
PK	Pharmacokinetics
PS	Performance status
PT	Preferred term, prothrombin time
PTT	Partial thromboplastin time
Q2W	Every 2 weeks
Q3W	Every 3 weeks
QD	Once daily
RBC	Red blood cell
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SOC	System organ class
SOPs	Standard operating procedures
SUSAR	Suspected unexpected serious adverse reactions
T1DM	Type 1 diabetes mellitus
$t_{1/2}$	Terminal half-life
tbd	To be determined
TEAEs	Treatment-emergent adverse events
TEMAV	Treatment-emergent markedly abnormal laboratory values
t_{max}	Time to maximum concentration
TME	Tumor microenvironment
TNBC	Triple-negative breast cancer
TTR	Time to response
UA	Urinalysis
UC	Urothelial carcinoma
ULN	Upper limit of normal
US	United States
V _z /F	Oral volume of distribution
WBC	White blood cell
WHO DD	World Health Organization Drug Dictionary

4 ETHICS

4.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation (ICH) E6 (Good Clinical Practice), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (e.g., change in contract research associate(s) [CRAs], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the Sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (or if regionally required, the head of the medical institution) with a copy to the Sponsor before study start and the release of any study treatment to the site by the Sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the Sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or Sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the Sponsor at the time of each periodic report. The investigator(s) or the Sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the investigator and the relevant IRB via the head of the medical institution) of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

At the end of the study, the Sponsor should notify the IRB/IEC and Competent Authority within 90 days. 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 Sponsor should also provide the IRB/IEC with a summary of the study's outcome.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and Competent Authority within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

4.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the Sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions (SUSARs) will be reported, as required, to the Competent Authorities of all involved EU member states.
- Other applicable regulatory authorities' requirements or directives

4.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to the subject is read and explained to him/her, and after the subject has orally consented to the his/her participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject (or legal guardian) will be asked to sign an ICF at the Screening Visit before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the Sponsor or designee and kept on file according to local procedures at the site.

The subject should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

With regard to the biomarker assessments described in [Section 11.4.2](#), an informed consent for collection of samples during the study for gene analysis will be included in the study-specific ICF or will be prepared separately.

5 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of RAPT Therapeutics (the Sponsor) at approximately 30 investigational sites in the US and internationally.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the Sponsor and of the contract research organizations (CROs) are listed in the Investigator Study File provided to each site.

6 INTRODUCTION

6.1 Background

6.1.1 *Immunotherapy for Cancer*

6.1.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades ([Disis, 2010](#)). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8⁺ T-cells and the ratio of CD8⁺ effector T cells (T_{eff}) to FoxP3⁺ regulatory T-cells (T_{reg}) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma ([Dudley, et al., 2005](#); [Hunder, et al., 2008](#)).

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) ([Greenwald, et al., 2005](#); [Okazaki, et al., 2001](#)).

The structure of murine PD-1 has been resolved ([Zhang et al., 2004](#)). PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable-type (IgVtype) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade ([Okazaki et al., 2001](#); [Chemnitz et al., 2004](#); [Sheppard et al., 2004](#); and [Riley, 2009](#)). The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins ([Parry et al., 2005](#); [Francisco, 2010](#)). As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in advanced cancers.

6.1.1.1.1 Pre-clinical and Clinical Trials

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8⁺ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities (Hirano, 2005; Blank, 2004; Weber, 2010; Strome, 2003; Spranger, 2014; Curran, 2010; Pilon, 2010). Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma (Strome, 2003; Curran, 2010; Pilon, 2010; Nomi, 2007; Zhang, 2004). In such studies, tumor infiltration by CD8⁺ T cells and increased IFN- γ , granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T cell function *in vivo* (Curran, 2010). Experiments have confirmed the *in vivo* efficacy of anti-mouse PD-1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (see the [Keytruda Investigator's Brochure](#)).

The recent use of antibodies (known as checkpoint inhibitors, or CPIs) to block immune checkpoints such as PD-1 and CTLA-4 has resulted in meaningful anti-tumor immune responses in multiple types of cancer (Pardoll, 2012, Sharma and Allison, 2015, Shin and Ribas, 2015). However, only a minor subset of patients experiences deep and durable responses to these treatments. Because activated immune responses are naturally controlled from running unchecked and causing autoimmunity not only by these suppressive checkpoint signals, but also by immunosuppressive cells such as T_{reg} and suppressive myeloid cells, more effective anti-tumor immunotherapy treatments may also need to address the accumulation of T_{reg} in and around tumors which can inhibit cytotoxic (effector) T-cells (T_{eff}) from killing tumor cells (Fridman, et al., 2017).

T_{reg} are recruited into tumors by small secreted protein signals called chemokines – specifically C-C motif chemokine ligand 17 (CCL17, or Thymus and activation-regulated chemokine) and C-C motif chemokine ligand 22 (CCL22, macrophage-derived chemokine) – produced by tumor cells and other cells in the tumor microenvironment (TME). These chemokines serve as a “homing signal” to T_{reg} by binding to their cognate receptor, C-C-chemokine receptor type 4 (CCR4), which is expressed on nearly all human T_{reg} (Curiel, et al., 2004, Li, et al., 2013). Thus, specifically blocking the CCR4 mediated “homing signal” from tumors to T_{reg} could prevent the accumulation of these immunosuppressive cells and enable the immune system to elicit a more robust anti-tumor response, particularly when combined with other immune modulating agents such as CPIs.

6.1.2 Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical *in vitro* data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for

advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the [Investigator's Brochure](#).

6.1.3 FLX475

FLX475, also known as F003475, is an orally available, potent and selective small-molecule antagonist of CCR4. In preclinical models of cancer, it has been shown to inhibit the recruitment of T_{reg} into tumors, and to improve tumor control and eradication in combination with CPIs.

6.1.3.1 Preclinical Experience with FLX475

6.1.3.1.1 Non-clinical Pharmacology

FLX475 potently inhibits CCL22- and CCL17-induced CCR4-mediated chemotaxis with excellent selectivity over other chemokine receptors. Daily oral dosing of FLX475 (10 mg/kg) in preclinical models reduced migration of T_{reg} to subcutaneous Pan02 tumors in mice by over 75%. The tumors had a corresponding 3-fold increase in numbers of activated CD8⁺ T cells. In the CT26 syngeneic subcutaneous mouse tumor model, FLX475 (10 mg/kg PO) or an antagonistic anti-PD-L1 antibody had minimal tumor growth inhibition when used alone. However, median survival was greater with the combination of FLX475 and anti-PD-L1 compared to anti-PD-L1 alone (40.5 days vs 26.5 days, respectively). Additionally, FLX475 enhanced the efficacy of an agonistic anti-CD137 antibody. Treatment of animals with anti-CD137 alone resulted in 4 out of 10 tumor-free animals, whereas FLX475 combined with anti-CD137 resulted in 7 out of 10 tumor-free animals. In the EMT6 breast tumor model, FLX475 (10 mg/kg PO) enhanced the tumor growth inhibition of anti-CTLA-4 antibody treatment resulting in delayed tumor growth. The combination of anti-CTLA-4 treatment and FLX475 resulted in 3 of 10 tumor free animals compared to 0 of 10 tumor free animals treated with anti-CTLA-4 alone. Taken together, these data suggest that FLX475 may inhibit recruitment of T_{reg} to tumors and augment the immune response in tumors. Furthermore, FLX475 may enhance the therapeutic efficacy of immune checkpoint inhibitors or other immune modulating agents. For more details on non-clinical studies, refer to the FLX475 Investigator's Brochure.

Consistent with the observation that CCR4 is not associated with any immune activation pathways, FLX475 did not stimulate secretion of cytokines (IFN- γ , TNF- α , IL-2, IL-6, IL-4, or IL-10) from PBMC in vitro at doses up to 5 μ M.

6.1.3.1.2 Preclinical Pharmacokinetics

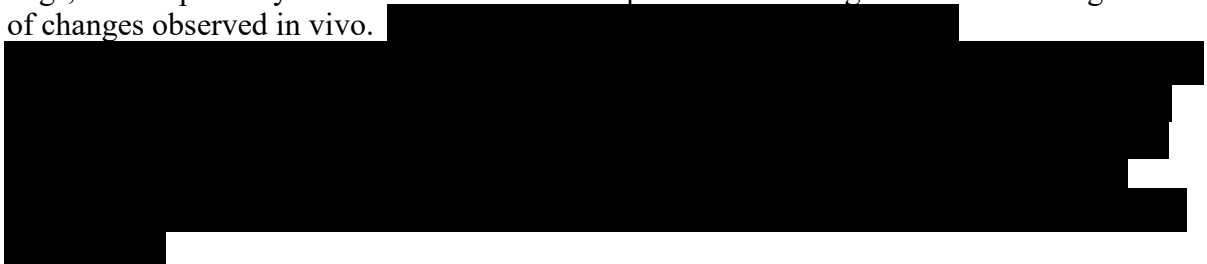
FLX475 has been given orally and intravenously to mice, rats, dogs, and monkeys and was absorbed and bioavailable in all species tested. Following single and repeated doses in mice and dogs, exposure is similar in males and females. Exposure (C_{max} and AUC₀₋₂₄), increases with the increase in dose level in both species and there is a small degree of accumulation (~2 fold) with repeated dosing.

CYP3A4 is likely responsible for the metabolism of FLX475. Metabolites present in human hepatocyte incubations were also detected in the incubation of at least one of the species used for toxicity assessment (mouse or dog).

FLX475 showed no significant competitive or time-dependent inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6 or CYP3A4, nor induction of CYP1A2, CYP2B6, or CYP3A4 mRNA. Thus, at clinically relevant doses and exposures in humans, FLX475 is unlikely to inhibit or induce the activity of the major drug-metabolizing CYP450 enzymes. Based on its low efflux ratio (1.3) in a Caco-2 cell assay, FLX475 is unlikely to be affected by inhibitors of drug transporters such as P-gp and BCRP.

6.1.3.1.3 Preclinical Toxicology

The non-clinical toxicology program in support of FLX475 included both in vivo and in vitro evaluations, consisting of a core battery of safety pharmacology, genotoxicity, and repeat-dose toxicity studies with a treatment duration of up to 4 weeks. The in vivo studies were conducted in mice and dogs administered FLX475 via daily oral dosing, the intended frequency and route of administration in humans. FLX475 was not genotoxic in Ames and chromosome aberration tests in vitro. Minimal QTc prolongation (< 10%) was noted in dogs, but the proarrhythmic risk in humans is expected to be low given the small magnitude of changes observed in vivo.



In the 4-week dog study, the no-observed-adverse-effect level (NOAEL) was 5 mg/kg/day and highest non-severely toxic dose (HNSTD) was 15 mg/kg/day. In the 4-week mouse study, the NOAEL was 10 mg/kg/day and severely toxic dose was at least 60 mg/kg/day. The results from these studies support a proposed starting dose of 25 mg FLX475 in oncology patients.

6.1.3.2 Clinical Experience with FLX475

6.1.3.2.1 Phase 1 Healthy Volunteer Study

FLX475 has been studied in a Phase 1, first-in-human, randomized, double-blind, placebo-controlled trial in the Netherlands examining the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of both single and repeat dosing of FLX475 in healthy volunteers (van Marle, 2018). Seven cohorts of 8 subjects each (6 drug, 2 placebo) were administered single doses ranging from 5 mg to 1000 mg. Six cohorts were administered daily doses of FLX475 for 14 days ranging from 25 mg to 150 mg, including two cohorts evaluating a 300 mg loading dose administered on Day 1.

FLX475 was well-tolerated, with no significant laboratory abnormalities or dose-limiting clinical adverse events. Dose-dependent increases in exposure were observed with low peak-to-trough ratios and a half-life of approximately 72 hours. [REDACTED]

[REDACTED] A receptor occupancy (RO) PD assay using study subject peripheral blood T_{reg} demonstrated a tight PK/PD relationship, suggesting that doses of approximately 75 mg PO QD and above are sufficient to maintain target drug exposure above the IC_{90} for human in vitro T_{reg} migration.

6.1.4 *Dose Rationale for Combination Therapy*

6.1.4.1 FLX475

[REDACTED] The similarity of concentrations of FLX475 needed for in vitro and in vivo activity in mouse models provides the rationale for using human in vitro data to guide human target exposure.

[REDACTED]

Based on the PK data obtained in healthy volunteers, FLX475 administered at doses of 75 mg PO QD or greater are predicted to achieve C_{trough} levels of drug above the human exposure target for clinical efficacy. Given the approximately 72-hour half-life of FLX475 observed, it may take up to approximately two weeks of continuous daily dosing to reach steady state. Therefore, a loading dose regimen that could minimize the time needed to reach the target exposure range (e.g. 300 mg single dose on Cycle 1 Day 1, followed by a maintenance dose of 100 mg PO QD starting from Day 2 onward) may be evaluated in this study.

6.1.4.2 Pembrolizumab

The planned dose of pembrolizumab (Keytruda®) for this study is 200 mg every 3 weeks (Q3W), which is the currently approved dosage for treatment of advanced cancer. Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all cancer indications, regardless of tumor type. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Refer to the approved labeling and Investigator's Brochure for more details on Keytruda® (pembrolizumab, MK-3475) ([Keytruda Investigator's Brochure](#)).

6.2 Risk-Benefit Assessment

FLX475, also known as F003475, is an orally-available, potent, and selective small molecule antagonist of CCR4. In preclinical models of cancer, it has been shown to inhibit the recruitment of T_{reg} into tumors, and to improve tumor control and eradication in combination with CPIs. Refer to the FLX475 Investigator's Brochure for details.

[REDACTED]

At the time of study initiation, the clinical experience of FLX475 in humans was limited to a first-in-human study with seven SAD cohorts (single doses of 5, 25, 75, 200, 400, 750, and 1000 mg) of 8 subjects each (6 drug, 2 placebo) and six MAD cohorts administered daily

doses of FLX475 for 14 days ranging from 25 mg to 150 mg, including two cohorts evaluating a 300 mg loading dose administered on Day 1. No significant safety findings have been observed (refer to [Section 6.1.3.2.1](#) and the current [FLX475 Investigator's Brochure](#)) that would alter the risk-benefit profile of this proposed Phase 1/2 study testing both FLX475 monotherapy and combination therapy with pembrolizumab in subjects with advanced cancer.

Because the proposed mechanism of action of FLX475 is the specific CCR4-mediated inhibition of recruitment of T_{reg} into tumors, and not a global inhibition or depletion of T_{reg} activity, it is not expected that FLX475 will result in significant autoimmunity or generalized immune activation. Consistent with this hypothesis, no clinical or histopathologic signs of cytokine release, autoimmunity, or inflammation were observed in non-clinical studies or in healthy volunteers to date. The safety profile of pembrolizumab has been well described, and does include immune-mediated toxicity ([Keytruda Investigator's Brochure](#)). Based on its proposed mechanism of action, FLX475 is not expected to significantly enhance immune-mediated toxicity when administered with pembrolizumab. However, signs and symptoms of immune-mediated toxicity (e.g., autoimmunity) will be closely monitored in the clinic and appropriate supportive care measures will be administered as indicated.

6.3 Study Rationale

This Phase 1/2 study will evaluate safety, PK, pharmacodynamics (PD), in addition to potential changes in the TME and possible clinical efficacy of FLX475 as monotherapy and in combination with pembrolizumab in subjects with advanced cancer. The tumor types included in this study are those that have been associated with higher levels of T_{reg}, T_{eff}, and CCR4 ligand gene expression, suggesting that they may have a higher likelihood of responding to CCR4 antagonism ([Okal et al, 2017](#)).

The primary hypothesis of this study is that ≥ 1 dose level of FLX475 in repeated oral administrations will achieve an acceptable safety, tolerability, and PK profile in subjects with advanced cancer, both as monotherapy and in combination with pembrolizumab. In addition, it is hypothesized that FLX475 administration may block the CCR4-mediated recruitment of T_{reg} into tumors, thus increasing the intratumoral T_{eff}:T_{reg} ratio and favoring an antitumor immune response either when given as monotherapy, or in combination with pembrolizumab. The study design will permit selection of a recommended Phase 2 dose (RP2D) for each regimen in Parts 1a and 1b. In Parts 2a and 2b, the hypothesis addressed is that the RP2D of FLX475 as monotherapy or in combination with pembrolizumab will show evidence of anti-tumor activity, reductions in the intratumoral T_{reg}:T_{eff} ratio, or both.

In addition, it is also possible that the sequence of dosing may be important in optimizing the efficacy of the combination of FLX475 and pembrolizumab. For example, administering FLX475 as monotherapy for several weeks to modulate or decrease the immunosuppressive effects of T_{reg} prior to administering pembrolizumab could potentially allow for improved efficacy over co-administration of both drugs starting together. To test this, lead-in dosing (ie. FLX475 administered as monotherapy for one 3-week cycle before pembrolizumab started with Cycle 2) may be tested in one or more cohorts in Part 2b. If evidence is obtained suggesting that lead-in dosing may be superior in efficacy than standard concurrent dosing of

FLX475/pembrolizumab, other/all combination cohorts in Part 2b may be transitioned over to using lead-in dosing.

7 STUDY OBJECTIVES

7.1 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

7.2 Secondary Objectives

The secondary objectives of this study are:

- To define the maximum tolerated dose (MTD) and/or 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

8 INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan

This clinical trial 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 at approximately 30 sites in the United States (US) and internationally (potentially including, but not limited to, Australia, South Korea, Thailand, Taiwan, and Hong Kong).

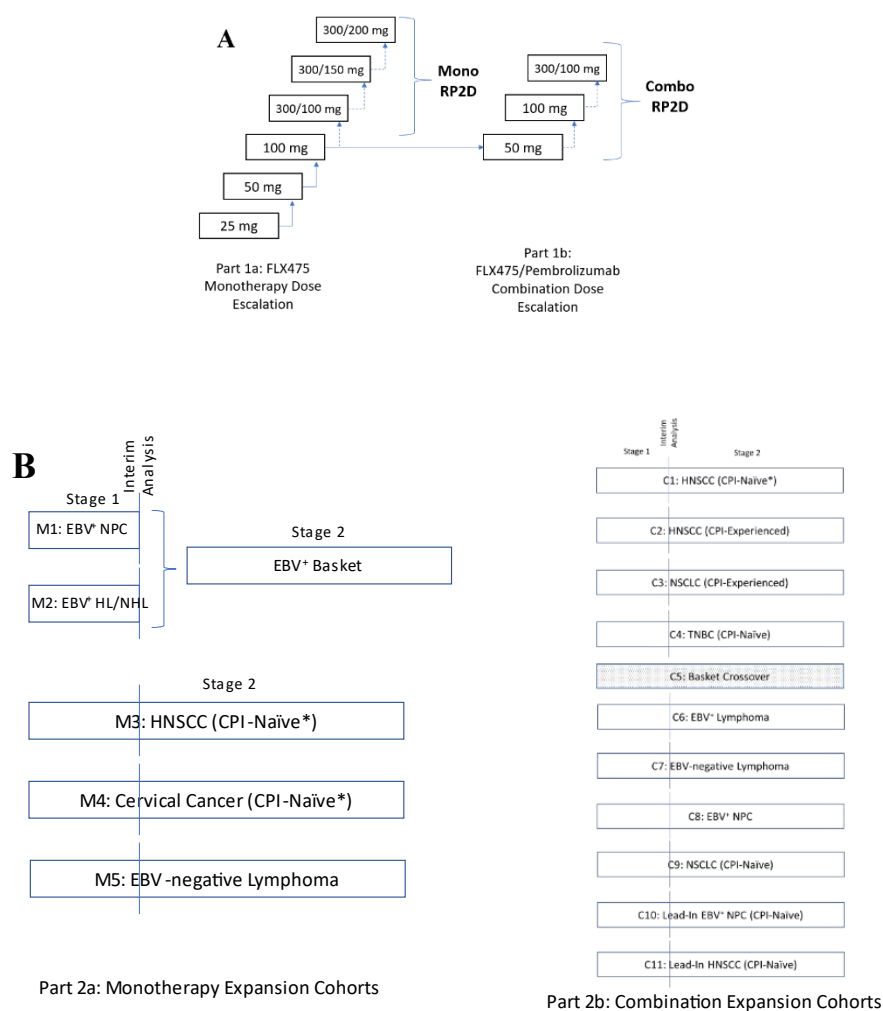
For each subject, the study consists of the following: screening period, treatment phase, and long-term follow-up:

- 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) as described in detail below. 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, up to 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); at least 19 additional subjects may be enrolled per cohort in Stage 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 for response.

Figure 1 Study Schema



A) Parts 1a and 1b: Dose Escalation; B) Parts 2a and 2b: Expansion Cohorts

3+3 design will be used for dose escalation with a 21-day DLT observation period. Pembrolizumab dose will be 200 mg IV Q3W. Intrasybect dose escalation will be permitted during dose escalation as per [Section 10.2.1.2](#). Crossover from monotherapy to combination therapy may be permitted as noted below. (Cohort C5 is a basket combination therapy cohort designated for eligible subjects who crossover from monotherapy expansion cohorts M1-M4. Note that as C5 is only 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. Enrollment to Stage 1 of Cohort C1 will only begin after Stage 1 enrollment has been completed in Cohort M3.

In addition to Cohorts C10 and C11 testing lead-in dosing in CPI-naïve EBV+ NPC and HNSCC, respectively, Cohorts C12 (CPI-experienced HNSCC) and C13 (CPI-naïve NSCLC) may also be enrolled to test lead-in dosing, depending upon Stage 1 results from C10 and C11.

X/Y = X mg PO Cycle 1 Day 1 loading dose, followed by Y mg PO QD maintenance dose starting Cycle 1 Day 2

RP2D = recommended Phase 2 dose, EBV+ = Epstein-Barr Virus positive, NPC = nasopharyngeal cancer, HL/NHL = Hodgkin lymphoma/Non-Hodgkin lymphoma, HNSCC = head & neck squamous cell carcinoma, CPI = checkpoint inhibitor, TNBC = triple-negative breast cancer, NSCLC = non-small cell lung cancer

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

This portion of the study will evaluate the safety and pharmacology of a range of FLX475 doses in subjects with designated types of advanced cancer. The MTD will be based on the occurrence of dose-limiting toxicity (DLT). The RP2D will be selected based on safety, PK, PD and efficacy findings, and may be determined prior to establishing an MTD.

In Part 1a, cohorts of subjects will be sequentially enrolled at progressively higher dose levels of FLX475 given as a single agent. Dose escalation will be performed with cohort sizes of at least 3 to 6 subjects using a standard 3+3 design.

In Part 1b, cohorts of subjects will be sequentially enrolled at progressively higher dose levels of FLX475 in combination with standard doses of pembrolizumab (200 mg Q3W). Once a full cohort of at least 3 subjects in the designated Part 1a monotherapy dose-escalation cohort (e.g. 100 mg) has completed 3 weeks of treatment (Cycle 1 in the DLT Observation Period) with no more than 0/3 or 1/6 DLTs, dose escalation in the combination-therapy cohort will begin with the previously-cleared dose of FLX475 (e.g., 50 mg). Combination dose escalation will proceed in parallel with, but staggered behind, dose escalation of FLX475 alone in Part 1a, and will also be performed with cohort sizes of at least 3 to 6 subjects using a standard 3+3 design, with a minimum of 10 subjects needed to determine a combination RP2D.

In both Parts 1a and 1b, dose escalation will proceed to the MTD (unless a RP2D is selected prior to establishing an MTD), defined as the highest tested dose level at which ≥ 6 subjects have been treated and which is associated with DLT during the first 3 weeks of treatment (the DLT Observation Period) in fewer than 33% of the subjects at that dose level. For Part 1b, at least 10 subjects should be evaluated at a dose level of FLX475 used in combination with pembrolizumab in order to designate it as the RP2D prior to initiation of Part 2b expansion cohorts. Additional higher dose escalation cohorts may be enrolled beyond those listed only if an MTD has not yet been reached and PK, PD, and safety data to date support exploring higher doses.

The RP2D for Parts 2a and 2b of the study will be selected based on safety, PK, PD and efficacy findings established in Parts 1a and 1b, respectively. The RP2D for single-agent FLX475 in Part 2a or combination therapy with FLX475-pembrolizumab in Part 2b will be a dose level at or below any MTD determined in Part 1a and Part 1b, respectively.

In addition, at least one dose escalation cohort in Parts 1a and 1b may test a loading dose of FLX475 to be given on Cycle 1 Day 1 followed by a lower daily maintenance dose. The

goal of using a loading dose will be to achieve steady-state drug levels earlier than if a loading dose is not used.

If 6 subjects at 9 dose levels are evaluated, as many as 54 subjects could be enrolled. To allow for the possibility that some subjects may not be fully evaluable for DLT, approximately 65 subjects may be enrolled. In addition, more than 3 to 6 subjects per cohort may be enrolled to collect additional safety data or to enroll subjects able to provide tumor biopsies before and during/after study treatment.

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 responses (CR) in the first 10 subjects) is observed in the first stage of enrollment. Note that either of the EBV⁺ indications that pass Stage 1 may be combined into a single Stage 2 EBV⁺ basket expansion.

If 13 expansion cohorts are fully accrued, as many as 377 subjects could be enrolled in Part 2 of the study. In addition, more than 29 subjects per cohort may be enrolled to collect additional safety data or to enroll subjects able to provide tumor biopsies before and during/after study treatment. 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. Accrual to specific expansion cohorts may also be discontinued prior to completing either Stage 1 or Stage 2 of enrollment, for reasons including, but not limited to, unacceptable safety, slow/insufficient enrollment, or changes in standard clinical practice.

- **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 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)

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

- **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 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]

Intrasubject Dose Escalation and Crossover

To maximize the collection of information at relevant doses and to minimize the exposure of subjects to potentially suboptimal doses, intrasubject dose escalation may be permitted in subjects enrolled in Parts 1a and 1b of the study as described in [Section 10.2.1.2](#).

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) if they meet all the following criteria: (1) documented disease progression (PD) during treatment with FLX475 monotherapy after completion of at least 3 cycles of monotherapy, (2) no occurrence of DLT related to FLX475, (3) meet all inclusion and exclusion criteria for eligibility, (4) judged by the investigator, in consultation with the Sponsor medical monitor, to be in the subject's best interest to re-enroll to a combination-therapy cohort, and (5) applicable cohort is open for enrollment. 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.

Potential crossover subjects will need to meet all screening entry criteria for combination cohort subjects (except QTcF values up to and including Grade 1 prolongation are acceptable if already receiving FLX475, and screening and on-study tumor biopsies for crossover subjects are optional). Assessments listed for combination therapy treatment should be obtained as noted in the corresponding Schedule of Visits and Procedures ([Table 9](#) and [Table 11](#)). Previously obtained lab and ECG results may be used for screening if obtained within the 21-day screening window for C1D1 of combination crossover (28 days for imaging).

8.2 Study Phases

8.2.1 *Pretreatment Phase*

The Pretreatment Phase will last no longer than 21 days and will include a Screening Period to establish protocol eligibility and disease characteristics and Baseline to confirm eligibility and establish disease characteristics prior to cohort assignment and treatment. See the Schedules of Assessments in [Table 8](#) through [Table 11](#) for complete details.

Screening Period

Screening will occur from Day -21 to Day -1. The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Repeated laboratory evaluation to establish eligibility is not allowed unless discussed and agreed upon with the Sponsor. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in [Section 4.3](#).

If the subject is eligible to participate in the study, the appropriate electronic case report form (eCRF) page must be completed. Procedures to be followed when obtaining both approval to screen a subject and approval to enroll a subject after screening are detailed in [Section 11](#).

Baseline Period

Baseline assessments must be performed on Cycle 1 Day 1 prior to administration of the first dose of study drug(s).

Subjects who complete the baseline assessments and meet all of the criteria for inclusion/exclusion ([Sections 9.1](#) and [9.2](#)) will begin the Treatment Phase.

8.2.2 *Treatment Phase*

The Treatment Period for each subject will begin at the start of dosing and will end with the completion of the End-of-Treatment Visit, which will occur within 90 days after the final dose of study treatment.

The following conditions apply:

- Subjects will receive study treatment with FLX475 or FLX475 and pembrolizumab as continuous 3-week (21-day) cycles. Treatment cycles will be counted continuously regardless of dose interruptions. Subjects will undergo safety and efficacy assessments as defined in the Schedule of Procedures/Assessments ([Table 8](#) through [Table 11](#)). Subjects will continue to receive study treatment for a maximum of 2 years (35 cycles) or until subject withdrawal from the study, confirmed progression of cancer, intolerable study treatment-related toxicity despite appropriate dose modification and supportive treatment, the development of intercurrent illness that precludes continued study treatment, pregnancy or breastfeeding, substantial noncompliance with study procedures, loss to follow-up, or study termination by the Sponsor, whichever occurs first.
- Subjects in a combination-therapy cohort who discontinue pembrolizumab due to toxicity may continue treatment with FLX475 alone only if it is determined to be in the subjects' best interest and upon agreement with the Sponsor medical monitor.
- Subjects in a combination-therapy cohort who discontinue FLX475 due to toxicity may continue treatment with pembrolizumab alone only if it is determined to be in the subjects' best interest and upon agreement with the Sponsor medical monitor.
- Discontinuation of treatment may be considered for those subjects who fulfill all of the following criteria: attain a confirmed CR, have been treated for at least 8 cycles (≥ 24 weeks) with pembrolizumab, and have received at least 2 infusions of pembrolizumab and at least 80% of the planned doses of FLX475 beyond the date when the initial CR is declared. In the presence of clinical benefit, subjects who complete treatment with pembrolizumab may continue to receive FLX475 alone after this time point if it is determined to be in the subject's best interest by the investigator in consultation with the Sponsor.

For subjects who have radiological PD by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 as determined by the investigator, the investigator will decide whether the subject can continue to receive study treatment until repeat, confirmatory imaging is obtained using modified RECIST for immunotherapies (iRECIST) for subject management (see [Appendix 5](#) for details). The investigator's decision is based on the subject's overall clinical condition. Lugano criteria will be used for subjects with lymphoma (see [Appendix 6](#) for details) other than those with CTCL, for which alternative criteria should be used ([Olsen et al., 2011](#)).

8.2.3 Follow-Up Phase

Unless they withdraw consent or are lost to follow-up, subjects who discontinue study treatment will be followed for acquisition of safety information for 90 days after the final dose of study treatment (or 30 days following cessation of study treatment if the subject initiates new anticancer therapy, whichever occurs first). Subjects will also be followed for long-term collection of information regarding further therapies for cancer and overall survival (OS).

If a subject discontinues study treatment and does not consent to continued follow-up, the investigator must not access confidential records that require the subject's consent. However, an investigator may consult public records to establish survival status, as well as for OS (until death or loss to follow-up).

During the Follow-up Phase, subjects will be treated by the investigator according to the prevailing local standard of care. Subjects will be followed at approximately 3- to 6-month intervals for survival and all subsequent anticancer treatments received. Long-term follow-up information will be collected during routine clinic visits, other study site contact with the subjects, or via telephone or e-mail with the subject/caregiver or referring physician's office. These data will be collected in the source documents (e.g., subject medical record) and recorded onto a specific eCRF. The information will be recorded unless not permitted because of confidentiality. The Sponsor may choose to discontinue survival follow-up following completion of the primary study analysis when appropriate, e.g., when only a minimal number of subjects remain in follow up.

If a subject becomes unavailable for follow-up (e.g., misses scheduled assessment, telephone contact), the investigator or designee will make every attempt to contact the subject to determine his or her status. All attempts at contact will be recorded in the subject's medical notes. A subject may be considered lost to follow-up after a minimum of two attempts to contact the subject (e.g. by email or telephone) have been unsuccessful.

All subjects who discontinue study treatment prior to PD will undergo tumor imaging at the time of treatment discontinuation ($\pm$ 4-week window). If previous tumor imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. For subjects who discontinue study treatment without documented PD, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used during study treatment (every 6 weeks $\pm$ 1 week in Year 1 or every 9 weeks $\pm$ 1 week in Year 2) until the start of a new anticancer treatment, PD, pregnancy, death, withdrawal of consent, loss to follow-up, or termination of the study, whichever occurs first.

For subjects who discontinue study treatment due to documented PD, no tumor imaging is required during follow-up if the investigator elects not to implement iRECIST.

8.3 Discussion of Study Design

This multicenter, nonrandomized, single arm, open-label, Phase 1/2 study was designed to evaluate the safety and activity of FLX475 alone and in combination with pembrolizumab in subjects with previously treated advanced solid tumors. The Part 1 portion of the study utilizes a 3+3 dose escalation design, commonly used in early phase drug testing to determine the MTD and RP2D, while limiting exposure to toxic doses. The dose escalation cohorts will be staggered such that only one cohort will be open to enrollment at a time. The 2-stage Simon design planned for Part 2 is an efficient method commonly used in oncology trials to identify anti-tumor activity and establish the level of response to an oncology agent, while minimizing exposure to a potentially ineffective therapy treatments will be open-label, since the dosage and administration of FLX475 must be carefully monitored and is different

between FLX475 and pembrolizumab. Pembrolizumab will be used as a comedication, since it is an approved checkpoint inhibitor with activity in patients with advanced solid tumors.

9 STUDY POPULATION

The target population comprises adult subjects with adequate performance status and organ function who have advanced cancer and have experienced failure of prior therapy or have experienced disease relapse after prior therapy or are ineligible for standard therapy and have no curative treatment options. The tumor types included in this study are those that have been associated with higher levels of T_{reg}, T_{eff}, and CCR4 ligand gene expression, suggesting that they may have a higher likelihood of responding to CCR4 antagonism (Okal et al, 2017).

9.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible to receive study treatment:

1. All subjects must have histologically or cytologically confirmed, advanced or metastatic tumors and (1) have disease progression after treatment with other available therapies for advanced or metastatic disease that are known to confer clinical benefit or (2) do not tolerate or refuse standard treatment(s). (Cohort C9 may include previously untreated subjects if recommended by the treating physician and agreed to by Sponsor.)
2. Subject must have one of the following diagnoses to be eligible for enrollment into a dose escalation cohort (Parts 1a and 1b), or otherwise have pre-approval from the Sponsor medical monitor for any diagnoses not listed below:
 - a. Stage IIIB/IV squamous or non-squamous non-small cell lung carcinoma (NSCLC)
 - b. Recurrent or metastatic head and neck squamous cell carcinoma (HNSCC; specifically of the oral cavity, oropharynx, hypopharynx, or larynx; and nasopharyngeal carcinoma)
 - c. Metastatic triple-negative breast cancer
 - d. Locally advanced or metastatic urothelial carcinoma (UC)
 - e. Locally advanced, recurrent, or metastatic gastric cancer (GC)
 - f. Locally advanced, recurrent, or metastatic esophageal or esophagogastric junction cancer
 - g. Recurrent or metastatic cervical squamous cell carcinoma or endocervical adenocarcinoma
 - h. Metastatic melanoma
 - i. Recurrent EBV+ classical Hodgkin lymphoma
3. Subject must have one of the following diagnoses to be eligible for enrollment into a corresponding expansion cohort (Parts 2a and 2b):

Part 2a

- Cohorts M1-M2 (FLX475 Monotherapy): Subjects with a documented Epstein-Barr virus positive (EBV⁺) malignancy (as determined by standard methods, e.g. EBER ISH or LMP-1 IHC) 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 will be combined into a single Stage 2 EBV⁺ basket expansion of up to 19 additional subjects, 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 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)
 - M5: EBV-negative lymphoma ineligible for standard therapy (specific subtypes permitted will be communicated by the Sponsor based upon available data) (N = 10-29)

Part 2b

- 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 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]
4. Men and women ≥ 18 years of age on day of signing informed consent.
 5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 or 1 (Subjects with stable ECOG PS of 2 due to a non-cancer-related condition may be permitted with the approval of the medical monitor.)

6. Evaluable disease (i.e., by imaging and/or tumor markers) at baseline for dose escalation (Parts 1a and 1b). For expansion cohorts (Parts 2a and 2b), subjects must have at least one measurable lesion at baseline by computed tomography (CT) or magnetic resonance imaging (MRI) per Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions. Liver metastases of eligible tumor types are permitted.

Note: Subjects with lymphoma in the expansion cohorts should have measurable disease, defined as at least 1 lesion that can be accurately measured in at least 2 dimensions with spiral CT scan (Cheson, et al., 2014). The minimum measurement must be > 15 mm in the longest diameter.

7. Subjects with brain metastases that improve or are stable upon repeat MRI after at least 4 weeks after radiation therapy (and who are not receiving steroids) are permitted.
8. Subjects who enroll and are treated in Parts 1a or 2a of this study (FLX475 monotherapy dose escalation or expansion cohorts), and who complete at least three 3-week cycles of study treatment including the first response assessment, but who have documented PD and discontinue study treatment without significant treatment-related toxicity, may be eligible to crossover to receive combination therapy, provided an appropriate combination-therapy cohort is open to enrollment, they otherwise meet selection criteria, and it is determined by the investigator, in consultation with the Sponsor's medical monitor, to be in the subjects' best interest to receive combination therapy. Subjects in Part 1a (monotherapy dose escalation) could potentially crossover to an available Part 1b (combination dose escalation) cohort, while subjects in Part 2a (monotherapy expansion) could potentially crossover to a basket combination therapy cohort (C5).
9. Considered by the investigator to be an appropriate candidate for a Phase 1 clinical study, with a life expectancy of ≥ 12 weeks
10. All acute toxic effects of any prior therapy have resolved to Grade 0 or 1 or to baseline level before the start of study treatment (except that up to Grade 2 alopecia, neurotoxicity, and bone marrow abnormalities, as well as endocrine insufficiency managed with replacement therapy, may be permitted with Sponsor agreement).
11. Adequate organ function as defined in [Table 1](#). Specimens must be collected within 21 days prior to the start of study treatment.

Table 1 Laboratory Values that Define Adequate Organ Function for Eligibility

System	Laboratory Value
Hematology	
Absolute neutrophil count (ANC)	$\geq 1500/\mu\text{L}^c$
Platelets	$\geq 100\,000/\mu\text{L}^c$
Hemoglobin	$\geq 9.0\text{ g/dL}$ or $\geq 5.6\text{ mmol/L}^{a,c}$
Renal	
Creatinine OR Measured or calculated ^b creatinine clearance (GFR can also be used in place of creatinine or CrCl)	$\leq 1.5 \times \text{ULN}$ OR $\geq 30\text{ mL/min}$ for subjects with creatinine levels $> 1.5 \times \text{institutional ULN}$
Hepatic	
Total bilirubin	$\leq 1.5 \times \text{ULN}$ OR direct bilirubin $\leq \text{ULN}$ for subjects with total bilirubin levels $> 1.5 \times \text{ULN}$
AST (SGOT) and ALT (SGPT)	$\leq 2.5 \times \text{ULN}$ ($\leq 5 \times \text{ULN}$ for subjects with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT) OR partial thromboplastin time (PTT)	$\leq 1.5 \times \text{ULN}$ unless subject is receiving anticoagulant therapy, as long as PT or aPTT/PTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase), AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GFR = glomerular filtration rate, ULN = upper limit of normal.

^a Criteria must be met without erythropoietin dependency.

^b Creatinine clearance (CrCl) should be calculated per institutional standard.

^c The following hematologic laboratory value parameters for eligibility should be used in Parts 2a and 2b (Phase 2 expansion cohorts) due to no significant effects on hematologic parameters being observed in Parts 1a and 1b: ANC $\geq 1000/\mu\text{L}$, hemoglobin $\geq 8.0\text{ g/dL}$ (transfusions permitted), and platelets $\geq 75,000/\mu\text{L}$ (or $\geq 50,000/\mu\text{L}$ in subjects with lymphoma and/or bone marrow involvement).

12. Subjects enrolled must be willing and able to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion not previously irradiated (unless subsequent progression demonstrated; minimum of 3 cores). Subjects in dose escalation for whom newly obtained pretreatment samples (i.e. tumor biopsies obtained at baseline screening, prior to initiation of study treatment) cannot be provided (e.g., inaccessible or subject safety concern) may submit an archived specimen only upon agreement from the Sponsor (not applicable for Part 2 expansion cohorts). Formalin-fixed, paraffin-embedded tissue blocks are preferred to slides for those escalation subjects who have been given prior approval by Sponsor (not applicable for Part 2 expansion cohorts). In addition, subjects must be willing to provide a tumor biopsy (minimum of 3 cores) while on treatment at Cycle 3 Day 1 (± 7 days) (or Cycle 2 Day 1 ± 3 days for subjects in lead-in cohorts such as C10-13) and may be asked to provide additional biopsies at other timepoints such as the time of discontinuation due to progression.

Notes: If submitting unstained cut slides (only after prior approval by Sponsor), newly cut slides should be submitted to the testing laboratory within 14 days from the date that slides are cut. Details pertaining to tumor tissue submission can be found in the Laboratory Manual.

Subjects with lymphoma should be able to provide a core or excisional lymph node biopsy for biomarker analysis at screening as above.

13. For women of childbearing potential, negative results on a serum pregnancy test prior to starting study treatment.
14. For women of childbearing potential, willingness to use an effective method of contraception (e.g., oral contraceptives, double-barrier methods such as a condom and a diaphragm, intrauterine device) during the study and for 120 days following the final dose of study treatment or to abstain from sexual intercourse for this period of time.

Note: A female subject is considered to be of childbearing potential unless she has had a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy; has medically documented ovarian failure (with serum estradiol and follicle-stimulating hormone levels within the institutional postmenopausal range and a negative result on serum or urine beta-human chorionic gonadotropin [β -HCG]) pregnancy test, or is postmenopausal (age ≥ 55 years with amenorrhea for ≥ 6 months).

15. For male subjects of childbearing potential having intercourse with females of childbearing potential, willingness to abstain from heterosexual intercourse or use of a protocol-recommended method of contraception (e.g., partner use of oral contraceptives or an intrauterine device, or double-barrier methods such as a condom and a diaphragm) from the start of study treatment to 120 days following the final dose of study treatment and to refrain from sperm donation from the start of study treatment to 120 days following the final dose of study treatment.

Note: A male subject is considered able to father a child unless he has had a bilateral vasectomy or a bilateral orchiectomy with confirmed azoospermia or has ongoing medical testicular suppression.

16. Ability to swallow tablets without difficulty
17. Willingness to comply with scheduled visits, drug administration plan, protocol-specified tumor biopsies, laboratory tests, other study procedures, and study restrictions.

Note: Psychological, social, familial, or geographical factors that might preclude adequate study participation should be considered.

18. Signed ICF by the subject or his/her legal guardian indicating that the subject is aware of the neoplastic nature of the disease and has been informed of and understands the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, possible side effects, potential risks and discomforts, and other pertinent aspects of study participation.

9.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria will not be eligible to receive study treatment:

1. History of known antidrug antibodies or severe allergic, anaphylactic, or other infusion-related reaction to a previous biologic agent (for subjects to be treated with pembrolizumab). Related reaction to a previous biologic agent (for subjects to be treated with pembrolizumab).
2. History of severe hypersensitivity ($\geq$ Grade 3) to pembrolizumab and/or any of its excipients (for subjects to be treated with pembrolizumab)
3. In subjects who received prior therapy with an anti-PD-1, anti-PD-L1, or anti PD-L2 agent or an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX-40, CD137), any history of discontinuing prior treatment due to Grade 3–4 immune-related adverse events (irAEs).
4. Has received prior systemic anticancer therapy including investigational agents within 4 weeks (or < 5 half-lives for investigational/noncytotoxic agents, whichever is shorter) prior to first dose of study treatment.
5. Any active autoimmune disease or documented history of serious autoimmune disease within the past 2 years requiring systemic therapy (i.e., with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
6. History of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, idiopathic pneumonitis, (non-infectious) pneumonitis that required steroids, or clinical symptoms of active pneumonitis.
7. Known carcinomatous meningitis and/or active central nervous system (CNS) metastasis. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e., without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable, and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.
8. History of another malignancy that has progressed or has required active treatment within the past 2 years except for the following: adequately treated local basal cell or squamous cell carcinoma of the skin; in situ cervical carcinoma; adequately treated papillary, noninvasive bladder cancer; asymptomatic prostate cancer without known metastatic disease and not requiring therapy or requiring only hormonal therapy, and with normal prostate specific antigen for ≥ 1 year prior to start of study treatment; other adequately treated Stage 1 or 2 cancers currently in complete remission, or any other cancer that has been in complete remission for ≥ 2 years.
9. Significant cardiovascular disease, including myocardial infarction, arterial thromboembolism, or cerebrovascular thromboembolism within 6 months prior to start of study treatment, symptomatic dysrhythmias or unstable dysrhythmias requiring medical

therapy, angina requiring therapy, symptomatic peripheral vascular disease, clinically significant history of syncope, New York Heart Association (NYHA) Class 3 or 4 congestive heart failure ([Appendix 3](#)), or chronic Grade 3 hypertension (diastolic blood pressure ≥ 100 mmHg or systolic blood pressure ≥ 160 mmHg).

10. Significant screening electrocardiogram (ECG) abnormalities including atrial fibrillation (unstable or newly diagnosed), double (left and right) bundle-branch block, second-degree atrioventricular block type II, third-degree atrioventricular block, Grade ≥ 2 bradycardia, QTcF interval ≥ 450 msec, or unstable cardiac arrhythmia requiring medication. Chronic asymptomatic atrial fibrillation stably controlled with medications is permitted.
11. Known family history of sudden cardiac death.
12. Ongoing risk for bleeding due to active peptic ulcer disease or bleeding diathesis.
13. Significant active gastrointestinal disease (e.g., malabsorption syndrome, resection of the stomach or small bowel, symptomatic inflammatory bowel disease, gastrointestinal perforation, or partial or complete bowel obstruction) that might impair absorption of study treatment.
14. Evidence of an ongoing, uncontrolled systemic bacterial, fungal, or viral infection or an uncontrolled local infection requiring therapy at the time of start of study treatment.
Note: Subjects with localized fungal infections of skin or nails are eligible.
15. Subjects with human immunodeficiency virus (HIV) infection who do not meet the following criteria are excluded: HIV-infected subjects must be on anti-retroviral therapy (ART) and have well-controlled HIV infection/disease defined as: (a) CD4⁺ T cell count > 350 cells/mm³ at time of screening, (b) achieved and maintained virologic suppression defined as confirmed HIV RNA level < 50 copies/mL or the lower limit of qualification (below the limit of detection) using the locally available assay at the time of screening and for at least 12 weeks prior to screening, (c) must have been on a stable anti-retroviral regimen, without changes in drugs or dose modification, for at least 4 weeks prior to start of study treatment (C1D1), and (d) the combination ART regimen must not contain any retroviral medications OTHER THAN abacavir, dolutegravir, emtricitabine, lamivudine, raltegravir, or tenofovir (due to potential CYP interactions, exceptions permitted only with prior Sponsor clearance). Subjects with a history of Kaposi Sarcoma and/or Multicentric Castlemann Disease are excluded.
16. Known history of Hepatitis B (defined as Hepatitis B surface antigen reactive) or known active Hepatitis C virus (defined as detection of HCV RNA [qualitative]) infection.
17. Diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (at doses exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 14 days prior to the first dose of study treatment.
18. Prior allogeneic organ transplant.
19. Receipt of live vaccine within 30 days prior to study entry or within 30 days of receiving study treatment. Examples of live vaccines include, but are not limited to, measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette-Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection

are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist[®]) are live attenuated vaccines and are not allowed.

20. Has undergone prior allogeneic hematopoietic stem cell transplantation within the last 5 years. (Subjects who have had a transplant more than 5 years before the start of study treatment are eligible as long as there are no symptoms of graft-versus-host-disease).
21. Females who are pregnant, breastfeeding, or expect to become pregnant within the projected duration of the study, starting with the screening visit through 120 days after the final dose of study treatment. Males who plan to father children within the projected duration of the study, starting with the screening visit through 120 days after the final dose of study treatment.
22. Major surgery within 28 days (or inadequate recovery from the toxicity or complications of the intervention) before the start of study treatment.
23. Radiotherapy within 14 days of start of study treatment. (NSCLC subjects who have received radiation therapy to the lung that is >30Gy within 6 months of start of study treatment are also excluded.) Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 7-day washout is permitted for palliative radiation (i.e., ≤ 14-day course of radiotherapy) to non-CNS lesions.
24. Subjects currently receiving treatment with any medications that have the potential to prolong the QT interval and that cannot be either discontinued or substituted with a different medication prior to starting study treatment.

Note: See [Appendix 8](#) for a list of proscribed drugs.
25. Subjects currently receiving treatment with strong cytochrome P450 (CYP)3A4 inhibitors or inducers should discontinue such treatment or be switched to a different medication prior to starting study treatment.

Note: See [Appendix 8](#) for a list of proscribed drugs.
26. Current participation in another study of an investigational agent or device.
27. Any illness, medical condition, organ system dysfunction, or social situation, including mental illness or substance abuse, deemed by the investigator to be likely to interfere with a subject's ability to sign informed consent, adversely affect the subject's ability to cooperate and participate in the study, or compromise the interpretation of study results.

9.3 Replacement of Subjects

Any subjects who do not receive at least 80% of planned doses in Cycle 1 due to reasons other than DLT, or who stop treatment prior to completing evaluation for the initial 3 weeks of therapy (DLT Observation Period) due to PD or refusal to participate further for reasons other than DLT, will be replaced at that dose level to permit full evaluation of that dose level before a decision regarding dose escalation can be made. See [Section 10.4](#) for the definition of a DLT.

9.4 Removal of Subjects from Therapy or Assessment

Discontinuation of study treatment does not represent withdrawal from the study.

The investigator may discontinue treating a subject with study treatment or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to discontinue study treatment or withdraw from the study at any time for any reason.

Pembrolizumab treatment must be discontinued but the subject should continue to be monitored in the study for any of the following reasons:

- Recurrent Grade 2 pneumonitis
- Completion of 35 treatments (approximately 2 years) with pembrolizumab

Discontinuation of pembrolizumab treatment may be considered for subjects who have attained a confirmed complete response (CR) and have been treated for at least 8 cycles (at least 24 weeks), receiving 2 cycles of the combination therapy including 2 doses of pembrolizumab and at least 80% of the planned doses of FLX475 beyond the date when the initial CR was declared.

The reason for discontinuation of FLX475, pembrolizumab, or both will be documented. If a subject discontinues study treatment, the subject will enter the Follow-Up Phase and complete protocol-specified End-of-Treatment and Follow-up visits, procedures, and survival follow-up unless the subject withdraws consent. The investigator should confirm whether a subject will discontinue study treatment but agree to continue protocol-specified, posttreatment study visits, procedures, and survival follow-up, or whether the subject withdraws consent or is lost to follow-up. If a subject withdraws consent, the date will be documented in the source documents. The investigator will complete the appropriate eCRF, indicating the primary reason for discontinuation. In addition, the date of final dose of study treatment(s) will be recorded on the appropriate eCRF.

All subjects who discontinue study treatment without having PD will continue to undergo tumor assessments using the same imaging schedule used during the Treatment Phase (i.e., every 6 weeks [± 1 week] in Year 1 or every 9 weeks [± 1 week] in Year 2) until the start of a new anticancer treatment, disease progression, pregnancy, or the end of the study, whichever occurs first, unless the subject withdraws consent, is lost to follow-up, or dies.

All subjects will be followed for survival until death, except for those subjects who withdraw consent or are lost to follow-up, or the Sponsor chooses to halt survival follow-up after completion of the primary study analysis.

10 TREATMENTS

10.1 Overview of Treatments Administered

Subjects in all cohorts will take FLX475 orally at their assigned dose (depending on cohort) once daily (QD) starting on Day 1 of Cycle 1. See [Section 10.2.1](#) for details of the planned dose administration schema.

Subjects assigned to a combination-therapy cohort (Parts 1b and 2b) will receive FLX475 in conjunction with pembrolizumab. Pembrolizumab 200 mg will be administered IV Q3W.

The treatments to be used in this study are outlined in [Table 2](#).

Table 2 Study Treatments

Study Treatment	Formulation	Dose Levels ^a	Route of Administration	Sourcing
FLX475	Tablets	Multiple: 25 mg to 200 mg qd	Oral	Provided centrally by the Sponsor
Pembrolizumab	Solution for infusion	200 mg Q3W	IV infusion	Provided centrally by the Sponsor

IV = intravenous, Q3W = once every 3 weeks, qd = once daily.

^a See [Section 10.8](#) of the protocol for details on planned strategy for dose escalation and expansion cohorts. FLX475 dosing may also include a single 300 mg Day 1 loading dose at higher dose cohorts.

10.2 FLX475 Administration

All subjects will take FLX475 orally once daily on a continual basis. On days when pembrolizumab is also administered (i.e., Day 1 of each cycle), FLX475 should be taken approximately 1 hour before the pembrolizumab infusion.

The dose administration schema for FLX475 is provided below, along with instructions for dose modification.

10.2.1 Dose Escalation Plan

10.2.1.1 Planned Dose Levels

Sequential cohorts of at least 3 to 6 evaluable subjects will be enrolled at progressively higher dose levels as illustrated in [Table 3](#). (Note that the actual dose of FLX475 used in a cohort may be different than those stated below, based on human PK/PD data or DLTs or other toxicity observed during dose escalation in this study [e.g., leading to smaller dose increments]). Actual dose levels will be determined by the Sponsor's medical monitor in consultation with the investigators. Subjects in particular cohorts may receive a loading dose of FLX475 on Cycle 1 Day 1. If an MTD has not been reached or exceeds the maximal doses listed in [Table 3](#), dose escalation may continue in up to 1 additional cohort each in

Parts 1a and 1b should it be determined to be needed by the Sponsor to better evaluate the PK, PD, and safety of FLX475. The initial cohort of subjects will be prescribed FLX475 monotherapy at Dose Level 1a (25 mg/dose QD).

Dose-escalation combination-therapy cohorts in Part 1b will begin enrollment once the corresponding dose-escalation monotherapy cohort (e.g., Cohort 3a: 100 mg QD) in Part 1a has completed (i.e., full cohort of subjects has completed the DLT Observation Period). (The starting dose in Cohort 1b may be lower or higher than 50 mg QD should initial human PK and PD data of FLX475 demonstrate greater than or lower than predicted exposure, respectively.) Enrollment of dose-escalation cohorts in Parts 1a and 1b will be staggered, such that only 1 cohort is open for enrollment at a time.

To maximize the collection of clinical sample data, once at least 3 subjects have been treated in a dose level cohort and have not exceeded the MTD, additional subjects may be enrolled at this cleared dose cohort (i.e., “back-fill slots,” to be enrolled in parallel with enrollment of the next higher dose cohort) only if they meet selection criteria and are able to and consent to provide fresh tumor biopsies both before and during study treatment.

Table 3 Anticipated Dose Levels of FLX475

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	100 mg QD	3–6	2.00-fold
4a	300/100 mg QD*	3–6	NA
5a	300/150 mg QD*	3–6	1.50-fold
6a	300/200 mg QD*	3–6	1.33-fold
Part 1b: Combination Dose Escalation			
1b	50 mg QD	3–6	NA
2b	100 mg QD	3–6	2.00-fold
3b	300/100 mg QD*	3–6	NA
Part 2a: Monotherapy Cohort Expansion			
Cohorts			
M1-M5	RP2D	10–29	NA
Part 2b: Combination Cohort Expansion			
C1-C13†	RP2D (combo)	10–29	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 MTD has not been reached and cumulative safety and PK/PD data support doing so.

10.2.1.2 Dose Escalation

The following dose-escalation rules will be employed:

- The first subject to be enrolled at the starting dose level (25 mg/dose QD) of FLX475 in Part 1a will be observed for ≥ 1 week after initiation of treatment before any subsequent subjects are treated at the same dose level.
- Each dose level cohort will initially enroll at least 3 subjects.
- If none (0) of the first 3 subjects in a cohort has a DLT, the next cohort of subjects will be treated at the next higher dose level of FLX475.
- If 1 subject in the first set of subjects experiences a DLT, additional subjects up to a cumulative total of 6 will be enrolled at that dose level. If none (0) of the additional subjects experience a DLT, the next cohort of subjects will be treated at the next higher dose level.
- If ≥ 2 of 3 to 6 subjects experience a DLT at a particular dose level, the Sponsor will consider the MTD to have been exceeded and additional subjects will be treated at the previous lower dose level, to a cumulative total of 6 if < 6 subjects were previously treated at that prior dose level. If none (0) of the additional subjects experience a DLT, that dose level will be considered the MTD. If 6 subjects were previously treated at the prior dose level, that prior dose level will be considered the MTD. (Note that a minimum of 10 subjects must be evaluated at a Part 1b combination dose in order for it to be designated a RP2D prior to opening Part 2b combination expansion cohorts for enrollment.)
- With the concurrence of the principal investigators and the Sponsor's medical monitor, intermediate dose levels between 2 planned dose levels may be added to the dose escalation scheme in order to further refine the estimation of the MTD.
- Each group of 3 to 6 subjects within a cohort must be observed for a minimum period of 3 weeks during Cycle 1 for the occurrence of DLTs (the DLT Observation Period) before subsequent subjects are enrolled to expand the cohort at the current dose level or before any subjects are enrolled at the next higher dose level.
- Escalation to the next higher dose level or progression to the expansion portion of the study can occur upon review of the safety data from all ongoing and previous subjects and with the concurrence of the principal investigators and the Sponsor's medical monitor.
- To maximize the collection of information at relevant doses and to minimize the exposure of subjects to potentially suboptimal doses, intrasubject dose escalation may be permitted in subjects enrolled in Parts 1a and 1b of the study under the following conditions:
 - Subjects must complete at least three 3-week (21-day) cycles at their originally assigned dose level prior to the dose escalation

- Subjects may only escalate their dose to the highest dose level cohort that has already been completed and cleared – i.e. in which at least 3 subjects have successfully completed at least one 3-week (21-day) cycle of FLX475 (the DLT Observation Period) with no more than 0/3 or 1/6 DLTs. (These subjects will not be included as part of the higher dose escalation cohort for dose escalation decisions.)
- All intrasubject dose escalation decisions will be made in coordination with the Sponsor's medical monitor based on an investigator's judgment of whether such an escalation is in the best interest of the subject.

After all subjects in a cohort have completed the 3-week safety observation period, a Safety Review Committee (SRC) will be convened. The SRC members will comprise appropriate Sponsor and 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). The SRC will carefully consider all available safety, laboratory, and PK information in consultation with the study investigators. Safety data from all enrolled subjects in preceding cohorts and dose levels will also be considered. After review of all available data, the SRC may recommend escalation to the next planned dose; escalation to an intermediate dose (a dose lower than the next planned dose); de-escalation to a lower dose; continuation, delay, or termination of dosing; or repetition or expansion of a cohort. Beyond Phase 1 dose escalation, the SRC will continue to meet at least quarterly during the Phase 2 expansion phase of the study to review accumulating safety data and may also recommend an amendment to the protocol to evaluate alternate study drug administration schedules or other changes in study design as may be appropriate based on emerging clinical data.

10.3 Pembrolizumab Administration

Pembrolizumab 200 mg will be administered as an IV infusion over 30 minutes on Day 1 of every 3-week treatment cycle (i.e., every 21 days [± 3 days]) after all procedures and assessments have been completed, and approximately 1 hour after the Day 1 dose of FLX475, unless for "lead-in" cohorts when pembrolizumab starts on Day 1 of cycles 2 and beyond. (Note that in the event that lead-in dosing is determined to potentially provide added clinical benefit over concurrent dosing, lead-in dosing may be implemented across additional/all combination cohorts within the study.) Pembrolizumab may be administered up to 7 days after cohort assignment in Cycle 1 and 3 days before or after the scheduled Day 1 of Cycle 2 and beyond due to administrative reasons.

The investigational staff should make every effort to ensure that the infusion duration be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (i.e., infusion time of 25 to 40 minutes).

The Pharmacy Manual contains specific instructions for the preparation and administration of the pembrolizumab infusion.

10.4 Dose-Limiting Toxicity and Stopping Criteria

A DLT is defined as an AE or abnormal laboratory value observed in a Phase 1 dose escalation subject assessed by the investigator as possibly, probably, or definitely related to study treatment, excluding toxicities clearly not related to study treatment, such as PD, environmental factors, unrelated trauma, etc. occurring during Days 1–21 of Cycle 1 (“DLT Observation Period”), that meets any of the following criteria:

- Grade 4 hematological laboratory abnormality lasting ≥ 7 days, except thrombocytopenia, or:
 - Grade 4 thrombocytopenia of any duration; or
 - Grade 3 thrombocytopenia associated with clinically significant bleeding
- Nonhematological Grade 3 or 4 laboratory abnormalities:
 - Grade 3 or 4 liver enzyme elevation, including aspartate aminotransferase (AST)/gamma glutamyl transferase and alanine aminotransferase (ALT), that does not return to baseline level within 7 days and requires systemic immunosuppression
 - Hepatocellular injury caused by drug ingestion consistent with Hy’s Law with the following acute changes:
 - ALT or AST $> 3X$ ULN
 - Total bilirubin $> 2X$ ULN
 - No signs of cholestasis (ALP $< 2X$ ULN)
 - No other assignable cause such as liver metastases, pre-existing hepatic disease, viral hepatitis, alcohol abuse, ischemia, etc.
 - Grade 3 or 4 serum electrolyte or mineral abnormalities (i.e., hypermagnesemia, hyperkalemia, hypernatremia, hypomagnesemia, hypokalemia, hyponatremia, or hypophosphatemia) unresponsive to supplementation within 72 hours
 - Grade 3 or 4 amylase or lipase abnormalities that are not associated with diabetes mellitus, associated liver or gall bladder inflammation, clinical manifestations of pancreatitis, and which did not decrease to Grade ≤ 2 within 7 days (isolated asymptomatic Grade 3 amylase abnormalities or lipase abnormalities are excluded)
- Any Grade 4 non-hematologic AE of any duration, with the following exception:
 - Grade 4 diarrhea lasting 48–72 hours in subjects who have received suboptimal anti-diarrheal therapy
- Grade 3 rash that does not resolve to Grade 1 or baseline level (whichever is higher) within 7 days
- Grade 3 fever that does not resolve to Grade 1 or baseline level (whichever is higher) within 7 days

- Grade 3 fatigue that does not resolve to Grade 2 or baseline level (whichever is higher) within 7 days
- Grade ≥ 3 creatinine increase
- Grade 3 nausea, vomiting, colitis, or diarrhea requiring total parenteral nutrition or hospitalization (e.g., duration >48 hours despite optimal management) that does not resolve to Grade 1 or baseline level (whichever is higher) within 7 days
- Grade 2–3 uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 0 or 1 within 7 days
- Grade ≥ 2 nonhematological toxicity requiring systemic immunosuppressive therapy. This includes, but is not limited to, autoimmune diseases of the lung, heart, kidney, bowel, CNS, pituitary, or eye
- Grade ≥ 2 endocrine toxicity requiring hormone replacement, with the exception of Grade 2 thyroiditis and thyroid dysfunction
- Grade ≥ 3 adrenal insufficiency
- Grade ≥ 3 febrile neutropenia:
 - Grade 3 is defined as absolute neutrophil count (ANC) $< 1000/\text{mm}^3$ with a single temperature of $> 38.3^\circ\text{C}$ (101°F) or a sustained temperature of $\geq 38^\circ\text{C}$ (100.4°F) for more than 1 hour
 - Grade 4 is defined as ANC $< 1000/\text{mm}^3$ with a single temperature of $> 38.3^\circ\text{C}$ (101°F) or a sustained temperature of $\geq 38^\circ\text{C}$ (100.4°F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated
- QTcF interval ≥ 501 msec and > 60 msec prolongation from baseline (defined as average QTcF value from C1D1 pre-dose ECGs), or associated with Torsades de pointes, polymorphic ventricular tachycardia, or serious arrhythmia
- Prolonged delay (> 2 weeks) in initiating Cycle 2 due to treatment-related toxicity;
- Any treatment-related toxicity that causes the subject to discontinue treatment during Cycle 1.
- Missing $> 20\%$ of FLX475 doses as a result of drug-related AE(s) during the first cycle.
- Any Grade 5 toxicity.

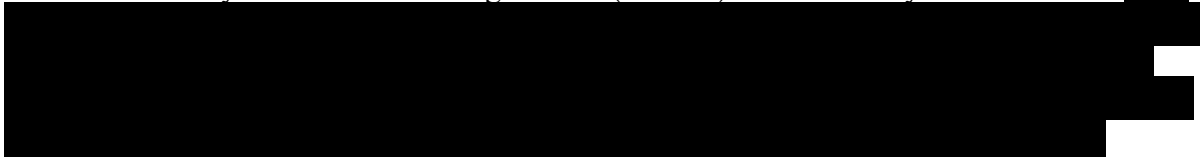
Refer to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 ([Appendix 1](#)) for grading of the severity of AEs and laboratory abnormalities.

10.5 Dose Modifications for Toxicity

The investigator will decide whether any AE that occurs is related to either or both drugs and determine whether dose modification or discontinuation of one or both drugs is required per the guidance below.

10.5.1 FLX475

For ongoing toxicity assessment throughout both parts of the study, subjects will be monitored closely for treatment-emergent AEs (TEAEs) and laboratory abnormalities.



If a subject experiences an AE, appropriate supportive care (e.g., antiemetics, antidiarrheals) should be instituted according to the nature of the event. In general, dose modifications of FLX475 are not permitted during the DLT Observation Period (Days 1–21 of Cycle 1) in Phase 1. Subjects who experience a DLT during Cycle 1 should discontinue study treatment (unless it is determined to be in the subject's best interest to continue treatment by the investigator in consultation with the Sponsor's medical monitor).

For subjects receiving study treatment beyond Cycle 1, the following dose modification and discontinuation guidelines must be followed:

- For any organ-related Grade 4 TEAE (neurologic, pulmonary, cardiac, gastrointestinal, genitourinary, renal, hepatic, cutaneous) at least possibly related to FLX475, discontinue drug use permanently (unless it is determined by the investigator, in consultation with the Sponsor's medical monitor, to be in the subject's best interest to continue treatment, at a reduced dose).
- For any Grade 3 gastrointestinal (GI) AE, interrupt treatment with FLX475 until resolution to Grade 0 or 1 or to pretreatment severity grade, then resume treatment at the previous lower dose level. (Exceptions may be made in Phase 2 subjects if accumulated Phase 1 data suggest no significant GI effects of FLX475, and in subjects with potential alternative etiology of GI toxicity, such as concomitant pembrolizumab.)
- For subjects requiring dose reduction based on QTcF prolongation (see criteria below), interrupt treatment with FLX475 until resolution to Grade 0 or 1 or to the pretreatment severity grade, then resume treatment at the next lower dose (i.e. from 75 or 100 mg reduced to 50 mg, or from 50 mg to 25 mg). Any subjects with observed QTcF prolongation of potential significance should have the ECG repeated for confirmation and electrolytes assessed and replaced as needed prior to action with study drug being taken. Subjects previously reduced to the 25 mg dose who exhibit QTcF prolongation meeting criteria for dose reduction below should discontinue FLX475.
 - For average Grade 1 QTcF prolongation at any time (or for average $\leq$ Grade 2 QTcF prolongation $\leq$ 6 hours after FLX475 dose), no dose reduction is required

- For average Grade 2-3 QTcF prolongation immediately prior to FLX475 dose (or > 6 hours after FLX475 dose), dose interruption and reduction guidelines should be followed as described above
- For average Grade 3 QTcF prolongation $\leq$ 6 hours after FLX475 dose, dose interruption and reduction guidelines should be followed as described above
- Any subjects with observed Grade 4 QTcF prolongation (including symptomatic/serious arrhythmia) should be treated appropriately and permanently discontinued from FLX475 treatment (unless it is later determined by the investigator, in consultation with the Sponsor's medical monitor, to be in the subject's best interest to continue treatment).
- The investigator may interrupt treatment with FLX475 for any other AE considered unacceptable for the individual subject and at least possibly related to FLX475, and treatment may be resumed at the previous lower dose level when resolved to Grade 0 or 1 or to pretreatment severity grade.
- If no lower dose level exists to which the subject may de-escalate, FLX475 should be discontinued.
- Subjects with any of the following liver function abnormalities below should be discontinued from FLX475 therapy. (Exceptions to consider restarting FLX475 therapy may be made in Phase 2 subjects with such abnormalities initially receiving combination therapy if accumulated Phase 1 data suggest no significant hepatic effects of FLX475, and abnormalities resolve after stopping use of both drugs.)
 - ALT or AST > 8x ULN
 - ALT or AST > 5x ULN for more than 2 weeks
 - ALT or AST > 3x ULN and (total bilirubin > 2x ULN or INR > 1.5)

Other dose modifications may be acceptable but should be implemented at the investigator's discretion in consultation with the Sponsor's medical monitor, considering the subject's condition and the clinical benefit to the subject of continuing treatment at the current dose. If the subject requires a dose modification for an AE, then FLX475 administration should be interrupted, as necessary, until the AE resolves or stabilizes to an acceptable degree (generally to CTCAE Grade 0 or 1 or to pretreatment severity grade). Thereafter, treatment with FLX475 may be reinstituted at the previous lower dose level. Subsequent reductions to successively lower dose levels can be made, if needed, as shown in [Table 4](#). More frequent laboratory monitoring may be required. Once the dose of study treatment has been reduced, it may not be increased at a later date, unless the dose was mistakenly decreased; in this situation, the Sponsor's approval is required to increase the dose.

Table 4 Dose Modification Guidelines for FLX475-Related Toxicity*

Treatment-Related Toxicity ^{a,b}	Management	Dose Adjustment
Grade 1 or Tolerable Grade 2		
	Continue treatment	No change
Intolerable Grade 2^{c, d, e} or Grade 3^f		
First occurrence	Interrupt FLX475 until resolved to Grade 0–1 or tolerable Grade 2 (or baseline)	Reduce FLX475 dose by 1 level (or if no lower dose level exists, discontinue drug)
Second occurrence (same toxicity or new toxicity)	Interrupt FLX475	Discuss with Sponsor
Grade 4^g: Discontinue Study Treatment		

Note: For grading see CTCAE version 4.03 ([Appendix 1](#)). Collect all CTC grades of adverse events, decreasing and increasing grade.

BMI = body mass index, CTCAE = Common Terminology Criteria for Adverse Events.

- * As of Amendment 6 with >200 subjects treated with FLX475, the only AE that has been clearly associated with FLX475 treatment to date has been QT prolongation, for which dose modification guidelines provided above in [Section 10.5.1](#) should be followed. For AEs other than QT prolongation, dose modification of FLX475 may not be required. Any such considerations should be discussed with the Sponsor.
- ^a An interruption of study treatment for more than 21 days will require Sponsor's approval before treatment can be resumed.
- ^b Initiate optimal medical management for nausea, vomiting, hypothyroidism and/or diarrhea prior to any study treatment interruption or dose reduction.
- ^c Applicable only to Grade 2 toxicities judged by the subject or physician to be intolerable.
- ^d Obese subjects with weight loss do not need their weight to return to baseline weight or within 10% of baseline weight (i.e., Grade 1 weight loss). These subjects will restart the study treatment(s) at a lower dose once their weight remains stable for at least 1 week and they reach their normal BMI (if the weight loss occurs but is still above normal BMI, they can restart study treatment at a lower dose once their weight has been stable for at least 1 week). Normal BMI should be used as the new baseline for further dose reductions.
- ^e For Grade 3 toxicity, investigator will decide the probability of the event being related to 1 or both drugs and as to whether dose modification of either or both drugs is required.
- ^f For asymptomatic laboratory abnormalities, such as Grade ≥ 3 elevations of amylase and lipase that are not considered clinically relevant by the investigator, continuation of treatment should be discussed with the Sponsor.
- ^g Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.

10.5.2 Dose Modification for Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the final dose of pembrolizumab. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs are reversible and can be managed with interruptions of pembrolizumab, administration of corticosteroids, and/or other supportive care. Suspected irAEs should be adequately evaluated to confirm etiology or exclude other causes. Additional procedures or

tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Criteria for dose delay, modification, or discontinuation of pembrolizumab are described below, and are based on criteria in the [Keytruda Investigator's Brochure](#).

[Table 5](#) shows treatment guidelines, including premedications, for subjects who experience an infusion reaction associated with the administration of pembrolizumab.

Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in [Table 6](#).

Pembrolizumab may be interrupted for situations other than treatment-related AEs, such as medical/surgical events or logistical reasons not related to study treatment. Pembrolizumab should be restarted within 3 weeks or 21 days of the originally scheduled dose and within 42 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the subject's eCRF.

[illegible]

Table 6

	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Category	Item	Value	Unit	Notes
Category A	Item A1	100	kg	Weight of Item A1
	Item A2	200	kg	Weight of Item A2
	Item A3	300	kg	Weight of Item A3
	Item A4	400	kg	Weight of Item A4
Category B	Item B1	500	kg	Weight of Item B1
	Item B2	600	kg	Weight of Item B2
	Item B3	700	kg	Weight of Item B3
	Item B4	800	kg	Weight of Item B4

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]				

10.6 Identity of Investigational Products

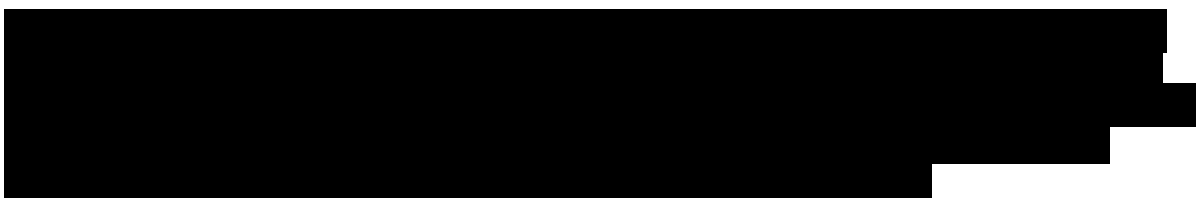
The study treatments under evaluation in this study are FLX475 and pembrolizumab. All study treatments will be provided to sites as open-label supplies by the Sponsor.

10.6.1 FLX475

FLX475 is a crystalline non-hydrosopic material that is moderately soluble in water. FLX475 will be supplied as tablets formulated with standard pharmaceutical-grade excipients designed to provide a release profile consisting of an immediate release of FLX475 drug substance over a period of approximately one hour.

10.6.2 Pembrolizumab

Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa.



The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion and administration of the infusion solution. An infusion of pembrolizumab in this study will require 2 vials of solution.

Refer to the latest [Keytruda® Investigator's Brochure](#) for complete details.

10.6.3 Supply, Packaging, and Labeling of Study Drug

FLX475 and pembrolizumab will be provided to the investigational sites by RAPT Therapeutics, Inc.

FLX475 for oral administration will be provided as tablets containing the active ingredient as well as standard pharmaceutical grade excipients. FLX475 will be packaged in bottles.

Pembrolizumab will be supplied in study-specific labeled vials packaged in individual cartons with study-specific labeling.

All study treatments will be labeled in accordance with text that is in full compliance with the requirements for each participating country and is translated into the required language(s) for each of those countries.

10.6.4 Storage Conditions

Bottles containing tablets of FLX475 should be stored at a controlled room temperature, 20-25°C (68-77°F). Study drug should be stored in the container in which it is supplied, in a

secured area to which access is limited to appropriate study personnel. FLX475 tablets should be stored protected from light and according to the storage information provided on the label.

Vials containing pembrolizumab (MK-3475) should be stored refrigerated at 2–8°C (36–46°F) in the original carton to protect from light.

10.7 Method of Assigning Subjects to Treatment Arms

This study is nonrandomized. Subjects will be assigned sequentially to treatment with FLX475 (Parts 1a and 2a) or FLX475 plus pembrolizumab (Parts 1b and 2b), as described in [Section 8.1](#) and shown in [Table 3](#) in [Section 10.2.1.1](#). For all cohorts in Parts 1a and 1b, eligible subjects will be assigned to the next available cohort once they have completed the Screening Phase and all baseline assessments ([Table 8](#) and [Table 9](#)). Eligible subjects in Parts 2a and 2b will be assigned to a cohort at the RP2D identified in Part 1 of the study, once they have completed the Screening Phase and all baseline assessments ([Table 10](#) and [Table 11](#)). Subjects enrolled in Part 2 of the study will further be assigned to a cohort based on their tumor type. (Subjects with CPI-naïve HNSCC will first enroll into Stage 1 of Cohort M3 before enrollment into Stage 1 of Cohort C1.)

10.8 Selection of Doses in the Study



Subjects will take FLX475 once daily. Each 3-week treatment period is considered to be 1 treatment cycle, based on administration of pembrolizumab. Subsequent dose levels of FLX475 will be selected according to the schema described in [Section 10.2.1](#). Dose increases of FLX475 in subsequent cohorts are no greater than 100% increments (i.e., doubling of the daily dose) until any subject at a given dose level experiences a Grade 2 or higher CTCAE treatment-related toxicity. From that time on, the dose will be increased for subsequent dose levels by 50% or less, depending upon the seriousness of the toxicity; all 3 initial subjects at a given dose level must complete a full cycle before the next dose level is opened for enrollment. Intrasubject dose escalation may be permitted in subjects enrolled in Parts 1a and 1b of the study under certain circumstances as described in [Section 10.2.1.2](#).

The dose of pembrolizumab used in this study, 200 mg as a 30-minute IV infusion Q3W, is the approved dosage in advanced cancer, based on clinical data from 8 randomized studies.

10.9 Selection of Dose and Timing for Each Subject

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting. Fasting is not required for FLX475 administration.

FLX475 tablets are to be taken with water orally once a day at approximately the same time each day in every 3-week cycle (21 days) from Cycle 1 Day 1 onward.

For subjects receiving combination treatment with FLX475 plus pembrolizumab, pembrolizumab will be administered at a dose of 200 mg as a 30-minute IV infusion (infusion durations of 25 minutes to 40 minutes are acceptable), Q3W, on Day 1 of each 3-week (21-day) cycle. For these subjects, FLX475 will be administered approximately 1 hour before administration of pembrolizumab on Day 1 of each cycle. (For lead-in dosing cohorts pembrolizumab will start on Day 1 of Cycle 2. Note that in the event that lead-in dosing is determined to potentially provide added clinical benefit over concurrent dosing, lead-in dosing may be implemented across additional/all combination cohorts within the study.)

Dose modifications may be acceptable for toxicity but should be implemented at the investigator's discretion in consultation with the Sponsor's medical monitor after considering the subject's condition and the clinical benefit to the subject of continuing treatment at the current dose.

See [Section 10.5](#) for details pertaining to the guidelines for dose modifications in this study.

10.10 Blinding

The study will not be blinded to the investigator or the subject. However, any independent radiologists reading the tumor assessment images for response/progression will be blinded per standard procedures.

10.11 Prior and Concomitant Therapy

10.11.1 Recording of Prior and Concomitant Treatments and Procedures

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medications taken by the subject within 30 days before the first dose of study treatment. The dates and doses of the most recent CPI administered (e.g. anti-PD-1 or anti-PD-L1 therapy) prior to study entry should be recorded even if beyond 30 days before the first dose of study treatment. Prior antibiotic usage (type, dose, and duration) for up to 6 months prior to study entry should also be recorded, if the information is readily available.

All prior medications (including over-the-counter medications) administered within 30 days before the first dose of study treatment and any concomitant therapy administered to the subject during the course of the study (starting at the date of informed consent) until 30 days after the final dose of study treatment will be recorded on the appropriate eCRF(s). Additionally, all diagnostic, therapeutic, or surgical procedures relating to malignancy should

be recorded. Any medication that is considered necessary for the subject's health and that is not expected to interfere with the evaluation of or interact with the study treatment may be continued during the study. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the appropriate eCRF.

10.11.2 *Drug-Drug Interactions*

FLX475 is metabolized by hepatocytes from mice, rats, dogs, monkeys, and humans; and the rates of metabolism suggest that FLX475 will have moderate clearance in humans. [REDACTED]

[REDACTED]

No formal PK drug interaction studies have been conducted between FLX475 and pembrolizumab. Pembrolizumab is a monoclonal antibody; PK interactions with FLX475 (and vice versa) are not expected.

Refer to the prescribing information and <http://medicine.iupui.edu/clinpharm/ddis/> for the most current information for drug-drug interaction studies conducted with pembrolizumab.

10.11.3 *Permitted Concomitant Therapies*

Treatment (including blood products, blood transfusions, fluid transfusions, antibiotics, antidiarrheal drugs, etc.) of complications or AEs, or therapy to ameliorate symptoms, may be given at the discretion of the investigator, unless it is expected to interfere with the evaluation of (or to interact with) the study treatment.

Any additional procedural or subject-specific particularities should be discussed with the Sponsor.

10.11.4 *Prohibited Concomitant Therapies and Drugs*

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during this trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation of study treatment or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination is at the discretion of the investigator or the subject's primary physician. However, the decision to allow the subject to continue to

receive study treatment requires the mutual agreement of the investigator, the Sponsor, and the subject.

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this study:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Investigational agents other than pembrolizumab or FLX475
- Radiation therapy

Note: Radiation therapy to a symptomatic solitary non-target lesion or to the brain may be allowed at the investigator's discretion.

- Live vaccines within 30 days prior to the first dose of study treatment and during participation in the study. Examples of live vaccines include, but are not limited to: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist[®]) are live attenuated vaccines and are not allowed.
 - Note: Any licensed COVID-19 vaccine (including for Emergency use) in a particular country is allowed in the study as long as they are mRNA vaccines, adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.
- Paxlovid[™] should not be given in combination with FLX475. If Paxlovid[™] is indicated, FLX475 should be held with ECG monitoring as indicated
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have an immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

Note: Inhaled steroids are allowed for management of asthma or seasonal allergies. The use of prophylactic corticosteroids to prevent allergic reactions (e.g., IV contrast dye or transfusions) is permitted.

Subjects who, in the investigator's judgment, require the use of any of the aforementioned treatments for clinical management should be removed from the study. If a subject receives additional anticancer therapies, this will be judged to represent evidence of PD, and study treatment will be discontinued. These subjects should complete all End-of-Treatment assessments and continue to be followed for survival in the Follow-up Phase unless they withdraw consent or are lost to follow-up.

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

All concomitant medication will be recorded on the eCRF, including all prescription, over-the-counter products, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

All medications received within 30 days prior to the first dose of study treatment and up to 30 days after the final dose of study treatment should be recorded. The date and dose of the most recent CPI administered (e.g. anti-PD-1 or anti-PD-L1 therapy) prior to study entry should be recorded even if beyond 30 days before the first dose of study treatment. Concomitant medications administered up to 90 days after the final dose of study treatment (or 30 days following cessation of study treatment if the subject initiates new anticancer therapy, whichever occurs first) should be recorded for SAEs and events of clinical interest (ECIs) as defined in [Section 11.5.2](#).

10.11.5 *Rescue Medication and Supportive Care*

Subjects should receive appropriate supportive care measures for an AE as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in [Section 10.5.2](#). Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Several courses of steroid tapering may be necessary, as symptoms may worsen when the steroid dose is decreased. For each disorder, an attempt should be made to rule out other causes, such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab (or FLX475). It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of the evaluation of the event.

Note: If, after evaluation, the event is determined to be not related to pembrolizumab (or FLX475), the investigator does not need to follow the treatment guidance.

10.12 *FLX475 Treatment Compliance*

FLX475 tablets will be self-administered by participating study subjects. Subjects will be provided with dosing instructions at the start of their participation in the study and at the time of any dosing modifications (e.g., dose reduction due to AE), and will be encouraged by study site personnel to take the study medication according to the instructions for the duration of the study. A diary card will be provided for subjects to record their adherence to the oral medication, which will be reviewed by qualified site personnel during study visits. Subjects will be instructed to bring the assigned bottles of study medication to the site staff at each study visit, whether empty or not. At the completion of each treatment cycle and at other times when the study drug dispensed might be returned (e.g., in the case of a dose

reduction), the returned study medication will be checked for any unused study drug, and a tablet count will be performed for any remaining study medication. This information will be recorded in the appropriate eCRF for each treatment cycle.

FLX475 plasma concentration measurements over the course of the study may also be used to assess subject compliance. Any events of non-compliance to the protocol will be documented in the study records.

10.13 Drug Accountability

FLX475 will be self-administered in this study. A diary card will be provided to each subject to record all dose administration information at home. On Day 1 of each cycle, FLX475 will be self-administered in the clinic, after a new supply of study treatment has been dispensed for that cycle, for drug accountability purposes.

The disposition of all FLX475 and pembrolizumab supplies should be documented from the time of receipt at the site through subject dispensing and return. The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study treatments/study supplies (dispensing, inventory, and record keeping) following the Sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study treatments to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study treatments, dispensing of study treatments to the subject, collection and reconciliation of unused study treatments that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study treatments to the Sponsor or (where applicable) destruction of reconciled study treatments at the site. This includes but may not be limited to: (a) documentation of receipt of study treatments, (b) study treatments dispensing/return reconciliation log, (c) study treatments accountability log, (d) all shipping service receipts, (e) documentation of returns to the Sponsor, and (f) certificates of destruction for any destruction of study treatments that occurs at the site. All forms will be provided by the Sponsor or designee. Any comparable forms that the site wishes to use must be approved by the Sponsor.

The study treatments and inventory records must be made available, upon request, for inspection by a designated representative of the Sponsor or a representative of a health authority (e.g., FDA, Medicines and Healthcare products Regulatory Agency). As applicable, all unused study treatments and empty and partially empty containers from used study treatments are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and, together with unused study treatments that were shipped to the site but not dispensed to subjects, are to be destroyed on-site during the study and at the conclusion of the study, unless the site cannot destroy on-site and requests to ship the returned and unused study treatments to the Sponsor's

designated depot. Site destruction Standard Operating Procedures (SOPs) must be reviewed and approved by Sponsor to ensure proper destruction will occur. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the Sponsor's personnel, study treatments that are to be returned to the Sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study treatments may be removed from the site and hand delivered to the central or local depot by Sponsor representatives. Where study treatments are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction or equivalent documentation of destruction will be provided to the Sponsor.

Drug accountability will be reviewed by Sponsor representatives during site visits and at the completion of the study.

Refer to [Section 14.7](#) of the protocol for further details pertaining to the handling of study drug.

11 STUDY PROCEDURES AND ASSESSMENTS

Complete information pertaining to all procedures and evaluations is provided in the Schedule of Assessments in [Table 8](#), [Table 9](#), [Table 10](#), and [Table 11](#) for Parts 1a, 1b, 2a, and 2b of the study, respectively.

11.1 Screening Assessments

The study center should confirm enrollment availability and obtain approval for screening from the Sponsor prior to initiation of screening. The approval to screen is requested by sending the appropriate screening approval form to the Sponsor or designee. The Sponsor or designee will approve the subject for screening and a unique subject identification number will be assigned and documented on the form. This number is used to identify the subject throughout the clinical study and must appear on all study related documentation and communications, including the enrollment authorization form used to approve enrollment of the subject. Subjects who fail to meet screening criteria may only be rescreened upon prior approval from the Sponsor.

The purpose of the Screening Period is to ensure that each subject meets all the specified inclusion ([Section 9.1](#)) and none of the exclusion criteria ([Section 9.2](#)). Screening will occur within 21 days before start of study treatment. Before performing any procedures or assessments, the nature of the study and the potential risks associated with the trial will be explained to all subjects and written informed consent will be obtained from them (or their legal guardian). Once signed informed consent is obtained, the following procedures and evaluations will be performed/recorded:

- Demographics/Baseline characteristics
- Physical examination, including height, weight, and vital sign measurements
- 12-Lead ECG
- Blood, urine, tissue and stool samples for laboratory tests and tumor biomarkers, as indicated on [Table 8](#) through [Table 11](#)
- Serum pregnancy test (female subjects who are premenopausal or amenorrheic for < 12 months)
- Tumor assessment (data collected before obtaining informed consent could be used if the data was collected within 28 days before start of study treatment)
- Adverse events
- Prior and concomitant drugs/therapy

Demography information will include date of birth (or age), sex, and race/ethnicity.

Baseline characteristics will include ECOG PS ([Appendix 2](#)), NYHA cardiac disease classification ([Appendix 3](#)), and cancer staging at the time of initial diagnosis. The subjects' medical and surgical histories, including those for their underlying cancer, will be obtained during the Screening Phase, along with a record of prior and concomitant medications.

Physical examinations (comprehensive or symptom-directed) will be performed as specified in the Schedules of Procedures/Assessments ([Table 8](#) through [Table 11](#)). A comprehensive physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and a complete neurological examination. Documentation of the physical examination will be included in the source documentation at the investigational site. Significant findings present before the signing of informed consent will be recorded on the appropriate eCRF. Changes from Screening in physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

Subjects must have measurable disease according to RECIST 1.1 ([Appendix 4](#)) as defined in Eligibility Criteria ([Section 9](#)). Lugano criteria will be used for subjects with lymphoma (see [Appendix 6](#) for details) other than those with CTCL, for which alternative criteria should be used ([Olsen et al., 2011](#)). Subjects must also fulfill the medical and physical characteristics identified in the inclusion criteria and not otherwise meet any of the exclusion criteria. Subjects who successfully complete the Screening process will be registered for the study and start study treatment within 21 days of initial screening. If judged to be ineligible, the reason(s) for screening failure will be described in the "Subject Screening Log" to the extent possible.

See the Schedules of Assessments ([Table 8](#) through [Table 11](#)) for a complete list of Screening assessments.

Subjects may be eligible to enroll once all screening assessments and procedures are completed and results indicate that all eligibility criteria are met.

Enrollment of a subject into the study will be performed according to the following procedure:

- To initiate enrollment of a subject, the study center will email a completed Subject Enrollment Approval Form to the Sponsor or designee.
- The Sponsor or designee will review the subject's information and notify the site of any additional information required or enrollment approval. Within 24 hours of receipt from the study center, the study Sponsor will complete the Subject Eligibility Form (Enrollment Authorization Form) to approve enrollment and to provide cohort allocation information. The study Sponsor will assign subjects sequentially to the cohort being evaluated at the time of subject enrollment.
- The Sponsor will return the approved Subject Eligibility Form (Enrollment Authorization Form) to the study center via fax/email. Subjects are only considered enrolled once the

Sponsor medical monitor or designee approves the subject enrollment. The enrollment date will be the date that the final approved form is received by the study center.

- The investigator or designee is responsible for ensuring that the confirmation of the cohort and dose level assignment from the Sponsor or its designee has been received prior to administration of study treatment on Day 1.

11.2 Baseline Assessments

The following assessments will be performed on Cycle 1 Day 1 prior to the start of study treatment:

- Physical examination and vital sign measurements
- ECOG performance status
- 12-Lead ECG
- Blood and urine samples for laboratory tests, PK assessments, and tumor biomarkers, as indicated on [Table 8](#) through [Table 11](#)
- Pregnancy test (female subjects who are premenopausal or amenorrheic for < 12 months)
- Adverse events
- Concomitant drugs/therapy

11.3 Efficacy Assessments

11.3.1 Tumor Imaging and Disease Assessment

RECIST 1.1 will be used as the primary measure for assessment of tumor response and progression, date of PD, and as a basis for all protocol guidelines related to disease status (e.g., discontinuation of study treatment). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant, to enable a broader sampling of tumor burden.

Investigator-determined response assessments will be performed at each assessment time point and recorded on the CRF. Tumor assessments for progression may also be performed by the investigator using iRECIST; this assessment will be performed following treatment discontinuation ([Appendix 5](#)).

Lugano criteria including PET-CT scans for FDG-avid lymphomas will be used for subjects with lymphoma, other than those with CTCL (see [Appendix 6](#) for details). Alternative criteria (utilizing visual assessment of skin and CT scans) should be used for subjects for CTCL ([Olsen et al., 2011](#)). Note that 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.

It is strongly preferred that tumor imaging be acquired by CT. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. The same imaging modality (and ideally the same scanner) and image-acquisition protocol (including use or nonuse of contrast) should be used consistently for each subject across all time points throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging. Note: for the purposes of assessing tumor imaging, the term “investigator” refers to the local investigator at the site or the radiological reviewer located at the site or at an offsite facility.

- In general, imaging should include the chest (CT), and abdomen and pelvis (CT or MRI)
- Imaging should include other known or suspected sites of disease
- If brain imaging is indicated, MRI is strongly preferred. However, CT imaging will be acceptable if MRI is medically contraindicated. The brain scan (MRI pre- and postgadolinium or CT with contrast) will be performed at Screening and as clinically indicated thereafter, and within a target of 1 week but no more than 2 weeks following achievement of a CR. For subjects with a history of protocol-eligible, treated brain metastases, a brain scan will be required at Screening (for all such subjects) and at all tumor assessment time points (for subjects treated for brain metastases within 6 months prior to C1D1).
- For subjects with HNSCC including NPC, baseline imaging should also include the head and neck as indicated by the known locations of disease
- For subjects with breast cancer who have a history of bone metastases and/or who have new bone pain, bone scans (^{99m}m-technetium-based scintigraphy, whole-body bone MRI, or ¹⁸F-sodium fluoride positron emission tomography) are also required for subjects. Any supplemental imaging done to support a positive or negative bone scan, such as plain X-rays that may be acquired for correlation, should be evaluated by the radiologist. Bone scans will be performed within 6 weeks prior to start of study treatment (historical is acceptable), at all tumor assessment time points, and within a target of 1 week but no more than 2 weeks following a CR as assessed by the investigator. Lesions identified on bone scans should be followed with cross-sectional imaging.

11.3.1.1 Timing of Tumor Imaging

Screening

Initial tumor imaging at Screening must be performed within 21 days prior to Cycle 1, Day 1. The investigator must review screening images to confirm that the subject has measurable disease per RECIST 1.1. Historical CT or MRI scans performed within 28 days before the start of study treatment, but before the signing of informed consent, may be used as screening scans.

Confirmation of measurable disease based on RECIST 1.1 using local assessment at Screening will be used to determine subject eligibility.

Lugano criteria including PET-CT scans for FDG-avid lymphoma will be used for subjects with lymphoma, other than those with CTCL (see [Appendix 6](#) for details). Alternative criteria (utilizing visual assessment of skin and CT scans) should be used for subjects for CTCL ([Olsen et al., 2011](#)).

During Treatment

The first imaging assessment during study treatment should be performed 9 weeks (± 7 days) from Cycle 1, Day 1. Subsequent tumor imaging should be performed every 6 weeks (± 7 days) or more frequently if clinically indicated for the first year of treatment. After 1 year, subjects who continue to receive study treatment will have imaging performed every 9 weeks (± 7 days) for up to 1 additional year. The timing of tumor imaging should follow calendar days and should not be adjusted for delays in cycle starts. Tumor imaging should continue to be performed until PD is identified by the investigator (unless the investigator elects to continue treatment and follow iRECIST), the start of new anticancer treatment, withdrawal of consent, loss to follow-up, death, 2 years of study treatment, or termination of the study by the Sponsor, whichever occurs first. Note that 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.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Subjects will then return to regularly scheduled imaging, starting with the next scheduled imaging time point. Subjects who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

Per iRECIST, investigator-assessed PD in the clinically stable subjects should be confirmed by the investigator 4 to 8 weeks after the first radiologic evidence of PD. A subject with unconfirmed PD may continue to receive study treatment at the discretion of the investigator until progression is confirmed by the investigator, provided the subject has met the conditions detailed in [Section 11.3.1.2](#). Subjects who have confirmatory imaging do not need to undergo the next scheduled tumor imaging assessment if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point, if clinically

stable. Subjects who have confirmed PD by iRECIST, as assessed by the investigator, will discontinue study treatment. Exceptions are detailed in [Section 11.3.1.2](#).

End of Treatment and Follow-up Tumor Imaging

Subjects who discontinue study treatment for a reason other than PD, tumor imaging should be performed at the time of treatment discontinuation (± 4 -week window). If previous imaging was performed within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. For subjects who discontinue study treatment due to documented PD, this is the final required tumor imaging if the investigator elects not to implement iRECIST.

For subjects who discontinue study treatment without documented PD, every effort should be made to continue monitoring disease status during the Follow-up Phase by tumor imaging using the same imaging schedule used during the Treatment Phase (i.e., every 6 weeks [± 1 week] for the first year and every 9 weeks [± 1 week] in the second year) until the start of a new anticancer treatment, PD, pregnancy, death, withdrawal of consent, loss to follow-up, or termination of the study, whichever occurs first.

11.3.1.2 Disease Assessment by iRECIST

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the investigator to assess solid tumor response and progression, and make treatment decisions. When clinically stable, subjects should not be discontinued until progression is confirmed by the investigator, in conjunction with the local radiologist, according to the rules outlined in [Appendix 5](#). This allowance to continue treatment despite initial radiologic PD takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. This data will be captured in the clinical database.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any subject deemed **clinically unstable** should discontinue study treatment at first radiologic evidence of PD as assessed by the investigator, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the investigator decides to continue treatment, the subject may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per investigator assessment.

If repeat imaging does not confirm PD per iRECIST, as assessed by the investigator, and the subject continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, subjects will be discontinued from study treatment.

If a subject has confirmed radiographic progression (iCPD) as defined in [Appendix 5](#), study treatment should be discontinued; however, if the subject is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in [Section 11.3.1.1](#).

A description of the adaptations and iRECIST process is provided in [Appendix 5](#), with additional details in the iRECIST publication ([Seymour, et al., 2017](#)). A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in [Table 13](#) in [Appendix 5](#).

11.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

11.4.1 Pharmacokinetic Assessments

Plasma concentrations of FLX475 (subjects in all cohorts) will be measured. Samples for serum concentrations of pembrolizumab (subjects in combination FLX475 plus pembrolizumab cohorts only) may be obtained for possible future analysis. Samples for serum antidrug antibodies and neutralizing antibodies to pembrolizumab may also be obtained for possible future analysis for subjects in the FLX475 plus pembrolizumab cohorts. (Note: As of Amendment 5, collection of pembrolizumab PK and antidrug antibody samples will be discontinued.)

Blood samples for PK analysis will be collected as specified in the Schedules of Assessments in [Table 8](#) through [Table 11](#). (Note that designated “Pre-dose” samples should be obtained at study visits even when study treatment is being held / not given.) In addition, blood samples may be drawn at the investigator’s discretion, e.g., during the occurrence of a clinically significant AE potentially related to study treatment. Study sites must have appropriately trained staff and adequate equipment for procuring and processing specimens. Instructions for the collection, handling, and shipping procedures of PK samples will be provided in the laboratory manual.

See [Sections 12.1.2.2](#) and [12.1.7](#) for more details.

11.4.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Blood samples for analysis of whole blood or serum biomarkers will be collected as specified in [Appendix 7](#) and in the Schedules of Assessments in [Table 8](#) through [Table 11](#). Blood samples may also be drawn at the investigator’s discretion, e.g., during the occurrence of a clinically significant AE potentially related to study treatment.

Biomarker discovery and/or validation may be performed to identify blood or tumor biomarkers that may be useful to predict subject response to study treatment, evaluation of

response-related and/or safety-related outcomes as well as for potential use in diagnostic development (if optional subject consent for sample banking is provided). Blood samples may undergo enzyme-linked immunosorbent assay-based analyses or multiplex bead-based immunoassay, and/or DNA/RNA analysis, but not limited to, in an effort to identify biomarkers. Stool samples will also be collected for microbiome analysis. In addition, biomarkers identified in other clinical studies of study treatment may also be assessed in samples collected from subjects enrolled in this study. The decision to perform biomarker analysis may be based on the clinical outcome of this study and/or the signals observed in other clinical studies or other information available at that time.

Pharmacodynamic and Pharmacokinetic/Pharmacodynamic:

Receptor Occupancy/Internalization: Blood samples for PD analysis of receptor occupancy/internalization will be collected as specified in the Schedules of Assessments in [Table 8](#) through [Table 11](#).

Immunophenotyping: Blood samples will be obtained for T/B/NK and T cell panels as specified in the Schedules of Assessments in [Table 8](#) through [Table 11](#).

Plasma concentration data for FLX475 from the monotherapy and combination FLX475 plus pembrolizumab cohorts of the study may be used to explore PK/pharmacodynamic relationships for effects of FLX475 in combination with pembrolizumab on objective response rate (ORR), other efficacy-related parameters including progression-free survival (PFS) and OS, and AEs/dose reduction. Exploratory/graphical analyses will be conducted for PK/pharmacodynamic evaluations and, if possible, may be followed by model-based analyses.

Any pharmacodynamic analyses will be detailed in a separate analysis plan and the results will be provided in a stand-alone report.

Pharmacogenetic/Pharmacogenomic (PG) Assessments

All subjects enrolled in the study, both in the dose escalation and expansion parts, will provide a core biopsy or excisional biopsy of a tumor lesion prior to starting treatment and on Cycle 3 Day 1 (± 7 days) (or Cycle 2 Day 1 ± 3 days for subjects in lead-in cohorts such as C10-13) (minimum of 3 cores). Optionally, additional biopsies may be obtained at clinically significant time points (e.g., early disease response or upon PD) with subject consent. Subjects in dose escalation for whom newly obtained samples cannot be provided (e.g., inaccessible or subject safety concern) may submit an archived, fixed tumor tissue specimen only upon agreement from the Sponsor.

Tissue from the biopsy of tumor lesions will be collected for potential assessment of mutations and other genetic alterations or genes or proteins that may be important in the development and progression of cancer as well as in response to study treatment for potential use in diagnostic development. Genetic alterations in selected molecular targets may be explored based on their potential involvement in tumor biology. Immune cell profiling and molecular targets and factors involved in immune checkpoint axis, such as PD-1 or PD-L1 levels, markers of Th1/Th2 phenotype, and inflammatory status, may also be explored.

Appropriate technology/methodologies will be used based on the amount of tumor tissue available.

A blood sample may be collected for potential pharmacogenomic analysis from all enrolled subjects (in accordance with regional or local laws). Variation in FLX475 exposure or the occurrence of AEs observed in the study population may be evaluated by correlating single-nucleotide polymorphisms with PK, safety, or pharmacodynamic data.

Any data obtained will be used for research purposes to assist in developing safer and more effective treatments and will not be used to change the diagnosis of the subject or alter the therapy of the subject. The DNA will not be used to determine or predict risks for diseases that an individual subject does not currently have. Any sample or derivatives (DNA, RNA, and protein) may be stored for up to 15 years (if optional subject consent for sample banking is provided) to assist in any research scientific questions related to study treatment, cancer and/or for potential diagnostic development.

Instructions for the processing, storage, and shipping of samples will be provided in the Laboratory Manual.

11.5 Safety Assessments

Safety assessments will consist of monitoring and recording of all AEs and SAEs using CTCAE v4.03 ([Appendix 1](#)), regular laboratory evaluation for hematology, blood chemistry, and urine values; regular performance of physical examinations and vital sign measurements; and periodic ECGs.

11.5.1 Adverse Events and Events of Clinical Interest

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. For this study, the study treatments are FLX475 and pembrolizumab. An AE does not necessarily have a causal relationship with the medicinal product. Progression of the cancer under study is not considered an AE.

Adverse events, SAEs, and other reportable safety events must be reported to the investigator by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE).
- Any new disease or exacerbation of an existing disease. However, worsening of the primary disease should be captured under efficacy assessments as PD rather than as an AE.

- Any deterioration in non-protocol-required measurements of a laboratory value or other clinical test (e.g., ECG or radiograph) that results in symptoms, a change in treatment, or discontinuation of study treatment
- Recurrence of an intermittent medical condition (e.g., headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study treatment, or withholding of study treatment, whether prescribed in the protocol or not

The investigator, who is a qualified physician, and any designees are responsible for detecting, assessing, documenting, and reporting events that meet the definition of an AE or SAE, as well as other reportable safety events (e.g., pregnancy). Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome.

All AEs observed during the study will be reported on the CRF. All AEs, SAEs, and other reportable safety events, regardless of relationship to study treatment or procedure, that occur after the consent form is signed but before treatment started, must be reported by the investigator if the event caused the subject to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to, washout or discontinuation of usual therapy, diet, or a procedure.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event eCRF.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTcF interval is ≥ 450 ms and there is an increase of more than 60 ms from baseline (defined as average QTcF value from C1D1 pre-dose ECGs). Any ECG abnormality that the investigator considers as an AE should be reported as such.

All AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before treatment must be reported by the investigator if the event causes the subject to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

All AEs or events of clinical interest (ECIs) that occur from the start of treatment through 30 days following cessation of study treatment must be reported on the eCRF by the investigator. See [Section 11.5.2](#) for further discussion of SAEs and ECIs.

All AEs present at time of cessation of study treatment must be followed for 90 days after the subject's final dose (or 30 days after final dose if the subject initiates new anticancer therapy), or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events

Adverse events will be graded on a 5-point scale according to CTCAE v4.03 ([Appendix 1](#)). Investigators will report CTCAE grades for all AEs (for both increasing and decreasing severity).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of non-study, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study treatment will be recorded on the eCRF in response to the following question:

Is there a reasonable possibility that the study treatment caused the AE?

Not Related	A causal relationship between the study treatment and the AE is not a reasonable possibility.
Possibly Related	Has a chronological relationship with the time of study drug administration and/or represents a known reaction to study drug but probably the result of another factor; not clearly the result of an external factor.
Probably Related	Has a chronological relationship with the time of study drug administration and/or represents a known reaction to study drug but

possibly the result of another factor; not clearly the result of another factor, disappears or decreases after discontinuation of the study drug.

Definitely Related Has a chronological relationship with the time of study drug administration and/or represents a known reaction to study drug, not the result of another factor, disappears or decreases after discontinuation of the study drug, and recurs on re-challenge (if restarted).

11.5.2 *Serious Adverse Events, Events of Clinical Interest, and Events Associated with Special Situations*

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (i.e., the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect (in the child of a subject who was exposed to the study treatment)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

Events of clinical interest (ECIs) in this study, whether serious or not, include:

1. An overdose of FLX475 or pembrolizumab, as defined in [Section 11.5.3, Overdose](#), that is not associated with clinical symptoms or abnormal laboratory results.
2. An elevated AST or ALT value that is ≥ 3 times the upper limit of normal ($\times$ ULN) and an elevated total bilirubin value that is $\geq 2 \times$ ULN and, at the same time, an alkaline phosphatase value that is $< 2 \times$ ULN, as determined by protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be made available. It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to

proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor's medical monitor. However, abnormalities of liver blood test values that do not meet the criteria noted above are not ECIs for this study.

3. QTcF interval ≥ 450 ms with a > 60 ms increase from baseline (defined as average QTcF value from C1D1 pre-dose ECGs)
4. Significant GI toxicity, e.g., nausea, vomiting, diarrhea, or constipation not easily managed with symptomatic medications in an outpatient setting

In addition to the above ECIs, events associated with special situations include pregnancy or exposure to study treatment through breastfeeding; AEs associated with study treatment overdose, misuse, abuse, or medication error. Events associated with special situations and ECIs are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with special situations are to be reported on the eCRF whether or not they meet the criteria for SAEs. Any occurrences of pregnancies and exposure during breastfeeding must be reported by the investigator from the start of treatment through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the subject initiates new anticancer therapy, whichever is earlier.

Serious AEs must be reported for 90 days after the subject's final dose of study treatment, or for 30 days after the final dose of study treatment if the subject initiates new anticancer therapy, whichever is earlier. Additionally, any SAE brought to the attention of an investigator at any time outside the time periods specified above must be reported immediately to the Sponsor if the event is considered to be drug-related. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (i.e., there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study treatment administration)
- Hospitalization for administration of study treatment or insertion of access for administration of study treatment
- Hospitalization for routine maintenance of a device (e.g., battery replacement) that was in place before study entry

If possible, blood sample(s) for the measurement of FLX475 and pembrolizumab plasma concentrations should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

11.5.3 *Overdose*

For this study, an overdose of FLX475 will be defined as any dose ≥ 2 times the indicated dose. An overdose of pembrolizumab will be defined as any dose of 1000 mg or ≥ 5 times the indicated dose. No specific information is available on the treatment of an overdose of FLX475 or pembrolizumab. In the event of an overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

11.5.4 *Pregnancy, Contraception, and Breastfeeding*

FLX475 and pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if FLX475 or pembrolizumab has transient adverse effects on the composition of sperm.

Subjects should be informed that taking the study drug(s) may involve unknown risks to the unborn baby if pregnancy were to occur during the study. In order to participate in the study, subjects of childbearing potential must adhere to the contraception requirement (from the start of study treatment [or 14 days prior to the initiation of study treatment for oral contraception] throughout the study period up to 120 days after the final dose of study treatment). If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

If a female subject inadvertently becomes pregnant while receiving treatment with FLX475, pembrolizumab or both, she must immediately discontinue study treatment. If a female partner of a male subject inadvertently becomes pregnant while the subject is receiving treatment with FLX475, pembrolizumab, or both, the investigator must be informed immediately. The investigator will contact the subject at least monthly and document the status of the mother and pregnancy until the pregnancy has been completed or terminated (spontaneously or through induced abortion). See [Section 11.7.2](#) for reporting requirement.

It is unknown whether FLX475 or pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions of drugs in the nursing infant, females who are breastfeeding are not eligible for enrollment in this study.

11.5.5 *Laboratory Measurements*

Clinical laboratory tests to be performed are summarized in [Table 7](#). Subjects should be in a seated or supine position during blood collection. The Schedules of Procedures/Assessments ([Table 8](#) through [Table 11](#)) show the visits and time points at which blood, urine, and stool samples for clinical laboratory testing will be collected in the study.

Stool samples will be analyzed by the central laboratory. All other laboratory tests during the study will be analyzed locally on the day of collection unless otherwise instructed.

Table 7 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, MCV, MCH, platelets, RBC count, ANC, and WBC count with differential
Coagulation	PT, PTT or aPTT INR
Chemistry	
Electrolytes	Bicarbonate, calcium, chloride, magnesium, phosphorous, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, total bilirubin
Renal function tests	Blood urea nitrogen, creatinine
Thyroid function tests	Triiodothyronine (T3) or free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH)
Other	Albumin, glucose ^a , lactate dehydrogenase, total protein, uric acid, amylase, lipase Pregnancy test (serum or urine β -hCG) ^b
Urinalysis	Glucose, blood, ketones, pH, protein, specific gravity, bilirubin (microscopic UA with WBC, RBC, epithelial cells, bacteria, casts and crystals, only if necessary)

See Schedules of Assessments (Table 8 through Table 11) for timing of all laboratory tests.

ANC = absolute neutrophil count, aPTT = activated partial thromboplastin time, β -hCG = Beta-human chorionic gonadotropin, INR = international normalized ratio, PT = prothrombin time, PTT = partial prothrombin time, RBC = red blood cell, UA = urinalysis, ULN = upper limit of normal, WBC = white blood cell.

^a For subjects with blood glucose >ULN at screening or clinically significant elevations on study (e.g. potentially considered an AE), a fasting (>6 h, water only) blood glucose sample should be obtained within 24 hours or as feasible

^b Females of childbearing potential.

Results from all hematology, clinical chemistry (including serum pregnancy test, as applicable), or urinalysis samples (including urine pregnancy test, as applicable) obtained prior to study treatment administration do not need to be reviewed prior to administration/dispensing of study treatment at each scheduled study visit, except at the investigator's discretion, or upon request of the Sponsor (e.g. due to borderline or abnormal values at screening).

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 11.5.1 and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

11.5.6 Vital Signs and Weight Measurements

Vital sign measurements (i.e., systolic and diastolic blood pressure [BP] [mmHg], heart rate [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained at the visits designated in the Schedules of

Procedures/Assessments ([Table 8](#) through [Table 11](#)) by a validated method. Blood pressure and pulse will be measured with the subject in the sitting position, after resting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.

Only 1 BP measurement is needed for subjects with systolic BP < 140 mmHg and diastolic BP < 90 mmHg. If the subject's initial BP measurement is elevated (systolic BP $\geq$ 140 mmHg or diastolic BP $\geq$ 90 mmHg), the BP measurement should be repeated at least 5 minutes later. The mean value of 2 measurements at least 5 minutes apart is defined as 1 BP assessment. If the BP assessment (i.e., the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (systolic BP $\geq$ 140 mm Hg or diastolic BP $\geq$ 90 mm Hg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.

11.5.7 *Physical Examinations*

Physical examinations (including a neurologic examination) will be performed as designated in the Schedules of Procedures/Assessments ([Table 8](#) through [Table 11](#)). Documentation of the physical examination will be included in the source documentation at the investigational site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF. A symptom-directed physical examination will be performed as clinically indicated.

11.5.8 *Electrocardiograms*

Electrocardiograms will be obtained as designated in the Schedules of Procedures/Assessments ([Table 8](#) through [Table 11](#)). (Note that designated "Pre-dose" ECGs should be obtained at study visits even when study treatment is being held / not given.) Complete, standardized, 12-lead ECG recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3 x 4 lead format are to be used. In addition to a rhythm strip, a minimum of 3 full complexes should be recorded from each lead simultaneously. Data should be collected using digital machines and electronically archived. Subjects must remain undisturbed in the supine position for a period of $\geq$ 10 minutes prior to the ECG.

An ECG abnormality may meet the criteria of an AE as described in [Section 11.5.1](#) of this protocol and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events eCRF.

11.6 *Schedule of Procedures/Assessments*

[Table 8](#), [Table 9](#), [Table 10](#), and [Table 11](#) present the schedules of procedures/assessments for Parts 1a, 1b, 2a, and 2b of the study, respectively.

Table 8 Schedule of Procedures/Assessments in Study FLX475-02: Part 1a: FLX475 Monotherapy Dose Escalation

Study Period/Cycle	Screening	Treatment										Early Discon./ End of Study Treatment (ED/EOST) ^v	Long-Term Follow-Up ^w
		Cycle 1				Cycle 2			Cycle 3		Cycle 4+		
Cycle Day		1	2	8	15	1	8	15	1	15	1		
Study Day	-21 to 0	1	2	8	15	22	29	36	43	57	64 ⁺		
Investigational Product Dispensing and Administration													
FLX475 In-clinic Administration ^a		X	X	X	X	X	X	X	X	X	X		
FLX475 Dispensing ^b		X				X			X		X		
General and Safety Assessments													
Written Informed Consent	X												
Inclusion/Exclusion Criteria	X												
Demographics	X												
Medical History ^c	X												
Clinical Evaluation ^d	X	X	X	X	X	X		X	X		X	X	
Vital Signs ^e	X	X	X	X	X	X		X	X		X	X	
Triplicate 12-Lead ECGs ^f	X	X	X	X	X	X		X	X		X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	
Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	
Drug Diary Cards		X				X			X		X	X	
Drug Accountability		X				X			X		X	X	
Laboratory Assessments and Sample Collection													
Serum Chemistry ^g	X	X	X	X	X	X	X	X	X	X	X	X	
CBC with Differential ^h	X	X	X	X	X	X	X	X	X	X	X	X	
Coagulation Tests ⁱ	X	X				X			X		X	X	
Thyroid Function Tests ^j	X	X							X		X	X	
Urinalysis ^k	X	X				X			X		X	X	
Pregnancy Test ^l	X	X				X					X ^k	X	
FLX475 PK Samples ^m		X	X	X	X	X			X		X	X	
Immunophenotyping ⁿ		X	X	X		X					X	X	
Serum Biomarkers ^o		X	X	X		X					X	X	
PD Samples (Receptor Occupancy) ^p		X	X			X						X	

Study Period/Cycle	Screening	Treatment										Early Discon./ End of Study Treatment (ED/EOST) ^v	Long-Term Follow-Up ^w
		Cycle 1				Cycle 2			Cycle 3		Cycle 4+		
Cycle Day		1	2	8	15	1	8	15	1	15	1		
Study Day	-21 to 0	1	2	8	15	22	29	36	43	57	64 ⁺		
Whole Blood Biomarkers ^q	X		X	X		X					X	X	
Fecal Microbiome Samples ^r	X										X	X	
Disease Assessments													
Disease Classification	X												
Tumor Imaging/Staging (CT/MRI Scan) ^s	X										X		
Tumor Biopsy ^t	X								X				
Response Assessment ^u											X	X	
Posttherapy Long-Term Follow-Up													X

ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; INR = international normalized ratio; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; MRI = magnetic resonance imaging; PD = pharmacodynamic; PK = pharmacokinetic; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; UA = urinalysis; WBC = white blood cell.

Cycle 1, Day 1 and Day 2 visits must occur as scheduled. Other study visits may occur within a window of ±3 days.

All “pre-dose” assessments (including PK and ECGs) should be obtained at study visits even when study treatment is being held or not given.

- ^a On days when a clinic visit with PK assessments occurs, the dose of FLX475 will be administered in the clinic after the specified visit assessments and procedures are performed. In addition, the dose of FLX475 should be self-administered in the clinic on Day 1 of each cycle only after a new supply of drug has been dispensed for that cycle, for drug accountability purposes. A diary card will be provided to each subject for recording of all dose administration information.
- ^b Dispensing of 3-week supply of FLX475 to the subject with instructions for self-administration at home.
- ^c Relevant medical history including current disease and prior treatment, including last prior therapy, best response to last prior therapy (PR, CR, SD, or PD) and either time on last therapy or duration of response
- ^d Clinical evaluation will include assessment of ECOG performance status, physical examination (at screening, response assessments, and as clinically indicated), and measurement of height (screening only) and weight.
- ^e Vital signs (blood pressure, pulse, respiratory rate, and temperature) will be collected with the subject in a sitting position. Vital signs will be assessed pre-dose and at 0.5, 1, 2, 4, and 6 hours post-dose on Cycle 1, Day 1; pre-dose on Cycle 1, Day 2; pre-dose and 2 hours post-dose on Cycle 1, Days 8 and 15; pre-dose and at 0.5, 1, 2, 4, and 6 hours post-dose on Cycle 2, Day 1; pre-dose and 2 hours post-dose on Cycle 2, Day 15. Vital signs will also be assessed pre-dose on Day 1 of all subsequent cycles and at Early Discontinuation/ End of Study Treatment (ED/EOST). Acceptable windows for collection are as follows: pre-dose samples must be within 6 hours prior to dosing; 0.5 hour post-dose ±15 minutes; 1 hour post-dose ±15 minutes; 2, 4, and 6 hour post-dose ±30 minutes.

- ^f Triplicate ECGs with tracings ≥ 30 seconds apart must be collected in digital format on designated calibrated ECG equipment after at least 10 minutes of quiet rest in supine position. Meals should not be served shortly before ECGs. Triplicate ECGs should be collected at Screening Visit; -0.75, -0.5, and -0.25 hours pre-dose and 0.5, 1, 2, 4, and 6 hours post-dose on Cycle 1, Day 1; pre-dose on Cycle 1, Day 2; pre-dose and 2 hours post-dose on Cycle 1, Days 8 and 15; pre-dose and at 0.5, 1, 2, 4, and 6 hours post-dose on Cycle 2, Day 1; pre-dose and 2 hours post-dose on Cycle 2, Day 15; pre-dose and 2 hours post-dose on Day 1 of Cycles 3 and beyond; and at Early Discontinuation / End of Study Treatment (ED/EOST). Acceptable windows for collection are as follows: general pre-dose ECGs must be within 2 hours prior to dosing; -0.75, -0.5, -0.25 hour pre-dose ± 5 minutes; 0.5 hour post-dose ± 5 minutes; 1 hour post-dose ± 15 minutes; 2, 4, and 6 hour post-dose ± 30 minutes. Pre-dose ECGs must also be obtained at designated study visits when study drug is being held / not given.
- ^g Serum Chemistry: including sodium, potassium, chloride, total protein, bicarbonate, albumin, calcium, magnesium, phosphorous, glucose, BUN, creatinine, uric acid, total bilirubin, ALP, LDH, AST, ALT, amylase and lipase. Serum Chemistry to be collected pre-dose (within 6 hours prior to dosing) on study visit days, including Days 1 and 15 for Cycle 3 and on Day 1 only for subsequent cycles.
- ^h Complete Blood Count and Differential: WBC, RBC, ANC, hemoglobin, hematocrit, MCV, MCH, platelets, and WBC differential. CBC with differential to be performed as noted pre-dose (within 6 hours prior to dosing) for Cycles 1 and 2, and on Days 1 and 15 for Cycle 3 and on Day 1 only for subsequent cycles.
- ⁱ Coagulation Tests should be obtained pre-dose (within 6 hours prior to dosing): PT, PTT or aPTT, and INR
- ^j Thyroid function tests should be obtained at screening and pre-dose (within 6 hours prior to dosing) Day 1 of Cycle 1 and every odd-numbered cycle during study treatment. Thyroid panel should include (1) Triiodothyronine (T3) or Free Triiodothyronine (FT3), (2) Free Thyroxine (FT4), and (3) Thyroid Stimulating Hormone (TSH).
- ^k Urinalysis should be obtained pre-dose (within 6 hours prior to dosing), and will include specific gravity, pH, blood, protein, glucose, ketones and bilirubin (microscopic UA with WBC, RBC, epithelial cells, bacteria, casts and crystals, only if necessary).
- ^l Serum pregnancy test only in women of childbearing potential during screening; urine or serum pregnancy test at all other time points. After Cycle 2, pregnancy testing will be performed on Day 1 of every even-numbered cycle (e.g., Cycle 4, 6, etc.).
- ^m FLX475 PK samples will be collected at the following time points: pre-dose and 0.5, 1, 2, 4, and 6 hours post-dose on Cycle 1, Day 1; pre-dose on Cycle 1, Day 2; pre-dose on Cycle 1, Days 8 and 15; pre-dose and at 0.5, 1, 2, 4, and 6 hours post-dose on Cycle 2, Day 1; pre-dose on Day 1 of odd-numbered cycles from Cycles 3 and beyond; and at Early Discontinuation / End of Study Treatment (ED/EOST). Samples may also be drawn at investigator discretion, e.g., during a clinically significant adverse event potentially related to study treatment. Acceptable windows for sampling include within 30 minutes prior to dose for pre-dose samples, ± 5 minutes for 0.5-hour post-dose samples, ± 15 minutes for 1 hour post-dose samples, and ± 30 minutes for other post-dose samples. PK samples should be obtained as close as possible both to protocol stipulated times and to concurrently scheduled ECGs. Pre-dose PK samples must also be obtained at designated study visits when study drug is being held / not given.
- ⁿ Immunophenotyping: Samples will be obtained for T/B/NK and T-cell panels pre-dose on Cycle 1, Days 1, 2 and 8; pre-dose on Day 1 of even-numbered Cycles 2 and beyond; and at Early Discontinuation / End of Study Treatment (ED/EOST). Acceptable window for pre-dose collection is within 2 hours prior to dosing.
- ^o Serum Biomarkers: Samples will be collected pre-dose and 6 hours post-dose on Cycle 1, Day 1; pre-dose on Cycle 1, Days 2 and 8; pre-dose on Day 1 of even-numbered Cycles 2 and beyond; and at Early Discontinuation / End of Study Treatment (ED/EOST). Acceptable windows for collection are as follows: pre-dose within 2 hours prior to dosing; 6 hours post-dose ± 30 minutes. Samples may also be drawn at investigator discretion, e.g., during a clinically significant adverse event potentially related to study treatment.

- ^p PD Samples for Receptor Occupancy/Internalization will be collected only for subjects at North American sites at pre-dose on Cycle 1, Day 1; pre-dose on Cycle 1, Day 2; pre-dose on Cycle 2, Day 1; and at Early Discontinuation / End of Study Treatment (ED/EOST). Acceptable window for pre-dose collection is within 2 hours prior to dosing.
- ^q Whole Blood Biomarkers: Samples will be collected at Screening Visit (2 samples); pre-dose on Cycle 1, Days 2 and 8; pre-dose on Day 1 of even-numbered Cycles 2 and beyond; and at Early Discontinuation / End of Study Treatment (ED/EOST). Acceptable window for pre-dose collection is within 2 hours prior to dosing.
- ^r Stool samples for fecal microbiome studies will be collected at baseline and timed with certain response assessments, including after the first 3 cycles, then every 4 cycles for the first year, followed by every 6 cycles thereafter for up to 2 years (i.e., within ± 5 days of Cycle 4, Day 1; Cycle 8, Day 1; etc.) and at any time per investigator's discretion and at Early Discontinuation / End of Study Treatment (ED/EOST). These samples should not be collected after August 1, 2021.
- ^s Tumor Imaging/Staging (CT/MRI Scan): After baseline scan, response assessments will be performed 9 weeks (± 1 week) from Cycle 1, Day 1, then every 6 weeks (± 1 week) for the first year, followed by every 9 weeks (± 1 week) thereafter for up to 2 years and at any time per investigator's discretion. Confirmatory scans should also be obtained 4–6 weeks following initial documentation of objective response. Response and progression will be evaluated in this study using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used. Lugano criteria will be used for subjects with lymphoma (see [Appendix 6](#) for details).
- ^t Tumor Biopsy: Subjects enrolled on the clinical trial must be willing and able to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion (minimum of 3 cores). Subjects in dose escalation for whom newly obtained samples cannot be provided (e.g., inaccessible or subject safety concern) may submit an archived specimen only upon agreement from the Sponsor (not applicable to any subject enrolled in Part 2 expansion). Subjects enrolled in either the dose escalation or expansion cohorts will undergo a core biopsy or excisional biopsy of a lesion (minimum of 3 cores) prior to starting treatment and in Cycle 3 Day 1 (± 7 days). There will be an option to also obtain additional biopsies at clinically significant time points (e.g., early disease response or upon progression of disease) with subject consent.
- ^u Response Assessment: Initial response assessment will be performed after the first 3 cycles, then every 2 cycles for the first year, followed by every 3 cycles thereafter for up to 2 years (i.e., within ± 7 days of Cycle 4, Day 1; Cycle 6, Day 1; etc.) and at any time per investigator's discretion and at Early Discontinuation / End of Study Treatment (ED/EOST) (unless clear PD has been documented previously).
- ^v All Early Discontinuation / End of Study Treatment (ED/EOST) assessments must be performed within 90 days following the subject's last administration of study treatment and prior to initiation of any other treatment, whichever comes first. After the final dose of study treatment, subjects should be followed for any drug-related AEs and/or ongoing SAEs for 90 days or until those events have resolved or become stable, whichever occurs later (or through 30 days following cessation of study treatment if the subject initiates new anticancer therapy, if that occurs earlier).
- ^w Data regarding poststudy anti-tumor therapy and survival will be collected from all subjects who receive ≥ 1 dose of FLX475 or pembrolizumab. Such information will be collected at ~ 3 to 6-month intervals as described in [Section 8.2.3](#) of the protocol. This long-term follow-up information will be gathered during routine clinic visits, other study site contact with the subjects, or via telephone or e-mail with the subjects/caregivers or referring physician offices. These data will be collected in the source documents (e.g., subject medical record) and transcribed into a specific eCRF.

Table 9 Schedule of Visits and Procedures in Study FLX475-02: Part 1b: FLX475/Pembrolizumab Combination Dose Escalation

Study Period/Cycle	Screening	Treatment										Early Discon./ End of Study Treatment (ED/EOST) ^v	Long-Term Follow-Up ^w
		Cycle 1				Cycle 2			Cycle 3		Cycle 4+		
		1	2	8	15	1	8	15	1	15	1		
Cycle Day		1	2	8	15	22	29	36	43	57	64 ⁺		
Study Day	-21 to 0	1	2	8	15	22	29	36	43	57	64 ⁺		
Investigational Product Dispensing and Administration													
FLX475 In-clinic Administration ^a		X	X	X	X	X	X	X	X	X	X		
Pembrolizumab Administration ^a		X				X			X		X		
FLX475 Dispensing ^b		X				X			X		X		
General and Safety Assessments													
Written Informed Consent	X												
Inclusion/Exclusion Criteria	X												
Demographics	X												
Medical History ^c	X												
Clinical Evaluation ^d	X	X	X	X	X	X		X	X		X	X	
Vital Signs ^e	X	X	X	X	X	X		X	X		X	X	
Triplicate 12-Lead ECGs ^f	X	X	X	X	X	X		X	X		X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	
Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	
Drug Diary Cards		X				X			X		X	X	
Drug Accountability		X				X			X		X	X	
Laboratory Assessments and Sample Collection													
Serum Chemistry ^g	X	X	X	X	X	X	X	X	X	X	X	X	
CBC with Differential ^h	X	X	X	X	X	X	X	X	X	X	X	X	
Coagulation Tests ⁱ	X	X				X			X		X	X	
Thyroid Function Tests ^j	X	X							X		X	X	
Urinalysis ^k	X	X				X			X		X	X	
Pregnancy Test ^l	X	X				X					X ^k	X	
FLX475 PK Samples ^m		X	X	X	X	X			X		X	X	
Immunophenotyping ⁿ		X	X	X		X					X	X	

Study Period/Cycle	Screening	Treatment										Early Discon./ End of Study Treatment (ED/EOST) ^v	Long-Term Follow-Up ^w
		Cycle 1				Cycle 2			Cycle 3		Cycle 4+		
Cycle Day		1	2	8	15	1	8	15	1	15	1		
Study Day	-21 to 0	1	2	8	15	22	29	36	43	57	64 ⁺		
Serum Biomarkers ^o		X	X	X		X					X	X	
PD Samples (Receptor Occupancy) ^p		X	X			X						X	
Whole Blood Biomarkers ^q	X		X	X		X					X	X	
Fecal Microbiome Samples ^r	X										X	X	
Disease Assessments													
Disease Classification	X												
Tumor Imaging/Staging (CT/MRI Scan) ^s	X										X		
Tumor Biopsy ^t	X								X				
Response Assessment ^u											X	X	
Posttherapy Long-Term Follow-Up													X

ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; INR = international normalized ratio; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; MRI = magnetic resonance imaging; PD = pharmacodynamic; PK = pharmacokinetic; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; UA = urinalysis; WBC = white blood cell.

Cycle 1, Day 1 and Day 2 visits must occur as scheduled. Other study visits may occur within a window of ±3 days.

All “pre-dose” assessments (including PK and ECGs) should be obtained at study visits even when study treatment is being held or not given.

- ^a On days when a clinic visit with PK assessments occurs, the dose of FLX475 will be administered in the clinic after the specified visit assessments and procedures are performed. In addition, the dose of FLX475 should be self-administered in the clinic on Day 1 of each cycle only after a new supply of drug has been dispensed for that cycle, for drug accountability purposes. A diary card will be provided to each subject for recording of all dose administration information.
Pembrolizumab will be administered at a dose of 200 mg IV over 30 minutes on Day 1 of each cycle. Pembrolizumab infusion should occur approximately 1 hour after the dose of FLX475 is administered in the clinic and after all 1 hour post-dose procedures have occurred.
- ^b Dispensing of 3-week supply of FLX475 to the subject with instructions for self-administration at home.
- ^c Relevant medical history including current disease and prior treatment, including last prior therapy, best response to last prior therapy (PR, CR, SD, or PD) and either time on last therapy or duration of response.
- ^d Clinical evaluation will include assessment of ECOG performance status, physical examination (at screening, response assessments, and as clinically indicated), and measurement of height (screening only) and weight.
- ^e Vital signs (blood pressure, pulse, respiratory rate, and temperature) will be collected with the subject in a sitting position. Vital signs will be assessed pre-dose and at 0.5, 1, 2, 4, and 6 hours post-dose on Cycle 1, Day 1; pre-dose on Cycle 1, Day 2; pre-dose and 2 hours post-dose on Cycle 1, Days 8 and 15; pre-dose and at 0.5, 1, 2, 4, and 6 hours post-dose on Cycle 2, Day 1; pre-dose and 2 hours post-dose on Cycle 2, Day 15. Vital signs will also be assessed

pre-dose on Day 1 of all subsequent cycles and at Early Discontinuation / End of Study Treatment (ED/EOST). Acceptable windows for collection are as follows: pre-dose samples must be within 6 hours prior to dosing; 0.5 hour post-dose ± 5 minutes; 1 hour post-dose ± 15 minutes; 2, 4, and 6 hour post-dose ± 30 minutes.

- ^f Triplicate ECGs with tracings ≥ 30 seconds apart must be collected in digital format on designated calibrated ECG equipment after at least 10 minutes of quiet rest in supine position. Meals should not be served shortly before ECGs. Triplicate ECGs should be collected at Screening Visit; -0.75, -0.5, and -0.25 hours pre-dose and 0.5, 1, 2, 4, and 6 hours post-dose on Cycle 1, Day 1; pre-dose on Cycle 1, Day 2; pre-dose and 2 hours post-dose on Cycle 1, Days 8 and 15; pre-dose and at 0.5, 1, 2, 4, and 6 hours post-dose on Cycle 2, Day 1; pre-dose and 2 hours post-dose on Cycle 2, Day 15; pre-dose and 2 hours post-dose on Day 1 of Cycles 3 and beyond; and at Early Discontinuation / End of Study Treatment (ED/EOST). Acceptable windows for collection are as follows: general pre-dose ECGs must be within 2 hours prior to dosing; -0.75, -0.5, -0.25 hour pre-dose ± 5 minutes; 0.5 hour post-dose ± 5 minutes; 1 hour post-dose ± 15 minutes; 2, 4, and 6 hour post-dose ± 30 minutes. Pre-dose ECGs must also be obtained at designated study visits when study drug is being held / not given.
- ^g Serum Chemistry: including sodium, potassium, chloride, total protein, bicarbonate, albumin, calcium, magnesium, phosphorous, glucose, BUN, creatinine, uric acid, total bilirubin, ALP, LDH, AST, ALT, amylase and lipase. Serum Chemistry to be collected pre-dose (within 6 hours prior to dosing) on study visit days, including Days 1 and 15 for Cycle 3 and on Day 1 only for subsequent cycles.
- ^h Complete Blood Count and Differential: WBC, RBC, ANC, hemoglobin, hematocrit, MCV, MCH, platelets, and WBC differential. CBC with differential to be performed as noted pre-dose (within 6 hours prior to dosing) for Cycles 1 and 2, and on Days 1 and 15 for Cycle 3 and on Day 1 only for subsequent cycles.
- ⁱ Coagulation Tests should be obtained pre-dose (within 6 hours prior to dosing): PT, PTT or aPTT, and INR
- ^j Thyroid function tests should be obtained at screening and pre-dose (within 6 hours prior to dosing) Day 1 of Cycle 1 and every odd-numbered cycle during study treatment. Thyroid panel should include (1) Triiodothyronine (T3) or Free Triiodothyronine (FT3), (2) Free Thyroxine (FT4), and (3) Thyroid Stimulating Hormone (TSH).
- ^k Urinalysis should be obtained pre-dose (within 6 hours prior to dosing), and will include specific gravity, pH, blood, protein, glucose, ketones and bilirubin (microscopic UA with WBC, RBC, epithelial cells, bacteria, casts and crystals, only if necessary).
- ^l Serum pregnancy test only in women of childbearing potential during screening; urine or serum pregnancy test at all other time points. After Cycle 2, pregnancy testing will be performed on Day 1 of every even-numbered cycle (e.g., Cycle 4, 6, etc.).
- ^m FLX475 PK samples will be collected at the following time points: pre-dose and 0.5, 1, 2, 4, and 6 hours post-dose on Cycle 1, Day 1; pre-dose on Cycle 1, Day 2; pre-dose on Cycle 1, Days 8 and 15; pre-dose and at 0.5, 1, 2, 4, and 6 hours post-dose on Cycle 2, Day 1; pre-dose on Day 1 of odd-numbered cycles from Cycles 3 and beyond; and at Early Discontinuation / End of Study Treatment (ED/EOST). Samples may also be drawn at investigator discretion, e.g., during a clinically significant adverse event potentially related to study treatment. Acceptable windows for sampling include within 30 minutes prior to dose for pre-dose samples, ± 5 minutes for 0.5-hour post-dose samples, ± 15 minutes for 1 hour post-dose samples, and ± 30 minutes for other post-dose samples. PK samples should be obtained as close as possible both to protocol stipulated times and to concurrently scheduled ECGs. Pre-dose PK samples must also be obtained at designated study visits when study drug is being held / not given.
- ⁿ Immunophenotyping: Samples will be obtained for T/B/NK and T-cell panels pre-dose Cycle 1, Days 1, 2, and 8; pre-dose on Day 1 of even-numbered Cycles 2 and beyond; and at Early Discontinuation / End of Study Treatment (ED/EOST). Acceptable window for pre-dose collection is within 2 hours prior to dosing.
- ^o Serum Biomarkers: Samples will be collected pre-dose and 6 hours post-dose on Cycle 1, Day 1; pre-dose on Cycle 1, Days 2 and 8; pre-dose on Day 1 of even-numbered Cycles 2 and beyond; and at Early Discontinuation / End of Study Treatment (ED/EOST). Acceptable windows for collection are as

follows: pre-dose within 2 hours prior to dosing; 6 hours post-dose ± 30 minutes. Samples may also be drawn at investigator discretion, e.g., during a clinically significant adverse event potentially related to study treatment.

- ^p PD Samples for Receptor Occupancy/Internalization will be collected only for subjects at North American sites pre-dose on Cycle 1, Day 1; pre-dose on Cycle 1, Day 2; pre-dose on Cycle 2, Day 1; and at Early Discontinuation / End of Study Treatment (ED/EOST). Acceptable window for pre-dose collection is within 2 hours prior to dosing.
- ^q Whole Blood Biomarkers: Samples will be collected at Screening Visit (2 samples); pre-dose on Cycle 1, Days 2 and 8; pre-dose on Day 1 of even-numbered Cycles 2 and beyond; and at Early Discontinuation / End of Study Treatment (ED/EOST). Acceptable window for pre-dose collection is within 2 hours prior to dosing.
- ^r Stool samples for fecal microbiome studies will be collected at baseline and timed with certain response assessments, including after the first 3 cycles, then every 4 cycles for the first year, followed by every 6 cycles thereafter for up to 2 years (i.e., within ± 5 days of Cycle 4, Day 1; Cycle 8, Day 1; etc.) and at any time per investigator's discretion and at Early Discontinuation / End of Study Treatment (ED/EOST). These samples should not be collected after August 1, 2021.
- ^s Tumor Imaging/Staging (CT/MRI Scan): After baseline scan, response assessments will be performed 9 weeks (± 1 week) from Cycle 1, Day 1, then every 6 weeks (± 1 week) for the first year, followed by every 9 weeks (± 1 week) thereafter for up to 2 years and at any time per investigator's discretion. Confirmatory scans should also be obtained 4-6 weeks following initial documentation of objective response. Response and progression will be evaluated in this study using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used. Lugano criteria will be used for subjects with lymphoma (see [Appendix 6](#) for details).
- ^t Tumor Biopsy: Subjects enrolled on the clinical trial must be willing and able to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion (minimum of 3 cores). Subjects in dose escalation for whom newly obtained samples cannot be provided (e.g., inaccessible or subject safety concern) may submit an archived specimen only upon agreement from the Sponsor (not applicable to any subject enrolled in Part 2 expansion). Subjects enrolled in either the dose escalation or expansion cohorts will undergo a core biopsy or excisional biopsy of a lesion (minimum of 3 cores) prior to starting treatment and in Cycle 3 Day 1 (± 7 days). There will be an option to also obtain additional biopsies at clinically significant time points (e.g., early disease response or upon progression of disease) with subject consent.
- ^u Response Assessment: Initial response assessment will be performed after the first 3 cycles, then every 2 cycles for the first year, followed by every 3 cycles thereafter for up to 2 years (i.e., within ± 7 days of Cycle 4, Day 1; Cycle 6, Day 1; etc.) and at any time per investigator's discretion and at Early Discontinuation/ End of Study Treatment (ED/EOST) (unless clear PD has been documented previously).
- ^v All Early Discontinuation / End of Study Treatment (ED/EOST) assessments must be performed within 90 days following the subject's last administration of study treatment and prior to initiation of any other treatment, whichever comes first. After the final dose of study treatment, subjects should be followed for any drug-related AEs and/or ongoing SAEs for 90 days or until those events have resolved or become stable, whichever occurs later (or through 30 days following cessation of study treatment if the subject initiates new anticancer therapy, if that occurs earlier).
- ^w Data regarding poststudy anti-tumor therapy and survival will be collected from all subjects who receive ≥ 1 dose of FLX475 or pembrolizumab. Such information will be collected at ~ 3 to 6-month intervals as described in [Section 8.2.3](#) of the protocol. This long-term follow-up information will be gathered during routine clinic visits, other study site contact with the subjects, or via telephone or e-mail with the subjects/caregivers or referring physician offices. These data will be collected in the source documents (e.g., subject medical record) and transcribed into a specific eCRF.

Table 10 Schedule of Visits and Procedures in Study FLX475-02 – Part 2a: FLX475 Monotherapy Expansion Cohorts

Study Period/Cycle	Screening	Treatment									Early Discon./ End of Study Treatment (ED/EOST) ^v	Long-Term Follow-Up ^w
		Cycle 1			Cycle 2			Cycle 3		Cycle 4+		
Cycle Day		1	8	15	1	8	15	1	15	1		
Study Day	-21 to 0	1	8	15	22	29	36	43	57	64 ⁺		
Investigational Product Dispensing and Administration												
FLX475 In-clinic Administration ^a		X	X	X	X	X	X	X	X	X		
FLX475 Dispensing ^b		X			X			X		X		
General and Safety Assessments												
Written Informed Consent	X											
Inclusion/Exclusion Criteria	X											
Demographics	X											
Medical History ^c	X											
Clinical Evaluation ^d	X	X	X	X	X		X	X		X	X	
Vital Signs ^e	X	X	X	X	X		X	X		X	X	
Triplicate 12-Lead ECGs ^f	X	X	X		X			X		X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	
Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	
Drug Diary Cards		X			X			X		X	X	
Drug Accountability		X			X			X		X	X	
Laboratory Assessments and Sample Collection												
Serum Chemistry ^g	X	X	X	X	X	X	X	X	X	X	X	
CBC with Differential ^h	X	X	X	X	X	X	X	X	X	X	X	
Coagulation Tests ⁱ	X	X			X			X		X	X	
Thyroid Function Tests ^j	X	X						X		X	X	
Urinalysis ^k	X	X			X			X		X	X	
Pregnancy Test ^l	X	X			X					X ^k	X	
FLX475 PK Samples ^m		X			X			X		X	X	
Immunophenotyping ⁿ		X	X		X					X	X	
Serum Biomarkers ^o		X	X		X					X	X	
PD Samples (Receptor Occupancy) ^p		X			X						X	
Whole Blood Biomarkers ^q	X		X		X					X	X	
Fecal Microbiome Samples ^r	X									X	X	

Study Period/Cycle	Screening	Treatment									Early Discon./ End of Study Treatment (ED/EOST) ^v	Long-Term Follow-Up ^w
		Cycle 1			Cycle 2			Cycle 3		Cycle 4+		
Cycle Day		1	8	15	1	8	15	1	15	1		
Study Day	-21 to 0	1	8	15	22	29	36	43	57	64 ⁺		
Disease Assessments												
Disease Classification	X											
Tumor Imaging/Staging (CT/MRI Scan) ^s	X									X		
Tumor Biopsy ^t	X							X				
Response Assessment ^u										X	X	
Posttherapy Long-Term Follow-Up												X

ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; INR = international normalized ratio; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; MRI = magnetic resonance imaging; PD = pharmacodynamic; PK = pharmacokinetic; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; UA = urinalysis; WBC = white blood cell.

Study visits after Cycle 1, Day 1 may occur within a window of ± 3 days.

All “pre-dose” assessments (including PK and ECGs) should be obtained at study visits even when study treatment is being held or not given.

- ^a On days when a clinic visit with PK assessments occurs, the dose of FLX475 will be administered in the clinic after the specified visit assessments and procedures are performed. In addition, the dose of FLX475 should be self-administered in the clinic on Day 1 of each cycle only after a new supply of drug has been dispensed for that cycle, for drug accountability purposes. A diary card will be provided to each subject for recording of all dose administration information.
- ^b Dispensing of 3-week supply of FLX475 to the subject with instructions for self-administration at home.
- ^c Relevant medical history including current disease and prior treatment, including last prior therapy, best response to last prior therapy (PR, CR, SD, or PD) and either time on last therapy or duration of response.
- ^d Clinical evaluation will include assessment of ECOG performance status, physical examination (at screening, response assessments, and as clinically indicated), and measurement of height (screening only) and weight.
- ^e Vital signs (blood pressure, pulse, respiratory rate, and temperature) will be collected with the subject in a sitting position. Vital signs will be assessed pre-dose and at 0.5, 1, 2, and 4 hours post-dose on Cycle 1, Day 1; pre-dose and 2 hours post-dose on Cycle 1, Days 8, and 15; pre-dose and at 0.5, 1, 2, and 4 hours post-dose on Cycle 2, Day 1; pre-dose and 2 hours post-dose on Cycle 2, Day 15. Vital signs will also be assessed pre-dose on Day 1 of all subsequent cycles and at Early Discontinuation / End of Study Treatment (ED/EOST). Acceptable windows for collection are as follows: pre-dose samples must be within 6 hours prior to dosing; 0.5 hour post-dose ± 5 minutes; 1 hour post-dose ± 15 minutes; 2 and 4 hour post-dose ± 30 minutes.
- ^f Triplicate ECGs with tracings ≥ 30 seconds apart must be collected in digital format on designated calibrated ECG equipment after at least 10 minutes of quiet rest in supine position. Meals should not be served shortly before ECGs. Triplicate ECGs should be collected at Screening Visit; -0.75, -0.5, and -0.25 hours pre-dose and 2 and 4 hours post-dose on Cycle 1, Day 1; pre-dose and 2 hours post-dose on Cycle 1, Day 8; pre-dose and 2 hours post-dose on Day 1 of Cycles 2-6; and at Early Discontinuation / End of Study Treatment (ED/EOST). Acceptable windows for collection are as follows: general

pre-dose ECGs must be within 2 hours prior to dosing; -0.75, -0.5, -0.25 hour pre-dose ± 5 minutes; 2 and 4 hour post-dose ± 30 minutes. Pre-dose ECGs must also be obtained at designated study visits when study drug is being held / not given.

- ^g Serum Chemistry: including sodium, potassium, chloride, total protein, bicarbonate, albumin, calcium, magnesium, phosphorous, glucose, BUN, creatinine, uric acid, total bilirubin, ALP, LDH, AST, ALT, amylase and lipase. Serum Chemistry to be collected pre-dose (within 6 hours prior to dosing) on study visit days, including Days 1 and 15 for Cycle 3 and on Day 1 only for subsequent cycles.
- ^h Complete Blood Count and Differential: WBC, RBC, ANC, hemoglobin, hematocrit, MCV, MCH, platelets, and WBC differential. CBC with differential to be performed as noted pre-dose (within 6 hours prior to dosing) for Cycles 1 and 2, and on Days 1 and 15 for Cycle 3 and on Day 1 only for subsequent cycles.
- ⁱ Coagulation Tests should be obtained pre-dose (within 6 hours prior to dosing): PT, PTT or aPTT, and INR
- ^j Thyroid function tests should be obtained at screening and pre-dose (within 6 hours prior to dosing) Day 1 of Cycle 1 and every odd-numbered cycle during study treatment. Thyroid panel should include (1) Triiodothyronine (T3) or Free Triiodothyronine (FT3), (2) Free Thyroxine (FT4), and (3) Thyroid Stimulating Hormone (TSH).
- ^k Urinalysis should be obtained pre-dose (within 6 hours prior to dosing), and will include specific gravity, pH, blood, protein, glucose, ketones and bilirubin (microscopic UA with WBC, RBC, epithelial cells, bacteria, casts and crystals, only if necessary).
- ^l Serum pregnancy test only in women of childbearing potential during screening; urine or serum pregnancy test at all other time points. After Cycle 2, pregnancy testing will be performed on Day 1 of every even-numbered cycle (e.g., Cycle 4, 6, etc.).
- ^m FLX475 PK samples will be collected at the following time points: pre-dose and 2 and 4 hours post-dose on Cycle 1, Day 1; pre-dose on Day 1 of Cycles 2-6; and at Early Discontinuation / End of Study Treatment (ED/EOST). Samples may also be drawn at investigator discretion, e.g., during a clinically significant adverse event potentially related to study treatment. Acceptable windows for sampling include within 30 minutes prior to dose for pre-dose samples and ± 30 minutes for other post-dose samples. PK samples should be obtained as close as possible both to protocol stipulated times and to concurrently scheduled ECGs. Pre-dose PK samples must also be obtained at designated study visits when study drug is being held / not given.
- ⁿ Immunophenotyping: Samples will be obtained for T/B/NK and T-cell panels pre-dose on Cycle 1, Days 1 and 8; pre-dose on Day 1 of even-numbered Cycles 2 and beyond; and at Early Discontinuation / End of Study Treatment (ED/EOST). Acceptable window for pre-dose collection is within 2 hours prior to dosing.
- ^o Serum Biomarkers: Samples will be collected pre-dose on Cycle 1, Day 1; pre-dose on Cycle 1, Day 8; pre-dose on Day 1 of even-numbered Cycles 2 and beyond; and at Early Discontinuation / End of Study Treatment (ED/EOST). Acceptable windows for collection are as follows: pre-dose within 2 hours prior to dosing. Samples may also be drawn at investigator discretion, e.g., during a clinically significant adverse event potentially related to study treatment.
- ^p PD Samples for Receptor Occupancy/Internalization will be collected only for designated subjects at North American sites (e.g. Hodgkin lymphoma) at pre-dose on Cycle 1, Day 1; pre-dose on Cycle 2, Day 1; and at Early Discontinuation / End of Study Treatment (ED/EOST). Acceptable window for pre-dose collection is within 2 hours prior to dosing. Collection of these samples will be discontinued as of November 1, 2021.
- ^q Whole Blood Biomarkers: Samples will be collected at Screening Visit (2 samples); pre-dose on Cycle 1, Day 8; pre-dose on Day 1 of even-numbered Cycles 2 and beyond; and at Early Discontinuation / End of Study Treatment (ED/EOST). Acceptable window for pre-dose collection is within 2 hours prior to dosing.
- ^r Stool samples for fecal microbiome studies will be collected at baseline and timed with certain response assessments, including after the first 3 cycles, then every 4 cycles for the first year, followed by every 6 cycles thereafter for up to 2 years (i.e., within ± 5 days of Cycle 4, Day 1; Cycle 8, Day 1; etc.) and at

any time per investigator's discretion and at Early Discontinuation / End of Study Treatment (ED/EOST). These samples should not be collected after August 1, 2021.

- ^s Tumor Imaging/Staging (CT/MRI Scan): After baseline scan, response assessments will be performed after the first 3 cycles, then every 2 cycles for the first year (i.e., within + 7 days of cycle 4, Day 1; Cycle 6, Day 1 etc.; until Cycle 20, Day 1), followed by every 3 cycles for up to 2 years (i.e., within $\pm$ 7 days of Cycle 23, Day 1; Cycle 26, Day 1 etc.; until Cycle 35, Day 1) and at any time per investigator's discretion and at Early Discontinuation / End of Study Treatment (ED/EOST) (unless clear PD has been documented previously).. Confirmatory scans should also be obtained 4–6 weeks following initial documentation of objective response. Response and progression will be evaluated in this study using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used. Lugano criteria will be used for subjects with lymphoma (see [Appendix 6](#) for details) other than those with CTCL, for which alternative criteria should be used ([Olsen et al., 2011](#)). Note that 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.
- ^t Tumor Biopsy: Subjects enrolled on the clinical trial must be willing and able to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion (minimum of 3 cores). Subjects enrolled in either the dose escalation or expansion cohorts will undergo a core biopsy or excisional biopsy of a lesion (minimum of 3 cores) prior to starting treatment and in Cycle 3 Day 1 ($\pm$ 7 days). There will be an option to also obtain additional biopsies at clinically significant time points (e.g., early disease response or upon progression of disease) with subject consent.
- ^u Response Assessment: Initial response assessment will be performed after the first 3 cycles, then every 2 cycles for the first year, (i.e., within $\pm$ 7 days of cycle 4, Day 1; Cycle 6, Day 1 etc.; until Cycle 20, Day 1), followed by every 3 cycles for up to 2 years (i.e., within $\pm$ 7 days of cycle 23, Day 1; Cycle 26, Day 1 etc.; until Cycle 35, Day 1) and at any time per investigator's discretion and at Early Discontinuation / End of Study Treatment (ED/EOST) (unless clear PD has been documented previously).
- ^v All Early Discontinuation / End of Study Treatment (ED/EOST) assessments must be performed within 90 days following the subject's last administration of study treatment and prior to initiation of any other treatment, whichever comes first. After the final dose of study treatment, subjects should be followed for any drug-related AEs and/or ongoing SAEs for 90 days or until those events have resolved or become stable, whichever occurs later (or through 30 days following cessation of study treatment if the subject initiates new anticancer therapy, if that occurs earlier).
- ^w Data regarding poststudy anti-tumor therapy and survival will be collected from all subjects who receive $\geq$ 1 dose of FLX475 or pembrolizumab. Such information will be collected at ~3 to 6-month intervals as described in [Section 8.2.3](#) of the protocol. This long-term follow-up information will be gathered during routine clinic visits, other study site contact with the subjects, or via telephone or e-mail with the subjects/caregivers or referring physician offices. These data will be collected in the source documents (e.g., subject medical record) and transcribed into a specific eCRF.

Table 11 Schedule of Visits and Procedures in Study FLX475-02: Part 2b: FLX475/Pembrolizumab Combination Expansion Cohorts

Study Period/Cycle	Screening	Treatment									Early Discon./ End of Study Treatment (ED/EOST) ^v	Long-Term Follow-Up ^w
		Cycle 1			Cycle 2			Cycle 3		Cycle 4+		
		1	8	15	1	8	15	1	15	1		
Study Day	-21 to 0	1	8	15	22	29	36	43	57	64 ⁺		
Investigational Product Dispensing and Administration												
FLX475 In-clinic Administration ^a		X	X	X	X	X	X	X	X	X		
Pembrolizumab Administration ^a		(X)			X			X		X		
FLX475 Dispensing ^b		X			X			X		X		
General and Safety Assessments												
Written Informed Consent	X											
Inclusion/Exclusion Criteria	X											
Demographics	X											
Medical History ^c	X											
Clinical Evaluation ^d	X	X	X	X	X		X	X		X	X	
Vital Signs ^e	X	X	X	X	X		X	X		X	X	
Triplicate 12-Lead ECGs ^f	X	X	X		X			X		X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	
Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	
Drug Diary Cards		X			X			X		X	X	
Drug Accountability		X			X			X		X	X	
Laboratory Assessments and Sample Collection												
Serum Chemistry ^g	X	X	X	X	X	X	X	X	X	X	X	
CBC with Differential ^h	X	X	X	X	X	X	X	X	X	X	X	
Coagulation Tests ⁱ	X	X			X			X		X	X	
Thyroid Function Tests ^j	X	X						X		X	X	
Urinalysis ^k	X	X			X			X		X	X	
Pregnancy Test ^l	X	X			X					X ^k	X	
FLX475 PK Samples ^m		X			X			X		X	X	
Immunophenotyping ⁿ		X	X		X					X	X	

Study Period/Cycle	Screening	Treatment									Early Discon./ End of Study Treatment (ED/EOST) ^v	Long-Term Follow-Up ^w
		Cycle 1			Cycle 2			Cycle 3		Cycle 4+		
Cycle Day		1	8	15	1	8	15	1	15	1		
Study Day	-21 to 0	1	8	15	22	29	36	43	57	64 ⁺		
Serum Biomarkers ^o		X	X		X					X	X	
PD Samples (Receptor Occupancy) ^p		X			X						X	
Whole Blood Biomarkers ^q	X		X		X					X	X	
Fecal Microbiome Samples ^r	X									X	X	
Disease Assessments												
Disease Classification	X											
Tumor Imaging/Staging (CT/MRI Scan) ^s	X									X		
Tumor Biopsy ^t	X				(X)			(X)				
Response Assessment ^u										X	X	
Post-Therapy Long-Term Follow-Up												X

ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; INR = international normalized ratio; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; MRI = magnetic resonance imaging; PD = pharmacodynamic; PK = pharmacokinetic; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; UA = urinalysis; WBC = white blood cell.

Study visits after Cycle 1, Day 1 may occur within a window of ±3 days.

All “pre-dose” assessments (including PK and ECGs) should be obtained at study visits even when study treatment is being held or not given.

^a On days when a clinic visit with PK assessments occurs, the dose of FLX475 will be administered in the clinic after the specified visit assessments and procedures are performed. In addition, the dose of FLX475 should be self-administered in the clinic on Day 1 of each cycle only after a new supply of drug has been dispensed for that cycle, for drug accountability purposes. A diary card will be provided to each subject for recording of all dose administration information.

Pembrolizumab will be administered at a dose of 200 mg IV over 30 minutes on Day 1 of each cycle, except in lead-in dosing cohorts (C10-13) when it will start with Day 1 of Cycle 2. Pembrolizumab infusion should occur at least 1 hour after the dose of FLX475 is administered in the clinic and after all 1-hour post-dose procedures have occurred

^b Dispensing of 3-week supply of FLX475 to the subject with instructions for self-administration at home.

^c Relevant medical history including current disease and prior treatment, including last prior therapy, best response to last prior therapy (PR, CR, SD, or PD) and either time on last therapy or duration of response.

^d Clinical evaluation will include assessment of ECOG performance status, physical examination (at screening, response assessments, and as clinically indicated), and measurement of height (screening only) and weight.

^e Vital signs (blood pressure, pulse, respiratory rate, and temperature) will be collected with the subject in a sitting position. Vital signs will be assessed pre-dose and at 0.5, 1, 2, and 4 hours post-dose on Cycle 1, Day 1; pre-dose and 2 hours post-dose on Cycle 1, Days 8, and 15; pre-dose and at 0.5, 1, 2, and

- 4 hours post-dose on Cycle 2, Day 1; pre-dose and 2 hours post-dose on Cycle 2, Day 15. Vital signs will also be assessed pre-dose on Day 1 of all subsequent cycles and at Early Discontinuation / End of Study Treatment (ED/EOST). Acceptable windows for collection are as follows: pre-dose samples must be within 6 hours prior to dosing; 0.5 hour post-dose ± 5 minutes; 1 hour post-dose ± 15 minutes; 2 and, 4 hour post-dose ± 30 minutes.
- ^f Triplicate ECGs with tracings ≥ 30 seconds apart must be collected in digital format on designated calibrated ECG equipment after at least 10 minutes of quiet rest in supine position. Meals should not be served shortly before ECGs. Triplicate ECGs should be collected at Screening Visit; -0.75, -0.5, and -0.25 hours pre-dose and 2 and 4 hours post-dose on Cycle 1, Day 1; pre-dose and 2 hours post-dose on Cycle 1, Day 8; pre-dose and 2 hours post-dose on Day 1 of Cycles 2-6; and at Early Discontinuation / End of Study Treatment (ED/EOST). Acceptable windows for collection are as follows: general pre-dose ECGs must be within 2 hours prior to dosing; -0.75, -0.5, -0.25 hour pre-dose ± 5 minutes; 2 and 4 hour post-dose ± 30 minutes. Pre-dose ECGs must also be obtained at designated study visits when study drug is being held / not given.
- ^g Serum Chemistry: including sodium, potassium, chloride, total protein, bicarbonate, albumin, calcium, magnesium, phosphorous, glucose, BUN, creatinine, uric acid, total bilirubin, ALP, LDH, AST, ALT, amylase and lipase. Serum Chemistry to be collected pre-dose (within 6 hours prior to dosing) on study visit days, including Days 1 and 15 for Cycle 3 and on Day 1 only for subsequent cycles.
- ^h Complete Blood Count and Differential: WBC, RBC, ANC, hemoglobin, hematocrit, MCV, MCH, platelets, and WBC differential. CBC with differential to be performed as noted pre-dose (within 6 hours prior to dosing) for Cycles 1 and 2, and on Days 1 and 15 for Cycle 3 and on Day 1 only for subsequent cycles.
- ⁱ Coagulation Tests should be obtained pre-dose (within 6 hours prior to dosing): PT, PTT or aPTT, and INR
- ^j Thyroid function tests should be obtained at screening and pre-dose (within 6 hours prior to dosing) Day 1 of Cycle 1 and every odd-numbered cycle during study treatment. Thyroid panel should include (1) Triiodothyronine (T3) or Free Triiodothyronine (FT3), (2) Free Thyroxine (FT4), and (3) Thyroid Stimulating Hormone (TSH).
- ^k Urinalysis should be obtained pre-dose (within 6 hours prior to dosing), and will include specific gravity, pH, blood, protein, glucose, ketones and bilirubin (microscopic UA with WBC, RBC, epithelial cells, bacteria, casts and crystals, only if necessary).
- ^l Serum pregnancy test only in women of childbearing potential during screening; urine or serum pregnancy test at all other time points. After Cycle 2, pregnancy testing will be performed on Day 1 of every even-numbered cycle (e.g., Cycle 4, 6, etc.).
- ^m FLX475 PK samples will be collected at the following time points: pre-dose and 2 and 4 hours post-dose on Cycle 1, Day 1; pre-dose on Day 1 of Cycles 2-6; and at Early Discontinuation / End of Study Treatment (ED/EOST). Samples may also be drawn at investigator discretion, e.g., during a clinically significant adverse event potentially related to study treatment. Acceptable windows for sampling include within 30 minutes prior to dose for pre-dose samples and ± 30 minutes for other post-dose samples. PK samples should be obtained as close as possible both to protocol stipulated times and to concurrently scheduled ECGs. Pre-dose PK samples must also be obtained at designated study visits when study drug is being held / not given.
- ⁿ Immunophenotyping: Samples will be obtained for T/B/NK and T-cell panels pre-dose on Cycle 1, Days 1 and 8; pre-dose on Day 1 of even-numbered Cycles 2 and beyond; and at Early Discontinuation / End of Study Treatment (ED/EOST). Acceptable window for pre-dose collection is within 2 hours prior to dosing.
- ^o Serum Biomarkers: Samples will be collected pre-dose \ on Cycle 1, Day 1; pre-dose on Cycle 1, Day 8; pre-dose on Day 1 of even-numbered Cycles 2 and beyond; and at Early Discontinuation / End of Study Treatment (ED/EOST). Acceptable windows for collection are as follows: pre-dose within 2 hours prior to dosing. Samples may also be drawn at investigator discretion, e.g., during a clinically significant adverse event potentially related to study treatment.

- ^p PD Samples for Receptor Occupancy/Internalization will be collected only for designated subjects at North American sites (e.g. Hodgkin lymphoma) at pre-dose on Cycle 1, Day 1; pre-dose on Cycle 2, Day 1; and at Early Discontinuation / End of Study Treatment (ED/EOST). Acceptable window for pre-dose collection is within 2 hours prior to dosing. Collection of these samples will be discontinued as of November 1, 2021.
- ^q Whole Blood Biomarkers: Samples will be collected at Screening Visit (2 samples); pre-dose on Cycle 1, Day 8; pre-dose on Day 1 of even-numbered Cycles 2 and beyond; and at Early Discontinuation / End of Study Treatment (ED/EOST). Acceptable window for pre-dose collection is within 2 hours prior to dosing.
- ^r Stool samples for fecal microbiome studies will be collected at baseline and timed with certain response assessments, including after the first 3 cycles, then every 4 cycles for the first year, followed by every 6 cycles thereafter for up to 2 years (i.e., within ± 5 days of Cycle 4, Day 1; Cycle 8, Day 1; etc.) and at any time per investigator's discretion and at Early Discontinuation / End of Study Treatment (ED/EOST). These samples should not be collected after August 1, 2021.
- ^s Tumor Imaging/Staging (CT/MRI Scan): After baseline scan, response assessments will be performed after the first 3 cycles, then every 2 cycles for the first year (i.e., within ± 7 days of cycle 4, Day 1; Cycle 6, Day 1 etc.; till Cycle 20, Day 1), followed by every 3 cycles for up to 2 years (i.e., within ± 7 days of cycle 23, Day 1; Cycle 26, Day 1 etc.; till Cycle 35, Day 1) and at any time per investigator's discretion and at Early Discontinuation / End of Study Treatment (ED/EOST) (unless clear PD has been documented previously). Confirmatory scans should also be obtained 4-6 weeks following initial documentation of objective response. Response and progression will be evaluated in this study using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used. Lugano criteria will be used for subjects with lymphoma (see [Appendix 6](#) for details) other than those with CTCL, for which alternative criteria should be used ([Olsen et al., 2011](#)). Note that 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.
- ^t Tumor Biopsy: Subjects enrolled on the clinical trial must be willing and able to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion (minimum of 3 cores). Subjects enrolled in either the dose escalation or expansion cohorts will undergo a core biopsy or excisional biopsy of a lesion (minimum of 3 cores) prior to starting treatment and at Cycle 3 Day 1 (± 7 days) (or Cycle 2 Day 1 ± 3 days for subjects in lead-in cohorts such as C10-13). There will be an option to also obtain additional biopsies at clinically significant time points (e.g., early disease response or upon progression of disease) with subject consent.
- ^u Response Assessment: Initial response assessment will be performed after the first 3 cycles, then every 2 cycles for the first year (i.e., within ± 7 days of cycle 4, Day 1; Cycle 6, Day 1 etc.; until Cycle 20, Day 1), followed by every 3 cycles for up to 2 years (i.e., within ± 7 days of cycle 23, Day 1; Cycle 26, Day 1 etc.; until Cycle 35, Day 1) and at any time per investigator's discretion and at Early Discontinuation / End of Study Treatment (ED/EOST) (unless clear PD has been documented previously).
- ^v All Early Discontinuation / End of Study Treatment (ED/EOST) assessments must be performed within 90 days following the subject's last administration of study treatment and prior to initiation of any other treatment, whichever comes first. After the final dose of study treatment, subjects should be followed for any drug-related AEs and/or ongoing SAEs for 90 days or until those events have resolved or become stable, whichever occurs later (or through 30 days following cessation of study treatment if the subject initiates new anticancer therapy, if that occurs earlier).
- ^w Data regarding poststudy anti-tumor therapy and survival will be collected from all subjects who receive ≥ 1 dose of FLX475 or pembrolizumab. Such information will be collected at ~ 3 to 6-month intervals as described in [Section 8.2.3](#) of the protocol. This long-term follow-up information will be gathered during routine clinic visits, other study site contact with the subjects, or via telephone or e-mail with the subjects/caregivers or referring physician offices. These data will be collected in the source documents (e.g., subject medical record) and transcribed into a specific eCRF.

11.6.1 *Appropriateness of Measurements*

All clinical assessments are standard measurements commonly used in studies of advanced solid tumors. The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urine dipstick testing, and assessment of AEs, are standard evaluations to ensure subject safety.

11.6.2 *Completion/Discontinuation of Subjects*

A subject may elect to discontinue treatment or withdraw from the study at any time for any reason. All subjects who withdraw are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments ([Table 8](#) through [Table 11](#)).

The investigator will promptly explain to the subject involved that study treatment and procedures will be discontinued for that subject, and appropriate medical treatment and other necessary measures will be provided. Subjects who consent to follow-up will be monitored for disease progression and/or survival. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms. If the subject cannot be successfully contacted (minimum of two documented attempts at contact), then the subject will be deemed lost to follow-up.

Study disposition information will be collected on the appropriate eCRF. Subjects who withdraw early from the study will be discontinued for 1 of these primary reasons: adverse event, progression of disease (as documented by response assessment scans), withdrawal of consent, pregnancy, study terminated by Sponsor, investigator decision, non-compliance, or other (including clinical progression not documented by tumor assessment imaging).

11.7 *Reporting of Adverse Events*

11.7.1 *Reporting of Serious Adverse Events*

All SERIOUS ADVERSE EVENTS, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event.

Serious AEs regardless of causality assessment must be collected through the last visit and for 90 days after the subject's final dose, or 30 days following the final dose if the subject initiates new anticancer therapy, whichever is earlier.

Regardless of treatment arm, all SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the Sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the investigator's Study File.

For urgent safety issues , please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.
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It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 24 hours of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the Sponsor.

For sites in the US, the investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by his/her institution. A copy of this communication must be forwarded to the Sponsor's designee for filing in the Sponsor's Trial Master File.

11.7.2 *Reporting of Pregnancy and Breastfeeding*

Any female subject who becomes pregnant must be withdrawn from the study.

Any pregnancy in which the estimated date of conception is either before the last visit or within 120 days of the final dose of study treatment or 30 days following the final dose of study treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported. Also, any exposure of an infant to study treatment through breastfeeding during study treatment or within 120 days of the final dose of study treatment, or 30 days following the final dose of study treatment if the subject initiates a new anticancer therapy, whichever is earlier, must be reported.

Regardless of study treatment agent, if an adverse outcome of a pregnancy is suspected to be related to study treatment exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment. A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see [Section 11.7.1](#), *Reporting of Serious Adverse Events*).

Pregnancies or exposure of an infant to study treatment through breastfeeding must be reported by fax or email as soon as possible but no later than 24 hours from the time that the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study treatment through breastfeeding is provided in the investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 24 hours from the time that the investigator becomes aware of the outcome, if the outcome is an SAE (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor.

11.7.3 *Reporting of Events Associated with Special Situations*

11.7.3.1 Reporting of Adverse Events Associated with Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of study treatment outside that specified by the protocol.

Overdose, misuse, abuse, and medication error are defined as follows:

- Overdose: Accidental or intentional use of the study treatment in an amount higher than the protocol-defined dose
- Misuse: Intentional and inappropriate use of study treatment not in accordance with the protocol
- Abuse: Sporadic or persistent intentional excessive use of study treatment accompanied by harmful physical or psychological effects
- Medication error: Any unintentional event that causes or leads to inappropriate study treatment use or subject harm while the study treatment is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event eCRF and also reported using the procedures detailed in [Section 11.7.1](#) (*Reporting of Serious Adverse Events*) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event eCRF.

Note: Overdose for pembrolizumab is defined as a dose > 5 times the 200 mg dose (i.e., 1000 mg). Overdose for FLX475 is defined as a dose > 2 times the assigned dose.

11.7.4 *Expedited Reporting*

The Sponsor must inform investigators (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (i.e., within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

11.7.5 *Regulatory Reporting of Adverse Events*

Adverse events will be reported by the Sponsor or designee to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the competent authorities of all involved European member states.

11.8 *Confirmation of Medical Care by Another Physician*

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he/she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

11.9 *Data Quality Assurance*

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. Site audits may be made periodically by the Sponsor's or designee's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

11.9.1 *Data Collection*

Data required by the protocol will be collected on eCRFs via a validated electronic data capture system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the Sponsor on each study subject.

Data collection on the eCRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee as identified on FDA Form 1572 must sign the completed eCRF to attest to its accuracy, authenticity, and completeness.

Completed eCRFs are the sole property of RAPT Therapeutics and should not be made available in any form to third parties without written permission from RAPT Therapeutics, except for authorized representatives of RAPT Therapeutics or appropriate regulatory authorities.

11.9.2 *Clinical Data Management*

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both eCRF and external data (e.g., laboratory data), will be entered into a clinical system.

12 STATISTICAL METHODS

12.1 General Statistical Considerations

Tabulations of summary statistics, graphical presentations, and statistical analyses will be performed using SAS® software. Descriptive statistics will be used to summarize data from this study, including mean, standard deviation, median, minimum, and maximum for continuous variables and frequency distributions and percentages for categorical variables. In general, data will be summarized by Cohort and by tumor type within Cohort for Stage 1 and Stage 2 separately, and overall (including data from the expansion phase). The specifics for these outputs will be described in detail within the Statistical Analysis Plan (SAP), which will be finalized before database lock.

The last observation prior to the first dose of study medication will be used as the baseline value for calculating post-administration changes from baseline. All data obtained on the eCRF will be presented in by-subject data listings.

Confidence intervals, both individual and simultaneous, will be at the 95% confidence level unless stated otherwise.

All summaries and analyses conducted will be by tumor type, assigned therapy, and combined total subjects. Statistical analyses will be performed using SAS® software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP), which will be finalized before the database lock.

12.1.1 *Statistical Design and Sample Size Determination*

12.1.1.1 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 12](#) shows the probability of escalating to the next dose level based on the true rate of DLT at the current dose level.

Table 12 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.

12.1.1.2 Statistical Basis for Study Design of 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. 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 be considered evaluable, subjects must meet criteria for the Efficacy Evaluable population, be evaluable for tumor response as per RECIST v1.1 at 9 weeks, and have no major protocol deviations.

Evaluability for tumor response will be based on the following:

- Subjects who remain on study until the first evaluation (at 9 weeks) and have a tumor assessment performed.
- Subjects who withdraw from the study due to disease progression before the first evaluation (at 9 weeks) will be considered as subjects with early progression
- Subjects who die from malignant disease before the first evaluation (at 9 weeks) will be considered as subjects with early death
- Subjects with measurable disease, for whom all baseline target lesions have been assessed at least once after 9 weeks, with the same method of measurement used at baseline.
- Subjects with only non-measurable disease, for whom non-target lesions have been assessed at least once after 9 weeks.

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 for response. 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 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.

12.1.2 *Statistical and Analytical Plans*

The statistical analyses of the primary analysis of the study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock.

Based on the FAS, information regarding study treatment administration, study treatment compliance, safety variables, and poststudy therapies will be described and summarized.

12.1.2.1 Study Endpoints

12.1.2.1.1 Safety Endpoints

The primary endpoint in Part 1 of the study is safety and tolerability by the determination of 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 (defined in [Section 10.4](#))
- Laboratory abnormalities
- Vital sign abnormalities
- Adverse ECG findings

12.1.2.1.2 Efficacy Endpoints

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 ([Appendix 4](#)) for subjects with solid tumors. Lugano criteria will be used for subjects with lymphoma (see [Appendix 6](#) for details) other than those with CTCL, for which alternative criteria should be used ([Olsen et al., 2011](#)).

Other 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, defined as the interval from start of study treatment to the first documentation of CR or PR
- Duration of Response, 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

12.1.2.2 Pharmacokinetic and Pharmacodynamic Endpoints

The following PK parameters for FLX475 will be analyzed:

- $AUC_{(0-t)}$: Area under the plasma concentration-time curve (AUC) calculated using linear trapezoidal summation from time 0 to time t, where t is the time of the last measurable concentration (C_t)
- $AUC_{(0-24)}$: Area under the plasma concentration-time curve from 0 to 24 hours, calculated using linear trapezoidal summation

- $AUC_{(0-\infty)}$: Area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: $AUC_{(0-\infty)} = AUC_{(0-t)} + C_t / \lambda_z$, where λ_z is the apparent terminal elimination rate constant (whenever possible)
- C_{max} : Maximum observed plasma concentration
- T_{max} : Time of the maximum plasma concentration (obtained without interpolation)
- $t_{1/2}$: Terminal half-life (whenever possible)
- λ_z : Terminal elimination rate constant (whenever possible)
- CL/F: Oral clearance of FLX475
- V_z/F : Oral volume of distribution of FLX475

Pharmacodynamic endpoints are as follows:

- Changes in CCR4 receptor occupancy on peripheral blood cells
- Changes in immune parameters, e.g., lymphocyte subpopulations and plasma cytokines or chemokines in peripheral blood or in tumor

Using data from the relevant evaluable data sets, study treatment plasma concentrations, PK parameters, and PD markers will also be described and summarized.

12.1.1.2.3 Analysis Sets

The allocation of subjects to analysis sets will be determined prior to database lock. For the purpose of analysis, the following populations will be defined:

Full Analysis Set: All subjects enrolled in the study, also known as the “Intent-to-Treat” (ITT) population.

Safety Analysis Set: All subjects who receive at least one dose of the investigational product, FLX475 (even a partial dose). Since the study design includes FLX475 monotherapy and FLX475 in combination with pembrolizumab, separate safety analyses will be performed using data from the monotherapy and combination therapy phases of the study, as well as for all safety data from the Safety Analysis Set.

Efficacy Eligible Set: All subjects who receive at least one dose of study treatment, have measurable disease at baseline per RECIST v1.1 (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 (Stage 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.

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.

Pharmacokinetic (PK) Analysis Set: All subjects who receive at least 1 dose of FLX475 as monotherapy or in combination with pembrolizumab, and have measurable plasma concentrations of FLX475.

Pharmacodynamic (PD) Analysis Set: All subjects who receive at least 1 dose of investigational product and have sufficient PD data to derive at least 1 PD measurement.

12.1.3 *Subject Disposition*

The number and percentage of subjects who are enrolled, treated, complete the study, and discontinue from the study will be presented for the Full Analysis Set by treatment (monotherapy vs. combination therapy) and by cohort for each phase of the study, Part 1 (dose escalation) and Part 2 (dose expansion). A summary of reasons for discontinuation will be provided. The number of subjects included in the Safety Analysis and Efficacy Evaluable Sets will be summarized and the reasons for excluding subjects from the Efficacy Analysis Set will be listed.

12.1.4 *Demographic and Other Baseline Characteristics*

Descriptive statistics will be used to summarize demographic and baseline characteristics of subjects in relevant analysis sets, overall and by cohort in each study phase. Subject characteristics to be tabulated include: age, sex, race, ethnicity, baseline performance status, primary diagnosis, disease stage at diagnosis and baseline, prior therapies (including systemic therapies, radiation, and surgeries), and best response to prior cancer therapies.

12.1.5 *Prior and Concomitant Therapy*

All investigator terms for medications recorded in the eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) drug codes. The number (percentage) of subjects who took prior and concomitant medications will be summarized for the FAS by treatment type (monotherapy vs combination therapy) and by cohort, Anatomical Therapeutic Chemical class, and WHO DD preferred term. Prior medications will be defined as medications that were stopped before the first dose of study treatment. Concomitant medications will be defined as medications that (1) started before the first dose of study treatment and were 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. All medications will be presented in subject data listings.

12.1.6 *Efficacy Analyses*

Efficacy analysis will be conducted separately for each tumor type in the Cohort Expansion phase (Parts 2a and 2b). The primary efficacy endpoint is ORR, and the secondary efficacy endpoints include PFS, TTR, DOR and OS. Tumor-related endpoints will be analyzed for the FAS and Efficacy Evaluable Sets, as appropriate. An additional sensitivity analysis of

ORR will be performed for the Efficacy Eligible Set. Efficacy will also be explored in subgroups of special interest, notably subjects who are anti-PD-(L)1 refractory (as defined in [Appendix 9](#)) and other prognostic subgroups pre-specified in the SAP.

ORR will be defined as the proportion of subjects who are responders, i.e., CR and PR; the exact 95% confidence interval for ORR will be calculated using the Clopper-Pearson method. The CBR (CR + PR + SD) will also be calculated; SD in the CBR determination is defined as SD that persists for ≥ 6 months. The ORR and CBR analysis will be based on RECIST v1.1 (or appropriate lymphoma criteria) and presented for each cohort of the Cohort Expansion phase, Part 2a (monotherapy) and Part 2b (combination therapy).

Time-to-event endpoints, including PFS and OS, will be summarized descriptively and graphically using Kaplan-Meier (KM) methodology. KM estimates for the median, first, and third quartiles will be determined along with 95% confidence intervals (CIs). The Brookmeyer-Crowley method will be used for the CI calculations. For the subset of subjects who have a CR or PR, DOR will be summarized similarly using the Kaplan-Meier method. TTR will be defined from the start of treatment to the first documented CR or PR and will be summarized descriptively as a continuous variable.

PFS is defined as the time from the date of initiation of FLX475 to the date measurement criteria are first met for irPD/PD or death from any cause, whichever occurs first. For subjects still alive at the time of analysis and without evidence of irPD/PD, PFS will be censored on the date of the most recent objective progression-free observation. For subjects who receive subsequent anticancer therapy prior to irPD/PD or death, PFS will be censored on the date of the last objective progression-free observation prior to the date of subsequent therapy.

DOR is defined as the time from first date measurement criteria are met for irPR/PR or irCR/CR (whichever status is recorded first) to the date measurement criteria are first met for irPD/PD or the date of death, whichever is sooner. For subjects not known to have died as of the data cut-off date and who do not have irPD/PD, DOR will be censored at the last progression-free assessment date. For responding subjects who receive subsequent anticancer therapy (after discontinuation from all study treatment) prior to disease progression, DOR will be censored at the date of last progression-free assessment prior to the initiation of a new anticancer therapy.

OS is defined as the time from the date of initiation of FLX475 to the date of death from any cause. For subjects who are still alive as of the data cut-off date, OS time will be censored on the date of the subject's last contact (last contact for subjects post-treatment = last known alive date in mortality status).

12.1.7 *Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses*

12.1.7.1 Pharmacokinetic Analyses

Plasma concentrations of FLX475, in the presence or absence of pembrolizumab, versus time data will be analyzed to estimate population PK parameters. Pembrolizumab concentrations, if analyzed, will be listed. No PK parameters will be calculated for pembrolizumab.

Using data from the relevant evaluable data sets, study treatment plasma concentrations and PK parameters will be described and summarized. Calculated PK parameters will be derived using noncompartmental methods.

Samples from all subjects receiving FLX475 or FLX475 plus pembrolizumab will be analyzed. Plasma concentrations of FLX475 will be quantified by liquid chromatography with tandem mass spectrometry (LC/MS/MS) methodology using previously validated assays. Serum concentrations of pembrolizumab will be measured using validated methods. Samples of plasma may be analyzed for metabolites of FLX475, and the results reported separately.

The following PK parameters for FLX475 will be analyzed:

- $AUC_{(0-t)}$: Area under the plasma concentration-time curve (AUC) calculated using linear trapezoidal summation from time 0 to time t, where t is the time of the last measurable concentration (C_t)
- $AUC_{(0-24)}$: Area under the plasma concentration-time curve from 0 to 24 hours, calculated using linear trapezoidal summation
- $AUC_{(0-\infty)}$: Area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: $AUC_{(0-\infty)} = AUC_{(0-t)} + C_t / \lambda_z$, where λ_z is the apparent terminal elimination rate constant (whenever possible)
- C_{max} : Maximum observed plasma concentration
- T_{max} : Time of the maximum plasma concentration (obtained without interpolation)
- $t_{1/2}$: Terminal half-life (whenever possible)
- λ_z : Terminal elimination rate constant (whenever possible)
- CL/F: Oral clearance of FLX475
- Vz/F: Oral volume of distribution of FLX475

12.1.7.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Soluble, tissue, genetic and/or imaging biomarkers (baseline and/or posttreatment) may be summarized using descriptive statistics and correlated with clinical outcomes-related endpoints for safety and/or efficacy (including OR, PFS and OS) as appropriate. Changes

from baseline in PD markers will be analyzed using appropriate methods. Details may be included in a separate analysis plan.

The effect of FLX475 alone or in combination with pembrolizumab on soluble, tissue, genetic and/or imaging biomarkers will be summarized using descriptive statistics based on the PK/PD analysis set. Pharmacokinetic/pharmacodynamic relationships (i.e., exposure-efficacy, and exposure-safety and exposure-biomarker relationships) will be modeled, if possible, using a mechanistic approach for effects of study treatment. Efficacy endpoints will include the primary endpoint of ORR and other efficacy-related metrics including but not limited to PFS (based on iRECIST) and OS. Safety endpoints will be the most frequent AEs of special interest and dose reductions. Exploratory/graphical analyses will be conducted for PK/PD evaluations, and, if possible, will be followed by model-based analyses.

The PK and PK/PD analyses will be detailed in a separate analysis plan that will be provided at a later date and the result will be provided in a standalone report.

12.1.8 *Safety Analyses*

Safety analyses will be based on the Safety Analysis Set. All safety analyses will be summarized by treatment (FLX475 or FLX475 plus pembrolizumab) and by dose level cohort. Adverse events and SAEs, laboratory test results, vital signs, and ECG results will be summarized. Safety data will be summarized using descriptive statistics. Categorical variables will be summarized by number and percentage. Continuous variables will be summarized using n (number of subjects with available data), mean, standard deviation, median, first and third quartile, and range (minimum and maximum) unless otherwise specified. The type, frequency, severity, timing of onset, duration, and relationship to study treatments of any TEAEs, DLTs, SAEs, or AEs leading to discontinuation or dose modification (reduction/interruption) of study treatment; laboratory abnormalities; vital sign abnormalities; and adverse ECG findings will be analyzed.

12.1.8.1 Extent of Exposure

The number of cycles/days on treatment, quantity of study treatments administered, and the number of subjects requiring dose reductions, treatment interruption, and treatment discontinuation due to AEs will be summarized. A by-subject listing of FLX475 administration data will be presented.

12.1.8.2 Adverse Events

Adverse events will be graded using CTCAE v4.03. The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA lower level term closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as an AE that starts or worsens in severity any time after the first dose of study treatment until 30 days after the last dose of study treatment. Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment (monotherapy vs combination therapy) and by FLX475 dose level. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (highest CTCAE grade).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include TEAEs that were considered by the investigator to be possibly or probably related to study treatment or TEAEs with a missing causality. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (by highest CTCAE grade).

The proportion of subjects who discontinue treatment due to toxicity will be summarized by frequency counts and percentages

12.1.8.3 Laboratory Values

Laboratory results will be summarized using Système International units, as appropriate. For all quantitative parameters listed in [Section 11.5.5](#), the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and cohort using descriptive statistics. Laboratory parameters will be categorized according to CTCAE v4.03 grade, and shifts from baseline CTCAE grade to worst postbaseline grade will be summarized using shift tables. Percentages will be based on the number of subjects with baseline and at least 1 post-baseline assessment.

Common Terminology Criteria for Adverse Events v4.03 will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAV). A more detailed definition of TEMAV will be specified in the SAP. A summary of TEMAVs will be presented by treatment arm.

12.1.8.4 Vital Signs

Descriptive statistics for vital signs parameters (i.e., systolic and diastolic BP, resting heart rate, respiratory rate, temperature, and weight) and changes from baseline will be presented by visit and cohort. Subjects will be included in the summary tables if they had both a baseline value and at least 1 post-baseline value for vital signs.

12.1.8.5 Electrocardiograms

Change from baseline (defined as average QTcF value from C1D1 pre-dose ECGs) to worst post-baseline result in ECG findings (categorized as normal; abnormal, not clinically

significant; and abnormal, clinically significant) will be summarized by cohort using shift tables. Descriptive statistics for ECG parameters and changes from baseline will be presented by visit and cohort.

12.1.9 *Interim Analysis*

Safety monitoring will be conducted throughout the study. A Safety Review Committee (SRC) will meet periodically (including at least quarterly during the Phase 2 expansion phase of the study) to review accumulating safety information for each cohort and make recommendations to continue or curtail enrollment. The SRC will comprise appropriate Sponsor and 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). 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.

Procedure for Revising the Statistical Analysis Plan

If the SAP needs to be revised after the study starts, the Sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

13 REFERENCE LIST

Blank, C., et al., PD-L1/B7H-1 inhibits the effector phase of tumor rejection by T cell receptor (TCR) transgenic CD8⁺ T cells. *Cancer Res*, 2004. 64(3): p. 1140-5.

Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 [published 28 May 2009 (v4.03: June 14, 2010)]. Available from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

Chaudhry A, Rudensky AY. Control of inflammation by integration of environmental cues by regulatory T cells. *J Clin Invest*. 2013;123(3):939.

Chemnitz, Jens M., Parry, Richard V., Nichols, Kim E., June, Carl H., Riley, James L., SHP-1 and SHP-2 Associate with Immunoreceptor Tyrosine-Based Switch Motif of Programmed Death 1 upon Primary Human T Cell Stimulation, but Only Receptor Ligation Prevents T Cell Activation. *The Journal of Immunology*.2004, 173: 945–954

Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, and Lister TA. Recommendation for initial evaluation staging and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano Classification. *J Clin Oncol*. 2014;32(27):3059-67.

Curiel TJ, Coukos G, Zou L, Alvarez X, Cheng, P, Mottram P, et al. Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. *Nature Med*. 2004;10(9):942.

Curran, M.A., et al., PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. *Proc Natl Acad Sci U S A*, 2010. 107(9): p. 4275-80.

Disis, Mary L. Immune Regulation of Cancer. *J Clin Oncol*. 2010; 28(29): 4531-8.

Dudley ME, Wunderlich JE, Yang JC, Sherry RM, Topalian SL, Restifo NP, et al. Adoptive cell transfer therapy following nonmyeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. *J Clin Oncol*. 2005;23(10): 2346-57.

Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD. Cancer immunoediting: from immunosurveillance to tumor escape. *Nature Immunology*. 2002;3(11):991-8.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-47.

Francisco, Loise M., Sage, Peter T., and Sharpe, Arlene H. The PD-1 pathway in tolerance and autoimmunity. *Immunological Reviews*.2010; 0105-2896

Fridman WH, Zitvogel L, Sautès-Fridman C, Kroemer G. The immune contexture in cancer prognosis and treatment. *Nat Rev Clin Oncol.* 2017;14(12):717-34.

Gobert M, Treilleux I, Bendriss-Vermare N, Bachelot T, Goddard-Leon S, Arfi, V, et al. Regulatory T cells recruited through CCL22/CCR4 are selectively activated in lymphoid infiltrates surrounding primary breast tumors and lead to an adverse clinical outcome. *Cancer Research.* 2009;69(5), 2000-9.

Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. *Annual Reviews.* 2005; 23:515–48.

Hirano, F., et al., Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. *Cancer Res*, 2005. 65(3): p. 1089-96.

Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. *N Engl J Med.* 2008;358(25):2698-703.

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Li YQ, Liu FF, Zhang XM, Guo XJ, Ren MJ, Fu L. Tumor secretion of CCL22 activates intratumoral Treg infiltration and is independent prognostic predictor of breast cancer. *PloS one.* 2013;8(10):e76379.

Nishikawa H, Sakaguchi S. Regulatory T cells in cancer immunotherapy. *Curr Opin Immuno*, 2014;27:1-7.

Nomi, T., et al., Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. *Clin Cancer Res*, 2007. 13(7): p. 2151-7.

Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptormediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. *PNAS.* 2001;98(24):13866-71.

Okal A, Ho W, Wong B, Kassner P, Cutler G. Patient selection strategies and pharmacodynamic assays for CCR4 antagonists [abstract]. In: Society for Immunotherapy of Cancer Annual Meeting; 2017 Nov 8-12; National Harbor, Maryland. 2017. Abstract P44.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP: Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-55.

Olsen EA, Whittaker S, Kim YH, Duvic M, Prince HM, Lessin SR, et al. Clinical end points and response criteria in mycosis fungoides and sézary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organization for Research and Treatment of Cancer. *J Clin Oncol.* 2011;29(18):2598-607.

Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer*. 2012;12(4):252.

Parry, Richard V., Chemnitz, Jens M., Frauwirth, Kenneth A., Lanfranco, Anthony R., Braunstein, Inbal., Kobayashi, Sumire V., Linsley, Peter S., Thompson, 4 Craig B. and Riley, James L. CTLA-4 and PD-1 Receptors Inhibit T-Cell Activation by Distinct Mechanisms. *Mol Cell Biol*. 2005 Nov; 25(21): 9543–9553.

Pilon-Thomas, S., et al., Blockade of programmed death ligand 1 enhances the therapeutic efficacy of combination immunotherapy against melanoma. *J Immunol*, 2010. 184(7): p. 3442-9.

Riley, James L., PD-1 signaling in primary T cells. *Immunological Reviews*. 2009; 0105-2896

Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al.; RECIST working group. iRECIST: Guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol*. 2017;18(3):e143-e152.

Sharma P, Allison JP. Immune checkpoint targeting in cancer therapy: toward combination strategies with curative potential. *Cell*. 2015;161(2):205-14.

Sheppard, Kelly-Ann., Fitz, Lori J., Lee, Julie M., Benander, Christina, George, Judith A., Wooter, Joe, Qiu, Yongchang, Jussif, Jason M., Carter, Laura L., Wood, Clive R., Chaudhary, Divya. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3 signalosome and downstream signaling to PKC. *FEBS Letters*. 2004; 0014-5793

Shin DS, Ribas A. The evolution of checkpoint blockade as a cancer therapy: what's here, what's next?. *Curr Opin Immuno*. 2015;33:23-35.

Spranger, S., et al., Mechanism of tumor rejection with doublets of CTLA-4, PD-1/PD-L1, or IDO blockade involves restored IL-2 production and proliferation of CD8(+) T cells directly within the tumor microenvironment. *J Immunother Cancer*, 2014. 2: p. 3.

Strome, S.E., et al., B7-H1 blockade augments adoptive T-cell immunotherapy for squamous cell carcinoma. *Cancer Res*, 2003. 63(19): p. 6501-5.

Tanaka A, Sakaguchi S. Regulatory T cells in cancer immunotherapy. *Cell Res*. 2017; 27(1):109-18.

van Marle S, van Hoogdalem EJ, Johnson D, Okal A., Kassner P., Wustrow DJ, et al. Pharmacokinetics, pharmacodynamics, and safety of FLX475, an orally-available, potent, and selective small-molecule antagonist of CCR4, in healthy volunteers. Society for Immunotherapy of Cancer Annual Meeting, 2018, P484.

Weber, J., Immune checkpoint proteins: a new therapeutic paradigm for cancer--preclinical background: CTLA-4 and PD-1 blockade. *Semin Oncol*, 2010. 37(5): p. 430-9.

Zhang, Xuewu, Schwartz, Jean-Claude D., Guo, Xiaoling, Bhatia, Sumeena, Cao, Erhu, Chen, Lieping, Zhang, Zhong-Yin, Edidin, Michael A., Nathenson, Stanley G. Almo, Steven C. Structural and Functional Analysis of the Costimulatory Receptor Programmed Death-1. *Immunity*.2004; 337-347.

14 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

14.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the Sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the Sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the Sponsor's medical monitor (or appropriate study team member) and the IRB/IEC for the site must be notified immediately. The Sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC (or if regionally required, the head of the medical institution) should be kept informed of such changes as required by local regulations. In these cases, the Sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities (or, if regionally required, the head of the medical institution) detailing such changes.

14.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

14.3 Monitoring Procedures

Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the Sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review. The Sponsor's/designee's CRA will maintain contact with the investigator and designated staff by telephone, letter, or electronic mail between study visits.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as interactive web/voice response system, radiographs, and other imaging reports (e.g., sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, electroencephalographs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (e.g., urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs

CRF components (e.g., questionnaires) that are completed directly by subjects and serve as their own source

14.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

14.5 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (e.g., Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the Sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the Sponsor, allowing the Sponsor the option of permanently retaining the study records.

14.6 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the Sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the Sponsor's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the Sponsor or designee immediately.

14.7 Handling of Study Drug

All study treatments will be supplied to the principal investigator (or a designated pharmacist) by the Sponsor. Drug supplies must be kept in an appropriate secure area (e.g., locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist, or other equivalent designee allowed by local regulations) must maintain an accurate record of each receipt, all dispensing, and final disposition of the study treatment in a drug accountability ledger, a copy of which must be given to the Sponsor at the end of the study. An accurate record of the date and amount of study treatment dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study treatment has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the Sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist, or other equivalent designee allowed by local regulations) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the Sponsor or designee or, when approval is given by the Sponsor, will destroy supplies and containers at the site.

14.8 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the Sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the Sponsor/CRO and the institution/investigator. The review is aimed at protecting the Sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the Sponsor or CRO, as appropriate.

14.9 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others or used for any purpose other than reviewing or performing the study, without the written consent of the Sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the Sponsor. These obligations of confidentiality and nonuse shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the Sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and nonuse set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the Sponsor/CRO.

14.10 Termination of the Study

The Sponsor reserves the right to terminate the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the Sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the Sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to terminate the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the Sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the Sponsor and the IRB/IEC and provide the Sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

14.11 Subject Insurance and Indemnity

The Sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

15 APPENDICES

APPENDIX 1 COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE) VERSION 4.03

The Common Terminology Criteria for Adverse Events (CTCAE v4.03, published 14 June 2010) provides descriptive terminology to be used for adverse event reporting in the clinical trials. A brief definition is provided to clarify the meaning of each AE term. To increase the accuracy of AE reporting, all adverse event terms in CTCAE v4.03 have been correlated with single-concept MedDRA terms.

The Common Terminology Criteria for Adverse Events v4.03 grading refers to the severity of the AE. The Common Terminology Criteria for Adverse Events grades 1 through 5, with unique clinical descriptions of severity for each AE, are based on this general guideline:

Grade	CTCAE Status
1	Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate: minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) ^a
3	Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL ^b
4	Life-threatening consequences: urgent intervention indicated
5	Death related to adverse event

ADL = activities of daily living, CTCAE = Common Terminology Criteria for Adverse Events.

^a Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

^b Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Adapted from the Cancer Therapy Evaluation Program, NCI. CTCAE v4.03

For further details regarding MedDRA, refer to the MedDRA website at:
<http://www.meddra.org>

**APPENDIX 2 EASTERN COOPERATIVE ONCOLOGY GROUP
PERFORMANCE STATUS SCALE**

ECOG Performance Status Scale*	
Definitions Rating Criteria	
Score (Grade)	Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

* As published in: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP: Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-55.

APPENDIX 3 NEW YORK HEART ASSOCIATION (NYHA) CARDIAC DISEASE CLASSIFICATION

The New York Heart Association Cardiac Disease Classification provides a functional and therapeutic classification for the prescription of physical activity for heart failure patients based on cardiac functional capacity. Based on NYHA definitions, subjects are to be classified as follows:

Class	NYHA Status
Class I:	Patients with cardiac disease but without resulting limitation of physical activity; ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
Class II:	Patients with cardiac disease resulting in slight limitation of physical activity; they are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III:	Patients with cardiac disease resulting in marked limitation of activity; they are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV:	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

NYHA = New York Heart Association.

Source: The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-6.

APPENDIX 4 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST)

Tumor response assessments in this clinical trial will use modified Response Evaluation Criteria in Solid Tumors (mRECIST) based on the 2009 article by Eisenhauer, et al., entitled *New Response Evaluation Criteria in Solid Tumors: revised RECIST guideline* (version 1.1).

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 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 up to 10 target lesions with up to 5 per organ to maintain consistency in target lesion selection across tumor types.

The Eisenhauer article published in the European Journal of Cancer, is available online at: <http://linkinghub.elsevier.com/retrieve/pii/S0959804908008733> .

APPENDIX 5 DESCRIPTION OF THE MODIFIED RESPONSE EVALUATION CRITERIA IN SOLID TUMORS 1.1 FOR IMMUNE-BASED THERAPEUTICS (iRECIST) PROCESS FOR ASSESSMENT OF DISEASE PROGRESSION

Tumor progression in this clinical trial may be evaluated by the investigator using modified Response Evaluation Criteria in Solid Tumors 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*. The Seymour article, published in the Lancet Oncology, is available online at:

[http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(17\)30074-8/supplemental](http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(17)30074-8/supplemental) .

These guidelines are an adaptation of RECIST 1.1. Although RECIST 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 up to 10 target lesions with up to 5 per organ to maintain consistency in target lesion selection across tumor types.

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic PD based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression

For subjects who show evidence of radiological PD by RECIST 1.1 as determined by the investigator, the investigator will decide whether to allow a subject to continue to receive study treatment until repeat imaging is obtained (using iRECIST for subject management (see Table 13)). This decision by the investigator should be based on the subject's overall clinical condition.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any subject deemed **clinically unstable** should be discontinued from study treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the investigator decides to continue treatment, the subject may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment.

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to $\geq 20\%$ and ≥ 5 mm from nadir
 - Note: the iRECIST publication uses the terminology “sum of measurements”, but “sum of diameters” will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of nontarget lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and nontarget lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or nonmeasurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

On the confirmatory imaging, the subject will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (immune-based stable disease/immune-based partial response/immune-based complete response [iSD/iPR/iCR]).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
 - For target lesions, worsening is a further increase in the sum of diameters of ≥ 5 mm, compared to any prior iUPD time point
 - For nontarget lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the “unequivocal” standard of RECIST 1.1

- For new lesions, worsening is any of these:
 - An increase in the new lesion sum of diameters by ≥ 5 mm from a prior iUPD time point
 - Visible growth of new nontarget lesions
 - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is “reset.” This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

If repeat imaging does not confirm PD per iRECIST, as assessed by the investigator, and the subject continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, subjects will be discontinued from study treatment.

NOTE: If a subject has confirmed radiographic progression (iCPD) as defined above, but the subject is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in [Section 11.3.1](#).

Detection of Progression at Visits After Pseudo-progression Resolves

After resolution of pseudo-progression (i.e., achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
 - Sum of diameters reaches the PD threshold ($\geq 20\%$ and ≥ 5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.
- Non-target lesions
 - If nontarget lesions have never shown unequivocal progression, their doing so for the first-time results in iUPD.
 - If nontarget lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of nontarget lesions, taken as a whole.
- New lesions
 - New lesions appear for the first time
 - Additional new lesions appear
 - Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of diameters, from the nadir value of that sum
 - Previously identified nontarget lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, with one exception: if new lesions occurred at a prior instance of iUPD, and at the confirmatory imaging the burden of new lesions has increased from its smallest value (for new target lesions, the sum of diameters is ≥ 5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details are provided in the iRECIST publication ([Seymour, et al., 2017](#)).

Table 13 **Imaging and Treatment after First Radiologic Evidence of Progressive Disease in Subjects Receiving FLX475 and Pembrolizumab**

	Clinically Stable		Clinically Unstable	
	Imaging	Treatment	Imaging	Treatment
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study treatment at the investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per investigator assessment	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study treatment at the investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule.
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study treatment at the investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue treatment

iCPD = iRECIST-confirmed progressive disease, iCR = iRECIST complete response, iRECIST = modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics, iSD = iRECIST stable disease, iUPD = iRECIST unconfirmed progressive disease, PD = progressive disease, RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1

APPENDIX 6 LUGANO CRITERIA FOR RESPONSE ASSESSMENT IN MALIGNANT LYMPHOMA (BASED ON [CHESON, 2014](#))

Lugano criteria for response assessment in lymphoma

Response and site	PET/ CT-based response	CT-based response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS [†] It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.	Target nodes/ nodal masses must regress to ≤ 1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesions	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5 [†] with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥ 50 percent decrease in SPD of up to six target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value When no longer visible, 0 x 0 mm For a node >5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by >50 percent in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse	Not applicable

Response and site	PET/ CT-based response	CT-based response
	uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan.	
No response or stable disease	No metabolic response	Stable disease
Target nodes/ nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50 percent decrease from baseline in SPD of up to six dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least one of the following
Individual target nodes/ nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/ lesion must be abnormal with: LD _i > 1.5 cm and Increase by 2:50 percent from PPD nadir and An increase in LD _i or SD _i from nadir 0.5 cm for lesions ≥ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50 percent of the extent of its prior increase beyond baseline (eg, a 15 cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another	Regrowth of previously resolved lesions

Response and site	PET/ CT-based response	CT-based response
	etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

5PS: 5-point scale; CT: computed tomography; FDG: fluorodeoxyglucose; IHC: immunohistochemistry; LD_i: longest transverse diameter of a lesion; MRI: magnetic resonance imaging; PET: positron emission tomography; PPD: cross product of the LD_i and perpendicular diameter; SD_i: shortest axis perpendicular to the LD_i; SPD: sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

† PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. J Clin Oncol 2014; 32(27):3059-67. Reprinted with permission. Copyright© 2014 American Society of Clinical Oncology. All rights reserved.

APPENDIX 7 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER RESEARCH

Subjects enrolled in this clinical study will have biologic samples collected for PD, PG, and other biomarker analysis. Optional subject consent must be obtained for banking of samples for future research. These samples may be used for discovery and validation to identify biomarkers that may be used for exploratory evaluation of response and/or safety-related outcomes as well as for use in diagnostic development.

The PG samples may be used to identify genetic factors that may influence a subject's exposure to the study treatment, as well as genetic factors that may have an effect on clinical response or potential adverse events related to study treatment, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or noncoding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the PK or therapeutic response of the study treatment.

Collection of the pharmacodynamic, PG, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for pharmacodynamic, PG, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

Sample Collection and Handling

The samples will be collected according to the study flow chart. If, for operational or medical reasons, the genomic DNA blood sample cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example DNA and/or RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the Sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the Sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The Sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double coded (according to the ICH E15 guidelines) in order to maintain subject privacy.

Right to Withdraw

If, during the time the samples are stored, a subject would like to withdraw his/her consent for participation in this research, RAPT Therapeutics will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

Subject Privacy and Return of Data

No subject-identifying information (e.g., initials, date of birth, government identifying number) will be associated with the sample. All pharmacodynamic and other biomarker samples will be single coded. Genomic DNA samples used to explore the effects on PK, treatment response, and safety will be single coded. Genomic DNA samples that will be stored for long-term use (defined as 15 years after the completion of the study) will be double coded. Double coding involves removing the initial code (subject ID) and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded, the first code being the subject number. Laboratory personnel performing genetic analysis will not have access to the “key.” Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID “key.”

The Sponsor will take steps to ensure that data are protected accordingly, and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The Sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- Clinical research organizations retained by the Sponsor
- Independent ethics committees or institutional review boards that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the coded data, in listing or summary format. Other publication (e.g., in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the pharmacodynamic, PG, and other biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the patients or their family members. Therefore, these results will not be disclosed to the patients or their physicians.

If at any time, pharmacodynamic, PG, and/or other biomarker results are obtained that may have clinical relevance, IRB review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments (CLIA)-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

APPENDIX 8 PROHIBITED MEDICATIONS AND THERAPIES

The following is a list of all medications, therapies (including procedures) that are prohibited while the subject is enrolled in this study. Subjects receiving any of these medications at study entry should discontinue the treatment or be switched to a different medication with similar pharmacology prior to starting study treatment. Subjects who receive any of these medications during the Treatment Phase must discontinue study treatment. However, the decision to allow the subject to continue to receive study treatment requires the mutual agreement of the investigator, the Sponsor, and the subject.

Medications that potentially prolong the QT interval

A list of medications known to cause QTc interval prolongation is provided in the table below and is also available at the following link:

<https://crediblemeds.org/pdftemp/pdf/CombinedList.pdf>. This list is not all-inclusive.

Compounds	Compound Half-Life	Possible Washout Period – Hours	Possible Washout Period – Days
Alfuzocin	~10 hours		7
Amantadine	17 +/- 4 hours (10–25)		4
Amiodarone (cordaron)	58 days (15–142) 36 days (active metabolite)		180
Amitriptyline*	> 24 hours, wide interpatient variability		
Arsenic trioxide	Not characterized		
Azithromycin	40 hours		
Bepiridil	42 hours (26-64)		10
Chloral hydrate	Readily converted to Trichloroethanol (active metabolite T1/2 = 7–10 hours)	48	
Chloroquine	Prolonged (days to weeks)		
Chlorpromazine	30 +/- 7 hours		
Clarithromycin	Non-linear PK3-4 hr (250mg Q12) 5–7 hr (500 mg Q12)	36	
Cloroquine	6 to 60 days; mean 20 days		
Desipramine*	> 24 hours, wide interpatient variability		
Disopyramide	6.7 hr (4-10)	36	
Dofetilide	10 hours	48	
Dolesetron	8.1 hours		
Domperidone	7-8 hours	48	
Doxepin*	> 24 hours, wide interpatient variability		
Droperidol	2.2 hours	10	
Erythromycin	*Each salt form has different Half-Life*		
Felbamate	20–23 hours		5
Flecainide	20 hours (12–27)		5
Foscarnet	87.5 +/-41.8 hours		20

Compounds	Compound Half-Life	Possible Washout Period – Hours	Possible Washout Period – Days
	distribution and release from bone		
Fosphenytoin	12–29 hours		6
Gatifloxacin	7–14 hours	48	
Gemifloxacin	7 hours	48	
Grepafloxacin	16 hours		3
Halofantrine	6–10 days (variable among individual)		45
Haloperidol	18 +/-5 hours		5
Ibutilide	6 hours (2–12) *variable among subject*	36	
Imipramine*	> 24 hours, wide interpatient variability		
Indapamide	14 hours (biphasic elimination)		3
Isardipine	8 hours (multiple metabolites)	48	
Levofloxacin	6–8 hours	48	
Levomethadyl	Multiple compartment PK with active metabolite 2.6 days for LAAM, 2 day for nor-LAAM, 4 day for dinor-LAAM		20
Lithium	24 hours (10–50)		7
Mesoridazine	24–48 hours (animal study)		10
Methadone	15–30 hours		7
Moexipril/HCTZ	2–9 hour (include active metabolite) for moexipril; 5.6–14.8 hours for HCTZ	48	
Moxifloxacin	12 +/-1.3 hours	72	
Naratriptan	6 hours	36	
Nicardipine	~ 2-hour post IV infusion	12	
Nortriptyline*	> 24 hours, wide interpatient variability		
Octreotide	1.7 hours	12	
Ofloxacin	5 to 7.5 hours		2
Ondansetron	4 hours (IV/IM); 3 hours (PO)		1 to 3
Pentamidine	6.4 +/- 1.3 hours	36	
Pimozide	55 hours		10
Procainamide	3–4 hours for PA and NAPA (active metabolite)	24	
Protriptyline*	> 24 hours, wide interpatient variability		
Quetiapine	6 hours	36	
Quinidine	6-8 hours in adult; 3–4 hours in children	36	
Quinine	4–5 hours		
Risperidone	3–20 hours (extensive to poor metabolizer) 9-hydroxyrisperidone (active metabolite) T _{1/2} = 21-30 hours (extensive to poor metabolizer)		4

Compounds	Compound Half-Life	Possible Washout Period – Hours	Possible Washout Period – Days
Salmeterol	5.5 hours (only one datum)	36	
Sotalol	12 hours	72	
Sparfloxacin	20 hours (16–30)		4
Sumatriptan	2.5 hours	12	
Tacrolimus	~34 hours in healthy; ~19 hours in Kidney transplant		7
Tamoxifen	5–7 days (biphasic)		30
Telithromycin	2-3 hours	24	
Thioridazine	20–40 hours (Phenothiazines)		7
Tizanidine	2.5 hours	12	
Vardenafil	4 to 5 hours		
Venlafaxine	5 +/- 2 hours for parent comp. 11 +/- 2 hours for OVD (active metabolite)	60	
Ziprasidone	7 hours	36	
Zolmitriptan	2.8–3.7 hours (higher in female)	18	

*Weakly associated with Torsades de pointes and/or QT prolongation but that are unlikely to be a risk for Torsades de pointes when used in usual recommended dosages and in patients without other risk factors (e.g., concomitant QT prolonged drugs, bradycardia, electrolyte disturbances, congenital long QT syndrome, concomitant drugs that inhibit metabolism).

References: 1. Physician's Desk Reference 2002; 2. Facts and Comparison (update to June 2005);
3. The Pharmacological Basis of Therapeutics 9th Edition, 1999.

Known Strong Cytochrome P450 (CYP)3A4 Inhibitors or Inducers

Medication Type	Drug Names
CYP3A4 Inhibitors	
Strong inhibitors	boceprevir, clarithromycin, conivaptan, grapefruit-containing products, indinavir, lopinavir, mibefradil, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, telithromycin
CYP3A4 Inducers	
Strong inducers	avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort

² This determination is made by the investigator. Once PD is confirmed, the initial date of PD documentation will be considered the date of disease progression.

APPENDIX 10 SUMMARY OF CHANGES

Amendment 6 (Section numbers refer to updated version):

- Added the following new combination cohorts to test lead-in dosing of FLX475 with pembrolizumab starting on Cycle 2 Day 1: C10 (CPI -naïve EBV+ NPC), C11 (CPI-naïve HNSCC), C12 (CPI-experienced HNSCC) and C13 (CPI-naïve NSCLC) in Synopsis, Inclusion Criteria, under section Part 2b, in Section 8.1 Overall Study Design and Plan, under section Part 2b: Combination Cohort Expansion (and Figure 1), and in Section 9.1 under Inclusion Criteria. Additional language describing lead-in dosing rationale and potential use in other cohorts added to Synopsis, Sections 6.3, 10.3, and 10.9.
- Changed timing of on-study tumor biopsy for subjects in lead-in dosing cohorts (C10-13) from Cycle 3 Day 1 ± 7 days to Cycle 2 Day 1 ± 3 days in Synopsis, Sections 9.1 and 11.4.2, and Table 11 Footnote “t”
- Removed exclusion for PR interval > 220 msec from Exclusion Criterion #10 (Synopsis and Section 9.2) given clinical data showing no effect of FLX475 on PR interval and no expected increased safety risk to subjects (Per protocol clarification letter (PCL) #8).
- Added reference for distinct response criteria (Olsen et al., 2011) for subjects with CTCL, and also clarified that on-study response assessment imaging for subjects with CTCL are only required 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 (Per PCL #8) to Synopsis, Sections 8.2.2, 11.1, 11.3.1, 11.3.1.1, Tables 10 and 11 (Footnote “s”), and 12.1.2.1.2.
- For NSCLC subjects, added exclusion criterion for prior radiation therapy to lungs that is > 30 Gy within 6 months of start of study treatment under Exclusion 23, in the Synopsis and under Section 9.2.
- Clarified, in Synopsis and under Statistical Methods, that Efficacy Eligible Set would include “lymphoma” criteria instead of “Lugano” criteria to include subjects with CTCL who will be assessed by alternative criteria.
- Updated background pembrolizumab-related language in Section 6.1: Background, under sections 6.1.1, 6.1.2, and 6.1.3.2.
- Updated Section 8.1 under Overall Study Design and Plan to reflect the previous addition of cohorts M5 and C6-C9 at Amendment 5 (Per PCL #6).
- Section 9.1 Inclusion Criteria, updated Table 1 footnote “c”, lowering platelet count threshold from $> 75,000/\mu\text{L}$ to $> 50,000/\mu\text{L}$ for eligibility in subjects with lymphoma and/or bone marrow involvement (Per PCL #6).

- Synopsis and Table 3 in Section 10.2.1.1: Updated Planned Dose Levels to reflect the previous addition of the M5 and C6-C9 cohorts from Amendment 5, and new lead-in cohorts C10-13.
- Section 10.5.1 and Table 4: Section updated to clarify that QT prolongation has been the only AE to date clearly related to FLX475 that may require dose modification.
- Section 10.5.2: Dose Modification for Pembrolizumab including Tables 5 and 6 have been revised to reflect the updated safety language in Edition 20 of the pembrolizumab Investigator's Brochure (Per PCL #6).
- Section 10.5.2: Dose Modification for Pembrolizumab. At the time of Amendment 5, in Table 6, the column header "Toxicity grade" inadvertently referenced CTCAE V5.0 instead of CTCAE V4.03. This has been corrected. (Per PCL #6).
- Added, under Section 10.11.4: Prohibited Medications and Therapies, guidance on COVID-19 vaccination and Paxlovid™ treatment.
- Section 11.4.2 and Tables 8-11 (Footnote "r") updated to indicate discontinuation of stool sample collection as of August 1, 2021.
- Section 11.5.5 modified to more clearly state that pre-dose lab results do not need to be reviewed prior to drug dispensing/administration at study visits except in certain circumstances (Per PCL #8).
- Section 11.6: Schedule of Procedures/Assessments, Subsections, Tables 10 and 11, footnotes modified to indicate discontinuation of sample collection for receptor occupancy/internalization from November 1, 2021 (Per PCL #8).
- Section 11.6, Table 10-11, footnotes "s" and "u" modified to clarify timing of scans and response assessments.
- Table 11: Table and Footnote "a" updated to note Cycle 1 Day 1 dose of pembrolizumab not given with lead-in dosing cohorts.
- Section 11.6.2 revised to clarify specific reasons for discontinuing treatment (Per PCL #7).
- Section 12.1.1.2 Statistical Basis for Study Design of Part 2 (Cohort Expansion): Text has been revised to reflect the addition of the new M5 and C6-C9 cohorts (Per PCL #6).
- Reference list updated

- Appendix 8 revised to align with Section 10.11.4: Prohibited Medications and Therapies.

Amendment 5 (Section numbers refer to updated version):

- Inclusion Criterion #3 updated to add new Phase 2 expansion cohorts based on evolving clinical data (Synopsis and Section 9.1; and Figure 1b). Total potential numbers of subjects in the study concurrently updated in Synopsis and elsewhere in protocol.
 - M5 (FLX475 Monotherapy): EBV-negative lymphoma
 - C6 (Combination Therapy): EBV+ lymphoma
 - C7 (Combination Therapy): EBV-negative lymphoma
 - C8 (Combination Therapy): EBV+ nasopharyngeal carcinoma
 - C9 (Combination Therapy): CPI-naïve NSCLC
- Inclusion Criterion #7 modified to align time window required for repeat scan after treatment of brain metastases with Exclusion Criterion #7 (Synopsis and Section 9.1)
- Inclusion Criterion #10 clarified to align with Exclusion Criterion #5 (Synopsis and Section 9.1)
- Exclusion Criterion #15 modified to permit enrollment of HIV-infected individuals with well-controlled disease consistent with FDA guidance
- Clarified that DLT definition applies to Phase 1 subjects only (Synopsis and Section 10.4)
- Clarified how baseline QTcF interval should be defined (Synopsis and Sections 10.4, 11.5.1, 12.1.8.5)
- Clarified entry requirements for crossover subjects (Section 8.1)
- Clarified dose modification guidelines for FLX475 based on accumulating safety data (e.g. GI and hepatic), including that dose reduction of FLX475 should be based on Grade 2 QTcF prolongation threshold when assessed pre-dose and Grade 3 for post-dose assessments (Section 10.5.1)
- Updated dose modification guidelines for pembrolizumab (Table 6) using updated standard guidance (Section 10.5.2)
- Clarified that baseline imaging for HNSCC including NPC should include head and neck imaging (Section 11.3.1)

- Removed reference to Imaging Core Lab (ICL) which is not being used (Section 11.3.1.1)
- Clarified that “pre-dose” assessments (including PK and ECGs) should be obtained at study visits even if study treatment is being held (Section 11.4.1 and Tables 8-11)
- Modified Section 11.4.1 and removed pembrolizumab PK and ADA samples from Tables 9 and 11, as determined these would no longer need to be collected for potential analysis.
- Updated link for reference for QTc prolonging drugs (Appendix 8)

Amendment 4 (Section numbers refer to updated version):

- Name of Sponsor updated from FLX Bio, Inc. to RAPT Therapeutics, Inc. due to corporate name change (throughout document)
- Inclusion Criterion #12 clarified to define “pretreatment” and to add that archival slides are only acceptable for Phase 1 subjects given prior approval by Sponsor
- Inclusion Criterion # 15 and Exclusion Criterion #21: Updated contraception requirement and sperm donation prohibition for men from 30 to 120 days to be consistent with local requirement in Korea
- Exclusion Criterion #10 clarified that QTcF cutoff is ≥ 450 msec (Grade 1 or above) and not > 450 msec; similar clarification made in Section 11.5.1 to define Events of Clinical Interest
- DLT criteria updated from “ ≥ 500 msec and > 60 msec” to “ ≥ 501 msec and > 60 msec” to align QTc cutoff with CTCAE Grade 3 value; also clarified QTcF value to be specifically used for QTc assessments in selected locations throughout protocol
- Language added in Statistical Methods and elsewhere to clarify potential overenrollment scenarios of Phase 2 expansion cohorts:
 - *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.*
- Section 8.1 “Intrasubject Dose Escalation and Crossover” section corrected to note that a minimum of 3 cycles of treatment at monotherapy are required to be eligible for crossover to combination therapy; language also added to clarify screening requirements and procedures for potential crossover patients
- Table 1 updated to clarify that either aPTT or PTT is acceptable

- Section 10.2.1.2 updated to clarify that a minimum of 10 subjects are needed to determine a RP2D for combination therapy
- Section 10.3 updated to increase the window between cohort assignment and C1D1 dose of pembrolizumab from 5 to 7 days to increase site flexibility
- Section 10.5.1: Dose modification criteria for FLX475 toxicity of Grade 2 or greater QTcF simplified to dose reduce to 50 mg or stop
- Section 10.6.4 updated to include pembrolizumab storage conditions
- Section 10.11.4 clarified that palliative radiation therapy to a symptomatic solitary lesion is permitted for non-target lesions only
- Section 11.1 updated to clarify that rescreening of candidates requires pre-approval from Sponsor
- Section 11.3.1 clarified that brain imaging at all tumor assessment time points (after Screening) are only required for subjects treated for brain metastases within 6 months prior to C1D1
- Section 11.5.1 clarified that 90-day follow up period after subject's last dose applies to AEs present at the time of cessation of study treatment (not for reporting of new AEs that occur after cessation of study treatment)
- Section 11.5.2 added overdose of pembrolizumab as event of clinical interest for consistency
- Section 11.5.8 clarified that subjects should be supine (not recumbent) for ECG collection to be consistent with the rest of the protocol
- Per Protocol Clarification Letter #4 (19Dec2019), Table 1 also updated to modify hematologic lab values defining adequate organ function for eligibility to allow lower values of absolute neutrophil count (ANC), platelets, and hemoglobin, particularly for patients with bone marrow involvement of cancer, given that no significant effects on hematologic parameters have been observed in Phase 1 of the study.
- As noted in Protocol Clarification Letter #3 (12DEC2019), Tables 10 and 11 were updated to remove the 6-hour post-dose vital signs and serum biomarker timepoints
- Per Protocol Clarification Letter #4 (19Dec2019), Section 11.5.1 updated to clarify that progression of cancer is not considered an AE and hospitalization or death due to progression of cancer does not need to be reported as an SAE.
- Appendix 4 corrected the maximum number of target lesions per organ from 2 to 5 to be consistent with Section 11.3.1.
- Clarified that the Safety Review Committee (SRC) will continue to meet in the Phase 2 portion of the study at least quarterly to review accumulating safety data

- Added language to clarify the rationale for possibly combining Stage 2 of expansion cohorts M1 and M2

Amendment 3 (Section numbers refer to updated version):

- Summary of Changes moved from Section 1 to Appendix 10
- (Section 5) Projected total site number updated
- (6.1.2) References to Keytruda Package Insert changed to IB
- (6.1.3.2.1) Phase 1 Healthy Volunteer Study summary updated
- (8.1) Total projected subject number updated with revised Phase 2 design
- Figure 1, study design, and inclusion criteria updated to refine the list of eligible indications for Phase 1 dose escalation
 - EBV⁺ and EBV⁻ gastric cancer cohorts were removed from Part 2a (monotherapy)
 - EBV⁺ cohorts were removed from Part 2b (combination)
 - CPI-naïve HNSCC cohort was added to Part 2b (combination)
 - Basket cohort was added for Part 2a monotherapy subjects eligible for crossover to combination therapy
 - Change to Simon 2-stage design decreased Stage 1 and Stage 2 cohort sizes from 15 to 10, and from 35 to 19, respectively
 - Expansion cohorts were renumbered M1-M4 and C1-C5
- Inclusion #12 updated to clarify minimum number of core biopsy samples and timing
- Exclusion #26 updated to remove redundant or contradictory criteria regarding prior or concurrent investigative treatment
- Tables 2 and 3 updated to remove references to unit dose strengths and tablet numbers, as different dose strengths will be used later in the study
- (11.3) Clarified that PET scans are part of lymphoma imaging for response assessments
- (11.5.1) Clarified the options available for Classification of Causality of AEs
- (11.5.5) Clarified the requirements for fasting glucose testing and for review of C1D1 pre-dose labs prior to dosing
- Safety follow-up period for AE and SAE reporting updated throughout (Sections 8.2.3, 10.11.4, 11.5.1, 11.5.2, 11.7.1, and Schedules of Assessments) for consistency
 - All AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before treatment must be reported by the investigator if the event causes

- the subject to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.
- AEs and ECIs should be reported through 30 days following cessation of study treatment
 - SAEs should be reported for 90 days after cessation of study treatment, or for 30 days after the final dose of study treatment if the subject initiates new anticancer therapy, whichever is earlier
 - Pregnancies and exposure during breastfeeding must be reported through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the subject initiates new anticancer therapy, whichever is earlier
 - Clarified timing of pembrolizumab PK samples in Tables 9 and 11
 - Response criteria for lymphoma updated from Cheson 2007 to Lugano (Cheson 2014) criteria in Appendix 6 and throughout protocol
 - Added/updated windows for assessments
 - Statistical Methods section language updated to reflect Simon 2-stage design
 - Administrative updates, editorial changes, and style and formatting revisions have also been made to improve clarity and consistency throughout the document

Amendment 2:

- Language describing previous treatment with anti-PD-1 or anti-PD-L1 requirement for specific expansion cohorts revised to clarify progression/relapse requirement (Synopsis, Sections 9.1, 10.1.1)
 - “Previously treated with anti-PD-1 or anti-PD-L1 therapy without disease progression within 3 months of therapy initiation”
 - Changed to “Subjects with documented disease progression or relapse more than 3 months after initiation of prior anti-PD-1 or anti-PD-L1 therapy”
- Table 11 title corrected
- Section 12.5.1 Deleted reference to screen failure eCRF which doesn’t exist.
- Expanded screening period from 14 to 21 days (Tables 8–11 and throughout protocol)
- Updated QTcF exclusion to > 450 msec for both men and women (Synopsis and Section 10.1.2)
- Clarified “FLX475 PK Samples” (Tables 8, 10, 11)
- Added study visit and PK sample windows to Tables 8–11

PROTOCOL SIGNATURE PAGE

Study Protocol Number: FLX475-02
Study Protocol Title: Phase 1/2 Dose-Escalation and Expansion Study of FLX475 Alone
and in Combination with Pembrolizumab in Advanced Cancer
Amendment Number: 6 (01 September 2022)
Investigational Product
Name: FLX475 (F003475) and pembrolizumab



INVESTIGATOR SIGNATURE PAGE

Study Protocol Number: FLX475-02
Study Protocol Title: Phase 1/2 Dose-Escalation and Expansion Study of FLX475 Alone and in Combination with Pembrolizumab in Advanced Cancer
Amendment Number: 6 (01 September 2022)
Investigational Product Name: FLX475 (F003475) and pembrolizumab
[REDACTED] [REDACTED]
EudraCT Number: xx

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator

Signature

Date

As regionally required

Head
Medicine Development
Center

Signature

Date