CLINICAL STUDY PROTOCOL

Study Protocol Number:	FLX475-03
Study Protocol Title:	Phase 2 Study of FLX475 in Combination with Ipilimumab in Advanced Melanoma
Investigational Product Name:	FLX475 (F003475)
Indication:	Advanced melanoma
Phase:	2
IND Number:	138286
Sponsor:	RAPT Therapeutics, Inc. 561 Eccles Avenue South San Francisco, CA 94080
Sponsor Contact:	[redacted]
Date:	Original Protocol: October 1, 2020 Amendment 1: October 19, 2020
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.

1 CLINICAL PROTOCOL SYNOPSIS

Investigational Product Name(s): FLX475

Study Protocol Title
Phase 2 Study of FLX475 in Combination with Ipilimumab in Advanced Melanoma

Sites
Approximately 3−5 sites in the United States (US)

Study Period and Phase of Development
Phase 2

Objectives
Primary Objectives

- To evaluate the objective response rate (ORR), defined as confirmed complete or partial response per RECIST 1.1, of FLX475 in combination with ipilimumab in subjects with advanced melanoma previously treated with an anti-PD-1 or anti-PD-L1 agent
- To evaluate the safety and tolerability of FLX475 in combination with ipilimumab in subjects with advanced melanoma previously treated with an anti-PD-1 or anti-PD-L1 agent

Secondary Objectives

- To evaluate the progression-free survival (PFS) of subjects with advanced melanoma treated with FLX475 in combination with ipilimumab who have been previously treated with an anti-PD-1 or anti-PD-L1 agent
- To evaluate the overall survival (OS) of subjects with advanced melanoma treated with FLX475 in combination with ipilimumab who have been previously treated with an anti-PD-1 or anti-PD-L1 agent
- To evaluate the objective response rate (ORR), defined as confirmed complete or partial response per iRECIST, of FLX475 in combination with ipilimumab in subjects with advanced melanoma previously treated with an anti-PD-1 or anti-PD-L1 agent
- To evaluate the plasma concentrations of FLX475 when it is given in combination with ipilimumab
- To assess the effects of FLX475 in combination with ipilimumab on pharmacodynamic (PD) markers relating to drug mechanism of action
- To characterize the onset, magnitude, and duration of tumor control in subjects receiving FLX475 in combination with ipilimumab

Number of Subjects
Approximately 20 subjects

Study Design:
This clinical trial is a Phase 2, open-label study to determine the anti-tumor activity of FLX475 in combination with ipilimumab in subjects with advanced melanoma previously treated with an anti-PD-1 or anti-PD-L1 agent.
The study will be conducted starting with a safety run-in portion in which 6 eligible subjects will be enrolled and treated for at least one 3-week cycle to determine if the safety profile of FLX475+

ipilimumab is acceptable to complete enrollment of the approximately 20-subject study. Should the safety profile be deemed not acceptable for the 100 mg FLX475 PO QD and 3 mg/kg ipilimumab IV Q3W combination regimen, an alternative (lower) dose regimen of either or both drug(s) may be selected and tested in an additional 6-subject safety run-in phase. Ultimately at least 20 subjects should be treated and evaluated with a single combination dose regimen.

Accrual to the study may be discontinued prior to completing 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 pathologically confirmed advanced melanoma that is either Stage IV or unresectable Stage III. Subjects may have cutaneous, mucosal or unknown primary lesions of origin. Subjects with uveal primary are not eligible.
2. Subjects must have had prior treatment with anti-PD-1 or anti-PD-L1 agents, with at least 2 months of therapy followed by documented disease progression either while on these agents or after stopping therapy with these agents. Subjects must have discontinued anti-PD-1 or anti-PD-L1 therapy at least 4 weeks prior to start of study treatment. Subjects who received prior treatment with anti-PD-1 or anti-PD-L1 agents in the adjuvant setting and whose disease recurred while on treatment, or within 6 months of completion of the treatment, are eligible.
3. Men and women ≥ 18 years of age on day of signing informed consent.
4. Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 or 1. (Subjects with stable ECOG PS of 2 due to non-cancer-related conditions may be permitted with the approval of the Sponsor's medical monitor.)
5. Subjects must have measurable disease per RECIST 1.1.
6. Subjects with central nervous system (CNS) metastases must have all lesions adequately treated with stereotactic radiation therapy, craniotomy, Gamma Knife therapy, or whole brain radiotherapy, with no subsequent evidence of CNS progression. Subjects must not have required steroids for at least 14 days prior to start of study treatment.
7. 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 may be permitted with Sponsor agreement, and subjects with immune-related endocrinopathies who are on stable doses of medications are permitted).
8. Subjects must have adequate hematologic function as evidenced by all of the following at time of screening within 21 days prior to start of study treatment: absolute neutrophil count (ANC) ≥ 1500/μL; hemoglobin ≥ 8 g/dL; and platelets ≥ 100,000/μL.
9. Human immunodeficiency virus (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/mm^3 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).

10. Subjects must have adequate hepatic function as evidenced by all of the following at time of screening within 21 days prior to start of study treatment: total bilirubin ≤ 2.5 x Institutional Upper Limit of Normal (IULN) (except subjects with Gilbert's syndrome); and AST and ALT both ≤ 5 x IULN.
11. Subjects must have adequate kidney function as evidenced by serum creatinine ≤ 2.0 x IULN at time of screening within 21 days prior to start of study treatment.
12. Subjects enrolled must be willing and able to provide tissue from a newly obtained core (minimum of 3 cores) or excisional (or skin punch) biopsy of a tumor lesion not previously irradiated (unless subsequent progression demonstrated). In addition, subjects must be willing to provide a tumor biopsy (minimum of 3 cores, or excisional or skin punch) while on treatment at Cycle 2 Day 8 (± 7 days) and may be asked to provide additional biopsies at other timepoints such as the time of discontinuation due to progression.
13. For women of childbearing potential, negative results on a serum pregnancy test within 2 days prior to study registration and willingness to use an effective method of contraception (e.g., oral contraceptives, double-barrier methods such as a condom and a diaphragm, intrauterine device) from the start of study treatment (or 14 days prior to the initiation of study treatment for oral contraception) 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).***
14. 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 (or 14 days prior to the initiation of study treatment for oral contraception) 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.***
15. Ability to swallow tablets without difficulty.
16. Signed Informed Consent Form by the subject or his/her legal guardian.

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.
2. Any history of discontinuing prior treatment due to Grade 3–4 immune-related adverse events (irAEs) of colitis or pneumonitis.
3. Prior treatment with ipilimumab or other CTLA-4 antagonists.
4. Prior systemic anticancer therapy including any anti-PD-1 or anti-PD-L1 agents within 4 weeks prior to start of study treatment.
5. Active autoimmune disease requiring disease-modifying therapy at the time of screening. 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 another malignancy that has progressed or has required active treatment within the past 2 years, unless it is clinically stable and does not require tumor-directed treatment. (Examples include 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; or other adequately treated Stage 0, 1 or 2 cancers currently in complete remission.) In addition, any other cancer treated with curative intent ≥ 2 years prior to screening with no evidence of disease is permitted.
7. 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).
8. 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, PR interval > 220 msec, or unstable cardiac arrhythmia requiring medication. Chronic asymptomatic atrial fibrillation stably controlled with medications is permitted.
9. 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.
10. 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.
11. HIV-infected subjects with a history of Kaposi sarcoma and/or Multicentric Castleman Disease.
12. 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.
13. 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. Inhaled or topical steroids, and adrenal replacement doses of ≤ 10 mg daily prednisone or equivalent are permitted in the absence of active autoimmune disease.
14. Prior allogeneic organ transplant.
15. 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.
16. Radiotherapy within 14 days prior to start of study treatment. Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis.

17. 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. (See Appendix 7)
18. 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. (See Appendix 7)
19. Current participation in another study of an investigational agent or device.
20. 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 100 mg FLX475 (or lower dose if subsequently modified) orally with water once daily at approximately the same time each day at their assigned dose on a continual basis. On days when ipilimumab is also administered (i.e., Day 1 of Cycles 1-4), FLX475 should be taken approximately 1 hour before the ipilimumab infusion.

Ipilimumab 3 mg/kg will be administered as an IV infusion over 30 or 90 minutes (per institutional protocol) on Day 1 of every 3-week treatment cycle (i.e., every 21 days [±3 days] for up to 4 doses), and approximately 1 hour after the Day 1 dose of FLX475.

Safety Run-In and Enrollment:

The first six subjects enrolled and treated at the recommended Phase 2 dose of FLX475 (100 mg/dose QD) plus ipilimumab (3 mg/kg IV q3W, up to 4 doses) will be followed for at least one 3-week cycle (21 days) to monitor for any unacceptable (or dose-limiting) toxicities prior to enrolling additional subjects.

After the first six subjects enrolled 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. pharmacokinetic [PK] scientist and/or biostatistician). The SRC will carefully consider all available safety, laboratory, and PK information in consultation with the study investigators. After review of all available data, the SRC may recommend continued enrollment of the entire study (e.g. if no unacceptable toxicities are observed); dose reduction of either FLX475 and/or ipilimumab; or discontinuation of the study. Beyond the safety run-in phase, the SRC will continue to meet at least quarterly during 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 Dose-Limiting Toxicity (DLT):

Reference should be made to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 (Appendix 1) for grading of the severity of AEs and laboratory abnormalities. The safety profile of ipilimumab monotherapy has been well described (Yervoy® Package Insert; Hodi et al., 2010) and includes a significant number of immune-related adverse events (irAEs) to be taken into account when determining what might be either unexpected or unacceptable toxicity for the combination of FLX475 with ipilimumab. Therefore, a DLT for this study will be defined as an AE or abnormal laboratory value 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:
  - Clinically significant medical intervention is required to treat the subject, or
  - The abnormality leads to hospitalization, or
  - The abnormality persists for >1 week, or
  - The abnormality results in a Drug-induced Liver Injury (DILI)
  - Exceptions: Clinically nonsignificant, treatable, or reversible laboratory abnormalities including liver function tests, uric acid, etc.
- 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 14 days with adequate medical management
- Grade 3 fever that does not resolve to Grade 1 or baseline level (whichever is higher) within 14 days with adequate medical management
- Grade 3 fatigue that does not resolve to Grade 2 or baseline level (whichever is higher) within 14 days with adequate medical management
- 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 14 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 14 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 adrenal insufficiency, thyroiditis and thyroid dysfunction (which are acceptable)
- Grade ≥ 3 febrile neutropenia:
  - Grade 3 is defined as absolute neutrophil count (ANC) < 1000/mm^3 with a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than 1 hour
  - Grade 4 is defined as ANC < 1000/mm^3 with a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°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 the average QTcF value from pre-dose C1D1 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
- Any Grade 5 toxicity.

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, or study discontinuation by Sponsor.

Study Endpoints:

Efficacy:

The primary efficacy endpoint 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 melanoma.

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.

Safety:

The primary safety endpoint in the safety run-in portion of the study is safety and tolerability by the determination of AEs, including DLTs. 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:

Plasma concentrations of FLX475 will be determined with a validated bioanalytical method, and listed and summarized by time point. No PK parameters (e.g. C_{max} and AUC) will be calculated.

Pharmacodynamics:

Changes in immune parameters, e.g., lymphocyte subpopulations and plasma cytokines or chemokines in peripheral blood or in tumor

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.

Efficacy Eligible Set: All subjects who receive at least one dose of FLX475 in combination with ipilimumab, have measurable disease at baseline per RECIST v1.1, 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 who complete at least one cycle of FLX475 in combination with ipilimumab 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 one dose of FLX475 in combination with ipilimumab, and have measurable plasma concentrations of FLX475.

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

Analysis Methods

Evaluation of data will consist primarily of descriptive statistics, summary displays, and data listings. Efficacy and safety data will be presented by treatment and tumor type.
The number of subjects enrolled and discontinued from the study (by reason) will be presented. 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. 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.

Rationale for Sample Size

The sample size of 20 subjects is considered adequate on clinical grounds to judge the safety of the combination therapy and obtain an initial estimate of its clinical efficacy. The ORR for the combination therapy is hypothesized to exceed the value observed with ipilimumab monotherapy (10−15%, Long et al., 2017).

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.

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LIST OF IN-TEXT TABLES

LIST OF APPENDICES

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)
CCL17	C-C motif chemokine ligand 17
CCL22	C-C motif chemokine ligand 22
CCR4	C-C chemokine receptor type 4
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendment
C_{max}	Maximum concentration
CNS	Central nervous system
CPI	Checkpoint inhibitor
CR	Complete response
CRA	Clinical research associate
CrCl	Creatinine clearance
CRF	Case report form
CRO	Contract research organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
CV	Curriculum vitae
DLT	Dose-limiting toxicity
DM	Diabetes mellitus
DOR	Duration of response
ECG	Electrocardiogram
ECI	Events of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EU	European Union

FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GI	Gastrointestinal
HBV	Hepatitis B virus
HCV	Hepatitis C virus
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
MTD	Maximum tolerated dose
NA	Not applicable
NCI	National Cancer Institute
NSAID	Nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease; pharmacodynamics
PD-1	Programmed cell death protein 1
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
RECIST	Response Evaluation Criteria In Solid Tumors
RO	Receptor Occupancy
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
$t_{½}$	Terminal half-life
TEAEs	Treatment-emergent adverse events
T_{eff}	Effector T cell
TEMAV	Treatment-emergent markedly abnormal laboratory values
TME	Tumor microenvironment
T_{reg}	Regulatory T cell
TTR	Time to response
UA	Urinalysis
ULN	Upper limit of normal
US	United States
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 or designee 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 3−5 investigational sites in the US.

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

6 INTRODUCTION

6.1 Background

6.1.1 Immunotherapy for Cancer

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 cytotoxic T lymphocyte-associated antigen 4 (CTLA-4, CD152) receptor serves as negative regulator of anti-tumor immunity. The normal function of CTLA-4, expressed on the cell surface of activated T cells under healthy conditions, is to mediate immune homeostasis, including prevention of autoimmune reactions. CTLA-4 is a homolog of cluster of differentiation 28 (CD28) that binds to CD80 and CD86 on the surface of antigen-presenting cells, outcompeting CD28, and serves as an "off switch" or "checkpoint" to immune activation (Walunas, et al., 1994; Sansom, 2000).

The recent use of antibodies (known as checkpoint inhibitors, or CPIs) to block immune checkpoints such as CTLA-4 and the programmed cell death 1 protein (PD-1) 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 Ipilimumab

Ipilimumab is a fully human immunoglobulin G1 (IgG1) monoclonal antibody (mAb) with high specificity of binding to the CTLA-4 receptor, thus inhibiting its interaction with CD80 and CD86. Ipilimumab has an acceptable preclinical safety profile and is approved as an intravenous (IV) immunotherapy for several advanced malignancies either as monotherapy, or in combination with the anti-PD-1 monoclonal antibody, nivolumab (Yervoy® Package Insert).

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 μM.

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 AUC_{0-24}), increases with the increase in dose level in both species and there is a small degree of accumulation (~2 fold) with repeated dosing.

[redacted] 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. [redacted]

In the 4-week dog study, the no-observed-adverse-effect level (NOAEL) was [redacted] and highest non-severely toxic dose (HNSTD) was [redacted]. In the 4-week mouse study, the NOAEL was [redacted] and severely toxic dose was at least [redacted]. The results from these studies supported the starting dose of 25 mg FLX475 in oncology patients.

6.1.3.2 Clinical Experience with FLX475

6.1.3.2.1 FLX475-01: 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 et al., 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. Daily dosing without a loading dose demonstrated approximately 4–5x accumulation of FLX475 over 14 days. The tablet formulation of FLX475 to be used in the oncology study was shown to provide equivalent exposure as the capsule formulation used in the healthy volunteer (HV) study, suggesting the HV PK data are applicable to the planned study in cancer patients. In addition, there was no significant effect of food on the bioavailability or PK profile of FLX475 tablets. 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.

The most common adverse events reported were transient low-grade headache and gastrointestinal symptoms (e.g. loose stool, abdominal discomfort, vomiting) that were considered not, unlikely, or possibly related to study medication. Asymptomatic transient Grade 1 and 2 prolongations in QTc interval were occasionally observed during dose escalation. An increased number of QTc interval increases were observed at the highest dose cohorts which achieved mean C_{max} values approximately 3–5-fold greater than the target therapeutic exposure level. There was no notable increase in QTc interval prolongation events observed at dose levels and exposures within the target exposure range for clinical efficacy.

6.1.3.2.2 FLX475-02: Phase 1/2 Dose-Escalation and Expansion Study of FLX475 Alone and in Combination with Pembrolizumab in Advanced Cancer

FLX475-02 is on ongoing study examining the safety and preliminary anti-tumor activity of FLX475 as monotherapy and in combination with pembrolizumab (Keytruda®) in subjects with several types of advanced cancer (Powderly et al., 2020). Phase 1 dose escalation has been completed for both FLX475 monotherapy and FLX475 + pembrolizumab combination therapy, and a recommended Phase 2 dose of 100 mg QD for FLX475 has been selected, based on the cumulative PK, PD, and safety data for both FLX475 monotherapy and combination therapy.

In Part 1a of the FLX475-02 study (Phase 1 dose escalation of FLX475 monotherapy), 19 subjects with advanced cancer have been treated in four dose escalation cohorts with daily dosing of FLX475 at 25 mg (3 subjects), 50 mg (3 subjects), 75 mg (7 subjects), and 100 mg (6 subjects). PK, PD, and safety findings have been consistent with what was observed in the healthy volunteer study. While one dose-limiting clinical adverse event of asymptomatic QTc prolongation (> 500 ms and > 60 ms prolongation from baseline) was observed in each of the 75 mg and 100 mg monotherapy dose escalation cohorts, both in subjects with confounding factors (including an elevated and increasing QTc at baseline in one, and hypokalemia in the other), no monotherapy maximum tolerated dose (MTD) was defined as no dose was determined to have exceeded the MTD. Preliminary PK data demonstrated that all 6 subjects in the 100 mg cohort achieved or exceeded the target minimum FLX475 drug exposure level of 130 ng/mL after 1 week of dosing. Available PD (RO) data suggested all subjects achieved target RO levels of 75% or more (see Section 6.1.4.1 for dose rationale). Based on the results of the healthy volunteer study, it was expected that additional dose escalation beyond 100 mg (e.g. 125 mg and beyond) was unnecessary to improve target drug exposure and RO, and would likely eventually exceed an MTD due to QTcF prolongation observed. Therefore 100 mg was chosen as the recommended Phase 2 dose (RP2D) for FLX475 monotherapy.

In Part 1b of the FLX475-02 study (Phase 1 dose escalation of FLX475 + pembrolizumab combination therapy), 18 subjects with advanced cancer have been treated in three dose escalation cohorts with standard-dose pembrolizumab plus daily dosing of FLX475 at 50 mg (3 subjects), 75 mg (4 subjects), and 100 mg (11 subjects). PK, PD, and safety findings have been consistent with what was observed in the healthy volunteer study (FLX475-01) and in Part 1a of FLX475-02. PK of FLX475 was similar between monotherapy and combination therapy cohorts. Preliminary PK data demonstrated that all evaluable subjects in the 100 mg combination cohort achieved or exceeded the target minimum FLX475 drug exposure level of 130 ng/mL after 1 week of dosing. Available PD (RO) data suggested all evaluable subjects in the 100 mg combination cohort achieved target RO levels of 75% or more. No new or unexpected treatment-emergent adverse events (TEAEs) were observed with the combination of FLX475 + pembrolizumab, i.e. all TEAEs observed were similar to those previously observed with either FLX475 monotherapy or pembrolizumab monotherapy alone. Finally, no DLTs were observed in all DLT-evaluable subjects , including at the highest combination dose of 100 mg FLX475 and therefore 100 mg FLX475 PO QD + 200 mg pembrolizumab IV Q3 weeks was selected as the RP2D for combination therapy, as additional dose escalation would be unnecessary to improve target drug exposure and RO, and would likely eventually exceed an MTD due to predicted QTcF prolongation at higher exposures.

6.1.4 Dose Rationale for Combination Therapy

6.1.4.1 FLX475

FLX475 administered to mice at a dose of 10 mg/kg orally QD resulted in maximal inhibition of in vivo T_{reg} migration into tumors (refer to the FLX475 Investigator's Brochure for details). The average plasma concentration of FLX475 in these mice was [redacted] at trough. This concentration is approximately equal to the IC_{90}

of FLX475 in the in vitro mouse T_{reg} chemotaxis assay of [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.

The corresponding IC_{90} in the human in vitro T_{reg} chemotaxis assay is [redacted]. Both the mouse and human in vitro IC_{90} values of FLX475 correspond to 75% receptor occupancy of CCR4 as measured by fluorescently labelled ligand (CCL22) in mouse and human T_{reg}, respectively. Thus, the human exposure target for clinical efficacy of FLX475 is [redacted]

Based on the PK data obtained in healthy volunteers, FLX475 administered at doses of [redacted] are predicted to achieve C_{trough} levels of drug above the human exposure target for clinical efficacy and a recommended Phase 2 dose of 100 mg PO QD has been selected in the ongoing FLX475-02 study for FLX475 given both as monotherapy and in combination with pembrolizumab. There has been no observed effect of pembrolizumab on the PK of FLX475 when administered in combination, and there similarly would be no effect of ipilimumab expected when given in combination with FLX475. Given the mechanism of action (and potential toxicity) of FLX475 and that it is not expected to have overlapping toxicities with checkpoint inhibitors, 100 mg PO QD will also be the dose of FLX475 used in combination with ipilimumab in this study.

6.1.4.2 Ipilimumab

The planned dose of ipilimumab (Yervoy®) for this study is 3 mg/kg every 3 weeks (Q3W) for 4 doses, which is the currently approved dosage for treatment of unresectable or metastatic melanoma. A lower dose level of 1 mg/kg has also been approved in other clinical settings.

Refer to the approved labeling for more details on Yervoy® (ipilimumab).

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.

Based on the non-clinical toxicology studies performed, a starting dose of [redacted] In the clinical

experience in healthy volunteers and in subjects with advanced cancer to date (Section 6.1.3.2.2), only asymptomatic and reversible QTcF prolongation has been observed as a dose-related effect of FLX475, and a daily oral dose of 100 mg FLX475 has been chosen as the recommended Phase 2 dose of FLX475 to be used in subjects with advanced cancer, both as monotherapy, and in combination with pembrolizumab.

Thus, based on the available preclinical, non-clinical, and clinical data, the risk-benefit profile of FLX475 is judged acceptable for this proposed Phase 2 study in subjects with advanced melanoma. No significant safety findings have been observed [Section 6.1.3.2] that would alter the risk-benefit profile of this proposed phase 2 study testing FLX475 combination therapy with ipilimumab in subjects with advanced or metastatic melanoma. 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 or cancer subjects to date.

The safety profile of ipilimumab has been well described, and does include immune-mediated toxicity (Yervoy® Package Insert). Based on its proposed mechanism of action, FLX475 is not expected to significantly enhance immune-mediated toxicity when administered with ipilimumab. Consistent with this, no overlapping toxicity with pembrolizumab has been observed to date. 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.

As part of a safety run-in, the first six subjects on study will be treated with both the recommended Phase 2 dose of FLX475 (100 mg PO QD) and the approved dose of ipilimumab (3 mg/kg IV) and observed for a minimum of one cycle of treatment (21 days) for any unacceptable toxicities (dose-limiting toxicities or DLTs as described in Section 10.4) prior to enrolling additional subjects. A DLT can be observed in no more than one of the first six subjects during the first cycle of treatment before enrollment of the remainder of the study subjects can continue. If a treatment-related DLT is observed during the first cycle of treatment in more than one of the first six (or fewer) subjects, dose modification of either or both drugs will be considered by the Safety Review Committee prior to continuing enrollment, potentially in an additional safety run-in.

6.3 Study Rationale

This Phase 2 study will evaluate safety and clinical efficacy, in addition to PK and potential changes in the TME of FLX475 in combination with ipilimumab in subjects with advanced melanoma. Ipilimumab is an approved treatment for advanced melanoma with a reported best overall response rate (ORR) ranging from 10.9% in previously-treated patients (Hodi, et al., 2010) to 19% in previously untreated patients (Larkin, et al., 2015), thus there remains room for clinical improvement.

The primary hypothesis of this study is 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 anti-tumor immune response when given in combination with ipilimumab, thus increasing the clinical activity of ipilimumab. The study design will first examine the safety of the combination of FLX475 and ipilimumab as part of a safety run-in phase, and will also examine the degree of anti-tumor activity (clinical responses) in subjects with advanced melanoma previously treated with an anti-PD-1 or anti-PD-L1 agent. Based upon available clinical data, the ORR of ipilimumab monotherapy in such subjects is expected to be approximately 14% (Long, et al., 2017). Thus an ORR of >20−30% with the combination of FLX475 and ipilimumab in this study would provide preliminary clinical evidence in support of the clinical hypothesis.

7 STUDY OBJECTIVES

7.1 Primary Objective

The primary objectives of the study are:

- To evaluate the objective response rate (ORR), defined as confirmed complete or partial response per RECIST 1.1, of FLX475 in combination with ipilimumab in subjects with advanced melanoma previously treated with an anti-PD-1 or anti-PD-L1 agent
- To evaluate the safety and tolerability of FLX475 in combination with ipilimumab in subjects with advanced melanoma previously treated with an anti-PD-1 or anti-PD-L1 agent

7.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the progression-free survival (PFS) of subjects with advanced melanoma treated with FLX475 in combination with ipilimumab who have been previously treated with an anti-PD-1 or anti-PD-L1 agent
- To evaluate the overall survival (OS) of subjects with advanced melanoma treated with FLX475 in combination with ipilimumab who have been previously treated with an anti-PD-1 or anti-PD-L1 agent
- To evaluate the objective response rate (ORR), defined as confirmed complete or partial response per iRECIST, of FLX475 in combination with ipilimumab in subjects with advanced melanoma previously treated with an anti-PD-1 or anti-PD-L1 agent
- To evaluate the plasma concentrations of FLX475 when it is given in combination with ipilimumab
- To assess the effects of FLX475 in combination with ipilimumab on PD markers relating to drug mechanism of action
- To characterize the onset, magnitude, and duration of tumor control in subjects receiving FLX475 in combination with ipilimumab

8 INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan

This clinical trial is a Phase 2, open-label study to determine the anti-tumor activity of FLX475 in combination with ipilimumab in subjects with advanced melanoma previously treated with an anti-PD-1 or anti-PD-L1 agent.

The study will be conducted starting with a safety run-in portion in which 6 eligible subjects will be enrolled and treated for at least one 3-week cycle to determine if the safety profile of FLX475+ ipilimumab is acceptable to complete enrollment of the approximately 20-subject study. Should the safety profile be deemed not acceptable for the 100 mg FLX475 PO QD and 3 mg/kg ipilimumab IV Q3W combination regimen, an alternative (lower) dose regimen of either or both drug(s) may be selected and tested in an additional 6-subject safety run-in phase. Ultimately at least 20 subjects should be treated and evaluated with a single chosen combination dose regimen.

Accrual to the study may be discontinued prior to completing enrollment, for reasons including, but not limited to, unacceptable safety, slow/insufficient enrollment, or changes in standard clinical practice. 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 a maximum of 4 cycles (4 doses) of ipilimumab and up to 35 treatment cycles (2 years) of FLX475, unless another intervening reason for discontinuation occurs. Each treatment cycle is 3 weeks in duration. Treatment beyond 35 cycles may be considered only if it is felt to be in the best interests of the subject by the investigator and upon Sponsor agreement (if feasible).
- 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 start with a safety run-in phase. The first six subjects enrolled and treated at the recommended Phase 2 dose of FLX475 (100 mg/dose QD) plus ipilimumab (3 mg/kg IV q3W, up to 4 doses) will be followed for at least one 3-week cycle (21 days) to monitor for any unacceptable (or dose-limiting) toxicities prior to enrolling additional subjects.

After the first six subjects enrolled 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. After review of all available data, the SRC may recommend continued enrollment of the entire study (e.g. if no unacceptable toxicities are observed); dose reduction of either FLX475 and/or ipilimumab; or discontinuation of the study. Beyond the safety run-in phase, the SRC will continue to meet at least quarterly during 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.

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 treatment. See the Schedule of Procedures/Assessments in Table 6 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. 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. Repeated laboratory evaluation to establish eligibility is not allowed unless discussed and agreed upon with the Sponsor.

Procedures to be followed when obtaining both approval to screen a subject and approval to enroll (i.e. register) 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 9.1.1 and 9.1.2) 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 and ipilimumab (first four (4) cycles) or FLX475 alone (Cycle 5 and beyond) as continuous 3-week (21-day) cycles. Treatment

cycles will be counted continuously regardless of dose interruptions (i.e. all study visits are anchored to Cycle 1 Day 1). Subjects will undergo safety and efficacy assessments as defined in the Schedule of Procedures/Assessments (Table 6). 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. Treatment beyond 35 cycles may be considered only if it is felt to be in the best interests of the subject by the investigator and upon Sponsor agreement (if feasible).

- Subjects who discontinue ipilimumab prior to receiving the planned four doses due to toxicity may continue treatment with FLX475 alone.

For subjects who have radiological disease progression (PD) by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 as determined by the investigator, the investigator will decide in consultation with the Sponsor's medical monitor 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.

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 (± 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 9 weeks ± 1 week in Year 1 or every 12 weeks ± 1 week beyond Year 1) 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 2 study was designed to evaluate the safety and activity of FLX475 in combination with ipilimumab in subjects with previously treated advanced melanoma. The study utilizes a safety run-in phase to confirm that the previously determined Phase 2 dose of FLX475 and the approved dose of ipilimumab are acceptable to be used in combination. The entire Phase 2 study will be used to evaluate the level of response to this novel combination. Ipilimumab will be used as a comedication since it is an approved checkpoint inhibitor with activity in patients with advanced melanoma.

9 STUDY POPULATION

The target population is composed of adult subjects with adequate performance status and organ function who have advanced melanoma previously treated with anti-PD-1 or anti-PD-L1.

9.1.1 Inclusion Criteria

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

1. All subjects must have pathologically confirmed melanoma that is either Stage IV or unresectable Stage III. Subjects may have cutaneous, mucosal or unknown primary lesions of origin. Subjects with uveal primary are not eligible.
2. Subjects must have had prior treatment with anti-PD-1 or anti-PD-L1 agents, with at least 2 months of therapy followed by documented disease progression either while on these agents or after stopping therapy with these agents. Subjects must have discontinued anti-PD-1 or anti-PD-L1 therapy at least 4 weeks prior to start of study treatment. Subjects who received prior treatment with anti-PD-1 or anti-PD-L1 agents in the adjuvant setting and whose disease recurred while on treatment or within 6 months of completion of the treatment are eligible.
3. Men and women ≥ 18 years of age on day of signing informed consent.
4. Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 or 1.(Subjects with stable ECOG PS of 2 due to non-cancer-related conditions may be permitted with the approval of the Sponsor's medical monitor.)
5. Subjects must have measurable disease per RECIST 1.1.
6. Subjects with central nervous system (CNS) metastases must have all lesions adequately treated with stereotactic radiation therapy, craniotomy, Gamma Knife therapy, or whole brain radiotherapy, with no subsequent evidence of CNS progression. Subjects must not have required steroids for at least 14 days prior to registration.
7. 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 may be permitted with Sponsor agreement, and subjects with immune-related endocrinopathies who are on stable doses of medications are permitted).
8. Subjects must have adequate hematologic function as evidenced by all of the following at time of screening within 21 days prior to start of study treatment: absolute neutrophil count (ANC) ≥ 1500/μL; hemoglobin ≥ 8 g/dL; and platelets ≥ 100,000/μL.
9. Human immunodeficiency virus (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/mm^3 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).

10. Subjects must have adequate hepatic function as evidenced by all of the following at time of screening within 21 days prior to start of study treatment: total bilirubin ≤ 2.5 x Investigational Upper Limit of Normal (IULN) (except subjects with Gilbert's syndrome); and AST and ALT both ≤ 5 x IULN.
11. Subjects must have adequate kidney function as evidenced by serum creatinine ≤ 2.0 x IULN at time of screening within 21 days prior to start of study treatment.
12. Subjects enrolled must be willing and able to provide tissue from a newly obtained core (minimum of 3 cores) or excisional (or skin punch) biopsy of a tumor lesion not previously irradiated (unless subsequent progression demonstrated). In addition, subjects must be willing to provide a tumor biopsy (minimum of 3 cores, or excisional or skin punch) while on treatment at Cycle 2 Day 8 (± 7 days) and may be asked to provide additional biopsies at other timepoints such as the time of discontinuation due to progression.
13. For women of childbearing potential, negative results on a serum pregnancy test within 2 days prior to study registration and willingness to use an effective method of contraception (e.g., oral contraceptives, double-barrier methods such as a condom and a diaphragm, intrauterine device) from the start of study treatment (or 14 days prior to the initiation of study treatment for oral contraception) 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).***
14. 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 (or 14 days prior to the initiation of study treatment for oral contraception) 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.***
15. Ability to swallow tablets without difficulty.
16. Signed Informed Consent Form by the subject or his/her legal guardian.

9.1.2 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.
2. Any history of discontinuing prior treatment due to Grade 3–4 immune related adverse events (irAEs) of colitis or pneumonitis.
3. Prior treatment with ipilimumab or other CTLA-4 antagonists.
4. Prior systemic anticancer therapy including any anti-PD-1 or anti-PD-L1 agents within 4 weeks prior to start of study treatment.
5. Active autoimmune disease requiring disease-modifying therapy at the time of screening. 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 another malignancy that has progressed or has required active treatment within the past 2 years, unless it is clinically stable and does not require tumor-directed treatment. (Examples include 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; or other adequately treated Stage 0, 1 or 2 cancers currently in complete remission.) In addition, any other cancer treated with curative intent ≥ 2 years prior to screening with no evidence of disease is permitted.
7. 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).
8. 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, PR interval > 220 msec, or unstable cardiac arrhythmia requiring medication. Chronic asymptomatic atrial fibrillation stably controlled with medications is permitted.
9. 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.

10. 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.
11. HIV-infected subjects with a history of Kaposi sarcoma and/or Multicentric Castleman Disease.
12. 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.
13. 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. Inhaled or topical steroids, and adrenal replacement doses of ≤ 10 mg daily prednisone or equivalent are permitted in the absence of active autoimmune disease.
14. Prior allogeneic organ transplant.
15. 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.
16. Radiotherapy within 14 days prior to start of study treatment. Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis.
17. 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. (See Appendix 7)
18. 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. (See Appendix 7)
19. Current participation in another study of an investigational agent or device.
20. 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.

9.1.3 Replacement of Subjects

Any subjects in the safety run-in phase 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 the safety run-in. See Section 10.4 for the definition of a DLT.

9.1.4 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, but should inform or discuss with the Sponsor's medical monitor prior to doing so (when feasible). The subject may decide to discontinue study treatment or withdraw from the study at any time for any reason.

The reason for discontinuation of FLX475, ipilimumab, 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, post-treatment 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, or designee, 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 9 weeks [±1 week] in Year 1 or every 12 weeks [±1 week] beyond Year 1) 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 will take FLX475 orally once daily (QD) starting on Day 1 of Cycle 1. See Section 10.2.1 for details of the planned dose administration schema.

Subjects will also receive ipilimumab. Ipilimumab 3 mg/kg will be administered IV Q3W for up to four doses.

The treatments to be used in this study are outlined in Table 1.

Table 1 Study Treatments

Study Treatment	Formulation		Dose Levels	Route of Administration	Sourcing
FLX475	Tablets		100 mg (with possible dose reduction to 75, 50, or 25 mg) qd	Oral	Provided centrally by the Sponsor
Ipilimumab	Solution for infusion		3 mg/kg Q3W	IV infusion	Provided by the site

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

10.2 FLX475 Administration

All subjects will take FLX475 orally once daily on a continual basis. On days when ipilimumab is also administered (i.e., Day 1 of Cycles 1−4), FLX475 should be taken approximately 1 hour before the ipilimumab infusion.

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

10.2.1 Dosing Plan

As noted in Section 6.1.4, the recommended Phase 2 dose of FLX475 of 100 mg PO QD has been selected both for monotherapy and for combination therapy with pembrolizumab in study FLX475-02. Therefore, this same dose will be used in this study in combination with ipilimumab. Should the safety run-in safety data suggest that the 100 mg of FLX475 dose is not acceptable in combination with ipilimumab, a lower dose (e.g. 75 or 50 mg PO QD) may be chosen to be used after evaluation in a new safety run-in cohort of six subjects. In the event of a change in FLX475 dose, additional subjects may be enrolled to ensure that a minimum of 20 subjects are treated at the chosen combination dose regimen.

After all subjects in the safety run-in phase have completed the 3-week safety observation period, a Safety Review Committee (SRC) will be convened. The SRC members will be composed of 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. After review of all available data, and if the safety profile of the combination therapy is deemed acceptable, the SRC will recommend continuation of the study and enrollment of the remainder of the subjects. If the safety profile of the combination regimen is not deemed to be acceptable (e.g. DLT observed in > 1 of 6 subjects), the SRC may recommend de-escalation of FLX475 to a lower dose (e.g. 75 or 50 mg PO QD); de-escalation of ipilimumab to a lower approved dose (e.g. 1 mg/kg); delay, or termination of dosing. Beyond the safety run-in, the SRC will continue to meet at least quarterly during 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 Ipilimumab Administration

Ipilimumab 3 mg/kg will be administered as an IV infusion over 30 or 90 minutes (per institutional protocol) on Day 1 of the first four 3-week treatment cycles (i.e., 21 days [± 3 days]) after all procedures and assessments have been completed, including any 1 hour post-FLX475 dose procedures, approximately 1 hour after the Day 1 dose of FLX475.

The investigational staff should make every effort to ensure that the infusion duration be as close to 30 or 90 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and + 10 minutes is permitted.

Ipilimumab should be prepared and administered per standard institutional protocol and the approved label instructions.

10.4 Dose-Limiting Toxicity and Stopping Criteria

The safety profile of ipilimumab monotherapy has been well described (Yervoy® Package Insert) and includes a significant number of immune-related adverse events (irAEs) to be taken into account when determining what might be either unexpected or unacceptable toxicity for the combination of FLX475 with ipilimumab. Therefore, a DLT for this study will be defined as an AE or abnormal laboratory value 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:
    - Clinically significant medical intervention is required to treat the subject, or
    - The abnormality leads to hospitalization, or
    - The abnormality persists for >1 week, or
    - The abnormality results in a Drug-induced Liver Injury (DILI)
    - Exceptions: Clinically nonsignificant, treatable, or reversible laboratory abnormalities including liver function tests, uric acid, etc.
- 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 14 days with adequate medical management
- Grade 3 fever that does not resolve to Grade 1 or baseline level (whichever is higher) within 14 days with adequate medical management
- Grade 3 fatigue that does not resolve to Grade 2 or baseline level (whichever is higher) within 14 days with adequate medical management
- 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 14 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 14 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 (which are acceptable)
- Grade ≥ 3 adrenal insufficiency
- Grade ≥ 3 febrile neutropenia:
    - Grade 3 is defined as absolute neutrophil count (ANC) < 1000/mm^3 with a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than 1 hour

  - Grade 4 is defined as ANC < 1000/mm^3 with a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°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 the average QTcF value from pre-dose C1D1 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.
- Any Grade 5 toxicity.

Refer to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 (Appendix 1) for grading of the severity of AEs and laboratory abnormalities.

10.5 Dose Modifications for Toxicity

The investigator (in consultation with the Sponsor's medical monitor as needed) 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 DLT assessment throughout both parts of the study, subjects will be monitored closely for treatment-emergent AEs (TEAEs) and laboratory abnormalities. [redacted]

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). 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 for FLX475 below should be considered. (Note that AEs known to be associated with ipilimumab but not previously observed with FLX475 monotherapy may not require modification of FLX475 dose.)

- For any clinically-significant 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 subjects with average Grade 2 or 3 QTcF prolongation at doses of 75 mg or greater (measured at times other than during the up to 6-hour period immediately following an FLX475 dose when a threshold of Grade 3 QTcF prolongation should be used), interrupt treatment with FLX475 until resolution to Grade 0 or 1 or to the pretreatment severity grade, then resume treatment at 50 mg. Subjects with average Grade 2 or 3 QTcF prolongation while at the 50 mg or lower dose level of FLX475 (measured at times other than during the up to 6-hour period immediately following an FLX475 dose when a threshold of Grade 3 QTcF prolongation should be used) should be permanently discontinued from FLX475 treatment (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 either at 50 mg or at a reduced dose of 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. 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 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.

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 (and upon consultation with the Sponsor's medical monitor), 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 2. 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 without approval from the Sponsor's medical monitor. (Note that AEs known to be associated with ipilimumab may not require interruption or modification of FLX475 dosing.)

Table 2 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] or Grade 3[d, e]		
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[f]: Discontinue Study Treatment		

Note: For grading see CTCAE version 5.0 (Appendix 1). Collect all CTC grades of adverse events, decreasing and increasing grade.

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

[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] 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.

[e] 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.

[f] Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.

10.5.2 Dose Modification for Ipilimumab

Adverse events associated with ipilimumab exposure may represent an immunologic etiology and may affect more than one body system simultaneously. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the final dose of ipilimumab. 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 ipilimumab, 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, ipilimumab should be withheld or permanently discontinued, and corticosteroids administered. Ipilimumab 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. Note that modification of dosing of ipilimumab (e.g. withholding or discontinuation) due to

potential/likely ipilimumab toxicity (e.g. irAE) does not require similar modification of FLX475 dosing unless there is evidence of concurrent FLX475-related toxicity.

Thorough dose modification and toxicity management guidelines for irAEs associated with immunotherapies including ipilimumab have been published and should be followed (Brahmer, et al., 2018). Criteria for dose delay, modification, or discontinuation of ipilimumab are described below. Additional guidance regarding dose modification for ipilimumab can be found in Section 2.3 of the approved label (Yervoy® Package Insert).

Table 3 shows treatment guidelines, including premedications, for subjects who experience an infusion reaction associated with the administration of ipilimumab. Examples of some of the most common irAEs are provided in Table 4.

Ipilimumab may be interrupted for situations other than treatment-related AEs, such as medical/surgical events or logistical reasons not related to study treatment. Ipilimumab should be restarted within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The timing of restarting ipilimumab should be discussed with and agreed to by the Sponsor's medical monitor. The reason for interruption should be documented in the subject's eCRF.

Table 3 Infusion Reaction Treatment Guidelines for Ipilimumab

NCI CTCAE Grade	Treatment	Premedication for Subsequent Doses of Ipilimumab
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h	**Stop infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate. Otherwise ipilimumab administration will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should permanently discontinue study treatment.**	Subject may be premedicated 1.5 h (± 30 minutes) prior to infusion of ipilimumab with: Diphenhydramine 50 mg orally (or equivalent dose of antihistamine). Acetaminophen 500−1000 mg orally (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication for Subsequent Doses of Ipilimumab
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Permanently discontinue study treatment.**	No subsequent dosing

Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.

CTCAE = Common Terminology Criteria for Adverse Events, version54.0, IV = intravenous, NCI = National Cancer Institute, NSAID = nonsteroidal anti-inflammatory drug.

Table 4 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Ipilimumab

Immune-related Adverse Event	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken with Ipilimumab	irAE Management with Corticosteroids and Other Therapies	Monitoring and Follow-up
General instructions: Corticosteroid taper should be initiated upon AE improving to Grade 0 or 1 and continue to taper over at least 4 weeks. For situations where ipilimumab has been withheld, ipilimumab can be resumed after AE has improved to Grade 0 or 1 and corticosteroid has been tapered. Ipilimumab should be permanently discontinued if AE does not resolve within 12 weeks of final dose or corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks. **For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.**				
Rash/Inflammatory Dermatitis	Grade 2	Consider withholding and monitor; if not resolved, interrupt until Grade 1	Treat with topical emollients, oral antihistamines, and medium- to high-potency topical corticosteroids. Consider initiating prednisone (or equivalent) at 1 mg/kg, tapering over at least four weeks.	Monitor for improvement, and for progression of Grade 4 rash to severe cutaneous adverse reaction. Consult with dermatology. Consider discontinuing ipilimumab if skin irAE does not resolve to Grade 1 or less.
	Grade 3 or 4	Withhold, consult dermatology to determine appropriateness of resuming	Treat with topical emollients, oral antihistamines, and medium- to high-potency topical corticosteroids. Initiate IV methylprednisolone (or equivalent) at 1−2 mg/kg, tapering over at least four weeks.	
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1–2 mg/kg prednisone or equivalent) followed by taper	Monitor subjects for signs and symptoms of pneumonitis. Evaluate subjects with suspected pneumonitis with radiographic imaging.
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		

Immune-related Adverse Event	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken with Ipilimumab	irAE Management with Corticosteroids and Other Therapies	Monitoring and Follow-up
			Add prophylactic antibiotics for opportunistic infections	
Diarrhea / Colitis	Grade 2	Withhold until symptoms recover to Grade 1; can consider permanently discontinuing	Administer corticosteroids (initial dose of 1–2 mg/kg prednisone or equivalent) followed by taper. Subjects with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.	Monitor subjects for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus). Subjects with Grade ≥ 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis.
	Grade 3 or 4	Permanently discontinue		
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5–1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returns to baseline level or is stable)
	Grade 3 or 4	Permanently discontinue	Administer corticosteroids (initial dose of 1–2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold until glucose control obtained with reduction to no greater than Grade 1 toxicity	Initiate insulin replacement therapy for subjects with T1DM. Administer antihyperglycemic in subjects with hyperglycemia.	Monitor subjects for hyperglycemia or other signs and symptoms of diabetes

Immune-related Adverse Event	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken with Ipilimumab	irAE Management with Corticosteroids and Other Therapies	Monitoring and Follow-up
Hypophysitis	Grade 2	Consider holding until stabilized on replacement hormones	Administer corticosteroids and initiate hormonal replacements as clinically indicated	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Consider holding until stabilized on replacement hormones or permanently discontinue[a]		
Hyperthyroidism	Grade 2	Continue	Treat with nonselective beta-blockers (e.g., propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Consider holding until symptoms return to baseline or permanently discontinue[a]		
Hypothyroidism	Grade 2−4	Continue	Initiate thyroid replacement hormones (e.g., levothyroxine or liothyroinine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Nephritis and Renal dysfunction	Grade 2	Withhold	Administer corticosteroids (prednisone 1–2 mg/kg or equivalent) followed by taper	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold, consider discontinuation if Grade 2	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		

Immune-related Adverse Event	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken with Ipilimumab	irAE Management with Corticosteroids and Other Therapies	Monitoring and Follow-up
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold		
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include but are not limited to: Guillain-Barre Syndrome, encephalitis	Based on type and severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 4 or recurrent Grade 3	Permanently discontinue		

NOTE: For subjects with Grade 3 or 4 immune-related endocrinopathy where withholding of ipilimumab is required, ipilimumab may be resumed when the AE improves to Grade ≤ 2 and is controlled with hormonal replacement therapy or metabolic control is achieved (in the case of T1DM).

AE = adverse event, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CTCAE = Common Terminology Criteria for Adverse Events: GI = gastrointestinal, irAE = immune-related adverse event, IV = intravenous, T1DM = Type 1 diabetes mellitus.

[a] Withholding or permanently discontinuing ipilimumab is at the discretion of the investigator or treating physician.

10.6 Identity of Investigational Products

The study treatments under evaluation in this study are FLX475 and ipilimumab. Ipilimumab is not considered an investigational product in this study. FLX475 will be provided to sites as open-label supplies by the Sponsor.

10.6.1 FLX475

FLX475 is a crystalline non-hydroscopic material that is moderately soluble in water. FLX475 will be supplied as tablets [redacted].

10.6.2 Ipilimumab

Ipilimumab is an IgG1 kappa immunoglobulin with an approximate molecular weight of 148 kDa. Commercial supplies of ipilimumab will be used in this study.

The Yervoy® Package Insert contains specific instructions for the preparation of the ipilimumab infusion and administration of the infusion solution.

10.6.3 Supply, Packaging, and Labeling of Study Drug

FLX475 will be provided to the investigational sites by RAPT Therapeutics, Inc. Ipilimumab will not be provided by the Sponsor and will be administered at the site according to its approved use paid for by insurance coverage in patients with unresectable and metastatic melanoma.

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.

FLX475 in all dose strengths, will be labeled in accordance with text that is in full compliance with FDA requirements.

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.

Storage of ipilimumab should follow institutional standards and per Yervoy® Package Insert.

10.7 Selection of Doses in the Study

As described in Section 6.1.4.1, a recommended Phase 2 dose of FLX475 of 100 mg PO QD has been selected in the ongoing FLX475-02 study. Dose reductions (e.g. to 50 mg) are

permitted as needed. Subjects will take FLX475 once daily. Each 3-week treatment period is considered to be 1 treatment cycle, based on administration of ipilimumab.

The dose of ipilimumab used in this study, 3 mg/kg mg as an IV infusion Q3W for a maximum of 4 doses, is the approved dosage in unresectable or metastatic melanoma. Additional dosage regimens of 10 mg/kg and 1 mg/kg are also approved in other clinical settings.

10.8 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.

Ipilimumab will be administered at a dose of 3 mg/kg as a 30- or 90-minute IV infusion (per institutional protocol), Q3W, on Day 1 of each 3-week (21-day) cycle for cycles 1−4, approximately 1 hour after the FLX475 dose and after the 1-hour post-FLX475 dose assessments have been completed.

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.

10.9 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, if used, will be blinded per standard procedures.

10.10 Prior and Concomitant Therapy

10.10.1 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.

10.10.2 Drug-Drug Interactions

[redacted]

FLX475 showed no significant inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. In human hepatocytes, FLX475 showed no induction of CYP1A2, CYP2B6, and CYP3A4. As FLX475 did not induce any of these three CYP450 enzymes, and the regulatory elements of these three CYP450 enzymes are also involved in the induction of most drug-metabolizing enzymes, FLX475 is considered unlikely to induce any other drug metabolizing pathways. 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 also unlikely to be affected by inhibitors of drug transporters such as P-gp and BCRP. Refer to the FLX475 Investigator's Brochure for details.

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

10.10.3 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.

10.10.4 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 ipilimumab 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.
- 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.

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.

10.10.5 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 ipilimumab (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 ipilimumab (or FLX475), the investigator does not need to follow the treatment guidance.

10.11 FLX475 Treatment Compliance

FLX475 tablets will be self-administered by participating study subjects, except on study visit days when FLX475 should only be administered by clinic staff after pre-dose procedures and assessments have been completed. 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.

10.12 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 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 FLX475 (dispensing, inventory, and record keeping) following the Sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

[As ipilimumab will not be provided by the Sponsor, but instead will come from local pharmacy supplies, local site staff should track the supplies of ipilimumab administered as part of study treatment in the event an issue or adverse event arises in a subject during the course of the study that requires an investigation and/or safety or regulatory reporting. At minimum, pharmacy logs should contain the following information: subject ID, date vial(s) administered, vial number, vial batch number, and expiration date.]

Under no circumstances will the investigator allow the study treatments provided by the Sponsor (i.e., FLX475) to be used other than as directed by this protocol. Study drug 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 FLX475, dispensing of FLX475 to the subject, collection and reconciliation of unused FLX475 that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled FLX475 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 FLX475, (b) FLX475 dispensing/return reconciliation log, (c) FLX475 accountability log, (d) all shipping service receipts, (e) documentation of returns to the Sponsor, and (f) certificates of destruction for any destruction of FLX475 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 drug 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 FLX475 and empty and partially empty containers from used FLX475 supplies 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, FLX475 may be removed from the site and hand delivered to the central or local depot by Sponsor representatives. Where FLX475 supplies 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 Procedures/Assessments in Table 6.

11.1 Screening Assessments

The study center should confirm enrollment availability and obtain approval for screening from the Sponsor prior to obtaining informed consent and 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 9.1.1) and none of the exclusion criteria (Section 9.1.2). 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 (triplicate)
- Blood, urine, and tissue samples for laboratory tests and tumor biomarkers, as indicated on Table 6
- Serum pregnancy test (female subjects who are premenopausal or amenorrheic for < 12 months)
- Tumor assessment (data collected before obtaining informed consent may 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 Schedule of Procedures/Assessments (Table 6). The physical examination should 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 eCRF.

Subjects must have measurable disease according to RECIST 1.1 (Appendix 4) as defined in Eligibility Criteria (Section 9). 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 Schedule of Procedures/Assessments (Table 6) 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 (i.e. registration) 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 one business day of receipt from the study center, the study Sponsor will complete the Subject Eligibility Form (Enrollment Authorization Form) to approve 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's medical monitor or designee approves the subject enrollment. The enrollment date will be the date of start of study treatment.
- The investigator or designee is responsible for ensuring that the confirmation of enrollment approval 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 6
- 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 eCRF. Tumor assessments for progression may also be performed by the investigator using iRECIST; this assessment will be performed following treatment discontinuation (Appendix 5).

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 post-gadolinium 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).
- Clinically assessed/visible lesions (including at minimum those being used as target lesions for disease assessment) should be followed by clinical caliper assessment and digital medical photography using standard equipment (including ruler) and light settings. The timing of cutaneous lesion photographs should follow the same schedule as imaging scans. Images should be archived per local site practice as part of the subject's medical record.

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, provided they meet minimum standards for RECIST assessment.

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

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 9 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 12 weeks (±7 days) . 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.

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 9 weeks [±1 week] for the first year and every 12 weeks [±1 week] thereafter) 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 7 in Appendix 5.

11.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

11.4.1 Pharmacokinetic Assessments

Plasma concentrations of FLX475 will be measured.

Blood samples for PK analysis will be collected as specified in the Schedule of Procedures/Assessments in Table 6. 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 6 and in the Schedule of Procedures/Assessments in Table 6. 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. 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:

Immunophenotyping: Blood samples will be obtained for T/B/NK and T cell panels as specified in the Schedule of Procedures/Assessments in Table 6.

Plasma concentration data for FLX475 from the study may be used to explore PK/pharmacodynamic relationships for effects of FLX475 in combination with ipilimumab 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 may be detailed in a separate analysis plan and the results provided in a stand-alone report.

Pharmacogenetic/Pharmacogenomic (PG) Assessments

All subjects enrolled in the study will provide a core biopsy (minimum of 3 cores) or excisional (or skin punch) biopsy of a tumor lesion prior to starting treatment and on Cycle 2 Day 8 (±7 days) (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.

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 T_{reg}/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 v5.0 (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 ipilimumab. 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 disease progression 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 appropriate eCRF.

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 has 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 $\geq$ 450 ms and there is an increase of more than 60 ms from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

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 v5.0 (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 ipilimumab, as defined in Section 11.5.3, *Overdose*, that is not associated with clinical symptoms or abnormal laboratory results.
2. QTcF interval ≥ 450 ms with a > 60 ms increase from baseline (defined as average QTcF value from C1D1 pre-dose ECGs)

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 plasma concentration 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 ipilimumab will be defined as any dose of ≥ 3 times the planned dose. No specific information is available on the treatment of an overdose of FLX475 or ipilimumab. 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 ipilimumab may have adverse effects on a fetus in utero. Furthermore, it is not known if FLX475 or ipilimumab 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, ipilimumab 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, ipilimumab, 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 ipilimumab 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 5. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 6) shows the visits and time points at which blood and urine samples for clinical laboratory testing will be collected in the study.

All laboratory tests during the study will analyzed locally on the day of collection unless otherwise instructed.

Table 5 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, 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 Schedule of Procedures/Assessments (Table 6) 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 should be reviewed prior to administration/dispensing of study treatment at the beginning of Cycle 1, at the investigator's discretion, and 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 eCRF 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 Schedule of

Procedures/Assessments (Table 6) 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 ≥ 140 mmHg or diastolic BP ≥ 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 ≥ 140 mm Hg or diastolic BP ≥ 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 Schedule of Procedures/Assessments (Table 6). 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 Schedule of Procedures/Assessments (Table 6). 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 ≥ 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 eCRF 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 6 presents the schedule of procedures/assessments for the study.

Table 6 Schedule of Procedures/Assessments in Study FLX475-03

Study Period/Cycle	Screening	Treatment							Early Discon./ End of Study Treatment (ED/EOST)[s]	Long-Term Follow-Up[t]
		Cycle 1			Cycle 2		Cycle 3-4	Cycle 5+		
Cycle Day		**1**	**8**	**15**	**1**	**8**	**1**	**1**		
Study Day	**-21 to 0**	**1**	**8**	**15**	**22**	**29**	**43, 64**	**85[+]**		
Investigational Product Dispensing and Administration										
FLX475 In-clinic Administration [a]		X	X	X	X	X	X	X		
Ipilimumab Administration [a]		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	
Vital Signs [e]	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	
Serious Adverse Events	X	X	X	X	X	X	X	X	X	
Concomitant Medications	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	
CBC with Differential [h]	X	X	X	X	X	X	X	X	X	
Coagulation Tests [i]	X	X			X				X	
Thyroid Function Tests [j]	X	X					X	X	X	
Urinalysis [k]	X	X			X		X	X	X	

Study Period/Cycle	Screening	Treatment							Early Discon./ End of Study Treatment (ED/EOST)[s]	Long-Term Follow-Up[t]
		Cycle 1			Cycle 2		Cycle 3-4	Cycle 5+		
Cycle Day		**1**	**8**	**15**	**1**	**8**	**1**	**1**		
Study Day	**-21 to 0**	**1**	**8**	**15**	**22**	**29**	**43, 64**	**85+**		
Pregnancy Test [l]	X	X			X		X	X	X	
FLX475 PK Samples [m]		X			X		X	X	X	
Immunophenotyping [n]		X	X		X		X	X	X	
Serum Biomarkers [o]		X	X		X		X	X	X	
Whole Blood Biomarkers [p]	X									
Disease Assessments										
Disease Classification	X									
Tumor Imaging/Staging (CT/MRI Scan) [q]	X						X	X		
Tumor Biopsy [r]	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 = lactose 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 visit must occur as scheduled. Other study visits may occur within a window of ±3 days.

[a] The dose of FLX475 will be administered in the clinic after the specified pre-dose visit assessments and procedures are performed. In addition, the dose of FLX475 should be 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.

Ipilimumab will be administered at the designated dose (e.g.3 mg/kg IV) over 30 or 90 minutes (per institutional protocol) on Day 1 of Cycles 1−4. Ipilimumab infusion should occur at least 1 hour after the dose of FLX475 is administered in the clinic and after all 1-hour post-FLX475 dose procedures have occurred.

[b] Dispensing of 3-week supply of FLX475 to the subject with instructions for self-administration at home and drug diary card.

[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 at Screening Visit, 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. 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.

[g] Serum Chemistry: including sodium, potassium, chloride, total protein, bicarbonate, albumin, calcium, magnesium, phosphorous, glucose, BUN, creatinine, total bilirubin, ALP, LDH, AST, ALT, amylase and lipase. Serum Chemistry to be collected at Screening Visit, pre-dose (within 24 hours prior to dosing) on study visit days, and at Early Discontinuation / End of Study Treatment (ED/EOST).

[h] Complete Blood Count and Differential: WBC, RBC, ANC, hemoglobin, hematocrit, MCV, MCH, platelets, and WBC differential. CBC with differential to be performed at Screening Visit, pre-dose (within 24 hours prior to dosing) on study visit days, and at Early Discontinuation / End of Study Treatment (ED/EOST).

[i] Coagulation Tests should be obtained at Screening Visit and pre-dose (within 24 hours prior to dosing) for Day 1 visits of Cycles 1-2 and at Early Discontinuation / End of Study Treatment (ED/EOST): PT, PTT or aPTT, and INR.

[j] Thyroid function tests should be obtained at Screening Visit, pre-dose (within 24 hours prior to dosing) Day 1 of Cycle 1 and every odd-numbered cycle during study treatment, and at Early Discontinuation / End of Study Treatment (ED/EOST). 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 at Screening Visit, pre-dose (within 24 hours prior to dosing) on Day 1 of each cycle, and at Early Discontinuation / End of Study Treatment (ED/EOST). It 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. Pregnancy testing will be performed at Screening Visit and on Day 1 of Cycles 1, 2, and of every even-numbered cycle thereafter (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.

[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 Cycle 2, Cycle 4, and every 4 cycles thereafter; 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] Whole Blood Biomarkers: Sample will be collected at Screening Visit

[q] 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 9 weeks (±1 week) for the first year, followed by every 12 weeks (±1 week) thereafter, and at any time per investigator's discretion. Confirmatory scans should also be obtained at least 4-6 weeks following initial documentation of objective response.

[r] Tumor Biopsy: Subjects enrolled on the clinical trial must be willing and able to provide tissue from a newly obtained core (minimum of 3 cores) or excisional (or skin punch) biopsy of a tumor lesion. Subjects will undergo a core biopsy (minimum of 3 cores) or excisional (or skin punch) biopsy of a lesion prior to starting treatment (during Screening) and at Cycle 2 Day 8 (±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.

[s] 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).

[t] Data regarding poststudy anti-tumor therapy and survival will be collected from all subjects who receive ≥ 1 dose of FLX475 or ipilimumab. 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 6).

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: AE(s), lost to follow-up, subject choice, progression of disease, withdrawal of consent, pregnancy, study terminated by Sponsor, or other.

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 the appropriate eCRF 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.

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.

It is very important that the eCRF or 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 eCRF or follow-up SAE form (if SAE occurred before first dose).

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, whether a female subject becomes pregnant or a female partner of a male subject becomes pregnant, 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 ipilimumab is defined as a dose > 3 times assigned dose. 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 eCRF 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. 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 will be at the 95% confidence level unless stated otherwise.

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 Rationale for Sample Size

The sample size of 20 subjects is considered adequate on clinical grounds to judge the safety of the combination therapy and obtain an initial estimate of its clinical efficacy.

The primary efficacy endpoint will be the overall response rate (ORR). The ORR for the combination therapy is hypothesized to exceed the value observed with ipilimumab monotherapy (10−15%, Long et al., 2017). A decision to officially expand enrollment beyond the planned approximately 20 subjects will depend on the number of responders in the first 20 evaluable subjects and will require a protocol amendment. 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.

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 safety endpoint of the study is safety and tolerability by the determination of AEs, including DLTs. 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 efficacy endpoint 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).

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

Plasma concentrations of FLX475 will be listed and summarized by time point. No PK parameters (e.g. C_{max} and AUC) will be calculated.

Pharmacodynamic endpoints are as follows:

- 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 and PD markers will also be described and summarized.

12.1.2.3 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).

Efficacy Eligible Set: All subjects who receive at least one dose of FLX475 in combination with ipilimumab, have measurable disease at baseline per RECIST v1.1, 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 who complete at least one cycle of FLX475 and ipilimumab 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 in combination with ipilimumab 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. 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 each analysis set. 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, 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

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 8) 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.

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

Samples from all subjects receiving FLX475 plus ipilimumab 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. Samples of plasma may be analyzed for metabolites of FLX475, and the results reported separately.

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 if done. Details may be included in a separate analysis plan.

The effect of FLX475 in combination with ipilimumab on soluble, tissue, genetic and/or imaging biomarkers may 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, if done) 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 and summarized. 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 either study treatment (FLX475 or ipilimumab); 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 v5.0. 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. 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 using descriptive statistics. Laboratory parameters will be categorized according to CTCAE v5.0 grade, and shifts from baseline CTCAE grade to worst post-baseline 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 v5.0 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. 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 to worst post-baseline result in ECG findings (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) will be summarized using shift tables. Descriptive statistics for ECG parameters and changes from baseline will be presented by visit.

12.1.9 Interim Analysis

Safety monitoring will be conducted throughout the study. A Safety Review Committee (SRC) will meet after the safety run-in phase and periodically to review accumulating safety information 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).

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.

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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 (e.g. via protocol clarification letter) 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 (= eCRF) 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

FLX475 will be supplied to the principal investigator (or a designated pharmacist) by the Sponsor. Ipilimumab will not be supplied by the Sponsor, but will come from local site pharmacies. 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 provided by the Sponsor 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 participation in 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 5.0

The Common Terminology Criteria for Adverse Events (CTCAE v5.0, published 27 November 2017) 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 v5.0 have been correlated with single-concept MedDRA terms.

The Common Terminology Criteria for Adverse Events v5.0 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 v5.0

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 to5 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.

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 to5 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 7). 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 ≥ 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 (≥ 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 7 Imaging and Treatment after First Radiologic Evidence of Progressive Disease in Subjects Receiving FLX475 and Ipilimumab

	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.

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 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 subjects or their family members. Therefore, these results will not be disclosed to the subjects 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 subjects should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

APPENDIX 7 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.

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		
Bepridil	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		
Disopryramide	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 *distribution and release from bone*		20

Compounds	Compound Half-Life	Possible Washout Period – Hours	Possible Washout Period - Days
Fosphenytoin	12–29 hours		6
Gatifloxacin	7–14 hours	48	
Gemiflozacin	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)		4

Compounds	Compound Half-Life	Possible Washout Period – Hours	Possible Washout Period - Days
	9-hydroxyrisperidone (active metabolite) T1/2 = 21-30 hours (extensive to poor metabolizer)		
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	
Vardenifil	4 to 5 hours		
Venlaflaxine	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

APPENDIX 8 ANTI-PD-(L)1 REFRACTORY DEFINITION

Subjects must have progressed on treatment with an anti-PD-(L)1 monoclonal antibody (mAb) administered either as monotherapy, or in combination with other checkpoint inhibitors or other therapies as defined below. Anti-PD-(L)1 treatment progression is defined by meeting all of the following criteria:

a. Has received at least 2 doses of an approved anti-PD-(L)1 mAb.

b. Has demonstrated disease progression after anti-PD-(L)1 as defined by RECIST v1.1. The initial evidence of disease progression (PD) is to be confirmed by a second assessment no less than four weeks from the date of the first documented PD, in the absence of rapid clinical progression. [1,2]

c. Progressive disease has been documented within 12 weeks from the last dose of anti-PD-(L)1 mAb.

[1] Seymour et al; iRECIST: Guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 18: e143-52

[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 9 SUMMARY OF CHANGES

Amendment 1 (Section numbers refer to updated version):

- Section 11.6, Table 6 updated to include Whole Blood Biomarker sample that had been omitted, and frequency of Immunophenotyping samples decreased

PROTOCOL SIGNATURE PAGE

Study Protocol Number:	FLX475-03
Study Protocol Title:	Phase 2 Study of FLX475 in Combination with Ipilimumab in Advanced Melanoma
Amendment Number:	1 (19 October 2020)
Investigational Product Name:	FLX475 (F003475)
IND Number:	138286

Approved by:

[redacted]

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	FLX475-03
Study Protocol Title:	Phase 2 Study of FLX475 in Combination with Ipilimumab in Advanced Melanoma
Amendment Number:	1 (19 October 2020)
Investigational Product Name:	FLX475 (F003475)
IND Number:	138286

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