Inclusion Criteria

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

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

Part 2a

- Cohorts M1-M2 (FLX475 Monotherapy): Subjects with a documented Epstein-Barr virus positive (EBV+) malignancy (as determined by standard methods, e.g. EBER ISH or LMP-1 IHC) who are ineligible for standard therapy
  - M1: EBV+Nasopharyngeal cancer (N = 10 Stage 1)
  - M2: EBV+ Hodgkin or non-Hodgkin lymphoma (N = 10 Stage 1)
  - Any EBV+ indications that pass Stage 1 will be combined into a single Stage 2 EBV+ basket expansion of up to 19 additional subjects, if emerging data suggest similar clinical activity across EBV+ NPC and lymphoma.
- Cohorts M3-M4 (FLX475 Monotherapy): Subjects with any of the following tumor types whose disease progressed during treatment with standard available therapies, or who are not eligible for such therapy, and who are also able to and consent to providing tumor biopsies at screening and during study treatment:
  - M3: Recurrent or metastatic HNSCC (specifically of the oral cavity, oropharynx, hypopharynx, or larynx) with no prior treatment with anti-PD-1 or anti-PD-L1 therapy (N = 10-29)

- M4: Recurrent or metastatic cervical squamous cell carcinoma with no prior treatment with anti-PD-1 or anti-PD-L1 therapy (N = 10-29)
- M5: EBV-negative lymphoma ineligible for standard therapy (specific subtypes permitted will be communicated by the Sponsor based upon available data) (N =
- 10-29)

Part 2b

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

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

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

• Cohort C4 (FLX475/Pembrolizumab Combination Therapy): Subjects with metastatic triple-negative breast cancer (TNBC) with disease progression after treatment with available therapies known to confer clinical benefit and with no prior treatment with anti-PD-1 or anti-PD-L1 therapy (N = 10–29)

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

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

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

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

4. Men and women ≥ 18 years of age on day of signing informed consent.
5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 or 1 (Subjects with stable ECOG PS of 2 due to a non-cancer-related condition may be permitted with the approval of the medical monitor.)
6. Evaluable disease (i.e., by imaging and/or tumor markers) at baseline for dose escalation (Parts 1a and 1b). For expansion cohorts (Parts 2a and 2b), subjects must have at least one measurable lesion at baseline by computed tomography (CT) or magnetic resonance imaging (MRI) per Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions. Liver metastases of eligible tumor types are permitted.

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

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

Table 1 Laboratory Values that Define Adequate Organ Function for Eligibility

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

12. Subjects enrolled must be willing and able to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion not previously irradiated (unless subsequent progression demonstrated; minimum of 3 cores). Subjects in dose escalation for whom newly obtained pretreatment samples (i.e. tumor biopsies obtained at baseline screening, prior to initiation of study treatment) cannot be provided (e.g., inaccessible or subject safety concern) may submit an archived specimen only upon agreement from the Sponsor (not applicable for Part 2 expansion cohorts). Formalin-fixed, paraffin-embedded tissue blocks are preferred to slides for those escalation subjects who have been given prior approval by Sponsor (not applicable for Part 2 expansion cohorts). In addition, subjects must be willing to provide a tumor biopsy (minimum of 3 cores) while on treatment at Cycle 3 Day 1 (±7 days) and may be asked to provide additional biopsies at other timepoints such as the time of discontinuation due to progression.
    Notes: If submitting unstained cut slides (only after prior approval by Sponsor), newly cut slides should be submitted to the testing laboratory within 14 days from the date that slides are cut. Details pertaining to tumor tissue submission can be found in the Laboratory Manual. Subjects with lymphoma should be able to provide a core or excisional lymph node biopsy for biomarker analysis at screening as above.
13. For women of childbearing potential, negative results on a serum pregnancy test prior to starting study treatment.

14. For women of childbearing potential, willingness to use an effective method of contraception (e.g., oral contraceptives, double-barrier methods such as a condom and a diaphragm, intrauterine device) during the study and for 120 days following the final dose of study treatment or to abstain from sexual intercourse for this period of time.
    Note: A female subject is considered to be of childbearing potential unless she has had a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy; has medically documented ovarian failure (with serum estradiol and follicle-stimulating hormone levels within the institutional postmenopausal range and a negative result on serum or urine beta-human chorionic gonadotropin [β-HCG]) pregnancy test, or is postmenopausal (age ≥ 55 years with amenorrhea for ≥ 6 months).
15. For male subjects of childbearing potential having intercourse with females of childbearing potential, willingness to abstain from heterosexual intercourse or use of a protocol-recommended method of contraception (e.g., partner use of oral contraceptives or an intrauterine device, or double-barrier methods such as a condom and a diaphragm) from the start of study treatment to 120 days following the final dose of study treatment and to refrain from sperm donation from the start of study treatment to 120 days following the final dose of study treatment.
    Note: A male subject is considered able to father a child unless he has had a bilateral vasectomy or a bilateral orchiectomy with confirmed azoospermia or has ongoing medical testicular suppression.
16. Ability to swallow tablets without difficulty
17. Willingness to comply with scheduled visits, drug administration plan, protocol-specified tumor biopsies, laboratory tests, other study procedures, and study restrictions.
    Note: Psychological, social, familial, or geographical factors that might preclude adequate study participation should be considered.
18. Signed ICF by the subject or his/her legal guardian indicating that the subject is aware of the neoplastic nature of the disease and has been informed of and understands the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, possible side effects, potential risks and discomforts, and other pertinent aspects of study participation.