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NCT Number:	NCT02826486
Sponsor Study Number:	BL-8040.PAC.201
Official Study Title:	A Phase IIa, Multicenter, Open-Label Study to Assess the Safety and Efficacy of the Combination of BL-8040 and Pembrolizumab in Subjects with Metastatic Pancreatic Cancer, the COMBAT Study
Document Version and Date:	Clinical Study Protocol, Version 4.1, 16 June 2019

CLINICAL STUDY PROTOCOL

A PHASE IIA, MULTICENTER, OPEN-LABEL STUDY TO ASSESS THE SAFETY AND EFFICACY OF THE COMBINATION OF BL-8040 AND PEMBROLIZUMAB IN SUBJECTS WITH METASTATIC PANCREATIC CANCER, THE COMBAT STUDY

Sponsors: BioLineRx, Ltd.

[redacted]

IND No. [redacted]

Investigational Medicinal Products: BL-8040 (previously BKT-140)
Pembrolizumab

Principal Investigator(s): [redacted]

Protocol Number: BL-8040.PAC.201

Study Phase: IIa

Sponsor Contact: [redacted]

Study Safety Officer: [redacted]

Protocol Version and Date: Version 4.1, June 16th, 2019

Protocol Signature Page

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Protocol Identification	BL-8040.PAC.201
Study Phase	IIa
Sponsor	BioLineRx Ltd., ISRAEL

Sponsor Representatives

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the trial and that the protocol is in compliance with International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines and applicable local regulations.

[redacted]

VP Clinical and Medical Affairs

[redacted]

Date

[redacted]

VP R&D

[redacted]

Date

Principal Investigator

By signing below, I, the Investigator, approve the protocol and agree to conduct the clinical trial according to all stipulations of the protocol as specified in both the clinical and administrative sections, Case Report Form (CRF) and any protocol-related documents (subject to any amendments agreed to in writing between the Sponsor and Principal Investigator). I agree to comply with the ICH-GCP, World Medical Association Declaration of Helsinki (and relevant updates) and applicable local regulations. I agree to ensure that the Confidential Information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of BioLineRx Ltd. I understand that the study may be terminated, or enrollment suspended at any time by Sponsor, or by me, at my center, if it becomes necessary in my opinion, to protect the best interests of the study subjects.

Name	Investigator Signature	Date

Center's Name	City, Country

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[redacted]

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Protocol Synopsis

Study Title	A phase IIa, multicenter, Open-Label Study to Assess the Safety and Efficacy of the **Com**bination of **B**L-8040 and Pembrolizum**a**b in Patients with Metastatic Pancrea**t**ic Cancer, **the COMBAT study**
Sponsor	BioLineRx
Protocol No.	BL-8040.PAC.201
Clinical Sites	~22 sites, globally in Israel, US and Spain
Study Phase	II
Planned Sample Size	Cohort 1: approximately 40 subjects Cohort 2: approximately 40 subjects
Therapeutic Indication	Cohort 1: Patients with unresectable metastatic pancreatic adenocarcinoma. Cohort 2: Patients with unresectable metastatic pancreatic adenocarcinoma who have progressed following a first-line gemcitabine-based therapy prior to enrollment.
Study Objectives	The objectives of the study are to assess the efficacy and safety of BL-8040 in combination with pembrolizumab and BL8040/ Pembrolizumab in combination with liposomal irinotecan (Onivyde®)/5-fluorouracil/leucovorin (5-FU/LV) in subjects with metastatic pancreatic adenocarcinoma. The mechanism of action of BL-8040, alone and when given in combination, will be studied further using blood and tumor tissue samples.
Study Design	This will be an open-label, two-cohort, Phase IIa study in subjects with metastatic pancreatic adenocarcinoma. The study consists of two periods: • *Monotherapy period:* One week, with BL-8040 administered daily on Days 1-5. • *Combination therapy:* o Cohort 1: Three-week cycles of a combination of BL-8040 administered three times a week (TIW) and pembrolizumab administered once every three weeks. o Cohort 2: Onivyde®/5-FU/LV every 2 weeks, pembrolizumab once every 3 weeks and BL-8040 twice a week. Cohort 1: Subjects with metastatic pancreatic adenocarcinoma will be enrolled and receive BL-8040 monotherapy for five days followed by a combination treatment of BL-8040 and pembrolizumab. During the monotherapy period, eligible subjects will receive daily subcutaneous (SC) injections of BL-8040 (1.25 mg/kg) on Days 1 - 5. From Day 8, subjects will begin a combination period consisting of treatment with SC BL-8040 (1.25 mg/kg) TIW and pembrolizumab (200mg) once every three weeks. The combination therapy will continue for up to 35 cycles of pembrolizumab

(approximately two years), or until progression, clinical deterioration or Early Termination, whichever comes first.

Cohort 2: Subjects with metastatic pancreatic adenocarcinoma that has progressed following first-line treatment with gemcitabine-based chemotherapy will be enrolled and receive BL-8040 monotherapy for five days followed by a combination treatment of BL-8040, pembrolizumab and chemotherapy. During the monotherapy period, eligible subjects will receive daily SC injections of BL-8040 (1.25 mg/kg) on Days 1 - 5.

From Day 8, subjects will begin a combination period consisting of:

- IV Onivyde® 70 mg/m^2 over 90 minutes followed by IV leucovorin (LV) 400 mg/m^2 over 30 minutes or according to local standard, followed by IV fluorouracil (5-FU) 2400 mg/m^2 over 46 hours, every 2 weeks.
- Pembrolizumab 200mg once every three weeks.
- Beginning on Day 10, BL-8040 twice a week and following the chemotherapy dosing.

The combination therapy will continue for up to 35 treatments (approximately two years), or until progression, clinical deterioration or Early Termination, whichever comes first.

An independent data monitoring committee (DMC) will review the accumulated study data according to the DMC charter in order to ensure subject welfare. Serious AEs will be monitored continuously throughout the study.

Safety review of the accumulated data of subjects enrolled to Cohort 2 (Cohort 1 already enrolled 37 subjects) will be performed by the independent DMC when the first 6 subjects and potentially when staggered to 12 subjects (Safety DLT Cohort) have completed 28 days of treatment including monotherapy and combination treatment. DMC recommendations will thereafter be presented to the Sponsor. The guidelines to be used by the DMC for the review of the Safety DLT Cohort are presented below:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Ongoing Safety Assessment and Dose-Limiting Toxicity

Adverse events (AEs) will be reported from the time of signing informed consent

	through 90 days after the last dose of the last study drug[a]. The period considered for DLT assessment is defined as the time from the first dose of BL-8040 and up to the end of the first cycle of combination therapy (i.e. Day 1 of monotherapy through Cycle 1/Day 21). Sites will be required to contact the Sponsor within 24 hrs if a subject presents with a DLT during the evaluation period. Beyond the DLT assessment period, data will be assessed continuously on an ongoing basis. AEs reported beyond the DLT assessment period will be captured within the Case Report Form (CRF); however, they will not be considered for DLT evaluation.
Study Procedures	**Visit Requirements** **Screening** From the time of Informed Consent Form (ICF) signature until Day 1 **before** dosing (Baseline visit). A window of 21 days is allowed for the Screening period procedures, with the exception of all laboratory assessments, which should be completed within 10 days prior to treatment initiation. Potential subjects will be assessed for fulfillment of the entry requirements as detailed below in the Inclusion and Exclusion Criteria sections of the synopsis. Screening period procedures: • Collect demographics and medical history • Collect MSI/dMMR status if available • Review prior and concomitant medications • AE recording • 12 lead electrocardiogram (ECG) • Full physical examination (PE) • Vital signs • Height • Eastern Cooperative Oncology Group (ECOG) performance status • Prothrombin Time (PT)/International Normalized Ratio (INR) and Activated Partial Thromboplastin Time (aPTT) • Complete Blood Count (CBC) with differential • Chemistry panel • Urinalysis • T3, free T4, and thyroid stimulating hormone (TSH) • HIV, HBV and HCV serology • Blood for carbohydrate antigen 19-9 (CA 19-9) and Carcinoembryonic antigen (CEA) • Blood for biomarker testing including immunophenotyping, CXCR4 and PD-1 expression. • Tumor tissues collection from metastasis for tumor and correlative studies assessments (including MSI/dMMR status if not previously tested) • Blood for cells, DNA and RNA for biomarker correlative studies

[a] Pregnancies will be followed until delivery or until pregnancy termination, as relevant.

	• Serum for biomarker correlative studies • Tumor imaging Subjects who failed the Screening procedures may be rescreened after consultation with the Sponsor. Rescreening should include all screening procedures listed in the protocol flow chart, including re-consent signature. **Baseline** Baseline visit refers to Day 1 of treatment **before** administration of study drug. A window of three days is allowed for the procedures and assessments of this visit. For the purpose of assessing efficacy, imaging procedures after monotherapy and before Cycle1/Day 1 of combination are considered Baseline imaging assessments. Baseline procedures: • AE recording • Prior and concomitant medications • Vital signs • Weight • Pregnancy test – serum or urine **Treatment Period** The treatment period is comprised of two periods: **Monotherapy:** This period will begin immediately after Baseline, preferably on the day of the Baseline assessments and will last for one week. During this period, BL-8040 will be administered daily on Days 1 to 5. The following activities will be performed during this week. Details on the specific days for each assessment are presented in the flow chart (Appendix A) • Review AEs • Prior and concomitant medications • Vital signs • 12 lead ECG • Directed PE • CBC with differential • Cohort 1: Blood for anti-BL8040 antibodies and complement activation Cohort 2: Blood for anti-BL8040 antibodies • Blood for immunophenotyping by FACS • Blood for CA 19-9 and CEA • Blood for CXCR4 and programmed death - 1 (PD-1) expression • Tumor tissues collection from metastasis (biopsy)[a] for tumor and correlative studies assessments for Cohort 1 only • Blood for cells, DNA and RNA for biomarker correlative studies • Serum for biomarker correlative studies • Tumor imaging

[a] Only for the first 15 patients enrolled

Combination: This period will begin after the monotherapy period, on Day 8, and will include treatment with the following:

Cohort 1: IV pembrolizumab followed by SC BL-8040 1 hr ± 30 min later.

Cohort 2:

- IV Onivyde® 70 mg/m^2 over 90 minutes, followed by IV LV 400 mg/m^2 over 30 minutes or according to local standard, followed by IV 5-FU 2400 mg/m^2 over 46 hours, every 2 weeks.
- IV Pembrolizumab 200mg once every three weeks
- Beginning on Day 10, SC BL-8040 1.25mg/kg twice a week after chemotherapy dosing.

Details on the specific days for each assessment are presented in the flow chart (Appendix A)

The following procedures will be performed during this period:

- Review prior and concomitant medications
- Review AEs
- Cohort 2 only: assess specific toxicities to decide on Onivyde® dose modifications
- 12 lead ECG
- Directed PE
- Vital signs
- Weight
- ECOG performance status
- CBC with differential
- Chemistry panel
- T3, free T4, and TSH
- Cohort 1: Blood for anti-BL8040 antibodies and complement activation

  Cohort 2: Blood for anti-BL8040 antibodies
- Blood for CA 19-9 and CEA
- Blood for immunophenotyping by FACS
- Blood for CXCR4 and PD-1 expression
- Blood for cells, DNA and RNA for biomarker correlative studies
- Serum for biomarker correlative studies
- Tumor tissue collection from metastasis (biopsy)[a] for tumor and correlative studies assessments- for Cohort 1 only
- Tumor imaging
- Pregnancy test
- BL-8040 administration three times a week for Cohort 1 and twice a week for Cohort 2
- Pembrolizumab administration every three weeks
- Cohort 2 only: Onivyde® with 5-FU/LV administered every 2 weeks.
- An ***optional*** newly-obtained core or excisional biopsy for Cohort 1 only.

	Termination visit The length of study treatment will be up to two years. A Termination visit will be conducted after two years, or before, in case of subject's Early Termination. The reason for Termination/Early Termination should be accordingly captured within the CRF[b]. Termination visit procedures: • Review prior and concomitant medications • Review AEs • 12 lead ECG • Full PE • Vital signs • ECOG performance status • CBC with differential • Chemistry panel • T3, free T4, and TSH • Cohort 1: Blood for anti-BL-8040 antibodies and complement activation Cohort 2: Blood for anti-BL-8040 antibodies • Blood for cells, DNA and RNA for biomarker correlative studies • Serum for biomarker correlative studies • Tumor imaging **Safety follow-up** A safety follow-up visit will be performed 90 days after the last dose of the last study drug. Exceptions that need a longer reporting period are as follow: • 120 days for pregnancy or 30 days following cessation of study treatment if a new anti-cancer therapy is initiated. Safety follow-up procedures: • Review prior and concomitant medications • Review AEs • CBC with differential • Chemistry panel • T3, free T4, and TSH • 12 lead ECG • Post- study anti-cancer therapy received **Long-term follow-up for survival** Subjects will be contacted by phone every 12 weeks after Termination/Early Termination in order to follow the subjects' survival status. Post-study cancer therapy will be captured within the CRF as well.

[a] [redacted]

Study Duration	**Core Study** Screening Period: 21 days Monotherapy period: 1 week Combination treatment period Cohort 1: repeated cycles every 3 weeks for up to 2 years Combination treatment period Cohort 2: for up to 2 years Safety Follow-up period: 90 days from the last of any of the study drugs **Long-term follow-up for survival** every 12 weeks until death
Inclusion Criteria	1. 18 years and older 2. Patients must sign a written informed consent prior to entering the study. 3. Histologically confirmed (either previously or newly biopsied) metastatic unresectable pancreatic adenocarcinoma, including intraductal papillary mucinous neoplasm. 4. Have measurable disease (≥ 1 measurable lesion) based on Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 as determined by the site study team. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions. 5. Previous treatment lines a. Cohort 1: Have documented objective radiographic progression after stopping treatment with first-line or further therapy, i.e. chemotherapy and or radiotherapy. Surgery not followed with neoadjuvant therapy will not be considered as first-line therapy. b. Cohort 2: Have documented objective radiographic progression after stopping treatment with first-line, gemcitabine-based chemotherapy. Only primary metastatic patients will be allowed to participate. Patients with previous surgery for their pancreatic cancer will not be allowed to participate. 6. Willing to submit an evaluable tumor tissue sample, preferably from a liver metastasis, unless tumor is considered inaccessible or biopsy is otherwise considered not in the subject's best interest 7. Complete resolution of toxic effect(s) of the most recent prior chemotherapy to Grade 1 or less (except alopecia). If the subject received major surgery or radiation therapy of > 30 Gy, they must have recovered from the toxicity and/or complications from the intervention. 8. ECOG status ≤1. 9. Life expectancy of at least 3 months. 10. Adequate organ function at Baseline as defined below. All laboratory assessments should be performed <u>within 10 days of treatment initiation</u> a. Hematological: • White blood cell (WBC) ≥ 2,500/mm^3 • Absolute neutrophil count o Cohort 1: ≥ 1000 /mm^3 o Cohort 2: ≥ 1500 /mm^3 • Platelet count ≥ 100,000/mm^3 • Hemoglobin ≥9 g/dL or ≥5.6 mmol/L • Hematocrit ≥30%

	b. Renal function: • Creatinine ≤1.5x Upper limit of normal (ULN) OR measured or calculated[a] creatinine clearance (glomerular filtration rate [GFR]) can also be used in place of creatinine or (CrCl) ≥ 60 mL/min for subject with creatinine levels > 1.5x institutional ULN c. Hepatic function: • Total Bilirubin: within institutional normal ranges • Aspartate Aminotransferase/Serum Glutamic Oxaloacetic Transaminase (AST/SGOT) and Alanine Transaminase/Serum Glutamic Pyruvic Transaminase (ALT/SGPT): ≤2.5xULN OR ≤5xULN for subjects with liver metastases d. Coagulation: • INR or PT: ≤1.5xULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants • Activated Partial Thromboplastin Time (aPTT): ≤1.5xULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants 11. Subjects must use effective contraception: a. Female subjects must be of non-childbearing potential or, if of childbearing potential, must have a negative urine or serum pregnancy test within 72 hours prior to taking study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the subject to be eligible. Non-childbearing potential is defined as (by other than medical reasons): • ≥45 years of age and has not had menses for over 2 years • Amenorrhoeic for > 2 years without a hysterectomy and oophorectomy and a Follicle Stimulating Hormone (FSH) value in the postmenopausal range upon pretrial (Screening) evaluation • Post hysterectomy, bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation at least 6 weeks prior to Screening. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure otherwise the subject must be willing to use two adequate barrier methods throughout the study, starting with the Screening visit through 120 days after the last dose of study therapy. Information must be captured appropriately within the site's source documents b. Male subjects must agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

[a] Creatinine clearance should be calculated per institutional standard

Exclusion Criteria	A subject must be excluded from participating in the trial if he/she: 1. Has a pancreatic tumor other than adenocarcinoma, including: acinar cell carcinoma, pancreaticoblastoma, malignant cystic neoplasms, endocrine neoplasms, squamous cell carcinoma, Vater and periampullary duodenal or common bile duct malignancies. 2. For Cohort 2 only: subjects with a bowel obstruction. 3. Has an active infection requiring systemic therapy or has an uncontrolled infection. 4. Has a known additional malignancy that is progressing or requires active treatment. Exceptions are adequately treated basal cell or squamous cell carcinoma that has undergone potentially curative therapy or carcinoma in situ of the cervix. 5. Has an underlying medical condition that would preclude study participation. 6. Has a disease that is suitable for therapy administered with curative intent. 7. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment. 8. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. 9. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at Baseline) from AE due to agents administered more than 4 weeks earlier. 10. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or has not recovered (i.e., ≤ Grade 1 or at Baseline) from AE due to a previously administered agent[a]. 11. An active autoimmune disease that has required systemic treatment in the 2 years preceding the study (i.e., with the use of disease-modifying agents, corticosteroids or immunosuppressive drugs*). Note: Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment and is allowed*. 12. Has received transfusions of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including Granulocyte Colony Stimulating Factor [G-CSF], GM-CSF or recombinant erythropoietin) within 4 weeks prior to study Day 1. 13. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis. 14. Has a history of interstitial lung disease. 15. O2 saturation < 92% (on room air).

[redacted]

	16. For both Cohorts: Has unstable angina, new onset angina within the last 3 months, myocardial infarction within the last 6 months, and current congestive heart failure New York Heart Association Class III or higher. For Cohort 2: has ventricular arrhythmias or uncontrolled blood pressure, or severe arterial thromboembolic events less than 6 months prior to study initiation. 17. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating Investigator. 18. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial. 19. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the trial, starting with the Screening visit through 120 days after the last dose of trial treatment. Women with a positive pregnancy test within 72 hours from Baseline. 20. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or if the subject has previously participated in Merck MK-3475 clinical trials. 21. Has a positive HIV test at Screening or at any time prior to Screening. Patients without a prior positive HIV test result will undergo an HIV test at Screening, unless not permitted per local regulations. 22. Has known active Hepatitis B (defined as having a positive Hepatitis B surface antigen (HBsAg) test at Screening) or Hepatitis C (defined as having a positive HCV antibody test or a positive HCV RNA test at Screening) 23. Has known history of Chronic Hepatitis B or C 24. Has received a live vaccine within 30 days of the planned start of study therapy. Seasonal flu vaccines that do not contain live virus are permitted. 25. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Note: Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging using the identical imaging modality for each assessment, either MRI or computerized tomography (CT) scan, for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to Baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 14 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability. 26. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients. 27. Cohort 2: Has clinical ascites requiring treatment

Investigational Product Route and Dosage Form	**BL-8040** BL-8040, a synthetic polypeptide highly selective antagonist of CXCR4. BL-8040, a white to off-white powder, is freely soluble in water. It is manufactured in accordance with Good Manufacturing Practice (cGMP) by [redacted]. During the monotherapy period, BL-8040 (1.25 mg/kg) will be administrated by SC injections daily on Days 1 - 5. From Day 8 subjects will begin the combination period which consists of treatment with SC BL-8040 (1.25 mg/kg) TIW. For Cohort 2 SC BL-8040 (1.25 mg/kg) will be provided twice a week beginning on Day 10. **Pembrolizumab** Pembrolizumab [Keytruda® (US)], is a humanized monoclonal antibody against the programmed death -1 (PD-1) receptor protein. Pembrolizumab will be administered at a dose of 200 mg every three weeks using a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (i.e., the infusion time is 30 minutes -5 min/+10 min). **Chemotherapy: Onivyde® with 5-FU/LV** Onivyde® is a liposomal irinotecan, an inhibitor of topoisomerase I that prevents re-ligation of the DNA and causes double-strand DNA breakage leading to cell death. 5-FU is a nucleoside metabolic inhibitor that interferes with the synthesis of DNA and to a lesser extent, inhibits the formation of RNA. LV is an active, chemically-reduced derivative of folic acid. It enhances the therapeutic and toxic effects of 5-FU, without changing its pharmacokinetics. The combination has been approved in the US and EU for treatment of pancreatic cancer patients who have progressed following treatment with gemcitabine-based chemotherapy. In this study, in Cohort 2 only, Onivyde® 70 mg/m^2 will be administered as an IV infusion over 90 minutes followed by IV LV 400 mg/m^2 over 30 minutes or according to the local standard, followed by IV 5-FU 2400 mg/m^2 over 46 hours, every 2 weeks.
Concomitant Medications	Medications or vaccinations specifically prohibited in the Exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation of trial therapy may be required. The Investigator should discuss any questions regarding this with the Sponsor's Medical Monitor. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the subject's primary physician. However, the decision to continue the subject's trial therapy requires the mutual agreement of the Investigator, the Sponsor, and the subject. **Acceptable Concomitant Medications** 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 CRF including all prescription, over-the-counter (OTC), herbal

	supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date should also be included in the CRF. All concomitant medications received within 30 days prior to the first dose of study treatment and 90 days after the last dose of trial treatment should be recorded. Concomitant medications administered more than 90 days after the last dose of trial treatment should be recorded for SAEs and events of clinical interest (ECIs). Several cases of transient hypotension were witnessed following the initial treatment with BL-8040. Therefore, caution should be taken with the use of negative chronotropic drugs such as beta blockers. When appropriate, beta blocker should be replaced to non-chronotropic negative drugs. **Prohibited Concomitant Medications** Subjects are prohibited from receiving the following therapies during the screening period and Treatment Phase of this trial: • Antineoplastic systemic chemotherapy (other than the one administered as part of the study in Cohort 2) or biological therapy. • Immunotherapy or other therapy not specified in this protocol. • Chemotherapy not specified in this protocol. • Investigational agents other than BL-8040 and pembrolizumab. • Radiation therapy: Radiation therapy to a solitary symptomatic lesion or to the brain may be considered on an exceptional case by case basis after consultation with the Sponsor. The subject must have clear, measurable disease outside the radiated field. Administration of palliative radiation therapy will be considered clinical progression for the purposes of determining Progression-free survival (PFS). • Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g. Flu - Mist®) are live attenuated vaccines and are not allowed. • Systemic glucocorticoids. Exceptions include the use of glucocorticoids for modulating symptoms from an event of clinical interest of suspected immunologic etiology, for systemic and local reactions secondary to BL-8040 and/or pembrolizumab treatment, and for premedication prior to Onivyde treatment in accordance with NCCN guidelines. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor[a].

[a] [redacted]

	○ Note: Inhaled steroids are allowed for management of asthma, and dermatological formulations are allowed to reduce the intensity of injection site reactions. • Cohort 2 only: ○ Strong CYP3A4 inducers are to be avoided if possible. Substitute non-enzyme inducing therapies at least 2 weeks prior to initiation of Onivyde®. ○ Strong CYP3A4 or UGT1A1 Inhibitors are to be avoided, if possible; discontinue strong CYP3A4 inhibitors at least 1 week prior to starting Onivyde®. ○ 5-FU may cause elevated coagulation times when administered with warfarin, possibly through inhibition of CYP2C9. Subjects who, in the assessment of the Investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the Investigator deems as medically necessary. The Exclusion Criteria describes other medications that are prohibited in this trial. There are no prohibited therapies during the Post-Treatment Follow-up Phase.
Study Endpoints	**Primary** • Objective Response Rate ($ORR_{RECIST1.1}$) determined according to RECIST 1.1 criteria[a]. **Secondary** • Objective Response Rate (ORRirRECIST) determined according to irRECIST criteria. • Overall Survival (OS) • PFS • Disease Control according to RECISIT 1.1 (DCRECIST1.1) is defined as the sum of PRs and CRs and SDs. **Safety and Tolerability** • Treatment Emergent Adverse Events (TEAEs) • Laboratory safety data • Vital signs • ECG • PE • Early study discontinuations, overall and due to AE

[a] [redacted]

	Exploratory • [redacted] • [redacted] • [redacted]
Statistical Analysis	As this is an open-label, phase IIa two-cohort study to evaluate the safety, tolerability and preliminary efficacy study of two potential treatment regimens, neither power assessment, nor between-cohort formal hypotheses testing are currently planned for study outcome measures. The planned sample size of a total of 40 subjects for each of the two study cohorts is considered clinically appropriate for further characterization of the safety, tolerability and preliminary efficacy of the proposed treatment regimens in subjects with metastatic pancreatic adenocarcinoma. Outcome results of all safety, tolerability and preliminary efficacy data will be compared between the two study cohorts descriptively. The primary efficacy endpoint is the Objective Response Rate according to RECIST1.1 ($ORR_{RECIST1.1}$) defined as the sum of PRs and CRs determined according to best response RECIST1.1 criteria. Principal analysis for inference will use the modified intent to treat (mITT) Analysis Set. The $ORR_{RECIST1.1}$ rate and its lower 95% one-sided confidence limit ([redacted]) will be displayed for each study cohort. Sensitivity analysis will be done for the ITT analysis set. A more detailed Statistical Analysis Plan (SAP), amending the plan written for Cohort 1, will be developed during the data collection period of the initial 6 subjects of Cohort 2.

Glossary

Subject and patient will be used interchangeably throughout this document.

Abbreviation/Term	Definition
AE	Adverse Event
ALT/SGPT	Alanine Transaminase/Serum Glutamic Pyruvic Transaminase
AML	Acute Myeloid Leukemia
aPTT	Activated Partial Thromboplastin Time
Ara-C	Arabinofuranosyl Cytidine / Cytarabine / Cytosine Arabinoside
AST/SGOT	Aspartate Aminotransferase/Serum Glutamic Oxaloacetic Transaminase
BIW	Twice Weekly
BM	Bone Marrow
CA 19-9	Carbohydrate Antigen 19-9
CBC	Complete Blood Count
CEA	Carcinoembryonic Antigen
CFR	Code of Federal Regulations
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CNS	Central Nervous System
CR	Complete Response
CRC	Colorectal cancer
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically Significant
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CXCR4	CXC Chemokine Receptor Type 4
DCR	Disease control rate
DILI	Drug Induce Liver Injury
DLT	Dose-Limiting Toxicity
DMC	Data monitoring committee
ECG	Electrocardiogram
ECI	Events of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EGFR	Endothelial Growth Factor Receptor
EMA	European Medicines Agency
ET	Early termination
FACS	Fluorescence-Activated Cell Sorting
FDA	Food and Drug Administration
FNA	Fine Needle Aspirate
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice

G-CSF	Granulocyte Colony Stimulating Factor
GFR	Glomerular Filtration Rate
GLP	Good-Laboratory Practice
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLT	High Level Term
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICI	Immune checkpoint inhibitor
IEC	Independent Ethics Committee
IHC	immunohistochemistry
INR	International Normalized Ratio (for blood coagulation tests)
IRB	Institutional Review Board
ITSM	Immunoreceptor Tyrosine-based Switch Motif
ITT	Intention To Treat
KIR	Killer-immunoglobulin-like receptor
LOV	Last Observed Value
MDSC	Myeloid-derived suppressor cells
MedDRA	Medical Dictionary for regulatory Activities
mITT	Modified Intention To Treat
MM	Multiple Myeloma
MTD	Maximum Tolerated Dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCS	Not Clinically Significant
NK cells	Natural Killer cells
NOAEL	No Observed Adverse Effect Level
NSCLC	Non-small cell lung carcinoma
ORR	Objective Response Rate
OS	Overall Survival
OTC	Over-The-Counter
PB	Peripheral Blood
PD-1	programmed death receptor 1
PDAC	pancreatic adenocarcinoma
PE	Physical Examination
PFS	Progression-Free Survival
PI	Principal Investigator
PK	Pharmacokinetic
PP	Per Protocol
PR	Partial Response

PT	Prothrombin Time
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	Stable disease
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Events
TIL	Tumor Infiltrating Lymphocytes
TIW	Three times a week
TLS	Tumor Lysis Syndrome
TMDD	Target-mediated drug disposition
TSH	Thyroid stimulating hormone
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization

1 INTRODUCTION

Cancer immunotherapy, a novel and rapidly growing field of research, investigates the use of therapies that harness the body's own immune system in the fight against cancer. Tumors utilize a variety of mechanisms to evade host immune detection. There is mounting evidence that tumor-infiltrating immune cells such as myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs) and tumor-associated macrophages, actively modulate the tumor microenvironment to suppress the effector arms of this response. The aim of the cancer immunotherapy approach is to prevent the tumor's ability to suppress its own detection and elimination by the host immune system. A number of biologic agents that target a range of immune signaling mechanisms, e.g., programmed-death receptor 1 (PD-1)/ programmed-death receptor ligand 1 (PD-L1), Lymphocyte-activation gene 3 (LAG-3), and killer-immunoglobulin-like receptor (KIR), are in clinical development for the treatment of a variety of cancers. However, a fraction of subjects do not respond to these therapies as a result of local immunosuppression mediated by stromal cells (mostly fibroblasts). It was found that activated fibroblasts in the tumor stroma mediate immune suppression in several mouse models of cancer. One suggestion for the basis of the immune suppression involves the production of the chemokine, CXCL12, by the fibroblastic stromal cells. Binding of CXCL12 by T cells leads to their exclusion from the vicinity of the cancer cells. T cell exclusion causes antagonists of T cell checkpoints to be ineffective, despite the presence of cancer-specific CD8+ T cells. Preclinical studies have demonstrated that this immune suppression is interrupted by administration of inhibitors of CXC chemokine receptor 4 (CXCR4), the receptor for CXCL12, which leads to the rapid accumulation of T cells among cancer cells, thereby uncovering the efficacy of immune checkpoints inhibitors.

[redacted]

1.1 BL-8040

BL-8040 (previously named BKT140) is a highly selective CXCR4 antagonist developed by BioLineRx Ltd. as a novel therapy for the treatment of cancer. [redacted]

1.1.1 Preclinical Studies

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

[a] [redacted]

[redacted]

1.2 PEMBROLIZUMAB

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications.

[redacted]

1.2.1 Pharmaceutical and Therapeutic Background

[redacted]

1.2.2 Preclinical and Clinical Trials

[redacted]

1.3 CHEMOTHERAPY: NANOLIPOSOMAL IRINOTECAN WITH FLUOROURACIL AND LEUCOVORIN (ONIVYDE® WITH 5-FU/LV)

Liposomal irinotecan is a liposome-encapsulated formulation of the topoisomerase-1 inhibitor irinotecan, developed to overcome the pharmacological and clinical limitations of non-liposomal irinotecan[26,27]. 5-FU is a nucleoside metabolic inhibitor indicated for the treatment of patients with pancreatic adenocarcinoma[28]. LV is a chemically-reduced derivative of folic acid. It can enhance the therapeutic and toxic effects of 5-FU. Concurrent administration of LV does not appear to alter the plasma pharmacokinetics of 5-FU. 5-FU is metabolized to fluorodeoxyuridylic acid, which binds to and inhibits the enzyme thymidylate synthase (an enzyme important in DNA repair and replication). LV is readily converted to another reduced folate, 5,10- methylenetetrahydrofolate, which acts to stabilize the binding of fluorodeoxyuridylic acid to thymidylate synthase and thereby enhances the inhibition of this enzyme[29]. IV liposomal irinotecan injection (Onivyde®) is approved for use in combination with 5-FU and LV (5-FU/LV) in patients with metastatic pancreatic adenocarcinoma that has progressed following gemcitabine-based therapy. [redacted]

1.4 THERAPEUTIC INDICATION

Pancreatic cancer is a malignant neoplasm of the pancreas with a low early- diagnosis rate and poor prognosis. Its incidence rate has risen in recent years and it now comprises 1%-2% of common tumors. Each year about 185,000 individuals globally are diagnosed with this condition. As its symptoms are usually non-specific, pancreatic cancer is often not diagnosed until it reaches an advanced stage. The only potentially curative therapy for pancreatic cancer is surgical resection. Unfortunately, tumors in only 20% patients are resectable at the time of diagnosis. Even among those patients who undergo resection for pancreatic cancer and have tumor-free margins, the 5-year survival rate is only 10%-25%[30,31]. The overall 5-year survival rate among patients is less than 5%, which constitutes the highest mortality rates among solid malignancies. The overall median survival is less than 1 year from diagnosis, highlighting the need for the development of newer therapeutic options.

The anatomical structure of the pancreas is very complicated. The high interstitial tension and inadequate blood perfusion of the pancreatic tumors give them extreme resistance to most chemotherapy drugs. Consequently, conventional systemic IV chemotherapy often fails to reach effective concentrations. High dosages may cause severe adverse reactions, thus impairing the immune system and reducing the potential therapeutic effect. The failure of clinical treatment in patients with pancreatic ductal adenocarcinoma is often attributed to the early metastatic growth, a high level of drug resistance to standard therapy options and high rates of local recurrence[32].

Despite recent advances in chemotherapeutics and in our understanding of the molecular biology of pancreatic cancer, there has been limited progress in therapeutic options for metastatic disease. Over the past four decades, studies of several combination therapies have demonstrated minimal or no survival benefit compared with gemcitabine alone. Gemcitabine monotherapy had been the standard of care for patients with metastatic pancreatic cancer for several years, until combination therapy with gemcitabine plus erlotinib was shown to increase median survival by 2 weeks. However, the modest survival benefit was tempered by a significant side effect profile and the high cost of treatment. Later, the multidrug combination of LV, 5-FU, irinotecan, and oxaliplatin (FOLFIRINOX) showed an increased median survival of 4.3 months; however, given its side effect profile, it is available only to a select group of patients with advanced pancreatic cancer. Recently, the gemcitabine plus nab-paclitaxel combination was shown to increase median survival by 1.8 months, with increased OS at 1 and 2 years; AEs were reasonable; they included cytopenias and peripheral neuropathy[33]. The current National Comprehensive Cancer Network recommendations suggest acceptable chemotherapy combinations for patients with good performance status (i.e., ECOG performance status of 0 or 1), good pain management, patent biliary stent, and adequate nutritional intake; these combinations include FOLFIRINOX, gemcitabine plus nab-paclitaxel, and gemcitabine plus erlotinib. The only recommended option for patients with poor performance status is gemcitabine monotherapy. In 2015, Onivyde® was the first chemotherapeutic agent approved in the US and in the EU in combination with 5-FU and LV, for the treatment of patients with metastatic adenocarcinoma of the pancreas in second line settings, after disease progression following gemcitabine-based therapy[26,34].

1.5 STUDY RATIONALE

Cancer immunotherapy is a novel and rapidly growing field of research investigating the use of therapies that harness the body's own immune system in the fight against the tumor. Tumors utilize a variety of mechanisms to evade host immune detection. Cancer cells, as well as infiltrating monocytic cells, including dendritic cells and macrophages—express PD-L1, which suppresses the proliferative and effector responses of T cells by engaging the inhibitory PD-1 receptor on these cells. In addition, there is mounting evidence that some tumor-infiltrating immune cells such as MDSCs, T-regulatory cells (Tregs) and tumor-associated macrophages, actively modulate the tumor microenvironment to suppress the effector arms of this response. The aim of cancer immunotherapy is to prevent the tumor's ability to suppress its own detection and elimination by the host immune system. The therapeutic effect of blocking antibodies to the immune checkpoint regulators CTLA-4 and PD-1/PD-L1 receptor-ligand pair is considered a major breakthrough in the treatment of several solid tumors. Nevertheless, it has become apparent that even if these T cell checkpoint antagonists overcome some of the immune-suppressive effects of the tumor microenvironment, other, more fundamental inhibitory reactions in the tumor microenvironment may constitute the underlying reason for the fact that many subjects— especially those with microsatellite stable colorectal cancer, ovarian cancer, prostate cancer, and pancreatic ductal adenocarcinoma — rarely exhibit objective responses to these therapies.

It was found that activated fibroblasts in the tumor stroma mediate immune suppression in several mouse models of cancer. The basis of the immune suppression involves the production of the chemokine, CXCL12, by cancer-associated fibroblasts. Binding of this CXCL12 by T cells leads to their exclusion from the vicinity of the cancer cells. T cell exclusion causes antagonists of T cell checkpoints to be ineffective, despite the presence of cancer-specific CD8+ T cells. The exclusion of CD8+ T cells from the vicinity of cancer cells in colorectal cancer (CRC) was shown to correlate with a poor long-term clinical outcome[35,36]. Exclusion of T cells from the vicinity of cancer cells was also found in ovarian cancer[37,38] and pancreatic ductal adenocarcinoma [39]. Thus, the tumor microenvironment can limit the capacity of T cells to accumulate among cancer cells. This immune suppression is interrupted by administering inhibitors of CXCR4, the receptor for CXCL12, which leads to the rapid accumulation of T cells among cancer cells, thereby uncovering the efficacy of immune checkpoint inhibitors [39,40].

BL-8040 (BKT-140) is a 14-residue, cyclic, synthetic peptide capped with an aromatic ring. BL-8040 was shown in vitro and in vivo to be a specific antagonist of CXCR4 with high affinity to the CXCR4 receptor (0.54-5.4 nM) and long receptor occupancy (>48hrs). BL-8040 is considered the most active CXCR4 peptide antagonist among inhibitors of the same class. In vitro and in vivo preclinical studies have shown that in addition to its activity as a mobilizer of hematopoietic cells, BL-8040 exhibits a CXCR4-dependent preferential antitumor effect against malignant cells overexpressing CXCR4 [41–43]. The efficacy of BL-8040 and its analogs for blocking CXCR4 in vitro and in vivo has been documented in numerous preclinical studies, including in vitro and in vivo models for small cell lung carcinoma, breast cancer, malignant melanoma, neuroblastoma and pancreatic cancer [44,45] (and unpublished). As a CXCR4 antagonist, BL-8040 affects the trafficking of immune cells to the tumor microenvironment. It was found that administration of BL-8040 induces the mobilization of NK cells, T cells and B cells from the BM and lymph nodes into the periphery. Using a syngeneic cancer model in mice, it was demonstrated that BL-8040 may eliminate the immunological barrier and allow the accumulation of immune cells within the tumor microenvironment (further details are available in the BL-8040 IB).

These findings raise the possibility that increasing the proportion of cancer-specific T cells may be more effective if immunotherapy is combined with a CXCR4 antagonist that alters the immune-suppressive tumor microenvironment. The aim of this study is to examine the effectiveness of combining BL-8040, a CXCR4 antagonist, with pembrolizumab, a PD-1 monoclonal antibody, in pancreatic ductal adenocarcinoma patients.

[redacted]

[redacted]

[redacted]

1.5.1 Rationale for Addition of Chemotherapy [redacted]

Pancreatic cancer remains an area of highly unmet medical need, with no new approved therapies since the approval of nab-paclitaxel in combination with gemcitabine (abraxene®) for first-line treatment in 2013 [46] and Onivyde® in combination with 5-FU and LV for second line treatment in 2015 [34]. The limited clinical benefits demonstrated by these existing standard treatment options reinforce the need for additional approaches.

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- [redacted]
- [redacted]

[redacted]

1.6 DOSE SELECTION RATIONALE

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

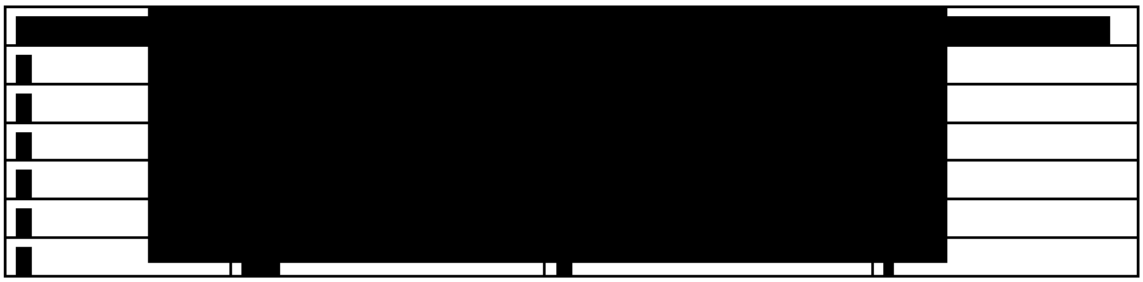
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

Based on the above safety, mobilization and preclinical effect on the tumor microenvironment the 1.25 mg/kg dose was selected for the combination study.

[redacted]

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- [redacted]

1.6.2 [redacted]

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- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]r.

[redacted]

[redacted]

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 OBJECTIVES

The objectives of the study are to assess the efficacy and safety of BL-8040 in combination with pembrolizumab and BL8040/ Pembrolizumab in combination with liposomal irinotecan (Onivyde®)/5-fluorouracil/leucovorin (5-FU/LV) in subjects with metastatic pancreatic adenocarcinoma. The mechanism of action of BL-8040, alone and when given in combination, will be studied further using blood and tumor tissue samples.

2.2 STUDY ENDPOINTS

2.2.1 Primary Endpoint

- Objective Response Rate (ORRRECIST1.1) determined according to Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 criteria.

2.2.2 Secondary Endpoint

- Objective Response Rate (ORRirRECIST) determined according to irRECIST criteria.
- OS.
- PFS.
- Disease Control according to RECISIT 1.1 (DCRECIST1.1) is defined as the sum of partial responses (PRs), CRs and SDs.

2.2.3 Safety and Tolerability

- TEAEs
- Laboratory safety data
- Vital signs
- ECG
- Physical examination (PE)
- Early study discontinuations, overall and due to AE

[redacted]

3 STUDY DESIGN

This will be an open-label, single arm, Phase IIa study in subjects with metastatic pancreatic adenocarcinoma. The study consists of two periods:

- *Monotherapy period:* One week, with treatment using BL-8040 on Days 1-5
- *Combination therapy:*
  - Cohort 1: Three-week cycles of a combination of BL-8040 TIW and pembrolizumab once every three weeks.
  - Cohort 2: Onivyde®/5-FU/LV every 2 weeks, pembrolizumab once every 3 weeks and BL-8040 twice a week.

Cohort 1: Subjects with metastatic pancreatic adenocarcinoma will be enrolled and receive BL-8040 monotherapy for five days followed by a combination treatment of BL-8040 and pembrolizumab. During the monotherapy period, eligible subjects will receive daily SC injections of BL-8040 (1.25 mg/kg) on Days 1 - 5.

From Day 8, subjects will begin a combination period consisting of treatment with SC BL-8040 (1.25 mg/kg) TIW and pembrolizumab (200 mg) once every three weeks. The combination therapy will continue for up to 35 cycles of pembrolizumab (approximately two years), or until progression, clinical deterioration or early Termination, whichever comes first.

Cohort 2: Subjects with metastatic pancreatic adenocarcinoma that have progressed following first-line treatment with gemcitabine-based chemotherapy will be enrolled and receive BL-8040 monotherapy for five days followed by a combination treatment of BL-8040, pembrolizumab and chemotherapy. During the monotherapy period, eligible subjects will receive daily SC injections of BL-8040 (1.25 mg/kg) on Days 1 - 5.

From Day 8, subjects will begin a combination period consisting of:

- IV Onivyde® 70 mg/m^2 over 90 minutes followed by IV leucovorin (LV) 400 mg/m^2 over 30 minutes or according to the local standard, followed by IV fluorouracil (5-FU) 2400 mg/m^2 over 46 hours, every 2 weeks.
- Pembrolizumab 200mg once every three weeks.
- Beginning on Day 10, BL-8040 twice a week and after chemotherapy dosing.

The combination therapy will continue for up to 35 treatments (approximately two years), or until progression, clinical deterioration or early Termination, whichever comes first.

An independent data monitoring committee (DMC) will review the accumulated study data according to the DMC charter in order to ensure subject welfare. Serious AEs (SAEs) will be monitored continuously throughout the study.

Safety review of the accumulated data of subjects enrolled to Cohort 2 (Cohort 1 already enrolled 37 subjects) will be performed by the independent DMC when the first 6 subjects and potentially when staggered to 12 subjects (Safety Dose-Limiting Toxicity (DLT) Cohort) have

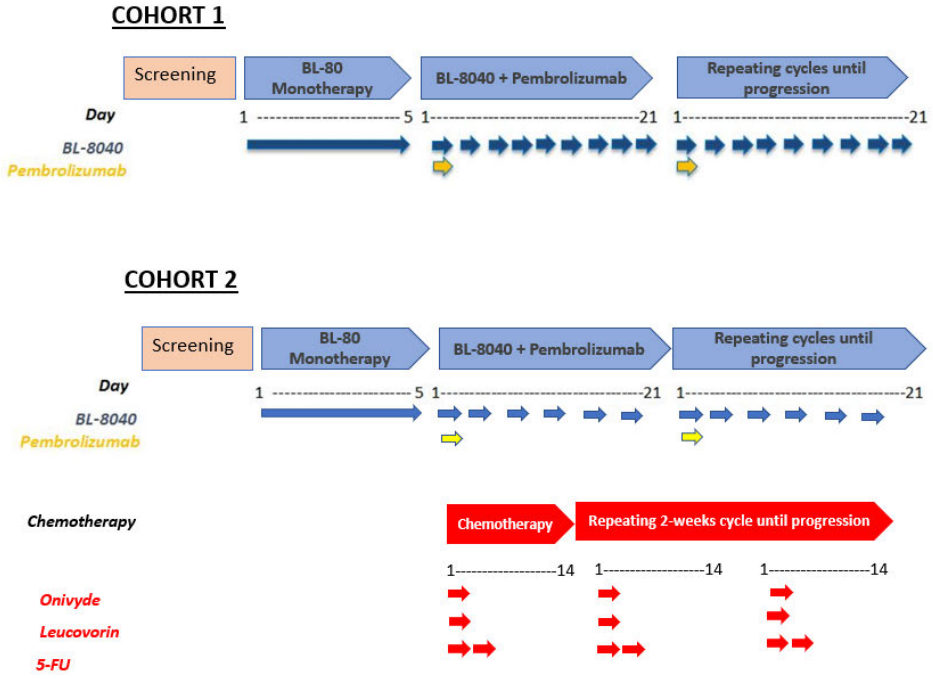
completed 28 days of treatment including monotherapy and combination treatment. DMC recommendations will thereafter be presented to the Sponsor. The guidelines to be used by the DMC for the review of the Safety DLT Cohort are presented below:

- If 0 out of 6 subjects experience a DLT during the first cycle of treatment, the combination treatment will be considered as eligible for further evaluation and recruitment will continue without a pause.
- If 1 out of 6 subjects experiences a DLT, the Safety DLT Cohort will be expanded to 12 subjects.
- If ≥ 2 out of 6 subjects experience a DLT, the DMC will assess the risk/benefit ratio of the combination treatment and recommend one or more of the following: 1) the Safety DLT Cohort should be expanded to 12 subjects, 2) the protocol should be modified, 3) the treatment schedule should be changed or 4) the study should be discontinued.
- If ≤ 2 out of 12 subjects experience a DLT in the expanded Safety DLT Cohort, recruitment can be continued to the full proposed study size.
- If > 2 out of 12 subjects experience a DLT in the expanded Safety DLT Cohort, the DMC will determine whether recruitment will be stopped, or recruitment can be continued with or without a protocol modification.

Efficacy data will be assessed throughout the study, without stopping recruitment. The assessment will include review all the available data, i.e. imaging, biopsies, safety assessment, etc. and will assess the clinical benefit of the investigated combination treatments.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Appendix A in Section 13.1.

3.1 TRIAL DIAGRAM



4 STUDY POPULATION

Male and female subjects 18 years old and older with metastatic *unresectable* PDAC will be enrolled in this trial. Inclusion/Exclusion criteria will be assessed during the Screening period unless otherwise specified within the specific criteria.

Entry criteria are absolute. Any subject not meeting one or more inclusion criteria or meeting one or more Exclusion Criteria is not allowed to enter the trial. If a variable's limit is presented in a criterion, then that limit may not be exceeded.

4.1 INCLUSION CRITERIA

In order to be eligible for participation in this trial, the subject must satisfy the following:

1. 18 years and older
2. Patients must sign a written informed consent prior to entering the study.
3. Histologically confirmed (either previously or newly biopsied) metastatic unresectable pancreatic adenocarcinoma, including intraductal papillary mucinous neoplasm.
4. Have measurable disease (≥ 1 measurable lesion) based on RECIST v1.1 as determined by the site study team. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
5. Previous treatment lines
    a. Cohort 1: Have documented objective radiographic progression after stopping treatment with first-line or further therapy, i.e. chemotherapy and or radiotherapy. Surgery not followed with neoadjuvant therapy will not be considered as first-line therapy.
    b. Cohort 2: Have documented objective radiographic progression after stopping treatment with first-line, gemcitabine-based chemotherapy. Only primary metastatic patients will be allowed to participate. Patients with previous surgery for their pancreatic cancer will not be allowed to participate.
6. Willing to submit an evaluable tumor tissue sample, preferably from a liver metastasis, unless tumor is considered inaccessible or biopsy is otherwise considered not in the subject's best interest
7. Complete resolution of toxic effect(s) of the most recent prior chemotherapy to Grade 1 or less (except alopecia). If the subject received major surgery or radiation therapy of > 30 Gy, they must have recovered from the toxicity and/or complications from the intervention.
8. ECOG status ≤1.
9. Life expectancy of at least 3 months.
10. Adequate organ function at Baseline as defined below. All laboratory assessments should be performed <u>within 10 days of treatment initiation</u>
    a. Hematological:
        - White blood cell (WBC) ≥ 2,500/mm^3
        - Absolute neutrophil count
            - Cohort 1: ≥ 1000 /mm^3
            - Cohort 2: ≥ 1500 /mm^3
        - Platelet count ≥ 100,000/mm^3
        - Hemoglobin ≥9 g/dL or ≥5.6 mmol/L

- Hematocrit ≥30%

b. Renal function:
   - Creatinine ≤1.5x Upper limit of normal (ULN) OR measured or calculated[a] creatinine clearance (glomerular filtration rate [GFR]) can also be used in place of creatinine or (CrCl) ≥ 60 mL/min for subject with creatinine levels > 1.5x institutional ULN

c. Hepatic function:
   - Total Bilirubin: within institutional normal ranges
   - Aspartate aminotransferase/ serum glutamic oxaloacetic transaminase (AST/SGOT) and Alanine amino transferase/ serum glutamate-pyruvate transaminase (ALT/SGPT): ≤2.5xULN OR ≤5xULN for subjects with liver metastases

d. Coagulation:
   - INR or PT: ≤1.5xULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
   - aPTT: ≤1.5xULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

11. Subjects must use effective contraception:
    a. Female subjects must be of non-childbearing potential or, if of childbearing potential, must have a negative urine or serum pregnancy test within 72 hours prior to taking study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the subject to be eligible. Non-childbearing potential is defined as (by other than medical reasons):
       - ≥45 years of age and has not had menses for over 2 years
       - Amenorrhoeic for > 2 years without a hysterectomy and oophorectomy and a Follicle Stimulating Hormone (FSH) value in the postmenopausal range upon pretrial (Screening) evaluation
       - Post hysterectomy, bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation at least 6 weeks prior to Screening. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure otherwise the subject must be willing to use two adequate barrier methods throughout the study, starting with the Screening visit through 120 days after the last dose of study therapy. Information must be captured appropriately within the site's source documents

    b. Male subjects must agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

    Please see Section 6.7.1 - Contraception for a list of acceptable birth control methods.

[a] Creatinine clearance should be calculated per institutional standard

4.2 EXCLUSION CRITERIA

A subject must be excluded from participating in the trial if he/she:

1. Has a pancreatic tumor other than adenocarcinoma, including: acinar cell carcinoma, pancreaticoblastoma, malignant cystic neoplasms, endocrine neoplasms, squamous cell carcinoma. Vater and periampullary duodenal or common bile duct malignancies.
2. For Cohort 2 only: subjects with a bowel obstruction.
3. Has an active infection requiring systemic therapy or has an uncontrolled infection.
4. Has a known additional malignancy that is progressing or requires active treatment. Exceptions are adequately treated basal cell or squamous cell carcinoma that has undergone potentially curative therapy or carcinoma in situ of the cervix.
5. Has an underlying medical condition that would preclude study participation.
6. Has a disease that is suitable for therapy administered with curative intent.
7. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.
8. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
9. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at Baseline) from AE due to agents administered more than 4 weeks earlier.
10. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or has not recovered (i.e., ≤ Grade 1 or at Baseline) from AE due to a previously administered agent[a].
11. An active autoimmune disease that has required systemic treatment in the 2 years preceding the study (i.e., with the use of disease-modifying agents, corticosteroids or immunosuppressive drugs*). Note: Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment and is allowed*.
12. Has received transfusions of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including Granulocyte Colony Stimulating Factor [G-CSF], GM-CSF or recombinant erythropoietin) within 4 weeks prior to study Day 1.
13. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
14. Has a history of interstitial lung disease.
15. O2 saturation < 92% (on room air).
16. For both Cohorts: Has unstable angina, new onset angina within the last 3 months, myocardial infarction within the last 6 months, and current congestive heart failure New

[a] Subjects with ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia are an exception to this criterion and may qualify for the study. If subject underwent major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

York Heart Association Class III or higher. For Cohort 2: has ventricular arrhythmias or uncontrolled blood pressure, or severe arterial thromboembolic events less than 6 months prior to study initiation.

17. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating Investigator.
18. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
19. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the trial, starting with the Screening visit through 120 days after the last dose of trial treatment. Women with a positive pregnancy test within 72 hours from Baseline.
20. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or if the subject has previously participated in Merck MK-3475 clinical trials.
21. Has a positive HIV test at Screening or at any time prior to Screening. Patients without a prior positive HIV test result will undergo an HIV test at Screening, unless not permitted per local regulations.
22. Has known active Hepatitis B (defined as having a positive Hepatitis B surface antigen (HBsAg) test at Screening) or Hepatitis C (defined as having a positive HCV antibody test or a positive HCV RNA test at Screening)
23. Has known history of Chronic Hepatitis B or C
24. Has received a live vaccine within 30 days of the planned start of study therapy. Seasonal flu vaccines that do not contain live virus are permitted.
25. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Note: Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging using the identical imaging modality for each assessment, either MRI or computerized tomography (CT) scan, for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 14 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.
26. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.
27. Cohort 2: Has clinical ascites requiring treatment

4.3 SUBJECT IDENTIFICATION

Each consented subject will receive a unique subject number that will be used to identify the subject for all procedures that occur from Screening throughout the end of study or until the subject terminates from the study. Each subject will be assigned only one subject number.

Subject numbers must not be re-used for different subjects.
Any subject who is screened multiple times will retain the original subject number assigned at the initial Screening visit. A single subject may not be assigned more than one subject number.
Specific details on the Screening visit requirements (Screening/rescreening) are provided in Section 5.1.

4.4 SCREENING FAILURES

Subjects who fail to meet the entrance criteria at any stage during the Screening period are defined as screening failures. All screening failures will be documented on the appropriate log which will be kept in the Investigator's Site File.

4.5 REMOVAL, REPLACEMENT, OR EARLY WITHDRAWAL OF SUBJECTS FROM THERAPY OR ASSESSMENT

Subjects are free to discontinue the study drugs and/or their participation in the study at any time and without prejudice to further treatment. The Investigator must withdraw any subject from the study if that subject requests to be withdrawn, or if it is determined that continuing in the study would result in a significant safety risk to the subject. Patients can terminate the study treatment early (i.e. before two years) in the case of CR (see Section 4.7). Subjects that discontinue the study drug will continue to participate in the survival follow-up of the study for up to 5 years, unless they withdrew their consent to continue their participation in the study as well.
Subjects withdrawn from the study prior to the Baseline visit or prior to first injection of any of the study drugs will be replaced by the Investigator to achieve the appropriate number of subjects, regardless of the reason for withdrawal.
If a subject discontinues from the trial during the DLT evaluation period for any reason other than safety, a replacement subject may be enrolled if deemed appropriate by the Investigator and Sponsor in order to reach the target number for DLT assessment. Subjects who discontinued the trial during the DLT period because of progression will not be considered for DLT assessment; however, they will be counted as having progressed for the efficacy analysis. The replacement subject will be assigned a unique treatment/ number. The trial site should contact the Sponsor for the replacement subject’s treatment number.
The subject's use of study drug may be discontinued for any of the following reasons:

- Toxicity
- Death
- Request of regulatory agency
- Sponsor request
- Primary care physician or Investigator request: Investigator decides that withdrawal from the study is in the best interest of the subject
- Withdrawal of consent by subject
- Disease Progression
- Female subject who becomes pregnant
- Lost to follow-up

- Subject is non-compliant with study procedures / study protocol
- Other
- See Section 6.7.4 for dose-modification and treatment attenuation recommendation for each study drug.

4.6 HANDLING OF WITHDRAWALS

If a subject is withdrawn from the study, every effort should be made to determine the reason. This information will be recorded on the subject's Case Report Form (CRF). All subjects who withdraw from the study prematurely, regardless of cause, should undergo all Early Discontinuation Study Visit procedures (see Section 5.4), safety follow-up visit and continue the long-term follow-up for survival.

If withdrawal is caused by an AE that the Investigator considers may be related to the study drug, the AE will be reported to the institutional review board/independent ethics committee (IRB/IEC) as per local guidelines if required.

Any SAE must be reported to the Sponsor or Sponsor's designee by telephone or fax within 24 hours of the Investigator's becoming aware of the event and to the IRB/IEC according to local regulations (for SAE notification procedures, refer to Section 7.2.5).

All AEs will be followed up with appropriate medical management until the outcome is determined or stabilized, according to the Investigator's clinical judgment. All follow-up information will be recorded in the subject's CRF until resolution of the AE.

4.7 DISCONTINUATION OF STUDY THERAPY AFTER CR

Discontinuation of study drugs may be considered for subjects who have attained a confirmed CR, that:

- Have been treated for at least 24 weeks with the combination therapy and
- Received at least two treatment cycles of combination therapy beyond the date when the initial CR was declared.

4.8 SPONSOR'S TERMINATION OF STUDY

The Sponsor reserves the right to discontinue the study at any time at the participating centers for any reason.

Regulatory Authorities also have the right to terminate the study for any reason.

5 STUDY PROCEDURES AND ASSESSMENTS

The schedule of events for this study is shown in Section 13.1, Appendix A1. No protocol-related procedures should be performed before the subject provides written informed consent. Study-related events and activities (including specific instructions, procedures, concomitant medications, dispensing of study medication, and descriptions of AEs) should be recorded in the appropriate source documents and CRF.

5.1 SCREENING PERIOD (DAY -21 TO DAY 0)

From the time of Informed Consent Form (ICF) signature until Day 1 before dosing (Baseline visit). A window of 21 days is allowed for the Screening period procedures, with the exception of all laboratory assessments, which should be completed within 10 days of treatment initiation. At the Screening visit the purpose and procedures of the study will be fully explained to participants. Those wishing to enroll in the study will sign a written ICF prior to

initiating any evaluations or study-related procedures. After signing informed consent, male and female subjects aged ≥18 years will be assessed for fulfillment of the entry requirements as detailed below in the Inclusion and Exclusion Criteria sections 4.1 and 4.2.

The following assessments should be done at Screening period-Visit 1 (exceptions are defined below):

1. Collect demographics and medical history
2. Collect MSI/dMMR status if available
3. Review prior and concomitant medications
4. AEs
5. 12 lead ECG
6. Full PE
7. Vital signs
8. Height
9. ECOG performance status
10. Laboratory assessments should be performed within 10 days of treatment initiation.
    a. PT/INR and aPTT
    b. Complete blood count (CBC) with differential
    c. Chemistry panel
    d. Urinalysis
    e. T3, free T4, and thyroid stimulating hormone (TSH)[a]
11. HIV, HBV and HCV serology
12. Blood for CA 19-9 (in Cohorts 1 and 2) and CEA (in Cohort 2 only)
13. Tumor tissue collection from metastasis (biopsy) for tumor and correlative studies assessments (including MSI/dMMR status if not previously tested)
14. Blood for cells, DNA and RNA for biomarker correlative studies.
15. Serum for biomarker correlative studies.
16. Tumor imaging assessment CT or MRI

Subjects who failed the Screening procedures may be rescreened after consultation with the Sponsor. Rescreening should include all screening procedures listed in the protocol flow chart, including re-consent signature.

5.2 BASELINE VISIT (DAY 1 BEFORE FIRST DOSE OF ANY OF THE STUDY DRUGS)

Baseline visit refers to Day 1 of treatment before administration of study drug. A window of

[a] in case of TSH is out of normal limits, the subject may still eligible if Total T3 or free T3 and free T4 are within normal limits

three days is allowed for the procedures and assessments of this visit.

For the purpose of assessing efficacy, imaging procedures after monotherapy and before Cycle1/Day 1 of combination are considered Baseline imaging assessments.

Baseline procedures:

1. AE recording
2. Prior and concomitant medications
3. Vital signs
4. Weight
5. Pregnancy test – serum or urine

5.3 TREATMENT PERIOD

The treatment period is comprised of two periods:

- *Monotherapy period:* One week, with BL-8040 administered daily on Days 1-5.
- *Combination therapy:*
  - Cohort 1: Three-week cycles of a combination of BL-8040 administered three times a week (TIW) and pembrolizumab administered once every three weeks.
  - Cohort 2: Chemotherapy: Onivyde®/5-FU/LV every 2 weeks, pembrolizumab once every 3 weeks and BL-8040 twice a week.

5.3.1 Monotherapy

This period will begin immediately after Baseline, preferably on the day of the Baseline assessments and will last for one week. During this period, BL-8040 will be administered daily on Days 1 to 5. Pre-medication with systemic antihistamines is recommended in order to minimize the occurrence of BL-8040 related local injection site reactions and/or systemic reactions. Details on the specific days for each assessment are presented in the flow chart (Appendix A).

5.3.1.1 Week 1 (Days 1-5) Procedures

1. Review of AEs at each visit
2. Prior and concomitant medications
3. CBC with differential, daily on Days 1-5 pre-dose and 4 hr (± 2 hr) post-dose on Day 1 and 5
4. a. Cohort 1: Blood for anti-BL8040 antibodies and complement activation on Day 1, pre-dose and 4 hr (± 2hr) post-dose. .

   b. Cohort 2: Blood for anti-BL8040 antibodies pre-dose on Day 1.
5. Blood for immunophenotyping by FACS on Day 1 and 5 pre-dose and 4 hr (± 2 hr) post-dose.
6. Directed PE on Day 5 (+ up to 3 days, but before the beginning of the combination period)
7. Vital signs Day 5 pre-dose of BL-8040, post-dose assessment maybe collected upon Investigator decision
8. 12 lead ECG- Pre dose on Day 1

9. Blood for CA 19-9 (in Cohorts 1 and 2) and CEA (in Cohort 2 only) on Day 5 (+ up to 3 days, but before the beginning of the combination period)
10. Blood for CXCR4 and PD-1 expression on Day 1 and 5 pre-dose and 4 hr (± 2 hr) post-dose.
11. Tumor tissue collection from metastasis (biopsy) for assessment according to Section 5.12.2, on Day 5 (+ up to 4 days, but before the beginning of the combination period). Biopsy during the monotherapy period will be performed only for the first 15 subjects enrolled in Cohort 1.
12. Tumor imaging assessment on Day 5 (+ up to 4 days, but before the beginning of the combination period).
13. Blood for cells, DNA and RNA for biomarker correlative studies on Day 5 (+ up to 3 days, but before the beginning of the combination period).
14. Serum for biomarker correlative studies on Day 5 (+ up to 3 days, but before the beginning of the combination period).

5.3.2 Combination Treatment

Cycles are defined according to the pembrolizumab three-week-cycle schedule of treatment.

From Day 8 (+ up to 4 days) subjects will begin a combination period consisting of treatment with:

Cohort 1: IV pembrolizumab every 3 weeks, followed by SC BL-8040 1.25mg/kg, 1 hr ± 30 min later TIW.

Cohort 2:

- IV Onivyde® 70 mg/m^2 over 90 minutes, followed by IV LV 400 mg/m^2 over 30 minutes or according to local standard, followed by IV 5-FU 2400 mg/m^2 over 46 hours, every 2 weeks.
- IV Pembrolizumab 200mg once every three weeks.
- Beginning on Day 10, SC BL-8040 1.25mg/kg twice a week after chemotherapy dosing.

The combination therapy will continue until progression, clinical deterioration or early Termination.

Pre-medication with systemic antihistamines is recommended in order to minimize the occurrence of BL-8040 related local injection site reactions and/or systemic reactions. Premedication with dexamethasone is allowed prior to Onivyde dosing, and on days 2 and 3 post-dosing, for acute and delayed emesis prevention in accordance with the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for Antiemesis, V.1 (Feb 2019), if deemed necessary by the study investigator.

The following assessments should be done at each cycle (time window will be ± 3 days unless otherwise specified):

1. Review prior and concomitant medications at all visits
2. Review of AEs at all visits
3. Directed PE on Day 1 pre-dose beginning in Cycle 2

4. Vital signs will be assessed on Day 1 of each cycle before study drug administration, post-dose vital sign assessment may be collected upon Investigator decision
5. Weight will be assessed at the beginning of each week during the combination treatment period before the first injection of the week. BL-8040 dose will be adjusted accordingly
6. ECOG performance status on Day 1 of each cycle
7. Chemistry panel on Day 1 of each cycle before study drug administration
8. Treatment administration:
   a. Cohort 1:
      i. BL-8040 administration three times a week
      ii. Pembrolizumab administration on Day 1 of each cycle
   b. Cohort 2:
      i. BL-8040 administration two times a week
      ii. Pembrolizumab administration on Day 1 of each 3-week cycle
      iii. Onivyde®/5-FU/LV every 2 weeks
9. An optional additional core or excisional biopsy (not Fine needle aspiration [FNA]) may be performed during the study provided the subject has agreed to it specifically. Only for Cohort 1.

The following assessments should be done at specific cycles (time window will be ± 3 days unless otherwise specified):

1. CBC with differential
   a. Cycle 1:
      - Before each BL-8040 dose for assessment of WBC (no window is allowed for CBC prior to BL-8040 injection). Further assessments will be performed as deemed necessary by the Investigator.
      - 4 hr (±2 hr) post-injection for the first three doses of BL-8040 for assessment of WBC.
   b. Cycle 2 and onward:
      - Before the first three doses of BL-8040 for assessment of WBC (no window is allowed for CBC prior to BL-8040 injection). Further assessments should be performed as deemed necessary by the Investigator.
2. 12 lead ECG on Day 1 of Cycle 1 pre-dose and 4 hr (± 2 hr) after the combination treatment
3. T3 (total or free), free T4 and TSH on Day 1 of Cycle 1 and thereafter on Day 1 of every two cycles beginning in Cycle 2 prior to dosing
4. Pregnancy test – serum or urine every two cycles beginning in Cycle 2
5. a. Cohort 1: Blood for anti-BL8040 antibodies and complement activation: Day 1 before administration of any of the study drugs, every two cycles beginning in Cycle 1.

b. Cohort 2: Blood for anti-BL8040 antibodies on Day 1 before administration of any of the study drugs, every two cycles beginning Cycle 1.

6. Blood for CA 19-9 (in Cohorts 1 and 2) and CEA (in Cohort 2 only) on Day 1 of every two cycles beginning in Cycle 2.
7. Blood for immunophenotyping by FACS:
   a. Cohort 1: on Day 21 of Cycle 2
   b. Cohort 2: on Day 15 of Cycle 1 and Day 21 of Cycle 2
8. Blood for CXCR4 and PD-1 expression on Day 15 of Cycle 1 and Day 21 of Cycle 2
9. Blood for DNA and RNA for biomarker correlative studies:
   a. Cohort 1: at the time of the biopsies
   b. Cohort 2: Blood for cells, DNA and RNA correlative studies will be collected on Cycle 1/Day 15 prior to the second cycle of chemotherapy and on Day 21 of every two cycles beginning in Cycle 3.
10. Cohort 1: Tumor tissue collection from metastasis (biopsy): on Day 21 of Cycle 2 (± 4 days) during the combination period will be performed beginning with subject 16 and up to the last enrolled subject as detailed in Section 5.12.2.
11. Tumor imaging assessment will be done at the end of Cycle 2, and then every 3 cycles up to one year of treatment (Cycle 17) and then every 4 cycles until end of Cycle 34 /Termination visit (two years of treatment).
12. Serum for biomarker correlative studies will be collected on Cycle 1/Day 15 prior to the second cycle of chemotherapy and on Day 21 of every two cycles beginning in Cycle 3.

5.4 TERMINATION OR EARLY DISCONTINUATION STUDY VISIT

A Termination visit will be performed after two years of treatment.

An Early Discontinuation Study Visit will be performed for subjects who withdraw from the study for the reasons specified in Section 4.5 (time window will be ± 14 days).

All reasons for treatment discontinuation will be documented in the source documents. Only one reason (the most severe) for early discontinuation should be recorded in the CRF. If one of the reasons for discontinuation is an AE, this should be chosen as the reason. Every effort should be made to follow-up these subjects until resolution or stabilization of the AE.

At this visit the following activities will be performed. Exceptions for assessments may be provided in case these assessments were done 1-2 cycles prior to Termination visit

1. Review prior and concomitant medications
2. Review of AEs
3. 12 lead ECG
4. Full PE
5. Vital signs
6. ECOG performance status
7. CBC with differential
8. Chemistry panel

9. T3 (total or free), free T4, and TSH
10. a. Cohort 1: Blood for anti-BL8040 antibodies and complement activation
    b. Cohort 2: Blood for anti-BL8040 antibodies
11. For Cohort 1: Blood for DNA and RNA for correlative studies
12. Tumor imaging

5.5 SAFETY FOLLOW-UP VISIT

After Termination/Early Termination visit, a safety follow-up visit will be performed approximately 90 days after the last dose of the last study drug (or within 7 days prior to initiation of a new anti-cancer treatment, whichever comes first). The subject will be monitored for AEs up to the safety follow-up visit or until resolution of toxicity to Grade 0-1 or AE stabilization, whichever occurs later. SAEs should be reported when occur within 90 days and pregnancies when occurred within 120 days of study termination, or, in both cases, 30 days following cessation if a new anti-cancer therapy is initiated (see Section 7.2.1).

The following assessment will be performed during this visit.

1. Review of AEs
2. Review prior and concomitant medications
3. Post- study anti-cancer therapy received
4. CBC with differential
5. Chemistry Panel
6. T3 (total or free), freeT4, TSH
7. 12 lead ECG

5.6 LONG-TERM FOLLOW-UP OF SURVIVAL

All subjects will be contacted by phone every 12 weeks (± 4 weeks) in order to assess their survival status regardless of the reason for discontinuation (i.e. early termination [ET] or after two years). This Follow-up will continue for up to 5 years unless they withdrew their consent to continue their participation in the study. During these phone calls, subjects will be asked to provide, among others, an update about disease status and post- study anti-cancer therapy received. All the data will be collected and entered within the CRF as well.

5.7 UNSCHEDULED VISIT

An unscheduled visit may be performed at any time during the study at the subject's request or as deemed necessary by the Investigator. The date and reason for the unscheduled visit will be recorded. AE monitoring and concomitant medication recording will be performed by the Investigator. Other procedures and evaluations will be completed as deemed necessary by the Investigator and may include (but are not limited to) laboratory safety tests, vital signs and physical examination.

5.8 SAFETY ASSESSMENTS

Safety assessments will be based on changes from Baseline of clinical signs and symptoms reported by the subject or observed by the Investigator, including AEs, concomitant medication use, treatment compliance, tolerability (e.g. dropouts due to AEs), vital signs, ECGs, physical examination and laboratory safety assessments.

5.8.1 Adverse Events (AEs)

Adverse Events (AEs) will be assessed at all study visits throughout the study.

Any new AE that occurs between scheduled assessment visits should be brought to the attention of the Investigator and recorded in the subject's medical file and on the appropriate CRF page.

AEs will be reported and graded in accordance with the latest National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version (currently version 5.0) and coded by Data Management using the latest version of Medical Dictionary for Regulatory Activities (MedDRA; see Section 7.1 for more details).

5.8.2 Concomitant Medications

Concomitant medication use will be recorded from Baseline through all study visits.

5.8.3 Vital Signs, Height and Weight

Vital signs will be measured at Screening, at Baseline and pre-dose on Day 5 of the monotherapy treatment. Post-dose assessment may be performed as deemed necessary by the Investigator. During the combination period, vital signs will be assessed on Day 1 of each cycle before study drug administration. Further assessment may be performed upon Investigator decision.

Vital signs will include blood pressure, pulse, oral temperature, O2 saturation and respiration rate following a minimum of 5 minutes of rest as per standard practice at the study site. Significant findings noticed after the start of study drug which meet the definition of an AE must be recorded on the AE CRF module.

Height will be recorded only at Screening.

Weight will be recorded at Baseline and on at the beginning of each week (combination period) before dosing in order to calculate the BL-8040 dose.

5.8.4 Electrocardiogram

An ECG will be performed at the Screening and Baseline (Day 1 pre-dose) visits.

During the combination period, an ECG will be performed on Cycle 1/Day 1 pre-dose and 4 hours (± 2 hours) after the last study drug administered. An ECG will be performed at the Termination visit and at any safety follow-up visit as well.

Additional ECGs will be performed at the discretion of the Investigator or upon the Sponsor's request. The subject should rest for at least 10 minutes before the measurement is taken.

ECG printouts will be evaluated by the Investigator or designee, signed and dated and filed in the source documentation file. When potentially Clinically Significant findings are detected by the Investigator or designee; a cardiologist should be consulted for a definitive interpretation and appropriate treatment if required. All communications and diagnoses should be filed in the source documentation file. The Investigator/Investigator's designee/local cardiologist is responsible for determining whether the ECG findings are of clinical significance. All abnormalities shall be closely monitored until stabilized or resolved. Clinically significant finding should be reported within the AEs CRF page.

5.8.5 Physical Examination and Directed Physical Examination

A full PE will be conducted at Screening and at the time of discontinuation. The PE will include assessment of the following body systems: head, neck, thyroid, respiratory, cardiovascular,

ophthalmologic, gastrointestinal, hepatic, endocrine/metabolic, musculoskeletal system, dermatological, lymph nodes, neurological system and, where appropriate, other body systems as indicated in the study schedule.

A directed PE will be conducted on Day 5 of the monotherapy period (± 3 days but before the first dose of the combination) and on Day 1 of each cycle beginning at Cycle 2 (± 3 days but before the first dose of the combination of Cycle 2) (see Study Flow Chart–Appendix A). During a directed PE, particular attention should be focused on identifying possibly drug-related AEs and managing these AEs effectively.

Information about the PE must be present in the source documentation at the study site. Significant findings that are present prior to the start of study drug must be included in the Relevant Medical History/ Current Medical Conditions CRF. Significant findings made after the start of study drug which meet the definition of an AE must be recorded on the AE CRF module.

5.8.6 Laboratory Safety Assessments

[redacted]

Table 1: Laboratory Tests

[redacted]

[a] For menopause confirmation

[b] if abnormal results are noted

[c] if total bilirubin is elevated above the upper limit of normal

A serum pregnancy test, if applicable, will be collected at Baseline and performed at the local laboratory.

Laboratory safety test abnormalities that arise after study drug administration will be repeated as clinically indicated until the values return to normal or until the etiology has been determined and the condition considered stable. Abnormal laboratory test results that are considered to be clinically important by the Investigator will be reported as AEs in the AE CRF module. A laboratory abnormality will not be considered an AE unless:

- Intervention is required
- Changes in dose are required (decrease, discontinued, interrupted)
- Other treatment/therapy is required
- Associated with other diagnoses

Laboratory results will be reported to the Investigator or designee who will review, sign and date abnormal laboratory findings for clinical significance. The Investigator will note any laboratory test results of clinical concern or values that were outside normal ranges and provide details of the relationship to the investigational product and the action taken. If a change in a laboratory value represents a medical condition, the medical condition will be listed in the AE record. If no correlation is possible, the direction of change (increase or decrease) in addition to the actual value will be recorded.

5.9 ECOG PERFORMANCE STATUS

ECOG performance status (see Appendix B in Section 13.2) will be collected at Screening and on Day 1 of each combination cycle (± 3 days) and at treatment discontinuation unless otherwise specified.

5.10 PHARMACODYNAMIC EVALUATIONS

[redacted]

[redacted]

5.11 PLANNED GENETIC ANALYSIS

[redacted]

5.12 EFFICACY ASSESSMENTS

5.12.1 Imaging Assessment

Imagining will be used for assessment of response. CT or MRI may be used according to institutional practice. The same imaging method should be used throughout the study for each subject.

The imaging assessment will be done at:

- Screening.
- End of Monotherapy period, Day 5.
- Combination treatment at the end of Cycle 2 and then every 3 cycles up to one year of treatment (Cycle 17) and then every 4 cycles until end of cycle 34[a].
- Termination visit: imaging for Cycle 34 will be considered as Termination visit imaging as well and should be captured as such in the CRF. In case of ET, all efforts should be done in order to have an additional imaging assessment.

Primary and secondary imaging related endpoints will be assessed by RECIST 1.1 and immune-related RECIST (irRECIST), respectively.

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment of immunotherapeutic agents. Agents such as pembrolizumab and BL-8040 may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Therefore, RECIST 1.1 will be used with the following general adaptations:

[redacted]

- If radiologic imaging verifies initial progressive disease, tumor assessment should be repeated ≥4 weeks later in order to confirm progressive disease with the option of continuing treatment per below.
- If repeat imaging shows less than a 20% increase in tumor burden compared to nadir, stable or improved previous new lesion (if identified as cause for initial progressive disease), and stable/improved non-target lesions (if identified as cause for initial progressive disease), treatment may be continued/resumed.
- If repeat imaging confirms progressive disease due to any of the scenarios list below, subjects will be discontinued from study therapy (exception noted in Table 3).
- In determining whether or not the tumor burden has increased or decreased, site study team should consider all target lesions as well as non-target lesions (please refer to the irRECIST TIP Sheet).

Scenarios where progressive disease is confirmed at repeat imaging:

- Tumor burden remains increased by ≥ 20% and at least 5 mm absolute increase compared to nadir
- Non-target lesions resulting in initial progressive disease is worse (qualitative)
- New lesion resulting in initial progressive disease is worse (qualitative)
- Additional new lesion(s) since last evaluation

In subjects who have initial evidence of radiological progressive disease, it is at the discretion of the treating physician whether to continue a subject on study treatment until repeat imaging is obtained. This clinical judgment decision should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may continue to receive treatment while waiting for confirmation of progressive disease if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

When feasible, subjects should not be discontinued until progression is confirmed. This allowance to continue treatment despite initial radiologic progression takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, but with subsequent disease response. Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation of progressive disease.

If the site study team assessed disease progression and the subject is clinically stable (described above), it is at the discretion of the site Investigator to continue to treat and image the subject at least 4 weeks after the first tumor imaging indicating progressive disease. irRECIST would then be followed by the study site to determine if the follow-up tumor imaging confirms progressive disease. Subjects who have unconfirmed disease progression may continue on treatment and follow the regular imaging schedule intervals until progression is confirmed, provided they have met the conditions detailed above.

irRECIST Assessment of Disease

As noted above, if tumor imaging shows initial disease progression, the study site may elect to continue treatment, repeat imaging ≥ 4 weeks later and assess tumor response or confirmed progression per irRECIST (see Table 3).

irRECIST is RECIST 1.1 adapted as described below to account for the unique tumor response seen with immunotherapeutic drugs. irRECIST will be used by site Investigator/local radiology review to assess tumor response and progression and make treatment decisions. This data will be collected in the clinical database.

Table 3: Imaging and Treatment after 1st Radiologic Evidence of PD

	Clinically Stable		**Clinically Unstable**	
	Tumor Imaging	**Treatment**	**Tumor Imaging**	**Treatment**
1st radiologic evidence of progressive disease by RECIST 1.1	Repeat tumor imaging ≥4weeks at site to confirm progressive disease	May continue study treatment at the Investigator's discretion while awaiting confirmatory tumor imaging by site by irRECIST	Repeat tumor imaging at ≥ 4 weeks to confirm progressive disease per physician discretion only	Discontinue treatment
Repeat tumor imaging confirms progressive disease by irRECIST at the local site	No additional tumor imaging Required	Discontinue treatment (exception is possible upon consultation with Sponsor)	No additional tumor imaging required	N/A
Repeat tumor imaging shows SD, PR or CR by irRECIST by the local site	Continue regularly scheduled tumor imaging assessments	Continue study treatment at the Investigator's discretion	Continue regularly scheduled tumor imaging assessments	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next tumor image should occur according to the study schedule.

In determining whether or not the tumor burden has increased or decreased, study site Investigators should consider all target lesions as well as non-target lesions (please refer to the irRECIST TIP Sheet). Subjects that are deemed clinically unstable are not required to have repeat tumor imaging for confirmation.

For a **clinically stable** subject with first radiologic evidence of progressive disease by RECIST 1.1 (i.e., **unconfirmed progression of disease**), it is at the discretion of the site Investigator to continue treating the subject with the assigned treatment per protocol until progression of disease is confirmed at least 28 days from the date of the scan first suggesting progressive disease. If radiologic progression is confirmed by subsequent scan, then the subject will be discontinued from trial treatment. If radiologic progression is not confirmed by irRECIST per the site, then the subjects may continue on treatment and follow the regular imaging schedule intervals until progression is confirmed at a later time point by the site.

***NOTE**: If a subject has confirmed radiographic progression (i.e. two scans at least 4 weeks apart demonstrating progressive disease) per irRECIST, but the subject is achieving a clinically meaningful benefit, and there is no further increase in the tumor burden at the*

confirmatory tumor imaging, an exception to continue treatment may be considered following consultation with the Sponsor. In this case, if treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Appendix 13.1 Study Flowchart

Any subject deemed **clinically unstable** should be discontinued from trial treatment at the first radiologic evidence of progressive disease and is not required to have repeat imaging for progressive disease confirmation.

In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment (every 2 cycles ± 7 days), until (1) the start of new anti-cancer treatment, (2) disease progression (3) death, or (4) the end of the study, whichever occurs first.

irRECIST data will be collected in the CRF

5.12.2 Planned Biopsy Analysis

5.13 BLOOD SAMPLING AND PROCESSING

Samples will be collected for safety and efficacy analysis, anti-drug antibodies titer and determination of BL-8040 plasma concentrations at the time points indicated in Study Flow Chart (see Section 13.1)

Instructions for the collection, processing, storage and shipment of samples are detailed in the Laboratory Manual provided by the Sponsor.

5.14 TIME WINDOWS FOR SAFETY AND EFFICACY ASSESSMENTS

Time windows are provided in Section 5 for each specific assessment and in Appendix A- Flow chart.

6 INVESTIGATIONAL PRODUCT

6.1 IDENTITY OF INVESTIGATIONAL PRODUCT

6.1.1 BL-8040

BL-8040 is a highly selective CXCR4 antagonist co-developed by [redacted]. and BioLineRx Ltd. as a novel investigational therapy for the treatment of cancer.

BL-8040, a white to off-white powder synthetic polypeptide, is freely soluble in water and in 0.45% Sodium Chloride (half normal saline). It is manufactured in accordance with current Good Manufacturing Practice (cGMP) by [redacted].

6.1.2 Pembrolizumab

[redacted]

6.1.3 Chemotherapy: Onivyde®/5-FU/LV

Onivyde is an injection: 43 mg/10 mL irinotecan free base as a white to slightly yellow, opaque, liposomal dispersion in a single-dose vial.

Fluorouracil injection is supplied as a pharmacy bulk package as a vial containing 2.5 g/50 mL (50 mg/mL) fluorouracil.

Leucovorin Calcium for injection is supplied as a sterile lyophilized powder. The 350 mg vial is preservative-free. The inactive ingredient is sodium chloride 140 mg/vial for the 350 mg vial. Sodium hydroxide and/or hydrochloric acid are used to adjust the pH to approximately 8.1 during manufacture. 1 mg of leucovorin calcium contains 0.002 mmol of leucovorin and 0.002 mmol of calcium.

6.2 STUDY DRUG ADMINISTRATION AND DOSAGE

6.2.1 BL-8040

Trial treatment with BL-8040 will be administrated by SC injection of 1.25 mg/kg daily as monotherapy for 1 week, beginning on Day 1 daily through Day 5. Subjects will receive once daily SC injections of BL-8040 in the morning. Pre-medication with systemic antihistamines with or without analgesics is recommended in order to minimize the occurrence of BL-8040 related local injection site reactions and/or systemic reactions.

[redacted]

6.2.2 Pembrolizumab

Treatment with pembrolizumab will begin following the monotherapy period and as a part of the combination therapy. During the combination period pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion on Day 1 of each 3-week treatment cycle after all procedures and assessments have been completed as detailed on the Section 13.1 Appendix A-Trial Flow Chart. Pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons[a].

Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes -5 min/+10 min).

[redacted]

[redacted]

[redacted]

6.2.3 Onivyde/5-FU/LV

Onivyde should be administered prior to LV and 5-FU. Onivyde 70 mg/m^2 as an IV infusion over 90 minutes, followed by LV 400 mg/m^2 IV over 30 minutes or according to local standard, followed by 5-FU 2400 mg/m^2 IV over 46 hours, every 2 weeks. Patients homozygous for the UGT1A1*28 allele will initiate Onivyde® at 50 mg/m^2, and the dose can be increased if tolerated at later cycles. Due to the moderate emetic risk of Onivyde, premedication with 12 mg Dexamethasone PO/IV is allowed once prior to Onivyde dosing. An additional 8 mg Dexamethasone PO/IV may be given on days 2 and 3 post-dosing in accordance with the NCCN guideline for antiemesis V.1 (Feb 2019), if deemed necessary by the study investigator.

Specific instructions on the reconstitution and administration of chemotherapy during the study are included in the Pharmacy Manual.

6.3 STUDY MEDICATION SOURCE AND INSTRUCTIONS FOR USE

6.3.1 BL-8040

BL-8040 drug substance (4F-benzoyl-TN14003 peptide) is a white or off-white powder synthetic polypeptide, freely soluble in water and in 0.45% Sodium Chloride (half normal saline). It is manufactured in accordance with (cGMP) requirements by [redacted]

Reconstitution and administration instructions will be provided in a separate Pharmacy Manual.

6.3.2 Pembrolizumab

Pembrolizumab is a monoclonal antibody (mAb) and is provided as a solution for infusion administered via IV infusion. The drug product is a clear to opalescent liquid essentially free of visible particles. The product is manufactured according to good manufacturing practice by Merck & Co, Inc. Administration instructions will be provided in a separate Pharmacy Manual.

6.3.3 Chemotherapy

6.3.3.1 Onivyde®

Dosage Form and Strength

Injection: 43 mg/10 mL irinotecan free base as a white to slightly yellow, opaque, liposomal dispersion in a single-dose vial.

Preparation and Administration

Onivyde® is a cytotoxic drug. Follow applicable special handling and disposal procedures.1

Preparation

- Withdraw the calculated volume of Onivyde® from the vial. Dilute Onivyde in 500 mL 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP and mix diluted solution by gentle inversion.

- Protect diluted solution from light.
- Administer diluted solution within 4 hours of preparation when stored at room temperature or within 24 hours of preparation when stored under refrigerated conditions [2ºC to 8ºC (36ºF to 46ºF)]. Allow diluted solution to come to room temperature prior to administration.
- Do NOT freeze.

For more details please refer to the Onivyde® label:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207793lbl.pdf

6.3.3.2 5-FU and LV

5-FU and LV drugs will be provided according to institutional guidelines at each study site.

6.4 DISTRIBUTION AND SHIPMENT OF STUDY MEDICATION

The study drugs product will be packed and shipped in appropriate boxes. If, upon arrival at the clinical investigation site, study drug supplies appear to be damaged, the study monitor should be contacted immediately.

Each shipment of study drug supplies for the study will be accompanied by a shipment form describing the contents of the shipment, product certificate of analysis, acknowledgment of receipt and other appropriate documentation. The shipment form will assist in maintaining current and accurate inventory records. The study staff will confirm the receipt of clinical supply to the study monitor.

All study supplies should arrive at the pharmacy/Investigational site in sufficient quantity and in time to enable dosing as scheduled. The Sponsor or its representative must notify the site Investigator's designee prior to dispatch of drug supplies, with the anticipated date of their arrival.

6.5 STORAGE, DISPENSING AND RETURN OF THE INVESTIGATIONAL MEDICINAL PRODUCT

6.5.1 BL-8040

Vials of BL-8040 for injection should be stored in the refrigerator (2-8°C) in its original packaging, protected from light.

Records should also be kept by the Investigator or designee as to how much study drug was dispensed to each subject. The study monitors must periodically check the study drug supplied to ensure expiry date and sufficient amount of study drug, and be sure that drug accountability is being performed at each visit, and the drug accountability logs are maintained.

All investigational products must be kept in a secure area with access to the study drug limited to designated study personnel.

Only trained personnel under the supervision of either the Investigator or the local pharmacist are authorized to dispense and administer study drug to participating subjects.

Further details and instructions will be provided in the Pharmacy Manual.

6.5.2 Pembrolizumab

Pembrolizumab (MK-3475) Solution for infusion, 100 mg/ 4 mL vial should be stored at refrigerated conditions (2 – 8 °C) and protected from light.

Records should also be kept by the Investigator or designee as to how much study drug was dispensed to each subject. The study monitors must periodically check the study drug supplied to ensure expiry date and sufficient amount of study drug and be sure that drug accountability is being performed at each visit, and the drug accountability logs are maintained.

All investigational products must be kept in a secure area with access to the study drug limited to designated study personnel.

Only trained personnel under the supervision of either the Investigator or the local pharmacist are authorized to dispense and administer study drug to participating subjects.

Further details and instructions will be provided in the Pharmacy Manual.

6.5.3 Chemotherapy

Chemotherapy will be provided at each site according to the standard of care.

6.6 ACCOUNTABILITY AND COMPLIANCE OF INVESTIGATIONAL MEDICINAL PRODUCT

Each delivery must be acknowledged by the hospital pharmacist (or authorized study team member responsible for the investigational medicinal product) by filling in the receipt record form and returning it by fax/email to the Sponsor or designee. Accurate, complete and timely documentation of study drug distribution will be maintained by the pharmacy and the study staff of the investigational site which may include confirmation of receipts of clinical supply, drug accountability logs and other forms.

The medical center pharmacist (or authorized study team member responsible for the investigational medicinal product) is responsible for ensuring the supervision of the storage and allocation of these supplies, which will be forwarded to the Investigator at the appropriate time before administration. The Investigator may dispense investigational drug only to subjects enrolled in the study.

Drug accountability records must be maintained by the clinical investigation site at all times. At the last study visit, all used and unused investigational drug will be collected, and drug accountability performed by the study staff. The study monitor will check these regularly during monitoring visits.

The subject number, the date, batch number/pack number and quantity of study drug used by the subject will be checked for correctness and recorded on the appropriate accountability forms. Unused drug supplies will be returned to the Sponsor. At the end of the study, all clinical supplies and the corresponding accountability forms must be returned to the Sponsor, the study monitor, or designee for reconciliation or destruction. A photocopy of these records must be kept at the clinical investigation site.

The inventory will be made available to the study monitor who will verify accountability and verify dose during the course of the study.

Study drug orders, records of study drug receipts, dispensing records and inventory forms located at the site will be examined and reconciled by the study monitor periodically during and at the end of the study

6.7 CONCOMITANT THERAPY

At the Screening visit, relevant treatments currently received by the subject will be recorded in the subject’s CRF including treatment's name, indication, dose, total daily dose and start and stop dates.

Any medications (including prescription, over-the-counter (OTC), herbal supplements and other health store-type products) to be taken during the study must be approved by the Investigator.

Concomitant medication use will be recorded from Screening through the safety follow visit. Treatment provided after study termination will be captured as part of the survival status assessment. The following information should be recorded: treatment's name (generic, if possible), indication, dose and start and stop dates.

Medications or vaccinations specifically prohibited in the Exclusion Criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation of trial therapy may be required. The Investigator should discuss any questions regarding this with the Sponsor's Medical Monitor. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the subject's primary physician. However, the decision to continue the subject's trial therapy requires the mutual agreement of the Investigator, the Sponsor, and the subject.

6.7.1 Contraception, use in Pregnancy and Nursing Women

6.7.1.1 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. BL-8040 effect on fetus in utero was not tested to date.

For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Males and non-pregnant, non-breastfeeding females may only be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 2 years will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study visit 1 (or 21 days prior to the initiation of study medication for oral contraception) and throughout the study period up to 120 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), or sponge, all of which are to be combined with a spermicide, or a copper intrauterine device as per local regulations or guidelines. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (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 (described above) for the duration of the study and during the follow-up period defined in Section 7.4 Reporting of Pregnancy and Lactation to the Sponsor. 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.

6.7.1.2 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with study drugs, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study 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. If a male subject impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and followed as described above and in Section 7.4- Reporting of Pregnancy and Lactation to the Sponsor.

6.7.1.3 Use in Nursing Women

It is unknown whether pembrolizumab or BL-8040 are excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breastfeeding are not eligible for enrollment.

6.7.2 Allowed Medications

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 CRF including all prescription, OTC, herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included in the CRF.

All concomitant medications received within 30 days prior to the first dose of study treatment and 90 days after the last dose of trial treatment should be recorded. Concomitant medications administered more than 90 days after the last dose of trial treatment should be recorded for SAEs and events of clinical interest (ECIs).

[redacted]

6.7.3 Prohibited Concomitant Medications

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

- [redacted]

[redacted]

- [redacted]
- [redacted]
- Cohort 2 only:
  - [redacted]

Subjects who, in the assessment by the Investigator, require the use of any of the aforementioned prohibited treatments for clinical management should be removed from the trial. Subjects may receive other medications that the Investigator deems to be medically necessary.

The Exclusion Criteria describes other medications that are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

6.7.4 Dose Modifications

[redacted]

[a] [redacted]

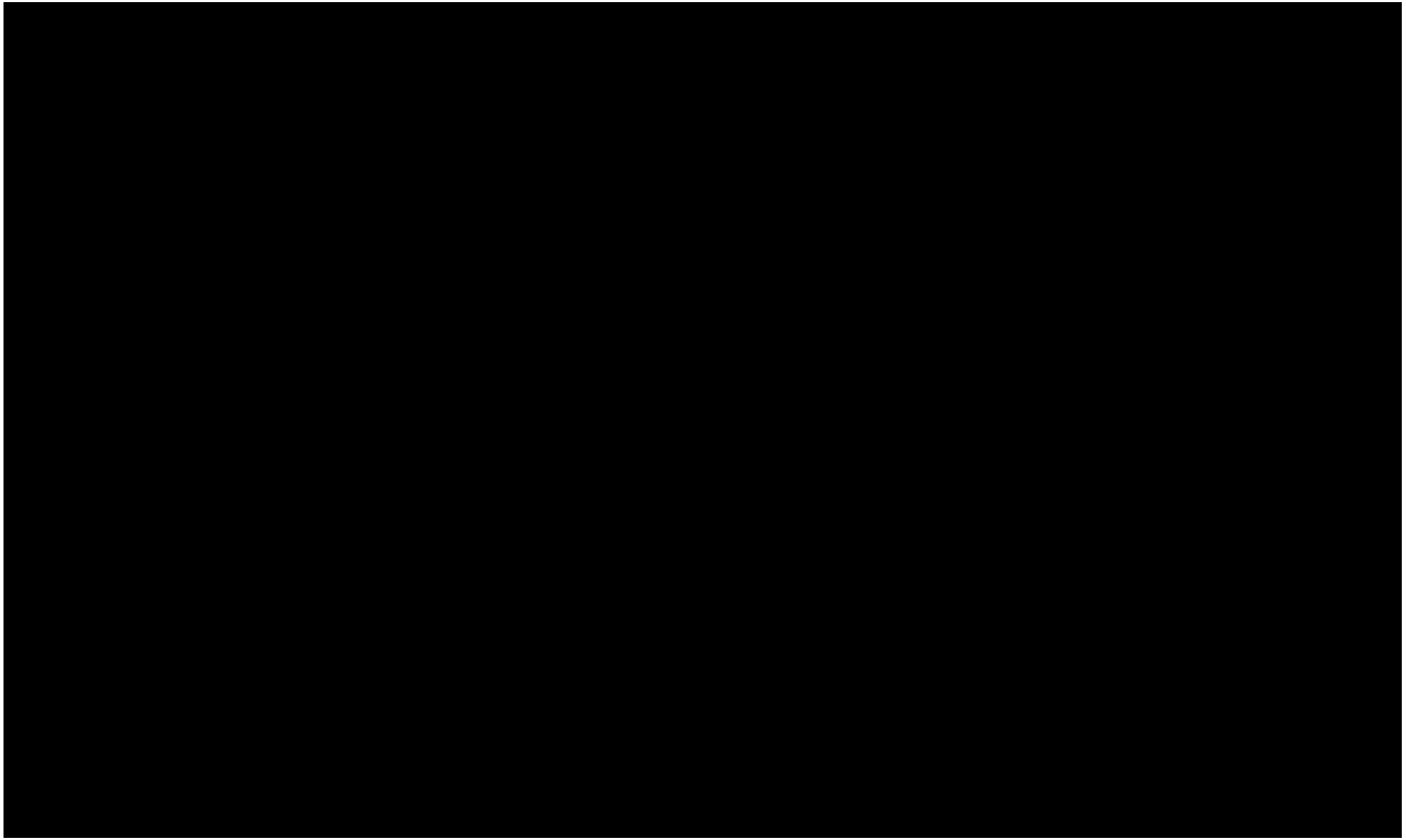
[redacted]

6.7.4.1 BL-8040

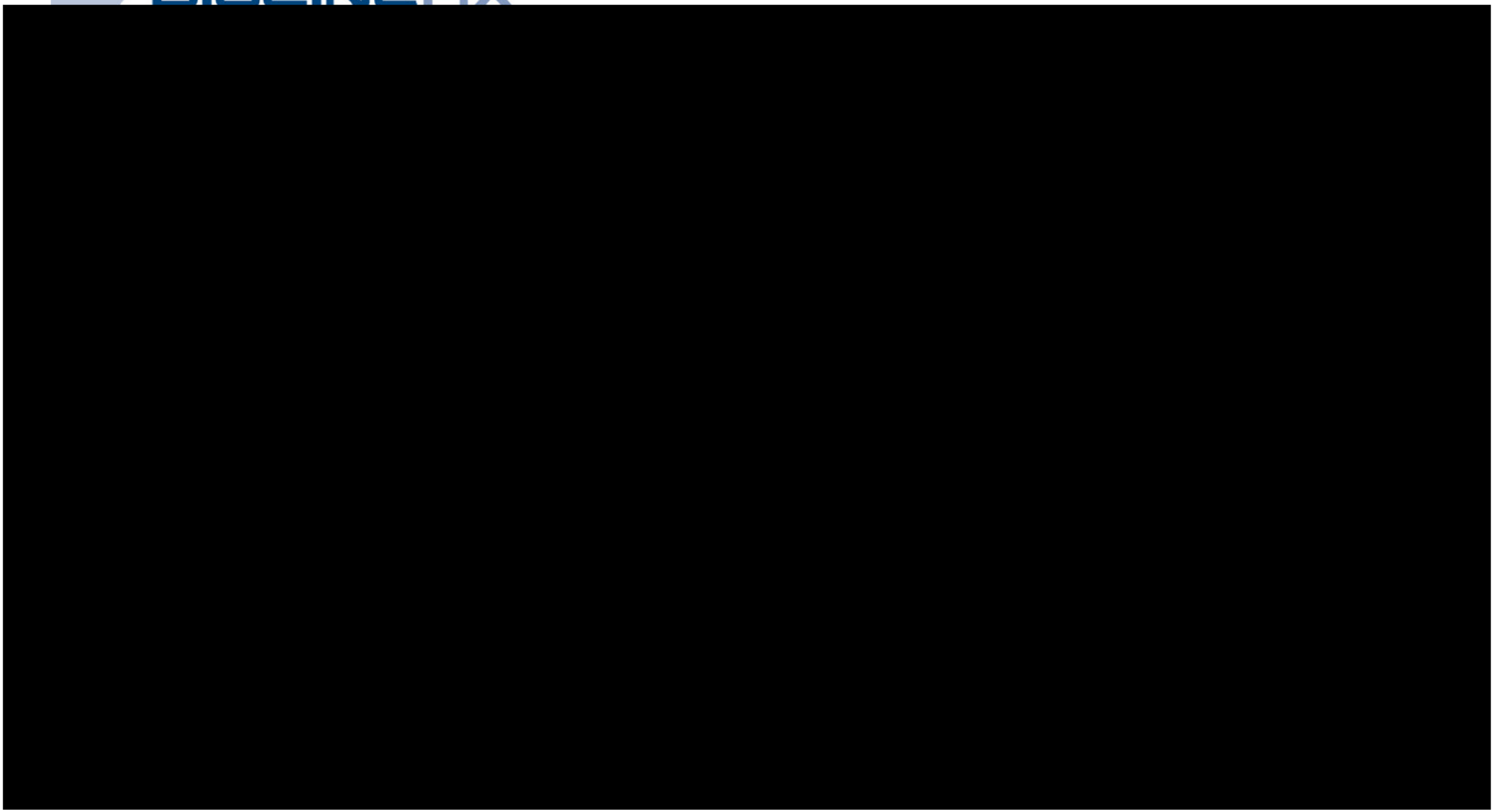
[redacted]

6.7.4.2 Dose-Modification and Toxicity Management for Immune-Related AEs Associated with Pembrolizumab

[redacted]



[redacted]



[redacted]

6.7.4.3 Onivyde®

The recommended[26] dose modifications for Onivyde® are listed in.

Table 5: Recommended Dose Modifications for Onivyde®

Toxicity NCI-CTCAE v4.0	Occurrence	Onivyde® adjustment in patients receiving 70 mg/m^2	Patients homozygous for UGT1A1*28 without previous increase to 70 mg/m^2
Grade 3 or 4 adverse reactions	Withhold Onivyde®. Initiate loperamide for late onset diarrhea of any severity. Administer intravenous or subcutaneous atropine 0.25 to 1 mg (unless clinically contraindicated) for early onset diarrhea of any severity. Upon recovery to ≤ Grade 1, resume Onivyde® at:		
	First	50 mg/m^2	43 mg/m^2
	Second	43 mg/m^2	35 mg/m^2
	Third	Discontinue Onivyde	Discontinue Onivyde
Interstitial Lung Disease	First	Discontinue Onivyde	Discontinue Onivyde
Anaphylactic Reaction	First	Discontinue Onivyde	Discontinue Onivyde

6.7.4.4 Dose Modifications for 5-FU

Withhold fluorouracil for any of the following[28]:

- Development of angina, myocardial infarction/ischemia, arrhythmia, or heart failure in patients with no history of coronary artery disease or myocardial dysfunction
- Hyperammonemic encephalopathy
- Acute cerebellar syndrome, confusion, disorientation, ataxia, or visual disturbances
- Grade 3 or 4 diarrhea
- Grade 2 or 3 palmar-plantar erythrodysesthesia (hand-foot syndrome)
- Grade 3 or 4 mucositis
- Grade 4 myelosuppression

Upon resolution or improvement to Grade 1 diarrhea, mucositis, myelosuppression, or palmar-plantar erythrodysesthesia, resume fluorouracil administration at a reduced dose.

There is no recommended dose for resumption of fluorouracil administration following development of any of the following adverse reactions:

- Cardiac toxicity
- Hyperammonemic encephalopathy
- Acute cerebellar syndrome, confusion, disorientation, ataxia, or visual disturbances

6.7.4.5 Dose Modifications for Leucovorin

No specific dose recommendations within the label[29].

6.7.4.6 Dose Modifications Guidelines for Managing Overlapping Toxicity

Oncology patients with advanced disease often experience adverse events that may be a result of their underlying disease, the study medications, or a combination of these. Furthermore, different study drugs have the potential to cause overlapping toxicities, making it difficult to determine the causality of these reactions. In such cases, the treating physician should use his or her best judgement in evaluating which drug is most suspect (e.g. based on his knowledge and experience, the patients' clinical condition and the temporal relation between the dosing and the reaction onset, etc.), and dose modifications should be implemented accordingly. The treating physician may consult with the study medical monitor when additional guidance is needed on a case by case basis. Specific guidance for the management of diarrhea is provided below, in section 6.7.4.6.1.

6.7.4.6.1 EVALUATION AND MANAGEMENT OF DIARRHEA DURING PEMBROLIZUMAB, 5-FU AND BL-8040 COMBINATION THERAPY

[redacted]

[a] Stein A, Voigt W, Jordan K. Chemotherapy-induced diarrhea: pathophysiology, frequency and guideline-based management. Ther Adv Med Oncol 2010; 2(1):51-63. doi: 10.1177/1758834009355164.

[redacted]

[redacted]

[redacted]

3. [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

6.7.5 Rescue Medications & Supportive Care

6.7.5.1 Allowed Concomitant Medications

- Pre-medication prior to BL-8040 injection with antihistamines in order to minimize the occurrence of BL-8040 related systemic reactions is recommended. Systemic steroids are allowed for the treatment (and not as pre-medication) of these reactions. Premedication with dexamethasone is allowed prior to Onivyde dosing, and on days 2 and 3 post-dosing, for acute and delayed emesis prevention in accordance with the NCCN guideline V.1, if deemed necessary by the study investigator.
- Clinically appropriate measures in case of BL-8040-related local injection site reactions e.g., local corticosteroids, systemic and local painkillers, antihistamines, local treatments etc.
- Antiemetic drugs (e.g., Ondansetron) as required clinically based on local guidelines for subjects experiencing nausea.
- Prophylactic antibiotics when appropriate. (e.g., quinolone or cephalosporin), anti-fungals (e.g., voriconazole) and antivirals (e.g., valacyclovir).
- Blood products, commonly required in oncology subjects.
- [redacted]

Additional medications/therapies to manage treatment or disease emergent conditions will be allowed at the discretion of the Investigator in consultation with the Sponsor, in advance where possible. In case there is a change in therapy related to an AE, the Sponsor or Investigator may decide to withdraw the subject (refer to Section 4.6).

6.7.5.2 Supportive Care Guidelines for BL-8040

[redacted]

6.7.5.2.1 [redacted]

[redacted]

6.7.5.3 Supportive Care Guidelines for Pembrolizumab

[redacted]

[redacted]

[redacted]

[redacted]nformation, please refer to the Common Terminology Criteria for Adverse Events v5.0 [redacted]

6.7.5.4 Supportive Care Guidelines for Chemotherapy

[redacted]

[redacted] [26,28,29].

7 SAFETY AND PHARMACOVIGILANCE

7.1 ADVERSE EVENT (AE)

An AE is defined in the International Conference on Harmonization (ICH) E6 as "any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product."

An abnormal result of diagnostic procedures including abnormal laboratory findings will be considered an AE if it fulfills one or more of the following:

- Results in subject's withdrawal by the Investigator
- Is associated with an SAE
- Is associated with clinical signs or symptoms
- Is considered by the physician to be of clinical significance

A new condition or the worsening of a pre-existing condition will be considered an AE.

AEs do not include the following:

- Medical/surgical procedures are not AEs (e.g., surgery, endoscopy, tooth extraction, transfusion). The condition that leads to the procedure is an AE if the procedure was not planned at Screening visit.
- Overdose of concomitant medication without any signs or symptoms unless the subject is hospitalized for observation.
- Hospitalization for elective surgery planned prior to study (situation where an untoward medical occurrence has not occurred).
- Progression of the cancer under study, unless it is considered to be drug-related by the Investigator.

All AEs, whether observed by the Investigator or designee or volunteered by or elicited from the subject, should be recorded individually on an AE CRF page with the following information: the specific event or condition, whether the event was present pre-Baseline or not, the dates and times (using the 24 hour clock, where midnight is 00:00 and noon is 12:00) of occurrence, duration, severity, relationship to study medication, action taken to study drug, outcome, and whether considered non-serious or serious, drug-related or not.

Once the subject has signed the ICF, AEs will be recorded until the end of the Follow-up period. The severity of the AE will be assessed by the investigating physician in accordance with the definitions below. A SAE must fulfill the requirements listed in Section 7.2.

AEs severity (Table 7) will be recorded and graded according to the latest version of the NCI-CTCAE (currently version 5.0) and coded into the database according to the latest version of MedDRA (currently version 22.0).

Table 7: Severity of Adverse Events According to CTCAE (Version 5.0)

Grade	Description

0	No AE or within normal limits
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)
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
4	Life-threatening consequences; urgent intervention indicated
5	Death related to AE

A semi-colon indicates 'or' within the description of the grade.

A single dash (-) indicates a grade is not available

The following definitions should be used for toxicities/AEs that are not defined in the CTCAE:

- Mild (Grade 1): The AE is noticeable to the subject but does not interfere with routine activity, no medical intervention is required;
- Moderate (Grade 2): The AE interferes with routine activity but responds to symptomatic therapy or rest;
- Severe (Grade 3): The AE significantly limits the subject's ability to perform routine activities despite symptomatic therapy;
- Life-threatening (Grade 4): The subject is at immediate risk of death.

The Investigator will document his opinion of the relationship of the AE to treatment with investigational product using the criteria outlined in Table 8.

Outcome to Date are classified as follows:

- Recovered: The subject has fully recovered from the AE with no residual effects observable
- Recovered with sequelae: The subject has recovered from the AE with residual effects observable
- Improved: the subject status improved but has not been fully recovered
- Ongoing: AE is not recovered
- Fatal
- Unknown

AEs will be coded by Data Management using the latest version of MedDRA (currently version 22.0) AE dictionary.

All AEs, serious and not serious, will be recorded on the AE Case Report Form, and if relevant, the Concomitant Medications Record in the CRF will be updated. Severity and relationship to study drug will be assessed by the Investigator as described in and treatment respectively. Particular attention should be made to ensure no discrepancies between the AE and the SAE form (i.e., outcome, severity, relationship must be consistent). TEAEs are defined as AEs observed after 1st dose of study drug.

The relationship of an AE to the study drug is characterized as follows:

Table 8: Relationship of Adverse Event to Treatment

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to AEs which, after careful consideration, are clearly due to extraneous causes (disease, environment, etc) or to AEs, which, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the study drug.	The relationship of an AE may be considered "no reasonable possibility" if it is clearly due to extraneous causes or if at least 2 of the following apply: • It does not follow a reasonable temporal sequence from the administration of the test drug. • It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It does not follow a known pattern of response to the test drug. • It does not reappear or worsen when the drug is re-administered.
Reasonable possibility (related)	This category applies to AEs for which, after careful medical consideration at the time they are evaluated, a connection with the test drug administration cannot be ruled out with certainty nor felt with a high degree of certainty to be related to the study drug.	The relationship of an AE may be considered "reasonable possibility" if at least 2 of the following apply: • It follows a reasonable temporal sequence from administration of the drug. • It cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists. • It follows a known pattern of response to the test drug.

7.2 SERIOUS ADVERSE EVENTS (SAE)

An SAE is any AE occurring at any dose that suggests a significant hazard or side effect, regardless of the Investigator or Sponsor's opinion concerning the relationship to the investigational medicinal product and that result in, but may not be limited to, any of the following outcomes:

- Death (regardless of the cause)
- A life-threatening experience

- Inpatient hospitalization or prolongation of existing hospitalization (any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility)
- A persistent or significant disability/incapacity
- A congenital anomaly or birth defect in an offspring of a study subject.

Significant medical events that may not result in death, be life-threatening, or require hospitalization may be **serious** when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Inpatient hospitalization or prolongation of existing hospitalization means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of AE, or that they occurred as a consequence of the event.

Hospitalization for elective treatment of a pre-study condition (pre-Baseline) that did not worsen while on study and optional hospitalizations not associated with a clinical AE (e.g. elective cosmetic surgery) are not considered SAEs.

Significant medical events are those that may not be immediately life-threatening, but may jeopardize the subject and may require intervention to prevent one of the other serious outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; such an AE will normally be considered serious by this criterion.

Progression of the cancer under study is not considered an AE unless it is considered to be drug-related by the Investigator.

In addition to the above criteria, AEs meeting any of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs as significant medical events to meet certain local requirements.

Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a new cancer (that is not a condition of the study)
- Is associated with an overdose, refer to Section 7.3 events of clinical interest

Methods for follow-up for these criteria can be found in the Investigator Trial File Binder (or equivalent).

A **life-threatening** adverse drug experience is any AE that places the subject, in the view of the Investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Any newly emergent SAE, after treatment is discontinued or the subject has completed the study, and that is considered to be related to the study drug or study participation, should be recorded and reported immediately to Sponsor or delegate.

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

Pembrolizumab

[redacted]

[redacted]

BL-8040

[redacted]

[redacted]

[redacted]

7.2.2 Reporting Period of Serious Adverse Event

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

All AEs or ECIs from the time of treatment/ allocation through 90 days following cessation of study treatment must be reported by the investigator.

All AEs meeting serious criteria, from the time of treatment/ allocation through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anti-cancer therapy, whichever is earlier must be reported by the investigator.

All pregnancies and exposure during breastfeeding, from the time of treatment/ allocation through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anti-cancer therapy must be reported by the investigator.

Additionally, any SAE brought to the attention of an Investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered to be drug-related.

All subjects with SAEs must be followed up for outcome.

7.2.3 Definition of an Unexpected Adverse Event

An **unexpected** adverse drug event is any AE, the specificity or severity of which is not consistent with information in the current IB for an unapproved investigational product.

Suspected Unexpected Serious Adverse Reaction (SUSAR) is a SAE assessed as unexpected by the Sponsor and that is judged by either the reporting Investigator or the Sponsor to have a reasonable causal relationship to the investigational medicinal product.

7.2.4 Exceptions in the Reporting of SAE

Elevations of blood cells are expected with BL-8040 treatment as a part of the mechanism of action. These elevations should not be reported as AEs or SAEs provided they are not

associated with clinical symptoms. In case of clinical symptoms, the final diagnosis should be reported accordingly as an AE or SAE depending of the severity.

7.2.5 Notification of Serious Adverse Event (SAE)

Initial Notification of SAEs

An initial SAE report form must be completed and sent via email/fax to the sponsor within 24 hours of the Investigator's knowledge of the event. Any fatal or life-threatening event should be reported immediately by phone, fax or email. Reporting SAEs to regulatory authorities and/or IRBs must comply with local regulations.

PhV representative:

[redacted]

[redacted]

[redacted]

The initial SAE report will be followed within 24 hours by a completed SAE report including a sufficiently detailed narrative to allow for a medical assessment of the case, as well as copies of hospital case reports, results of applicable diagnostic tests, laboratory results, biopsy results, autopsy reports and other documents when requested and applicable.

Minimum Criteria for a Valid Initial SAE Case:

For regulatory purposes, initial SAE reports should be submitted to the Sponsor's Medical Monitor or designee immediately and should include:

1. A suspected study drug (whether or not it is suspected to be related to one or both study drugs)
2. An identifiable subject (e.g. study subject code number)
3. An AE with the Investigator's assessment of seriousness
4. An identifiable reporting source (Investigator contact details)

Once sent, the SAE form and accompanying documentation should be placed in the SAE section of the Investigator's site file.

SAEs will be reported to the IRB/IEC and regulatory authorities as required by local regulations and ICH-GCP guidelines.

Follow-up of SAEs:

Follow-up of all SAEs that occur during the study will continue until their satisfactory resolution or stabilization. In outstanding cases, an SAE may be defined as "ongoing without further follow-up" if mutually agreed by the Investigator and Sponsor.

A Follow-up SAE report form must be completed by the site (marked as "Follow-up report") and sent to the Medical Monitor within a reasonable timeframe (an SAE Follow-up report is required whether or not there is any additional information to the initial report).

The contact information for Follow-up SAE reporting is the same as for initial SAE reports (see above section).

As for the initial SAE report, once sent, the Follow-up SAE report and accompanying documentation should be placed in the SAE section of the Investigator's site file.

7.3 EVENTS OF CLINICAL INTEREST

[redacted]

7.4 REPORTING OF PREGNANCY AND LACTATION TO THE SPONSOR

Although pregnancy and lactation are not considered AEs, it is the responsibility of Investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before Baseline must be reported by the Investigator and the subject should be excluded from the trial.

Pregnancies and lactations that occur from the time of Baseline through 120 days following cessation of study drugs, or 30 days following cessation of treatment if the subject initiates new anti-cancer therapy, whichever is earlier, must be reported by the Investigator. All reported pregnancies must be followed to the completion/Termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (under Important Medical Event). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

8 STATISTICAL METHODOLOGY

As this is an open-label, Phase IIa two-cohort study to evaluate the safety, tolerability and preliminary efficacy study of two potential treatments regimens, neither power assessment, nor between cohorts formal hypotheses testing are currently planned for study outcome measures.

The planned sample size of a total of 40 subjects for each of the two study cohorts is considered clinically appropriate for further characterization of the safety, tolerability and preliminary efficacy of the proposed treatment regimens in subjects with metastatic pancreatic adenocarcinoma.

Outcome results of all safety, tolerability and preliminary efficacy data will be compared between the two study cohorts descriptively.

The primary efficacy endpoint is the ORR according to RECIST1.1 ($ORR_{RECIST1.1}$) defined as the sum of PRs and CRs determined according to best response RECIST1.1 criteria.

Principal analysis for inference will use the mITT Analysis Set. The $ORR_{RECIST1.1}$ rate and its lower 95% One-Sided Confidence Limit ([redacted]) will be displayed for each study cohort. Sensitivity analysis will be done for the ITT analysis set.

A more detailed Statistical Analysis Plan (SAP), amending the plan written to Cohort 1, will be developed during the data collection period of the initial 6 subjects of Cohort 2.

8.1 SAMPLE SIZE CONSIDERATION

The planned sample size of a total of 40 subjects for each of the two study cohorts is considered clinically appropriate for further characterization of the safety, tolerability and preliminary efficacy of the proposed treatment regimens in subjects with metastatic pancreatic adenocarcinoma.

8.2 DATA ANALYSES SETS

The following data analysis sets are defined for this study:

8.2.1 Intent-to-Treat (ITT) Analysis Set

The Intent-to-Treat (ITT) analysis set will consist of all data collected for all subjects who have been enrolled into the study and treated for at least once with any of the study drugs. This analysis set will serve as the principal analysis set for safety inference and for OS and PFS inference.

8.2.2 Modified Intent-to-Treat (mITT) Analysis Set

The Modified Intent-to-Treat (mITT) analysis set is a subset of the ITT set. This set will consist of data from all subjects who met all of the below criteria:

- Treated with and of study drugs at least once, and,
- Underwent at least 1 post-Baseline CT scan.

The mITT analysis set will serve as the principal analysis set for efficacy inference (except for the OS and PFS analyses).

8.3 EFFICACY ENDPOINTS AND ANALYSES

All efficacy endpoints will be evaluated for the mITT analysis set with the exception of the PFS and OS that will be evaluated for the ITT Analysis Set. The two study cohorts will be compared descriptively.

8.3.1 Significance Level

No between-cohort significance tests are planned for this study. 95% One-Sided Confidence Limits for each cohort response estimates will be provided when applicable.

8.3.2 Primary Efficacy Endpoint: Objective Response Rate According to RECIST1.1 ($ORR_{RECIST1.1}$)

The primary efficacy endpoint is the Objective Response Rate according to RECIST1.1 ($ORR_{RECIST1.1}$) defined as the sum of PRs and CRs determined according to best response RECIST1.1 criteria. Principal analysis for inference will use the mITT Analysis Set. The $ORR_{RECIST1.1}$ rate and its lower 95% One-Sided Confidence Limit ([redacted]) will be displayed for each study cohort separately. Sensitivity analysis will be done for the ITT analysis set.

8.3.3 Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be assessed:

8.3.3.1 $ORR_{irRECIST}$

The Objective Response Rate according to irRECIST ($ORR_{irRECIST}$) is defined as the sum of PRs and CRs determined according to best response irRECIST criteria.

Principal analysis for inference will use the mITT Analysis Set. The $ORR_{irRECIST}$ rate and its lower 95% One-Sided Confidence Limit ([redacted]) will be displayed for each study cohort separately.

Sensitivity analysis will be done for the ITT analysis set.

8.3.3.2 Overall Survival (OS)

The analysis of OS will be performed for the ITT Analysis Set for each study cohort separately.

The distribution of the time to event from first dose of either study drug will be presented using Kaplan-Meier Plot. Censoring, for event free subjects, will use the last day subject is alive.

Median time to event as well as its lower 95% One-Sided Confidence Limit will be extracted from the [redacted] table. The 6-Months OS estimate and its lower 95% One-Sided Confidence Limit (extracted from SAS dataset generated while using the [redacted]) will be presented as well.

Number of deaths and death rate as well as its lower 95% One-Sided Confidence Limit ([redacted]) will also be displayed.

8.3.3.3 Progression-Free Survival (PFS)

The analysis of PFS will be performed for the ITT Analysis Set.

The distribution of the time to event from first dose of either study drug will be presented using Kaplan-Meier Plot. Censoring, for event free subjects, will use the last day subject is alive. The

distribution of the time to event will be presented using Kaplan-Meier Plots. Censoring, for event free subjects, will use the last day subject is alive.

Median time to event as well as its lower 95% One-Sided Confidence Limit will be extracted from the [redacted] table. The 6-Months PFS estimate and its lower 95% One-Sided Confidence Limit (extracted from SAS dataset generated while using the [redacted]) will be presented as well.

8.3.3.4 Disease Control (DC)

DC is defined as the sum of PRs and CRs and SDs determined according to:

- **DC$_{RECIST1.1}$** is defined as the best response according to RECIST1.1.
- **DC$_{irRECIST}$** is defined as the best response according to irRECIST.

Number of events and event rates as well as lower 95% One-Sided Confidence Limit ([redacted]) will be provided.

8.3.3.5 [redacted]

[redacted]

8.4 SAFETY ANALYSES

All safety assessments will use the ITT analysis set and will consist of all data collected for all subjects who have been enrolled into the study and treated for at least once with either study drugs. This analysis set will serve as the principal analysis set for safety inference.

8.4.1 Treatment Emergent Adverse Events (TEAEs)

AEs are to be recorded from the time a subject has signed the ICF until the end of subject's study participation in the study (including the safety follow-up period), regardless of study drug administration.

The MedDRA dictionary Version 22 will be used to standardize the terms used by the investigator to describe the AEs.

AE analyses will include only the TEAEs, namely, those events which started at the time of first study drug administration or afterwards.

The following analyses are pre-planned for AEs:

- The incidence (no. of patients) and frequency (no. of events) of most frequent TEAEs (>10% of subjects) by Preferred Term.

- The incidence (no. of patients) and frequency (no. of events) of most frequent TEAEs (>10% of subjects) by High Level Term (HLT).
- The incidence (no. of patients) and frequency (no. of events) by System Organ Class (SOC).
- The incidence (no. of patients) and frequency (no. of events) of TEAEs broken down by SOC, HLT and Preferred Term.
- For each attribute of AEs (e.g. seriousness, severity) a summary table will be provided displaying the incidence (no. of patients) and frequency (no. of events) when broken down by event attribute classification, by SOC and Preferred Term.
- The incidence (no. of patients) and frequency (no. of events) of serious TEAEs broken down by SOC, Preferred Term and by study drugs relationship.
- The incidence (no. of patients) and frequency (no. of events) of injection site reactions will be provided when broken down by Preferred Term.
- The incidence (no. of patients) and frequency (no. of events) of systemic reactions will be provided when broken down by Preferred Term as described below:

8.4.2 Laboratory Data

Analyses of safety laboratory data will be performed in the following manner:

- The proportion (%) of patients who reach WBC > 60,000/µL will be presented by study visits and across all post-Baseline visits.
- Laboratory measurements were categorized with reference to the local sites normal ranges as Low, Normal or High. The incidence (no. of subjects) of abnormal values at any time first study drug administration, calculated for subjects with normal values at Baseline will be provided. Analysis will include, per tested parameter, those subjects with normal baseline and at least one post-treatment measurement. Summary table will display the number and relative percentage of subjects with at least one abnormal value at any time post 1st study drug administration.
- Abnormal laboratory measurements of potentially clinical significance were also been classified by the sites as Clinically Significant (CS) or Not Clinically Significant (NCS). Summary table will display the number and relative percentage of subjects with at least one CS assessment, for each laboratory parameter and across all laboratory parameters at any time post 1st study drug administration.
- Quantitative laboratory parameters will be summarized by study visits according to the below:
  - Descriptive statistics of measured values and changes from Screening Visit (Note: Laboratory assessments were not collected at Baseline Visit).
  - Graphical display of measured values will be presented using Box-Plots and figures of mean values ±SE across study visits.

8.4.3 Vital Signs

Analyses of vital signs data will be performed in the following manner:

- Descriptive statistics of quantitative parameters measured at scheduled visits and at Last Observed Value (LOV) will be provided along with changes from Baseline.
- Graphical presentation of mean values ± 1 standard error of the mean as well as Box-Plots of quantitative parameters measured at scheduled visits and at LOV will be provided as well.
- Summary table of the number and percent (%) of subjects with at least one post 1st study drug CS assessment, along with data listing of all vital signs data of these subjects will be provided. The denominator for this analysis will be number of subjects with at least one post 1st study drug vital signs assessment.
- The distribution of Investigator's assessment (Normal, Abnormal NCS and Abnormal CS) done for each parameter evaluated will be provided by study visit.

8.4.4 ECG

Analyses of ECG data will be performed in the following manner:

- Descriptive statistics of quantitative parameters measured at scheduled visits and at LOV will be provided along with changes from baseline.
- Graphical presentation of mean values ± 1 standard error of the mean as well as Box-Plots of quantitative parameters measured at scheduled visits and at LOV will be provided as well.
- Summary table of the number and percent (%) of subjects with at least one post 1st study drug administration CS overall assessment, along with data listing of all ECG data of these subjects will be provided. The denominator for this analysis will be number of subjects with at least one post Monotherapy D1 ECG assessment.
- QTcF prolongation is defined as QTcF>440(msec) for males and QTcF>460(msec) for females at any time post 1st study drug administration. Summary table of the number and percent (%) of subjects with at least one post Monotherapy D1 QTcF prolongation, along with data listing of all ECG data of these subjects will be provided. The denominator for this analysis will be number of subjects with at least one post 1st study drug administration.
- The distribution of overall Investigator's assessment of ECG (Normal, Abnormal NCS and Abnormal CS) will be provided by study visit.

8.4.5 Safety Assessment - Physical Examinations

Physical examinations and directed physical examinations were to be performed as described in the study scheme. Accordingly:

- Full PE will be conducted at Screening and at the time of discontinuation. These data will be summarized as outlined below:
  - Assessment results, for each body system, were classified as Normal, Abnormal NCS or Abnormal CS. The distribution of number of subjects by body system examined and result assessments made will be presented by scheduled visit.
  - Shift analysis from Screening to End of Treatment will be provided.

- The number and the proportion of subjects with abnormal assessments of clinical significance will be displayed.

- Directed PE will be conducted on Day 5 of the monotherapy period (± 3 days but before the first dose of the combination) and on Day 1 of each cycle beginning at Cycle 2 (± 3 days but before the first dose of the combination of cycle 2).

  These data will be summarized in a frequency table displaying the number and proportion (%) of subjects with any change in physical examination by visit and overall, across all post-Baseline visits.

8.5 TOLERABILITY ASSESSMENT

Tolerability and drop-out assessments will be performed for the ITT Analysis Set for the below metrics:

- Proportion of subjects (%) who prematurely discontinued from the study by reason of discontinuation.
- Time of early study discontinuation for whatever reason.
- Time of early study discontinuation due to AEs.

The distribution of the time to event will be presented using Kaplan-Meier Plots. Median time to event will be extracted from the [redacted] table. The 6-Months early-Termination-frees-subjects estimate and its lower 95% One-Sided Confidence Limit (extracted from SAS dataset generated while using the [redacted]) will be presented as well.

8.6 MORE DETAILED STATISTICAL ANALYSIS PLAN (SAP)

A more detailed SAP, amending the plan written to Cohort 1, will be developed during the data collection period of the initial 6 subjects of Cohort 2.

8.7 STATISTICAL SOFTWARE

All data listings, summary tables and statistical analyses will be generated using SAS® Version 9.4 or higher (SAS is a registered trademark of the SAS Institute Inc., Cary, NC, USA).

8.8 ONGOING SAFETY ASSESSMENT AND DOSE-LIMITING TOXICITY (DLT)

AEs will be reported from the time of informed consent signature through 90 days of the last dose of the last study drug.

An independent DMC will review the accumulated study data according the DMC charter in order to ensure subjects welfare. Serious AEs will be monitored continuously throughout the study.

[redacted]

[redacted]

[a] First cycle of combination, Day 1 to 21, for the first six to twelve patients that complete this period

9 ETHICS

9.1 INSTITUTIONAL REVIEW BOARD OR INDEPENDENT ETHICS COMMITTEE

Prior to initiation of the study, the Investigator will submit the study protocol and amendments, IB and amendments, ICF and any other documents that may be provided to the subject or any other documents requested by the IRB/IEC for review and approval.

The names and affiliations of all members of the IRB/IEC must be provided to the PI and BioLineRx. In lieu of this, the IRB/IEC must certify that it has been officially authorized/recognized according to the national legislation.

The IRB/IEC must provide written approval of the study to keep in the Investigator's file. Records of approval of all documents pertaining to this study, including the local Regulatory Authority, should be filed as such. The Investigator will not begin the study until the protocol, ICF and any other document provided to the subject have been approved by the IRB/IEC. The Investigator must agree to make any required progress reports to the IRB/IEC, as well as reports of SAEs, life-threatening conditions or death. The IRB/IEC will also be notified of Part 1 preliminary results.

9.2 ETHICAL CONDUCT OF THE STUDY

All clinical work conducted under this protocol is subject to ICH-GCP (E6) guidelines. This includes an inspection by Sponsor or its designee, health authority or IRB/IEC representatives at any time. The Investigator must agree to the inspection of study-related records by health authority representatives and/or Sponsor or its designee.

The study will be conducted in accordance with Sponsor and/or designee's standards operating procedures and the following guidelines:

- GCP: Consolidated Guideline (International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use, May 1996).
- Declaration of Helsinki: Brazil, 2013.
- US Code of Federal Regulations (Title 21, CFR Part 11, 50, 54, 56 and 312) and/or EU Directives; and/or local country regulations and guidelines.

9.3 SUBJECT INFORMATION AND CONSENT

Prior to Screening for the study each subject will be informed in detail about the study drugs to be administered and the nature of the clinical investigation including the risks and discomforts to be expected. The basic elements of informed consent as specified by the US Government (21 CFR 50.25) and ICH-GCP will be followed. The subjects will also be instructed that they are free to withdraw their consent and discontinue their participation in the study at any time without prejudice. Written consent will be obtained from each subject to be involved in the clinical trial by using the IRB/IEC-approved ICF prior to the conduct of any study-related activity. A copy of the ICF will be submitted together with this protocol and must be approved by the IRB/IEC prior to study commencement. Each subject will be given a copy of the written ICF, and each subject's chart will include the signed ICF for study participation. The original subject signed and dated ICFs will be maintained per ICH record retention requirements. Regulatory authorities may check the existence of the signed ICF in this central study folder if not having performed so during the study.

The initial ICF, any subsequent revised written ICF and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative 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 trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

9.4 SUBJECT INSURANCE

A product liability to cover against injury and damages arising from the use of investigational products in this project is provided by the Sponsor for the total duration of the study covering the subjects and Investigators in respect of the risks involved in conducting this study according to this protocol. The insurance policy will be filed in the Investigator's site file or can be made available to the Investigator and to the IRB/IEC upon request.

Subjects will be insured through contract between an insurance company and the Sponsor.

9.5 INFORMING THE GENERAL PRACTITIONER

When required by location regulation, the Investigator will inform the subject's primary care physician of his/her participation in the study, by sending a letter to the physician.

9.6 PERSONAL DATA PROTECTION

The Sponsor will comply with local regulations and with the principle of a subject's right to protection against invasion of privacy. Throughout this trial, all subject data will be identified only by a subject identification number and subject initials and date of birth. The subject must be informed and consent to authorized personnel of the Sponsor, such as study monitor, auditor, etc. and relevant health regulatory agencies having direct access to personal medical data to assure a high-quality standard of the study. At the subject's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

9.7 DATA REVIEW MONITORING

[redacted]

9.8 PROTOCOL EXCEPTIONS AND DEVIATIONS

Departures from the protocol should be avoided, unless required for the safety of the subject. Protocol deviations, and if possible the reason for occurrence, will be documented by the study monitor in visit reports and will be included in the final clinical study report. The Investigator must report any protocol deviations to the Sponsor or the Sponsor's designee, should they occur. If required, the Investigator should also report deviations to the IRB/IEC in accordance with local regulations and within a reasonable time. No prospective waivers will be allowed for subjects who do not fulfill the inclusion/Exclusion Criteria.

9.9 PROTOCOL AMENDMENTS

Changes to the protocol may be made only by the Sponsor (with or without consultation with the Investigator). All protocol modifications must be submitted to the site IRB/IEC in accordance with local requirements and, if required, to the Regulatory Authority, either as an amendment or a notification. Approval for amendments must be received before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial subjects, or when the changes involve only logistical or administrative aspects of the trial. No approval is required for notifications.

10 QUALITY CONTROL AND QUALITY ASSURANCE

The study will be conducted according to GCP as outlined by ICH Topic E6 step 5 guidelines. The Sponsor's SOPs will be followed to ensure that clinical trials are conducted, and data are generated, documented and reported in compliance with the protocol, GCP and applicable regulatory requirements.

10.1 AUDITS AND INSPECTIONS

The study may be audited according to the Sponsor's or its designee's Quality Assurance inspection program. The purpose of the audit is to determine whether or not the study is being conducted and monitored in compliance with the study protocol and ICH-GCP guidelines. Audit visit(s) will be arranged in advance with site personnel at a mutually acceptable time.

The Investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Sponsor or its designees or the Regulatory Authority inspectors after appropriate notification. The verification of the CRF data must be made by direct inspection of source documents. The auditor may ask to visit the

facilities where laboratory samples are collected, where the investigational product is stored and prepared and any other facility used during the study. These audits or inspections may take place at any time, during or after the study, and are based on the national regulations, as well as ICH guidelines.

10.2 STUDY MONITORING

Monitoring of the study, which is the responsibility of the Sponsor, may be delegated to a CRO. The study monitor will advise the Investigator regarding the practical conduct of the study and maintaining compliance with the protocol, GCP and all applicable regulatory requirements.

Before study initiation, at the site initiation visit or at an Investigator's meeting, a Sponsor or CRO representative will review the protocol and CRFs with the Investigator and staff. The Sponsor/CRO will also be responsible for training study personnel in the study-specific procedures.

Throughout the course of the study, the study monitor will oversee the conduct and the progress of the study by frequent contacts with the Investigator and his staff. Contact will include telephone calls and on-site visits. During the on-site visits, the CRF will be reviewed for completeness and accuracy with corresponding source documents. As part of the data audit, source documents will be made available for review by the study monitor. The study monitor will also perform drug accountability checks and will periodically review the Investigator study file to ensure completeness of documentation in all respects of clinical study conduct.

Periodically, some or all of the facilities used in the study (e.g., local laboratory, pharmacy) may be reviewed. Monitoring visits will be arranged in advance with site personnel at a mutually acceptable time. Sufficient time must be allowed by the site personnel for the monitor to review CRFs and relevant source documents. The Investigator should be available to answer questions or resolve data clarifications. The Investigator or appointed delegate will receive the study monitor during these on-site visits, cooperate in providing the documents for inspection and respond to enquiries.

The Investigator will ensure that the study participants are aware of and consent to their personal information being scrutinized during the data verification process, as part of study-related monitoring, inspection and/or auditing, by properly authorized persons associated with Sponsor or by domestic and/or foreign regulatory authorities. However, the subject's participation and personal information will be treated as strictly confidential to the extent that the applicable law permits and will not be made publicly available.

Upon completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period.

10.3 QUALITY LABORATORY STANDARDS

Laboratory tests or evaluations described in this protocol will be conducted in accordance with quality laboratory standards as described in the SOPs of the central and local institution laboratories.

Before the study begins, where applicable, the laboratories to be used in the study will provide a list of the reference ranges for all laboratory tests to be undertaken and details of the method used for quality control. These will be held in the Investigator Site File and the Trial Master File. The methods employed for each assay should be available on request. Any change in the laboratory, its procedures, references, values, etc. during the study must be notified promptly to the Sponsor.

When academic laboratories are used in this study, they may be exempt from some or all of the above requirements on a case by case basis.

10.4 STUDY DOCUMENTATION

Study documents will include the following:

- Signed ICFs
- Source documents (e.g. subject files, medical notes)
- Investigator copies of the CRFs and SAE reports
- Investigator site file and its content
- Study manual (including imaging tip sheet)
- Laboratory Manual
- Study Pharmacy Manual (includes instructions for use)
- Training materials

Upon completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period.

10.4.1 Source Document

The Investigator will permit study-related monitoring, audits by or on behalf of the Sponsor, IRB/IEC review and regulatory inspections providing direct access to source data documents. Source documents are original records in which raw data are first recorded. These may be office/clinic/hospital records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records or completed scales for each study participant. Source documents should be kept in a secure and limited access area. All source documents must be accurate, clear, unambiguous, permanent and capable of being audited. They should be made using a permanent form of recording (ink, typing, printing, optical disc etc). They should not be obscured by correcting fluid or have temporary attachments (such as removable self-stick notes). Source documents that are computer generated and stored electronically must be printed, signed and dated by the Investigator.

Source data for subjects registered to the study should indicate the date the ICF was signed, participation in a clinical trial with the clinical protocol number and title, treatment number and evidence that inclusion/Exclusion Criteria have been met.

10.4.2 Recording of Data on Case Report Form (CRF)

The development of the CRF will be the responsibility of the Sponsor or its designee.

All the pertinent data will be recorded on an electronic Case Report Form (eCRF). All eCRFs will be completed in English and will be reviewed by study monitors for accuracy and completeness. All data pertaining to the visit should be recorded in the eCRF no later than five days after the completion of the visit. The Investigator is responsible for verifying that all data entries in the eCRFs are accurate and correct. The PI must sign the completed CRF prior to its submission to the Sponsor.

A representative of the Sponsor or designee will instruct the Investigator and his/her staff prior to the enrollment of the first subject and will train them on recording the findings into the EDC system.

EDC System on the Electronic CRFs (eCRFs):

After the enrollment of the first subject, a study monitor will periodically monitor the progress of the study. The study monitor will also have the ability to review query statuses remotely which may warrant more frequent contact with the Investigator and his/her staff. The Investigator will make available to the study monitor the computer that accesses the eCRFs, source documents, signed consent forms and all other study-related documents. The Investigator will be responsible for reviewing eCRFs, providing resolution to data queries generated by the study monitor via the EDC system, providing missing or corrected data, and approving all changes performed on his/her data, and endorsing the subject data within the EDC system. This approval method will include applying an electronic signature, a uniquely assigned username and a password, that together would represent a traditional handwritten signature.

The Investigator will agree to the inspection of study-related records by the Sponsor, external auditor and/or health authority representatives.

10.4.3 Investigator Site File

All documents required for the conduct of the study as specified in the ICH-GCP guidelines will be maintained by the Investigator in an orderly manner and made available for monitoring and/or auditing by the Sponsor/or designee and regulatory agencies.

10.5 CLINICAL TRIAL SUPPLIES

The Sponsor or designee will be responsible for supplying clinical trial supplies to the sites. The PI will be responsible for the administration, inventory and accountability of all clinical trial supplies provided to the site, exercising accepted medical and pharmaceutical practices. An accurate and timely record of the disposition of all clinical supplies must be maintained. The supplies and inventory record must be made available for inspection upon request. Upon completion or Termination of the study, the Investigator will return the remaining clinical supplies along with a copy of the inventory record and a record of the clinical supplies returned. A copy of these records should be maintained in the site study files. **Under no circumstances will the Investigator allow the study drugs to be used other than as directed by this protocol.**

Clinical trial supplies include, but are not limited to: CRFs, lab supplies, and study drugs.

10.6 DATA MANAGEMENT

Data Management services will be provided by the Sponsor or designee. The Data Management system will be specified in the Data Management Plan.

After the data has been entered and verified, various edit checks will be performed to ensure the accuracy, integrity and validity of the database. These edit checks may include:

- Missing value checks
- Range checks
- Consistency checks
- Sequence checks
- Protocol adherence checks

Queries generated from these checks will be sent to the investigational site for resolution, and the database will be updated to reflect query resolutions as appropriate.

AEs will be coded using the latest version of MedDRA (currently version 22.0). Prior and concomitant medications will be coded according to the World Health Organization (WHO) Drug Dictionary.

11 STUDY ADMINISTRATION

11.1 PARTICIPATING CENTERS

Five to ten sites

11.2 REQUIRED DOCUMENTS PRIOR TO STUDY INITIATION

Prior to the start of this study, all pre-investigational requirements must be met by the Investigator and study site. These may include:

- Appropriate local health authority documentation properly signed and dated by the required Investigator (i.e., documents required for submission to the local IRB/IECs or applicable regulatory authorities).
- Signed copy (original) of the approved protocol.
- Completed and signed statement of Investigator.
- A signed Clinical Trial Agreement.
- Curriculum vitae for the Investigator and sub-Investigator (may be collected at site initiation visit).
- IRB/IEC name and address; and membership list (may be collected at site initiation visit).
- Letter of approval from the IRB/IEC for both protocol (identified by protocol title and number) and ICF (identified by protocol title and number).
- Copy of the IRB/IEC-approved written ICF to be used in the study (that has also been approved by the Sponsor).
- Provisions for direct access to source/data documents, if necessary, for trial-related monitoring, audits, IRB/IEC review and regulatory inspection.
- Name and location of the laboratory utilized for laboratory assays and other facilities conducting tests, as well as a copy of the laboratory certificate and list of normal laboratory values (can be collected at site initiation visit).

In case a laboratory certification is not available, a written statement as to how the laboratory complies with quality assurance should be provided.

Upon satisfactory receipt of all required regulatory documents, the Sponsor will arrange for study drugs to be delivered to the study site. Supply of all other study materials will be the responsibility of the Sponsor and/or designee. Subject entry should not begin until after the required regulatory documents are confirmed as received and the Investigator Meeting/Initiation Meeting has occurred. All personnel expected to be involved in the conduct of the study will undergo study initiation which will include review of study protocol, instructions for CRF completion, AE reporting and overall responsibilities including those for drug accountability and study file maintenance.

The Investigator and/or designee (study monitor) will be provided with an Investigator's file. This file should be used for all trial-related documents. The Investigator will be responsible for

keeping the Investigator's file updated and ensuring that all required documents are filed. The file will be inspected during monitoring visits.

11.3 STUDY COMPLETION

This study is expected to end when all required subjects have been enrolled and the last subject has completed the study and all query resolutions have been completed.

Data and materials that are required before the study can be considered complete and/or terminated include, but are not limited to:

- Laboratory findings, clinical data and all special test results from Screening through the end of the follow-up period
- CRF properly completed by appropriate study personnel and signed by the Investigator
- Completed Drug Accountability Records
- Statement of outcome for each SAE reported
- Copies of protocol amendments and IRB/IEC as well as relevant health authority approval/notification (if applicable)
- Retention of Study Documents Statement

11.4 CLINICAL STUDY REPORT

A clinical study report will be developed by the Sponsor on completion of data analysis. This report will be a clinical and statistical integrated report, according to the ICH E3 guidelines.

11.5 RETENTION OF STUDY RECORDS

The Investigator will retain copies of the approved protocol, completed CRF, signed ICFs, relevant source documents and all other supporting documentation related to the project as defined in ICH-E6 Section 8 related to the project per ICH-E6 record retention requirements 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 2 years have elapsed since the formal discontinuation of clinical development of the investigational product in a secure and safe facility with limited access. If the Investigator is unable to retain the study documents for the required amount of time, the Sponsor or designee must be informed of the individual who will be assuming this responsibility.

The Sponsor will notify, in writing, the Investigator when the clinical study data may be discarded. The Investigator will take measures to prevent accidental or premature destruction of these documents.

These files must be made available for inspection upon reasonable request by authorized representatives of the Sponsor and/or the relevant regulatory agencies.

11.6 CONFIDENTIALITY AND PUBLICATION OF STUDY RESULTS

11.6.1 General

All data and information supplied by or on behalf of the Sponsor or otherwise acquired or obtained by any Research Institution, the Principal Investigator and other Investigators ("**Recipients**") in any manner, in connection with or in performance of this study, is considered "**Confidential Information**." This Confidential Information includes, but is not limited to, the IB, this protocol and any information relating thereto, CRFs and other scientific data,

information relating to Sponsor's Investigational Product and treatment methodology and information relating to Sponsor's (or its affiliates') commercial, technical and financial information, research technology, products, inventions, trade secrets and research and development. The results produced in performance of the study and any data, information or other material collected or generated in the course of performing the study shall be promptly disclosed to Sponsor in full, in writing, and are also considered Confidential Information. This Confidential Information shall be the sole property of the Sponsor.

Except for Publishable Results (defined below) to the extent it may be published under Section 11.6.2, throughout the duration of the study and after its completion, Recipients shall

(i) not disclose Confidential Information to others without the written consent of the Sponsor, except to those of its employees who have a need to know the Confidential Information in order to enable Recipients' to fulfill their obligations hereunder, and where such employees are bound by written contractual obligations covering Confidential Information that are no less restrictive or protective than those contained herein, *provided that* Recipients shall remain liable for any disclosure or use of Confidential Information by such employees;

(ii) use the same degree of care to preserve confidentiality of Confidential Information as they use for their own information of like nature, which shall not be less than reasonable degree of care; and

(iii) not use Confidential Information for any purpose except in the performance of this study. Promptly at Sponsor's request, or upon completion of the study, Recipients will discontinue use and return to Sponsor or destroy, in accordance with Sponsor's instructions, all copies or other manifestations of Confidential Information that may be in their possession or control, except to the extent expressly required hereunder and to comply with applicable laws (defined below).

Should a recipient be required to disclose Confidential Information pursuant to law, regulation, judicial or administrative order or request by a governmental or other entity authorized by law to make such request, recipient shall (i) promptly notify Sponsor prior to such disclosure, (ii) cooperate with Sponsor and provide assistance in seeking a protective order or other suitable protection with respect to the Confidential Information, and (iii) only disclose such Confidential Information to the extent pursuant to said law, regulation, judicial or administrative order, or request by a governmental or other authorized entity.

At the subject's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. The personal physician will be notified by site personnel of subject participation in the study.

11.6.2 Published Data

The original CRFs and the data generated from the CRFs or otherwise obtained during the study under this study protocol will become the property of the Sponsor. Publication of the results of this study ("**Publishable Results**") in an appropriate peer-reviewed journal after the conclusion of the study ("**Publication**") made be made as provided herein. Publication must be undertaken in a responsible and ethical manner, taking into account relevant external standards regarding the manner and content of scientific, technical and medical publications and in subject to applicable laws, rules, regulations, policies and guidelines ("**Applicable Laws**"). Authorship will be determined by mutual agreement between Sponsor and Principal Investigator. Sponsor shall be mentioned in all Publications unless contrary instruction is given by Sponsor. Review and comment by Sponsor authorized personnel on draft abstracts and

manuscripts for Publication or presentation is required prior to publication or presentation. Authors shall submit a copy of any abstracts, manuscripts or other material proposed for publication or presentation ("**Draft Publications**") to the Sponsor for its approval no fewer than sixty (60) days prior to the intended date of submission of such Draft Publications to any journal, publisher, and/or third party. The Sponsor has the right, at its discretion (a) to evaluate Draft Publications for accuracy and concurrence regarding data, evaluations, and conclusions, (b) to provide an opportunity for Sponsor to share with the Investigator(s) any new or unpublished information of which he or she may be unaware, (c) to ensure that no Confidential Information or other Sponsor proprietary information is being utilized and has been included, and (d) evaluate Draft Publications to determine if patent applications need to be filed on any information disclosed therein. If the Sponsor determines that such Draft Publication contains Confidential Information or could otherwise be detrimental to Sponsor's intellectual property interest or have other adverse effects on its business, and notifies Principal Investigator of its determination, the Principal Investigator, Research Institutions and other Investigators/authors shall remove such Confidential Information from the Draft Publication or at Sponsor's election, modify it to remove language that is detrimental to Sponsor's intellectual property or other interests, and refrain from submitting such Draft Publication to a journal, publisher and/or other third party for additional ninety (90) days from Sponsor's notification to allow for filing of patent applications or the taking of such other measures as Sponsor deems appropriate to establish, preserve and protect its intellectual property or other interests. Principal Investigator, other Investigators and Research Institutions further agree to redact or modify those sections of the Draft Publication which Sponsor in good faith determines falls within (a) to (d) above

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13 APPENDICES

13.1 APPENDIX A- FLOW CHART

13.1.1 Cohort 1

Trial Period:	**Screening Phase**	**Baseline Assessments**	**Monotherapy**	**Combination Treatment Cycles[1]**					**End of Treatment**	**Post-Treatment**	
Treatment Cycle:	**Screening (Visit 1)**	**D1 Pre-dose**	**D1-D5**	**1**	**2**	**3**	**4**	**5-34 every two cycles ± 3**	**Discontinuation (± 14 days)**	**Safety Follow-up**	**Survival Follow-up[2,3]**
Scheduling Window (Days)[4]:	**-21 to 0**	**-3 to 1 Pre-dose**	**± 3**	**+4**	**± 3**	**± 3**	**± 3**		**At time of discontinuation**	**90 days post discontinuation**	**Every 12 weeks[5] (± 4 weeks)**
Administrative Procedures											
Informed Consent	X[6]										
Inclusion/Exclusion Criteria	X										
Demographics and Medical History	X										
Prior and Concomitant Medication Review[7]	X	X	X	X	X	X	X	X	X	X	
Clinical Procedures/Assessments											
Review Adverse Events[8]	X	X	X	X	X	X	X	X	X	X	
12-Lead Electrocardiogram (ECG)	X		X[9]	X[10]					X	X	
Full PE	X								X		
Directed Physical Examination			X[11]		X[12]	X[12]	X[12]	X[12]			
Vital Signs[13]	X	X	X[14]	X[15]	X[15]	X[15]	X[15]	X[15]	X		
Weight[16]		X		X	X	X	X	X			
Height	X										
ECOG performance status[17]	X			X	X	X	X	X	X		
BL-8040 administration			X[18]	X[19]	X[19]	X[19]	X[19]	X[19]			

Trial Period:	Screening Phase	Baseline Assessments	Monotherapy	Combination Treatment Cycles[1]					End of Treatment	Post-Treatment	
Treatment Cycle:	**Screening (Visit 1)**	**D1 Pre-dose**	**D1-D5**	**1**	**2**	**3**	**4**	**5-34 every two cycles ± 3**	**Discontinuation (± 14 days)**	**Safety Follow-up**	**Survival Follow-up[2,3]**
Scheduling Window (Days)[4]:	**-21 to 0**	**-3 to 1 Pre-dose**	**± 3**	**+4**	**± 3**	**± 3**	**± 3**		**At time of discontinuation**	**90 days post discontinuation**	**Every 12 weeks[5] (± 4 weeks)**
Pembrolizumab Administration [20]				X	X	X	X	X			
Post-study Anti-Cancer Therapy Status										X	X
Survival Status											X
Laboratory Procedures/Assessments: Analysis performed by LOCAL laboratory											
Pregnancy Test – Serum or Urine[21]		X			X		X	X			
PT/INR and aPTT	X[22]										
CBC with Differential	X[22]		X[23]	X[24]	X[25]	X[25]	X[25]	X[25]	X	X[26]	
Chemistry Panel	X[22]			X[27]	X[27]	X[27]	X[27]	X[27]	X	X[26]	
Urinalysis	X[22]										
T3 (free or total), freeT4 and TSH	X[22]			X[28]	X[28]		X[28]		X	X[26]	
HIV, HBV and HCV serology	X										
Blood for CA19-9	X		X[29]		X[30]		X[30]	X[30]			
Laboratory Procedures/Assessments: Analysis performed by CENTRAL laboratory											
[redacted]											

[redacted]

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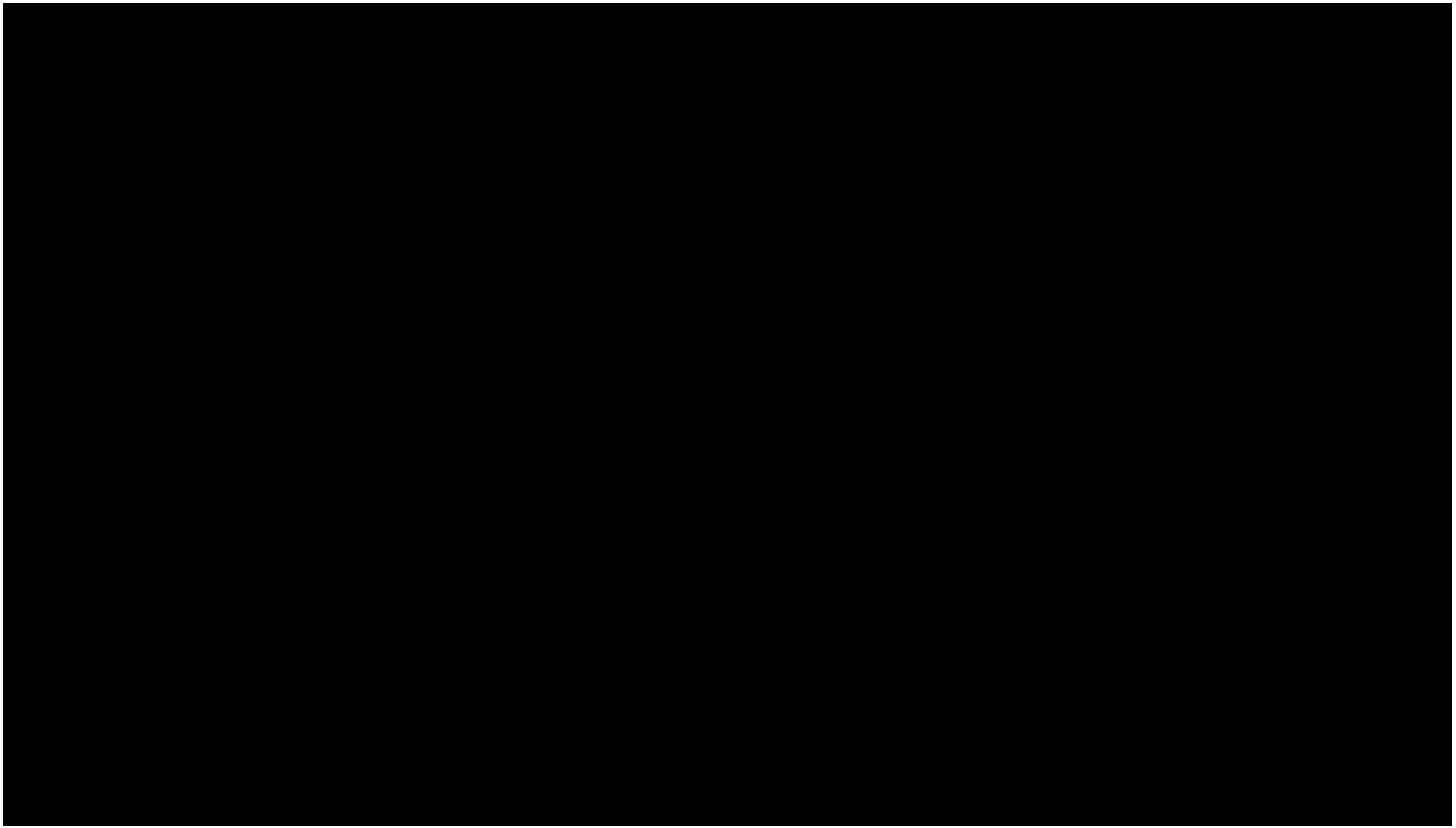
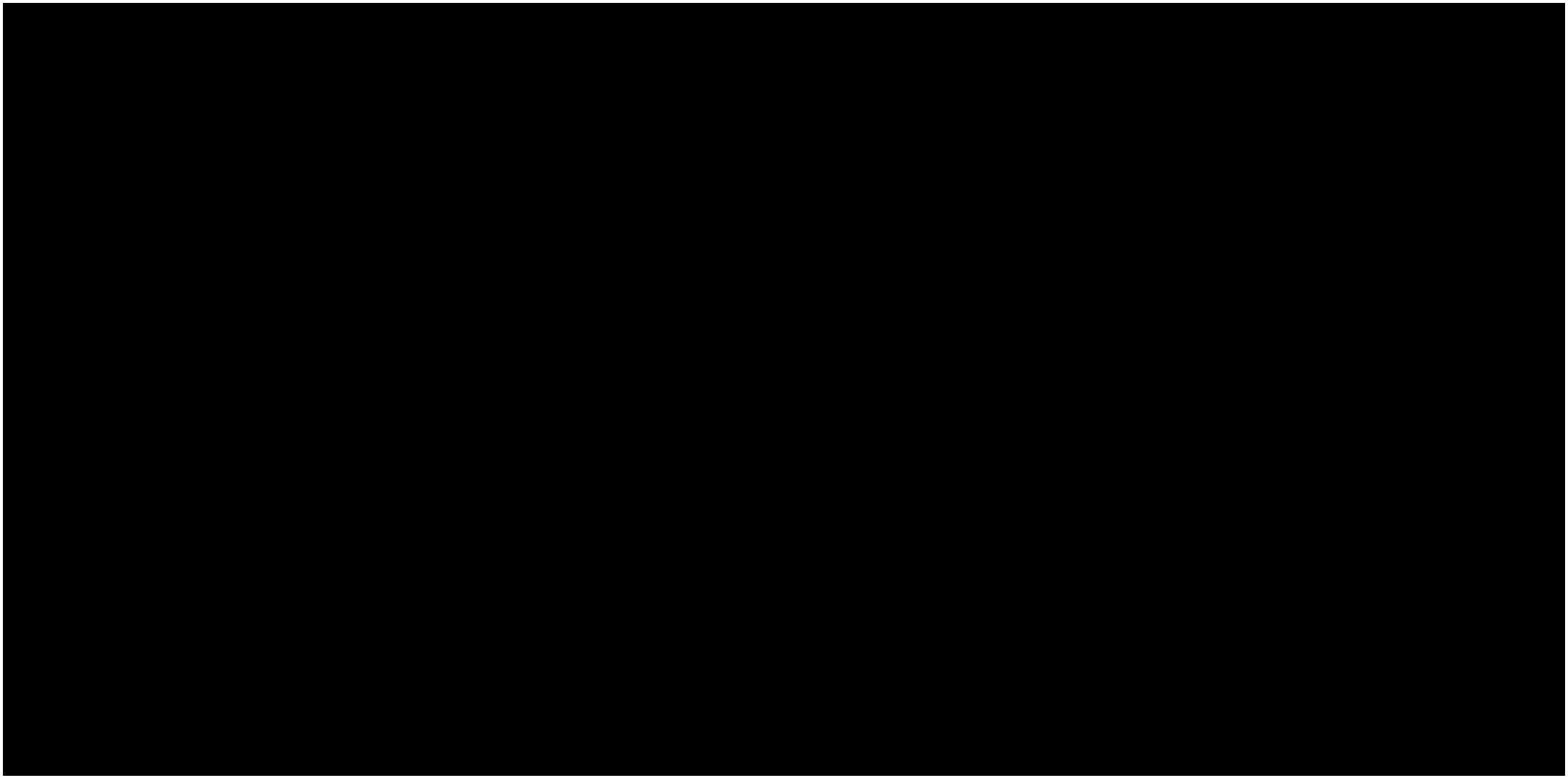




13.1.2 Cohort 2

Trial Period:	Screening Phase	Baseline Assessments	Monotherapy	Combination Treatment Cycles[45]					End of Treatment	Post-Treatment	
Treatment Cycle is defined according to Pembrolizumab 3-week cycle:	Screening (Visit 1)	D1 Pre-dose	D1-D5	1	2	3	4	5-34 every two cycles ± 3	Discontinuation (± 14 days)	Safety Follow-up	Survival Follow-up[46,47]
Scheduling Window (Days)[48]:	-21 to 0	-3 to 1 Pre-dose	± 3	+4	± 3	± 3	± 3		At time of discontinuation	90 days post discontinuation	Every 12 weeks[49] (± 4 weeks)
Administrative Procedures											
Informed Consent	X[50]										
Inclusion/Exclusion Criteria	X										
Demographics and Medical History	X										
[redacted]	X										
Prior and Concomitant Medication Review[52]	X	X	X	X	X	X	X	X	X	X	
Clinical Procedures/Assessments											
Review Adverse Events[53]	X	X	X	X	X	X	X	X	X	X	
12-Lead Electrocardiogram (ECG)	X		X[54]	X[55]					X	X	
Full PE	X								X		
Directed Physical Examination			X[56]		X[57]	X[57]	X[57]	X[12]			
Vital Signs[58]	X	X	X[59]	X[60]	X[60]	X[60]	X[60]	X[60]	X		
Weight[61]		X		X	X	X	X	X			
Height	X										
ECOG performance status[62]	X			X	X	X	X	X	X		
BL-8040 administration			X[63]	X[64]	X[64]	X[64]	X[64]	X[64]			
Pembrolizumab Administration[65]				X	X	X	X	X			

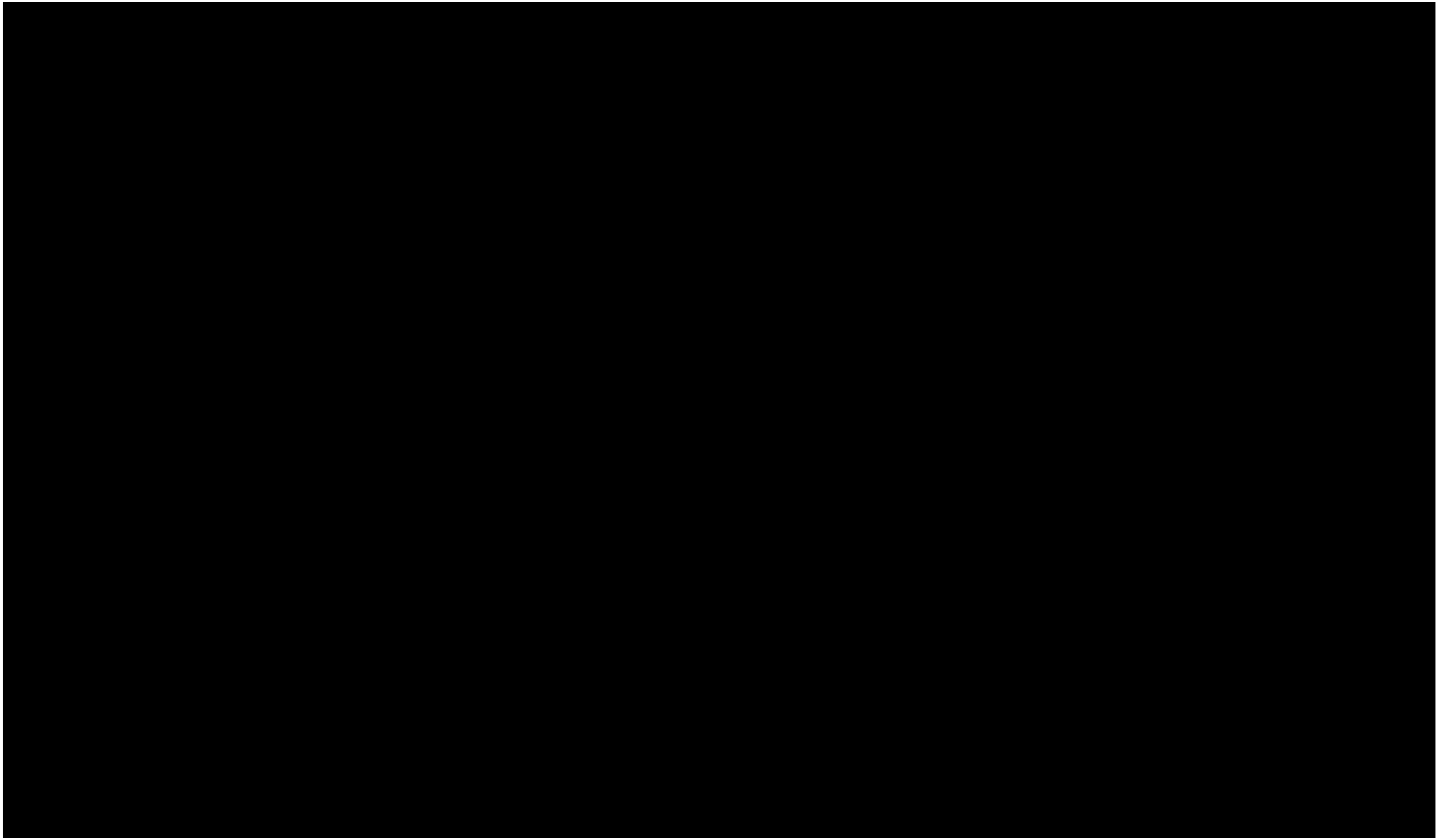
Trial Period:	**Screening Phase**	**Baseline Assessments**	**Monotherapy**	**Combination Treatment Cycles[45]**					**End of Treatment**	**Post-Treatment**	
Treatment Cycle is defined according to Pembrolizumab 3-week cycle:	**Screening (Visit 1)**	**D1 Pre-dose**	**D1-D5**	**1**	**2**	**3**	**4**	**5-34 every two cycles ± 3**	**Discontinuation (± 14 days)**	**Safety Follow-up**	**Survival Follow-up[46,47]**
Scheduling Window (Days)[48]:	**-21 to 0**	**-3 to 1 Pre-dose**	**± 3**	**+4**	**± 3**	**± 3**	**± 3**		**At time of discontinuation**	**90 days post discontinuation**	**Every 12 weeks[49] (± 4 weeks)**
Chemotherapy				Starting on day 1 cycle 1 of Pembrolizumab, Chemotherapy will be provided **every two weeks:** ONIVYDE 70 mg/m^2, with leucovorin 400 mg/m^2 and fluorouracil 2400 mg/m^2 over 46 hours every 2 weeks							
Post-study Anti-Cancer Therapy Status										X	X
Survival Status											X
Laboratory Procedures/Assessments: Analysis performed by LOCAL laboratory											
Pregnancy Test – Serum or Urine[66]		X			X		X	X			
PT/INR and aPTT	X[67]										
CBC with Differential	X[67]		X[68]	X[69]	X[70]	X[70]	X[70]	X[70]	X	X[71]	
Chemistry Panel	X[67]			X[72]	X[72]	X[72]	X[72]	X[72]	X	X[71]	
Urinalysis	X[67]										
T3 (free or total), freeT4 and TSH	X[67]			X[73]	X[73]		X[73]		X	X[71]	

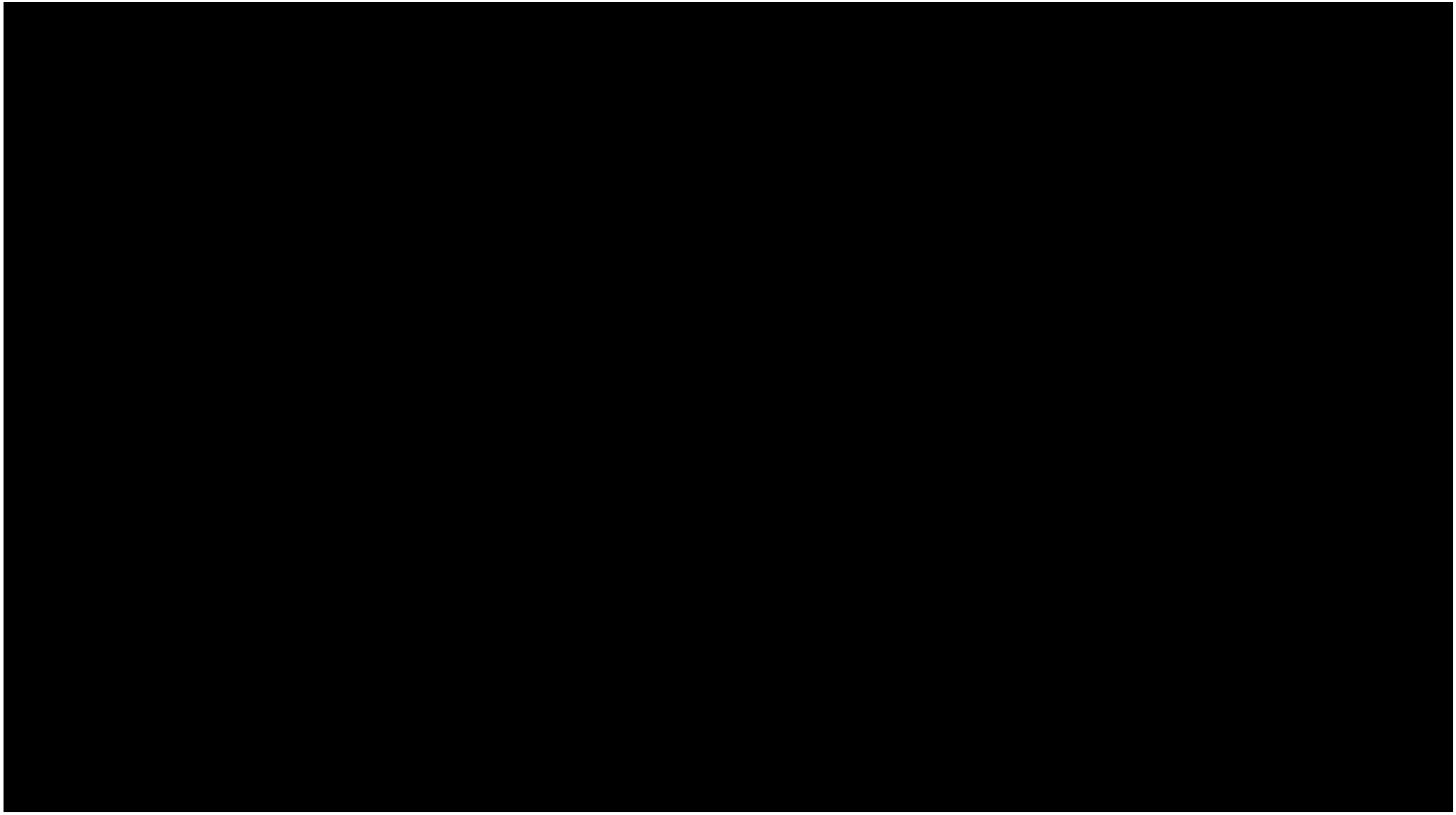
[redacted]

Trial Period:	Screening Phase	Baseline Assessments	Monotherapy	Combination Treatment Cycles[45]					End of Treatment	Post-Treatment	
Treatment Cycle is defined according to Pembrolizumab 3-week cycle:	Screening (Visit 1)	D1 Pre-dose	D1-D5	1	2	3	4	5-34 every two cycles ± 3	Discontinuation (± 14 days)	Safety Follow-up	Survival Follow-up[46,47]
Scheduling Window (Days)[48]:	-21 to 0	-3 to 1 Pre-dose	± 3	+4	± 3	± 3	± 3		At time of discontinuation	90 days post discontinuation	Every 12 weeks[49] (± 4 weeks)

[redacted]

[redacted]





13.2 APPENDIX B - EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Eastern Cooperative Oncology Group (Zubrod-ECOG)[1,2]	
Description	**Grade**
Fully active, able to carry on all pre-disease activities without restriction.	0
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.	1
Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care, confirmed to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4

[1]Zubrod, C.G., et al. *Appraisal of Methods for the Study of Chemotherapy of Cancer in Man*. Journal of Chronic Diseases, 11:7-33, 1960.

[2]Oken, M.M., et al. *Toxicity and response criteria of the Eastern Cooperative Oncology Group*. Am J Clin Oncol (CCT) 5: 649-655, 1982