Clinical Study Protocol

Title: A Phase 1/2, Multicenter, Single-Arm, Open-Label, Dose-Escalation Study of Birinapant in Combination with Pembrolizumab (KEYTRUDA™) in Patients with Relapsed or Refractory Solid Tumors

Date: 16 August 2018

NCT number: NCT02587962

TITLE PAGE

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Study Title:	A Phase 1/2, Multicenter, Single-Arm, Open-Label, Dose-Escalation Study of Birinapant in Combination with Pembrolizumab (KEYTRUDA™) in Patients with Relapsed or Refractory Solid Tumors
Sponsor:	Medivir AB Box 1086 141 22 Stockholm Phone: + (46) 08 546 831 00
Investigational Product:	Birinapant Injection and Pembrolizumab (KEYTRUDA™)
Indication:	Relapsed or refractory solid malignant tumors
Phase:	Phase 1/2
Protocol Version:	V 5.0 incl. amendment 04
Protocol Date:	16 Aug 2018

Statement of Compliance

This clinical study will be conducted in compliance with the protocol, the Guidelines of the World Medical Association Declaration of Helsinki (2013), International Conference on Harmonization (ICH) Good Clinical Practice (GCP), and applicable regulatory requirements.

Confidentiality Statement

The confidential information in the following document is provided to you as an Investigator, potential Investigator, or consultant for review by you, your staff and applicable ethical review committee or institutional review board. By accepting this document, you agree the information contained herein will not be disclosed to others, without written authorization from Medivir AB, except to the extent necessary to obtain informed consent from those persons to whom the study drug is administered.

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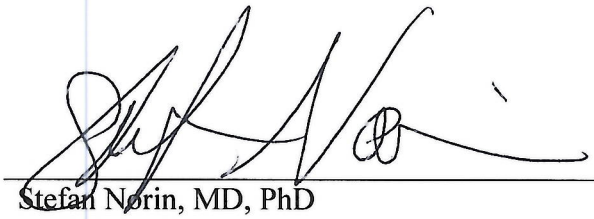
PROTOCOL APPROVAL

Protocol Title: A Phase 1/2, Multicenter, Single-Arm, Open-Label, Dose-Escalation Study of Birinapant in Combination with Pembrolizumab (KEYTRUDA™) in Patients with Relapsed or Refractory Solid Tumors

I, the undersigned, have read this original protocol and agree that it contains all necessary information required to conduct the study.



07-SEP-2018

Stefan Norin, MD, PhD
Associate Director Clinical R&D,
Medivir AB

Date

SYNOPSIS

Sponsor: Medivir AB

Study drug: Birinapant Injection (hereafter referred to as birinapant) and pembrolizumab

Title of Study: A Phase 1/2, Multicenter, Single-Arm, Open-Label, Dose-Escalation Study of Birinapant in Combination with Pembrolizumab (KEYTRUDA™) in Patients with Relapsed or Refractory Solid Tumor

Protocol Number: BPT-201 v 4.0 incl. amendment 03

Number of Centers Planned: Approximately 10 sites

Phase of development: Phase 1/2

Study Objectives:

Dose Escalation Phase

Primary Objective:

To determine the safety and tolerability of the recommended phase 2 dose (RP2D) of birinapant when given in combination with pembrolizumab IV

Secondary Objective:

To assess preliminary efficacy of the combination of pembrolizumab and birinapant in patients with relapsed or refractory cancer by effects on tumor size as measured by imaging (CT or MRI) assessed by RECIST 1.1

Exploratory Objectives:

1. To assess preliminary efficacy of the combination of pembrolizumab and birinapant in patients with relapsed or refractory cancer by effects on tumor size as measured by imaging (CT or MRI) assessed by iRECIST
2. To determine the pharmacodynamic markers of birinapant and of pembrolizumab when given in combination at the schedule and dose as defined by the protocol, to include but not be limited to mechanism of action (inhibition of cIAP1), and of immune surveillance and activation.
3. To assess biomarkers that might predict for responders to the combination treatment and allow comparison to know potential predictive biomarkers of pembrolizumab response
4. To evaluate birinapant pharmacokinetics in plasma when administered in combination with pembrolizumab.

Dose Expansion Phase

Primary Objective

The primary objective in each of the cohorts is as follows:

1. To determine whether the combination of pembrolizumab and birinapant has sufficient antitumor activity, as assessed by ORR, against colorectal cancer to warrant more extensive development.
2. To determine whether the combination of pembrolizumab and birinapant has sufficient antitumor activity, as assessed by ORR against ovarian cancer to warrant more extensive development.
3. To determine whether the combination of pembrolizumab and birinapant has sufficient antitumor activity, as assessed by ORR against cervical cancer to warrant more extensive development.
4. To determine the safety and tolerability of the RP2D of birinapant when given in combination with pembrolizumab to patients in the various solid tumors cohort

Secondary Objectives

1. To assess the safety and tolerability of the combination of pembrolizumab and birinapant; overall and in the defined tumor types, colorectal cancer, ovarian cancer and cervical cancer.
2. To assess efficacy of the combination of pembrolizumab and birinapant in the defined tumor types by effects on tumor response, including CBR, time to response and duration of response, assessed by RECIST v1.1
3. To assess efficacy of the combination of pembrolizumab and birinapant in the defined tumor types by effect on overall survival
4. To assess efficacy of the combination of pembrolizumab and birinapant in the defined tumor types by effect on progression free survival.

Exploratory Objectives

1. To assess efficacy of the combination of pembrolizumab and birinapant in the defined tumor types by effects on tumor response, including; CBR, time to response, duration of response, iBOR, duration of iBOR and time to iCPD, assessed by iRECIST
2. To assess the pharmacodynamic markers of birinapant and of pembrolizumab when given in combination at the schedule and dose as defined by the protocol, to include but not to be limited to mechanism of action (inhibition of cIAP1), and of immune surveillance and activation.
3. To determine biomarkers that might predict for response and/or indicate response to the combination treatment and allow comparison to known potential predictive biomarkers of pembrolizumab response.
4. To evaluate birinapant pharmacokinetics in plasma when administered in combination with pembrolizumab

Number of Patients Planned: Up to 24 patients in the dose-escalation phase. The dose expansion phase will comprise of four patient cohorts totaling up to 111 patients defined as follows:

- Colorectal cancer (28 patients)
- Ovarian cancer (27 patients)
- Cervical cancer (26 patients)
- Various solid tumors (30 patients, including 5 patients with each of the following 6 tumor types: [Small cell lung cancer; Cholangiocarcinoma; Gastroesophageal carcinoma; Mesothelioma; Head and Neck Squamous Cell Carcinoma (HNSCC)-checkpoint inhibitor-naïve; and HNSCC checkpoint inhibitor-experienced]

Predefined interim analyses for futility and safety will be conducted in each of the cohorts in colorectal cancer, ovarian cancer and cervical cancer to limit undue exposure before further inclusion into a given cohort. The design of the various solid tumors cohort will limit undue exposure in any of the selected tumor types by limiting the number of enrolled patient to five in each tumor type.

Selection of Study Population:

Inclusion Criteria: All inclusion criteria for the study are listed below. **Unless otherwise stated, inclusion criteria apply to all phases and cohorts in the study**. Patients will be eligible for study participation if they meet ALL of the following inclusion criteria, applicable for the cohort/tumor type, after patient has provided written informed consent.

1. The patient is male or female ≥ 18 years of age on the day of signing informed consent.
2. The patient is able to understand and voluntarily sign a written informed consent, and is willing and able to comply with the protocol requirements.
3. The patient must have a histologically confirmed solid malignancy that is metastatic or unresectable and for which standard curative or palliative measures do not exist or are no longer effective. Patients with

tumors with mutations for which there are FDA-approved therapies must have progressed following these therapies in order to be eligible for this study. Patients with metastatic colorectal cancer should have progressed on prior fluoropyrimidine-based therapies, and have no curative therapies available to them, in order to be eligible for this study. Colorectal cancer patients should be assessed for microsatellite instability (MSI) status as per the local site routines. (*Dose Escalation Phase only*)

4. Patients must have measurable disease based on RECIST 1.1 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. Patients must have an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1 at screening.
6. Patients must have a life expectancy of greater than 12 weeks.
7. Patients must have amylase and lipase values < ULN
8. Patients must demonstrate adequate organ function as defined in Table 1.. All screening labs should be performed within 10 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5xULN **OR** ≥60 mL/min for patient with creatinine levels >1.5x institutional ULN
Hepatic	
Total bilirubin	≤1.5xULN **OR** Direct bilirubin ≤ULN for patients with total bilirubin levels >1.5xULN), unless known Gilbert's Syndrome has been diagnosed
AST (SGOT) and ALT (SGPT)	≤2.5xULN OR ≤5.0xULN for patients with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5xULN unless patient 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 patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a] Creatinine clearance should be calculated per institutional standard.	

9. Female patients of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

10. Female patients of childbearing potential must be willing to use an adequate method of contraception for the course of the study through 120 days after the last dose of study medication.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient.

11. Male patients with female partners of childbearing potential 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. *(Not applicable for ovarian cancer cohort or cervical cancer cohort)*

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient.

12. An tumor tissue sample for PD-L1 biomarker analysis from archival material, a newly obtained core or excisional biopsy is available for submission. Repeat samples may be required if adequate tissue is not provided.
13. Have resolution of toxic effect(s) of the most recent prior chemotherapy to Grade 1 or less (except neuropathy or alopecia; see Exclusion criteria below). If patients received major surgery or radiation therapy of > 30 Gy, they must have recovered from the toxicity and/or complications from the intervention.

Dose expansion phase cohort-specific inclusion criteria

14. Patients with metastatic colorectal cancer with no available therapy options that are known to provide clinical benefit per institutional standard of care. Patients with tumors with mutations for which there are available therapies that are known to provide clinical benefit, as defined by national authority and/or ratified by national guidelines or equivalent, must have progressed following these therapies in order to be eligible for this study. (*colorectal cancer cohort only*)
15. Patients with histological or cytologically confirmed metastatic colorectal cancer which is Microsatellite Stable (MSI-Stable) accordingly to local laboratory testing. (*colorectal cancer cohort only*)
16. Patients must have a histologically confirmed epithelial ovarian cancer, primary peritoneal cancer or fallopian tube solid tumor cancer that is locally advanced or metastatic with no available therapy options that are known to provide clinical benefit per institutional standard of care. Patients with tumors with mutations for which there are available therapies that are known to provide clinical benefit, as defined by national authority and/or ratified by national guidelines or equivalent, must have progressed following these therapies in order to be eligible for this study. (*ovarian cancer cohort only*)
17. Patients must have histologically or cytologically confirmed cervical squamous cell carcinoma that is locally advanced or metastatic with no available therapy options that are known to provide clinical benefit per institutional standard of care. Patients with tumors with mutations for which there are available therapies that are known to provide clinical benefit, as defined by national authority and/or ratified by national guidelines or equivalent, must have progressed following these therapies in order to be eligible for this study (c*ervical cancer cohort only*)
18. Patients must have histologically or cytologically confirmed head and neck squamous cell carcinoma that is locally advanced or metastatic with no available therapy options that are known to provide clinical benefit per institutional standard of care. Patients with tumors with mutations for which there are available therapies that are known to provide clinical benefit, as defined by national authority and/or ratified by national guidelines or equivalent, must have progressed following these therapies in order to be eligible for this study (*various solid tumors cohort: head and neck squamous cell carcinoma groups only*).
19. Patients with head and neck squamous cell carcinoma who are to participate in the group of checkpoint inhibitor experienced patients must have received prior therapy with an anti-PD-1 or anti-PD-L1 antibody, administered either as monotherapy, or in combination with other therapies. Patients must have received at least two doses of an approved anti-PD-1/anti-PD-L1 antibody and have experienced documented radiographic progression of disease by RECIST v1.1. The initial evidence of disease progression is to be confirmed by a second assessment no less than four weeks from the date of the first documented disease progression in the absence of rapid clinical progression. The date for documentation of initial progression will be considered the date for disease progression. Progressive disease must have been documented during or within 12 weeks after last dose of such treatment. (*various solid tumors cohort head and neck squamous cell carcinoma, checkpoint inhibitor experienced group only*).
20. Patients must have histologically or cytologically confirmed small cell lung carcinoma that is locally

advanced or metastatic with no available therapy options that are known to provide clinical benefit per institutional standard of care. Patients with tumors with mutations for which there are available therapies that are known to provide clinical benefit, as defined by national authority and/or ratified by national guidelines or equivalent, must have progressed following these therapies in order to be eligible for this study (v*arious solid tumors cohort, SCLC group only*)

21. Patients must have histologically or cytologically confirmed cholangiocarcinoma that is locally advanced or metastatic with no available therapy options that are known to provide clinical benefit per institutional standard of care. Patients with tumors with mutations for which there are available therapies that are known to provide clinical benefit, as defined by national authority and/or ratified by national guidelines or equivalent, must have progressed following these therapies in order to be eligible for this study (v*arious solid tumors cohort, cholangiocarcinoma group only*)

22. Patients must have histologically or cytologically confirmed pleural mesothelioma that is locally advanced or metastatic with no available therapy options that are known to provide clinical benefit per institutional standard of care. Patients with tumors with mutations for which there are available therapies that are known to provide clinical benefit, as defined by national authority and/or ratified by national guidelines or equivalent, must have progressed following these therapies in order to be eligible for this study (v*arious solid tumors cohort, mesothelioma group only*)

23. Patients must have histologically or cytologically confirmed carcinoma of the esophagus including the gastroesophageal junction that is locally advanced or metastatic with no available therapy options that are known to provide clinical benefit per institutional standard of care. Patients with tumors with mutations for which there are available therapies that are known to provide clinical benefit, as defined by national authority and/or ratified by national guidelines or equivalent, must have progressed following these therapies in order to be eligible for this study (v*arious solid tumors cohort, gastroesophageal carcinoma group only*)

Exclusion Criteria: All exclusion criteria for the study are listed below. **Unless otherwise stated, exclusion criteria apply to all phases and cohorts in the study.** Patients are excluded from participating in this study if one or more of the following criteria, applicable for the specific cohort/tumor type, are met:

1. Patients who have 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 adverse events due to agents administered more than 4 weeks earlier prior to study Day 1.
2. Patients who have had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who have not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

   Note: Patients with ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia are an exception to this criterion and may qualify for the study.

   Note: If patients have received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

3. Patients who are currently participating and receiving study therapy or who have participated in a study of an investigational agent and received study therapy or who have used an investigational device within 4 weeks of the first dose of treatment.

4. Patients who have received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways) or if the patient has previously participated in Merck MK-3475 clinical trials. (*Not applicable for various solid tumors cohort, head and neck squamous cell carcinoma, checkpoint inhibitor experienced group*)

5. Patients with known active central nervous system (CNS) metastases and/or carcinomatous meningitis.

   Note: Patients 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 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 systemic steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

6. Patients with a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

7. Patients who have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to birinapant or pembrolizumab or their constituents.
8. Patients requiring the use of anti-tumor necrosis factor (anti-TNF) therapies, such as infliximab, or patients who have received treatment with anti-TNF therapies within 5 half-lives of the drug.
9. Patients with a diagnosis of immunodeficiency or who are receiving systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days before the first dose of study drug. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
10. Patients with an uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure, hypertension, unstable angina pectoris, cardiac arrhythmia, autoimmune or inflammatory diseases, or psychiatric illness that would limit compliance with study requirements.
11. Patients with an active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.

12. Patients who have evidence of active, non-infectious pneumonitis. Patients with a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.

13. Patients with a history of interstitial lung disease.

14. Patients who are 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. Pregnant women and men who expect to conceive a child are excluded from this study because birinapant and pembrolizumab are agents with unknown potential for teratogenic or abortifacient effects in humans. Because there is an unknown risk for AEs in nursing infants secondary to treatment of the mother with birinapant and pembrolizumab, breastfeeding should be discontinued if the mother is treated on this study.
15. Patients who have a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies), or active Hepatitis B (e.g., HBsAg reactive). Patients with active Hepatitis C (e.g., HCV RNA [qualitative] is detected).
16. Patients who have received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.
17. Patients who have disease that is suitable for local therapy administered with curative intent.
18. Patients who have received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including G-CSF, GM-CSF or recombinant erythropoietin)

within 4 weeks prior to study Day 1.

19. Patients who have a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating investigator.

20. Patients who have known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

21. Patients who have severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.

22. Patient who have received anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways) *(various solid tumors cohort, head and neck squamous cell carcinoma checkpoint inhibitor experienced group only)*

23. Patient who have previously received birinapant treatment

Study Drug Dose, Mode of Administration, and Administration Rate:

During a 21-day treatment cycle, patients will receive 200 mg pembrolizumab intravenously (IV) on Day 1 and IV birinapant on Days 1 and 8. A week without treatment (i.e., Days 15-21) will follow the second week of treatment, immediately after which the next 21-day treatment cycle will start. All doses will be administered via a 30-minute (+10 min) IV infusion. Pembrolizumab will be administered first on Day 1. The birinapant infusion will begin 30 minutes (+ 10 minutes) following the completion of the pembrolizumab infusion on Day 1. Patients will be eligible to receive study medication for 35 treatment cycles or until documentation of disease progression or unacceptable toxicity.

Study drug will be administered in the arm opposite to the site of blood-sample collection or via other venous access as appropriate.

Dose-escalation phase

Inter-patient dose escalation of birinapant will proceed at the birinapant dose indicated in the dose-escalation table, below. A minimum of 3 and up to 6 evaluable patients will be enrolled per dose level.

Dose-Escalation Schedule	
Dose Level	Pembrolizumab + Birinapant (per 21-day cycle)
Level -1	200 mg pembrolizumab on Day 1 + **birinapant 2.8 mg/m^2/week** on Days 1 and 8
Level 1	200 mg pembrolizumab on Day 1 + **birinapant 5.6 mg/m^2/week** on Days 1 and 8
Level 2	200 mg pembrolizumab on Day 1 + **birinapant 11 mg/m^2/week** on Days 1 and 8
Level 3	200 mg pembrolizumab on Day 1 + **birinapant 17 mg/m^2/week** on Days 1 and 8
Level 4	200 mg pembrolizumab on Day 1 + **birinapant 22 mg/m^2/week** on Days 1 and 8

The inter-patient dose escalation of birinapant will be based on the number of patients that experience a protocol-defined dose-limiting toxicity (DLT). A DLT is a clinically significant event attributed to birinapant, pembrolizumab, or the combination of the 2 study drugs, during the first cycle of drug therapy and is defined as follows:

Non-hematological toxicity:

- Common Toxicity Criteria for Adverse Event (CTCAE; v4.03) Grade 3 nausea, vomiting, or diarrhea despite maximal anti-emetic or anti-diarrheal treatment and lasting > 48 hours; or Grade 4 vomiting or diarrhea;

- ≥ Grade 3 other non-hematological toxicity, excluding isolated laboratory abnormalities without clinical sequelae, except for the following:
    - Prolonged (> 7 days) serum amylase or lipase elevation;
    - Prolonged (> 7 days) aspartate aminotransferase (AST) elevation;
    - Prolonged (> 7 days) alanine aminotransferase (ALT) elevation;

    All of which will be considered dose limiting.

Hematological toxicity:

- Grade 4 neutropenia;
- Grade ≥ 3 neutropenia with fever > 38.3°C or > 38°C (> 100.9°F or > 100.4°F) for more than one hour;
- Grade ≥ 3 thrombocytopenia with bleeding.

If Day 8 of treatment is held due to toxicity, then the event will be considered a DLT. A prolonged delay (> 2 weeks) in initiating Cycle 2 secondary to drug-related toxicity may be considered a DLT. Events related to disease progression, intercurrent illness, or concomitant medication will not constitute a DLT. If a patient experiences a DLT that is deemed related to birinapant, the dose of birinapant may be reduced and the patient may remain on study.

The decisions on when to dose escalate birinapant for each Dose Level are indicated in the table below.

Number of Patients with DLT at a Given Dose Level	Escalation-decision Rule
Zero of 3 to 6	Enter 3 to 6 patients at the next dose level.
1 out of 3 to 6	Enter up to a total of 6 patients at this dose level. • If 1 of these 3 to 6 patients experiences a DLT, proceed to the next dose level, if the next highest dose has not already been declared intolerable*. • If 1 of these 3 to 6 patients experiences a DLT and the next highest dose has already been declared intolerable, enroll a minimum of 6 patients at this dose level.
≥ 2	Dose escalation will be stopped. This dose level may be declared the maximally administered dose (highest dose administered) and may be declared intolerable. Three additional patients may be entered at the next lowest dose level if only 3 patients were treated previously at that dose.

*Defined as ≥2 patients from 3-6 experiencing a DLT

Safety data at each dose-escalation level will be reviewed by a Safety Review Committee (SRC), which will consist of representatives from the Sponsor and the study sites before each dose escalation. A separate safety review will be performed by the SRC to determine the recommended phase 2 dose (RP2D) of the combination of birinapant and pembrolizumab and to begin the dose-expansion phase of the study.

Dose-expansion phase

Once the RP2D of birinapant combined with pembrolizumab is defined, additional patients with relapsed or refractory carcinoma will be enrolled in the dose-expansion phase of the study.

Dose Level	Pembrolizumab + Birinapant (per 21-day cycle)
Expansion	200 mg pembrolizumab on Day 1+ **birinapant at the RP2D mg/m^2/week** on Days 1 and 8

The dose expansion phase will comprise 4 cohorts of 26-30 patients.

The 4 cohorts will include the following:

- Colorectal cancer
- Ovarian Cancer
- Cervical cancer
- Various solid tumors (30 patients, including 5 patients with each of the following 6 tumor types: Head and Neck Squamous Cell Carcinoma (HNSCC)-checkpoint-inhibitor naïve; and HNSCC checkpoint-inhibitor experienced; Gastroesophageal carcinoma; Mesothelioma; Small cell lung cancer (SCLC); Cholangiocarcinoma

Predefined interim analyses for futility and safety will be conducted in each of the cohorts in colorectal cancer, ovarian cancer and cervical cancer to limit undue exposure before further inclusion into a given cohort. The design of the various solid tumors cohort will limit undue exposure in any of the selected tumor types by limiting the number of enrolled patient to five in each tumor type. During the dose-expansion phase of the study the SRC will be replaced by an independent Data Monitoring Committee (DMC). The DMC will meet approximately biannually to review the complete analysis of combined observed toxicities including emerging safety reports and reported SAEs. Specifically, they will monitor AEs and SAEs related to the treatments received in accordance with the recommendations of performing a clinical study of an IMP.

Duration of Patient Participation:

Patients are to receive study treatment for up to 35 treatment cycles or until documented progressive disease (PD) or unacceptable toxicity (See Section 6.1).

General Design and Methodology:

This is a Phase 1/2, multicenter, single-arm, open-label, dose-escalation study in patients with relapsed or refractory solid tumors.

The study will determine the recommended Phase 2 birinapant dose in combination with pembrolizumab and will assess the tolerability, safety, pharmacokinetics, and pharmacodynamics of this birinapant dose in combination with pembrolizumab in male and female patients with relapsed or refractory solid tumors. Study visits to investigate the objectives of the study will be conducted as follows:

- Screening is conducted ≤ 28 days before dosing.
- Patients will be required to attend the investigative unit for screening to confirm eligibility. Eligible patients will be required to return to the investigative unit to receive, via IV infusion, 200 mg pembrolizumab on Day 1 and the assigned dose of birinapant on Days 1 and 8 of every 21-day cycle.
- The active treatment phase commences on Day 1 and patients will be treated on a 21-day cycle for a maximum of

35 cycles, until disease progression or unacceptable toxicity. While on active treatment study assessments to monitor safety and pharmacodynamics will be conducted.

- Patients will also be required to return to the clinic for radiological tumor assessment (according to RECIST v 1.1 and iRECIST) at the end of the third week (± 3 days) of every notional third 21-day cycle (every 9 weeks).
- A follow-up visit to monitor safety, including ECOG performance status, will be conducted 30 days after study-drug discontinuation.
- For patients that discontinue therapy for reasons other than progressive disease, a follow-up visit to confirm/document disease progression or initiation of a new therapy for patients' disease must be performed every 30 days after study-drug discontinuation.
- A survival follow-up telephone contact visit must also be completed every 3 months to confirm survival status and the date of the next cancer therapy and type of therapy.

Study Parameters:

Dose escalation phase:

Primary Endpoint

Safety and tolerability, will be assessed by monitoring:

- Incidence and severity of adverse events (AEs) experienced by patients receiving birinapant in combination with pembrolizumab.
- Incidence and magnitude of clinically significant changes in clinical laboratory parameters experienced by patients receiving birinapant and pembrolizumab, or overall pattern of shifts by treatment group in individual laboratory values suggestive of possible trends, but not necessarily establishing, clinical abnormality.
- Incidence and severity of clinically significant adverse findings in vital signs, electrocardiogram (ECGs), and other physical examination parameters identified among patients receiving birinapant and pembrolizumab.

Secondary Endpoints

Efficacy:

Tumor response and progression evaluated using RECIST v 1.1

Measures defined by the ORR, will be assessed through RECIST v 1.1 until response or progression and will be subsequently analyzed through iRECIST as an exploratory endpoint.

Exploratory Endpoints

Efficacy:

Tumor response and progression evaluated using iRECIST.

a) iBOR

b) Duration of iBOR

c) Time to iCPD

Efficacy, as defined by the ORR, will be assessed through RECIST v 1.1 until response or progression and will be subsequently analyzed through iRECIST (iCR, or iPR or iSD or after iUPD iCR, iPR or iSD or iCPD). iBOR will also be assessed.

Overall survival will also be assessed.

Pharmacokinetics:

The pharmacokinetics of birinapant in plasma when administered in combination with pembrolizumab will be evaluated.

Pharmacodynamics:

Translational biomarker assessments obtained from blood will be evaluated at a central laboratory:

- Pre- and post-treatment levels in the expression of cIAP1
- Cytokines levels such as GM-CSF, IFNγ, IL10, IL2, IL3, IL4, IL5, IL6, IL7, IL8, MIP-1α, MIP-1β, MCP-1, TNFα, and TNFβ
- Gene expression analysis by Nanostring

Blood samples looking at $CD3^+$, $CD4^+$, $CD8^+$, and $CD19^+$ cell counts as well as absolute neutrophil count and absolute lymphocyte count will be analyzed by each investigational site's local laboratory.

Translational biomarker assessments such as listed below, will be evaluated from archival or fresh pre-treatment biopsy samples, and optional post-treatment tumor biopsy samples, which will be analyzed at central laboratory:

- Pre-treatment PD-L1 levels by immunohistochemistry
- Gene expression analysis by Nanostring
- cIAP1 expression by immunohistochemistry
- Inhibition of apoptosis protein (IAP) gene copy number
- Tumor infiltrating lymphocytes (TILs) CD3, CD4, CD8, CD20 and FOXP3

Note that the exploratory biomarker analyses listed are planned but may not be conducted if deemed as obsolete during later stages of the study; other exploratory analyses may be added based on emerging new findings.

Dose expansion phase:

Primary Endpoint

The primary endpoint in each of the cohorts is as follows:

1. The overall response assessed through RECIST v.1.1 until response or progression in colorectal cancer
2. The overall response assessed through RECIST v1.1 until response or progression in ovarian cancer
3. The overall response assessed through RECIST v1.1 until response or progression in cervical cancer
4. Safety and tolerability in cohort with various solid tumor types will be assessed by monitoring:

- Incidence and severity of adverse events (AEs) experienced by patients receiving birinapant in combination with pembrolizumab.
- Incidence and magnitude of clinically significant changes in clinical laboratory parameters experienced by patients receiving birinapant and pembrolizumab, or overall pattern of shifts by treatment group in individual laboratory values suggestive of possible trends, but not necessarily establishing, clinical abnormality.
- Incidence and severity of clinically significant adverse findings in vital signs, electrocardiogram (ECGs), and other physical examination parameters among patients receiving birinapant and pembrolizumab.

Secondary Endpoints

Safety and tolerability will be assessed in colorectal cancer, ovarian cancer and cervical cancer by monitoring:

- Incidence and severity of adverse events (AEs) experienced by patients receiving birinapant in combination with pembrolizumab.
- Incidence and magnitude of clinically significant changes in clinical laboratory parameters experienced by patients receiving birinapant and pembrolizumab, or overall pattern of shifts by treatment group in individual laboratory values suggestive of possible trends, but not necessarily establishing, clinical abnormality.
- Incidence and severity of clinically significant adverse findings in vital signs, electrocardiogram (ECGs), and other physical examination parameters among patients receiving birinapant and pembrolizumab.

Clinical Activity: Tumor response will be assessed in all four cohorts by monitoring:

- Progression Free Survival (PFS)
- Clinical Benefit Rate (CBR) defined as CR+PR+SD
- Time to response
- Duration of response
- Overall Survival (OS)

Measures of tumor response will be evaluated using RECIST v1.1 until response or progression and will be subsequently analyzed through iRECIST.

Exploratory endpoints

Clinical Activity

Tumor response and progression evaluated in all four cohorts using iRECIST.

- Overall Response
- iBOR
- Duration of iBOR
- Time to iCPD
- Clinical Benefit Rate (CBR) defined as iCR+iPR+iSD
- Time to response
- Duration of response

Pharmacokinetics

The pharmacokinetics of birinapant in plasma when administered in combination with pembrolizumab will be evaluated.

Pharmacodynamics

Translational biomarker assessments obtained from blood will be evaluated at a central laboratory.

- Pre- and post-treatment levels of cIAP1 expression
- Cytokine levels such as GM-CSF, IFNγ, IL10, IL2, IL3, IL4, IL5, IL6, IL7, IL8, MIP-1α, MIP-1β, MCP-1, TNFα, and TNFβ
- Gene expression analysis by Nanostring may be performed

Blood samples looking at CA-125 (for ovarian cancer patients), CEA (for CRC patients), $CD3^+$, $CD4^+$, $CD8^+$, and $CD19^+$ cell counts as well as absolute neutrophil count and absolute lymphocyte count will be analyzed by each investigational site's local laboratory.

Translational biomarker assessments such as listed below, will be evaluated from archival or fresh pre-treatment biopsy samples, and optional post-treatment tumor biopsy samples, which will be analyzed at central laboratory:

- Pre-treatment PD-L1 levels by immunohistochemistry
- Gene expression analysis by Nanostring
- cIAP1 expression by immunohistochemistry
- Inhibition of apoptosis protein (IAP) gene copy number
- Tumor infiltrating lymphocytes (TILs) CD3, CD4, CD8, CD20, FoxP3

The exploratory biomarker analyses listed are planned but may not be conducted if deemed as obsolete during later stages of the study; other exploratory analyses may be added based on emerging new findings. Details regarding the processing and shipping of all pharmacodynamic samples will be outlined in the study specific laboratory manual.

Statistical Considerations:

The analysis of all the clinical activity, safety, pharmacokinetic and pharmacodynamic parameters will be performed by Medivir AB or its designee.

Demographics and Baseline Characteristics

Descriptive statistics will be provided to summarize demographics and baseline characteristics.

Dose Escalation phase:

Primary Endpoint: Safety

The safety and tolerability of pembrolizumab and birinapant will be based on results of DLT incidence, reported SAEs, AEs, vital sign measurements, physical examinations, clinical laboratory information, ECOG performance status, and concomitant medications. Exposure to study drug and reasons for discontinuation will be tabulated. These data will be summarized descriptively for the ITT population overall.

Adverse events will be coded using the current *Medical Dictionary for Regulated Activities* (MedDRA) classification system, and will be summarized by system organ class and preferred term.

Additional safety analyses may be determined in order to most clearly describe toxicity rates and to further define the safety profile of pembrolizumab and birinapant.

Secondary Endpoints: Efficacy

Efficacy, as defined by ORR, will be assessed through RECIST v 1.1 until response or progression. Overall survival will also be assessed.

Results will be summarized descriptively. For parameters measured over time, data and changes from baseline will be summarized for each time point. **Exploratory Endpoints: Efficacy, Pharmacodynamics and Pharmacokinetics**

Efficacy, as defined by the ORR, will be assessed through RECIST v 1.1 until response or progression and will be subsequently analyzed through iRECIST (iCR, or iPR or iSD or after iUPD iCR, iPR or iSD or iCPD). iBOR will also be assessed. Results will be summarized descriptively.

Pharmacodynamic results will be summarized descriptively.

Pharmacokinetics results will be summarized descriptively. Population PK modeling may also be applied.

Dose Expansion phase:

Primary Endpoints:

Cohorts in colorectal cancer, ovarian cancer and cervical cancer: Clinical Activity

The primary objective will be evaluated using Simon's two-stage design. The null hypothesis that the true ORR is (5%, 7% and 10% for colorectal cancer, ovarian cancer and cervical cancer, respectively) will be tested against a one-sided alternative. The design yields a type I error rate of 5% and power of 80% for each of the three indications individually. No correction for multiplicity will be done. In addition to tabulate the result of the statistical tests, results will be summarized descriptively.

Various solid tumors cohort: Safety

The safety and tolerability of pembrolizumab and birinapant will be based on results of reported SAEs, AEs, vital sign measurements, physical examinations, clinical laboratory information, ECOG performance status, and concomitant medications. Safety data will be summarized descriptively. Exposure to study drug and reasons for discontinuation will be tabulated.

Adverse events will be coded using the current *Medical Dictionary for Regulated Activities* (MedDRA) classification system, and will be summarized by system organ class and preferred term.

Additional safety analyses may be determined in order to most clearly describe toxicity rates and to further define the

safety profile of pembrolizumab and birinapant.

Secondary Endpoints:

Cohorts in colorectal cancer, ovarian cancer and cervical cancer: Safety

The safety and tolerability of pembrolizumab and birinapant will be based on results of reported SAEs, AEs, vital sign measurements, physical examinations, clinical laboratory information, ECOG performance status, and concomitant medications. Safety data will be summarized descriptively by cohort and also summarized descriptively over cohorts within each of the two phases of the protocol. Exposure to study drug and reasons for discontinuation will be tabulated.

Adverse events will be coded using the current *Medical Dictionary for Regulated Activities* (MedDRA) classification system, and will be summarized by system organ class and preferred term.

Additional safety analyses may be determined in order to most clearly describe toxicity rates and to further define the safety profile of pembrolizumab and birinapant.

All Cohorts: Clinical Activity

Efficacy, as defined by PFS, CBR, Time to response and Duration of response, will be assessed through RECIST v 1.1 and until response or progression. Overall survival will also be assessed.

Results will be summarized descriptively. For parameters measured over time, data and changes from baseline will be summarized for each time point.

Exploratory Endpoints: Clinical Activity, Pharmacodynamics and Pharmacokinetics

All Cohorts:

Clinical Activity, as defined by PFS, CBR, Time to response and duration of response, iBOR, Duration of iBOR and Time to iCPD, will be assessed through iRECIST. Results will be summarized descriptively.

Pharmacodynamic results will be summarized descriptively.

Pharmacokinetics results will be summarized descriptively. Population PK modeling may also be applied.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADL	Activities of daily living
AE	Adverse Event
ALC	Absolute lymphocyte count
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BCG	Bacillus Calmette–Guérin
BSA	Body surface area
BUN	Blood urea nitrogen
CBC	Complete blood count
CCA	Cholangiocarcinoma
CEA	Carcinoembryonic antigen
CDMS	Clinical Data Management System
CI	Confidence interval
CLcr	Creatinine Clearance
CR	Complete Response
CRS	Cytokine release syndrome
CRC	Colorectal carcinoma
CRO	Clinical Research Organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4
CYP	Cytochrome P450
DLT	Dose limiting toxicity
dMMR	Deficient in mismatch repair
ECG	Electrocardiogram
ECI	Event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form

FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEJ	Gastroesophageal Junction
GFR	Glomerular Filtration Rate
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papillomavirus
HSV	Herpes Simplex Virus
IAP	Inhibitor of Apoptosis Protein
IB	Investigator's Brochure
iBOR	Immune response for immuno-therapeutics (i) Best Overall Response
ICH	International Conference on Harmonization
iCPD	Immune response for immune-therapeutics (i) Confirmed Progressive Disease
IRB	Institutional Review Board
iRECIST	Immune Response Evaluation Criteria in Solid Tumors (Lancet Oncology 18, 143 – 152. 2017)
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
iUPD	Immune response for immuno-therapeutics (i) Unconfirmed Progressive Disease
ITS	Investigator initiated study
ITT	Intent-to-treat
IV	Intravenous
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MM	Malignant Mesothelioma
MPM	Malignant Pleural Mesothelioma
MSI	Microsatellite instability
MSS	Microsatellite stable
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells

NCCN	National Comprehensive Cancer Network
NSAID	Non-steroidal anti-inflammatory drug
NSCLC	Non small cell lung cancer
ORR	Overall Response Rate
OS	Overall survival
pCCA	Perihilar Cholangiocarcinoma
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
P-gp	P-glycoprotein
PK	Pharmacokinetic
PR	Partial Response
PS	Performance Status
Q2W	Every 2 weeks
Q3W	Every 3 weeks
RBC	Red Blood Cell
RIPK1	Receptor interacting protein kinase-1
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SC	Subcutaneous
SCLC	Small cell lung cancer
SMAC	Second mitochondria-derived activator of caspase
SOP	Standard Operating Procedure
SRC	Safety Review Committee
T1DM	Type I diabetes mellitus
TIL	Tumor Infiltrating Lymphocytes
TNF	Tumor necrosis factor
TRAF-2	TNF receptor-associated factor 2
ULN	Upper limit of normal
US	United States
USP	US Pharmacopeia
VZV	Varicella Zoster Virus

WBC	White blood cell count
WHO	World Health Organization
XIAP	X-linked inhibitors of apoptosis protein

INVESTIGATOR STATEMENT

I have read and understood the protocol and agree to conduct this study as detailed herein, in compliance with current Good Clinical Practice[1] (GCP) and the applicable regulatory requirements, and will make every reasonable effort to complete the study within the time designated.

I will provide adequate protocol training to my associates, colleagues, and employees assisting in the conduct of the study. The protocol and all relevant information on the study drug relating to pre-clinical and prior clinical experience, which was furnished by the Sponsor, will be made available to all physicians, nurses and other personnel who participate in the conduct of this study. I will discuss this material with them to assure that they are fully informed regarding the drug(s) and the conduct of the study.

I will obtain approval from, the institutional review board (IRB) for the protocol and Informed Consent Form (ICF) before enrollment of patients in the study. I understand that any modifications to the protocol made during the course of the study must first be approved by the IRB except when such modification is made to remove an immediate hazard to the patient.

I will ensure that a fully executed ICF is obtained from each patient before initiation of any study procedures.

I will report any Serious Adverse Event (SAE), adverse events of clinical interest, overdose, and new cancer that occur during the course of the study in accordance with the procedures described in Section 8.3 and Section 8.4 of the protocol.

I will allow the Sponsor, Medivir AB and its agents, as well as the United States Food and Drug Administration (US FDA) and other regulatory agencies, to inspect study facilities and pertinent records at reasonable times and in a reasonable manner, ensuring patient confidentiality. If I am notified that this study is to be inspected by a regulatory agency, I will notify Medivir AB as soon as possible thereafter.

This document contains information that is privileged or confidential. As such, it may not be disclosed unless specific prior permission is granted in writing by Medivir AB or such disclosure is required by federal or other laws or regulations. Persons to whom any of this information is to be disclosed must first be informed that the information is confidential. These restrictions on disclosure will apply equally to all future information supplied, which is indicated as privileged or confidential.

Medivir AB will have access to any source documents from which Case Report Form (CRF) information may have been generated. The CRF and other data pertinent to this study are the sole property of Medivir AB, which may utilize the data in various ways, such as for submission to government regulatory authorities, or in publication of the results of the study.

Signature of Principal Investigator	Date
Print Name	Site Number

1 INTRODUCTION

1.1 Inhibitors of Apoptosis Proteins and Cancer

The dysregulation of apoptosis is recognized as a fundamental contributor to the pathogenesis of cancer. Apoptosis is a highly-regulated process that enables cells in non-tumor tissues to respond to either external death receptor signals or intracellular stress signals (such as deoxyribonucleic acid (DNA) damage) in order to rapidly eliminate damaged cells through the activation of intracellular caspases. In many tumors however, the ability to undergo apoptosis is impaired and the transformed cell can remain in a viable, pro-survival state, even in the presence of strong pro-apoptotic signals. Therefore, dysregulation of apoptosis in tumors contributes to the malignant phenotype and is associated with resistance to certain chemotherapeutics and biological therapies (Hanahan et al. 2000).

A family of proteins known as the Inhibitors of Apoptosis (IAPs) plays a critical role in blocking the apoptotic signals at multiple points in the apoptotic pathway. The IAP gene family encodes a group of structurally-related proteins (including X-linked inhibitor of apoptosis protein [XIAP], cellular IAP1 [cIAP1], cIAP2, and Melanoma-IAP [ML-IAP]) that can suppress apoptotic cell death (Hunter et al. 2007, LaCasse et al. 2008). Many of the IAP proteins are known to be over-expressed in cancer cells, and can contribute to resistance to apoptosis in response to certain biological and conventional cytotoxic drug therapies (Fesik 2005, Bertrand et al. 2008). Members of the IAP family of proteins including cIAP1, cIAP2, and XIAP can block caspase activation at the cell death receptor pathway level (cIAP1 and cIAP2) and at the last step in the pathway by directly binding to and suppressing caspase-3/7 activity. In addition, cIAP1 and cIAP2 critically regulate nuclear factor-kappa B (NF-κB), leading to the activation of pro-survival canonical NF-κB signaling pathways (Gyrd-Hansen et al. 2010, Fulda 2012).

Dysregulation of IAPs may be critical for the development and progression of certain malignancies. Over-expression of IAPs has been linked to resistance to chemotherapy and radiation in multiple tumor types (Tamm et al. 2000, Janzen et al. 2015), (Eytan et al. 2016))(Eytan et al. 2016). Similarly, there is data demonstrating IAP gene amplification in the majority of tumor types including pancreatic, non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), glioblastoma multiforme, head and neck, cervical, bladder, gastric, ovarian, breast and esophageal tumors, as noted below. The evidence of widespread IAP gene amplification across multiple human tumors underlines the importance of this pathway in mechanisms of oncogenesis and drug-resistance.

The activity of IAPs is regulated by a protein known as a second mitochondria-derived activator of caspases (SMAC) (Du et al. 2000, Verhagen et al. 2000, Condon 2011). SMAC is a natural IAP antagonist that, once released from mitochondria following cellular stress, rapidly antagonizes the IAPs, resulting in caspase activation and apoptosis (Du et al. 2000, Vince et al. 2007). Small molecule SMAC mimetics mimic endogenous SMAC, resulting in the rapid and irreversible initiation of apoptotic cell death. Bivalent SMAC mimetics also potently suppress pro-survival NF-κB pathways (Li et al. 2004, Fesik 2005, Hunter et al. 2007, Petersen et al. 2007, Varfolomeev et al. 2007, Vince et al. 2007, Bertrand et al. 2008, LaCasse et al. 2008, Chen et al. 2009, Ndubaku et al. 2009) . cIAP1 and cIAP2 are critical

components of the Tumor Necrosis Factor (TNF) receptor I complex. This complex initiates canonical NF-κB signaling in response to receptor ligation by TNF. cIAP1 and cIAP2, through their intrinsic E3 ubiquitin ligase activity, catalyze the ubiquitination of several proteins (including cIAP1 itself, cIAP2, and receptor interacting protein kinase-1 [RIPK1]), a necessary modification for the activation of pro-survival NF-κB signaling. Antagonism of TNF receptor-associated factor 2 (TRAF-2)-bound cIAP1 and cIAP2 by SMAC mimetics such as birinapant results in their auto-ubiquitination and subsequent proteasomal degradation (Varfolomeev et al. 2007) (Vince et al. 2007). In the absence of cIAP proteins, ubiquitination does not occur and the non-ubiquitinated RIPK1 promotes the formation of a cytosolic complex (complex II), which includes the adaptor protein FADD, caspase 8, and RIPK1. Complex II mediates the activation of caspase 8, ultimately leading to apoptosis. Thus, SMAC mimetics can switch the function of TNFα from a proinflammatory, pro-survival role to an inducer of cell death.

cIAP1 and cIAP2 proteins are also negative regulators of the non-canonical NF-κB pathway, acting as ubiquitin ligases for the NF-κB Inducing Kinase (NIK) and directing it for proteasomal degradation (Demchenko et al. 2010). On stimulation of the non-canonical NF-κB pathway by the binding of ligands such as CD40L or BAFF, cIAP proteins are recruited to the cell membrane and can no longer ubiquitinate NIK, which is thus allowed to accumulate and then catalyzes NFKB2 p100 to p52 processing and activation of non-canonical signaling (Demchenko et al. 2010). Degradation of cIAP1 by SMAC mimetics such as birinapant also prevents ubiquitination and degradation of NIK and leads to activation of alternative NF-κB signaling, and increased expression of target genes including TNFα and other cytokines. Enhanced production of TNFα can then further catalyze TNF-dependent apoptosis as described above.

Activation of non-canonical NF-κB signaling by SMAC mimetics induces co-stimulatory activity in T cells and induces dendritic cell maturation leading to enhanced immune activation (Dougan et al. 2010, Muller-Sienerth et al. 2011, Knights et al. 2013). Proinflammatory cell death induction by SMAC mimetic also elicits the adaptive immune response, leading to increased Tumor Infiltrating Lymphocytes (TILs), interferon gamma production and activation of CD8 positive cytotoxic lymphocytes (Emeagi et al. 2012). The enhanced production of inflammatory cytokines in the local tumor microenvironment can be further enhanced by the combination of SMAC mimetics and anti-PD1 checkpoint inhibitors (Beug et al. 2017) which will then be expected to attract further immune cell infiltration to enhance the anti-tumor effect. These multiple mechanisms of enhanced immune activation lead to potent anti-tumor activity and synergistic combinations with multiple immunotherapy strategies (Dougan et al. 2010, Knights et al. 2013, Beug et al. 2015, Beug et al. 2017).

In particular, the combination of SMAC mimetics, including birinapant, with anti-PD1 checkpoint inhibitors leads to synergistic anti-tumor activity in preclinical models of glioblastoma, mammary tumors and multiple myeloma (Chesi et al. 2016, Beug et al. 2017). Birinapant was shown to enhance the TNF-dependent cytotoxic lymphocyte killing of tumor cells which was further enhanced by combination with anti-PD-1 antibodies (Kearney et al. 2017 Cell Death and Differentiation). These and other data provide a strong rationale for a potential benefit of combining birinapant with pembrolizumab due to two complementary

mechanisms:

(1) Increased efficiency of activation of immune cells by activation of non-canonical NF-κB signaling,
(2) Increased local delivery of TNFα by activated T cells is converted to an induction of apoptosis as described above

These arguments support investigation of the combination of birinapant and pembrolizumab in various cancer indications and underpin the rationale for the selection of indications in the expansion phase of this study, which is further described in section 1.5.

1.2 Birinapant Background

Birinapant is a potent, bivalent SMAC-mimetic (molecular weight 806.9 g/mol) that binds with differential affinity to multiple members of the IAP family including cIAP1, cIAP2, XIAP, and ML-IAP (Condon et al. 2014). Birinapant is differentiated from related bivalent SMAC-mimetics in that birinapant results in the loss of cIAP1 and selective degradation of cIAP2 bound to TRAF-2 in the TNF receptor complex, but sparing non-TRAF-2 bound cIAP2 (Benetatos et al. 2014). This unique IAP antagonism profile of birinapant is thought to result in the improved tolerability and therapeutic index observed with this agent compared to other bivalent SMAC-mimetics (Condon et al. 2014). Birinapant is differentiated from monovalent SMAC mimetics by the ability of birinapant to access TRAF 2-bound cIAP1 and target it for degradation (Mitsuuchi et al. 2017). In contrast, monovalent SMAC mimetic treatment leaves a residual inaccessible cIAP1-TRAF2 complex undegraded, which results in an incomplete shutdown compared to birinapant (Mitsuuchi et al. 2017).

1.2.1 *Pre-Clinical Studies*

Birinapant shows marked anti-tumor activity and a high therapeutic index in human tumor xenografts in mice following intraperitoneal or IV administration. The minimal efficacious dose when administered every 3 days to mice bearing an orthotopic MDA-MB-231 (birinapant-sensitive sub-clone) breast tumor was 1.25 mg/kg (3.75 mg/m^2) with no toxicity at doses up to 60 mg/kg (180 mg/m^2), the highest dose evaluated in this model. Single agent efficacy of birinapant was also observed in the SKOV-3 ovarian cancer xenograft model where the tumor was implanted subcutaneously in the axillary region. Birinapant also displays single agent efficacy in cell line and primary patient-derived tumors, transplanted into mice including ovarian, melanoma, ALL, AML, Diffuse Large B Cell Lymphoma and pancreatic tumor models (Benetatos et al. 2014, Carter et al. 2014, Condon et al. 2014, Yang et al. 2016). However, while some tumor models are sensitive to birinapant administration as a monotherapy, much greater efficacy in a wider variety of tumor models is observed in combination treatments. This is consistent with the concept of birinapant blocking the anti-apoptotic effect of IAP proteins, while a simultaneously applied inducer of apoptosis is required for a combined optimal anti-tumor effect. Potent anti-tumor activity in combination studies has been observed in preclinical models of e.g. ovarian cancer (Janzen et al. 2015) and head and neck cancer (Eytan et al. 2016), particularly in those tumors with a high expression of cIAP1. Taken together these findings indicate that birinapant therapy will elicit the maximal benefit when used in combination treatments (Fulda 2015).

1.2.2 *Birinapant and Clinical Trials*

Clinical trials with birinapant include 9 studies that are complete targeting oncology and HBV indications. As of 21 October 2017, 470 patients have been enrolled in these studies, of which 411 have received birinapant.

The oncology program includes 8 studies conducted under multiple sponsor-initiated and investigator-initiated clinical applications. As of 21 October 2017, 463 patients with solid tumors or hematological malignancies have been enrolled in studies designed to evaluate birinapant in the oncology setting, either as a single agent or in combination with other chemotherapeutics at doses up to 63 mg/m^2/dose. To date, 5 oncology studies sponsored by TetraLogic Pharmaceuticals (the previous owner of birinapant) and 3 investigator-sponsored studies have been completed.

Birinapant has demonstrated single-agent efficacy in combination when given with standard agent and investigational agent chemotherapy in patients with advanced cancers including but not limited to colorectal carcinoma (CRC), ovarian cancer and myelodysplastic syndrome (MDS).

For further information, please see the birinapant Investigator's Brochure.

1.3 Checkpoint Inhibition and Cancer

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades (Disis 2010). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and prognosis in various malignancies (Dunn et al. 2007, Uppaluri et al. 2008, Bellati et al. 2009, Oble et al. 2009, Nosho et al. 2010, Shirabe et al. 2010, Bremnes et al. 2011, Gooden et al. 2011, Schreiber et al. 2011, Talmadge 2011, Mei et al. 2014, Schatton 2014, Salgado et al. 2015). In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells seem to correlate with improved prognosis and long-term survival in many solid tumors (Kirk 2010, Nosho et al. 2010, Liu et al. 2011, Mathai et al. 2012, Yoon et al. 2012, Kim et al. 2013, Preston et al. 2013, Chang et al. 2014).

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control (Pedoeem et al. 2014). The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28, which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structures of murine PD-1 alone (Zhang et al. 2004) and in complex with its ligands were first resolved (Lazar-Molnar et al. 2008, Lin et al. 2008) and more recently the NMR-based structure of the human PD-1 extracellular region and analyses of its interactions with its ligands were also reported (Cheng et al. 2013). PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-

based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules, such as CD3ζ, PKCθ and ZAP70, which are involved in the CD3 T-cell signaling cascade (Sheppard et al. 2004). PD-1 was shown to be expressed on activated lymphocytes, including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells (Yao et al. 2014). Expression has also been shown during thymic development on CD4-CD8- (double negative) T cells (Nishimura et al. 1996), as well as subsets of macrophages (Huang et al. 2009) and dendritic cells (Pena-Cruz et al. 2010). The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types (Keir et al. 2008). PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments (Keir et al. 2008). Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T cell activation triggered through the T cell receptor. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T cell inhibitor (Karim et al. 2009, Taube et al. 2012), which, via its interaction with the PD-1 receptor on tumor-specific T cells, plays a critical role in immune evasion by tumors (Sanmamed et al. 2014). As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in cancer (Topalian et al. 2012a).

1.4 Pembrolizumab Background

1.4.1 *Pre-Clinical Studies*

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities (Strome et al. 2003, Blank et al. 2004, Hirano et al. 2005, Curran et al. 2010, Pilon-Thomas et al. 2010, Weber 2010, Spranger et al. 2014). Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma (Strome et al. 2003, Nomi et al. 2007, Zhang et al. 2009, Pilon-Thomas et al. 2010). In such studies, tumor infiltration by CD8+ T cells and increased IFN-γ, granzyme B and perforin expression were observed, indicating that the mechanism underlying the anti-tumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T cell function *in vivo* (Curran et al. 2010). Experiments have confirmed the *in vivo* efficacy of anti-mouse PD-1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (see the Investigator's Brochure [IB]).

1.4.2 *Pembrolizumab and Clinical use*

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus

inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical *ad* data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. KEYTRUDA™ (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator brochure.

1.5 Rationale for Patient Population

1.5.1 *Colorectal cancer*

Colorectal cancer is the second most common in cancer in women and the third most common in men. The American Cancer Society estimates that 95,520 new cases of colon cancer will be diagnosed in the United States in 2017. Estimates for mortality from colon and rectal cancer (the two are combined because of classification difficulties) are for 50,260 deaths in 2017 (Siegel et al. 2017). The approximate 5-year survival rate for colorectal cancer patients in the United States (all stages included) is 65%. Survival is inversely related to stage: approximate 5-year survival rates are 95% for patients with stage I disease, 60% for those with stage III disease, and 10% for those with stage IV (metastatic) disease (NCI 2017a).

Surgery is the only curative modality for localized colon cancer (stage I-III). Surgical resection potentially provides the only curative option for patients with limited metastatic disease in liver and/or lung (stage IV disease). Adjuvant chemotherapy is standard for patients with stage III disease and has been shown to reduce death rate by 33% (Moertel et al. 1990). At present, the role of radiation therapy is limited to palliative therapy for selected metastatic sites such as bone or brain metastases. Chemotherapy rather than surgery has been the standard management for patients with metastatic colorectal cancer. Biologic agents have assumed a major role in the treatment of metastatic cases, with selection increasingly guided by genetic analysis of the tumor. Biologic agents used in the treatment of colon cancer include monoclonal antibodies against vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR), as well as a kinase inhibitor and a decoy receptor for VEGF.

Combination regimens provide improved efficacy and prolonged progression-free survival (PFS) in patients with metastatic colon cancer, and the advent of new classes of active drugs and biologics for colorectal cancer has improved the expected survival (Kim et al. 2009). However, despite the improvements in the past decades, the long-term outcome is still dismal with a median overall survival of 11-15 months in published trials after start of second-line therapy with only a modest improvement in Overall Survival (OS) and PFS with regimens containing new compounds (Giantonio et al. 2007) , (Van Cutsem et al. 2012) (Tabernero et al. 2015). Therefore, an unmet medical need still exists in order to improve outcomes for patients progressing after initial therapy.

Microsatellite Instability (MSI) is a hypermutable phenotype of certain cancers caused by defects in the DNA mismatch repair system, most frequently due to hypermethylation of the

MLH1 gene or loss of MSH2 expression (Boland et al. 2010). Microsatellites are small regions of repeated sequences in DNA, and these can present challenges to the DNA replication machinery which can result in mismatches between the DNA strands which must be repaired by the DNA mismatch repair system. If these mismatches are unrepaired, they lead to a very high mutation rate and the consequent generation of thousands of neoantigens which are readily recognized as foreign by the immune system. This leads to a high degree of tumor infiltration by lymphocytes and a priming of the immune system for reactivation.

MSI occurs in approximately 15% of colorectal cancers, with ~ 3% arising from the hereditary Lynch syndrome and ~12% arising spontaneously (Boland et al. 2010). MSI status has been further categorized as MSI-High, in which >30% of the microsatellite marker panel is mutated, or MSI-Low where at least 1 but <30% are mutated, as defined in the Bethesda guidelines (Boland et al. 1998). Mismatch repair status can also be determined using immunohistochemistry, and termed as deficient mismatch repair (dMMR), which is equivalent phenotypically to MSI. Cancers with intact mismatch repair systems are termed microsatellite stable (MSS). MSI-High tumors are characterized with a high degree of Tumor Infiltrating Lymphocytes (TILs) whereas MSI-Low tumors have clinical features of microsatellite-stable tumors.

Rationale for birinipant in colorectal cancer

In microsatellite-stable CRC, birinapant was active in multiple CRC PDX models that were both KRAS wild-type (WT) and KRAS mutant (Benetatos et al. 2014). These data suggest that *KRAS* status is not decisive for SMAC-mimetic treatment. In addition, increased IAP gene copy number has been detected in 45% of 573 CRC tumors analyzed (http://cancergenome.nih.gov). IAP genes have been suggested as prognostic markers of colorectal cancer (Miura et al. 2011). Consistent with the preclinical data, birinapant showed evidence of clinical activity in patient studies. In the phase 1 monotherapy trial of birinapant, Amaravadi et al. (Amaravadi et al. 2015) reported evidence of clinical activity in CRC (1 patient prolonged SD, 2 patients radiographical shrinkage) and demonstration of target modulation (reduction in cIAP expression in PBMC and tumors) correlating with PK assessment. Furthermore, 6 PR seen in CRC in combination with irinotecan were seen in another of the studies (TL32711-POC-078-PTL) (For more details on specific indications refer to the Investigator's brochure).

Pembrolizumab in colorectal cancer

Pembrolizumab gained accelerated approval from the FDA in May 2017 due to its specific efficacy in unresectable or metastatic colon cancer that has tested positive for MSI-High or dMMR, and has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. The approval for pembrolizumab was based on data from 149 patients with MSI-High or dMMR cancers enrolled across 5 single-arm clinical trials (KEYNOTE-012, -016, -028, -154 and -164), that included ninety patients with colorectal cancer (CRC). The ORR with pembrolizumab was 39.6%, including 11 (7.4%) complete responses (CRs). Among patients who responded to pembrolizumab, 78% had responses that lasted for at least 6 months (Keytruda 2017).

However, despite these good response rates of immune checkpoint antibodies for MSI-High / dMMR colorectal cancer, there is little evidence of activity in microsatellite stable (MSS) colorectal cancers. In a phase II study by Le et al. investigating pembrolizumab, with an objective response rate of 40% in MSI CRC, no responses were recorded in the mismatch repair-proficient cohort (Le et al. 2015). Only 1/14 CRC patients responded to anti-PD1 antibody (MDX-1106, nivolumab), and the one responding patient was diagnosed as MSI-High (Brahmer et al. 2010). Subsequently, no objective responses were observed in 19 CRC patients with anti-PD1 antibody nivolumab not assessed for MSI status (aka BMS-936558; (Topalian et al. 2012b)). No objective responses are described with nivolumab or the combination of nivolumab and ipilumimab in MSS CRC (Overman 2016). No objective responses were observed in 18 CRC patients with anti-PD-L1 antibody BMS-936559 (Brahmer et al. 2012).

Thus, there is a substantial unmet medical need and opportunity to unlock immune responses in the MSS population of colorectal cancer patients.

1.5.2 *Ovarian cancer*

Ovarian cancer is the most common cause of cancer death from gynecologic tumors in the United States. Around the world, more than 200,000 women are estimated to develop ovarian cancer every year and about 100,000 die from the disease. (NCI 2017b) The American Cancer Society estimates that 22,440 new cases of ovarian cancer will be diagnosed in 2017 and 14,080 women will die from the disease (NCS 2017). Although the 5-year survival rate for ovarian cancer has improved significantly in the past 30 years, the prognosis for ovarian cancer remains poor overall, with a 46% 5-year survival rate. The prognosis of ovarian cancer is closely related to the stage at diagnosis (Chan et al. 2008);.

Standard treatment for ovarian cancer involves cytoreductive debulking surgery and neoadjuvant chemotherapy which offers some improvement in morbidity and possibly survival. Postoperative chemotherapy is indicated in all patients with ovarian cancer except those with surgical-pathologic stage I disease with low-risk characteristics. The standard is a platinum compound and taxanes combination therapy (e.g., carboplatin and paclitaxel). The National Comprehensive Cancer Network (NCCN) recommends three to six cycles of intravenous taxane/carboplatin adjuvant chemotherapy for high-risk stage IA, IB, or IC epithelial ovarian cancer (NCCN 2016a). For stage II-IV disease, the recommended options include intraperitoneal chemotherapy, in patients with <1 cm optimally debulked stage II and III disease; or intravenous taxane/carboplatin for six cycles. In addition, completion surgery, as indicated by tumor response and potential resectability, may be used in selected patients (NCCN 2016a). Additional agents may be used for recurrent disease including targeted therapy with bevacizumab and olaparib.

Recurrent ovarian cancer is classified into two categories, depending on the length of time the patient remained disease-free after completing chemotherapy: (1) relapse that occurs more than 6 months after initial chemotherapy is considered platinum-sensitive; (2) earlier relapse is considered platinum-resistant. Patients with platinum-sensitive disease may exhibit a good response if rechallenged with a platinum-based regimen (Parmar et al. 2003),

(Pfisterer et al. 2006). The probability of response increases with the duration of the disease-free interval.

Results from clinical trials suggest that combination chemotherapy offers an improvement in response rate, progression-free survival, and overall survival. Several chemotherapy agents elicit a response in patients whose disease is resistant to platinum-based therapies. These include liposomal doxorubicin, topotecan, oral etoposide, gemcitabine, docetaxel, and vinorelbine. Bevacizumab has approval for both platinum-resistant as well as platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in combination therapy (Aghajanian et al. 2015) (Coleman et al. 2017), In patients receiving third- line therapy, response rates are generally low with a short time to progression (Hanker et al. 2012). There is a clear need for more effective treatments.

Rationale for birinapant in ovarian cancer

Ovarian carcinomas often have an increased copy number of IAP genes. Published data suggests that ovarian carcinomas may be sensitive to birinapant / IAP antagonist treatment (Brunckhorst et al. 2012, Benetatos et al. 2014, Janzen et al. 2015). Birinapant has demonstrated activity against ~70% (8/11) ovarian cancer cell lines as a single-agent or in combination with TNF. Furthermore, birinapant treatment delayed growth in patient derived xenograft and cell line models (Benetatos et al. 2014, Gatti et al. 2014).High TNFα expression is common in ovarian cancers, and they are resistant to TNFα-dependent killing, suggesting that birinapant may be able to convert this TNFα towards a pro-apoptotic function by antagonizing cIAP1.

Birinapant was shown to significantly reduce cIAP1 expression levels in PBMCs and tumor biopsies in a clinical study in ovarian carcinoma (Noonan et al. 2016), demonstrating target engagement in this population. In combination with carboplatin/paclitaxel one out of two patients showed PR (for more details on specific indications refer to the Investigator brochure).

Pembrolizumab in ovarian cancer

The introduction of immune checkpoint inhibitors has revolutionized treatment of multiple cancers and has bolstered interest in this treatment approach. So far, emerging clinical data show limited clinical efficacy of these agents in ovarian cancer with objective response rates of 10–15% with some durable responses (Gaillard et al. 2016).

Overexpression of the PD-1 ligand PD-L1 has been demonstrated in ovarian cancer and may hinder an effective antitumor immune response. A preliminary analysis of the ovarian cancer cohort of the KEYNOTE-028 study (NCT02054806) showed pembrolizumab had only modest antitumor activity in patients with PD-L1+ advanced ovarian cancer. ORR was 11.5% (95% CI, 2.4%-30.2%). Tumor reduction was observed in 6/26 (23.1%); all 3 patients who responded completed 2 years of treatment. Median duration of response was not reached (range, 24.9+ to 26.5+ months). Median (95% CI) PFS and OS were 1.9 months (1.8 to 3.2 months) and 13.1 months (6.7 to 17.5 months) respectively (Varga 2017).

Other PD-1 antibodies have been evaluated in ovarian cancer. Nivolumab demonstrated a best overall response rate of 15% (Hamanishi et al. 2015). High PD-L1 expression was observed in 80% of ovarian cancers in this study, and although this did not correlate with response to nivolumab, it may indicate the possibility to reactivate immune-dependent responses in combination with drugs that can facilitate this.

1.5.3 *Cervical cancer*

Cervical cancer is the third most common malignancy in women worldwide and the fourth most common cause of cancer-related deaths in women worldwide (Torre et al. 2015). Human papillomavirus (HPV) infection must be present for cervical cancer to occur. Most cervical cancers are associated with oncogenic HPV subtypes, high-risk type HPV-16 and HPV-18 being the most frequently involved in cervical cancer development. (zur Hausen 2002). HPV plays an etiologic role in cervical cancer and is included in the screening regimen for young women. (Torre et al. 2015); (Sant et al. 2015). A significant number of women present with or develop advanced disease despite advances in screening (Pap test and HPV screening) and HPV vaccination. The prognosis is poor and depends on the disease stage. In general, the 5-year survival rates are as follows: Stage I - Greater than 90%; Stage II - 60-80%; Stage III - Approximately 50%, and Stage IV - Less than 30%.

The treatment of cervical cancer varies with the stage of the disease. Early-stage cervical cancer can be cured with surgery, while concurrent chemoradiation is the treatment of choice for locally advanced stages. Patients with recurrent or metastatic cancers have, however, limited treatment options. (NCCN 2016b).

For platinum-sensitive recurrent or metastatic tumors, the standard of care is chemotherapy with paclitaxel and cisplatin (Moore 2008) (Monk et al. 2009). Bevazicumab was approved by FDA in 2014 in combination with paclitaxel and cisplatin or paclitaxel and topotecan based on a phase III study that showed an improvement of overall survival by 3.5 months to 16.8 months compared to standard chemotherapy. No validated treatment options exist beyond this first-line treatment regimen. Chemotherapy regimens in this situation are associated with substantial toxicity and poor efficacy with a median overall survival of 7 months (Tewari et al. 2017). There is still a significant unmet medical need.

Rationale for birinapant in cervical cancer

Squamous carcinomas of the head and neck, the cervix and the esophagus have similar etiologies and high rate of amplification of IAP genes, and cervical carcinomas have a high frequency of amplification of cIAP1 and cIAP2 genes (Derakhshan et al. 2017). cIAP1 gene expression in cervical cancers has been linked to resistance to radiotherapy (Imoto et al. 2002). Squamous carcinomas of the head and neck with high expression and amplification of cIAP1/2 have recently been shown to be sensitive to birinapant (Eytan et al. 2016) and by analogy, these related cancers with high expression of cIAP1/2 are also expected to be sensitive to birinapant (Imoto et al. 2002) (Liu et al. 2001). HPV E6 and E7 proteins have been shown to activate NF-κB, induce cIAP2 expression and protect against TNFα-induced apoptosis (James et al. 2006). HPV 16 E6 protein has also been shown to directly bind to TNFR1 and to block TNFα-induced apoptosis (Filippova et al. 2002). Birinapant may be

able to resensitize HPV-infected cervical cancer cells to apoptosis through degradation of cIAP1 and cIAP2.

Pembrolizumab in cervical cancer

The central role of HPV infection in cervical cancer oncogenesis provides a strong rationale for the utility of immunotherapy. The presence of viral antigens may allow the development of an HPV-specific response that may facilitate tumor clearance. Pembrolizumab and multiple other checkpoint antibodies are being evaluated in cervical cancer and early evidence suggests a relatively modest response to date (Borcoman et al. 2017). In the cervical cancer cohort of the KEYNOTE-028 trial, 24 PD-L1 positive patients were treated with pembrolizumab. ORR was 17% (all PR) and the median duration of response was 5.4 (4.1-7.5) months. A phase II trial (KEYNOTE-158) in advanced cervical cancer is ongoing (Frenel et al. 2017). There remains a substantial fraction of patients who could derive benefit from a combination therapy that can enhance the effect of checkpoint antibodies.

1.5.4 *Various solid tumors cohort*

1.5.4.1 Head and Neck Squamous Cell Carcinoma

In the United States, 63,030 new cases of Head and neck squamous cell carcinoma (HNSCC) are expected in 2017, with nearly 13,360 deaths related to HNSCC. Tobacco smoking, alcohol consumption and HPV infection are risk factors for the development of HNSCC (Blot et al. 1988) (Chaturvedi 2012). HPV-related HNSCC is a distinct subgroup with a better prognosis (Schwartz et al. 2001).

Early-stage HNSCC disease is treated with relative success using single-modality therapy (either surgery or radiation alone). However, nearly 66% of patients present with advanced disease (stage III and IV), and fewer than 30% of these patients are cured, which underlines the present medical need in this indication.

The management of advanced HNSCC consists of multiple-modality therapy with surgery, radiation, and chemotherapy. Despite significant improvements in these modalities, long-term survival rates in patients with advanced-stage HNSCC have not increased significantly in the past 30 years.

Cetuximab is the only targeted molecule approved by the FDA for the treatment of HNSCC. In a phase III trial that included patients with locoregionally advanced HNSCC, radiotherapy and cetuximab was shown to be superior to radiotherapy alone. The median OS was 49.0 and 29.3 months in the two arms of the study (Bonner et al. 2006). In another phase III study, patients with recurrent or metastatic disease were randomized between cisplatin/carboplatin, 5-FU and cetuximab or cisplatin/carboplatin and 5-FU only. Patients treated with cetuximab survived a median of 10.1 months, compared with 7.4 months for those patients who received chemotherapy alone (Vermorken et al. 2008).

Rationale for Birinapant in HNSCC

HNSCC has been reported to have genomic amplification and gene expression increases in cIAP1, cIAP2 and XIAP genes as well as other components of the NF-κB and apoptosis pathways (Derakhshan et al. 2017). HNSCC cell lines containing these amplifications are sensitive to birinapant alone and in combination with radiation or chemotherapy (Eytan et al. 2016). Other IAP antagonists have also shown preclinical activity in HNSCC (Yang et al. 2011, Matzinger et al. 2015, Kadletz et al. 2017). Multiple studies have shown high TNFα expression is common and a negative prognostic factor in HNSCC. Birinapant may be able to convert this TNFα towards a pro-apoptotic function by antagonizing cIAP1. As described for cervical cancer, HPV infected cells may also be sensitive to birinapant treatment.

Pembrolizumab in HNSCC

Pembrolizumab has demonstrated clinical activity in HNSCC (Chow et al. 2016), and the FDA granted accelerated approval to pembrolizumab in August 2016 for patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy based on results from the open-label phase Ib KEYNOTE-012 trial.

The accelerated approval was specifically based on an efficacy analysis of 174 patients treated with a prior platinum-based agent. In this assessment, the ORR with pembrolizumab was 16% (95% CI, 11-22), which included a complete response (CR) rate of 5%. Responses lasted for ≥6 months for 82% of patients. Median PFS was 2.0 months with pembrolizumab (95% CI, 1.9-2.1). The 6-month PFS rate was 25% and the 12-month rate was 17%. Median OS across evaluable patients was 8.0 months (95% CI, 6-10). The 6-month OS rate was 58%. At 12 months, 38% of patients remained alive (Larkins et al. 2017).

There are no approved treatments for recurrent/metastatic head and neck squamous cell carcinoma refractory to platinum and cetuximab. The single-arm, phase II KEYNOTE-055 study evaluated pembrolizumab, in this platinum- and cetuximab-pre-treated (concurrent or sequential) population with poor prognosis.

Among 171 patients treated, 75% received two or more prior lines of therapy for metastatic disease, 82% were PD-L1 positive, and 22% were HPV positive. Overall response rate was 16% (95% CI, 11% to 23%), with a median duration of response of 8 months (range, 2+ to 12+ months); 75% of responses were ongoing at the time of analysis. Response rates were similar in all HPV and PD-L1 subgroups. Median progression-free survival was 2.1 months, and median overall survival was 8 months (Bauml et al. 2017). Even though these data are encouraging, the duration of clinical benefit is still modest which leaves a substantial need for additional treatments.

1.5.4.2 Gastroesophageal carcinoma

Gastroesophageal cancer (which comprises cancer of the stomach, esophagus, and gastroesophageal junction (GEJ) has one of the highest incidences of all cancers and is responsible for over one million annual deaths worldwide. Cancers of the upper gastrointestinal tract are a group of highly aggressive malignancies. In the USA alone, 16,910 new cases of esophageal cancer and 26,370 cases of stomach cancer are estimated to

be diagnosed in 2016, and approximately 15,690 and 10,730 deaths will be attributed to these diseases, respectively (Siegel et al. 2016).

Options for treatments in the first line settings are limited to the platinum/5-fluoropyrimidine (5FU) backbone which results in modest survival benefits in patients with good performance status (Wagner et al. 2006). This benefit was further enhanced by 2.7 months survival difference when adding trastuzumab to chemotherapy in the specific population of Her2/neu overexpression which accounts for 20%–30% of esophagogastric adenocarcinomas (Bang et al. 2010) (Kim et al. 2011) (Park et al. 2012).

In the second line treatment setting, vascular endothelial growth factor receptor (VEGF) inhibition with ramucirumab as monotherapy(Fuchs et al. 2014), or in combination with paclitaxel, resulted in a median OS of 9.6 months (Wilke et al. 2014). This target was also studied in the first line setting in a with bevacizumab in combination with cisplatin and capecitabine with a reported median PFS (6.7 vs. 5.3 months) and ORR 46.0% vs. 37.4%, with significant improvement for the bevacizumab arm versus placebo (Ohtsu et al. 2011). These survival numbers remain poor, urging the development of more effective treatment approaches for esophageal and gastric adenocarcinomas.

Rationale for birinapant in Gastroesophageal Cancer

Gastroesophageal cancer has frequent amplification of cIAP1 and cIAP2 genes (Derakhshan et al. 2017). SMAC was significantly downregulated in 63% of esophageal squamous cell carcinoma samples and SMAC expression by immunohistochemistry was significantly lower in chemoresistant patient tumors (Xu et al. 2011). SMAC mimetics showed activity in the SMAC-deficient tumor cells suggesting a rationale for increased response to birinapant.

Pembrolizumab in Gastroesophageal Cancer

Programmed death ligand 1 (PD-L1) overexpression, a possible biomarker predicting response to immune checkpoint inhibitors, approaches forty percent in esophageal and gastric cancers (Shaib et al. 2016). Translational and molecular studies have shown that esophageal cancers are possible candidate malignancies for immune checkpoint inhibition (Shaib et al. 2016). Muro et al. investigated the safety and activity of pembrolizumab in advanced gastric and GEJ cancer patients in a phase Ib KEYNOTE-012 trial. PD-L1 expression was demonstrated in 40% of the patients, 39 of whom were treated with pembrolizumab. The ORR was 22% (Muro et al. 2016).

In September 2017, the FDA granted accelerated approval for pembrolizumab for patients with recurrent locally advanced or metastatic gastric or GEJ adenocarcinoma who have received two or more lines of systemic therapy and whose tumors express PD-L1. This approval was based on promising ORR (11%) from one cohort of the Phase II KEYNOTE-059 study in heavily pre-treated patients (Fuchs 2017). Keytruda has also shown promise in an early-Phase esophageal cancer trial (KEYNOTE-028). ORR was 30%, and the stable disease rate was 9%; 6-months and 12-months PFS rates were 30% and 22%. The median duration of response was 15 months (Doi et al. 2017). Additional pembrolizumab studies

have been completed or are ongoing in various settings to further develop the treatment for gastroesophageal carcinoma.

1.5.4.3 Mesothelioma

Malignant mesothelioma (MM) is an aggressive tumor that arises from the mesothelial cells that line the pleural, pericardial, and peritoneal cavities. The incidence is predicted to rise in the coming years – as individuals with prior exposure to asbestos live longer: In the United States, an estimated 2500 people are diagnosed with MM each year.

Malignant pleural mesothelioma (MPM) has a median survival of 9–12 months even with trimodality therapy (chemotherapy, surgical resection, and thoracic radiation). The only currently recommended systemic therapy for MPM, based on the phase III EMPHACIS trial, is platinum/antifolate regimen that has extended the median OS of MPM patients to approximately 1 year with a median PFS of less than 6 months, and a 5-year survival rate of less than 5%. (Vogelzang et al. 2003) (Haas et al. 2013). Most patients are treated upfront by chemotherapy containing pemetrexed and a platinum agent; however, nearly all patients progress during or after first-line therapy, and no standard second-line and further-line therapies are available.

Recently, immunotherapy by targeting of immune checkpoints such as CTLA-4 and PD-1 has changed the treatment framework of several tumors including melanoma, lung cancer, renal cancer, and urothelial neoplasms. However, malignant pleural mesothelioma does not rank high in terms of mutational load which is an important determinant of the response to checkpoint blockade inhibitors (Bueno et al. 2016). Indeed, mesothelioma pathogenesis seems to be essentially driven by inflammation (Yamagishi et al. 2015). Tumor-associated macrophages, which are key inflammatory cells with potent immunosuppressive activity, are abundantly expressed in the stroma of malignant pleural mesothelioma; moreover, in malignant pleural mesothelioma, a low lymphocyte to monocyte ratio in peripheral blood and tissue is reported to have negative prognostic significance (Yamagishi et al. 2015).

Rationale for birinapant in mesothelioma

Despite high levels of TNF-α, mesothelioma cells are relatively resistant to apoptosis due to overexpression of IAP , that can be further upregulated by TNF-α by autocrine secretion (Gordon et al. 2002). TNF-α mediates resistance to cisplatin in vitro that can be reversed by NF-κB inhibition (Gordon et al. 2007b).(Gordon et al. 2007a) Birinapant can cause inhibition of TNFα-induced NF-κB signaling and promote TNFα-induced apoptosis suggesting a rationale for clinical benefit.

Pembrolizumab in Mesothelioma

Alley and colleagues reported the results of pembrolizumab, an anti-PD-1 antibody, in 25 patients with pre-treated malignant pleural mesothelioma expressing PD-L1 (KEYNOTE-028 trial). The ORR was 20%, PFS 5.4 months and OS 18 months – well beyond the survival observed with second line therapies in this setting (Alley et al. 2017).

1.5.4.4 Small Cell Lung Cancer

Lung cancer overall is the second most common malignancy in both sexes in the United States (ACS 2017). While the incidence of small cell lung cancer (SCLC) has declined over the last few years in the United States, as smoking rates have fallen, it still comprises about 15% of all lung cancers. (PDQ 2017). SCLC is a distinct type of lung cancer. It is a neuroendocrine tumor characterized by aggressive behavior, rapid growth, early dissemination, exquisite sensitivity to chemotherapy and radiation, and frequent association with distinct paraneoplastic syndromes. (Boffetta 2008) (Pietanza 2015) (Cascone 2016).

Approximately 60-70% of patients with SCLC have clinically disseminated or extensive disease at presentation. Extensive-stage SCLC (i.e. SCLC that has spread beyond the supraclavicular areas, or with distant metastases) is incurable. For individuals with limited-stage disease that is treated with combination chemotherapy plus chest radiation, a complete response rate of 80% and survival of 17 months have been reported; 12-15% of patients are alive at 5 years (Janne et al. 2002). Extensive-stage disease remains incurable with current management options median survival is only 7-9 months and only 2% are alive at 5 years (Jackman et al. 2005).

Several chemotherapy combinations are active in SCLC, but usually a platinum-containing regimen is chosen. However, despite strides in the management of SCLC, there has been little change in survival over the past 2 decades for limited- or extensive-stage disease. Indeed, very few new agents with activity in SCLC have been identified (compared to NSCLC) (Hanna et al. 2002, Lally et al. 2007). Unlike NSCLC, SCLC has not been shown to respond well to targeted therapies. Studies of vascular endothelial growth factor (VEGF) and VEGF receptor (VEGFR) inhibitors have yielded disappointing results: bevacizumab, aflibercept, and vandetanib have failed to demonstrate significant improvements in survival. (Spigel et al. 2011) (Hanna et al. 2002) (Lally et al. 2007). However, a phase II trial of sunitinib maintenance therapy in patients with untreated extensive-stage SCLC reported a modest but significant improvement in median progression-free survival, from 2.1 months with placebo to 3.7 months with sunitinib (Leighl 2015). The modest progress in improvements in life expectancy for patients diagnosed with this aggressive disease highlight the clear unmet medical need to develop more effective treatments.

Rationale for birinapant in lung cancer

cIAP1 expression has been shown to contribute to resistance to chemotherapy and apoptosis in SCLC (Pardo et al. 2003). TNFα can induce NF-κB signaling and differentiation in SCLC, but does not cause cell death (Haley et al. 1998), suggesting that birinapant may allow switching this to an apoptotic response.

Pembrolizumab in SCLC

SCLC has a very high mutational burden due to the carcinogenic effects of smoking (George et al. 2015), which is the most common cause of SCLC, suggesting a potential susceptibility to checkpoint inhibition, and pembrolizumab and a number of other checkpoint inhibitors are currently in clinical investigation.

The safety and efficacy of pembrolizumab, were assessed in patients with programmed death ligand 1 (PD-L1)–expressing extensive-stage SCLC in the multicohort, phase Ib open-label KEYNOTE-028 study (NCT02054806) (Ott et al. 2017).

Twenty-four patients with PD-L1–expressing SCLC were enrolled and received at least one pembrolizumab dose. At the data cutoff date (June 20, 2016), the median follow-up duration was 9.8 months (range, 0.5 to 24 months). One patient had a complete response, and seven patients had partial responses, resulting in an ORR of 33% (95% CI, 16% to 55%). Pembrolizumab demonstrated promising antitumor activity in patients with pre-treated, PD-L1–expressing SCLC.

1.5.4.5 Cholangiocarcinoma

Cholangiocarcinoma (CCA) is comprised of malignancy arising from the intrahepatic (iCCA), perihilar (pCCA) and distal biliary tree (dCCA) with features of cholangiocyte differentiation. Intrahepatic CCA (iCCA) is the second most common primary hepatic malignancy, after hepatocellular carcinoma, and accounts for 10-20% of primary liver cancers. In the past decade, iCCA has risen in incidence and mortality rate whereas those of extrahepatic CCA (eCCA) are either stable or decreasing.

Only 10-15% of the patients with CCA are amenable to potentially curative surgery due to late presentation at an advanced stage because no effective screening strategies exist. Despite resection, high recurrence rates of 50-60% persist, conferring a five-year OS of only 30% (Nathan et al. 2007) (Mavros et al. 2014). The prognosis of patients with unresectable or metastatic CCA is universally poor, with a median OS of less than one year (Valle et al. 2010).

Marginal advances with chemotherapy has shifted emphasis to molecularly targeted therapies, either as a single agent or in combination with chemotherapy. The poor understanding of the biology of CCA and the lack of known oncogenic addiction loops has hindered the development of effective targeted therapies and a high unmet medical need is still present

Rationale for birinapant in cholangiocarcinoma

Cholangiocarcinoma is a form of cancer that displays prominent inflammatory traits with high TNFα expression. Macrophage infiltration has been shown to lead to local TNFα release leading to epithelial-mesenchymal transition and increased invasiveness. Kupffer cell-derived TNFα can enhance tumorigenesis and cancer cell proliferation, and >50% of CCA stained positive for TNFα (Yuan et al. 2017). Birinapant may allow these local TNFα concentrations to induce an apoptotic response in cancer cells.

Pembrolizumab in Cholangiocarcinoma

PD-L1 expression, PD-1 expression and TNM stage are significantly associated with the survival time of patients. Furthermore, multivariate analysis revealed the PD-L1 expression as an independent prognostic factor of patients with eCCA. These preliminary results suggested that PD-L1 or PD-1 immunodetection may be a valuable prognostic marker for eCCA patients (Ma et al. 2017). Increased levels of tumor-infiltrating CD8+ cytotoxic T cells and/or CD4+ T cells have been shown to be associated with improved prognosis in biliary tract cancers (Oshikiri et al. 2003). Given the success of checkpoint inhibitors in the treatment of metastatic melanoma, there has been growing interest of the benefit of immunomodulation in biliary tract cancers. In a preclinical study of iCCA it has been shown that both gemcitabine and interferon -γ led to an upregulation of PD-L1, which suggests that treatment with PD-L1 blockade may be beneficial (Koido et al. 2014). KEYNOTE-028 included a group of biliary tract cancers of which 42% were positive for PD-L1., with a 17% overall response rate in PD-L1 positive patients (Bang 2015).

1.6 Rationale for Dose Selection

1.6.1 *Rationale for Birinapant Starting Dose*

The starting dose for the first in human study of birinapant (birinapant Investigator's Brochure) was 0.18 mg/m^2 and doses were escalated to 63 mg/m^2. Two patients out of three (67%) who received birinapant at 63 mg/m^2 developed Grade 2 AEs of Bell's palsy. Based upon these events the dose of 63 mg/m^2 of birinapant was considered to be above the maximum tolerated dose (MTD). The MTD of birinapant was defined at a dose of 47 mg/m^2 administered once weekly. Further clinical studies have utilized total weekly doses of birinapant up to and including 22 mg/m^2 weekly in combination with chemotherapy. The starting dose escalation cohort of 5.6 mg/m^2 weekly is consistent with these data, and is below the combination MTD seen previously in the birinapant program when used in combination with other cancer drugs.

1.6.2 *Rationale for Pembrolizumab Dose Selection*

The dose of pembrolizumab planned to be studied in this trial is 200 mg Q3W. The dose approved in the United States and several other countries is 2 mg/kg every 3 weeks (Q3W). Information on the rationale for selecting 200 mg Q3W is summarized below.

In KEYNOTE-001, an open-label Phase 1 study conducted to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics, and anti-tumor activity of pembrolizumab when administered as monotherapy. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg and 10 mg/kg, administered every 2 weeks (Q2W) and dose expansion cohorts evaluated 2 mg/kg Q3W and 10 mg/kg Q3W in subjects with advanced solid tumors. All dose levels were well tolerated and no dose-limiting toxicities were observed. This first-in-human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels. No MTD has been identified. In addition, two randomized cohort evaluations of melanoma subjects receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed,

and one randomized cohort evaluating 10 mg/kg Q3W versus 10 mg/kg Q2W has also been completed. The clinical efficacy and safety data demonstrate a lack of important differences in efficacy or safety profile across doses.

An integrated body of evidence suggests that 200 mg Q3W is expected to provide similar response to 2 mg/kg Q3W, 10 mg/kg Q3W and 10 mg/kg Q2W. Previously, a flat pembrolizumab exposure-response relationship for efficacy and safety has been found in subjects with melanoma in the range of doses between 2 mg/kg and 10 mg/kg. Exposures for 200 mg Q3W are expected to lie within this range and will be close to those obtained with 2 mg/kg Q3W dose.

A population pharmacokinetic (PK) model, which characterized the influence of body weight and other patient covariates on exposure, has been developed. The PK profile of pembrolizumab is consistent with that of other humanized monoclonal antibodies, which typically have a low clearance and a limited volume of distribution. The distribution of exposures from the 200 mg fixed dose is predicted to considerably overlap those obtained with the 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. Pharmacokinetic properties of pembrolizumab, and specifically the weight-dependency in clearance and volume of distribution are consistent with no meaningful advantage to weight-based dosing relative to fixed dosing.

In translating to other tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in subjects with melanoma can be expected, as the anti-tumor effect of pembrolizumab is driven through immune system activation rather than through a direct interaction with tumor cells, rendering it independent of the specific tumor type. In addition, available PK results in subjects with melanoma, NSCLC, and other tumor types support a lack of meaningful difference in pharmacokinetic exposures obtained at tested doses among tumor types. Thus the 200 mg Q3W fixed-dose regimen is considered an appropriate fixed dose for other tumor indications as well.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage. The existing data suggest 200 mg Q3W as the appropriate dose for pembrolizumab.

2 STUDY OBJECTIVES

2.1 Study Objectives Dose Escalation Phase

2.1.1 *Primary Objective*

To determine the safety and tolerability of the recommended phase 2 dose (RP2D) of birinapant when given in combination with pembrolizumab IV

2.1.2 *Secondary Objective*

To assess preliminary efficacy of the combination of pembrolizumab and birinapant in patients with relapsed or refractory cancer by effects on tumor size as measured by imaging (CT or MRI) assessed by RECIST 1.1.

2.1.3 *Exploratory Objectives*

1. To assess preliminary efficacy of the combination of pembrolizumab and birinapant in patients with relapsed or refractory cancer by effects on tumor size as measured by imaging (CT or MRI) assessed by iRECIST.
2. To determine the pharmacodynamic markers of birinapant and of pembrolizumab when given in combination at the schedule and dose as defined by the protocol, to include but not to be limited to mechanism of action (inhibition of cIAP1), and of immune surveillance and activation.
3. To assess biomarkers that might predict for responders to the combination treatment and allow comparison to known potential predictive biomarkers of pembrolizumab response.
4. To evaluate birinapant pharmacokinetics in plasma when administered in combination with pembrolizumab.

2.2 Study Objectives Dose Expansion Phase

2.2.1 *Primary Objective*

The primary objective in each of the cohorts is as follows:

1. To determine whether the combination of pembrolizumab and birinapant has sufficient antitumor activity, as assessed by ORR, against colorectal cancer to warrant more extensive development.
2. To determine whether the combination of pembrolizumab and birinapant has sufficient antitumor activity, as assessed by ORR, against ovarian cancer to warrant more extensive development.
3. To determine whether the combination of pembrolizumab and birinapant has sufficient antitumor activity, as assessed by ORR, against cervical cancer to warrant more extensive development.
4. To determine the safety and tolerability of the RP2D of birinapant when given in combination with pembrolizumab to patients in the various solid tumors cohort

2.2.2 *Secondary Objectives*

1. To assess the safety and tolerability of the combination of pembrolizumab and birinapant; Overall and in the defined tumor types, colorectal cancer, ovarian cancer and cervical cancer.

2. To assess clinical activity of the combination of pembrolizumab and birinapant in the defined tumor types by effects on tumor response, including CBR, time to response and duration of response, assessed by RECIST 1.1
3. To assess clinical activity of the combination of pembrolizumab and birinapant in the defined tumor types by effect on overall survival
4. To assess clinical activity of the combination of pembrolizumab and birinapant in the defined tumor types by effect on progression free survival.

2.2.3 *Exploratory Objectives*

1. To assess clinical activity of the combination of pembrolizumab and birinapant in the defined tumor types by effects on tumor response, including: CBR, time to response, duration of response, iBOR, duration of iBOR and time to iCPD, assessed by iRECIST
2. To assess the pharmacodynamic markers of birinapant and of pembrolizumab when given in combination at the schedule and dose as defined by the protocol, to include but not to be limited to mechanism of action (inhibition of cIAP1), and of immune surveillance and activation.
3. To determine biomarkers that might predict for response and/or indicate response to the combination treatment and allow comparison to known potential predictive biomarkers of pembrolizumab response.
4. To evaluate birinapant pharmacokinetics in plasma when administered in combination with pembrolizumab

3 INVESTIGATIONAL PLAN

3.1 Description of Study Design

This is a phase 1/2, multicenter, single-arm, open-label, dose-escalation, safety, tolerability, pharmacokinetic and pharmacodynamic study of birinapant and pembrolizumab, conducted in male and female patients, ≥18 years of age, who have relapsed or refractory solid tumors. Patients must qualify for study participation within 28 days before initiation of study-drug treatment; must have a histologically confirmed solid malignancy that is metastatic or unresectable and for which standard curative or palliative measures do not exist or are no longer effective; must have measurable disease according to RECIST v 1.1 and must have an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1.

3.1.1 *Description of Study Design Dose Escalation Phase*

The dose escalation phase of this study will employ a sequential group dose-escalation design to determine the dose-limiting toxicity (DLT) and RP2D of birinapant administered in combination with pembrolizumab, both administered as a 30-minute intravenous (IV) infusion. Pembrolizumab will be administered first on Day 1. The birinapant infusion will begin 30 minutes (+10 minutes) following the completion of the pembrolizumab infusion on

Day 1. An additional dose of birinapant only will be administered on Day 8. The dose levels of birinapant and pembrolizumab are outlined in Table 2.

Table 2 Dose Escalation Schedule

Dose-Escalation Schedule	
Dose Level	Pembrolizumab + Birinapant (per 21-day cycle)*
Level -1	200 mg pembrolizumab on Day 1 + **birinapant 2.8 mg/m^2/week** on Days 1 and 8
Level 1	200 mg pembrolizumab on Day 1 + **birinapant 5.6 mg/m^2/week** on Days 1 and 8
Level 2	200 mg pembrolizumab on Day 1 + **birinapant 11 mg/m^2/week** on Days 1 and 8
Level 3	200 mg pembrolizumab on Day 1 + **birinapant 17 mg/m^2/week** on Days 1 and 8
Level 4	200 mg pembrolizumab on Day 1 + **birinapant 22 mg/m^2/week** on Days 1 and 8

*Note: A week without treatment (i.e., Days 15-21) will follow the second week of treatment, immediately after which the next 21-day cycle commences.

A minimum of 3 and up to 6 evaluable patients will be enrolled per dose level. For patients enrolled in Dose Level 1, the birinapant starting dose will be 5.6 mg/m^2/week. Dose escalation of birinapant will occur in up to three steps. The Safety Review Committee (SRC) will review all the cumulative safety data up to and including completion of Day 21 for the last patient in a cohort from that treatment group prior to dose escalation. Upon review of the safety data the SRC will determine whether or not the safety data supports dose escalation to the next sequential dose level. If the first dose level (5.6 mg/m^2) is deemed intolerable, defined as ≥2 patients from 3-6 experiencing a DLT, the SRC may decrease the starting dose of the next dosing cohort to 2.8 mg/m^2 (dose level -1).

If 1 of the 3 to 6 patients enrolled at a given dose level experiences a DLT, enrollment at the next dose level will proceed, if the next highest dose has not already been declared intolerable. However, if 1 of these 3 to 6 patients experiences a DLT at the given dose level and the next highest dose has already been declared intolerable, a minimum of 6 patients are to be enrolled at the given level and the dose at the given level may be the RP2D. A separate safety review will be performed by the SRC to determine the RP2D of the combination of birinapant and pembrolizumab and to begin the dose-expansion phase of the study.

3.1.2 *Description of Study Design Dose Expansion Phase*

Once the RP2D of birinapant combined with pembrolizumab is defined, additional patients with relapsed or refractory carcinoma will be enrolled in the dose-expansion phase of the study.

Dose Level	Pembrolizumab + Birinapant (per 21-day cycle)
Expansion	200 mg pembrolizumab on Day 1+ **birinapant at the RP2D mg/m^2/week** on Days 1 and 8

The dose expansion phase will comprise of four patient cohorts defined as follows;: The 4 cohorts will include the following

a. Colorectal cancer (28 patients)
b. Ovarian cancer (27 patients)
c. Cervical cancer (26 patients)
d. Various solid tumors (30 patients, including 5 patients with each of the following 6 tumor types: [Small cell lung cancer; Cholangiocarcinoma; Gastroesophageal carcinoma; Mesothelioma; Head and Neck Squamous Cell Carcinoma (HNSCC)-checkpoint inhibitor-naïve; and HNSCC checkpoint inhibitor-experienced])

Predefined interim analyses for futility and safety will be conducted in each of the cohorts in colorectal cancer, ovarian cancer and cervical cancer to limit undue exposure before further inclusion into a given cohort. The design of the various solid tumors cohort will limit undue exposure in any of the selected tumor types by virtue of the fact that it limits the number of enrolled patient to five in each tumor type.

3.1.3 *Safety Review Committee Dose Escalation Phase*

A SRC will be involved in the conduct of the dose escalation phase of this study. The SRC will be comprised of representatives from the Sponsor and the study sites, and the SRC may recommend that the study be interrupted or terminated at any time if, in their judgment, serious or unexpected AEs of sufficient concern warrant such action. See reporting requirements (Section 8.3) for Serious AEs (SAEs). The SRC has the responsibility for monitoring the clinical study's progress and the safety of the participating patients

Following completion of a dosing level, an evaluation of the safety of that dose will be performed by the SRC (based on cumulative data to the time of SRC assessment). The SRC will review the safety, efficacy and pharmacodynamic data (when available) from all patients enrolled at each dose level to confirm any DLTs that were experienced and to make a recommendation regarding enrollment in the next dose level. Each of the 3 to 6 patients at a dose level must have completed Cycle 1 (21-day cycle) to be eligible for SRC review. On the basis of the findings, the committee will have several options:

1. Recommend escalation to the next dose level,
2. In case of unexpected or unacceptable toxicity during the dose escalation phase recommend early discontinuation of the study, or

   Alter the subsequent dose as per the dose escalation criteria presented in Section 5.4.

The SRC will make the decision on RP2D based on an MTD of the combination being the occurrence of greater than 2 defined grade 3 or above SAEs (for definition of DLTs see section 5.4) in the final cohort of 3 plus 3 subjects. In the absence of an MTD, the SRC will consider pharmacodynamic and PK of birinapant as applicable considering that birinapant monotherapy has been studied previously at 10 to 63 mg/m^2. Doses > 47 mg/m^2 will not be considered.

Further details on the SRC procedures are presented in the SRC-charter

3.1.4 *Data Monitoring Committee Dose Expansion Phase*

During the dose-expansion phase of the study the SRC will be replaced by an independent Data Monitoring Committee (DMC). The independent DMC will include an independent chair having specialist oncology expertise and experience of studies in this area, an independent statistician and one other member will also be appointed. The DMC will meet approximately biannually to review the complete analysis of combined observed toxicities including emerging safety reports and reported SAEs. Specifically, they will monitor AEs and serious SAEs related to the treatments received in accordance with the recommendations of performing a clinical study of an IMP. On the basis of the findings, the committee will have several options:

1. Recommend reappraisal of the MTD
2. Reconsider RP2D, including dose de-escalation, based on safety, tolerability, PK, pharmacodynamic data and preliminary clinical activity,
3. In case of unexpected or unacceptable toxicity during the dose expansion phase recommend early discontinuation of the study

It is also the main responsibility for the DMC to conduct the interim analyses in the cohorts applying the Simon's two-stage design; the independent DMC will make recommendations on continuation of each of the cohorts based on the predefined futility rules outlined in section 12.8, in addition to assessing the safety and tolerability overall and for the defined tumor types.

Considering the potential delayed clinical activity known for immune related cancer treatments, the DMC may delay the interim analysis by up to 4 months if indicated as beneficial for the involved patients as judged by the relevant investigators. The time extension would in such case increase the treatment time for all patients that are judged to still be benefitting from treatment up to the new set date of the interim.

Further details on the DMC procedures are presented in the DMC-charter.

3.2 Discussion of Study Design

3.2.1 *Design Rationale including Dose Rationale Dose Escalation Phase*

The study design is appropriate to evaluate safety, tolerability, pharmacokinetics, and pharmacodynamics in male and female patients, who have relapsed or refractory solid tumors. A low starting dose is initially used to evaluate safety with minimal risk and is selected based on previous safety data obtained in oncology studies.

See Section 1.5 for discussion of the patient population and Section 1.6 for discussion of the dose-selection rationale.

3.2.2 *Design Rationale Dose Expansion Phase Study Design*

The phase 2a part of this study is constituted by a number of individual single-arm treatment cohorts in order to obtain an estimate of the degree of the anti-tumor effect. Simon's two-stage design is used for the dose expansion component of this study. The intent is to expose as few patients as possible to an ineffective drug. It is ethically imperative that the study is terminated if the drug is shown to have little or no anti-tumor activity. Simon's two-stage design gives the option to stop development of the drug in a given indication after the first or second stage if insufficient activity is demonstrated. The design also enables an early readout of sufficiently promising activity to warrant further investigation in a phase 3 study. The design of the various solid tumors cohort will limit undue exposure in any of the selected tumor types by virtue of the fact that it limits the number of enrolled patients to five in each tumor type. Following any positive results, it is the sponsor may consider the initiation of an expansion cohort in any of the tumor types included in the various solid tumor cohort, following submission of a protocol amendment. For further information of the patient population and the specific rationale for including these groups with high unmet medical need in this trial, refer to section 1.5.

The dose of birinapant is the RP2D chosen from the dose escalation part of the study. All patients in this part of study will therefore receive birinapant at a dose within the expected therapeutic range with the possibility to halt dosing as described in section 5.5 in the case of adverse event and may reinitiate at a lower dose according to the schema in section 5.5.1. The dose of pembrolizumab is the manufacturer's standard recommended dose used in approved indications. Available preclinical data for birinapant discussed in section 1.1 indicates the potential for an added clinical benefit with the combination of birinapant and pembrolizumab. Birinapant has a favorable safety profile based on data from previous trials, which indicates that the combination has a low risk of generating unacceptable toxicity.

In all the phase 1 approach employing a stepwise definition of the recommended birinapant dose in combination with pembrolizumab together with the balanced evaluation allowed by Simons's two-stage design and taking the beneficial preclinical basis into consideration, it is judged that the proposed phase 2 design has a favorable benefit-risk ratio.

3.3 Expected Duration of Study

It is expected to take approximately 6 months to enroll patients to the dose-escalation phase of the study. In the dose expansion phase is it expected to take approximately 4 months to enroll patients into the colorectal cancer cohort participating in the interim analysis. Following the interim analysis, it is expected to take additional 4 months to enroll all remaining patients. It is expected that to take approximately 8 months to enroll patients into the cohorts in ovarian cancer and cervical cancer participating in the interim analysis. Following the interim analysis is it expected to take approximately 5 months to enroll to the additional patients to complete the cohorts. For the various solid tumors cohort it is expected to take approximately 15 months to enroll all patients.

Table 3 Expected enrollment duration for individual cohorts

Dose escalation phase		**Enrollment duration**	
		6 months	
		Enrollment duration to interim analysis	**Enrollment duration from interim analysis to full cohort size**
Dose expansion phase	**Colorectal cancer cohort**	4 months	4 months
	Ovarian cancer cohort	8 months	5 months
	Cervical cancer cohort	8 months	5 months
	Various solid tumor cohort	15 months	

Patients will be allowed to remain on active treatment for 35 treatment cycles or until documented progressive disease (PD) or unacceptable toxicity. All patients will be followed for survival.

3.4 Study Endpoints

3.4.1 *Study Endpoints: Dose Escalation Phase*

3.4.1.1 Primary Endpoint

Safety and tolerability will be assessed by monitoring:

- Incidence and severity of adverse events (AEs) experienced by patients receiving birinapant in combination with pembrolizumab.
- Incidence and magnitude of clinically significant changes in clinical laboratory parameters experienced by patients receiving birinapant and pembrolizumab, or overall pattern of shifts by treatment group in individual laboratory values suggestive of possible trends, but not necessarily establishing, clinical abnormality.
- Incidence and severity of clinically significant adverse findings in vital signs, electrocardiogram (ECGs), and other physical examination parameters among patients receiving birinapant and pembrolizumab.

3.4.1.2 Secondary Endpoints

Efficacy:

- Tumor response and progression evaluated using RECIST v 1.1

Measures defined by the ORR, will be assessed through RECIST v 1.1 until response or progression and will be subsequently analyzed through iRECIST as an exploratory endpoint (see below).

3.4.1.3 Exploratory endpoints

3.4.1.3.1 Efficacy

Tumor response and progression evaluated using iRECIST.

a) iBOR
b) Duration of iBOR
c) Time to iCPD

Efficacy, as defined by the ORR, will be assessed through RECIST v 1.1 until response or progression and will be subsequently analyzed through iRECIST (iCR, or iPR or iSD or after iUPD iCR, iPR or iSD or iCPD). iBOR will also be assessed.

Overall survival will also be assessed.

3.4.1.3.2 Pharmacokinetics

The pharmacokinetics of birinapant in plasma when administered in combination with pembrolizumab will be evaluated.

3.4.1.3.3 Pharmacodynamics

Translational biomarker assessments obtained from blood will be evaluated at a central laboratory.

- Pre- and post-treatment levels in the expression of cIAP1
- Cytokine levels such as GM-CSF, IFNγ, IL10, IL2, IL3, IL4, IL5, IL6, IL7, IL8, MIP-1α, MIP-1β, MCP-1, TNFα, and TNFβ
- Gene expression analysis by Nanostring may also be performed

Blood samples looking at $CD3^+$, $CD4^+$, $CD8^+$, and $CD19^+$ cell counts as well as absolute neutrophil count and absolute lymphocyte count will be analyzed by each investigational site's local laboratory.

Translational biomarker assessments such as listed below, will be evaluated from archival or fresh pre-treatment biopsy samples, and optional post-treatment tumor biopsy samples, which will be analyzed at central laboratory:

- Pre-treatment PD-L1 levels by immunohistochemistry
- Gene expression analysis by Nanostring
- cIAP1 expression by immunohistochemistry
- Inhibition of apoptosis protein (IAP) gene copy number
- Tumor infiltrating lymphocytes (TILs) CD3, CD4, CD8, CD20 and FOXP3

The exploratory biomarker analyses listed are planned but may not be conducted if deemed as obsolete during later stages of the study; other exploratory analyses may be added based

on emerging new findings. Details regarding the processing and shipping of all pharmacodynamic samples will be outlined in the study specific laboratory manual.

3.4.2 *Study Endpoints; Dose Expansion Phase*

3.4.2.1 Primary Endpoint

The primary endpoint in each of the cohorts is as follows:

1. The overall response assessed through RECIST v.1.1 until response or progression in colorectal cancer
2. The overall response assessed through RECIST v1.1 until response or progression in ovarian cancer
3. The overall response assessed through RECIST v1.1 until response or progression in cervical cancer
4. Safety and tolerability in the cohort with various solid tumor types will be assessed by monitoring:
    - Incidence and severity of adverse events (AEs) experienced by patients receiving birinapant in combination with pembrolizumab.
    - Incidence and magnitude of clinically significant changes in clinical laboratory parameters experienced by patients receiving birinapant and pembrolizumab, or overall pattern of shifts by treatment group in individual laboratory values suggestive of possible trends, but not necessarily establishing, clinical abnormality.
    - Incidence and severity of clinically significant adverse findings in vital signs, electrocardiogram (ECGs), and other physical examination parameters among patients receiving birinapant and pembrolizumab.

Measures of tumor response will be evaluated using RECIST v1.1 until response or progression and will be subsequently analyzed through iRECIST as an exploratory endpoint (see below).

3.4.2.2 Secondary Endpoints

Safety and tolerability will be assessed in colorectal cancer, ovarian cancer and cervical cancer by monitoring:

- Incidence and severity of adverse events (AEs) experienced by patients receiving birinapant in combination with pembrolizumab.
- Incidence and magnitude of clinically significant changes in clinical laboratory parameters experienced by patients receiving birinapant and pembrolizumab, or overall pattern of shifts by treatment group in individual laboratory values suggestive of possible trends, but not necessarily establishing, clinical abnormality.
- Incidence and severity of clinically significant adverse findings in vital signs, electrocardiogram (ECGs), and other physical examination parameters among patients receiving birinapant and pembrolizumab.

Clinical Activity: Tumor response will be assessed in all four cohorts by monitoring:

- Progression Free Survival (PFS)
- Clinical Benefit Rate (CBR) defined as CR+PR+SD
- Time to response
- Duration of response
- Overall Survival (OS)

Measures of tumor response will be evaluated using RECIST v1.1 until response or progression and will be subsequently analyzed through iRECIST as an exploratory endpoint (see below).

3.4.2.3 Exploratory endpoints

3.4.2.3.1 Clinical Activity

Tumor response and progression evaluated in all four cohorts using iRECIST:

- Overall response
- iBOR
- Duration of iBOR
- Time to iCPD
- Clinical Benefit Rate (CBR) defined as iCR+iPR+iSD
- Time to response
- Duration of response

3.4.2.3.2 Pharmacokinetics

The pharmacokinetics of birinapant in plasma when administered in combination with pembrolizumab will be evaluated.

3.4.2.3.3 Pharmacodynamics

Translational biomarker assessments obtained from blood will be evaluated at a central laboratory.

- Pre- and post-treatment levels of cIAP1 expression
- Cytokine levels such as GM-CSF, IFNγ, IL10, IL2, IL3, IL4, IL5, IL6, IL7, IL8, MIP-1α, MIP-1β, MCP-1, TNFα, and TNFβ
- Gene expression analysis by Nanostring may also be performed

Blood samples looking at CA-125 (for ovarian cancer patients), CEA (for CRC patients), $CD3^+$, $CD4^+$, $CD8^+$, and $CD19^+$ cell counts as well as absolute neutrophil count and absolute lymphocyte count will be analyzed by each investigational site's local laboratory.

Translational biomarker assessments such as listed below, will be evaluated from archival or fresh pre-treatment biopsy samples, and optional post-treatment tumor biopsy samples, which will be analyzed at central laboratory:

- Pre-treatment PD-L1 levels by immunohistochemistry
- Gene expression analysis by Nanostring
- cIAP1 expression by immunohistochemistry
- Inhibition of apoptosis protein (IAP) gene copy number
- Tumor infiltrating lymphocytes (TILs) CD3, CD4, CD8, CD20 and FOXP3

The exploratory biomarker analyses listed are planned but may not be conducted if deemed as obsolete during later stages of the study; other exploratory analyses may be added based on emerging new findings. Details regarding the processing and shipping of all pharmacodynamic samples will be outlined in the study specific laboratory manual.

4 STUDY POPULATION

In the dose-escalation phase the study population will consist of approximately 24 male and female patients, ≥ 18 years of age, with relapsed or refractory solid tumors, who meet all of the inclusion criteria and none of the exclusion criteria.

Additional patients with relapsed or refractory carcinoma will be enrolled in the dose-expansion phase of the study. The dose expansion phase will comprise 4 cohorts of 26-30 patients. Three cohorts will enroll distinct cancer subtypes (colorectal cancer, ovarian cancer and cervical cancer) while the 4th cohort will include patients with one of 6 candidate tumors: small cell lung cancer; cholangiocarcinoma; gastroesophageal, mesothelioma; head and neck squamous cell carcinoma (HNSCC)-checkpoint naïve; and HNSCC check-point experienced).

4.1 Inclusion Criteria

All inclusion criteria for the study are listed below. **Unless otherwise stated, inclusion criteria apply to all phases and cohorts in the study**. Individual lists of inclusion and exclusion criteria applicable for the dose escalation phase and for each tumor type of the dose expansion phase can be found in Appendices 2.1 to 2.5.6.

Patients will be eligible for study participation if they meet ALL of the following inclusion criteria, after patient has provided written informed consent.

1. The patient is male or female ≥ 18 years of age on the day of signing informed consent.
2. The patient is able to understand and voluntarily sign a written informed consent, and is willing and able to comply with the protocol requirements.
3. The patient must have a histologically confirmed solid malignancy that is metastatic or unresectable and for which standard curative or palliative measures do not exist or are no longer effective. Patients with tumors with mutations for which there are FDA-approved therapies must have progressed following these therapies in order to be eligible for this study. Patients with metastatic colorectal cancer should have progressed on prior fluoropyrimidine-based therapies, and have no curative therapies available to them, in

order to be eligible for this study. Colorectal cancer patients should be assessed for microsatellite instability (MSI) status as per the local site routines. (*Dose Escalation Phase only*)

4. Patients must have measurable disease based on RECIST 1.1 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. Patients must have an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1 at screening.
6. Patients must have a life expectancy of greater than 12 weeks.
7. Patients must have amylase and lipase values < ULN.
8. Patients must demonstrate adequate organ function as defined in Table 4. All screening labs should be performed within 10 days of treatment initiation.

Table 4 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5xULN **OR** ≥60 mL/min for patient with creatinine levels >1.5x institutional ULN
Hepatic	
Total bilirubin	≤1.5xULN **OR** Direct bilirubin ≤ULN for patients with total bilirubin levels >1.5xULN), unless known Gilbert's Syndrome has been diagnosed
AST (SGOT) and ALT (SGPT)	≤2.5xULN OR ≤5.0xULN for patients with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5xULN unless patient 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 patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a] Creatinine clearance should be calculated per institutional standard.	

9. Female patients of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

10. Female patients of childbearing potential must be willing to use an adequate method of contraception for the course of the study through 120 days after the last dose of study medication.

    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient.

11. Male patients with female partners of childbearing potential 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. *(Not applicable for ovarian cancer cohort or cervical cancer cohort)*

    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient.

12. A tumor tissue sample for PD-L1 biomarker analysis from archival material, a newly obtained core or excisional biopsy is available for submission. Repeat samples may be required if adequate tissue is not provided.
13. Have resolution of toxic effect(s) of the most recent prior chemotherapy to Grade 1 or less (except neuropathy or alopecia). If patients have received major surgery or radiation therapy of > 30 Gy, they must have recovered from the toxicity and/or complications from the intervention.

Dose expansion phase cohort-specific inclusion criteria

14. Patients with metastatic colorectal cancer with no available therapy options that are known to provide clinical benefit per institutional standard of care. Patients with tumors with mutations for which there are available therapies that are known to provide clinical benefit, as defined by national authority and/or ratified by national guidelines or equivalent, have progressed following these therapies in order to be eligible for this study. (c*olorectal cancer cohort only*)
15. Patients with histological or cytologically confirmed metastatic colorectal cancer which is Microsatellite Stable (MSI-Stable) accordingly to local laboratory testing. (c*olorectal cancer cohort only*)
16. Patients must have a histologically confirmed epithelial ovarian cancer, primary peritoneal cancer or fallopian tube solid tumor cancer that is locally advanced or metastatic with no available therapy options that are known to provide clinical benefit per institutional standard of care. Patients with tumors with mutations for which there are available therapies that are known to provide clinical benefit, as defined by national authority and/or ratified by national guidelines or equivalent, must have progressed following these therapies in order to be eligible for this study. (o*varian cancer cohort only*)

17. Patients must have histologically or cytologically confirmed cervical squamous cell carcinoma that is locally advanced or metastatic with no available therapy options that are known to provide clinical benefit per institutional standard of care. Patients with tumors with mutations for which there are available therapies that are known

to provide clinical benefit, as defined by national authority and/or ratified by national guidelines or equivalent, must have progressed following these therapies in order to be eligible for this study (*cervical cancer cohort only*)

18. Patients must have histologically or cytologically confirmed head and neck squamous cell carcinoma that is locally advanced or metastatic with no available therapy options that are known to provide clinical benefit per institutional standard of care. Patients with tumors with mutations for which there are available therapies that are known to provide clinical benefit, as defined by national authority and/or ratified by national guidelines or equivalent, must have progressed following these therapies in order to be eligible for this study (*various solid tumors cohort: head and neck squamous cell carcinoma groups only*).

19. Patients with head and neck squamous cell carcinoma who are to participate in the group of Checkpoint inhibitor experienced patients must have received prior therapy with an anti-PD-1 or anti-PD-L1 antibody, administered either as monotherapy, or in combination with other therapies. Patients must have received at least two doses of an approved anti-PD-1/anti-PD-L1 antibody and have experienced documented radiographic progression of disease by RECIST v1.1. The initial evidence of disease progression is to be confirmed by a second assessment no less than four weeks from the date of the first documented disease progression in the absence of rapid clinical progression. The date for documentation of initial progression will be considered the date for disease progression. Progressive disease must have been documented during or within 12 weeks after last dose of such treatment. (*various solid tumors cohort head and neck squamous cell carcinoma, Checkpoint inhibitor experienced group only*).

20. Patients must have histologically or cytologically confirmed small cell lung carcinoma that is locally advanced or metastatic with no available therapy options that are known to provide clinical benefit per institutional standard of care. Patients with tumors with mutations for which there are available therapies that are known to provide clinical benefit, as defined by national authority and/or ratified by national guidelines or equivalent, must have progressed following these therapies in order to be eligible for this study (*various solid tumors cohort, SCLC group only*)

21. Patients must have histologically or cytologically confirmed cholangiocarcinoma that is locally advanced or metastatic with no available therapy options that are known to provide clinical benefit per institutional standard of care. Patients with tumors with mutations for which there are available therapies that are known to provide clinical benefit, as defined by national authority and/or ratified by national guidelines or equivalent, must have progressed following these therapies in order to be eligible for this study (*various solid tumors cohort, cholangiocarcinoma group only*)

22. Patients must have histologically or cytologically confirmed pleural mesothelioma that is locally advanced or metastatic with no available therapy options that are known to provide clinical benefit per institutional standard of care. Patients with

tumors with mutations for which there are available therapies that are known to provide clinical benefit, as defined by national authority and/or ratified by national guidelines or equivalent, must have progressed following these therapies in order to be eligible for this study (*various solid tumors cohort, mesothelioma group only*)

23. Patients must have histologically or cytologically confirmed carcinoma of the esophagus including the gastroesophageal junction that is locally advanced or metastatic with no available therapy options that are known to provide clinical benefit per institutional standard of care. Patients with tumors with mutations for which there are available therapies that are known to provide clinical, as defined by national authority and/or ratified by national guidelines or equivalent, must have progressed following these therapies in order to be eligible for this study (*various solid tumors cohort, gastroesophageal carcinoma group only*)

4.2 Exclusion Criteria

All exclusion criteria for the study are listed below. **Unless otherwise stated, exclusion criteria apply to all phases and cohorts in the study.** Individual lists of inclusion and exclusion criteria applicable for the dose escalation phase and for each tumor type of the dose expansion phase can be found in Appendices 2.1 to 2.5.6.

A patient will be excluded from the study for any one or more of the following reasons:

1. Patients who have 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 adverse events due to agents administered more than 4 weeks earlier prior to study Day 1.
2. Patients who have had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who have not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

   Note: Patients with ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia are an exception to this criterion and may qualify for the study.

   Note: If patients have received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

3. Patients who are currently participating and receiving study therapy or who have participated in a study of an investigational agent and received study therapy or who have used an investigational device within 4 weeks of the first dose of treatment.
4. Patients who have received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways) or if the patient has previously participated in Merck MK-3475 clinical trials. (*Not applicable for various solid tumors cohort, head and neck squamous cell carcinoma check-point inhibitor experienced group*)

5. Patients with known active central nervous system (CNS) metastases and/or carcinomatous meningitis.

   Note: Patients 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 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 systemic steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

6. Patients with a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

7. Patients who have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to birinapant or pembrolizumab or their constituents.
8. Patients requiring the use of anti-tumor necrosis factor (anti-TNF) therapies, such as infliximab, or patients who have received treatment with anti-TNF therapies within 5 half-lives of the drug.
9. Patients with a diagnosis of immunodeficiency or who are receiving systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days before the first dose of study drug. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
10. Patients with an uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure, hypertension, unstable angina pectoris, cardiac arrhythmia, autoimmune or inflammatory diseases, or psychiatric illness that would limit compliance with study requirements.
11. Patients with an active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.

12. Patients who have evidence of active, non-infectious pneumonitis. Patients with a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.

13. Patients with a history of interstitial lung disease

14. Patients who are 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. Pregnant women and men who want to conceive a child are excluded from this study because birinapant and pembrolizumab are agents with unknown potential for teratogenic or abortifacient effects in humans. Because there is an unknown risk for AEs in nursing infants secondary to treatment of the mother with birinapant and pembrolizumab, breastfeeding should be discontinued if the mother is treated on this study.

15. Patients who have a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies), or active Hepatitis B (e.g., HBsAg reactive). Patients with active Hepatitis C (e.g., HCV RNA [qualitative] is detected).

16. Patients who have received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.

17. Patients who have disease that is suitable for local therapy administered with curative intent.

18. Patients who have received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including G-CSF, GM-CSF or recombinant erythropoietin) within 4 weeks prior to study Day 1.

19. Patients who have a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or it is not in the best interest of the patient to participate, in the opinion of the treating investigator.

20. Patients who have known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

21. Patients who have severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.

22. Patients who have received anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways) (*Various solid tumor cohort, head and neck squamous cell carcinoma check point inhibitor experienced group only)*

23. Patients who have previously received birinapant treatment.

4.3 Withdrawal Criteria and Procedures

In accordance with the Declaration of Helsinki (and consistent with the applicable country's acceptance), each patient is free to withdraw from the study at any time. Medivir AB reserves the right to terminate the study at any time for any reason.

The Investigator also has the right to withdraw a patient from the study in the event of any of the following:

- Confirmed disease progression (refer to Section 9.1.5)

- Pregnancy or intent to become pregnant
- Occurrence of AEs or drug toxicities requiring permanent discontinuation of birinapant or pembrolizumab
- Intercurrent illness that prevents further administration of study drug
- Patient decides to withdraw consent for study participation
- General or specific changes in the patient's condition that, in the judgment of the Investigator, render the patient unacceptable for further treatment
- Protocol Violation: Study-related findings or conduct fail to meet the protocol entry criteria or the patient fails to adhere to the protocol requirements.

A patient discontinued from study participation will continue the follow-up procedures specified in Section 6. All AEs will be monitored until resolution or stabilization, or if not study related, until transfer of medical responsibility to non-study medical personnel. Patients discontinuing from treatment will be assessed for possible AEs and SAEs up to 30 days after the last dose of study drug. If an AE is identified or suspected, the patient will be required to return to the clinical site, if possible, for full evaluation, regardless of causal relationship to study-drug administration.

The reason for and date of discontinuation of study-drug treatment and the reason for and date of withdrawal from the study must be recorded on the source documentation and transcribed into the case report form (CRF). If a patient withdraws consent, every attempt will be made to determine the reason. If the reason for withdrawal is an AE or a clinically significant abnormal laboratory test result, monitoring will be continued by the Investigator until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made. The specific AE or test result(s) must be recorded on the source documentation and transcribed into the CRF.

5 INVESTIGATIONAL PRODUCT AND CONCOMINANT MEDICATIONS

Investigational product (IP) refers to birinapant and pembrolizumab. Other medications consumed either before dosing or concomitantly with study drug, may be permitted or result in the patient's exclusion or discontinuation, respectively as described below (see Section 5.5 and Section 5.6).

5.1 Formulation, Packaging and Labeling

Birinapant is supplied as a sterile-filled, clear, colorless-to-pale yellow, liquid solution. Birinapant will be supplied by the Sponsor in single use 10 mL amber glass vials, formulated in 50 mM citrate buffer (pH 5.0) at a concentration of 1 mg/mL containing a total fill volume of approximately 10.5 mL. Each vial is packaged in secondary packaging (carton) to further prevent the product from potential degradation on exposure to light.

Pembrolizumab is provided by the Sponsor as a solution for injection (100 mg/4 mL).

5.2 Storage, Preparation, Stability and Accounting

5.2.1 *Investigational Product Storage, Preparation and Stability*

Birinapant must be stored frozen in secondary packaging (below -10ºC) in a secured area until ready to use. When ready to prepare the birinapant solution, the desired dose is to be removed from the vial, under aseptic conditions, and the contents injected into an IV bag containing 250 mL of 0.9% sodium chloride for injection USP. The prepared solution of birinapant is stable under typical in-use conditions (i.e., ambient light and temperature) for 4 hours (time of preparation through to the end of infusion). Birinapant is stable through at least 5 freeze/thaw cycles.

Pembrolizumab must be stored under refrigerated conditions at 2°C to 8°C (36°F to 46°F). Details regarding preparation of pembrolizumab can be found in the pharmacy manual.

5.2.2 *Investigational Product Accountability*

The Investigator must maintain an accurate inventory log of all investigational product received, used, returned, and destroyed. Investigational product dispensed for all patients must be recorded on the drug accountability log. Information to be documented for each dispensed vial includes:

- Patient number and initials
- Treatment cohort number
- Dose level
- Date that investigational product was dispensed
- Amount dispensed (volumes and number of vials) per patient

The investigational product accountability log and remaining investigational product inventory will be reviewed at each monitoring visit by the Sponsor's clinical monitor.

The investigational products supplied for this study are for use only in patients properly consented and enrolled into this protocol.

5.2.3 *Retention of Samples*

It will be the responsibility of the Sponsor to ensure that adequate samples of all investigational products are retained in accordance with the relevant regulatory guidelines.

5.2.4 *Investigational Product Waste Handling*

It is recommended that healthcare workers follow the institution's standard procedures for handling cytotoxic drugs during preparation and administration of study drugs. The waste generated during the preparation and administration of study drug, including materials that come into direct contact with study drug (e.g., needles, gauze, and sponges), should be disposed in accordance with applicable governmental, and institutional policies regarding the disposal of hazardous biological materials and medical waste. Although birinapant did not

exhibit any evidence of mutagenicity in the Ames assay at 10 μM and does not demonstrate significant activity in the *in vitro* micronucleus assay at concentrations up to 130 μM in either the presence or absence of S9 metabolic activation.

Handling of pembrolizumab study drug waste is detailed in the study-specific pharmacy manual.

5.3 Dose Administration

All doses of investigational product will be administered via a 30-minute (± 10 minutes) peripheral or central IV infusion. During each 21-day treatment cycle, pembrolizumab will be administered first on Day 1 as a 30-minute (± 10 minutes) 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). Birinapant will be administered 30 minutes (+10 minutes) following the completion of the pembrolizumab infusion. Birinapant will be administered alone on Day 8. A week without treatment (i.e., Days 15-21) will conclude each 21-day cycle, immediately after which the treatment cycle will be repeated (i.e., with pembrolizumab on Day 1 and birinapant on Days 1 and 8). Study drugs will be administered in the arm opposite to the site of blood-sample collection.

The birinapant dose will be administered according to the dose-escalation schedule and in the dose-expansion phase of the study, according to the RP2D that will be determined in the dose escalation phase of the study.

Dose Level	Pembrolizumab + Birinapant (per 21-day cycle)
Expansion	200 mg pembrolizumab on Day 1+ **birinapant at the RP2D mg/m^2/week** on Days 1 and 8

The dose will be prepared by the site's Pharmacy and administered using materials known to be compatible with birinapant formulation. A filter should not be used during the birinapant infusion.

The birinapant dose calculation will be based on the patient's body surface area (BSA) using the Mosteller or institutional standard formula (to be calculated to the first decimal place) determined by height and weight at Screening (see the Pharmacy Manual). If a patient's BSA is > 2.5, then 2.5 will be used to calculate the patient's study-drug dose. If the patient's body weight has changed > 10% from that used to calculate the prior BSA, the BSA will be recalculated and the dose adjusted.

Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion.

The pharmacy manual contains specific instructions for the preparation of the pembrolizumab infusion and administration of infusion solution. The dosing arm will be noted and all study blood samples for collection of safety and pharmacodynamic samples must be drawn from the contralateral arm.

5.4 Dose-Limiting Toxicity and Recommended Phase 2 Dose

The inter-patient dose escalation of birinapant will be based on the number of patients that experience a DLT. A DLT is a clinically significant event attributed to birinapant, pembrolizumab, or the combination of the 2 study drugs, during the first cycle of drug therapy and is defined as follows:

Non-hematological toxicity:

- Common Toxicity Criteria for Adverse Event (CTCAE; 4.03) Grade 3 nausea, vomiting, or diarrhea despite maximal (according to treating investigator) anti-emetic or anti-diarrheal treatment and lasting > 48 hours; or Grade 4 vomiting or diarrhea;
- ≥ Grade 3 other non-hematological toxicity, excluding isolated laboratory abnormalities without clinical sequelae, except for the following:
    - Prolonged (> 7 days) serum amylase or lipase elevation;
    - Prolonged (> 7 days) aspartate aminotransferase (AST) elevation;
    - Prolonged (> 7 days) alanine aminotransferase (ALT) elevation;

  All of which will be considered dose limiting.

Hematological toxicity:

- Grade 4 neutropenia;
- Grade ≥ 3 neutropenia with fever > 38.3°C or > 38°C (> 100.9°F or > 100.4°F) for more than one hour;
- Grade ≥ 3 thrombocytopenia with bleeding

Specific toxicity:

- Cytokine release syndrome (CRS); Grade 3 or 4. Furthermore, if a Grade >2 CRS occurs during the DLT period (Cycle 1), this also triggers the permanent discontinuation of all study dosing (birinapant AND pembrolizumab) with subsequent adequate care to treat the condition (see also sections 5.5.1 and 5.5.3).

If Day 8 of treatment is held due to toxicity then the event will be considered a DLT. A prolonged delay (> 2 weeks) in initiating Cycle 2 secondary to drug-related toxicity may be considered a DLT as judged by the SRC. Events related to disease progression, intercurrent illness, or concomitant medication will not constitute a DLT. Since patients are assessed for DLTs during the first cycle, dose modifications may not be performed. If a patient experiences a DLT that is deemed related to birinapant, the dose of birinapant may be restarted at a reduced level for Cycle 2 according to dose levels indicated in Table 2/section 3 and the rules stated in section 5.5, and the patient may remain on study.

The decisions to dose-escalate birinapant for each Dose Level are indicated in Table 5 below.

Table 5 Escalation Decision Rules

Number of Patients with DLT at a Given Dose Level	Escalation-decision Rule
Zero of 3 to 6	Enter 3 to 6 patients at the next dose level.
1 out of 3 to 6	Enter up to a total of 6 patients at this dose level. • If 1 of these 3 to 6 patients experiences a DLT, proceed to the next dose level, if the next highest dose has not already been declared intolerable*. • If 1 of these 3 to 6 patients experiences a DLT and the next highest dose has already been declared intolerable, enroll a minimum of 6 patients at this dose level.
≥ 2 out of 3 to 6	Dose escalation will be stopped. This dose level may be declared the maximally administered dose (highest dose administered) and may be declared intolerable. Three additional patients may be entered at the next lowest dose level if only 3 patients were treated previously at that dose.

*Defined as ≥2 patients from 3-6 experiencing a DLT

Once the RP2D of birinapant combined with pembrolizumab is defined, additional patients with relapsed or refractory carcinoma will be enrolled in the dose-expansion phase of the study.

During the dose-expansion phase, an independent DMC will meet at least biannually to review the complete analysis of combined observed toxicities including emerging safety issues and reported SAEs. Such meetings may result in a reappraisal of the MTD and /or RP2D. In the event that dose de-escalation is to occur the same dose levels as indicated in Table 2 / section 3.1.1 should be applied.

5.5 Dosing Delays/Dose Modifications

During the dose escalation phase dose modifications of birinapant will only be permitted in Cycle 2 and beyond (section 5.5.1). During the first cycle, patients are assessed for DLTs and dose modifications may not be performed.

Following the completion of the first cycle of therapy and in the dose expansion phase, if an AE is assessed as related to study drug the dosing may be modified according to the starting cohort dose by reducing the dose of birinapant according to the schema in Section 5.5.1 . In the case where causality cannot be assigned to only one of the agents, the Investigator should first dose de-escalate birinapant, followed by withholding pembrolizumab if required. There will be no pembrolizumab dose reductions permitted in this study (for pembrolizumab dosing rules, see Table 6)

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Section 5.5.2 and Section 5.5.3 for supportive care guidelines, including use of corticosteroids. Dosing interruptions are permitted in the case of medical or surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Patients should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

If a patient experiences an AE in cycle 2 or beyond in the dose escalation phase or in the dose expansion phase of the study, the Investigator may hold birinapant for up to 14 days. On resolution of the AE (or return to baseline) birinapant may be restarted at their prior dose, or de-escalated, depending on the type and severity of the event. After a delay of > 14 days, the Investigator should consider removing the patient from the study.

5.5.1 *Dose Modifications Schema and Supportive Care Guidelines for Birinapant*

The following dose modification schemas for **birinapant** are required for selected AEs below.

Cranial Nerve Palsy	Birinapant
≤ Grade 1	No change; initiate corticosteroids[1,2]
≥ Grade 2	Interrupt up to 14 days; may restart at same or one dose below initial dose received[2]
[1]Corticosteroids should be considered at the onset of any Grade cranial nerve palsy; the recommended dose is 1-2 mg/kg day of prednisone or prednisone-equivalent, until resolution or return to baseline. [2] All patients that develop a cranial nerve palsy should have a blood sample taken to assess for HSV and VZV. Sites may also consider sending the patient for a MRI.	

In the event of facial pain, ear pain, retro-orbital pain, or atypical or new-onset headache, it is recommended that birinapant be held, and that a course of nonsteroidal anti-inflammatory agents (NSAIDs), such as ibuprofen, be initiated, at an appropriate anti-inflammatory dose. If within 24 hours symptoms do not resolve, or worsen, or the patient develops a cranial neuropathy, a course of steroids (prednisone) should be initiated. Birinapant may be re-introduced at the resolution of the event, at the same dose or at a reduced dose (by 1 dose level) depending on the severity of the event, if the Investigator and the patient are in agreement.

Cytokine Release Syndrome	Birinapant
≤ Grade 1	Interrupt up to 14 days; initiate diphenhydramine, acetaminophen*. Restart at same dose.
Grade 2	Interrupt up to 14 days; initiate diphenhydramine, corticosteroids. Restart treatment at one dose level down
> Grade 2	Interrupt permanently; initiate diphenhydramine, corticosteroids.
*Diphenhydramine, acetaminophen or intravenous fluids should be considered at the onset of cytokine release syndrome, until resolution.	

Management of Cytokine Release Syndrome (CRS): Cytokine release syndrome is defined in CTCAE v4.03 as a disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breath. CRS occurs when lymphocytes (B cells, T cells, and/or natural killer cells) and/or myeloid cells (macrophages, dendritic cells, and monocytes) become activated and release inflammatory cytokines. In addition to the symptomatology defined under CTCAE, CRS may present with fever, chills, myalgias, and malaise.

Amylase or lipase Elevation	Birinapant
≤ Grade 1	No change
≥Grade 2	Interrupt up to 14 days; restart at same dose*.
*On second occurrence, after resolution or return to baseline, a dose reduction to one dose level down should be considered.	

5.5.2 *Dose Modification Schema for Pembrolizumab*

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs. See Section 5.5.3 for supportive care guidelines, including use of corticosteroids.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

5.5.3 *Supportive Care Guidelines for Pembrolizumab*

5.5.3.1 Dose Modification and Toxicity Management Guidelines for Pembrolizumab

Dose modification and toxicity management for immune-related AEs associated with pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 6.

Table 6 Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

General instructions:
Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of pneumonitis Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		

AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	Initiate insulin replacement therapy for participants with T1DM Administer anti-hyperglycemic in participants with hyperglycemia	Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue1		
Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (e.g., propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue1		
Hypothyroidism	Grade 2-4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes

	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	Based on type and severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		
Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. NOTE: For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).				

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 7.

Table 7 Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.03 (CTCAE) at http://ctep.cancer.gov		

Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

5.6 Concomitant Medications

All patients will be required to be administered 800 mg of ibuprofen (or equipotent and equivalent alternative NSAID) prior to administration of birinapant on Day 1 and Day 8 as prophylaxis for possible events of cranial nerve palsy associated with the administration of birinapant. Patients with a history of peptic ulcer disease or gastritis will receive proton pump inhibitor for prophylaxis.

5.6.1 *Restricted and prohibited medications*

Patients are prohibited from receiving the following therapies during screening and the treatment phase (dose-escalation and dose-expansion) of this study:

- Antineoplastic systemic chemotherapy or biological, immune- or chemotherapy not specified in this protocol;
- Granulocyte-macrophage colony-stimulating factor (GM-CSF)
- Investigational agents other than pembrolizumab and birinapant;
- Radiation therapy
    - Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on an exceptional case by case basis after consultation with Sponsor's Medical Monitor. The patient 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.
- Live vaccines within 30 days before the first dose of trial treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, 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 for any purpose other than to modulate symptoms from adverse event of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor's Medical Monitor.
    - Inhaled steroids are allowed for management of asthma.
- Anti-TNF agents are excluded while on study treatment and must be discontinued prior to Cycle 1 Day 1 for a period of 5 half-lives. Examples include:
    - Infliximab (Remicade®)
    - Entanercept (Enbrel®)
    - Adalimumab (Humira®)
    - Certolizumab (Cimzia®)
    - Golimumab (Simponi®)

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

Based on *in vitro* studies, birinapant is a weak-to-moderate inhibitor of CYP3A4. Co-administration of medications that are substrates for CYP3A4 may result in an increase in their systemic exposures. Therefore, drugs with a narrow therapeutic index (e.g. alfentanil, cyclosporine, sirolimus, tacrolimus, cisapride, pimozide, fentanyl, quinidine, ergotamine, dihydroergotamine, astemizole, terfenadine) should be avoided. Birinapant is also an inhibitor of P-glycoprotein (P-gp), therefore digoxin should be used with caution. Birinapant is a substrate for the hepatic uptake transporter OATP1B3 and medications that are OATP1B3 inhibitors (e.g. cyclosporine, rifampicin, lopinavir, ritonavir) should be avoided.

Because there is a potential for interaction of birinapant with other concomitantly administered drugs through the cytochrome P450 system and transporters such as P-gp and OATP1B3, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Investigator should be alerted if the patient is taking any agent known to affect or has the potential to affect selected CYP450 isoenzymes, P-gp or OATP1B3.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study treatment or vaccination 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 patient's primary physician. However, the decision to continue the patient on study treatment or vaccination schedule requires the mutual agreement of the Investigator, the Sponsor and the patient.

All treatments that the Investigator considers necessary for a patient'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) medication, herbal supplements, and IV medications and fluids. Details regarding the generic name, reason for use, dose, route, and frequency of all prescription medications, OTC medications, or alternative therapies taken within 14 days before administration of first study dose and through 7 days after the last study-drug dose will be recorded.

5.7 Diet/Activity/Other considerations

5.7.1 *Diet*

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

5.7.2 *Contraception*

Pembrolizumab or birinapant may have adverse effects on a fetus in utero. Furthermore,

it is not known if either have adverse effects on sperm.

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 (two forms of highly effective contraception (e.g. oral contraceptive and condom, or intra uterine device and condom, abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of study treatment. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.7.3 *Use in Nursing Women*

It is unknown whether birinapant and/or pembrolizumab 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 breast-feeding are not eligible for enrollment.

5.7.4 *Phototoxicity*

The initial assessment of phototoxicity (UV/visible light absorption and the MEC value) indicates for possible phototoxic reactions by birinapant. Therefore. as a precaution, it is advised that patients avoid prolonged exposure to natural or artificial sunlight (UVA/B, such as a tanning bed) while taking the study drug by wearing sun-protective clothes, applying effective sunblock to your skin, and by wearing UV protective sunglasses.

5.8 Patient Compliance

Investigational product will be administered as an IV infusion by study staff and administration information will be recorded in the appropriate CRF. There will be no self-administration of investigational product by the study patients.

6 STUDY PROCEDURES

Study procedures and assessments to be performed for all subjects are summarized in Table 8.

Table 8 Schedule of Study Procedures and Assessments

Study Procedures	Screening (Within 28 Days of Cycle 1 Day 1)	Cycle 1			Subsequent Cycles		End of the Third Week of Every Third 21-Day Cycle	Every six weeks	Every 12 weeks	Follow up		
		Day 1	Day 2	Day 8	Day 1	Day 8				Safety Follow up Visit (30 Days After Study Drug Discontinuation)	Progressive Disease/ Study Drug Discontinuation[20]	Overall Survival Follow-up[21]
Visit Window				± 2 Days		± 2 Days	± 3 Days			+7 Days	± 3 Days	
Informed Consent	X											
Inclusion/ Exclusion Criteria	X											
Demographics	X											
Medical History and Disease Characteristics[1]	X											
ECOG Performance Status	X	X			X					X	X	
Serology[2] (HSV, VZV)	X											
Review Prior/ Concomitant Medications	X	X		X	X	X				X		
Measurement of Vital Signs[3]	X	X		X	X	X				X		

Study Procedures	Screening (Within 28 Days of Cycle 1 Day 1)	Cycle 1			Subsequent Cycles		End of the Third Week of Every Third 21-Day Cycle	Every six weeks	Every 12 weeks	Follow up		
		Day 1	Day 2	Day 8	Day 1	Day 8				Safety Follow up Visit (30 Days After Study Drug Discontinuation)	Progressive Disease/ Study Drug Discontinuation[20]	Overall Survival Follow-up[21]
Visit Window				± 2 Days		± 2 Days	± 3 Days			+7 Days	± 3 Days	
Physical Examination	X	X			X					X		
Weight and Height[4]	X	X			X							
BSA Calculation[5]		X			X							
Serum Chemistry[6]	X	X		X	X	X				X	X	
Hematology[7]	X	X		X	X	X				X	X	
Urinalysis[8]	X	X			X					X		
Hepatitis C antibody	X											
CA-125 (Ovarian Cancer patients only)	X	X			X					X		
CEA (CRC patients only)	X								X	X		
MSI for CRC patients[16]	X											
Pregnancy Test [9]	X	X			X					X		
12-Lead Electrocardiogram	X	X		X	X	X				X		
Adverse Events[10]		X	X	X	X	X				X		

Study Procedures	Screening (Within 28 Days of Cycle 1 Day 1)	Cycle 1			Subsequent Cycles		End of the Third Week of Every Third 21-Day Cycle	Every six weeks	Every 12 weeks	Follow up		
		Day 1	Day 2	Day 8	Day 1	Day 8				Safety Follow up Visit (30 Days After Study Drug Discontinuation)	Progressive Disease/ Study Drug Discontinuation[20]	Overall Survival Follow-up[21]
Visit Window				± 2 Days		± 2 Days	± 3 Days			+7 Days	± 3 Days	
Administration of pembrolizumab[11]		X			X							
Administration of NSAIDs[12]		X		X	X	X						
Administration of birinapant[13]		X		X	X	X						
Pharmacodynamic Blood Sampling[14]		X	X	X								
CD3+, CD4+, CD8+, CD19+, ANC, ALC Blood Sampling		X[15]		X[17]								
Archival Tumor Tissue Sample for Pharmacodynamic Analysis[18]	X											
Optional Tumor Biopsy Sample for Pharmacodynamic Analysis	X[18]				X[18]							
Radiological Tumor Assessment[19]	X						X				X	

Study Procedures	Screening (Within 28 Days of Cycle 1 Day 1)	Cycle 1			Subsequent Cycles		End of the Third Week of Every Third 21-Day Cycle	Every six weeks	Every 12 weeks	Follow up		
		Day 1	Day 2	Day 8	Day 1	Day 8				Safety Follow up Visit (30 Days After Study Drug Discontinuation)	Progressive Disease/ Study Drug Discontinuation[20]	Overall Survival Follow-up[21]
Visit Window				± 2 Days		± 2 Days	± 3 Days			+7 Days	± 3 Days	
ANC and ALC			X									
Survival Status												X
Pharmacokinetic Blood Sampling[22]		X	X	X								
Thyroid testing[6]	X							X				

1 Medical history and disease characteristics should include the date of the initial cancer diagnosis, a listing of relevant past and current diseases, and the details of active disease.

2 For those patients that may develop cranial nerve palsy, a second sample will be collected at the time of the event to assess for HSV (herpes simplex virus) and VZV (varicella zoster virus) viral titers.

3 Vital signs will be collected at Screening and on Days 1, and 8 of every 21-day cycle and will include blood pressure, respiration rate, heart rate, and body temperature. Vital signs should be collected pre- and post-administration of pembrolizumab, and; pre- and post-administration of birinapant).

4 Height and weight is to be measured at screening. Weight should be measured for each BSA calculation.

5 If a patient's BSA is > 2.5, then 2.5 will be used to calculate the patient's study-drug dose. If the patient's body weight has changed > 10% from that used to calculate the prior BSA, the BSA will be recalculated and the dose adjusted.

6 Serum chemistry will be performed at screening (within 10 days of Cycle 1 Day 1) and on Days 1 and 8 of every cycle beginning with Cycle 1 Day 1. Chemistry panel is to include the following parameters: lipase, amylase, albumin, total protein, blood glucose (non-fasting), sodium, potassium, chloride, bicarbonate, magnesium, calcium, blood urea nitrogen (BUN), creatinine, AST, ALT, alkaline phosphatase (ALP), total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), gamma glutamyltransferase (GGT), and phosphate. If screening chemistry is performed within 72 hours of Cycle 1 Day 1, the sample does not need to be repeated. Thyroid function testing includes triiodothyronine (T3) or free triiodothyronine (FT3), Thyroxine (T4) or free thyroxine (FT4), and TSH

7 Hematology will include CBC and differentials. Hematology will be performed at screening (within 10 days of Cycle 1 Day1) and on Days 1 and 8 of every cycle beginning with Cycle 1 Day 1. If screening hematology is performed within 72 hours of Cycle 1 Day 1, the sample does not need to be repeated

8 Urinalysis will be performed at screening and on Day 1 of every 21-day cycle. If screening urinalysis is performed within 72 hours of Cycle 1 Day 1, the sample does not need to be repeated

9 For women of child bearing potential, a serum pregnancy test must be performed at screening only. Urine or serum pregnancy tests must be done within 72 hours before the first dose of study drug. A urine pregnancy test can be performed at all other study visits. Monthly pregnancy testing should be conducted as per local regulations where applicable.

10 The adverse event reporting period is from the time the patient signs consent until 30 days after study-drug discontinuation.
Adverse events that lead to study-drug discontinuation should be followed until resolution or stabilization.
11 Pembrolizumab 200 mg will be administered first on Day 1 of each 21-day cycle.
12 All patients will be required to be administered All patients will be required to be administered 800 mg of ibuprofen (or equipotent and equivalent alternative NSAID) prior to administration of birinapant on Day 1 and Day 8 as prophylaxis for possible events of cranial nerve palsy associated with the administration of birinapant.
13 Birinapant will be administered 30 minutes (+10 minutes) after pembrolizumab on Day 1 and by itself on Day 8 of each 21-day cycle.
14 Pharmacodynamic blood samples will be collected from all patients in Cycle 1. These samples will be sent to a central laboratory for analysis.

- Day 1: prior to pembrolizumab (sample 1) and 4 hours post-birinapant dose (sample 2)
- Day 2: 24 hours post-birinapant dose (from Day 1) (sample 3)
- Day 8: prior to birinapant (sample 4) and 4 hours post-birinapant dose (sample 5)

15 A peripheral blood sample will be collected to assess for $CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, ANC and ALC on cycle 1 day 1 prior to the pembrolizumab infusion A CBC is required prior to dosing. This sample will be analyzed locally.
16 MSI testing for CRC patients done at local laboratory. Results from an historical sample can be used if done within 24 months of C1D1
17 A peripheral blood sample will be collected to assess for $CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, ANC and ALC on cycle 1 day 8 4 hours after the completion of the birinapant infusion. A CBC is required prior to dosing. This sample will be analyzed locally.
18 Archival tumor tissue sample for biomarkers should be obtained during screening (pre-dose; paraffin embedded archival); if no archival sample is available, a fresh biopsy, though not required, may be obtained. A subsequent second optional fresh tumor biopsy may be requested at any time during Cycle 2 (time of sampling post-dose will be recorded) or after to assess the pharmacodynamics of birinapant and pembrolizumab in this patient population. For further information, consult the laboratory manual.
19 All patients will be required to have a CT scan of their chest, abdomen and pelvis during screening. MRIs will be allowed but the same radiological modality must be used at each repeat assessment. Repeat radiological assessments will be performed every 9 weeks (last week of every 3rd cycle). In the event of a response, a confirmatory scan must be performed 4 weeks following initial assessment of response. All radiological assessments will be reviewed according to both RECIST v 1.1 and iRECIST criteria.
20 Patients who discontinue from study treatment due to reasons other than disease progression will need to be followed every 30 days until documentation of disease progression or initiation of a new therapy for their disease. Once disease progression is documented or new therapy is initiated the patient will move into the survival follow up stage of the protocol.
21 Patients will be contacted by telephone every 3 months after last study-drug treatment for survival information and subsequent therapy information
22 Pharmacokinetic blood samples will be collected from all patients in Cycle 1. These samples will be sent to a bioanalytical laboratory for analysis.

- Day 1: 4 hours after completion of birinapant infusion (sample 2)
- Day 2: 24 hours after completion of birinapant infusion (from Day 1) (sample 3)
- Day 8: prior to birinapant (sample 4) and 4 hours after completion of birinapant infusion (sample 5)

6.1 Duration of Patient Participation

The anticipated duration of participation for the screening and treatment periods, for each patient, is determined by the following:

Screening may not exceed 28 days before the first dose of study drug. In the absence of treatment delays due to AE(s), treatment may continue until one of the following criteria applies:

1. Confirmed disease progression (refer to Section 9.1.2 and Section 9.1.5),
2. Intercurrent illness or unacceptable AE(s) that prevents further administration of treatment,
3. Patient decides to withdraw from the study, or
4. General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the Investigator.

Patients will be allowed to remain on active treatment for 35 treatment cycles or until documented progressive disease (PD) or unacceptable toxicity. All patients will be followed for survival.

Patients will be followed for survival until death, withdrawal of consent, or study closure, whichever occurs first. Patients removed from study treatment for unacceptable AE(s) should be followed until resolution or stabilization of the AE, and should be followed for disease progression and or initiation of a new therapy and survival where feasible.

In addition, the study may be terminated by the study Sponsor; in this case all efforts will be made to continue to provide study drug to patients who are continuing to benefit clinically from them. However, this cannot be guaranteed.

6.2 Timing of Study Procedures

6.2.1 *Screening*

Potential patients will be contacted to determine their interest in participating in this study and, after providing written informed consent, will be evaluated for eligibility by screening tests and conformity to study inclusion and exclusion criteria.

Once a patient is determined to be eligible for Screening and satisfy all initial inclusion and exclusion criteria (Section 4.1 and Section 4.2 respectively), screening procedures will be performed as listed below. If at any point during Screening, a finding disqualifies the patient from study participation, no further screening tests will be performed.

The Screening visit will occur within 28 days before dosing with study drug unless otherwise specified.

The following assessments will be performed at the Screening visit:

- Demographics

- Medical history and disease characteristics, including the following:
    - Date of initial cancer diagnosis
    - Listing of relevant past and current diseases
    - Details of active disease
- Serology (Hepatitis C Antibody, HSV and VZV)
- Review prior/concomitant medications
- Vital signs (blood pressure, respiratory rate, heart rate, and body temperature)
- CT Scan (chest, abdomen, pelvis)
- RECIST 1.1 entry measurements.
- Physical examination
- Height and weight
- ECOG performance status
- 12-lead electrocardiogram (ECG)
- Safety laboratory studies (chemistry, urinalysis, and other studies including serum pregnancy test in females of childbearing potential), complete blood count (CBC) and differential within 10 days of Cycle 1 Day 1
- CA-125 sampling for ovarian cancer patients
- MSI testing for CRC patients done at local laboratory. Results from an historical sample can be used if done within 24 months of C1D1
- CEA sampling for CRC patients
- Thyroid function testing:
    - Triiodothyronine (T3) or free triiodothyronine (FT3)
    - Thyroxine (T4) of free thyroxine (FT4)
    - TSH
- Mandatory archival sample for pharmacodynamic analysis (pre-dose; paraffin embedded archival); if no archival sample is available, a fresh pre-dose biopsy, though not required, may be obtained.

The patient may be enrolled upon confirmation by the Sponsor/Designee CRO that the patient meets the enrollment criteria.

The Investigator will review each patient's screening data and document the patient's acceptability for study participation. If results are acceptable, the patient will be asked to return to the study site for the treatment phase of the study.

For patients who fail screening, the Investigator will record demographics and reason for screen fail in the appropriate sections of the CRF and note the reason for exclusion. These documents and the patient's signed informed consent will be retained in the study files.

6.2.2 *During Active Protocol Treatment*

The following procedures will be performed during active protocol treatment at the times specified in the Study Procedures table. (Refer to Table 8)

Day 1 of Each Cycle

- ECOG performance status
- Concomitant medications
    - Any medication other than the investigational products are considered concomitant medication and will be documented in the eCRF. This includes natural supplements.
- Physical examination and vital signs
    - Vital signs including temperature, respiratory rate, blood pressure, and heart rate before administration of investigational product, and immediately following administration of investigational product. (Pre- and post-administration of pembrolizumab, and; pre- and post-administration of birinapant) Temperatures for individual patients must be measured using the same method at all visits.
- Weight and BSA
    - If the patient's BSA is greater than 2.5, 2.5 will be used to calculate the dose. If the patient's body weight has changed >10% from that used to calculate the prior BSA, the BSA will be recalculated and the dose adjusted.
- Hematology, chemistries, urinalysis and pregnancy (if applicable)
- CA-125 sampling for ovarian cancer patients
- 12-lead ECG
- $CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, ANC and ALC peripheral blood sample [Cycle 1 only (pre pembrolizumab infusion)]
- Pharmacodynamic blood sample collection (Cycle 1 only)
- Pharmacokinetic blood sample collection (Cycle 1 only)
- Pharmacodynamic optional fresh tumor biopsy (Cycle 2 onwards)
- Adverse events
- Administration of pembrolizumab
- Administration of NSAIDs prior to birinapant
- Administration of birinapant followed by observation for 4 hours after completed infusion

Day 2 of Cycle 1 Only

- Pharmacodynamic blood sample collection
- Pharmacokinetic blood sample collection
- Absolute neutrophil count (ANC) and lymphocyte (ALC)
- Adverse events

Day 8 of Each Cycle

- Concomitant medications
- Vital signs (pre- and post-administration of birinapant)
- Adverse events
- Pharmacodynamic blood sample collection (Cycle 1 only)
- Pharmacokinetic blood sample collection (Cycle 1 only)
- $CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, ANC and ALC peripheral blood sample [Cycle 1 only (4 hours post birinapant infusion)]
- Hematology, serum chemistry
- 12-lead ECG
- Administration of NSAIDs prior to birinapant

Administration of birinapant followed by observation for 4 hours after completed infusion

End of the Third Week of Every Third Cycle

- Radiological tumor assessment (RECIST v1.1 and iRECIST) at the end of Weeks 9, 18, 27, 36, etc.

Every Six weeks

- Thyroid function testing:
  - Triiodothyronine (T3) or free triiodothyronine (FT3)
  - Thyroxine (T4) or free thyroxine (FT4)
  - TSH

Every Twelve weeks

- CEA sampling for CRC patients

6.3 Procedures After Active Protocol Treatment Phase

Patients will be treated until unacceptable toxicity, confirmed disease progression (refer to Section 9.1.5), or another criterion for treatment discontinuation is encountered.

Patients who discontinue treatment because of adverse events will be followed until resolution to baseline or stabilization of the adverse event. All patients will return for a safety evaluation 30 days (+ 7 days) following the last dose of study drug.

Those patients that are discontinued from study treatment due to reasons other than disease progression, but have not withdrawn consent to be followed for survival will need to be followed every 30 days until documentation of disease progression or initiation of a new therapy for their disease. Once there is documentation of disease progression or initiation of a new therapy for their disease, the patient will move into the long-term survival follow up phase of the study.

All patients will be followed every 3 months for survival.

Patients will be considered lost-to-follow-up only if no contact has been established by the time the study is completed such that there is insufficient information to determine the patient's status at the end of the study. Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, follow-up should resume according to the protocol.

6.3.1 *Safety Follow up Visit*

The following procedures will be performed at the safety follow-up visit:

- Physical examination
- Vital signs
- ECOG performance status
- Clinical laboratory evaluations including hematology, serum chemistry, urinalysis and pregnancy test
- Concomitant medication inquiry
- Adverse events
- 12-lead Electrocardiogram
- CA-125 sampling for ovarian cancer patients
- CEA sampling for CRC patients

6.3.2 *Disease Progression Follow up Visit*

Those patients that are discontinued from study treatment due to reasons other than disease progression, but have not withdrawn consent to be followed for survival; will need to be followed every 30 days until documentation of disease progression or initiation of a new therapy for their disease. Once there is documentation of disease progression or initiation of a new therapy for their disease, the patient will move into the long-term survival follow up phase of the study.

The following procedures will be performed at this follow up visit:

- Hematology, serum chemistry
- ECOG PS
- Radiological tumor assessment (RECIST v1.1 and iRECIST) until documentation of disease progression as defined by RECIST or iRECIST
- Initiation of any new cancer therapy and type of therapy

6.3.3 *Overall Survival Follow up Visit*

Patients will be monitored by telephone every 3 months for the following:

- Survival status
- Date of next cancer therapy and type of therapy. Participation in any other interventional clinical study during follow-up is permitted.

7 STUDY ASSESSMENTS

7.1 Safety Measurements

The primary objective of the dose escalation phase and the secondary objective of the dose expansion phase is to assess the safety and tolerability of birinapant in combination with pembrolizumab, which in addition to adverse events assessments will be evaluated using the assessments described below. For timing of each of the safety assessments for all enrolled subjects refer to Section 6 and Table 8.

7.1.1 *Medical History and Disease Characteristics*

A complete medical history will include evaluation for past or present cardiovascular, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, metabolic, lymphatic, hematologic, immunologic, dermatologic, psychiatric, and genitourinary disorders, medication and surgical history, and review of any other diseases or disorders.

7.1.2 *Concomitant Therapy or Medication*

Concomitant therapy or medication usage will be monitored throughout the study. Details of restricted medications and potential drug interactions are found in Section 5.6.

7.1.3 *Eastern Cooperative Oncology Group Performance Status*

Eastern Cooperative Oncology Group (ECOG) performance status will be will be assessed throughout the study.

7.1.4 *Physical Examination*

The physical examination will include examination of the following: general appearance, head, ears, eyes, nose, throat, neck (including thyroid), skin, cardiovascular system, respiratory system, gastrointestinal system, musculoskeletal system, lymph nodes and nervous system. Any findings made during the physical examination must be noted regardless of if they are part of the patient's medical history.

7.1.5 *Vital Signs*

Vital signs include sitting blood pressure, heart rate, respiratory rate, and temperature.

Temperature for individual patients must be measured using the same methodology on each occasion. Respiratory rate and sitting heart rate will be counted for at least 30 seconds. Serial measurements of heart rate and blood pressure will be obtained using the same arm, after two minutes' rest, preferably using a mercury sphygmomanometer. Blood pressure will be recorded to the nearest mm.

7.1.6 *Electrocardiograms*

12-lead ECGs will be taken in the supine position, after the patient has been lying down for at least three minutes.

The following parameters will be assessed: heart rate; PR, QRS, QT, QTcF (Fridericia's correction) intervals. The Investigator (or a qualified observer at the investigational site) will interpret the ECG using one of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant.

7.1.7 *Clinical Laboratory Tests*

7.1.7.1 Hematology, Serum Chemistry, Immunology and Urinalysis, Serology

The following samples will be analyzed by the local laboratory.

Hematology with Differential: to include; hemoglobin, hematocrit, red blood cells (RBCs), white blood cells (WBCs), platelet count, WBC subset count (neutrophils, eosinophils, basophils, lymphocytes, and monocytes), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean cell hemoglobin concentration (MCHC).

Clinical Chemistry - to include; lipase, amylase, albumin, total protein, blood glucose (non-fasting), sodium, potassium, chloride, bicarbonate, magnesium, calcium, blood urea nitrogen (BUN), creatinine, AST, ALT, alkaline phosphatase (ALP), total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), gamma glutamyltransferase (GGT), and phosphate, thyroid function testing (triiodothyronine (T3) or free triiodothyronine (FT3), Thyroxine (T4) or free thyroxine (FT4), TSH).

Immunology: to include CD3, CD4, CD8 and CD19

Urinalysis – Urine collected to determine pH, blood, protein, ketones, leukocyte elastase, nitrite, glucose, specific gravity, urobilinogen, and bilirubin. If blood, leukocytes or nitrites are detected, microscopy will be completed.

Serology: to include Hepatitis C Antibody

7.1.7.2 Pregnancy Testing

The following samples will be analyzed at local laboratory.

For women of childbearing potential, a negative serum β-HCG pregnancy test is required at screening to confirm eligibility. A stat negative urine pregnancy test is required before dosing on Days 1 of each cycle.

7.1.7.3 Histology

Submission of formalin-fixed paraffin embedded tumor tissue sample blocks are preferred; if submitting unstained slides, the slides should be freshly cut and submitted to

the testing laboratory within 7 days from site slide sectioning date otherwise a new specimen will be requested. See laboratory manual.

Note: Subjects for whom an archived sample cannot be obtained may submit a newly obtained specimen only upon agreement from the Sponsor.

8 ADVERSE EVENTS

8.1 Definition of Adverse Events

As defined by the ICH/GCP (CPMP/ICH/135/95), an AE is:

- Any untoward medical occurrence in a study patient 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 product, whether or not considered related to the medicinal product.

An AE includes but is not limited to:

- Any clinically significant worsening of a patient's pre-existent condition
- An overdose, whether accidental or deliberate, defined as a dose higher than that prescribed by a healthcare professional for clinical reasons, or a dose higher than that described in the approved labelling for a marketed product, or in available clinical data for a study drug
- Abuse (i.e., use for nonmedical reasons) of an investigational or marketed product

Note: Progression of the cancer under study is not considered an adverse event.

A protocol-related AE is any AE that bears a direct relationship to a study procedure or the alteration of ongoing pre-study drug regimens, medical procedures, or treatments discontinued as required by the protocol.

8.1.1 *Recording and Reporting of Adverse Events*

All adverse events that occur after the consent form is signed but before treatment start must be reported by the investigator if they cause the subject to be excluded from the study, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

From the time of treatment start through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section Immediate Reporting of Adverse Events to the Sponsor. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

AEs will be reported in accordance with the NCI CTCAE v4.03, using a recognized medical term or diagnosis that accurately reflects the event. AEs will be assessed by the Investigator for severity and relationship to investigational product (birinapant/pembrolizumab), for other possible etiologies, and whether the event meets criteria as an SAE and therefore requires immediate notification to the Sponsor. If an AE has not resolved at the end of the study reporting period, it will be documented as ongoing. If an AE evolves into a condition that becomes "serious," it will be reported as an SAE.

For hematological toxicity fluctuations, record the highest grade during the cycle on the patient's eCRF.

8.1.2 *Severity of an Adverse Event*

Severity of AEs will be graded according to NCI CTCAE version 4.03.

AEs that are not included in the NCI CTCAE lists will be graded according to the NCI CTCAE general guideline for grades as follows:

Grade 1 Mild, asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate, minimal, local intervention, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL), e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL, e.g., bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to adverse event

8.1.3 *Relationship of an Adverse Event*

Causal relationship to study drug will be rated as follows:

- **Not Related** –
    - A medical condition that is present before the administration of study drug unless the condition worsens or episodes increase in frequency after administration of investigational product;
    - Symptoms that are reasonably determined to be the normal course of the disease state (NOTE: life-threatening complications from cancer are considered SAEs);
    - An event for which sufficient information exists to indicate the etiology is related to a concomitant medication;

- Medical events (e.g., unrelated illness, accident, or trauma) that occur during the clinical study for which sufficient information exists to indicate that the etiology is not related to the investigational product;
- Symptoms from procedures such as surgery or radiation which are not a direct result of receiving investigational product.

- **Possibly Related** –
  - An event that follows a reasonable temporal sequence from administration of the investigational product;
  - An event that follows a known or expected response pattern to the suspected investigational product but could readily have been produced by a number of other factors.
- **Probably Related** -
  - An event that follows a reasonable temporal sequence from investigational product administration;
  - An event that follows a known or expected response pattern to the suspected investigational product;
  - Is confirmed by stopping or reducing the dosage of the investigational product;
  - Cannot be reasonably explained by the known characteristics of the patient's clinical state or by other factors.
- **Definitely Related -**
  - An event that follows a reasonable temporal sequence from investigational product administration;
  - Follows a known or expected response pattern to the suspected investigational product;
  - Is confirmed by improvement on stopping or reducing the dosage of the investigational product and reappearance of the reaction on repeated exposure unless the latter is considered to be medically unethical.

Certain drug-mediated AEs and laboratory abnormalities may not resolve promptly upon dechallenge. While dechallenge-rechallenge may afford the Investigator greater confidence regarding causality of an AE, the welfare and consent of the patient must be primary in any decision to rechallenge with discontinued investigational product. In the absence of rechallenge, the Investigator will use his/her best judgment and consider all available information when determining the most likely relationship between the AE and investigational product treatment.

The designee CRO pharmacovigilance physician will review AE attribution independently. This is not a conclusive determination of causal association between the investigational product and the event. Whenever the Investigator's assessment is

unknown or unclear, the AE will be treated as investigational product-related for the purposes of reporting to regulatory authorities.

8.2 Serious Adverse Events

8.2.1 *Definition of a Serious Adverse Event*

A SAE is an AE that results in any of the following outcomes:

- Results in death
- Is life threatening (i.e. the patient is at immediate risk of death at the time the event occurred; it does not refer to an event which might hypothetically have caused death had it been more severe)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Other (medically important) events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

If there is any doubt whether the AE constitutes an SAE, it should be treated as serious and reported as such, until confirmation can be obtained.

8.2.2 *Expectedness*

An AE is considered unexpected if it has not been described previously in either published descriptions of the investigational product (e.g., package inserts), in the medical literature, or in reports of previous clinical trials of the investigational product, including the IB.

8.3 Notification/Reporting of a Serious Adverse Event

In addition to the criteria listed in Section 8.2.1, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements.

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

- A new cancer (that is not a part of the cancer being studied); or
- Associated with an overdose.

For the time period beginning when the consent form is signed until treatment start, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (refer to Section 9.1 for additional details), that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment start through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (refer to Section 9.1 for additional details), whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor by paper.. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent)

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

After submitting an initial SAE report for a patient, the Investigator is required to follow the patient proactively and provide further information on the patient's condition to Diamond PV Services Ltd.

	Diamond PV Services Ltd
Central Email	pvservices@diamondpharmaservices.com
Fax number	+44 (0) 1279 418 964

All subjects with SAEs should be followed to resolution or stabilization by the Investigator or until 30 days after the last dose of any investigational product. All related SAEs should continue to be followed, even if this extends beyond the study reporting period. Resolution of an SAE is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

To the Institutional Review Board

In addition to reporting the SAE to the Sponsor or representative, the Investigator must also notify the IRB which approved the study according to their requirements.

Copies of all correspondence relating to reporting of any SAEs should be maintained in the site's study files and will be checked routinely by the Study Monitor.

8.4 Notification of Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

Events of clinical interest for this study include:

1. An overdose of Sponsor's product, as defined for pembrolizumab as ≥1000 mg (5 times the dose) and for birinapant as any dose ≥15% greater than the protocol assigned cohort dose that may or may not be associated with clinical symptoms or abnormal laboratory results. No specific information is available on the treatment of overdose of pembrolizumab or birinapant. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing. Corresponding redacted local laboratory report must be sent in with the SAE reporting form.

   The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

3. A cranial nerve palsy

For the time period beginning when the consent form is signed until treatment start, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment start through 30 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, by paper. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

8.5 Withdrawal Due to an Adverse Event

Any patient who experiences an AE may be withdrawn from investigational product treatment and/or the study at any time, at the discretion of the Investigator. If a patient is withdrawn wholly or in part because of an AE, both the AE page and termination page (end of treatment termination and/or study termination) of the CRF will be completed at that time, especially if the patient may not be able to return to the investigative site for the regularly scheduled follow-up visit.

The patient's condition will be monitored until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made.

8.6 Pregnancy

Based on information solicited by the Investigator at scheduled study follow-up or provided spontaneously by patients at any time, if a patient becomes pregnant or the partner of a male patient participating in the study becomes pregnant during the study or within 3 months of discontinuing the investigational product (birinapant/pembrolizumab), the Investigator will report the pregnancy to Diamond PV Services Ltd within 24 hours. If treatment with investigational product is ongoing at the time, the investigational product will be immediately discontinued for any female patient who becomes pregnant.

The female patient or the partner of a male patient should be followed at least monthly by the Investigator and the subject's status documented 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 the pregnancy ends for any reason before the anticipated date, the Investigator will attempt to determine the cause and will notify the Sponsor. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e. postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly) the Investigator will 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.

8.6.1 *Reporting of Pregnancy and Lactation to the Sponsor*

Although pregnancy and lactation are not considered adverse events, 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 study.

Pregnancies and lactations that occur after the consent form is signed but before treatment start must be reported by the investigator if they cause the subject to be excluded from the study, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and lactations that occur from the time of treatment start through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer 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 (Important Medical Events). 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 by paper. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

9 EFFICACY

Although the clinical benefit of the combination of these drug(s) has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability. Patients with measurable disease will be assessed using RECIST v 1.1 and iRECIST (Seymour et al. 2017). For the purposes of this study, all patients will be required to have a CT scan of their chest, abdomen, and pelvis within 28 days of Cycle 1 Day 1 and then will be re-evaluated every 9 weeks (end of every 3rd treatment cycle). The same radiological imagining modality used at screening must be used throughout the patient's course of treatment (CT or MRI; X-ray is not adequate to assess measurable disease). In the event of a response, a confirmatory scan must be performed 4 weeks following initial assessment of response.

9.1 Antitumor Effect

Response and progression will be evaluated in this study using Response Evaluation Criteria in Solid Tumors (RECIST) guideline version 1.1. and iRECIST.

9.1.1 *Tumor Imaging*

Tumor imaging should be performed by computed tomography (CT) (preferred). MRI should only be used when CT is contraindicated or for imaging in the brain, but the same imaging technique should be used in a patient throughout the study. An MRI can be utilized if clinically appropriate. X-ray may not be used to assess disease.

All patients are required to have a CT of the chest, abdomen, and pelvis within 28 days of Cycle 1 Day 1. Local site study team reading (Investigator assessment with site radiology reading) based on RECIST 1.1 and iRECIST will be used to determine patient eligibility and response.

Scans performed as part of routine clinical management are acceptable for use as initial tumor imaging if they are of diagnostic quality and performed within 28 days before Cycle 1 Day 1.

9.1.2 *RECIST 1.1 Response Criteria*

Table 9 Disease Response Criteria for Target and Non-Target Lesions

Category	Response Criteria	
	Target Lesions	**Non-Target Lesions**
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (target or non-target) must have reduction in short axis to < 10mm.	Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10mm short axis).
Partial Response (PR)	A ≥ 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter	N/A
Non-CR/Non PD	N/A	Persistence of one or more non-target lesion(s).
Not Evaluable	When no imagining/measurement is done at a particular time-point or if only a subset of lesions is made at an assessment.	When no imagining/measurement is done at a particular time-point or if only a subset of lesions is made at an assessment.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum longest diameter since treatment started.	N/A
Progressive Disease (PD)	A ≥ 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started, or the appearance of one or more new lesions.	Appearance of one or more new lesions, and/or unequivocal progression of existing non-target lesions.

Source: (Eisenhauer et al. 2009).

Table 10 Time Point Response: Patients with Target (+/- Non-Target) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non CR/Non-PD	No	PR
CR	Not Evaluated	No	PR
PR	Non-PD or Not all Evaluated	No	PR
SD	Non-PD or Not all Evaluated	No	SD
Not All Evaluated	Non-PD	NO	NE
PD	Any	Yes or NO	PD
Any	PD	Yes or NO	PD
Any	Any	Yes	PD
CR=complete response, PR=partial response, SD=stable disease, PD=progressive disease, and NE=not evaluated			

Source: (Eisenhauer et al. 2009).

9.1.2.1 Lesions that become too small to measure

As patients respond to treatment, target lesions may be too small to measure. The radiologist performing the tumor evaluation must provide clear documentation that the lesion is either 'present, but too small to measure' or must document that the lesion has in fact disappeared. In the case where the lesion has disappeared then the measurement would be recorded as 0 mm. However, in all cases the radiologist must make an attempt to provide an actual measurement of all target lesions, even if the lesion measures less than 5mm. In cases where the lesion is too small to measure and the radiologist cannot provide a measurement, a measurement of 5 mm will be documented.

9.1.2.2 Lesions that split or grow together

If a target lesion splits into two separate lesions, the lesion diameters need to be added together to calculate the sum of the lesions. If two target lesions grow together, the vector of the longest diameter of the now merged lesions will be recorded as the lesion measurement.

9.1.3 *On-Study Tumor Imaging*

Following the screening CT scans, patients are to have repeat radiological assessments at the end of Cycle 3 [9 weeks (63 days ±3 days) from Cycle 1 Day 1]. Subsequent radiological assessments are to be performed every 9 weeks (at the end of every 3rd treatment cycle) until documentation of disease progression. If cycles become delayed, for whatever reason, the imaging schedule will as a default follow a nine-week pattern regardless of where in terms of cycles the subject is. If there is a large mismatch the PI can discuss frequency with the medical monitor

Per RECIST 1.1, if a patient has a documented partial or complete response, a

confirmatory tumor radiological assessment is to be performed not less than 4 weeks from the date the response was first documented.

Patients are to continue to have tumor assessments performed until whichever of the following occurs first:

- Site-assessed disease progression is documented
- The start of new anti-cancer treatment
- Withdrawal of consent
- Death
- The end of the study

9.1.4 *Immune RECIST (iRECIST)*

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment of pembrolizumab. Immunotherapeutic agents such as pembrolizumab 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 adaptations:

- If radiologic imaging verifies initial progressive disease (PD), tumor assessment should be repeated ≥4 (iRECIST 4-8) weeks later in order to confirm PD with the option of continuing treatment per below while awaiting radiologic confirmation of progression.

At initial progressive disease based on RECIST 1.1 criteria, iRECIST: can have iUPD (Unconfirmed Progressive Disease). Imaging must then be repeated 4-8 weeks later. Progression is defined as the time of the first iUPD followed by the next confirmatory scan showing progression. Thus, iPFS is defined as the time to iUPD if the next scan (4-8 weeks later) confirms PD (state change from iUPD to iCPD, time to progression defined in this instance as iUPD). Note: following iUPD, if the next assessment is not a CPD, treatment can continue until iCPD is documented.

- iRECIST criteria:
    - For iUPD; if repeat imaging shows < 20% tumor burden increase compared to nadir, stable or improved previous new lesion (if identified as cause for initial PD), and stable/improved non-target disease (if identified as cause for initial PD), treatment may be continued/resumed.
    - NOTE; if repeat imaging confirms PD due to any of the scenarios listed below, patients will be discontinued from study therapy.

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.

Scenarios where PD is confirmed at repeat imaging (iCPD):

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

In patients who have initial evidence of radiological PD, it is at the discretion of the treating physician whether to continue a patient on study treatment until repeat imaging is obtained. This clinical judgment decision should be based on the patient's overall clinical condition, including performance status, clinical symptoms, and laboratory data.

iRECIST criteria include the above RECIST 1.1 derived criteria (see Table 11 and Table 12 below) with the proviso that the increase in tumor burden must be shown to increase, but in the case of iUSD, iUPR or iCR, the assessment time bar is reset.

For target lesions, iCR, iPR and iSD can all be assigned after iUPD has been documented as long as iCPD has not been confirmed. Progression is confirmed in the target lesion category if the next imaging assessment after iUPD (4-8 weeks later) confirms an increase in the sum of target lesions dimensions of greater than 5 mm. However, iCPD is not met if the imaging assessment after iUPD is followed by CR, PR or SD (compared to baseline as defined in RECIST 1.1). The status is reset and assessment continues. Please note this is different from RECIST 1.1

Thus iUPD can be assigned on multiple occasions, as long as iCPD is not declared.

Table 11 Comparison of RECIST 1.1, iRECIST and irRECIST

	RECIST 1.1	iRECIST	irRECIST
Definitions of disease: numbers, sites and target or non	Measurable are diameters greater than 10 mm (15 for nodes maximum of 5 (2 per organ)	No change from RECIST 1.1	No change from RECIST 1.1
CR, PR or SD	Cannot have met criteria for progression	Can have had iUPD (more than once) but not iCPD before iCR, iPR or iSD	Use of terminology based around RECIST 1.1
Confirmation of CR or PR	Only in non-randomized studies	As per RECIST 1.1	As per RECIST 1.1
Confirmation of SD	Not required	As per RECIST 1.1	As per RECIST 1.1
New lesions	Progression: recorded but not measured	iUPD but only becomes iCPD if on the next scan there are new lesions or the size increases by greater than 5 mm	Unclear
Confirmation of progression	Not required	Required	Required
Consideration of clinical status	Not required	Clinical stability considered at iUPD to decide treatment continuation	As iRECIST without terminology considering unconfirmed findings

Table 12 Trajectory of progression in iRECIST

Target Lesions: iCR, Non-target: iCR, no new lesions	iCR	iCR
Target lesions: iCR, Non-target: non iCR/non iUPD, no new lesions	iPR	iPR
Target Lesions: iPR, Non-target: non iCR/non iUPD, no new lesions	iPR	iPR
Target lesions: iSD, Non-target: non iCR/non iUPD, no new lesions	iSD	iSD
Target lesions: iUPD with no change or with a decrease from the last time point, Non-target: iUPD with no change or decrease from last time point, new lesions	NA	New lesions confirm iCPD if new lesions previously identified and increased in size (≥ 5 mm in sum of measures for new lesions or any increase for new lesion non-target) or increase in number. If no change is seen in new lesions assignment remains iUPD
Target lesions: iSD, iPR, iCR, non-target: iUPD, no new lesions	iUPD	Remains iUPD unless iCPD is confirmed by increase in the size of non-targets (does not need to meet RECIST 1.1 criteria)
Target lesions: iUPD, non-target: non iCR/non iUPD, no new lesions	iUPD	Remains iUPD unless iCPD confirmed on the basis of further increase ≥ 5 mm; otherwise stays as iUPD
Target lesions: iUPD, non-target: iUPD, no new lesions	iUPD	Remains iUPD unless iCPD confirmed on previously identified targets iUPD ≥ 5 mm or non-target iUPD

Target lesions: iUPD, non-targets: iUPD, new lesions	iUPD	Remains iUPD unless iCPD confirmed by increase of ≥ 5 mm previously identified target, or non-target or an increase in size or number of new lesions
Target lesions non iUPD or progression, non-targets: non iUPD or progression, new lesions	iUPD	Remains iUPD unless iCPD confirmed by increase in size or number of new lesions previously identified.

Target lesions, non-target lesions and new lesions are defined according to RECIST 1.1 criteria: if no pseudoprogression occurs, RECIST 1.1 and iRECIST categories for CR, PR and SD are the same. * Previously identified in the assessment prior to this time point. 'I' indicates immune responses assigned using iRECIST

Patients may receive study drugs treatment while waiting for confirmation of PD 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
- No requirement for intensified management of disease related symptoms exists, including analgesia, radiotherapy and palliative care

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

9.1.5 *In Study iRECIST Assessment of Disease*

As noted above, if tumor imaging shows initial disease progression, the study site may elect to continue treatment, repeat imaging 4-8 weeks later and assess tumor response or confirmed progression per iRECIST.

iRECIST is the adaptation of RECIST 1.1 as described below to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST 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. Treatment efficacy based on iRECIST as assessed by central imaging vendor review will be

evaluated retrospectively.

Table 13 Imaging and treatment after first radiologic evidence of PD (iRECIST designation iUPD)

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of PD by RECIST 1.1	Repeat imaging at ≥ 4 weeks at site to confirm PD	May continue study treatment at the local site Investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at ≥ 4 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat tumor imaging confirms PD by iRECIST at the local site	No additional imaging required	Discontinue treatment (exception is possible upon consultation with sponsor)	No additional imaging required	N/A
Repeat tumor imaging shows SD, PR or CR by iRECIST by the local site	Continue regularly scheduled imaging assessments	Continue study treatment at the local site Investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next tumor image should occur according to the every 9 week (63 ± 7 days) imaging schedule

- In determining whether or not the tumor burden has increased or decreased, local study site investigators should consider all target lesions as well as non-target lesions. 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 or iUPD**), it is at the discretion of the site investigator to continue treating the subject with the assigned treatment per protocol until progression of disease (iCPD) is confirmed at least 28 days from the date of the scan first suggesting PD. If radiologic progression is confirmed by subsequent scan then the subject will be discontinued from trial treatment. If radiologic progression is not confirmed by iRECIST per the site, then the patient should resume or continue trial treatment and have their next tumor imaging according to the protocol schedule of every 9 weeks (end of every 3rd treatment cycle) until progression is confirmed at a later timepoint by the site. In applying iRECIST, the appropriate documentation at

each time point must be made (i.e. iSD, iUPR, iUCR). For a more comprehensive and detailed account of the application of RECIST 1.1 and iRECIST for in-study imaging assessments please refer to the imaging guide document Note that RECIST 1.1 must always serve as the primary imaging assessment guide up to the first indication of disease progression after which iRECIST may be used as described.

- Any subject deemed **clinically unstable** should be discontinued from trial treatment at 1st radiologic evidence of PD and is not required to have repeat imaging for PD 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 9 weeks), until (1) the start of new anti-cancer treatment, (2) disease progression (3) death, or (4) the end of the study, whichever occurs first.

If a subject has confirmed radiographic progression (i.e. 2 scans at least 4 weeks apart demonstrating progressive disease) per iRECIST, 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's Medical Monitor. In this case, if treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in sections 6.0 Study Flowchart and be submitted to the central imaging vendor. iRECIST: for the sequences of imaging assessments following iUPD please see Table 11 and Table 12.

10 PHARMACODYNAMIC SAMPLING

Pharmacodynamic blood samples will be collected on Cycle 1 Day 1 before the dose of pembrolizumab and 4 hours post-birinapant dose and on Cycle 1 Day 2 at 24 hours post-birinapant dose. On Cycle 1 Day 8, pharmacodynamics blood samples will be collected before the dose of birinapant, and 4 hours post-birinapant dose. Refer to Table 14.

Table 14 Timing of Pharmacodynamic Sampling

Birinapant Infusion (Cycle 1 Day 1)	
Sample 1	Prior to pembrolizumab infusion
Sample 2	4 hours after the end of the birinapant infusion
Birinapant Infusion (Cycle 1 Day 2)	
Sample 3	24 hours after completion of birinapant infusion
Birinapant Infusion (Cycle 1 Day 8)	
Sample 4	Prior to birinapant infusion
Sample 5	4 hours after the end of the birinapant infusion

Blood samples will be collected to evaluate changes in cIAP1 expression in pre- and post-treatment samples as a pharmacodynamic marker of birinapant activity. Blood samples (PBMCs) may also be evaluated for gene expression studies to understand the mechanism of action of the combination of birinapant and pembrolizumab.

Serum samples will be evaluated for cytokines such as GM-CSF, IFNγ, IL10, IL2, IL3, IL4, IL5, IL6, IL7, IL8, MIP-1α, MIP-1β, MCP-1, TNFα, and TNFβ.

Paraffin embedded archival tumor tissue will be obtained if available from all patients for gene expression studies, immunohistochemistry for PD-L1 and cIAP1 expression and for assessment of Tumor Infiltrating Lymphocytes (TILs). In patients for whom a paraffin embedded archival tissue sample is not available, a pre-dose fresh tumor biopsy may be performed however this is not required for participation on the study, and patients without a paraffin embedded archival sample or a fresh biopsy may still be enrolled.

Patients may also consent to have an optional post-dose tumor biopsy at a single time-point any time during or after Cycle 2.

Translational biomarker assessments of blood, archival tumor samples and optional tumor biopsy samples will be evaluated (see Table 15). Pre- and post-treatment changes in the expression of cIAP1 in peripheral blood samples will be assessed. Pre-treatment PD-L1, cIAP1 and Tumor Infiltrating Lymphocytes (TILs) will also be evaluated in archival tumor samples and / or pre- and post-treatment optional tumor biopsy. Inhibitor of apoptosis protein (IAP) gene copy number studies in archival tumor samples or pre-treatment optional tumor biopsy samples will be conducted. Blood or serum samples may also be evaluated for cytokines such as GM-CSF, IFNγ, IL10, IL2, IL3, IL4, IL5, IL6, IL7, IL8, MIP-1α, MIP-1β, MCP-1, TNFα, and TNFβ. CD3, CD4, CD8, and CD19 and FOXP3 as well as absolute neutrophil count and absolute lymphocyte count will be assessed through peripheral blood pre- and post-dosing of birinapant and pembrolizumab.

Table 15 Summary of Pharmacodynamic Assessments

Marker	**Tissue**	**Purpose of analysis**

Pre- and post-treatment levels of cIAP1 expression	Blood (PBMC)	Evidence of target engagement of birinapant
Gene expression analysis	Blood (PBMC)	Evidence of immune system modulation
Serum Cytokines such as GM-CSF, IFNγ, IL10, IL2, IL3, IL4, IL5, IL6, IL7, IL8, MIP-1α, MIP-1β, MCP-1, TNFα, and TNFβ	Blood (serum)	Evidence of immune system modulation
Blood samples looking at CD3, CD4, CD8, and CD19 as well as absolute neutrophil count and absolute lymphocyte count	Blood	Peripheral changes in WBC populations
Pre-treatment PD-L1 expression	Archival tumor	May predict pembrolizumab sensitivity
Gene expression analysis by Nanostring	Archival tumor or pre-treatment optional biopsy	May predict pembrolizumab sensitivity. May allow derivation of predictive response signature of combination
	Post-treatment optional biopsy	Evidence of treatment-induced changes
cIAP1 expression	Archival tumor	May predict birinapant or combination sensitivity
	Post-treatment optional biopsy	Evidence of target expression and modulation in tumor
Inhibition of apoptosis protein (IAP) gene copy number	Archival tumor	May predict birinapant or combination sensitivity
Tumor infiltrating lymphocytes (TILs) CD3, CD4, CD8 and CD20 and FOXP3	Archival tumor	May predict birinapant or combination sensitivity
	Post-treatment optional biopsy	May provide evidence of increased anti-tumor immune activity
MSI mismatch repair assessment (CRC only)	Archival tumor	May predict pembrolizumab sensitivity

11 PHARMACOKINETIC SAMPLING

Pharmacokinetic blood samples will be collected on Cycle 1 Day 1 4 hours after completion of birinapant infusion and on Cycle 1 Day 2 at 24 hours after completion of birinapant infusion. On Cycle 1 Day 8, pharmacokinetic blood samples will be collected before the dose of birinapant, and 4 hours after completion of birinapant infusion (Table 16).

Table 16 Timing of Pharmacokinetic Sampling

Birinapant Infusion (Cycle 1 Day 1)	
Sample 2	4 hours after completion of birinapant infusion
Birinapant Infusion (Cycle 1 Day 2)	
Sample 3	24 hours after completion of birinapant infusion
Birinapant Infusion (Cycle 1 Day 8)	
Sample 4	Prior to birinapant infusion
Sample 5	4 hours after completion birinapant infusion

All blood samples will be collected from the arm opposite the site of infusion or distal to the site of infusion, in collection tubes containing K_2EDTA. If there is a delay in completion of birinapant infusion, this must be noted in the CRF. If birinapant infusion is resumed to completion, PK sample collection will continue with end of infusion and post-infusion timepoints.

Blood samples (2mL) for pharmacokinetic analyses will be drawn into pre-labeled tubes containing K_2EDTA anticoagulant at the time points specified in Table 16. Within 30 minutes of collection, blood samples will be centrifuged under refrigeration (approximately +4°C at 1500 g RCF) for approximately 10 minutes. Plasma will be harvested and divided into 2 separate aliquots. Samples will be stored frozen (-70ºC preferred, or -20 ºC - for specifications see Laboratory Manual) in pre-labeled cryovials prior to bioanalysis.

12 STATISTICAL CONSIDERATIONS

12.1 General Considerations

Details of the scope and nature of statistical analyses to be utilized in analyzing data from this study will be found in the Statistical Analysis Plan (SAP). The analysis of all the safety and pharmacodynamic parameters will be performed by Medivir or its designee.

Safety analyses will include all patients who receive at least one dose of either investigational product. All data collected for these patients will be used in the analyses, and no imputation will be performed for missing data. AEs that are unrelated to treatment and that occur more than 30 days after treatment administration will not be reported or analyzed. The statistical methods employed in this protocol will be primarily

descriptive since the study was not sized for a specific level of power. No inferential statistics will be utilized in the safety analyses.

For all analyses, baseline is defined as the last measurement for a variable before the dose of pembrolizumab or birinapant. All data collected on the eCRF will be included in data listings. Routine data listing or tabulation review during the study conduct will be performed to identify missing data, anomalies, and outliers.

Unless otherwise stated, continuous variables will be summarized using number of observations, mean standard deviation, median (as appropriate), minimum, and maximum. Categorical variables will be tabulated with frequencies and percentages.

All analyses will be performed using SAS® version 9.3 or later (SAS Institute, Cary NC), or comparable software. A complete description of data handling rules and planned statistical analyses will be detailed in a separate SAP before conducting any planned analysis.

12.2 Determination of Sample Size

No formal sample size or power calculations will be performed for the dose-escalation phase of the study. A sample size of 3 to 6 patients per cohort is a feasible sample size to assess safety for dose escalation and dose-limiting toxicity. Additional patients may be needed for cohort expansion during dose escalation, for the replacement of non-evaluable patients. Only patients who do not complete the first cycle due to study drug related toxicity will be replaced.

Once the RP2D of birinapant combined with pembrolizumab is defined, additional patients with relapsed or refractory carcinoma will be enrolled in the dose-expansion phase of the study.

The dose expansion phase will comprise 4 cohorts of 26-30 patients, as follows:

- Colorectal cancer (28 patients)
- Ovarian cancer (27 patients)
- Cervical cancer (26 patients)
- Various solid tumors (30 patients, including 5 patients with each of the 6 following tumor types: (Small cell lung cancer; Cholangiocarcinoma; Gastroesophageal carcinoma; Mesothelioma; Head and Neck Squamous Cell Carcinoma (HNSCC)-checkpoint inhibitor-naïve; and HNSCC checkpoint inhibitor-experienced)

A Simon's 2-stage design (Simon 1989) will be used for each of the cohorts in colorectal cancer, ovarian cancer and cervical cancer, as outlined in Table 17. A predefined interim analysis allowing stopping each of these cohorts for futility and safety will be conducted in the first stage to limit undue exposure before further inclusion into a given cohort.

The interim analyses will be based on at least 6 and most 13 patients having completed from 9 up to 27 weeks of treatment (3 to 9 cycles) in the colorectal cancer cohort and based on at least 6 and at most 16 and 15 patients in the ovarian cancer cohort and

cervical cancer cohort, respectively. Note that one additional patient will be included in each cohort. This patient will only be included in the interim analysis in case a patient drops out in that cohort. Thus, the number of included patients in each cohort will be 27+ 1 (CRC), 26+1 (ovarian) and 25+1 (cervical). In all cases this extra patient will be included in the main/end analysis. If the predefined level for success in a given cohort is reached prior to the stipulated number of patients being enrolled/completed, enrollment in that cohort may be discontinued.

The Simon's two-stage design yields a type I error rate of 0.05 and statistical power of 0.80 for each of the three main cohorts described above using a one-sided test when the true response rate is 20% for colorectal cancer, 25% for ovarian cancer and 30% for cervical cancer. No formal sample size or power calculation will be performed for the fourth cohort.

12.3 Randomization and Stratification

No randomization or stratification will be utilized in this study.

12.4 Analysis Population

The following four populations will be defined for this study:

- Intent-to-Treat Population (ITT): will comprise any patient that is enrolled to the study and receives a dose of pembrolizumab and birinapant. Note that the ITT population can be considered equivalent to the Full Analysis Set population as no randomization is done in this study.
- Safety Population: will be the same as the ITT population.
- Efficacy Evaluable Population: will comprise all patients in the ITT population who have baseline and at least one post-baseline efficacy assessment, unless the patient dies or experiences an AE that results in study drug termination prior to assessment. At that point, the patient will be considered to have progressed in the absence of other data.
- Pharmacodynamic Population: The pharmacodynamic population will include all treated patients for whom pre- and post- infusion pharmacodynamic data are available.

12.5 Demographics and Baseline Characteristics

Descriptive statistics will be provided to summarize demographics and baseline characteristics.

12.6 Analysis of Safety Data

The safety and tolerability of pembrolizumab and birinapant will be based on results of DLT incidence, reported SAEs, AEs, vital sign measurements, physical examinations, clinical laboratory information, ECOG performance status, and concomitant medications. Exposure to study drug and reasons for discontinuation will be tabulated. These data will

be summarized descriptively for the dose escalation phase and for the dose expansion phase of the protocol separately for the ITT population. Safety data will be summarized descriptively by cohort and also summarized descriptively over cohorts within each of the two phases of the protocol.

For parameters measured over time, data and changes from baseline will be summarized for each time point. Adverse events will be coded using the current *Medical Dictionary for Regulatory Activities* (MedDRA) classification system, and will be summarized by system organ class and preferred term.

Additional safety analyses may be determined in order to most clearly describe toxicity rates and to further define the safety profile of pembrolizumab and birinapant.

12.7 Efficacy Analysis

Efficacy, as measured by the ORR, will be assessed through RECIST v1.1 and iRECIST measurements and clinical response per Investigator. Results will be summarized descriptively (See SAP for further details).

In the dose expansion phase of the protocol, the null hypothesis that the true response rate is p_0 will be tested against the one-sided alternative $H_A: ORR > p_0$ in each of the three cohorts in Simon's two-stage design (Simon 1989). The statistical test will be performed for each cohort with p_0 , p_1, n_1, n, r_1 and r_2 as in Table 17 as follows. In the first stage, n_1 patients will be accrued. If there are r_1 or fewer responses in these n_1 patients, the study will be stopped. Otherwise, n - n_1 additional patients will be accrued for a total of n patients. The null hypothesis will be rejected if r_2+1 or more responses are observed in n patients. This design yields a type I error rate of 0.05 and power of 0.80 when the true response rate is p_1 for each of the three main cohorts. No correction for multiple comparisons are done.

Table 17 Simon's two-stage design settings in each of the three main cohorts

Indication	**Response rate** (ORR)		n_1 (# patient in the 1st stage)	n (Total #patients)	r_1 (Continue with stage 2 if >r_1 responses in stage 1)	r_2 (p-value <=0.05 if >r_2 responses after stage 2)
	Poor drug (p_0)	Good drug (p_1)				
Colorectal cancer	<=5%	>=20%	13	27	0	3
Ovarian cancer	<=7%	>=25%	16	26	1	4
Cervical cancer	<=10%	>=30%	15	25	1	5

Note that one additional patient will be included in each cohort. This patient will only be included in the interim analysis in case a patient drops out in that cohort. Thus, the number of included patients in in each cohort will be 27+1 (CRC), 26+1 (ovarian) and 25+1 (cervical). In all cases this extra patient will be included in the main/end analysis. The final statistical analysis will take account of the actual number of patients evaluable for efficacy.

12.8 Analysis of Pharmacodynamic Parameters

Descriptive statistics will be provided to summarize pharmacodynamic parameters. For parameters measured over time, observed data and changes from baseline will be summarized for each time point.

Descriptive statistics will be provided to summarize pharmacodynamic parameters. For parameters measured over time, observed data and changes from baseline will be summarized for each time point.

12.9 Analysis of Pharmacokinetic data

The plasma PK data of birinapant will be summarized descriptively. Population PK modeling may also be applied to analyze the data and will, in that case, be reported separately.

13 DATA COLLECTION, STUDY MONITORING AND DATA DISCLOSURE

Data will be collected using CRFs that are specifically designed for this study. The data collected on the CRFs will be captured in a clinical data management system (CDMS) that meets the technical requirements described in US 21 Code of Federal Regulations (CFR) Part 11. The CDMS will be fully validated to ensure that it meets the scientific, regulatory, and logistical requirements of the study before it is used to capture data from this study. Before using the CDMS, all users will receive training on the system and study specific training. After they are trained, users will be provided with individual system access rights.

All required study data will be collected from primary source documents (or direct electronic capture from validated instrument operating systems, where applicable) by appropriately designated and trained personnel at the clinical facility, and CRFs must be completed for each patient screened consistent with the data source. Patients' actual identity will be coded appropriately and should not be discernible from the data provided on the CRF. CRF content will be verified against data sources by the study monitor, and reviewed for consistency by Data Management using both automated logical checks and manual review. All data collected will be approved by the Investigator at the clinical site. This approval acknowledges the Investigator's review and declaration that the data are complete and accurate.

Queries regarding study data in CRFs will be provided to the clinical site and will be reviewed and responded to, based on all raw study data, in the manner dictated by the Sponsor.

14 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents include Investigator's Study Files and patients' clinical source documents.

The Investigator will ensure the Study Files are maintained with copies of the CRFs and data query forms, protocol/amendments, IRB and regulatory approvals with associated correspondence, all versions of informed consent templates, all original, signed informed consents, study drug shipment and accountability records, staff curricula vitae and training records, authorization forms, all correspondence, and all other appropriate documents. The Study File will be inspected by the study monitor periodically and as part of the study closeout visit and must be made available in the event of a regulatory inspection or Sponsor's quality assurance audit.

Patients' clinical source documents may include, but need not be limited to, patient's hospital/clinic records, physicians' and nurses' notes, study visit appointment book, original laboratory reports, ECG, radiograph, laboratory, pathology and special assessment reports, and consultant communications, including all information relating to study patient referrals from other medical institutions or individuals.

Financial information related to conduct of the study by both the Sponsor and the Investigator are to be kept separate from files relating to study conduct and are confidential, privileged information with respect to regulatory audits.

15 QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, a quality assurance audit may be performed by the Sponsor or its designees. Regulatory authorities may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the Investigator and institution agree to provide the auditors/inspectors direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditors/inspectors to discuss findings and any relevant issues.

The Investigator and study staff are responsible for maintaining a comprehensive and accurate filing system of all study-related documentation in a manner suitable for inspection at any time by the Sponsor, its designees, and/or regulatory authorities. By signing this protocol, the Investigator attests that he/she understands and agrees to provide access to the necessary documentation and files.

As applicable, both the Investigator and Sponsor are responsible for implementing and maintaining quality control and quality assurance systems, each with written standard operating procedures (SOPs), to ensure that this study is conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of GCP, and all applicable governmental legal/regulatory requirements of both the US and the country in which the study is conducted.

16 ETHICS AND GOOD CLINICAL PRACTICE COMPLIANCE

This study will be carried out according to the Declaration of Helsinki, the Notes for Guidance on GCP (2000) (CPMP/ICH/135/95) and with ICH GCP.

This protocol and any accompanying material, including information that will be provided to prospective patients (such as advertisements, patient information sheets, or study descriptions used to induce study participation or obtain informed consent) must be submitted by the Investigator to the IRB. Approval of each such submission must be obtained from the committee before it may be used in the study and must be documented in a written notification to the Investigator specifying the protocol number, protocol version, documents reviewed, and date on which the committee met and granted the approval. In particular, each informed consent document must bear clear evidence (written, stamp, date of approval, etc.) of IRB approval before it may be presented to prospective (or ongoing, as appropriate) study patients for signature.

Written evidence of the approval must be made available to the Sponsor. Any modifications made to the protocol and of correspondingly modified informed consent documents made after receipt of IRB approval must also be submitted to the committee for approval before implementation unless the modification is made on an emergency basis to protect the welfare of study patients. In the latter case, the IRB must be notified promptly and their written approval must be obtained as soon after the fact as possible.

Appropriate reports on the progress of the study will be made to the IRB and the Sponsor by the Investigator in accordance with applicable regulatory regulations and in conformity with policies established by both the IRB and the Sponsor. The shortest time interval between required reports required by either party or by regulations will prevail.

The Investigator at each investigative site, or his/her nominee, will be responsible for reporting any SAEs to the IRB as soon as possible, and in accordance with the guidelines of the IRB.

The Sponsor or its designee will be responsible for reporting all serious, life threatening or fatal adverse study drug events with a causal relationship to the study drug to appropriate regulatory agencies within their required timelines.

The Investigator will submit the site-specific informed consent to the Sponsor for approval before submitting to the IRB. The Investigator is responsible for obtaining written, informed consent(s) from each prospective patient interested in participating in this study before performing any study-related procedures. Written informed consent must be obtained after adequate, thorough, and clear explanation of the aims, methods,

objectives, and potential hazards of the study, as well as any use of the patient's genetic information from the study. The Investigator must use the most current IRB-approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the patient and the person obtaining consent and each page not signed must be initialed and dated by the patient. The investigational site must retain the original signed consent and provide a copy to the patient.

Information concerning the protocol, the study information, patent applications, and processes, scientific data, or other pertinent information is confidential and remains the property of the Sponsor. The Investigator may use this information for the purpose of the study only and may not disseminate it in whole or in part to third parties except for a participating CRO, the IRB, regulatory authorities, or, after Sponsor approval, to others involved in study conduct.

The Sponsor will use information developed in this clinical study in connection with the development of birinapant and, therefore, may disclose it as required to other clinical Investigators participating in other studies and to regulatory agencies. In order to allow the use of the information derived from this clinical study, the Investigator understands that he/she has an obligation to provide all data produced during this study to the Sponsor.

The Sponsor considers that clinical data (complete or incomplete) constitute financially sensitive information. Consequently, the Sponsor requires that discussion of results in any form, electronic, verbal, or written before study completion and full reporting should only be undertaken with the Sponsor's prior written consent.

Individual patients' medical information obtained as a result of this study is considered confidential. The Investigator and the study center will adhere to all applicable laws relating to the protection of patient information. To assure that patients' confidentiality is maintained, patients' data will be identified by a study-assigned number and date of birth only.

All Sponsor personnel will handle patients' data in a confidential manner in accordance with applicable regulations governing clinical research. Patients' records will be inspected only in connection with this research project. Information generated as a result of a patient's participation in this study may be disclosed to third parties for research and regulatory purposes in any country as determined by the Sponsor. However, patients will not be individually identified but will be referred to only by the study assigned number and the patient's date of birth.

16.1 Patient Information and Consent

All patients will receive written and verbal information regarding the study. This information will emphasize that participation in the study is voluntary and that the patient may withdraw from the study at any time and for any reason. All patients will be given

the opportunity to ask questions about the study and will be given sufficient time to decide whether to participate in the study.

Before any study-related procedures will be performed the ICF will be signed and personally dated by the patient (or their legally acceptable representative and/or witness, as applicable) and by the qualified person who conducted the informed consent discussion. Local regulations and laws regulate who is authorized to conduct the informed consent procedure.

The consent includes information that the patient's identity will be kept confidential, except as required by the law, and except for inspections by Agencies that regulate experimental drug studies, auditors, members of Independent Review Boards or Ethics Committees, and the study Sponsor or agents of the sponsor.

A copy of the patient information including the signed consent form will be provided to the patient.

The patient 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.

17 STUDY SITE CLOSURE

Upon completion or termination of the study, the Sponsor/CRO monitor will conduct site closure activities with the Investigator and site staff (as appropriate), in accordance with applicable regulations, GCP, and Medivir AB's and the designee CRO's SOPs.

FDA can temporarily suspend or terminate the study upon receipt of information that raises doubts about the safety or scientific validity of the study.

Medivir AB reserves the right to temporarily suspend or to terminate the study or close a site at any time for reasons including (but not limited to) lack of recruitment, futility, safety issues, ethical issues, or severe noncompliance. If Medivir AB determines that such action is required, Medivir AB will discuss the reasons for taking such action with the Investigator or head of the medical institution (where applicable). When feasible, Medivir will provide advance notice to the Investigator or head of the medical institution of the impending action. If a study is suspended or terminated for safety reasons, Medivir will promptly inform all Investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. Medivir AB will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the Investigator or head of the medical institution must inform the IRB promptly and provide the reason(s) for the suspension/termination.

18 RECORD RETENTION

All clinical study documents must be secured and retained by the Investigator until at least two years after the last approval of a marketing application in an ICH region (i.e., US, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until two (2) years after the investigation is discontinued and regulatory authorities have been notified. Investigators may need to retain documents longer if required by applicable regulatory requirements or if requested by the Sponsor. The Investigator must notify the Sponsor before destroying any clinical study records.

The Investigator will notify the Sponsor of the intended storage location for all study records. Should the Investigator have reason to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

If the Investigator cannot guarantee this archiving requirement at the investigative site for any or all of the documents, special arrangements must be made between the Investigator and the Sponsor to store these in sealed containers in an off-site storage location so that they can be returned to the Investigator in case of a regulatory audit. Where source documents are required for the continued care of the patient, appropriate copies will be made for off-site storage.

No study document should be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, the Investigator must notify the Sponsor in writing of the new responsible person and/or the new location.

19 PROVISION OF STUDY RESULTS AND INFORMATION TO INVESTIGATORS

A Clinical Study Report (CSR) will be prepared after the study has been completed, and all data have been entered, reviewed, and analyzed. The CSR will be signed off by the Sponsor's representative, and where required by applicable regulatory requirements, the Investigator.

The sponsor reserves the right to collate preliminary data from this open label study as ad hoc analyses that enables update reporting at scientific conferences. In such cases, the data will be handled as outlined in the SAP and protocol sections 12 as well as 13.

The Investigator must submit to the Sponsor, any proposed publication or presentation, along with information about the scientific journal or presentation forum, at least 30 days before submission of the publication or presentation (2 weeks for abstracts). The Investigator will comply with requests from the Sponsor to delete references to its confidential information (other than the study results) in any publication or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

No such interim communication, presentation or publication will include the Sponsor's confidential information.

After conclusion of the study, the Investigator may make oral presentations of study results or publish such results in scientific journals or other scholarly media without prior written approval from the Sponsor, only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of the Sponsor in an abstract, manuscript, or presentation forum;
- The Investigator has complied with all requests from the Sponsor to delete any references to its confidential information (other than study results);
- The study has been completed for at least 2 years.

20 FINANCING AND INSURANCE

Agreements about the appropriate payment will be made between the Sponsor and the Investigator(s) and will be known as the Clinical Trial Agreement. Payment will relate to the number of patients as well as the cost of clinical visits, laboratory investigations, and other services outside of normal routine examinations and specifically connected with the conduct of this study. This agreement will cover payment for CRFs fully completed in conformity with the protocol. The fee for participants who withdraw prematurely from the study will be on a pro-rata basis reflecting the percentage of study activities completed.

Patients may be compensated for the time that they spend participating in the study using a formula determined by the investigative site.

Insurance will be provided in conformity with US guidelines and institutional requirements for all patients involved in the study. The patient should not take part in any other clinical study while enrolled in this study. The patient should report any health injury that could have occurred as a result of the clinical study to the Investigator without delay.

21 STUDY ADMINISTRATIVE INFORMATION

21.1 Protocol Amendments

Alterations to study procedures not previously provided for in the protocol will require a protocol amendment. The amendment must be approved in writing by the IRB before implementation and may require a revised informed consent document to be signed by all patients who are ongoing or about to enroll in the study.

An exception will be made only if immediate changes to treatment are necessary to protect the health and welfare of study patients. In such a case, the IRB will be notified promptly and the protocol will be amended and submitted for IRB approval as promptly as possible.

21.2 Biological Specimens

The identity and contact information for the laboratories responsible for analyzing biological specimens (e.g., pharmacodynamic samples) is located in the study reference documents. Instructions for handling and shipment of biological samples will be provided in the study reference documents.

22 REFERENCES

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23 APPENDICES

Appendix 1 Blood Volume

During the study blood will be drawn at the study visit. Limited blood volumes will be taken at each single occasion. Approximate blood volume per study visit have been listed below:

Study Procedures	Screening	Cycle 1			Subsequent Cycles				Follow up	
		Day 1	Day 2	Day 8	Day 1	Day 8	Every 6 weeks	Every 12 weeks	Safety Follow up Visit	PD/ Study Drug Discontinuation
Serum Chemistry	X	X		X	X	X			X	X
Hematology	X	X		X	X	X			X	X
Pregnancy test serum at screening	X									
PD blood sampling		X	X	X						
CD3+, CD4+, CD8+, CD19+ ANC, ALC		X		X						
ANC, ALC			X							
Serology (HSV, VZV)	X									
Hepatitis C antibody	X									
PK blood sampling		X	X	X						
Hepatitis C antibody	X									
Thyroid testing	X						X			
CEA for CRC patients	X							X	X	
MSI for CRC patients	X									
CA-125 for Ovarian cancer patients	X	X			X				X	
Approximate Blood Volume per visit (mL)	**45**	**60**	**45**	**45**	**45**	**45**	**15**	**15**	**45**	**45**

Appendix 2 Inclusion/Exclusion criteria for individual cohorts

Appendix 2.1 Inclusion/Exclusion criteria Dose Escalation Phase

NB: Inclusion/exclusion criteria numbering is derived from the complete set of criteria defined in sections 4.1 and 4.2.

Inclusion criteria

Patients will be eligible for study participation if they meet ALL of the following inclusion criteria, after patient has provided written informed consent.

1. The patient is male or female ≥ 18 years of age on the day of signing informed consent.
2. The patient is able to understand and voluntarily sign a written informed consent, and is willing and able to comply with the protocol requirements.
3. The patient must have a histologically confirmed solid malignancy that is metastatic or unresectable and for which standard curative or palliative measures do not exist or are no longer effective. Patients with tumors with mutations for which there are FDA-approved therapies must have progressed following these therapies in order to be eligible for this study. Patients with metastatic colorectal cancer should have progressed on prior fluoropyrimidine-based therapies, and have no curative therapies available to them, in order to be eligible for this study. Colorectal cancer patients should be assessed for microsatellite instability (MSI) status as per the local site routines. (*Dose Escalation Phase only*)
4. Patients must have measurable disease based on RECIST 1.1 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. Patients must have an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1 at screening.
6. Patients must have a life expectancy of greater than 12 weeks.
7. Patients must have amylase and lipase values < ULN.
8. Patients must demonstrate adequate organ function as defined in Table A2.1. All screening labs should be performed within 10 days of treatment initiation.

Table A2.1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L

Renal	
Creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5xULN **OR** ≥60 mL/min for patient with creatinine levels >1.5x institutional ULN
Hepatic	
Total bilirubin	≤1.5xULN **OR** Direct bilirubin ≤ULN for patients with total bilirubin levels >1.5xULN), unless known Gilbert's Syndrome has been diagnosed
AST (SGOT) and ALT (SGPT)	≤2.5xULN OR ≤5.0xULN for patients with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5xULN unless patient 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 patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a] Creatinine clearance should be calculated per institutional standard.	

9. Female patients of childbearing potential must have a negative urine or serum serum pregnancy test will be required.

10. Female patients of childbearing potential must be willing to use an adequate pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a method of contraception for the course of the study through 120 days after the last dose of study medication.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient.

11. Male patients with female partners of childbearing potential 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.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient.

12. A tumor tissue sample for PD-L1 biomarker analysis from archival material, a newly obtained core or excisional biopsy is available for submission. Repeat samples may be required if adequate tissue is not provided.

13. Have resolution of toxic effect(s) of the most recent prior chemotherapy to Grade 1 or less (except neuropathy or alopecia). If patients have received major surgery or radiation therapy of > 30 Gy, they must have recovered from the toxicity and/or complications from the intervention.

Exclusion Criteria

A patient will be excluded from the study for any one or more of the following reasons:

1. Patients who have 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 adverse events due to agents administered more than 4 weeks earlier prior to study Day 1.
2. Patients who have had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who have not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

Note: Patients with ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia are an exception to this criterion and may qualify for the study.

Note: If patients have received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

3. Patients who are currently participating and receiving study therapy or who have participated in a study of an investigational agent and received study therapy or who have used an investigational device within 4 weeks of the first dose of treatment.
4. Patients who have received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways) or if the patient has previously participated in Merck MK-3475 clinical trials. (*Not applicable for various solid tumors cohort, head and neck squamous cell carcinoma check-point inhibitor experienced group*)
5. Patients with known active central nervous system (CNS) metastases and/or carcinomatous meningitis.

Note: Patients 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 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 systemic steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

6. Patients with a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

7. Patients who have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to birinapant or pembrolizumab or their constituents.
8. Patients requiring the use of anti-tumor necrosis factor (anti-TNF) therapies, such as infliximab, or patients who have received treatment with anti-TNF therapies within 5 half-lives of the drug.
9. Patients with a diagnosis of immunodeficiency or who are receiving systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days before the first dose of study drug. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
10. Patients with an uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure, hypertension, unstable angina pectoris, cardiac arrhythmia, autoimmune or inflammatory diseases, or psychiatric illness that would limit compliance with study requirements.
11. Patients with an active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
12. Patients who have evidence of active, non-infectious pneumonitis. Patients with a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
13. Patients with a history of interstitial lung disease.
14. Patients who are 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. Pregnant women and men who want to conceive a child are excluded from this study because birinapant and pembrolizumab are agents with unknown potential for teratogenic or abortifacient effects in humans. Because there is an unknown risk for AEs in nursing infants secondary to treatment of the mother with birinapant and pembrolizumab, breastfeeding should be discontinued if the mother is treated on this study.
15. Patients who have a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies), or active Hepatitis B (e.g., HBsAg reactive). Patients with active Hepatitis C (e.g., HCV RNA [qualitative] is detected).
16. Patients who have received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.

17. Patients who have disease that is suitable for local therapy administered with curative intent.

18. Patients who have received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including G-CSF, GM-CSF or recombinant erythropoietin) within 4 weeks prior to study Day 1.

19. Patients who have a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or it is not in the best interest of the patient to participate, in the opinion of the treating investigator.

20. Patients who have known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

21. Patients who have severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.

23. Patients who have previously received birinapant treatment.

Appendix 2.2 Inclusion/Exclusion criteria Dose Expansion Phase Colorectal cancer cohort

NB: Inclusion/exclusion criteria numbering is derived from the complete set of criteria defined in sections 4.1 and 4.2.

Inclusion Criteria

Patients will be eligible for study participation if they meet ALL of the following inclusion criteria, after patient has provided written informed consent.

1. The patient is male or female ≥ 18 years of age on the day of signing informed consent.
2. The patient is able to understand and voluntarily sign a written informed consent, and is willing and able to comply with the protocol requirements.
4. Patients must have measurable disease based on RECIST 1.1 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. Patients must have an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1 at screening.
6. Patients must have a life expectancy of greater than 12 weeks.
7. Patients must have amylase and lipase values < ULN.
8. Patients must demonstrate adequate organ function as defined in Table A2.2. All screening labs should be performed within 10 days of treatment initiation.

Table A2.2 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5xULN **OR** ≥60 mL/min for patient with creatinine levels >1.5x institutional ULN
Hepatic	
Total bilirubin	≤1.5xULN **OR** Direct bilirubin ≤ULN for patients with total bilirubin levels >1.5xULN), unless known Gilbert's Syndrome has been diagnosed

AST (SGOT) and ALT (SGPT)	≤2.5xULN OR ≤5.0xULN for patients with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5xULN unless patient 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 patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a] Creatinine clearance should be calculated per institutional standard.	

9. Female patients of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

10. Female patients of childbearing potential must be willing to use an adequate method of contraception for the course of the study through 120 days after the last dose of study medication.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient.

11. Male patients with female partners of childbearing potential 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.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient.

12. A tumor tissue sample for PD-L1 biomarker analysis from archival material, a newly obtained core or excisional biopsy is available for submission. Repeat samples may be required if adequate tissue is not provided.

13. Have resolution of toxic effect(s) of the most recent prior chemotherapy to Grade 1 or less (except neuropathy or alopecia). If patients have received major surgery or radiation therapy of > 30 Gy, they must have recovered from the toxicity and/or complications from the intervention.

14. Patients with metastatic colorectal cancer with no available therapy options that are known to provide clinical benefit per institutional standard of care. Patients with tumors with mutations for which there are available therapies that are known to provide clinical benefit, as defined by national authority and/or ratified by national guidelines or equivalent, must have progressed following these therapies in order to be eligible for this study.

15. Patients with histological or cytologically confirmed metastatic colorectal cancer which is Microsatellite Stable (MSI-Stable) accordingly to local laboratory testing.

Exclusion Criteria

A patient will be excluded from the study for any one or more of the following reasons:

1. Patients who have 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 adverse events due to agents administered more than 4 weeks earlier prior to study Day 1.
2. Patients who have had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who have not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

Note: Patients with ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia are an exception to this criterion and may qualify for the study.

Note: If patients have received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

3. Patients who are currently participating and receiving study therapy or who have participated in a study of an investigational agent and received study therapy or who have used an investigational device within 4 weeks of the first dose of treatment.
4. Patients who have received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways) or if the patient has previously participated in Merck MK-3475 clinical trials. (*Not applicable for Head and Neck Squamous Cell Carcinoma Check point inhibitor experienced group*)
5. Patients with known active central nervous system (CNS) metastases and/or carcinomatous meningitis.

Note: Patients 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 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 systemic steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

6. Patients with a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
7. Patients who have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to birinapant or pembrolizumab or their

constituents.

8. Patients requiring the use of anti-tumor necrosis factor (anti-TNF) therapies, such as infliximab, or patients who have received treatment with anti-TNF therapies within 5 half-lives of the drug.
9. Patients with a diagnosis of immunodeficiency or who are receiving systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days before the first dose of study drug. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
10. Patients with an uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure, hypertension, unstable angina pectoris, cardiac arrhythmia, autoimmune or inflammatory diseases, or psychiatric illness that would limit compliance with study requirements.
11. Patients with an active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
12. Patients who have evidence of active, non-infectious pneumonitis. Patients with a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
13. Patients with a history of interstitial lung disease.
14. Patients who are 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. Pregnant women and men who want to conceive a child are excluded from this study because birinapant and pembrolizumab are agents with unknown potential for teratogenic or abortifacient effects in humans. Because there is an unknown risk for AEs in nursing infants secondary to treatment of the mother with birinapant and pembrolizumab, breastfeeding should be discontinued if the mother is treated on this study.
15. Patients who have a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies), or active Hepatitis B (e.g., HBsAg reactive). Patients with active Hepatitis C (e.g., HCV RNA [qualitative] is detected).
16. Patients who have received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.
17. Patients who have disease that is suitable for local therapy administered with curative intent.

18. Patients who have received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including G-CSF, GM-CSF or recombinant erythropoietin) within 4 weeks prior to study Day 1.

19. Patients who have a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or it is not in the best interest of the patient to participate, in the opinion of the treating investigator.

20. Patients who have known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

21. Patients who have severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.

23. Patients who have previously received birinapant treatment.

Appendix 2.3 Inclusion/Exclusion criteria Dose Expansion Phase Ovarian cancer cohort

NB: Inclusion/exclusion criteria numbering is derived from the complete set of criteria defined in sections 4.1 and 4.2.

Inclusion Criteria

Patients will be eligible for study participation if they meet ALL of the following inclusion criteria, after patient has provided written informed consent.

1. The patient is male or female ≥ 18 years of age on the day of signing informed consent.
2. The patient is able to understand and voluntarily sign a written informed consent, and is willing and able to comply with the protocol requirements.
4. Patients must have measurable disease based on RECIST 1.1 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. Patients must have an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1 at screening.
6. Patients must have a life expectancy of greater than 12 weeks.
7. Patients must have amylase and lipase values < ULN.
8. Patients must demonstrate adequate organ function as defined in Table A2.3. All screening labs should be performed within 10 days of treatment initiation.

Table A2.3 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5xULN **OR** ≥60 mL/min for patient with creatinine levels >1.5x institutional ULN
Hepatic	
Total bilirubin	≤1.5xULN **OR** Direct bilirubin ≤ULN for patients with total bilirubin levels >1.5xULN), unless known Gilbert's Syndrome has been diagnosed
AST (SGOT) and ALT (SGPT)	≤2.5xULN OR ≤5.0xULN for patients with liver metastases

Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5xULN unless patient 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 patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a] Creatinine clearance should be calculated per institutional standard.	

9. Female patients of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

10. Female patients of childbearing potential must be willing to use an adequate method of contraception for the course of the study through 120 days after the last dose of study medication.

    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient.

11. A tumor tissue sample for PD-L1 biomarker analysis from archival material, a newly obtained core or excisional biopsy is available for submission. Repeat samples may be required if adequate tissue is not provided.

12. Have resolution of toxic effect(s) of the most recent prior chemotherapy to Grade 1 or less (except neuropathy or alopecia). If patients have received major surgery or radiation therapy of > 30 Gy, they must have recovered from the toxicity and/or complications from the intervention.

13. Patients must have a histologically confirmed epithelial ovarian cancer, primary peritoneal cancer or fallopian tube solid tumor cancer that is locally advanced or metastatic with no available therapy options that are known to provide clinical benefit per institutional standard of care. Patients with tumors with mutations for which there are available therapies that are known to provide clinical benefit, as defined by national authority and/or ratified by national guidelines or equivalent, must have progressed following these therapies in order to be eligible for this study.

    16. Patients must have a histologically confirmed epithelial ovarian cancer, primary peritoneal cancer or fallopian tube solid tumor cancer that is locally advanced or metastatic with no available therapy options that are known to provide clinical benefit per institutional standard of care. Patients with tumors with mutations for which there are available therapies that are known to provide clinical benefit, as defined by national authority and/or ratified by national guidelines or equivalent, must have progressed following these therapies in order to be eligible for this study.

Exclusion Criteria

A patient will be excluded from the study for any one or more of the following reasons:

1. Patients who have 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 adverse events due to agents administered more than 4 weeks earlier prior to study Day 1.
2. Patients who have had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who have not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

Note: Patients with ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia are an exception to this criterion and may qualify for the study.

Note: If patients have received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

3. Patients who are currently participating and receiving study therapy or who have participated in a study of an investigational agent and received study therapy or who have used an investigational device within 4 weeks of the first dose of treatment.
4. Patients who have received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways) or if the patient has previously participated in Merck MK-3475 clinical trials.
5. Patients with known active central nervous system (CNS) metastases and/or carcinomatous meningitis.

   Note: Patients 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 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 systemic steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

6. Patients with a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

7. Patients who have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to birinapant or pembrolizumab or their constituents.
8. Patients requiring the use of anti-tumor necrosis factor (anti-TNF) therapies, such as infliximab, or patients who have received treatment with anti-TNF therapies within 5 half-lives of the drug.
9. Patients with a diagnosis of immunodeficiency or who are receiving systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days before the first dose of study drug. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
10. Patients with an uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure, hypertension, unstable angina pectoris, cardiac arrhythmia, autoimmune or inflammatory diseases, or psychiatric illness that would limit compliance with study requirements.
11. Patients with an active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
12. Patients who have evidence of active, non-infectious pneumonitis. Patients with a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
13. Patients with a history of interstitial lung disease.
14. Patients who are 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. Pregnant women and men who want to conceive a child are excluded from this study because birinapant and pembrolizumab are agents with unknown potential for teratogenic or abortifacient effects in humans. Because there is an unknown risk for AEs in nursing infants secondary to treatment of the mother with birinapant and pembrolizumab, breastfeeding should be discontinued if the mother is treated on this study.
15. Patients who have a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies), or active Hepatitis B (e.g., HBsAg reactive). Patients with active Hepatitis C (e.g., HCV RNA [qualitative] is detected).
16. Patients who have received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.

17. Patients who have disease that is suitable for local therapy administered with curative intent.
18. Patients who have received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including G-CSF, GM-CSF or recombinant erythropoietin) within 4 weeks prior to study Day 1.
19. Patients who have a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or it is not in the best interest of the patient to participate, in the opinion of the treating investigator.
20. Patients who have known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
21. Patients who have severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.
23. Patients who have previously received birinapant treatment.

Appendix 2.4 Inclusion/Exclusion criteria Dose Expansion Phase Cervical cancer cohort

NB: Inclusion/exclusion criteria numbering is derived from the complete set of criteria defined in sections 4.1 and 4.2.

Inclusion Criteria

Patients will be eligible for study participation if they meet ALL of the following inclusion criteria, after patient has provided written informed consent.

1. The patient is male or female ≥ 18 years of age on the day of signing informed consent.
2. The patient is able to understand and voluntarily sign a written informed consent, and is willing and able to comply with the protocol requirements.
4. Patients must have measurable disease based on RECIST 1.1 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. Patients must have an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1 at screening.
6. Patients must have a life expectancy of greater than 12 weeks.
7. Patients must have amylase and lipase values < ULN.
8. Patients must demonstrate adequate organ function as defined in Table A2.4. All screening labs should be performed within 10 days of treatment initiation.

Table A2.4 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5xULN **OR** ≥60 mL/min for patient with creatinine levels >1.5x institutional ULN
Hepatic	
Total bilirubin	≤1.5xULN **OR** Direct bilirubin ≤ULN for patients with total bilirubin levels >1.5xULN), unless known Gilbert's Syndrome has been diagnosed

AST (SGOT) and ALT (SGPT)	≤2.5xULN OR ≤5.0xULN for patients with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5xULN unless patient 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 patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a] Creatinine clearance should be calculated per institutional standard.	

9. Female patients of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

10. Female patients of childbearing potential must be willing to use an adequate method of contraception for the course of the study through 120 days after the last dose of study medication.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient.

12. A tumor tissue sample for PD-L1 biomarker analysis from archival material, a newly obtained core or excisional biopsy is available for submission. Repeat samples may be required if adequate tissue is not provided.

13. Have resolution of toxic effect(s) of the most recent prior chemotherapy to Grade 1 or less (except neuropathy or alopecia). If patients have received major surgery or radiation therapy of > 30 Gy, they must have recovered from the toxicity and/or complications from the intervention.

17. Patients must have histologically or cytologically confirmed cervical squamous cell carcinoma that is locally advanced or metastatic with no available therapy options that are known to provide clinical benefit per institutional standard of care. Patients with tumors with mutations for which there are available therapies that are known to provide clinical benefit, as defined by national authority and/or ratified by national guidelines or equivalent, must have progressed following these therapies in order to be eligible for this study.

Exclusion Criteria

A patient will be excluded from the study for any one or more of the following reasons:

1. Patients who have 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 adverse events due to agents administered more than 4 weeks earlier prior to study Day 1.

2. Patients who have had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who have not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

   Note: Patients with ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia are an exception to this criterion and may qualify for the study.

   Note: If patients have received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

3. Patients who are currently participating and receiving study therapy or who have participated in a study of an investigational agent and received study therapy or who have used an investigational device within 4 weeks of the first dose of treatment.
4. Patients who have received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways) or if the patient has previously participated in Merck MK-3475 clinical trials.

5. Patients with known active central nervous system (CNS) metastases and/or carcinomatous meningitis.

   Note: Patients 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 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 systemic steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

6. Patients with a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

7. Patients who have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to birinapant or pembrolizumab or their constituents.
8. Patients requiring the use of anti-tumor necrosis factor (anti-TNF) therapies, such as infliximab, or patients who have received treatment with anti-TNF therapies within 5 half-lives of the drug.
9. Patients with a diagnosis of immunodeficiency or who are receiving systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other

form of immunosuppressive therapy within 7 days before the first dose of study drug. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

10. Patients with an uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure, hypertension, unstable angina pectoris, cardiac arrhythmia, autoimmune or inflammatory diseases, or psychiatric illness that would limit compliance with study requirements.
11. Patients with an active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
12. Patients who have evidence of active, non-infectious pneumonitis. Patients with a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
13. Patients with a history of interstitial lung disease.
14. Patients who are 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. Pregnant women and men who want to conceive a child are excluded from this study because birinapant and pembrolizumab are agents with unknown potential for teratogenic or abortifacient effects in humans. Because there is an unknown risk for AEs in nursing infants secondary to treatment of the mother with birinapant and pembrolizumab, breastfeeding should be discontinued if the mother is treated on this study.
15. Patients who have a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies), or active Hepatitis B (e.g., HBsAg reactive). Patients with active Hepatitis C (e.g., HCV RNA [qualitative] is detected).
16. Patients who have received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.
17. Patients who have disease that is suitable for local therapy administered with curative intent.
18. Patients who have received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including G-CSF, GM-CSF or recombinant erythropoietin) within 4 weeks prior to study Day 1.
19. Patients who have a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or it is not in the best interest of the patient to participate, in the opinion of the treating investigator.

20. Patients who have known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

21. Patients who have severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.

23. Patients who have previously received birinapant treatment.

Appendix 2.5 Inclusion/Exclusion criteria Dose Expansion Phase various solid tumors cohort

Appendix 2.5.1 Inclusion/Exclusion criteria Dose Expansion Phase various solid tumors cohort, head and neck squamous cell carcinoma (HNSCC)-check-point-inhibitor naïve group

NB: Inclusion/exclusion criteria numbering is derived from the complete set of criteria defined in sections 4.1 and 4.2.

Inclusion criteria

Patients will be eligible for study participation if they meet ALL of the following inclusion criteria, after patient has provided written informed consent.

1. The patient is male or female ≥ 18 years of age on the day of signing informed consent.
2. The patient is able to understand and voluntarily sign a written informed consent, and is willing and able to comply with the protocol requirements.
4. Patients must have measurable disease based on RECIST 1.1 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. Patients must have an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1 at screening.
6. Patients must have a life expectancy of greater than 12 weeks.
7. Patients must have amylase and lipase values < ULN.
8. Patients must demonstrate adequate organ function as defined in A2.5.1. All screening labs should be performed within 10 days of treatment initiation.

Table A2.5.1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5xULN **OR** ≥60 mL/min for patient with creatinine levels >1.5x institutional ULN
Hepatic	
Total bilirubin	≤1.5xULN **OR** Direct bilirubin ≤ULN for patients with total

	bilirubin levels >1.5xULN), unless known Gilbert's Syndrome has been diagnosed
AST (SGOT) and ALT (SGPT)	≤2.5xULN OR ≤5.0xULN for patients with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5xULN unless patient 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 patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a] Creatinine clearance should be calculated per institutional standard.	

9. Female patients of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

10. Female patients of childbearing potential must be willing to use an adequate method of contraception for the course of the study through 120 days after the last dose of study medication.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient.

11. Male patients with female partners of childbearing potential 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.

    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient.

12. A tumor tissue sample for PD-L1 biomarker analysis from archival material, a newly obtained core or excisional biopsy is available for submission. Repeat samples may be required if adequate tissue is not provided.

13. Have resolution of toxic effect(s) of the most recent prior chemotherapy to Grade 1 or less (except neuropathy or alopecia). If patients have received major surgery or radiation therapy of > 30 Gy, they must have recovered from the toxicity and/or complications from the intervention.

18. Patients must have histologically or cytologically confirmed head and neck squamous cell carcinoma that is locally advanced or metastatic with no available therapy options that are known to provide clinical benefit per institutional standard of care. Patients with tumors with mutations for which there are available therapies that are known to provide clinical benefit, as defined by national authority and/or ratified by national guidelines or equivalent, must have progressed following these therapies in order to be eligible for this study.

Exclusion Criteria

A patient will be excluded from the study for any one or more of the following reasons:

1. Patients who have 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 adverse events due to agents administered more than 4 weeks earlier prior to study Day 1.
2. Patients who have had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who have not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

   Note: Patients with ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia are an exception to this criterion and may qualify for the study.

   Note: If patients have received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

3. Patients who are currently participating and receiving study therapy or who have participated in a study of an investigational agent and received study therapy or who have used an investigational device within 4 weeks of the first dose of treatment.
4. Patients who have received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways) or if the patient has previously participated in Merck MK-3475 clinical trials.
5. Patients with known active central nervous system (CNS) metastases and/or carcinomatous meningitis.

   Note: Patients 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 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 systemic steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

6. Patients with a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
7. Patients who have a history of allergic reactions attributed to compounds of similar

chemical or biologic composition to birinapant or pembrolizumab or their constituents.

8. Patients requiring the use of anti-tumor necrosis factor (anti-TNF) therapies, such as infliximab, or patients who have received treatment with anti-TNF therapies within 5 half-lives of the drug.
9. Patients with a diagnosis of immunodeficiency or who are receiving systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days before the first dose of study drug. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
10. Patients with an uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure, hypertension, unstable angina pectoris, cardiac arrhythmia, autoimmune or inflammatory diseases, or psychiatric illness that would limit compliance with study requirements.
11. Patients with an active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
12. Patients who have evidence of active, non-infectious pneumonitis. Patients with a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
13. Patients with a history of interstitial lung disease.
14. Patients who are 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. Pregnant women and men who want to conceive a child are excluded from this study because birinapant and pembrolizumab are agents with unknown potential for teratogenic or abortifacient effects in humans. Because there is an unknown risk for AEs in nursing infants secondary to treatment of the mother with birinapant and pembrolizumab, breastfeeding should be discontinued if the mother is treated on this study.
15. Patients who have a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies), or active Hepatitis B (e.g., HBsAg reactive). Patients with active Hepatitis C (e.g., HCV RNA [qualitative] is detected).
16. Patients who have received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.
17. Patients who have disease that is suitable for local therapy administered with curative intent.

18. Patients who have received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including G-CSF, GM-CSF or recombinant erythropoietin) within 4 weeks prior to study Day 1.

19. Patients who have a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or it is not in the best interest of the patient to participate, in the opinion of the treating investigator.

20. Patients who have known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

21. Patients who have severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.

23. Patients who have previously received birinapant treatment.

Appendix 2.5.2 Inclusion/Exclusion criteria Dose Expansion Phase various solid tumors cohort, HNSCC check-point -inhibitor experienced group

NB: Inclusion/exclusion criteria numbering is derived from the complete set of criteria defined in sections 4.1 and 4.2.

Inclusion Criteria

Patients will be eligible for study participation if they meet ALL of the following inclusion criteria, after patient has provided written informed consent.

1. The patient is male or female ≥ 18 years of age on the day of signing informed consent.
2. The patient is able to understand and voluntarily sign a written informed consent, and is willing and able to comply with the protocol requirements.
4. Patients must have measurable disease based on RECIST 1.1 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. Patients must have an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1 at screening.
6. Patients must have a life expectancy of greater than 12 weeks.
7. Patients must have amylase and lipase values < ULN.
8. Patients must demonstrate adequate organ function as defined in Table A.2.5.2. All screening labs should be performed within 10 days of treatment initiation.

Table A2.5.2 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5xULN **OR** ≥60 mL/min for patient with creatinine levels >1.5x institutional ULN
Hepatic	
Total bilirubin	≤1.5xULN **OR** Direct bilirubin ≤ULN for patients with total bilirubin levels >1.5xULN), unless known Gilbert's Syndrome has been diagnosed
AST (SGOT) and ALT (SGPT)	≤2.5xULN OR ≤5.0xULN for patients with liver metastases

Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5xULN unless patient 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 patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a] Creatinine clearance should be calculated per institutional standard.	

9. Female patients of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

10. Female patients of childbearing potential must be willing to use an adequate method of contraception for the course of the study through 120 days after the last dose of study medication.

    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient.

11. Male patients with female partners of childbearing potential 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. (*Not applicable for Ovarian cancer cohort or Cervical cancer cohort*)

    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient.

12. A tumor tissue sample for PD-L1 biomarker analysis from archival material, a newly obtained core or excisional biopsy is available for submission. Repeat samples may be required if adequate tissue is not provided.

13. Have resolution of toxic effect(s) of the most recent prior chemotherapy to Grade 1 or less (except neuropathy or alopecia). If patients have received major surgery or radiation therapy of > 30 Gy, they must have recovered from the toxicity and/or complications from the intervention.

18. Patients must have histologically or cytologically confirmed head and neck squamous cell carcinoma that is locally advanced or metastatic with no available therapy options that are known to provide clinical benefit per institutional standard of care. Patients with tumors with mutations for which there are available therapies that are known to provide clinical benefit, as defined by national authority and/or ratified by national guidelines or equivalent, must have progressed following these therapies in order to be eligible for this study (*various solid tumor cohort: head and neck squamous cell carcinoma groups only*).

19. Patients with Head and Neck Squamous Cell Carcinoma who are to participate in the group of Checkpoint inhibitor experienced patients must have received prior therapy with an anti-PD-1 or anti-PD-L1 antibody administered either as monotherapy, or in combination with other therapies. Patients must have received at least two doses of an approved anti-PD-1/anti-PD-L1 antibody and have experienced documented radiographic progression of disease by RECIST v1.1. The initial evidence of disease progression is to be confirmed by a second assessment no less than four weeks from the date of the first documented disease progression in the absence of rapid clinical progression. The date for documentation of initial progression will be considered the date for disease progression. Progressive disease must have been documented during or within 12 weeks after last dose of such treatment. (*various solid tumor cohort head and neck squamous cell carcinoma, check-point inhibitor experienced group only*).

Exclusion Criteria

A patient will be excluded from the study for any one or more of the following reasons:

1. Patients who have 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 adverse events due to agents administered more than 4 weeks earlier prior to study Day 1.
2. Patients who have had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who have not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

   Note: Patients with ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia are an exception to this criterion and may qualify for the study.

   Note: If patients have received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

3. Patients who are currently participating and receiving study therapy or who have participated in a study of an investigational agent and received study therapy or who have used an investigational device within 4 weeks of the first dose of treatment.
5. Patients with known active central nervous system (CNS) metastases and/or carcinomatous meningitis.

   Note: Patients 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 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 systemic steroids for at least 7 days prior to trial treatment. This exception

does not include carcinomatous meningitis which is excluded regardless of clinical stability.

6. Patients with a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

7. Patients who have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to birinapant or pembrolizumab or their constituents.
8. Patients requiring the use of anti-tumor necrosis factor (anti-TNF) therapies, such as infliximab, or patients who have received treatment with anti-TNF therapies within 5 half-lives of the drug.
9. Patients with a diagnosis of immunodeficiency or who are receiving systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days before the first dose of study drug. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
10. Patients with an uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure, hypertension, unstable angina pectoris, cardiac arrhythmia, autoimmune or inflammatory diseases, or psychiatric illness that would limit compliance with study requirements.
11. Patients with an active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.

12. Patients who have evidence of active, non-infectious pneumonitis. Patients with a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.

13. Patients with a history of interstitial lung disease.

14. Patients who are 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. Pregnant women and men who want to conceive a child are excluded from this study because birinapant and pembrolizumab are agents with unknown potential for teratogenic or abortifacient effects in humans. Because there is an unknown risk for AEs in nursing infants secondary to treatment of the mother with birinapant and pembrolizumab, breastfeeding should be discontinued if the mother is treated on this study.

15. Patients who have a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies), or active Hepatitis B (e.g., HBsAg reactive). Patients with active Hepatitis C (e.g., HCV RNA [qualitative] is detected).

16. Patients who have received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.

17. Patients who have disease that is suitable for local therapy administered with curative intent.

18. Patients who have received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including G-CSF, GM-CSF or recombinant erythropoietin) within 4 weeks prior to study Day 1.

19. Patients who have a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or it is not in the best interest of the patient to participate, in the opinion of the treating investigator.

20. Patients who have known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

21. Patients who have severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.

22. Patients who have received anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

23. Patients who have previously received birinapant treatment.

Appendix 2.5.3 Inclusion/Exclusion criteria Dose Expansion Phase various solid tumor cohort, gastroesophageal carcinoma group

NB: Inclusion/exclusion criteria numbering is derived from the complete set of criteria defined in sections 4.1 and 4.2.

Inclusion Criteria

Patients will be eligible for study participation if they meet ALL of the following inclusion criteria, after patient has provided written informed consent.

1. The patient is male or female ≥ 18 years of age on the day of signing informed consent.
2. The patient is able to understand and voluntarily sign a written informed consent, and is willing and able to comply with the protocol requirements.
4. Patients must have measurable disease based on RECIST 1.1 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. Patients must have an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1 at screening.
6. Patients must have a life expectancy of greater than 12 weeks.
7. Patients must have amylase and lipase values < ULN.
8. Patients must demonstrate adequate organ function as defined in A2.5.3. All screening labs should be performed within 10 days of treatment initiation.

Table A2.5.3 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5xULN **OR** ≥60 mL/min for patient with creatinine levels >1.5x institutional ULN
Hepatic	
Total bilirubin	≤1.5xULN **OR** Direct bilirubin ≤ULN for patients with total bilirubin levels >1.5xULN), unless known Gilbert's Syndrome has been diagnosed

AST (SGOT) and ALT (SGPT)	≤2.5xULN OR ≤5.0xULN for patients with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5xULN unless patient 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 patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a] Creatinine clearance should be calculated per institutional standard.	

9. Female patients of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

10. Female patients of childbearing potential must be willing to use an adequate method of contraception for the course of the study through 120 days after the last dose of study medication.

    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient.

11. Male patients with female partners of childbearing potential 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. *(Not applicable for Ovarian cancer cohort or Cervical cancer cohort)*

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient.

12. A tumor tissue sample for PD-L1 biomarker analysis from archival material, a newly obtained core or excisional biopsy is available for submission. Repeat samples may be required if adequate tissue is not provided.

13. Have resolution of toxic effect(s) of the most recent prior chemotherapy to Grade 1 or less (except neuropathy or alopecia). If patients have received major surgery or radiation therapy of > 30 Gy, they must have recovered from the toxicity and/or complications from the intervention.

23. Patients must have histologically or cytologically confirmed carcinoma of the esophagus including the gastroesophageal junction that is locally advanced or metastatic with no available therapy options that are known to provide clinical benefit per institutional standard of care. Patients with tumors with mutations for which there are available therapies that are known to provide clinical benefit, as defined by national authority and/or ratified by national guidelines or equivalent, must have progressed following these therapies in order to be eligible for this study.

Exclusion Criteria

A patient will be excluded from the study for any one or more of the following reasons:

1. Patients who have 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 adverse events due to agents administered more than 4 weeks earlier prior to study Day 1.
2. Patients who have had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who have not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

   Note: Patients with ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia are an exception to this criterion and may qualify for the study.

   Note: If patients have received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

3. Patients who are currently participating and receiving study therapy or who have participated in a study of an investigational agent and received study therapy or who have used an investigational device within 4 weeks of the first dose of treatment.
4. Patients who have received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways) or if the patient has previously participated in Merck MK-3475 clinical trials.

5. Patients with known active central nervous system (CNS) metastases and/or carcinomatous meningitis.

   Note: Patients 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 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 systemic steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

6. Patients with a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

7. Patients who have a history of allergic reactions attributed to compounds of similar

chemical or biologic composition to birinapant or pembrolizumab or their constituents.

8. Patients requiring the use of anti-tumor necrosis factor (anti-TNF) therapies, such as infliximab, or patients who have received treatment with anti-TNF therapies within 5 half-lives of the drug.
9. Patients with a diagnosis of immunodeficiency or who are receiving systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days before the first dose of study drug. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
10. Patients with an uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure, hypertension, unstable angina pectoris, cardiac arrhythmia, autoimmune or inflammatory diseases, or psychiatric illness that would limit compliance with study requirements.
11. Patients with an active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
12. Patients who have evidence of active, non-infectious pneumonitis. Patients with a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
13. Patients with a history of interstitial lung disease.
14. Patients who are 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. Pregnant women and men who want to conceive a child are excluded from this study because birinapant and pembrolizumab are agents with unknown potential for teratogenic or abortifacient effects in humans. Because there is an unknown risk for AEs in nursing infants secondary to treatment of the mother with birinapant and pembrolizumab, breastfeeding should be discontinued if the mother is treated on this study.
15. Patients who have a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies), or active Hepatitis B (e.g., HBsAg reactive). Patients with active Hepatitis C (e.g., HCV RNA [qualitative] is detected).
16. Patients who have received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.
17. Patients who have disease that is suitable for local therapy administered with curative intent.

18. Patients who have received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including G-CSF, GM-CSF or recombinant erythropoietin) within 4 weeks prior to study Day 1.

19. Patients who have a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or it is not in the best interest of the patient to participate, in the opinion of the treating investigator.

20. Patients who have known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

21. Patients who have severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.

23. Patients who have previously received birinapant treatment.

Appendix 2.5.4 Inclusion/Exclusion criteria Dose Expansion Phase various solid tumor cohort, mesothelioma group

NB: Inclusion/exclusion criteria numbering is derived from the complete set of criteria defined in sections 4.1 and 4.2.

Inclusion Criteria

Patients will be eligible for study participation if they meet ALL of the following inclusion criteria, after patient has provided written informed consent.

1. The patient is male or female ≥ 18 years of age on the day of signing informed consent.
2. The patient is able to understand and voluntarily sign a written informed consent, and is willing and able to comply with the protocol requirements.
4. Patients must have measurable disease based on RECIST 1.1 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. Patients must have an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1 at screening.
6. Patients must have a life expectancy of greater than 12 weeks.
7. Patients must have amylase and lipase values < ULN.
8. Patients must demonstrate adequate organ function as defined in Table A2.5.4. All screening labs should be performed within 10 days of treatment initiation.

Table A2.5.4 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5xULN **OR** ≥60 mL/min for patient with creatinine levels >1.5x institutional ULN
Hepatic	
Total bilirubin	≤1.5xULN **OR** Direct bilirubin ≤ULN for patients with total bilirubin levels >1.5xULN), unless known Gilbert's Syndrome has been diagnosed
AST (SGOT) and ALT (SGPT)	≤2.5xULN OR ≤5.0xULN for patients with liver metastases

Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5xULN unless patient 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 patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a] Creatinine clearance should be calculated per institutional standard.	

9. Female patients of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

10. Female patients of childbearing potential must be willing to use an adequate method of contraception for the course of the study through 120 days after the last dose of study medication.

    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient.

11. Male patients with female partners of childbearing potential 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. (Not applicable for Ovarian cancer cohort or Cervical cancer cohort)

    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient.

12. A tumor tissue sample for PD-L1 biomarker analysis from archival material, a newly obtained core or excisional biopsy is available for submission. Repeat samples may be required if adequate tissue is not provided.

13. Have resolution of toxic effect(s) of the most recent prior chemotherapy to Grade 1 or less (except neuropathy or alopecia). If patients have received major surgery or radiation therapy of > 30 Gy, they must have recovered from the toxicity and/or complications from the intervention.

22. Patients must have histologically or cytologically confirmed pleural mesothelioma that is locally advanced or metastatic with no available therapy options that are known to provide clinical benefit per institutional standard of care. Patients with tumors with mutations for which there are available therapies that are known to provide clinical benefit, as defined by national authority and/or ratified by national guidelines or equivalent, must have progressed following these therapies in order to be eligible for this study.

Exclusion Criteria

A patient will be excluded from the study for any one or more of the following reasons:

1. Patients who have 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 adverse events due to agents administered more than 4 weeks earlier prior to study Day 1.
2. Patients who have had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who have not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

   Note: Patients with ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia are an exception to this criterion and may qualify for the study.

   Note: If patients have received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

3. Patients who are currently participating and receiving study therapy or who have participated in a study of an investigational agent and received study therapy or who have used an investigational device within 4 weeks of the first dose of treatment.
4. Patients who have received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways) or if the patient has previously participated in Merck MK-3475 clinical trials.

5. Patients with known active central nervous system (CNS) metastases and/or carcinomatous meningitis.

   Note: Patients 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 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 systemic steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

6. Patients with a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

7. Patients who have a history of allergic reactions attributed to compounds of similar

chemical or biologic composition to birinapant or pembrolizumab or their constituents.

8. Patients requiring the use of anti-tumor necrosis factor (anti-TNF) therapies, such as infliximab, or patients who have received treatment with anti-TNF therapies within 5 half-lives of the drug.
9. Patients with a diagnosis of immunodeficiency or who are receiving systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days before the first dose of study drug. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
10. Patients with an uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure, hypertension, unstable angina pectoris, cardiac arrhythmia, autoimmune or inflammatory diseases, or psychiatric illness that would limit compliance with study requirements.
11. Patients with an active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
12. Patients who have evidence of active, non-infectious pneumonitis. Patients with a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
13. Patients with a history of interstitial lung disease.
14. Patients who are 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. Pregnant women and men who want to conceive a child are excluded from this study because birinapant and pembrolizumab are agents with unknown potential for teratogenic or abortifacient effects in humans. Because there is an unknown risk for AEs in nursing infants secondary to treatment of the mother with birinapant and pembrolizumab, breastfeeding should be discontinued if the mother is treated on this study.
15. Patients who have a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies), or active Hepatitis B (e.g., HBsAg reactive). Patients with active Hepatitis C (e.g., HCV RNA [qualitative] is detected).
16. Patients who have received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.
17. Patients who have disease that is suitable for local therapy administered with curative intent.

18. Patients who have received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including G-CSF, GM-CSF or recombinant erythropoietin) within 4 weeks prior to study Day 1.

19. Patients who have a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or it is not in the best interest of the patient to participate, in the opinion of the treating investigator.

20. Patients who have known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

21. Patients who have severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.

23. Patients who have previously received birinapant treatment.

Appendix 2.5.5 Inclusion/Exclusion criteria Dose Expansion Phase various solid tumor cohort, Small cell lung cancer group

NB: Inclusion/exclusion criteria numbering is derived from the complete set of criteria defined in sections 4.1 and 4.2.

Inclusion Criteria

Patients will be eligible for study participation if they meet ALL of the following inclusion criteria, after patient has provided written informed consent.

1. The patient is male or female ≥ 18 years of age on the day of signing informed consent.
2. The patient is able to understand and voluntarily sign a written informed consent, and is willing and able to comply with the protocol requirements.
4. Patients must have measurable disease based on RECIST 1.1 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. Patients must have an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1 at screening.
6. Patients must have a life expectancy of greater than 12 weeks.
7. Patients must have amylase and lipase values < ULN.
8. Patients must demonstrate adequate organ function as defined in TableA2.5.5. All screening labs should be performed within 10 days of treatment initiation.

Table A2.5.5 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5xULN **OR** ≥60 mL/min for patient with creatinine levels >1.5x institutional ULN
Hepatic	
Total bilirubin	≤1.5xULN **OR** Direct bilirubin ≤ULN for patients with total bilirubin levels >1.5xULN), unless known Gilbert's Syndrome has been diagnosed
AST (SGOT) and ALT (SGPT)	≤2.5xULN OR ≤5.0xULN for patients with liver metastases

Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5xULN unless patient 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 patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a] Creatinine clearance should be calculated per institutional standard.	

9. Female patients of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

10. Female patients of childbearing potential must be willing to use an adequate method of contraception for the course of the study through 120 days after the last dose of study medication.

    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient.

11. Male patients with female partners of childbearing potential 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. (Not applicable for Ovarian cancer cohort or Cervical cancer cohort)

    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient.

12. A tumor tissue sample for PD-L1 biomarker analysis from archival material, a newly obtained core or excisional biopsy is available for submission. Repeat samples may be required if adequate tissue is not provided.

13. Have resolution of toxic effect(s) of the most recent prior chemotherapy to Grade 1 or less (except neuropathy or alopecia). If patients have received major surgery or radiation therapy of > 30 Gy, they must have recovered from the toxicity and/or complications from the intervention.

20. Patients must have histologically or cytologically confirmed small cell lung carcinoma that is locally advanced or metastatic with no available therapy options that are known to provide clinical benefit per institutional standard of care. Patients with tumors with mutations for which there are available therapies that are known to provide clinical benefit, as defined by national authority and/or ratified by national guidelines or equivalent, must have progressed following these therapies in order to be eligible for this study.

Exclusion Criteria

A patient will be excluded from the study for any one or more of the following reasons:

1. Patients who have 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 adverse events due to agents administered more than 4 weeks earlier prior to study Day 1.
2. Patients who have had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who have not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

   Note: Patients with ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia are an exception to this criterion and may qualify for the study.

   Note: If patients have received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

3. Patients who are currently participating and receiving study therapy or who have participated in a study of an investigational agent and received study therapy or who have used an investigational device within 4 weeks of the first dose of treatment.
4. Patients who have received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways) or if the patient has previously participated in Merck MK-3475 clinical trials.

5. Patients with known active central nervous system (CNS) metastases and/or carcinomatous meningitis.

   Note: Patients 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 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 systemic steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

6. Patients with a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

7. Patients who have a history of allergic reactions attributed to compounds of similar

chemical or biologic composition to birinapant or pembrolizumab or their constituents.

8. Patients requiring the use of anti-tumor necrosis factor (anti-TNF) therapies, such as infliximab, or patients who have received treatment with anti-TNF therapies within 5 half-lives of the drug.
9. Patients with a diagnosis of immunodeficiency or who are receiving systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days before the first dose of study drug. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
10. Patients with an uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure, hypertension, unstable angina pectoris, cardiac arrhythmia, autoimmune or inflammatory diseases, or psychiatric illness that would limit compliance with study requirements.
11. Patients with an active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
12. Patients who have evidence of active, non-infectious pneumonitis. Patients with a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
13. Patients with a history of interstitial lung disease.
14. Patients who are 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. Pregnant women and men who want to conceive a child are excluded from this study because birinapant and pembrolizumab are agents with unknown potential for teratogenic or abortifacient effects in humans. Because there is an unknown risk for AEs in nursing infants secondary to treatment of the mother with birinapant and pembrolizumab, breastfeeding should be discontinued if the mother is treated on this study.
15. Patients who have a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies), or active Hepatitis B (e.g., HBsAg reactive). Patients with active Hepatitis C (e.g., HCV RNA [qualitative] is detected).
16. Patients who have received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.
17. Patients who have disease that is suitable for local therapy administered with curative intent.

18. Patients who have received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including G-CSF, GM-CSF or recombinant erythropoietin) within 4 weeks prior to study Day 1.

19. Patients who have a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or it is not in the best interest of the patient to participate, in the opinion of the treating investigator.

20. Patients who have known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

21. Patients who have severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.

23. Patients who have previously received birinapant treatment.

Appendix 2.5.6 Inclusion/Exclusion criteria Dose Expansion Phase various solid tumor cohort, cholangiocarcinoma group

NB: Inclusion/exclusion criteria numbering is derived from the complete set of criteria defined in sections 4.1 and 4.2.

Inclusion Criteria

Patients will be eligible for study participation if they meet ALL of the following inclusion criteria, after patient has provided written informed consent.

1. The patient is male or female ≥ 18 years of age on the day of signing informed consent.
2. The patient is able to understand and voluntarily sign a written informed consent, and is willing and able to comply with the protocol requirements.
4. Patients must have measurable disease based on RECIST 1.1 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. Patients must have an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1 at screening.
6. Patients must have a life expectancy of greater than 12 weeks.
7. Patients must have amylase and lipase values < ULN.
8. Patients must demonstrate adequate organ function as defined in TableA2.5.6. All screening labs should be performed within 10 days of treatment initiation.

Table A2.5.6 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5xULN **OR** ≥60 mL/min for patient with creatinine levels >1.5x institutional ULN
Hepatic	
Total bilirubin	≤1.5xULN **OR** Direct bilirubin ≤ULN for patients with total bilirubin levels >1.5xULN), unless known Gilbert's Syndrome has been diagnosed
AST (SGOT) and ALT (SGPT)	≤2.5xULN OR ≤5.0xULN for patients with liver metastases

Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5xULN unless patient 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 patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
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9. Female patients of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

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Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient.

11. Male patients with female partners of childbearing potential 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. (Not applicable for Ovarian cancer cohort or Cervical cancer cohort)

    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient.

12. A tumor tissue sample for PD-L1 biomarker analysis from archival material, a newly obtained core or excisional biopsy is available for submission. Repeat samples may be required if adequate tissue is not provided.

13. Have resolution of toxic effect(s) of the most recent prior chemotherapy to Grade 1 or less (except neuropathy or alopecia). If patients have received major surgery or radiation therapy of > 30 Gy, they must have recovered from the toxicity and/or complications from the intervention.

21. Patients must have histologically or cytologically confirmed cholangiocarcinoma that is locally advanced or metastatic with no available therapy options that are known to provide clinical benefit per institutional standard of care. Patients with tumors with mutations for which there are available therapies that are known to provide clinical benefit, as defined by national authority and/or ratified by national guidelines or equivalent, must have progressed following these therapies in order to be eligible for this study.

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4. Patients who have received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways) or if the patient has previously participated in Merck MK-3475 clinical trials.

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chemical or biologic composition to birinapant or pembrolizumab or their constituents.

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11. Patients with an active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
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