Statistical Analysis Plan

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: 13 June 2018

NCT number: NCT02587962

Scandinavian Development Services

Statistical Analysis Plan

Client Study Code:	BPT-201
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
SDS Project Code:	

Document Control

Control

Document Name	BPT-201_SAP_final
Based on clinical study protocol and amendment versions	Final version 4.0/incl amendment 03. Dated 18 Jan 2018
Version	Final Version 1.0
Study statistician	Niclas Sjögren, Scandinavian Development Services (SDS)
Trial coordinating investigator	
Author	Niclas Sjögren, Scandinavian Development Services (SDS)
Status	Final
Approval Date	
Approved by	

Signatures

13 June 2018

John Öhd, Chief Medical Officer, Medivir AB Date

13 June 2018

Niclas Sjögren Date

History

Version	*Modified By*	*Date*	*Description of Changes*
0.1	Niclas Sjögren, SDS	2018-03-01	SAP for first review
0.2	Niclas Sjögren, SDS	2018-03-16	Updated after comments at 1st review
0.3	Niclas Sjögren, SDS	2018-04-03	Updated after review 2.
0.4	Niclas Sjögren, SDS	2018-04-27	Updated after 3rd review
1.0	Niclas Sjögren, SDS	2018-06-13	Final version

Table of Contents

Signatures 2

Abbreviations 5

1. Introduction 7

2. Study Objectives 7

2.1 Study Objectives Dose Escalation Phase 7

2.1.1 Primary Objective 7

2.1.2 Secondary Objective 7

2.1.3 Exploratory Objectives 7

2.2 Study Objectives Dose Expansion Phase 7

2.2.1 Primary Objective 7

2.2.2 Secondary Objectives 8

2.2.3 Exploratory Objectives 8

3. Study Details 8

3.1 Study Design and Study Population 8

3.1.1 Dose-escalation phase 8

3.1.2 Dose expansion phase 9

3.1.3 Study Flow Chart 10

3.2 Randomization and Blinding 10

3.3 Number of Patients 10

3.3.1 Sample Size Calculation 10

3.3.1.1 Dose escalation phase 10

3.3.1.2 Dose expansion phase 10

4. Assessments 11

4.1 Disposition and Other Supporting Assessments 11

4.1.1 Patient Compliance 11

4.1.2 Protocol Deviations 11

4.1.3 Demographic and Baseline Characteristics 11

4.1.4 Medical History 11

4.1.5 Prior and Concomitant Medications 11

4.1.6 Eastern Cooperative Oncology Group-Performance Status 12

4.2 Efficacy Endpoints 12

4.2.1 Dose Escalation Phase 12

4.2.1.1 Primary Efficacy Endpoint 12

4.2.1.2 Secondary Efficacy Endpoints 12

4.2.1.3 Exploratory Efficacy Variable 12

4.2.2 Dose Expansion Phase 12

4.2.2.1 Primary Efficacy Endpoint 12

4.2.2.2 Secondary Efficacy Endpoints 13

4.2.2.3 Exploratory Efficacy Variable 13

4.2.3 Definition of Efficacy Endpoints 13

4.2.3.1 Overall response (and ORR) assessed through RECIST 1.1 14

4.2.3.2 Progression Free Survival (PFS) 15

4.2.3.3 Clinical Benefit Rate (CBR) 15

4.2.3.4 Time to response 15

4.2.3.5 Duration of response 15

4.2.3.6 Overall Survival (OS) 15

4.2.3.7 Overall response assessed through iRECIST 15

4.2.3.8 Immune Best Overall Response (iBOR) 16

4.2.3.9 Duration of iBOR 16

4.2.3.10 Time to iCPD 17

4.2.3.11 Immune Clinical Benefit Rate (iCBR) 17

4.2.3.12 Time to immune response 17

4.2.3.13 Duration of immune response 17

4.3 Safety Endpoints 17

4.3.1 Adverse Events 17

4.3.2 Clinical Laboratory Tests 17

4.3.2.1 Hematology, Serum Chemistry, Immunology and Urinalysis, Serology 17

4.3.2.2 Pregnancy Testing 18

4.3.2.3 Histology 18

4.3.3 Physical Examination 18

4.3.4 Vital Signs 18

4.3.5 ECGs 18

4.4 Pharmacokinetic Assessments 18

5. Analysis Methods 19
5.1 Clean File and Timing of Analysis 19
5.2 Analysis Populations 19
5.2.1 Intent-to-Treat Population (ITT) 19
5.2.2 Efficacy Evaluable Population 19
5.2.3 Safety Population 19
5.2.4 Pharmacodynamic Evaluable Population 19
5.2.5 Pharmacokinetic Analysis Population 19
5.3 General Principles for Presenting Study Data 19
5.4 Statistical/Analytical issues 20
5.4.1 Missing Data and Handling of Dropouts 20
5.4.2 Data Transformations and Derived Variables 21
5.4.2.1 Calculation of change from baseline 21
5.4.3 Interim Analysis and Data Monitoring 21
5.4.3.1 Colorectal Cancer Cohort 21
5.4.3.2 Ovarian Cancer Cohort 21
5.4.3.3 Cervical Cancer Cohort 21
5.4.4 Multiple Comparisons/Multiplicity 21
5.4.5 Examination of Subgroups 22
5.5 Patient Disposition Summary 22
5.5.1 Patient Disposition 22
5.5.2 Protocol Deviations 22
5.5.3 Demographic and Baseline Characteristics 22
5.5.4 Medical History 22
5.5.5 Prior and Concomitant Medications 22
5.5.6 Exposure to Study Treatment 22
5.5.7 Premature Termination 23
5.6 Efficacy Analyses 23
5.6.1 Primary Efficacy Analysis 23
5.6.2 Secondary Efficacy Analyses 24
5.6.3 Exploratory Efficacy Analyses 24
5.6.4 Subgroup Analyses 24
5.6.5 Sensitivity Analyses 24
5.7 Safety Analyses 25
5.7.1 Adverse Events 25
5.7.2 Clinical Laboratory Tests 25
5.7.3 Physical Examination 25
5.7.4 Vital Signs 26
5.7.5 Electrocardiogram 26
5.8 Pharmacokinetic Analyses 26
5.9 Changes to Planned Analysis 26

6. References 27

7. Appendix 1 28

Abbreviations

Abbreviation	Term
AE	Adverse Event
ALAT	Alanine Transaminase
ALP	Alkaline Phosphatase
ANCOVA	Analysis of Covariance
ASAT	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemicals
CI	Confidence Interval
CBR	Clinical Benefit Rate
CR	Complete Response
CRP	C-reactive protein
DLT	Dose Limiting Toxicity
DSMB	Data and Safety Monitoring Board
FAS	Full Analysis Set
HDL	High Density Lipoprotein
IAP	Interim Analysis Plan
iBOR	Immune Best Overall Response
iCBR	Immune Clinical Benefit Rate
ICH	International Conference on Harmonization
iCPD	Immune Confirmed Progressive Disease
iCR	Immune Complete Response
IMP	Investigational Medicinal Product
iPR	Immune Partial Response
iRECIST	Immune Response Evaluation Criteria in Solid Tumours
iSD	Immune Stable Disease
iUPD	Immune Unconfirmed Progressive Disease
LLOQ	Lower Limit Of Quantification
LSmeans	Least Square Means
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
N	Number of observations
Nmiss	Number of Missing Observations
ORR	Overall Response Rate
OS	Overall Survival
OTC	Over-the-counter
PFS	Progression Free Survival
PD	Progressive Disease
PR	Partial Response
PT	Preferred Term
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria in Solid Tumours
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SD	Stable Disease
SOC	System Organ Class
SD	Standard Deviation
SRC	Safety Review Committee
TEAE	Treatment Emergent Adverse Event
TLF	Tables Listing Figures
WBC	White Blood Cells

1. Introduction

This Statistical Analysis Plan (SAP) provides a detailed and technical description of the planned statistical evaluation of the Medivir study BPT-201: "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". The study consists of two phases, a dose-escalation phase followed by a dose-expansion phase.

Mock-up TFLs and an analysis plan for the exploratory objectives regarding biomarkers will be provided in separate documents.

Details regarding the investigational plan, patient selection criteria, dose administration, and schedule of assessments are given in the Clinical Study Protocol (CSP) "BPT-201 v4.0/incl amendment 03".

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. Study Details

Details of the study design, inclusion/exclusion criteria applicable to the dose escalation phase and for each tumor type of the dose expansion phase are given in the CSP.

3.1 Study Design and Study Population

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.

The study will have two parts, one dose escalation part followed by a dose-expansion phase.

3.1.1 Dose-escalation phase

The dose escalation part employs a sequential group dose-escalation design to determine the dose-limiting toxicity (DLT) and recommended phase 2 dose (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 1.

Table 1 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/m2/week** on Days 1 and 8
Level 1	200 mg pembrolizumab on Day 1 + **birinapant 5.6 mg/m2/week** on Days 1 and 8
Level 2	200 mg pembrolizumab on Day 1 + **birinapant 11 mg/m2/week** on Days 1 and 8
Level 3	200 mg pembrolizumab on Day 1 + **birinapant 17 mg/m2/week** on Days 1 and 8
Level 4	200 mg pembrolizumab on Day 1 + **birinapant 22 mg/m2/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/m2/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/m2) 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/m2 (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 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.

Table 2. Dose Expansion Phase

Pembrolizumab + Birinapant (per 21-day cycle)*
200 mg pembrolizumab on Day 1 + **birinapant at the RP2D mg/m2/week** on Days 1 and 8

The dose expansion phase will comprise of four patient cohorts 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 three main cohorts, i.e. 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 Study Flow Chart

An overview of the study including the different periods (screening, baseline visit, treatment period and follow-up period) overview of the time points of measurements for each assessment are given in Table 5 (Schedule of Study Procedures and Assessments) in Appendix 1.

3.2 Randomization and Blinding

This study is an open-label study, no randomization and blinding are needed.

3.3 Number of Patients

3.3.1 Sample Size Calculation

3.3.1.1 Dose escalation phase

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.

3.3.1.2 Dose expansion phase

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

1. Colorectal cancer (28 patients will be recruited)
2. Ovarian cancer (27 patients will be recruited)
3. Cervical cancer (26 patients will be recruited)
4. Various solid tumors (30 patients will be recruited, 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 4. 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.

The Simon's two-stage design as outlined in Table 4 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.

Note that one additional patient will be included in each cohort compared to what is stated in Table 4. 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.

4. Assessments

An overview of the time points of measurements for each assessment is given in Table 5 (Schedule of Study Procedures and Assessments) in Appendix 1.

4.1 Disposition and Other Supporting Assessments

4.1.1 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.

4.1.2 Protocol Deviations

Protocol deviations will be classified into minor and major and logged as described in the Protocol Deviation Plan.

4.1.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be collected at the screening visit and will include age, gender, ethnicity, race, height, weight and body surface area.

4.1.4 Medical History

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

4.1.5 Prior and Concomitant Medications

Prior medication is defined as medication stopped prior to baseline.

Concomitant medication refers to medication, or therapy, other than the study medication, taken during the study treatment period.

All prescribed drugs, herbal products, vitamins, minerals, and OTC medications are regarded as prior/concomitant medications.

Concomitant therapy or medication usage will be monitored throughout the study.

4.1.6 Eastern Cooperative Oncology Group-Performance Status

Eastern Cooperative Oncology Group Performance (ECOG) Status will be assessed throughout the study.

4.2 Efficacy Endpoints

Details of the assessment of efficacy endpoints are given in Section 9 in the CSP. Definitions of the endpoints are given in Section 4.2.3.

4.2.1 Dose Escalation Phase

4.2.1.1 Primary Efficacy Endpoint

The primary objective of the dose escalation phase concerns safety and tolerability.

4.2.1.2 Secondary Efficacy Endpoints

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).

4.2.1.3 Exploratory Efficacy Variable

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.

4.2.2 Dose Expansion Phase

4.2.2.1 Primary Efficacy Endpoint

The primary endpoint in each of the three main 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

The primary objective for the cohort with various tumor types concerns safety and tolerability of the RP2D dose of birinapant when given in combination with 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).

4.2.2.2 Secondary Efficacy Endpoints

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).

4.2.2.3 Exploratory Efficacy Variable

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

4.2.3 Definition of Efficacy Endpoints

All patients will have a tumor measurement after cycle 3 (week 9) and subsequently after every third cycle. Measures will be assessed through RECIST 1.1 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

After progression, measures will subsequently be analyzed through iRECIST as an exploratory endpoint.

The outcome of a tumor measurement for RECIST 1.1 is a categorization into one of the following categories:

- CR – Complete Response
- PR – Partial Response
- SD – Stable Disease
- PD – Progressive Disease
- Non-CR/Non-PD
- Not Evaluable

For iRECIST, a tumor measurement is categorized into one of the following:

- iCR
- iPR
- iSD
- iUPD
- iCPD
- Non-iCR/Non-iPD
- Not Evaluable

Note that RECIST 1.1 and iRECIST is equivalent until Progressive Disease (PD).

There will be two RECIST 1.1 and iRECIST categorizations, one made in the clinic and one made by an independent radiologist at MEDIAN Technologies. The categorization by the independent radiologist is the one that will be used in the analyses detailed in this SAP. The categorizations at the clinic will be reported descriptively as pure explorative purpose.

A tumour measurement may consist of scans conducted at different days (during the visit window) but there will be only one date associated to the categorization for each visit. That date will be set by the independent radiologist and will be the date used in the derivation of the time to event endpoints below. The overall process for image receipt, review and reporting conducted by MEDIAN Technologies is detailed in the Imaging Review Charter -01, dated 7 February 2018.

4.2.3.1 Overall response (and ORR) assessed through RECIST 1.1

The primary endpoint in the dose expansion phase is the overall response assessed through RECIST v.1.1 until response or progression. A patient with a best overall response of either CP or PR is defined as a patient with an overall response according to RECIST 1.1. A tumor measurement categorized as CP or PR needs a confirmed response of either CP or PR at least 4 weeks after the intial response assessment to be classified as best overall response CP or PR. Examples of patients with an overall response are the following (observations in cycle 3 (week 9) and subsequent every 3rd cycles (9 weeks between each measurement):

- SD, SD, PR, PR, ; SD, SD, PD (overall response as PR in cycle 9 which is confirmed in cycle 12 (9 weeks after))
- SD, SD, SD, CR, CR (overall response as CR in cycle 12)

Example of patients with no overall response as assessed through RECIST 1.1:

- SD, SD, SD, SD, SD, SD, SD, SD, SD
- SD, PD(iUPD), iSD, iSD, iCPD
- SD, PD(iUPD), iSD, iSD
- SD, SD, PR, SD, SD, PD (PR in cycle 9 is not confirmed)
- SD, PD(iUPD), iPR, iSD, iSD (no overall response according to RECIST 1.1)

The overall respose rate (ORR) is defined as the proportion of patients that are classified as overall responders assessed through RECIST 1.1 as described above.

4.2.3.2 Progression Free Survival (PFS)

The PFS is defined as the length of time from the start of treatment the patient lives and does not progress (PD as assessed by RECIST 1.1). Patients who do not die or progress will be censored at the date "last known to be alive", i.e. the latest date of contact with the patient based on all collected evaluation dates.

4.2.3.3 Clinical Benefit Rate (CBR)

The CBR is defined as the percentage of patients with the best measurement of response categorized as CR, PR or SD. Note that SD requires no confirmation as is required for the best overall response of either CR or PR. The first tumor assessment is planned to occur 9 weeks after first dose and therefore, iSD documented at the first assessment would typically qualify as iSD. However, an iSD with actual assessment time less than 6 weeks after first dose will not be qualifyed as iSD. Patients with no post-baseline tumor assessments are considered to have achieved no clinical benefit.

4.2.3.4 Time to response

The time to response is defined as the length of time from start of treatment until the date of the first documented CRor PR assessed through RECIST 1.1. CR or PR requires confirmation on imaging dates that are at least 4 weeks apart. Once it is confirmed, the first documented CR or PR will be considered the start of the response.

Patients not obtaining an overall response (CR or PR) will be censored at the the date of their last tumor assessment.

4.2.3.5 Duration of response

Duration of response will be calculated as the length of time from the first date of confirmed CR/PR to the date of death or the date of first documented tumor progression (PD), whichever is earlier, using RECIST v1.1. Patients who remain alive and do not progress are censored on the date of their last tumor assessment. Response duration is only evaluated in patients with an overall response of CR or PR.

4.2.3.6 Overall Survival (OS)

Overall survival (OS) is defined as the time from the first dose of study treatment to the date of death due to any cause. For patients who do not die, the OS time will be censored on the date when the patient was last known to be alive. The date "last known to be alive" will be defined as the latest date of contact with the patient based on all collected evaluation dates, including the telephone contacts for the survival follow-up.

4.2.3.7 Overall response assessed through iRECIST

The categorization using iRECIST is equivalent with the categorization using RECIST 1.1 until PD. Once PD is obtained, RECIST 1.1 will stop whereas iRECIST will continue to characterize disease state also in cycles after PD.

A patient with a best overall response of either iCP or iPR is defined as a patient with an overall response according to iRECIST. A tumor measurement categorized as iCP or iPR needs a confirmed response of either iCP or iPR at least 4 weeks after the intial response assessment to be classified as best overall response iCP or iPR.

Examples of patients with an overall response are patients with the following outcome of iRECIST at cycle 3 (week 9) and subsequent every 3rd cycles:

- iSD, iSD, iPR, iPR, iSD; iPD (overall response as iPR in cycle 9 and confirmed in cycle 12)
- iSD, iSD, iSD, iCR, iCR (overall response as iCR in cycle 4)
- iSD, PD(iUPD), iPR, iPR, iSD (overall response as iPR as assessed by iRECIST in cycle 9 and confirmed in cycle 12)

Example of patients with no overall response:

- iSD, iSD, iSD, iSD, iSD, iSD, iSD, iSD, iSD
- iSD, (iUPD), iSD, iSD, iCPD
- iSD, iSD, iPR, iSD, iSD, iUPD (iPR in cycle 9 is not confirmed)
- iSD, (iUPD), iSD,

The overall respose rate (ORR) using iRECIST is defined as the percentages of patients that are classified as overall responders assessed through iRECIST as described above.

4.2.3.8 Immune Best Overall Response (iBOR)

The immune best overall response (iBOR) is the best timepoint response recorded from the start of the study treatment until the last assessment of tumor response recorded during study period or the start of post treatment cancer therapy (whichever is sooner), taking into account any requirement for confirmation. iUPD will not override a subsequent best overall response of iSD, iPR, or iCR, meaning that iPR or iSD can be assigned (timepoint response or iBOR) even if new lesions have not regressed, or if unequivocal progression (non-target lesions) remains unchanged, providing that the criteria for iCPD are not met. Table 3 gives scenarios for assignment of iBOR (Seymour (2017)).

Table 3 Scenarios of assignments of best overall response using iRECIST

	Timepoint response 1	Timepoint response 2	Timepoint response 3	Timepoint response 4	Timepoint response 5	iBOR
Example 1	iCR	iCR, iPR, iUPD, or NE	iCR, iPR, iUPD, or NE	iUPD	iCPD	iCR
Example 2	iUPD	iPR, iSD, or NE	iCR	iCR, iUPD, or NE	iCR, iPR, iSD, iUPD, iCPD, or NE	iCR
Example 3	iUPD	iPR	iPR, iSD, iUPD, or NE	iPR, iSD, iUPD, NE, or iCPD	iPR, iSD, iUPD, NE, or iCPD	iPR
Example 4	iUPD	iSD or NE	iPR	iPR, iSD, iUPD, or NE	iPR, iSD, iUPD, iCPD, or NE	iPR
Example 5	iUPD	iSD	iSD, iUPD, or NE	iSD, iUPD, iCPD, or NE	iSD, iUPD, iCPD, or NE	iSD
Example 6	iUPD	iCPD	Any	Any	Any	iCPD
Example 7	iUPD	iUPD (no iCPD)	iCPD	Any	Any	iCPD
Example 8	iUPD	NE	NE	NE	NE	iUPD

4.2.3.9 Duration of iBOR

The duration of iBOR is defined as the length of time from the date when iBOR is first documented until the date of death or the date when a change in disease state using iRECIST is objectively documented, whichever is earlier. Patients who remain alive and do not change from iBOR in disease state are censored on the date of their last tumor assessment. Patients who start a new therapy and do not change from iBOR in disease state are censored at the last tumor assessment prior to initiating the subsequent anticancer therapy. Duration of iBOR is only evaluated in patients with a documented diease state.

4.2.3.10 Time to iCPD

The time to immune Clinical Progressive Disease (iCPD) is the length of time from start of treatment until the date iCPD assessed through iRECIST is obtained. Patients not obtaining iCPD will be sensored on the date of their last tumor assessment.

4.2.3.11 Immune Clinical Benefit Rate (iCBR)

The iCBR is defined as the percentage of patients with the best measurement of response categorized as iCR, iPR or iSD. Note that iSD requires no confirmation as is required for the immune best overall response of either iCR or iPR. The first tumor assessment is planned to occur 9 weeks after first dose and therefore, iSD documented at the first assessment would typically qualify as iSD. However, an iSD with actual assessment time less than 6 weeks after first dose will not be qualifyed as iSD. Patients with no post-baseline tumor assessments are considered to have achieved no clinical benefit according to iRECIST.

4.2.3.12 Time to immune response

The time to immune response is defined as the length of time from start of treatment until the date of the first documented iCRor iPR assessed through iRECIST. iCR or iPR requires confirmation on imaging dates that are at least 4 weeks apart. Once it is confirmed, the first documented iCR or iPR will be considered the start of the response.

Patients not obtaining an overall response (iCR or iPR) will be censored at the the date of their last tumor assessment.

4.2.3.13 Duration of immune response

Duration of immune response is defined as the length of time from the first date of confirmed iCR/iPR to the date of death or the date of first documented tumor progression (iUPD) provided that iCPD is confirmed at the next assessment, whichever is earlier, using iRECIST. Patients who remain alive and do not progress are censored on the date of their last tumor assessment. Patients who start a new therapy without a prior iUPD are censored at the last tumor assessment prior to initiating the subsequent anticancer therapy. Response duration is only evaluated in patients with an overall immune response of iCR or iPR.

4.3 Safety Endpoints

4.3.1 Adverse Events

All adverse events (AEs) and serious adverse events (SAEs) will be reported by the investigator as specified in Section 8 in the CSP.

4.3.2 Clinical Laboratory Tests

4.3.2.1 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

4.3.2.2 Pregnancy Testing

For women of childbearing potential, the following tests are performed:

- At screening: serum β-HCG pregnancy test (a negative test is required to confirm eligibility).
- Before dosing on Days 1 of each cycle: urine pregnancy test (a negative test is required before dosing).

4.3.2.3 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.

4.3.3 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 will be noted regardless of if they are part of the patient's medical history.

4.3.4 Vital Signs

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

4.3.5 ECGs

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.

4.4 Pharmacokinetic Assessments

Pharmacokinetic blood samples will be collected at four different time points during Cycle 1:

- Day 1, 4 hours after completion of birinapant infusion.
- Day 2, 24 hours after completion of birinapant infusion.
- Day 8, before the infusion of birinapant.

- Day 8, 4 hours after completion of birinapant infusion.

See Section 11 in the CSP for more details.

5. Analysis Methods

5.1 Clean File and Timing of Analysis

When the database has been declared to be complete and accurate, the database will be locked and declared clean file. Any changes to the database after that time can only be made by joint written agreement between the project manager, the data manager and the statistician.

The final analysis will be performed after declared clean file, and after finalization and approval of this SAP document.

5.2 Analysis Populations

The analysis of data will be based on different subsets according to the purpose of analysis, i.e. for efficacy and safety respectively. The classification of each patient with respect to each analysis population will be done prior to database lock.

5.2.1 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 FAS population, which is also the safety population, as no randomization is done in this study.

5.2.2 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.

5.2.3 Safety Population

Will be the same as the ITT population.

5.2.4 Pharmacodynamic Evaluable Population

The pharmacodynamic population will include all treated patients for whom pre- and post-infusion pharmacodynamic data are available.

5.2.5 Pharmacokinetic Analysis Population

The PK population will include all treated patients for whom at least one pharmacokinetic sample is quantified.

5.3 General Principles for Presenting Study Data

All statistical analyses will be performed at SDS using SAS® (Version 9.3 or higher, SAS Institute Inc., Cary, NC, USA). All statistical analyses will be performed after this SAP is finalised and approved and the study database is locked.

Continuous data will be summarized using descriptive statistics where the following parameters will be reported:

- Number of observations (n),
- Mean,
- Median,
- Standard deviation (SD),

- Range (Min, Max)

Categorical data will be presented as the number and percentage of patients.

Time to event endpoints defined in Section 4.2.3 (e.g. duration of response, OS and time to iCPD) will be analysed using Kaplain-Meier methods taking censoring into account. The Kaplain-Meier plot and corresponding estimate of the median value with 95% confidence interval will be reported.

All tests will be one-sided and performed at the 5% significance level. When reporting the results of significance tests, p-values will be reported together with 2-sided 90% confidence intervals.

Throughout the report, the number of decimal places given for the summary statistics; mean, STD, confidence interval and median values will exceed that of the source data by one. Minimum and maximum will have the same number of decimal places as the source data. For relative frequencies, integer with one decimal and %-sign will be presented and for p-values four (three) decimals will be reported.

Percentages will be based on number of patients with data at a certain time point with the exception of presentations of medical history, medications and AEs where the percentages will be based on the number of patients in the study population.

In general, all data will be listed, sorted by phase of study, cohort and patient, and when appropriate by cycle within patient. All summary tables will be structured with a column for cohort and will be annotated with the total population size relevant to that table/cohort, including any missing observations. Summary tables will include summaries for visits for Cycle 1 (Screening, Day 1 pre dose, Day 1 post dose, Day 8 pre dose, Day 8 post dose and Day 22 End of Cycle 1 as appropriate) whereas subsequent cycles will be summarized with summary statistics for the minimum and maximum observed value during the subsequent cycles.

The two phases of the study will be summarized separately. In addition, cohorts from phase 1 and phase 2 may be combined and summarized if appropriate.

5.4 Statistical/Analytical issues

5.4.1 Missing Data and Handling of Dropouts

Missing values will not be imputed/replaced in the efficacy analysis.

Laboratory values which are greater/smaller than a stated value will be replaced by the stated value (for example <1 will be replaced by 1) when summarized in tables.

If the start and/or stop dates for medication, AEs and medical history are unknown the date will be imputed to calculate the duration of AE or to decide if the medication was ongoing at baseline or not. No imputation will be presented in individual patient listings. An unknown date will be imputed as follows:

- If the month and date are unknown, the date will be set to June 30th.
- If the day is unknown, the day will be set to the 15th.
- If the year is unknown, the date will not be imputed.

5.4.2 Data Transformations and Derived Variables

5.4.2.1 Calculation of change from baseline

Baseline is defined as the last measurement before the first dose of pembrolizumab or birinapant. The change from baseline value for visit X is derived as 'value at visit X' minus 'value at baseline'.

5.4.3 Interim Analysis and Data Monitoring

An independent Data Monitoring Committee (DMC) will meet approximately biannually during the dose expansion phase to review the complete analysis of combined observed toxicities including emerging safety reports and reported SAEs.

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 interim analysis constitutes the first stage in Simon's two-stage design controlling the overall type I error to 5% within each cohort. The interim analysis for each of the three cohorts will be as follows:

5.4.3.1 Colorectal Cancer Cohort

The interim analysis 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.

The second stage will continue, i.e. the remaining patients in the cohort will be recruited according to the plan, if at least 1 patient (out of 6-13 patients) responds in the overall tumor response assessed through RECIST v1.1. (provided the DMC decides not to stop the second stage because of safety issues).

5.4.3.2 Ovarian Cancer Cohort

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

The second stage will continue if at least 2 patients (out of 6-16 patients) respond in the overall tumor response assessed through RECIST v1.1. (provided the DMC decides not to stop the second stage because of safety issues).

5.4.3.3 Cervical Cancer Cohort

The interim analysis will be based on at least 6 and most 15 patients having completed from 9 up to 27 weeks of treatment (3 to 9 cycles) in the cervical cancer cohort.

The second stage will continue if at least 2 patients (out of 6-16 patients) respond in the overall tumor response assessed through RECIST v1.1. (provided the DMC decides not to stop the second stage because of safety issues).

5.4.4 Multiple Comparisons/Multiplicity

The four cohorts will be handled separately, no adjustment for multiple comparisons will be made between cohorts. No adjustment for multiple comparisons will be performed within a cohort as there is only one primary endpoint in each of the three main cohorts.

For the secondary efficacy variables, no statistical inference will be performed. Thus, no adjustment for multiple comparisons will be made.

5.4.5 Examination of Subgroups

No pre-defined analysis on subgroups are planned.

5.5 Patient Disposition Summary

Descriptive summaries for continuous data and for categorical data will be provided in accordance with Section 5.3 if other not stated.

5.5.1 Patient Disposition

Number of patients screened, enrolled, discontinued for treatment (by reason), continuing in follow-up, and discontinued from the study (by reason) will be summarized by cancer cohort.

5.5.2 Protocol Deviations

Protocol deviations will be displayed in listings.

5.5.3 Demographic and Baseline Characteristics

Demographics and baseline characteristics (gender, age, ethnicity, race, height, weight and body surface area) will be presented as a table for the screening visit.

5.5.4 Medical History

Medical history and medical conditions ongoing at Screening will be coded by system organ class (SOC) and preferred term (PT) using MedDRA (version 20.0) and presented as number and percentage of patients in each SOC and PT by cancer cohort and in total over cohorts.

5.5.5 Prior and Concomitant Medications

Prior and concomitant medication will be coded according to the WHO-Drug Dictionary Enhanced (Version Mar 2017) and ATC classification. Prior and concomitant medication will be reported as a listing for all enrolled patients and tabulated by ACT level 1 and level 3 by cancer cohort and in total over cohorts.
Prior anti cancer therapies, prior medications and concomitant medications will be tabulated separately.

5.5.6 Exposure to Study Treatment

The Investigational products will be administered as IV infusions by study staff and administration information will be recorded in the appropriate CRF.

The following variables will be derived for birinapant and Pembrolizumab separately:

- Cumulative dose = Sum of all administred doses.
- Treatment duration (weeks) = (Date of last dose – date of first dose + planned treatment duration(days))/7.
- Dose intensity = Cumulative dose/Treatment duration
- Relative dose intensity (%) = 100*Dose intensity/Planned dose intensity

Planned treatment duration(days) is 21 days for Pembrolizab and 13 days (21-8) for birinapant (this is the number of days between the last dose of a treatment cycle and the first dose in the subsequent cycle).

The unit of the dose will be in milligram (mg) for Pembrolizumab and in mg/m^2 for birinapant. For birinapant, the total dose in 'mg' is divided by the patient body surface area (m^2) to get dose expressed as mg/ m^2.

Cumulative dose, treatment duration, dose intensity, relative dose intensity, number of infusions administered, number of cycles started, and infusion time per administration will be summarized using descriptive statistics by cohort, treatment (Pembrolizumab) and cycle (cycle 1 and the minimum and maximum observed value during the subsequent cycles) and in total over cycles as appropriate.

5.5.7 Premature Termination

Patients who terminated prematurely will be summarized by reason for early termination and cancer cohort.

5.6 Efficacy Analyses

The only formal statistical analysis in the study concerns the ORR, assessed through RECIST 1.1, in each of the three main cancer cohort in the dose expansion phase of the study. That analysis is detailed in Section 5.6.1. The remaining efficacy endpoints will be summarized using descriptive statistics in accordance with Section 5.3 if other not stated.

5.6.1 Primary Efficacy Analysis

The primary endpoint will be summarized for the Efficacy Evaluable Population in accordance with Section 5.3.

The primary efficacy analysis for each of the three main cohorts in the dose expansion phase of the protocol will be evaluated using Simon's two-stage design (Simon 1989). The null hypothesis that the true response rate (π) is π_0 will be tested against the one-sided alternative $H_A: \pi > \pi_0$ in each of the three cohorts with π_0 , π_1, n_1, n, r_1 and r_2 as in Table 4 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 cohort will be stopped and the p-value for the test will be reported as not significant (no p-value will be calculated). 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.

Table 4 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 (π_0)	Good drug (π_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

In case the total number of evaluable patients do not equal the planned number of patients (n in Table 4), the statistical inference of the ORR will take account of the actual total number of evaluable patients, n^*, as suggested in Koyama and Chen (2007). With a modified stage 2 sample size, the p-value will be calculated as follows.

i. Find π^* such that $P_{\pi}(X_2 > r_2 - x_1 | n_2) = P_{\pi_0}(X_2 \geq x_2 | n_2^*)$
ii. Compute the p-value by

$$\sum_{x=r_1+1}^{n_1} P_{\pi_0}(X_1 = x | n_1)\, A(x, n_2, \pi^*)$$

Here $n_2 (= n - n_1)$ denotes the planned number of patients in the second stage, n_2^* the actual number of patients in the second stage and X_2 denotes the number of responses among those n_2 patients. The p-value will be calculated as above even if $n_2^* = n_2$. In that case it simplifies to the original Simon's 2-stage design with rejection regions as in Table 4.

The point estimate of response rate and the corresponding 90% confidence interval will be obtained by inverting the hypothesis testing. Compute the p-value for testing $H_0: \pi \leq \pi'_0$ versus $H_A: \pi > \pi'_0$ as above. The 90% confidence interval for π is the collection of π'_0 such that the corresponding p-value is within $[0.05, 0.95]$. The value of π'_0 which gives a p-value of 0.5 will be the point estimate of the response rate (π).

5.6.2 Secondary Efficacy Analyses

The secondary endpoints will be summarized with descriptive statistics in accordance with Section 5.3 for the Efficacy Evaluable Population.

5.6.3 Exploratory Efficacy Analyses

The exploratory endpoints will be summarized with descriptive statistics in accordance with Section 5.3 for the Efficacy Evaluable Population.

5.6.4 Subgroup Analyses

No pre-defined analysis on subgroups are planned.

5.6.5 Sensitivity Analyses

A sensitivity analysis of the primary endpoint will be conducted if there are patients that are wrongly included into the study and receives a dose of pembrolizumab and birinapant. In that case, the primary efficacy analysis will be repeated when those patients are excluded from the efficacy evaluable population, for the cohorts it concerns, as a sensitivity analysis. Also other major protocol deviations may be considered in this sensitivity analysis.

5.7 Safety Analyses

No formal statistical analyses will be performed, although descriptive summaries for continuous data and for categorical data will be provided in accordance with Section 5.3 if other not stated. Complete listings of all patient safety evaluations will be provided to support each summary table.

All presentations will be based on the safety analysis set.

5.7.1 Adverse Events

Adverse Events (AEs) will be coded by system organ class (SOC), preferred term (PT) and Verbatim name using MedDRA Version 20.0

All AEs will be listed whereas the treatment emergent AEs (TEAEs), i.e. any AE with onset or worsening on or after the first dose of any IMP and within 30 days after the last dose of IMP, will be summarized as follows.The number of TEAEs, as well as the number and percentage of patients reporting any TEAE will be summarised for Cycle 1, subsequent cycles and Safety follow-up by cohort. Separate summary tables will be produced for the following:

1. TEAEs related to IMP by Verbatim names
2. TEAEs related to IMP by SOC and PT
3. TEAEs not related to IMP by Verbatim name
4. TEAEs not related to IMP by SOC and PT
5. Serious Adverse Events (SAEs) by Verbatim name
6. SAEs by SOC and PT.
7. TEAEs related to IMP by AE grade
8. TEAEs not related to IMP by AE grade

AEs leading to withdrawals or death will be presented by cohort.

All percentages will be based on the number of patients in the safety set.

5.7.2 Clinical Laboratory Tests

All laboratory parameters for individual patients will be listed and patients with abnormal values (out of normal range reported by the laboratory) and with clinically significant abnormalities (according to the Investigator's criteria) will be flagged.

Clinical Laboratory Tests (hematology, clinical chemistry, immunology, serology, urinalysis, pregnancy testing and histology) will be summarized regarding observed values, change from baseline and abnormal findings in accordance with Section 5.3 by cancer cohort and in total over cohorts. In addition, the categorization of the observed values into 'low', 'normal' and 'high' will be summarized in max/min shift from baseline tables by cohort and in total over cohorts. There will be two variants of each shift table, one where the max/min is taken over the samples taken after the first dose but before the 2nd dose and one where the max/min is taken over all samples taken after the first dose.

5.7.3 Physical Examination

Physical examination will be presented as the number and percentage of patients with normal, abnormal not clinically significant, abnormal clinically significant result over time by Body System and cancer cohort.

Findings that are present during screening and prior to drug administration will be included under Medical History. Significant findings made after drug administration that meet the definition of an AE will be reported under the AE section.

5.7.4 Vital Signs

Vital signs will be summarized regarding observed values and change from baseline in accordance with Section 5.3 by cancer cohort and in total over cohorts.

In case several measurements are taken for the same planned sample time, average values will be used.

5.7.5 Electrocardiogram

ECG results will be summarized regarding observed values, change from baseline values and findings (normal, abnormal not clinically significant and abnormal clinical significant) in accordance with Section 5.3 by cancer cohort.

If one of the measurements within a triplicate ECGs is classified as abnormal the value for that visit is classified as abnormal.

5.8 Pharmacokinetic Analyses

The raw PK data (actual drug concentrations) will be summarized in accordance with Section 5.3. The PK data will be summarized by dose and (nominal) sampling time in the dose escalation phase of the study. Whereas in the dose expansion phase, the data will be summarized by cohort and scheduled (nominal) sampling time and over cohorts by scheduled (nominal) sampling time, as appropriate. A sample with actual sample time outside the acceptable time window will not be included in the summary statistics, but will appear in the listings.

Concentration-time data that are below lower limit of quantification (LLOQ) will be treated as zero for PK analysis. The number (and the percentage) of samples below LLOQ will be shown in the summary tables.

Individual graphs on PK (plasma concentration versus actual time point) will be reported for each patient separately, and summarized by cohort/dose group.

The PK analysis will be performed on the PK population set.

Population PK modeling may also be applied to analyze the PK data and will, in that case, be reported separately.

5.9 Changes to Planned Analysis

The statistical analysis of the primary endpoint has been supplemented with how the analysis will be done in case of the number of patients evaluable for efficacy differs from the planned number of patients in the Simon's design.

6. References

BPT-201 v4.0/incl amendment 03, final version dated 18 January 2018.

Eisenhauer, EA, Therasse, P, Bogaerts, J, Schwartz, LH, Sargent, D, Ford, R, et al. New response evaluation criteria in solid tumours: Revised recist guideline (version 1.1). Eur J Cancer. 2009;45(2):228-247.

Imaging Review Charter for BPT-201, MEDIAN Technologies, 7 February 2018.

Koyama T, Chen H. Proper inference from Simon's two-stage designs. Stat. Med. 2008;27:3145–154

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

Simon R. Optimal two-stage designs for phase II clinical trials. Controlled Clinical Trials. 1989; 10(1):1–10. [PubMed: 2702835]

Statistical Principles for Clinical Trials (ICH Topic E 9). EMEA. September 1998, CPMP/ICH/363/96.

7. Appendix 1

Table 5 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		
Physical Examination	X	X			X					X		
Weight and Height[4]	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	
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		
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								

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	
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	
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)