STATISTICAL ANALYSIS PLAN

Clinical Study ARRAY-382-201

A Phase 1b/2 Study of ARRY-382 in Combination with Pembrolizumab, a Programmed Cell Death Receptor 1 (PD-1) Antibody, for the Treatment of Patients with Advanced Solid Tumors

PROTOCOL NUMBER:	ARRAY-382-201
VERSION:	1.0
DATE:	20 February 2020

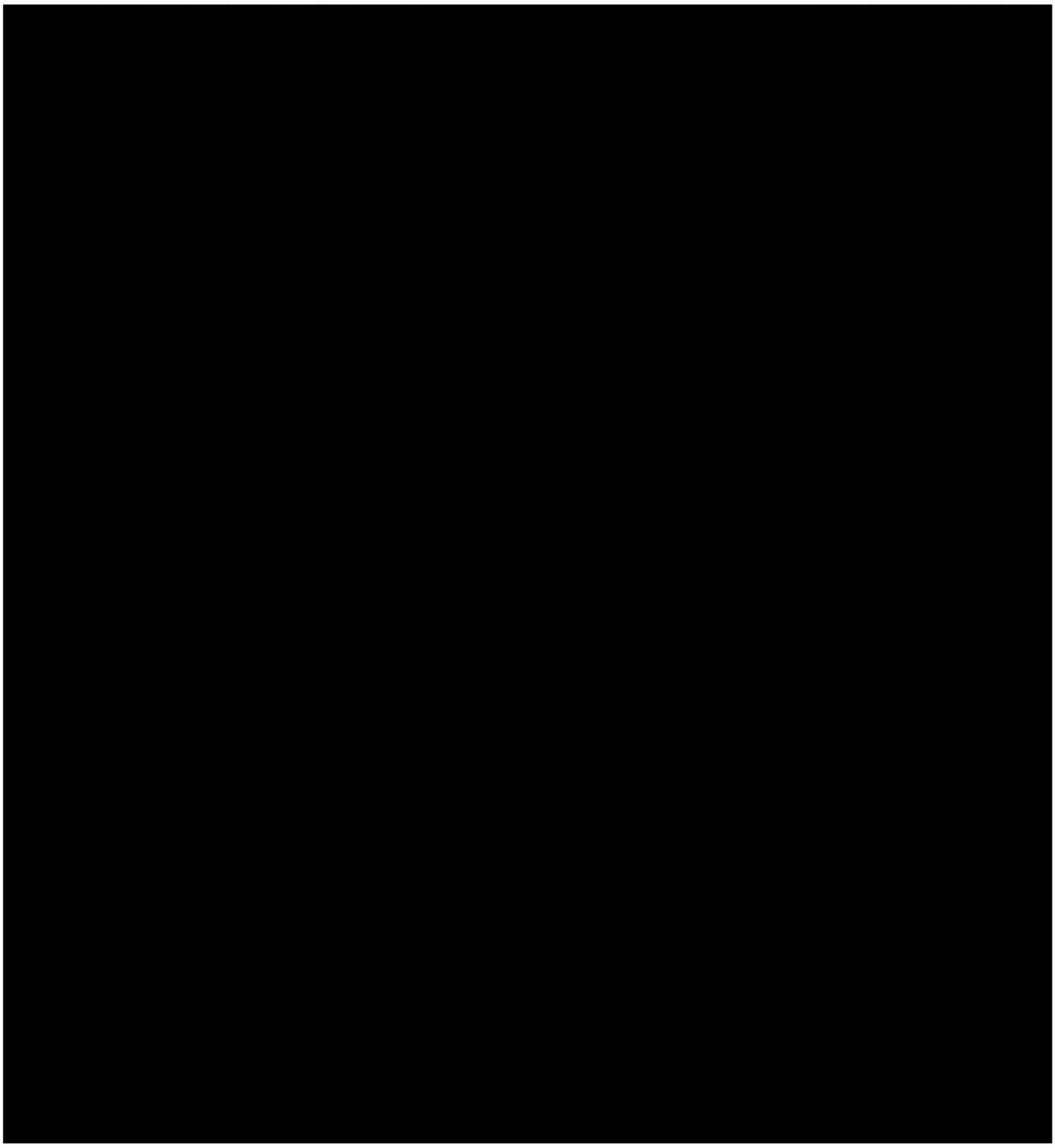
Prepared by:

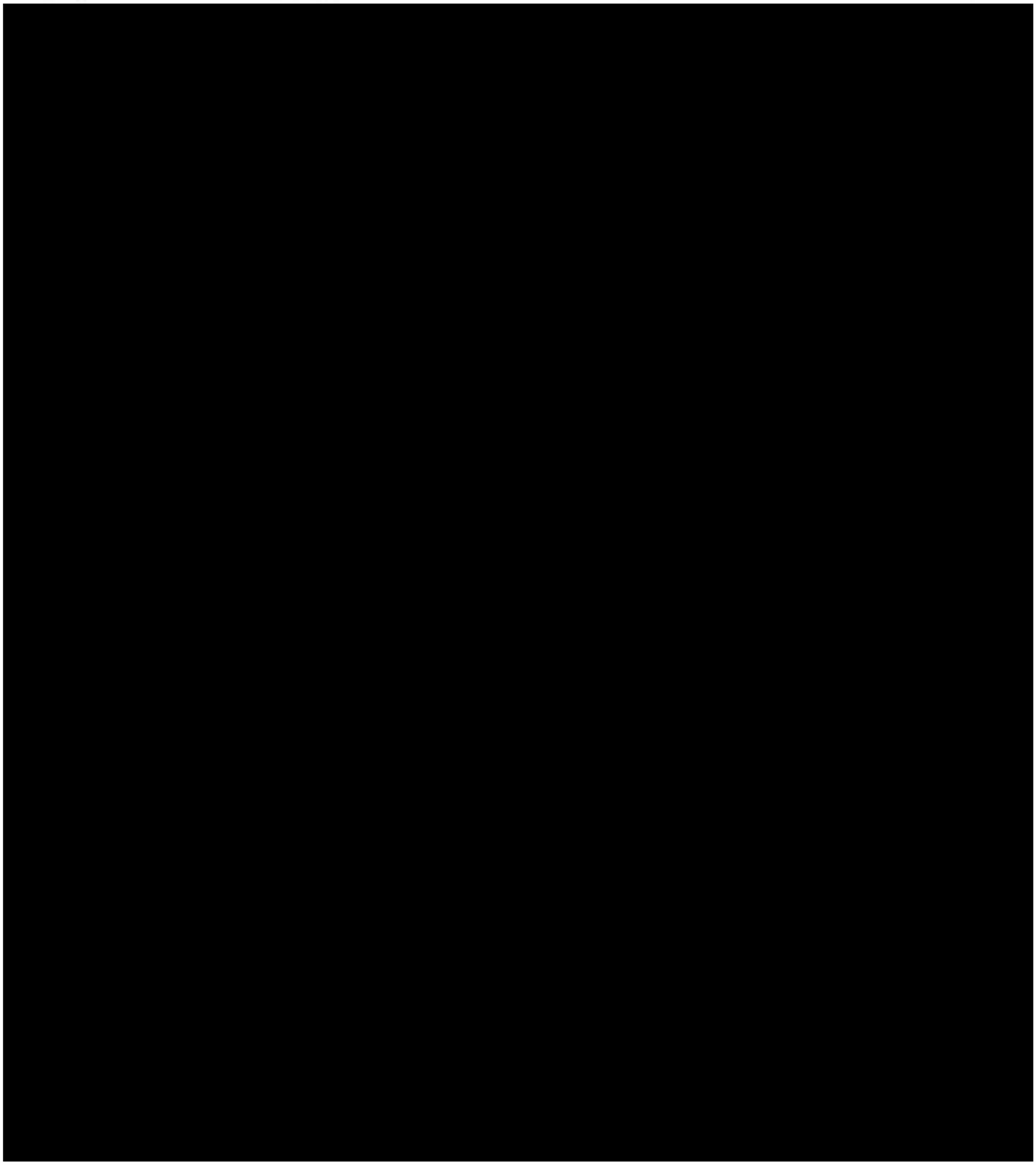
PPD

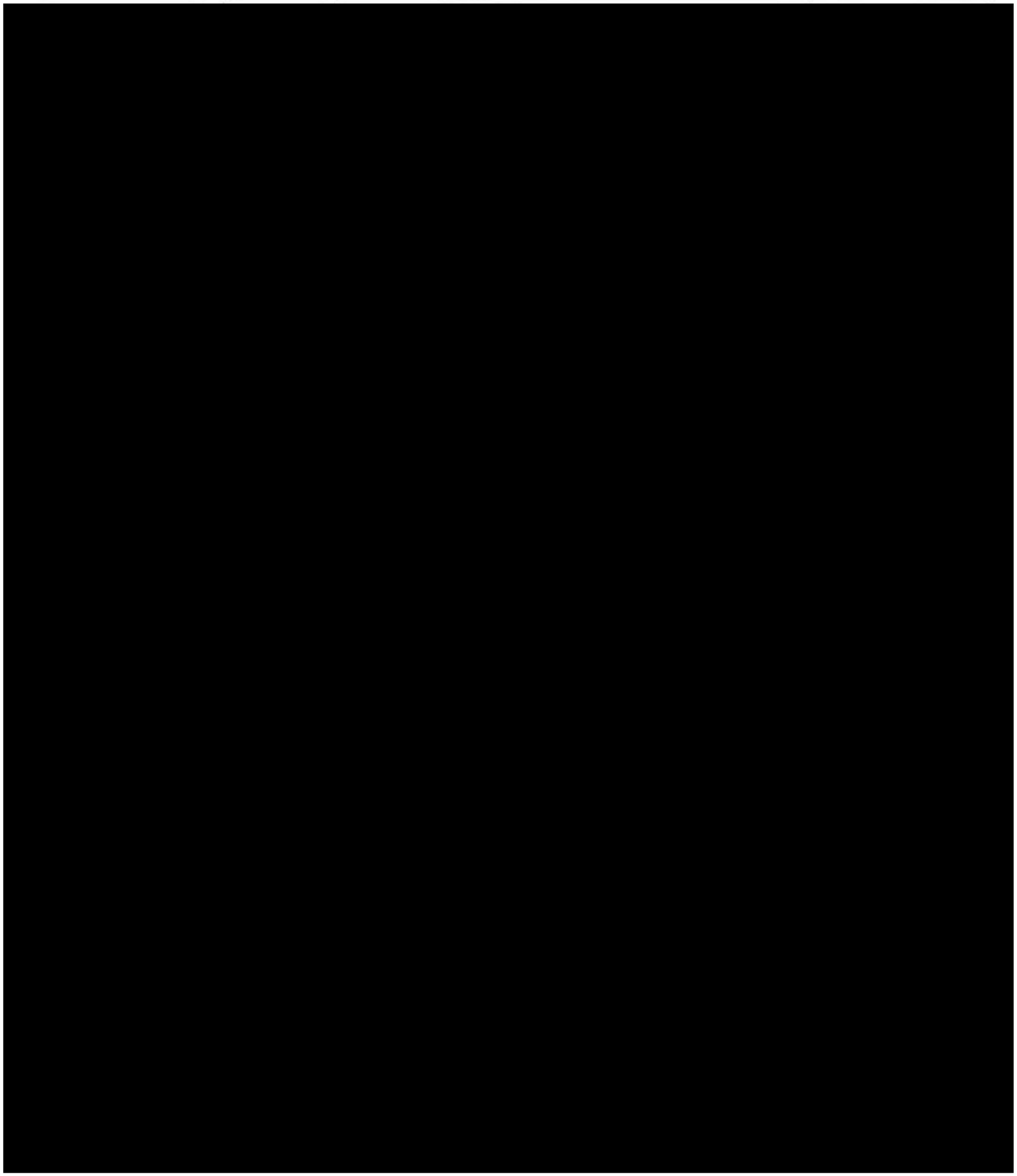
Array BioPharma Inc.
(a wholly owned subsidiary of Pfizer Inc.)

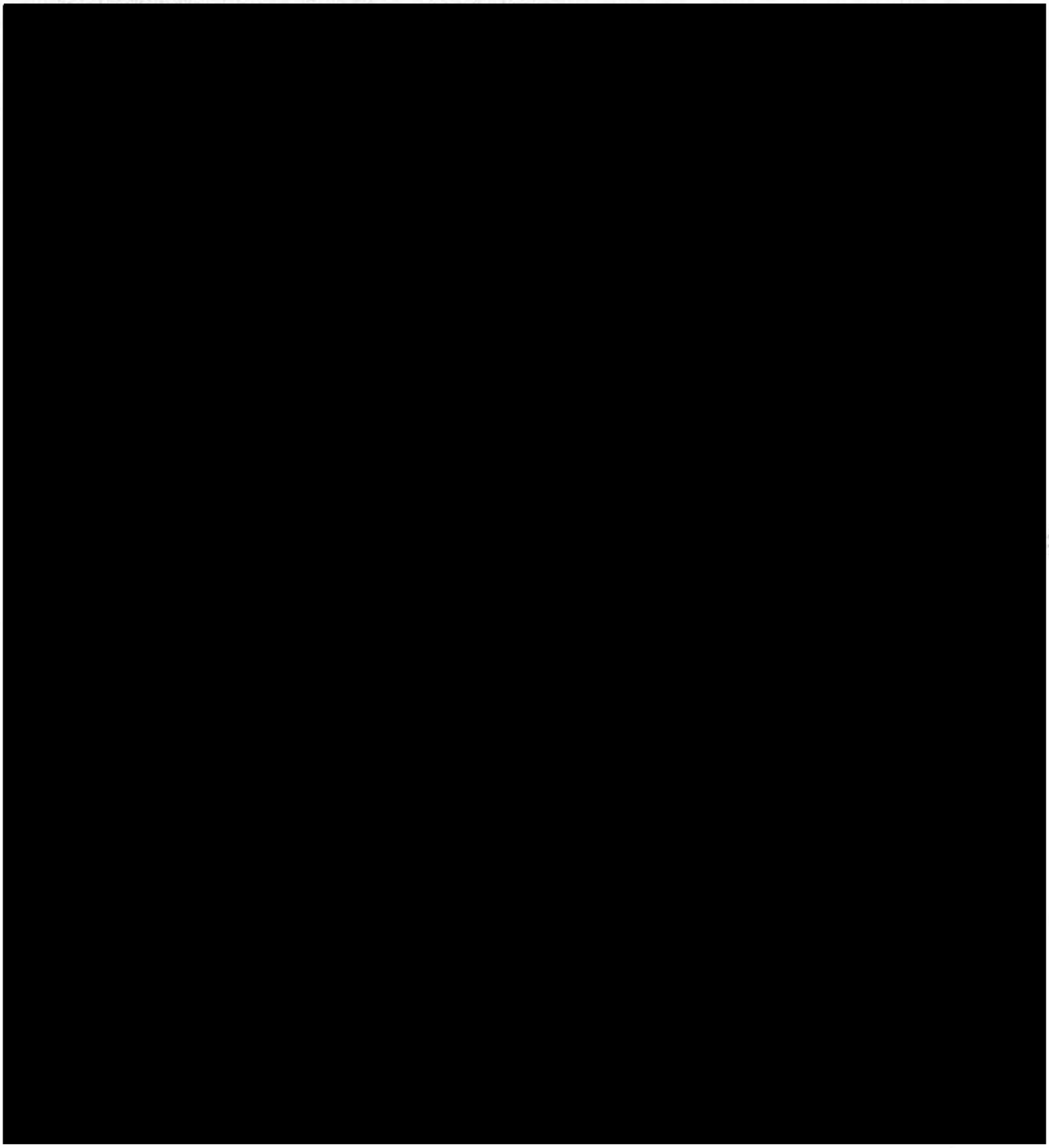
3200 Walnut Street
Boulder, CO 80301

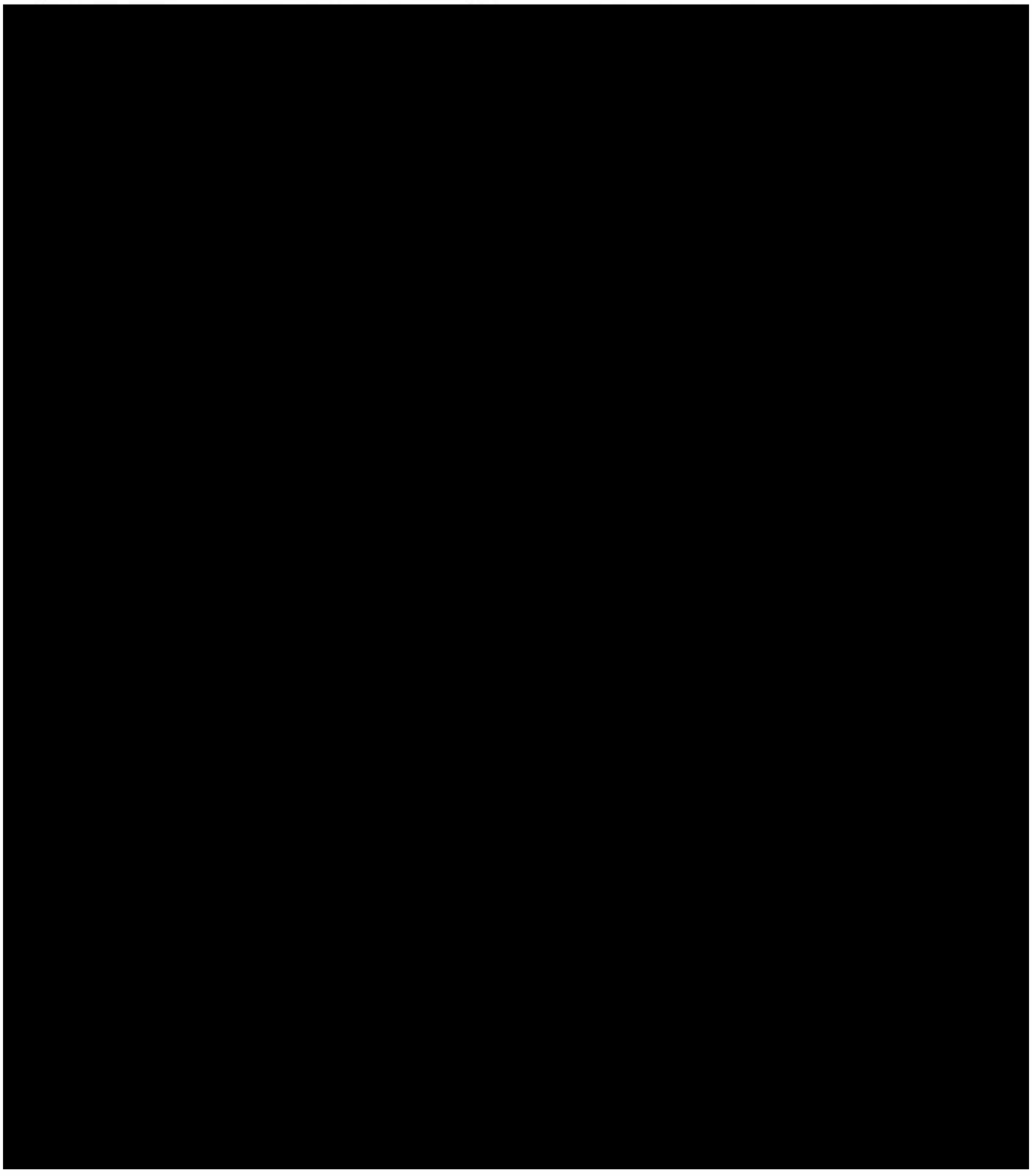
TABLE OF CONTENTS

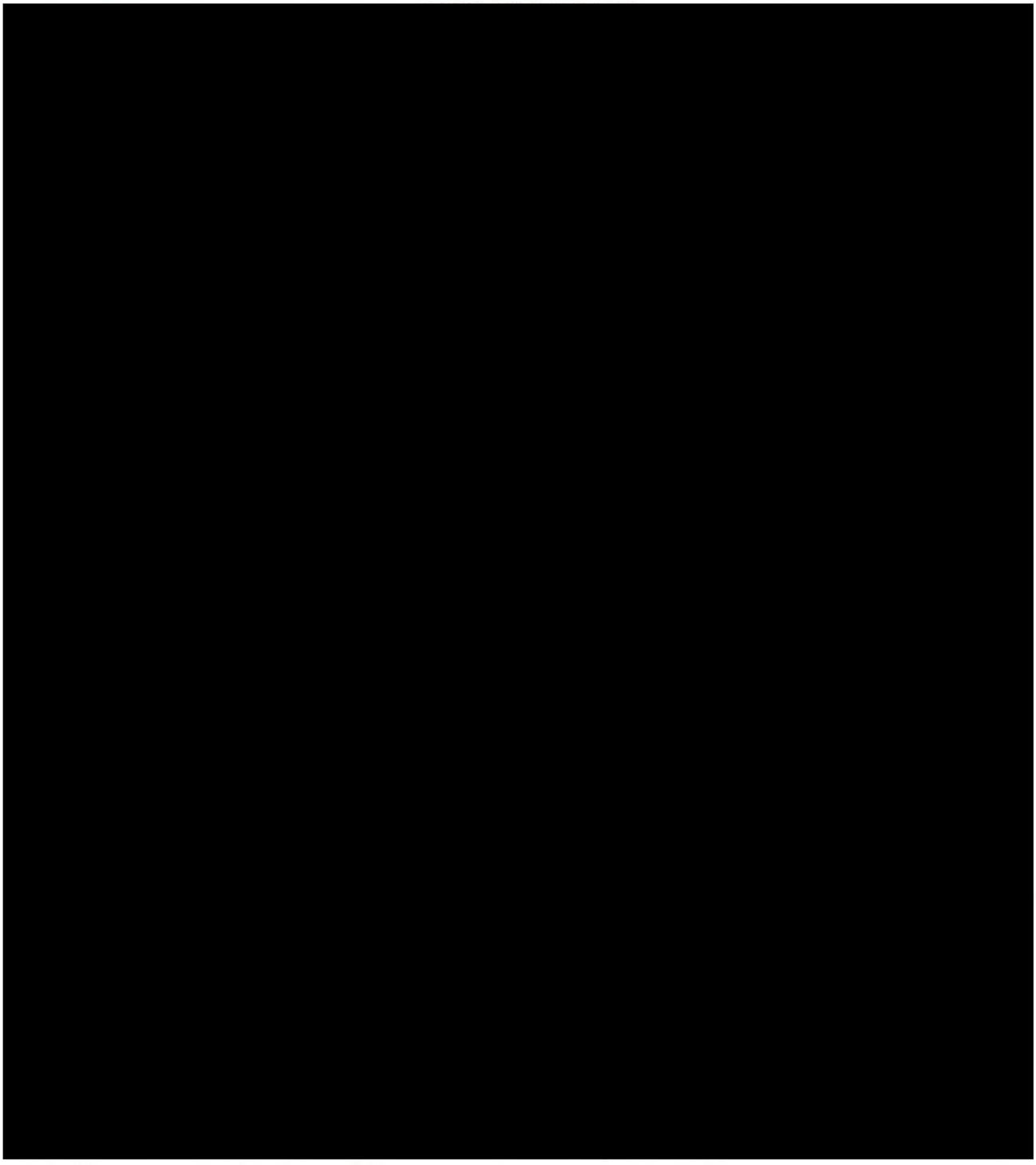


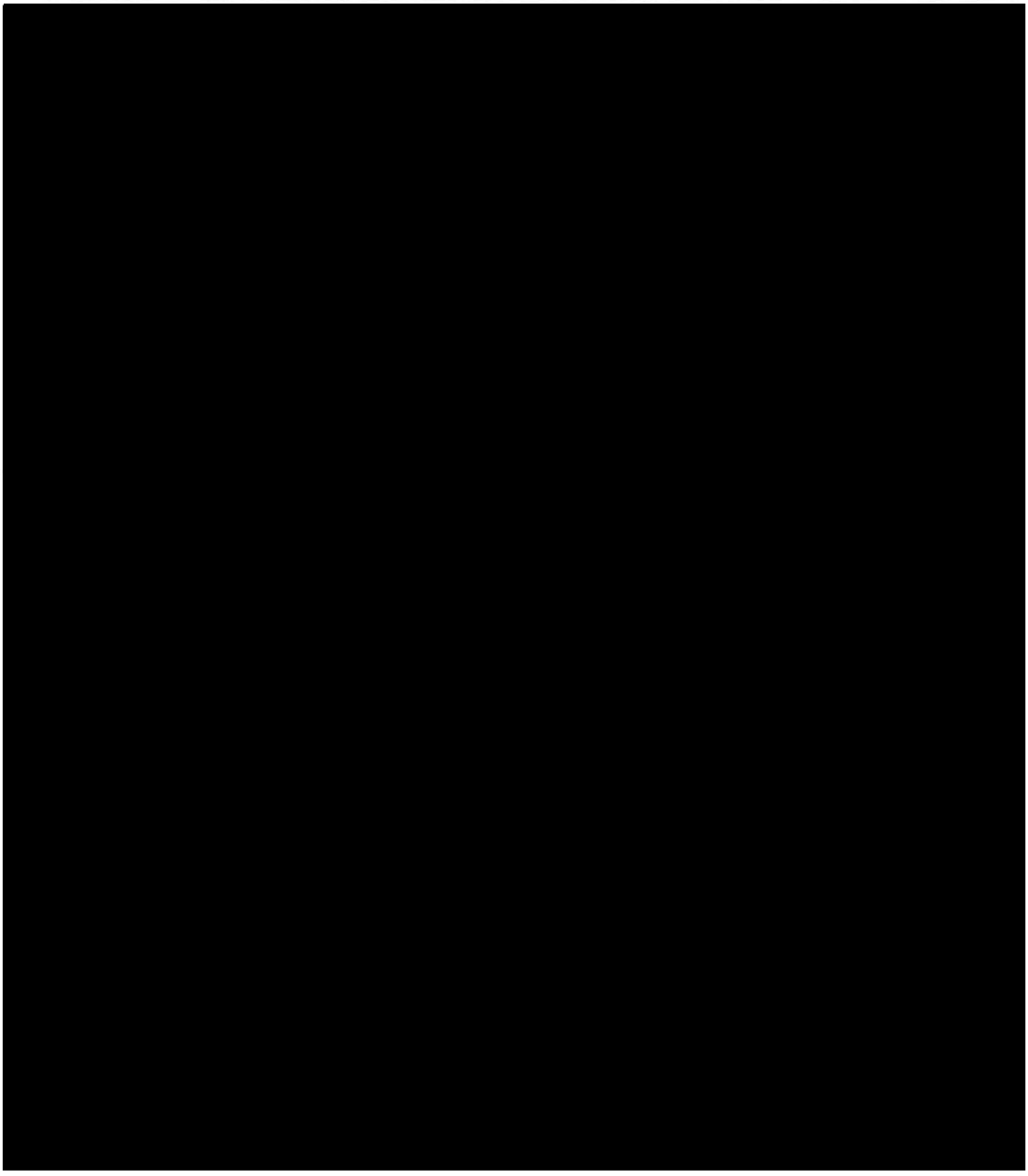












LIST OF ABBREVIATIONS

Abbreviation or Special Term	Explanation
AE	adverse event
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Array	Array BioPharma Inc.
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the plasma concentration-time curve
AUC_{0-x}	area under the plasma concentration-time curve from zero to the specified time point
AUC_{last}	area under the plasma concentration-time curve from zero to the last measurable time point
AUC_{tau}	area under the plasma concentration-time curve over the dosing interval
BLQ	below the limit of quantification
BP	blood pressure
BRAF	B-RAF proto-oncogene, serine/threonine-protein kinase
C1D1	Day 1 of Cycle 1
CXDY	Day Y of Cycle X
CI	confidence interval
CK	creatine kinase
C_{max}	observed maximum plasma concentration
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
C_{trough}	trough (predose) concentration at steady state
CV	coefficient of variation
DCR	disease control rate
DOR	duration of response
DRL	Drug Reference Listing

Abbreviation or Special Term	Explanation
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EOT	end of treatment
FA	fluorescein angiography
FAS	full analysis set
FDA	United States Food and Drug Administration
ICF	informed consent form
KM	Kaplan-Meier
LFT	liver function test
LLOQ	Lower limit of quantification
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MR_{Cmax}	ratio of C_{max} values of the metabolite compared to parent, corrected for molecular weight
$MR_{AUClast}$	ratio of AUC_{last} values of the metabolite compared to parent, corrected for molecular weight
ms	millisecond(s)
MUGA	multi-gated acquisition
NCA	noncompartmental analysis
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
OCT	Optical Coherence Tomography
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death protein ligand 1

Abbreviation or Special Term	Explanation
PFS	progression-free survival
PK	pharmacokinetic(s)
PKS	PK set
PPS	Per-protocol set
PR	partial response
PT	preferred term
QT	QT interval
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fredericia's formula
R_{AUC}	accumulation ratio based on AUC values
RBC	red blood cell(s)
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SI units	International System of Units
SOC	system organ class
SOP	standard operating procedure
SS	safety set
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
T_{last}	observed time of last measured concentration
T_{max}	observed time of C_{max}
ULN	upper limit of normal
WBC	white blood cell(s)
WHO	World Health Organization

1.0 INTRODUCTION

This document describes the statistical analyses and data presentations to be performed for the clinical protocol ARRAY-382-201 entitled "A Phase 1b/2 Study of ARRY-382 in Combination with Pembrolizumab, a Programmed Cell Death Receptor 1 (PD-1) Antibody, for the Treatment of Patients with Advanced Solid Tumors".

This statistical analysis plan (SAP) should be read in conjunction with the study protocol and electronic case report forms (eCRFs). This document has been developed using the protocol Version 5 dated 02 January 2019 and eCRFs dated 13 June 2018. Any further changes to the protocol or eCRFs may necessitate updates to the SAP.

This SAP provides a comprehensive and detailed description of the strategy, rationale and statistical techniques to be used to assess the safety, efficacy, pharmacokinetics (PK) CCI analyses in adult patients with selected advanced solid tumors (Part A/Phase 1b); in adult patients with advanced solid tumors that have progressed on prior PD-1/PD-L1 inhibitors, in adult patients with platinum-resistant ovarian cancer (prOVCA) and in patients with pancreatic ductal adenocarcinoma (PDA) (Phase 2). The purpose of this SAP is to ensure the credibility of the study findings by specifying the statistical approaches for the final analysis of study data. This SAP will be finalized and signed prior to the clinical database lock.

Statistical analyses detailed in this SAP will be conducted using SAS®, Version 9.4 or higher (SAS Institute, Inc., Cary, NC USA). Noncompartmental PK analyses will be performed with Phoenix® WinNonlin® Version 8.0 or higher (Certara USA, Inc., Princeton, NJ). Original sample size calculations for Phase 2 were conducted using R, Version 3.4.3.

1.1 Responsibilities

An Array or CRO-designated Biostatistician or Statistical Programmer will perform any statistical analyses required for patient disposition, protocol deviations, patient characteristics, efficacy and safety; an Array or CRO-designated Biostatistician is responsible for the production and quality control of all tables, figures and listings associated with these analyses. An Array or CRO-designated Clinical Pharmacology representative will perform any PK statistical analyses and is responsible for the production and quality control of all tables, figures and listings associated with these analyses. An Array Translation Science representative will perform any CCI statistical analyses and is responsible for the production and quality control of all tables, figures and listings associated with these analyses.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

Phase 1b/Part A:

- To determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of ARRY-382 in combination with pembrolizumab in patients with selected solid tumors

Phase 2: PD-1 or PD-L1 Inhibitor Refractory:

- To estimate the efficacy of ARRY-382 in combination with pembrolizumab in patients with advanced solid tumors following progression on prior PD-1/PD-L1 inhibitor therapy

Phase 2: Platinum-resistant Ovarian Cancer:

- To estimate the efficacy of ARRY-382 in combination with pembrolizumab in patients with microsatellite stable (MSS)/mismatch repair (MMR)-proficient platinum-resistant ovarian cancer (prOVCA)

Phase 2: Pancreatic Ductal Adenocarcinoma:

- To estimate the efficacy of ARRY-382 in combination with pembrolizumab in patients with MSS/MMR-proficient pancreatic ductal adenocarcinoma (PDA)

2.2 Secondary Objectives

Phase 1b/Part A:

- To describe the preliminary antitumor activity of the combination based on the Response Criteria In Solid Tumors, version 1.1 (RECIST v1.1)
- To describe the preliminary antitumor activity of the combination based on immune-related response criteria (irRC)
- To characterize the safety and tolerability of the combination, including acute and chronic toxicities
- To evaluate the pharmacokinetics (PK) of ARRY-382 in combination with pembrolizumab

Phase 2: PD-1 or PD-L1 Inhibitor Refractory:

- To further estimate the efficacy of the combination

- To estimate the efficacy of the combination, as assessed by changes in tumor markers from baseline
- To characterize the safety and tolerability of the combination, including acute and chronic toxicities
- To evaluate the PK of ARRY-382 in combination with pembrolizumab

Phase 2: Platinum-resistant Ovarian Cancer:

- To further estimate the efficacy of the combination in patients with MSS/MMR-proficient prOVCA
- To estimate the efficacy of the combination, as assessed by changes in tumor markers from baseline
- To characterize the safety and tolerability of the combination, including acute and chronic toxicities
- To evaluate the PK of ARRY-382 in combination with pembrolizumab

Phase 2: Pancreatic Ductal Adenocarcinoma:

- To further estimate the efficacy of the combination in patients with MSS/MMR-proficient PDA
- To characterize the safety and tolerability of the combination, including acute and chronic toxicities
- To evaluate the PK of ARRY-382 in combination with pembrolizumab

CC

[redacted]


CCI

3.0 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is an open-label, multicenter Phase 1b/2 study to determine the MTD and/or RP2D of ARRY-382 in combination with pembrolizumab in adult patients with selected advanced solid tumors (Part A/Phase 1b); and to estimate the efficacy of the combination in patients with advanced solid tumors that have progressed on prior PD-1/PD-L1 inhibitors, in patients with prOVCA and in patients with PDA (Phase 2).

Phase 1b/Part A:

Part A includes a dose-escalation component with 2 planned dose cohorts (200 mg once daily [QD] and 400 mg QD). Oral doses of ARRY-382 will be administered QD in combination with pembrolizumab 2 mg/kg intravenously (iv) every 3 weeks (Q3W). Patients in Cohort 1 will be enrolled on a rolling basis up to 6 evaluable patients or until DLTs are observed in more than 1 patient during Cycle 1. If fewer than 2 of 6 patients experience a DLT during Cycle 1, patients in Cohort 2 will receive ARRY-382 400 mg QD. If 2 or more patients in Cohort 1 experience DLTs during Cycle 1, the dosage of ARRY-382 in Cohort 2 will be 100 mg QD. If a Grade 3 immune-related adverse event (irAE) (first occurrence) is reported in a given cohort, enrollment in that cohort will continue at the same dose until the toxicity is evaluated. If a second Grade 3 irAE is reported or a first Grade 3 irAE is reported in addition to a previous DLT in a given cohort, enrollment of new patients in that cohort will be stopped until the Grade 3 irAE is evaluated. If the event is not a DLT (as determined by the Investigators in consultation with the Sponsor), then enrollment may be resumed, or the cohort may be expanded to include up to 9 patients. If the Grade 3 irAE is deemed a DLT, the MTD has been achieved and additional patients will be enrolled at the previous dose level or at an intermediate dose level.

Intermediate doses and doses higher than 400 mg QD may also be considered upon review of the safety and PK results from the planned dose cohorts. In the absence of identification of an MTD, a dose of 400 mg or lower may be selected as the RP2D as long as the DLT rate is $< 33\%$ (e.g., fewer than 2 of 6 patients experience a DLT).

Part A has been completed and the MTD/RP2D of ARRY-382 was determined to be 300 mg QD in combination with pembrolizumab.

Phase 2

The Phase 2 part will consist of 3 separate cohorts of patients. The Phase 2 PD-1/PD-L1 Inhibitor Refractory cohort will consist of patients with advanced solid tumors who progressed on a PD-1/PD-L1 inhibitor-containing regimen as their most recent prior line of therapy are who are naïve to prior CSF-1R or CSF-1 inhibitors. The Phase 2 prOVCA and PDA cohorts will consist of

patients with prOVCA and patients with PDA, respectively, who have had at least one prior line of therapy and who are naïve to prior checkpoint inhibitor (CPI) therapy and to prior CSF-1R or CSF-1 inhibitors.

In Phase 2, at baseline, submission of archived tumor tissue from the most recent sample collection available or a fresh biopsy will be required.

All patients in Phase 2 will receive ARRY-382 at 300 mg QD, the MTD/RP2D determined during Part A, in combination with pembrolizumab 200 mg iv Q3W.

Efficacy assessments include determination of objective response using RECIST v1.1. For patients who have initial evidence of radiological progressive disease (PD) by RECIST v1.1, it will be at the discretion of the Investigator to keep a patient on study treatment or to stop study treatment until repeat imaging is performed approximately 4 weeks later in order to confirm PD per irRC. Patients with confirmed irPD should discontinue treatment. Patients with a declining Eastern Cooperative Oncology Group performance status (ECOG PS), deteriorating clinical symptoms or rapid progression of disease/progression at critical anatomical sites (i.e., central nervous system [CNS]) should be considered for treatment discontinuation based on clinical judgment.

CCI [redacted]

Pharmacokinetic assessments include determination of plasma concentrations of ARRY-382 and its metabolites.

Safety assessments include monitoring of AEs, clinical laboratory tests (hematology, coagulation, clinical chemistry, thyroid panel, and urinalysis), physical examinations, vital signs, and electrocardiograms (ECGs). ECOG PS will also be assessed.

3.2 Sample Size Considerations

Overall, approximately 90 patients are planned for enrollment.

For Part A, the sample size of approximately 18 evaluable patients (i.e., 6 to 9 patients in each dose cohort) is standard for purposes of determining the MTD and RP2D. Patients will be considered evaluable if they receive at least 67% of protocol-specified doses of ARRY-382 during Cycle 1 or have an adverse event (AE) or other event as described in Protocol Section 9.3. The binomial probabilities of observing a DLT in a cohort of 6 and 9 patients, assuming a true rate of 33%, are provided in Table 1 and Table 2, respectively.

Table 1: Binomial Probabilities of Dose-Limiting Toxicity in a Cohort of 6 Patients

	Binomial Probability		
K	Exactly k DLTs	≤ k DLTs	>k DLTs
0	0.0878	0.0878	0.9122
1	0.2634	0.3512	0.6488
2	0.3292	0.6804	0.3196
3	0.2194	0.8998	0.1002
4	0.0823	0.9821	0.0179
5	0.0165	0.9986	0.0014
6	0.0014	1.0000	0.0000

DLT = dose-limiting toxicity; k = number of dose-limiting toxicities

Table 2: Binomial Probabilities of Dose-Limiting Toxicity in a Cohort of 9 Patients

	Binomial Probability		
K	Exactly k DLTs	≤ k DLTs	>k DLTs
0	0.0260	0.0260	0.9740
1	0.1171	0.1431	0.8569
2	0.2341	0.3772	0.6228
3	0.2731	0.6503	0.3497
4	0.2048	0.8552	0.1448
5	0.1024	0.9576	0.0424
6	0.0341	0.9917	0.0083
7	0.0073	0.9990	0.0010
8	0.0009	0.9999	0.0001
9	0.0001	1.0000	0.0000

DLT=dose-limiting toxicity; k=number of dose-limiting toxicities

For the Phase 2 PD-1/PD-L1 Inhibitor Refractory cohort, the sample size of approximately 20 patients will be evaluated for initial evidence of activity in this PD-1/PD-L1 refractory population.

For the Phase 2 prOVCA cohort, a Simon's 2-stage optimal design (Simon 1989) will be used in the MSS/MMR-proficient prOVCA population. The null hypothesis of the true response rate is

15% will be tested at one-sided type I error rate of 10%. The alternative hypothesis is the true response rate is at least 35%. Accrual of patients in Stage 1 will continue until 9 evaluable MSS/MMR-proficient patients have been enrolled, with evaluable defined as having received at least one dose of study drug. The analysis for Stage 1 will not occur until all evaluable patients in Stage 1 have had the opportunity to have at least 2 post-baseline tumor assessments (or have discontinued tumor assessments beforehand). If there are fewer than 2 responders in these 9 patients, enrollment into this cohort of the study will be stopped. Otherwise, 14 additional patients will be accrued during Stage 2, for a total of 23 patients enrolled in this cohort. The null hypothesis will be rejected if 6 or more responses are observed in 23 patients. With this sample size, the actual Type I error is 9.9%, and the power is 80%. If the null hypothesis is true, the expected sample size is 15 patients, and the probability of stopping enrollment into this cohort of the study early is 60%. Patients who are MSI-H/mismatch repair-deficient (dMMR) will not be included in the Simon's 2-stage analyses and the study will ensure that the sample size requirements are met by enrolling the required number of MSS/MMR-proficient prOVCA patients.

For the Phase 2 PDA cohort, a Simon's 2-stage optimal design (Simon 1989) will be used in the MSS/MMR-proficient PDA population. The null hypothesis of the true response rate is 4%, versus alternative of 15%. Accrual of patients in Stage 1 will continue until 15 evaluable MSS/MMR-proficient patients have been enrolled, with evaluable defined as having received at least one dose of study drug. The analysis for Stage 1 will not occur until all evaluable patients in Stage 1 have had the opportunity to have at least 2 post-baseline tumor assessments (or have discontinued tumor assessments beforehand). If there are no responders in these 15 patients, enrollment into this cohort of the study will be stopped. Otherwise, 14 additional MSS/MMR-proficient patients will be accrued during Stage 2, for a total of 29 patients enrolled in this cohort. The null hypothesis will be rejected if 3 or more responses are observed in 29 MSS/MMR-proficient patients. With this sample size, the actual Type I error is 9.9%, and the power is 80%. If the null hypothesis is true, the expected sample size is 21 patients, and the probability of stopping enrollment into this cohort of the study early is 54%. PDA patients who are MSI-H/dMMR will not be included in the Simon's 2-stage analyses and the study will ensure that the sample size requirements are met by enrolling the required number of MSS/MMR-proficient PDA patients.

4.0 STUDY ENDPOINTS

4.1 Primary Endpoint

Phase 1b/Part A:

- Incidence of dose limiting toxicity (DLT), as a function of the dose of ARRY-382 when administered in combination with pembrolizumab

Phase 2: PD-1 or PD-L1 Inhibitor Refractory:

- Objective response rate (ORR), per RECIST v 1.1, as determined by the Investigator

Phase 2: Platinum-resistant Ovarian Cancer:

- ORR, per RECIST v 1.1, as determined by the Investigator

Phase 2: Pancreatic Ductal Adenocarcinoma:

- ORR, per RECIST v 1.1, as determined by the Investigator

4.2 Secondary Endpoints

Phase 1b/Part A:

- ORR, as determined by the Investigator
- Duration of response (DOR), as determined by the Investigator
- Progression-free survival (PFS), as determined by the Investigator
- Overall survival (OS)
- Immune-related response (irRR), as determined by the Investigator
- Immune-related progression-free survival (irPFS), as determined by the Investigator
- Type, frequency, and severity of AEs, using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)
- Serious adverse events (SAEs), using the NCI CTCAE
- Clinical laboratory values
- Vital signs
- Plasma concentration-time profiles
- PK parameters (e.g., area under the plasma concentration-time curve over the dosing interval [AUC_{τ}], maximum observed plasma concentration [C_{max}], time of maximum observed plasma concentration [T_{max}], plasma concentration measured just before the

next dose of study drug [C_{trough}], accumulation ratio, and metabolite- to-parent ratio) for ARRY-382 and its metabolites, AR00469099, AR00469100, and AR00470870

Phase 2: PD-1 or PD-L1 Inhibitor Refractory:

- DOR, per RECIST v1.1, as determined by the Investigator
- PFS, per RECIST v1.1, as determined by the Investigator
- irRR, per irRC, as determined by the Investigator
- irPFS, per irRC, as determined by the Investigator
- OS
- Type, frequency, and severity of AEs, using the NCI CTCAE
- SAEs, using the NCI CTCAE
- Clinical laboratory values
- Vital signs
- Plasma concentration-time profiles
- PK parameters (e.g., AUC_{τ}, C_{max}, T_{max}, C_{trough}, accumulation ratio, and metabolite-to-parent ratio) for ARRY-382 and its metabolites, AR00469099, AR00469100, and AR00470870

Phase 2: Platinum-resistant Ovarian Cancer:

- DOR, per RECIST v1.1, as determined by the Investigator
- PFS, per RECIST v1.1, as determined by the Investigator
- irRR, per irRC, as determined by the Investigator
- irPFS, per irRC, as determined by the Investigator
- OS
- Changes from baseline in relevant tumor markers
- Type, frequency, and severity of AEs, using the NCI CTCAE
- SAEs, using the NCI CTCAE
- Clinical laboratory values
- Vital signs
- Plasma concentration-time profiles

- PK parameters (e.g., AUC_{τ}, C_{max}, T_{max}, C_{trough}, accumulation ratio, and metabolite-to-parent ratio) for ARRY-382 and its metabolites, AR00469099, AR00469100 and AR00470870

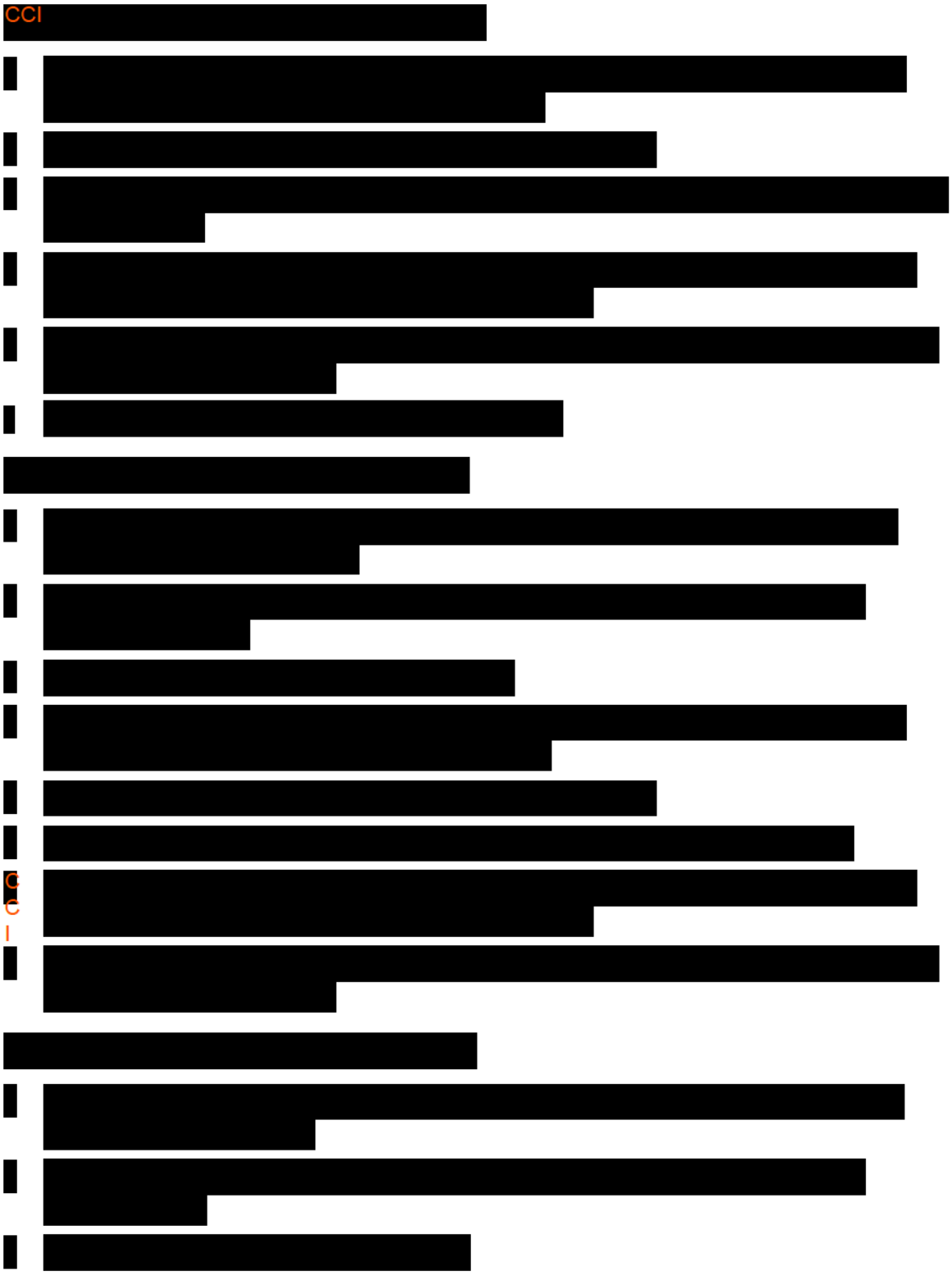
Phase 2: Pancreatic Ductal Adenocarcinoma:

- DOR, per RECIST v1.1, as determined by the Investigator
- PFS, per RECIST v1.1, as determined by the Investigator
- irRR, per irRC, as determined by the Investigator
- irPFS, per irRC, as determined by the Investigator
- OS
- Type, frequency, and severity of AEs, using the NCI CTCAE
- SAEs, using the NCI CTCAE
- Clinical laboratory values
- Vital signs
- Plasma concentration-time profiles
- PK parameters (e.g., AUC_{τ}, C_{max}, T_{max}, C_{trough}, accumulation ratio, and metabolite-to-parent ratio) for ARRY-382 and its metabolites, AR00469099, AR00469100, and AR00470870

CC
I

[redacted]

CCI



5.0 ANALYSIS SETS

5.1 Screened

Screened patients include all patients who sign the Informed Consent Form (ICF).

5.2 Dose-Determining Set

The dose-determining set (DDS) includes all patients in Phase 1b who receive at least 67% of the planned cumulative dose of ARRY-382 during Cycle 1 or discontinue the treatment because of DLT.

5.3 Full Analysis Set

The full analysis set (FAS) will include all patients who have received at least 1 dose (partial or full) of ARRY-382 or pembrolizumab. The FAS will be used for the summary of demographics, baseline characteristics, patient disposition data, and all efficacy analyses.

5.4 Safety Set

The safety set (SS) includes all patients who receive at least 1 dose (partial or full) of ARRY-382 or pembrolizumab. The SS is the same as the FAS in this study.

Unless otherwise specified, the SS will be the default analysis set used for all safety analyses.

5.5 Pharmacokinetic Set

The pharmacokinetic set (PKS) includes all patients from SS who have received any active study treatment (ARRY-382), with at least one post-dose blood draw to determine plasma concentration of ARRY-382 and its metabolites (AR00469099, AR00469100 and AR00470870), and who have no protocol deviations or other circumstances that would exclude them from analysis.

6.0 CHANGES FROM THE STUDY PROTOCOL

There are no changes from the statistical analyses described in the study protocol at this time.

7.0 STATISTICAL METHODS

7.1 Reporting Conventions and Definitions

7.1.1 Study Drug

Study drug is defined as ARRY-382 or pembrolizumab.

7.1.2 Study Treatment

Study treatment is defined as the combination of ARRY-382 + pembrolizumab or single-agent ARRY-382.

7.1.3 Baseline

Baseline is defined as the last available and valid assessment before or at date of start of study treatment. If an assessment is planned to be performed prior to the first dose of study drug in the protocol and the assessment is performed on the same day as the first administration of study drug and the time is unknown, it will be assumed that it was performed prior to study drug administration unless the protocol specifies it otherwise. Unscheduled assessments will be used in the determination of baseline. Data reported at the End of Treatment (EOT) visit are not eligible for baseline selection. The ECG baseline will be the average of triplicate ECG measurements obtained at pre-dose on Day 1 of the study treatment.

7.1.4 Last Contact Date

Last contact date will be derived for patients not known to have died on or before the analysis cutoff date. Imputed dates will not be considered for the determination of last contact date. Only dates associated with patient visits or the actual assessment of the patient will be used in the derivation. Dates associated with a technical operation unrelated to patient status (e.g. the date a blood sample was processed) will not be used. Assessment dates after the cutoff date will not be used to derive the last contact date. Last contact date will only be derived using the latest complete date among the following:

- Study drug start and end dates with non-missing dose (doses of 0 are allowed)
- RECIST assessment date with evaluation marked as done
- Laboratory/PK collection date with sample collection marked as done
- Vital sign, ECG, physical exam, dermatologic exam and ophthalmic exam assessment date with non-missing parameter value
- Performance status date with non-missing performance status
- Start/end date of adverse events with non-missing verbatim term

- Start/end date of anticancer therapies administered after study treatment; discontinuation with non-missing medication/procedure term
- Date of contact for most recent post-treatment survival assessment with the status as "Alive"
- Cardiac imaging assessment date
- [redacted]

7.1.5 Treatment Start Date

Treatment start date is defined as the date patient receives the first non-zero dose of study drug.

7.1.6 Study Day

Study day is defined in the following manner:

- On or after the start date of study treatment: (date of assessment) – (treatment start date) + 1. Study day 1 will therefore be the first day of study treatment.
- Before the start date of study treatment: (date of assessment) – (treatment start date).

7.1.7 Reporting Conventions

Unless specified otherwise, durations of events (e.g., duration of treatment) will be calculated in days as (stop date – start date + 1).

The following conversion factors will be used to convert days into weeks, months or years:

1 week = 7 days, 1 month = 30.4375 days, 1 year = 365.25 days.

Demographics and physical measurements:

- Age (years):
  - (date of given informed consent - date of birth + 1) / 365.25
  - In case of only year and month given: Age (years): (year/month of given informed consent – year/month of birth)
  - In case only year of birth is given: Age (years): (year of given informed consent – year of birth)
  - The integer part of the calculated age will be used for reporting purposes.

All data collected in the database will be used for the statistical analysis. For each analysis a cutoff date will be determined. Only data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) before or on the cutoff date will be included in the analysis.

All events with a start date before or on the cutoff date and an end date after the cutoff date will be considered as continuing at the cutoff date. The same rule will be applied to events starting before or on the cutoff date and not having a documented end date.

In general, missing values will be handled as follows unless otherwise specified. For continuous variables at Baseline, missing values will be excluded from calculation of summary statistics, and the number and percent of patients with missing values will be displayed. For categorical values at Baseline, the number and percent of patients with a missing value will be displayed. For missing post-Baseline values, the method for reporting missing values will depend on the summary table.

Qualitative/categorical data will be summarized by frequency counts and percentages. Percentages will be calculated using the number of patients or subgroup as the denominator. Continuous data will be summarized using appropriate descriptive statistics (e.g. mean, standard deviation, median, minimum, and maximum).

For reporting conventions, minimum and maximum values will be presented with the same decimal precision as collected in the raw data; mean, median, and quartiles should generally be presented to one more decimal place than the raw data; standard deviation should be displayed to two more decimal places than the raw data. Percentages will be reported to one decimal place. Unless otherwise noted, for all percentages, the number of patients in the analysis set who have an observation will be the denominator.

All analyses will be performed and summarized for Phase 1b and Phase 2 separately. All Phase 1b tables will be presented by the following 4 groups, and the listings will be presented by the first 3 groups:

200 mg ARRY-382 + 2 mg/kg Pembro	400 mg ARRY-382 + 2 mg/kg Pembro	300 mg ARRY-382 + 2 mg/kg Pembro	All Phase 1b Patients

All Phase 2 tables, listings and figures will be presented by the following 3 groups:

PD-1/PD-L1 Inhibitor Refractory	prOVCA	PDA

Data listings will be created for Phase 1b and Phase 2 separately, and will be sorted by patient identifier, parameter, and the corresponding date of assessment. The listing source will be included in the footer of the listings.

7.1.8 Unscheduled Visits

Generally, data collected at unscheduled visits will be included and analyzed for both safety and non-safety analyses in the same fashion as the data collected at scheduled visits except where otherwise noted in the sections that follow. Descriptive statistics (mean, standard deviation, median, minimum, maximum, quartiles) by nominal visit or time point for safety endpoints such as laboratory measurements, ECGs and vital signs will include data from scheduled visits only.

7.1.9 Imputation Rules for Partial or Missing Dates

7.1.9.1 Prior and Concomitant Medications

Incomplete concomitant medication dates will be imputed as follows:

Medication start date

- If only day of the month is missing,
  - If month and year match that of the treatment start date, then impute as (treatment start date + 1).
  - If month and year fall before the study treatment start date, then impute the concomitant medication start date as the 15th day of the month.
  - If month and year fall after the treatment start date, then impute as the 1st day of the month.
- If both day and month are missing,
  - If the year matches that of the treatment start date, then impute as the start date for concomitant medication (treatment start date + 1).
  - If the year is prior to the treatment start date, then impute start of the concomitant medication as July 1$^{st.}$
  - If the year is after the treatment start date, then impute as January 1$^{st.}$
- In all other cases the incomplete medication start date will not be imputed.

Medication end date

- If only day is missing,
  - If month and year match that of last contact date, and the medication was ongoing, then impute the end date to be the last day of the month. Otherwise, impute as last contact date.

  - If month and year are prior to the last contact date, then impute as the last day of the month.

- If both day and month are missing,
  - If the year matches that of last contact date, and the medication is ongoing, then impute as December 31st. Otherwise, impute as last contact date.
  - If the year is prior to or after last contact date, then impute as December 31st.
- If the medication end date is completely missing and the medication is ongoing, impute as last contact date.
- In all other cases the incomplete medication end date will not be imputed.

Table 3 and Table 4 provide examples for different scenarios for imputing concomitant medication start and end dates, respectively. The imputation of the start date of prior and concomitant non-drug therapy will follow the same conventions as for concomitant medication start date. However, imputation of non-drug therapy end date will be different, as the data collected on non-drug therapy does not include whether the therapy is ongoing. The imputation of non-drug therapy end date is as follows: completely missing end dates will not be imputed, end dates with only day missing will be imputed to the last day of the month, and end dates with both day and month missing will be imputed to December 31.

Table 3: Concomitant Medication Start Date Imputation Example Scenarios

Partial conmed start date	Treatment start date	Temporal relationship compared to treatment start	Imputed Date
12MMMYYYY	20OCT2001	Uncertain	<blank>
DDMMM2000	20OCT2001	Before	01JUL2000
DDMMM2002	20OCT2001	After	01JAN2002
DDMMM2001	20OCT2001	Uncertain	21OCT2001
DDSEP2001	20OCT2001	Before	15SEP2001
DDOCT2001	20OCT2001	Uncertain	21OCT2001
DDNOV2001	20OCT2001	After	01NOV2001

Table 4: Concomitant Medication End Date Imputation Example Scenarios

Partial conmed end date	Last contact date	Ongoing	Imputed Date
Missing	20OCT2001	Yes	20OCT2001
DDMMM2000	20OCT2001	No	31DEC2000
DDMMM2002	20OCT2001	No	31DEC2002
DDMMM2001	20OCT2001	No	20OCT2001
DDMMM2001	20OCT2001	Yes	31DEC2001
DDSEP2001	20OCT2001	No	30SEP2001
DDOCT2001	20OCT2001	No	20OCT2001
DDOCT2001	20OCT2001	Yes	31OCT2001

7.1.9.2 Adverse Events

The imputation of the start date and end date of AEs will follow the same conventions as for concomitant medication start date and end date.

AEs that are completely missing a start date will be considered as treatment emergent if the end date of the AE is either missing or occurs after the treatment start date. In this case, impute AE start date to be treatment start date.

7.1.9.3 Death Date

Missing or partial death dates will be imputed based on the last contact date:

- If the date is completely missing, it will be imputed as the day after last contact date.
  - Note: A special case is the patient's last contact date is the same as the data cutoff date. In this case, his death date will be imputed as the day after the last contact date. Therefore, he would be still alive as of the data cutoff date.

- If the day or both day and month are missing, death date will be imputed to the maximum of the full (non-imputed) [last contact date (excluding the date of death) + 1] and the following:
  - Missing day: 15th day of the month and year of death
  - Missing day and month: July 1st of the year of death

7.1.9.4 Exposure Date

No imputation will be done for start date of treatment. Date of last dose of study drug if unknown or partially unknown will be imputed as follows:

- If the last date of study drug is completely missing and there is no EOT eCRF page and no death date, the patient should be considered to be on-going and the data cutoff date will be used as the last dosing date for the analysis.
- If the last date of study drug is completely or partially missing and there is either an EOT eCRF page or a death date available (within the data cutoff date), then imputed last dose date will be as follows:
    - = 31DECYYYY, if **only Year** is available and Year < Year of min (EOT date, death date)
    - = Last day of the month, if **both Year and Month** are available and **Year = Year** of min (EOT date, death date) and Month < the month of min (EOT date, death date)
    - = Last day of the month, if **both Year and Month** are available and **Year < Year** of min (EOT date, death date)
    - = min (EOT date, death date), for all other cases

The imputed date will be compared with start date of study treatment:

- If the imputed date < start date of study drug, then last date of study drug is set to start date of study drug;
- Otherwise, use the imputed date.

7.1.9.5 Date of Initial Diagnosis of Cancer

Incomplete dates of initial diagnosis of cancer will be imputed as follows:

- If only day is missing, impute as the 15th day of the month.
- If both day and month are missing and the year is prior to the year of the first study treatment, impute as July 1st.
- If both day and month are missing and the year is same as the year of the first study treatment, impute as January 1st.
- If the date is completely missing, no imputation will be performed.

7.1.9.6 Dates of Anticancer Therapies

Prior therapies:
Incomplete start dates will be handled by applying the same imputation rules as AE/concomitant medications start date except:

- If only day is missing, and month and year match that of the treatment start date, impute as date of first dose of study drug -1;

- If both day and month are missing, and the year matches that of the treatment start date, then impute as date of first dose of study drug – 1;
- Completely missing start date is imputed as date of first dose of study drug – 1.

Incomplete end dates and dates of progression on the prior anticancer therapies will be handled using the following rule:

- If only day is missing**,** imputed date = min (first dose of study drug -1, last day of the month);
- If both month and day are missing, imputed date = min (first dose of study drug -1, 31DEC);
- Completely missing end dates will not be imputed.

If the end date or the date of progression is not missing, and the imputed start date is after the end date or after the date of progression, use the min (end date, date of progression) as the imputed start date.

Subsequent therapies:
Incomplete subsequent anticancer therapy start dates will be imputed using the following rule:

- Imputed date = max (EOT date + 1, first day of the month), if day is missing;
- Imputed date = max (EOT date + 1, 01JAN), if day and month are missing;
- Impute date = EOT date+ 1 if the date is completely missing.

End of Treatment Date is the date of treatment discontinuation as collected from the disposition eCRF page.

There will be no imputation for missing end dates.

7.2 Patient Disposition

Patient disposition analyses will use the FAS unless otherwise stated.

The following disposition categories will be summarized:

- Number (%) of patients enrolled
- Number (%) of patients enrolled but not treated
- Number (%) of patients who received at least one dose of study drug
- Number (%) of patients who are still on treatment
- Number (%) of patients who discontinued the treatment
    - Primary reasons for treatment discontinuation
- Number (%) of patients who discontinued the treatment but are still in follow-up

- Number (%) of patients who were no longer being followed for study evaluation completion
    - Primary reasons for study evaluation completion

Inclusion and exclusion for each of the analysis sets will also be summarized.

Patient disposition data will also be listed.

Screen failure patients are those who were screened, but never started the study treatment for any reason. The data collected on these patients will not be included in any analyses. A listing of reasons for screen failure will be presented.

A separate listing will describe each patient's inclusion or exclusion status for each of the analysis sets defined in Section 5.0.

7.3 Protocol Deviations

Protocol deviations will be determined and documented prior to database lock as outlined in the *Specifications of Protocol Deviations*. The number and percentage of patients in the FAS with any protocol deviations will be tabulated by deviation category, study part and cohort. Protocol deviations will be presented in a data listing.

7.4 Patient Characteristics

Patient characteristic analyses will be performed using the FAS.

7.4.1 Demographics and Pretreatment Characteristics

Demographic and other pretreatment characteristics including age, gender, race, ethnicity, height, weight, and ECOG performance status, will be summarized.

A demographics listing by patient will be created.

7.4.2 Medical and Disease History

Summary of disease history will be created including date of initial diagnosis, stage at diagnosis and stage at study entry.

Medical and disease history will also be listed for each patient.

7.4.3 Substance Use

Data on tobacco use and alcohol use as collected on the Substance Use eCRF page will be included in a listing.

CCI [redacted]

[redacted]

[redacted]

7.4.5 Prior Anticancer Therapy

Prior anticancer therapy will be summarized for three distinct subtypes - systemic treatment, radiotherapy and surgery. Number (%) of patients who received, separately, any prior systemic treatment, radiotherapy, or surgery will be summarized.

For prior systemic treatment, the following data as collected on the "Prior Systemic Cancer Treatments" eCRF page will be summarized:

- Number of patients with at least one prior systemic treatment
- Total number of regimens (there can be more than one medication per regimen)
- Type of prior treatments
- Indication at the last prior therapy (based on the end date)
- Best response at the last prior therapy (defined as the best response during the last treatment regimen recorded)

Prior systemic treatments will also be summarized by Anatomical Therapeutic Chemical (ATC) class and PT.

For prior anticancer radiotherapy, the following information about *the last radiotherapy* (based on end date) will be summarized: location, intent of the radiation and best response.

For prior anticancer surgery, type of procedure and result of procedure will be summarized.

All prior anticancer therapies will be listed separately for systemic treatment, radiotherapy, and surgery.

Incomplete dates will be handled as described in Section 7.1.9.6 .

7.4.6 Other Prior Medications and Procedures

Prior medications (defined as any medications, excluding study drug and prior anticancer treatments) and significant non-drug therapies (including physical therapy, herbal/natural medications, and blood transfusions) recorded in the "Prior and Concomitant Medications" eCRF will be summarized. These medications and therapies will be coded using the World Health Organization Drug Reference Listing (WHO DRL) dictionary that employs the WHO ATC classification system.

The number and percentage of patients will be summarized for medications/non-drug therapies that were stopped prior to start of study drug.

A listing will be produced for medications/non-drug therapies that were stopped prior to start of study drug.

Incomplete dates will be handled as described in Section 7.1.9.

7.5 Efficacy Analysis

Efficacy analyses will be performed using the FAS.

7.5.1 Objective Response Rate

ORR is defined as the proportion of patients who have achieved a best overall response (BOR) of complete response (CR) or partial response (PR) as determined by Investigator review of radiographic disease assessments per RECIST v1.1. Both confirmed and unconfirmed ORR will be summarized, but the primary analysis will be based on confirmed responses.

The BOR is defined as the best response recorded from the study start date until progression and will be determined programmatically based on the Investigator's assessment of tumor response at each time point per RECIST v1.1. Only tumor assessments performed before the start of any subsequent anticancer therapies and not later than 30 days after last dose of study drug will be considered in the assessment of best overall response. Clinical deterioration or clinical progression noted on the End of Treatment Disposition eCRF will not be considered as documented disease progression for the purposes of the ORR calculation.

The confirmed BOR for each patient is determined from the sequence of overall timepoint (lesion) responses according to the following rules below:

> CR = at least two determinations of CR at least 4 weeks apart before progression, where confirmation required, or one determination of CR prior to progression, where confirmation not required.

PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR), where confirmation required, or one determination of PR prior to progression, where confirmation not required.

SD = an assessment of SD or better > 6 weeks after start of treatment (and not qualifying for PD, PR or CR).

PD = progression ≤ 9 weeks after start of treatment (and not qualifying for CR, PR, or SD).

NE (Not Evaluable) = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 9 weeks).

Patients with confirmed best overall response 'Not Evaluable' will be summarized by reason for having unknown status. The following reasons will be used:

- No baseline assessment
- No adequate post-baseline assessment
- All post-baseline assessments have overall response of "NE"
- New anticancer therapy started before first post-baseline assessment
- SD occurred ≤ 6 weeks after the start of treatment
- Progression >9 weeks after the start of treatment (i.e. tumor assessment of PD was >9 weeks after start of treatment and there was no tumor assessment in between)

Special (and rare) cases where BOR is 'Not evaluable' due to both SD occurring ≤ 6 weeks after start of treatment and progression > 9 weeks after the start of treatment will be classified as "SD occurred ≤ 6 weeks after the start of treatment".

The ORR will be calculated with an exact two-sided 95% CI. The 95% CI will be derived using the Clopper-Pearson[4] exact binomial CI method. In addition, the number and percentage of patients in each BOR category (i.e., CR, PR, stable disease (SD), progressive disease (PD), and Not Evaluable) will be summarized.

A figure for duration of exposure and best overall response (confirmed) will be created.

A waterfall plot will be created to show the best percentage change from the baseline in the sum of longest diameters. Patients with baseline and at least one post-baseline tumor assessment will be included in the waterfall plot.

Individual lesion measurements and overall response assessments per RECIST v1.1 will be listed by patient and assessment date.

7.5.2 Duration of Response

DOR is defined as the time from the date of the first documented response (CR or PR) to the earliest date of disease progression, as determined by Investigator review of radiographic disease assessments per RECIST v1.1, or death due to any cause. If a patient with a CR or PR has neither progressed nor died at the time of the analysis cutoff or at the start of any new anticancer therapy, the patient will be censored at the date of last adequate tumor assessment. DOR will be calculated for patients who have achieved a confirmed overall response (i.e., CR or PR).

An estimate of the DOR survival function will be constructed using the Kaplan-Meier (product-limit) method (Kaplan & Meier, 1958) as implemented in PROC LIFETEST. The 25%, median, and 75% DOR (in months) will be summarized along with 95% CIs as calculated from the PROC LIFETEST output (using method of [Brookmeyer & Crowley, 1982]).

Frequency counts and percentages of patients with each event type (PD or death) and censoring reasons will be summarized. Censoring reasons are as follows:

- Ongoing in the study without an event
- No baseline assessment
- No post-baseline assessment
- New anticancer therapy was given
- Progression after 2 or more missed assessments
- Death after 2 or more missed assessments
- Adequate assessment no longer available
- Withdrawal of consent
- Lost to follow-up

A Kaplan-Meier plot of the survival function will be provided as well.

Duration of response will be listed.

7.5.3 Progression-free Survival

PFS is defined as the time from the date of first dose of study drug to the earliest date of disease progression, as determined by Investigator review of radiographic disease assessments per RECIST v1.1, or death due to any cause.

If a patient has not had a PFS event at the time of the analysis cutoff or at the start of any new anticancer therapy, PFS will be censored at the date of last adequate tumor assessment. If a PFS event is observed after more than one missing or inadequate tumor assessment, PFS will be

censored at the last adequate tumor assessment. If a PFS event is observed after a single missing or non-adequate tumor assessment, the actual date of event will be used. Patients who do not have baseline or post-baseline tumor assessments will be censored at the study start date.

The last adequate tumor assessment is defined as a tumor assessment result that is not "NE", "ND", "NA" or missing.

The survival distribution function for PFS will be estimated using the Kaplan-Meier (KM) method as described for DOR in Section 7.5.2. The PFS rate at 2, 4 and 6 months will be estimated with corresponding two-sided 95% CIs.

Frequency counts and percentages of patients with each event type (PD or death) and censoring reasons will be summarized as described in Section 7.5.2.

In addition, time to progression/censoring, event and censoring reasons will be listed.

7.5.4 Overall Survival

OS is defined as the time from the date of first dose of study drug to the date of death due to any cause. If a death has not been observed by the date of the analysis cutoff, OS will be censored at the date of last contact.

The survival distribution function for OS will be estimated using the KM method as described for DOR in Section 7.5.2. The OS rate at 2, 4, 6, 8 and 10 months will be estimated with corresponding two-sided 95% CIs.

Frequency counts and percentages of patients with an event (death) and censoring reasons will be summarized. Censoring reasons are as follows:

- Ongoing and no death
- Lost to follow-up

7.5.5 Immune-related Response Rate

Immune-related RR (irRR) is defined as the proportion of patients who achieve immune-related best overall response (irBOR) of immune-related CR (irCR) or immune-related PR (irPR), as determined by the Investigator per irRC, where irBOR is the best response using irRC recorded from the start of study treatment until the end of treatment.

The confirmed irBOR for each patient is determined from the sequence of overall timepoint (lesion) responses per irRC as summarized in Appendix 6 in the study protocol. The derivation of BOR with confirmation requirement as defined in Section 7.5.1 will be used to determine the

irBOR. In addition, Immune-related PD (irPD) needs to be confirmed by a repeat, consecutive assessment no less than 4 weeks from the first documented date.

The irRR will be calculated along with the two-sided exact Clopper-Pearson 95% CIs. In addition, the number and percentage of patients in each BOR category, i.e., irCR, irPR, immune-related SD (irSD), irPD, and immune-related Unevaluable (irUnevaluable) will be summarized.

7.5.6 Immune-related Progression-free Survival

Immune-related PFS (irPFS) is defined as the time from the start of treatment to the time of first documented progression per irRC, as determined by the Investigator or death due to any cause.

For the analysis of irPFS, the Kaplan-Meier method as defined in Section 7.5.3 will be performed, and the same censoring rules as described in Section 7.5.3 will be applied.

7.6 Safety Analysis

All safety analyses will be performed using the appropriate data for all patients in the SS unless otherwise stated.

7.6.1 Extent of Study Drug Exposure

Duration of exposure is defined as follows and will be summarized with descriptive statistics (n, mean, median, minimum, maximum).

ARRY-382:

Duration of exposure (days) = date of last (non-zero) dose of ARRY-382 – date of first dose of ARRY-382 + 1

Pembrolizumab:

Duration of exposure (weeks) = (date of last (non-zero) dose of pembrolizumab - date of first dose of pembrolizumab + 21)/7

Cumulative dose is defined as:

ARRY-382:

- **Planned cumulative dose** (mg) = sum of all protocol specified doses across each planned day of dosing
- **Actual cumulative dose** (mg) = sum of all actual doses taken during the dosing period

Pembrolizumab:

- **Planned cumulative dose** (mg/kg) = sum of all protocol specified doses across the dosing period
- **Actual cumulative dose** (mg/kg) = sum of all actual doses taken during the dosing period

The dose of pembrolizumab taken at each visit is calculated as total (planned and actual) dose administered (mg) at each visit / weight (kg) at that visit.

For patients who did not take any drug the actual cumulative dose is by definition equal to zero.

Dose intensity and relative dose intensity are defined as follows:

ARRY-382:

- **Planned dose intensity** (mg/day) = planned cumulative dose (mg) / [duration of exposure (days)]
- **Actual dose intensity** (mg/day) = actual cumulative dose (mg) / [duration of exposure (days)]
- **Relative dose intensity** = 100*[actual dose intensity (mg/day) / planned dose intensity (mg/day)]

Pembrolizumab:

- **Planned dose intensity** (mg/kg/cycle) = planned cumulative dose (mg/kg) / [duration of exposure (weeks)/3]
- **Actual dose intensity** (mg/kg/cycle) = actual cumulative dose (mg/kg) / [duration of exposure (weeks)/3]
- **Relative dose intensity** = 100*[actual dose intensity (mg/kg/cycle) / planned dose intensity (mg/kg/cycle)]

A summary of exposure, including duration, cumulative dose, actual dose intensity, and relative dose intensity (including categories <50%, 50%-<75%, 75%-<90%, 90%-<110%, and ≥110%, if applicable), will be presented for each study drug. Duration of exposure, cumulative dose, actual dose intensity, and relative dose intensity will also be listed for each patient.

7.6.1.1 Dose Modifications

Dose reduction:

Dose reductions are permitted for ARRY-382. A dose reduction is defined as a decrease in dose from the protocol planned dose and a decrease from the previous non-zero dose, even if this decrease has been directly preceded by an interruption.

If a patient's dose decreases from a higher than protocol planned dose to the planned dose, this is not counted as a reduction; however, if the dose is reduced directly from a higher than planned dose to a lower than protocol planned dose or the planned dose on a less frequent regimen, this is counted as a reduction.

If the dose on the first dosing record is lower than protocol planned dose this is also counted as a reduction.

Dose reduction will be summarized based on the dose modification data collected on the eCRF page.

Dose interruption:

A dose interruption will be indicated in the eCRF by a dosing record with a total daily dose of 0 mg for one or more days.

Dose interruption will be summarized based on the dose modification data collected on the eCRF page. However, in order not to over count interruptions, dosing records with 0 mg entered as last dosing record will not be counted as interruptions. Those represent the reason for permanent discontinuation and will therefore be presented in the reason for treatment discontinuation analysis.

Frequency counts and percentages of patients who have dose reductions or any study drug interruptions, and the corresponding reasons, will be provided. The number of dose interruptions per patient, and the duration of dose interruptions (days) will also be summarized for each study drug.

7.6.2 Concomitant Medications

Concomitant medications are defined as any medications (excluding study drug and prior anticancer treatments) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered in the study and recorded in the Prior and Concomitant Medications eCRF.

Concomitant medications will be coded using the latest version of the WHO Drug Reference Listing dictionary available at the time of reporting and will be summarized by ATC (level 2) and PT (level 4). These summaries will include:

1. medications starting on or after the start of study treatment but no later than 30 days after last dose of study treatment, and

2. medications starting prior to the start of study treatment and continuing after the start of study treatment.

All concomitant medications will be listed.

Incomplete dates will be handled as described in Section 7.1.9.1.

7.6.3 Subsequent Anticancer Therapies

Subsequent anticancer therapies include anticancer systemic therapy, anticancer radiation or anticancer surgery.

Subsequent anticancer systemic therapy will be summarized by ATC class (level 2) and PT.

Subsequent anticancer systemic therapy, radiotherapy, and surgery will be listed.

Incomplete dates will be handled as described in Section 7.1.9.6.

7.6.4 Adverse Events

AEs and serious adverse events (SAEs) will be coded by PT and SOC using the latest available MedDRA version.

The severity of an AE will be assessed by the investigator using the NCI CTCAE, Version 4.03. For patients with more than 1 AE within a SOC or PT, only the highest grade will be included in by-severity summaries.

The investigator will also assess whether the AE is suspected to be related to study drug (i.e., a treatment-related AE). For patients with more than 1 AE within a SOC or PT, the highest level of relationship (related is higher than not related) will be included in the by-relationship summaries.

For summaries by SOC and PT, each patient will be counted at most once per SOC and at most once per PT. For summaries by PT, each patient will be counted at most once per PT.

Treatment-emergent AEs (TEAEs) will be defined as:

- Any new event that starts after administration of study drug and ≤ 30 days after treatment discontinuation.
- Any event that was ongoing when treatment with study drug started and the severity/grade after treatment was higher than the Baseline value (fluctuations below the Baseline severity/grade are not considered as treatment emergent).
- Any new event that starts > 30 days after treatment discontinuation and is assessed by the Investigator as related to study treatment.

Every effort should be made to obtain start dates for adverse events (AEs). If an AE is missing the start date, and the timing of the start date relative to treatment start is not known, it should be considered as treatment emergent for reporting and analysis purposes.

Unless otherwise stated, only TEAEs will be presented in summary tables. However, all AEs will be presented in listings.

Overall summary of safety table will include numbers and percentages of the following:

- Patients who died on study or within 30 days of last treatment
- Patients with at least 1 TEAE regardless of causality
- Patients with at least 1 treatment related TEAE
- Patients with treatment related TEAEs by worst severity
- Patients with at least 1 treatment-emergent SAE (TESAE)
- Patients with at least 1 treatment-related TESAE
- Patients who discontinued study drug due to a TEAE regardless of causality
- Patients who discontinued study drug due to a treatment-related TEAE
- Patients with a dose reduction due to a TEAE
- Patients with a dose interruption due to a TEAE

All TEAE summaries will be displayed (frequency counts and percentages) alphabetically by system organ class (SOC) and preferred term (PT) by descending frequency within SOC, if not otherwise noted. Individual summary tables showing the incidence of patients with the following subsets of TEAEs will be generated:

- TEAEs, regardless of causality, by SOC, PT and maximum severity
- TEAEs, regardless of causality, by SOC and PT
- TEAEs, regardless of causality, by PT
- Treatment-related TEAEs with suspected relationship to ARRY-382 by SOC, PT and maximum severity
- Treatment-related TEAEs with suspected relationship to pembrolizumab by SOC, PT and maximum severity
- Treatment-related TEAEs with suspected relationship to ARRY-382 by PT
- Treatment-related TEAEs with suspected relationship to pembrolizumab by PT
- TESAEs, regardless of causality, by SOC, PT and maximum severity
- TESAEs, regardless of causality, by SOC and PT
- TESAEs, regardless of causality, by PT
- TESAEs with suspected relationship to ARRY-382 by SOC, PT and maximum severity
- TESAEs with suspected relationship to pembrolizumab by SOC, PT and maximum severity

- TEAEs, regardless of causality, that led to discontinuation of study drug, by SOC and PT
- Treatment-related TEAEs with suspected relationship to ARRY-382 leading to study drug discontinuation by SOC and PT
- Treatment-related TEAEs with suspected relationship to pembrolizumab leading to study drug discontinuation by SOC and PT
- TEAEs that led to dose reduction in ARRY-382 by SOC and PT
- TEAEs that led to dose interruption /delay of ARRY-382 by SOC and PT
- TEAEs that led to dose interruption /delay of pembrolizumab by SOC and PT
- Non-serious TEAEs, regardless of causality, by SOC and PT
- TEAEs that resulted in death on study or within 30 days of last study treatment by SOC and PT

Separate listings for AEs, serious AEs (SAEs), AEs requiring dose interruption, AEs leading to any study drug discontinuation, and death recorded during the study will be provided.

All AEs and their attributes will be presented in data listings sorted by patient identifier, AE and date of onset of the AE.

7.6.5 Clinical Laboratory Evaluations

Required hematology, coagulation, clinical chemistry, thyroid panel and urinalysis tests are described in Table 9 of the protocol. Hematology, clinical chemistry, coagulation, thyroid panel and urinalysis test results will be presented using the International System of Units (SI units) and, where appropriate, will be graded using NCI CTCAE, Version 4.03.

For laboratory data, baseline is the last available assessment performed prior to the treatment start date/time. If more than one value is available, priority is given to the central assessment versus the local assessment. If more than one central sample is available, priority is given to the assessment marked as Unscheduled or Repeat assessment. Patients who start treatment and discontinue from the study on the same day may have 2 different sets of data collected on study day 1, one being reported to the cycle 1 day 1 visit, the other reported to the EOT visit. Data reported at the EOT visit are not eligible for baseline selection.

The following laboratory parameters will be summarized by CTCAE grade:

- Hematology:

  Hemoglobin (anemia/hemoglobin increased), Platelets (platelet count decreased), WBC (white blood cell decreased/increased), Neutrophils (neutrophil count decreased), Lymphocytes (lymphocyte count increased/decreased).

- Chemistry:

Albumin (hypoalbuminemia), Alkaline phosphatase (ALP) (alkaline phosphatase increased), Alanine aminotransferase (ALT) (ALT increased), Aspartate aminotransferase (AST) (AST increased), Total bilirubin (TBL) (blood bilirubin increased), Creatinine (creatinine increased), Corrected calcium (hypocalcemia/ hypercalcemia), Creatine Kinase (CPK increased), Glucose (hypoglycemia/hyperglycemia), Amylase (serum amylase increased), Lipase (lipase increased), Phosphate (hypophosphatemia), Magnesium (hypomagnesemia/hypermagnesemia), Potassium (hypokalemia/hyperkalemia), Sodium (hyponatremia/hypernatremia).

- Coagulation: INR (INR increased), PTT or aPTT (Activated partial thromboplastin, time prolonged)

The following rules will be used for grading elevated glucose:

- If a glucose value falls within normal ranges it should be graded as zero, irrespective of fasting status.
- If fasting status is unknown and the result falls within the ranges for hyperglycemia grades 1 or 2, grade should be set to missing.
- If fasting status is known and fasting did not occur, and the result falls within the ranges for hyperglycemia grades 1 or 2, grade should be set to 0.

The following laboratory parameters will be summarized by normal range:

- Hematology:

  Hematocrit, RBC, Monocytes (absolute), Eosinophils (absolute), Basophils (absolute).

- Chemistry:

  Bicarbonate (CO2), BUN or urea, Chloride, Glucose (non-fasting), LDH, Total protein, Direct bilirubin.

- Urinalysis:

  Specific gravity, Glucose, Ketones, Blood, Nitrite, Leukocytes.

- Thyroid panel:

  Thyroid-Stimulating Hormone (TSH)

  Triiodothyronine (T3), free

  Thyroxine (T4), free

The Corrected Calcium will be derived from Calcium and Albumin results as per the following formula:

Corrected calcium (mmol/L) = [4*calcium(mmol/L) – 0.8*(0.1*albumin(g/L) – 4)]/4

The normal range of the Calcium will be used as normal range for Corrected Calcium.

The following summaries will be produced for the hematology, coagulation, clinical chemistry, thyroid panel and urinalysis laboratory data (by laboratory parameter):

- Shift tables using CTCAE grades to compare baseline to the worst post-baseline value for laboratory parameters with CTCAE grades. For the laboratory parameters like blood glucose where patients can be graded for decreased or increased values, the worst post-baseline CTCAE grade will be presented for decrease and increase separately (e.g. hyperglycemia and hypoglycemia). In the description of worst grade increase, a decrease of a grade >= 1 will be described as grade 0. The reciprocal will be applied for grade decrease categorization.
- Shift tables using low, normal, high (as well as low and high combined) classifications to compare baseline to the worst post-baseline value for laboratory parameters where CTCAE grades are not defined.
- The following listings will be produced for the laboratory data for all laboratory parameters where CTCAE grades are defined:
  - Listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory reference ranges.
  - Listing of patients with laboratory abnormalities of CTCAE grade 3 or 4.

Serology test results will be summarized.

All lab test results will be presented in listings sorted by patient identifier, lab test, and date/time of collection. Values outside laboratory normal ranges will be flagged where appropriate.

Hepatic Toxicity

Hepatic toxicity will be assessed based on the following Liver Function Tests (LFTs): ALT, AST, ALP, and TBL.

LFTs will be summarized as follows:

- Frequency counts and percentages of patients having a newly occurring value in the categories in Table 3 will be provided.

In addition, a listing of all LFTs values for patients having a newly occurring value in the categories presented in Table 3 will be provided.

Table 3: Hepatic Toxicity Criteria

Parameter	Criterion
ALT	>3xULN; >5xULN; >8xULN;>10xULN;>20 ULN
AST	>3xULN; >5xULN; >8xULN >10xULN;>20 ULN
AT (ALT or AST)	>3xULN; >5xULN; >8xULN >10xULN;>20 ULN
TBL	>1.5xULN, >2xULN
ALP	>2xULN, >3xULN
AT & TBL	AT >3xULN & TBL >2xULN; AT >5xULN & TBL >2xULN; AT >10xULN & TBL >2xULN
ALP & TBL	ALP >3xULN & TBL >2xULN
AT & TBL & ALP	AT >3xULN & TBL >2xULN & ALP <2xULN

7.6.6 Pregnancy Tests

Results of all pregnancy tests will be presented in a data listing.

7.6.7 Vital Signs and Body Measurements

The following criteria define clinically notable vital sign abnormalities:

Clinically notable elevated values

- Systolic Blood Pressure (BP): ≥ 160 mmHg and an increase ≥ 20 mmHg from baseline
- Diastolic BP: ≥ 100 mmHg and an increase ≥ 15 mmHg from baseline
- Heart rate (collected as pulse rate in the vital signs eCRF): ≥ 120 bpm with increase from baseline of ≥15 bpm
- Weight: increase from baseline of ≥ 10%
- Body temperature [C]: ≥ 37.5 C

Clinically notable low values

- Systolic BP: ≤ 90 mmHg with decrease from baseline of ≥ 20 mmHg
- Diastolic BP: ≤ 50 mmHg with decrease from baseline of ≥ 15 mmHg
- Heart rate (collected as pulse rate in the vital signs eCRF): ≤ 50 bpm with decrease from baseline of ≥ 15 bpm
- Weight: ≥ 20% decrease from baseline
- Body temperature [C]: ≤ 36 C

Number and percentage of patients with at least one post-baseline vital sign abnormality will be summarized.

Descriptive statistics will be tabulated for baseline and change from baseline to worst post-baseline value (both directions) for each vital sign parameter.

Patients with clinically notable vital sign abnormalities will be listed. All vital sign assessments will be listed by patient and vital sign parameter. Clinically notable values will also be flagged in this listing.

7.6.8 ECG

Potential effects of treatment with study drug on ECG parameters will be assessed by ECG interval analysis of heart rate, pulse rate, QRS, QT, and QT interval corrected for heart rate (QTc). Triplicate measurements will be obtained at each assessment according to the schedule of assessments in the protocol. Results from triplicate readings will be averaged.

The average of the machine-read triplicate ECG measurements collected closest to but prior to the first dose of study drug will serve as each patient's Baseline-QTc value for all post-dose comparisons. The QTcF data collected on the eCRF page will be used in the summary.

Data from ECGs will be listed, notable values will be flagged, and any other information collected will be listed as appropriate. The following summaries will be provided for each applicable ECG parameter:

- Frequency counts and percentages of patients having notable ECG values according to Table 4.
- For each QT interval (QT, QTcF), shift tables based on notable QT interval categories (≤450, >450 - ≤480, >480 - ≤500, >500 ms) at baseline to the worst post-baseline value observed.

Table 4: Criteria for Notable ECG Criteria

Parameter	Criterion
QT, QTcF	increase from baseline > 30 ms
	increase from baseline > 60 ms
	new > 450 ms
	new > 480 ms
	new > 500 ms
Heart rate	Increase from baseline > 25% to a value > 100 bpm
	Decrease from baseline > 25% and to a value < 50 bpm

7.6.9 Physical Examinations

Physical examination dates will be presented in a data listing. Any abnormal findings were to have been reported as AEs and will be reported in the appropriate AE listings and summary tables.

7.6.10 Eastern Cooperative Oncology Group Performance Status Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status is used to assess the physical health of patients, and ranges from 0 (most active) to 5 (dead). Frequency counts and percentages of patients in each score category will be provided by assessment visit.

In addition, the ECOG shift from baseline to highest score during the post-baseline period will be summarized.

ECOG performance status at each time point will be listed.

7.6.11 Clinically Significant Procedures

All clinically significant procedures related to cancer while on study (from first dose through end of study) will be listed.

7.6.12 Transfusion

Data on transfusions of blood products received while on study will be listed.

7.7 Pharmacokinetic Analysis

The Pharmacokinetic Analysis Set will be used for all PK analysis, listings and figures. C1D1 is defined as single dose (i.e., first dose), and C2D1 is defined as steady state.

7.7.1 Plasma Concentrations of ARRY-382 and its three metabolites (AR00469099, AR00469100 and AR00470870)

Plasma concentrations of ARRY-382 and its three metabolites (AR00469099, AR00469100 and AR00470870) will be collected and then determined using a validated bioanalytical method at the time points as specified in protocol. All plasma concentration values for each patient in the PK set will be included in the bioanalytical plasma concentration listings. Individual concentration records will be flagged for the affected visit if any of the following occur:

a. Patient had vomiting within 4 hours following study drug administration on the day of series PK sampling.

b. Plasma levels were not considered to be at steady-state (i.e. dosing was not performed for at least 4 consecutive days prior to C2D1).

c. Subject received a higher or lower dose compared to planned treatment.

d. PK sampling time was outside the allowed window or the elapsed time was not calculable.

The plasma concentrations of ARRY-382 and its three metabolites (AR00469099, AR00469100 and AR00470870) will be summarized by phases, dose levels and cohorts for all nominal time points, including predose (trough) concentrations for C1D15, C3D1, C4D1, C5D1 and C6D1, using the following descriptive statistics: n (number of patients with non-missing values), m (number of non-zero concentrations), arithmetic mean, standard deviation, coefficient of variation (CV), geometric mean, geometric standard deviation, geometric CV, minimum, median and maximum. An individual concentration-time data point be excluded from the calculation of summary statistics if any of the above flags [a-d] apply. For each time point, statistical values will only be calculated if at least two-thirds of the individual concentration data measured are above the limit of quantitation. BLQs will be set to zero for the calculation of arithmetic mean, SD, CV, minimum, median and maximum. For the calculation of geometric means and geometric CVs, BLQ concentrations will be replaced by ½ LLOQ. When greater than one-third of data points are BLQ, the means, standard deviations and CVs will be reported as not calculated (NC). When all data points are BLQ, the mean will be reported as BLQ and standard deviations and CVs will be reported as NC. If there are less than 3 values for calculation of standard deviation or CV, the value will be reported as NC.

The geometric mean with standard deviation plasma concentration-versus-time profiles will be presented graphically for each analyte using both linear and semi-logarithmic scales on C1D1 and C2D1 for Phase 1b/Part A and Phase 2. Geometric mean plasma concentrations will only be plotted for a specific time point if at least two-thirds of the concentrations are above the limit of quantitation and the actual time of sample collection was within the protocol-specified time window. Individual plasma concentration-time profiles will also be presented graphically using linear and semi-logarithmic scales by study day. For ease of presentation, nominal time will be used to present results in summary and actual time for individual figures.

7.7.2 Plasma Pharmacokinetic Parameters for ARRY-382 and its three metabolites (AR00469099, AR00469100 and AR00470870)

PK parameters for patients in the PK set will be derived for ARRY-382 and its three metabolites (AR00469099, AR00469100 and AR00470870) on C1D1 and C2D1 when possible and appropriate. Parameters may include but not limited to AUC_{τ}, C_{max}, T_{max}, C_{trough}, accumulation ratio, and metabolite-to-parent ratio.

The individual plasma concentration-time data for each analyte will be evaluated with noncompartmental analysis (NCA) using Phoenix WinNonlin®, Version 8.0 or higher. Actual blood collection times and doses will be used for PK calculations. All BLQ values before the observed maximum plasma concentration (C_{max}) will be set to 0; all BLQ values after C_{max} will be considered as missing. The AUC parameters will be calculated according to the linear-up log-down trapezoidal rule. Additional PK parameters may be calculated at the discretion of the pharmacokineticist.

All PK parameter values will be presented in data listings by phases, dose levels and cohorts for analyte, cycle and study day. Each parameter will be summarized in tables by phases, dose levels and cohorts for analyte, cycle and study day using the following descriptive statistics: n, arithmetic mean, standard deviation, CV, geometric mean, geometric CV, minimum, median and maximum. Summary descriptive statistics for in-text summary tables will include geometric mean with geometric CV for AUC, C_{max}, and R_{AUC}. For T_{max} and $t_{1/2}$ values, median, minimum and maximum will be presented. Pharmacokinetic parameters will be excluded from the calculation of summary statistics if any of the above flags [a-c] apply.

Table 5: Definitions of Pharmacokinetic Parameters

PK Parameter	Definition
C1D1	
AUC_{0-8}	Area under the plasma concentration-time curve from zero to 8 hours after drug administration
AUC_{last}	Area under the plasma concentration-time curve from zero to the last measurable time point
C_{max}	Maximum observed plasma concentration after drug administration
T_{max}	Time to reach C_{max}
T_{last}	Time of last PK sample
MR_{Cmax}	Ratio of C_{max} values of the metabolite compared to parent, corrected for molecular weight,
$MR_{AUClast}$	Ratio of AUC_{last} values of the metabolite compared to parent, corrected for molecular weight,
C2D1	
$AUC_{0-8,ss}$	Area under the plasma concentration-time curve from zero to 8 hours after drug administration at steady-state
$AUC_{last,ss}$	Area under the plasma concentration-time curve from zero to the last measurable time point at steady-state
$AUC_{tau,ss}$	Area under the plasma concentration-time curve over a dosing interval at steady-state To estimate $AUC_{tau,ss}$, the concentration measured at predose on steady state (C1D15 for Phase 1b/Part A and Phase 2) will be imputed as the concentration at the end of the dosing interval (i.e., 12 or 24 hours, as appropriate) assuming steady-state has been attained
$C_{max,ss}$	Maximum observed plasma concentration after drug administration
$C_{trough,ss}$	Measured concentration at the end of a dosing interval at steady-state
$T_{max,ss}$	Time to reach C_{max}
$T_{last,ss}$	Time of last PK sample
$MR_{Cmax,ss}$	Ratio of $C_{max,ss}$ values of the metabolite compared to parent, corrected for molecular weight,
$MR_{AUCtau,ss}$	Ratio of $AUC_{tau,ss}$ values of the metabolite compared to parent, corrected for molecular weight,
R_{AUC}	Accumulation ratio, calculated as: $AUC_{0-8,ss}$ / AUC_{0-8}
R_{Cmax}	Accumulation ratio, calculated as: $C_{max,ss}$ / C_{max}

CC [redacted]

[redacted]

7.9 Interim Analysis

No formal interim analysis is planned in this study.

8.0 DATA AND ANALYSIS QUALITY ASSURANCE

This protocol was conducted under the sponsorship of Array BioPharma. Personnel within Array BioPharma or CRO designee provided statistical and data management input for the design of the clinical trial protocol; data management, statistical analysis and generation of tables, listings and figures; and medical writing support for the clinical study report.

All parties mentioned above will work diligently and collaboratively to ensure that data collection and analysis for this study are of the highest quality. This will be accomplished through programmed edit checks, quality control processes, and clinical and statistical review of data displays. Quality and accuracy of statistical analyses will be verified though established statistical programming validation processes.

9.0 REFERENCES

1. E.A. Eisenhauer. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1)
2. Jedd D. Wolchok. Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria
3. Simon R. Optimal two-stage designs for Phase II Clinical Trials. Control Clin Trials 1989; 10(1):1-10.
4. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26(4):404-13

10.0 STANDARD OPERATING PROCEDURES, FORMS AND WORK INSTRUCTIONS

Array Biopharma SOPs will be utilized.