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 Version 1: 12 April 2016

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Protocol Version 4: 24 July 2018

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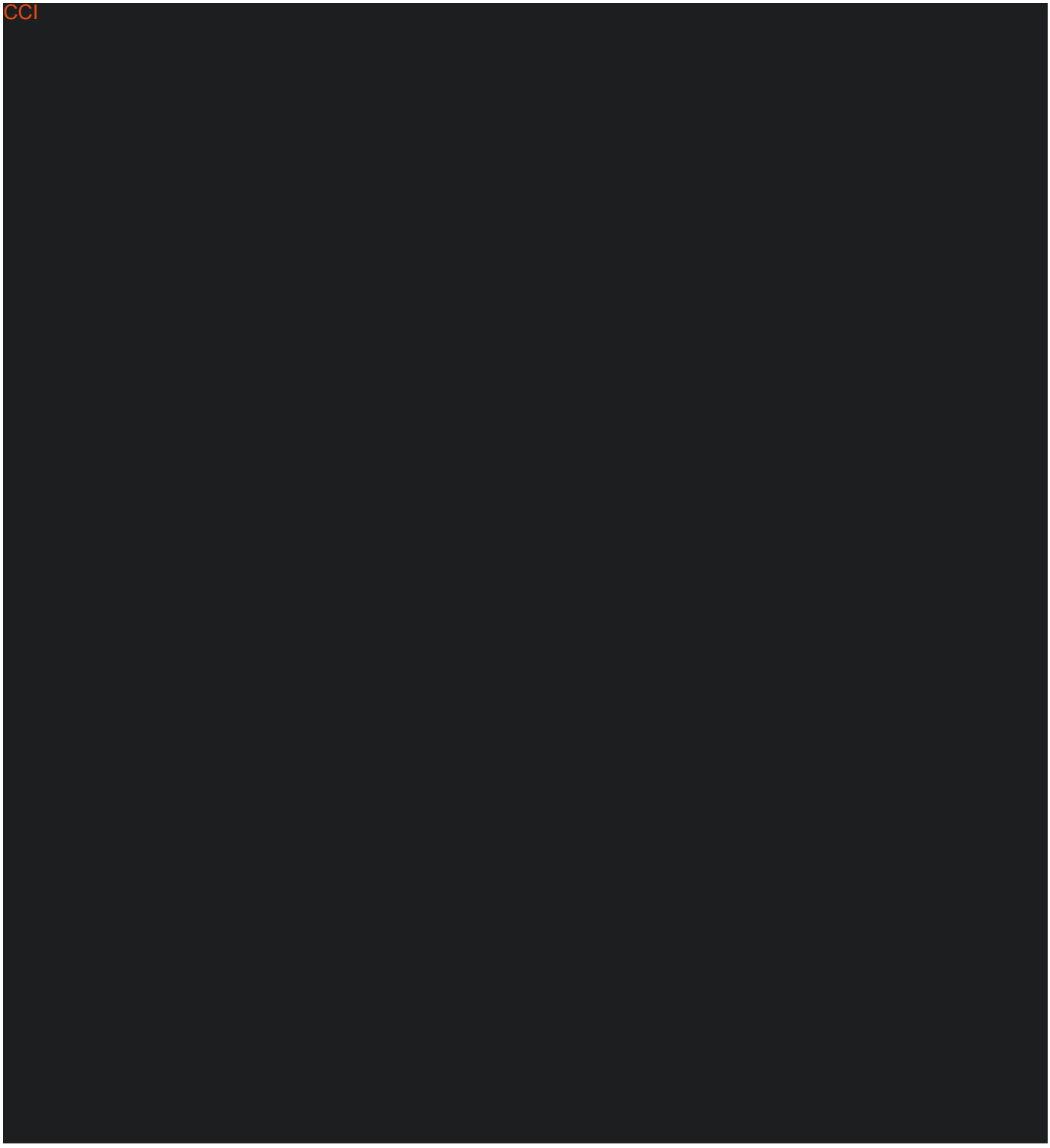
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PROTOCOL SYNOPSIS

Title	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
Phase	Phase 1b/2
Study Center(s)	Approximately 30 centers
Objectives and Endpoints	**Phase 1b/Part A** Primary objective: • 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 Primary endpoint: • Incidence of dose-limiting toxicities (DLTs), as a function of the dose of ARRY-382 when administered in combination with pembrolizumab Secondary objectives: • 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 Secondary endpoints: • Objective response rate (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 rate (irRR), as determined by the Investigator • Immune-related progression-free survival (irPFS), as determined by the Investigator • Type, frequency, and severity of adverse events (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 CCI [redacted]

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[redacted]

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

Primary objective:

- 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

Primary endpoint:

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

Secondary objectives:

- To further estimate the efficacy of the combination
- 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

Secondary endpoints:

- 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

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	C C I [redacted] **Phase 2: Platinum-resistant Ovarian Cancer** Primary objective: • 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) Primary endpoint: • ORR, per RECIST v1.1, as determined by the Investigator Secondary objectives: • 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 Secondary endpoints: • 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

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Phase 2: Pancreatic Ductal Adenocarcinoma

Primary objective:

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

	Primary endpoint: • ORR, per RECIST v 1.1, as determined by the Investigator Secondary objectives: • 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 Secondary endpoints: • 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 CCI [redacted]

	
Design	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). Part A (Phase 1b) 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 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.
Treatment Regimens	ARRY-382: Patients in Part A (Phase 1b dose escalation) will receive oral doses of single-agent ARRY-382 capsules in combination with pembrolizumab; planned dose levels of ARRY-382 are 200 mg QD and 400 mg QD. Patients in Phase 2 will receive oral doses of ARRY-382 capsules at 300 mg QD, the MTD/RP2D determined during Part A, in combination with pembrolizumab. Pembrolizumab: Patients in Part A will receive 2 mg/kg pembrolizumab administered by study site personnel as an iv infusion over 30 minutes Q3W. Patients in Phase 2 will receive 200 mg pembrolizumab administered by study site personnel as an iv infusion over 30 minutes (within -5 to +10 minutes) Q3W. In all phases of the study, patients will continue to receive ARRY-382 in combination with pembrolizumab until disease progression as determined by the Investigator, withdrawal of consent, initiation of subsequent anticancer therapy, the patient is lost to follow-up, or death, whichever occurs first.
Study Population	Overall, approximately 90 patients are planned for enrollment. Part A (Phase 1b) will consist of approximately 18 patients with advanced/metastatic melanoma, PD-L1–positive NSCLC, ovarian cancer, triple-negative breast cancer, head and neck squamous cell

	carcinoma (HNSCC), bladder cancer, metastatic colorectal cancer (CRC), PDA, or gastric cancer. Patients who had prior treatment with an immune CPI (e.g., programmed cell death receptor 1 [PD-1], PD-L1, or cytotoxic T-lymphocyte antigen 4 [CTLA-4] inhibitor) will be excluded. Prior treatment with ipilimumab administered as adjuvant therapy in patients with melanoma is allowed. Prior treatment with a CSF-1R or CSF-1 (or macrophage colony-stimulating factor [MCSF]) inhibitor is allowed. The Phase 2 PD-1/PD-L1 Inhibitor Refractory cohort will consist of up to 20 patients with advanced solid tumors who progressed on a PD-1/PD-L1 inhibitor-containing regimen as their most recent prior line of therapy. If clinical activity is observed, enrollment may be focused to include up to 10 additional patients with particular tumor histologies of interest. The Phase 2 prOVCA cohort will consist of approximately 23 patients with prOVCA who are naïve to prior CPI therapy. The Phase 2 PDA cohort will consist of approximately 29 patients with PDA who have had at least one prior therapy who are naïve to prior CPI therapy.
Duration of Study Participation	Each phase of the study consists of a 28-day screening period; 21-day treatment cycles with the combination of ARRY-382 and pembrolizumab until disease progression as determined by the Investigator, unacceptable toxicity, withdrawal of consent, or death (or other discontinuation criteria are met); and a 30-day safety follow-up period. Patients will be monitored for OS until 1 year after the date of the last patient's first visit.
Statistical Considerations	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 complete Cycle 1 or discontinue treatment due to DLT during Cycle 1. For the Phase 2 PD-1/PD-L1 Inhibitor Refractory cohort, the sample size of up to 20 patients will be evaluated for initial evidence of activity in this PD-1/PD-L1 inhibitor-refractory population. For the Phase 2 prOVCA cohort, a Simon's 2-stage optimal design will be used in the MSS/MMR-proficient prOVCA population. The null hypothesis of the true response rate is 15%, versus alternative of 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 less 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 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. Objective response rate and 95% confidence intervals (CIs) will be reported. For time-to-event variables (i.e., DOR, PFS, OS), the survival distribution functions will be estimated using the Kaplan-

	Meier method. Data for tumor genomic alterations, gene expression profiles CCI [redacted] will be presented in tabular and/or graphical format and summarized descriptively. Absolute data, change from baseline and/or percentage change from baseline will be summarized by dose level, as appropriate. Plasma concentrations of ARRY-382 and metabolites, AR00469099, AR00469100, and AR00470870, will be determined using a validated bioanalytical method. Standard noncompartmental and/or compartmental PK parameters (e.g., C_{max} and area under the curve [AUC]) will be estimated for each patient. Descriptive statistics of PK parameters will be reported for each cohort and summarized. Dose proportionality, metabolite-to-parent ratio and drug accumulation will be assessed as appropriate. Other model-dependent PK analysis approaches (e.g., maximum a posteriori Bayesian parameter estimation, nonlinear mixed effects modeling) may also be applied to the data as appropriate. CCI [redacted] CCI [redacted] Parametric PK/CCI [redacted] models may be assessed for suitability and used in describing PKCCI [redacted] results. Results may be summarized graphically or with summary statistics. Safety data will be presented in tabular and/or graphical format and summarized descriptively by treatment group and study day, where appropriate. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). Incidence tables will be presented for DLTs, all AEs by maximum severity, SAEs, AEs assessed as related to study drug and AEs resulting in discontinuation of study drug. Dose-limiting toxicities will be listed for Part A. Changes in ECG and laboratory measurements will be summarized. Listings of all safety data sorted by treatment group, patient and assessment date will be provided.
Sponsor	Array BioPharma Inc.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study protocol.

Abbreviation or special term	Explanation
AE	adverse event
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{τ}	area under the plasma concentration-time curve over the dosing interval
BCE	bone collagen equivalents
BUN	blood urea nitrogen
CA-125	cancer antigen 125
CA 19-9	cancer antigen 19-9
cFMS	cellular homolog of the V-FMS oncogene product of the Susan McDonough strain of feline sarcoma virus, also known as colony-stimulating factor 1 receptor (CSF-1R)
CI	confidence interval
CK	creatine kinase
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CPI	checkpoint inhibitor
CR	complete response
CRC	colorectal cancer
CRO	contract research organization
CSF-1	colony-stimulating factor 1
CSF-1R	colony-stimulating factor 1 receptor
CT	computed tomography
CTC	circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte antigen 4

Abbreviation or special term	Explanation
C_{trough}	plasma concentration measured just before the next dose of study drug
CCI	[redacted]
CV	curriculum vitae
CYP	cytochrome p450
DLT	dose-limiting toxicity
dMMR	mismatch repair-deficient
DNA	deoxyribonucleic acid
DOR	duration of response
EC	Ethics Committee (includes institutional review board, research ethics board, and institutional ethics committee)
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	electronic case report form
ED_{50}	dose required for 50% of maximum effect
EDC	electronic data capture
EGFR	epidermal growth factor receptor
ERK	extracellular signal-regulated kinase
EU	European Union
FDA	United States Food and Drug Administration
FDG-PET	fluorodeoxyglucose positron emission tomography
FMO	flavin-containing monooxygenase
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HEK-293	human embryonic kidney cell line
hERG	human ether a-go-go gene
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma

Abbreviation or special term	Explanation
IC_{50}	concentration required for 50% inhibition
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IL	interleukin
INR	international normalized ratio
irAE	immune-related adverse event
IRB	Institutional Review Board
irBOR	immune-related best overall response
irCR	immune-related complete response
irPD	immune-related progressive disease
irPFS	immune-related progression-free survival
irPR	immune-related partial response
irRC	immune-related response criteria
irRR	immune-related response rate
irSD	immune-related stable disease
ISH	International Society of Hypertension
iv	intravenously
k	number of dose-limiting toxicities
LLC-PK1	pig kidney epithelial cell line
mAb	monoclonal antibody
MCP-1	monocyte chemoattractant protein 1
MCSF	macrophage colony-stimulating factor
MDSC	myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Affairs
MIP-1b	macrophage inflammatory protein 1 beta
MMR	mismatch repair
Mo-MDSC	monocytic myeloid-derived suppressor cell
MRI	magnetic resonance imaging
MSI	microsatellite instability
MSI-H	microsatellite instability-high
MSS	microsatellite stable

Abbreviation or special term	Explanation
MTD	maximum tolerated dose
NCI	National Cancer Institute
NCM	nonclassical monocytes
NOAEL	no observed adverse effect level
NSCLC	non–small cell lung cancer
CCI	[redacted]
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death receptor 1
PDA	pancreatic ductal adenocarcinoma
PDF	portable document format
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PET	positron emission tomography
PFS	progression-free survival
P-gp	permeability glycoprotein
pH	hydrogen ion concentration
PK	pharmacokinetic
po	by mouth
PR	partial response
prOVCA	platinum-resistant ovarian cancer
PTH	parathyroid hormone
PT	prothrombin time
PTT	partial thromboplastin time
Q3M	every 3 months
Q3W	every 3 weeks
Q8W	every 8 weeks
QD	once daily
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula

Abbreviation or special term	Explanation
RBC	red blood cell(s)
RECIST v1.1	Response Criteria in Solid Tumors, version 1.1
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SJS	Stevens-Johnson Syndrome
SOP	standard operating procedure
SPD	sum of the products of the 2 largest perpendicular diameters
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal half-life
T3	triiodothyronine
T4	thyroxine
TAM	tumor-associated macrophage
TEAE	treatment-emergent adverse event
TEN	toxic epidermal necrolysis
TKI	tyrosine kinase inhibitor
T_{max}	time of maximum observed plasma concentration
TME	tumor microenvironment
TNF-α	tumor necrosis factor-alpha
TPS	tumor proportion score
TRAP5b	tartrate-resistant acid phosphatase 5b
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
CCI	[redacted]
WBC	white blood cell(s)
WHO	World Health Organization

SUMMARY OF CHANGES FOR PROTOCOL VERSION 4

Rationale:

At the time of this protocol amendment, the study had been initiated at 11 study centers, 31 patients have been treated (19 in Part A, 1 melanoma patient in previous Part B, 2 NSCLC in previous Part C and 9 in Phase 2) and enrollment in Part A has been completed.

The rationale for the key changes to the protocol includes:

- Detailed information regarding dose modification and discontinuation of pembrolizumab was removed and, as the prescribing information for pembrolizumab varies across countries, sites are instructed to follow the most current local Prescribing Information for dose modification guidelines. In addition, information on a pembrolizumab formulation now available in the European Union (EU) was added. Furthermore, it was clarified that pembrolizumab will be administered at 200 mg in Phase 2.
    - Rationale: To account for the changes in pembrolizumab formulation and the rapidly evolving changes in pembrolizumab indication and administration and for clarity.
- A correction was made to add mismatch repair (MMR) proficiency in places where microsatellite instability (MSI) status was noted.
    - Rationale: To be consistent with the study sample and the statistical considerations.

Changes to the Protocol:

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strikethrough font for deletions and underlined font for insertions.

Abbreviations have been updated throughout to account for changes to the protocol and are not otherwise noted in section changes below.

Summary of Changes for Protocol Version 4:
Section added to discuss this amendment.

Protocol Synopsis:
Section was updated to match the body of the protocol.

Section 2.4 Dose Selection
Section was modified to remove "according to the Prescribing Information for Keytruda® (pembrolizumab)" in the Phase 2 instructions for pembrolizumab administration.

Section 6.1.1 Manufacturing and Formulation
Section was updated to provide information on the 2 currently available pembrolizumab formulations in the European Union.

Section 6.1.2 Packaging and Labeling
Section was updated to state that the Sponsor, or designee, will provide each site with the most current local pembrolizumab Prescribing Information and distribute any updates as they become available.

Section 6.2.2 Pembrolizumab
Section was modified to remove "as instructed on the local label" in the Phase 2 instructions for pembrolizumab administration.

Section 6.3.3 Pembrolizumab
Section was modified to remove details regarding dose modification and discontinuation of pembrolizumab and instead added instructions to follow the current locally approved Prescribing Information.

Section 6.5.3 Prohibited Medications
Section was updated to add instructions to consult the most current local pembrolizumab Prescribing Information for any additional prohibited medications.

Section 7.1.1 Medical History/Disease History
Section was updated with administrative changes/corrections regarding the study population.

Section 7.1.5 Tumor and Blood Samples for Retrospective Testing of Tumor Genomic Alterations, Tumor Mutation Burden and/or Gene Expression Profiling (Phase 2 Only)
Section was updated with administrative changes/corrections regarding the study population.

Section 7.5.2 Clinical Laboratory Tests
Section/Table 9 was updated to allow for urine myoglobin to only be collected if blood CK levels are elevated.

Section 8.1 Screening Evaluations
Section was updated with administrative changes/corrections regarding the study population.

Section 9.3 Replacement of Patients
Section was updated with administrative changes/corrections regarding the study population.

Section 11.1.1 Sample Size
Section was updated with administrative changes/corrections regarding the study population.

Section 15.0 References
Section updated with new references to reflect changes to protocol content.

Appendices
Previous Appendix 4 (Immune-Related Adverse Reactions Associated with Pembrolizumab) was removed and previous Appendices 5, 6, 7 were renumbered to Appendices 4, 5, 6, respectively.

SUMMARY OF CHANGES FOR PROTOCOL VERSION 3

Rationale:

At the time of this protocol amendment, the study had been initiated at 11 study centers, 21 patients have been treated (19 in Part A, 1 melanoma patient in previous Part B and 1 NSCLC in previous Part C) and enrollment in Part A has been completed.

The rationale for the key changes to the protocol includes:

- The Phase 1b Expansion cohort in melanoma patients (Part B) and the Phase 2 cohort in non-small cell lung cancer (NSCLC) patients (Part C) have been removed and replaced with 3 new Phase 2 cohorts in programmed cell death receptor 1 (PD-1)/programmed cell death ligand 1 (PD-L1) inhibitor-refractory patients, platinum-resistant ovarian cancer (prOVCA) patients and pancreatic ductal adenocarcinoma (PDA) patients. As such, specific objectives/endpoints, background information and rationale, inclusion/exclusion criteria, assessments and statistical methods were added for each cohort in Phase 2 and sections and content pertaining specifically to previous Parts B and C have been removed.
    - Rationale: Preclinical data in the literature suggests that activated macrophages may represent one potential mechanism of PD-1/PD-L1 inhibitor resistance. Thus, there is the potential that the addition of a colony-stimulating factor 1 receptor (CSF-1R) inhibitor to a patient with progression on a prior PD-1/PD-L1 inhibitor-containing regimen may result in clinical activity. Phase 2 indications were modified as a result of clinical evidence of activity with combined PD-1 and CSF-1R inhibition in patients with advanced PDA and initial evidence of activity seen in Part A of this study in patients with PDA and ovarian cancer. Another consideration for changing the Phase 2 indications was the changing clinical landscape regarding the use of PD-1 inhibitors in the treatment of patients with NSCLC.
- To modify the dose of pembrolizumab to be used in combination with ARRY-382 in Phase 2 from 2 mg/kg to a flat dose of 200 mg intravenously (iv) every 3 weeks (Q3W).
    - Rationale: To conform to the current pembrolizumab label.
- To update the number of study centers from approximately 10 to approximately 30.
    - Rationale: To account for the additional patients planned to be enrolled in Phase 2.
- To modify the overall sample size from approximately 71 patients to approximately 90 patients.

  - Rationale: To account for the additional patients planned to be enrolled in Phase 2.

- To clarify that, with the exception of Cycle 1, the pembrolizumab dose does not have to occur on Day 1 of each cycle.

  - Rationale: To clarify that administration of either ARRY-382 or pembrolizumab will define the re-start of subsequent cycles following temporary dosing hold.

- To clarify that patients may remain on study treatment until the confirmation of disease progression by the Investigator per immune-related response criteria (irRC).

  - Rationale: To allow study treatment beyond initial progressive disease (PD) per Response Criteria in Solid Tumors, version 1.1 (RECIST v1.1) criteria to align with irRC criteria for establishing disease progression.

- To clarify that tumor assessments should be performed once every 6 weeks (± 7 days), regardless of treatment interruptions.

  - Rationale: To ensure that tumor assessments are performed at consistent time intervals in all patients and not based on treatment cycles which may be of varying durations due to patient tolerability.

- To add that all data acquired for efficacy purposes obtained at Screening and while on study, including any off-schedule imaging studies performed, should be made available if requested by the Sponsor for central assessment by an independent reviewer.

  - Rationale: To allow for independent confirmation of the tumor assessment data if it is required to better understand the observed activity in the trial.

- To clarify that the Treatment Discontinuation Visit and the 30-Day Safety Follow-up Visit should occur as specified or prior to the initiation of subsequent anticancer therapy, whichever occurs first.

  - Rationale: To conduct these visits prior to the initiation of subsequent anticancer therapy.

- To add that any subsequent anticancer therapies should be recorded throughout the survival follow-up period.

  - Rationale: To collect this information as these treatments can impact overall survival (OS).

- To add ARRY-382 dose modifications for hepatic enzyme elevations.
    - Rationale: To provide more specific dose modifications for elevations of hepatic enzyme based on time to resolution in order ensure that the patients receive the adequate dose that is safe.
- To update the pembrolizumab dose modification information based on updated data and to clarify that modification should be based on the most recent, local pembrolizumab label.
    - Rationale: To provide the latest information on dose modification based on recent label updates and to note that the most current local label should be referenced in the future.
- To modify predose blood collections for PK from within 60 minutes to within 120 minutes prior to administration of ARRY-382.
    - Rationale: Broadens the collection window for ease of sample collection without significantly impacting the quality of the PK data.
- To modify hepatitis testing such that hepatitis C virus (HCV) ribonucleic acid (RNA) qualitative will be required only if HCV serology is positive.
    - Rationale: To avoid unnecessary additional testing in patients.
- To clarify that direct bilirubin only needs to be collected when total bilirubin values are above normal.
    - Rationale: Any increase in direct bilirubin will be reflected in the total bilirubin levels. Thus, if the total bilirubin is not elevated, evaluation of the direct bilirubin levels is not necessary.
- To clarify that creatine kinase (CK) isoenzymes only need to be collected when total CK is ≥ Grade 2; unless there are cardiac signs and symptoms.
    - Rationale: To avoid unnecessary additional testing in patients with mild, asymptomatic CK elevations.
- To permit the substitution of a telephone call for the Day 15 clinic visit of Cycles ≥ 5.
    - Rationale: To improve patient convenience while still requiring oversight by the site.
- To update protocol instructions regarding documentation of adverse events (AEs).

- Rationale: To align with current Sponsor language.

- Other (clarifications and corrections).

Changes to the Protocol:

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strikethrough font for deletions and underlined font for insertions.

Abbreviations have been updated throughout to account for changes to the protocol and are not otherwise noted in section changes below.

References have been modified from a numbered format to an alphabetical format and are not otherwise noted in section changes below.

Summary of Changes for Protocol Version 3:
Section added to discuss this amendment.

Protocol Synopsis:
Section has been updated to match the body of the protocol.

Section 2.1.1 PD-1 and PD-L1 Inhibitor Resistance:
Section added to provide background information for the PD-1/PD-L1 inhibitor refractory population.

Section 2.1.3 Non-Small Cell Lung Carcinoma:
Section modified to provide additional details of pembrolizumab treatment in patients with NSCLC.

Section 2.1.4 Ovarian Cancer:
Section added to include background information for the ovarian cancer population and literature results of treatment of these patients.

Section 2.1.5 Pancreatic Cancer:
Section added to provide background information for the pancreatic cancer population and literature results of treatment of these patients.

Section 2.2.2 Clinical Experience with ARRY-382 (Clinical Study ARRAY-382-101):
Section title updated with administrative changes/corrections.

Section 2.2.2.1 Clinical Safety:
Section modified to provide a mechanistic rationale for observed hepatic enzyme elevations and

Table 1 (All Adverse Events Reported in ≥ 15% of All Patients [Clinical Study ARRAY-382-101]) updated with administrative changes/corrections.

Section 2.2.2.2 Clinical Pharmacokinetics:
Section updated with administrative changes/corrections.

Section 2.3 Rationale for the Current Study:
Section updated with administrative changes/corrections.

Section 2.3.1 Phase 1b (Part A):
Section updated with results from Part A.

Section updated with administrative changes.

Previous Section 2.3.2 Phase 1b Expansion (Part B):
Section deleted as it is no longer applicable.

Section 2.3.2 Phase 2:
Section title and section text modified to provide the rationale for the new patient populations in Phase 2 (PD-1/PD-L1 inhibitor refractory patients, prOVCA patients and PDA patients) and to remove information pertaining specifically to previous Part C.

Section 2.4 Dose Selection:
Section modified to clarify the dosing and administration information for ARRY-382 and pembrolizumab in Phase 2 and to include the MTD/RP2D for ARRY-382 of 300 mg QD, determined during Part A which will be used in the Phase 2 cohorts.

Previous Section 3.2 Phase 1b Expansion (Part B):
Section and previous Table 3 deleted as no longer applicable.

Section 3.2 Phase 2:
Section header modified, previous Table 4 deleted and Table 3 (Objectives and Endpoints [Phase 2: PD-1 or PD-L1 Inhibitor Refractory]), Table 4 (Objectives and Endpoints [Phase 2: prOVCA]) and Table 5 (Objectives and Endpoints [Phase 2: PDA]) added to account for the new objectives and endpoints for each of the 3 Phase 2 cohorts noted above.

Section 4.1 Study Design Overview:
Section modified to account for changes/additions to study design for each of the Phase 2 cohorts of the study.

Section modified to include the MTD/RP2D for ARRY-382 of 300 mg QD, determined during Part A, which will be used in the Phase 2 cohorts.

Section modified to include mention of previous Part B and Part C of the study that are being removed per this amendment.

Section modified to include that submission of tumor tissue will be required for patients in the Phase 2 cohorts at baseline.

Section modified to clarify the dosing and administration information for ARRY-382 and pembrolizumab in Phase 2.

Section modified to clarify that irRC may be used by the Investigator for treatment decisions and that patients may remain on study treatment until confirmation of disease progression by the Investigator per irRC.

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Section 4.2 Dose-Limiting Toxicities (Part A):
Section updated with administrative changes.

Section 4.3 End of Study:
Section added to define the end of the study.

Section 5.1 Number of Patients:
Section updated to adjust the number of patients planned overall and for each part of the study based on changes to the study design.

Section 5.2.1 Inclusion Criteria:
Inclusion criterion #3, pertaining to the diagnosis of cancer that has been histologically or cytologically confirmed, was modified to update to add the criteria for the additional tumor types to be enrolled in the Phase 2 cohorts. The criteria pertaining to Part A was updated with administrative changes/corrections.

Inclusion criterion #8, pertaining to agreement to use an effective method of contraception, was updated to require an acceptable method of contraception as defined in the protocol and to modify the timeframe that contraception is required after last dose of pembrolizumab.

Inclusion criterion #11, pertaining to the availability of a fresh biopsy (preferred) or an archival tumor sample for the Phase 2 patients, was added.

Section 5.2.2 Exclusion Criteria:
Exclusion criterion #1, pertaining to prior treatment, was modified to update/add the criteria for the Phase 2 patients.

Exclusion criteria #9, pertaining to patients with symptomatic ascites or symptomatic pleural effusion, was modified for clarity and to add a consideration for the prOVCA patients.

Exclusion criteria #18, pertaining to prior therapy, was modified for clarity.

Exclusion criteria #19, pertaining to residual Common Terminology Criteria for Adverse Events (CTCAE) ≥ Grade 2 side effects of any prior therapy, was modified for clarity.

Exclusion criteria #21, pertaining to hepatitis B and C testing, was modified such that HCV RNA qualitative will be required only if HCV serology is positive.

Section 5.3 Contraception:
Section added to define contraception requirements for patients.

Section 6.1.1 Manufacturing and Formulation:
Section updated to clarify the manufacturer of ARRY-382 capsules and added details about market authorization holder for pembrolizumab in the European Union (EU) and specified formulation that is available in the EU.

Section 6.1.2 Packaging and Labeling:
Section modified to update the packaging and labeling details for ARRY-382 and pembrolizumab.

Section 6.1.3 Shipping, Storage and Handling:
Section updated with administrative changes/corrections.

Previous Section 6.2.1.2 Part B:
Section deleted as no longer applicable.

Section 6.2.1.2 Phase 2:
Title and section updated to account for the changes to Phase 2.

Section 6.2.2 Pembrolizumab:
Section modified to modify/add pembrolizumab administration details for Phase 2.

Section 6.3 Dose Modifications and Reductions:
Section updated to clarify that Cycle 1 Day 1 is defined as the first day of study drug treatment with both ARRY-382 and pembrolizumab and administration of either ARRY-382 or pembrolizumab will define the re-start of subsequent cycles following temporary dosing hold.

Section 6.3.1 General Guidelines:
Section updated with administrative changes/corrections.

Section 6.3.2 ARRY-382:

Table 8 (Recommended Dose Modifications for ARRY-382 Treatment-Related Adverse Events) updated to add ARRY-382 dose modifications for hepatic enzyme elevations and to modify footnote "a" pertaining to increased CK.

Section modified to account for the different phases of the study and to clarify that ARRY-382 dose reductions should occur in 100 mg increments.

Text pertaining to dose reductions in Parts B and C with a possible starting dose of ≥ 400 mg was removed as no longer applicable.

Section 6.3.3 Pembrolizumab:
Section updated to state that pembrolizumab should be withheld or discontinued for any of the specified toxicities listed in the most current, local label unless they are considered to be clearly attributable to ARRY-382, concurrent illness, or underlying disease. Additional toxicities were added for consideration of dose modification or discontinuation, per the most current label.

Section updated with other administrative changes/corrections.

Section 7.1.1 Medical History/Disease History:
Section title and section text updated to include collection of disease history information.

Section 7.1.3 Hepatitis Tests:
Section title was changed for clarity and section text was modified such that HCV RNA qualitative will be required only if HCV serology is positive.

Section 7.1.4. Local and Retrospective Testing for PD-L1 Expression (Part A Patients with Non-Small Cell Lung Carcinoma Only):
Section updated to remove reference to Part C as no longer applicable.

Section 7.1.5 Tumor and Blood Samples for Retrospective Testing of Tumor Genomic Alterations, Tumor Mutation Burden and/or Gene Expression Profiling (Phase 2 Only):
Section added to state that in Phase 2, patients must have a fresh biopsy (preferred) or an archival tumor sample from the most recent sample available submitted to be eligible for participation in the study and to provide instructions for obtaining PD-L1 expression, tumor genomic alterations including microsatellite instability (MSI) status, tumor mutation burden and/or gene expression profiling status.

Section 7.2 Efficacy Assessments:
Section modified to clarify that patients may remain on study treatment until the confirmation of disease progression by the Investigator per irRC and to add that all data acquired for efficacy

purposes should be made available if requested by the Sponsor for central assessment by an independent reviewer.

Section 7.2.2 Immune-Related Response Criteria:
Section updated with administrative changes/corrections.

Previous Section 7.3.1 Macrophages, T Cells, and Other Immune Markers in Tumor Tissue:
Section deleted as no longer applicable.

Section 7.3.1.1 Markers of CSF-1R Inhibition:
Section updated with administrative changes/corrections and to include the measurement of NCM in peripheral blood in Phase 2.

Section 7.3.1.3 Tumor Markers (Phase 2 Only):
Section added to include details regarding measurement of tumor markers.

Section 7.4 Pharmacokinetic Assessments:
Section modified to clarify that pembrolizumab concentrations are not planned to be measured but that remaining PK plasma samples may be used to assess pembrolizumab concentrations on an ad hoc basis.

Section modified to move predose blood collections for PK from within 60 minutes to within 120 minutes prior to administration of ARRY-382.

Section updated with administrative changes/corrections.

Section 7.5.1 Adverse Events:
Section updated to include reference to Table 10 (Schedule of Events [Part A/Phase 1b]) and Table 11 (Schedule of Events [Phase 2]).

Section 7.5.2 Clinical Laboratory Tests:
Table 9 (Clinical Laboratory Tests) updated to clarify that direct bilirubin will only be collected when total bilirubin values are above normal.

Table 9 (Clinical Laboratory Tests) updated to clarify that CK isoenzymes will only be collected when total CK is ≥ Grade 2, unless there are cardiac signs and symptoms.

Table 9 (Clinical Laboratory Tests) was modified such that HCV RNA qualitative will be required only if HCV serology is positive.

Section 7.5.5 Electrocardiogram:
Section updated to clarify that triplicate 12-lead electrocardiogram (ECG) collections should occur over a period of approximately 5 to 10 minutes.

Section 8.0 Schedule of Procedures and Assesssments:
Section updated to clarify that any patients enrolled in previous Part C/Phase 2 should follow the Phase 2 procedures and assessments and schedule of events.

Section 8.1 Screening Evaluations:
Section modified to remove text specific to Parts B and C as no longer applicable.

Section updated to include collection of disease history information.

Section modified to add information about obtaining a fresh biopsy or an archived tumor specimen plus a blood sample for patients in Phase 2.

Section updated to clarify that triplicate 12-lead ECG collections should occur over a period of approximately 5 to 10 minutes.

Section updated to clarify collection of blood samples for hepatitis testing.

Section 8.2.1.1.1 Cycle 1 Day 1:
Section updated to clarify that triplicate 12-lead ECG collections should occur over a period of approximately 5 to 10 minutes.

Section modified to move predose blood collections for PK from within 60 minutes to within 120 minutes prior to administration of ARRY-382.

Section 8.2.1.1.3 Cycle 1 Day 15 (± 1 Day):
Section modified to move predose blood collections for PK from within 60 minutes to within 120 minutes prior to administration of ARRY-382.

Section 8.2.1.2.1 Subsequent Cycles Day 1 (± 2 days):
Section updated to clarify that triplicate 12-lead ECG collections should occur over a period of approximately 5 to 10 minutes.

Section modified to move predose blood collections for PK from within 60 minutes to within 120 minutes prior to administration of ARRY-382.

Section modified to clarify that tumor assessments should be performed once every 6 weeks (± 7 days).

Section 8.2.1.2.2 Subsequent Cycles Day 15 (± 2 days):
Section modified to permit the substitution of a telephone call for the Day 15 clinic visit for Cycles ≥ 5.

Previous Section 8.2.2 Part B:
Section and subsections deleted as no longer applicable.

Section 8.2.2 Phase 2:
Section title modified and corresponding subsections added for the procedures and assessments for the new cohorts in Phase 2.

Previous Section 8.2.3 Part C:
Section and subsections deleted as no longer applicable.

Section 8.3 Treatment Discontinuation Visit (to be completed within 2 weeks after treatment discontinuation or prior to the initiation of subsequent anticancer therapy, whichever occurs first):
Section title updated to clarify that this visit should occur as specified or prior to the initiation of subsequent anticancer therapy, whichever occurs first.

Section updated to include collection of a CCI [redacted] for measurement of tumor markers in Phase 2, if applicable for tumor type.

Section 8.4 30-Day (± 3 Days) Safety Follow-up Visit:
Section title updated to indicate this is a follow-up visit.

Section updated to clarify that this visit should occur as specified or prior to the initiation of subsequent anticancer therapy, whichever occurs first.

Section updated to include that if the treatment discontinuation visit was performed ≥ 21 days from last dose of study drug, the 30-day safety follow-up visit does not need to be performed.

Section 8.5 Follow-up Visits for Disease Progression:
Section updated to clarify that disease progression is determined by the Investigator.

Section also updated with administrative changes/corrections.

Section 8.6 Monitoring for Survival Status:
Section updated to add that subsequent anticancer therapies should be recorded in the electronic case report form (eCRF).

Section 8.7 Collection of Data for Ongoing Patients Following Database Lock:
Table 10 (Schedule of Events [Part A/Phase 1b]) footnotes updated to reflect the changes to the schedule of procedures and assessments for Part A described above.

Previous Tables 10 and 11 deleted as no longer applicable.

Table 11 (Schedule of Events [Phase 2]) added to include the schedule of procedures and assessments for Phase 2.

Section 9.3 Replacement of Patients:
Section updated with administrative changes/corrections.

Section updated to add information about replacement of patients in the cohorts of Phase 2.

Section 10.0 Safety Monitoring: Definitions and Reporting:
Section heading updated to reflect updated Sponsor language.

Section 10.1 Adverse Events:
Section updated to reflect updated Sponsor terminology.

Previous Section 10.1.2 Adverse Events Related to Subsequent Anticancer Therapy:
Section removed to reflect updated Sponsor terminology.

Section 10.2 Assessment of Severity:
Section updated to clarify that severity of each AE will be determined by the Investigator and to reflect updated Sponsor terminology.

Section 10.3 Assessment of Causality:
Section updated with administrative changes/corrections.

Section 10.4 Assessment of Seriousness:
Section updated to reflect updated Sponsor terminology.

Section 10.5 Reporting of Serious and Nonserious Adverse Events:
Sponsor language regarding documentation of AEs updated. Section also updated with administrative changes/corrections.

Section 10.6 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs):
Section heading and section updated to reflect updated Sponsor terminology.

Section 10.7 Pregnancy or Drug Exposure During Pregnancy:
Section updated to reflect updated Sponsor terminology.

Section 10.8 Review of Safety Data:
Section updated to clarify that the Medical Monitor will be responsible for the ongoing review and evaluation of safety data, no longer including the Sponsor's Drug Safety Department.

Section 11.1.1 Sample Size:
Section updated to adjust the number of patients planned overall and for each cohort of the study based on changes to the study design.

Section 11.1.2.1 Efficacy Analyses Using Response Criteria in Solid Tumors:
Section updated to clarify that duration of response will be calculated for patients who achieve an objective response (i.e., CR or PR, as determined by the Investigator) and is defined as the time from the first documented response to the date of documented progression or death after achieving a response.

Section updated to clarify that duration of response for a patient who achieves a CR or PR and progression has not been documented and the patient is still alive at the time of analysis is to be censored on the date of the last tumor assessment.

Section updated with administrative changes/corrections.

Section 11.1.2.2 Efficacy Analyses Using Immune-Related Response Criteria:
Section updated to clarify that disease progression is determined by the Investigator.

Section updated to clarify that duration of response for a patient who achieves a CR or PR and progression has not been documented and the patient is still alive at the time of analysis is to be censored on the date of the last tumor assessment.

Section updated with administrative changes/corrections.

CCI [redacted]

Section 15.0 References:
Section updated with new references to reflect changes to protocol content.

Section modified from a numbered format to an alphabetical format.

APPENDIX 3 CHILD PUGH CLASSIFICATION:
Section updated with administrative changes/corrections and to provide an additional reference.

APPENDIX 7 IMMUNE-RELATED RESPONSE CRITERIA IN SOLID TUMORS:
Section updated to correct the definition of confirmation of progression as representing an increase in tumor burden ≥ 25% compared with nadir at 2 consecutive time points at least 4 weeks apart (was incorrectly noted as 2 weeks apart).

SUMMARY OF CHANGES FOR PROTOCOL VERSION 2

The rationale for the key changes to the protocol includes:

- Revision of inclusion criteria to allow previously untreated patients with PD-L1 positive advanced/metastatic NSCLC
    - Rationale: addresses a recent shift in first-line treatment of advanced NSCLC with pembrolizumab and maintains consistency with prescribing information
- Pembrolizumab dosing changed to 200 mg iv Q3W in patients with NSCLC in Part C
    - Rationale: maintains consistency with prescribing information

[redacted]

- Revision of inclusion criteria to allow ipilumumab adjuvant treatment for patients with melanoma
    - Rationale: the inclusion criteria have been changed to reflect the standard-of-care therapy in patients with melanoma which includes treatment with ipilumumab and is consistent with prescribing information
- Allow tumor sampling by either punch biopsies or core biopsies
    - Rationale: to allow patients without accessible cutaneous skin lesions to enroll
- Modifications to DLT criteria and the replacement of patients
    - Rationale: to clarify specific DLT criteria for nonhematological AEs, hematological AEs/lab abnormalities and dose intensity
- Added Exclusion Criterion for patients with ocular melanoma

Changes to the Protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

Protocol Synopsis

Adjusted the approximate number of investigational sites to 10.

Protocol Synopsis – objectives and endpoints; Protocol Table 3, Table 4, Section 7.3.2

CCI [redacted]

Deleted requirement for blood sample for DNA analysis from **Table 10** and **Table 11**.

Deleted interferon gamma [IFNγ] assay as secondary endpoint for Part B. Rationale: there is no validated reagent to assay this protein.

Protocol Synopsis – statistical considerations; Protocol Section 11.1.1 Sample Size

Revised to reflect new statistical design of Part C due to change in patient population which includes patients who receive frontline checkpoint inhibitor therapy.

Added: For Part C, a Simon's 2-stage optimal design will be used. The response rate expected in Part C will depend on the mixture of patients enrolled in the 1st or the 2nd line, where the null hypothesis of the true response rates are 44.8% and 30%, respectively, versus alternatives of 68% and 56%. The null and alternative response rate percentages will be calculated at the end of Stage 1 as well as at the end of the study. If the observed mixture of 1st and 2nd line patients is 50%/50%, the null hypothesis that the true response rate is 37% will be tested against a 1-sided alternative that the true response rate is 62%. Accrual of patients in Stage 1 will continue until 10 evaluable patients have been enrolled, with evaluable defined as having had at least one dose of study drug.

If there are 4 or fewer responses in these 10 patients, the study will be stopped. Otherwise, 23 additional patients will be accrued during Stage 2, for a total of 33 patients in Part C. The null hypothesis will be rejected if 17 or more responses are observed in 33 patients. With this sample size, and assuming a 50%/50% mixture of 1st and 2nd line patients, the actual Type I error is 4.7%, and the power actual Type II error is 82%. If the null hypothesis is true, the expected sample size is 17 patients, and the probability of stopping the study early is 71%.

Section 2.1.2 Non-Small Cell Lung Carcinoma

Added the following to account for novel therapy shift for frontline treatment of patients with advanced lung cancer: Recently, based on results from the KEYNOTE-024 study, a Phase 3 trial that evaluated the efficacy of pembrolizumab versus platinum-based chemotherapy as first-line treatment for metastatic NSCLC that expressed PD-L1, the FDA approved the use of pembrolizumab for the frontline treatment of metastatic NSCLC in patients who have 50% or

higher PDL1 expression based on an FDA-approved test, and who do not express EGFR/ALK mutations. Additionally, the pembrolizumab label was expanded to include patients with lower PD-L1 expression (TPS ≥1%) who progressed on prior platinum therapy.

Section 2.4 Dose Selection

Clarified dosing for Pembrolizumab: In Parts A and B, pembrolizumab will be administered at the dose of 2 mg/kg intravenous infusion over 30 minutes every 3 weeks.

In Part C, pembrolizumab will be administered at the approved dose of 200 mg intravenous infusion over 30 minutes every 3 weeks according to the Prescribing Information for Keytruda® (pembrolizumab).

Section 4.1 Study Design Overview

Table 5 was updated to remove ambiguity of cohort names and dose levels. The name of the first cohort is "Cohort 1", and the name of the second cohort is "Cohort 2". The dose of ARRY-382 in Cohort 2 will depend on the number of patients with DLTs.

Section 4.2 Dose-limiting Toxicities (Part A)

Table 6 was revised for consistency with the pembrolizumab label.

Added: Patients who require a dose interruption or reduction during the initial 21-day treatment period (Cycle 1) will remain evaluable for tolerability decisions if the reason for the reduction and/or interruption represents a DLT. Patients will be replaced if they have received less than 67% dose intensity [(administered dose in mg/planned dose in mg) x 100] of ARRY-382 or if they did not receive pembrolizumab for any reason other than an AE or abnormal laboratory value that is not related to disease, disease progression, intercurrent illness or concomitant medications/therapies before completing Cycle 1.

Section 5.2.1 Inclusion Criteria

Inclusion criterion #3 was revised for consistency with the pembrolizumab label. Language was added to allow patients on study who have front-line treatment with pembrolizumab in those with advanced NSCLC; TPS percentage of 50% is also stated for clarity.

Section 5.2.2 Exclusion criteria

Exclusion criterion #1 was revised due to change in treatment for patients which have adjuvant ipilimumab treatment. Language was added to clarify that prior treatment with ipilimumab is allowed under the conditions shown.

Patients with ocular melanoma are excluded.

Section 6.3.2 ARRY-382 Dose Modifications

Language was added to allow decreasing doses from ≥ 400 mg QD to 300, 200 or 100 mg QD for Parts B and C.

Section 6.3.3 Pembrolizumab Dose Modifications

Updated label reference from 2014 to OCT 2016

Section 7.3.1 Macrophages, T Cells, and Other Immune Markers in Tumor Tissue

Language was added to allow the option of punch biopsies or core needle biopsies.

Section 7.4 PK Assessments

Added the following to allow more flexibility with obtaining PK samples: Predose PK samples must be collected within 60 minutes prior to administration of ARRY-382. Postdose PK samples will be collected at 1hr (±5 min), 2hr (±10 min), 4hr (±20 min), and 8hr (±30 min) after administration of ARRY-382 on Cycle 1 Day 1 and Cycle 2 Day 1. Trough PK blood samples will be collected predose on Cycle 1 Day 15 and Day 1 of Cycles 3 through 6.

Section 8.7 Collection of Data for Ongoing Patients Following Database Lock

Modified the text in order to allow more flexibility in procedures and data collection following database lock: If the primary objective of the study has been met or the Sponsor decides to stop the study early, the database may be locked for the purpose of analyzing and reporting data. Patients may continue to receive study treatment per protocol beyond database lock if the Investigator and the Sponsor agree that patients' best interests are served by continuing to receive study treatment. In patients who continue on study treatment, the Sponsor may decide to only follow for safety (*i.e.*, collect only SAE information, not require any study-specific procedures, and mandate that patients be followed according to standard-of-care), where allowable per local laws or jurisdictions.

Section 9.3 Replacement of Patients

Modified the text to indicate patients who do not receive a dose intensity of at least 67% of study drug will be replaced: For Part A, patients will be replaced if they have received less than 67% dose intensity [(administered dose in mg/planned dose in mg) x 100] of ARRY-382 or if they did not receive pembrolizumab for any reason other than an AE or abnormal laboratory value that is not related to disease, disease progression, intercurrent illness or concomitant medications/therapies before completing Cycle 1.

Other minor changes/corrections in the protocol text, tables and footnotes were made for consistency and/or clarifications.

Appendix 3

Minor corrections made to align with reference publication.

1.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The Investigator at each investigational site is responsible for the conduct of the study. A subinvestigator is any member of the clinical study team designated and supervised by the Investigator to perform critical study-related procedures and/or to make important study-related decisions.

Prior to study initiation, the Investigator at each site must provide to Array BioPharma Inc. (Array BioPharma/Sponsor) a signed protocol signature page, a fully executed and signed United States Food and Drug Administration (FDA) Form 1572, a current curriculum vitae (CV), medical license, and a financial disclosure form. Financial disclosure forms, current CVs and medical licenses must also be provided for all subinvestigators listed on Form 1572 who will be directly involved in the treatment or evaluation of patients in this study.

The study will be administered and monitored by employees or representatives of Array BioPharma and/or a contract research organization (CRO) in accordance with all applicable regulations. Clinical research associates will monitor each site on a periodic basis and perform verification of source documentation for each patient. The Array BioPharma Drug Safety Department (and/or the CRO, if applicable) will be responsible for ensuring timely reporting of expedited serious adverse event (SAE) reports to regulatory authorities and Investigators.

2.0 INTRODUCTION

2.1 Background Therapeutic Information

Recent advances in immunobiology have resulted in novel agents with potent antitumor activity in patients with solid tumors. The tumor microenvironment, comprised of the tumor cells, fibroblasts, immune inflammatory cells, and endothelial cells, plays an important role in suppressing the immune system, leading to decreased antitumor effects. Increasing evidence suggests that interactions between cancer cells, stromal cells, macrophages, and the extracellular matrix are pivotal to the processes of tumorigenesis, metastasis, and neovascularization. Colony-stimulating factor 1 receptor (CSF-1R, also known as the cellular homolog of the V-FMS oncogene product of the Susan McDonough strain of feline sarcoma virus [cFMS]), is the primary receptor for colony-stimulating factor 1 (CSF-1), a regulator of the survival and proliferation of mononuclear phagocytes from undifferentiated precursors to fully differentiated nondividing macrophages (Stanley et al 1997). Binding of CSF-1 to the CSF-1R extracellular domain induces receptor dimerization and trans-autophosphorylation of the intracellular kinase domain. Expression of CSF-1R is robust on monocytes, tissue macrophages, and osteoclasts. Therefore, CSF-1 inhibitors may be useful in treating diseases in which osteoclasts and macrophages play a pathogenic role, such as cancer, autoimmune/inflammatory disease, and bone-related diseases.

Tumor-associated macrophages (TAMs) were once thought to play a beneficial role in controlling cancer, engulfing tumor cells and mounting an immune response to cancer by presenting tumor antigens to effector T-cells. More recently, however, emerging data suggest that subsets of tumor macrophages, particularly those with M2 polarization, promote tumor progression by suppressing immune response and promoting angiogenesis, tumor cell migration, and invasion (Qian and Pollard 2010; Mantovani et al 2002). Consistent with these findings, the presence of tumor macrophages (particularly M2-polarized TAMs) and increased levels of CSF-1 and CSF-1R, have been associated with poor prognosis and survival in a number of cancer types, including breast (Leek et al 1996; Kluger et al 2004; Tsutsui et al 2005), ovarian (Shah et al 2008; Huang et al 2002), prostate (Lissbrant et al 2000), and lung cancers (Takanami et al 1999; Chen et al 2005; Kaminska et al 2006). CSF-1 promotes the differentiation of myeloid progenitors into monocytes, macrophages, dendritic cells, and osteoclasts. In the periphery, CSF-1 regulates the migration, proliferation, function, and survival of macrophages (Hume and MacDonald 2012).

Critical drivers of immune escape in the tumor microenvironment include TAMs, monocytic myeloid-derived suppressor cells (Mo-MDSCs) and granulocytic MDSCs (Zhu et al 2014). Tumor-associated macrophages and MDSCs are both regulated in part by CSF-1, which signals via its receptor (i.e., CSF-1R). Depleting or modifying these regulatory cells has been shown to reverse immunosuppression in nonclinical models (Devaud et al 2013). Based on the role of

CSF-1R in promoting tumor cell-induced osteolysis, angiogenesis, and macrophage-stimulated tumor invasion, selective inhibition of CSF-1R presents an attractive therapeutic approach for the treatment of patients with cancer.

2.1.1 PD-1 and PD-L1 Inhibitor Resistance

Despite strategies aimed at harnessing the immune system to fight cancer, the majority of patients that are treated with immune checkpoint inhibitors (CPIs) fail to respond. One mechanism that is utilized for primary (or intrinsic) resistance to these treatments is the ability of the tumor to avoid recognition by the immune system, preventing infiltration of immune cells into the tumor microenvironment (TME) which therefore cannot elicit an immune response against the tumor (Kim and Chen 2016). Studies have shown that an intrinsic or primary resistance to anti-programmed cell death receptor 1 (PD-1) therapy arises from immune regulatory factors in the tumor microenvironment which suppress specific immune responses to the tumor or which allows the tumor to evade recognition all together (Restifo et al 2016; Jenkins et al 2018). Hugo et al 2016 revealed an innate PD-1 resistance signature ("IPRES") at the heart of anti-PD-1 nonresponders, in which tumors displayed elevated immunosuppressive factors like interleukin (IL)-10 and other anti-inflammatory molecules which likely contribute to the overall evasion of the tumor from an immune response. Furthermore, they suggested that genetic data from The Cancer Genome Atlas database indicate that only a subset of tumors display the IPRES (lung renal cell, pancreatic and colon carcinomas). One strategy is to turn these "cold" tumors, which have minimal immune cell infiltrate, into "hot" tumors by reducing or inhibiting the immunosuppressive factors present in the TME. Zhu et al 2014 found that CSF-1R inhibition in preclinical models not only decreased the number of tumor infiltrative macrophages (e.g., TAMs) in the TME, but improved the response to PD-1 inhibitor treatments and converted macrophages to support T-cell activation and increase antigen presentation. Thus, these data suggest that CSF-1R inhibition may be able to contribute to the repopulation of infiltrative T-cells and other pro-inflammatory cells in the TME resulting in the ability to respond to PD-1/programmed cell death ligand 1 (PD-L1) inhibition.

2.1.2 Malignant Melanoma

For more than 30 years, cytotoxic chemotherapies and biologic agents such as IL-2 and interferon (alone and in combinations) have been used to treat unresectable, metastatic or advanced melanoma. Progress has been made with the regulatory approval of ipilimumab in 2011 and other immune CPIs. Programmed cell death receptor 1 is a well described immune checkpoint protein that is a negative regulator of T-cell activity, and when bound to its ligands, PD-L1 and programmed cell death ligand 2 (PD-L2), is a negative regulator of cytokine production and T-cell proliferation. Pembrolizumab and nivolumab are monoclonal antibodies (mAbs) targeted to PD-1 that act to block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Both CPIs were approved by the FDA for the treatment of melanoma in 2014. The

combination of ipilimumab and nivolumab for the treatment of metastatic melanoma demonstrated impressive antitumor activity, including a median progression-free survival (PFS) of 11.5 months and an objective response rate (ORR) of approximately 58% (Larkin et al 2015), albeit with increased toxicity over single-agent therapy.

2.1.3 Non-Small Cell Lung Carcinoma

Lung cancer is the most common cause of death from cancer with an estimated 264,800 and 157,423 cancer deaths per year in Europe and the United States (US), respectively (Ferlay et al 2013; U.S. Cancer Statistics Working Group 2015). For patients with advanced disease, first-line therapies, including epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in patients with EGFR mutations, and platinum-based chemotherapy, have shown improved survival outcomes. However, most of these patients progress and require second-line therapy with a chemotherapy-based regimen. Until recently, docetaxel and pemetrexed have been standard second-line treatment regimens for non–small cell lung cancer (NSCLC) and have demonstrated a median PFS of 3 months (Hanna et al 2004). In early clinical trials, anti-PD-1 and anti-PD-L1 antibodies produced durable responses in 20% of unselected patients with advanced NSCLC (Brahmer et al 2012; Topalian et al 2012). Pembrolizumab, a PD-1–blocking antibody, was initially approved for a NSCLC indication in 2015 on the basis of a subgroup analysis within a larger trial. Those patients who had received a prior platinum-based chemotherapy regimen and had tumors expressing PD-L1 with a tumor proportion score (TPS) of ≥ 50% achieved a median PFS of approximately 6.1 months and an ORR of approximately 44% (Garon et al 2015). It was recently reported that in a study of patients with advanced NSCLC who had received a prior platinum-based chemotherapy regimen, pembrolizumab (2 mg/kg every 3 weeks [Q3W]) resulted in a median PFS of 5.0 months and an ORR of 30% in patients with TPS ≥ 50%, generally confirming the earlier study (Herbst et al 2016). Based on results from the KEYNOTE-024 study, a Phase 3 trial that evaluated the efficacy of pembrolizumab versus platinum-based chemotherapy as first-line treatment for metastatic NSCLC that expressed PD-L1, the FDA recently approved the use of single-agent pembrolizumab for the frontline treatment of metastatic NSCLC in patients who have 50% or higher PD-L1 expression based on an FDA-approved test, and who do not express EGFR/anaplastic lymphoma kinase (ALK) mutations. In patients treated with pembrolizumab, the median PFS was 10.3 months, and the ORR was 44.8%. The estimated rate of overall survival at 6 months was 80.2% (Reck et al 2016). Additionally, the pembrolizumab label was expanded to include patients with lower PD-L1 expression (TPS ≥ 1%) who progressed on prior platinum therapy (Keytruda® [pembrolizumab] summary of product characteristics). In the KEYNOTE-001 study, in the cohort of treatment-naïve NSCLC patients with tumor TPS of 1% to 49%, the ORR was 17%, the median PFS was 4.2 months, and the PFS rate at 12 months was 25% (Hui et al 2017). In May 2017, pembrolizumab was also approved under accelerated approval in combination with pemetrexed and carboplatin as first-line treatment of patients with

metastatic nonsquamous NSCLC, irrespective of PD-L1 expression (Keytruda® [pembrolizumab] summary of product characteristics).

2.1.4 Ovarian Cancer

Ovarian cancer ranks fifth in cancer deaths among women, accounting for more deaths than any other cancer of the female reproductive system (American Cancer Society 2018). Despite surgery and platinum- and taxane-based chemotherapies, greater than 70% of patients with advanced ovarian cancer who achieve remission ultimately experience relapse. Because there are few effective treatments for these patients the development of new treatment strategies is urgently required (Hamanishi et al 2015). In platinum-resistant ovarian cancer (prOVCA), current standard-of-care includes single-agent chemotherapeutic agents which have ORRs of 20% to 25% and median PFS of approximately 3 months (Herzog and Monk 2017). In a recent Phase 3 study, bevacizumab added to chemotherapy resulted in ORR of 27% and PFS of 6.7 months (Pujade-Lorraine et al 2014).

In recent years, there has been some progress made with achieving response with immunotherapy. In the KEYNOTE-028 trial of pembrolizumab in patients with advanced solid tumors, data were reviewed for the 26 patients enrolled with PD-L1-positive ovarian cancer. In this patient population, the ORR was 11.5% with 1 complete response (CR) and 2 partial responses (PRs) achieved. Median PFS and overall survival (OS) were 1.9 months and 13.1 months, respectively (Varga et al 2017). Results are pending for a follow-up Phase 2 study (KEYNOTE-100; NCT02674061) in women with advanced ovarian cancer (ClinicalTrials.gov NCT02674061).

2.1.5 Pancreatic Cancer

Pancreatic cancer is one of the most treatment-resistant human malignancies, due in part to its heterogenic tumor microenvironment. Patients with pancreatic ductal cancer have extremely poor prognoses with the 5-year survival rate of 5–20% of patients who undergo a potentially curative operation (Nakata et al 2002). The existing treatment modalities, including surgical resection and conventional chemotherapies, prolong survival but fail to cure the disease (Johansson et al 2016). A number of immunotherapeutic agents are currently being tested in patients with pancreatic cancer. In unselected patients, cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitors and PD-1/PD-L1 inhibitors appear to have limited activity with best response of stable disease (Johansson et al 2016). In patients with microsatellite instability high (MSI-H) pancreatic ductal cancer, partial responses were observed in 5/6 (83%) patients (Keytruda® [pembrolizumab] summary of product characteristics). Recently, the combination of the PD-1 inhibitor nivolumab and the antibody targeting CSF-1R, cabiralizumab, resulted in an overall ORR of 13% in 30 patients with microsatellite stable (MSS) pancreatic cancer. The

safety profile of the combination was generally tolerable and consistent with nivolumab and cabiralizumab monotherapy (Wainburg et al 2017).

2.2 Investigational Medicinal Product

ARRY-382 is a potent, highly specific, orally available small-molecule inhibitor of CSF-1R (also known as cFMS) kinase activity.

2.2.1 Nonclinical Studies with ARRY-382

Detailed information regarding nonclinical studies of ARRY-382 is presented in the Investigator's Brochure.

2.2.1.1 Nonclinical Pharmacology

The biological activity of ARRY-382 has been evaluated in a panel of cell culture and in vivo studies. In cellular studies, ARRY-382 was a potent inhibitor of CSF-1R (concentration required for 50% inhibition [IC_{50}] = 9 nM). In cell culture experiments, ARRY-382 markedly inhibited the CSF-1R pathway both mechanistically and functionally. Using human osteoclast precursor cells, ARRY-382 was shown to significantly inhibit osteoclast differentiation and bone resorption in vitro.

In vivo, ARRY-382 was evaluated for its ability to inhibit inflammatory processes and CSF-1R phosphorylation in human embryonic kidney cell line (HEK-293) cells. In a lipopolysaccharide-induced cytokine model in mice, single administrations of 3, 10, 30, and 100 mg/kg significantly inhibited tumor necrosis factor-alpha (TNF-α) production. In a pharmacodynamics model (engineered HEK-293 cell line expressing doxycycline-induced CSF-1R), the dose required for 50% of the maximum effect (ED_{50}) of ARRY-382 was 3 mg/kg. ARRY-382 was also efficacious in inhibiting osteolytic bone destruction and allodynia in a breast cancer bone metastasis model.

Based on in vitro metabolism studies, ARRY-382 in humans is predicted to be eliminated by multiple metabolic pathways and enzymes including Phase 1 (cytochrome P450 [CYP] 3A4 and flavin-containing monooxygenase [FMO] 1, 3, and 5) and Phase 2 metabolism. Human recombinant CYPs responsible for the metabolism of ARRY-382 include primarily CYP3A4, but also included CYP2C9, CYP2C19, and CYP2D6. ARRY-382 was a substrate for permeability glycoprotein (P-gp) expressed in pig kidney epithelial cell line (LLC-PK1) cells and may be an inhibitor of P-gp at concentrations greater than 30 μM.

2.2.1.2 Nonclinical Safety and Toxicity

Safety pharmacology studies were conducted to assess the effects of ARRY-382 on cardiovascular function. In the in vitro human ether a-go-go gene (hERG) channel assay, ARRY-382 showed a free IC_{50} of 4.12 µg/mL. This is significantly higher than the expected unbound plasma concentration of ARRY-382 at a dose of 400 mg, which is approximately 100 ng/mL. These results indicate a low risk of hERG channel-influenced conduction abnormalities.

In vivo, cynomolgus monkeys received single oral doses of 0, 10, 30, or 100 mg/kg ARRY-382. The only cardiovascular change noted was a marked increase in QT interval corrected for heart rate (QTc) interval observed in 1 of the 6 animals treated at the highest dose level (i.e., 100 mg/kg). Although values for QT interval and QTc for other animals treated at the high dose level were not affected, a potential effect of ARRY-382 on ventricular repolarization could not be fully excluded at the dose of 100 mg/kg.

Two toxicity studies have been conducted in accordance with international regulatory guidelines for nonclinical toxicity studies and in adherence to current Good Laboratory Practice (GLP) guidelines. ARRY-382, administered orally at doses up to 300 mg/kg/day in rats and 100 mg/kg/day in cynomolgus monkeys, demonstrated an acceptable safety profile in both studies.

The no observed adverse effect level (NOAEL) for daily oral dosing of ARRY-382 in rats for 28 days was 30 mg/kg/day (180 mg/m^2). Findings in rats included dose-related elevations in alanine transaminase (ALT), aspartate transaminase (AST), sorbitol dehydrogenase, and amylase, with no adverse effects in associated organs. Increased kidney weights at 300 mg/kg and decreased spleen weights at all doses of ARRY-382 were noted, but the significance of these findings is unclear. Statistically significant increases in adrenal gland weights were noted in males and females given 100 and 300 mg/kg, correlating with minimal to slight cortical hypertrophy that was histologically evident. Study-related stress may have contributed to increased adrenal gland weight. Other changes relating to increases or changes in macrophages and bone changes were consistent with the pharmacologic activity of ARRY-382.

The NOAEL for daily oral dosing of ARRY-382 in cynomolgus monkeys for 28 days was 10 mg/kg (120 mg/m^2). Findings in monkeys included elevations in ALT, AST, and creatine kinase (CK) in animals receiving 30 and 100 mg/kg. Lower levels of amino-terminal crosslinking telopeptides of type I collagen (NTX) were noted in animals receiving 30 and 100 mg/kg compared with pretest. A slight increase in bioactive parathyroid hormone (PTH) was also noted, though these data were highly variable. The only test-article-related macroscopic finding or change in organ weight was a statistically significant lower thymus weight in both sexes at 100 mg/kg, which appeared to be partly due to individual variations. None of these

findings were associated with obvious adverse effects, tissue damage, or histological changes in associated organs, and all changes were reversed or reversing at recovery. Other findings relating to changes in CCI and increases or changes in macrophages were consistent with the pharmacologic activity of ARRY-382.

2.2.2 Clinical Experience with ARRY-382 (Clinical Study ARRAY-382-101)

ARRY-382 has been assessed in one Phase 1 clinical study (Clinical Study ARRAY-382-101, hereafter referred to as Study 101) in patients with advanced or metastatic cancer that was refractory to standard treatment, for which no standard therapy was available or for which the patient refused standard therapy. Twenty-six patients were enrolled and received ascending doses of ARRY-382 at 6 dose levels (25, 50, 100, 200, 400, and 500 mg), administered orally once daily (QD) in 28-day cycles.

2.2.2.1 Clinical Safety

No treatment-related SAEs or deaths were reported during Study 101.

The most frequently reported adverse events (AEs) were fatigue, nausea, vomiting, peripheral edema, increased blood CK, and decreased appetite (Table 1). Treatment-related AEs observed in more than 2 patients included fatigue (11 patients), increased blood CK (7 patients), nausea (6 patients), decreased appetite (4 patients), and vomiting (3 patients). Adverse events appeared to be dose-related, as all treatment-related Grade 3 and 4 AEs were reported in the 2 highest dose cohorts (400 and 500 mg QD). Grade 3 treatment-related AEs included CK elevation in 6 patients and pyrexia, increased AST, hyponatremia, and anemia in 1 patient each. Hepatic enzyme elevations may reflect on-target effects of CSF-1 inhibitors based on their inhibition of Kupffer cells in the liver resulting in decreased clearance of transaminases (Radi et al 2011). Grade 4 treatment-related AEs included elevated lipase and hypophosphatemia in 1 patient each. Two patients who received 200 mg discontinued ARRY-382 due to treatment-related AEs (petechiae at Day 70 of treatment and increased ALT at Day 21 of treatment, respectively).

Table 1: All Adverse Events Reported in ≥ 15% of All Patients (Clinical Study ARRAY-382-101)

MedDRA Preferred Term	25 mg QD (n=1) n (%)	50 mg QD (n=1) n (%)	100 mg QD (n=1) n (%)	200 mg QD (n=6) n (%)	400 mg QD (n=11) n (%)	500 mg QD (n=6) n (%)	Total (N=26) n (%)
Total patients with any AE	1 (100)	1 (100)	1 (100)	6 (100)	11 (100)	5 (83)	25 (96)
Fatigue	1 (100)	1 (100)	1 (100)	3 (50)	7 (64)	3 (50)	16 (62)
Nausea	1 (100)	1 (100)	0	1 (17)	2 (18)	3 (50)	8 (31)
Vomiting	1 (100)	1 (100)	0	1 (17)	3 (27)	2 (33)	8 (31)
Oedema peripheral	0	0	0	1 (17)	4 (36)	2 (33)	7 (27)
Blood creatine phosphokinase increased	0	0	0	0	4 (36)	3 (50)	7 (27)
Decreased appetite	1 (100)	0	1 (100)	0	2 (18)	2 (33)	6 (23)
Constipation	0	0	0	0	2 (18)	3 (50)	5 (19)
Dyspnoea	0	0	0	1 (17)	2 (18)	2 (33)	5 (19)
Anaemia	0	0	0	2 (33)	1 (9)	2 (33)	5 (19)
Pyrexia	1 (100)	0	0	1 (17)	0	2 (33)	4 (15)
Dehydration	0	0	0	0	3 (27)	1 (17)	4 (15)
Pruritus	0	0	0	1 (17)	3 (27)	0	4 (15)
Cough	1 (100)	0	0	0	1 (9)	2 (33)	4 (15)
Pneumonia	1 (100)	0	0	0	2 (18)	1 (17)	4 (15)

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Affairs; QD = once daily

Grade 1 increases in QT interval corrected for heart rate using Fridericia's formula (QTcF) (absolute values) were observed in 9 (35%) of 26 patients, all of whom were in the higher dose levels (i.e., 200 mg QD, 400 mg QD, or 500 mg QD cohorts). Grade 1 increases (31 to 60 msec) from baseline in QTcF intervals were observed in 6 (23%) patients, and did not appear to be dose-related. No patient had a QTcF interval that exceeded 480 msec or an increase from baseline that exceeded 60 msec.

Dose-limiting toxicities (DLTs) were reported for 1 of 11 patients in the 400 mg QD cohort (Grade 3 increase in blood CK) and 2 of 6 patients in the 500 mg QD cohort (Grade 2/3 increase in AST and Grade 3 pyrexia in 1 patient). The maximum tolerated dose (MTD) was determined to be 400 mg QD.

2.2.2.2 Clinical Pharmacokinetics

In Study 101 (n=26 patients), concentrations of ARRY-382 and 3 metabolites (AR00469099 [an N-oxide metabolite], AR00649100 [an N-desmethyl metabolite], and AR00470870 [a sulfate

metabolite]) were measured. Exposure (maximum observed plasma concentration [C_{max}] and area under the plasma concentration-time curve over the dosing interval [AUC_{τ}]) to ARRY-382 increased with increasing doses over the 25 mg to 500 mg QD dose range on Cycle 1 Day 1 and Day 15, with median time of the maximum observed plasma concentration (T_{max}) values of approximately 2 hours across all doses at both time points. The overall median apparent terminal half-life ($t_{1/2}$) values were 18 and 19 hours on Cycle 1 Day 1 and Day 15, respectively.

For the 3 metabolites (AR00469099, AR00649100, and AR00470870), exposure (C_{max} and AUC_{τ}) to ARRY-382 increased with increasing doses over the 25 mg to 500 mg QD dose range on Cycle 1 Day 1 and Day 15. The overall median T_{max} values for the 3 metabolites on Cycle 1 Day 1 and Day 15 were approximately 4 and 5.5 hours, 2 and 2 hours, and 4 and 3 hours, respectively.

A preliminary assessment of food effect on the exposure of ARRY-382 was included in Study 101. Plasma concentrations in samples collected 24 hours after administration of ARRY-382 in the fasted state (Cycle 1 Day 15) were compared with those in the fed state (with full or light meal, Cycle 1 Day 14). Information related to food consumption was collected using food diaries for each patient. Although there was no significant variation in trough plasma concentrations of ARRY-382 when administered in the fasted or fed condition, there was a trend toward increased exposure to ARRY-382 when administered with a heavy meal. Limitations of these findings included the long median $t_{1/2}$ values (approximately 19 hours across all doses at Cycle 1 Day 15) and high intrapatient variability.

2.2.2.3 Clinical Biomarker Analysis

In Study 101, biomarkers included CSF-1 and circulating cytokines, nonclassical monocytes (NCMs), CSF-1–stimulated extracellular signal-regulated kinase (ERK) phosphorylation in monocytes, markers of bone turnover, and circulating tumor cells (CTCs). Twenty-six patients were included in the blood pharmacodynamic population, and 25 patients were included in the urine pharmacodynamic population. However, data for each marker were not available for all patients, as noted in the following sections.

2.2.2.3.1 Markers of CSF-1R Inhibition

Serum concentrations of CSF-1, as well as macrophage inflammatory protein 1 beta [MIP-1b], monocyte chemoattractant protein 1 [MCP-1], interleukin [IL]-8, IL-10, IL-6, and other circulating cytokines that are produced by or affect macrophages, were evaluated as potential markers of CSF-1R inhibition. For CSF-1, mean (standard deviation [SD]) percentage increases from baseline following treatment with ARRY-382 ranged from 328% (325) to 1845% (2022) and were observed at all time points. Increases in CSF-1 trended in a dose- and time-dependent manner, with minimal (< 2-fold) increases being observed for the lowest dose levels (25, 50, and

100 mg QD) and increases being higher and generally similar for the 400 and 500 mg QD dose levels. The maximum effect for the 2 highest dose levels was observed on Cycle 1 Day 22.

Another potential marker of CSF-1 inhibition was the abundance of an NCM subpopulation in blood. Assessment of NCM subpopulation was not performed for the 25, 50, and 100 mg QD dose levels, and available data are limited to 15 patients in the higher dose cohorts (200, 400, and 500 mg QD). Review of individual patient data indicated no notable changes in the percentage of total monocytes following treatment with ARRY-382. When the abundance of NCM was evaluated as a percentage of baseline at Cycle 1 Day 15, decreases were observed in all cohorts tested. Overall, the mean (SD) percentage of the NCM subpopulation was reduced to 15.2% (27.2) of the baseline value. Intermediate reductions in NCM subpopulation compared with baseline were observed in the 200 mg QD cohort, with a mean (SD) percentage of 35.5% (42.2) of the baseline value present on Cycle 1 Day 15. The largest reductions were observed for the 400 and 500 mg QD cohorts, when the NCM subpopulation was reduced to mean (SD) values of 4.3% (4.4) and 5.9% (2.4) of the baseline values, respectively.

Finally, ex vivo CSF-1-stimulated ERK phosphorylation in circulating monocytes was also evaluated as a potential marker of CSF-1R inhibition. Data are not available for the 25 and 100 mg QD dose levels due to sample processing issues. Inhibition of ERK phosphorylation relative to baseline was observed at each time point in all cohorts tested. At the time point corresponding with steady-state trough plasma concentrations of ARRY-382 (Cycle 1 Day 15 predose), decreases in phosphorylated ERK were observed in a dose-dependent manner, with complete inhibition observed at the 400 and 500 mg QD dose levels. At the 200 mg QD level, complete inhibition was observed at 4 hours postdose on Cycle 1 Day 15.

2.2.2.3.2 Markers of Bone Turnover

Urine concentrations of NTX, serum concentrations of NTX, and serum tartrate-resistant acid phosphatase 5b (TRAP5b) were evaluated as markers of bone turnover. Values of NTX > 64 nmol bone collagen equivalents (BCE)/mmol creatinine at baseline were classified as being elevated. Of 7 patients with elevated urinary NTX levels at baseline, 5 had reductions in absolute values to within the normal range (≤ 64 nmol BCE/creatinine) on or before Cycle 2 Day 1, including 2 patients with known bone metastases. Another patient with elevated urinary NTX levels at baseline and known bone metastasis had a reduction in absolute values to within the normal range by Cycle 3 Day 1. Mean NTX levels were reduced relative to baseline at all time points for the 100, 200, 400, and 500 mg QD cohorts.

Review of individual patient data indicated a trend in serum NTX concentrations similar to that of urinary NTX and no notable changes in TRAP5b levels.

2.2.2.3.3 Markers of Metastasis

Circulating tumor cells were quantified as a marker of intravasation and/or metastasis. Changes in the number of CTCs relative to baseline levels following treatment were variable, and no conclusions regarding the effect of ARRY-382 on CTCs was drawn.

2.2.2.4 Clinical Efficacy

In Study 101 (n=26 patients), no objective responses were observed. Four patients with heavily pretreated cancer experienced a best response of stable disease, which lasted > 3 months for 2 patients.

2.3 Rationale for the Current Study

ARRY-382 is a potent, highly specific, orally available small molecule inhibitor of CSF-1R. Pembrolizumab is a potent and highly selective humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. PD-1 is a well described immune checkpoint protein that is upregulated on tumors and acts as a negative regulator of T-cell activity and cytokine production, thereby suppressing immune-mediated surveillance of tumor growth (Postow et al 2015). Pembrolizumab acts to release the PD-1 pathway-mediated inhibition of the immune response, including the antitumor immune response.

The exploration of ARRY-382 in combination with pembrolizumab is a logical approach to treat certain cancers by affecting a double-blockade of cancer-induced immune suppression through inhibition of 2 pathways that negatively regulate immune-mediated tumor control. Nonclinical studies have demonstrated that the T-cell antitumor responses elicited by treatment with anti-PD-L1 can be limited by immunosuppressive myeloid cells such as M2 macrophages. Treatment with ARRY-382 in mice bearing MCF-7 or MD-MB-231 breast carcinoma xenografts markedly reduced TAM infiltration into these tumors (data on file). Combining anti-PD-L1 with CSF-1R inhibitors (antibodies or small molecules) reverses this immune suppression and leads to a stronger anti-tumor response than that seen with anti-PD-L1 alone (Zhu et al 2014). In addition, studies with nonclinical tumor xenografts show that inhibition of CSF-1R kinase can augment antitumor responses (e.g., with chemotherapy or immunotherapy) (DeNardo et al 2011). Agents targeting CSF-1R in combination with anti-PD-1 or anti-PD-L antibodies are under active clinical development (ClinicalTrials.gov NCT02323191; ClinicalTrials.gov NCT02452424; ClinicalTrials.gov NCT02526017).

2.3.1 Phase 1b (Part A)

The Phase 1b portion (Part A) of the study has a standard dose-escalation design to determine the MTD and/or recommended Phase 2 dose (RP2D) of ARRY-382 in combination with pembrolizumab. The patient population for Part A of this study will consist of patients with

advanced/metastatic melanoma, PD-L1–positive NSCLC, ovarian cancer, triple-negative breast cancer, head and neck squamous cell cancer (HNSCC), bladder cancer, metastatic colorectal cancer (CRC), pancreatic ductal adenocarcinoma (PDA), or gastric cancer.

Selection of the tumor types included in this portion of the study is based on evidence that increased TAM or signaling through the CSF-1 receptor is associated with poor outcome in these indications. Increased levels of CSF-1 and CSF-1R, have been associated with poor prognosis and survival in a number of cancer types, including breast (Leek et al 1996; Kluger et al 2004; Tsutsui et al 2005), ovarian (Shah et al 2008; Huang et al 2002), prostate (Lissbrant et al 2000), and lung cancers (Takanami et al 1999; Chen et al 2005; Kaminska et al 2006).

Part A (Phase 1b) has been completed and the MTD/RP2D of ARRY-382 was determined to be 300 mg QD in combination with pembrolizumab. A total of 19 patients were treated in Part A at doses of 200 mg QD (n=6), 400 mg QD (n=7) and 300 mg QD (n=6). Dose-limiting toxicities were observed in 2 patients at 400 mg QD, including Grade 3 CK increase in 1 patient and Grade 3 AST/ALT and bilirubin increase in another patient. One patient treated at 300 mg QD experienced a DLT of Grade 3 pancreatitis. There were 2 confirmed responses including 1 patient with PDA treated at the 200 mg dose level and 1 patient with ovarian cancer at the 300 mg dose level. In addition to the patients with objective responses per the Response Criteria in Solid Tumors, version 1.1 (RECIST 1.1), tumor regressions were observed in 1 patient with melanoma and 2 patients with ovarian cancer (Harb et al 2017).

2.3.2 Phase 2

The purpose of the Phase 2 cohorts of the study is to assess whether the efficacy of pembrolizumab can be enhanced with the addition of ARRY-382 at the RP2D in these patient populations.

The Phase 2 PD-1/PD-L1 Inhibitor Refractory cohort is based on nonclinical data that suggests that CSF-1R inhibition can increase infiltrating T-cells and other pro-inflammatory markers that may enhance the effects of a PD-1 inhibitor (Section 2.1.1). All tumor types to be included are those in which PD-1/PD-L1 inhibitors are currently being used and are consistent with the indications selected in Part A of the study.

The Phase 2 prOVCA and PDA cohorts are based on the preliminary activity that was observed in Part A suggesting that the addition of ARRY-382 to pembrolizumab may be effective in patients with ovarian cancer and in patients with PDA in whom effective therapies are not available. In Part A (dose-escalation) of this study, all 3 patients with ovarian cancer in the study achieved tumor regression with 1 patient experiencing a PR. The only other response in Part A was observed in a patient with PDA who had been treated with 2 prior lines of therapy who remained on study for greater than 17 cycles.

2.4 Dose Selection

ARRY-382:

For Part A, the starting dosage of ARRY-382 is 200 mg QD by mouth (po), with planned escalation to 400 mg QD.

The starting dosage of ARRY-382 in this study is 50% of the MTD identified in Study 101. In that study (see Section 2.2.2), evidence of biologic activity, including decreases in ex vivo CSF-1-stimulated phosphorylated ERK in monocytes and decreased numbers of NCM, was observed in patients treated at dose levels of 200 mg QD or higher. Maximal inhibition of these markers was observed at the 400 mg QD and 500 mg QD dose levels. Reductions in urinary levels of NTX were observed at dose levels of 50 mg QD and higher.

In Phase 2, the dose of ARRY-382 will be 300 mg QD, the MTD/RP2D determined during Part A (see Section 2.3.1), in combination with pembrolizumab.

Pembrolizumab:

In Part A, pembrolizumab will be administered at the dose of 2 mg/kg intravenous (iv) infusion over 30 minutes Q3W.

In Phase 2, pembrolizumab will be administered as 200 mg iv infusion over 30 minutes (within -5 to +10 minutes) Q3W.

3.0 STUDY OBJECTIVES AND ENDPOINTS

3.1 Phase 1b (Part A)

Objectives and endpoints for the Phase 1b portion (Part A) of the study are presented in Table 2.

Table 2: Objectives and Endpoints (Phase 1b/Part A)

Primary Objective	**Primary Endpoint**
To determine the MTD and/or RP2D of ARRY-382 in combination with pembrolizumab in patients with selected solid tumors	Incidence of DLTs, as a function of the dose of ARRY-382 when administered in combination with pembrolizumab
Secondary Objectives	**Secondary Endpoints**
• To describe the preliminary antitumor activity of the combination based on RECIST v1.1	• ORR, as determined by the Investigator • DOR, as determined by the Investigator • PFS, as determined by the Investigator • OS
• To describe the preliminary antitumor activity of the combination based on irRC	• irRR, as determined by the Investigator • irPFS, as determined by the Investigator
• To characterize the safety and tolerability of the combination, including acute and chronic toxicities	• Type, frequency, and severity of AEs, using the NCI CTCAE • SAEs, using the NCI CTCAE • Clinical laboratory values • Vital signs
• To evaluate the PK of ARRY-382 in combination with pembrolizumab	• 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
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

AE = adverse event; AUC_{τ} = area under the plasma concentration-time curve over the dosing interval; C_{max} = maximum observed plasma concentration; CSF-1 = colony-stimulating factor 1; CTCAE = Common Terminology Criteria for Adverse Events; C_{trough} = plasma concentration measured just before the next dose of study drug; CCI ; DLT = dose-limiting toxicity; DOR = duration of response; FDA=United States Food and Drug Administration; irRC = immune-related response criteria; irRR = immune-related response rate; irPFS = immune-related progression-free survival; MTD = maximum tolerated dose; NCI = National Cancer Institute; CCI ORR = objective response rate; OS = overall survival; CCI 1; PFS = progression-free survival; PK = pharmacokinetic(s); RECIST, v1.1 = Response Criteria in Solid Tumors, version 1.1; RP2D = recommended Phase 2 dose; SAE = serious adverse event; T_{max} = time of maximum observed plasma concentration; CCI

3.2 Phase 2

Objectives and endpoints for the Phase 2 portion of the study are presented in Table 3 for the PD-1/PD-L1 Inhibitor Refractory cohort, in Table 4 for the prOVCA cohort and in Table 5 for the PDA cohort.

Table 3: Objectives and Endpoints (Phase 2: PD-1 or PD-L1 Inhibitor Refractory)

Primary Objective	Primary Endpoint
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	ORR, per RECIST v 1.1, as determined by the Investigator
Secondary Objectives	**Secondary Endpoints**
• To further estimate the efficacy of the combination	• 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
• To characterize the safety and tolerability of the combination, including acute and chronic toxicities	• Type, frequency, and severity of AEs, using the NCI CTCAE • SAEs, using the NCI CTCAE • Clinical laboratory values • Vital signs
• To evaluate the PK of ARRY-382 in combination with pembrolizumab	• 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
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

AE = adverse event; AUC_{τ} = area under the plasma concentration-time curve over the dosing interval; C_{max} = maximum observed plasma concentration; CSF-1 = colony-stimulating factor 1; CTCAE = Common Terminology Criteria for Adverse Events; C_{trough} = plasma concentration measured just before the next dose of study drug; CCI [redacted] DOR = duration of response; response rate; irPFS = immune-related progression-free survival; irRC = immune-related response criteria; irRR = immune-related response rate; NCI = National Cancer Institute; CCI [redacted] ORR = objective response rate; OS = overall survival; PD-1 = programmed cell death receptor 1; PD-L1 = programmed cell death ligand 1; PFS = progression-free survival; PK = pharmacokinetic(s); RECIST, v1.1 = Response Criteria in Solid Tumors, version 1.1; SAE = serious adverse event; T_{max} = time of maximum observed plasma concentration; CCI [redacted]

Table 4: Objectives and Endpoints (Phase 2: prOVCA)

Primary Objective	Primary Endpoint
To estimate the efficacy of ARRY-382 in combination with pembrolizumab in patients with MSS/MMR-proficient prOVCA	ORR, per RECIST v1.1, as determined by the Investigator
Secondary Objectives	**Secondary Endpoints**
• To further estimate the efficacy of the combination in patients with MSS/MMR-proficient prOVCA	• 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
• To estimate the efficacy of the combination, as assessed by changes in tumor markers from baseline	• Changes from baseline in relevant tumor markers
• To characterize the safety and tolerability of the combination, including acute and chronic toxicities	• Type, frequency, and severity of AEs, using the NCI CTCAE • SAEs, using the NCI CTCAE • Clinical laboratory values • Vital signs
• To evaluate the PK of ARRY-382 in combination with pembrolizumab	• Plasma concentration-time profiles • PK parameters (e.g., AUCτ, C_{max}, T_{max}, C_{trough}, accumulation ratio, and metabolite-to-parent ratio) for ARRY-382 and its metabolites, AR00469099, AR00469100, and AR00470870
CCI [redacted]	[redacted]

AE = adverse event; AUCτ = area under the plasma concentration-time curve over the dosing interval; C_{max} = maximum observed plasma concentration; CSF-1 = colony-stimulating factor 1; CTCAE = Common Terminology Criteria for Adverse Events; C_{trough} = plasma concentration measured just before the next dose of study; CCI [redacted] dMMR = mismatch repair-deficient; DOR = duration of response; FDA = United States Food and Drug Administration; irPFS = immune-related progression-free survival; irRC = immune-related response criteria; irRR=immune-related response rate; MMR = mismatch repair; MSI-H = microsatellite instability-high; MSS = microsatellite stable; NCI = National Cancer Institute; NCM = nonclassical monocytes; NSCLC = non–small cell lung cancer; CCI [redacted] ORR = objective response rate; OS = overall survival; CCI [redacted] 1; PFS = progression-free survival; PK = pharmacokinetic(s); prOVCA = platinum-resistant ovarian cancer; RECIST, v1.1 = Response Criteria in Solid Tumors, version 1.1; SAE = serious adverse event; T_{max} = time of maximum observed plasma concentration; TPS = tumor proportion score; CCI [redacted]

Table 5: Objectives and Endpoints (Phase 2: PDA)

Primary Objective	Primary Endpoint
To estimate the efficacy of ARRY-382 in combination with pembrolizumab in patients with MSS/MMR-proficient PDA	ORR per RECIST v1.1, as determined by the Investigator
Secondary Objectives	**Secondary Endpoints**
• To further estimate the efficacy of the combination in patients with MSS/MMR-proficient PDA	• 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
• To characterize the safety and tolerability of the combination, including acute and chronic toxicities	• Type, frequency, and severity of AEs, using the NCI CTCAE • SAEs, using the NCI CTCAE • Clinical laboratory values • Vital signs
• To evaluate the PK of ARRY-382 in combination with pembrolizumab	• Plasma concentration-time profiles • PK parameters (e.g., AUCτ, C_{max}, T_{max}, C_{trough}, accumulation ratio, and metabolite-to-parent ratio) for ARRY-382 and its metabolites, AR00469099, AR00469100, and AR00470870
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

AE = adverse event; AUCτ = area under the plasma concentration-time curve over the dosing interval; C_{max} = maximum observed plasma concentration; CSF-1 = colony-stimulating factor 1; CTCAE = Common Terminology Criteria for Adverse Events; C_{trough} = plasma concentration measured just before the next dose of study; CCI [redacted] dMMR = mismatch repair-deficient; DOR = duration of response; FDA = United States Food and Drug Administration; irPFS = immune-related progression-free survival; irRC = immune-related response criteria; irRR=immune-related response rate; MMR = mismatch repair; MSI-H = microsatellite instability-high; MSS = microsatellite stable; NCI = National Cancer Institute; NCM = nonclassical monocytes; CCI [redacted] ORR = objective response rate; OS = overall survival; PDA = pancreatic ductal adenocarcinoma; CCI [redacted]; PFS = progression-free survival; PK = pharmacokinetic(s); RECIST, v1.1 = Response Criteria in Solid Tumors, version 1.1; SAE = serious adverse event; T_{max} = time of maximum observed plasma concentration; CCI [redacted]

4.0 STUDY DESIGN

4.1 Study Design Overview

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).

Each phase of the study consists of a 28-day screening period; 21-day treatment cycles with the combination of ARRY-382 and pembrolizumab until disease progression as determined by the Investigator, unacceptable toxicity, withdrawal of consent, or death (or other discontinuation criteria are met [see also Section 9.2]); and a 30-day safety follow-up period. Patients in all cohorts/phases will be monitored for OS until 1 year after the date of the last patient's first visit.

Part A (Phase 1b) includes a dose-escalation component with 2 planned dose cohorts (Table 6). Oral doses of ARRY-382 will be administered QD in combination with pembrolizumab 2 mg/kg iv Q3W. Patients in Cohort 1 will be enrolled on a rolling basis up to 6 evaluable patients or until DLTs (see Section 4.2) 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 AE (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.

Table 6: Planned Dose Cohorts (Part A)

	Planned dose regimen		
	ARRY-382		**Pembrolizumab**
Cohort 1	200 mg po QD		2 mg/kg iv every 3 weeks
Cohort 2	If patients with DLTs ≥ 2 of 6 in Cycle 1:	100 mg po QD	2 mg/kg iv every 3 weeks
	If patients with DLTs ≤ 1 of 6 in Cycle 1:	400 mg po QD	2 mg/kg iv every 3 weeks

DLT = dose limiting toxicity; iv = intravenously; kg = kilogram(s); mg = milligram(s); po = by mouth; Q3W = every 3 weeks; QD = once daily

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. Cohorts evaluating patients with metastatic melanoma (previous Part B) and PD-L1-positive NSCLC (previous Part C) were removed by protocol amendment after enrollment of 1 patient in each cohort due to changes in the respective treatment paradigms.

Phase 2 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

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.

4.2 Dose-Limiting Toxicities (Part A)

For Part A, DLTs are defined as a treatment-emergent adverse event (TEAE) or abnormal laboratory value not clearly attributable to an extraneous cause, such as disease progression, intercurrent illness, or concomitant medications occurring during Cycle 1 and meeting one of the criteria shown in Table 7.

Table 7: Dose-Limiting Toxicities (Part A)

Toxicity	DLT Definition Criteria
Nonhematologic AEs	• Recurring Grade 2 pneumonitis • Grade 3 irAE that does not resolve or return to baseline with immunosuppressive therapy within 28 days of onset • Grade 3 QTcF prolongation or > 60 msec increase in QTcF over baseline • Grade 3 rash that does not resolve or return to baseline in <10 days with symptomatic management • Any other Grade 3 or 4 nonhematologic AE, with the **following exceptions**: o Alopecia o Grade 3 nausea, diarrhea, or vomiting lasting less than 72 hours with optimal medical management o Grade 3 AE of tumor flare or pseudoprogression (defined as local pain, irritation, or rash localized at sites of known or suspected tumor) o Grade 3 endocrinopathy that is adequately controlled by hormonal replacement
Hematology AEs/ Laboratory abnormalities	• Any Grade 4 hematologic AEs or Grade 4 laboratory abnormalities, with the **following exceptions**: o Grade 4 lymphopenia o Grade 4 neutropenia lasting ≤ 48 hours that is not associated with fever or other clinically significant symptoms o Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within72 hours of onset • Grade 3 thrombocytopenia with clinically significant bleeding that requires platelet transfusion • Febrile neutropenia defined as a fever with or without clinically or microbiologically documented infection with absolute neutrophil count (ANC) < 1.0×10^9/L, and a fever ≥ 38.5 °C • Any Grade 4 AST or ALT elevation unless clearly attributable to disease progression • Grade 3 AST or ALT elevation lasting > 7 days unless clearly attributable to disease progression • Grade 3 AST or ALT elevation associated with bilirubin levels ≥ 2 × ULN or an international normalized ratio (INR) > 1.5 unless clearly attributable to disease progression • Any Grade ≥ 3 bilirubin elevation unless clearly attributable to disease progression • CK elevation ≥ Grade 3 lasting > 7 days OR associated with an increase in creatinine ≥ 1.5 × the baseline value for creatinine
Dose delay	• Interruption of dosing for greater than 14 days, if due to AEs not related to the underlying disease or intercurrent illness
Other	• Inability to receive at least 67% of protocol-specified doses of ARRY-382 during Cycle 1 due to AEs not related to the underlying disease or intercurrent illness

AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CK = creatine kinase; DLT = dose-limiting toxicity; INR = International Normalized Ratio; irAE = immune-related adverse event; QTcF = QT interval corrected for heart rate using Fridericia's formula; ULN = upper limit of normal

For the purposes of dose escalation and determination of the MTD in Part A, only DLTs that occur during Cycle 1 will be necessarily considered for decisions regarding dose escalation. Other clinically significant toxicities or TEAEs that meet the definition of DLT occurring after Cycle 1 (i.e., dose-modifying events) may be considered when determining the RP2D.

In Part A, patients who require a dose interruption or reduction during the initial 21-day treatment period (Cycle 1) will remain evaluable for tolerability decisions if the reason for the reduction and/or interruption represents a DLT. Patients will be replaced if they have received less than 67% dose intensity [(administered dose in mg/planned dose in mg) x 100] of ARRY-382 or if they did not receive pembrolizumab for any reason other than an AE or abnormal laboratory value that is not related to disease, disease progression, intercurrent illness or concomitant medications/therapies before completing Cycle 1.

Dose modifications of study drug are described in Section 6.3.

For Part A, after the last patient in a given cohort has completed 1 cycle of study treatment, the Sponsor Medical Monitor and Investigators will meet to review all safety data and decide whether to continue or halt dose escalation, expand individual dose levels to gain additional safety data, determine the MTD and/or RP2D, or explore other dose levels. In addition to end-of cohort meetings, safety meetings including the Sponsor Medical Monitor and Investigators will be scheduled periodically (e.g., every 4 weeks) during the conduct of Phase 2 to review safety data for ongoing patients and patients who are being monitored during the follow-up period.

4.3 End of Study

End of study will be defined as the point when all patients have had the opportunity to be followed for at least 1 year after the date the last patient enrolled receives first treatment. Any patients still receiving study drugs at the end of the study will be allowed to continue at the discretion of the Investigator and as long as none of the treatment discontinuation criteria are met (see Section 9.2). The Sponsor will notify all applicable regulatory agencies in accordance with local requirements when the study has ended. After the end of the study, access to study drugs will be provided only in accordance with local regulations and requirements.

5.0 PATIENT POPULATION

This clinical study can fulfill its objectives only if appropriate patients are enrolled. The eligibility criteria described in this study protocol are designed to identify patients for whom treatment is considered appropriate. All relevant medical and nonmedical conditions should be considered when deciding whether a patient is suitable for enrollment in the study.

5.1 Number of Patients

Overall, approximately 90 patients at approximately 30 study sites are planned for enrollment.

Part A (Phase 1b) will consist of approximately 18 patients with selected solid tumors.

The Phase 2 PD-1/PD-L1 Inhibitor Refractory cohort will consist of up to 20 patients with advanced solid tumors who progressed on a PD-1/PD-L1 inhibitor-containing regimen as their most recent prior line of therapy. If clinical activity is observed, enrollment may be focused to include up to 10 additional patients with particular tumor histologies of interest.

The Phase 2 prOVCA cohort will consist of approximately 23 patients with prOVCA who are naïve to prior CPI therapy. The Phase 2 PDA cohort will consist of approximately 29 patients with PDA who have had at least one prior therapy who are naïve to prior CPI therapy.

5.2 Selection of Patients

Questions regarding patient eligibility should be addressed with the Sponsor prior to enrollment of a particular patient. Patients must fulfill all of the following inclusion criteria and none of the exclusion criteria to be eligible for admission to the study.

5.2.1 Inclusion Criteria

1. Personally signed and dated informed consent form
2. Male or female ≥ 18 years of age
3. Diagnosis of cancer that has been histologically or cytologically confirmed as follows:

   Part A (1 of the following):

   a. Ovarian cancer, triple-negative breast cancer, HNSCC, bladder cancer, metastatic CRC, PDA, or gastric cancer that is measurable or evaluable, nonmeasurable as defined by RECIST v1.1 and meets 1 of the following criteria:

      - is refractory to standard of care

- no standard therapy available
- patient refuses standard therapy

b. Advanced, unresectable, or metastatic melanoma with or without prior treatment and measurable or evaluable, nonmeasurable disease as defined by RECIST v1.1

c. Advanced/metastatic PD-L1–positive NSCLC (defined as TPS ≥ 50%) with measurable or evaluable, nonmeasurable disease as defined by RECIST v1.1 (1 of the following):

- 1) Patients with metastatic PD-L1 positive NSCLC with no EGFR or ALK genomic tumor aberrations and no prior systemic chemotherapy
- 2) Patients with advanced/metastatic PD-L1 positive NSCLC with disease progression on or after platinum-containing chemotherapy
- 3) Patients with advanced/metastatic PD-L1 positive NSCLC with EGFR or ALK genomic tumor aberrations, with disease progression on FDA-approved therapy for these aberrations

  All patients with NSCLC must provide documentation of positive PD-L1 expression, defined as a TPS ≥ 50% on a fresh tumor biopsy (preferred) or the most recent archived tumor sample available. If test results documenting positive PD-L1 expression were not obtained using an FDA-approved test, then tumor tissue must be submitted to a central laboratory and it will be tested retrospectively using an FDA-approved test at a central laboratory (please see the laboratory manual for additional details).

Phase 2 (1 of the following):

a. Advanced/metastatic solid tumor with PD as defined by RECIST 1.1 or irRC on an anti-PD-1- or anti-PD-L1-containing regimen as their most recent prior therapy

b. Advanced/metastatic epithelial ovarian cancer, peritoneal cancer or tubal cancer with measurable disease as defined by RECIST 1.1, that had progressed within 6 months of completing ≥ 4 cycles of platinum-based therapy

c. Advanced/metastatic PDA that is locally advanced, unresectable or metastatic with measurable disease as defined by RECIST v1.1 in patients who have received at least one prior line of systemic therapy for their disease

4. Eastern Cooperative Oncology Group Performance Status of 0 or 1 (see APPENDIX 1)

5. Adequate bone marrow function at screening, characterized by the following:

   a. absolute neutrophil count (ANC) ≥ 1.0×10^9/L

b. platelets ≥ 75 × 10^9/L

c. hemoglobin ≥ 9.0 g/dL
Note: Transfusions will be allowed to achieve the acceptable hemoglobin value.

6. Adequate renal function characterized by serum creatinine ≤ 1.5 × upper limit of normal (ULN) or calculated or directly measured creatinine clearance ≥ 50 mL/min at screening

7. Adequate hepatic function at screening, characterized by the following:

   a. serum total bilirubin ≤ 1.5 × ULN and < 2 mg/dL
   Note: Patients who have a total bilirubin level > 1.5 × ULN will be allowed if their indirect bilirubin level is ≤ 1.5 × ULN

   b. ALT and/or AST ≤ 2.5 × ULN, or ≤ 5 × ULN in presence of liver metastases

8. For male patients and female patients of childbearing potential, agreement to use an acceptable method of contraception as defined in the protocol (see Section 5.3) from the start of study treatment until 7.5 months after the last dose of pembrolizumab for males and until 5.5 months after the last dose of pembrolizumab for females
   Note: Women are considered not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy with hysterectomy or tubal ligation at least 6 weeks prior to Screening. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of childbearing potential.

9. For females of childbearing potential only, negative serum human chorionic gonadotropin (hCG) pregnancy test result at baseline and nonlactating

10. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures

11. **Phase 2 only**: Availability of a fresh biopsy (preferred) or an archival tumor sample from the most recent sample available. Between 10 to 15 slides or an archival block are required.

    This requirement may be waived under certain circumstances (e.g., sufficient archived tissue is no longer available and fresh specimen collection is deemed medically unsafe or not feasible by the Investigator due to the location of the tumor) after discussion and agreement between the Sponsor and the Investigator.

5.2.2 Exclusion Criteria

Patients meeting any of the following criteria are ineligible for enrollment in the study.

1. Prior treatment as follows:

   Part A:

   - An immune CPI (e.g., PD-1, PD-L1, or CTLA-4 inhibitor)

     NOTE: Prior treatment with a CSF-1R or CSF-1 (or macrophage colony-stimulating factor [MCSF]) inhibitor is allowed. For patients with melanoma, prior treatment with ipilimumab is allowed if it was administered as adjuvant therapy and treatment was completed at least 3 months prior to enrollment.

   Phase 2:

   - A CSF-1R inhibitor or CSF-1 (or MCSF) inhibitor
   - prOVCA and PDA patients only: an immune CPI (e.g., PD-1, PD-L1, or CTLA-4 inhibitor)

2. Symptomatic brain metastasis at screening
   NOTE: Patients who are asymptomatic will be allowed, regardless of whether they received previous treatment for the metastases. Any brain metastases present at screening must be stable by imaging (e.g., magnetic resonance imaging [MRI] or computed tomography [CT]) demonstrating no evidence of progression at screening; patients must not be receiving anticonvulsant therapy and must have completed treatment with corticosteroids or be taking a decreasing dose of corticosteroids.

3. Active autoimmune disease, documented history of autoimmune syndrome or disease, or a chronic medical condition that requires chronic steroid therapy or immunosuppressive medication
   NOTE: Exceptions include patients with vitiligo, resolved childhood asthma/atopy, patients who require intermittent use of bronchodilators or local steroid injections, and patients with a history of hypothyroidism taking a stable dose of replacement therapy. In addition, patients requiring physiological replacement doses of hydrocortisone or its equivalent (i.e., up to 20 mg hydrocortisone [or 5 mg prednisone] in the morning, and 10 mg hydrocortisone [or 2.5 mg prednisone] in the evening) will be considered eligible for the study.

4. Impaired gastrointestinal function or disease that may significantly alter the absorption of ARRY-382 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection)

5. Presence of risk factors for bowel obstruction or bowel perforation (e.g., history of acute diverticulitis, intra-abdominal abscesses, or abdominal carcinomatosis)

6. History of severe hypersensitivity to mAb

7. Active infection requiring therapy

8. History of pneumonitis or interstitial lung disease

9. Symptomatic ascites or symptomatic pleural effusion

   NOTE: For prOVCA patients, paracentesis or pleurocentesis to relieve symptoms prior to and during treatment will be permitted.

10. Leptomeningeal disease

11. Ocular melanoma

12. Use of herbal medications/supplements or any medications or foods that are strong inhibitors or inducers of CYP3A4/5 within 2 weeks before the start of study treatment

13. Clinically significant cardiac disease, including any of the following:

    a. congestive heart failure requiring treatment (New York Heart Association Grade ≥ 2)
    b. uncontrolled hypertension per World Health Organization (WHO)/International Society of Hypertension (ISH) 2003 guidelines
    c. presence of clinically significant and uncontrolled atrial fibrillation
    d. unstable angina pectoris ≤ 3 months prior to enrollment
    e. acute myocardial infarction ≤ 3 months prior to enrollment

14. QT abnormality or risk of QT abnormality, as follows:

    a. a prolonged QTcF ≥ 450 msec at screening (based on average of 3 readings)
    b. history or evidence of congenital long QT syndrome
    c. use of concomitant medications that may prolong QT/QTc interval or induce torsades de pointes (see APPENDIX 2) within 2 weeks before the start of study treatment

15. Impaired hepatic function, defined as Child Pugh (Schwartz et al 2007) Class B or C (see APPENDIX 3)

16. Previous tumor malignancy within the last 3 years, or has a concurrent malignancy, with the exception of adequately treated basal cell or squamous cell carcinoma, in situ carcinoma of the cervix, in situ breast cancer, or in situ prostate cancer without evidence of active disease for 2 years before enrollment

17. History of thromboembolic or cerebrovascular events, including transient ischemic attacks, cerebrovascular accidents, deep vein thrombosis, or pulmonary emboli within 6 months before enrollment

18. Prior therapy consisting of any of the following:

    a. cyclical chemotherapy within a period of time that was shorter than the cycle length used for that treatment (e.g., 6 weeks for nitrosourea, mitomycin-C)

    b. biologic therapy (e.g., antibodies), continuous or intermittent small-molecule therapeutics, or any other investigational agents within a period of time that is ≤ 5 half-lives ($t_{1/2}$) or ≤ 2 weeks (whichever is shorter)

19. Residual Common Terminology Criteria for Adverse Events (CTCAE) ≥ Grade 2 side effects of any prior therapy, with the exception of residual Grade 2 alopecia

20. Known history of human immunodeficiency virus (HIV) infection

21. Active hepatitis B (hepatitis B surface antigen-[HBsAg-]reactive) or hepatitis C serology infection (hepatitis C virus [HCV] ribonucleic acid [RNA] [qualitative] will be required if serology is positive)

22. Severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or that may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient an inappropriate candidate for the study

5.3 Contraception

Female patients of childbearing potential must agree to use acceptable or highly effective methods of contraception to avoid pregnancy for the duration of study treatment through 5.5 months after the last dose of pembrolizumab (i.e., 30 days [duration of ovulatory cycle] plus the time required for the investigational drug to undergo approximately 5 half-lives).

Non-sterile male patients who are sexually active with female partners of childbearing potential must agree to use acceptable or highly effective methods of contraception to avoid fathering a child for the duration of study treatment and for 7.5 months after the last dose of pembrolizumab

(i.e., 90 days [duration of sperm turnover] plus the time required for the investigational drug to undergo approximately 5 half-lives).

The permitted contraceptive methods listed below (CTFG Guidelines 2014) should be communicated to the patients and their understanding confirmed.

The following methods have been determined to be highly effective (i.e., can achieve a failure rate < 1% per year when used consistently and correctly):

- Complete abstinence from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient
- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner (considered highly effective provided the vasectomized male has received medical assessment of surgical success and that the male is a female patient's sole sexual partner)

Acceptable birth control methods that result in a failure rate of more than 1% per year include:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide
- Cap, diaphragm or sponge with spermicide

6.0 STUDY TREATMENT AND CONCOMITANT MEDICATIONS

The term "study treatment" is defined as ARRY-382 or pembrolizumab.

6.1 Study Treatment Supplies

6.1.1 Manufacturing and Formulation

ARRY-382 is manufactured by Avista Pharma Solutions and supplied by the Sponsor as powder in a capsule. Drug product will be provided in Swedish orange opaque size "00" (100 mg) gelatin capsules.

Pembrolizumab is marketed in the United States by Merck, Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (Whitehouse, NJ) in 2 formulations. Keytruda® (pembrolizumab) for injection, for iv use is supplied as 50 mg lyophilized powder in a single-use vial for reconstitution, and Keytruda® (pembrolizumab) injection, for iv use is supplied as 100 mg/4 mL (25 mg/mL) solution in a single-use vial.

Pembrolizumab is marketed by Merck Sharp & Dohme Limited (Hoddesdon, UK) in the European Union in 2 formulations. Keytruda® (pembrolizumab) for injection, for iv use is supplied as 50 mg lyophilized powder for concentrate for solution for infusion in a single-use vial, and Keytruda® (pembrolizumab) injection, for iv use is supplied as 100 mg/4 mL (25 mg/mL) solution in a single-use vial.

6.1.2 Packaging and Labeling

ARRY-382 capsules are packaged in high density polyethylene bottles with child-resistant plastic caps and safety-seal features and sent to the site in bulk. Label content will include, at a minimum, the lot number, storage information, and a statement that the contents are investigational in nature. Each bottle will be labeled in compliance with local regulations.

Commercially available pembrolizumab will be used in this study according to local regulations in each participating country. Pembrolizumab for injection (lyophilized powder) and pembrolizumab injection (solution) is packaged in individual cartons containing single-use vials. Pembrolizumab will be supplied either locally or by the Sponsor. Pembrolizumab preparation must be in accordance with the label and with local institutional guidelines. The Sponsor, or designee, will provide each site with the most current local pembrolizumab Prescribing Information and distribute any updates as they become available (see also Section 6.3.3).

6.1.3 Shipping, Storage and Handling

Labeled, packaged study drug will be shipped to each study site by the Sponsor or designee following receipt of the necessary regulatory documents. The Investigator or an approved representative (e.g., registered pharmacist) will ensure that all study drug is stored as outlined in the Pharmacy Manual and in accordance with applicable regulatory requirements. The drug storage area at the site must be secure, with access limited to authorized personnel.

Stability studies to support drug storage conditions have been conducted by the Manufacturer or an affiliate. The Manufacturer will continue to monitor the stability of the study drug and the Sponsor will alert the site if a lot is nearing the end of its anticipated shelf life.

ARRY-382 capsules are to be stored at controlled room temperature (15°C to 30°C). Detailed instructions for storage and handling of investigational product will be provided in the Pharmacy Manual.

Pembrolizumab for injection (lyophilized powder) is to be stored under refrigeration at 2°C to 8°C (36°F to 46°F). Pembrolizumab injection (solution) is to be stored under refrigeration at 2°C to 8°C (36°F to 46°F) in the original carton to protect it from light.

6.1.4 Accountability and Return of Study Drug Supply

The Investigator or an approved representative (e.g., pharmacist) must maintain accurate records of dates and quantities of study drug received, to whom study drug is dispensed (patient-by-patient accounting), and accounts of any study drug accidentally or deliberately destroyed. The Investigator must retain all unused or expired study drug supplies until the study monitor has confirmed the accountability data. If a study site's policy prohibits holding study drug supplies for monitor review, then a copy of the standard operating procedure (SOP) for processing drug returns must be provided to the Sponsor.

To ensure adequate records, all study drug will be accounted for on a drug accountability inventory form as instructed by the Sponsor. Instructions for processing all unused or expired study supplies will be included in the Pharmacy Manual.

6.2 Study Drug Dispensing and Administration

6.2.1 ARRY-382

ARRY-382 oral capsules will be administered QD (approximately 24 ±2 hours) as a fixed dose either without food or after a light meal (e.g., breakfast) with approximately 240 mL of water. ARRY-382 should not be taken within 4 hours after a full meal because preliminary results

suggest a modest increase in exposure with larger meals (Section 2.2.2.2). Patients will be instructed not to crush study drug capsules.

The pharmacist or study nurse will ensure that the appropriate dosage is dispensed and will provide the patient with at least the appropriate number of capsules for the number of doses to be taken prior to the next scheduled visit.

Study site personnel will train the patient and/or the patient's caregiver on dosing procedures for the study drug. Patients will receive a diary to document self-administered dosing of study drug in each cycle to include the dose of study drug taken, the date and timing of dosing, if any doses were missed and the reason for the missed dose, and timing and type of meals eaten in relation to dosing. One diary will be provided per cycle. Patients will be instructed to return unused study drug and the patient diary to the site at each visit.

Complete dispensing instructions, dosing instructions (including the timing of study drug administration), dosing in relation to meals and instructions for missed doses will be provided in the Pharmacy Manual.

6.2.1.1 Part A

Patients with selected solid tumors in Part A will receive oral doses of single-agent ARRY-382 capsules in combination with pembrolizumab. Planned dose levels of ARRY-382 are 200 mg QD and 400 mg QD; the dose escalation scheme is described in Section 4.1.

6.2.1.2 Phase 2

Patients in the Phase 2 cohorts (PD-1/PD-L1 Inhibitor Refractory, prOVCA and PDA) will receive oral doses of ARRY-382 capsules at 300 mg QD, the MTD/RP2D determined during Part A, in combination with pembrolizumab.

6.2.2 Pembrolizumab

For Part A: Pembrolizumab 2 mg/kg will be administered by study site personnel as an iv infusion over 30 minutes Q3W. The initial patient dose will be based on baseline body weight determined by the pharmacist. Dosing will be updated throughout the study based on body weight on Day 1 of each cycle or at a frequency determined by local practices.

For Phase 2: Pembrolizumab will be dosed at 200 mg and will be administered by study site personnel as an iv infusion over 30 minutes (within -5 to +10 minutes) Q3W.

6.3 Dose Modifications and Reductions

Doses of ARRY-382 and pembrolizumab may be modified throughout the study.

Cycle 1 Day 1 is defined as the first day of study drug treatment with both ARRY-382 and pembrolizumab. Per the schedule of events, cycles are defined as 21 days and pembrolizumab should be administered Q3W. In the event of temporary dose interruptions, the re-start of subsequent cycles may correspond with administration of either ARRY-382 or pembrolizumab. Doses of ARRY-382 withheld during a cycle will not be made up.

6.3.1 General Guidelines

If assessment of the toxicity can be clearly attributed to ARRY-382 or pembrolizumab, administration of the offending drug should be interrupted and the toxicity should be followed until resolution or return to baseline according to the respective dose modification guidelines described in Sections 6.3.2 and 6.3.3. Treatment with the other agent in the combination may continue without alterations.

If attribution of the toxicity cannot be clearly ascribed to either ARRY-382 or pembrolizumab, then both agents should be stopped and the toxicity should be followed until resolution or return to baseline. For patients with melanoma, long-term single-agent treatment with ARRY-382 is not recommended; if pembrolizumab is permanently discontinued for these patients, ARRY-382 may also be discontinued. In special circumstances, if a patient is benefitting from therapy, that patient may continue to receive single-agent ARRY-382 after discussion with the Sponsor.

If the toxicity recurs after a dose reduction, the process outlined above should be followed once again to determine attribution to either study drug or both study drugs.

6.3.2 ARRY-382

General guidelines for dose modifications of ARRY-382 are provided in Table 8. However, Investigators are to use their judgment when assessing the clinical significance of individual AEs.

Table 8: Recommended Dose Modifications for ARRY-382 Treatment-Related Adverse Events

Severity of Event	Action to be Taken
Grade 0-1	• Maintain ARRY-382 dose level and provide treatment to control symptoms, if applicable.
Grade 2	• Provide treatment to control symptoms, if applicable. If the symptoms cannot be controlled, withhold ARRY-382 until resolution or return to baseline. Then, resume at the original dose. • In the event of a persistent Grade 2 AE that is not responsive to treatment measures or that prevents the patient from resuming treatment, ARRY-382 treatment may be resumed at the next lower dose level. • In the event of irAEs: o At first occurrence, withhold ARRY-382 until resolution or return to baseline. Then, resume treatment with ARRY-382 at the same dose level. o At second occurrence, withhold ARRY-382 until resolution or return to baseline. Then resume treatment with ARRY-382 at the next lower dose level. o At third occurrence, discontinue ARRY-382.
Grade 3	• Withhold ARRY-382 until the AE recovers to resolution, or return to baseline. Then, resume treatment with ARRY-382 at the next lower dose level.[a] • In the event of a Grade 3 QTcF prolongation or > 60 msec increase in QTcF interval seen on ≥ 2 ECGs (on at least 2 separate ECGs). o At first occurrence, interrupt ARRY-382 until QTcF decreases below 500 msec. Then resume treatment at next lower dose level o At second occurrence, discontinue ARRY-382.
Grade 4	• Discontinue administration of ARRY-382[b]
Dose delay > 21 days due to AEs and not underlying disease progression, concomitant illness, or non-medical issues	• Discontinue administration of ARRY-382 (unless it is in the best interest of the patient to continue treatment, as judged by the Investigator)
ALT or AST elevations	• ALT or AST > 8 × ULN ≤ 20 × ULN (Grade 3) o Withhold ARRY-382. Resume treatment at the next lower dose level if ALT or AST resolves to Grade 1 or baseline (or ≤ 5 × ULN in presence of liver metastases) in ≤ 7 days o Discontinue ARRY-382 if ALT or AST > 8 × ULN for > 7 days • ALT or AST ≥ 5 × ULN and ≤ 8 × ULN (Grade 3) o Withhold ARRY-382. Resume treatment at the next lower dose level if ALT or AST resolves to Grade 1 or baseline in ≤ 14 days o Discontinue ARRY-382 if ALT or AST > 5 × ULN for > 14 days • ALT or AST > 3 × ULN and bilirubin levels ≥ 2 × ULN or an INR > 1.5 unless clearly attributable to disease progression o Discontinue ARRY-382 • ALT or AST >20 × ULN (Grade 4) o Discontinue ARRY-382

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; ECG = electrocardiogram; INR = international normalized ratio; irAE = immune-related adverse event; QTcF = QT interval corrected for heart rate using Fridericia's formula; ULN = upper limit of normal

[a] The following exceptions apply: 1) ARRY-382 should not be withheld for increased CK unless it is associated with an increase in creatinine ≥ 1.5 × the baseline value for creatinine OR until the CK increase remains ≥ Grade 3 for > 7 days. 2) In the event of Grade 3 nausea, vomiting or diarrhea, the patient can continue at the same dose of ARRY-382 if the patient is responsive to treatment measures.

[b] A patient with a Grade 4 AE may resume treatment at the next lower dose level if the AE recovers to Grade 0 or 1 and, if in the opinion of the Investigator and Sponsor, the patient can be monitored for recurrence of AE.

Patients should be evaluated weekly, at a minimum for nonlaboratory, ARRY-382-related toxicities until resolution or return to baseline, and then at least monthly until return to baseline, whichever comes first. For abnormal laboratory values that qualify as AEs, patients should be followed twice weekly until resolution or return to baseline.

Doses of ARRY-382 withheld during a cycle will not be made up. When a dose reduction is required because of AEs, no dose re-escalation will be permitted for the duration of study treatment.

For ARRY-382 dose modifications or reductions because of AEs in patients enrolled in Part A of the study, please refer to Table 6 in Section 4.1. Only 2 dose reductions (in 100 mg increments) are allowed in all patients in any study part/phase with 100 mg QD as the lowest possible dose.

6.3.3 Pembrolizumab

Pembrolizumab belongs to a class of cancer therapies commonly referred to as immune checkpoint inhibitors. Despite important clinical benefits, checkpoint inhibition is associated with a unique spectrum of side effects termed immune-related adverse events (irAEs) or, occasionally, AEs of special interest (Naidoo et al 2015; Champiat et al 2016). IrAEs include dermatologic, gastrointestinal, hepatic, endocrine, and other less common inflammatory events. IrAEs are believed to arise from general immunologic enhancement, and temporary immunosuppression with corticosteroids, tumor necrosis factor-alpha antagonists, mycophenolate mofetil, or other agents can be an effective treatment in most cases.

In general, treatment of moderate or severe requires interruption of the checkpoint inhibitor and the use of corticosteroid immunosuppression. Patients should be carefully monitored during treatment for initial evidence of Grade 1 AEs. Treatment is based upon the severity of the observed toxicity.

Instructions for monitoring and treating irAEs associated with pembrolizumab are described fully in the most current local Prescribing Information for Keytruda® (pembrolizumab). The Sponsor, or designee, will ensure that each site will be provided with the most current local

Prescribing Information for pembrolizumab. The Sponsor will notify applicable sites and distribute updated information as it is approved and becomes available in each country. Investigators should apply the guidelines within this document to treat patients experiencing an irAE(s) suspected to be due to pembrolizumab. These instructions include when and for how long to withhold pembrolizumab, when to reduce the dose of pembrolizumab and when pembrolizumab must be discontinued. If the Investigator has any questions on how to proceed with patient treatment for a pembrolizumab-associated irAE following review of the most current local pembrolizumab Prescribing Information, the Investigator should consult with their local medical monitor and/or the Sponsor.

6.4 Treatment Compliance

Compliance will be evaluated at each visit by a review of patient diary entries, an accounting of returned drug product, and patient interviews.

6.5 Prior and Concomitant Medications

6.5.1 Prior Treatments

All prior cancer treatments are to be recorded in the electronic case report form (eCRF). Other prior treatments (i.e., other than cancer treatments) taken within 4 weeks of screening should also be recorded.

6.5.2 Concomitant Medications

Unless specifically prohibited, concomitant medications can be administered at the Investigator's discretion to conform to standard practice during the treatment period. All concomitant medications are to be recorded on the eCRF using generic drug names when possible.

Antacids should be taken approximately 4 hours after administration of ARRY-382. The aqueous solubility of ARRY-382 is pH-dependent. Therefore, antacid medications (including proton pump inhibitors such as omeprazole, lansoprazole or esomeprazole) may decrease the absorption of ARRY-382.

Moderate or weak CYP3A4 inhibitors and inducers, and P-gp inhibitors and substrates should be used with caution as they may affect the clearance of ARRY-382 (see APPENDIX 4).

ARRY-382 is not a potent inhibitor or inducer of human CYP enzymes in isolated enzyme systems and its probability to interact with other medications that are substrates of CYP metabolism is expected to be low. However, Investigators should use normal caution when prescribing concomitant medications, as with any novel therapeutic for which there is limited clinical experience.

Investigators should contact the Sponsor when they are unsure whether a drug should be prescribed to a patient in the clinical study.

6.5.3 Prohibited Medications

The following therapies are prohibited during the study (unless otherwise noted):

- Chronic steroid therapy or immunosuppressive medication
  Note: Physiological replacement doses of hydrocortisone or its equivalent (i.e., up to 20 mg hydrocortisone [or 5 mg prednisone] in the morning and 10 mg hydrocortisone [or 2.5 mg prednisone] in the evening) will be allowed.

- Medications that may prolong the QT/QTc interval or induce torsades de pointes (see APPENDIX 2).

- Strong inhibitors or inducers of CYP3A

  In vitro drug metabolism studies suggest that ARRY-382 is a substrate of CYP3A and its systemic exposure may be affected by medications that are strong CYP3A inhibitors and inducers. Known strong inhibitors of CYP3A include, but are not limited to, ketoconazole, itraconazole, clarithromycin, erythromycin, grapefruit juice, troleandomycin, diltiazem, fluoxetine, and verapamil. Known inducers of CYP3A include, but are not limited to, rifampicin, phenytoin, carbamazepine, barbiturates, and St. John's Wort. For a more complete list of strong CYP3A inhibitors and inducers, see APPENDIX 2.

- Anticancer agents (e.g., cytotoxic chemotherapy, small-molecule targeted agents, biological agents, immune response modifiers or hormonal therapy)

- Herbal remedies

- Investigational drugs and devices

- Consult the most current local pembrolizumab Prescribing Information for possible other prohibited medications

7.0 STUDY PROCEDURES AND ASSESSMENTS

The procedures and assessments that will be conducted during this study are described in this section in narrative form, described by study visit in Section 8.0, and summarized in Table 10 and Table 11.

Written informed consent must be granted by each patient prior to the initiation of any study procedure or assessment (other than those considered standard of care).

7.1 Screening and Continued Eligibility Tests

7.1.1 Medical History/Disease History

Significant (at the Investigator's discretion) past and present medical history, including alcohol and nicotine history over the 3 months before screening, will be recorded. Any ongoing condition observed prior to the initiation of study treatment will be recorded.

Document cancer diagnosis, molecular alterations and extent of disease (i.e., stage at diagnosis and at study start and any previously determined biomarker data including germline or somatic mutation status, MSI status/MMR proficiency, tumor mutation burden level, PD-L1 status or any disease-specific gene expression subtype).

7.1.2 Pregnancy Tests

All females of childbearing potential are required to have a serum pregnancy test at Screening; serum or urine pregnancy tests will be allowed at subsequent time points specified in Table 10 and Table 11. Any positive test result will result in immediate cessation of study drug administration.

Patients of nonchildbearing potential do not require pregnancy tests. Women are considered not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy with hysterectomy or tubal ligation at least 6 weeks prior to Screening. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of childbearing potential.

All blood or urine collections for pregnancy tests occurring on dosing days must be performed prior to study drug administration.

7.1.3 Hepatitis Tests

Blood samples for testing of hepatitis B virus (HBV; HBsAg-reactive) and HCV serology (HCV RNA [qualitative] will be required if serology is positive) will be collected at screening.

7.1.4 Local and Retrospective Testing for PD-L1 Expression (Part A Patients with Non-Small Cell Lung Carcinoma Only)

Patients with NSCLC in Part A must have documentation of positive PD-L1 expression to be eligible for participation in the study. Testing should be performed locally on a fresh tumor biopsy (preferred) or the most recent archived tumor sample available. Instructions for obtaining the tissue sample will be provided in the Laboratory Manual.

If tests results documenting positive PD-L1 expression were not obtained using an FDA-approved test, then tumor tissue will be tested retrospectively using an FDA-approved test at a central laboratory.

7.1.5 Tumor and Blood Samples for Retrospective Testing of Tumor Genomic Alterations, Tumor Mutation Burden and/or Gene Expression Profiling (Phase 2 Only)

Patients in Phase 2 must have a fresh biopsy (preferred) or an archival tumor sample from the most recent sample available submitted to be eligible for participation in the study. This requirement may be waived under certain circumstances (e.g., sufficient archived tissue is no longer available and fresh specimen collection is deemed medically unsafe or not feasible by the Investigator due to the location of the tumor) after discussion and agreement between the Sponsor and the Investigator.

All patients in Phase 2 will have PD-L1 expression, tumor genomic alterations including microsatellite instability (MSI) status/MMR proficiency, tumor mutation burden and/or gene expression profiling obtained from patient records when available and will be confirmed by retrospective testing of the fresh or archived tumor specimen plus a blood sample at a central laboratory.

Information regarding tissue specimen requirements, preparation and shipment of tumor blocks or slides, and sample handling will be provided in the Laboratory Manual.

7.2 Efficacy Assessments

Tumor assessments will include imaging (e.g., CT, MRI, x-ray, fluorodeoxyglucose positron emission tomography [FDG-PET]) and caliper measurements, as applicable, and will be performed at the time points specified in Table 10 and Table 11.

Efficacy assessments include determination of objective response using RECIST v1.1. For patients who have initial evidence of radiological 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 ECOG PS, deteriorating clinical symptoms or rapid progression of disease/progression at critical anatomical sites (i.e., CNS) should be considered for treatment discontinuation based on clinical judgment.

All data acquired for efficacy purposes (e.g., CT, MRI, x-ray, FDG-PET, pathology reports, caliper measurements and measurements of tumor markers) obtained at Screening and while on study, including any off-schedule imaging studies performed, should be made available if requested by the Sponsor for central assessment by an independent reviewer.

7.2.1 Response Criteria in Solid Tumors

Response to treatment will be measured using RECIST v1.1 (APPENDIX 5), as assessed by the Investigators. Confirmation of CR and PR will be required by a repeat, consecutive assessment no less than 4 weeks from the date first documented.

7.2.2 Immune-Related Response Criteria

Response to treatment will also be measured using irRC (Wolchok et al 2009), as assessed by the Investigators. Confirmation of an immune-related complete response (irCR), immune-related partial response (irPR) and immune-related disease progression will be required by a repeat, consecutive assessment no less than 4 weeks from the date first documented. The details of the irRC assessment can be found in APPENDIX 6.

CC

7.3.1.3 Tumor Markers (Phase 2 Only)

Tumor markers, such as cancer antigen 19-9 (CA 19-9) and cancer antigen 125 (CA-125), will be measured as appropriate for tumor type from serum samples obtained from patients in Phase 2.

7.4 Pharmacokinetic Assessments

Venous blood samples for measurement of plasma concentrations of ARRY-382 and its metabolites (AR00469099 [an N-oxide metabolite], AR00469100 [an N-desmethyl metabolite], and AR00470870 [a sulfate metabolite]) will be drawn at the time points specified in Table 10 and Table 11. Pembrolizumab concentrations are not planned to be measured because no drug-drug interaction is expected. However, remaining PK plasma samples may be used to assess pembrolizumab concentrations, CCI or concomitant medications on an ad hoc basis. Complete instructions for sample collection, processing, handling and shipment will be provided in the Laboratory Manual.

Predose PK samples must be collected within 120 minutes prior to administration of ARRY-382. Postdose PK samples will be collected at 1 hr (±5 min), 2 hr (±10 min), 4 hr (±20 min), and 8 hr (±30 min) after administration of ARRY-382 on Cycle 1 Day 1 and Cycle 2 Day 1. Trough PK blood samples will be collected predose on Cycle 1 Day 15 and Day 1 of Cycles 3 through 6.

If a patient experiences an AE that results in an unscheduled visit or meets SAE criteria, a blood sample for measurement of plasma concentrations of ARRY-382 and its metabolites (AR00469099, AR00469100, and AR00470870) should be collected if less than 24 hours has elapsed since the last dose of study drug, if possible.

If vomiting occurs within 4 hours following study drug administration on the day of PK blood sampling, the time (using the 24-hour clock) of vomiting should be recorded on the transmittal forms that accompany the sample and that dose of study drug should not be re-administered.

7.5 Safety Assessments

7.5.1 Adverse Events

Adverse events will be assessed by direct observation and patient interviews. Patients should be questioned using non-leading questions. Assessment and reporting of AEs is described in detail in Section 10.0 and will be completed at the time points specified in Table 10 and Table 11.

7.5.2 Clinical Laboratory Tests

Clinical laboratory tests include hematology, coagulation, clinical chemistry, thyroid panel, and urinalysis (Table 9) and will be collected at the time points specified in Table 10 and Table 11. It is expected that local laboratories will be used for all protocol-specified and unscheduled laboratory tests related to safety. Depending on the availability of certain tests at local laboratories, some protocol-specified laboratory tests may be performed outside of local laboratories.

Table 9: Clinical Laboratory Tests

Hematology	Chemistry	Urinalysis	Others
Hemoglobin Hematocrit RBC Platelets WBC Neutrophils Lymphocytes Monocytes Eosinophils Basophils	BUN Urea Uric acid Creatinine Creatinine clearance[a] Total protein Albumin Alkaline phosphatase AST ALT Lactate dehydrogenase Total bilirubin Indirect bilirubin Direct bilirubin (if total bilirubin values are above normal) Amylase Lipase Aldolase CK CK isoenzymes[c] Glucose Sodium Potassium Chloride Bicarbonate Calcium Magnesium Phosphorus	Appearance Color Specific gravity pH Myoglobin[c] Protein Glucose Ketones Blood Nitrite Leukocyte esterase If urinalysis is abnormal, then microscopy: • WBC • RBC • Bacteria • Epithelial cells • Casts	• HBsAg and HCV serology (RNA, qualitative if serology positive) (screening only) • Serum or urine pregnancy test[b] (females of childbearing potential only)
Coagulation			
INR PT aPTT/PTT			
Thyroid Panel			
TSH T3, free T4, free			

ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatine kinase; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; INR = International Normalized Ratio; PT = prothrombin time; PTT=partial thromboplastin time; RBC = red blood cells; RNA = ribonucleic acid; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WBC = white blood cells

[a] Creatinine clearance will be calculated using the Cockcroft-Gault formula [(140 – age)*body mass (kg) / creatinine (mg/dL)*72]*0.85 for females or 1.00 for males.

[b] Serum pregnancy test required at screening only; serum or urine pregnancy tests will be allowed at subsequent time points.

[c] Measurement of CK isoenzymes and urine myoglobin only necessary if total CK is ≥ Grade 2, unless there are cardiac signs and symptoms. If cardiac signs and symptoms are present, measure CK isoenzymes and urine myoglobin if total CK is any grade above normal.

Site-specific handling instructions for hematology, coagulation, clinical chemistry, thyroid panel, and urinalysis samples should be followed. Screening results will be assessed by the Investigator to determine patient eligibility. Day 1 results (or assessments allowed within 96 hours prior to Day 1) will be assessed by the Investigator prior to first dose of study treatment; clinical chemistry and coagulation test results must be reviewed before the first dose of study drug is administered in each cycle. Additional clinical laboratory tests may be obtained at any time during the study at the Investigator's discretion. Clinically significant findings should be followed to resolution or stabilization.

Blood and urine sample collections on dosing days must be performed prior to study treatment administration. Laboratory test results required to make decisions regarding potential dose modifications (as specified in Section 6.3) should be reviewed prior to study treatment administration.

7.5.3 Physical Examination

Physical examinations, including weight, will be performed by trained medical personnel at the time points specified in Table 10 and Table 11. Height will be measured only at screening. All physical examinations occurring on dosing days must be performed prior to study drug administration.

7.5.4 Vital Signs

Vital signs (blood pressure, pulse, and temperature) will be measured per institutional standards at the time points specified in Table 10 and Table 11. Any treatment-emergent abnormal findings will be recorded as AEs.

7.5.5 Electrocardiogram

Triplicate 12-lead ECGs will be performed at the time points specified in Table 10 and Table 11. At each measurement, 3 serial ECGs will be obtained over a period of approximately 5 to 10 minutes. The mean of the triplicate ECG measurements performed at predose on Day 1 will serve as each patient's baseline value for all postdose comparisons.

In some cases, it may be appropriate to repeat an abnormal ECG. However, if the Investigator is able to interpret the ECG, then an abnormal ECG does not need to be repeated. When ECGs are to be performed at the same time point as a blood collection, ECGs should be performed first.

QT interval values will be corrected using Fridericia's formula (QTcF).

All ECGs will be submitted for central assessment.

7.6 Eastern Cooperative Oncology Group Performance Status

Assessment of ECOG PS (APPENDIX 1) will be conducted at the time points specified in Table 10 and Table 11.

8.0 SCHEDULE OF PROCEDURES AND ASSESSMENTS

Before recruitment of patients into the study, written Ethics Committee (EC) approval of the protocol, informed consent, and any additional patient information must be obtained.

During screening, the Sponsor will assign a unique number to each patient who provides written informed consent. Once a patient is in screening or is enrolled in the study, that patient will be identified only by the assigned patient number.

The Investigator or designee is responsible for verifying that the patient is eligible before requesting registration.

At the site, the Investigator will maintain a log for all screened patients (including patients who fail screening after providing written informed consent) and all enrolled patients.

Patients should be treated within 5 working days of the registration/enrollment date. The registration/enrollment date is the date that the Sponsor assigns a patient to a given dose level.

The procedures and assessments that will be conducted during this study are described in this section by study visit, described in narrative form in Section 7.0 and summarized in Table 10 and Table 11.

Any patients enrolled in previous Part C/Phase 2 should follow the Phase 2 procedures and assessments (Section 8.2.2) and schedule of events (Table 11).

8.1 Screening Evaluations

All screening procedures to determine eligibility must be performed within 28 days prior to the first dose of study treatment. Eligibility is determined by results of screening assessments performed prior to the first dose of study treatment and up to and including Cycle 1 Day 1. If a particular assessment is repeated, the results obtained closest to the first dose of study treatment should be used to assess eligibility.

Within 28 days of Day 1 dosing:

- Administration of written informed consent (must be obtained prior to performance of any study-specific tests or evaluations that are not considered standard of care)
- Demographics
- Medical history, including alcohol and nicotine use for the 3 months before screening, and disease history

- Verification of eligibility criteria
- Prior treatments, including all cancer treatments, and any other prior treatments (i.e., other than cancer treatments) taken within 4 weeks before screening
- Confirmation of positive PD-L1 expression for patients with NSCLC in Part A. Prior documentation of TPS ≥ 50%, or fresh tumor biopsy or most recent archived tumor tissue sample for local testing for PD-L1 expression.
  Note: If test results documenting positive PD-L1 expression for purposes of determining eligibility were not obtained using an FDA-approved test, then tumor tissue will be tested retrospectively using an FDA-approved test at a central laboratory.
- **All patients in Phase 2**: Obtain and send a fresh biopsy plus a blood sample, or the most recent archived tumor tissue sample available plus a blood sample to the central laboratory for testing of PD-L1 expression, MMR proficiency, tumor genomic alterations including MSI status and/or gene expression profiling.
- Tumor assessments, i.e., imaging (e.g., CT, MRI, x-ray, FDG-PET) and caliper measurements, as applicable

Within 14 days of Day 1 dosing:

- ECOG PS
- Physical exam, including body weight and height
- Vital signs, including blood pressure, pulse, and temperature
- Triplicate 12-lead ECG over a period of approximately 5 to 10 minutes
- Blood samples for the following tests:
  - Serum pregnancy test (females of childbearing potential only)
  - Hepatitis testing (HBV and HCV)
  - Clinical chemistry, thyroid panel, hematology, and coagulation
- Urine sample for urinalysis

8.2 Study Evaluations

8.2.1 Part A

8.2.1.1 Cycle 1

8.2.1.1.1 Cycle 1 Day 1

- Verification of eligibility criteria
- Updates to prior treatments
- ECOG PS (need not be repeated if performed within 96 hours before Cycle 1 Day 1)
- Physical exam, including body weight (need not be repeated if performed within 96 hours before Cycle 1 Day 1)
- Vital signs, including blood pressure, pulse, and temperature
- Triplicate 12-lead ECG over a period of approximately 5 to 10 minutes
    - Predose (need not be repeated if performed within 96 hours before Cycle 1 Day 1) and 4 hours postdose
- Serum or urine pregnancy test (females of childbearing potential only, need not be repeated if performed within 96 hours before Cycle 1 Day 1)
- Blood sample for the following tests:
    - Clinical chemistry, thyroid panel, hematology, and coagulation (need not be repeated if performed within 96 hours before Cycle 1 Day 1)
    - C [redacted] C I
    - Pharmacokinetics
        - Predose (i.e., within 120 minutes prior to administration of ARRY-382) and at 1, 2, 4, and 8 hours postdose
- Urine samples for the following tests:
    - Urinalysis (need not be repeated if performed within 96 hours before Cycle 1 Day 1)

[redacted]

- Administration/dispensing of ARRY-382
- Administration of pembrolizumab
- Review of concomitant medications
- Review of AEs

8.2.1.1.2 Cycle 1 Day 8 (± 1 Day)

- Blood sample for the following tests:
  - Clinical chemistry and hematology

[redacted]

- Administration/dispensing of ARRY-382
- Review of concomitant medications
- Review of AEs

8.2.1.1.3 Cycle 1 Day 15 (± 1 Day)

- Blood sample for the following tests:
  - Clinical chemistry and hematology

[redacted]

  - Pharmacokinetics, predose (i.e., within 120 minutes before administration of ARRY-382)

[redacted]

- Administration/dispensing of ARRY-382
- Review of concomitant medications
- Review of AEs

8.2.1.2 Subsequent Cycles

8.2.1.2.1 Subsequent Cycles Day 1 (± 2 days)

- ECOG PS
- Physical exam, including body weight
- Vital signs, including blood pressure, pulse, and temperature
- Serum or urine pregnancy test (females of childbearing potential only)
- Triplicate 12-lead ECG over a period of approximately 5 to 10 minutes (Cycle 2 only)
    - Predose and 4 hours postdose
- Single 12-lead ECG (all cycles subsequent to Cycle 2)
- Blood sample for the following tests:
    - Clinical chemistry, thyroid panel, hematology, and coagulation
    - [redacted]
    - Pharmacokinetics
        - Predose (i.e., within 120 minutes prior to administration of ARRY-382) and at 1, 2, 4, and 8 hours postdose (Cycle 2 only)
        - Predose (i.e., within 120 minutes prior to administration of ARRY-382) (Cycles 3, 4, 5, and 6)
- Urine samples for the following tests:
    - Urinalysis
    - [redacted]
- Tumor assessments, i.e., imaging (e.g., CT, MRI, x-ray, FDG-PET) and caliper measurements, as applicable (Cycle 3 Day 1 [± 7 days] and approximately every 6 weeks thereafter [e.g. Cycle 5 Day 1 [± 7 days], Cycle 7 Day 1 (± 7 days), etc.])
- Administration/dispensing of ARRY-382

- Administration of pembrolizumab
- Review of concomitant medications
- Review of AEs

8.2.1.2.2 Subsequent Cycles Day 15 (± 2 Days)*

- Blood sample for the clinical chemistry and hematology (Cycles 2, 3, and 4 only)
- Administration/dispensing of ARRY-382
- Review of concomitant medications
- Review of AEs

* For Cycles ≥ 5, on each Day 15 where only AEs and concomitant medications are assessed, a telephone call to the patient can substitute for a clinical visit. However, if the Investigator feels that there are AEs that need to be further assessed, a clinic visit may be warranted.

8.2.2 Phase 2

8.2.2.1 Cycle 1

8.2.2.1.1 Cycle 1 Day 1

- Verification of eligibility criteria
- Updates to prior treatments
- ECOG PS (need not be repeated if performed within 96 hours before Cycle 1 Day 1)
- Physical examination, including body weight (need not be repeated if performed within 96 hours before Cycle 1 Day 1)
- Vital signs, including blood pressure, pulse, and temperature
- Triplicate 12-lead ECG over a period of approximately 5 to 10 minutes
    - Predose (need not be repeated if performed within 96 hours before Cycle 1 Day 1) and 4 hours postdose

- Serum or urine pregnancy test (females of childbearing potential only, need not be repeated if performed within 96 hours before Cycle 1 Day 1)
- Blood sample for the following tests:
    - Clinical chemistry, thyroid panel, hematology, and coagulation (need not be repeated if performed within 96 hours before Cycle 1 Day 1)
    - [redacted]
    - [redacted]
    - Pharmacokinetics
        - Predose (i.e., within 120 minutes prior to administration of ARRY-382) and at 1, 2, 4, and 8 hours postdose
- Urine samples for the following tests:
    - Urinalysis (need not be repeated if performed within 96 hours before Cycle 1 Day 1)
    - [redacted]
- Administration/dispensing of ARRY-382
- Administration of pembrolizumab
- Review of concomitant medications
- Review of AEs

8.2.2.1.2 Cycle 1 Day 8 (± 1 Day)

- Blood sample for the following tests:
    - Clinical chemistry and hematology
    - [redacted]

[redacted]

- Administration/dispensing of ARRY-382
- Review of concomitant medications
- Review of AEs

8.2.2.1.3 Cycle 1 Day 15 (± 1 Day)

- Blood sample for the following tests:
  - Clinical chemistry and hematology
  - CCI [redacted]
  - CCI [redacted]
  - Pharmacokinetics, predose (i.e., within 120 minutes before administration of ARRY-382)
- CCI [redacted]
- Administration/dispensing of ARRY-382
- Review of concomitant medications
- Review of AEs

8.2.2.2 Subsequent Cycles

8.2.2.2.1 Subsequent Cycles Day 1 (± 2 days)

- ECOG PS
- Physical exam, including body weight
- Vital signs, including blood pressure, pulse, and temperature
- Serum or urine pregnancy test (females of childbearing potential only)
- Triplicate 12-lead ECG over a period of approximately 5 to 10 minutes (Cycle 2 only)
  - Predose and 4 hours postdose

- Single 12-lead ECG (all cycles subsequent to Cycle 2)
- Blood sample for the following tests:
  - Clinical chemistry, thyroid panel, hematology, and coagulation
  - [redacted]
  - Pharmacokinetics
    - Cycle 2 only: Predose (i.e., within 120 minutes prior to administration of ARRY-382) and at 1, 2, 4, and 8 hours postdose
    - Cycles 3, 4, 5 and 6: Predose (i.e., within 120 minutes prior to administration of ARRY-382)
- Urine samples for the following tests:
  - Urinalysis
  - [redacted]
- Tumor assessments, i.e., imaging (e.g., CT, MRI, x-ray, FDG-PET) and caliper measurements, as applicable (Cycle 3 Day 1 [± 7 days] and approximately every 6 weeks thereafter [e.g. Cycle 5 Day 1 [± 7 days], Cycle 7 Day 1 (± 7 days), etc.])
- Administration/dispensing of ARRY-382
- Administration of pembrolizumab
- Review of concomitant medications
- Review of AEs

8.2.2.2.2 Subsequent Cycles Day 15 (± 2 Days)*

- Blood sample for the clinical chemistry and hematology (Cycles 2, 3, and 4 only)
- Administration/dispensing of ARRY-382
- Review of concomitant medications

- Review of AEs

  * For Cycles ≥ 5, on each Day 15 where only AEs and concomitant medications are assessed, a telephone call to the patient can substitute for a clinical visit. However, if the Investigator feels that there are AEs that need to be further assessed, a clinic visit may be warranted.

8.3 Treatment Discontinuation Visit (to be completed within 2 weeks after treatment discontinuation or prior to the initiation of subsequent anticancer therapy, whichever occurs first)

- ECOG PS
- Physical exam, including body weight
- Vital signs, including blood pressure, pulse, and temperature
- Single 12-lead ECG
- Serum or urine pregnancy test (females of childbearing potential only)
- Blood sample for the following tests:
  - Clinical chemistry, thyroid panel, hematology, and coagulation

CCI [redacted]

- Urine sample for the following tests:
  - Urinalysis

CCI [redacted]

- Review of concomitant medications
- Review of AEs

8.4 30-Day (± 3 Days) Safety Follow-up Visit

All patients will return for a 30-Day Safety Follow-up Visit approximately 30 days after the last dose of study treatment or prior to the initiation of subsequent anticancer therapy, whichever occurs first.

- ECOG PS
- Physical exam, including body weight
- Vital signs, including blood pressure, pulse, and temperature
- Serum or urine pregnancy test (females of childbearing potential only)
- Blood sample for the following tests:
    - Clinical chemistry, thyroid panel, hematology, and coagulation
- Urine sample for urinalysis
- Review of AEs

Additional safety assessments may be performed to monitor any safety concerns identified at the treatment discontinuation visit. If the treatment discontinuation visit was performed ≥ 21 days from last dose of study drug, the 30-day safety follow-up visit does not need to be performed.

8.5 Follow-up Visits for Disease Progression

Tumor assessments are to be performed only if clinically indicated after the 30-day safety follow-up visit. Patients who discontinue study treatment for a reason other than disease progression should be encouraged to continue with tumor assessments every 8 weeks ± 1 week until disease progression as determined by the Investigator, withdrawal of consent, initiation of subsequent anticancer therapy, the patient is lost to follow-up, or death, whichever occurs first.

8.6 Monitoring for Survival Status

After patients have completed all other follow-up visits (i.e., 30-day safety follow-up visit or follow-up visits for disease progression), they will be contacted via telephone or electronic means every 3 months (Q3M; ± 2 weeks) for survival status for 1 year after the date of the last patient's first visit. During this follow-up period, any subsequent anticancer therapies should be recorded in the eCRF.

8.7 Collection of Data for Ongoing Patients Following Database Lock

If the primary objective of the study has been met or the Sponsor decides to stop the study early, the database may be locked for the purpose of analyzing and reporting data. Patients may continue to receive study treatment per protocol beyond database lock if the Investigator and the Sponsor agree that patients' best interests are served by continuing to receive study treatment. In patients who continue on study treatment, the Sponsor may decide to only follow for safety (i.e., collect only SAE information, not require any study-specific procedures, and mandate that patients be followed according to standard of care), where allowable per local laws or jurisdictions.

Table 10: Schedule of Events (Part A/Phase 1b)

Procedure or Assessment	Screening		Treatment					Follow-up			
			Cycle 1 Day			Subsequent cycles Day					
	(–28 to –1)	(–14 to –1)	1	8 (± 1)	15 (± 1)	1 (± 2)	15 (± 2)	Treatment Discontin-uation (within 2 weeks)	30-day Safety (± 3 days)[a]	For Progression Q8W (± 1 week)	For Survival Q3M (± 2 weeks)
Informed consent	x										
Demographics	x										
Medical history[b]	x										
Eligibility criteria	x		x								
Prior treatments[c]	x		x								
ECOG PS		x	x[d]			x		x	x		
Physical exam, including body weight		x[e]	x[d]			x		x	x		
Vital signs[f]		x	x			x		x	x		
Pregnancy test[g]		x	x[d]			x		x	x		
Tumor biopsy/archived tumor tissue sample for PD-L1 expression[h]	x										
HBsAg, HCV RNA (qualitative)		x									
Triplicate 12-lead ECG[i]		x	x[d]			x[j]					
Single 12-lead ECG						x[k]		x			
Clinical chemistry		x	x[d]	x	x	x	x[l]	x	x		
Thyroid panel		x	x[d]			x		x	x		
Hematology		x	x[d]	x	x	x	x[l]	x	x		
Coagulation		x	x[d]			x		x	x		

	Screening		Treatment					Follow-up			
			Cycle 1			Subsequent cycles					
			Day			Day					
Procedure or Assessment	**(–28 to –1)**	**(–14 to –1)**	**1**	**8 (± 1)**	**15 (± 1)**	**1 (± 2)**	**15 (± 2)**	**Treatment Discontin-uation (within 2 weeks)**	**30-day Safety (± 3 days)[a]**	**For Progression Q8W (± 1 week)**	**For Survival Q3M (± 2 weeks)**
Urinalysis		x	x[d]			x		x	x		
CCI [redacted]			[redacted]	[redacted]	[redacted]	[redacted]		[redacted][n]			
CCI [redacted]			[redacted]	[redacted]	[redacted]	[redacted]		[redacted]			
Tumor assessments[o]	x					x[p]				x[q]	
PK Blood sample			x[r]		x[s]	x[r,s]					
Administer/dispense ARRY-382			Daily			Daily					
Administer pembrolizumab			x[u]			x[u]					
AEs			Review on ongoing basis					x	x		
Concomitant medications			Review on ongoing basis					x			
Survival status/subsequent anticancer therapies											x[t]

AE = adverse event; CT = computed tomography; CSF-1 = colony-stimulating factor 1; CCI [redacted] ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; FDA = United States Food and Drug Administration; FDG-PET = fluorodeoxyglucose positron emission tomography; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; MRI = magnetic resonance imaging; NSCLC = non–small-cell lung cancer; CCI [redacted] PD-L1 = programmed cell death ligand 1; PK = pharmacokinetic; Q3M = every 3 months; Q8W = every 8 weeks; RNA = ribonucleic acid; TPS = tumor proportion score; CCI [redacted]

a. The 30-day safety follow-up visit should occur 30 days (± 3 days) after last dose of study treatment. Additional safety assessments may be performed at the 30-day safety follow-up visit to monitor any safety concerns identified at the treatment discontinuation visit.
b. Medical history includes alcohol and nicotine history over the 3 months before screening.
c. All prior cancer treatments are to be recorded; other prior treatments (i.e., other than cancer treatments) taken within 4 weeks of screening should also be recorded.

d. These assessments do not need to be repeated if they were performed within 96 hours of Cycle 1 Day 1. For the triplicate 12-lead ECG, the predose assessment need not be repeated if it was performed within 96 hours of Cycle 1 Day 1, but the assessment at 4 hours postdose (± 10 minutes) must be performed regardless of when the predose assessment was performed.
e. Physical examination includes height at screening only.
f. Vital signs include blood pressure, pulse, and temperature.
g. For females of childbearing potential only (see Section 7.1.2), serum pregnancy tests are to be performed at screening; serum or urine pregnancy tests will be allowed at subsequent time points.
h. For patients with NSCLC only, if documentation of positive PD-L1 expression is not already available (TPS ≥ 50%), tumor tissue from a fresh biopsy (preferred) or most recent archived tumor tissue sample available will be tested locally for determination of PD-L1 expression for purposes of eligibility. If test results for PD-L1 expression were not obtained using an FDA-approved test, tumor tissue will be tested retrospectively using an FDA-approved test at a central laboratory.
i. Three 12-lead ECGs are to be performed over a period of approximately 5 to 10 minutes. Triplicate 12-lead ECGs will be performed at predose and 4 hours (± 10 minutes) for all postbaseline assessments.
j. For subsequent cycles, triplicate 12-lead ECGs are to be performed on Day 1 of Cycle 2 only.
k. Single 12-lead ECGs will be performed beginning on Cycle 3 Day 1 and Day 1 of subsequent cycles.
l. Clinical chemistry and hematology tests are to be performed on Day 15 of Cycles 2, 3, and 4 only. After Cycle 4, the Day 15 visit can be replaced with a telephone call to assess AEs and concomitant medications.

CCI [redacted]

o. Tumor assessments include imaging (e.g., CT, MRI, x-ray, FDG-PET) and caliper measurements, as applicable.
p. Tumor assessments are to be performed on Cycle 3 Day 1 (± 7 days) and approximately every 6 weeks thereafter [e.g., Cycle 5 Day 1 (± 7 days), Cycle 7 Day 1 (± 7 days), etc.].
q. Tumor assessments are to be performed only if clinically indicated. Patients who discontinue the study for a reason other than disease progression should be encouraged to continue with tumor assessments every 8 weeks ± 1 week until disease progression as determined by the Investigator, withdrawal of consent, initiation of subsequent anticancer therapy, the patient is lost to follow-up, or death, whichever occurs first.
r. Predose PK blood samples must be collected within 120 minutes prior to administration of ARRY-382. Postdose PK samples will be collected at 1hr (±5 min), 2hr (±10 min), 4hr (±20 min), and 8hr (±30 min) after administration of ARRY-382 on Cycle 1 Day 1 and Cycle 2 Day 1.
s. Trough PK blood samples will be collected predose (i.e., within 120 minutes before administration of ARRY-382) on Cycle 1 Day 15 and Day 1 of Cycles 3 through 6. If ARRY-382 is being held, the trough PK blood sample should still be collected.
t. Patients are to be contacted via telephone or electronic means for survival status and any subsequent anticancer therapies for 1 year after the date of the last patient's first visit.
u. Pembrolizumab should be administered Q3W according to instructions in Section 6.2.2.

Table 11: Schedule of Events (Phase 2)

Procedure or Assessment	Screening		Treatment					Follow-up			
			Cycle 1 Day			Subsequent cycles Day					
	(–28 to –1)	(–14 to –1)	1	8 (± 1)	15 (± 1)	1 (± 2)	15 (± 2)	Treatment Discontin-uation (within 2 weeks)	30-day Safety (± 3 days)[a]	For Progression Q8W (± 1 week)	For Survival Q3M (± 2 weeks)
Informed consent	x										
Demographics	x										
Medical history[b] / Disease history	x										
Eligibility criteria	x		x								
Prior treatments[c]	x		x								
ECOG PS		x	x[d]			x		x	x		
Physical exam, including body weight		x[e]	x[d]			x		x	x		
Vital signs[f]		x	x			x		x	x		
Pregnancy test[g]		x	x[d]			x		x	x		
Fresh tumor biopsy and blood sample or archived tumor tissue and blood sample[h]	x										
Hepatitis testing (HBV and HCV)		x									
Triplicate 12-lead ECG[i]		x	x[d]			x[j]					
Single 12-lead ECG						x[k]		x			
Clinical chemistry		x	x[d]	x	x	x	x[l]	x	x		
Thyroid panel		x	x[d]			x		x	x		
Hematology		x	x[d]	x	x	x	x[l]	x	x		

	Screening		Treatment					Follow-up			
			Cycle 1			Subsequent cycles					
			Day			Day					
Procedure or Assessment	**(–28 to –1)**	**(–14 to –1)**	**1**	**8 (± 1)**	**15 (± 1)**	**1 (± 2)**	**15 (± 2)**	**Treatment Discontin-uation (within 2 weeks)**	**30-day Safety (± 3 days)[a]**	**For Progression Q8W (± 1 week)**	**For Survival Q3M (± 2 weeks)**
Coagulation		x	x[d]			x		x	x		
Urinalysis		x	x[d]			x		x	x		
CCI [redacted]			[redacted]		[redacted]	[redacted]					
[redacted]			[redacted]	[redacted]	[redacted]	[redacted]		[redacted]			
CCI [redacted]			[redacted]	[redacted]	[redacted]	[redacted]		[redacted]			
Tumor assessments[o]	x					x[p]				x[q]	
PK Blood sample			x[r]		x[s]	x[r,s]					
Administer ARRY-382			Daily			Daily					
Administer pembrolizumab			x[u]			x[u]					
AEs			Review on ongoing basis					x	x		
Concomitant medications			Review on ongoing basis					x			
Survival status/subsequent anticancer therapies											x[t]

AE = adverse event; CT = computed tomography; CSF-1 = colony-stimulating factor 1; CCI [redacted] ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; FDA = United States Food and Drug Administration; FDG-PET = fluorodeoxyglucose positron emission tomography; HBV = hepatitis B virus; HCV = hepatitis C virus; MRI = magnetic resonance imaging; CCI [redacted] NSCLC = non–small cell lung cancer; CCI [redacted] PD-L1 = programmed cell death ligand 1; PK = pharmacokinetic; Q3M = every 3 months; Q3W = every 3 weeks; Q8W = every 8 weeks; CCI [redacted]

a. The 30-day safety follow-up visit should occur 30 days (± 3 days) after last dose of study treatment. Additional safety assessments may be performed at the 30-day safety follow-up visit to monitor any safety concerns identified at the treatment discontinuation visit.

b. Medical history includes alcohol and nicotine history over the 3 months before screening.
c. All prior cancer treatments are to be recorded; other prior treatments (i.e., other than cancer treatments) taken within 4 weeks of screening should also be recorded.
d. These assessments do not need to be repeated if they were performed within 96 hours of Cycle 1 Day 1. For the triplicate 12-lead ECG, the predose assessment need not be repeated if it was performed within 96 hours of Cycle 1 Day 1, but the assessment at 4 hours postdose must be performed regardless of when the predose assessment was performed.
e. Physical examination includes height at screening only.
f. Vital signs include blood pressure, pulse, and temperature.
g. For females of childbearing potential only (see Section 7.1.2), serum pregnancy tests are to be performed at screening; serum or urine pregnancy tests will be allowed at subsequent time points.
h. All patients are to have a fresh biopsy plus a blood sample obtained at screening, or submit archived tumor samples from the most recent sample available plus a blood sample. The requirement of tumor tissue may be waived only with Sponsor approval (see Section 7.1.5).
i. Three 12-lead ECGs are to be performed over a period of approximately 5 to 10 minutes. Triplicate 12-lead ECGs will be performed at predose and 4 hours (± 10 minutes) for all postbaseline assessments.
j. For subsequent cycles, triplicate 12-lead ECGs are to be performed on Day 1 of Cycle 2 only.
k. Single 12-lead ECGs will be performed on Cycle 3 Day 1 and Day 1 of subsequent cycles.
l. Clinical chemistry and hematology tests are to be performed on Day 15 of Cycles 2, 3, and 4 only. For Cycles ≥ 5, the Day 15 visit can be replaced with a telephone call to assess AEs and concomitant medications.
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o. Tumor assessments include imaging (e.g., CT, MRI, x-ray, FDG-PET) and caliper measurements, as applicable.
p. Tumor assessments are to be performed on Cycle 3 Day 1 (± 7 days) and approximately every 6 weeks thereafter (e.g., Cycle 5 Day 1 [± 7 days], Cycle 7 Day 1 [± 7 days], etc.).
q. Tumor assessments are to be performed only if clinically indicated. Patients who discontinue the study for a reason other than disease progression should be encouraged to continue with tumor assessments every 8 weeks ± 1 week until disease progression as determined by the Investigator, withdrawal of consent, initiation of subsequent anticancer therapy, the patient is lost to follow-up, or death, whichever occurs first.
r. Predose PK blood samples must be collected within 120 minutes prior to administration of ARRY-382. Postdose PK samples will be collected at 1hr (±5 min), 2hr (±10 min), 4hr (±20 min), and 8hr (±30 min) after administration of ARRY-382 on Cycle 1 Day 1 and Cycle 2 Day 1. Postdose PK samples should not be collected if ARRY-382 is on hold.
s. Trough PK blood samples will be collected predose (i.e., within 120 minutes before administration of ARRY-382) on Cycle 1 Day 15 and Day 1 of Cycles 3 through 6. If ARRY-382 is being held, the trough PK blood sample should still be collected.
t. Patients are to be contacted via telephone or electronic means for survival status and any subsequent anticancer therapies for 1 year after the date of the last patient's first visit.
u. Pembrolizumab should be administered Q3W according to instructions in Section 6.2.2.

9.0 STUDY DISCONTINUATION

9.1 Sponsor Discontinuation Criteria

This study may be discontinued at any time due to safety concerns, failure to meet expected enrollment goals, administrative reasons, or at the discretion of the Sponsor. Should the study be terminated prematurely, the Sponsor will provide written notification to all Investigators and regulatory authorities and will specify the reason(s) for early termination. The Investigator must inform the Institutional Review Board (IRB) promptly and provide the reason(s) for the termination.

9.2 Treatment Discontinuation for Individual Patients

Patients may withdraw their consent to participate in the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. If a patient withdraws consent, the date and stated reason for consent withdrawal should be documented. Patient data collected up to the date of consent withdrawal will be included in the analyses. Any blood or tissue samples collected up to the date of consent withdrawal will be analyzed.

Wherever possible, the tests and evaluations listed for the Treatment Discontinuation Visit should be carried out and efforts should be made to continue follow-up. The Sponsor should be notified of all study withdrawals through the designated eCRFs in a timely manner.

Patients meeting any of the following criteria should discontinue study drug treatment:

- Withdrawal of consent (no further participation and thus no further protected health information may be collected)
- Patient decision to discontinue study treatment (but agree to return for treatment discontinuation assessments (Section 8.3), safety follow-up (Section 8.4) and/or additional follow-up, if applicable (Section 8.5 and Section 8.6)
- Unacceptable AEs or failure to tolerate study drug
  Note: For patients with melanoma, single-agent treatment with ARRY-382 is not recommended; if pembrolizumab is permanently discontinued for these patients, ARRY-382 must also be discontinued.
- Delay of > 21 days to start a subsequent treatment cycle unless judged by the Investigator to be in the best interest of the patient to continue treatment
- Changes in the patient's condition or development of an intercurrent illness which renders the patient unacceptable for further treatment in the judgment of the Investigator
- Disease progression, as determined by the Investigator

- Patient becomes pregnant or begins breastfeeding
- Significant protocol deviation that, in the opinion of the Investigator and/or Sponsor, renders the patient unsuitable for further study drug administration
- Lost to follow-up
- Discretion of Investigator
- Termination of the study by the Sponsor (described in Section 9.1)

9.3 Replacement of Patients

For Part A, patients will be replaced if they have received less than 67% dose intensity [(administered dose in mg/planned dose in mg) × 100] of ARRY-382 or if they did not receive pembrolizumab for any reason other than an AE or abnormal laboratory value that is not related to disease, disease progression, intercurrent illness or concomitant medications/therapies before completing Cycle 1.

For the Phase 2 PD-1/PD-L1 Inhibitor Refractory cohort, patients who discontinue prior to study completion will not be replaced.

For the Phase 2 prOVCA and PDA cohorts, additional patients will be enrolled to account for those who are found to be MSI-H/dMMR in order to evaluate the targeted patient population and to satisfy the Simon's 2-stage design.

10.0 SAFETY MONITORING: DEFINITIONS AND REPORTING

10.1 Adverse Event

An AE is defined as any untoward medical occurrence, including the exacerbation of a pre-existing condition, in a patient administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

10.1.1 Events Related to Progression of Disease

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors) will be designated as progression of disease in the eCRF and should not be reported as an AE or SAE unless a causal relationship to study drug is suspected.

10.1.2 Clinical Laboratory Abnormalities

An abnormal laboratory value that is not associated with an already reported AE is to be recorded as an AE only if an action on the study drug is made as a result of the abnormality, if intervention for management of the abnormality is required, or at the discretion of the Investigator.

Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or baseline, or per Investigator discretion.

10.1.3 Overdose

An overdose of study drug (whether symptomatic or asymptomatic) will be reported as an AE.

10.2 Assessment of Severity

The severity rating of an AE refers to its intensity. The severity of each AE will be determined by the Investigator using the National Cancer Institute (NCI) CTCAE, version 4.03 (US Department of Health and Human Services 2010). For any term that is not specifically listed in the CTCAE scale, severity should be assigned a grade of 1 through 5 using the following CTCAE guidelines:

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

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Fatal

10.3 Assessment of Causality

An assessment of causal relationship of study drug to each AE must be performed by the Investigator. Medical judgment should be used to determine the cause of the AE, considering all relevant factors such as (but not limited to) the underlying study indication, coexisting disease, concomitant medication, relevant history, pattern of the AE, temporal relationship to the study medication and de-challenge or re-challenge.

Yes (possibly, probably or definitely related): there is a reasonable possibility that the study drug caused the event; 1 or more of the following criteria apply:

- The event follows a reasonable temporal sequence from administration of study drug.
- The event could not be reasonably attributed to the known characteristics of the patient's clinical state, environmental or toxic factors or other modes of therapy administered to the patient.
- The event follows a known pattern of response to study drug.
- The event disappears or decreases on cessation or reduction in dose of the study drug. (It should be noted that in some situations an AE will not disappear or decrease in intensity upon discontinuation of study drug despite other clear indications of relatedness).
- The event reappears or worsens when the study drug is re-administered.

No (unlikely, probably not related or definitely not related): there is no reasonable possibility that the study drug caused the event; 1 or more of the following criteria apply:

- The event does not follow a reasonable temporal sequence from administration of study drug.

- The event could be reasonably attributed to the known characteristics of the patient's clinical state, concurrent illness, environment or toxic factors or other modes of therapy administered to the patient.

- The event does not follow a known pattern of response to study drug.

- The event does not disappear or decrease on cessation or reduction in dose of the study drug, and it does not reappear or worsen when the study drug is re-administered.

10.4 Assessment of Seriousness

An AE is considered "serious" if it results in any of the following outcomes:

- Results in death

    - Death is an outcome of an SAE and not an SAE in itself. When death is an outcome, the event(s) resulting in death should be reported (e.g., "pulmonary embolism" with a fatal outcome) and assigned severity Grade 5.

    - Death should only be reported as an SAE term when no additional information is known about a fatal event.

- Is immediately life-threatening (its occurrence places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death)

- Requires inpatient hospitalization or prolongation of existing hospitalization

    Note: Hospitalization includes any hospital admission, even if for less than 24 hours. The following <u>do not</u> meet hospitalization serious criteria:

    - A visit to the emergency room, or outpatient observation that does not result in admission

    - Elective surgery, planned prior to signing consent

    - Routine health assessment requiring admission

- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- Is a congenital anomaly/birth defect

- Based upon appropriate medical judgment, represents an important medical event that may jeopardize the patient or may require intervention to prevent one of the outcomes described above

10.5 Reporting of Serious and Nonserious Adverse Events

All AEs, serious and nonserious (including the exacerbation of a pre-existing condition) and regardless of causality to study drug will be fully recorded on the appropriate eCRF. For each AE, the Investigator must provide its duration (start and end dates or ongoing), severity (intensity), assessment of causality, whether specific action or therapy was required, and whether action was taken with regard to study drug treatment.

Any AE that occurs from the signing of the informed consent until the first dose of study drug is to be recorded on the AE eCRF only if the event was related to a study procedure. All other AEs/findings prior to the first dose of study drug should be recorded on the medical history eCRF. All AEs occurring from the first dose of study drug until 30 days after the last dose of study drug must be recorded on the AE eCRF, regardless of causal relationship to investigational product. SAEs occurring greater than 30 days after the last dose of study drug should be reported only if considered related to investigational product.

In addition to recording SAEs on the AE eCRF, all SAEs must be reported to the Sponsor within 24 hours of the Investigator's knowledge by faxing the completed SAE form to the Sponsor at the number provided on the SAE form or fax cover sheet. If new information becomes available for a previously reported SAE, a follow-up SAE report should be sent within 24 hours.

Investigators must follow patients with AEs/SAEs until the event has resolved, the condition has stabilized, withdrawal of consent, the patient is lost to follow-up or death OR until 30 days after the last dose of study drug, whichever occurs first. Ongoing treatment-related SAEs may be followed beyond this time period if clinically indicated.

10.6 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

Suspected unexpected serious adverse reactions (SUSARs) will be collected and reported by the Sponsor and/or designee to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

10.7 Pregnancy or Drug Exposure During Pregnancy

If a patient becomes pregnant during the study, administration of study drug is to be discontinued immediately.

Pregnancies (both those of female patients and female partners of male patients) must be reported to the Sponsor or designee within 24 hours of the Investigator's knowledge using the pregnancy reporting form. All pregnancies will be followed through to outcome and the outcome must be reported to the Sponsor or designee using the pregnancy outcome form.

Pregnancies themselves are not considered AEs or SAEs. However, any AEs or SAEs occurring during pregnancy are to be reported following AE and SAE reporting guidelines.

10.8 Review of Safety Data

The Medical Monitor will be responsible for the ongoing review and evaluation of safety data, including AEs, laboratory data, and any other safety evaluations, throughout the duration of the study.

11.0 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

11.1 General Considerations

A detailed statistical analysis plan (SAP) will be prepared by the Sponsor or designee. This plan may modify the statistical methods outlined in the protocol; however, any major modifications of the primary endpoint definition or analysis (in any part of the study) will also be described in a protocol amendment.

11.1.1 Sample Size

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 AE or other event as described in 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 12 and Table 13, respectively.

Table 12: 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 13: 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%, versus alternative of 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 less 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.

11.1.2 Efficacy Analysis

11.1.2.1 Efficacy Analyses Using Response Criteria in Solid Tumors

Objective response using RECIST will be defined as CR + PR, as determined by the Investigator. Objective response rate is defined as the proportion of patients who achieve an objective response. The objective response rate along with exact 95% CIs (Clopper and Pearson 1934) will be reported.

Duration of response will be calculated for patients who achieve an objective response (i.e., CR or PR, as determined by the Investigator) and is defined as the time from the first documented response to the date of documented progression or death after achieving a response. If a patient has not had a PFS event at the time of the analysis cutoff or at the start of any new antineoplastic therapy, duration of response is censored at the date of last adequate tumor assessment. The survival distribution function for duration of response will be estimated using the Kaplan-Meier method.

Progression-free survival is defined as the time from the start of treatment to the time of first documented progression or death, whichever occurs first. If a patient has not had a PFS event at the time of the analysis cut-off or at the start of any new anti-neoplastic therapy, PFS is censored at the date of last adequate tumor assessment. The survival distribution function for PFS will be estimated using the Kaplan-Meier method.

Overall survival is defined as the time from the start of treatment 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 Kaplan-Meier method.

If the patient achieves a CR or PR and progression has not been documented and the patient is still alive at the time of analysis, the duration of response is censored on the date of the last tumor assessment.

11.1.2.2 Efficacy Analyses Using Immune-Related Response Criteria

Analyses of immune-related endpoints will be the same as those described for endpoints using RECIST (see Section 11.1.2.1).

Immune-related objective response is defined as irCR + irPR, as determined by the Investigator. Immune-related ORR is defined as the proportion of patients who achieve an objective response using the irRC.

Immune-related PFS will be defined as the time from the start of treatment until disease progression as determined by the Investigator, or death, whichever occurs first.

If the patient achieves an irCR or irPR and progression has not been documented and the patient is still alive at the time of analysis, the duration of response is censored on the date of the last tumor assessment.

CCI [redacted]

[redacted]

11.1.4 Pharmacokinetic Analysis

Plasma concentrations of ARRY-382 and metabolites, AR00469099, AR00469100, and AR00470870, will be determined using a validated bioanalytical method. Standard noncompartmental and/or compartmental PK parameters (e.g., C_{max} and area under the curve [AUC]) will be estimated for each patient. Descriptive statistics of PK parameters will be reported for each cohort and summarized. Dose proportionality, metabolite-to-parent ratio and drug accumulation will be assessed as appropriate. Other model-dependent PK analysis approaches (e.g., maximum a posteriori Bayesian parameter estimation, nonlinear mixed effects modeling) may also be applied to the data as appropriate. CCI [redacted]

CCI [redacted]

Parameters will include but are not limited to AUC_{τ}, C_{max}, T_{max}, C_{trough}, accumulation ratio, and metabolite-to-parent ratio.

CCI [redacted]

11.1.6 Safety Analysis

All patients who receive at least 1 dose of study drug will be included in the safety analyses.

Safety data will be presented in tabular and/or graphical format and summarized descriptively by treatment group and study day, where appropriate. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Incidence tables will be presented for DLTs, all AEs by maximum severity, SAEs, AEs assessed as related to study drug and AEs resulting in discontinuation of study drug. Dose-limiting toxicities will be listed for Part A. Changes in ECG and laboratory measurements will be summarized. Listings of all safety data sorted by treatment group, patient and assessment date will be provided.

12.0 DATA RECORDING, RETENTION AND MONITORING

12.1 Case Report Forms

Data will be collected using an electronic data capture system (EDC) at the clinical site. The Investigator or designee will record data specified in the protocol using eCRFs. Changes or corrections to eCRFs will be made by the Investigator or an authorized member of the study staff according to the policies and procedures at the site.

It is the Investigator's responsibility to ensure eCRFs are complete and accurate. Following review and approval, the Investigator will electronically sign and date the pages. This signature certifies that the Investigator has thoroughly reviewed and confirmed all data on the eCRF.

A portable document format (PDF) file of the eCRFs will be provided to the site after all data have been monitored and reconciled. An electronic copy will be archived at the site.

12.2 Data Monitoring

This study will be closely monitored by representatives of the Sponsor throughout its duration. Monitoring will include personal visits with the Investigator and study staff as well as appropriate communications by telephone, fax, mail, email or use of the EDC system, if applicable. It is the monitor's responsibility to inspect eCRFs at regular intervals throughout the study to verify the completeness, accuracy and consistency of the data and to confirm adherence to the study protocol and to Good Clinical Practice (GCP) guidelines. The Investigator agrees to cooperate with the monitor to ensure that any problems detected during the course of this study are resolved promptly. The Investigator and site will permit study-related monitoring, audits, EC review and regulatory inspection, including direct access to source documents.

It is understood that study monitors and any other personnel authorized by the Sponsor may contact and visit the Investigator and will be permitted to inspect all study records (including eCRFs and other pertinent data) on request, provided that patient confidentiality is maintained and that the inspection is conducted in accordance with local regulations.

Every effort will be made to maintain the anonymity and confidentiality of patients during this study. However, because of the experimental nature of this treatment, the Investigator agrees to allow representatives of the Sponsor as well as authorized representatives of regulatory authorities to inspect the facilities used in the conduct of this study and to inspect, for purposes of verification, the hospital or clinic records of all patients enrolled in the study.

12.3 Quality Control and Quality Assurance

Quality control procedures will be conducted according to the Sponsor's internal procedures. The study site may be audited by a quality assurance representative of the Sponsor. All necessary data and documents will be made available for inspection.

13.0 REGULATORY, ETHICAL AND LEGAL OBLIGATIONS

13.1 Good Clinical Practice

The study will be performed in accordance with the protocol, guidelines for GCP established by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and applicable local regulatory requirements and laws.

13.2 Ethics Committee Approval

The Investigator must inform and obtain approval from the EC for the conduct of the study at named sites, the protocol, informed consent documents and any other written information that will be provided to the patients and any advertisements that will be used. Written approval must be obtained prior to recruitment of patients into the study and shipment of study drug.

Proposed amendments to the protocol and aforementioned documents must be submitted to the Sponsor for review and approval, then to the EC. Amendments may be implemented only after a copy of the approval letter from the EC has been transmitted to the Sponsor. Amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented prior to receiving Sponsor or EC approval. However, in this case, approval must be obtained as soon as possible after implementation.

Per GCP guidelines, the Investigator will be responsible for ensuring that an annual update is provided to the EC to facilitate continuing review of the study and that the EC is informed about the end of the study. Copies of the update, subsequent approvals and final letter must be sent to the Sponsor.

13.3 Regulatory Authority Approval

The study will be performed in accordance with the requirements of each country's regulatory authorities, e.g., US FDA and will also meet all of the requirements of ICH GCP guidance. Amendments to the protocol will be submitted to the relevant authorities prior to implementation in accordance with applicable regulations.

13.4 Other Required Approvals

In addition to EC and regulatory authority approval, all other required approvals (e.g., approval from the local research and development board or scientific committee) will be obtained prior to recruitment of patients into the study and shipment of study drug.

13.5 Informed Consent

Informed consent is a process that is initiated prior to the patient's agreeing to participate in the study and continues throughout the patient's study participation. It is the Investigator's

responsibility (or designee) to obtain written informed consent from each patient after adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study and before any study procedures are initiated. Each patient should be given a copy of the informed consent document and associated materials. The original copy of the signed and dated informed consent document must be retained at the site and is subject to inspection by representatives of the Sponsor or regulatory authorities. If any amendments occur throughout the course of the study that affect the informed consent form (i.e., when new study procedures or assessments have been added), all active patients should be reconsented using the same process for the initial consent.

13.6 Patient Confidentiality

The Investigator must ensure that the patient's privacy is maintained. On the eCRF or other documents submitted to the Sponsor, patients will be identified by a patient number only. Documents that are not submitted to the Sponsor (e.g., signed informed consent documents) should be kept in a confidential file by the Investigator.

The Investigator shall permit authorized representatives of the Sponsor, regulatory authorities and ethics committees to review the portion of the patient's medical record that is directly related to the study. As part of the required content of informed consent documents, the patient must be informed that his/her records will be reviewed in this manner.

13.7 Disclosure of Information

Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The Investigator may use this information for the purposes of the study only.

It is understood by the Investigator that the Sponsor will use information obtained in this clinical study in connection with the clinical development program, and therefore may disclose it as required to other clinical Investigators and to regulatory authorities. In order to allow the use of the information derived from this clinical study, the Principal Investigator understands that he/she has an obligation to provide complete test results and all data obtained during this study to the Sponsor.

Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Sponsor.

13.8 Publication of Study Data

The conditions regulating dissemination of the information derived from this study are described in the Clinical Trial Agreement.

14.0 ADHERENCE TO THE PROTOCOL

Investigators must apply due diligence to avoid protocol deviations, and the Sponsor (and designee[s]) will not pre-authorize deviations. If the Investigator believes a change to the protocol would improve the conduct of the study, this must be considered for implementation in a protocol amendment. Protocol deviations will be recorded.

14.1 Amendments to the Protocol

Only the Sponsor may modify the protocol. Amendments to the protocol will be made only after consultation and agreement between the Sponsor and the Investigator. The only exception is when the Investigator considers that a patient's safety is compromised without immediate action. In these circumstances, immediate approval of the chairman of the EC must be sought, and the Investigator should inform the Sponsor and the full EC within 5 working days after the emergency occurred. All amendments that have an impact on patient risk or the study objectives or require revision of the informed consent document must receive approval from the EC prior to implementation.

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Appendix 1 Eastern Cooperative Oncology Group Performance Status

ECOG PS	Definition
0	Asymptomatic
1	Symptomatic, but fully ambulatory
2	Symptomatic, in bed less than 50% of the day
3	Symptomatic, in bed more than 50% of the day, but not bedridden
4	Bedridden
5	Dead

ECOG PS = Eastern Cooperative Oncology Group performance status

Appendix 2 Drugs with Risk of TDP/Potential to Prolong QT Interval and CYP3A Inhibitors/Inducers

DRUGS WITH RISK OF TORSADES DE POINTES/POTENTIAL TO PROLONG QT INTERVAL		
amiodarone	clarithromycin	[haloperidol]
arsenic trioxide	disopyramide	ibutilide
[astemizole]	dofetilide	[levomethadyl]
azithromycin	[domperidone]	mesoridazine
bepridil	droperidol	methadone
chlorpromazine	erythromycin	moxifloxacin
chloroquine	flecainide	pentamidine
[cisapride]	halofantrine	pimozide
citalopram		

Notes: Substantial evidence supports the conclusion that these drugs prolong QT intervals and have a risk of torsade de pointes when used as directed in labeling.

Drugs in brackets are not marketed in US.

STRONG CYP3A INHIBITORS AND INDUCERS		
Category	**Drugs**	
Strong CYP3A inhibitors	boceprevir clarithromycin cobicistat conivaptan elvitegravir indinavir itraconazole ketoconazole, lopinavir mibefradil	nefazodone nelfinavir, posaconazole ritonavir saquinavir telaprevir, telithromycin tipranavir troleandomycin voriconazole
Strong CYP3A inducers	avasimibe carbamazepine mitotane phenobarbital	phenytoin rifabutin rifampin (rifampicin) St. John's wort (hypericum perforatum)

Note: Compiled from the Indiana University School of Medicine “Clinically Relevant” Table, FDA Guidance for Industry, Drug Interaction Studies and the University of Washington Drug Interaction Database

Appendix 3 Child Pugh Classification

Measure	Points		
	1	**2**	**3**
Bilirubin (mg/dL)	<2.0	2.0-3.0	>3.0
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
PT (INR)	<1.7	1.7-2.3	>2.3
Ascites	Absent	Mild to moderate	Severe/refractory
Encephalopathy (grade)*	Absent	Mild (1-2)	Severe (3-4)

*Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity

Class A=5-6 points; Class B=7-9 points; Class C=10-15 points; Abbreviations: PT, prothrombin time; INR, International Normalized Ratio.

Schwartz M, Roayaie S, Konstadoulakis M. Strategies for the management of hepatocellular carcinoma. Nat Clin Pract Oncol 2007;424-32.

US Department of Health and Human Services, Food and Drug Administration. Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling. May 2003. Available from: <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072123.pdf> (Accessed on 06 November 2017).

Appendix 4 Concomitant Medications to Be Used with Caution

CONCOMITANT MEDICATIONS TO BE USED WITH CAUTION		
Category	**Drugs**	
P-gp inhibitors	amiodarone azithromycin captopril carvedilol clarithromycin conivaptan cyclosporine diltiazem dronedarone elacridar (GF120918) erythromycin felodipine fexofenadine fluvoxamine indinavir indinavir/ritonavir	itraconazole ketoconazole lopinavir/ritonavir mibefradil nelfinavir paroxetine quercetin quinidine ranolazine telaprevir saquinavir/ritonavir ticagrelo tipranavir/ritonavir valspodar (PSC 833) verapamil
P-gp inducers	avasimibe carbamazepine phenytoin	rifampin St John's wort tipranavir/ritonavir
Moderate CYP3A inhibitors	amprenavir aprepitant atazanavir atazanavir/ritonavir casopitant cimetidine ciprofloxacin crizotinib cyclosporine duranavir darunavir/ritonavir diltiazem dronedarone	erythromycin fluconazole fosamprenavir grapefruit juice imatinib lomitapide netupitant nilotinib schisandra sphenanthera tofisopam verapamil

CONCOMITANT MEDICATIONS TO BE USED WITH CAUTION (continued)		
Weak CYP3A inhibitors	almorexant alprazolam amiodarone amlodipine atorvastatin azithromycin berberine bicalutamide blueberry juice cilostazol cimetidine clotrimazole clozoxazone cranberry juice cyclosporine delavirdine evrolimus fluoxetine fluvoxamine fosaprepritantranolaxine ginkgo goldenseal	isoniazid ivacaftorlacipidine linagliptin nilotinib oral contraceptives pazopanib peppermint oil propiverine ranitidine ranolazine resveratrol roxithromycin Seville orange simeprevir tabimorelin tacrolimus ticagrelor tolvaptan sitaxentan teriflunomide tipranavir/ritonavir zileuton

Note: Compiled from the Indiana University School of Medicine “Clinically Relevant” Table, FDA Guidance for Industry, Drug Interaction Studies and the University of Washington Drug Interaction Database

Appendix 5 Response Criteria in Solid Tumors, Version 1.1

1.0 Response and Evaluation Endpoints

Response and progression will be evaluated in this study using the revised international criteria (1.1) proposed by the RECIST (Response Evaluation Criteria in Solid Tumors) committee.

1.1.1 Measurable Disease

Measurable tumor lesions are defined as those that can be accurately measured in at least 1 dimension (longest diameter to be recorded) as ≥ 20 mm with chest x-ray and as ≥ 10 mm with computerized tomography (CT) scan or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component > 10 mm by CT scan). Malignant lymph nodes must be ≥ 15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

1.1.2 Nonmeasurable Disease

All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

1.1.3 Target Lesions

When more than 1 measurable tumor lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. Note that pathological nodes must meet the criterion of a short axis of ≥ 15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered nonpathological and should not be recorded or followed. At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the eCRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

1.1.4 Nontarget Lesions

All nonmeasurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered non-target lesions. Measurements are not required but these lesions should be noted at baseline and should be followed as "present" or "absent".

1.1.5 Response

All patients will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): Disappearance of target and non-target lesions and normalization of tumor markers. Pathological lymph nodes must have short axis measures < 10 mm (Note: continue to record the measurement even if < 10 mm and considered CR). Residual lesions (other than nodes < 10 mm) thought to be non-malignant should be further investigated (by cytology or positron emission tomography [PET] scans) before CR can be accepted. To qualify as CR, CR must be confirmed by repeat disease assessment studies performed no less than 4 weeks after the criteria for response were first met to qualify as CR.

Partial Response (PR): At least a 30% decrease in the sum of measures (longest diameter for tumor lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non-target lesions must be non-PD. To qualify as PR, PR must be confirmed by repeat disease assessment studies performed no less than 4 weeks after the criteria for response were first met to qualify as CR.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥ 5 mm. Appearance of new lesions will also constitute progressive disease (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment or where the tumor burden appears to have increased by at least 73% in volume. Modest increases in the size of 1 or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or nontarget), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

Table 1: Integration of Target, Nontarget and New Lesions into Response Assessment

Target Lesions	Nontarget Lesions	New Lesions	Overall Response	Best Response for this Category also Requires
Target Lesions ± Nontarget lesions				
CR	CR	No	CR	Normalization of tumor markers, tumor nodes < 10 mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	Documented at least once ≥ 6 to 8 weeks from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Nontarget lesions ONLY				
No Target	CR	No	CR	Normalization of tumor markers, tumor nodes < 10 mm
No Target	Non-CR/non-PD	No	Non-CR/non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes	PD	

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.

For nonrandomized trials, where confirmation of response is required, best overall response can be interpreted as follows:

Table 2: Interpretation of Best Overall Response

Response: First Time Point	Subsequent Time Point	BEST Overall Response	Also Requires
CR	CR	CR	Normalization of tumor markers, tumor nodes < 10 mm
CR	PR	SD, PD or PR (see comment*)	
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD	
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD	
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE	
PR	CR	PR	
PR	PR	PR	
PR	SD	SD	
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD	
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE	
NE	NE	NE	

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease

* may consider PR providing initial "CR" likely PR on subsequent review – then original CR should be corrected. Recurrence of lesion after true CR is PD.

1.2 Response Duration

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

1.3 Stable Disease Duration

Stable disease duration will be measured from the time of start of treatment (or randomization for randomized studies) until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

1.4 Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy, which may be treatment-arm dependent. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. If feasible, imaging is preferred.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions > 20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans). While PET scans are not considered adequate to measure lesions, positron emission tomography-computerized tomography [PET-CT] scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with intravenous [iv] and oral contrast).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain).When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Appendix 6 Immune-Related Response Criteria in Solid Tumors

Response to treatment will be measured using immune-related response criteria (irRC),[1] which have been defined for use with immunotherapy.

To systematically characterize additional patterns of response in patients with advanced melanoma, underlying WHO criteria (hereafter referred to as RECIST) formed the basis for irRC.

Antitumor Response Based on Total Measurable Tumor Burden

For the irRC, only index and measurable new lesions are taken into account (in contrast to conventional RECIST, which does not require the measurement of new lesions, nor do they include new lesion measurements in the characterization of evolving tumor burden). At the baseline tumor, the sum of the products of the 2 largest perpendicular diameters (SPD) of all index lesions (5 lesions per organ, up to 10 visceral lesions and 5 cutaneous index lesions) is calculated. At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (≥5 x 5 mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total tumor burden:

$$\text{Tumor burden} = SPD_{\text{index lesions}} + SPD_{\text{new, measurable lesions}}$$

Use of tumor burden in irRC criteria is presented in Table A.

[1] Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15(23):7412-20.

Table A Definitions of Overall Responses

	irRC
New, measurable lesions (i.e., ≥5 x 5 mm)	Incorporated into tumor burden
New, nonmeasurable lesions (i.e., <5 x 5 mm)	Do not define progression (but preclude irCR)
Non-index lesions	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions in 2 consecutive observations not less than 4 weeks apart
PR	≥ 50% decrease in tumor burden compared with baseline in 2 observations at least 4 weeks apart
SD	>50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir
PD	At least 25% increase in tumor burden compared with nadir (at any single time point) in 2 consecutive observations at least 4 weeks apart

CR = complete response; irCR = complete response; irRC = immune-related response criteria; PD = progressive disease; PR = partial response; SD = stable disease

Time Point Response Assessment Using irRC

Percentage changes in tumor burden per assessment time point describe the size and growth kinetics of both conventional and new, measurable lesions as they appear. At each tumor assessment, the response in index and new, measurable lesions is defined based on the change in tumor burden (after ruling out immune-related progressive disease [irPD]). Decreases in tumor burden must be assessed relative to baseline measurements (i.e., the SPD of all index lesions at screening). The irRC were derived from RECIST and, therefore, the thresholds of response remain the same (Table B). However, the irRC response categories have been modified from those of RECIST, as detailed in Tables A and B.

Table B Derivation of Overall Responses Using Immune-Related Response Criteria

Measurable response	Nonmeasurable response		Overall response
Index and new measurable lesions (tumor burden),[a] %	Nonindex lesions	New nonmeasurable lesions	Using irRC
↓100	Absent	Absent	irCR[b]
ie	Stable	Any	irPR[b]
↓100	Unequivocal progression	Any	irPR[b]
↓≥50	Absent/stable	Any	irPR[b]
↓≥50	Unequivocal progression	Any	irPR[b]
↓<50 to <25↑	Absent/stable	Any	irSD
↓<50 to <25↑	Unequivocal progression	Any	irSD
≥25?	Any	Any	irPD[b]

↑ = increase in tumor burden; ↓ = decrease in tumor burden; irCR = immune-related complete response; irPD = immune-related progressive disease; irPR = immune-related partial response; irRC = immune-related response criteria; irSD = immune-related stable disease
[a] Decreases assessed relative to baseline, including measurable lesions only (>5 x 5 mm)
[b] Assuming response (i.e., irCR) and progression (i.e., irPD) are confirmed by a second, consecutive assessment at least 4 weeks apart.

Overall Response Using the irRC

The overall response according to the irRC is derived from time point assessment (based on tumor burden) as follows:

- irCR, complete disappearance of all lesions (whether measurable or not, and no lesions); confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented
- irPR, decrease in tumor burden ≥50% relative to baseline confirmed by a consecutive assessment at least 4 weeks after first documentation
- immune-related stable disease (irSD), not meeting criteria for irCR or irPR, in absence of irPD
- irPD, increase in tumor burden ≥25% relative to nadir (minimum recorded tumor burden); confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented

Patients are considered to have irPR or irSD even if new lesions are present, as long as they met the respective thresholds of response described above. Furthermore, patients are not considered to have irPD if new lesions are present and the tumor burden of all lesions did not increase by ≥25%. In contrast to irCR, irPR, and irPD, a response of irSD does not require confirmation. It is important to note that irCR, irPR, and irSD include all patients with CR, PR or SD by RECIST as well as those patients who shift to these irRC categories from RECIST PD. Patients with irSD, particularly those with slow-declining tumor burden ≥25% from baseline at the last tumor assessment, are considered clinically meaningful because they show an objectively measurable reduction in tumor burden without reaching the 50% threshold that defines irPR (ie, this represents an objectively measured reduction not commonly observed in the natural history of advanced melanoma patients).

If a patient is classified as having irPD at a postbaseline tumor assessment, then confirmation of irPD by a second scan in the absence of a rapid clinical deterioration is required. The definition of confirmation of progression represents an increase in tumor burden ≥25% compared with nadir at 2 consecutive time points at least 4 weeks apart. It is recommended that this be done at the discretion of the Investigator because follow-up with observation alone may not be appropriate for patients with a rapid decline in performance status. Confirmation of irPD allows for the capture of all observed responses using the irRC (Table B), as most of these late-responding patients have a trend toward response within 4 weeks after initial irPD. Whereas

RECIST consider any new measurable lesion to indicate PD, determination of immune-related best overall response (irBOR) is based on changes in total tumor burden from baseline (nadir, for irPD) tumor assessment, regardless of any initial increase in baseline lesions or the appearance of new lesions.