Protocol J2I-MC-JZMA(d)

A Phase 1 Multicenter Global First in Human Study of the CD73 Inhibitor LY3475070 as Monotherapy or in Combination with Pembrolizumab in Patients with Advanced Solid Malignancies

NCT04148937

Approval Date: 02-Sep-2020

Title Page

Protocol Title: A Phase 1 Multicenter Global First in Human Study of the CD73 Inhibitor LY3475070 as Monotherapy or in Combination with Pembrolizumab in Patients with Advanced Solid Malignancies

Protocol Number: J2I-MC-JZMA

Amendment Number: d

Compound Number: LY3475070

Study Phase: Early Phase 1

Short Title: A Phase 1 Study of the CD73 Inhibitor LY3475070 in Patients with Advanced Solid Malignancies

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana USA 46285

Regulatory Agency Identifier Number(s)

IND: 144903

EudraCT: 2019-003270-64

Approval Date: Protocol Electronically Signed and Approved by Lilly: 23-Aug-2019 GMT.
Protocol Amendment (a) Electronically Signed and Approved by Lilly on: 02-Oct-2019 GMT.
Protocol Amendment (b) Electronically Signed and Approved by Lilly on: 24-Feb-2020 GMT.
Protocol Amendment (c) Electronically Signed and Approved by Lilly on: 22-Mar-2020 GMT.
Protocol Amendment (d) Electronically Signed and Approved by Lilly on the date below.

Approval Date: 02-Sep-2020 GMT

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Protocol J2I-MC-JZMA	23-Aug-2019
Protocol J2I-MC-JZMA Amendment (a)	02-Oct-2019
Protocol J2I-MC-JZMA Amendment (b)	24-Feb-2020
Protocol J2I-MC-JZMA Amendment (c)	22-Mar-2020

Amendment d

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The purpose of this amendment is to allow metastatic castrate-resistant prostate cancer (mCRPC) patients with non-measurable disease for trial participation.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis; Section 4.1 Overall Design; 4.1.1 Dose Escalation; Section 9.2 Sample Size Determination	Added language for backfill patients; updated language for sample size	Backfill patients included to improve understanding of safety, PK, and pharmacodynamics of LY3475070
Section 1.1 Synopsis; Section 4.1 Overall Design; Section 6.1 Study Intervention(s) Administered	Added additional guidance on BID dosing	Additional guidance and clarity regarding BID dosing
Section 1.3, Schedule of Activities (Baseline, On-Study and Post-Study Treatment Follow-up)	Revised CT/MRI assessment window	Updated to correct discrepancy between Section 1.3 and Section 8.1 for enrollment and study participation purposes
Section 1.3, Schedule of Activities (Baseline, On-Study and Post-Study Treatment Follow-up)	Added additional PSA sampling, radionuclide bone scan	Updated for enrollment and study participation purposes
Section 1.3, Schedule of Activities (Continued Access Follow-up Visits)	Clarified pregnancy testing requirements during continued access period	Clarification
Section 1.3.1 Sampling Schedule for Pharmacokinetics and Biomarkers	Added sampling for circulating tumor cells for mCRPC patients only	Updated for enrollment and study participation purposes

Section # and Name	Description of Change	Brief Rationale
Section 5.1 Inclusion Criteria	For Inclusion Criteria 3f and 7f, added exclusion for CRPC patients with small-cell or neuroendocrine histologies. Inclusion Criteria 11, added exception for patients in Phase 1a portion of trial (dose escalation) and mCRPC patients in Cohorts D1 and D2 that these patients are not required to have measurable disease.	Updated for enrollment and study participation purposes
Section 6.5 Concomitant Therapy	Updated concomitant medication language to reflect greater certainty regarding enzymes involved in the metabolism of LY3475070. Updated language regarding concomitant use of zoledronic acid and denosumab. Removed references to specific foods or behaviors to avoid.	Clarification
Section 8.1.3 Efficacy Assessment for mCRPC Patients	Added new section to describe assessments to be used for mCRPC patients with measurable or non-measurable disease.	Updated for enrollment and study participation purposes
Section 8.8 Biomarkers	Added text to allow for submission of archival tissue from recent biopsy. Added text for use of fine-needle aspiration specimens for NSCLC patients only upon discussion with Lilly CRP/CRS.	Updated for enrollment and study participation purposes
Section 10.2 Appendix 2: Clinical Laboratory Tests	Added amylase and lipase to local clinical chemistry analytes	Amylase and lipase were added in order to detect any possible cases of immune-mediated pancreatitis
CCI		
Throughout protocol	Minor formatting and editorial changes	Minor, therefore not detailed

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 1 Multicenter Global First in Human Study of the CD73 Inhibitor LY3475070 as Monotherapy or in Combination with Pembrolizumab in Patients with Advanced Solid Malignancies

Short Title: A Phase 1 Study of the CD73 Inhibitor LY3475070 in Patients with Advanced Solid Malignancies

Rationale: Approximately 50 to 80% of advanced cancers patients experience progressive disease (PD) as their best objective response to immune checkpoint inhibitors (ICIs) such as ipilimumab, nivolumab, pembrolizumab or atezolizumab, suggesting the presence of tumor clones that are primarily resistant to ICI monotherapy. In addition, most patients whose tumor initially responded to ICI eventually develop PD, further suggesting that tumor clones can acquire resistance in the face of active therapies.

While immune escape by cancer is likely a multi-faceted phenomenon, adenosine signaling within the tumor microenvironment has been shown to promote immunosuppression and cancer growth. CD73, an ecto-5′-nucleotidase, catalyzes the conversion of adenosine monophosphate to adenosine, an immune suppressive metabolite. The CD73-adenosine axis facilitates cancer cell immune escape and promotes resistance to ICIs; therefore, targeting CD73 has the potential to become a novel cancer treatment. J2I-MC-JZMA (hereafter known as JZMA) will evaluate safety, tolerability and anti-tumor activity of LY3475070 alone or in combination with pembrolizumab in advanced cancer patients.

Objectives and Endpoints:

Phase 1a:

Objectives	Endpoints
Primary	
• To determine a safe dose of LY3475070 as monotherapy and in combination treatment with pembrolizumab to be further evaluated and confirmed in the Phase 1b portion of the study (recommended Phase 1b dose)	• DLTs • Assessment of safety including, but not limited to, TEAEs, SAEs, deaths, and clinical lab abnormalities per CTCAE v5.0
Secondary	
• To characterize the LY3475070 PK profile as monotherapy and in combination with pembrolizumab	• $C_{max,}$ trough ($C_{min,}$ $C_{steady\ state}$), $AUC_{steady\ state}$

Objectives	Endpoints
• To characterize the clinical activity of LY3475070 as monotherapy and in combination with pembrolizumab as assessed by the investigator using RECIST v1.1	• ORR • DCR • PFS

Abbreviations: AUC = area under the curve; C_{max} = maximum blood plasma concentration; C_{min} = minimum blood plasma concentration; CTCAE = Common Terminology Criteria in Adverse Events; DLT = dose limiting toxicities; DCR = disease control rate; ORR = overall response rate; PFS = progression-free survival; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Phase 1b:

Objectives	Endpoints
Primary	
• To establish the RP2D of LY3475070 as monotherapy and in combination treatment with pembrolizumab • To assess the safety, tolerability and clinical activity of LY3475070 as monotherapy and in combination with pembrolizumab	• Assessment of safety including, but not limited to, TEAEs, SAEs, deaths, and clinical lab abnormalities per CTCAE v5.0 • Investigator assessed ORR per RECIST v 1.1
Secondary	
• To characterize the LY3475070 PK profile as monotherapy and in combination with pembrolizumab	• $C_{max,}$ trough ($C_{min,}$ $C_{steady\ state}$), $AUC_{steady\ state}$
• To characterize the clinical activity of LY3475070 as monotherapy and in combination with pembrolizumab as assessed by the investigator using RECIST v1.1	• DOR • DCR • TTR • PFS • OS

Abbreviations: AUC = area under the curve; C_{max} = maximum blood plasma concentration; C_{min} = minimum blood plasma concentration; CD73 = cluster of differentiation 73;CTCAE = Common Terminology Criteria in Adverse Events; DCR = disease control rate; DOR = duration of response; NSCLC = non-small cell lung cancer; ORR = overall response rate; OS = overall survival; PD-1/L1 = programmed cell death protein-1/ligand 1; PFS = progression-free survival; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; RCC = renal cell carcinoma; RP2D = recommended phase 2 dose; TEAE = treatment-emergent adverse event; TTR = time to response.

Overall Design:

Study JZMA is an open-label, multi-center, Phase 1 study of LY3475070, a CD73 inhibitor, alone or in combination with pembrolizumab in patients with advanced solid tumors.

In **Cohort A** of Phase 1a, single agent LY3475070 will be evaluated in at least 3 evaluable patients per dose level (DL). Dose escalation will be guided by the modified toxicity probability interval 2 (mTPI-2) method. It is anticipated that 4 dose levels will be evaluated to determine the recommended phase 1b dose of single agent LY3475070. Once the dose level DL2 (300 mg once a day [QD]) for single agent LY3475070 has been determined safe and tolerable, LY3475070 in combination with pembrolizumab is planned to be evaluated at 3 dose levels in **Cohort B**, starting at combination dose level 1 (150 mg QD).

Phase 1b of the study aims to confirm the recommended phase 2 dose (RP2D) for LY3475070 monotherapy and LY3475070 in combination with pembrolizumab, and to further evaluate safety and preliminary efficacy in 3 patient cohorts:

- **Cohort C** will consist of patients with programmed cell death protein-1/ligand 1 (PD-1/L1) refractory non-small cell lung cancer, renal cell cancer, or melanoma who are positive for CD73 expression centrally-assessed by immuno-histochemistry. To minimize physician/patient selection bias, patients will be randomized to either single agent LY3475070 (Cohort C2) or combination therapy of LY3475070 and pembrolizumab (Cohort C1).
- **Cohort D** will consist of men with metastatic castrate resistant prostate cancer; eligible patients must be naïve to PD-1/L1 therapy. To minimize physician/patient selection bias, patients will be randomized to either single agent LY3475070 (Cohort D2) or combination therapy of LY3475070 and pembrolizumab (Cohort D1).
- **Cohort E** will consist of patients with metastatic triple negative breast cancer who have received at least 1 line of systemic treatment for metastatic disease; prior PD-1/L1 inhibitor is allowed but not required. Patients will receive combination therapy of LY3475070 and pembrolizumab.

Disclosure Statement: This is a treatment study with dose escalation and dose expansion phases that has no blinding or masking.

Number of Participants:

Dose Escalation (Phase 1a): Maximum of 62 patients

- Monotherapy Cohort (Cohort A): Approximately 12 to 24 patients will be enrolled.
- Combination Cohort (LY3475070 with pembrolizumab; Cohort B): Approximately 9 to 18 patients will be enrolled.
- Backfill patients to both Cohort A and Cohort B: up to 20 patients.

In the dose escalation phase, once a given DL is cleared for DLT evaluation and is deemed safe, the dose cohort may be expanded (i.e., backfilled) to further investigate the safety, pharmacokinetic (PK), pharmacodynamic, and clinical activity.

Dose expansion (Phase 1b): Approximately up to 140 patients

- Cohort C (patients with CD73+ tumors): up to 50 patients will be enrolled

- Cohort D (castrate resistant prostate cancer): up to 50 patients will be enrolled
- Cohort E (triple negative breast cancer): up to 40 patients will be enrolled

Intervention Groups and Duration

Cohort	Dose Level	Oral LY3475070	IV Pembrolizumab
Cohort A	DL1	150mg QD	N/A
	DL2	300mg QD	N/A
	DL3	600mg QD	N/A
	DL4	1000mg QD	N/A
Cohort B	CDL1	150mg QD	200 mg Q3W
	CDL2	300mg QD	200 mg Q3W
	CDL3	600mg QD	200mg Q3W
Cohorts C1, D1 and E	$RP1D_c$	RP1D/MTD	200 mg Q3W
Cohorts C2 and D2	$RP1D_m$	RP1D/MTD	N/A

Abbreviations: CDL = combination dose level; DL = dose level; IV = intravenous; MTD = maximum tolerated dose; N/A = not applicable; Q3W = every 3 weeks; QD = once a day; RP1D = recommended phase 1 dose; $RP1D_c$ = recommended phase 1 dose (for combination therapy); $RP1D_m$ = recommended phase 2 dose (for monotherapy).

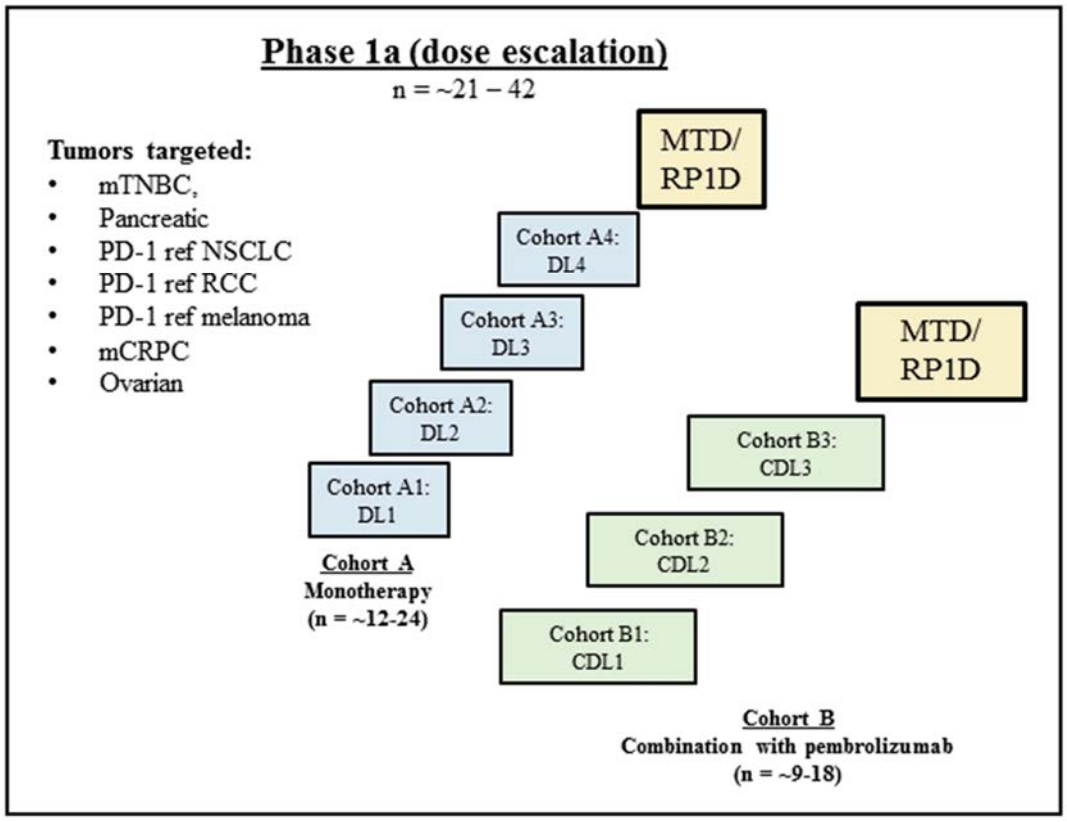
Note: Pembrolizumab should be administered for a maximum duration of 24 months (35 cycles).

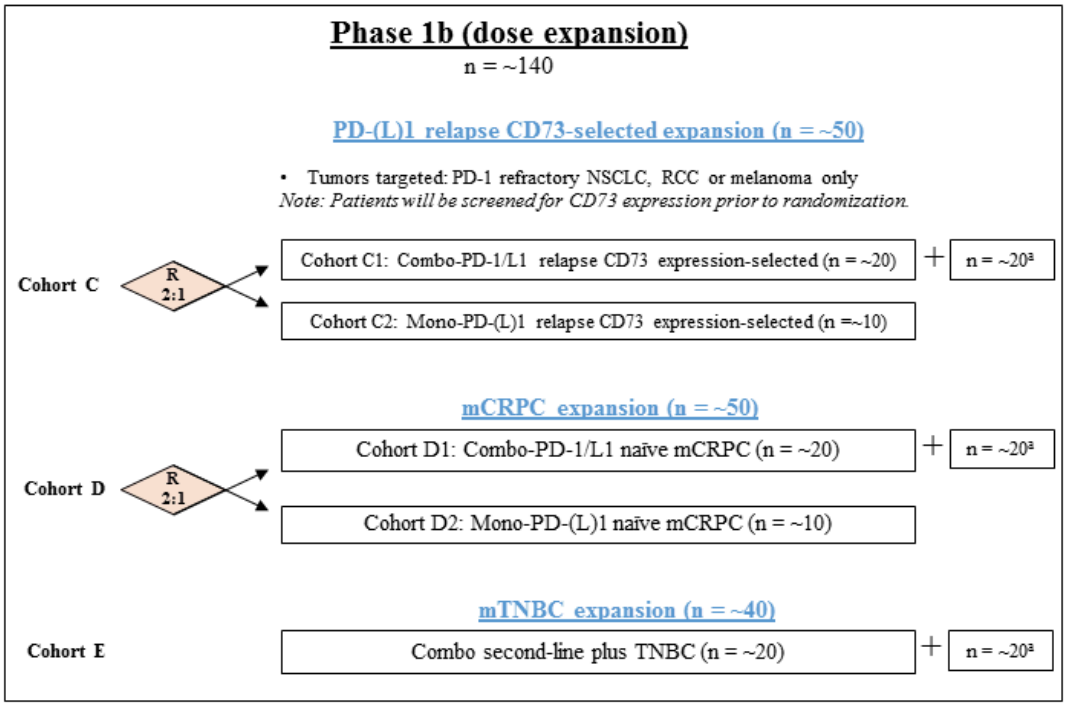
LY3475070 is to be administered until PD, unacceptable toxicity or other criterion for study discontinuation is met. In the absence of PD, unacceptable toxicity or other criterion for study discontinuation is met; pembrolizumab may be administered for a maximum duration of 24 months (35 cycles).

The above table shows the provisional dose levels that will be explored, ranging from 150 mg to 1000 mg QD of LY 3475070. Depending on PK, pharmacodynamic, and safety data observed, not all the provisional dose levels may be explored. A dose level −1 (DL−1 = 75 mg) may be explored if a dose of 150 mg QD (DL1) is not tolerated or if otherwise warranted based on the assessment of PK, PD, and safety data. Intermediate and/or higher dose levels as well as alternative schedules (e.g., 2 times a day [BID] dosing instead of QD) may be explored after discussion between Lilly and investigators if deemed appropriate based on the assessment of patient safety, PK, and PD data. The total dose of LY3475070 is not planned to exceed 1200 mg per 24 hours. If BID dosing is evaluated, patients will take doses 12±2 hours apart (i.e., 10 to 14 hours between doses). There should at least be 10 hours between each subsequent dose.

Data Monitoring Committee: No

1.2. Schema


Phase 1a (dose escalation)
n = ~21 – 42
Tumors targeted:
• mTNBC,
• Pancreatic
• PD-1 ref NSCLC
• PD-1 ref RCC
• PD-1 ref melanoma
• mCRPC
• Ovarian
Cohort A1: DL1
Cohort A2: DL2
Cohort A3: DL3
Cohort A4: DL4
MTD/ RP1D
Cohort A
Monotherapy
(n = ~12-24)
Cohort B1: CDL1
Cohort B2: CDL2
Cohort B3: CDL3
MTD/ RP1D
Cohort B
Combination with pembrolizumab
(n = ~9-18)


Phase 1b (dose expansion)
n = ~140
PD-(L)1 relapse CD73-selected expansion (n = ~50)
• Tumors targeted: PD-1 refractory NSCLC, RCC or melanoma only
Note: Patients will be screened for CD73 expression prior to randomization.
Cohort C
R 2:1
Cohort C1: Combo-PD-1/L1 relapse CD73 expression-selected (n = ~20)
Cohort C2: Mono-PD-(L)1 relapse CD73 expression-selected (n =~10)
n = ~20[a]
mCRPC expansion (n = ~50)
Cohort D
R 2:1
Cohort D1: Combo-PD-1/L1 naïve mCRPC (n = ~20)
Cohort D2: Mono-PD-(L)1 naïve mCRPC (n = ~10)
n = ~20[a]
mTNBC expansion (n = ~40)
Cohort E
Combo second-line plus TNBC (n = ~20)
n = ~20[a]

Abbreviations: CD73 = cluster of differentiation 73; CDL = combination dose level; DL = dose level; mCRPC = metastatic castrate resistant prostate cancer; MTD = maximum tolerated dose; NSCLC = non-small cell lung cancer; PD-1 = programmed cell death-1; PD-1/L1 = programmed cell death-1/ligand 1; R = randomization; RCC = renal cell carcinoma; ref = refractory; RP1D = recommended phase 1 dose; TNBC = triple negative breast cancer.

[a] If supported by data analysis, an additional 20 patients will be added (i.e., backfilled)

1.3. Schedule of Activities (SoA)

This section includes the following SoAs:

- Baseline, On-Study and Post-Study Treatment Follow-Up SoA
- Continued Access SoA

Baseline, On-Study and Post-Study Treatment Follow-up SoA														
	Baseline		**Cycle = 21 days**							**Short-Term Follow Up[a]**			**Long-Term Follow-Up[b]**	
	(Day Relative to C1D1)		**Cycle 1**				**Cycle 2**		**Cycle 3-n**	**801**	**802**	**803**	**804-X**	**Instructions**
			(±3 days)				(±3 days)		(±3 days)	30 day follow-up ±5 days	60 day follow-up ±5 days	90 day follow-up ±5 days	Q90D	
	≤28	≤7	D1	D2	D8	D15	D1	D2	D1					
Procedure														
Informed consent (Main and Phase 1b Cohort C consent)	X													Main ICF must be signed before any protocol-specific procedures are performed and Phase 1b Cohort C ICF prior to tissue collection for CD73 testing
Inclusion/exclusion criteria	X													
Medical history	X													Including assessment of preexisting conditions and historical illnesses, and habits (such as tobacco and alcohol use).
Cancer treatment history	X													Record prior anticancer therapy
Concomitant medication	X		X							X	X	X		See Section 6.5
Physical examination	X		X		X	X	X		X					Collect weekly during Cycle 1, and then on D1 of every cycle thereafter. A partial physical examination may be performed by a healthcare professional other than the physician on C1D8 and C1D15.
Vital signs	X		See Section 1.3.1.						X	X				Collect weekly during Cycle 1, and then on D1 of every cycle thereafter. Please collect vitals as follows: - At baseline only: Height, - At D1 of every cycle: Weight, - At every schedule visit: Temperature, blood pressure, pulse rate, respiratory rate, and pulse oximetry. Please refer to Section 1.3.1. for detailed collection pertaining to collection on C1D1-C3-n (D1).

Baseline, On-Study and Post-Study Treatment Follow-up SoA														
	Baseline		**Cycle = 21 days**							**Short-Term Follow Up[a]**			**Long-Term Follow-Up[b]**	
	(Day Relative to C1D1)		**Cycle 1**				**Cycle 2**		**Cycle 3-n**	**801**	**802**	**803**	**804-X**	**Instructions**
			(±3 days)				(±3 days)		(±3 days)	30 day follow-up ±5 days	60 day follow-up ±5 days	90 day follow-up ±5 days	Q90D	
	≤28	≤7	D1	D2	D8	D15	D1	D2	D1					
Procedure														
AE collection	X		X											Collect continuously at every visit and throughout the study using CTCAE Version 5.0. During the 30-, 60-, and 90-day follow-up visits, collect all AEs/SAEs. Thereafter, collect only SAEs related to study treatment or protocol procedures
Collection of survival information										X				Telephone contact is acceptable.
Collection of poststudy-treatment anticancer therapy information										X				
ECOG PS	X		X				X		X	X				During study treatment, perform ≤3 days prior to scheduled visits
ECHO or MUGA	X													Please perform locally.
ECG	See Section 1.3.1.		See Section 1.3.1.							See Section 1.3.1.				Please perform locally.
Hematology	X		X		X	X	X		X	X				See Appendix 2. Please collect weekly during cycle 1, then Q3W thereafter. If baseline testing is collected ≤3 days prior to C1D1, repeat testing is not required.
Coagulation	X		X		X	X	X		X	X				See Appendix 2. Please collect weekly during cycle 1, then Q3W thereafter. If baseline testing is collected ≤3 days prior to C1D1, repeat testing is not required.

Baseline, On-Study and Post-Study Treatment Follow-up SoA														
	Baseline		Cycle = 21 days							Short-Term Follow Up[a]			Long-Term Follow-Up[b]	
	(Day Relative to C1D1)		Cycle 1 (±3 days)				Cycle 2 (±3 days)		Cycle 3-n (±3 days)	801 30 day follow-up ±5 days	802 60 day follow-up ±5 days	803 90 day follow-up ±5 days	804-X Q90D	Instructions
	≤28	≤7	D1	D2	D8	D15	D1	D2	D1					
Procedure														
Clinical chemistry	X		X		X	X	X		X	X				Please collect weekly during cycle 1, then Q3W thereafter. If baseline testing is collected ≤3 days prior to C1D1, repeat testing is not required. See Appendix 2.
Urinalysis	X		X				X		X	X				Please collect per SoA. If baseline testing is collected ≤3 days prior to C1D1, repeat testing is not required. See Appendix 2.
CCI	X		X				X		X	X				Please collect D1 of first 3 cycles. Then Q6W thereafter (e.g., C5D1, C7D1 etc.). If baseline testing is collected ≤7 days prior to C1D1, repeat testing is not required. See Appendix 2.
Thyroid function testing	X		X						See Instructions	X				Starting C3D1, then D1 every other cycle. If baseline testing is collected ≤3 days prior to C1D1, repeat testing is not required. See Appendix 2.
Tumor markers	X		See Instructions											Collect tumor markers only for corresponding to cancer type: PSA- Prostate For mCRPC patients with nonmeasureable disease, PSA should be collected every 3 weeks (for the first 12 weeks of therapy) and evaluated every 9 weeks for progression after the first evaluation period (at 12 weeks). See Section 8.1.3 and Appendix 2 for further details. CEA - Pancreatic CA-125 - Ovarian CA 19-9 - Pancreatic For other indications please collect relevant tumor markers (e.g., CA 19-9) Q6W

Baseline, On-Study and Post-Study Treatment Follow-up SoA														
	Baseline		**Cycle = 21 days**							**Short-Term Follow Up[a]**			**Long-Term Follow-Up[b]**	
	(Day Relative to C1D1)		**Cycle 1**				**Cycle 2**		**Cycle 3-n**	**801**	**802**	**803**	**804-X**	**Instructions**
			(±3 days)				(±3 days)		(±3 days)	30 day follow-up ±5 days	60 day follow-up ±5 days	90 day follow-up ±5 days	Q90D	
	≤28	≤7	D1	D2	D8	D15	D1	D2	D1					
Procedure														
														throughout the study (C1D1, C3D1, etc.). See Appendix 2.
Pregnancy test	X	≤24h	See Instructions							X	X	X		Applies only to women of childbearing potential. See Section 8.3.4. for pembrolizumab-specific requirements and Appendix 2. Pregnancy test required at monthly intervals during study treatment in both treatment arms and up to 120 days after study treatment discontinuation for patients receiving LY3475070 and pembrolizumab and at 7 days after study treatment discontinuation for patients receiving LY3475070 monotherapy per Section 8.3.4.
Tumor assessment-radiological imaging	X		See Instructions							See Instructions				Perform locally according to RECIST 1.1, using the same imaging method (e.g., CT or MRI) at each assessment every 9 weeks ± 7 days for the first year and every 12 weeks (±7 days) thereafter until a discontinuation criteria is met. Disease progression should be confirmed per iRECIST by the site 4 to 8 weeks after site-assessed first radiologic evidence of PD in clinically stable participants. Participants, who have unconfirmed disease progression may continue on treatment at the discretion of the investigator until progression is confirmed by the site. Note: Imaging must be performed within 28 days before C1D1. See Section 8.1
Radionuclide bone scan	X		See Instructions							See Instructions				

Baseline, On-Study and Post-Study Treatment Follow-up SoA														
	Baseline		**Cycle = 21 days**							**Short-Term Follow Up[a]**			**Long-Term Follow-Up[b]**	
	(Day Relative to C1D1)		**Cycle 1**				**Cycle 2**		**Cycle 3-n**	**801**	**802**	**803**	**804-X**	**Instructions**
			(±3 days)				(±3 days)		(±3 days)	30 day follow-up ±5 days	60 day follow-up ±5 days	90 day follow-up ±5 days	Q90D	
	≤28	≤7	D1	D2	D8	D15	D1	D2	D1					
Procedure														
														Radionuclide bone scans should be performed only for patients with mCRPC. See Section 8.1.3.
Tumor assessment-measurement of palpable and/or visible lesions	X		See Instructions							See Instructions				See Section 8.1
Whole blood (PK)			See Section 1.3.1.											See Section 8.5.
Urine (PK)			See Section 1.3.1.											See Section 8.5.
Serum (Pharmacodynamics)			See Section 1.3.1.											See Section 8.6.
Whole Blood (PGx)			See Section 1.3.1.											See Section 8.8.
Plasma			See Section 1.3.1.							See Section 1.3.1.				See Section 8.8.
Serum (Biomarkers)			See Section 1.3.1.											See Section 8.8.
Whole Blood (CTCs)	See Section 1.3.1		See Section 1.3.1							See Section 1.3.1				For mCRPC patients only. Samples to be taken every 3 weeks. See Section 8.8.
Tissue	See Section 1.3.1		See Section 1.3.1.											See Section 8.8., 8.8.1.
Patient dosing diary			X											

Baseline, On-Study and Post-Study Treatment Follow-up SoA														
	Baseline		Cycle = 21 days							Short-Term Follow Up[a]			Long-Term Follow-Up[b]	
	(Day Relative to C1D1)		Cycle 1				Cycle 2		Cycle 3-n	801	802	803	804-X	Instructions
			(±3 days)				(±3 days)		(±3 days)	30 day follow-up ±5 days	60 day follow-up ±5 days	90 day follow-up ±5 days	Q90D	
	≤28	≤7	D1	D2	D8	D15	D1	D2	D1					
Procedure														
Administer LY3475070			X											See Section 6.1
Administer pembrolizumab (for patients assigned to combination treatment)			X				X		X					See Section 6.1

Abbreviations: AE = adverse event; CA-125 = cancer antigen; CA 19-9 = carbohydrate antigen 19-9; CEA = carcinoembryonic antigen; CCI [redacted] CCI [redacted]; CT = computed tomography; CTC = circulating tumor cell; CTCAE = Common Terminology; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; ICF = informed consent form; iRECIST = immune Response Evaluation Criteria in Solid Tumors; mCRPC = metastatic castrate-resistant prostate cancer; MRI = magnetic resonance imaging; MUGA= multigated acquisition; PD = progressive disease; PGx = pharmacogenetics; PK = pharmacokinetics; PSA = prostate-specific antigen; Q3W = every 3 weeks; Q6W = every 6 weeks; Q90D = every 90 days; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SOA = schedule of activities.

[a] Short-term follow-up begins when the patient and investigator agree that the patient will no longer continue study treatment.

[b] Long-term follow-up begins when short-term follow-up period is completed and continues until death, study withdrawal, or the patient is lost to follow-up. In all cases, no follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

Continued Access Schedule of Activities							
	Continued Access Treatment			Continued Access Follow-Up Visits[a]			
				30-Day	60-Day	90-Day	
Visit	501-5XX			901	902	903	
Procedure							Instructions
AE collection	X			X	X	X	Per CTCAE v5.0, for post follow-up, the investigator should only be made aware of collected SAEs related to study regimen or protocol procedures. As part of AE collection, monitor vital signs and perform standard laboratory tests (hematology, chemistry, urinalysis, and pregnancy testing) at the same frequency as during the study treatment period. All laboratory tests during the continued access period will be performed in the local laboratories only. Pregnancy testing applies only to women of childbearing potential. See Section 8.3.4 for pembrolizumab-specific requirements and Appendix 3. Pregnancy test required at monthly intervals during study treatment in both treatment arms and up to 120 days after study treatment discontinuation for patients receiving LY3475070 and pembrolizumab and at 7 days after study treatment discontinuation for patients receiving LY3475070 monotherapy per Section 8.3.4 and Appendix 3. Collect AEs for 30 days following cessation of study treatment and SAEs for 90 days or 30 days following cessation of study treatment if the participant initiates new anticancer treatment, whichever comes first. **Note**: All pregnancies and exposure during breastfeeding must be reported, from time of treatment through 120 days following cessation of treatment, or 30 days following cessation of treatment.
PK, IG and exploratory hypersensitivity							In the event of hypersensitivity, blood samples will be collected for PK, IG and exploratory hypersensitivity analyses at the following time points, as close as possible to: (i) the onset of the hypersensitivity, (ii) the resolution of the hypersensitivity, and (iii) 30 [±3] days following the hypersensitivity. Exploratory hypersensitivity samples may be analyzed for markers of: • Tryptase • ADA and LY3475070 concentration (PK)

Continued Access Schedule of Activities					
	Continued Access Treatment	**Continued Access Follow-Up Visits**[a]			
		30-Day	60-Day	90-Day	
Visit	501-5XX	901	902	903	
Procedure					**Instructions**
Administer LY3475070	X				See Section 6.1 for Dosing.
Administer pembrolizumab	X				See Section 6.1 for Dosing.

Abbreviations: ADA= antidrug antibody; AE = adverse event; IG = immunoglobulin; PK = pharmacokinetics.

a Continued access follow-up begins when the patient and the investigator agree that the patient will no longer continue treatment in the continued access period and lasts approximately 90 days.

1.3.1. Sampling Schedule for Pharmacokinetics and Biomarkers

Sampling Day	Time relative to LY3475070 dose	Vital Signs[d]	ECG	Whole Blood (PK)	Urine (PK)	Serum (Pharmaco dynamics)	Whole Blood (PGx)	Plasma	Serum (Bio-markers)	Whole Blood for CTCs – mCRPC Patients Only	Tissue
Baseline ≤28 days prior C1D1		X	X							X	X[a]
Cycle 1 Day 1	Predose	X	X	X		X	X	X	X	X	
Cycle 1 Day 1	0.5h±5m	X[c]		X	X[e]	X					
Cycle 1 Day 1	1h±5m	X[c]		X		X					
Cycle 1 Day 1	2h±10m	X[c]	X	X		X					
Cycle 1 Day 1	4h±30m	X[c]		X		X					
Cycle 1 Day 1	6h±30m	X[c]		X		X					
Cycle 1 Day 1	8h±30m	X[c]		X		X					
Cycle 1 Day 2	Predose	X	X	X		X					
Cycle 1 Day 2	1h±5m	X[c]									
Cycle 1 Day 8	Predose	X	X	X		X					
Cycle 1 Day 15	Predose	X	X	X		X		X	X		X[b]
Cycle 2 Day 1	Predose	X	X	X		X				X	
Cycle 2 Day 1	0.5h±5m	X[c]		X		X					

Sampling Day	Time relative to LY3475070 dose	Vital Signs[d]	ECG	Whole Blood (PK)	Urine (PK)	Serum (Pharmaco dynamics)	Whole Blood (PGx)	Plasma	Serum (Bio-markers)	Whole Blood for CTCs – mCRPC Patients Only	Tissue
Cycle 2 Day 1	1h±5m	X[c]		X		X					
Cycle 2 Day 1	2h±10m	X[c]		X		X					
Cycle 2 Day 1	4h±30m	X[c]		X		X					
Cycle 2 Day 1	6h±30m	X[c]		X		X					
Cycle 2 Day 1	8h±30m	X[c]		X		X					
Cycle 2 Day 2	Predose	X		X		X					
Cycle 3 Day 1	Predose	X	X	X		X		X	X	X	
Cycle 4-6 Day 1	Predose	X	X	X		X				X	
Cycle 7-n Day 1	Predose	X	X							X	
At progression								X	X	X	X[f]
V801		X	X					X	X	X	X[f]

Abbreviations: C1D1 = cycle 1 day 1; CTCs = circulating tumor cells; ECG=electrocardiogram; h = hour; m = min; mCRPC = metastatic castrate resistant prostate cancer; PGx = pharmacogenetics; PK = pharmacokinetics.

[a] Phase 1a = optional; Phase1b = mandatory (exceptions apply to Cohorts D1 and D2, see section 8.8) fresh biopsy collection required following determination of eligibility and before initiating study treatment. This final screening procedure will serve as the pre-treatment sample for biomarker testing (See Sections 5.1, 8.8, and 8.8.1).

[b] Phase 1a = optional; Phase 1b = mandatory (exceptions apply to Cohorts D1 and D2, see section 8.8) fresh biopsy collection required on-treatment (see Section 8.8) within C1D15 to C2D1 window.

[c] Only blood pressure and pulse are required at postdose collections

[d] Vital signs should be taken after at least 5 minutes supine and prior to any scheduled blood draws at the same time point.

[e] Urine output following dose administration, from 0 to 8 hours on Cycle 1 Day 1 will be pooled for a total collection and sampled for PK and creatinine.

[f] Optional collection

2. Introduction

2.1. Study Rationale

The immune system has developed multiple regulatory mechanisms to control for self-tolerance and limit tissue and organ damage during active responses to pathogens. This is partly achieved by a host of inhibitory receptors expressed on cells of the immune system that upon activation suppresses the inflammatory responses of immune cells. These pathways are referred to as "immune checkpoints" (Brahmer and Pardoll 2013). Several such checkpoints have been identified over the last decades, with programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) now having been validated as targets to modulate the immune system to fight cancer. In addition to the inhibitory receptors expressed on the immune cells, there are also soluble ligands and metabolites within the tumor microenvironment that can trigger the check point pathways (Leone et al. 2015).

Extracellular nucleotides such as adenosine-triphosphate (ATP) play an important role in cell metabolism and biological processes (Dubyak and El-Moatassim 1993). In the extracellular space, ATP gets converted to adenosine monophosphate (AMP) by the ecto-5'-nucleotidase CD39. Subsequently, CD73, a downstream ecto-5′-nucleotidase, catalyzes the conversion of AMP to adenosine, which acts as an immune suppressive metabolite (Horenstein et al. 2019). Adenosine signals by binding through four G protein-coupled receptors, A_{1A}, A_{2A}, A_{2B} and A_3 (Robeva et al. 1996). The most ubiquitously expressed receptor subtype on immune cells is A_{2A} and upon activation exerts a suppressive effect of the inflammatory immune response by modulating CD4 and $CD8^+$ T-cells and downregulating cytokine expression (Fishman et al. 2009). The immune suppressive effect of $A_{2A}R$ activation is so profound that in $A_{2A}R$ knockout mice, triggering an inflammatory response by external stimuli has a lethal effect (Ohta and Sitkovsky 2001). Other adenosine receptors, such as $A_{2B}R$ and A_3 receptors, have also been shown to be expressed by immune cells (Leone and Emens 2018; Van Der Putten et al. 2019), suggesting adenosine can signal through different receptor subtypes that have different binding affinity towards adenosine as well as distinct downstream effects, resulting in context dependent immune-modulation. Due to the complexity and the different expression of adenosine receptors on the various immune cells, and the various affinity adenosine receptors have to its ligand, lowering adenosine concentrations within the tumor microenvironment (TME) by targeting the ecto-enzymes may be a better strategy than targeting specific adenosine receptor subtypes. CCI

CCI [redacted]

Immune checkpoint inhibitors (ICI) have yielded significant improvements in tumor response rates, duration of tumor responses and overall survival in multiple advanced cancer settings such as melanoma, renal cell carcinoma, and non-small cell lung cancer (Fukumura et al. 2018). However, despite the observed efficacy with ICIs, depending upon the tumor type, 50 to 80% of advanced cancer patients will experience disease progression while receiving ICI treatment or within 3 to 6 months of treatment completion. This variability may be due to variability in the TME that can suppress T cell activation, necessitating novel combination treatment approaches to overcome resistance that develops to ICI treatment (O'Donnell 2016; Fukumura et al. 2018).

Several $A_{2A}R$ inhibitors, some of which having been evaluated in large Phase 3 trials for neurodegenerative diseases, have recently entered the clinic, evaluating their utility in treating patients with advanced solid malignancies (Leone and Emens 2018). CPI-444, an antagonist of $A_{2A}R$, has shown responses as a single agent and in combination with atezolizumab in patients with metastatic non-small cell lung cancer (NSCLC) and metastatic renal cell carcinoma (RCC) (Fong et al. 2017). Patients that had been on a programmed cell death protein-1/ligand 1 (PD-1/L1) for a prolonged duration prior to study entry showed evidence of elevated $A_{2A}R$ and CD73 expression, suggesting the adenosine pathway may play a role in acquired resistance to PD-1/L1 treatment (Hotson et al. 2017). Recent published data from an ongoing Phase 1 trial evaluating the $A_{2A}R$ antagonist AZD4635 as single agent or in combination with the PD-1/L1 targeted antibody durvalumab, has shown radiological responses in metastatic castrate resistant prostate patients, an indication that has not generally been responsive to anti- PD-1/L1 treatment alone (De Bono et al. 2018; Bendell et al., 2019). Additionally, CD73 upregulation has also been demonstrated in tumors with oncogenic driver mutations such as epidermal growth factor receptor mutation (EGFRm) NSCLC, and may explain the limited response patients with EGFRm have to ICI treatment (Streicher et al. 2017; Higgs et al. 2018).

Given the role the adenosine balance plays in the immune system, the current study, J2I-MC-JZMA (JZMA), will evaluate safety, tolerability and anti-tumor control of CD73 inhibitor LY3475070 (administered as monotherapy or in combination with pembrolizumab) in advanced cancer patients with malignancies traditionally unresponsive to single agent ICI treatment.

2.2. Background

2.2.1. LY3475070

LY3475070 is an orally bioavailable uncompetitive, potent, and selective inhibitor of CD73 with clearance that appears related to metabolism by CCI [redacted]. The mode of action is by binding to the enzyme-phosphate complex of CD73. In preclinical models, LY3475070 has demonstrated robust rescue of adenosine-mediated suppression of T-cell proliferation and cytokine secretion, correlated with a reduction in adenosine levels under experimental conditions where AMP/adenosine levels are high. An immune-suppressive TME is often characterized by significantly elevated levels of adenosine, likely limiting the clinical utility of competitive inhibitors of CD73 and adenosine receptor antagonists. Owing to its distinct uncompetitive mechanism of action (MOA), it is anticipated that LY3475070 may demonstrate more complete target inhibition and suppression of immune-suppressive adenosinergic signaling.

The pharmacological properties of LY3475070 were characterized both in vivo and in vitro in nonclinical pharmacology studies, and can be summarized as follows:

- It is orally bioavailable
- It shows robust target inhibition ex vivo in whole blood and in tumors models with a well-defined pharmacokinetic (PK)/pharmacodynamic relationship
- It demonstrates an acceptable toxicology profile in 1-month rat and dog repeat dose toxicology studies (see Section 2.3 of clinical protocol and Section 4.2.1 of IB)
- The projected human efficacious dose (148 mg once a day [QD]) and high Maximum Absorbable Dose (860 mg) projections allow greater dosing flexibility in clinic

Additional information may be found in the IB for LY3475070.

2.2.2. Pembrolizumab

Pembrolizumab is potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator's a Brochure.

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475 (Pembrolizumab).

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities (Strome et al. 2003; Blank et al. 2004; Hirano 2005; Curran 2010; Pilon et al.2010; Weber 2010; Spranger 2014). Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma (Strome et al. 2003; Zhang et al. 2004; Nomi et al. 2007; Curran et al. 2010; Pilon et al. 2010). In such studies, tumor infiltration by CD8+ T cells and increased IFN-γ, granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T cell function in vivo (Curran 2010). Experiments have confirmed the in vivo efficacy of anti-mouse PD-1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (see the IB).

2.3. Benefit/Risk Assessment

LY3475070 was evaluated in 1-month daily oral-dosing toxicology studies in Sprague-Dawley rats and Beagle dogs. Safety pharmacology parameters were evaluated in vitro (human ether á-go-go–related gene) and as part of the repeat-dose toxicity study in dogs. Genetic toxicity was evaluated in a bacterial mutation (Ames) assay, an in vitro micronucleus (MN) assay and an in vivo rat MN assay. Based on nonclinical study findings, potential toxicities include CCI

CCI

CCI All nonclinical toxicology findings in rats and dogs were reversible after a 1-month recovery period.

The experience so far with other $A_{2A}R$ antagonists and CD73 inhibitors in clinic suggest treatment to be well tolerated (Hauser et al. 2014; Fong et al. 2017; Hotson et al. 2017; Chiappori et al. 2018; Sui et al. 2018; Bendell et al. 2019; Luke et al 2019). The main toxicities that have emerged have been mainly gastro-intestinal (nausea, vomiting, diarrhea), neurological (headache, dizziness, somnolence, insomnia), and constitutional (weight loss, fatigue). Possible

immune related adverse events (irAEs), such as pruritis, pneumonitis, rash, hypothyroidism and hepatitis have also been reported. Based on these reports and the preclinical safety of LY3475070, GI-related events such as vomiting, nausea and fatigue may be expected. Due to the immune stimulatory mechanism of action, irAEs such as rash, colitis, and hypothyroidism may also be experienced. In combination treatment with other checkpoint inhibitors, there may be potential for increased incidence of irAEs. More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated adverse events (AEs) of LY3475070 may be found in the IB.

More detailed information about the known and expected benefits and risks of pembrolizumab may be found in the locally approved product label.

Pembrolizumab is a PD-1 blocking antibody with global regulatory approvals in several indications (pembrolizumab USPI). The risk profile of pembrolizumab is well characterized, and the management of irAEs associated with pembrolizumab is part of national guidelines and clearly described in this protocol.

Section 2.1 provides the rationale for the expected benefit, supporting the investigation of LY3475070 in combination with pembrolizumab. Preclinical and clinical data suggest that adenosine mediated signaling may be involved in mediating resistance to inhibition of PD-1/L1 signaling. Therefore, combining the CD73 inhibitor LY3475070 with PD-1/L1 blockade is hypothesized to increase efficacy in settings where adenosine mediated immune-suppression may limit clinical responses seen with PD-1/L1 blockade. Agents targeting the purinergic pathway, such as $A_{2A}R$ antagonists or CD73 monoclonal antibodies, have not shown incidence of irAEs to the same degree as PD-1 or CTLA-4 inhibitors. However, a combination of 2 agents targeting the immune system has the possibility to induce more frequent irAEs than each agent alone. Although it is not possible to extrapolate findings from other studies that have combined 2 checkpoint inhibitors to the combination of LY3475070 and pembrolizumab, the treatment protocol will provide clear dose modifications for irAEs to mitigate for possible irAEs. Given limited treatment options for the targeted patient population, and well established protocols for the management of irAEs, the risk remains acceptable.

3. Objectives and Endpoints

Phase 1a:

Objectives	Endpoints
Primary	
• To determine a safe dose of LY3475070 as monotherapy and in combination treatment with pembrolizumab to be further evaluated and confirmed in Phase 1b portion of the study (recommended Phase 1b dose)	• DLTs • Assessment of safety including, but not limited to, TEAEs, SAEs, deaths, and clinical lab abnormalities per CTCAE v5.0
Secondary	
• To characterize the LY3475070 PK profile as monotherapy and in combination with pembrolizumab	• $C_{max,}$ trough ($C_{min,}$ $C_{steady\ state}$), $AUC_{steady\ state}$
• To characterize the clinical activity of LY3475070 as monotherapy and in combination with pembrolizumab as assessed by the investigator using RECIST v1.1	• ORR • DCR • PFS
Tertiary/Exploratory	
• To evaluate target occupancy of LY3475070	• Percentage of target inhibition of adenosine in peripheral serum
• To assess the relationship between biomarkers, dose/exposure, and clinical outcomes	• Results of biomarker assessments • Clinical outcomes data
• To characterize the anti-tumor activity, as determined by the investigator, of LY3475070 in combination with pembrolizumab in subjects with indicated tumor types based on iRECIST criteria	• iORR • iPFS • iDCR
• To estimate the renal clearance of LY3475070 and conduct exploratory metabolite identification on blood and urine samples.	• Metabolite profiling • Renal clearance

Abbreviations: AUC = area under the curve; C_{max} = maximum blood plasma concentration; C_{min} = minimum blood plasma concentration; CTCAE = Common Terminology Criteria in Adverse Events; DLT = dose limiting toxicities; DCR = disease control rate; iDCR = immune disease control rate; iORR = immune overall response rate; iPFS = immune progression-free survival; iRECIST = immune Response Evaluation Criteria in Solid Tumors; ORR = overall response rate; PFS = progression-free survival; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Phase 1b:

Objectives	Endpoints
Primary	
• To establish the RP2D of LY3475070 as monotherapy and in combination treatment with pembrolizumab • To assess the safety, tolerability and clinical activity of LY3475070 as monotherapy and in combination with pembrolizumab	• Assessment of safety including, but not limited to, TEAEs, SAEs, deaths, and clinical lab abnormalities per CTCAE v5.0 • Investigator assessed ORR per RECIST v 1.1
Secondary	
• To characterize the LY3475070 PK profile as monotherapy and in combination with pembrolizumab	• C_{max}, trough (C_{min}, $C_{steady\ state}$), $AUC_{steady\ state}$
• To characterize the clinical activity of LY3475070 as monotherapy and in combination with pembrolizumab as assessed by the investigator using RECIST v1.1	• DOR • DCR • TTR • PFS • OS
Tertiary/Exploratory	
• To assess the relationship between biomarkers, dose/exposure, and clinical outcomes	• Results of biomarker assessments • Clinical outcomes data
• To characterize the immune mediated anti-tumor activity of LY3475070 as monotherapy or in combination with pembrolizumab based on iRECIST criteria	• iORR • iPFS • iDOR • iDCR
• To evaluate the relationship between anti-tumor activity of LY3475070, as monotherapy and in combination with pembrolizumab, and biomarkers predicting efficacy and resistance in obtained tumor tissues or blood samples	• Results of biomarker analyses • Clinical outcomes
• To evaluate target occupancy of LY3475070	• Percentage of target inhibition of adenosine in peripheral serum
• To estimate the renal clearance of LY3475070 and conduct exploratory	• Metabolite profiling • Renal clearance

metabolite identification on blood and urine samples.	

Abbreviations: AUC = area under the curve; C_{max} = maximum blood plasma concentration; C_{min} = minimum blood plasma concentration; CD73 = cluster of differentiation 73;CTCAE = Common Terminology Criteria in Adverse Events; DCR = disease control rate; DOR = duration of response; iDCR = immune disease control rate; iDOR = immune duration of response; iORR = immune overall response rate; iPFS = immune progression-free survival; iRECIST = immune Response Evaluation Criteria in Solid Tumors; NSCLC = non-small cell lung cancer; ORR = overall response rate; OS = overall survival; PD-1/L1 = programmed cell death protein-1/ligand 1; PFS = progression-free survival; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended phase 2 dose; SAE = serious adverse event; RCC = renal cell carcinoma; RP2D = recommended phase 2 dose; TEAE = treatment-emergent adverse event; TTR = time to response

4. Study Design

4.1. Overall Design

Study JZMA is an open-label, multicenter, global, 2-part Phase 1 study of LY3475070 alone or in combination with pembrolizumab in advanced cancer patients.

Phase 1a of the study will target the following tumor types: triple negative breast cancer, pancreatic cancer, PD-1 refractory NSCLC, PD-1 refractory RCC, PD-1 refractory melanoma, metastatic castrate resistant prostate cancer (mCRPC) and ovarian cancer. In **Cohort A** in Phase 1a, escalating doses of single agent LY3475070 will be evaluated in at least 3 evaluable patients per dose level (i.e., DLA1-A4, see Schema in Section 1.2). However, based on the observed PK, pharmacodynamic, and safety data observed, not all provisional dose levels may be explored. Intermediate and/or higher dose as well as alternative schedules of administration (BID dosing) will be explored if deemed necessary after discussion between Lilly and investigators. The dose limiting toxicity (DLT) observation period will be 28 days. The first patient of each DL will be observed for 48 hours before additional patients are enrolled to that DL. The totality of safety data will be reviewed by the Lilly clinical research physician/clinical research scientist (CRP/CRS) and study investigators prior to escalating to a next DL. Intrapatient dose escalation is not allowed. In the dose escalation phase, once a given DL is cleared for DLT evaluation and is deemed safe, the dose cohort may be expanded (i.e., backfilled) to a maximum of 20 patients to further investigate the safety, PK, pharmacodynamic, and clinical activity. Enrollment of patients to the dose cohort for DLT evaluation/dose escalation will take precedent. To ensure that patients are not unnecessarily enrolled to subtherapeutic dose levels, these backfills will not be undertaken until a DL already declared safe also demonstrates evidence of therapeutic exposures. However, continuous safety monitoring (Section 9.2) will be implemented to ensure ongoing evaluation of patient safety in backfill patients. In the event that backfill enrollment/escalation is paused, the aggregated safety data will be evaluated to determine if the dose level in question (and higher dose levels) should be permanently discontinued. In general, all available toxicity and PK data will be utilized, including DLT equivalents observed from backfill patients, to recommend an escalation/de-escalation decision, and to inform the selection of the RP2D.

It is anticipated that a minimum of 4 DLs will be evaluated in Cohort A to determine the MTD of single agent LY3475070, or, in the absence of MTD, a recommended Phase 1b dose of single agent LY3475070. The MTD will be the dose for which the estimated toxicity rate is the closest to the target toxicity rate of 30% and less than 35%. The recommended Phase 2 dose (RP2D) to be formally established in Phase 1b part of the study will be based upon the totality of safety, PK and pharmacodynamic data, and thus may be lower than the MTD or the recommended Phase 1b dose identified in the Phase 1a part of the study.

Once the DLA2 (300 mg QD) for single agent LY3475070 is determined safe and tolerable, LY3475070 in combination with pembrolizumab is planned to be evaluated in **Cohort B** starting at combination DL1 (150 mg QD LY3475070 and pembrolizumab) and escalated, independently from ongoing monotherapy dose escalation, to the recommended Phase 1b dose or MTD of LY3475070 single agent. At the first dose level, there will be at least a 48-hour delay between

dosing the first patient and additional patients. There will be no dose escalations for pembrolizumab, which will be given at 200 mg every 3 weeks (Q3W). The dose given in the dose escalation in Cohort B should not exceed the maximum dose shown to be safe in Cohort A.

In Phase1b of the study, the recommended phase 1 dose (RP1D) or MTD, as determined in the Phase 1a part, of LY3475070 alone or in combination with pembrolizumab will be evaluated in 3 distinct cohorts: Cohorts C, D, and E. The RP2D will be determined at the end of the Phase 1b part of the study based on the totality of data.

Cohort C will consist of patients that have been treated with and are refractory to PD-1/L1 inhibitor treatment with the following malignancies: NSCLC, RCC or melanoma. To be eligible, Cohort C will consist of patients with NSCLC, RCC, or melanoma that progressed on anti-PD1-L1 inhibitor therapy. Exception for prior anti- PD-1/L1 requirement will be given for NSCLC patients with EGFR activating mutations, as these patients do not respond to PD-1/L1 directed therapy, which may be due to high CD73 expression (Higgs et al. 2017; Streicher et al. 2017). In addition, patients must undergo a pretreatment biopsy and be positive for CD73 expression by central immunohistochemistry (IHC) testing.

Cohort D will consist of men with mCRPC; eligible patients must be PD-1/L1 inhibitor naïve.

To minimize physician/patient bias and to promote balanced patient characteristics between treatments, patients in Cohorts C and D will be randomized to either single agent LY3475070 or LY3475070 and pembrolizumab.

Cohort E will consist of patients with previously treated metastatic triple negative breast cancer (mTNBC) who will receive LY3475070 and pembrolizumab. Patients must have received at least one prior cytotoxic regimen. Prior anti PD-1/L1 treatment is not a requirement.

4.1.1. Dose Escalation

Dose escalation of LY3475070 will be driven by the modified toxicity probability interval-2 (mTPI-2) method (Guo et al. 2017) where a pre-calculated decision table (Appendix 8) will guide the dose recommendations until the MTD is determined (e.g., when all planned patients have been tested, or when no higher candidate DL can be tested). Dose escalation decision will also take into consideration available PK and pharmacodynamic data from previous DLs. Although mTPI-2 allows flexible number of patients in each dosing cohort, a minimum of 3 evaluable patients are required for the DLT evaluation at each DL. The first patient of each DL (in Phase 1a) will be observed for 48 hours before additional patients are enrolled to that DL. Intrapatient dose escalation is not allowed.

Like the 3+3 design, the mTPI-2 method incorporates prespecified escalation rules. In contrast, the mTPI-2 method is based on quantitative models that incorporate uncertainty into the decision rules, thereby allowing more precise RP2D selection. If 3 or 6 patients are enrolled in a cohort, the escalation rule parallels a traditional 3+3 design. However, it allows flexible number of patients in a cohort. For example, with 2 DLTs per 6 patients enrolled, the mTPI-2 would recommend staying at the current dose, as analogy to 1 DLT per 3 patients enrolled in 3+3 design; therefore, it allows more patients for a more precise estimate of the DLT rate at this DL.

Following a discussion between the Lilly CRP/CRS and the investigators, a more conservative dose selection may be applied to the next cohort (for instance, if PK/pharmacodynamics data suggest that further dose increase would not be expected to yield additional benefit). For

example, if the rule indicates "E" to escalate, the dose may stay at the current DL, be de-escalated to a lower level, or escalation may cease. In the mTPI-2, the cohort size is not fixed. However, each DL in this study will be tested with a minimum of 3 evaluable patients, unless the escalation rules dictate that the dose should be de-escalated ("D" or "DU"). Doses can be escalated, de-escalated, and re-escalated. If the dose decision was "DU," the dose cannot be re-escalated to that level.

This study is designed to identify a DL with a dose-limiting target toxicity rate of 30%. The mTPI-2 method considers an equivalence interval (EI) around the target toxicity rate. For this study, the EI is elicited to be (25%, 35%), resulting in the rules below.

Safety data, in particular DLTs, will be the primary criteria for the dose escalation. In addition, if available at the time of dose escalation decision, PK/pharmacodynamics results (for example, C_{max}, area under the concentration curve (AUC), pharmacodynamics results) will be used as secondary/supporting data for dose escalation.

Intermediate and/or higher dose as well as alternative schedules of administration will be explored if deemed necessary after discussion between Lilly and investigators and taking into account patient safety and PK/pharmacodynamics data. If needed, additional patients may be enrolled to further assess PK/pharmacodynamics or tolerability.

In order to be DLT-evaluable, patients must have received 75% of LY3475070 scheduled dose within the 28-day DLT period unless patients have a DLT qualifying event. For patients treated with the combination treatment, patients must have received 75% of LY3475070 and a minimum of 1 pembrolizumab infusion within the 28-day DLT period.

In the dose escalation phase, once a given DL is cleared for DLT evaluation and is deemed safe, the dose cohort may be expanded to further investigate the safety, PK, pharmacodynamic, and clinical activity of LY3475070 and the combination with pembrolizumab. There will be up to 20 backfill patients enrolled across all dose levels in cohorts A and B combined in the phase 1a study. Any AEs reported by those backfilled patients that meet the DLT criteria as defined in Section 6.1.1.1 and occur in the DLT period are considered DLT-equivalent toxicities (Section 6.1.1.2). The cumulative safety data from the cohorts previously declared safe and the current dose cohort under evaluation will be continuously monitored. A Bayesian toxicity monitoring rule will be implemented for DLT-equivalent toxicities added from backfill patients (Section 9.2). These aggregate safety data will be included in defining the RP2D.

4.1.2. In Vitro Diagnostic Utilization

An investigational CD73 IHC assay will be utilized to determine CD73 protein expression status in patients that otherwise meet all other eligibility criteria for enrollment in Phase 1b Cohort C. The test will be performed at a central laboratory following routine processing for histological evaluation using a commercial autostainer platform and will be interpreted by qualified pathologists. Patients will be required to undergo a mandatory fresh biopsy of a primary or metastatic site to obtain tumor tissue for determining CD73 expression. Patients that are not positive for CD73 expression, despite meeting all other eligibility criteria, will be screen failures.

In an initial survey of CCI formalin-fixed paraffin-embedded (FFPE) tumor samples conducted with an investigational IHC assay, CD73 expression was observed in CCI of lung tumors CCI . Recently disclosed external studies, using IHC-based assessment of CD73 expression,

have reported an overall prevalence of CD73 in RCC of 22% (25/112 [Tripathi et al. 2019]). Tumor cell CD73 expression has been detected in 54% (62/114) of metastatic melanoma (Monteiro et al. 2018), and in 73% and 40% of adenocarcinoma and squamous cell carcinoma of the lung respectively (Salazar et al. 2018).

4.2. Scientific Rationale for Study Design

Multiple tumor types have shown CD73 expression to have a prognostic value (Allard et al. 2019), including tumors insensitive to PD-1/L1 or CTLA-4 checkpoint blockade such as TNBC (Loi et al. 2013) and mCRPC (Leclerc et al. 2015). In preclinical models of such "immune cold" tumors, combined treatment targeting CD73 and checkpoints CTLA4 or PD-1/L1 showed synergy in comparison to single agent treatment (Allard et al. 2012). Several agents targeting $A_{2A}R$ and CD73 have recently entered the clinic and are being evaluated in patients with solid tumors (Leone and Emens 2018). Responses have been noted either as single agent treatment, or in combination with PD-1/L1 targeting antibodies, including in immune "cold" tumors not sensitive to ICI such as mCRPC, ovarian and pancreatic cancer (Sui et al. 2018; Bendell et al. 2019). In addition, translational data from the ongoing Phase 1/2 study with CPI-444, an antagonist of $A_{2A}R$, has suggested that patients with higher tumoral expression of CD73 and $A_{2A}R$ benefit from treatment (Hotson et al. 2017). Interestingly, patients that had been on a PD-1/L1 for a prolonged duration prior to study entry had elevated $A_{2A}R$ and CD73 expression suggesting the adenosine pathway may play a role in acquired resistance to PD-1/L1 treatment. Additional work on patient samples from this study also revealed patients that had a high intratumoral activation of the adenosine pathway to benefit from study treatment in comparison to patients with a low activation signature (Willingham et al. 2018).

Study JZMA will evaluate the safety and efficacy of LY3475070 either as single agent or in combination with pembrolizumab in tumors known to be immune "cold" such as mCRPC, as well as immune "inflamed" tumors that are unresponsive to check point inhibition, as a consequence of an immune suppressive TME infiltrated by myeloid and other immune regulatory cells. The underlying clinical hypothesis is that targeting CD73 within the TME will reduce local adenosine levels, an important immune-suppressive metabolite. This can be expected to reduce the inhibitory signals of immune suppressive cells, which may lead to increased T-cell infiltration and activation within the TME and lead to improved clinical responses.

Owing to the primary focus on patient safety in early clinical development an open label study is appropriate and an mTPI-2 based dose escalation is an appropriate design feature as it allows for more comprehensive and nuanced decision making in Phase 1a of this study. In Phase 1b, randomization of patients to monotherapy or combination therapy in 2 of 3 cohorts is an appropriate means of ensuring balanced patient characteristics in both treatment arms.

4.3. Justification for Dose

4.3.1. LY3475070

A clinical starting dose of 150 mg QD of LY3475070 administered orally in humans is anticipated to be safe and have the potential for clinical efficacy. Based on predicted human pharmacokinetics and a PK/pharmacodynamic model established on the basis of

pharmacodynamic data [redacted] a dose of 150 mg QD is anticipated to result in an average target inhibition of [redacted] over the dosing interval and [redacted] at C_{min} (refer to Section 4.2.3 of the IB for details). Target inhibition of this magnitude is expected to result in clinically meaningful reduction of adenosine formation by CD73. Margin of Safety for oral administration of LY3475070 based on administered dose and predicted exposure is presented below.

Margin of Safety for Oral Administration of LY3475070 Based on Administered Dose and Predicted Exposure

	Dose (mg/kg)	Dose (mg/m^2)	Dose Multiple[a] to Starting Dose (to maximum dose)	AUC (ng*h/mL)	Exposure Multiple[b] to Starting Dose (to maximum dose)
Human (150 mg)[c]	[redacted]	[redacted]	–	[redacted]	–
Human (1000 mg)[d]			–		–
Rat NOAEL[e]			32x (4.9x)		43x (6.5x)
Dog NOAEL[f]			22x (3.2x)		14x (2.2x)

Abbreviations: AUC = area under the curve; IVIVE = in vitro to in vivo extrapolation; NOAEL = no-observed-adverse-effect level.

a Dose multiple is the dose in animals/dose in humans based on mg/m2. Doses were converted from mg/kg to mg/m^2 using a km conversion factor of 6 for the rat, 20 for the dog, and 37 for a 60-kg human.

b Exposure multiple is the calculated AUC in animals/predicted AUC in humans.

c Clinical starting dose (150 mg). Exposure is predicted AUC using IVIVE of hepatocyte clearance.

d Maximum planned clinical dose (1000 mg). Exposure is predicted AUC using IVIVE of hepatocyte clearance.

e NOAEL in a rat 1-month repeat dose toxicity study (Study 8401913). Average of male and female rat AUC on Day 28.

f NOAEL in a dog 1-month repeat dose toxicity study (Study 8401914). Average of male and female dog AUC on Day 28.

4.3.2. Pembrolizumab

The planned dose of pembrolizumab for this study is 200 mg Q3W. Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA (Section 1.3) for the last participant in the study globally.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Type of Participant and Disease Characteristics for Phase 1a

Participants are eligible to be included in the study only if the following **cohort-specific** criteria apply:

1. Patients must be, in the judgement of the investigator, an appropriate candidate for experimental therapy and must have progressed through or be intolerant to therapies known to confer clinical benefit.
2. Patients must have archived tumor tissue available for biomarker analysis or be able and willing to undergo a baseline biopsy. On-treatment biopsy is optional (See Section 8.8).
3. Male or female participant with histological or cytological evidence of 1 of the following cancers that is metastatic, unresectable locally advanced, or locally recurrent:
   a. Triple negative breast cancer. Triple-negative receptor status is defined as ≤10% for estrogen and progesterone receptor expression, and human epidermal growth factor receptor 2 (HER2) negative per ASCO/CAP HER2 testing guideline.
      i. Patient must have received treatment for metastatic disease
      ii. Prior PD-1/L1 inhibitor is allowed;
   b. Pancreatic cancer
      i. Must have received chemotherapy for advanced or metastatic disease (e.g. gemcitabine containing regimen or modified FOLFIRINOX);
      ii. Patients with known microsatellite instability-high (MSI-H) tumor should have received prior PD-1/L1 inhibitor therapy;
   c. Non-small cell lung cancer
      i. Patient must have experienced progressive disease on or within 3 months of completing prior PD-1/L1 based inhibitor therapy (i.e., have refractory disease).
      ii. Patients must have received treatment for metastatic disease. Patients with targetable mutations (e.g., ROS1, ALK, BRAF, and EGFR) must have received approved mutation-targeted therapy;
      iii. Patients with targetable mutations are not required to have received PD-1/L1 inhibitors
   d. Renal cell carcinoma, clear cell predominant subtype
      i. Patient must have experienced progressive disease on or within 3 months of completing prior PD-1/L1-based inhibitor therapy (i.e., have refractory disease).
   e. Cutaneous melanoma (CM)
      i. Patient must have experienced progressive disease on or within 3 months of completing prior-PD-1/L-based inhibitor therapy (i.e., have refractory disease).
   f. Castrate resistant prostate cancer

i. Patient must have received treatment for metastatic disease; which should have included at least 1 next generation hormonal agent (e.g., Abiraterone, enzalutamide)
ii. Patients with small-cell or neuro-endocrine histologies will be excluded

g. Epithelial ovarian cancer
i. Patient must have received treatment for metastatic disease, including a platinum-based therapy. Patients in first relapse after adjuvant platinum therapy whose disease is platinum-sensitive should have received treatment with platinum-based therapy for recurrent disease.

Type of Participant and Disease Characteristics for Phase 1b

4. Patients must be, in the judgement of the investigator, an appropriate candidate for experimental therapy and must have either refused, progressed through or be intolerant to therapies known to confer clinical benefit.
5. Patients must have metastatic, unresectable locally advanced, or locally recurrent disease.
6. Patients must be able and willing to provide the protocol required biopsies at baseline and during study treatment period (See Section 8.8). For patients enrolled in Cohorts D1 and D2, biopsies are only required if patient has accessible soft tissue metastasis.
7. Cohorts C1 and C2: Patients positive for CD73 expression (CD73 expression determined by central IHC testing of pretreatment tumor biopsy; cut-off will be determined by the Sponsor)
   a) Patients must have NSCLC, RCC or melanoma;
   b) Patients must be refractory to prior PD-1/L1 inhibitor defined as: patients must have had prior PD-1/L1 therapy within 12 weeks of starting dosing on this study. Patients must have progressed on treatment with an anti-PD-1/L1 mAb administered either as monotherapy, or in combination with other checkpoint inhibitors or other therapies, with no intervening therapy prior to the start of study.
      PD-1/L1 treatment progression is defined by meeting all of the following criteria:
      i. Patients must have had complete response (CR)/partial response (PR) or stable disease (SD) for a duration of at least 6 months prior to progression.
      ii. Disease progression must have been demonstrated per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Eisenhauer et al. 2009).
      iii. The initial evidence of disease progression is to be confirmed by a second assessment no less than 4 weeks from the date of the first documented disease progression, in the absence of rapid clinical progression.
   c) NSCLC patients with targetable mutations (e.g., ROS1, ALK, BRAF, and EGFR) must have received prior targeted therapy with an approved agent. PD-1/L1 directed treatment is not a requirement for EGFR-mutant patients.

   Cohorts D1 and D2: Patients with metastatic CRPC

   d) Patients must be PD-1/L1 inhibitor therapy naïve;
   e) Patients must have received treatment for metastatic disease; which should have included at least 1 next generation hormonal agent (e.g., Abiraterone, enzalutamide)
   f) Patients with small-cell or neuro-endocrine histologies will be excluded

Cohort E: Patients with mTNBC

g) Prior PD-1/L1 inhibitor therapy allowed;
h) Patients must have received treatment for metastatic disease (at least 1 regimen of cytotoxic chemotherapy for metastatic disease);

Participants are eligible to be included in the study only if **all** of the following criteria apply:

8. Must be able to provide informed consent, as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol, according to local regulations and are at least 18 years of age.
9. Men with partners of childbearing potential must use a condom during intercourse. Men with partners of childbearing potential or women with childbearing potential must agree to use 2 effective methods of contraception including a highly effective contraceptive method of birth control (Appendix 3) during study treatment and for at least 120 days following the last dose of LY3475070 and pembrolizumab or country requirements, whichever is longer. For patients receiving LY3475070 only, contraception should be maintained for 7 days following the last dose. Additional guidance for contraception during and after study intervention are located in Appendix 3.
10. Women of childbearing potential must have a negative urine pregnancy test at the screening visit followed by a negative serum pregnancy test documented within 24 hours prior to initiation of treatment. If the screening urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Additional guidance for pregnancy testing during and after study intervention is located in Appendix 2 and Appendix 3.
11. Have at least 1 measurable lesion using standard techniques by RECIST version 1.1 (Eisenhauer et al. 2009). **Exception**: patients enrolled in the dose escalation phase and mCRPC patients enrolled in Cohort D1 and D2 are **not** required to have measurable disease.
12. Have a performance status (PS) of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale (Oken et al. 1982).
13. Previous treatments: Have discontinued all previous treatments for cancer and recovered from the acute effects of therapy (except alopecia). Patients must have discontinued from previous treatments, as shown below:

Previous Treatment	Length of Time Prior to First Dose of LY3475070
Endocrine therapies	≥14 days
Cytotoxic therapies or targeted agents that are small molecule inhibitors	≥21 days or ≥ 5 half-lives, whichever is shorter
Biologic agents that are large molecules including immunotherapy (except for patients enrolled in cohorts C1 and C2)	≥28 days
Limited-field radiotherapy (eg, stereotactic body radiation therapy [SBRT]) with palliative intent	≥14 days
Other radiotherapy	≥28 days Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis.
Major surgery, excluding biopsy	Patients with recent major surgery must have recovered, in the opinion of the investigator, from the toxicity and/or complications from the intervention before starting therapy.

14. Have adequate organ function, as defined below:

System	Laboratory Value
Hematologic	
ANC	≥1.5×10^9/L
Platelets	≥100×10^9/L
Hemoglobin	≥9 g/dL
Note: transfusions to increase a patient's hemoglobin level or initiation of erythropoietin or G-CSF therapy to meet enrollment criteria are not allowed in the 14 days preceding the first dose of study drug. If a patient receives transfusions, erythropoietin, or G-CSF therapy ≥14 days prior to the first dose, the hematologic criteria listed above must be met following the 14-day window and prior to the first dose of study therapy.	
Hepatic	
Total bilirubin	≤1.5×ULN
	Isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin is within normal limits, total serum bilirubin <3xULN, and Gilbert's Syndrome is confirmed.
ALT and AST	<2.5x ULN
Renal	
Calculated creatinine clearance based upon the Cockcroft-Gault formula	≥50 mL/min/1.73 m^2

(see Appendix 6)	

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; G-CSF = granulocyte-colony stimulating factor; ULN = upper limit of normal

5.2. Exclusion Criteria

Participants are excluded from the study if **any** of the following criteria apply:

Medical Conditions

15. For patients who have received prior immunotherapy, the following patients will be excluded:
    a) Experienced a Grade 4 immune-related toxicity or any immune-related toxicity that led to permanent discontinuation of prior anti-PD-1, anti-PD-L1, or other immunotherapy
    b) Experienced a less than or equal to Grade 3 irAE that has not recovered to Grade 1 after use of high dose corticosteroids that occurred during prior immunotherapy [exceptions: endocrine disorders where patients with prior endocrine AEs are permitted to enroll if they are asymptomatic, considered clinically stable, and maintained on appropriate replacement therapy]
    c) Any grade:
        i. ocular irAE,
        ii. serious neurologic irAE (e.g., Guillain-Barre syndrome, myasthenia gravis, encephalitis)
        iii. Serious cardiovascular irAE (e.g., myocarditis)
    d) Required immunosuppressive agents other than corticosteroids for the management of irAE; or currently requires maintenance doses of ≥10 mg prednisone/prednisolone (or equivalent) per day for irAE
16. Have interstitial lung disease or (noninfectious) pneumonitis; patients with a history of (noninfectious) pneumonitis Grade 2 or greater that required steroids (>7 days) to assist with management
17. Have a serious concomitant systemic disorder that, in the opinion of the investigator, would compromise the patient's ability to adhere to the protocol
18. Human Immunodeficiency Virus (HIV) positive patients (HIV 1 and/or 2; screening not required) are excluded **unless** they are well controlled on highly active antiretroviral therapy with
    - No evidence of acquired immunodeficiency syndrome (AIDS)-defining opportunistic infections within the last 2 years, and
    - CD4 count >350 cells/µl

- HIV infected participants with a history of Kaposi's sarcoma and/or Multicentric Castleman's Disease are not eligible.

19. Have active hepatitis B or C virus infection (screening required)
20. Have current untreated tuberculosis
21. Have active infection requiring systemic therapy
22. Have prior or second concurrent primary malignancies that, in the judgment of the investigator and the Lilly CRP/CRS, may affect the interpretation of results. Patients with carcinoma in situ of any origin and patients with prior malignancies who are in remission and whose likelihood of recurrence is very low (such as basal cell carcinoma), as judged by the Lilly CRP/CRS, are eligible for this study
23. Have active or suspected autoimmune disease (e.g., autoimmune vasculitis, autoimmune myocarditis) or any illness or treatment that could compromise the immune system (e.g., prior solid organ transplant) within the past 2 years, or a syndrome or condition that requires continuous systemic corticosteroids or immunosuppressive agents.

    This criterion does not apply to patients with: (i) vitiligo, alopecia, or type I diabetes mellitus; (ii) residual hypothyroidism due to an autoimmune condition requiring only hormone replacement; or (iii) psoriasis not requiring chronic systemic immunosuppressive treatment within the past 2years, not expected to recur in the absence of an external trigger, (iv) autoimmune-mediated hypothyroidism that is stable on hormone replacement; (v) Raynaud's syndrome; or (vi) Sjogren's syndrome. Patients with resolved childhood asthma/atopy are allowed.

24. Are at risk of vascular inflammation, such as those with a history of angiitis, arteritis, or hypersensitivity vasculitis as an adverse reaction to medication, for example, are not eligible.
25. Are being treated with escalating or chronic supraphysiologic doses of corticosteroids or immunosuppressive agents (such as, exceeding 10 mg/day of prednisone or equivalent). Use of topical, ophthalmic, inhaled, intermittent steroid injections, and intranasal corticosteroids permitted.
26. Patients with conditions that may impact absorption of LY3475070, such as bowel obstruction, uncontrolled diarrhea, or extensive intestinal resection.
27. Have moderate or severe cardiovascular disease, such as the following:

    a) presence of cardiac disease, including a myocardial infarction or any other arterial thrombotic event, blood clots not limited to deep vein thrombosis, cerebrovascular accident or transient ischemic attack within 6 months prior to enrollment; unstable angina pectoris; New York Heart Association Class III/IV congestive heart failure; aneurysm of major vessels or heart; left ventricular ejection fraction <50% (evaluation based on institutional lower limit of normal); or uncontrolled hypertension

b) severe, moderate, or clinically significant valvulopathy; documented major ECG abnormalities that, in the judgment of the investigator, are clinically significant (for example, symptomatic arrhythmias or arrhythmias requiring treatment; myocardial infarction within the last 3 months; or mean corrected QT interval (QTc) >450 msec for male participants or QTc >470 msec for female participants or QTc >480 msec in participants with bundle branch block calculated using Fredericia's correction and confirmed by triplicate ECG.

c) previous cardiotoxic cancer treatment associated with type 1 damage such as anthracyclines (e.g., daunorubicin, doxorubicin, epirubicin, idarubicin) and previous thoracic radiotherapy with a field involving the heart.

28. Have symptomatic central nervous system (CNS) malignancy or metastasis and/or carcinomatous meningitis (screening not required). Patients with treated CNS metastases are eligible for this study if they are not currently receiving corticosteroids (exceeding 10 mg/day prednisone or equivalent) and/or anticonvulsants to treat CNS metastases, and their disease is asymptomatic and radiographically stable for at least 30 days.
29. Have received a live vaccine within 30 days before the first dose of study treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines are live attenuated vaccines and are not allowed.
30. Post-partum patient who is or plans to breast-feed during the study
31. Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study
32. Have current or history of allergy or hypersensitivity to LY3475070 components including allergy to beta lactam antibiotics.
33. Has severe hypersensitivity to pembrolizumab and/or any of its excipients.
34. Has had an allogenic tissue/solid organ transplant.

Prior Therapy

35. Has received prior purinergic based inhibitors defined as adenosine $A_{2A}R$, $A_{2B}R$, A_3, CD39 or CD73.
36. Has undergone prior allogeneic hematopoietic stem cell transplantation within the last 5 years. Patients who have had a transplant greater than 5 years ago are eligible as long as they have no symptoms of graft versus host disease.

Prior/Concurrent Clinical Study Experience

37. Patient is currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study by the investigator and Lilly CRP/CRS.

5.3. Lifestyle Considerations

Not applicable.

5.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned a new participant identification number. The interval between rescreening should be ≥2 weeks. Each time rescreening is performed, the individual must sign a new ICF and will be assigned a new identification number. A patient may not be rescreened in an effort to obtain a different CD73 result. Repeating of laboratory tests during the screening period or repeating screening tests to comply with the protocol designated screening period does not constitute rescreening. This includes 1 repeat for CD73 expression to determine Phase 1b Cohort C eligibility if CD73 expression was not able to be determined by the patient's initial sample.

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Cohort	Dose Level	Oral LY3475070	IV Pembrolizumab
Cohort A	DL1	150mg QD	N/A
	DL2	300mg QD	N/A
	DL3	600mg QD	N/A
	DL4	1000mg QD	N/A
Cohort B	CDL1	150mg QD	200 mg Q3W
	CDL2	300mg QD	200 mg Q3W
	CDL3	600mg QD	200mg Q3W
Cohorts C1, D1 and E	$RP1D_c$	RP1D/MTD	200 mg Q3W
Cohorts C2 and D2	$RP1D_m$	RP1D/MTD	N/A

Abbreviations: CDL = combination dose level; DL = dose level; IV = intravenous; N/A = not applicable; MTD = maximum tolerated dose; RP1D = recommended phase 1 dose; $RP1D_c$ = recommended phase 1 dose (for combination therapy); $RP1D_m$ = recommended phase 1 dose (for monotherapy); Q3W = every 3 weeks; QD = once a day.

Note: Pembrolizumab should be administered for a maximum duration of 24 months (35 cycles).

A delay of a treatment day up to 7 days due to holidays, weekends, bad weather, unrelated medical events, or other unforeseen circumstances will be permitted and not be counted as a protocol deviation. The reason for interruption should be documented on the electronic case report form (eCRF).

The doses of LY3475070 will be administered at approximately the same times on each day, generally at home. Patients should be instructed take LY3475070 on an empty stomach, if possible. Otherwise, drug capsules may be taken a minimum of 1 hour before eating or 2 hours after consumption of food. A LY3475070 administration patient diary must be kept for dosing compliance monitoring. The actual time of dose administrations will be transcribed and provided to the sponsor.

If BID dosing is evaluated, patients will take doses 12±2 hours apart (i.e., 10 to 14 hours between doses). There should at least be 10 hours between each subsequent dose.

At clinic visits, patients will be directed to take LY3475070 at the site. LY3475070 will be administered 30 to 60 minutes post administration of pembrolizumab.

Pembrolizumab will be administered using IV infusion on Day 1 of each 3-week treatment cycle after all procedures and assessments have been completed. Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of

infusion pumps from site to site, a window between 5 minutes prior to and 10 minutes after administration is permitted (i.e., infusion time is 30 minutes (-5 min/+10 min).

The actual time of dose administrations will be transcribed and provided to the sponsor.

If LY3475070 is discontinued, pembrolizumab may be continued alone for up to 2 years (35 cycles). Conversely, if pembrolizumab is discontinued, LY3475070 may be continued alone.

6.1.1. Definition of DLT and DLT-ET

6.1.1.1. DLT

A **DLT** is defined as any of the events listed in the table below, if both of the following criteria are met:

- the event occurs during the DLT observation period (28 days) in Phase 1a, and
- the event cannot, in the opinion of the investigator, be definitely attributed to primary disease or extraneous causes, such as accident.

Patients who experience a DLT in the DLT observation period will be discontinued from study treatment.

Dose-Limiting Toxicities

Hematologic Toxicity
• Grade 3 thrombocytopenia associated with clinically significant bleeding and requiring platelet transfusion or Grade 4 thrombocytopenia of any duration
• Grade ≥3 febrile neutropenia
• Grade ≥3 anemia requiring a blood transfusion
• Other Grade ≥ 4 toxicity, excluding toxicities listed below this table
Nonhematologic Toxicity – Nonlaboratory
• Grade ≥3 irAE
• Grade ≥3 colitis or noninfectious pneumonitis
• Grade ≥3 pneumonitis or Grade 2 pneumonitis that does not show clinical improvement within 3 days after initiation of optimal medical management including corticosteroids therapy, which is then treated as Grade 3
• Grade ≥3 nausea, vomiting or diarrhea that lasts more than 48 hrs despite optimal supportive care
• Grade ≥3 fatigue lasting >7 days
• Grade ≥3 hypertension despite maximal medical therapy
• Grade ≥3 tachycardia
• Any other Grade ≥3 toxicity
• Immune-related adverse event that necessitated permanent discontinuation of study drug(s), regardless of grade
Nonhematologic Toxicity – Laboratory/Investigations
• Any Grade ≥3 laboratory abnormality except for specific exceptions listed below
• ALT or AST: o >8 × ULN o ≥2-fold above the patient's baseline value that lasts >7 days, o ≥3 × ULN with concomitant bilirubin >2 × ULN, in the absence of cholestasis o Total bilirubin >3 × ULN o ≥Grade 3 amylase or lipase that is associated with symptoms or clinical manifestations of pancreatitis Please refer to Section 8.2.1.1 for additional hepatic safety monitoring guidance.

Other Hematologic or Nonhematologic Toxicity That May Be a DLT.
• Toxicity deemed by the investigator and Lilly CRP to be dose limiting, such as: o toxicity that is possibly related to study treatment and requires discontinuation of the patient from the study at any time within the DLT observation period, or o persistent Grade >2 toxicities causing a delay of LY3475070 study treatment >14 days during the DLT observation period.

Abbreviations: AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase; CRP = clinical research physician; HCC = hepatocellular carcinoma; irAE = immune-related adverse event; IV = intravenous; ULN = upper limit of normal.

The following adverse events are not considered DLTs:

- Toxicity that is clearly and directly related to the primary disease or to another etiology
- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency), if both the following criteria are met:
  - the disorder is manageable with or without systemic corticosteroid therapy and/or hormone replacement therapy, and
  - the patient is asymptomatic
- Grade 3 inflammatory reaction attributed to a local antitumor response (such as, inflammatory reaction in the lymph nodes or at sites of metastatic disease)
- Any grade vitiligo or alopecia
- ≥Grade 3 electrolyte abnormality that lasts <72 hours, is not clinically complicated and resolves spontaneous or responds to conventional medical interventions
- ≥Grade 3 amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis
- Grade 3 or 4 neutropenia, provided **both** of the following criteria are met:
  - is not associated with fever or systemic infection, and
  - improves by at least 1 grade within 5 days
- Grade 3 or 4 lymphopenia

6.1.1.2. DLT-ET

A **DLT-equivalent toxicity** (ET) is any event listed in Section 6.1.1.1 occurring after the DLT observation period in Phase 1a or any cycle in Phase 1b.

A DLT-ET is an AE that meets the DLT criteria as defined above and occurs in any cycle other than the DLT assessment period (28 days for Cohorts A1 through A4 and B1 through B3). In addition to the DLT assessment period, available safety data beyond the DLT assessment period may also be taken into consideration prior to a decision to advance to the next DL or the determination of the RP2D.

Potential DLTs that are AEs, which are reasonably anticipated AEs for concomitant medication should be reviewed by the treating investigator and Lilly CRP/CRS before final determination as a DLT. Review and discussion may include additional participating investigators. Such review

may determine that confounding factors render the case to be not evaluable for the purposes of dose selection.

6.1.2. Definition of RP2D

The RP2D will be chosen following discussion between the Lilly CRP/CRS and the investigators based on consideration of the totality of the data during interim analyses and upon completion of Phase 1, including but not limited to LY3475070 dose adjustments, AEs, chronic intolerance, PK/pharmacodynamics data, and irAEs.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.
5. Investigators should consult the site training, Pharmacy Manual or label for the specific study drug information.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label dose finding study.

The Phase 1b dose expansion part will implement a randomization design for Cohorts C and D to mitigate the selection bias in allocating patients to either monotherapy dose expansion or combination therapy dose expansion.

6.4. Study Intervention Compliance

Participant compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned capsules/tablets/packages, and reviewing patient diaries. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF. Seventy-five percent of LY3475070 treatment doses must have been received by the patient in order to be considered compliant.

For IV medication, study intervention that is administered intravenously will be administered only at the investigational sites by the authorized study personnel. As a result, treatment compliance is ensured.

6.5. Concomitant Therapy

At baseline, record prior and concurrent medications. Record all premedication, supportive care, and concomitant medication continuously at every visit and throughout the study.

The Lilly CRP/CRS should be contacted if there are any questions regarding concomitant or prior therapy. Patients with metastatic CRPC may continue with luteinizing hormone-releasing hormone analogue for testosterone suppression. Zoledronic acid or denosumab given for bone support is allowed to be continued if started 1 week prior to study treatment dosing. However, zoledronic acid or densoumab should not be initiated, especially in metastatic CRPC patients, after study treatment has commenced. No other chemotherapy, immunotherapy, herbal supplements and/or herbal drugs intended to treat cancer, or experimental drugs will be permitted while the patients are in this study.

CCI

CCI If patients can't be switched to alternative therapy Lilly CRP/CRS must be consulted. For a list please consult Appendix 5. Immune-suppressive glucocorticosteroids other than to treat treatment related irAE are also prohibited.

Administration of live vaccines is prohibited during the study and for 3 months following the final dose of study drug. Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, Lilly CRP/CRS, and the participant.

Listed below are specific restrictions for concomitant therapy or vaccination during the course of the study:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.

- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines are live attenuated vaccines and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have an immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Lilly CRP/CRS.

  Note: Inhaled steroids are allowed for management of asthma.

Participants who, in the assessment of the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study.

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

All concomitant medication will be recorded on the eCRF including all prescription, over-the-counter products, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

All concomitant medications received within 28 days prior to the first dose of study treatment and up to 90 days after the last dose of study treatment should be recorded. Concomitant medications administered up to 90 days after the last dose of study treatment should be recorded for SAEs and events of clinical interest (Section 8.3.7).

6.5.1. Palliative Medicine and Supportive Care for LY3475070

The need for any form of radiotherapy (including palliative) in Cycles 1 and 2 will be cause for early discontinuation from the study. In Cycle 3 and beyond, palliative radiotherapy will be allowed.

In addition, any disease progression requiring other forms of specific antitumor therapy will also necessitate early discontinuation from the study. Appropriate documentation for all forms of premedications, supportive care, and concomitant medications must be captured on the case report form.

Patients should receive full supportive care. The use of granulocyte-colony stimulating factor (G-CSF) is permitted at the discretion of the investigator based on American Society for Clinical Oncology (ASCO) (Smith et al. 2015) and European Society for Medical Oncology (Crawford et al. 2009) guidelines.

If clinically indicated at any time during the study, erythropoietin and packed red blood cell transfusions may be used according to ASCO guidelines (Rizzo et al. 2008). Prophylactic antibiotic treatment should be consistent with ASCO guidelines (Flowers et al. 2013).

All concomitant medications should be recorded throughout the patient's participation in the study.

6.6. Dose Modification

6.6.1. Dose Modification and Toxicity Management of LY3475070 for Non-immune-mediated AEs Associated with LY3475070 and/or in Combination with Pembrolizumab

Patient may receive up to 2 dose reductions for AEs attributed to LY3475070. LY3475070 treatment may be interrupted, dose reduced or discontinued due to toxicity per the tables below.

Patients who have dose delays of more than 14 days, unless a different duration is specified in the above table, should permanently discontinue from the study.

Due to its MOA, LY3475070 may induce irAEs that could affect any organ of the body. Previous trials with agents inhibiting the adenosine pathway have not reported irAEs to the same incidence rate as seen with other check point inhibitors such as CTLA4 or PD-1/L1. From the ongoing $A_{2A}R$ antagonist single agent data only rash/pruritus, and elevated LFTs have been reported. In the event other irAEs occur please consult the table provided in Section 6.6.1.2 for management of irAEs.

Related AEs	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken to Therapy	AE Management	Monitor and Follow-up
Non hematologic				
Acneiform Rash	Grade 1	Continue treatment	Initiate topical prophylactic antibiotic (e.g., clindamycin). Consider using low potency topical steroids (e.g., hydrocortisone 2.5%)	Monitor for worsening signs and symptoms.
	Grade 2	Withhold therapy until ≤ Grade 1 (for recurrent Grade 2, or toxicity lasting more than 2 weeks proceed as Grade 3). If immune mediated rash is suspected see below table for management of immune mediated AE's).	Initiate oral antibiotic (e.g., doxycycline). Initiate low potency topical steroid, if not already started. Consider skin biopsy if immune mediated toxicity is suspected	Monitor for worsening signs and symptoms weekly
	Grade 3	Withhold therapy until ≤ grade 1 then dose reduce LY3475070 (if rash worsens or does not improve in two weeks permanently discontinue) If Stevens–Johnson syndrome or toxic epidermal necrosis permanently discontinue patient	Initiate oral antibiotic (e.g., doxycycline). Initiate systemic corticosteroid (e.g., prednisone 0.5 mg/kg daily (maximum dose, 40 mg). Consider dermatology consultation.	Monitor for worsening signs and symptoms weekly until improvement to ≤Grade 1. Resume LY treatment with 1 DL reduction. If rash does not improve or worsens after 2 weeks of treatment, discontinue LY permanently. If Stevens–Johnson syndrome or toxic epidermal necrolysis is suspected, discontinue permanently.
	Grade 4	Permanently discontinue	Initiate oral antibiotic (e.g., doxycycline). Initiate systemic corticosteroid (e.g., prednisone 0.5 mg/kg daily (maximum dose, 40 mg). Consider dermatology consultation.	
Diarrhea	Grade 1	Continue LY3475070 treatment. Start loperamide 4 mg initially, followed by 2 mg every 4 hours or after each stool.	Consider discontinue of lactose containing products	

Related AEs	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken to Therapy	AE Management	Monitor and Follow-up
	Grade 2	Continue LY3475070 treatment if Grade 2 diarrhea lasts <48 hours. Hold LY3475070 treatment if Grade 2 diarrhea lasts ≥48 hrs treatment until resolution to ≤ Grade 1.	Start loperamide 4 mg initially, followed by 2 mg every 4 hours or after each stool. Encourage oral hydration. If immune mediated colitis is suspected, consider GI consultation and biopsy.	
	Grade 3	Hold LY3475070 until resolution to Grade ≤ 1. Resume LY at 1 DL lower upon recovery.	If not already done, start loperamide 4 mg initially, followed by 2 mg every 4 hours or after each stool. Consider hospitalization for symptom and fluid management and GI consultation.	
	Grade 4	Permanently discontinue LY3475070 treatment	Consider hospitalization for symptom and fluid management, hydration and GI consultation.	
AST/ALT elevation or Increased bilirubin	Grade 1	Continue LY3475070 treatment	Review concomitant medications and alcohol use	
	Grade 2	Continue treatment if immune mediated transaminitis is not suspected. Hold LY3475070 if immune mediated transaminitis is suspected (see below table for management of immune mediated AE's).	Review concomitant medications and alcohol use Consider hepatology consultation and rule out biliary obstruction due to disease progression Consider biopsy if immune mediated transaminitis suspected.	Monitor LFTs every 2-5 days until ≤Grade 1 (see protocol section 8.2.1.1)
	Grade 3	Hold LY3475070 until ≤Grade 1. Resume LY3475070 treatment at 1 DL lower if the patient has no evidence of drug induced hepatocellular injury. Patients with evidence of drug induced hepatocellular injury (i.e., transaminase ≥3XULN and total bilirubin ≥2XULN should	Review concomitant medications and alcohol use Consider hepatology consultation	Monitor LFTs every 2-5 days until ≤Grade 1 (see protocol section 8.2.1.1)

Related AEs	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken to Therapy	AE Management	Monitor and Follow-up
		permanently discontinue LY3475070 treatment.		
	Grade 4	Permanently discontinue LY3475070 treatment	Review concomitant medications and alcohol use Consider hepatology consultation.	Monitor LFTs every 2-5 days until ≤Grade 1 (see protocol section 8.2.1.1).
[redacted]				
Fatigue	Grade 1	Continue treatment	Manage per routine clinical practice and/or institutional guidelines	
	Grade 2	Continue treatment	Manage per routine clinical practice and/or institutional guidelines	
	Grade 3	Withhold LY3475070 until resolution ≤ grade 1, if resolved within 7 days then resume treatment.	Manage per routine clinical practice and/or institutional guidelines	

Related AEs	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken to Therapy	AE Management	Monitor and Follow-up
		If grade 3 persist over 7 days then dose reduce one level. If recurrence after continuing treatment dose reduce one level.		
Non-Hematologic Toxicity CCI	Grade 1	Continue LY3475070 treatment	Manage per routine clinical practice and/or institutional guidelines	
	Grade 2	Withhold LY3475070 treatment until resolution to ≤ grade 1 for recurrent Grade 2, or toxicity lasting more than 2 weeks proceed as Grade 3	Manage per routine clinical practice and/or institutional guidelines	
	Grade 3 or recurrent Grade 2	Withhold treatment until resolution to ≤grade 1 and then reduce dose one level.	Manage per routine clinical practice and/or institutional guidelines	
	Grade 4	Permanently discontinue	Manage per routine clinical practice and/or institutional guidelines.	
Hematologic toxicity				
Neutropenia	Grade 1	Continue treatment		
	Grade 2	Continue treatment		
	Grade 3	Withhold LY3475070 until resolution ≤ grade 1 for recurrent Grade 3, or toxicity lasting more than 2 weeks proceed as grade 4. If febrile neutropenia then dose reduce one level upon resolution ≤ grade 1	If patient is above 38.0° C on 2 separate occasions and or associated with signs or symptoms of sepsis start intravenous in accordance with the local hospital neutropenic sepsis guidelines G-CSF support may be given as deemed appropriate by the physician per institutional guidelines	Perform CBC weekly ≤Grade 3
	Grade 4	Withhold LY3475070 until resolution ≤ grade 1 then resume at one reduced DL. If neutropenia is longer than 5 days discontinue patient	If patient is above 38.0° C on two separate occasions and or associated with signs or symptoms of sepsis start intravenous in accordance with the local hospital neutropenic sepsis guidelines.	Perform CBC weekly ≤Grade 3

Related AEs	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken to Therapy	AE Management	Monitor and Follow-up
			G-CSF support may be given as deemed appropriate by the physician per institutional guidelines.	
Anemia	Grade 1	Continue dose		
	Grade 2	Continue dose		
	Grade 3	Withhold LY3475070 until resolution ≤ grade 1 then resume at one reduced DL	Blood transfusions as per local institutional guidelines	Perform CBC weekly ≤Grade 3
	Grade 4	Discontinue treatment	Blood transfusions as per local institutional guidelines	
Thrombocytopenia	Grade 1 (LLN > 75,000 mcL)	Continue dose		
	Grade 2 (75,000>25,000)	Continue dose		
	Grade 3 (<25,000 mcL) with significant bleeding	Withhold LY3475070 until resolution ≤ Grade 1 and resume treatment. If associated with bleeding, or Grade 3 reoccurs, then resume at one reduced DL. If thrombocytopenia Grade 3 reoccurs at lower DL discontinue patient.	Platelet transfusion per local institutional guidelines.	Perform CBC weekly ≤Grade 3.
	Grade 4 life threatening spontaneous bleeding	Permanently discontinue.	Platelet transfusion per local institutional guidelines	

Abbreviations: CBC = complete blood count; CCI ; CCI ; G-CSF = granulocyte colony-stimulating factor; LFTs = liver function tests; CCI .

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

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

Pembrolizumab Infusion-Related Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated.	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr. to 50 mL/hr.). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment.	Participant may be premedicated 1.5 hrs (±30 minutes) prior to infusion of pembrolizumab with: • Diphenhydramine 50 mg po (or equivalent dose of antihistamine). • Acetaminophen 500 to 1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 **Grade 3:** Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement;	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilator support indicated	• Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.	
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

Abbreviations: IV = intravenous; NSAID = non-steroidal anti-inflammatory drug; po = by mouth

6.6.2. Dose Modification and Toxicity Management for Immune-Related AEs Associated with LY3475070 and/or in Combination with Pembrolizumab

An immune-related AE (irAE) may be defined as an AE consistent with an immune-mediated chronic inflammatory reaction associated with drug exposure. These irAEs may occur shortly after the first dose or several months after the last dose of drug and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data of immune checkpoint inhibitors, most irAEs are reversible and can be managed with interruptions of therapy, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue therapy and administer corticosteroids. Dose modification and toxicity management guidelines for potential irAEs are provided in the table below.

Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Study Treatment

General Instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab and LY3475070	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3, or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood, or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST or ALT elevation or Increased Bilirubin	Grade 2[a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3[b] or 4[c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent)	

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab and LY3475070	Corticosteroid and/or other therapies	Monitoring and follow-up
			followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold[d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue[d]		
Hypothyroidism	Grade 2, 3, 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab and LY3475070	Corticosteroid and/or other therapies	Monitoring and follow-up
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event[e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

[a] AST/ALT: >3.0 to 5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin: >1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin: >3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include but are not limited to: Guillain-Barre Syndrome, encephalitis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis.

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate transaminase; GI = gastrointestinal; irAE = immune-related adverse event; IV = intravenous; ULN = upper limit of normal

NOTE: The frequency or severity of known potential irAEs with pembrolizumab may be increased in combination with LY3475070. Therefore, particularly close monitoring for irAEs should be standard. For all irAEs of grade 2 or above would consider specialist consultation and/or additional work-up including labs and biopsy to confirm diagnosis. For certain toxicities of more serious clinical consequence, such as myocarditis, neurologic, or ophthalmologic irAE, consider withholding therapy for grade 2 toxicities and early hospitalization for close monitoring for grade 3 toxicities. For any grade 2 or greater suspected irAE, please consult with Lilly CRS/CRP.

For any other dose modifications, toxicities, or infusion-related reactions related to pembrolizumab, please consult the product label.

6.6.3. Other allowed dose interruption for pembrolizumab

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

6.7. Intervention after the End of the Study

The end of study definition is defined in Section 4.4. Investigators will continue to follow the SoA provided in Section 1.3 until notified by Lilly that end of study has occurred.

6.7.1. Treatment after Study Completion

Study completion will occur following the final analysis of primary and secondary objectives, as determined by Lilly. Investigators will continue to follow the SoA (Section 1.3) for all patients until notified by Lilly that study completion has occurred.

6.7.1.1. Continued Access

Participants who are still on study intervention at the time of study completion may continue to receive study intervention if they are experiencing clinical benefit and no undue risks.

The continued access period will apply to this study only if at least 1 participant is still on study intervention when study completion occurs. Lilly will notify investigators when the continued access period begins.

If LY3475070 is discontinued, pembrolizumab may be continued alone for up to 2 years (35 cycles). Conversely, if pembrolizumab is discontinued, LY3475070 may be continued alone.

Participants are not required to sign a new ICF before treatment is provided during the continued access period; the initial ICF for this study includes continued access under this protocol.

The participant’s continued access to study intervention will end when a criterion for discontinuation is met (Section 7). Continued access follow-up will begin when the participant and the investigator agree to discontinue study intervention and lasts approximately 90 days. Follow-up procedures will be performed as shown in the Continued Access SoA.

Participants who are in short-term follow-up when the continued access period begins will continue in short-term follow-up until the 90-day short-term follow-up visit is completed. Long-term follow-up does not apply.

Participants who are in long-term follow-up when the continued access period begins will be discontinued from long-term follow-up.

In all cases, no follow-up procedures will be performed for a participant who withdraws informed consent unless he or she has explicitly provided permission and consent.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

The reasons for treatment and study discontinuation and dates of discontinuation will be collected for all patients.

Patients who discontinue during the study treatment period, whether or not they received study treatment, will have follow-up procedures performed as shown in the SoA (Section 1.3).

If a patient withdraws informed consent, he or she must not be contacted unless he or she has explicitly provided permission and consent. Lilly may continue to use previously collected medical research data prior to the withdrawal consistent with the original authorization.

7.1. Discontinuation of Study Intervention

Discontinuation of study treatment does not represent withdrawal from the study.

Participants may discontinue study treatment at any time for any reason or be discontinued from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the sponsor if enrollment into the trial is inappropriate, the trial plan is violated or for administrate and/or other safety reasons.

A subject must be discontinued from the trial for the following reasons:

- the participant or the participant's designee, for example, parents or legal guardian requests to discontinue investigational product.
- the subject is lost to follow -up

A subject must be discontinued from trial treatment but continue to be followed for any of the following reasons:

- the patient becomes pregnant during the study
- the patient is significantly noncompliant with study procedures and/or treatment
- disease progression. Disease progression should be confirmed per iRECIST 4 to 8 weeks after site-assessed first radiologic evidence of PD in clinically stable participants. Participants, who have unconfirmed disease progression may continue on treatment at the discretion of the investigator until progression per iRECIST. Any participant deemed clinically unstable should be discontinued from study treatment at first radiologic evidence of PD and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.
- unacceptable toxicity
- the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. Discontinuation from study invention will occur prior to introduction of the new agent.
- Recurrent Grade 2 pneumonitis
- Discontinuation of treatment may be considered for participants who have attained a confirmed complete response (CR) and have been treated for at least 8 cycles (at least 24 weeks), receiving [for monotherapy: at least 2 doses of pembrolizumab; for

combination treatment: 2 cycles of the combination including 2 doses of pembrolizumab and at least 75% of the planned doses of LY3475070] beyond the date when the initial CR was declared.

- Pembrolizumab will be discontinued after completion of approximately 2 years of treatment with pembrolizumab (completion of 35 treatments with pembrolizumab). Note: The number of treatments is calculated starting with the first dose of pembrolizumab.

Participants discontinuing from the investigational product prematurely for any reason should complete adverse event and other follow-up procedures per Section 1.3 (Schedule of Activities), Section 8.3 (Adverse Events and Serious Adverse Events), and Section 8.2 (Safety Assessments) of the protocol.

7.2. Participant Discontinuation/Withdrawal from the Study

Participants will be discontinued in the following circumstances:

- enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- subject decision
    - the participant or the patient's designee, for example, parents or legal guardian requests to be withdrawn from the study
- the patient becomes pregnant during the study. See Section 8.3 regarding regulatory reporting requirements on fetal outcome.
- Participants discontinuing from the study prematurely for any reason should complete AE and other safety follow-up per Section 1.3 (Schedule of Activities), Section 8.3 (Adverse Events and Serious Adverse Events), and Section 8.2 (Safety Assessments) of this protocol.

7.2.1. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identify a participant who did not meet enrollment criteria and was inadvertently enrolled, then the patient should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the patient to continue on study treatment. If the investigator and the sponsor CRP agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled participant to continue in the study with or without treatment with investigational product. Safety follow up is as outlined in Section 1.3 (Schedule of Activities), Section 8.3 (Adverse Events and Serious Adverse Events), and Section 8.2 (Safety Assessments) of the protocol.

Please refer to Appendix 7 for discontinuation of inadvertently enrolled patients in the United Kingdom.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get investigational product. Public sources may be searched for vital status information. If vital status is determined, this will be documented and the participant will not be considered lost to follow-up.

Lilly personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.7.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).

8.1. Efficacy Assessments

8.1.1. RECIST V1.1 for Tumor Response Assessment

Please follow the guidelines below when assessing tumor response:

- Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 will be applied as the primary criteria for assessment of tumor response (Eisenhauer et al. 2009).
- The extent of computed tomography (CT) or magnetic resonance imaging needed to establish baseline tumor burden is based upon the investigator's determination.
- Tumor assessments will be performed for each patient at the times shown in the SoA (Section 1.3). Counting from C1D1, for the first year of study treatment, disease status should be evaluated radiologically per RECIST v1.1 guidelines every 9 weeks (±7 days) for the first year, and every 12 weeks (±7 days) thereafter (until a discontinuation criterion is met).
- Perform assessments as scheduled, even if study treatment is delayed or omitted, except when deemed not feasible in the opinion of the investigator because of the patient's clinical status.
- Standard of care scan (pre-ICF) may be used as baseline provided it meets technical requirements for inclusion criteria and occurred within 28 days of treatment.

Per RECIST v1.1 imaging guidelines:

- imaging modality (e.g., CT or magnetic resonance imaging [MRI]) obtained for the study baseline should be repeated throughout the study as described in SoA;
- Intravenous and oral contrast should be used as clinically indicated;
- While CT imaging with slices ≤5 mm, MRI imaging is also acceptable;

- CT images from positron emission tomography-CT scans may be used for response assessment if the associated CT scan has the same quality as a diagnostic CT.

Best overall response (BOR; e.g., complete or partial response, stable disease or unknown) will be determined locally by the investigator per RECIST v1.1; there will be no independent review of BOR. When the RECIST v1.1 criteria for progressive disease are met, clinically stable patients may undergo additional radiologic imaging progression for confirmation of PD per iRECIST (Section 8.1.1, Seymour et al 2017). For patients who meet criteria to continue treatment after initial progression (either awaiting confirmation by iRECIST or have iUPD by iRECIST), reconsenting is required. Patients who discontinue treatment without documented progression should continue to be assessed for patients who discontinue study treatment without confirmed PD, periodic imaging per SoA (Section 1.3) for PD confirmation will continue until PD, or initiation of subsequent therapy or withdrawal of consent. If the patient is still on study treatment after 1 year, perform tumor imaging Q12W.

8.1.2. iRECIST For Confirmation of PD in Clinically Stable Patients and Radiologic PD per RECIST v1.1.

RECIST v1.1 will be applied as the primary criteria for assessment of tumor response (Eisenhauer et al. 2009). The response to immunotherapy may differ from the typical responses observed with cytotoxic chemotherapy, including the following (Wolchok et al. 2009; Nishino et al. 2013):

- Response to immunotherapy may be delayed.
- Response to immunotherapy may occur after progressive disease by conventional criteria.
- The appearance of new lesions may not represent progressive disease with immunotherapy.

Therefore, to adequately characterize additional patterns of response and progression specific to patients treated with immunotherapy, which cannot be captured using conventional criteria such as RECIST v1.1, alternative measures of tumor assessment have been developed. The iRECIST standard was developed by the RECIST working group for the use of modified RECIST version 1.1 in cancer immunotherapy trials (Seymour et al. 2017).

After initial disease progression defined by RECIST v1.1, iRECIST guidelines will be applied in the following tumor assessments. In iRECIST, any new lesions are categorized as measurable or non-measurable. Up to 5 lesions total (up to 2 per organ) can be selected as new lesion-target (NL-T). All other new lesions will be followed as new lesion-non-target (NL-NT). The NL-T sum of diameters will be calculated and recorded separately from the sum of diameters for target lesions identified at baseline.

Tumor response by iRECIST will be classified as confirmed progression (iCPD), or unconfirmed progression (iUPD), or stable disease or response (iSD/iPR/iCR) at all subsequent imaging. The initial tumor scan showing disease progression by RECIST v1.1 will be assigned as unconfirmed progression (iUPD) for overall response.

Progression is considered confirmed (iCPD), if the previous response status was iUPD and any of the following happens:

- For target lesions: any further increase in the previously identified target lesion sum of diameters by 5mm or more after iUPD.
- For non-target lesions: any further increase in the size of previously identified non-target lesion iUPD (the increase doesn't need to meet RECIST v1.1 criteria for unequivocal progression)
- For new lesions:
    - an increase in the NL-T previously identified as iUPD and increase ≥5mm in sum of diameter OR
    - any increase for NL-NT OR
    - any appearance of additional new lesions

The overall response remains iUPD, IF

- target lesions were the cause of the initial iUPD AND
- target lesions haven't worsened, but they are still above PD threshold (20% increase from the nadir), AND
- no above factors of iCPD occur.

When progression is considered not unconfirmed, the overall response can become iSD/iPR/iCR instead of iUPD if any of the following criteria are met:

- iCR: Target lesions and non-target lesions have regressed completely AND no new lesions.
- iPR: Target lesions have regressed to ≥30% decrease from baseline (iCR or iPR) AND non-target lesions remain non-iCR/non-iUPD AND no new lesion
- iSD: Target lesions have regressed to <20% increase from nadir AND non-target lesions remain non-iCR/non-iUPD AND no new lesion.

Management Guidelines for Patients Who Have Radiologic Evidence of Progressive Disease by RECIST v1.1

If a patient is clinically stable at the first radiologic PD by RECIST v1.1 (Eisenhauer et al 2009), the patient may be considered for continuation on the study until progression is confirmed. Confirmation of progression must occur no less than 4 weeks later by iRECIST. For patients to be considered for continuation, the following criteria must **all** be met:

a. Absence of symptoms and signs indicating clinically significant progression of disease;
b. No decline in ECOG or Karnofsky performance status;
c. Absence of symptomatic rapid disease progression requiring urgent medical intervention (e.g., symptomatic pleural effusion, spinal cord compression).

The continuation of treatment after initial radiologic PD takes into consideration the observation that some patients may experience transient tumor flare or pseudo-progression with immunotherapy but could have disease response later. Patients may continue to receive treatment after reconsenting. For patients who meet criteria to continue treatment after initial progression (either awaiting confirmation by iRECIST or have iUPD by iRECIST), reconsenting is required. Patients who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor assessment will resume at the next

scheduled imaging time point, if clinically stable. Patients will be discontinued from study treatment if disease progression is confirmed by iRECIST (Seymour et al. 2017).

If a patient is clinically unstable, the patient should be discontinued from the study treatment at the first radiological PD by RECIST v1.1. The repeat tumor imaging for confirmation of PD by iRECIST is not required.

Clinical stability is defined as the following (Seymour et al. 2017): no worsening of performance status; absence of signs or symptoms that are associated with clinically significant disease progression; no requirement for intensified management, including increased analgesia, radiotherapy, or other palliative care. Clinical stability is ultimately defined by the treating investigator.

A summary of imaging and treatment guidelines for patients who have first radiologic PD is listed in the table below.

Imaging and Treatment Guideline for Patients who have First Radiologic PD by RECIST v1.1

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST v1.1	Repeat imaging at 4 to 8 weeks to confirm PD by iRECIST	May continue study treatment while waiting for confirmatory scan by iRECIST	Not required; Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST	No additional imaging required	Discontinue treatment	No additional imaging required	Not applicable
Repeat tumor imaging shows iUPD by iRECIST	Repeat imaging at 4 to 8 weeks to confirm PD by iRECIST. May occur at next regularly scheduled imaging visit	Continue treatment at the investigator's discretion	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only	Discontinue treatment.
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per Investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study treatment at the Investigator's discretion.	Continue regularly scheduled imaging assessments.	Discontinue treatment

Abbreviations: iCPD = iRECIST confirmed progressive disease; iCR = iRECIST confirmed complete response; iSD = iRECIST confirmed stable disease; iUPD = iRECIST unconfirmed progressive disease; PD = progressive disease; RECIST= Response Evaluation Criteria in Solid Tumors.

8.1.3. Efficacy Assessment for mCRPC Patients

For mCRPC patients enrolled in this trial (both during dose escalation, Cohorts A and B, and dose expansion Cohorts D1 and D2), response criteria set forth by the Prostate Cancer Clinical Trials Working Group 3 will be utilized (Scher et al. 2016). Efficacy will be evaluated on a combination of RECIST v.1.1 (if patient has measurable disease), prostate-specific antigen (PSA) measurements, and bone scintigraphy using ^{99m}Tc-methylene diphosphonate radionucleotide (^{99m}Tc MDP). Multi-parametric MRI may also be used to evaluate response or progression in bone-only disease. Central measurement of circulating tumor cells is planned at a frequency of every 3 weeks but will not be required for efficacy evaluation.

For patients with measurable disease, RECIST v1.1, as described above in Section 8.1.1, will be utilized with the following caveats:

I. For nodal lesions, separate pelvic vs extra-pelvic disease and record up to 5 nodal lesions in total.
II. In order to classify as progression, previously normal lymph nodes (<1 cm) must have grown by at least 0.5 cm in the short axis from baseline scan or nadir and be ≥1 cm in the short axis.
III. Nodes that have progressed to ≥1.5 cm in the short axis are considered measurable; nodes that have progressed to 1 cm to <1.5 cm are considered pathologic but subject to clinical discretion and non-measurable.
IV. Visceral disease should be designated separately as lung, liver, adrenal, or CNS.

All mCRPC patients will undergo a ^{99m}Tc MDP scintigraphy at baseline to evaluate skeletal disease involvement. Bone lesions should be evaluated every 9 weeks (±7 days) and can be scheduled around CT/MRI disease staging. Due to possible bone flare that can be part of bone healing in response to treatment, and not actual progression, a 2+2 rule should be used for assessment. Progression should only be called if at least 2 new lesions are seen on the first on-treatment scan, followed by at least 2 additional lesions on the second or subsequent post-treatment scans.

For patients with non-measurable disease, PSA evaluations will be utilized for response assessment to treatment. Prostate-specific antigen will be measured at each treatment cycle (every 3 weeks), but because favorable PSA response to treatment may be delayed, early PSA rises should be ignored until 12 weeks unless patient is rapidly progressing (new lesions on image assessment) with clinical deterioration. After the first evaluation at 12 weeks, PSA response should be evaluated at every 9 weeks for progression. A PSA increase of ≥25% and ≥2 ng/dL from baseline/nadir, confirmed with a second measurement at least 3 weeks apart, will be considered progression. A PSA decrease from baseline that is ≥50% will be considered a response and should be confirmed with a repeat measurement at least 3 weeks apart.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

For each patient, ECGs, vital signs, laboratory tests, and other tests should be collected as shown in the SoA (Section 1.3).

Refer to Section 8.3 for details on the recording of AEs.

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

8.2.1. Clinical Safety Laboratory Assessments

- Lilly or its designee will provide the investigator with the results of safety laboratory tests analyzed by a central vendor, if a central vendor is used for the clinical trial.
- See Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or until the completion of Visit 803 should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
    - If there is an abnormal laboratory value or abnormal value for any other diagnostic or screening test (for example, blood pressure increased, neutrophils decreased, etc.) and it is known to be related to a disease diagnosis (for example, hypertension, neutropenia, etc.) this should be reported in the CRF as an AE. Do not enter the test abnormality, enter the disease diagnosis or categorical term. If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the event(s) must be reported in the CRF as AE(s).

8.2.1.1. Hepatic Safety Monitoring

In study participants with baseline ALT/AST< 1.5× ULN

If a study participant enrolled with baseline alanine aminotransferase (ALT)/aspartate aminotransferase (AST) <1.5× ULN, experiences elevated ALT/AST ≥3× ULN, liver testing (Appendix 4) should be repeated within 2 to 5 days including ALT, AST, alkaline phosphatase

(ALP), total bilirubin (TBL), direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring and evaluation for possible causes of abnormal liver tests, should be initiated by the investigator in consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels.

In study participants with baseline ALT/AST ≥1.5x ULN

If a study participant enrolled with baseline ALT/AST ≥1.5× ULN, experiences elevated ALT/AST ≥2× baseline, liver testing (Appendix 4) including ALT, AST, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase should be repeated within 3 to 5 days to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring and evaluation for possible causes of abnormal liver tests, should be initiated by the investigator in consultation with the study CRP/CRS. Monitoring of ALT, AST, and TBL should continue until levels normalize or return to approximate baseline levels.

8.2.1.1.1. Special Hepatic Safety Data Collection

Additional safety data should be collected via the CRF/electronic data entry/designated data transmission methods if 1 or more of the following conditions occur:

In participants enrolled with baseline ALT/AST <1.5× ULN:

- Elevation of serum ALT/AST to ≥5× ULN on 2 or more consecutive blood tests
- Elevated ALT/AST ≥3× ULN and elevated TBL ≥2× ULN

In participants enrolled with baseline ALT/AST ≥1.5× ULN

- Elevated ALT/AST ≥3× baseline on 2 consecutive tests
- Elevated ALT/AST ≥2× baseline and elevated TBL ≥2× ULN

In all study participants

- Discontinuation from study treatment due to a hepatic event or abnormality of liver tests
- Occurrence of a hepatic event considered to be a SAE

8.2.1.2. Allergic reaction and Hypersensitivity

For suspected hypersensitivity reaction, laboratory tests may be obtained at the following time points:

- In the presence of generalized urticaria or if anaphylaxis is suspected.
- After the subject has been stabilized, obtain a sample within 1 to 2 hours of the event, however, samples may be obtained as late as 12 hours after the event as analytes can remain altered for an extended period of time. Record the time at which the sample was collected.

Obtain a follow-up sample at the next regularly scheduled visit or after 4 weeks, whichever is later.

All biologic agents carry the risk of systemic allergic/hypersensitivity reactions. Clinical manifestations of these reactions may include but are not limited to:

- Skin rash
- Pruritus (itching)
- Dyspnea
- Urticarial (hives)
- Angioedema (for example, swelling of the lips and/or tongue)
- Hypotension
- Anaphylactic reaction

Participants with clinical manifestations of systemic allergic/hypersensitivity reactions should be treated per local standard of care. Additional data describing each symptom should be provided to the sponsor in the CRF.

In case of anaphylaxis or generalized urticaria, additional blood samples should be collected as close as possible to the onset of the event (see Section 8.2.1 Clinical Safety Laboratory Assessments). Follow-up samples should be obtained at the next regularly scheduled visit or 4 weeks after the event, whichever is later. The lab results are provided to the sponsor via the central laboratory or via CRF.

8.3. Adverse Events and Serious Adverse Events

Investigators are responsible for monitoring the safety of participants who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the participant.

The investigator is responsible for the appropriate medical care of participants during the study.

Investigators must document their review of each laboratory safety report.

The investigator should provide AE verbatim terms and then the terms will be mapped by Lilly or its designee to corresponding terminology within the Medical Dictionary for Regulatory Activities (MedDRA) Lower Level Term (LLT) dictionary. The investigator will use Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 to assign AE severity grades.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the participant to discontinue the investigational product before completing the study. The participant should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is otherwise explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the ICF is signed, study site personnel will record via CRF the occurrence and nature of each participant's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure, investigational product, via CRF.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, study device, or a study procedure, taking into account the disease, concomitant treatment or pathologies.

A "reasonable possibility" means that there is a cause and effect relationship between the investigational product, study device and/or study procedure and the AE.

The investigator answers yes/no when making this assessment.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a participant's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via CRF, clarifying if possible, the circumstances leading to any dosage modifications, or discontinuations of treatment.

Serious Adverse Events

An SAE is any AE from this study that results in 1 of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All AEs occurring after signing the ICF are recorded in the CRF and assessed for serious criteria. The SAE reporting to the sponsor begins after the participant has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, the SAE should be reported to the sponsor as per SAE reporting requirements and timelines (see Section 8.3.1) if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Participants with a serious hepatic AE should have additional data collected using the CRF.

Pregnancy (during maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in participants once they have discontinued and/or completed the study (the participant disposition CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the identification, recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

Although all AEs after signing the ICF are recorded by the site in the CRF/electronic data entry, SAE reporting to Lilly begins after the patient has signed the ICF and has received study treatment. However, if an SAE occurs after signing the ICF, but prior to receiving study treatment, it needs to be reported ONLY if it is considered reasonably possibly related to study procedures.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be reported on the adverse events CRF.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available. Serious adverse events, including death, caused by disease progression should not be reported unless the investigator deems them to be possibly related to study treatment.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.2. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

8.3.3. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for SUSAR according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.4. Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until the completion of Visit 803.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 3.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
- Additional requirements for pregnancy testing during and after study intervention are located in Appendix 3.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy
- All pregnancies and exposure during breastfeeding, from the time of treatment through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator

8.3.5. Cardiovascular and Death Events

Events leading to the clinical outcome of death due to study disease that are part of the efficacy analyses for this study will not be reported to Lilly or its designee as SAEs unless the investigator believes the event may have been caused by the investigational product.

8.3.6. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Participants will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

8.3.7. Events of Clinical interest

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

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 8.4 – Treatment of Overdose, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3× the ULN and an elevated total bilirubin lab value that is greater than or equal to 2× the ULN and, at the same time, an alkaline phosphatase lab value that is less than 2× the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be made available. It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Lilly CRP/CRS. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this trial.

8.4. Treatment of Overdose

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or ≥5 times the indicated dose.

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

8.5. Pharmacokinetics

At the visits and times specified in the SoA (Section 1.3), venous blood samples of approximately 2 mL will be collected to determine the plasma concentrations of LY3475070. Aberrations to specified sampling times in the SoA (Section 1.3) will not be considered protocol deviations as long as the samples are taken and the actual sampling time is recorded.

Prior to dosing, patient should void bladder. Following administration of LY3475070, the total urine output from 0 (post dose) to 8 hours will be collected, pooled, and refrigerated (Section 1.3). Urine should not be fractionated unless scientifically justified. From the time period, 1 aliquot will be used to measure LY3475070 for urinary creatinine concentration and 2 aliquots of approximately 10 mL each will be stored frozen until further analysis. The total volume of urine will be recorded and the remaining urine will be discarded. Serum samples for creatinine measurement should be collected as specified in the study SoA in Section 1.3 (Clinical Chemistry).

Blood and urine samples will be analyzed at a laboratory approved by the sponsor. Plasma and urine concentrations of LY3475070 will be assayed using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method.

Bioanalytical samples collected to measure investigational product concentrations and metabolism and/or protein binding will be retained for a maximum of 2 years following last participant visit for the study. During this time, blood and urine samples remaining after the bioanalyses will be analyzed for exploratory metabolite identification, as deemed appropriate by the sponsor. The results of such exploratory metabolism work may only be included in the clinical study report if deemed appropriate by the sponsor or may be reported in a separate exploratory metabolism report.

8.6. Pharmacodynamics

See Section 1.3.1 for a schedule of serum collection for CD73 inhibition ex vivo pharmacodynamic assay to be collected in this study.

8.7. Genetics

8.7.1. Whole Blood Sample for Pharmacogenetic Research

A whole blood sample will be collected for pharmacogenetic analysis as specified in the SoA (Section 1.3) where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to LY3475070 and to investigate genetic variants thought to play a role in cancer. Samples may also be used to determine the somatic or germline origin of identified genetic alterations in tumor samples. Assessment of variable response may include evaluation of AEs or differences in efficacy.

All samples will be coded with the patient identification number. These samples and any data generated can be linked back to the patient only by the investigator site personnel.

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last participant visit for the study, or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3475070 or after LY3475070 become(s) commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome wide association studies, and candidate gene studies. Regardless of technology utilized, data generated will be used only for the specific research scope described in this section.

8.8. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, pharmacodynamics, MOA, variability of participant response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including deoxyribonucleic acid, ribonucleic acid, proteins, lipids, and other cellular elements.

Serum, plasma, tumor tissue, and whole blood for biomarker research will be collected at the times specified in the SoA (Section 1.3) where local regulations allow. A maximum of 5 samples may be drawn, collected, or removed at additional time points during the study if warranted and agreed upon by the investigator and Lilly. If these additional samples are requested, they will be used to further investigate biomarkers that may explain treatment response and resistance mechanisms.

Samples will be used for research on the drug target, disease process, variable response to LY3475070, pathways associated with cancer, MOA of LY3475070, and/or used to develop research methods or to validate diagnostic tools or assay(s) related to cancer.

Collection of the following tumor tissue sample(s) is **required** for patients to participate in this study:

- Phase 1a:
  - A mandatory archival FFPE tumor tissue sample. While the tissue can be from either initial diagnosis or later, the sample should be the most recent available specimen containing adequate material. Sites should confirm the availability of archival tumor tissue with the pathology laboratory during screening and prior to enrollment. Tumor tissue should be submitted within 30 days following enrollment.
  - If an archival sample is unavailable, then a pretreatment biopsy (core or excisional) of a tumor lesion from a primary or metastatic site may be submitted to meet eligibility requirements.
- Phase 1b:
  - A newly obtained core or excisional baseline biopsy of a tumor lesion from a primary or metastatic site. Archived tissue obtained from a recent biopsy may be permitted in lieu of the baseline biopsy after discussion between the Lilly CRP/CRS and investigator if a patient has not received any therapies for the disease between the time the archived tissue was collected to the start of LY345070 treatment; the decision to use an archived tissue sample will be documented.
  - A tumor tissue sample from a newly obtained core or excisional biopsy specimen collected during the study treatment period as shown in the SoA (Section 1.3).

Patients must be willing to undergo baseline and on-study biopsies that should not put patients at undue risk greater than that which comes with a core biopsy.

Collection of biopsies, as outlined above, is mandatory for patients enrolled in Cohorts D1 and D2 only in cases in which these patients present with accessible soft tissue metastasis that can be safely biopsied. Exceptions will be made in all other cases.

Collection of the following tumor tissue sample(s) is **optional** for patients participating in this study:

- Phase 1a:
  - If archival tissue is submitted to meet eligibility requirements, a newly obtained core or excisional pretreatment biopsy of a tumor lesion from a primary or metastatic site.
  - A tumor tissue sample from a newly obtained core or excisional biopsy specimen collected during the study treatment period as shown in the SoA (Section 1.3).
- Phase 1b:
  - An archival FFPE tumor tissue obtained from the primary tumor site, if available and not restricted by local regulations. Regardless of whether or not the archival tissue is submitted, patients are still required to undergo pretreatment and on-treatment biopsies, as indicated above and in the SoA (section 1.3).
- All patients:
  - A tumor tissue sample from a newly obtained biopsy specimen collected after disease progression or at additional study time points, if warranted and agreed upon by the investigator and Lilly. Such additional biopsies are optional and should be performed only if clinically feasible. If these additional samples are requested, they will be used to further investigate biomarkers that may explain treatment response and resistance mechanisms. If a biopsy is performed as part of clinical care after the patient signs the ICF, Lilly may request a tissue sample from the biopsy for additional biomarker testing at any time during the study including post-progression.

The tissue samples should be obtained using an appropriate method. Tumor tissue should be submitted as a newly acquired endoscopic core needle (minimum 18 gauge) or surgical biopsy. Cytological or fine-needle aspiration specimens may be acceptable for NSCLC patients upon discussion with the Lilly CRP/CRS, but are not acceptable for other cancer types. An attempt to obtain up to 4 core-needle biopsies, surgical biopsy, or endoscopic biopsy is required, unless medically contraindicated or unsafe and discussed with the Lilly CRP/CRS. Optimally, biopsies should be taken from the same metastatic lesion and from areas not previously irradiated (except if the lesion progressed after radiation). See the Laboratory Manual for details regarding sample collection and handling. If additional tumor biopsies are collected as part of clinical care, they should be submitted, along with pathology reports, for further analysis. When a biopsy is submitted, due diligence should be used to ensure that tumor specimens (not a normal adjacent or a tumor margin sample) are provided and that the tumor sample contains tumor cells prior to shipment to the central laboratory. If a pre-treatment sample does not contain adequate tissue for analysis, the patient may be replaced. Lilly may replace up to 10% of the total patients who are unable to submit an adequate tumor sample. The pathology report accompanying archival tissue

may also be requested. The pathology report must be coded with the patient number. Personal identifiers, including the patient's name and initials, must be removed from the institutional pathology report prior to submission. Lilly has a right to retain a portion of the submitted tissue. Archival blocks will be sectioned and returned to the study site. Slides and tissue samples collected on-study will not be returned.

All samples will be coded with the participant identification number. These samples and any data generated can be linked back to the participant only by the investigator site personnel.

Samples will be retained at a facility selected by Lilly or its designee for a maximum 15 years after the last participant visit for the study, or for a shorter period if local regulations and ERBs impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3475070 or after LY3475070 become(s) commercially available.

Technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. Existing approaches, including mutation profiling, copy number variability analysis, gene expression assays, multiplex assays, and/or immunohistochemistry may be performed on these tissue samples to assess potential associations between these biomarkers and clinical outcomes.

It is possible that biomarker data for patients in the study have already been generated from samples that were collected and analyzed prior to enrolling in this study. This may include data generated from genetic analyses. If available, these data may be requested from medical records for use in the research described in Sections 8.7 and 8.8.

8.8.1. Tumor Tissue Samples for Determination of CD73 Expression

Patients must submit all samples from the pretreatment biopsy and be positive for CD73 expression as determined at a central laboratory to confirm study eligibility into Phase 1b Cohort C. Patients that are not positive for CD73 expression, despite meeting all other eligibility criteria, will be screen failures. Unused tissue from screen failures will be returned to the sites. Samples from patients that are positive for CD73 expression and proceed to enroll into the study will be retained for biomarker testing.

8.9. Medical Resource Utilization and Health Economics

Health economics and medical resource utilization parameters will not be evaluated in this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

In the dose escalation phase, our hypothesis is that there is a tolerable DL for LY3475070 in both monotherapy and in combination treatment with pembrolizumab.

In the dose expansion phase, the objective is to assess the safety and tolerability, as well as clinical activity of LY3475070 as monotherapy and in combination with pembrolizumab. No formal hypothesis testing will be performed to demonstrate any statistically significant improvement in objective response rate. Therefore, specification of alternative hypothesis on the objective response rate does not apply.

9.2. Sample Size Determination

The primary objective of this study is to assess the safety and tolerability of LY3475070, thereby identifying and confirming the RP2D of LY3475070, to be administered as monotherapy and in combination with pembrolizumab, in patients with advanced solid malignancies. The primary objective of the Phase 1b portion of this study also includes preliminary clinical activity evaluation by overall response rate (ORR) per RECIST v1.1, as monotherapy and in combination with pembrolizumab. The secondary objective is to evaluate PK and any observed evidence of clinical efficacy.

With a total sample size of N=20 or N=40, example point estimates of incidence rates and corresponding 2-sided 95% confidence intervals (CIs) are summarized in the table below. The values are provided as a reference for estimation rather than a basis of any decision criteria. The RP2D may be revised based on the safety data obtained in the expansion phase (Iasonos and O'Quigley 2013).

Estimated Incidence Rate and 2-Sided 95% CI

N=20				N=40			
Number of Cases	Estimated Rate	95% CI[a]		Number of Cases	Estimated Rate	95% CI[a]	
		Lower Limit	Upper Limit			Lower Limit	Upper Limit
0	0.0	0.0	0.17	0	0.0	0.0	0.09
3	0.15	0.03	0.38	5	0.12	0.04	0.27
5	0.25	0.09	0.49	10	0.25	0.13	0.41
10	0.50	0.27	0.73	15	0.38	0.23	0.54
15	0.75	0.51	0.91	20	0.50	0.34	0.66

Abbreviations: CI = confidence interval; N = number of patients.

[a] 95% Clopper-Pearson interval for binomial distribution.

In the dose escalation phase, once a given DL is cleared for DLT evaluation and is deemed safe, the dose cohort may be expanded with backfill patients to further investigate the safety, PK, pharmacodynamic, and clinical activity of LY3475070 and the combination with

pembrolizumab. There will be up to 20 backfill patients enrolled across all DLs in Cohorts A and B combined in the phase 1a study. Enrollment of patients to the dose cohort for DLT evaluation/dose escalation decision will take precedent. A Bayesian toxicity monitoring rule will be implemented to ensure continuous safety monitoring, assuming DLT or DLT-equivalent events arise from a beta-binomial model. Specifically, if the *Prob(true DLT or DLT-equivalent rate >35%) >55%* in any given cohort, the enrollment to that cohort will be halted. A 35% rate is targeted to be consistent with the mTPI-2 equivalence interval upper bound. A Beta(1, 1) prior for the true rate is utilized. The stopping boundaries for this safety monitoring rule based on the aggregated data is listed in the following table.

Bayesian Toxicity Monitoring Rules

Number of Patients	Pause if Number of Patients with DLT or DLT Equivalent
4-5	≥2
6-8	≥3
9-11	≥4
12-14	≥5
15-16	≥6
17-19	≥7
20	stop

Abbreviations: DLT = dose-limiting toxicity.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Entered	All participants who sign informed consent
DLT evaluable	All patients enrolled in the dose escalation phase (phase 1a) who either complete 3 weeks of follow-up and treatment or discontinue treatment prior to 3 weeks due to a DLT.
PK Evaluable	All enrolled patients who have at least 1 post baseline evaluable PK sample
Safety	All participants who take at least 1 dose of study treatment. Participants will be included in the treatment group corresponding to their initial dose of study treatment, even if it is not the treatment to which they were assigned. In the event of a treatment error, participants will be analyzed according to the treatment they actually received. "Enrolled" population also refers to the "Safety" population in this study.
Phase 1a	All patients assigned to a treatment cohort during the dose escalation portion of the study.
Phase 1b	All patients assigned to a treatment cohort during the dose expansion portion of the study.
CD73+	CD73+ by IHC

Abbreviations: DLT = dose-limiting toxicity; IHC = immuno-histochemistry; PK = pharmacokinetics.

9.4. Statistical Analyses

9.4.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee.

Efficacy analyses will be conducted on the set of all enrolled patients. This set includes all data from all participants receiving at least 1 dose of the investigational product according to the treatment the participants were assigned.

All tests of treatment effects will be conducted at a 1-sided 0.05 alpha level, as appropriate for the comparison, unless otherwise stated.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

9.4.2. Treatment Group Comparability

9.4.2.1. Participant Disposition

A detailed description of participant disposition will be provided at the end of the study, including a summary of the number and percentage of patients entered into the study, enrolled in the study, and treated as well as number and percentage of patients completing the study, as

defined in the statistical analysis plan (SAP), or discontinuing (overall and by reason for discontinuation). A summary of all important protocol deviations will be provided.

9.4.2.2. Participant Characteristics

Demographic data are collected and reported to demonstrate that the study population represents the target patient population considered for regulatory approval. A summary of baseline patient and disease characteristics, historical diagnoses, preexisting conditions, and prior therapies will be reported using descriptive statistics.

9.4.2.3. Concomitant Therapy

A summary of prior and concomitant medications will be reported.

9.4.2.4. Treatment Compliance

Study treatment compliance will be assessed as the proportion of treatment that is actually taken, relative to what is expected, after accounting for protocol-defined dose adjustments. Study treatment taken will be derived from the difference between the total number of capsules/tablets dispensed and returned over the course of the patient's treatment. The number of cycles received, dose omissions, dose reductions, dose delays, and dose intensity will be summarized for all treated patients by treatment arm.

9.4.3. Efficacy Analyses

9.4.3.1. Primary Analyses

Overall response rate is defined as the number of patients who achieve a best overall response of CR or PR divided by the total number of patients treated (safety population). The ORR, with 95% CI, will be summarized for each study part.

9.4.3.2. Secondary Analyses

The **disease control rate** (DCR), defined as the proportion of patients who achieved a CR or PR or SD) out of all patients treated, will also be summarized. Best response is determined from a sequence of responses assessed. Two objective status determinations of CR before progression are required for a best response of CR. Two determinations of PR or better before progression, but not qualifying for a CR, are required for a best response of PR.

Duration of response (DoR) is defined as the time from the date measurement criteria for CR or PR (whichever is first recorded) are first met until the first date that disease is recurrent or objective progression is observed, per RECIST v1.1 criteria, or the date of death from any cause in the absence of objectively determined disease progression or recurrence. Duration of SD will be calculated only for patients with best response of SD. It is measured from the date of start of treatment to the date of first progression of disease or the date of death due to any cause, whichever is earlier. For each patient who is not known to have died or to have had a progression of disease as of the data-inclusion cut-off date, duration of SD will be censored at the date of last objective response assessment prior to the date of any subsequent systemic anticancer therapy.

Progression-free survival (PFS) is defined as the time from the date of start of treatment to the first date of the observed clinical or radiologically documented PD or death due to any cause,

whichever occurs first. For patients who are not known to have died or progressed as of the data-inclusion cut-off date, PFS time will be censored at the date of the last objective progression-free disease assessment prior to the date of any subsequent systematic anticancer therapy.

PFS Event/Censoring Scheme

Situation[a]	Event/Censor	Date of Event or Censor
Tumor progression or death	Event	Earliest date of PD or death
No tumor progression and no death	Censored	Date of last adequate tumor assessment per RECIST v1.1, or date of first dose (whichever is later)[b]
Unless		
No baseline radiologic tumor assessment available	Censored	Date of first dose
No adequate postbaseline tumor assessment available and death reported after 2 scan intervals following the first dose[b, c]	Censored	Date of first dose
Tumor progression or death documented immediately after 2 or more scan intervals following last adequate tumor assessment or randomization (whichever is later)[b,c]	Censored	Date of last adequate tumor assessment, per RECIST v1.1, or date of first dose (whichever is later)[b]
New therapeutic anticancer treatment started prior to tumor progression or death	Censored	Date of last adequate radiological assessment prior to new therapeutic anticancer therapy[b]

Abbreviations: CR = complete response; PD = progressive disease; PFS = progression-free survival; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

[a] Symptomatic deterioration (i.e., symptomatic progression that is not confirmed per RECIST v1.1) will not be considered as tumor progression.

[b] Adequate tumor assessment per RECIST v1.1 refers to an assessment with one of the following responses: CR, PR, SD, or PD.

[c] Refer to the statistical analysis plan for the definition of 2 scan intervals, including any adjustment for scan window.

Time to response (TTR) is defined as the time from the date of start of treatment to the date measurement criteria for confirmed CR or PR (whichever is first recorded) are first met. For patients who are not known to have achieved CR or PR as of the data-inclusion cut-off date, TTR will be censored at the date of the last objective disease assessment prior the date of any subsequent systematic anticancer therapy.

9.4.3.3. Tertiary/Exploratory Analyses

Overall survival (OS), as well as the efficacy parameters based on iRECIST will also be analyzed as the exploratory objectives. The definition of efficacy endpoints based on iRECIST will be described in the SAP.

Overall survival is defined as the time from the first start of study treatments until death from any cause. If the patient is alive, lost to follow-up, or withdrawn from study at the time of data analysis, OS data will be censored on the last date the patient is known to be alive.

9.4.4. Safety Analyses

All patients who receive at least 1 dose of any study therapy will be evaluated for safety and toxicity.

The MedDRA Version 22.0 (or higher) will be used when reporting AEs by MedDRA terms. The MedDRA Lower Level Term (LLT) will be used in the treatment-emergent computation. Treatment-emergent adverse events will be summarized by System Organ Class (SOC) and by decreasing frequency of Preferred Term (PT) within SOC.

Safety analyses will include summaries of the following:

- DLTs at each DL in the dose escalation phase and DLT-equivalent AEs for expansion cohorts;
- AEs, including severity and possible relationship to study drug;
- SAEs, including possible relationship to study drug;
- AEs leading to dose adjustments;
- discontinuations from study treatment due to AEs or death;
- treatment emergent abnormal changes in laboratory values;
- treatment emergent abnormal changes in vital signs and ECGs.

9.4.5. Pharmacokinetic/Pharmacodynamic Analyses

Selected PK descriptors for LY3475070 (based on actual sampling times), including C_{max}, approximate time of C_{max} (t_{max}), and AUC will be calculated by noncompartmental analysis methods and/or model simulations. As an exploratory analysis, PK descriptor estimates for trough concentrations (C_{min}) at steady state following repeated dose may be evaluated.

In addition, PK parameter estimates for LY3475070 as single agent and in combination with pembrolizumab may be calculated, data allowing. The version of any software used for the analysis will be documented, and the program will meet the Lilly requirements of software validation. It is possible that other validated, equivalent PK software programs may be used if appropriate, warranted, and approved by Global PK/pharmacodynamics management.

PK/pharmacodynamics analyses may be conducted to explore exposure-response relationships between LY3475070 concentrations in systemic circulation and various pharmacodynamic measures as second step if dose-response relationship is positively assessed.

Renal clearance of LY3475070 will be calculated as the ratio of amount excreted/AUC from time 0 to time t (AUC_{0-t}), and will be compared with unbound glomerular filtration rate,

estimated using creatinine renal clearance and plasma unbound fraction (Fu) (Fu × amount of creatinine excreted/creatinine AUC_{0-t}).

9.4.6. Other Analyses

Subgroup Analyses A prespecified list of subgroups will be identified in the SAP. The treatment effect within each subgroup will be summarized. Other subgroup analyses not specified in the SAP may be performed as deemed appropriate. These subgroups will be based on important characteristics, for example, prognostic significance.

9.4.6.1. Biomarker Analyses

Single-marker and/or multi-marker statistical analysis may be performed to explore the association between biomarkers, dose/exposure, and clinical outcomes. For an example, an association analysis between CD73 expression and clinical benefit may be triggered after data in Phase 1b Cohort C is collected.

9.5. Interim Analyses

In the Phase 1a portion of this study, dose-escalation data (monotherapy and combination) will be reviewed for safety on a cohort-by-cohort basis, until the MTDs (or the highest DLs if MTDs are not reached) are determined for each treatment part. The purpose of these cohort-by-cohort reviews is to evaluate the safety data at each DL and determine if a DLT has been observed that would suggest MTD has been met or exceeded. The investigators and the Lilly study team will make the determination regarding dose escalation based upon their review of the safety and tolerability data as described in this protocol.

In the Phase 1b portion of this study, a safety review will be performed after the first 20 patients across all dose-expansion cohorts are enrolled and treated for 1 cycle, and then every 6 months afterward. For preliminary efficacy evaluations, the following interim analyses are planned:

- Cohort C (patients with CD73+ tumors) and Cohort D (castrate resistant prostate cancer): for each cohort, an interim analysis of safety and efficacy is planned after 10 patients in the monotherapy arm are treated and completed 2 cycles or have discontinued before the first postbaseline tumor assessment. Per 2:1 randomization ratio, at this interim analysis approximately 20 patients in the combination arm are treated. Preliminary efficacy will be evaluated on these 20 patients in the combination arm and on these 10 patients in the monotherapy arm, and the combination arm may be expanded with additional 20 patients if the totality of efficacy, safety, and PK/pharmacodynamics data warrant expansion. If no objective responses are observed, both as monotherapy or combination therapy, the combination arm(s) will not continue enrollment.
- Cohort E (TNBC): an interim of safety and efficacy is planned after approximately 20 patients are treated and completed 2 cycles or have discontinued before the first postbaseline tumor assessment. The trial may continue to enroll 20 additional patients for the final analysis if the totality of efficacy, safety, and PK/pharmacodynamics data supports the addition of patients. If no objective responses are observed, additional patient enrollment to Cohort E will be terminated.

The interim analyses may be combined if they are expected to occur within a similar timeframe; interim analyses may also be combined with any prespecified safety review or annual reporting (such as an update to the IB or Development Safety Update Review, etc.).

If it is deemed that enough data are obtained to assess the primary objective and the secondary objectives, a CSR might be created before the last patient visit. In this case, all data until the data-cutoff date will be used for the analysis of safety, efficacy, PK, and pharmacodynamic biomarkers. All data defined in the protocol will continue to be collected from patients on treatment after the data-cutoff date. These data may be reported separately and the analyses on all patients including these data may not be performed.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

The CSR coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

10.1.2. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- Participants otherwise eligible for Phase 1b Cohort C will sign the Cohort C informed consent prior to collection of the fresh tissue sample for determination of CD73 expression and potentially retained for biomarker testing.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and is kept on file.

Participants who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.3. Data Protection

- Participants will be assigned a unique identifier by the investigator. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.4. Dissemination of Clinical Study Data

10.1.5. Data Quality Assurance

To ensure accurate, complete, and reliable data, the sponsor or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- provide sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site

- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and verify data reported to detect potential errors

In addition, the sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by the sponsor or its representatives and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

Data Capture System

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An electronic data capture system (EDC) will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Additionally, clinical outcome assessment (COA) data will be collected by the subject, via a paper source document and will be transcribed by the investigator site personnel into the EDC system.

Data collected via the sponsor-provided data capture system will be stored at third party. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system. Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and the results will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

10.1.6. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.7. Study and Site Closure

10.1.7.1. Discontinuation of the Study

The study will be discontinued if Lilly or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

10.1.7.2. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly or its designee, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed below will be performed as indicated in the table below.
- Local laboratory results are required for inclusion/exclusion determination, study intervention administration, and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the clinically significant abnormalities must be entered into the AE CRF. If there is an abnormal laboratory value or abnormal value for any other diagnostic or screening test (for example, blood pressure increased, neutrophils decreased, etc.) and it is known to be related to a diagnosis (for example, hypertension, neutropenia, etc.) this should be reported in the CRF as an AE. Do not enter the test abnormality; enter the disease diagnosis or categorical term.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations and clinically significant findings should be recorded reported in the CRF as an AE.

Enrollment and treatment decisions may be based upon local laboratory results. Discrepancies between local and central laboratory results will not be considered a protocol deviation.

Clinical Laboratory Tests

Hematology[a] -local laboratory	
Leukocytes (WBC)	Basophils
Neutrophils	Erythrocytes (RBC)
Lymphocytes	Hemoglobin (HGB)
Monocytes	Hematocrit (HCT)
Eosinophils	Platelets (PLT)

Coagulation -local laboratory	
PT/INR	PTT/aPTT

Clinical chemistry[a] -local laboratory Serum concentrations of:	
Alanine aminotransferase (ALT)	Calcium
Albumin	Creatinine
Alkaline phosphatase	Glucose (random)
Amylase	Lipase
Aspartate aminotransferase (AST)	Potassium
Bilirubin, direct	Protein
Bilirubin, total	Sodium
Blood urea nitrogen (BUN) or blood urea	

Urinalysis -local laboratory	
Blood	Protein
Glucose	Specific gravity
Ketones	Urine leukocyte esterase[d]
pH	

Pregnancy Test[c] -local laboratory	
Urine pregnancy test	Serum pregnancy test
Note: Urine pregnancy test at a minimum sensitivity of 25 IU/L or equivalent units of β-hCG. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required	

Thyroid panel -local laboratory	
Triiodothyronine (T3) or Free Triiodothyronine (FT3)	Thyroid-stimulating hormone (TSH)
Free Thyroxine (FT4)	

CCI

Tumor markers -local laboratory	
PSA	CA-125
CEA	CA 19-9

IHC - Central laboratory
CD73 expression for Phase 1b Cohort C

Selected tests may be obtained in the event of anaphylaxis or generalized urticaria.

Hypersensitivity Tests[b] – Central laboratory	
Anti-LY antibodies (immunogenicity)	Basophil Activation Test
LY concentration (PK)	Complements
Tryptase	Cytokine Panel
N-methylhistamine	

Abbreviations: aPTT = activated partial thromboplastin time; CA-125 = cancer antigen 125; CA 19-9 = cancer antigen 19-9; CEA = carcinoembryonic antigen; CRF = case report form; hCG = human chorionic gonadotropin; HCT = hematocrit; HGB = hemoglobin; INR = international normalized ratio; MB = muscle and brain; PLT = platelets; PK = pharmacokinetics; PT = prothrombin time; PTT = partial thromboplastin time; PSA = prostate specific antigen; RBC = red blood cells; WBC = white blood cells.

a Treatment and enrollment decisions will be based on local laboratory results.

Note: Neutrophils reported by automated differential hematology instruments include both segmented and band forms. When a manual differential is needed to report the neutrophils, the segmented and band forms should be added together and recorded on the CRF, unless the CRF specifically provides an entry field for bands.

b Central laboratory. In addition, local labs may be collected at investigator's discretion.

c For female patients of childbearing potential.

d Urine microscopy may be used in place of the urine leukocyte esterase assessment to test for the presence of WBC.

10.3. Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
    a. Documented hysterectomy
    b. Documented bilateral salpingectomy
    c. Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

1. Women of child-bearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same sex relationship without sexual relationships with males. Periodic abstinence methods (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial, and withdrawal) are not acceptable methods of contraception.

2. Women of child-bearing potential must use 2 effective methods of contraception for the entirety of the study. Abstinence or contraception must continue following completion of study drug administration, LY3475070 and pembrolizumab, for at least 120 days following the last dose of study drugs or country requirements, whichever is longer. For patients receiving LY3475070 only, contraception should be maintained for 5 half-lives or until plasma concentrations are equal to 1/25th of the nonclinical NOAEL exposure, (NOAEL/25) predicted to be 7 days.
   a. Women of child-bearing potential participating must test negative for pregnancy prior to initiation of treatment as indicated by a negative urine pregnancy test at the screening visit followed by a negative serum pregnancy test within 24 hours prior to study drug exposure. Pregnancy testing is conducted at monthly intervals during study treatment in both treatment arms, and up to 120 days after study discontinuation for patients receiving LY3475070 and pembrolizumab, and at 7 days after study discontinuation for patients receiving LY3475070 monotherapy.
   b. Two effective methods of contraception, such as male or female condoms with spermicide, diaphragms with spermicide or cervical sponges, will be used. The subject may choose to use a double barrier method of contraception. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. Thus, each barrier method must include use of a spermicide. It should be noted that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these methods are combined.
      i. One of the 2 methods of contraception must be a highly effective (less than 1% failure rate) method of contraception, such as combination oral contraceptives, implanted contraceptives or intrauterine devices.

Collection of Pregnancy Information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of obtaining informed consent from the pregnant female partner. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for

longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.2. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be discontinued from study treatment.

10.4. Appendix 4: Liver Safety: Suggested Actions and Follow-up Assessments

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with participants in consultation with the Lilly, or its designee, CRP/CRS.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin (HGB)	
Hematocrit (HCT)	**Hepatic Coagulation[a]**
Erythrocytes (RBC)	Prothrombin time (PT)
Leukocytes (WBC)	Prothrombin time, INR
Neutrophils[b]	
Lymphocytes	**Hepatic Serologies[a,c]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets (PLT)	Hepatitis B surface antibody
	Hepatitis B core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
Alanine aminotransferase (ALT)	**Antinuclear Antibody[a]**
Aspartate aminotransferase (AST)	
Gamma-glutamyl transferase (GGT)	**Anti-smooth Muscle Antibody [a]**
Creatine phosphokinase (CPK)	
	Anti-actin Antibody[a]

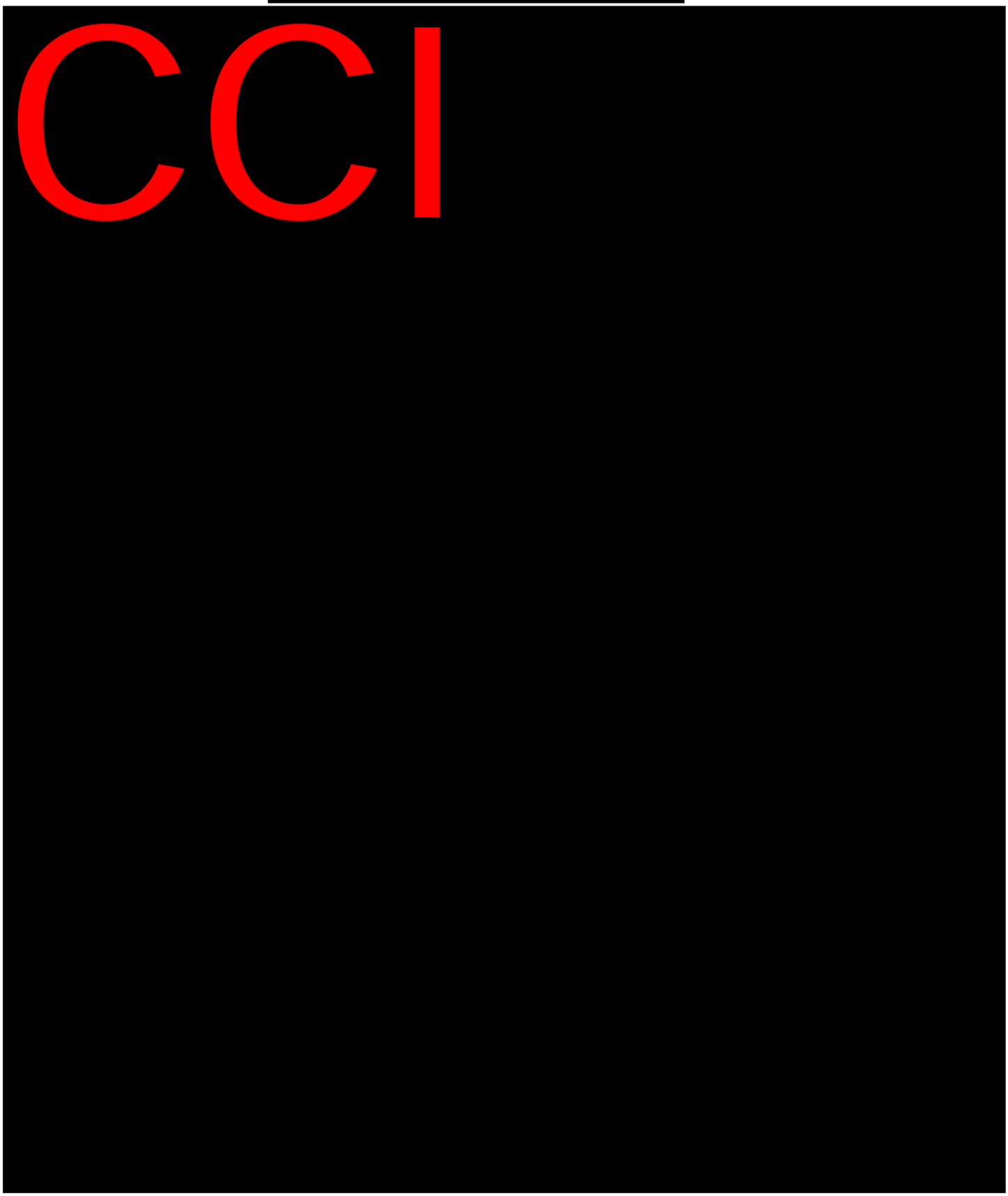
Abbreviations: IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio.

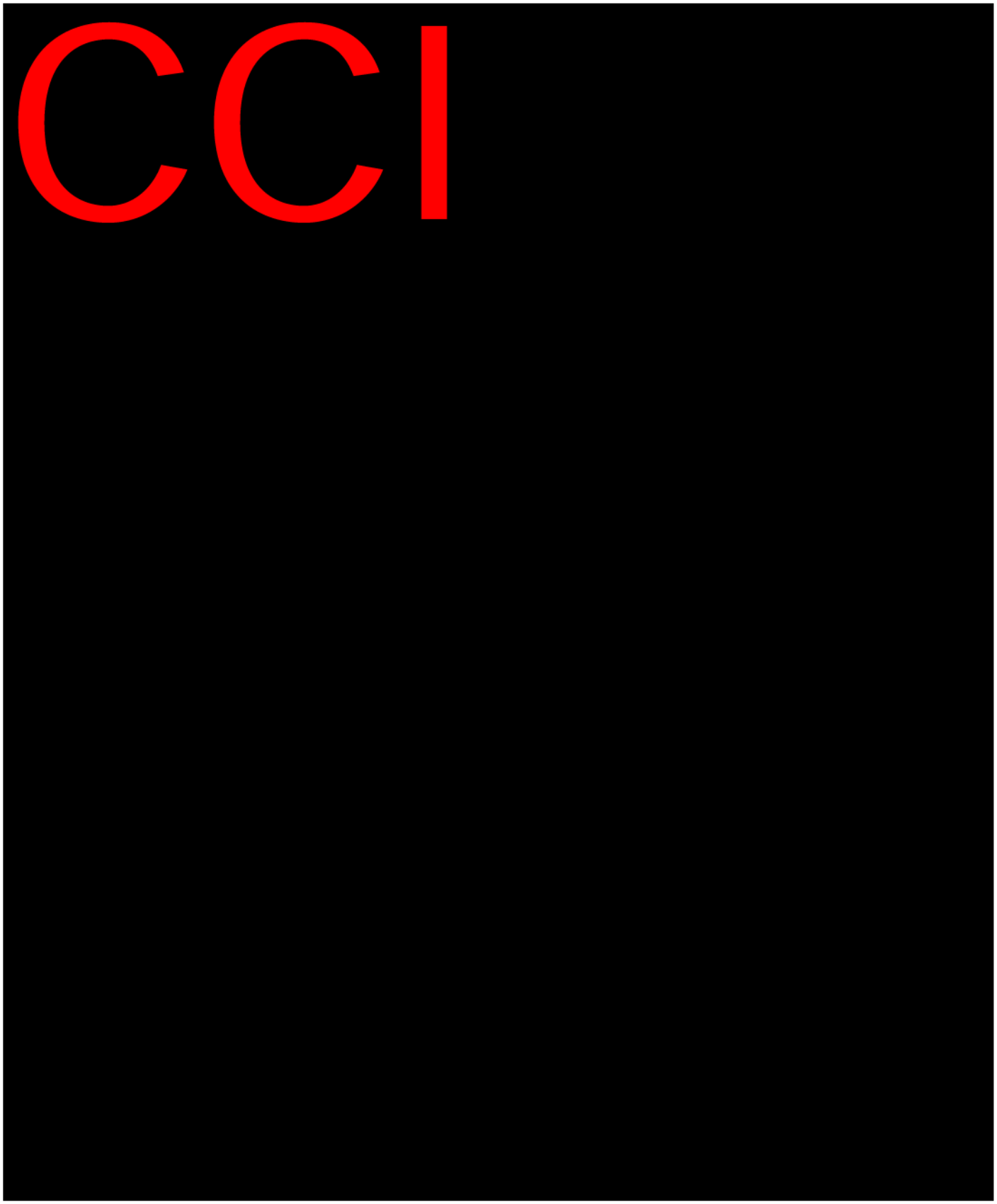
[a] Assayed by local laboratory.

[b] Neutrophils reported by automated differential hematology instruments include both segmented and band forms. Whenever a manual differential is needed to report the neutrophils, the segmented and band forms should be added together and recorded on the CRF, unless the CRF specifically provides an entry field for bands.

[c] Reflex/confirmation dependent on regulatory requirements and/or testing availability.

10.5. Appendix 5: CCI




CCI

10.6. Appendix 6: Creatinine Clearance Formula

Note: This formula is to be used for calculating creatinine clearance (CrCl) from **local laboratory results only.**

For serum creatinine concentration in mg/dL:

$$\text{CrCl (mL/min)} = \frac{(\mathbf{140 - age}^{a}) \times (\mathbf{wt}) \times \mathbf{0.85} \text{ (if female), or} \times \mathbf{1.0} \text{ (if male)}}{\mathbf{72} \times \mathbf{serum\ creatinine}\ (mg/dL)}$$

For serum creatinine concentration in μmol/L:

$$\text{CrCl (mL/min)} = \frac{(\mathbf{140 - age}^{a}) \times (\mathbf{wt}) \times \mathbf{0.85} \text{ (if female), or} \times \mathbf{1.0} \text{ (if male)}}{\mathbf{0.81\ x\ serum\ creatinine}\ (\mu mo/L)}$$

a age in years, weight (wt) in kilograms.

Reference: Cockcroft and Gault 1976.

10.7. Appendix 7: Country-specific Requirements

10.7.1. Discontinuation of Inadvertently Enrolled Patients in the UK

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study treatment and safety follow up should be performed as outlined in Section 1.3 (Schedule of Activities), Section 8.3 (Adverse Events and Serious Adverse Events), and Section 8.2 (Safety Assessments) of the protocol.

10.8. Appendix 8: Dose-Finding Algorithm of the Modified Toxicity Probability Interval-2 Method Showing Number of Patients Treated

Number of Patients

Number of Patients with DLTs

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	D	D	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
2		DU *	D	D	D	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E
3			DU	DU	D	D	D	D	S	S	S	S	E	E	E	E	E	E	E	E
4				DU	DU	DU	D	D	D	D	D	S	S	S	S	S	E	E	E	E
5					DU	DU	DU	DU	DU	D	D	D	D	D	S	S	S	S	S	S
6						DU	DU	DU	DU	DU	DU	D	D	D	D	D	D	S	S	S
7							DU	DU	DU	DU	DU	DU	DU	D	D	D	D	D	D	D
8								DU	DU	DU	DU	DU	DU	DU	DU	DU	D	D	D	D
9									DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	D
10										DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
11											DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
12												DU	DU	DU	DU	DU	DU	DU	DU	DU
13													DU	DU	DU	DU	DU	DU	DU	DU
14														DU	DU	DU	DU	DU	DU	DU
15															DU	DU	DU	DU	DU	DU
16																DU	DU	DU	DU	DU
17																	DU	DU	DU	DU
18																		DU	DU	DU
19																			DU	DU
20																				DU

$n = 20$, $p_T = 0.3$, $\varepsilon_1 = 0.05$, $\varepsilon_2 = 0.05$

E: Escalate to the next higher dose; S: Stay at the same dose; D: De-escalate to the previous lower dose; DU: De-escalate to the previous lower dose and the current dose will never be used again in the trial;

* If at the first dose level, users can choose to early-terminate the trial or not based on their own discretion.

The number of patients dosed at a given DL is shown in the columns (X-axis), while the number of DLTs experienced is shown in the rows (Y-axis). The rules in this figure will be used for each DL evaluated; the patient numbers and DLTs do not carry over from cohort to cohort. By locating the intersection of the number of patients dosed and the number of DLTs, 1 of 4 predefined rules is used:

- E: Escalate the dose
- S: Stay at the same dose
- D: De-escalate the dose
- DU: De-escalate the dose due to unacceptable toxicity. The dose cannot be re-escalated to this DL at a future point in the escalation.

For example, within a cohort:

- If 1 of 3 patients experiences a DLT, stay at the same dose (see "S" in column 3, row 1). The fourth patient must be treated at the same DL.
- If 1 of 6 patients experiences a DLT, escalate the dose (see "E" at column 6, row 1).
- If 2 of 3 patients experience a DLT the dose to treat the next patient is de-escalated (see "D" at column 3, row 2).
- If 5 of 7 patients experience a DLT, the dose is determined to be unacceptably toxic, and the previous dose is defined as the MTD.

10.9. Appendix 9: Abbreviations

Term	Definition
^{99m}Tc MDP	^{99m}Tc-methylene diphosphonate
$A_{1A}R$	adenosine $_{1A}$ receptor
$A_{2A}R$	adenosine $_{2A}$ receptor
$A_{2B}R$	adenosine $_{2B}$ receptor
A_3R	adenosine $_3$ receptor
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMP	adenosine monophosphate
ASCO/CAP	American Society of Clinical Oncology/College of American Pathologists
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	Area under the curve
BID	two times a day
BOR	best overall results
CD73	ecto-5′-nucleotidase
CIOMS	Council for International Organizations of Medical Sciences
CCI	[redacted]
CM	cutaneous melanoma
CNS	central nervous system
COA	clinical outcome assessment

complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRF/eCRF	case report form/electronic case report form
CRP/CRS	clinical research physician/clinical research scientist: Individual responsible for the medical conduct of the study. Responsibilities of the CRP/CRS may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DCR	disease control rate
DL	dose level
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture system
EGFR	epidermal growth factor receptor
EI	equivalence interval
enroll	the act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
ET	equivalent toxicity
FFPE	formalin-fixed paraffin-embedded
FSH	follicle stimulating hormone
GCP	good clinical practice

G-CSF	granulocyte-colony stimulating factor
HER2	human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICI	immune checkpoint inhibitor
ICH	International Council for Harmonisation
IHC	immunohistochemistry
Informed consent	a process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	an interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
irAE	immune-related adverse event
IRB/IEC	Institutional Review Board/Independent Ethics Committee
ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participant allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IV	intravenous
IVRS/IWRS	interactive voice-response system/interactive web-response system
LLT	lower level term
mAb	monoclonal antibody
mCRPC	metastatic castrate resistant prostate cancer

MedDRA	Medical Dictionary for Regulatory Activities
MOA	mechanism of action
MRI	magnetic resonance imaging
mTNBC	metastatic triple negative breast cancer
MN	micronucleus
MSI-H	microsatellite instability-high
MTD	maximum tolerated dose
mTPI-2	modified toxicity probability interval
NL-NT	new lesion-non-target
NL-T	new lesion-target
NOAEL	no observed adverse effect level
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PBPK	physiologically-based pharmacokinetics
PD	progressive disease
PD-1	programmed cell death protein 1
PD-1/L1	programmed cell death protein 1/ligand 1
PD-L2	programmed cell death protein/ligand 2
PFS	progression-free survival
PK	pharmacokinetics
PPS	per-protocol set: The set of data generated by the subset of participant who sufficiently complied with the protocol to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model.
PS	performance status
PSA	prostate-specific antigen
PT	preferred term
Q2W	every 2 weeks

Q3W	every 3 weeks
QD	once a day
QTc	corrected QT interval
RCC	renal cell carcinoma
RECIST/iRECIST	Response Evaluation Criteria in Solid Tumors/immune Response Evaluation Criteria in Solid Tumors
RP1D	recommended phase 1 dose
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
screen	the act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SoA	schedule of activities
SOC	System Organ Class
SUSARs	suspected unexpected serious adverse reactions
TBL	total bilirubin
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TME	tumor microenvironment
TNBC	triple negative breast cancer
TTR	time to response

10.10. Appendix 10: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment a (02-Oct-2019)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

This amendment incorporates changes requested by regulatory agencies. In addition, this amendment includes changes made to correct and clarify information for sites.

Section # and Name	Description of Change	Brief Rationale
Section 6.6.1 Dose Modification and Toxicity Management	Addition of monitoring and management guidelines for infusion-related reactions	Based on regulatory agency feedback
Section 5.1 Inclusion Criteria	Amended criteria to specify minimum treatments patients should have received for phase 1a	Based on regulatory agency feedback
Section 5.1 Inclusion Criteria	Amended criteria to specify minimum treatments patients should have received for phase 1b	Based on regulatory agency feedback
Section 1.3.1 Sampling Schedule for Pharmacokinetics and Biomarkers	Revised ECG monitoring plan to add an ECG collection	Based on regulatory agency feedback
Section 6.1.1 Definition of DLT and DLT-ET	Modification of dose limiting toxicity criteria and clarification of definition of DLT-ET	Based on regulatory agency feedback
Section 5.2 Exclusion Criteria	Separated exclusion criteria a through j from Criterion 17 into numbered criteria	Based on regulatory agency feedback
Section 8.1.2 iRECIST for Confirmation of PD in Clinically Stable Patients and Radiologic PD per RECIST v1.1	Modification of management guidelines for patients who have radiologic evidence of progressive disease by RECIST v1.1	Based on regulatory agency feedback
Section 4.1 Overall Design	Clarification regarding dose escalation timeline	Based on regulatory agency feedback
Section 1.1 Synopsis,	Resolved inconsistencies	Based on regulatory agency

Section # and Name	Description of Change	Brief Rationale
Section 1.2 Schema, Section 4.1 Overall Design, Section 6.1 Study Intervention(s) Administered	regarding naming of recommended dose	feedback
Section 6.1 Study Intervention(s) Administered	Added instruction on how to administer LY3475070 with regards to food intake	Based on regulatory agency feedback
Section 5.1 Inclusion Criteria	Removed duplicate inclusion criteria related to informed consent	Duplication
Section 1.3 Schedule of Activities	Specification of requirements related to short- and long-term follow-up visits	Clarification for sites
Throughout protocol	Minor formatting and editorial changes	Minor, therefore not detailed

Amendment b (24-Feb-2020)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The purpose of this amendment is to add updated informative language for pembrolizumab and address regulatory concerns.

Section # and Name	Description of Change	Brief Rationale
Throughout	Addition of pembrolizumab-specific language	Language added as a result of pembrolizumab language requirements
Section 1.3 SoA	Added language regarding iRECIST evaluation	Clarification
Section 1.3 SoA	Amended language regarding urinalysis collection	Clarification
Section 1.3 SoA, Section 5.1 Inclusion Criteria, Section 5.2 Exclusion Criteria, Section 6.5 Concomitant Therapy, Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information	Added and amended pregnancy/contraception language	Per regulatory feedback

Section 5.1 Inclusion Criteria	Amended hepatic inclusion language	Per regulatory feedback
Section 5.1 Inclusion Criteria	For Inclusion Criteria 2 and 5, revised requirements for prior lines of therapy for all indications	Per investigator feedback
Section 10.2 Appendix 2: Clinical Laboratory Tests	Amended language regarding local laboratory results	Clarification
Throughout protocol	Minor formatting and editorial changes	Minor, therefore not detailed.

Amendment c (22-Mar-2020)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The purpose of this amendment is to add updated informative language for pembrolizumab and address regulatory concerns.

Section # and Name	**Description of Change**	**Brief Rationale**
Section 1.3. Schedule of Activities	Removal of stool sample collection	Clarification; site/investigator feedback
Section 1.3.1 Sampling Schedule for Pharmacokinetics and Biomarkers	Change of mandatory biopsies to optional for Phase 1a patients; removal of collection of stool samples	Updated for enrollment and study participation purposes
Section 5.1 Inclusion Criteria	Addition of inclusion criterion 2 for archival sample collection; changed mandatory biopsies to optional for Phase 1a patients	Updated for enrollment and study participation purposes
Section 5.1 Inclusion Criteria	Removed language regarding intervening treatment for PD-1 indications in Phase 1a for inclusion criterion 3; amended language of “activating EGFR mutations” to “targetable mutations”	Updated for enrollment and study participation purposes
Section 5.1 Inclusion Criteria	Moved inclusion criterion 9 to criterion 6 and amended language	Updated for enrollment and study participation purposes
Section 5.1 Inclusion Criteria	Addition of language for inclusion criterion 13; amended language regarding wash-out period for prior therapy	Clarification; site/investigator feedback

Section 5.1 Inclusion Criteria	Updated platelet lab value in inclusion criterion 14 to 100×10^9/L	Clarification; site/investigator feedback
Section 5.2 Exclusion Criteria	Amended language for exclusion criterion 26	Clarification
Section 5.2 Exclusion Criteria	Deletion of exclusion criterion 37 regarding prior participation in a clinical trial	Clarification; site/investigator feedback
Section 8.8 Biomarkers	Amended language regarding the collection of tumor tissue sample(s) and stool collection	Updated for enrollment and study participation purposes
Throughout protocol	Minor formatting and editorial changes	Minor, therefore not detailed.

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Approval Date & Time: 02-Sep-2020 18:58:20 GMT

Signature meaning: Approved