J2I-MC-JZMA Statistical Analysis Plan Version 1

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

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Approval Date: 23-Oct-2019

1. Statistical Analysis Plan: J2I-MC-JZMA: 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

CD73 Inhibitor (LY3475070)

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Protocol J2I-MC-JZMA
Phase 1

Statistical Analysis Plan electronically signed and approved by Lilly on date provided below.

Approval Date: 23-Oct-2019 GMT

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3. Revision History

Statistical Analysis Plan (SAP) Version 1 was approved prior to the first visit when a subject receives study drug or any other protocol intervention. The SAP Version 1 is based on Protocol J2I-MC-JZMA(a), approved on 02-Oct-2019.

4. Study Objectives

4.1. Primary Objective

Primary Objectives	Endpoints
Phase 1a	
• 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
Phase 1b	
• 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 v1.1

Abbreviations: CTCAE = Common Terminology Criteria in Adverse Events; DLT = dose limiting toxicities; ORR = overall response rate; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; RP2D = recommended phase 2 dose; TEAE = treatment-emergent adverse event.

4.2. Secondary Objectives

Secondary Objectives	Endpoints
Phase 1a	
• To characterize the LY3475070 PK profile as monotherapy and in combination with pembrolizumab • To characterize the clinical activity of LY3475070 as monotherapy and in combination with pembrolizumab as assessed by the investigator using RECIST v1.1	• $C_{max,}$ trough ($C_{min,}$ $C_{steady\ state}$), $AUC_{steady\ state}$ • ORR • DCR • PFS

Secondary Objectives	Endpoints
Phase 1b	
• To characterize the LY3475070 PK profile as monotherapy and in combination with pembrolizumab • To characterize the clinical activity of LY3475070 as monotherapy and in combination with pembrolizumab as assessed by the investigator using RECIST v1.1	• $C_{max,}$ trough ($C_{min,}$ $C_{steady\ state}$), $AUC_{steady\ state}$ • DOR • DCR • TTR • PFS • OS

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; DCR = disease control rate; DOR = duration of response; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; TTR = time to response.

4.3. Exploratory Objectives

Tertiary/Exploratory Objectives	Endpoints
Phase 1a	
• 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

Tertiary/Exploratory Objectives	Endpoints
Phase 1b	
• 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 identification on blood and urine samples.	• Metabolite profiling • Renal clearance

Abbreviations: 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.

5. Study Design

5.1. Summary of Study 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. Table JZMA.5.1. summaries the study intervention(s) administered and duration.

Table JZMA.5.1. Study Intervention(s) Administered and Duration

Cohort	Dose Level	Oral LY3475070	IV Pembrolizumab
Cohort A	DL1	150 mg QD	N/A
	DL2	300 mg QD	N/A
	DL3	600 mg QD	N/A
	DL4	1000 mg QD	N/A
Cohort B	CDL1	150 mg QD	200 mg Q3W
	CDL2	300 mg QD	200 mg Q3W
	CDL3	600 mg QD	200 mg 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).

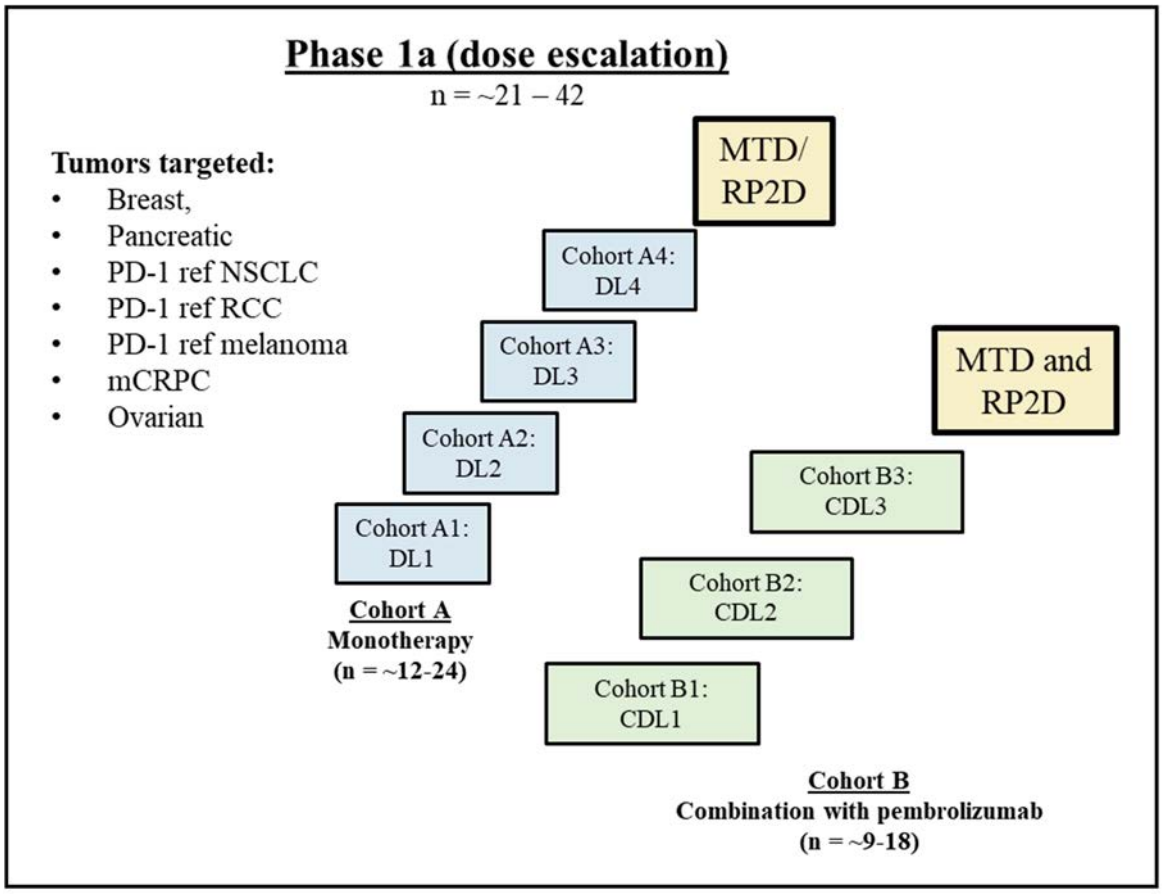
5.1.1. Phase 1a Dose Escalation

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). 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. Intra-patient dose escalation is not allowed.

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 final 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 enrollment to DL3 has commenced, LY3475070 in combination with pembrolizumab will be evaluated in **Cohort B** in 3 to 6 patients 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. The first patient of each DL will be observed for 48 hours before additional patients are enrolled to that DL. 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.

Figure JZMA.5.1 illustrates the study design for Phase 1a dose escalation. Section 5.1.3 describes the details of the dose-escalation method used in this study.



Abbreviations: 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; RCC = renal cell carcinoma; ref = refractory; RP2D = recommended phase 2 dose.

Figure JZMA.5.1. Illustration of study design for Phase 1a (dose escalation).

5.1.2. Phase 1b Dose Expansion

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.

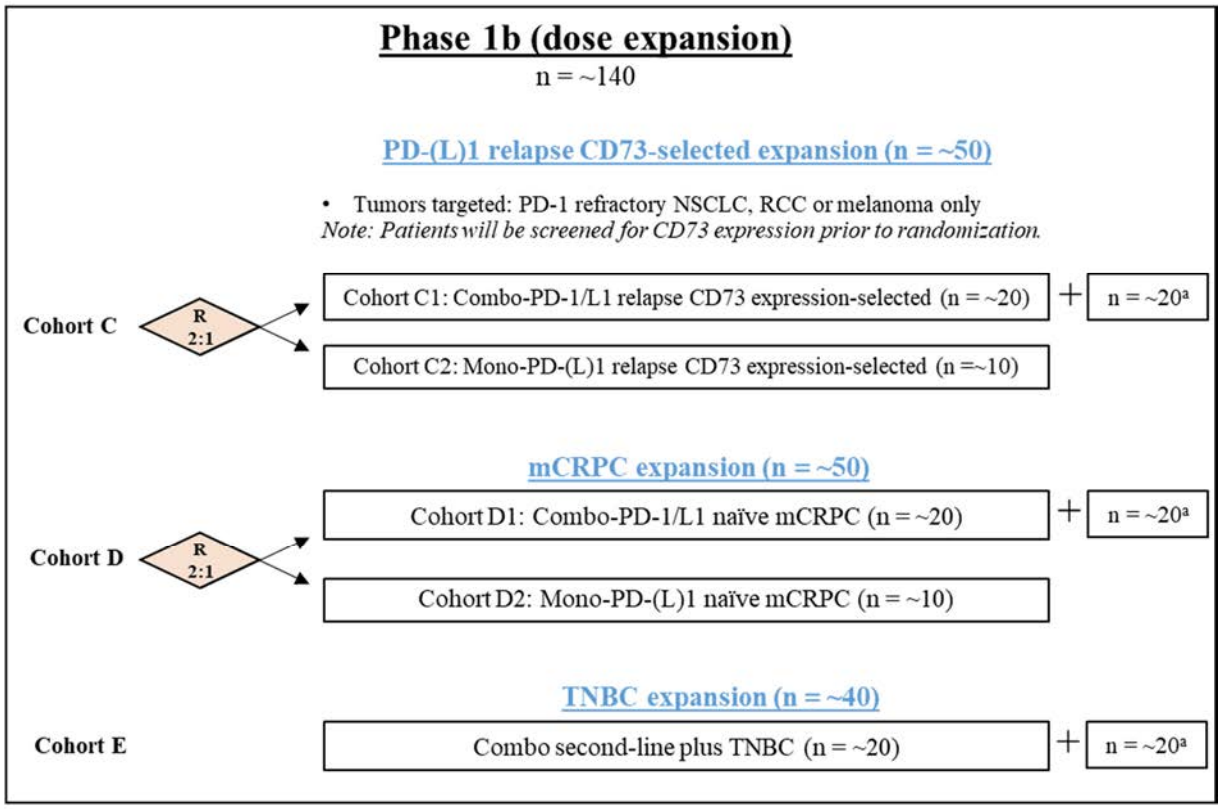
Cohort C will consist of patients that have been treated with and are refractory to PD-1/L1 inhibitor treatment with the following malignancies: NSCLC, RCC or melanoma. To be eligible, Cohort C will consist of patients with NSCLC, RCC, or melanoma that progressed on anti-PD1-L1 inhibitor therapy. Exception 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. 2018; 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.

Table JZMA.5.2 illustrates the study design for Phase 1b dose expansion.



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

Figure JZMA.5.2. Illustration of study design for Phase 1b (dose expansion).

5.1.3. Dose-Escalation Methodology

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 (Figure JZMA.5.3) 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.

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
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14														DU	DU	DU	DU	DU	DU	DU
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16																DU	DU	DU	DU	DU
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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.

Figure JZMA.5.3. Dose-finding algorithm of the mTPI-2 method showing number of patients treated and number of patients with DLTs.

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%). 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.

5.2. Determination of Sample Size

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).

Table JZMA.5.2. 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.

6. A Priori Statistical Methods

6.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company. The interpretation of the study results will be the responsibility of the investigator with the Lilly CRP or CRS, pharmacokineticist, and statistician. The CRP or CRS and statistician will also be responsible for the appropriate conduct of an internal review for both the final study report and any study-related material to be authorized by Lilly for publication.

Sponsor standard tables, figures, and listings (TFLs) and supporting programs and software (e.g., TAFFY, BEACH) will be utilized for all analyses where a suitable standard exists. Data derivations in this SAP are defined, based upon current Sponsor reporting standards at the time of writing, and may be updated at the time of analysis in order to maintain accordance with the most current Sponsor standards at that time.

In general, continuous variables will be presented using the mean, standard deviation, coefficient of variation, median, minimum, maximum and number of patients with an observation (n). For categorical variables, the population size (N), the number of patients with events (n) and the percentage of patients with events are usually reported.

All confidence intervals (CIs) will be given at a 2-sided 95%, unless otherwise stated.

The data handling conventions and analysis populations are outlined in Table JZMA.6.1.

Table JZMA.6.1. Data Handling Conventions and Analysis Populations

Term	Definition or Rule
Relative Study Day	If assessment is on or after date of first dose then (date of assessment) – (date of first study drug dose) +1
	If assessment precedes first dose of drug then (date of assessment) – (date of first study drug dose)
	There is no Study Day 0. Study Day 1 is the date of first dose and Study Day -1 is the day before the first dose.
Cycle Day	If assessment is on or after date of first dose in cycle then (date of assessment) – (date of first study drug dose in cycle) +1
	There is no Cycle Day 0. Cycle Day 1 is the date of first dose in that cycle.
Baseline	For change from baseline analyses, baseline value is defined as the last reported measure on or before the first dose date (prior to the dose administration) unless, otherwise, specified.
Entered	All participants who sign informed consent
DLT evaluable	All patients enrolled in the dose escalation phase (Phase 1a) who either complete 28 days of follow-up and at least 75% of treatment doses or discontinue treatment prior to 28 days due to a DLT.
Randomized	(Phase 1b portion only). All patients in cohorts C and D who are randomized to a treatment regimen, regardless of whether they take any study drug.
PK evaluable	All enrolled patients who have at least 1 postbaseline 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.
Screen Failures	Patients who have signed informed consent, do not meet eligibility criteria and are not enrolled.

Abbreviations: DLT = dose-limiting toxicity; PK = pharmacokinetic(s).

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

6.2. Handling of Dropouts or Missing Data

Missing data, except dates, will not be imputed. Historical data such as historical diagnosis, historical illness, preexisting conditions and prior therapies should be collected in a sufficiently informative way. For example, in order to be considered as historical illness, events occurring in the same year as study entry should have at least a known month and year for the end date, while events occurring in previous years should have at least a known year for the end date. The start

dates and end dates for adverse events and concomitant medications will be imputed following the most recent Sponsors' standards. Partial dates should be reported in all listings and not the imputed date.

6.3. Patient Disposition

A detailed summary of patient disposition will be provided. It will include a summary of the number and percentage of patients entered into the study, and treated as well as number and percentage of patients completing the study (patients who receive 1 cycle of study dose or are evaluable for DLT for Phase 1a and patients who have at least 1 postbasline tumor assessment for Phase 1b), or discontinuing (overall and by reason for discontinuation of LY3475070). Reason for discontinuation from both the study treatment and the study will be summarized by predetermined categories.

A listing of primary reasons for study treatment and study discontinuation will also be provided.

6.4. Patient Characteristics

Patient demographics (including age, sex, screening height, weight, body mass index, race, ethnicity, and country) will be reported using descriptive statistics. The summary will include the number of patients for each treatment group and the total across treatment groups.

The following baseline disease characteristics will be summarized by treatment arm: Eastern Cooperative Oncology Group (ECOG) performance status, initial pathological diagnosis, and basis of initial pathological diagnosis.

Patient preexisting condition, historical illness, prior anti-cancer therapies, and other baseline characteristics such as biomarker and genetic alterations at baseline will be summarized as deemed appropriate.

6.5. 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.

6.6. Concomitant Therapy

All medications will be coded to the generic preferred name according to the current World Health Organization (WHO) drug dictionary. All concomitant medications will be summarized for the safety population using the preferred name.

6.7. Efficacy Analyses

The antitumor activity of LY3475070 monotherapy and in combination with pembrolizumab will be assessed based on RECIST 1.1 and iRECIST (Seymour et al. 2017), respectively. The

efficacy analyses will be focused on treated participants (safety populations) in Phase 1a part of the study (dose escalation), and in Phase 1b part of the study (dose expansion).

The Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the curves, median time and 95% CI of time to event parameters such as OS, PFS and DoR based on RECIST 1.1, iPFS and iDOR based on iRECIST for each arm of Cohorts C and D, and Cohort E. Overall response rate (ORR based on RECIST 1.1 and iORR based on iRECIST), with corresponding 95% exact CI, will be summarized for each arm of Cohorts C and D, and Cohort E. ORR with corresponding 95% exact CI will also be summarized for the monotherapy and combination cohorts in Phase 1a part of the study.

The following definitions for efficacy endpoints will be used:

Primary Endpoint

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

Secondary Endpoints

The **disease control rate** (DCR), defined as the proportion of patients who achieved a CR or PR or stable disease (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 1.1 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 1.1, 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 1.1, 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 1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; SD = stable disease.

[a] Symptomatic deterioration (ie, symptomatic progression that is not confirmed per RECIST 1.1) will not be considered as tumor progression.

[b] Adequate tumor assessment per RECIST 1.1 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.

Exploratory Endpoints

As the exploratory objective, the efficacy parameters based on iRECIST will also be analyzed.

Overall response rate (iORR) is measured by the percentage of patients who achieved a complete response (iCR) or partial response (iPR) as their best overall response (iBOR) out of all

treated patients (safety population). The best overall response (iBOR) is defined as the best response across all time point assessments based on RECIST 1.1 and iRECIST.

Progression-free survival (iPFS) should be the date of randomization (the date of first dose for single arm study) to the date at which progression criteria are first met (ie, the date of first iUPD) provided that iUPD or a sequence of consecutive iUPD is confirmed by an iCPD, or the iUPD followed by only iUPDs at subsequent assessments, or no more tumor assessments, or to the death date from any cause in the absence of progressive disease. Patients known to be alive and without the iUPD as mentioned above as of the data inclusion cut-off date for a particular analysis will be censored at the time of the last adequate tumor assessment (a detailed iPFS event/censoring scheme is provided in the table below).

iPFS Event/Censoring Scheme

Situation[a]	Event/Censor	Date of Event or Censor
iUPD confirmed at next assessment (iCPD), or Consecutive iUPD followed by an iCPD	Event	(First) iUPD date
iUPD followed by only iUPD at subsequent assessments and no further tumor assessment available.	Event	First iUPD date of the consecutive iUPDs
iUPD without subsequent assessment	Event	iUPD date
Death	Event	Death date if no iUPD date as in the above 3 situations before death.
No Death and no iUPD or iUPD is followed by iSD/iPR/iCR/	Censored	Date of last adequate tumor assessment per iRECIST, or date of randomization (first dose for single arm study) (whichever is later)[b]
Confirmed iUPD (including all the first 3 Event cases)or death reported after 2 scan intervals following the last adequate tumor scan	Censored	Date of last adequate tumor scan prior to Confirmed IUPD (iCPD) or Death.
No baseline radiologic tumor assessment available	Censored	Date of randomization (first dose for single arm study)
No adequate postbaseline tumor assessment available and death reported after 2 scan intervals following the first dose[b, c]	Censored	Date of randomization (first dose for single arm study)

iPFS Event/Censoring Scheme

Abbreviations: "i" indicates immune responses assigned using iRECIST. iCR = complete response; iPR = partial response; iSD = stable disease; iUPD=unconfirmed progression; iCPD=confirmed progression.; iPFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors;

[a] Symptomatic deterioration (ie, symptomatic progression that is not confirmed per iRECIST) will not be considered as tumor progression.

[b] Adequate tumor assessment per iRECIST refers to an assessment with one of the following responses: iCR, iPR, iSD, iUPD, or iCPD.

[c] Refer to the statistical analysis plan for the definition of 2 scan intervals, including any adjustment for scan window. (new anti-cancer therapy in SAP)

Duration of response (iDoR) is defined as the time from the date measurement criteria for iCR or iPR (whichever is first recorded) are first met until the first date that disease is recurrent or objective progression (as assessed by investigators) is observed, or the date of death from any cause in the absence of objectively determined disease progression or recurrence. Patients known to be alive and without disease progression as of the data inclusion cut-off date for a particular analysis will be censored at the time of the last adequate tumor assessment. iDoR will follow the same censoring scheme as iPFS. iDoR will be analyzed for the treated patients who achieve iCR/iPR as the best of overall response (iBOR).

6.8. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

Unless stated otherwise, the Lilly pharmacokineticist will be responsible for the PK/PD 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}).

6.9. 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.

6.9.1. Extent of Exposure

LY3475070 will be administered PO QD on a 28-day cycle 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).

Pembrolizumab will be administered IV 200mg Q3W in cohorts B, C1, D1 and E.

The actual cumulative dose taken of LY3475070 will be derived from the difference between the total number of tablets/capsules dispensed and returned over the course of the patient's treatment taking into account the dose strengths.

The duration of therapy for the QD schedule will be calculated as last dose date-first dose date+1.

A summary of exposure will be provided for each study drug, including cycle received, cumulative dose, and duration of therapy.

A summary of dose intensity will be provided for each study drug. Dose intensity (per day) is calculated as total actual dose taken/duration of therapy (day). Relative dose intensity is calculated as 100 × (actual dose intensity per day/planned dose intensity per day).

Note that planned dose is the same as actual dose if there is no dose modification or cycle delays.

A summary of dose adjustments will be provided for each study drug, including dose omissions, dose reductions, cycle delays, and the corresponding reasons for dose adjustment.

6.9.2. Adverse Events

Adverse event (AE) verbatim terms will be provided by the investigators and then will be mapped by Lilly or its designee to corresponding terminology within the Medical Dictionary for Regulatory Activities (MedDRA) Lower Level Term (LLT) dictionary Version 22.0 (or higher).

The investigator will use Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (NCI 2009) to assign AE severity grades.

Preexisting conditions are defined as AEs that begin but do not resolve prior to the first dose of study drug in each study period. Preexisting conditions will be presented by patient and can be combined with the listing of AE, so that the history of the preexisting conditions/AEs can be traced.

A treatment emergent adverse event (TEAE) is defined as any AE that begins on or after the day of first dose in the reporting study period or any preexisting condition that increases in CTCAE grade on or after the day of first dose in the reporting study period. The MedDRA LLT will be used in the treatment-emergent computation.

The number of patients who experienced a TEAE, or TEAE possibly related to study drug, will be summarized. Treatment-emergent adverse events will be summarized by System Organ Class (SOC), by Preferred Term (PT) of decreasing frequency within SOC, and by maximum CTCAE grade and grade categories (any, Grade 3 or higher).

Adverse events leading to dose adjustments, treatment discontinuation, or death will also be summarized.

Dose-limiting toxicities in Phase 1a and DLT-equivalent toxicities occurring after Cycle 2 in Phase 1a or any cycle in Phase 1b will be summarized by cohort.

6.9.3. Deaths, Other Serious Adverse Events, and Other Notable Adverse Events

All deaths in this study, including the reasons for death, will be listed by treatment. The reasons for death will be summarized, separately for on-therapy, and within 30 days of last dose of study drug.

Serious AEs will be summarized for each treatment by decreasing frequency of PT within SOC. The summary will be provided for events, regardless of study drug causality, and repeated for events deemed by the investigator to be related to study medication.

6.9.4. Clinical Laboratory Evaluation

Listings of laboratory results will be provided. All relevant hematology and chemistry laboratory values will be graded according to CTCAE Version 5.0. Shift tables showing the change from baseline to the worst grade on study will be presented.

Laboratory analytes below/above quantifiable levels (data in the database recorded as "<x" and ">x") will be reported as such in listings, and imputed to the lower or upper limit of quantification in any summaries or analyses.

6.9.5. Vital Signs and Other Physical Findings

Vital signs measurements, including height, weight, temperature, blood pressure, pulse, and ECOG performance status will be listed and summarized.

6.9.6. *Electrocardiograms*

Local electrocardiograms (ECGs) will be summarized by cycle and overall. The summary by cycle will classify patients as having normal or abnormal. Adverse events that could be associated with abnormal ECGs will be presented, if appropriate.

Quantitative ECG results including PR, QRS, Bazett's corrected QT (QTcB), Fridericia's corrected QT (QTcF), and RR intervals will be provided in patient listings for absolute and change from baseline. In addition, summaries of outlying corrected QT (QTc) intervals (QTc, QTcB, and QTcF) will be provided. Outlying intervals include absolute values >450 for males, >470 for females, >480 and >500 msec, and change from baseline >30 and >60 msec.

6.10. Subgroup Analyses

The treatment effect within each subgroup of interest will be summarized. Other subgroup analyses not specified in this SAP may be performed as deemed appropriate. These subgroups will be based on important characteristics, for example, prognostic significance.

Single-marker and/or multi-marker statistical analysis may be performed to explore the association between biomarkers, dose/exposure, and clinical outcomes. CCI

CCI

6.11. Protocol Violations

All significant protocol violations will be summarized by pre-determined categories (e.g., inclusion/exclusion criteria, noncompliance with protocol procedures, drug dosage/intervention, use of excluded treatments, informed consent/assent process, continuing after meeting withdrawal criteria, or other). These violations will include deviations which can be identified programmatically and those which can only be identified by the clinical research associate (CRA) during monitoring.

6.12. Interim Analyses and Data Monitoring

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 post-baseline 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 data support.

- 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 post-baseline tumor assessment. The trial may continue to enroll 20 additional patients for the final analysis if the totality of data supports the addition of patients.

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.

Data Monitoring Committee: No

6.13. Annual Report Analyses

The following reports are needed as requested for annual reporting purposes.

Development Safety Update Report:

- Cumulative Subject Exposure by Age Group and Sex
- Cumulative Subject Exposure by Racial Group
- Estimated Cumulative Subject Exposure
- Exposure Information
- Listing of Discontinuations Due to AE During the Reporting Period
- Listing of Subjects Who Died During the Reporting Period

Clinical IB:

- Listing and Summary of Serious Adverse Event (SAE)
- Listing and Summary of Death
- Listing and Summary of TEAE (and by maximum CTCAE grade)
- Listing and Summary of Patient Disposition

- Listing and Summary of Study Drug Adjustment

Other reports may be requested if deemed appropriate for the IB.

6.14. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

Summary of adverse events, provided as a dataset which will be converted to an XML file. Both Serious Adverse Events and 'Other' Adverse Events are summarized: by treatment group, by MedDRA preferred term.

- An adverse event is considered 'Serious' whether or not it is a treatment emergent adverse event (TEAE).
- An adverse event is considered in the 'Other' category if it is both a TEAE and is not serious. For each Serious AE and 'Other' AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

In addition, a participant flow will be created that will describe how many enrolled patients completed the study, and for those who did not, the frequency of each reason for not completing. This analysis will be based on study discontinuation, not treatment discontinuation. A patient will be identified as having completed the study if the patient is observed until event (PD or death) or the patient had discontinued study treatment and is in follow up at the time of the final analysis. Patients who withdraw consent or are lost to follow-up before the final analysis, or who are still on treatment at the time of the final analysis will be identified as not completing the study.

7. References

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