J1E-MC-JZEA Protocol (b)

A Phase 1 Study of LY3434172, a Bispecific Antibody Monotherapy in Advance Solid Tumors

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A Phase 1 Study of LY3434172, a Bispecific Antibody Monotherapy in Advanced Solid Tumors

LY3434172

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1. Synopsis

Protocol Title:

A Phase 1 study of LY3434172, a bispecific antibody administered as a monotherapy in advanced solid tumors.

Rationale:

T-cells play a central role in immune response to tumor. However, tumors have adopted multiple mechanisms to evade host immune surveillance. One of the key mechanisms is the up-regulation of immune suppressive co-inhibitory molecules (immune checkpoint molecules) on the tumor cells. The programmed cell death protein-1 receptor (PD-1) axis is one of the dominant co-inhibitory pathways in T-cell activation. This axis involves three interactions. Both programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2) ligands, expressed by antigen presenting cells (APC), can bind to PD-1 receptor on T-cells. In addition, PD-L1 can also bind to B7-1, which is upregulated along with PD-1 upon initial T-cell activation by antigen stimulation. These interactions lead to suppression of T-cell activation. In a variety of tumors, PD-L1 is frequently over-expressed by tumor cells, contributing to the immune tolerant state known as T-cell exhaustion. However, blocking the PD-1 axis has been shown to remove this suppression and reinvigorate T-cell activation.

While anti-PD-1 and anti-PD-L1 antibodies have demonstrated durable clinical responses in multiple tumor indications, only a subset of patients benefit from these treatments and there is room for further improvement. In vitro experiments have demonstrated that LY3434172 can bridge cells engineered to express PD-1 and those that express PD-L1. This enhances cell-based functional activity in vitro and antitumor efficacy in vivo compared to monoclonal antibody (mAb) monotherapy or combination; hence, the bispecific antibody (bsAb) may have the potential to improve upon the biological activity of existing PD-1 and PD-L1 agents, either alone or in combination. Clinical relevance of bridging is unknown at this time. The goal of this study is to establish the safety and recommended Phase 2 dose (RP2D) of LY3434172 administered as monotherapy to patients with advanced solid tumors.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the safety and tolerability of LY3434172, thereby identifying a RP2D of LY3434172, administered to patients with advanced solid tumors.	• DLTs • Safety (including but not limited to): TEAEs, DLT-equivalent toxicities, SAEs, deaths, and clinical laboratory abnormalities per CTCAE (Version 5.0)
Secondary	
To assess the PK in patients with solid tumors of LY3434172.	• AUC, C_{min} and approximate C_{max} of LY3434172
To assess preliminary antitumor activity[a] of LY3434172	• ORR • DOR • TTR • DCR

Abbreviations: AUC = area under the curve; C_{max} = maximum serum/plasma concentration; C_{min} = minimum serum/plasma concentration; CTCAE = Common Terminology Criteria in Adverse Events; DCR = disease control rate; DLT = dose-limiting toxicity; DOR = duration of response; ORR = objective response rate; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TTR = time-to-response.

[a] Response assessment using RECIST 1.1 and RECIST 1.1 with confirmatory scan for disease progression.

Overall Design:

Study J1E-MC-JZEA (JZEA) is a multicenter, nonrandomized, open-label Phase 1 study in patients with advanced solid tumors.

Phase 1 study will assess the safety and tolerability of LY3434172, administered as a monotherapy in patients with select advanced solid tumors. Study JZEA will facilitate a thorough safety evaluation and exploration of pharmacokinetics (PK) and pharmacodynamics effects CCI [redacted]. Once dose-limiting toxicity (DLT) period is completed for respective Cohorts A1 to A5/6 up to approximately 12 to 15 additional patients may be added to two dose levels selected from these cohorts. For example, if 300mg is a dose level selected, additional patients may be enrolled in parallel with Cohort A5 after Cohort A4 has cleared DLT. Dose escalation will be driven by modified toxicity probability interval 2 (mTPI2) method, enrolling at least 3 patients per cohort.

In addition, an every three weeks (Q3W) dosing schedule (Cohorts A7 and A8) will be evaluated to allow for flexibility for future combinations with standard-of-care agents that may use a Q3W dose regimen. The Q3W dosing schedule could be initiated as Cohorts A7 and A8 in parallel with the Q2W expansion respectively.

Interim analyses will be conducted at the end of dose escalation from Cohort A1 to A5/6 at completion of DLT period across these cohorts. The RP2D will be identified after final analyses upon completion of this Phase 1 study.

Number of Patients:

Approximately 15 to 20 patients will be enrolled in Q2W dose escalation (Cohorts A1 to A6), approximately 12 to 15 additional patients may be added to two cohorts after dose level has cleared the DLT period. The sample size of Q3W depends primarily on PK profiles and clinical considerations.

Treatment Arms and Duration:

Patients enrolled in Phase 1 will receive LY3434172 monotherapy, as shown in the following table. Patients may continue to receive study treatment until they meet a criterion for discontinuation.

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2. Schedule of Activities

Table JZEA.1 presents the Baseline and On-study Schedule of Activities for all patients (for each of the 28-day cycle).

Table JZEA.2 presents the Baseline and On-study Schedule of Activities for all patients (for each of the 21-day cycle).

Table JZEA.3 presents the Post Treatment Follow-up Schedule of Activities for all patients (for each of the 21-day and 28-day cycle).

Table JZEA.4 presents the Continued Access Schedule of Activities for patients receiving LY3434172.

Table JZEA.1 Baseline and On-Study Treatment Schedule of Activities (Cohort A1, A2, A3, A4, A5, and A6)

	Baseline (Day Relative to C1D1)		Cycle = 28 days								Instructions
			Cycle 1 (±3 days)		Cycle 2 (±3 days)		Cycle 3 (±3 days)		Cycle 4-n (±3 days)		
	≤28	≤7	D1	D15	D1	D15	D1	D15	D1	D15	
Procedure											
Informed consent	X										ICF must be signed before any protocol-specific procedures are performed
Inclusion/exclusion criteria	X										
Medical history	X										Including assessment of preexisting conditions and historical illnesses
Cancer treatment history	X										Record prior anticancer therapy
Concomitant medication	X		X								• At baseline, record prior and concurrent medications • Record all premedication, supportive care, and concomitant medication continuously at every visit and throughout the study
Physical examination	X		X	X	X	X	X	X	X	X	• D1 visit should be completed by a physician. • Should include palpable tumor measurement.

Vital signs	X		X	X	X	X	X	X	X	X	**Measure vital signs (height (at baseline), weight, temperature, blood pressure, pulse rate, oxygen saturation, and respiration rate) as follows (±5 minutes):**
											• **In Cycles 1 through 3:**
											  • within 15 minutes prior to each LY3434172 infusion
											  • every 15 minutes during each LY3434172 infusion
											  • at the end of each LY3434172 infusion
											
											A 4-hour observation period (See Section 5.1.1 and 7.4) following the end of LY3434172 administration will occur in Cycles 1 to 3.
											• every 30 (±5) minutes for the first hour and 60 (±5) minutes thereafter during the 4-hour observation period

	Baseline (Day Relative to C1D1)		Cycle = 28 days								Instructions
			Cycle 1 (±3 days)		Cycle 2 (±3 days)		Cycle 3 (±3 days)		Cycle 4-n (±3 days)		
	≤28	≤7	D1	D15	D1	D15	D1	D15	D1	D15	

											• **In Cycle 4 and beyond, if the patient has not experienced an infusion-related reaction or other infusion-related AE:**
											  • up to 15 minutes prior to each LY3434172 infusion
											  • at least once during each LY3434172 infusion
											  • at the end of each LY3434172 infusion

AE collection	X		X								• Collect continuously at every visit and throughout the study • CTCAE Version 5.0
ECOG PS	X		X	X	X	X	X	X	X	X	During study treatment, perform ≤3 days prior to D1 and D15 of each cycle.
ECHO	X								See Instructions		Perform locally, at baseline, Cycle 4 Day 1, and as clinically indicated
ECG											See Appendix 4 for ECG collection instructions
Blood tumor markers		X	X		X		X		X		As appropriate for particular tumor types (local testing). For example, include alpha-fetoprotein for patient with HCC.
Hematology		X	X	X	X	X	X	X	X	X	See Appendix 2
Coagulation	X										See Appendix 2. Perform at baseline and as clinically indicated.
Fibrinogen	X										See Appendix 2. Perform at baseline and as clinically indicated when CRP and/or ESR are elevated from baseline
TSH and free T4		X					X				See Appendix 2. Perform at baseline, C3D1, every 2 cycles thereafter, and more frequently as clinically indicated.
C3a complement		X			X		X				See Appendix 2. Perform at baseline, C2D1, C3D1, every other cycle thereafter and more frequently as clinically indicated.
C-ANCA/ P-ANCA		X									See Appendix 2. Perform at baseline and more frequently as clinically indicated.

	Baseline (Day Relative to C1D1)		Cycle = 28 days								Instructions
			Cycle 1 (±3 days)		Cycle 2 (±3 days)		Cycle 3 (±3 days)		Cycle 4-n (±3 days)		
	≤28	≤7	D1	D15	D1	D15	D1	D15	D1	D15	
Troponin-I		X									See Appendix 2. Perform at baseline and more frequently as clinically indicated.
Clinical chemistry		X	X	X	X	X	X	X	X	X	See Appendix 2
C-reactive protein		X	X		X		X		X		
ESR		X	X		X		X		X		
Urinalysis		X		X	X	X	X	X	X	X	See Appendix 2. Perform at specified timepoint and as clinically indicated.
Pregnancy test		X	See Instructions								• Applies only to women of childbearing potential • **Note:** during study treatment, perform monthly or as required per local regulations and/or institutional guidelines. • See Appendix 2
Tumor imaging/ assessment	X						X		See Instructions		• Perform locally according to RECIST 1.1, using the same method at each assessment • Perform 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 • Note: After C1D1, perform Q8W (±7 days) according to RECIST 1.1 for the first year, until a discontinuation criterion is met. If radiologic imaging verifies an initial assessment of PD, apply RECIST 1.1 with confirmatory scan for disease progression (Section 9.1.1). • If the patient is still on study treatment after 1 year, perform tumor imaging approximately every 12W.
Sample collection											See Appendix 4 for pharmacodynamics, pharmacokinetics, immunogenicity, pharmacogenetics, tumor tissue, and other biomarkers.

	Baseline (Day Relative to C1D1)		Cycle = 28 days								Instructions
			Cycle 1 (±3 days)		Cycle 2 (±3 days)		Cycle 3 (±3 days)		Cycle 4-n (±3 days)		
	≤28	≤7	D1	D15	D1	D15	D1	D15	D1	D15	
Administer LY3434172			X	X	X	X	X	X	X	X	LY3434172 will be administered as an IV infusion over approximately 60 minutes, depending on dose level (doses <100 mg may require bolus IV injection administration over approximately 5 to 10 minutes). A 4-hour observation period following the end of LY3434172 administration will occur in Cycles 1 to 3.

Abbreviations: AE = adverse event; C = Cycle; C-ANCA = cytoplasmic antineutrophil cytoplasmic antibody; CRP = C-reactive protein; CTCAE = Common Terminology Criteria for Adverse Events; D = day; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; ESR = erythrocyte sedimentation rate; free T4 = free thyroxine; HCC = hepatocellular carcinoma; ICF = informed consent form; IV = intravenous; P-ANCA = perinuclear antineutrophil cytoplasmic antibody; PD = progressive disease; Q = every; RECIST 1.1 = Response Criteria in Solid Tumors Version 1.1; TSH = thyroid stimulating hormone; W = weeks.

Table JZEA.2 Baseline and On-Study Treatment Schedule of Activities (Cohort A7 and A8)

	Baseline (Day Relative to C1D1)		Cycle = 21 days						Instructions
			Cycle 1 (±3 days)		Cycle 2 (±3 days)		Cycle 3 (±3 days)	Cycle 4-n (±3 days)	
	≤28	≤7	D1	D8	D1	D8	D1	D1	
Procedure									
Informed consent	X								ICF must be signed before any protocol-specific procedures are performed
Inclusion/exclusion criteria	X								
Medical history	X								Including assessment of preexisting conditions and historical illnesses
Cancer treatment history	X								Record prior anticancer therapy
Concomitant medication	X		X						• At baseline, record prior and concurrent medications • Record all premedication, supportive care, and concomitant medication continuously at each visit and throughout the study.
Physical examination	X		X	X	X	X	X	X	• D1 visit should be completed by a physician. • Should include palpable tumor measurement.

Vital signs	X		X		X		X	X	**Measure vital signs (height (at baseline), weight, temperature, blood pressure, pulse rate, oxygen saturation, and respiration rate) as follows (±5 minutes):**
									• **In Cycles 1 through 3:**
									  • up to 15 minutes prior to each LY3434172 infusion
									  • every 15 minutes during each LY3434172 infusion
									  • at the end of each LY3434172 infusion
									
									A 4-hour observation period (See Section 5.1.1 and 7.4) following the end of LY3434172 administration will occur in Cycles 1 to 3.
									• every 30 (±5) minutes for the first hour and every 60 (±5) minutes thereafter during the 4-hour observation period.

	Baseline (Day Relative to C1D1)		Cycle = 21 days						Instructions
			Cycle 1 (±3 days)		Cycle 2 (±3 days)		Cycle 3 (±3 days)	Cycle 4-n (±3 days)	
	≤28	≤7	D1	D8	D1	D8	D1	D1	

									• **In Cycle 4 and beyond, if the patient has not experienced an infusion-related reaction or other infusion-related AE:**
									  • up to 15 minutes prior to each LY3434172 infusion
									  • at least once during each LY3434172 infusion
									  • at the end of each LY3434172 infusion

AE collection	X		X						• Collect continuously at each visit and throughout the study • CTCAE Version 5.0
ECOG PS	X		X	X	X	X	X	X	During study treatment, perform ≤3 days prior to D1 of each cycle.
ECHO	X							See instructions	Perform locally, at baseline, at Cycle 4 Day 1, and as clinically indicated.
ECG									See Appendix 4 for ECG collection instructions
Blood tumor markers		X	X		X		X	X	As appropriate for particular tumor types (local testing). For example, include alpha-fetoprotein for patients with HCC.
Hematology		X	X	X	X	X	X	X	See Appendix 2
Coagulation	X								See Appendix 2. Perform at baseline and as clinically indicated.
Fibrinogen	X								See Appendix 2. Perform at baseline and as clinically indicated when CRP and/or ESR are elevated from baseline
TSH and free T4		X					X		See Appendix 2. Perform at baseline, C3D1, every 2 cycles thereafter, and more frequently as clinically indicated.
C3a complement		X			X		X		See Appendix 2. Perform at baseline, C2D1, C3D1, every other cycle thereafter and more frequently as clinically indicated.
C-ANCA/P-ANCA		X							See Appendix 2. Perform at baseline and more frequently as clinically indicated.

	Baseline (Day Relative to C1D1)		Cycle = 21 days						Instructions
			Cycle 1 (±3 days)		Cycle 2 (±3 days)		Cycle 3 (±3 days)	Cycle 4-n (±3 days)	
	≤28	≤7	D1	D8	D1	D8	D1	D1	
Troponin-I		X							See Appendix 2. Perform at baseline and more frequently as clinically indicated.
Clinical chemistry		X	X	X	X	X	X	X	See Appendix 2
C-reactive protein		X	X		X		X	X	
ESR		X	X		X		X	X	
Urinalysis		X		X	X	X	X	X	See Appendix 2. Perform at specified timepoint and as clinically indicated.
Pregnancy test		X	See Instructions						• Applies only to women of childbearing potential • **Note:** during study treatment, perform monthly or as required per local regulations and/or institutional guidelines • See Appendix 2
Tumor imaging/ assessment	X						X	See Instructions	• Perform locally according to RECIST 1.1, using the same method at each assessment • Perform 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. • Note: After C1D1, perform Q6W (±7 days) according to RECIST 1.1 for the first year, until a discontinuation criterion is met. If radiologic imaging verifies an initial assessment of PD, apply RECIST 1.1 with confirmatory scan for disease progression (Section 9.1.1). • If the patient is still on study treatment after 1 year, perform tumor imaging approximately every 12W.
Sample collection									See Appendix 4 for pharmacodynamics, pharmacokinetics, immunogenicity, pharmacogenetics, tumor tissue, and other biomarkers.

	Baseline (Day Relative to C1D1)		Cycle = 21 days						Instructions
			Cycle 1 (±3 days)		Cycle 2 (±3 days)		Cycle 3 (±3 days)	Cycle 4-n (±3 days)	
	≤28	≤7	D1	D8	D1	D8	D1	D1	
Administer LY3434172			X		X		X	X	LY3434172 will be administered as an IV infusion over approximately 60 minutes, depending on dose level (doses <100 mg may require bolus IV injection administration approximately 5 to 10 minutes). A 4-hour observation period following the end of LY3434172 administration will occur in Cycles 1 to 3.

Abbreviations: AE = adverse event; C = Cycle; C-ANCA = cytoplasmic antineutrophil cytoplasmic antibody; CTCAE = Common Terminology Criteria for Adverse Events; D = day; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; ESR = erythrocyte sedimentation rate; free T4 = free thyroxine; HCC = hepatocellular carcinoma; ICF = informed consent form; IV = intravenous; P-ANCA = perinuclear antineutrophil cytoplasmic antibody; PD = progressive disease; Q = every; RECIST 1.1 = Response Criteria in Solid Tumors Version 1.1; TSH = thyroid stimulating hormone; W = weeks.

Table JZEA.3. Poststudy Treatment Schedule of Activities (All Parts)

	Follow-Up Visit (±7 days)				
	Short-Term[a]			Long-Term (Q90D)[b]	
Visit	30-Day 801	60-Day 802	90-Day 803	804 to 8XX	
Procedure					**Instructions**
Pregnancy test	X	X	X		Perform pregnancy test for women of childbearing potential
ECG					See Appendix 4 for ECG collection instructions
Physical examination	X				Including weight and vital signs (temperature, blood pressure, pulse rate, oxygen saturation, and respiration rate)
Concomitant medication	X				
AE collection	X	X	X	X	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
ECOG performance status	X				
Tumor imaging/assessment	X				For patients who discontinue study treatment without objectively measured PD, continue to perform tumor assessment and imaging every 8 to 12 weeks according to the standard-of-care
Collection of survival information	X	X	X	X	In-person office visits are not required; the site may confirm survival by contacting the patient directly via telephone or other means of communication (for example, email)
Collection of poststudy-treatment anticancer therapy information	X	X	X	X	Discontinuation from study treatment must occur prior to introduction of the new agent
Hematology	X				See Appendix 2
Clinical Chemistry	X				See Appendix 2
Coagulation	X				See Appendix 2
Sample collection					See Appendix 4 for pharmacodynamics, pharmacokinetics, immunogenicity, pharmacogenetics, tumor tissue, and other biomarkers.

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2017); ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group (Oken et al. 1982); F/U = follow-up; PD = progressive disease; PK = pharmacokinetics; SAE = serious adverse event.

[a] Short-term follow-up begins when the patient and investigator agree that the patient will discontinue study treatment and ends on the day of the 90-day (±7 days) follow-up visit.

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

Table JZEA.4. Continued Access Schedule of Activities

	Continued Access Treatment		Continued Access Follow-up Visits[a]			
			30-Day	60-Day	90-Day	
	501-5XX		901	902	903	
Visit	D1	D15				Instructions:
LY3434172 Schedule	All	Q2W				
Procedure						
AE collection	X	X	X	X	X	As part of AE collection, monitor vital signs and perform standard laboratory tests (hematology, chemistry, urinalysis, and pregnancy testing) at the same frequency as the study treatment period (see Table JZEA.1 and Table JZEA.2). All laboratory tests during the continued access period will be performed in the local laboratories only.
PK, IG and exploratory hypersensitivity						In the event of an IRR, 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 IRR, (ii) the resolution of the IRR, and (iii) 30 [±3] days following the IRR.CCI [redacted]
Administer LY3434172	X	X				

Abbreviations: AE = adverse event; D = day; IG = immunogenicity; IRR = infusion-related reaction; 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 30 days.

3. Introduction

3.1. Study Rationale

T-cells play a central role in immune response to tumors. However, tumors have adopted multiple mechanisms to evade host immune surveillance. One of the key mechanisms is programmed cell death protein-1 receptor (PD-1) and its ligands, programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2), coinhibitory molecules (immune checkpoints) that suppress T-cell-mediated immune responses. Both PD-L1 and PD-L2 ligands can bind to the PD-1 receptor on T-cells.

In addition, PD-L1 can also bind to B7-1 on T-cells. These PD-1 axis interactions lead to suppression of T-cell activation. In a variety of tumors, PD-L1 is frequently over-expressed by tumor cells. Blocking the PD-1/PD-L1 axis has been shown to remove this suppression and reinvigorate T-cell activation (Zou et al. 2016).

While anti-PD-1 and anti-PD-L1 antibodies have demonstrated durable clinical responses in multiple tumor indications, only a subset of patients benefit from these treatments with room for further improvement (Jenkins et al. 2018). Eli Lilly & Company (Lilly) has designed a novel approach using a bispecific antibody (BsAb) to target both PD-L1 and PD-1. Such a BsAb will be capable of blocking all interactions of the PD-1/PD-L1 axis (PD-1 with PD-L1 and PD-L2, B7-1 with PD-L1) whereas anti-PD-1 does not block PD-L1-B7-1 interactions and anti-PD-L1 does not block PD-L2-PD1 interactions. In addition, in vitro experiments have demonstrated that LY3434172 can bridge cells engineered to express PD-1 and those that express PD-L1; the clinical relevance of bridging will be assessed in this study.

The goal of this study is to establish the safety of the PD-1/PD-L1 bsAb as monotherapy in patients with advanced solid tumors. If the product has an acceptable clinical safety profile and shows sufficient activity, additional studies and/or cohorts may be added to determine a safe dose alone or in combination with other anticancer therapies.

3.2. Background

While inhibitors of both PD-1 and PD-L1 have shown clinical activity and manageable safety profiles as monotherapy in a variety of tumor types, their efficacy in various tumor types could potentially be improved (Wu et al. 2015). The possible benefit of targeting the PD-1/PD-L1 pathway with another immune checkpoint inhibitor, which can further augment the response, is an important area of interest.

LY3434172 is a human bsAb (effectorless IgG1-Fc) consisting of two different sets of light and heavy chains. One pair of the heavy-light chain is a human immunoglobulin G1 (IgG1) variant that binds PD-L1 and the other pair is a human IgG1 variant that binds PD-1.

The in vitro and in vivo biological properties of LY3434172 were characterized in nonclinical pharmacology studies. LY3434172 blocks all interactions of the programmed death (PD) axis: PD-1 binding to PD-L1 and PD-L2 ligands, as well as B7-1 binding to PD-L1. In vitro, LY3434172 can bridge a PD-L1 expressing target cell and a PD-1 expressing T-cell to enable

T-cell activation that is superior to parental PD-1 and PD-L1 monoclonal antibodies (mAbs) or their combination. Furthermore, LY3434172 demonstrates in vivo antitumor efficacy in humanized mouse model systems. Collectively, LY3434172 fully blocks the PD-1 and PD-L1 axes and more effectively releases immune inhibitory signals to promote T-cell activation and enhance antitumor efficacy.

The toxicity profile of LY3434172 was investigated in cynomolgus monkeys administered intravenous (IV) bolus doses of 0, 30, and 100 mg/kg twice weekly for 1-month (9 doses total; Table JZEA.5). LY3434172 binds to and antagonizes both human and monkey PD-1 and PD-L1 with similar affinity and potency, establishing cynomolgus monkeys as a pharmacologically-relevant species for toxicity testing.

No mortality or significant clinical signs were observed and all animals survived to scheduled necropsy. LY3434172-related clinical pathology changes at both doses were largely limited to minimal decreases in albumin with minimal to mild increases in globulins, compatible with an acute phase response. LY3434172-related microscopic findings of minimal to marked vascular/perivascular mononuclear cell infiltrates in multiple organs were observed in 14 of 16 animals (7 at 30 mg/kg, 7 at 100 mg/kg). The histological features, spectrum of affected organs, and distribution of microscopic findings at both dose levels were consistent with immune complex deposition secondary to an immune response to LY3434172. Microscopic changes similar in appearance and location have been observed in preclinical studies for other biopharmaceuticals, and have been determined to be the result of an immune response to the therapeutic compound (Rojko et al. 2014). Commonly affected organs included brain, heart, gall bladder, and organs of the reproductive and gastrointestinal tracts – a tissue/ organ spectrum which is also compatible with published reports (Heyen et al. 2014; Leach et al. 2014; Rojko et al. 2014; Husar et al. 2017; Kronenberg et al. 2017). Immunohistochemical detection of granular deposits containing LY3434172, endogenous monkey immunoglobulin M (IgM) and immunoglobulin G (IgG), and/or complement C3 at sites of vascular lesions in many of the tissues tested provided definitive evidence of immune complex deposition in development of vascular/ perivascular infiltrates.

These findings are consistent with a Type III hypersensitivity response, which have been described in monkey studies for a number of therapeutic monoclonal antibodies (Heyen et al. 2014; Leach et al. 2014; Rojko et al. 2014; Husar et al. 2017; Kronenberg et al. 2017). Importantly in this case, a high incidence of anti-drug antibody (ADA) in LY3434172-treated animals and detection of granular deposits in affected tissues of representative animals provided robust evidence of immune complex disease. In monkeys, immune complex-related vascular/perivascular inflammation is commonly found in varied organs/tissues such as the gastrointestinal tract, gall bladder, heart, and tissues of the reproductive tract, consistent with the organs affected in this study. Based on historical examples, there is low potential risk for clinical translation of both preclinical immunogenicity (IG) and immune complex-related pathology (Husar et al. 2017; Kronenberg et al. 2017).

No LY3434172-related effects were observed on other standard toxicology endpoints in the study with the exception of heart rate (HR) increases noted in a subset of animals affected by

vasculitis (Table JZEA.5). While transient increases in HR were observed in the light photoperiod, most pronounced changes (with maximal increases ranging up to +23 bpm) were observed during the dark phase of the recording period (100 mg/kg only) on Day 5. By Day 22, HR changes of similar magnitude (with maximal changes up to +39 bpm) were observed at both dose levels, with evidence of a carryover effect during predose recording (+17 to 19 bpm) indicative of a reduced but sustained heart rate effect. No changes in QTc or any waveform abnormalities were noted in any animal on either day.

As the vascular findings were considered adverse to the animals in the study at both 30 mg/kg and 100 mg/kg, a no-observed-adverse-effect level (NOAEL) was not identified for this study. The proposed starting dose of 3 mg every two weeks (Q2W) has a multiple of ≥2,000-fold based on dose and projected maximum observed drug concentration (C_{max}), and a >10,000-fold multiple based on projected average drug concentration (C_{av}) over the dose interval, compared to the lowest dose of 30 mg/kg tested in monkeys in the 1-month repeat-dose study.

Table JZEA.5. Summary of 1-month Repeat-Dose Monkey Toxicity Study with LY3434172

Study Type Study Number	Species Number	Doses (mg/kg) Route Duration	Parameters Evaluated	Low Dose[e]	High Dose[e]
1-month GLP toxicity study 20134606	Monkey Cynomolgus 4/sex/group	0[a], 30, 100 IV twice-weekly for 1 month (9 total doses)	Mortality, BW, clin signs, phys, temp, resp, neuro, ophthal, ECG, TK/ADA, immuno[b], clin path[c], path[d]	30 mg/kg IV (Exposure Day 29: mean $AUC_{0\text{-}96hr}$= 103000 µg*hr/mL; C_0=1540 µg/mL)	100 mg/kg IV (Exposure Day 29: mean $AUC_{0\text{-}96hr}$= 400000 µg*hr/mL; C_0=5610 µg/mL)
Microscopic findings:	LY3434172-related adverse findings included minimal to marked vascular/perivascular mononuclear or mixed cell infiltrates in 14 of 16 animals (7 animals at 30 mg/kg, 7 animals at 100 mg/kg). The histological nature, tissue locations, and distribution of the lesions were consistent with an indirect ADA response to LY3434172 and resultant immune complex deposition and damage. Subsequent investigative work demonstrated immune complex deposition in lesions from multiple tissues/ organs from a representative subset of affected animals				
Cardio-vascular findings:	Increases in heart rate (HR) were observed in several animals on Day 5 (100 mg/kg; up to +23 bpm) and Day 22 (30 and 100 mg/kg; up to +39 bpm), most notably pronounced during the dark photoperiod. Changes on Day 22 were elevated at predose (+17-19 bpm) and were of a similar magnitude in both dose groups during the dark photoperiod.				

Abbreviations: ADA = anti-drug antibody; mean $AUC_{0\text{-}96hr}$ = average area under the plasma concentration-time curve from time zero to 96 hours for both males and females; BW = body weight; clin = clinical; mean C_0 = mean maximal plasma concentration for both males and females extrapolated to t=0 time point; ECG = electrocardiogram; immuno = immunophenotyping; IV = intravenous; neuro = neurological evaluations; NOAEL = no-observed-adverse-effect level; NK = natural killer; ophthal = ophthalmic examinations; path = pathology; phys = physical examinations; resp = respiratory rate and depth; temp = body temperature; TK = toxicokinetics (plasma LY3434172).

[a] Vehicle control group.

[b] Peripheral blood immunophenotyping.

[c] Hematology, coagulation, cytokines, complement, clinical chemistry, and urinalysis.

[d] Organ weights, gross pathology, histopathology, immunohistochemistry.

[e] An NOAEL was not identified in this study due to indirect adverse effects in animals that were driven by an immune response to LY3434172.

Additional information pertaining to nonclinical efficacy and safety may be found in Section 4.2 of the Investigator's Brochure (IB).

Information pertaining to nonclinical pharmacokinetics (PK) and metabolism may be found in Section 4.1 of the IB.

3.3. Benefit/Risk Assessment

More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated adverse events (AEs) of LY3434172 are to be found in the Investigator's Brochure (IB).

4. Objectives and Endpoints

Table JZEA.6 shows the objectives and endpoints of the study.

Table JZEA.6. Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the safety and tolerability of LY3434172, thereby identifying a RP2D of LY3434172, administered to patients with advanced solid tumors.	• DLTs • Safety (including but not limited to): TEAEs, DLT-equivalent toxicities, SAEs, deaths, and clinical laboratory abnormalities per CTCAE (Version 5.0)
Secondary	
To assess the PK in patients with solid tumors of LY3434172.	• AUC, C_{min} and approximate C_{max} of LY3434172
To assess preliminary antitumor activity[a] of LY3434172	• ORR • DOR • TTR • DCR
Tertiary/Exploratory	
To characterize tumor tissue and blood biomarkers relevant to LY3434172, including but not limited to immune cells/immune functioning, mechanism of action of study drugs, cancer-related pathways, and disease state	• Results of biomarker analyses • Clinical outcomes
To explore the association between biomarkers and dose, concentrations and clinical outcomes	• Results of biomarker analyses • Clinical outcomes
To assess the IG of LY3434172 in patients with advanced solid tumors.	• Relationship between TE ADA and safety • Relationship between TE ADA and LY3434172 pharmacokinetics.
To assess PFS and OS of patients receiving LY3434172.	• PFS • OS

Abbreviations: C_{max} = maximum serum/plasma concentration; C_{min} = minimum serum/plasma concentration; CTCAE = Common Terminology Criteria in Adverse Events; DCR = disease control rate; DLT = dose-limiting toxicity; DOR = duration of response; IG = immunogenicity; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TE ADA = Treatment-emergent anti-drug antibodies; TTR = time-to-response.

[a] Response assessment using RECIST 1.1 and RECIST 1.1 with confirmatory scan for disease progression.

5. Study Design

5.1. Overall Design

Study J1E-MC-JZEA (JZEA) is a multicenter, nonrandomized, open-label, first in human Phase 1 study in patients with advanced solid tumors.

Phase 1 study will assess the safety and tolerability of LY3434172, administered as a monotherapy in patients with select advanced solid tumors (see Figure JZEA.1). LY3434172 will be administered as an IV bolus injection for doses less than 100 mg (approximately 5 to 10 minutes) and for doses ≥100 mg, IV infusion over approximately 60 minutes. Patients enrolled into Cohorts A1 through A5/6 will be administered LY3434172 on a Q2W dose schedule. Cohort A6 is an optional cohort that may be explored at a dose not exceeding 1000 mg of LY3434172 based on safety, PK, and pharmacodynamic data. Dose escalation will be driven by modified toxicity probability interval 2 (mTPI2) method (Guo et al. 2017), enrolling at least three patients per cohort. Further discussion on dose escalation is explained in Section 5.1.1.

To facilitate a thorough safety evaluation and exploration of PK and pharmacodynamics effects of the every two week (Q2W) dosing schedule (Cohorts A1 to A6) will be explored. Once dose-limiting toxicity (DLT) period is completed for respective Cohorts A1 to A5/6 up to approximately 12 to 15 additional patients may be added to two dose levels selected from these cohorts (see Figure JZEA.1). After evaluating PK/pharmacodynamic data from these cohorts, any doses from the dose escalation range could be used in order to cover the entire predicted biologically effective dose (BED) and allow for uncertainty around it (see Section 5.5). For example, if 300 mg is a dose level selected, additional patients may be enrolled in parallel with Cohort A5 after Cohort A4 has cleared DLT.

In addition, an every three-week (Q3W) dosing schedule (Cohorts A7 and A8) will be evaluated to allow for flexibility for future combinations with standard-of-care agents that may use a Q3W dose regimen. The Q3W dosing schedule could be initiated as Cohorts A7 and A8 in parallel with the enrollment of additional patients enrolled into two dose levels of the Q2W schedule, respectively.

Ongoing safety reviews between the Lilly and the investigators will be conducted after completion of the DLT period for each cohort to ensure it is safe to continue with the next dose-escalation cohort.

Interim analyses will be conducted at the end of dose escalation from Cohorts A1 to A5/6 at completion of DLT period across these cohorts. The recommended Phase 2 dose (RP2D) will be identified after final analyses upon completion of this Phase 1 study. If LY3434172 has an acceptable clinical safety profile and shows sufficient activity, additional studies and/or cohorts may be added to determine a safe dose alone or in combination with other anticancer therapies. As noted in Section 9.8, PD-L1 expression and other biomarkers will be evaluated, and may influence enrichment strategies for subsequent studies and/or cohorts.

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5.1.1. Dose Escalation

The first patient will be enrolled in Cohort A1 and treated according to a Q2W dosing regimen (see Figure JZEA.1). CCI [redacted] A DLT observation period of 28 days (42 days in Cohort A1) will apply to all patients on the Q2W dosing regimen in subsequent cohorts. Ongoing safety reviews between the Lilly clinical research physician/clinical research scientist (CRP/CRS) and the investigators will be conducted during and upon completion of the DLT period for each cohort, to ensure it is safe to continue with the next dose-escalation cohort.

After the first patient in Cohort A1 receives the first dose of LY3434172, there will be a delay of 1 week before the second patient receives LY3434172 to allow for safety observation. In all subsequent cohorts, the first patient in each dose level will be observed for approximately 24 hours before any additional patients are treated; no additional delays are required for subsequent patients in the same cohort.

Patients in Cohorts A2, A3, A4, A5, and A6 (optional), respectively, CCI [redacted] provided safety is established in the preceding cohorts. Once DLT period of 28 days for Q2W, except Cohort A1 with 42 day DLT, is completed for respective dose levels within Cohorts A1 to A5/A6, two dose

levels, yet to be determined but will be selected from these cohorts, can be expanded between 12 and 15 patients in total. Pharmacokinetic, pharmacodynamic and safety data evaluated during the course of the dose escalation will be used to select these two dose levels. The purpose of expanding to additional 12-15 patients is to further inform safety, PK and pharmacodynamics. These cohorts will continue to enroll while interim analysis (IA) is ongoing.

Cohorts of patients will be treated with escalating doses of LY3434172 according to an mTPI-2 method until the criteria for reaching the maximum-tolerated dose (MTD) are met. For some immuno-oncology compounds that have manageable safety profiles and do not reach a MTD, additional information such as pharmacodynamic markers may be helpful in determining the appropriate RP2D (Agrawal et al. 2016; Parchment et al. 2016).

A Q3W dosing regimen will be explored in Cohorts A7, A8 at doses yet to be determined. The Q3W dosing regimen will use the LY3434172 dose anticipated to have drug exposure similar to two selected Q2W dose levels where additional patients were enrolled. The Q3W dosing schedule could be initiated as Cohorts A7 and A8 in parallel with the Q2W expansion respectively.

5.2. Number of Patients

Enrollment in each cohort will be adjusted if needed to allow adequate assessment of safety and preliminary antitumor activity at the LY3434172 RP2D. Planned enrollment is as follows:

Approximately 15 to 20 patients will be enrolled in Q2W dose escalation, approximately 12 to 15 additional patients may be added to two dose levels selected from Cohorts A1 to A5/A6 after selected dose level has cleared the DLT period for adequate assessment of safety and exploration of PK and pharmacodynamic effects. The additional patients for the two selected dose levels can be enrolled in parallel to dose escalation in Q2W as long as the dose level explored has cleared DLT. In parallel, patients will be enrolled in Q3W cohorts (A7 and A8) to allow flexibility for future combinations with standard-of-care agents. The sample size of Q3W depends primarily on PK profiles and clinical considerations. A minimum of three patients will be enrolled in each cohort.

5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last patient.

5.4. Scientific Rationale for Study Design

See Sections 3.1 and 3.3.

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6. Study Population

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

6.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all the following criteria:

[1] Melanoma, NSCLC, squamous cell carcinoma of the head and neck (SCCHN), urothelial cancer, gastric cancer, colorectal cancer, biliary tract cancer, anal cancer, nasopharyngeal cancer, esophageal cancer, SCLC, ovarian cancer, mesothelioma, pan-tumor MSIhi solid tumors, hepatocellular carcinoma, merkel cell cancer, cutaneous squamous cell carcinoma, endometrial cancer, breast cancer, cervical cancer, thyroid cancer, salivary cancer, and prostate cancer who have received at least one line of standard systemic therapy for their respective tumor type in the metastatic setting with progressive locally advanced or metastatic disease and that is not amenable/resistant to approved standard-of-care therapy. Prior anti-PD-1 and anti-PD-L1 allowed if they received another therapy immediately prior to this study or there has been a lapse of approximately ≥90 days from prior therapy. If patients received prior anti-PD-1 or anti-PD-L1, the following criteria need to be met:

a) did not experience a toxicity that led to permanent discontinuation of prior anti-PD-1, anti-PD-L1, or other immunotherapy.
b) have completely recovered to at least his or her previous baseline level prior to screening from any clinically significant AEs that occurred during prior immunotherapy.
c) did not experience any of the following irAEs during prior anti-PD-1, anti-PD-L1, or other immunotherapy:
   - a Grade ≥3 irAE
   - any grade neurologic or ocular irAE
   - any grade immune-related pneumonitis or cardiomyopathy

Patients with an endocrine AE are permitted to enroll if they are stably maintained on appropriate replacement therapy and are asymptomatic

d) did not require immunosuppressive agents, other than corticosteroids for the management of an AE, did not experience recurrence of a Grade ≥3 AE if rechallenged, and does not currently require maintenance doses of >10 mg prednisone (or equivalent) per day.

[2] have at least one measurable lesion assessable using standard techniques by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) (Eisenhauer et al. 2009). Bone metastases are not considered measurable.

[3] are able and willing to provide the protocol required biopsies from a newly obtained core or excisional pre-treatment biopsy of a tumor lesion and a newly obtained core or excisional biopsy collected during the study treatment period (See Section 9.8.1). (Note: An archived tumor sample also will be requested, if not restricted by local regulations).

[4] have an Eastern Cooperative Oncology Group performance status of 0 or 1 (Oken et al. 1982).

[5] have discontinued all previous treatments for cancer for at least 14 days and recovered from the acute effects of therapy. Patients must have discontinued from previous treatments, as shown below:

Previous Treatment[a]	**Length of Time Prior to First Dose of Study Treatment**
Cytotoxic therapies or targeted agents that are small-molecule inhibitors	≥14 days
Mitomycin-C or nitrosoureas	>42 days
Biologic agents (excludes anti-PD-1, anti-PD-L1)	≥14 days
Radiotherapy	≥28 days
Limited field radiotherapy (i.e. <25% bone marrow affected)	≥14 days
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.

[a] At the discretion of the investigator, patients with hormone-refractory prostate cancer who are stable on gonadotropin-releasing hormone agonist therapy and patients with breast cancer who are stable on antiestrogen therapy (for example, an aromatase inhibitor) may continue that treatment while enrolled in this study.

[6] have adequate organ function, as defined below, with all screening laboratory assessments performed within 28 days of treatment initiation.

System	**Laboratory Value**
Hematologic	
ANC	≥1.5 × 10^9 cells/L
Platelets	≥100 × 10^9/L
Hemoglobin	≥9 g/dL At the discretion of the investigator, patients may receive erythrocyte transfusions to achieve this hemoglobin level; however, study treatment may not begin until 2 days after erythrocyte transfusion and after confirmation of hemoglobin ≥9 g/dL.
aPTT	≤1.5 × ULN

Hepatic	
Total bilirubin	≤1.5 × ULN OR <3.0 x ULN for patients who have Gilbert's syndrome
ALT and AST	≤2.5 × ULN OR ≤5 × ULN if the liver has tumor involvement
Renal	
Serum creatinine OR Calculated creatinine clearance	≤1.5 × ULN OR ≥50 mL/min

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; HCC = hepatocellular carcinoma; ULN = upper limit of normal.

Note: Adequate organ function should be confirmed within 7 days prior to first dose on Cycle 1 Day 1.

[7] are, at the time of screening, ≥18 years old or of an acceptable age to provide informed consent according to local regulations, whichever is older

[8] Men with partners of childbearing potential or women with childbearing potential must agree to use a highly effective contraceptive method of birth control (Appendix 1) during study treatment and for at least 6 months following the last dose of study drug.

[9] Women of childbearing potential must have a negative serum pregnancy test documented within 7 days prior to initiation of treatment (see Appendix 9).

[10] have given written informed consent/assent prior to any study-specific procedures

[11] have an estimated life expectancy of ≥12 weeks, in the judgment of the investigator

[12] are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures

6.2. Exclusion Criteria

Patients will be excluded from the study if they meet any of the following criteria:

[13] Are currently enrolled in a clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

[14] Have a serious concomitant systemic disorder that, in the opinion of the investigator, would compromise the patient's ability to adhere to the protocol, such as the following:

a. 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 (HAART) therapy with

- No evidence of AIDS-defining opportunistic infections within the last 2 years, and
- CD4 count > 350 cells/μL

b. active hepatitis B or C virus infection according to local standards (screening not required) (e.g., with no evidence of known positive hepatitis B surface antigen or known positive hepatitis C antibody and quantitative hepatitis C RNA greater than the lower limit of detection of the assay).

c. current active tuberculosis

d. active infection requiring systemic therapy

e. 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

f. Active or suspected autoimmune disease (e.g., autoimmune vasculitis, autoimmune myocarditis) or any illness that could compromise the immune system (e.g., prior organ transplant) within the past two years, or a syndrome or condition that requires systemic corticosteroids or immunosuppressive agents. Patients at risk of vascular adverse events, such as those with a history of angiitis, arteritis, or hypersensitivity vasculitis as an adverse reaction to medication, for example, are not eligible.

   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 2 years, not expected to recur in the absence of an external trigger.

g. use of 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, and intranasal corticosteroids permitted.

   This criterion does not apply to patients with: (i) resolved childhood asthma/atopy or who require intermittent use of bronchodilators or local corticosteroid injections; (ii) hypothyroidism that is stable on hormone replacement; (iii) Raynaud's syndrome; or (iv) Sjogren's syndrome.

h. bowel obstruction, history or presence of inflammatory enteropathy or extensive intestinal resection (hemicolectomy or extensive small intestine resection, either condition with chronic diarrhea), Crohn's disease, ulcerative colitis, or chronic diarrhea

i. evidence of (i) interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity; (ii) active, noninfectious pneumonitis; or (iii) history of noninfectious pneumonitis that required corticosteroid therapy

j. moderate or severe cardiovascular disease, such as the following:

(i) 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

(ii) severe, moderate, or clinically significant valvulopathy; documented major electrocardiogram (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 QTc ≥470 ms calculated using Fredericia's correction and confirmed by triplicate ECG).

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

[15] Have symptomatic central nervous system (CNS) malignancy or metastasis (screening not required). Patients with treated CNS metastases are eligible for this study if they are not currently receiving corticosteroids and/or anticonvulsants to treat CNS metastases, and their disease is asymptomatic and radiographically stable for at least 30 days.

[16] Unresolved toxicities from prior anticancer therapy, including immune-related adverse event (irAE), that have not resolved to the baseline levels prior to starting the prior anticancer therapy.

[17] 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 (for example, FluMist®) are live attenuated vaccines and are not allowed.

[18] are pregnant, breastfeeding, or planning to become pregnant during the study or within 6 months of the last dose of LY3434172.

[19] have a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study, or is not in the best interest of the patient to participate, in the opinion of the treating investigator

[20] have current or history of allergy or hypersensitivity to study drug components

6.3. Lifestyle Restrictions

There are no specific lifestyle restrictions for this protocol.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) within the 28-day baseline-screening period may be rescreened. Individuals may be rescreened up to 2 times after initial screening. The interval between rescreening should be at least 1 week. Each time rescreening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number. All required tests (see Section 2) must be repeated for patients who are rescreened in a new 28-day baseline-screening period.

Repeating laboratory tests (including ECGs) that did not meet eligibility criteria during the 28-day baseline-screening period does not constitute rescreening. However, laboratory tests may not be repeated more than twice.

7. Treatment

7.1. Treatment Administered

LY3434172 will be administered as an IV infusion over approximately 60 minutes, depending on dose level (doses <100 mg may require bolus IV infusion, approximately over 5 to 10 minutes). A 4-hour observation period following the end of LY3434172 administration will occur in Cycles 1 to 3.

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The investigator or his/her designee is responsible for the following:

- explaining the correct use of the drug(s) and the planned duration of each individual's treatment to the patient and study site personnel
- verifying that instructions are followed properly
- maintaining accurate records of study drug dispensing and collection
- at the end of the study returning all unused medications to Lilly, or its designee, unless Lilly and sites have agreed all unused medications are to be destroyed by the site, as allowed by local law

7.1.1. Packaging and Labeling

All study drug will be provided by Lilly. Clinical study materials will be labeled according to the country's regulatory requirements.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be assigned to receive LY3434172 in this study.

An interactive web-response system (IWRS) will be used to dispense study drugs and to ensure that the correct number of patients is assigned to each cohort.

No dose escalations (i.e. to the next cohort) can occur without prior discussion of clinical data and agreement with the responsible Lilly CRP/CRS.

If investigators have eligible patients who have consented concurrently, more than the assigned patients may be entered at a particular dose level if accrual has not ceased due to excessive toxicity. This enrollment procedure is allowed because of the advanced disease state of this patient population and the screening involved in defining eligibility. This event should be approved by the Lilly CRP/CRS following discussions with the investigators.

7.2.1. Selection and Timing of Doses

The doses will be administered at approximately the same times on each day. The actual time of all dose administrations will be recorded in the electronic case report form (eCRF).

A cycle is defined as an interval of 28 days (Q2W regimen) and 21 days (Q3W regimen) as shown in Table JZEA.7. A delay of a cycle due to holiday, weekend, bad weather, or other unforeseen circumstances will be permitted for a maximum of 7 days and not counted as a protocol deviation. The reason for the delay should be documented on the eCRF.

The first study treatment will be administered within 7 days after the patient is assigned to a treatment cohort. There should be a minimum of 14 days between doses of study drug for all cohorts in Q2W schedule and 21 days between doses of study drug for the Q3W schedule. However, if there is a delay due to holiday, weekend, bad weather, or other unforeseen circumstances, a flexibility of ±3 days is permitted.

A patient may continue to receive LY3434172 until he or she meets one or more of the specified reasons for discontinuation (see Section 8).

7.2.2. Dose Escalation

Safety data, in particular AEs, will be the primary criteria for the dose escalation. In addition, if available at the time of dose escalation decision, PK (for example, approximate C_{max}, minimum plasma concentration (C_{min}), area under the concentration (AUC) versus time curve, pharmacodynamics results) will be used as secondary/supporting data for dose escalation. No dose escalation can occur without prior discussion and agreement between the investigator(s) and the Lilly CRP/CRS; the decision will be documented in writing.

7.2.2.1. Dose Escalation Method

An mTPI-2 method will be used to identify an RP2D for LY3434172, taking into consideration available PK and pharmacodynamic data from previous dose levels. Each cohort in this study will enroll at least three patients.

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 three or six 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 two DLTs per six patients enrolled, the mTPI-2 would recommend staying at the current dose, as analogy to one DLT per three patients enrolled in 3+3 design; therefore, it allows more patients for a more precise estimate of the DLT rate at this dose level.

Appendix 8 provides the mTPI-2 escalation rules for any cohort size up to 20 patients.

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/pharmacodynamic 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 dose level, be de-escalated to a lower level, or escalation may cease. In the mTPI-2, the cohort size is not fixed. However, each cohort in this study will contain a minimum of three 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 following the rules in Appendix 8. If the dose decision was "DU," the dose cannot be re-escalated to that level. This study is designed to identify a dose level 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 in Appendix 8.

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 necessary, additional patients may be enrolled to further assess PK/pharmacodynamics or tolerability.

7.2.2.2. Dose-Limiting Toxicity Determination

A DLT is defined as any of the events listed in Table JZEA.8, if both the following criteria are met:

- the event occurs during the DLT observation period (Cycle 1, 42 days) for Cohort A1, (Cycle 1, 28 days) for Cohorts A2 to A5 (A2 to A6 if Cohort A6 is opened), (Cycle 1 and 2, 42 days) for Cohorts A7 and A8, and
- the event is clinically significant and definitely, probably, or possibly related to LY3434172, in the opinion of the investigator.

Patients in Cohorts A1 to A5/6, A7, and A8 who experience a DLT in Cycle 1 will be discontinued from study treatment.

Table JZEA.8. Dose-Limiting Toxicity

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 lasting >7 days, excluding toxicities listed in Section 7.2.2.1
Nonhematologic toxicity – nonlaboratory
• Grade 4 irAE, except as stated otherwise below • Grade ≥3 colitis or noninfectious pneumonitis • Other Grade 3 irAE, excluding colitis or pneumonitis, that: o does not downgrade to Grade 2 within 3 days after onset of the event despite optimal medical management including corticosteroid therapy, or o does not downgrade to Grade ≤1 or the patient's baseline level within 14 days after onset of the event • 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 toxicity despite optimal supportive care (e.g., nausea, vomiting, and diarrhea) • Grade ≥3 fatigue lasting >7 days • Grade ≥3 hypertension despite maximal medical therapy
Nonhematologic toxicity – laboratory/investigations
• Other Grade 3 or 4 laboratory value lasting >14 days or requiring medical intervention • ALT or AST: o >8 × ULN, if the patient does not have HCC or liver metastasis • ≥2-fold above the patient's baseline value that lasts >7 days, if the patient has HCC or liver metastasis and had ALT or AST >3.0 × ULN at baseline • >3 × ULN with concomitant bilirubin >2 × ULN, in the absence of cholestasis • Total bilirubin >3 × ULN • ≥Grade 3 amylase or lipase that is associated with symptoms or clinical manifestations of pancreatitis
Other hematologic or nonhematologic toxicity
• Grade 5 toxicity (i.e. death) • ≥Grade 3 electrolyte abnormality that lasts >72 hours unless the patient has clinical symptoms, in which case all Grade 3+ electrolyte abnormality regardless of duration should count as a DLT. • Toxicity deemed by the investigator and the Lilly CRP/CRS 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 during Cycle 1, or o persistent Grade >2 toxicities causing a delay of >14 days in initiating Cycle 2 o Grade 3 vasculitis

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

Potential DLTs that are adverse events, 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.

7.2.2.2.1. Events That Are Not Considered to Be DLTs

The following events will not be considered to be 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
- First occurrence of Grade 3 infusion-related reaction (IRR) during infusion of LY3434172, if both of the following criteria are met:
  - the patient did not receive corticosteroid prophylaxis, and
  - the Grade 3 IRR resolves within 6 hours with appropriate clinical management
  - If symptoms reappear, the event would be considered a DLT.
  - If this first occurence is anaphylaxis of any grade, the event would be considered a DLT.
- Grade 3 or 4 neutropenia meeting both of the following criteria are met:
  - is not associated with fever or systemic infection, and
  - improves by at least 1 grade within 7 days
- Grade 3 or 4 lymphopenia

It should be recognized that for patients who have received prior immune therapy, including checkpoint inhibitor therapy, there is the potential for delayed manifestation of serious irAEs such as colitis, hepatitis, pneumonitis, and endocrinopathies. Patients manifesting potential delayed irAEs should receive prompt evaluation and treatment.

7.2.2.2.2 DLT-Equivalent Toxicities

A DLT-equivalent toxicity (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 Q2W schedule and 42 days for Q3W schedule). 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 dose level or the determination of the RP2D.

7.2.2.3. Recommended Phase 2 Dose Determination

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 LY3434172 dose adjustments, AEs, chronic intolerance, PK and pharmacodynamic data, and irAEs. If LY3434172 has an acceptable clinical safety profile and shows sufficient activity, additional studies and/or cohorts may be added to determine a safe dose alone or in combination with other anti-cancer therapies. PD-L1 expression and other

biomarkers will be evaluated, and may influence enrichment strategies for subsequent studies and/or cohorts.

7.3. Blinding

This is an open-label study.

7.4. Dose Modification

No dose modification is allowed during the DLT observation period (Cycle 1). See Section 8 for discontinuation criteria. See Section 7.6.1.1 for the definition of DLT-evaluable patients.

After the DLT observation period (Cycle 1), doses of the study drug may be delayed or discontinued to manage specific AEs or other toxicities. Dose reductions are not permitted. All dose modifications should be documented, including the approach taken and a clear rationale for the need for modification.

The investigator must assess whether the toxicity is at least possibly due to study treatment and apply the dose-modification guidelines. Investigators are encouraged to consult Lilly for additional guidance.

If a patient requires a dose delay, study treatment should be resumed within 1 cycle, if possible and appropriate. If study treatment cannot be resumed within 1 cycle, every effort should be made to restart on the first day of the next cycle. In rare circumstances, a delay of >28 days may be permitted before permanent treatment discontinuation, as long as the patient demonstrates clinical benefit, does not have objective progression, and is recovering from the toxicity. Such circumstances must be discussed with the Lilly CRP/CRS.

Adverse events of immune-related etiology are expected because of the study drug's mechanism of action and may occur shortly after the first dose or several months after the last dose. Study treatment must be withheld if the patient experiences a drug-related toxicity or a severe or life-threatening AE. Dose reductions are not permitted.

A 4-hour observation period following the end of LY3434172 administration will occur in Cycles 1 to 3. During observation period, patients treated with LY3434172 should be closely monitored for signs and symptoms indicative of an infusion-related reaction by medical staff from the start of the infusion, in an area where emergency medical resuscitation equipment and other agents (epinephrine, prednisolone, or equivalents, etc.) are available. LY3434172 infusion-related reactions will be defined according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 definition of IRRs.

Table JZEA.9 presents instructions for management of infusion-related reactions associated with LY3434172.

Table JZEA.9. Management of Infusion-Related Reactions (IRR)

Grade	Management	
2	First occurrence	Immediately and permanently discontinue treatment if hypersentivity reaction is due to anaphylaxis of any grade. Stop the infusion for other infusion-related reactions. 1. If resolved to baseline or Grade 1 within 1 hour after stopping the infusion a. restart the infusion at 50% of the original rate (e.g., reduce from 100 mL/hr to 50 mL/hr) 2. If NOT resolved to Grade 0 or 1 within 1 hour after stopping the infusion: a. delay study treatment until the symptoms resolve in ≤48 hours, and b. premedicate prior to the next scheduled dose. Premedication should be administered 1.5 hours (±30 minutes) prior to the LY3434172 infusion with diphenhydramine (or other antihistamine), acetaminophen (or other antipyretic), steroids, etc., at the discretion of treating physician.
	Second occurrence	Immediately and permanently discontinue study treatment
3 or 4		Immediately and permanently discontinue study treatment except for situation below: Patients who experience Gr3 IRR that resolves within 6 hours may continue on study treatment. For subsequent infusions, the patient should be premedicated 1.5 hours (±30 minutes) prior to the LY3434172 infusion with diphenhydramine (or other antihistamine), acetaminophen (or other antipyretic), steroids, etc., at the discretion of treating physician.

American Society of Clinical Oncology (ASCO) guideline (Brahmer et al. 2018) for irAE management (including use for corticosteroids) will guide criteria for dose delays and discontinuations if the patient experiences a potential irAE considered at least possibly related to LY3434172.

Because of the potential for rapid and serious sequelae associated with irAEs, early intervention with corticosteroids is encouraged, concurrent with further diagnostic medical evaluations for possible nonimmune-related causes of AEs. The treatment plan should always include a thorough workup of the issue to rule out other potential etiologies such as infection. Local standards may supersede the guidelines provided in table below if deemed appropriate by the investigator. If a patient experiences an irAE that is not listed in this table, consult the Lilly CRP/CRS to discuss appropriate management.

Other corticosteroid options can be given at equivalent doses. Corticosteroids should be tapered over 1 month once symptoms improve to Grade ≤1, and study treatment should not be restarted until corticosteroid tapering is complete. During corticosteroid use, use prophylactic antibiotics to prevent opportunistic infections.

Table JZEA.10. Dose Modification Guidelines and AE Management for Toxicities At Least Possibly Related to Study Drug

SOC	Toxicity	CTCAE Grade and/or Symptoms[a]		Treatment Plan[b]
		Grade	Symptoms	
Endocrine	Thyroid issues		If asymptomatic with TSH <0.5 × LLN or >2 × ULN	Continue study treatment; perform free T4 in subsequent cycles.
			If symptomatic	• Start thyroid replacement therapy and/or medical management and continue study treatment • For Grade 3 hyperthyroidism, withhold study treatment until hyperthyroidism improves to Grade ≤1 • For Grade 4 hyperthyroidism, discontinue study treatment
Endocrine	Hypotension, altered mental status, headache, fatigue, hyperglycemia		For endocrine issues other than thyroid issues (for example, hypophysitis)	• For Grade 2, withhold study treatment and administer prednisone 1 to 2 mg/kg/day • Resume study treatment when symptoms resolve and the patient is stable on hormone replacement therapy • For Grade 3 or 4, discontinue study treatment • For severe adrenal crisis, give stress dose of IV corticosteroids with mineralocorticosteroid
Gastrointestinal	Diarrhea, Abdominal pain, Blood in stool, Colitis	2		• Withhold study treatment, give anti-diarrheal medication, and check etiology • If the event continues for >5 days despite the use of antidiarrheal medications, start prednisone 0.5 to 1 mg/kg/day • Resume study treatment after the event resolves to Grade ≤1

SOC	Toxicity	CTCAE Grade and/or Symptoms[a]		Treatment Plan[b]
		Grade	Symptoms	
Gastrointestinal	Diarrhea, Ileus, Perforation, Colitis	≥3		• Withhold study treatment and administer prednisone 1 to 2 mg/kg/day (no corticosteroids if possible perforation) • If the event persists >3 days despite use of corticosteroids, add a nonsteroidal immunosuppressive agent and discontinue study treatment.[c] • Resume study treatment after the event resolves to Grade ≤1 • Discontinue study treatment if Grade 3 persists • For Grade 4, discontinue study treatment
Hepatobiliary	Transaminitis, elevated bilirubin	2	• AST or ALT between 2.5 × ULN and 5 × ULN, or • TB between 1.5 × ULN and 3 × ULN	• Withhold study treatment and administer prednisone 1 to 2 mg/kg/day • Resume study treatment after symptoms resolve to Grade ≤1
		≥3	• AST or ALT >5 × ULN, or • TB >3 × ULN	• Discontinue study treatment and administer IV methylprednisolone 2 to 4 mg/kg/day • If the event continues for >3 days despite corticosteroids, add a nonsteroidal immunosuppressive agent[c]
Nervous system	Weakness, paresthesia (for example, Guillain–Barre syndrome or myasthenia gravis)		Moderate symptoms with no impact on ADL	Withhold study treatment until symptoms resolve.
		≥2 irAE	Impact on ADL	Discontinue study treatment. Give appropriate medical intervention and prednisone 1 to 2 mg/kg/day.
	Instructions if vasculitis suspected: New onset loss of motor function			• Follow management guidelines above as clinically indicated • Consult neurologist/ rheumatologist, preferably with vasculitis expertise

SOC	Toxicity	CTCAE Grade and/or Symptoms[a]		Treatment Plan[b]
		Grade	Symptoms	
Respiratory	Pneumonitis	1		Consider withholding study treatment and monitoring for radiographic improvement.
		2	Mild to moderate symptoms	• Withhold study treatment and administer prednisone 1 to 2 mg/kg/day • Resume study treatment after the event resolves to Grade ≤1
		≥3	Severe	• Discontinue study treatment and administer: o IV methylprednisolone 2 to 4 mg/kg/day and o prophylactic antibiotics • If the event remains at Grade ≥3 for >2 days despite corticosteroids, add a nonsteroidal immunosuppressive agent[c]
	Instructions if vasculitis suspected: Hemoptysis, appearance of new lung nodules or rapidly progressing respiratory failure.			• Consult pulmonologist/rheumatologist with vasculitis expertise in addition to following management instructions above. • Signs of additional nodules and infiltrates (compared to baseline) from thoracic CT scans could be suggestive of vasculitis (See Section 9.4.2.1)
Cardiac	Myocarditis, cardiac function abnormalities (for example. dysrhythmia, valvular abnormalities)	≥1		• Discontinue study treatment and administer o IV methylprednisolone 2 to 4 mg/kg/day o Consider immunosuppressives without immediate response to steroids (for example, mycophenolate, infliximab, or anti-thymocyte globulin) • Consult with cardiology immediately and; if available, transfer to cardiac care unit

SOC	Toxicity	CTCAE Grade and/or Symptoms[a]		Treatment Plan[b]
		Grade	Symptoms	
Renal and urinary	Elevated creatinine, decreased urine output, blood in urine, edema, nephritis	1	<1.5 x baseline	Continue study treatment
		2-3	1.5 × ULN< × ≤6 × ULN or >1.5 × baseline	• Withhold study treatment and administer prednisone 0.5 to 1 mg/kg/day • Resume study treatment after the event resolves to Grade ≤1 • If elevations persist for >7 days or worsen, follow the guidelines for a Grade 4 event
		4	>6 × ULN	Discontinue study treatment and administer prednisone 1 to 2 mg/kg/day.
	Instructions if vasculitis suspected: Elevated creatinine, decreased urine output, blood in urine, RBC casts, proteinuria		Creatinine: 1.5 × ULN< × ≤6 × ULN or >1.5 × baseline Proteinuria: >1+ on dipstick or regular urine analyses	• Follow management guidelines above as clinically indicated • Repeat creatinine and proteinuria and RBC casts in 7 days and if levels of creatinine and proteinuria still elevated and RBC casts still present, consult nephrologist and/or rheumatologist, preferably with vasculitis expertise. See Section 9.4.2.1.
Skin	Rash, pruritus		Moderate rash (diffuse, ≤30% BSA)	• Withhold study treatment • For rash on <10% of the patient's BSA, administer intermediate or high-potency topical corticosteroid • For rash on 10%-30% of the patient's BSA, administer systemic corticosteroids • Resume study treatment if the rash improves to mild (localized) and the corticosteroid dose is <7.5 mg/day
	Instructions if vasculitis suspected: Palpable purpura, skin ulcers			• Follow management guidelines above as clinically indicated • Consult dermatologist/rheumatologist preferably with vasculitis expertise. • Confirmation of vasculitis with skin punch biopsy required (See Section 9.4.2.1)

SOC	Toxicity	CTCAE Grade and/or Symptoms[a]		Treatment Plan[b]
		Grade	Symptoms	
Skin	Stevens–Johnson syndrome, toxic epidermal necrolysis, necrosis, bullous or hemorrhagic lesions			Discontinue study treatment and administer prednisone 1 to 2 mg/kg/day
Ophthalmological	Eye disorders (for example, uveitis, episcleritis)	≥2		• Consider topical steroids (for example, 1% prednisolone); temporarily discontinue study treatment until ophthalmology consult and administer ○ Oral or IV methylprednisolone 2 to 4 mg/kg/day
	Instructions if vasculitis suspected: blurred vision, vision loss, periorbital swelling			• Follow management guidelines above as clinically indicated • Consult ophthalmologist/rheumatologist preferably with vasculitis expertise. • See Section 9.4.2.1.

Abbreviations: ADL = activities of daily living; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BSA = body surface area; CRP = clinical research physician; CTCAE = Common Terminology Criteria for Adverse Events, version 5.0; irAE = immune-related adverse event; IV = intravenous; LLN = lower limit of normal; SOC = system organ class; TB = total bilirubin; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

[a] If symptoms of grade is not specified, use CTCAE version 5.0 definitions; otherwise, use the definitions provided in this table.

[b] Discontinuation of study treatment is permanent; resumption of study treatment is not allowed. If a toxicity does not resolve to Grade 0-1 or if the corticosteroid dose cannot be reduced to ≤10 mg/day of prednisone or equivalent within 12 weeks, consult with the Lilly CRP about discontinuing study treatment. In cases where corticosteroids are used, they should be appropriately tapered.

[c] Immunosuppressive refers to infliximab or cyclophosphamide.

7.5. Preparation/Handling/Storage/Accountability

Investigators should consult the study drug information provided in the Pharmacy Manual.

7.6. Treatment Compliance

The study medication will be administered only at the investigational site by the authorized study site personnel. As a result, treatment compliance is ensured.

7.6.1. Evaluable Patients

7.6.1.1 DLT-Evaluable Patients in Phase 1 Dose Escalation

Dose escalation refers to Cohort A1 to A5 or Cohort A1 to A6 (if Cohort A6 is opened).

A patient will be DLT evaluable if he or she experiences a DLT during the DLT observation period and has received at least one dose of study drug.

If a patient does not experience a DLT during the DLT observation period, he or she will be DLT evaluable if he or she receives all assigned doses of study drug(s) during the DLT observation period

Patients who receive all doses of study drug but discontinue from study treatment before the end of the DLT observation period will be considered DLT evaluable for the assessment of a dose level, provided it can be documented that the patient did or did not experience a DLT within the DLT observation period.

Patients who are not DLT evaluable may be replaced to ensure that enough patients complete the DLT observation period at each dose level, unless accrual to that cohort has stopped due to a DLT.

A patient may be deemed non-evaluable for assessment of a dose level in the event the patient experiences an AE which would meet DLT criteria, and furthermore has been determined through discussion between investigator and Lilly CRP/CRS to most likely be related to a concomitant medication or a prior line of immune therapy (in the case of irAEs) due to previously established linkage.

To ensure collection of adequate PK or biomarker data, patients who complete the DLT observation period but who do not have a valid PK or biomarker assay result may be replaced, upon consultation with the investigator(s) and the Lilly CRP/CRS, unless accrual to that cohort has stopped because of a DLT. Patients who are replaced for purposes of the PK or biomarker analysis are still considered DLT evaluable.

7.7. Concomitant Therapy

Appendix 5 describes medications, treatments, and drug classes that are restricted or prohibited for use during the study treatment period, including exceptions and conditions. There are no prohibited therapies during the post discontinuation follow-up period. Patients who, in the opinion of the investigator, require the use of any of the prohibited treatments for clinical

management should be discontinued from the trial. Patients may receive other supportive therapy that the investigator deems to be medically necessary.

In general, medications or live vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial except with approval from Lilly CRP/CRS.

No other chemotherapy, systemic radiotherapy, immunotherapy, cancer-related hormone therapy, experimental drugs, herbal supplements intended to treat cancer will be permitted while the patients are on this study.

Palliative radiation therapy to small areas of painful metastases that cannot be adequately managed with systemic or local analgesics is permitted after discussion with and agreement of the Lilly CRP/CRS.

In addition, any disease progression requiring other forms of specific antitumor therapy will also necessitate early discontinuation from study treatment. Appropriate documentation for all forms of premedication, supportive care, and concomitant medications must be captured on the eCRF. Replacement hormonal therapy initiated before study entry will be allowed.

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 ASCO (Smith et al. 2015) and European Society for Medical Oncology (Crawford et al. 2010) 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.

7.8. Treatment after the End of Study

The end of study definition is defined in Section 5.3. Investigators will continue to follow the schedule of activities provided in Section 2 until notified by Lilly that end of study has occurred.

7.8.1. 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 Schedule of Activities (Section 2) for all patients until notified by Lilly that study completion has occurred.

7.8.1.1. Continued Access

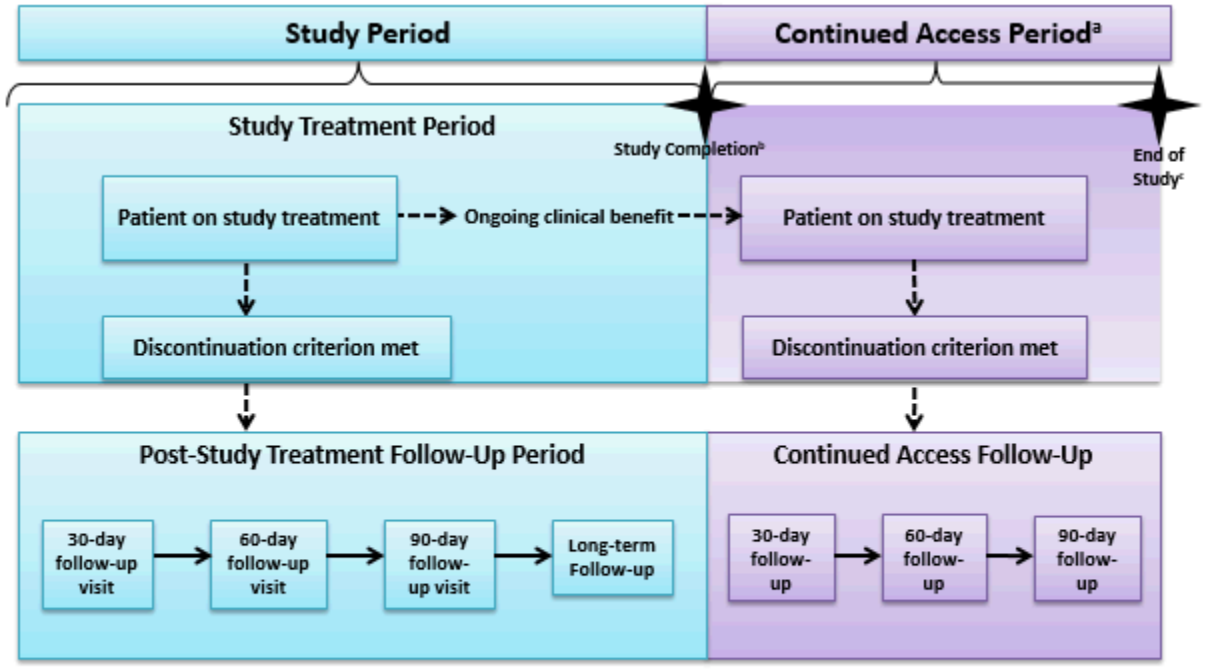
Patients who are still on study treatment at the time of study completion may continue to receive study treatment if they are experiencing clinical benefit and no undue risks.

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

Lilly may allow patients to enroll in a "rollover" protocol to provide long-term continued access for patients enrolled in this study.

Patients 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.

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



[a] Lilly will notify sites when the continued access period begins and ends.
[b] Final analysis of overall survival. Lilly will notify sites when study completion occurs.
[c] End of study occurs at the last visit or last scheduled procedure for the last patient.

Figure JZEA.2. Continued access diagram.

8. Discontinuation Criteria

The reasons for treatment and study discontinuation and the 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 Schedule of Activities (Section 2).

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.

8.1. Discontinuation from Study Treatment

Patients will be discontinued from study treatment in the following circumstances:

- the patient is 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.
- the patient becomes pregnant during the study
- the patient is significantly non-compliant with study procedures and/or treatment as described in Section 7.6
- The patient experiences a DLT (see Section 7.2.2.2) during Cycle 1, a DLT-ET (see Section 7.2.2.2.2), or other unacceptable toxicity
- the patient requires a dose delay of >28 days for Q2W schedule and >21 days for Q3W schedule, except as described in Section 7.4
- 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 treatment will occur prior to introduction of the new agent
- the investigator decides that the patient should be discontinued from study treatment, for reasons such as but not limited to confirmed disease progression (see Section 9.1.1).
- the patient requests to be discontinued from study treatment

Patients who are discontinued from study treatment will have follow-up procedures performed as shown in the Schedule of Activities (Section 2).

Discontinuation of study treatment may be considered for patients who meet **all** of the following criteria:

- have a confirmed complete response (CR)**, and**
- have received study treatment for at least 24 weeks**, and**
- have received at least 2 cycles of study treatment beyond the date when the initial CR was declared.

8.1.1. Discontinuation of Inadvertently Enrolled Patients

If Lilly or the investigator site identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, a discussion must occur between Lilly CRP/CRS and the investigator to determine if the patient may continue in the study. If both agree that it is medically appropriate to continue ,the investigator must obtain documented approval from Lilly CRP/CRS to allow the inadvertently enrolled patient to continue in the study with or without study treatment. Safety follow-up is as outlined in the Schedule of Activities (Section 2).

8.2. Discontinuation from the Study

Patients will be discontinued from the study in the following circumstances:

- 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).
- the patient becomes pregnant during the study. See Section 9.1.1.3 regarding regulatory reporting requirements on fetal outcome and breast-feeding
- the investigator decides that the patient should be discontinued from the study
- the patient requests to be discontinued from the study
- the patient's legal representative requests that the patient be discontinued from the study

Patients who discontinue from the study early will have end-of-study procedures performed as shown in the Schedule of Activities (Section 2).

8.3. Lost to Follow-Up

A patient would 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. Study site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or who the site is otherwise unable to follow-up.

9. Study Assessments and Procedures

Section 2 provides the Schedule of Activities for this study.

Appendix 2 provides a list of the laboratory tests that will be performed for this study.

Appendix 4 provides the schedule for collection of samples in this study.

Unless otherwise stated in the following subsections, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.1. Efficacy Assessments

Tumor assessments will be performed for each patient at the times shown in the Schedule of Activities (Section 2). A secondary objective of the study is to document efficacy.

RECIST 1.1 (Eisenhauer et al. 2009) will be applied as the primary criteria for assessment of tumor response and disease progression. Local tumor imaging (investigator assessment with site radiological reading) will be used.

Computed tomography (CT) is the preferred imaging method for the majority of patients. Magnetic resonance imaging should only be used when CT is contraindicated or for imaging in the brain. The same imaging technique should be used for a patient throughout the trial. Imaging should include the chest, abdomen, and pelvis. Intravenous and oral contrast is required unless medically contraindicated.

At Study Baseline:

- Must be performed within 28 days prior to the first dose of study drug.
- Scans performed as part of routine clinical management are acceptable for use as initial tumor imaging if they are of diagnostic quality and performed within protocol-required time frame as described above.

During Study Treatment:

- Performed every 8 weeks (±7 days) for the 28-day cycle cohorts and every 6 weeks (±7 days) for the 21-day cycle cohorts, by the investigator, with confirmatory assessment obtained at the next routine scheduled imaging time point (See Section 9.1.1).
- Per RECIST v1.1, partial response (PR) or complete response (CR) should be confirmed by a repeat tumor imaging assessment, preferably at the next scheduled imaging visit, and not less than 4 weeks from the date the response was first documented. Thus, for Study JZEA, tumor imaging for confirmation of response may be performed at the earliest four weeks after the first indication of response, or at the next scheduled scan, whichever is clinically indicated.
- Continue to perform imaging until whichever of the following occurs **first**:
    - disease progression confirmed by the second radiographic examination

- the start of new anticancer treatment
- withdrawal of consent
- death
- study completion

If radiologic imaging verifies an initial assessment of progressive disease (PD), apply RECIST 1.1 with confirmatory scan for disease progression (Section 9.1.1).

During the Poststudy Treatment Period: Tumor assessments may continue for patients who are withdrawn from the study treatment for reasons other than disease progression every 8 to 12 weeks depending on standard-of-care.

See Section 10.3.2 for definitions of the efficacy endpoints.

9.1.1. RECIST 1.1 with Confirmatory Scan for Disease Progression

9.1.1.1. Rationale for RECIST 1.1 with Confirmatory Scan for Disease Progression

Response to immunotherapy may differ from responses typically 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 PD by conventional criteria.
- The appearance of new lesions may not represent PD with immunotherapy.
- Stable disease while on immunotherapy may be durable and represent clinical benefit.

Therefore, to adequately characterize additional patterns of response and progression specific to patients treated with immunotherapy, which cannot be captured by conventional criteria such as RECIST 1.1, alternative measures of tumor assessment have been developed, such as RECIST 1.1 with confirmatory scan for disease progression. Clinically stable patients may continue treatment until disease progression (per standard RECIST 1.1) is confirmed. See Table JZEA.11 for further details and timing of confirmatory scans for PD.

Table JZEA.11. Summary of Response Assessment by RECIST, RECIST with Confirmatory Scan for PD, and irRC

Definition	Used in Study JZEA		Not Used in Study JZEA
	RECIST v1.1	RECIST 1.1 with Confirmatory Scan for PD	irRC (Wolchock et al. 2009), irRECIST (Nishino et al. 2013) iRECIST (Seymour et al. 2017)
New lesion	The presence of new lesion defines progression	The presence of new lesion defines progression	The presence of new lesion does not define progression. The measurements of the new lesion(s) are included in the sum of the measurements.
Confirmation of PD	Not required	PD, in the absence of clinically significant deterioration, requires confirmation with repeat imaging after 4 to 6 weeks. After initial PD following RECIST v1.1, shift to "RECIST 1.1 with confirmatory scan for PD".	Required

Abbreviations: irRC = immune-related response criteria; irRECIST = immune-related Response Evaluation Criteria in Solid Tumors; PD = progressive disease; RECIST = Response Evaluation Criteria in Solid Tumors.

9.1.1.2. Application of RECIST 1.1 with Confirmatory Scan for Disease Progression

For Study JZEA, based on the unique response to immunotherapy and guidelines from regulatory agencies (for example, the EMA guideline on the evaluation of anticancer medicinal products in man for immune-modulating anticancer compounds [EMA 2013]), the following will be applied, in addition to standard RECIST 1.1 criteria:

- If radiologic imaging verifies initial PD, tumor assessment should be repeated 4 to 6 weeks later in order to confirm PD in the absence of clinically significant deterioration. Study treatment will continue between the initial assessment of progression and confirmation for progression.

"Clinically significant deterioration" is considered to be rapid tumor progression that necessitates treatment with anticancer therapy other than study treatment, or symptomatic progression that requires urgent medical intervention (for example, central nervous system metastasis, respiratory failure due to tumor compression, or spinal cord compression).

- In the case of clinically significant deterioration, the patient will be discontinued from study treatment (Section 8.1).
- Patients who continue to receive clinical benefit and who do not have clinically significant deterioration despite evidence of objective PD by the confirmatory scan may continue study treatment at the discretion of the investigator, in consultation with the Lilly CRP/CRS.

In determining whether or not progression can be confirmed, the site study team should consider all target lesions, nontarget lesions, and new lesions, and assess according to RECIST 1.1.

9.1.1.3. Criteria Required to Receive Treatment during Confirmatory Scan Period

In order for patients to continue receiving LY3415244, the following criteria apply:

- absence of clinically significant deterioration (defined in Section 9.1.1.2)
- absence of clinical symptoms indicating clinically significant disease progression
- no decline in performance status
- no significant, unacceptable or irreversible toxicities related to study treatment
- patient must sign the addendum consent prior to being treated during this time period

9.2. Adverse Events

The investigator will use Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (NCI 2017) to assign severity grades.

Investigators are responsible for:

- monitoring the safety of patients who have entered into 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 patient.
- providing appropriate medical care of the patient during the study.
- documenting their review of each laboratory safety report.
- following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to study treatment or the study, or that caused the patient to discontinue study treatment before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. Frequency of follow-up evaluation 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 safety and toxicity.

After the ICF is signed, study site personnel will record via eCRF the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. Study site personnel will record via eCRF any change in preexisting conditions and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to study treatment or study procedure via eCRF.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment 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 study treatment and/or study procedure and the AE.

Adverse Event grading of toxicities related to estimated Glomerular Filtration Rate (GFR) should be evaluated based on the Cockcroft-Gault method (Cockcroft and Gault 1976) or measured GFR.

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

Study site personnel must report any dose modifications or treatment discontinuation that results from AEs to Lilly or its designee via eCRF, clarifying, if possible, the circumstances leading to dose modification or discontinuation of treatment.

9.2.1. Serious Adverse Events

An SAE is any AE during this study that results in one 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 require hospitalization, may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above.

Although all AEs after signing the ICF are recorded in the eCRF, 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 procedure.

Where permitted, study site personnel must notify Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a Lilly-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.

Pregnancy (during maternal or paternal exposure to study treatment) does not meet the definition of an AE but should be reported. 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 patients once they have discontinued and/or completed the study (the patient disposition eCRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a patient 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.

Planned hospitalizations or procedures for preexisting conditions that were recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study treatment or other protocol-required procedure) should not be considered SAEs.

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.

9.2.2. 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 study treatment or study procedure. The United States 21 CFR 312.32, the Regulation (EU) No 536/2014 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 recording and expedited reporting of SUSARs that are consistent with global regulatory regulations and the associated detailed guidances.

Regular communication will occur between investigators and the Lilly CRP/CRS via various channels (that is, email, regularly scheduled teleconference, Safety Reporting Notification System, etc.) to ensure that all parties are aware of how patients are tolerating LY3434172. If in the event that sites need to be made aware of an emerging safety issue in a timely manner, Lilly will, upon confirmation of the event, communicate to site staff via email and/or direct telephone calls to ensure receipt of all of the information. Lilly will follow-up with individual sites until receipt of the information is confirmed and that the site has taken the appropriate safety measures.

9.2.3. Complaint Handling

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

Patients 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.

9.3. Treatment of Overdose

Refer to the IB for intervention or comparator for available information on the signs, symptoms, and treatment of overdose.

9.4. Safety

9.4.1. Safety Measures

Refer to the Schedules of Activities (Section 2) regarding the timing of vital signs, laboratory tests, and other tests.

9.4.1.1. Electrocardiograms

Perform ECGs as shown in Appendix 4. Triplicate ECGs will be collected in Study JZEA at indicated time points in Appendix 4. During posttreatment follow-up period, single ECGs are collected. ECGs should be recorded according to the study-specific recommendations included in the ECG manual.

ECG recording and vital sign measurements should occur prior to any blood draws scheduled at the same time point. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

ECGs will be initially interpreted by a qualified physician at the site (the investigator or qualified designee) as soon after the time of ECG collection as possible (ideally while the patient is still present) to determine whether the patient meets entry criteria and for immediate patient management.

If a clinically significant quantitative or qualitative change from baseline is identified after enrollment, the investigator will assess the patient for symptoms (for example, palpitations, near-syncope, or syncope) and to determine if the patient can continue in the study. The investigator or qualified designee is responsible for determining if any change in patient management is needed and must document his/her review of the ECG printed at the time of evaluation.

Any clinically significant findings that result in a diagnosis and that occur after the patient receives the first dose of study treatment should be reported to Lilly or its designee as an AE via eCRF.

All digital ECGs will be electronically transmitted to a designated central ECG laboratory. The central ECG laboratory will perform a basic quality control check (for example, demographics and study details) and store the ECGs in a database. At a future time, the stored ECG data may be overread at the central ECG laboratory for further evaluation of machine-read measurements or to meet regulatory requirements.

The machine-read ECG intervals and heart rate may be used for data analysis and report writing purposes unless a central ECG laboratory cardiologist overread of the ECGs is conducted prior to completion of the final study report (in which case the overread data would be used).

For each set of replicates, the cardiologist will determine the R-R and QT intervals and heart rate on the ECGs. These data are not routinely reported back to the investigative site. However, any clinically significant finding that was not present on the fully overread ECG will be reported to the investigator and to Lilly. All data from the overreads will be placed in the Lilly database for analytical and study report purposes.

The investigator’s (or qualified designee’s) ECG interpretation will be used for decisions about study entry and immediate patient management will be based on the investigator's or qualified designee's ECG interpretation. Data analysis will be based on ECG interpretations performed by the cardiologist at the central ECG laboratory.

9.4.2. Safety Monitoring

Lilly will review safety data on a cohort by cohort basis and periodically review evolving aggregate safety data within the study by appropriate methods.

Lilly has systematic and robust internal processes in place that ensure safety surveillance of development compounds in line with the US Food and Drug Administration (FDA)'s expectations for safety assessment committees (SACs) (FDA Draft Guidance: "Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics"; FDA Draft Guidance: "Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics"; FDA Draft Guidance: "Safety Assessment for IND Safety Reporting"; FDA Guidance: "Safety Reporting Requirements for INDs and BA/BE Studies"). This includes processes with clearly described roles and responsibilities that are owned by Lilly's Global Patient Safety organization. These processes are designed to monitor the evolving safety profile (i.e., review of cumulative SAEs, other important safety information) by designated cross-functional teams in a timely manner at pre-defined intervals or on an ad-hoc basis. In addition, a dedicated process may be used to perform unblinded comparisons of event rates for SAEs as necessary.

This system ensures that the accumulating safety data derived from individual and multiple trials across a development program is reviewed on a regular basis and that important new safety information, such as the need for protocol modification or other relevant safety related material, is identified and communicated to regulators and investigators appropriately and in a timely fashion. An internal review of aggregate safety data occurs on at least a quarterly basis or more frequently, as appropriate. Any serious adverse reactions are reported within the required timeline for expedited reporting.

In addition to annual periodic safety updates and to further inform investigators, a line listing report of SUSARs is created and distributed to investigators on a biannual (twice yearly) basis. Any significant potential risk/safety concerns that are being monitored as well as any results being reported in other periodic reports for the compound; SAC decisions; and other significant safety data (for example, nonclinical or clinical findings, removal of serious adverse reactions) are included in the report.

If a study patient experiences elevated alanine aminotransferase (ALT) >5X upper limit of normal (ULN) and elevated total bilirubin (TBL) >2X ULN, or ALT ≥8X ULN, liver tests (Appendix 6) should be repeated within 3 to 5 days including ALT, AST, TBL, direct bilirubin (D.TBL), gamma-glutamyl transferase (GGT), and creatine phosphokinase (CPK) to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator based on the hepatic monitoring tests (Appendix 6) and in consultation with the Lilly CRP/CRS. Monitoring of ALT, AST, and TBL should continue until levels normalize or return to approximate baseline levels.

9.4.2.1. Guidance for Monitoring Vasculitis

In the preclinical toxicology studies with LY3434172, vascular/perivascular mononuclear or mixed cell infiltrates were observed in both large and small vessels, whereby various organs were affected. While this is not an uncommon finding with human antibodies in non-human primates, it is unknown if vasculitis poses a potential risk in humans.

Given the nature of the findings in animals and heterogeneity associated with vasculitis, patients should be monitored for clinical signs and systemic laboratory tests described below for possible signs of vasculitis. There are some overlapping clinical features and laboratory tests to those observed for irAE and management of these AEs should be in accordance with local guidelines (Brahmer et al. 2012, Hannen et al. 2017, Puzanov et al. 2017) or Table JZEA.11. A rheumatologist (preferably with specialist knowledge in diagnosis and treatment of vasculitis) should be consulted if vasculitis is suspected.

Clinical signs of potential vasculitis:

- Skin: palpable purpura, skin ulcers. In the case of cutaneous vasculitis, 2 skin punch biopsies (deep dermis should be captured as part of the biopsy) of the affected area should be obtained. One core could be collected in formalin and processed for H&E assessment and the second core biopsy flash frozen.
- Mucous membranes: new onset oral ulcers that do not resolve within a week
- Ophthalmologic symptoms: blurred vision, vision loss, periorbital swelling
- Ear, nose or throat: New onset bloody nasal discharge/crust/ulcers that does not resolve within a week, sinusitis, sudden onset of hearing loss
- Lungs/respiratory: Hemoptysis, respiratory failure, infiltrates, appearance of nodules on imaging (thoracic CT scan) not attributable to other causes (e.g., immune related pneumonitis)
- Gastrointestinal: Bloody diarrhea, ischemic abdominal pain
- Renal and urinary: Hypertension, proteinuria, hematuria ≥10 RBCs/hpf, RBC casts, elevated serum creatinine
- Nervous system: New onset loss of motor function

Systemic laboratory test:

- Complete blood count (CBC), liver enzymes, creatinine, urinalysis with microscopy should be evaluated together with clinical features listed above for hematologic, renal or other organ involvement.
- Erythrocyte sedimentation rate (ESR) elevation suggestive of inflammation if not already elevated due to underlying malignancy.
- C-reactive protein elevation suggestive of inflammation if not already elevated due to underlying malignancy.
- C3a complement will be tested as indicated in table (Table JZEA.1 and Table JZEA.2).
- C-ANCA and P-ANCA values will be captured at baseline and as indicated
    - if positive, additional tests for myoperoxidase (MPO) and proteinase-3 (PR3) antibodies are required.

9.4.2.2. Special Hepatic Safety Data Collection

Hepatic data should be collected (see Appendix 6) in the event that a patient meets one of the following conditions during the course of the study:

- elevation of serum ALT to ≥10X ULN
- patients without liver tumors or liver metastasis: ALT≥5X ULN and TBL≥ 2X ULN
- patients with liver tumors or liver metastasis: ALT≥8X ULN and TBL≥ 2X ULN
- discontinuation from treatment due to a hepatic event or abnormality of liver tests
- occurrence of a hepatic event considered to be a SAE

9.5. Pharmacokinetics

Pharmacokinetic samples will be collected as shown in Appendix 4.

Blood samples will be used to determine the study drug concentrations of LY3434172 (also known as bioanalytical samples).

Instructions for the collection and handling of bioanalytical blood samples will be provided by Lilly. The actual start and end date and time of LY3434172 infusion must be recorded on the eCRF. The actual date and time that each bioanalytical blood sample is drawn must be recorded on the laboratory requisition page after the sample is drawn.

All study drug concentrations in bioanalytical serum samples will be measured using a validated enzyme-linked immunosorbent assay in a laboratory designated by Lilly.

Bioanalytical samples collected to measure study drug concentrations will be retained for a maximum of 1 year following last subject visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory metabolism studies or exploratory analyses such as bioanalytical assay validation or cross-validation exercises.

9.6. Pharmacodynamics

Pharmacodynamic samples will be collected as shown in Appendix 4 to assess target engagement and activity for LY3434172. Potential pharmacodynamic markers may include measuring soluble markers (sPD-L1 and sPD-1) in serum, cytokine levels (i.e. IL-2 and IFNy) in blood samples after ex vivo stimulation with staphylococcal enterotoxin B (SEB) and anti-CD28 agonist, and immune cell subsets characterization and distribution. Tumor tissue, plasma, serum, and whole blood may be used for additional exploratory pharmacodynamics testing as deemed appropriate by Lilly (see also Section 9.8). Samples collected to measure pharmacodynamic biomarkers will be identified by the patient number (coded) and retained at a facility selected by the Lilly for a maximum of 15 years following last patient visit for the study.

9.6.1. Immunogenicity Assessments

Blood samples for IG testing will be collected as shown in Appendix 4 to determine antibody production against LY3434172. Immunogenicity will be assessed by a validated assay designed

to detect ADAs in the presence of LY3434172. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of LY3434172.

In the event of an IRR, blood samples will be collected for PK, ADA and exploratory immune safety analyses at the following time points, as close as possible to: (i) the onset of the IRR, (ii) the resolution of the IRR, and (iii) 30 [±3] days following the IRR. CCI [redacted] Instructions for the collection and handling of blood samples will be provided by the Lilly CRP/CRS. The actual date and time (24-hour clock time) of each sampling will be recorded.

Samples will be retained at a facility selected by Lilly for a maximum of 15 years after last the patient visit for the study, or for a shorter period if regulations and ethical review boards (ERBs)/institutional review boards (IRBs) impose shorter time limits. The duration allows Lilly to respond to future regulatory requests related to LY3434172. Any samples remaining after 15 years will be destroyed.

9.7. Genetics

9.7.1. Whole Blood Sample for Pharmacogenetic Research

A whole blood sample will be collected for pharmacogenetic analysis as specified in Appendix 4, 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 LY3434172 and to investigate genetic variants thought to play a role in cancer. Assessment of variable response may include evaluation of AEs or differences in efficacy.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the study site personnel. Samples will be retained at a facility selected by Lilly for a maximum of 15 years after the last patient 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 questions from regulatory agencies, and investigation of variable response that may not be observed until later in the development of LY3434172 or after LY3434172 becomes commercially available.

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

9.8. Biomarkers

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

As part of Lilly's ongoing efforts to understand the relationship between cancer, genetics, and response to therapy, this study will analyze systemic and tumor tissue-associated biomarkers relevant to LY3434172, mechanism of action of LY3434172, the variable response to study drug(s), immune function, and pathways associated with cancer. These samples may also be used to develop related research methods or to validate diagnostic tools or assays.

Samples for biomarker research will be collected as specified in Appendix 4, where local regulations allow. It is possible that biomarker data for patients in the study has 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 9.7.1, 9.8.1, and 9.8.2.

9.8.1. Tissue Samples for Biomarker Research

Tissue samples for biomarker research will be collected for the purposes described in Section 9.8. The following samples for biomarker research will be collected as specified in Appendix 4, where local regulations allow.

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

For patients participating in all cohorts:

- a newly obtained core or excisional pre-treatment biopsy of a tumor lesion from metastatic site **and**
- a tumor tissue sample from a newly obtained core or excisional biopsy specimen collected during the study treatment period as shown in Appendix 4.
- an archival formalin-fixed paraffin-embedded 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).

An attempt to obtain up to 4 core-needle biopsies or a surgical biopsy is required, unless medically contraindicated or unsafe and discussed with Lilly CRP/CRS. Optimally, biopsies should be taken from the same metastatic lesion and from areas not previously irradiated (except if the patient had progressed after radiation). For tumor tissue samples that are not archived, the subject has to be willing to undergo baseline and on-study biopsies that should not put subjects at undue risk greater than that which comes with a core biopsy, in other words, a procedure to obtain biopsy should have a serious/severe complication risk no greater than 2%.

If a biopsy does not contain adequate tissue for analysis, the patient may be replaced. Lilly may replace up to 25% patients, if unable to submit an adequate tumor sample.

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

For patients participating in all cohorts

- 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 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.

Newly acquired tumor biopsies are requested because they provide the most current biomarker characteristics of the tumor compared with biopsies taken at the time of diagnosis (tumor characteristics may shift during subsequent lines of treatment). Pre- and on-treatment assessments are critical to evaluate changes in molecular markers over time and to document any potential immunomodulatory activity of treatment with LY3434172 and should be performed if clinically feasible. Samples will be examined for biomarkers as described in Section 9.8, including but not limited to, PD-L1 expression by immunohistochemistry.

The tissue samples should be obtained using an appropriate method. Tumor tissue should be submitted as a newly acquired excisional or core needle (minimum 18 gauge) or surgical biopsy in formalin. Cytological or fine-needle aspiration, bone specimens are not acceptable. If additional tumor biopsies are collected as part of clinical care, they should be submitted, along with pathology reports, for further analysis. See the Laboratory Manual for details regarding sample handling. At the time of tissue collection process, due diligence should be used to make sure that the tumor sample (not a normal adjacent tissue sample or a tumor margin sample) is provided and contains tumor cells prior to shipment to the central laboratory. This will help ensure that a quality biopsy sample has been taken.

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.

Samples will be retained at a facility selected by Lilly for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits. This retention period enables the use of new technologies, response to questions from regulatory agencies, and investigation of variable response that may not be

observed until later in the development of LY3434172 or after LY3434172 becomes commercially available.

Technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. Existing approaches, including but not limited to 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.

9.8.2. Other Samples for Biomarker Research

The following samples for biomarker research will be collected for the purposes described in Section 9.8, and as specified in Appendix 4, where local regulations allow.

- Whole blood
- Serum
- Plasma
- Stool (when applicable, stool specimens may be collected for microbiome analyses)
- A maximum of 5 samples may be collected 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.

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

Samples will be retained at a facility selected by Lilly for a maximum of 15 years after the last patient 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 questions from regulatory agencies, and investigation of variable response that may not be observed until later in the development of LY3434172 or after LY3434172 becomes commercially available.

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

9.9. Health Economics

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

10. Statistical Considerations

10.1. Sample Size Determination

The primary objective of this study is to assess the safety and tolerability of LY3434172, thereby identifying and confirming the RP2D of LY3434172 to be administered as monotherapy to patients with solid tumors. The secondary objective is to evaluate PK and any observed evidence of clinical efficacy.

The total sample size in Cohorts A1 to A5/A6 will be determined by the incidence of DLTs. The RP2D could be chosen after the corresponding Q2W cohorts have been enrolled. After the DLT period (Cohorts A1 to A5/A6) is completed, an additional 12 to 15 patients at two dose levels selected from these cohorts will be enrolled for adequate assessment of safety and exploration of PK and pharmacodynamic effects. In parallel, patients will be enrolled in Q3W cohorts (A7 and A8) to allow flexibility for future combinations with standard-of-care agents. The sample size of Q3W depends primarily on PK profiles and clinical considerations.

10.2. Populations for Analyses

The following analysis sets will be defined for this study.

Enrolled/Safety population: will include all patients who received any quantity of study treatment, regardless of their eligibility for the study. The safety and efficacy evaluation will be performed based on the first dose of study treatment a patient actually received. This population will be used for all dosing/exposure, safety, and efficacy analyses.

Pharmacokinetic analysis set: will include all enrolled patients who received at least one dose of LY3434172 and have at least one evaluable PK sample.

Biomarker analysis set: will include the subset of enrolled patients from whom a valid assay result has been obtained. No imputation will be performed for missing data due to the limitation of small sample size.

10.3. Statistical Analyses

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

Unless otherwise stated, all confidence interval (CIs) will be given at a 2-sided 95% level.

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 Statistical Analysis Plan (SAP) and clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

10.3.1. Safety Analyses

All patients who receive any quantity of LY3434172 will be evaluated for safety and toxicity. Severity grades will be assigned by the investigator using CTCAE Version 5.0.

Safety analyses will include summaries of the following:

- DLTs: the number of patients who experience any DLTs during Cycle 1 will be summarized by cohort by treatment arm
- DLT-equivalent: the number of patients who experience any AE that qualifies as a DLT during any period of study will be summarized by the first dose by treatment arm and by tumor type
- AEs, including severity and possible relationship to study drug
- AEs by Medical Dictionary for Regulatory Activities system organ class (SOC) by decreasing frequency of Preferred Term within an SOC
- laboratory and non-laboratory AEs by CTCAE Version 5.0 term, maximum CTCAE grade, and CTCAE Grade 3 and above (regardless of causality and at least possibly related to study treatment)
- changes in vital signs and ECGs

10.3.2. Efficacy Analyses

The study was not designed to make an efficacy assessment. However, any tumor response data will be tabulated, where appropriate, for all patients in the enrolled/safety analysis set.

The efficacy endpoints are listed and defined as follows:

Objective response rate (ORR) is the proportion of enrolled patients who have received any amount of either study drug, have at least one postbaseline tumor image, and achieved a best overall response (BOR) of confirmed CR or PR.

Duration of response (DoR) is defined only for responders (patients with a confirmed CR or PR). It is measured from the date of first evidence of a confirmed CR or PR to the date of the first observed radiographically documented PD, or the date of death due to any cause, whichever is earlier. If a responder is not known to have died or have objective progression as of the data inclusion cutoff date, DoR will be censored at the date of the last complete objective progression-free disease assessment.

Time-to-response (TTR) is the time from the date of first study treatment until the first evidence of a confirmed CR or PR.

Disease control rate (DCR) is the proportion of enrolled patients who have a BOR of confirmed CR, confirmed PR, or stable disease (SD).

Progression-free survival is defined as the time from the date of first study treatment until the date of the first observed radiographically documented PD or death due to any cause, whichever is earlier. The censoring is taken in the following order:

- If a patient does not have a complete baseline disease assessment, then the PFS time will be censored at the enrollment date, regardless of whether or not objectively determined disease progression or death has been observed for the patient; otherwise,

- if a patient is not known to have died or have objective progression as of the data inclusion cutoff date for the analysis, the PFS time will be censored at the last complete objective progression-free disease assessment date.

Overall survival, an exploratory objective, is determined from the date of first study treatment until death due to any cause. If the patient is not known to have died at the data inclusion cutoff date for the analysis (or is lost to follow-up), OS will be censored on the last date the patient was known to be alive. This endpoint will be followed up for 12 months after the last patient has entered treatment.

The objective response rate, TTR, DCR, DoR, and PFS will be assessed based on RECIST v1.1 (Eisenhauer et al. 2009) and RECIST v1.1 with confirmatory scan for disease progression (Section 9.1.1).

The estimate of ORR and DCR, and the corresponding CI, will be provided by dose-level (cohort) according to RECIST v1.1 and RECIST v1.1 with confirmatory scan for disease progression (Section 9.1.1). Time-to-event variables, such as TTR, DoR, PFS (as an exploratory objective), and OS (as an exploratory objective), will be summarized by Kaplan and Meier (1958) method by dose-level (cohort) where appropriate. Presentations of antitumor activity may include patients enrolled in the dose-level (cohort) with the same tumor type and dosing scheme. Individual changes in the tumor burden over time will be presented graphically within a tumor type. Subgroup analysis of interest will be further defined in the SAP.

10.3.3. Other Analyses

10.3.3.1. Patient Disposition

A detailed description of patient disposition will be provided, 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 SAP, or discontinuing (overall and by reason for discontinuation). A summary of all important protocol deviations will be provided.

10.3.3.2. Patient Characteristics

Demographic data are collected and reported using descriptive statistics.

A summary of baseline patient and disease characteristics, historical diagnoses, preexisting conditions, and prior therapies will be reported using descriptive statistics.

Other patient characteristics at baseline will be summarized as deemed appropriate.

10.3.3.3. Concomitant Therapy

A summary of prior and concomitant medications will be reported.

10.3.3.4. Treatment Compliance

The number of cycles received, dose omissions, dose reductions (if any), dose delays, and dose intensity will be summarized for all treated patients by treatment arm.

LY3434172 will be administered at the investigator site, therefore treatment compliance is assured.

10.3.3.5. Pharmacokinetic/Pharmacodynamic Analyses

Selected PK descriptors (based on actual sampling times), including approximate C_{max} and AUC will be calculated by noncompartmental analysis methods. 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 LY3434172 may be calculated by population PK analysis methods using nonlinear mixed effects modeling (NONMEM). 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/pharmacodynamic management.

Following review of the biomarker analyses (see Section 10.3.3.6), pharmacodynamics biomarker analysis with tumor type, changes in biomarker levels over time, and association to dose levels or exposure might be explored if applicable. Pharmacokinetics/Pharmacodynamics analyses may be conducted to explore exposure-response relationships between LY3434172 concentrations in systemic circulation and relevant pharmacodynamics measures such as soluble PD-1, soluble PD-L1 and IL-2 stimulation. Either summary metrics of exposure and effect (for example, individual trough concentrations) or concentration time profiles of exposure and effect could be used for these analyses.

10.3.3.6. Biomarker Analyses

The relationship between biomarkers and clinical outcome may be assessed. If the ORR is greater than or equal to 10%, the baseline biomarkers that potentially predict better response to LY3434172 may be explored using single- or multi-marker approach. Association analysis from selected biomarkers to the clinical endpoints will be explored if applicable.

10.3.3.7. Immunogenicity Analyses

The frequency and percentage of patients with preexisting ADA, ADA at any time point postbaseline, and with treatment-emergent ADA positivity (TE ADA+) to LY3434172 will be tabulated. Treatment-emergent ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA). For the TE ADA+ patients, the distribution of maximum titers will be described. The frequency of neutralizing antibodies may also be tabulated in TE ADA+ patients.

The relationship between the presence of antibodies and the PK parameters and pharmacodynamic response including safety and efficacy to LY3434172 may be assessed.

10.3.4. Interim Analyses

Safety, PK, and biomarker data (if available) will be reviewed on a cohort-by-cohort basis during the study, until the MTD and/or RP2D is determined. The purpose of these cohort-by-cohort data reviews is to evaluate the safety data at each dose level and determine if a DLT has been observed. The decision whether to advance to the next dose level will be made following discussion between the investigators and Lilly and will be relayed to the sites prior to patients being treated on the subsequent cohort.

Safety and available PK data will be reviewed during the study to inform dose escalation, modifications to the dose-escalation strategy, or other design elements.

An interim analyses will be performed after all patients from cohorts A1 to A5/6 have completed the DLT evaluation period. Additional enrolment of 12-15 patients from these cohorts at two dose levels (yet to be determined) can continue during IA.

Interim analyses may also be combined with any prespecified safety review or reporting (i.e. Trial Level Safety Reviews, Development Safety Update Reviews, or IB update reviews).

The final overall analysis of Study JZEA will coincide with the safety and efficacy primary analysis of the last cohort.

If it is deemed that enough data have been obtained to assess the primary and 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 data-cutoff date and results may be listed. However, summary tables including data after data-cutoff date will not be created.

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	anti-drug antibody
AE	Adverse event: any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and 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 medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BED	biologically effective dose
BOR	best overall response
C_{avg}	2-week average concentration
C_{max}	maximum plasma concentration
C_{min}	trough concentration
CBC	complete blood count
cDNA	complementary DNA
CI	confidence interval
CL	clearance
CNS	central nervous system
collection database	A computer database where clinical study data are entered and validated.

CR	complete response
CrCl	creatinine clearance
CRP	clinical research physician: individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRS	clinical research scientist
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	lowest concentration of drug just prior to the next dose
DCR	disease control rate: the percentage of patients with a best response of CR, PR, or SD.
DLT	dose-limiting toxicity
DLT-ET	DLT-equivelant toxicity
DoR	duration of response: 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.
ECG	electrocardiogram
eCRF	electronic case report form
EI	equivalence interval
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment and have received at least one dose of study treatment.
ERBs/IRBs	ethical review boards/institutional review boards
Enter	Patients entered in the study are those who have signed the informed consent form directly or through their legally acceptable representatives.
ESR	erythrocyte sedimentation rate
FDA	Food and Drug Administration
FIH	first in human
GCP	good clinical practice

G-CSF	granulocyte colony stimulating factors
GFR	glomerular filtration rate
HCC	hepatocellular
highly effective method of contraception	Methods include • combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: o oral o intravaginal o transdermal • progestogen-only hormonal contraception associated with inhibition of ovulation: o oral o intravaginal o transdermal • intrauterine device • intrauterine hormone-releasing system • bilateral tubal occlusion • vasectomized partner (vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential who is the trial participant and that the vasectomized partner has received medical assessment of the surgical success.) • sexual abstinence (sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.)
HIV	human immunodeficiency virus
IB	Investigator's Brochure
irAEs	immune-related adverse events
IRR	infusion-related reaction
ICF	informed consent form
ICH	International Conference on Harmonization
IG	immunogenicity
IgG	immunoglobulin G
IgG1	immunoglobulin G1
IgM	immunoglobulin M

interim analysis	An analysis of clinical study data that is conducted before the final reporting database is authorized for datalock.
IRR	infision-related reaction
irRC	immune-related response criteria
Investigational product	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, marketed products used for an unauthorized indication or marketed products used to gain further information about the authorized form.
IV	intravenous
IWRS	interactive web-response system
LPET	last patient enters/starts study treatment
mAb	monoclonal antibody
MABEL	minimum anticipated biological effect level
MPO	myoperoxidase
MTD	maximum tolerated dose
mTPI-2	modified toxicity probability interval-2
NK cells	natural killer cells
NOAEL	no-observed-adverse-effect-level
NONMEM	nonlinear mixed effects modeling
NSCLC	non-small cell lung cancer
NSG	nod-SCID gamma
open-label	A study in which there are no restrictions on knowledge of treatment allocation, therefore the investigator and the study participants are aware of the drug therapy received during the study.
ORR	objective response rate: the percentage of patients who achieve a best overall response (BOR) of CR or PR
OS	overall survival
PD	progressive disease
PD-1	programmed death 1
PD-L1	programmed death ligand 1

PFS	progression-free survival: the time from randomization until the first radiographic documentation of progression or death from any cause in the absence in progressive disease.
PK	pharmacokinetic
PR	partial response
PR3	proteinase-3
RECIST	Response Evaluation Criteria in Solid Tumors
reporting database	A point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.
Re-screen	to screen a patient who was previously declared a screen failure for the same study
RP2D	recommended Phase 2 dose
SAC	safety assessment committee
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.
Screen failure	A patient who does not meet one or more criteria required for participation in a study
SEC	staphylococcal enterotoxin B
sPD-L1	soluble programmed death ligand 1
SOC	system organ class
SUSAR	suspected unexpected serious adverse reactions
TBL	total bilirubin
TE	target engagement
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.
TMDD	Target Mediated Drug Disposition
TTR	Time-to-response

Vd	volume of distribution
WOCBP	Women of childbearing potential; females who have attained menarche and are not menopausal or surgically sterile.

Appendix 2. Clinical Laboratory Tests

Hematology – local laboratory

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

Coagulation – local laboratory

Activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT)
International normalized ratio (INR) or prothrombin time (PT)

Fibrinogen – local laboratory

Clinical chemistry – local and central laboratory[b]

Serum concentrations of:

- Alanine aminotransferase (ALT)
- Albumin
- Alpha-fetoprotein (AFP; required only for patients with HCC)
- Alkaline phosphatase
- Aspartate aminotransferase (AST)
- Amylase
- Bicarbonate
- Bilirubin, direct
- Bilirubin, total
- Blood urea nitrogen (BUN) or blood urea
- C-reactive protein
- Calcium
- Chloride
- Creatinine
- Creatine kinase (CK)
- Gamma glutamyl transferase (GGT)
- Glucose, random
- Lactate dehydrogenase (LDH)
- Lipase
- Potassium
- Sodium
- Total protein

TSH and free T4 – central laboratory

Erythrocyte sedimentation rate (ESR) – local laboratory

C3a complement - central laboratory

C-ANCA/P-ANCA/Troponin-I – central laboratory

Tumor markers – local laboratory

Urinalysis – local laboratory

A microscopic examination is required for abnormal results. Microscopy should be used as appropriate to investigate white blood cells and use the high-power field for red blood cells. Perform the 24-hour urine protein analysis if urine protein is ≥2+ at baseline or during study treatment

- Bilirubin
- Blood
- Color and appearance
- Glucose
- Ketones
- pH
- Protein
- Specific gravity
- Urine leukocyte esterase

Pregnancy test (for female patients of childbearing potential) – local laboratory

- 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

CCI [redacted]
CCI [redacted]

Abbreviations: DNA = deoxyribonucleic acid; Ig = immunoglobulin; LY = LY3434172; PK = pharmacokinetic; RBC = red blood cells; RNA = ribonucleic acid; T4 = thyroxine; TSH = thyroid-stimulating hormone; WBC = white blood cells.

Note: Study eligibility and decisions about treatment will be based on local laboratory results.

a 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 Performed centrally (required) and locally if clinically indicated.

c CCI

Appendix 3. Study Governance, Regulatory and Ethical Considerations

Informed Consent

The investigator is responsible for:

- ensuring that the patient understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary
- ensuring that informed consent is given by each patient. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any study protocol procedures and prior to the administration of study treatment.
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue the patient's participation in the study.
- providing a copy of the ICF to the patient and retaining a copy of the signed ICF in the site file

Ethical Review

Documentation of ERB/IRB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve all ICFs, including any changes made by the ERBs/IRBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on GCP.

The study site's ERB/IRB should be provided with the following:

- the protocol, protocol amendments, and relevant protocol addenda, and the current IB and updates during the course of the study
- ICF
- other relevant documents (for example, curricula vitae, advertisements)

Regulatory Considerations

This study will be conducted in accordance with:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- the ICH GCP guidelines
- applicable laws and regulations

The investigator or designee will promptly submit the protocol to applicable ERB(s).

Some of the obligations of Lilly will be assigned to a third party organization.

Investigator Information

Licensed physicians with a specialty in oncology will participate as investigators in this clinical study

Protocol Signatures

Lilly's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

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.

Final Report Signature

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. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the CSR coordinating investigator.

Lilly's responsible medical officer and statistician will approve the final CSR for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly 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, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly 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 Systems

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 (questionnaires, scales, self-reported diary data, rating scales etc.) will be collected by the subject/investigator site personnel, 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(s) will be stored at third parties. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system(s). 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 reports/electronic transfers 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.

Study and Site Closures

Discontinuation of Study Sites

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

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.

Appendix 4. Sampling Schedule

Pharmacokinetic, Immunogenicity and Biomarker samples will be collected for all patients receiving LY3434172.

Preferred time windows for each PK/IG sample collection are provided in the tables in this section. While best effort should be done to draw the blood samples within the time windows provided, it is more important to ensure predose sample is actually collected before the start of first infusion of the day and postdose samples are collected after the respective infusion has completed. It is also equally important to record ACTUAL date and time of blood sample collection on the Requisition Form AFTER drawing the sample (that is, do not record planned time of collection) and to record the ACTUAL infusions start and end dates and times on the eCRF in order to facilitate the data analyses.

Blood sample collection must be from the opposite arm to that used for study drug infusion. If drug was administered via a central venous catheter, the sample collection should be from a different site.

In the event of an infusion-related reaction (IRR), blood samples will be collected for PK, IG and exploratory immune safety analyses at the following time points, as close as possible to: (i) the onset of the IRR, (ii) the resolution of the IRR, and (iii) 30 [±3] days following the IRR.

CCI [redacted]

Pharmacokinetic, Immunogenicity, Biomarker, and ECG Collection Time Points Cohorts with Q2W Dosing (Cohort A1, A2, A3, A4, A5, and A6)

Pharmacokinetic, Immunogenicity, Biomarker, and ECG Collection Time Points Cohorts with Q2W Dosing (Cohort A1, A2, A3, A4, A5, and A6)													
						Biomarker Collection							
Cycle/Day	Study Day	Sample Time (Relative to the END of LY3434172 Infusion)	PK[a]	IG[a]	Whole Blood (PGx)	Plasma	Ex vivo	Whole Blood & PBMC[b]	Serum	Tissue	sPD-1 and sPD-L1	Stool[c]	ECG
Baseline		≤28 days prior to C1D1 • ECG: 2-3 sets of ECGs (each set is a triplicate), with approximately 15 minutes between each set.[d] Tumor tissue: required see Section 9.8.1.								X		X	X
Baseline		≤7 days prior to C1D1					X	X					
C1D1	1	• **0 hour predose**[e] • PK, IG, and biomarkers • ECG: 2-3 sets of ECGs (each set is a triplicate), with approximately 15 minutes between each set.[d] Before blood draw.	X	X	X	X	X	X	X		X		X
C1D1		• **1 hour post LY3434172 infusion**[f] • ECG (triplicate) Before blood draw.[d]	X				X	X	X		X		X

Pharmacokinetic, Immunogenicity, Biomarker, and ECG Collection Time Points Cohorts with Q2W Dosing (Cohort A1, A2, A3, A4, A5, and A6)													
						Biomarker Collection							
Cycle/Day	Study Day	Sample Time (Relative to the END of LY3434172 Infusion)	PK[a]	IG[a]	Whole Blood (PGx)	Plasma	Ex vivo	Whole Blood & PBMC[b]	Serum	Tissue	sPD-1 and sPD-L1	Stool[c]	ECG
C1D1	1	• **3 hours post LY3434172 infusion**[f] • ECG (triplicate) Before blood draw[d]	X					X	X		X		X
C1D2	2	• **24 hours post LY3434172 infusion**[f] • ECG (triplicate) Before blood draw.[d]	X				X	X	X		X		X
C1D4	4	72 hours post LY3434172 infusion[f]	X								X		
C1D8	8	168 hours post LY3434172 infusion[f]	X	X		X	X	X	X		X		
C1D15	15	• **0 hour predose**[e] • PK, IG, and biomarkers	X	X			X	X	X		X		
C1D15	15	• **1 hour post LY3434172 infusion**[f] • ECG (triplicate) Before blood draw.[d]	X				X (only cohort A1)		X (only A1)		X		X
C1D15	15	• **3 hours post LY3434172 infusion**[f]	X								X		
C1D16	16	• **24 hours post LY3434172 infusion**[f]	X				X (only cohort A1)		X (only A1)		X		

Pharmacokinetic, Immunogenicity, Biomarker, and ECG Collection Time Points Cohorts with Q2W Dosing (Cohort A1, A2, A3, A4, A5, and A6)													
						Biomarker Collection							
Cycle/Day	Study Day	Sample Time (Relative to the END of LY3434172 Infusion)	PK[a]	IG[a]	Whole Blood (PGx)	Plasma	Ex vivo	Whole Blood & PBMC[b]	Serum	Tissue	sPD-1 and sPD-L1	Stool[c]	ECG
C1D22	22	168 hours post LY3434172 infusion[f]	X				X (only cohort A1)	X	X (only A1)		X		
C2D1	29	• **0 hour predose**[e] • PK, IG, and biomarkers	X	X		X	X	X	X	X[g]	X	X	
C2D1	29	• **1 hour post LY3434172 infusion**[f] • ECG (triplicate) Before blood draw.[d]	X								X		X
C2D2	30	• **24 hours post LY3434172 infusion**[f]	X								X		
C2D15	43	• **0 hour predose**[e]	X				X (only cohort A1)	X	X (only A1)		X		
C2D15	43	• **1 hour post LY3434172 infusion**[f] • ECG (triplicate) Before blood draw.[d]	X								X		X
C2D16	44	• **24 hours post LY3434172 infusion**[f]	X								X		
C3D1	57	• **0 hour predose**[e] • PK, IG, and biomarkers	X	X		X		X	X		X		

Pharmacokinetic, Immunogenicity, Biomarker, and ECG Collection Time Points Cohorts with Q2W Dosing (Cohort A1, A2, A3, A4, A5, and A6)													
						Biomarker Collection							
Cycle/Day	Study Day	Sample Time (Relative to the END of LY3434172 Infusion)	PK[a]	IG[a]	Whole Blood (PGx)	Plasma	Ex vivo	Whole Blood & PBMC[b]	Serum	Tissue	sPD-1 and sPD-L1	Stool[c]	ECG
C3D1	57	• **1 hour post LY3434172 infusion**[f] • ECG (triplicate) Before blood draw.[d]	X								X		X
C4D1	85	• **0 hour predose**[e] • PK and biomarkers	X	X							X		
C4D1	85	• **1 hour post LY3434172 infusion** • ECG (single)											X
C5D1	113	• **0 hour predose**[e] • PK and biomarkers	X	X							X		
C5D1	113	• **1 hour post LY3434172 infusion** • ECG (single)											X
C6D1	141	• **0 hour predose**[e] • PK and biomarkers	X	X							X		
C6D1	141	• **1 hour post LY3434172 infusion** • ECG (single)											X
C7D1; then, Q3 (C10D1…)	169, 197…	• **0 hour predose**[e] • PK and biomarkers	X	X							X		

Pharmacokinetic, Immunogenicity, Biomarker, and ECG Collection Time Points Cohorts with Q2W Dosing (Cohort A1, A2, A3, A4, A5, and A6)													
						Biomarker Collection							
Cycle/Day	Study Day	Sample Time (Relative to the END of LY3434172 Infusion)	PK[a]	IG[a]	Whole Blood (PGx)	Plasma	Ex vivo	Whole Blood & PBMC[b]	Serum	Tissue	sPD-1 and sPD-L1	Stool[c]	ECG
When/if any DLT or DLT equivalent occurs		Anytime	X	X							X		
Last LY3434172 dose (if known)		• 0 hour predose[e] • PK, IG, and biomarkers	X	X							X		
30 days post last LY3434172 dose		Anytime[f] • ECG (single). Before blood draw.	X			X					X		X
60 days post last LY3434172 dose		Anytime[f] • ECG (single). Before blood draw.	X	X							X		X
90 days post last LY3434172 dose		Anytime[f] • ECG (single). Before blood draw.	X								X		X
Disease Progression		Anytime before start of next anticancer treatment. • Highly recommended				X				X (optional)		X	

Abbreviations: ADA = antidrug antibody; C = Cycle; D = Day; DLT = dose-limiting toxicity; ECG = electrocardiogram; IG = immunogenicity; IRR = infusion-related reaction; PGx = pharmacogenomics; PK = pharmacokinetics; Q = every; W = week.

[a] In the event of an infusion-related reaction (IRR), blood samples will be collected for PK, IG and exploratory immune safety analyses at the following time points, as close as possible to: (i) the onset of the IRR, (ii) the resolution of the IRR, and (iii) 30 [±3] days following the IRR. CCI [redacted]

[b] For exploratory research, including but not limited to immunophenotyping.
[c] Fecal collections will begin at baseline with any new patients starting the trial at that time, and as the collection materials become available.
[d] Triplicate ECGs: the 3 replicates should be approximately 1 minute apart, with all 3 replicates within a set conducted within a 5-minute timeframe.
[e] Collect samples in the morning of infusion day prior to the start of first infusion of the day.
[f] The 1-, 3-, 24-, 72-, and 168-hour samples are relative to the END of the corresponding dosing event. These samples must be collected after completion of the infusion. Their sampling windows are ±15 minutes (1- and 3-hour), ± 4 hours (24-hour), ± 24 hours (72- and 168-hour), respectively. The samples at 30, 60, and 90 days post last LY3434172 dose have sampling windows of ±7 days.
[g] Tissue biopsy sample within 3 days prior to C2D1.

Pharmacokinetic, Immunogenicity, Biomarker, and ECG Collection Time Points Cohorts with Q3W Dosing (Cohort A7 and A8)

Pharmacokinetic, Immunogenicity, Biomarker, and ECG Collection Time Points Cohorts with Q3W Dosing (Cohort A7 and A8)														
						Biomarker Collection								
Cycle/Day	Study Day	Sample Time (Relative to the END of LY3434172 Infusion)	PK[a]	IG[a]	Whole Blood (PGx)	Plasma	Ex vivo	Whole Blood & PBMC[b]	Serum	Tissue	sPD-1 and sPD-L1	Stool[c]	ECG
Baseline		≤28 days prior to C1D1 • ECG: 2-3 sets of ECGs (each set is a triplicate), with approximately 15 minutes between each set.[d] Tumor tissue: required see Section 9.8.1								X		X	X
Baseline		≤7 days prior to C1D1					X	X					
C1D1	1	• **0 hour predose**[e] • PK, IG, and biomarkers • ECG: 2-3 sets of ECGs (each set is a triplicate), with approximately 15 minutes between each set. Before blood draw.[d]	X	X	X	X	X	X	X		X		X

Pharmacokinetic, Immunogenicity, Biomarker, and ECG Collection Time Points Cohorts with Q3W Dosing (Cohort A7 and A8)													
						Biomarker Collection							
Cycle/Day	Study Day	Sample Time (Relative to the END of LY3434172 Infusion)	PK[a]	IG[a]	Whole Blood (PGx)	Plasma	Ex vivo	Whole Blood & PBMC[b]	Serum	Tissue	sPD-1 and sPD-L1	Stool[c]	ECG
C1D1	1	• **1 hour post LY3434172 infusion**[f] • ECG (triplicate). Before blood draw.[d]	X				X	X	X		X		X
C1D1	1	• **3 hours post LY3434172 infusion**[f] • ECG (triplicate). Before blood draw.[d]	X					X	X		X		X
C1D2	2	• **24 hours post LY3434172 infusion**[f] • ECG (triplicate) Before blood draw.[d]	X				X	X	X		X		X
C1D4	4	72 hours post LY3434172 infusion[f]	X								X		
C1D8	8	168 hours post LY3434172 infusion[f]	X	X		X	X	X	X		X		
C1D15	15	336 hours post LY3434172 infusion[f]	X					X			X		

Pharmacokinetic, Immunogenicity, Biomarker, and ECG Collection Time Points Cohorts with Q3W Dosing (Cohort A7 and A8)													
						Biomarker Collection							
Cycle/Day	Study Day	Sample Time (Relative to the END of LY3434172 Infusion)	PK[a]	IG[a]	Whole Blood (PGx)	Plasma	Ex vivo	Whole Blood & PBMC[b]	Serum	Tissue	sPD-1 and sPD-L1	Stool[c]	ECG
C2D1	**22**	• **0 hour predose**[e] • PK, IG, and biomarkers	X	X		X	X	X	X		X		
C2D1	**22**	• **1 hour post LY3434172 infusion**[f] • ECG (triplicate). Before blood draw.[d]	X								X		X
C2D1	**22**	• **3 hours post LY3434172 infusion**[f]	X								X		
C2D2	24	24 hours post LY3434172 infusion[f]	X								X		
C2D8	30	168 hours post LY3434172 infusion[f]	X	X				X			X		
C3D1	43	• **0 hour predose**[e] • PK, IG, and biomarkers	X	X		X	X	X	X	X[g]	X	X	

Pharmacokinetic, Immunogenicity, Biomarker, and ECG Collection Time Points Cohorts with Q3W Dosing (Cohort A7 and A8)													
						Biomarker Collection							
Cycle/Day	Study Day	Sample Time (Relative to the END of LY3434172 Infusion)	PK[a]	IG[a]	Whole Blood (PGx)	Plasma	Ex vivo	Whole Blood & PBMC[b]	Serum	Tissue	sPD-1 and sPD-L1	Stool[c]	ECG
C3D1	43	• **1 hour postdose infusion**[f] • ECG (triplicate). Before blood draw.[d]	X								X		X
C4D1	64	• 0 hour predose[e] • PK, and IG	X	X							X		
C6D1		• 0 hour predose[e] • PK: collect sample for all patients	X	X							X		
C8D1; then, Q4C (Cycle 12…)	148, 232…	• 0 hour predose[e] • PK: collect PK sample for all patients	X	X							X		
When/if any DLT or DLT equivalent occurs		Anytime	X	X							X		
Last LY3434172 dose (if known)		• 0 hour predose[e] sample • PK, IG, and biomarkers	X	X							X		
30 days post last LY3434172 dose		Anytime[f] • ECG (single). Before blood draw.	X			X					X		X

Pharmacokinetic, Immunogenicity, Biomarker, and ECG Collection Time Points Cohorts with Q3W Dosing (Cohort A7 and A8)													
						Biomarker Collection							
Cycle/Day	Study Day	Sample Time (Relative to the END of LY3434172 Infusion)	PK[a]	IG[a]	Whole Blood (PGx)	Plasma	Ex vivo	Whole Blood & PBMC[b]	Serum	Tissue	sPD-1 and sPD-L1	Stool[c]	ECG
60 days post last LY3434172 dose		Anytime[f] • ECG (single). Before blood draw.	X	X							X		X
90 days post last LY3434172 dose		Anytime[f] • ECG (single). Before blood draw.	X								X		X
Disease progesssion		Anytime before next anticancer treatment. • Highly recommended				X				X (optional)		X	

Abbreviations: ADA = antidrug antibody; C = Cycle; D = Day; DLT = dose-limiting toxicity; ECG = electrocardiogram; IG = immunogenicity; IRR = infusion-related reaction; PGx = pharmacogenomics; PK = pharmacokinetics; Q = every; W = week.

a In the event of an infusion-related reaction (IRR), blood samples will be collected for PK, IG and exploratory immune safety analyses at the following time points, as close as possible to: (i) the onset of the IRR, (ii) the resolution of the IRR, and (iii) 30 [±3] days following the IRR. CCI [redacted]

b For exploratory research, including but not limited to immunophenotyping.

c Fecal collections will begin at baseline with any new patients starting the trial at that time, and as the collection materials become available.

d Triplicate ECGs: the 3 replicates should be approximately 1 minute apart, with all 3 replicates within a set conducted within a 5-minute timeframe.

e Collect samples in the morning of infusion day prior to the start of first infusion of the day.

f The 1-, 36-, 24-, 72-, 168- and 336-hour samples are relative to the END of the corresponding dosing event. They must be collected after the completion of the infusion. Their sampling windows are ±15 minutes (1- and 3-hour), ± 4 hours (24-hour), ± 24 hours (72-, 168- and 336-hour), respectively. The samples at 30, 60, and 90 days post last LY3434172 dose have sampling windows of ± 7 days.

g Tissue biopsy sample within 3 days prior to C3D1.

Appendix 5. Restricted and Prohibited Concomitant Medications

The table below describes the drug class and associated medications that will be restricted during the study treatment period. Patients who, in the opinion of the investigator, require the use of any of the prohibited treatments for clinical management should be discontinued from the trial. Patients may receive other supportive therapy that the investigator deems to be medically necessary.

Therapy	As Needed	Chronic Use	Exceptions or Conditions for Use
Antiplatelet therapy	Yes	Yes, with restrictions	Chronic use of aspirin up to 325 mg/day is permitted
Anticoagulation therapy	No	Yes, with restrictions	Patients who are on full-dose anticoagulation must be on a stable dose (minimum duration 14 days) of oral anticoagulant or low-molecular-weight heparin or similar agent. If on warfarin, the patient must have an INR of ≤ 3 and no active bleeding or pathological condition present that carries a high risk of bleeding (for example, tumor involving major vessels or known varices).
Colony-stimulating factors	Yes	No	Follow local guidelines. No prophylactic use
Erythroid growth factors	Yes	No	Follow local guidelines
Experimental medicines or investigational agents	No	No	
Glucocorticoids	Yes, with restrictions	Yes, with restrictions	Use of corticosteroids for the management of investigational product-related AEs or in patients with contrast allergies is acceptable. A temporary course of corticosteroids will be allowed for other indications, at the discretion of the principal investigator (for example, chronic obstructive pulmonary disease, radiation, nausea). Systemic corticosteroids doses should not exceed 10 mg/day of prednisone or equivalent (except as stated otherwise in this protocol). The use of physiologic doses of corticosteroids may be approved after consultation with Lilly. The use of topical, ophthalmic, inhaled, and intranasal corticosteroids is permitted.

Therapy	As Needed	Chronic Use	Exceptions or Conditions for Use
Immunosuppressive medications other than glucocorticoids (including, but not limited to methotrexate, azathioprine, and TNF-α blockers)	No	No	Use of immunosuppressive medications for the management of AEs related to LY3434172 or in patients with contrast allergies is acceptable
NSAIDs	Yes	No	See guidance for aspirin on the "antiplatelet therapy" line above. Chronic use of other NSAIDs is not permitted. However, in certain medical situations, NSAIDs may be the best treatment option (for example, for pain management) and are therefore permissible as needed.

Abbreviations: AE = adverse event; INR = international normalized ratio; NSAIDs = nonsteroidal anti-inflammatory drugs; TNF = tumor necrosis factor.

Appendix 6. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment emergent hepatic abnormality and may be required in follow up with patients in consultation with the Lilly 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)	**Recommended Autoimmune Serology:**
Aspartate aminotransferase (AST)	Anti-nuclear antibody[a]
Gamma-glutamyl transferase (GGT)	Anti-smooth muscle antibody[a]
Creatine phosphokinase (CPK)	Anti actin antibody[a]

Abbreviations: Ig = immunoglobulin; INR = International Normalised Ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by Lilly-designated 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.

Appendix 7. 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:

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

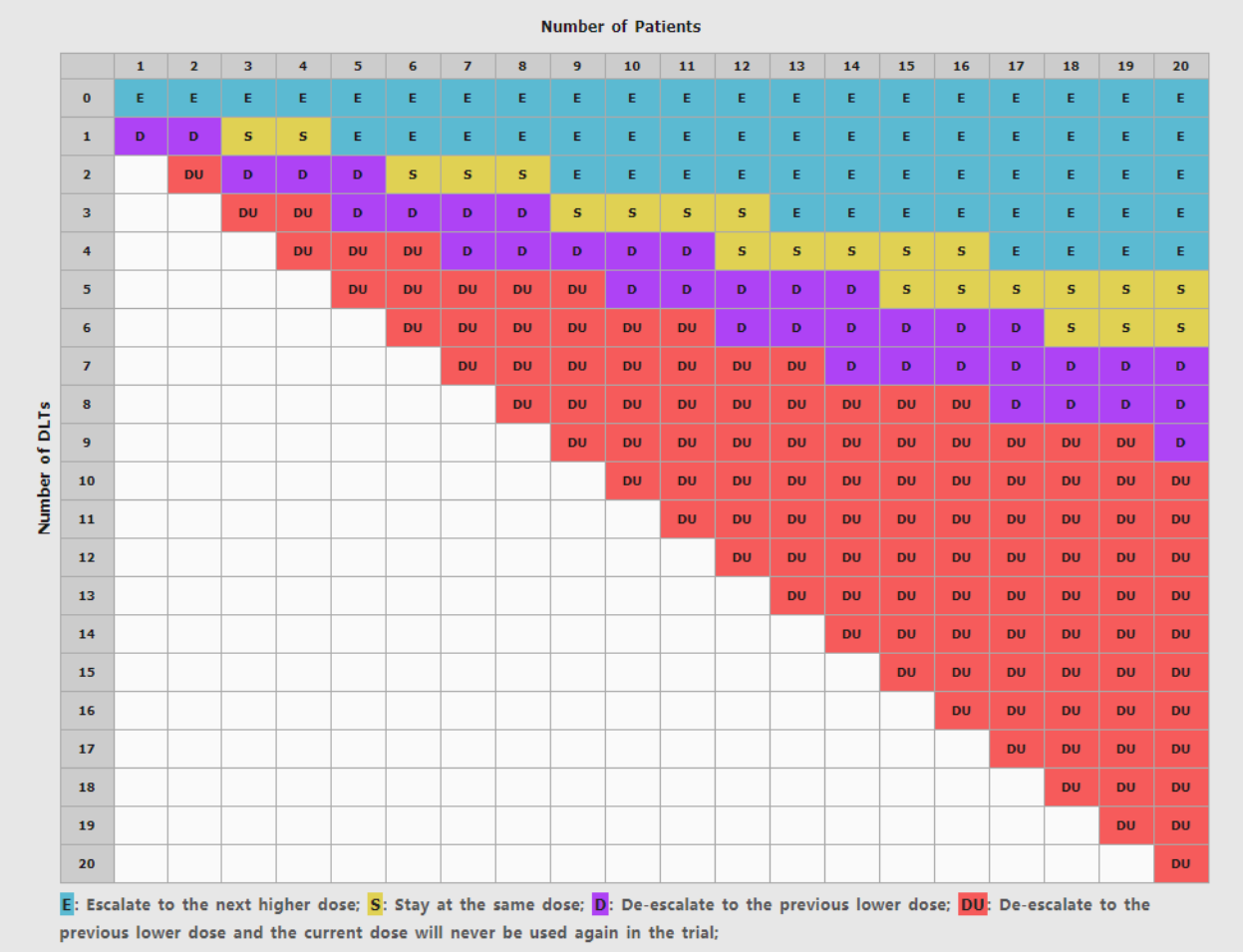
For serum creatinine concentration in μmol/L:

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

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

Reference: Cockcroft and Gault 1976.

Appendix 8. Dose-Finding Algorithm of the Modified Toxicity Probability Interval (mTPI-2) Method Showing Number of Patients Treated



	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

Source: Guo et al. 2016.

The number of patients dosed at a given dose level 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 dose level 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 dose level 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 dose level.
- 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.

Appendix 9. Definition of Woman of Childbearing Potential

Definitions:

Woman of Childbearing Potential (WOCBP)
A female is not considered to be of childbearing potential due to surgical sterilization confirmed by medical history (at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy or tubal ligation) or menopause.

Menopausal women include women with either:

a. spontaneous amenorrhea for at least 12 months, not induced by a medical condition such as anorexia nervosa, and not taking medications during the amenorrhea that induced the amenorrhea (for example, oral contraceptives, hormones, gonadotropin-releasing hormone, antiestrogens, selective estrogen receptor modulators, or chemotherapy), or
b. spontaneous amenorrhea for 6 to 12 months and a follicle-stimulating hormone level >40 mIU/mL.

For individuals with permanent infertility due to an alternate medical cause other than the above, (for example, 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.

Exceptions to those listed above would be if female and of childbearing potential, has a negative serum or urine pregnancy test within 7 days prior to the first dose of study medication, agrees to use a highly effective method of birth control during the study and for 6 months following the last dose of the study drugs, and is not breastfeeding. If the urine pregnancy test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Appendix 10. Protocol Amendment J1E-MC-JZEA(b) Summary A Phase 1 Study of LY3434172, a Bispecific Antibody Administered as a Monotherapy in Advanced Solid Tumors

Overview

Protocol J1E-MC-JZEA(a), A Phase 1 study of LY3434172, a bispecific antibody administered as a monotherapy in advanced solid tumors, has been amended. The new protocol is indicated by Amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

- The following phrase was made applicable for Cohorts A1 to A5/A6: "Once dose-limiting toxicity (DLT) period is completed for respective Cohorts A1 to A5/6 up to approximately 12 to 15 additional patients may be added to two dose levels selected from these cohorts." Corresponding revisions were made to Synopsis (Overall Design), Section 5.1 (Overall Design), Section 7.1 (Treatment Administered), Section 10.1 (Sample Size Determination), and Section 10.3.4 (Interim Analyses).
- A clarification of the 4-hour observation period and the sampling times relative to infusion time was made throughout the document. All observation periods and post-dose sampling times are now relative to the end of LY3434172 administration/infusion.
- A correction to the timing of tumor imaging for Cohorts A7 and A8 after Cycle 1 Day 1 was made. For Cycle 3 and beyond, Day 8 visits were deleted from the Schedule of Activities for these cohorts, since there are no infusions and sample collections for the D8 visits.
- A correction to vital signs collected during the post study treatment schedule was made to include oxygen saturation.
- A change was made to exclusion criterion 14 in Section 6.2 to clarify active hepatitis and active tuberculosis.
- A statement about repeating screening tests was deleted from Section 6.4.
- A clarification that anaphylaxis will be considered a DLT was made to Section 7.2.2.2.1 and a clarification that study treatment will be immediately and permanently discontinued was added to Table JZEA 9.
- Additional standard safety monitoring language was added to Section 9.4.2.
- Stool sample collections were added to Appendix 4 and clarification of the timing of predose and post dose samples was added to the footnotes.

Revised Protocol Sections

Note:	All deletions have been identified by ~~strikethroughs~~. All additions have been identified by the use of underscore.

Section 1. Synopsis

Overall Design:

Study J1E-MC-JZEA (JZEA) is a multicenter, nonrandomized, open-label Phase 1 study in patients with advanced solid tumors.

Phase 1 study will assess the safety and tolerability of LY3434172, administered as a monotherapy in patients with select advanced solid tumors. Study JZEA will facilitate a thorough safety evaluation and exploration of pharmacokinetics (PK) and pharmacodynamics effects for the every two-week (Q2W) dosing schedule (Cohorts A1 to A6). Once dose-limiting toxicity (DLT) period is completed for respective Cohorts A1 to A5/6 up to approximately 12 to 15 additional patients may be added to two dose levels selected from ~~Cohorts A4, A5/6.~~these cohorts.

...

Treatment Arms and Duration:

CCI

[redacted]

Table JZEA.1 Baseline and On-Study Treatment Schedule of Activities (Cohort A1, A2, A3, A4, A5, and A6)

	Baseline (Day Relative to C1D1)		Cycle = 28 days								Instructions
			Cycle 1 (±3 days)		Cycle 2 (±3 days)		Cycle 3 (±3 days)		Cycle 4-n (±3 days)		
	≤ 28	≤7	D1	D15	D1	D15	D1	D15	D1	D15	

Vital signs	X		X	X	X	X	X	X	X	X	**Measure vital signs (height (at baseline), weight, temperature, blood pressure, pulse rate, oxygen saturation, and respiration rate) as follows (±5 minutes):**
											• **In Cycles 1 through 3:**
											  • within 15 minutes prior to each LY3434172 infusion
											  • every 15 minutes during each LY3434172 infusion
											  • at the end of each LY3434172 infusion
											
											A 4-hour observation period (See Section 5.1.1 and 7.4) ~~from the end of~~ following the end of LY3434172 administration will occur in Cycles 1 to 3.
											  • every 30 (±5) minutes for the first hour and 60 (±5) minutes thereafter during the 4-hour observation period
											
											• **In Cycle 4 and beyond, if the patient has not experienced an infusion-related reaction or other infusion-related AE:**
											  • up to 15 minutes prior to each LY3434172 infusion
											  • at least once during each LY3434172 infusion
											  • at the end of each LY3434172 infusion

Administer LY3434172			X	X	X	X	X	X	X	X	LY3434172 will be administered as an IV infusion over approximately 60 minutes, depending on dose level (doses <100 mg may require bolus IV injection administration over approximately 5 to 10 minutes). A 4-hour observation period ~~from the start of~~following the end of LY3434172 administration will occur in Cycles 1 to 3.

Table JZEA.2 Baseline and On-Study Treatment Schedule of Activities (Cohort A7 and A8)

	Baseline (Day Relative to C1D1)		Cycle = 21 days								Instructions
			Cycle 1 (±3 days)		Cycle 2 (±3 days)		Cycle 3 (±3 days)		Cycle 4-n (±3 days)		
	≤ 28	≤7	D1	D 8	D 1	D 8	D 1	~~D 8~~	D 1	~~D 8~~	
Procedure											
Physical examination	X		X	X	X	X	X	~~X~~	X	~~X~~	• D1 visit should be completed by a physician. • Should include palpable tumor measurement.
Vital signs	X		X		X		X		X		**Measure vital signs (height (at baseline), weight, temperature, blood pressure, pulse rate, oxygen saturation, and respiration rate) as follows (±5 minutes):** • **In Cycles 1 through 3:** • up to 15 minutes prior to each LY3434172 infusion • every 15 minutes during each LY3434172 infusion • at the end of each LY3434172 infusion A 4-hour observation period (See Section 5.1.1 and 7.4) ~~from~~following the end of LY3434172 administration will occur in Cycles 1 to 3. every 30 (±5) minutes for the first hour and every 60 (±5) minutes thereafter during the 4-hour observation period
ECOG PS	X		X	X	X	X	X	~~X~~	X	~~X~~	During study treatment, perform ≤3 days prior to D1 of each cycle.
ECHO	X								See instructions		Perform locally, at baseline, at Cycle 4 Day 1, and as clinically indicated.
ECG											See Appendix 4 for ECG collection instructions
Blood tumor markers		X	X		X		X		X		As appropriate for particular tumor types (local testing). For example, include alpha-fetoprotein for patients with HCC.
Hematology		X	X	X	X	X	X	~~X~~	X	~~X~~	See Appendix 2

Clinical chemistry		X	X	X	X	X	X	~~X~~	X	~~X~~	See Appendix 2
Tumor imaging/ assessment	X						X		See Instructions		• Perform locally according to RECIST 1.1, using the same method at each assessment • Perform 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. • Note: After C1D1, perform ~~Q8W~~Q6W (±7 days) according to RECIST 1.1 for the first year, until a discontinuation criterion is met. If radiologic imaging verifies an initial assessment of PD, apply RECIST 1.1 with confirmatory scan for disease progression (Section 9.1.1). • If the patient is still on study treatment after 1 year, perform tumor imaging approximately every 12W.
Sample collection											See Appendix 4 for pharmacodynamics, pharmacokinetics, immunogenicity, pharmacogenetics, tumor tissue, and other biomarkers.
Administer LY3434172			X		X		X		X		LY3434172 will be administered as an IV infusion over approximately 60 minutes, depending on dose level (doses <100 mg may require bolus IV injection administration approximately 5 to 10 minutes). A 4-hour observation period ~~from~~following the ~~start~~end of LY3434172 administration will occur in Cycles 1 to 3.

Table JZEA.3. Poststudy Treatment Schedule of Activities (All Parts)

	Follow-Up Visit (±7 days)				
	Short-Term[a]			Long-Term (Q90D)[b]	
Visit	30-Day 801	60-Day 802	90-Day 803	804 to 8XX	
Procedure					**Instructions**
Physical examination	X				Including weight and vital signs (temperature, blood pressure, pulse rate, oxygen saturation, and respiration rate)

5.1. Overall Design

...

To facilitate a thorough safety evaluation and exploration of PK and pharmacodynamics effects of the every two week (Q2W) dosing schedule (Cohorts A1 to A6) will be explored. Once dose-limiting toxicity (DLT) period is completed for respective Cohorts A1 to A5/6 up to approximately 12 to 15 additional patients may be added to two dose levels selected from ~~Cohorts A4, A5/6~~these cohorts (see Figure JZEA.1). After evaluating PK/pharmacodynamic data from these cohorts, any doses from the dose escalation range could be used in order to cover the entire predicted biologically effective dose (BED) and allow for uncertainty around it (see Section 5.5). CCI [redacted]

CCI [redacted]

CCI

[redacted]

5.1.1. Dose Escalation

...

CCI

[redacted] Once DLT period of 28 days for Q2W, except Cohort A1 with 42 day DLT, is completed for respective dose levels within Cohorts A1 to A5/A6, ~~Cohorts A4, A5, and A6 can be expanded between 12 and 15 patients in total at~~ two dose levels, yet to be determined but will be selected from these ~~three~~ cohorts, can be expanded between 12 and 15 patients in total. Pharmacokinetic, pharmacodynamic and safety data evaluated during the course of the dose escalation will be used to select these two dose levels. The purpose of expanding ~~Cohorts A4, A5, and A6~~to additional 12-15 patients is to further inform safety, PK and pharmacodynamics. These cohorts will continue to enroll while interim analysis (IA) is ongoing.

5.2. Number of Patients

...

Approximately 15 to 20 patients will be enrolled in Q2W dose escalation, approximately 12 to 15 additional patients may be added to two dose levels selected from Cohorts ~~A4,~~A1 to A5/A6 after selected dose level has cleared the DLT period for adequate assessment of safety and exploration of PK and pharmacodynamic effects.

6.1 Inclusion Criteria

Patients are eligible to be included in the study only if they meet all the following criteria:

[1] Melanoma, NSCLC, squamous cell carcinoma of the head and neck (SCCHN), urothelial cancer, gastric cancer, colorectal cancer, biliary tract cancer, anal cancer, nasopharyngeal cancer, esophageal cancer, SCLC, ovarian cancer, mesothelioma, pan-tumor MSIhi solid tumors, hepatocellular carcinoma, merkel cell cancer, cutaneous squamous cell carcinoma, endometrial cancer, breast cancer, cervical

cancer, thyroid cancer, salivary cancer, and prostate cancer who have received at least one line of standard systemic therapy for their respective tumor type in the metastatic setting with progressive locally advanced or metastatic disease and that is not amenable/resistant to approved standard-of-care therapy. Prior anti-PD-1 and anti-PD-L1 allowed if they received another therapy immediately prior to this study or there has been a lapse of approximately ≥90 days from prior therapy. If patients received prior anti-PD-1 or anti-PD-L1, the following criteria need to be met:

6.2 Exclusion Criteria

Patients will be excluded from the study if they meet any of the following criteria:

[14] Have a serious concomitant systemic disorder that, in the opinion of the investigator, would compromise the patient's ability to adhere to the protocol, such as the following:

b. active hepatitis B or C virus infection according to local standards (screening not required) (e.g., with no evidence of known positive hepatitis B surface antigen or known positive hepatitis C antibody and quantitative hepatitis C RNA greater than the lower limit of detection of the assay).

c. current active ~~or known history of~~ tuberculosis

6.4. Screen Failures

Repeating laboratory tests (including ECGs) that did not meet eligibility criteria during the 28-day baseline-screening period does not constitute rescreening. However, laboratory tests may not be repeated more than twice. ~~If the results of a repeated laboratory test meet the eligibility criteria, that laboratory test must be repeated again to confirm eligibility.~~

7.1. Treatment Administered

LY3434172 will be administered as an IV infusion over approximately 60 minutes, depending on dose level (doses <100 mg may require bolus IV infusion, approximately over 5 to 10 minutes). A 4-hour observation period ~~from the start of~~ following the end of LY3434172 administration will occur in Cycles 1 to 3.

CCI

[redacted]

7.2.1. Selection and Timing of Doses

…

The first study treatment will be administered within 7 days after the patient is assigned to a treatment cohort. There should be a minimum of 14 days between doses of study drug for all cohorts in Q2W schedule and 21 days between doses of study drug for the Q3W schedule. However, if there is a delay due to holiday, weekend, bad weather, or other unforeseen circumstances, a flexibility of ±3 days is permitted.

7.2.2.2.1. Events That Are Not Considered to Be DLTs

The following events will not be considered to be DLTs:

…

- First occurrence of Grade 3 infusion-related reaction (IRR) during infusion of LY3434172, if both of the following criteria are met:
  - the patient did not receive corticosteroid prophylaxis, and
  - the Grade 3 IRR resolves within 6 hours with appropriate clinical management
  - If symptoms reappear, the event would be considered a DLT.
  - If this first occurence is anaphylaxis of any grade, the event would be considered a DLT.

7.4. Dose Modification

…

A 4-hour observation period ~~from the start of~~following the end of LY3434172 administration will occur in Cycles 1 to 3. During observation period, patients treated with LY3434172 should be closely monitored for signs and symptoms indicative of an infusion-related reaction by medical staff from the start of the infusion, in an area where emergency medical resuscitation equipment and other agents (epinephrine, prednisolone, or equivalents, etc.) are available. LY3434172 infusion-related reactions will be defined according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 definition of IRRs.

Table JZEA.9. Management of Infusion-Related Reactions (IRR)

Grade	Management	
2	First occurrence	Immediately and permanently discontinue treatment if hypersentivity reaction is due to anaphylaxis of any grade. Stop the infusion for other infusion-related reactions. 1. If resolved to baseline or Grade 1 within 1 hour after stopping the infusion a. restart the infusion at 50% of the original rate (e.g., reduce from 100 mL/hr to 50 mL/hr) 2. If NOT resolved to Grade 0 or 1 within 1 hour after stopping the infusion: a. delay study treatment until the symptoms resolve in ≤48 hours, and b. premedicate prior to the next scheduled dose. Premedication should be administered 1.5 hours (±30 minutes) prior to the LY3434172 infusion with diphenhydramine (or other antihistamine), acetaminophen (or other antipyretic), steroids, etc., at the discretion of treating physician.

9.1. Efficacy Assessments

…

During Study Treatment:

- Performed every 8 weeks (±7 days) for the 28-day cycle cohorts and every 6 weeks (±7 days) for the 21-day cycle cohorts, by the investigator, with confirmatory assessment obtained at the next routine scheduled imaging time point (See Section 9.1.1.).

9.4.2. Safety Monitoring

Lilly will review safety data on a cohort by cohort basis and periodically review evolving aggregate safety data within the study by appropriate methods.

Lilly has systematic and robust internal processes in place that ensure safety surveillance of development compounds in line with the US Food and Drug Administration (FDA)'s expectations for safety assessment committees (SAC) (FDA Draft Guidance: "Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics"; FDA Draft Guidance: "Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics"; FDA Draft Guidance: "Safety Assessment for IND Safety Reporting"; FDA Guidance: "Safety Reporting Requirements for INDs and BA/BE Studies"). This includes processes with clearly described roles and responsibilities that are owned by Lilly's Global Patient Safety organization. These processes are designed to monitor the evolving safety profile (i.e. review of cumulative SAEs, other important safety information) by designated cross-functional teams in a timely manner at pre-defined intervals or on an ad-hoc basis. In addition, a dedicated process may be used to perform unblinded comparisons of event rates for SAEs as necessary.

This system ensures that the accumulating safety data derived from individual and multiple trials across a development program is reviewed on a regular basis and that important new safety information such as the need for protocol modification or other relevant safety related material is identified and communicated to regulators and investigators appropriately and in a timely

fashion. An internal review of aggregate safety data occurs on at least a quarterly basis or more frequently, as appropriate. Any serious adverse reactions are reported within the required timeline for expedited reporting.

In addition to annual periodic safety updates and to further inform investigators, a line listing report of SUSARs is created and distributed to investigators on a biannual (twice yearly) basis. Any significant potential risk/safety concerns that are being monitored as well as any results being reported in other periodic reports for the compound; SAC decisions; and other significant safety data (for example, nonclinical or clinical findings, removal of serious adverse reactions) are included in the report.

9.8.2 Other Samples for Biomarker Research

The following samples for biomarker research will be collected for the purposes described in Section 9.8, and as specified in Appendix 4, where local regulations allow.

…

- Stool (when applicable, stool specimens may be collected for microbiome analyses)

10.1. Sample Size Determination

…

The total sample size in Cohorts A1 to A5/A6 will be determined by the incidence of DLTs. The RP2D could be chosen after the corresponding Q2W cohorts have been enrolled. After the DLT period (Cohorts A1 to A5/A6) is completed, ~~Cohorts A4, A5, or A6 may include~~an additional ~~enrollment of approximately~~12 to 15 patients at two ~~selected~~ dose levels selected from these cohorts will be enrolled for adequate assessment of safety and exploration of PK and pharmacodynamic effects.

10.3.4. Interim Analyses

…

An interim analyses will be performed after all patients from cohorts A1 to A5/6 have completed the DLT evaluation period. Additional enrolment of 12-15 patients ~~to~~from these cohorts ~~A4 to A5/6~~at two dose levels (yet to be determined) can continue during IA.

Appendix 2 Clinical Laboratory Tests

[b] Performed centrally (required)~~only, unless~~ and locally ~~laboratory is~~if clinically indicated.

Appendix 4 Sampling Schedule

Pharmacokinetic, Immunogenicity, Biomarker, and ECG Collection Time Points Cohorts with Q2W Dosing (Cohort A1, A2, A3, A4, A5, and A6)

Pharmacokinetic, Immunogenicity, Biomarker, and ECG Collection Time Points Cohorts with Q2W Dosing (Cohort A1, A2, A3, A4, A5, and A6)													
						Biomarker Collection							
Cycle/Day	Study Day	Sample Time (Relative to ~~START~~the END of LY3434172 Infusion)	PK[a]	IG[a]	Whole Blood (PGx)	Plasma	Ex vivo	Whole Blood & PBMC[b]	Serum	Tissue	sPD-1 and sPD-L1	Stool[c]	ECG
Baseline		≤28 days prior to C1D1 • ECG: 2-3 sets of ECGs (each set is a triplicate), with approximately 15 minutes between each set.[d] Tumor tissue: required see Section 9.8.1.								X		X	X
Baseline		≤7 days prior to C1D1					X	X					
C1D1	1	• **0 hour predose**[e] • PK, IG, and biomarkers~~: collect samples in the morning of infusion day prior to start of first infusion of the day~~ • ECG: 2-3 sets of ECGs (each set is a triplicate), with approximately 15 minutes between each ~~set~~[d]~~.~~set.[d] Before blood draw.	X	X	X	X	X	X	X		X		X

Pharmacokinetic, Immunogenicity, Biomarker, and ECG Collection Time Points Cohorts with Q2W Dosing (Cohort A1, A2, A3, A4, A5, and A6)													
						Biomarker Collection							
Cycle/Day	**Study Day**	**Sample Time (Relative to ~~START~~the END of LY3434172 Infusion)**	**PK[a]**	**IG[a]**	**Whole Blood (PGx)**	**Plasma**	**Ex vivo**	**Whole Blood & PBMC[b]**	**Serum**	**Tissue**	**sPD-1 and sPD-L1**	**Stool[c]**	**ECG**
C1D1		• **1 hour post LY3434172 ~~infusion~~[e]infusion[f]** • ECG (triplicate) Before blood draw.[d]	X				X	X	X		X		X
C1D1	1	• **3 hours post LY3434172 ~~infusion~~[e]infusion[f]** • ECG (triplicate) Before blood draw[d]	X					X	X		X		X
C1D2	2	• **24 hours post LY3434172 ~~infusion~~[e]infusion[f]** • ECG (triplicate) Before blood draw.[d]	X				X	X	X		X		X
C1D4	4	72 hours post LY3434172 ~~infusion~~[e]infusion[f]	X								X		
C1D8	8	168 hours post LY3434172 ~~infusion~~[e]infusion[f]	X	X		X	X	X	X		X		
C1D15	15	• **0 hour ~~predose~~predose[e]** • PK, IG, and biomarkers~~: collect samples ≤2 hours prior to start of first infusion of the day~~	X	X			X	X	X		X		

Pharmacokinetic, Immunogenicity, Biomarker, and ECG Collection Time Points Cohorts with Q2W Dosing (Cohort A1, A2, A3, A4, A5, and A6)													
						Biomarker Collection							
Cycle/Day	Study Day	Sample Time (Relative to ~~START~~the END of LY3434172 Infusion)	PK[a]	IG[a]	Whole Blood (PGx)	Plasma	Ex vivo	Whole Blood & PBMC[b]	Serum	Tissue	sPD-1 and sPD-L1	Stool[c]	ECG
C1D15	15	• **1 hour post LY3434172 ~~infusion~~[e]infusion**[f] • ECG (triplicate) Before blood draw.[d]	X				X (only cohort A1)		X (only A1)		X		X
C1D15	15	• **3 hours post LY3434172 ~~infusion~~[e]infusion**[f]	X								X		
C1D16	16	• **24 hours post ~~start of~~ LY3434172 infusion**[f]	X				X (only cohort A1)		X (only A1)		X		
C1D22	22	168 hours post LY3434172 ~~infusion~~[e]infusion[f]	X				X (only cohort A1)	X	X (only A1)		X		
C2D1	29	• **0 hour predose**[e] • PK, IG, and biomarkers~~: collect samples in the morning of infusion day prior to start of first infusion of the day~~	X	X		X	X	X	X	~~X~~[e]X[g]	X	X	
C2D1	29	• **1 hour post LY3434172 ~~infusion~~[e]infusion**[f] • ECG (triplicate) Before blood draw.[d]	X								X		X
C2D2	30	• **24 hours post ~~start of~~ LY3434172 infusion**[f]	X								X		
C2D15	43	• **0 hour ~~predose~~predose**[e]	X				X (only cohort A1)	X	X (only A1)		X		

Pharmacokinetic, Immunogenicity, Biomarker, and ECG Collection Time Points Cohorts with Q2W Dosing (Cohort A1, A2, A3, A4, A5, and A6)													
						Biomarker Collection							
Cycle/Day	Study Day	Sample Time (Relative to ~~START~~the END of LY3434172 Infusion)	PK[a]	IG[a]	Whole Blood (PGx)	Plasma	Ex vivo	Whole Blood & PBMC[b]	Serum	Tissue	sPD-1 and sPD-L1	Stool[c]	ECG
C2D15	43	• **1 hour post LY3434172 ~~infusion~~[e]infusion**[f] • ECG (triplicate) Before blood draw.[d]	X								X		X
C2D16	44	• **24 hours post LY3434172 infusion**[f]	X								X		
C3D1	57	• **0 hour predose**[e] • PK, IG, and biomarkers~~: collect samples in the morning of infusion day prior to start of first infusion of the day~~	X	X		X		X	X		X		
C3D1	57	• **1 hour post LY3434172 ~~infusion~~[e]infusion**[f] • ECG (triplicate) Before blood draw.[d]	X								X		X
C4D1	85	• **0 hour predose**[e] • PK and biomarkers	X	X							X		
C4D1	85	• **1 hour post LY3434172 infusion** • ECG (single)											X
C5D1	113	• **0 hour predose**[d] • PK and biomarkers	X	X							X		

Pharmacokinetic, Immunogenicity, Biomarker, and ECG Collection Time Points Cohorts with Q2W Dosing (Cohort A1, A2, A3, A4, A5, and A6)													
						Biomarker Collection							
Cycle/Day	**Study Day**	**Sample Time (Relative to ~~START~~the END of LY3434172 Infusion)**	**PK[a]**	**IG[a]**	**Whole Blood (PGx)**	**Plasma**	**Ex vivo**	**Whole Blood & PBMC[b]**	**Serum**	**Tissue**	**sPD-1 and sPD-L1**	**Stool[c]**	**ECG**
C5D1	113	• **1 hour post LY3434172 infusion** • ECG (single)											X
C6D1	141	• **0 hour predose[e]** • PK and biomarkers	X	X							X		
C6D1	141	• **1 hour post LY3434172 infusion** • ECG (single)											X
~~C4D1~~C7D1; then, Q3 (~~C7…~~)C10D1…)	~~85,~~ 169, 197 …	• **0 hour predose[e]** • PK and biomarkers~~: collect samples in the morning of infusion day prior to start of first infusion of the day~~	X	X							X		
When/if any DLT or DLT equivalent occurs		Anytime	X	X							X		
Last LY3434172 dose (if known)		• **0 hour predose[e]** • PK, IG, and biomarkers~~: collect samples in the morning of infusion day prior to start of first infusion of the day.~~	X	X							X		
30 days post last LY3434172 dose		~~Anytime[e]~~ Anytime[f] • ECG (single). Before blood draw.	X			X					X		X

Pharmacokinetic, Immunogenicity, Biomarker, and ECG Collection Time Points Cohorts with Q2W Dosing (Cohort A1, A2, A3, A4, A5, and A6)													
						Biomarker Collection							
Cycle/Day	Study Day	Sample Time (Relative to ~~START~~the END of LY3434172 Infusion)	PK[a]	IG[a]	Whole Blood (PGx)	Plasma	Ex vivo	Whole Blood & PBMC[b]	Serum	Tissue	sPD-1 and sPD-L1	Stool[c]	ECG
60 days post last LY3434172 dose		~~Anytime[e]~~ Anytime[f] • ECG (single). Before blood draw.	X	X							X		X
90 days post last LY3434172 dose		~~Anytime[e]~~ Anytime[f] • ECG (single). Before blood draw.	X								X		X
Disease Progression		Anytime before start of next anticancer treatment. • Highly recommended				X				X (optional)		X	

[c] Fecal collections will begin at baseline with any new patients starting the trial at that time, and as the collection materials become available.

[d] Triplicate ECGs: the 3 replicates should be approximately 1 minute apart, with all 3 replicates within a set conducted within a 5-minute timeframe.

[e] Collect samples in the morning of infusion day prior to the start of first infusion of the day.

[f] The 1-, ~~2-, 4~~3-, 24-, 72-, 120- and 168-hour samples are relative to the ~~START~~END of the corresponding dosing event. These samples must be collected after completion of the infusion. Their sampling windows are ±15 minutes (1~~-, 2-~~ and 43-hour), ± 4 hours (24-hour), ± 24 hours (72~~-, 120-~~ and 168-hour), respectively. The samples at 30, 60, and 90 days post last LY3434172 dose have sampling windows of ±7 days.

[g] Tissue biopsy sample within 3 days prior to C2D1.

Pharmacokinetic, Immunogenicity, Biomarker, and ECG Collection Time Points Cohorts with Q3W Dosing (Cohort A7 and A8)

Pharmacokinetic, Immunogenicity, Biomarker, and ECG Collection Time Points Cohorts with Q3W Dosing (Cohort A7 and A8)													
						Biomarker Collection							
Cycle/Day	Study Day	Sample Time (Relative to ~~START~~the END of LY3434172 Infusion)	PK[a]	IG[a]	Whole Blood (PGx)	Plasma	Ex vivo	Whole Blood & PBMC[b]	Serum	Tissue	sPD-1 and sPD-L1	Stool[c]	ECG
Baseline		≤28 days prior to C1D1 • ECG: 2-3 sets of ECGs (each set is a triplicate), with approximately 15 minutes between each set.[d] Tumor tissue: required see Section 9.8.1								X		X	X
Baseline		≤7 days prior to C1D1					X	X					

Pharmacokinetic, Immunogenicity, Biomarker, and ECG Collection Time Points Cohorts with Q3W Dosing (Cohort A7 and A8)													
						Biomarker Collection							
Cycle/Day	Study Day	Sample Time (Relative to ~~START~~the END of LY3434172 Infusion)	PK[a]	IG[a]	Whole Blood (PGx)	Plasma	Ex vivo	Whole Blood & PBMC[b]	Serum	Tissue	sPD-1 and sPD-L1	Stool[c]	ECG
C1D1	1	• **0 hour predose**[e] • PK, IG, and biomarkers~~:~~ ~~collect samples in the morning of infusion day prior to start of first infusion of the day~~ • ECG 2-3 sets of ECGs (each set is a triplicate), with approximately 15 minutes between each set. Before blood draw.[d]	X	X	X	X	X	X	X		X		X
C1D1	1	• **1 hour post LY3434172 ~~infusion~~**[e] **infusion**[f] • ECG (triplicate). Before blood draw.[d]	X				X	X	X		X		X

Pharmacokinetic, Immunogenicity, Biomarker, and ECG Collection Time Points Cohorts with Q3W Dosing (Cohort A7 and A8)													
						Biomarker Collection							
Cycle/Day	Study Day	Sample Time (Relative to ~~START~~the END of LY3434172 Infusion)	PK[a]	IG[a]	Whole Blood (PGx)	Plasma	Ex vivo	Whole Blood & PBMC[b]	Serum	Tissue	sPD-1 and sPD-L1	Stool[c]	ECG
C1D1	1	• **3 hours post LY3434172 ~~infusion~~[e]infusion**[f] • ECG (triplicate). Before blood draw.[d]	X					X	X		X		X
C1D2	2	• **24 hours post LY3434172 ~~infusion~~[e]infusion**[f] • ECG (triplicate) Before blood draw.[d]	X				X	X	X		X		X
C1D4	4	72 hours post LY3434172 ~~infusion~~[e]infusion[f]	X								X		
C1D8	8	168 hours post LY3434172 ~~infusion~~[e]infusion[f]	X	X		X	X	X	X		X		
C1D15	15	336 hours post LY3434172 ~~infusion~~[e]infusion[f]	X					X			X		

Pharmacokinetic, Immunogenicity, Biomarker, and ECG Collection Time Points Cohorts with Q3W Dosing (Cohort A7 and A8)													
						Biomarker Collection							
Cycle/Day	**Study Day**	**Sample Time (Relative to ~~START~~the END of LY3434172 Infusion)**	**PK[a]**	**IG[a]**	**Whole Blood (PGx)**	**Plasma**	**Ex vivo**	**Whole Blood & PBMC[b]**	**Serum**	**Tissue**	**sPD-1 and sPD-L1**	**Stool[c]**	**ECG**
C2D1	**22**	• **0 hour predose**~~[e]~~ • PK, IG, and biomarkers~~:~~ ~~collect samples in the morning of infusion day prior to start of first infusion of the day~~	X	X		X	X	X	X		X		
C2D1	**22**	• **1 hour post LY3434172 infusion**[f] • ECG (triplicate). Before blood draw.[d]	X								X		X
C2D1	**22**	• **3 hours post LY3434172 infusion**[f]	X								X		
C2D2	24	24 hours post LY3434172 ~~infusion[e]~~infusion[f]	X								X		
C2D8	30	168 hours post LY3434172 ~~infusion[e]~~infusion[f]	X	X				X			X		

Pharmacokinetic, Immunogenicity, Biomarker, and ECG Collection Time Points Cohorts with Q3W Dosing (Cohort A7 and A8)														
						Biomarker Collection								
Cycle/Day	**Study Day**	**Sample Time (Relative to ~~START~~the END of LY3434172 Infusion)**	**PK[a]**	**IG[a]**	**Whole Blood (PGx)**	**Plasma**	**Ex vivo**	**Whole Blood & PBMC[b]**	**Serum**	**Tissue**	**sPD-1 and sPD-L1**	**Stool[c]**	**ECG**
C3D1	43	• **0 hour predose~~de~~** • PK, IG, and biomarkers~~:~~ ~~collect samples in the morning of infusion day prior to start of first infusion of the day~~	X	X		X	X	X	X	~~X~~[e]X[g]	X	X	
C3D1	43	• **1 hour postdose infusion**[f] • ECG (triplicate). Before blood draw.[d]	X								X		X
C4D1	64	• 0 hour predose~~de~~ • PK, IG~~, and collect samples in the morning of infusion day prior to start of first infusion of the day~~	X	X							X		

Pharmacokinetic, Immunogenicity, Biomarker, and ECG Collection Time Points Cohorts with Q3W Dosing (Cohort A7 and A8)													
						Biomarker Collection							
Cycle/Day	**Study Day**	**Sample Time (Relative to ~~START~~the END of LY3434172 Infusion)**	**PK[a]**	**IG[a]**	**Whole Blood (PGx)**	**Plasma**	**Ex vivo**	**Whole Blood & PBMC[b]**	**Serum**	**Tissue**	**sPD-1 and sPD-L1**	**Stool[c]**	**ECG**
C6D1		• 0 hour predose[~~d~~e] • PK: collect sample for all patients	X	X							X		
C8D1; then, Q4C (Cycle 12…)	148, 232…	• 0 hour predose[~~d~~e] • PK: collect PK sample for all patients	X	X							X		
When/if any DLT or DLT equivalent occurs		Anytime	X	X							X		
Last LY3434172 dose (if known)		• 0 hour predose[~~d~~e] sample • PK, IG, and biomarkers~~:~~ ~~collect sample ≤2 hours prior to start of first infusion of the day~~	X	X							X		
30 days post last LY3434172 dose		~~Anytime[c]~~ Anytime[f] • ECG (single). Before blood draw.	X			X					X		X

Pharmacokinetic, Immunogenicity, Biomarker, and ECG Collection Time Points Cohorts with Q3W Dosing (Cohort A7 and A8)													
						Biomarker Collection							
Cycle/Day	**Study Day**	**Sample Time (Relative to ~~START~~the END of LY3434172 Infusion)**	**PK[a]**	**IG[a]**	**Whole Blood (PGx)**	**Plasma**	**Ex vivo**	**Whole Blood & PBMC[b]**	**Serum**	**Tissue**	**sPD-1 and sPD-L1**	**Stool[c]**	**ECG**
60 days post last LY3434172 dose		~~Anytime[e]~~ Anytime[f] • ECG (single). Before blood draw.	X	X							X		X
90 days post last LY3434172 dose		~~Anytime[e]~~ Anytime[f] • ECG (single). Before blood draw.	X								X		X
Disease progesssion		Anytime before next anticancer treatment. • Highly recommended				X				X (optional)		X	

[c] Fecal collections will begin at baseline with any new patients starting the trial at that time, and as the collection materials become available.

[d] Triplicate ECGs: the 3 replicates should be approximately 1 minute apart, with all 3 replicates within a set conducted within a 5-minute timeframe.

[e] Collect samples in the morning of infusion day prior to the start of first infusion of the day.

[f] The ~~2-, 4~~1-, 36-, 24-, 72-, ~~and~~ 168- and 336-hour samples are relative to the ~~START~~END of the corresponding dosing event. They must be collected after the completion of the infusion. Their sampling windows are ±15 minutes (~~2-,~~1- and 43-hour), ± 4 hours (24-hour), ± 24 hours (72-, 168- and 336-hour), respectively. The samples at 30, 60, and 90 days post last LY3434172 dose have sampling windows of ± 7 days.

[g] Tissue biopsy sample within 3 days prior to C3D1.

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