Protocol J1C-MC-JZDA (b)

A Phase 1a/1b Study of LY3415244, a Bispecific Antibody in Patients with Advanced Solid Tumors

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LY3415244

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1. Synopsis

Protocol Title: A Phase 1a/1b Study of LY3415244, a Bispecific Antibody in Patients with Advanced Solid Tumors

Rationale:
While inhibitors of either programmed death 1 (PD-1) or programmed death ligand 1 (PD-L1) have shown clinical activity and manageable safety profiles as monotherapy in a variety of tumor types, efficacy can be low in some tumor types (Wu et al. 2015). The possible benefit of other immunotherapy agents alone or in combination with PD-1 or PD-L1 inhibitor, which can further augment the response, is an important area of interest.

T-cell immunoglobulin and mucin-domain-containing molecule-3 (TIM-3), a co-inhibitory molecule, is expressed on T cells during activation and has been identified as a cell surface marker for "exhausted" T cells following chronic exposure to antigen (Wherry 2011) and marks the most exhausted or dysfunctional populations of T cells in the tumor microenvironment and during chronic viral infection. TIM-3 is often co-expressed with PD-1 and cytotoxic T-lymphocyte antigen 4 on tumor-antigen-specific T cells in cancer patients. Blocking TIM-3 provides the opportunity to enhance antitumor T-cell immunity, much like targeting the PD-1 axis, and provides the opportunity to combine anti-TIM-3 therapy with clinically validated checkpoint inhibitor antibodies such as PD-1 or PD-L1.

Dual-targeting of the TIM-3 and PD-1/PD-L1 pathway has been pursued preclinically. For example, in vitro treatment of tumor-infiltrating lymphocytes harvested from CT26 tumor bearing mice with anti-TIM-3 and anti-PD-L1 resulted in more robust interferon gamma production than with either antibody alone. In vivo, combined targeting of the TIM-3 and PD-L1 is more effective in controlling tumor growth than targeting either pathway alone in a CT26 model, in a B16F10 model, and in a 5T33 myeloma model with low dose irradiation (Sakuishi et al. 2010, Anderson 2015 [WWW], and Jing et.al. 2015, respectively). Synergistic antitumor effects have been observed for combinations of anti-TIM-3 with anti-PD-1 in CT26, MC38, and established methylcholanthrene-induced sarcomas (Ngiow et al. 2011). TIM-3 expression is upregulated in PD-1 refractory patients and there is survival advantage with the addition of a TIM-3 blocking antibody following failure of PD-1 blockade in $EGFR^{T790M/L858R}$ or $Kras^{G12D}$ transgenic tumor model (Koyama et al. 2016). Collectively, these data suggest that blockade of both TIM-3 and PD-1/PD-L1 immune checkpoints is a promising approach for improved efficacy of immunotherapy.

LY3415244, a TIM-3/PD-L1 bispecific antibody, can block both PD-L1 and TIM-3, thereby overcoming immune checkpoints and T-cell exhaustion. In vitro experiments have demonstrated that LY3415244 can bridge cells engineered to express TIM-3 with those that express PD-L1. The clinical relevance of bridging is unknown at this time. The goal of this study is to evaluate the safety of LY3415244 administered as monotherapy to patients with advanced solid tumors.

Objectives and Endpoints:

Phase	Objectives	Endpoints
1a – Dose Escalation	**Primary**	
	To assess the safety and tolerability of LY3415244 in patients with advanced solid tumors, thereby identifying RP2D to be administered to patients in the Phase 1b portion of the study	• DLTs • Safety (including but not limited to): TEAEs, DLT-equivalent toxicities, SAEs, deaths, and clinical laboratory abnormalities per CTCAE (Version 4.0)
	Secondary	
	To assess the PK of LY3415244	• AUC, C_{min}, and approximate C_{max} of LY3415244
1b - Dose Expansion	**Primary**	
	To assess the safety and tolerability of the RP2D dose of LY3415244 in patients with advanced solid tumors.	• Safety (including but not limited to): TEAEs, SAEs, deaths, and clinical laboratory abnormalities per CTCAE (Version 4.0)
	Secondary	
	To assess the PK of LY3415244 in patients in each of 4 expansion cohorts	• C_{min} and approximate C_{max} of LY3415244
	To assess early antitumor activity[a] of LY3415244 in patients in each of 4 expansion cohorts	• ORR • DOR • TTR • DCR • PFS

Abbreviations: AUC = area under time-concentration 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; PFS = progression-free survival; 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 version 1.1

Overall Design:

Study J1C-MC-JZDA is a multicenter, nonrandomized, open-label, dose-escalation Phase 1a study followed by Phase 1b cohort expansion of intravenous LY3415244 in patients with advanced solid tumors.

Number of Patients:

Approximately 27 to 30 patients will be enrolled in the Phase 1a portion of the study; approximately 80 patients will be enrolled in the Phase 1b portion of the study.

Treatment Arms and Duration:

Phase 1a (dose escalation): Patients will receive LY3415244 monotherapy, as shown in the following table:

	Cohort	Dose of LY3415244	Route	Dosing Schedule
Phase 1a: Dose Escalation	A1	3 mg	IV	D1 and D15 of each 28-day cycle (Q2W)
	A2	10 mg		
	A3	30 mg		
	A4	70 mg		
	A5	200 mg		
	A6	600 mg		
	A7	1000 mg		
	A8	Optional, TBD[a]		
Phase 1b: Dose Expansion	B	RP2D	IV	D1 and D15 of each 28-day cycle (Q2W)
	C			
	D			
	E			

Abbreviations: C = cycle; D = day; IV = intravenously; Q2W = every 2 weeks; PK/PD = pharmacokinetic/pharmacodynamic; RP2D = recommended Phase 2 dose; TBD = to be determined.

a Enrollment of Cohort A8 is optional. It will be initiated if PK/PD analyses suggest that another dose level may be appropriate. The dose will not exceed 1500 mg.

Patients may continue to receive study treatment for a maximum of 12 months or until a criterion for discontinuation is met.

Phase 1b (dose expansion): Patients in each of 4 expansion cohorts will receive the recommended Phase 2 dose (RP2D) of LY3415244 intravenously at a schedule to be determined at Phase 1a, until a criterion for discontinuation is met.

The data from Phase 1a will determine the RP2D but the RP2D dose may be modified in Phase 1b if supported by additional safety and/or PK/PD data.

Short-term follow-up period (Phase 1a and 1b)
Short-term follow-up (includes 30-, 60-, and 90-day follow-up visits) begins when the patient and investigator agree that the patient will discontinue study treatment and ends on the day of the 90-day follow-up visit.

Long-term follow-up period (Phase 1a and 1b)
Long-term follow-up begins the day after the patient completes the 90-day follow-up visit and ends with the patient's death, upon loss to follow-up, or upon overall study completion, whichever is earlier.

2. Schedule of Activities

Table JZDA.2.1. Baseline and On-Study Treatment Schedule of Activities

	Baseline (Day Relative to C1D1)		Cycle 1		Cycle 2		Cycle 3		Cycle 4–n		Instructions: Perform all cycle-related procedures on the specified day (±3 days), unless stated otherwise in this schedule of activities. See Section 7 regarding administration of study treatment.
	≤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 throughout the study
Physical examination	X		X		X		X		X		• At baseline, perform full examination including recent medical history, height and weight • Thereafter, perform a focused examination, including weight and vital signs • For vital sign measurements, see additional instructions below

Baseline and On-Study Treatment Schedule of Activities

	Baseline (Day Relative to C1D1)		Cycle 1		Cycle 2		Cycle 3		Cycle 4-n		**Instructions:** Perform all cycle-related procedures on the specified day (±3 days), unless stated otherwise in this schedule of activities. See Section 7 regarding administration of study treatment.
	≤28	≤7	D1	D15	D1	D15	D1	D15	D1	D15	

Vital signs	X		X	X	X	X	X	X	X	X	**Measure vital signs (temperature, blood pressure, pulse rate, and respiration rate) as follows (±5 minutes):**
											• **In Cycles 1 through 3:**
											  • up to 15 minutes prior to each LY3415244 infusion
											  • every 15 minutes during each LY3415244 infusion
											  • at the end of each LY3415244 infusion
											
											A 4-hour postinfusion observation period is required after the end of each LY3415244 infusion in Cycles 1 through 3.
											  • every 30 minutes during the 4-hour postinfusion 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 LY3415244 infusion
											  • at least once during each LY3415244 infusion
											  • at the end of each LY3415244 infusion

AE collection	X		X								• Collect continuously throughout the study • CTCAE Version 4.0
ECOG PS	X		X		X		X		X		During study treatment, perform ≤3 days prior to D1 of each cycle.
ECHO and/or MUGA	X										Perform locally, at baseline and as clinically indicated
ECG											See Appendix 4 for ECG collection instructions

Baseline and On-Study Treatment Schedule of Activities

	Baseline (Day Relative to C1D1)		Cycle 1		Cycle 2		Cycle 3		Cycle 4-n		**Instructions:** Perform all cycle-related procedures on the specified day (±3 days), unless stated otherwise in this schedule of activities. See Section 7 regarding administration of study treatment.
	≤28	≤7	D1	D15	D1	D15	D1	D15	D1	D15	
Laboratory Tests	• If baseline laboratory tests were performed ≤7 days prior to C1D1 and the results are deemed to be clinically valid by the investigator, laboratory tests do not need to be repeated on C1D1 • After C1D1, perform laboratory tests ≤3 days prior to infusion • Perform more frequent assessments as clinically indicated • The investigator must review results of blood tests prior to start of infusion										
Blood tumor markers		X	X	X	X	X	X	X	X	X	As appropriate for particular tumor types (local testing). For example, include alpha-fetoprotein for patient with HCC.
HIV testing	X										Local testing
Hepatitis panel	X										Local testing
Hematology		X	X	X	X	X	X	X	X	X	
Coagulation	X										Perform at baseline and as clinically indicated
Clinical chemistry		X	X	X	X	X	X	X	X	X	
C-reactive protein		X	X		X		X		X		
ESR		X	X		X		X		X		
Urinalysis		X					X			X	Perform as clinically indicated
Pregnancy test		X	See Note								• Applies only to women of childbearing potential • **Note:** during study treatment, perform as clinically indicated or as required per local regulations and/or institutional guidelines

Baseline and On-Study Treatment Schedule of Activities

	Baseline (Day Relative to C1D1)		Cycle 1		Cycle 2		Cycle 3		Cycle 4-n		**Instructions:** Perform all cycle-related procedures on the specified day (±3 days), unless stated otherwise in this schedule of activities. See Section 7 regarding administration of study treatment.
	≤28	≤7	D1	D15	D1	D15	D1	D15	D1	D15	
Tumor imaging/ assessment	X						X		See Note		• Perform locally according to RECIST 1.1, with the addition of modified RECIST for mesothelioma patients, 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 Q6-12W.
Tumor measurement (palpable or visible lesions)	X		X		X		X		X		
Sample collection											See Appendix 4 for pharmacodynamics, pharmacokinetics, immunogenicity, pharmacogenetics, tumor tissue, and other biomarkers.
Administer LY3415244			X	X	X	X	X	X	X	X	LY3415244 will be administered as an IV infusion over approximately 60 minutes, depending on dose level (doses ≤70 mg may require bolus IV injection administration over 5 to 10 minutes). In Cycles 1 to 3, the LY3415244 infusion will be followed by a 4-hour observation period.

Baseline and On-Study Treatment Schedule of Activities

Abbreviations: AE = adverse event; C1D1 = Cycle 1 Day 1; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; ESR = erythrocyte sedimentation rate; HCC = hepatocellular carcinoma; HIV = human immunodeficiency virus; ICF = informed consent form; IV = intravenous; MUGA = multiple-gated acquisition; Q = every; RECIST 1.1 = Response Criteria in Solid Tumors Version 1.1; W = weeks.

Table JZDA.2.2. Poststudy Treatment Follow-Up Schedule of Activities

	Follow-Up Visit				Instructions
	Short-Term[a]			Long-Term (Q90D)[b]	• Perform all procedures on the specified day (±7 days), unless stated otherwise in this schedule of activities • No follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent
Visit	30-Day 801	60-Day 802	90-Day 803	804 to 8XX	
Procedure					
Pregnancy test	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, and respiration rate)
Concomitant medication	X				
AE collection	X	X	X	X	CTCAE Version 4.0. 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 6 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
Laboratory tests	X				Perform hematology, coagulation, clinical chemistries, and thyroid function tests
Sample collection					See Appendix 4 for pharmacodynamics, pharmacokinetics, immunogenicity, and other biomarkers

Poststudy Treatment Follow-Up Schedule of Activities

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; PD = progressive disease; SAE = serious adverse event; Q = every; W = week.

[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 follow-up visit. No follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

[b] Long-term follow-up begins the day after the patient completes the 90-day follow-up visit and ends with the patient's death, upon loss to follow-up, or upon overall study completion, whichever is earlier. 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 JZDA.2.3. Continued Access Schedule of Activities

	Continued Access Treatment		Continued Access Follow-Up Visits[a]			Instructions:
			30-Day	60-Day	90-Day	• No follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent • Efficacy assessments will be done at the investigator's discretion based on the standard of care.
	501-5XX		901	902	903	
Visit	**D1**	**D15**				
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 during the study treatment period (see Table JZDA.2.1). 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. Exploratory hypersensitivity samples may be analyzed for markers of basophil/mast cell activation (e.g., tryptase), immune complex formation (e.g., C3 levels) and cytokine release (e.g., IL-6) as appropriate for the clinical presentation. If treatment-emergent ADAs are identified during continued access follow-up, the patient will continue to be followed until ADA levels return to 2-fold above baseline (60-day posttreatment sample, every 3 months over the first year, and then yearly thereafter until return to 2-fold above baseline unless deemed clinically unnecessary after 1 year), provided the patient has not been lost to follow up or withdrawn consent.
Administer LY3415244	X	X				

Continued Access Schedule of Activities

Abbreviations: ADAs = antidrug antibodies; AE = adverse event; D = day; IG = immunogenicity; IRR = infusion-related reaction; PK = pharmacokinetics; Q = every; W = week.

[a] Continued access follow-up begins when the patient and the investigator agree that the patient will no longer continue treatment in the continued access period and lasts approximately 90 days. No follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

3. Introduction

3.1. Study Rationale

Targeted checkpoint inhibitors such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed death 1 (PD-1), and programmed death ligand 1 (PD-L1) have shown great promise in the treatment of cancer and have resulted in durable responses across many tumor types, demonstrating that the targeting of checkpoint inhibitors is a clinically validated approach (Brahmer et al. 2012; Topalian et al. 2012; Hamid et al. 2013; Reck et al. 2016; Bellmunt et al. 2017). However, there remains a large proportion of patients who do not respond.

The PD-1 checkpoint is known to be upregulated after activation of T-cell receptor and subsequently during T-cell exhaustion (Zou et al. 2016). T-cell immunoglobulin and mucin-domain-containing molecule-3 (TIM-3) is another co-inhibitory molecule that marks exhausted or dysfunctional populations of T cells in the tumor microenvironment and during chronic viral infection. In fact, it is often co-expressed with PD-1 and CTLA-4 on tumor-antigen-specific T cells in cancer patients and negatively regulates T-cell activity (Fourcade 2010, Baitsch et al. 2011; Pauken and Wherry 2015). More importantly, TIM-3 expression is found to be upregulated in PD-1-refractory patients. In addition, administration of a TIM-3-blocking antibody to epidermal growth factor receptor $(EGFR)^{T790M/L858R}$ or Kirsten rat sarcoma $(Kras)^{G12D}$ transgenic mice with tumors that progress upon treatment with anti-PD-1 appears to confer a survival advantage (Koyama et al. 2016).

LY3415244, a TIM-3/PD-L1 bispecific antibody, has been demonstrated to block PD-L1 and TIM-3, in respective in vitro assays. In line with the biology of PD-L1 and TIM-3, this blockade could result in overcoming immune checkpoints and T-cell exhaustion. In vitro experiments have demonstrated that LY3415244 can bridge cells engineered to express TIM-3 with those that express PD-L1. The clinical relevance of bridging is unknown at this time.

The goal of this study is to evaluate the safety of LY3415244 administered as monotherapy to patients with advanced solid tumors.

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.

T-cell immunoglobulin and TIM-3 were first discovered as a negative regulators of interferon gamma (IFN-γ) secreting T cells (Monney et al. 2002). TIM-3 is expressed on T cells during activation and has been identified as a cell surface marker for “exhausted” T cells following chronic exposure to antigen (Wherry 2011). Multiple ligands have been described for TIM-3, including phosphatidylserine (PtdSer), galectin-9 (Gal-9), and carcinoembryonic antigen cell adhesion molecule-1 (Zhu et al. 2005; DeKruyff et al. 2010; Huang et al. 2015). Binding of TIM-3 with TIM-3 ligand leads to T-cell dysfunction, but the precise signaling mechanism for

these receptors has not been fully elucidated. In the context of chronic viral infection, TIM-3 expression on virus-specific T cells has been associated with T-cell dysfunction, and inhibition of TIM-3 signaling has been shown to restore T-cell functionality (Jin et al. 2010). Recently, TIM-3 expression on T-lymphocytes has also been shown to mediate T-cell exhaustion during chronic mycobacterium tuberculosis infection (Jayararman et al. 2016).

Consistent with its inhibitory role in autoimmune and chronic viral and bacterial infections, TIM-3 has been shown to mark the most exhausted or dysfunctional populations of CD8+ T cells in animal models of solid and hematologic malignancies (Sakuishi et al. 2010; Zhou et al. 2011). TIM-3 has also been implicated in modulating antitumor immunity in a number of preclinical models. The growth of 4T1 mammary tumors was inhibited in TIM-3-deficient mice and anti-TIM-3-monoclonal antibody (mAb) inhibited the growth of established EL4 lymphoma, suggesting that TIM-3 is a potential target for cancer immunotherapy (Dardalhon et al. 2010). TIM-3 blockade in WT3, TRAMP-C1, and CT26 mouse models resulted in antitumor activities similar to anti-CTLA-4/PD-1 antibody and a greater efficacy with combined use of TIM-3 and PD-1 antibodies (Ngiow et al. 2011). NY-ESO-1-specific CD8+ T cells from patients with melanoma showed dysfunctional phenotypes and TIM-3 blockade restored IFN-γ and tumor necrosis factor-α production as well as cell proliferation (Fourcade et al. 2010). TIM-3 has also been reported to promote myeloid-derived suppressor cells (Dardalhon et al. 2010) and suppress natural killer (NK) cell activity (da Silva et al. 2014).

Dual-targeting of the TIM-3 and PD-1/PD-L1 pathway has been evaluated preclinically. For example, in vitro treatment of tumor-infiltrating lymphocytes (TILs) harvested from CT26 tumor-bearing mice with anti-TIM-3 and anti-PD-L1 resulted in more robust IFNγ production than with either antibody alone. In vivo, combined targeting of the TIM-3 and PD-L1 is more effective in controlling tumor growth than targeting either pathway alone in a CT26 model, in a B16F10 model, and in a 5T33 myeloma model with low dose irradiation (Sakuishi et al. 2010, Anderson 2015 [WWW], and Jing et.al. 2015, respectively). Synergistic antitumor effects have been observed for combinations of anti-TIM-3 with anti-PD-1 in CT26, MC38, and established methylcholanthrene-induced sarcomas (Ngiow et al. 2011). TIM-3 expression is upregulated in PD-1 refractory patients and there is survival advantage with the addition of a TIM-3 blocking antibody following failure of PD-1 blockade in $EGFR^{T790M/L858R}$ or $Kras^{G12D}$ transgenic tumor model (Koyama et al. 2016). Collectively, these data suggest that blockade of both TIM-3 and PD-1/PD-L1 immune checkpoints is a promising approach for improved efficacy of immunotherapy.

3.2.1. LY3415244

3.2.1.1. Nonclinical Pharmacokinetics

The pharmacokinetics (PK) of LY3415244 were evaluated in male cynomolgus monkeys following a single bolus intravenous (IV) administration CCI [redacted]

CCI

CCI

CCI

CCI

The toxicity profile of LY3415244 was investigated CCI

CCI

CCI

CCI

CCI

CCI

CCI

[redacted]

3.3. Benefit/Risk Assessment

LY3415244 targets TIM-3 and PD-L1 T cell checkpoint inhibitors and is predicted to share a similar profile of potential immune-related adverse drug reactions. The constellation of immune-related adverse events (irAEs) observed across the immune checkpoint inhibitor class (see Section 7.4) is generally considered to be clinically monitorable and manageable (Chow 2013). Currently, there is limited safety data published from ongoing clinical trials evaluating several anti-TIM-3. Clinical data from Phase 1 dose escalation of TSR-022, an anti-TIM-3 mAb, reported TSR-022 as being well-tolerated across multiple dose levels with safety profiles consistent with those of other checkpoint inhibitors (Weiss et al. 2017). Data from nonclinical models predicts a similar immune-related toxicity profile, as TIM-3 pathway blockade has been shown to enhance immune-driven pathology in murine autoimmunity models (Monney et al. 2002; Sánchez-Fueyo et al. 2003). It is currently unknown whether a bispecific antibody like LY3415244 that targets both TIM-3 and PD-L1 would have an effect on the severity, onset, and/or frequency of adverse drug reactions as compared to monotherapy administration.

CCI

[redacted]

CCI [redacted]

CCI [redacted]

More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated adverse events (AEs) of LY3415244 are to be found in the Investigator's Brochure (IB).

4. Objectives and Endpoints

Table JZDA.4.1 shows the objectives and endpoints of the study.

Table JZDA.4.1. Objectives and Endpoints

Phase	Objectives	Endpoints
1a – Dose Escalation	**Primary**	
	To assess the safety and tolerability of LY3415244 in patients with advanced solid tumors, thereby identifying a RP2D to be administered to patients in the Phase 1b portion of the study	• DLTs • Safety (including but not limited to): TEAEs, DLT-equivalent toxicities, SAEs, deaths, and clinical laboratory abnormalities per CTCAE (Version 4.0)
	Secondary	
	To assess the PK of LY3415244	• AUC, C_{min} and approximate C_{max} of LY3415244
1b - Dose Expansion	**Primary**	
	To assess the safety and tolerability of the RP2D dose of LY3415244 in patients with advanced solid tumors.	• Safety (including but not limited to): TEAEs, SAEs, deaths, and clinical laboratory abnormalities per CTCAE (Version 4.0)
	Secondary	
	To assess the PK of LY3415244 in patients in each of 4 expansion cohorts	• C_{min} and approximate C_{max} of LY3415244
	To assess early antitumor activity[a] of LY3415244 in patients in each of 4 expansion cohorts	• ORR • DOR • TTR • DCR • PFS
	Tertiary/Exploratory	
Phase 1a and 1b	To characterize tumor tissue and blood biomarkers relevant to LY3415244, including but not limited to immune cells/immune functioning, mechanism of action of study drugs, cancer-related pathways, and disease state To explore the association between biomarkers and clinical outcomes	• Results of biomarker analyses • Clinical outcomes
	To assess the immunogenicity of LY3415244	• Relationship between TEADA and safety • Relationship between TEADA and LY3415244 pharmacokinetics.

Objectives and Endpoints

Phase	Objectives	Endpoints
	To assess overall survival (OS) of patients receiving LY3415244 administered as monotherapy	• OS

Abbreviations: AUC = area under time-concentration 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; PFS = progression-free survival; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TEADA = 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 JZDA is a multicenter, nonrandomized, open-label, Phase 1a/1b study of intravenous LY3415244 in patients with advanced solid tumors. Inclusion and exclusion criteria are provided in Sections 6.1 and 6.2, respectively.

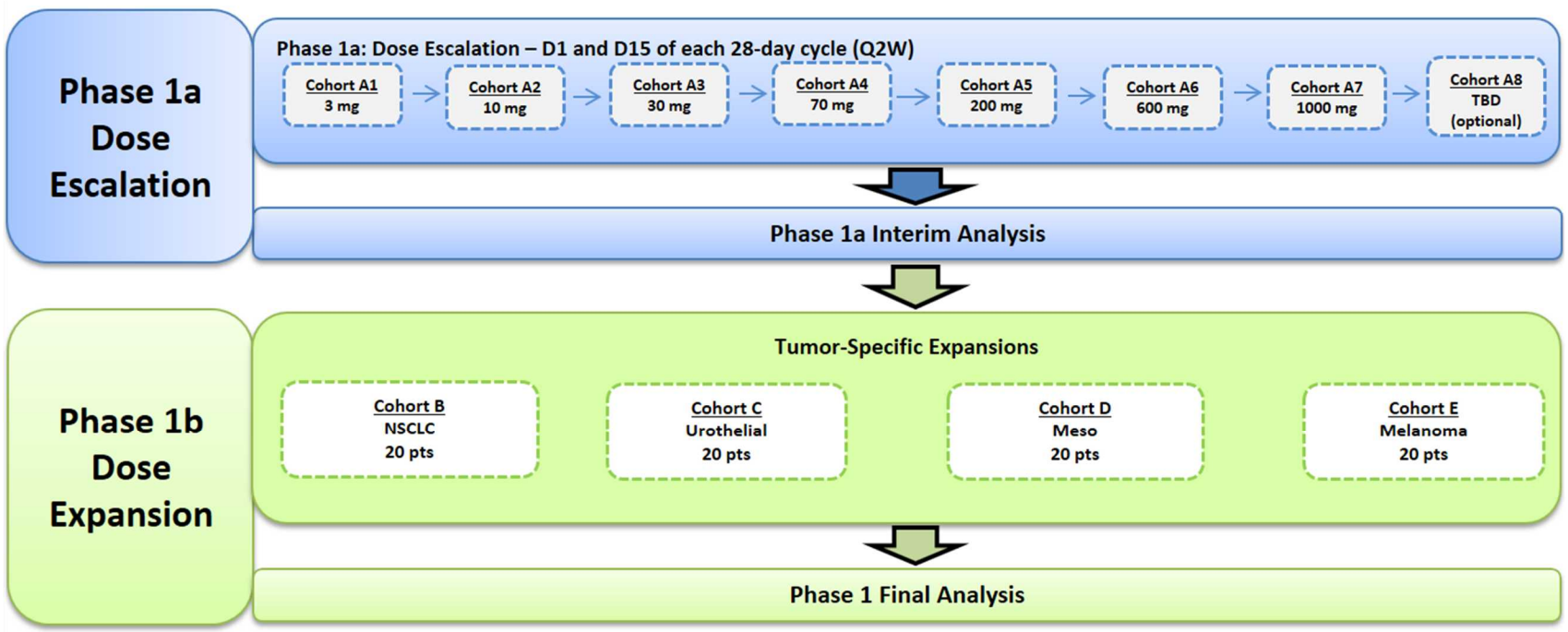
Phase 1a (dose escalation) will assess the safety and tolerability of LY3415244, administered as monotherapy in patients with advanced solid tumors. The RP2D to be tested in Phase 1b will be identified in Phase 1a, as described in Section 7.2.2. Late toxicities of available data up to 90 days will be considered for RP2D determination. Dose escalation of LY3415244 will be driven by a mTPI-2 method (Guo et al. 2016 [WWW]; see Section 7.2.2.1).

Phase 1b (dose expansion) will assess the safety and tolerability of LY3415244, administered as monotherapy in 4 expansion cohorts of patients with selected advanced solid tumor types of non-small cell lung cancer (NSCLC), urothelial cancer, mesothelioma, and melanoma.

Patients in both phases will receive study treatment for a maximum of 12 months (see Section 8.1).

The data from Phase1 a will determine the RP2D but the RP2D dose may be modified in Phase 1b if supported by additional safety and/or PK/PD data. For the primary objective of establishing safety, patients will be followed for at least 24 weeks after the last patient is enrolled. For the secondary objective of progression-free survival (PFS) and the tertiary objective of overall survival (OS), patients will be followed until death or until study completion (defined in Section 5.3), whichever occurs first.

Figure JZDA.5.1 illustrates the study design.



Abbreviations: D = day; Meso = mesothelioma; mg = milligrams; NSCLC = non-small-cell lung cancer; pts = patients; Q = every; TBD = to be determined; W = week.

Note: Cohort A8 is optional and may be explored at a dose not exceeding 1500 mg of LY3415244.

Figure JZDA.5.1. Illustration of study design.

5.1.1. Dose Escalation Phase

Patients in Cohorts A1, A2, A3, A4, A5, A6, A7, and A8, respectively, will receive doses of 3 mg, 10 mg, 30 mg, 70 mg, 200 mg, 600 mg, 1000 mg, and a dose not exceeding 1500 mg according to an every-2-weeks (Q2W) dosing regimen, provided safety is established in the preceding cohorts (see Table JZDA.7.1).

After the first patient in Cohort A1 receives the first dose of LY3415244, there will be a delay of 1 week to allow for safety observation before the second and third patients receive LY3415244. There will be no additional delays for subsequent patients.

Cohorts of patients will be treated with escalating doses of LY3415244 according to a mTPI-2 method until the criteria for reaching the maximum-tolerated dose (MTD) are met (see Section 7.2.2.1). The RP2D of LY3415244 to be tested in the Phase 1b portion of the study will be identified in Phase 1a. The RP2D may be below the MTD, which may or may not be reached during Phase 1a. 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). Late toxicities of available data up to 90 days will be considered for RP2D determination.

A 1-cycle (28 days) dose-limiting toxicity (DLT) observation period will apply to all cohorts in Phase 1a.

5.1.2. Dose Expansion Phase

Phase 1b will begin after Eli Lilly and Company (Lilly) reviews the Phase 1a data and communicates the LY3415244 doses to the study investigators.

In Phase 1b, patients will enroll concurrently to each of the 4 expansion cohorts.

Individual patient, delays and discontinuations may occur as outlined in Section 7.4. No dose reductions will be allowed.

Phase 1b will provide additional safety, tolerability, PK, pharmacodynamics, and efficacy data for LY3415244 given as monotherapy.

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 LY3415244 RP2D.

- **Phase 1a:** Total enrollment will be determined by the incidence of DLTs.
  - Cohorts A1 through A8: approximately 27 patients (minimum of 3 patients per cohort) will be enrolled. During Phase 1a DLT assessment period, a maximum of 10 patients, per dose level, may be enrolled.
- **Phase 1b:**
  - Expansion cohorts: approximately 80 patients (20 patients with NSCLC, 20 patients with urothelial cancer, 20 patients with mesothelioma, and 20 patients with melanoma)

Because of the advanced disease state of this patient population and the screening involved in defining eligibility, more than the planned number of patients may be enrolled in a particular cohort, if approved by Lilly.

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.

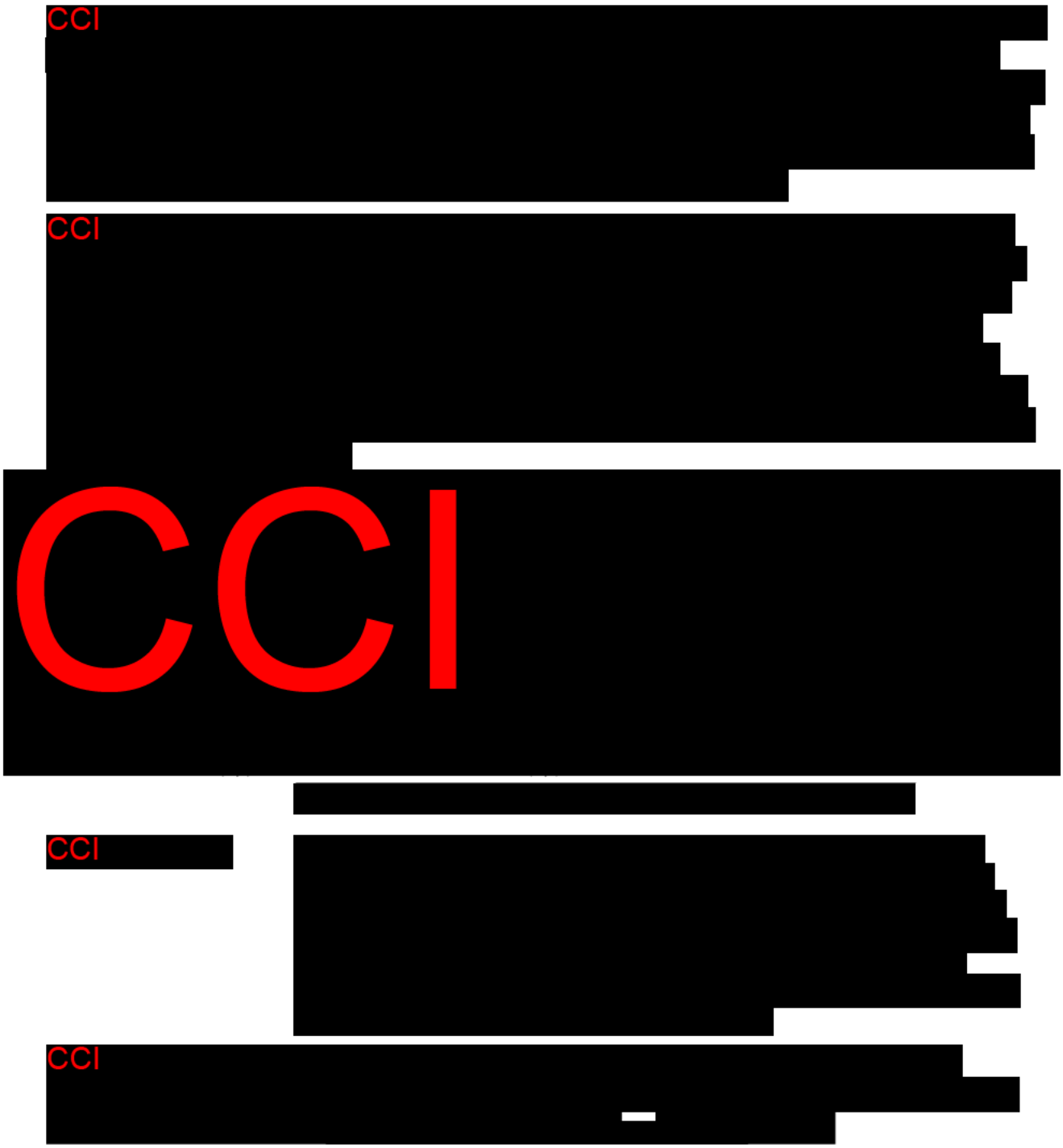
5.4. Scientific Rationale for Study Design

See Sections 3.1 and 3.3.

5.5. Justification for Dose

Plasma concentrations of LY3415244, total soluble sTIM-3, and sPD-L1 plasma concentrations in cynomolgus monkeys following a single IV dose of CCI [redacted] LY3415244 were used to build a population PK/PD model that simultaneously describes the temporal profiles of PK of both soluble targets. The developed population PK/PD model was translated to humans based on allometric scaling (body weight) and similar affinity between species (Kd). The model was then used for the prediction of soluble TE% CCI [redacted] in humans. Concentrations needed for reaching CCI [redacted] TE CCI [redacted] were estimated. CCI [redacted]

CCI [redacted]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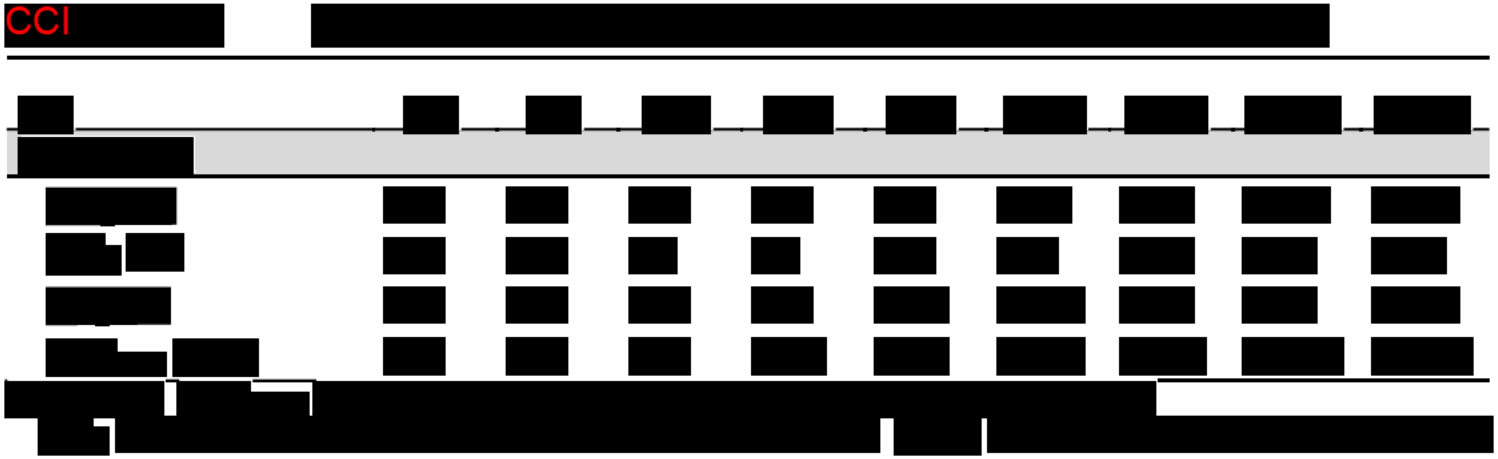

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6. Study Population

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 of the following criteria:

[1] Have histological or cytological evidence of a diagnosis of cancer that is advanced and/or metastatic. The patient must be, in the judgment of the investigator, an appropriate candidate for experimental therapy after available standard therapies (per available local guidelines) have failed to provide clinical benefit for their disease.

[2] For patients enrolled to Phase 1a, prior anti-PD-1 or anti-PD-L1 therapy or other immunotherapy is allowed. For Phase 1b, prior anti-PD-1 or anti-PD-L1 therapy is required for patients with NSCLC, urothelial cancer, and melanoma. For Phase 1a and Phase 1b, 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:

i. a Grade ≥3 irAE (Table JZDA.7.4)

ii. any grade neurologic or ocular irAE

iii. 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 re-challenged, and does not currently require maintenance doses of >10 mg prednisone (or equivalent) per day

[3] For patients enrolled to Phase 1b expansion cohorts, have a histologically or cytologically confirmed diagnosis of:

a. disease that did not initially respond to prior anti-PD-1 or anti-PD-L1 therapy

OR

b. disease that initially responded to anti-PD-1 or anti-PD-L1 therapy (considered to have partial response [PR] or complete response [CR] for any duration) and later progressed

AND one of the following:

c. metastatic NSCLC (Stage IV, any histological type) with 1 prior line of therapy. Patients with an EGFR-sensitizing mutation, an ALK gene rearrangement, ROS1 rearrangements, or BRAF V600E mutations must also have progressed after treatment with an appropriate tyrosine kinase inhibitor.

d. locally advanced, unresectable or metastatic transitional cell carcinoma of urothelium (bladder, urethra, or renal pelvis) (patients with tumors of mixed pathology are eligible if predominantly transitional cell tumor) with at least 1 prior line of systemic therapy.

e. metastatic cutaneous melanoma with advanced unresectable disease. Acral lentiginous melanoma, uveal, and mucosal melanoma are excluded.

[4] Patients with mesothelioma are not required to have received prior anti-PD-1 or anti-PD-L1 therapy. If the patient has received prior anti-PD-1 or anti-PD-L1 therapy, then inclusion criteria [2]a through [2]d and [3]a and [3]b would apply. Additionally, patients must have:

a. confirmed unresectable or medically inoperable malignant mesothelioma and progressive disease (PD) after at least one prior systemic treatment with a platinum-based doublet (both cisplatin and carboplatin are allowed) for unresectable MPM. All prior cytotoxic toxicities must have resolved to Grade ≤2 prior to registration.

Note: Inclusion criteria [5] through [15] apply to patients enrolled to Phase 1a and Phase 1b portions of the study.

[5] are able and willing to provide required, newly obtained core or excisional biopsy of a tumor lesion prior to study enrollment and undergo a biopsy procedure during the study treatment period for collection of an additional tumor tissue sample (see Section 9.8.1 for additional details). (Note: An archived tumor sample will be requested, if not restricted by local regulations).

[6] Have at least 1 measurable lesion as defined by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) (Eisenhauer et al. 2009). Bone metastases are not considered measurable.

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

[8] Have given written informed consent prior to any study-specific procedures.

[9] Have adequate organ function as defined in the table below:

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 (see Appendix 6)	≤1.5 × ULN OR ≥50 mL/min

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

[10] Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group scale (Oken et al. 1982).

[11] Have discontinued previous treatments for cancer and recovered from the acute effects of therapy. Patients must have discontinued from previous treatments, as shown in the table below:

Previous Treatment	Length of Time Prior to First Dose of Study Treatment
Cytotoxic therapies or targeted agents (small molecule inhibitors)	≥14 days
Mitomycin-C or nitrosoureas	>42 days
Biologic agents (including immunotherapy)	≥21days
Radiotherapy	≥28 days
Limited field radiotherapy for palliative intent	≥14 days
Major surgery, excluding biopsy	Patients with major surgery within 28 days prior to starting therapy must have recovered in the opinion 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.

[13] 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.

[14] Women of childbearing potential must have a negative serum pregnancy test documented within 7 days prior to initiation of treatment.

[15] Have an estimated life expectancy ≥12 weeks, in the judgement of the investigator.

6.2. Exclusion Criteria

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

[16] 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.

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

a. known human immunodeficiency virus (HIV) infection (HIV 1 and/or 2 antibodies)

b. active hepatitis B or C virus infection according to local standards

c. current or known history of tuberculosis

d. active infection requiring systemic therapy

e. prior or second concurrent primary malignancies that, in the judgment of the investigator and the Lilly Clinical Research Physician (CRP)/Clinical Research Scientist (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 known or suspected autoimmune disease or any illness that could compromise the immune system (for example, prior organ transplant) within the past 2 years or a syndrome that requires systemic corticosteroids or immunosuppressive agents

   This criterion does not apply to patients with: (i) vitiligo, alopecia, or type I diabetes mellitus; (ii) residual hypothyroidism due to an autoimmune condition requiring only hormone replacement; or (iii) psoriasis not requiring chronic systemic immunosuppressive treatment within the past 2 years, and 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, cyclosporine). 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 (for example, interstitial lung disease or radiation pneumonitis); (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 including 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 ECG abnormalities that, in the judgment of the investigator, are clinically significant (for example, arrhythmias requiring treatment; recent myocardial infarction within the last 3 months; or mean QTc ≥470 ms calculated using Fridericia's correction and confirmed by triplicate ECG)

[18] 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 requiring concurrent treatment, including but not limited to surgery, radiation, corticosteroids and/or anticonvulsants to treat CNS metastases, and their disease is asymptomatic and radiographically stable for at least 30 days.

[19] 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.

[20] Are pregnant, or planning to become pregnant during the study or within 6 months following the last dose of LY3415244. Plan to be breastfeeding from C1D1 of study or within 6 months following the last dose of LY3415244.

[21] 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

[22] 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 re-screened 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, and the repeated laboratory test must meet the eligibility criteria.

7. Treatment

7.1. Treatment Administered

LY3415244 will be administered as an IV infusion over approximately 60 minutes, depending on dose level (doses ≤70 mg may require bolus IV infusion). In Cycles 1 through 3, the LY3415244 infusion will be followed by a 4-hour observation period.

Table JZDA.7.1 shows the treatment regimen.

Table JZDA.7.1. Treatment Regimen

	Cohort	Dose of LY3415244	Route	Dosing Schedule
Phase 1a: Dose Escalation	A1	3 mg	IV	D1 and D15 of each 28-day cycle (Q2W)
	A2	10 mg		
	A3	30 mg		
	A4	70 mg		
	A5	200 mg		
	A6	600 mg		
	A7	1000 mg		
	A8	Optional: TBD[a]		
Phase 1b: Dose Expansion	B	RP2D	IV	D1 and D15 of each 28-day cycle (Q2W)
	C			
	D			
	E			

Abbreviations: C = cycle; D = day; IV = intravenously; mg = milligrams; Q2W = every 2 weeks; RP2D = recommended Phase 2 dose; TBD = to be determined.

a Enrollment of Cohort A8 is optional. It will be initiated if Cohort A7 is tolerated and PK/PD analyses suggest that another dose may be appropriate. The dose will not exceed 1500 mg.

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

LY3415244 drug product is a clear to opalescent, colorless to slightly yellow to slightly brown, sterile, preservative-free solution for IV infusion supplied in glass vials.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be assigned to receive LY3415244 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 (that is, 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 provided that 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 Lilly 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) as shown in Table JZDA.7.1. 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.

A patient may continue to receive LY3415244 until he or she meets one or more of the specified reasons for discontinuation (see Section 8).

7.2.2. Dose Escalation: Phase 1a

7.2.2.1. Dose Escalation Method

Dose escalation of LY3415244 (at the levels shown in Figure JZDA.5.1) will be driven by a mTPI-2 method (Guo et al. 2016 [WWW]), taking into consideration available PK and pharmacodynamic data from previous dose levels. Each cohort in this study will contain a minimum of 3 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 3 or 6 patients are enrolled in a cohort, the escalation rule parallels a traditional 3+3 design. However, it allows flexible number of patients in a cohort. For example, with 2 DLTs per 6 patients enrolled, the mTPI-2 would recommend staying at the current dose, as analogy to 1 DLT per 3 patients enrolled in 3+3 design; therefore, it allows more patients for a more precise estimate of the DLT rate at this dose level.

Appendix 7 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 3 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 7. 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 7.

Safety data, in particular DLTs, will be the primary criteria for the dose escalation. In addition, if available at the time of dose escalation decision, PK (for example, Cmax, AUC, pharmacodynamics results) will be used as secondary/supporting data for dose escalation.

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

7.2.2.2. Dose-Limiting Toxicity Determination

A DLT is defined as any of the events listed in Table JZDA, if the event occurs during the DLT observation period (Cycle 1) in Phase 1a, and toxicity that is not clearly and directly related to the primary disease or another etiology.

All AEs of Grade 3 or higher that occur during the DLT observation period will be included in the DLT definition except for toxicities with a clear, alternative explanation, including the exceptions listed in Section 7.2.2.2.1.

Patients who experience a DLT in Cycle 1 will be discontinued from study treatment.

Table JZDA.7.2. Dose-Limiting Toxicity

Hematologic toxicity
• Grade 3 thrombocytopenia 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 7.2.2.2.1
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:
  • does not downgrade to Grade 2 within 3 days after onset of the event despite optimal medical management including corticosteroid therapy, or
  • does not downgrade to Grade ≤1 or the patient's baseline level within 14 days after onset of the event
• Grade 2 pneumonitis that does not resolve to Grade ≤1 within 3 days after initiation of optimal medical management including corticosteroids therapy
• Grade ≥3 toxicity lasting an extended period of time despite optimal supportive care (for example, nausea, vomiting, and diarrhea lasting >3 days)
• Grade ≥3 fatigue lasting >7 days
• Grade ≥3 hypertension despite of maximal medical therapy

Nonhematologic toxicity – laboratory/investigations

• Grade 3 or 4 amylase or lipase elevation that leads to discontinuation of study drug
• Other Grade 3 or 4 laboratory value lasting >14 days or requiring medical intervention
• ALT or AST:
  • >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

Other hematologic or nonhematologic toxicity

• Grade 5 toxicity (that is, death)
• Toxicity deemed by the investigator and Lilly CRP/CRS to be dose limiting, such as:
  • toxicity that is possibly related to study treatment and requires discontinuation of the patient from the study at any time during Cycle 1, or
  • persistent Grade >2 toxicities causing a delay of >14 days in initiating Cycle 2

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.

7.2.2.2.1. Events That Are Not Considered to Be DLTs

The following events listed in this section will not be considered to be DLTs:

- Adverse event that is clearly and directly related to the primary disease or to another etiology
- Known class effects that have been observed with immunotherapy:
  - Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency), if both the following criteria are met:

  - the disorder is manageable with or without systemic corticosteroid therapy and/or hormone replacement therapy, and
  - the patient is asymptomatic
- Grade 3 inflammatory reaction attributed to a local antitumor response (such as, inflammatory reaction in the lymph nodes or at sites of metastatic disease)
- Any grade vitiligo or alopecia
- Grade 3 or 4 lymphopenia

- First occurrence of Grade 3 infusion-related reaction (IRR) during infusion of LY3415244, 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.

- Grade 3 or 4 neutropenia meeting both of the following criteria:
  - not associated with fever or systemic infection, and
  - improves by at least 1 grade within 7 days with treatment

- In order to exclude potential detection of electrolyte abnormalities that cannot be associated with clinical signs of symptoms, or laboratory test error. Isolated Grade 3 electrolyte abnormalities meeting both of the following criteria:
  - not associated with clinical signs or symptoms, and
  - reversed with appropriate maximal medical intervention within 2 days

It should be recognized that for patients who have received prior immune therapy, including check point 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 is any event listed in Table JZDA.7.2 occurring after Cycle 1 in Phase 1a or in any cycle of Phase 1b that would have met criteria for DLT if it had occurred during the DLT observation period. For individual patients experiencing a DLT-equivalent toxicity, dose modifications will be made as outlined in Section 7.4.

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, including but not limited to LY3415244 dose adjustments (delays, reductions, or omissions), AEs, chronic intolerance, PK and pharmacodynamic data, and irAEs. The final RP2D to be carried forward into any future studies will be confirmed or changed based on the combined data from Phase 1a and Phase 1b.

7.3. Blinding

This is an open-label study.

7.4. Dose Modification

No dose modification is allowed during Phase 1a DLT observation period (Cycle 1).

After the Phase 1a 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 is required after the administration of LY3415244 in Cycles 1 to 3. During observation period, patients treated with LY3415244 should be closely monitored for signs and symptoms indicative of an infusion-related reaction by medical staff from the start of the infusion until 4 hours after the end of the infusion, in an area where emergency medical resuscitation equipment and other agents (epinephrine prednisolone equivalents, etc.) are available. LY3415244 infusion-related reactions will be defined according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 definition of IRRs.

Table JZDA.7.3 presents instructions for management of infusion-related reactions associated with LY3415244.

Table JZDA.7.3. Management of Infusion-Related Reactions

Grade	Management	
2	First occurrence	Stop the infusion and proceed with following: 1. If resolved to Grade 0 or 1 within 1 hour after stopping the infusion a. restart the infusion at 50% of the original rate (for example, reduce from 100 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 LY3415244 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. Patients who experience a Grade 3 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 LY3415244 infusion with diphenhydramine (or other antihistamine), acetaminophen (or other antipyretic), steroids etc., at the discretion of treating physician. If symptoms reappear, immediately and permanently discontinue study treatment.

Table JZDA.7.4 presents guidance for irAE management (including use of corticosteroids) and criteria for dose delays and discontinuations if the patient experiences a potential irAE considered at least possibly related to LY3415244.

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. Guidelines used by local standards such as, but not limited to Haanen and colleagues (2017), Puzanov and colleagues (2017), or Brahmer and colleagues (2018), supersede the guidelines provided in Table JZDA.7.4 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 JZDA.7.4. 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 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, diabetes mellitus-type 1)	• Withhold study treatment and administer prednisone 1-2 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

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	
Gastrointestinal	Diarrhea, Abdominal pain, Blood in stool, Colitis	2		• Withhold study treatment, give antidiarrheal medication, and check etiology • If the event continues for >5 days despite the use of antidiarrheal medications, start prednisone 0.5-1 mg/kg/day • Resume study treatment after the event resolves to Grade ≤1
	Diarrhea, Ileus, Perforation, Colitis	≥3		• Withhold study treatment and administer prednisone 1-2 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
	Pancreatitis	1-2	Increase in amylase and lipase	• Withhold study treatment and administer prednisone 0.5-1 mg/kg/day • Resume study treatment after the event resolves to Grade ≤1
		≥3		• Discontinue study treatment and administer prednisone 1-2 mg/kg/day[d]

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	
Hepatobiliary	Transaminitis, elevated bilirubin	2	• AST or ALT between 3 × ULN and 5 × ULN, or • TB between 1.5 × ULN and 3 × ULN	• Withhold study treatment and administer prednisone 1-2 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 2-4 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 1-2 mg/kg/day
Respiratory	Dyspnea, hypoxia, pneumonitis	1		Consider withholding study treatment until the patient is stable
		2	Mild to moderate symptoms	• Withhold study treatment and administer prednisone 1-2 mg/kg/day • Resume study treatment after the event resolves to Grade ≤1
		≥3	Severe	• Discontinue study treatment and administer: o IV methylprednisolone 2-4 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]

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	
Cardiac	Myocarditis, cardiac function abnormalities (for example. dysrhythmia, valvular abnormalities)	≥1		• Discontinue study treatment and administer o IV methylprednisolone 2-4 mg/kg/day o Consider immunosuppressives without immediate response to steroids (for example, mycophenolate, infliximab, or anti-thymocyte globulin) • Consult with cardiology immediately and Lilly CRP/CRS; if available, transfer to cardiac care unit
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 0.5-1 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 1-2 mg/kg/day

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	
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
	Stevens–Johnson syndrome, toxic epidermal necrolysis, necrosis, bullous or hemorrhagic lesions			Discontinue study treatment and administer prednisone 1-2 mg/kg/day
Ophthalmological	Eye disorders (for example, uveitis, episcleritis)	≥2		• If mild, consider topical steroids (for example, 1% prednisolone); otherwise, discontinue study treatment and administer o Oral or IV methylprednisolone 2-4 mg/kg/day o Consult ophthalmologist and Lilly CRP/CRS.

Dose Modification Guidelines and AE Management for Toxicities At Least Possibly Related to Study Drug

Abbreviations: ADL = activities of daily living; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BSA = body surface area; CRP = clinical research physician; CRS = Clinical Research Scientist; CTCAE = Common Terminology Criteria for Adverse Events, Version 4.0; irAE = immune-related adverse event; IV = intravenous; SOC = system organ class; TB = total bilirubin; ULN = upper limit of normal.

[a] If symptoms of grade is not specified, use CTCAE Version 4 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/CRS about discontinuing study treatment.

[c] Immunosuppressive refers to infliximab or cyclophosphamide.

[d] Patients who have asymptomatic or clinically non-significant Grade 3 or 4 lipase or amylase elevations (for example, not associated with clinical symptoms or radiological signs of pancreatitis) that are transient as demonstrated by a decrease of at least 1 CTCAE Grade within 7days (± 3 days) of onset will not require discontinuation of LY3415244. If the elevation does not decrease by at least 1 CTCAE Grade within this time window, LY3415244 treatment may continue only after consultation and discussion with the Lilly CRP/CRS.

7.5. Preparation/Handling/Storage/Accountability

LY3415244 should be stored under refrigerated conditions (2°C to 8°C).

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 1a

A patient will be DLT evaluable if he or she experiences a DLT during the DLT observation period and has received at least 1 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. Adverse events from DLT non-evaluable patients will also be reviewed throughout the dose escalation process in Phase 1a.

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

Table JZDA.7.5 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 postdiscontinuation 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.

Table JZDA.7.5. Concomitant Medication Guidelines

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	

Concomitant Medication Guidelines

Therapy	As Needed	Chronic Use	Exceptions or Conditions for Use
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.
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 LY3415244 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.

No other chemotherapy, systemic radiotherapy, immunotherapy, cancer-related hormone therapy, experimental drugs, or 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 the study. 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 American Society of Clinical

Oncology (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 Study Completion

7.8.1. Continued Access

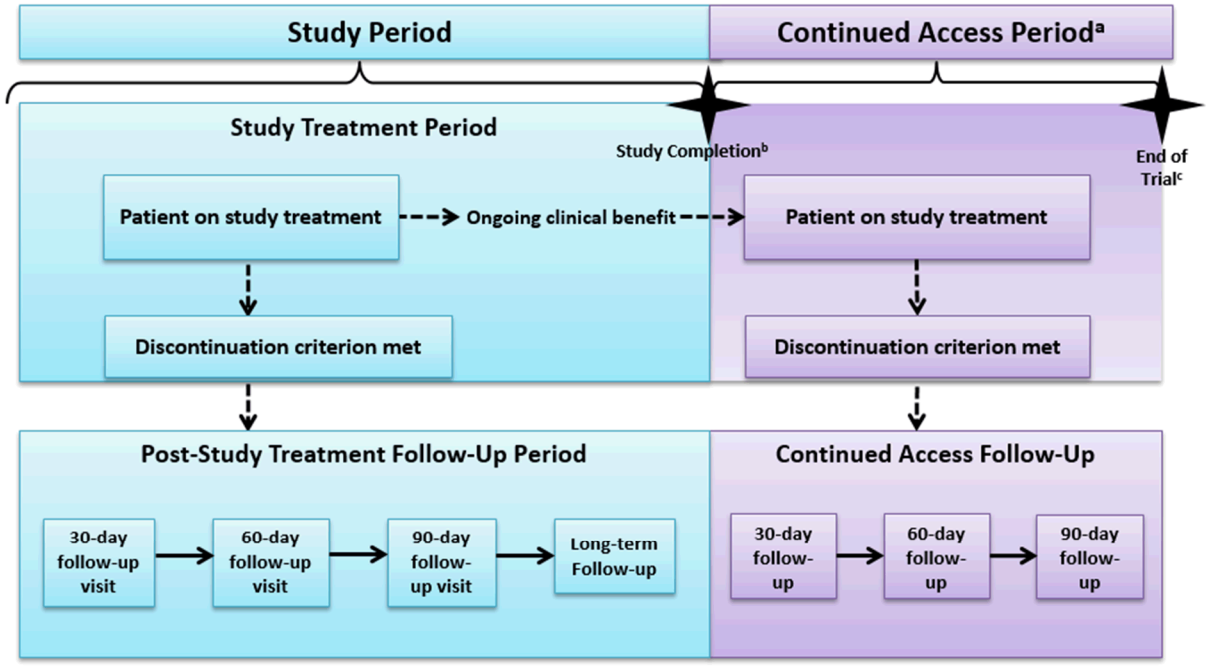
Patients who are still on study drug at the time of study completion may continue to receive study drug if they are experiencing clinical benefit and no undue risks.

The continued access period will apply to this study only if at least 1 patient is still on study drug 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 JZDA.7.1. 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 noncompliant 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-equivalent toxicity (see Section 7.2.2.2.2), or other unacceptable toxicity
- the patient requires a dose delay of >28 days, 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
- the patient requests to be discontinued from study treatment
- the patient has received the maximum duration of 12 months of study treatment (longer duration may be considered for a patient receiving clinical benefit, in consultation with the Lilly CRP/CRS). If tumor imaging shows initial disease progression, at the discretion of treating physician, patients may remain on study treatment with repeat imaging 4 to 6 weeks later to assess tumor response or confirm progression per RECIST 1.1 with confirmatory scan on disease progression

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 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 9.2 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 will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. 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. Modified RECIST will be applied for patients with pleural mesothelioma whereby tumor thickness (perpendicular to chest wall or mediastinum) would be measured at 2 positions on 3 separate levels on transverse cuts of CT scan (Byrne 2004).

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), by the investigator, with confirmatory assessment obtained at the next routine scheduled imaging time point.
- Per RECIST v1.1, PR or 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 JZDA, tumor imaging for confirmation of response may be performed at the earliest 4 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 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 6 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: (i) RECIST 1.1 with confirmatory scan for disease progression and (ii) immune-related response criteria (irRC, Wolchok et al. 2009). For both measures (i) and (ii), clinically stable patients may continue treatment until disease progression (per standard RECIST 1.1) is confirmed. As the irRC are still being developed and validated for various tumor types, Study JZDA will use RECIST 1.1 with confirmatory scan for disease progression, which may discourage the early discontinuation of study treatment and provide a more complete evaluation of its efficacy than would be seen with conventional response criteria.

Table JZDA.9.1. Summary of Response Assessment by RECIST, RECIST with Confirmatory Scan for PD, and irRC

Definition	Used in Study JZDA		Not Used in Study JZDA
	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 4-6 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 JZDA, 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 (see Section 9.1.1.3).

"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, rapid disease progression or threat to vital organs or critical anatomical sites, such as 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.

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 CTCAE, Version, 4.0 (NCI 2009) to assign AE terms and 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 to 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 drug 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 summary 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 (European Union) No 536/2014 and the associated detailed guidance 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 guidance.

Regular communication will occur between investigators and the sponsor 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 LY3415244. 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

If a patient receives a higher dose of LY3415244 than that specified in the protocol, patients should receive appropriate supportive care measures for any AEs, as deemed necessary by the treating investigator.

9.4. Safety

9.4.1. Other Safety Measures

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

Perform ECGs as shown in Appendix 4. Triplicate ECGs will be collected in Study JZDA. ECGs should be recorded according to the study-specific recommendations included in the ECG manual.

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.

9.4.2. Safety Monitoring

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

For Phase 1a, safety data will be reviewed on a cohort by cohort basis. For Phase 1b, a safety review will be performed when every 10 patients have been treated for approximately 1 cycle for the first 20 patients enrolled into Phase 1b across all expansion cohorts, then every 3 months after the last patient enters study treatment (LPET) for 1 year, and then at least once a year afterward. The purpose of this Phase 1b safety review is to evaluate the safety and tolerability for each expansion cohort and determine if a dose-limiting equivalent toxicity (DLET) has been observed. For the first 20 patients enrolled into Phase 1b, based on mTPI-2 method, if 7 or more DLETs are observed, accrual will be temporarily paused, and the available data from Phase 1a and 1b will be analyzed to potentially modify the RP2D, or the study; considerations for stopping recruitment should be given after discussion with investigator and sponsor.

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 5) 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 5) 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. Special Hepatic Safety Data Collection

Hepatic data, such as lab tests (see Appendix 5), liver related signs and symptoms, results from hepatic monitoring procedures, and liver biopsy assessment if available, should be collected 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 LY3415244 (also known as bioanalytical samples).

Bioanalytical samples collected to measure LY3415244 plasma concentration will be retained for a maximum of 1 year following last patient visit for the study.

Instructions for the collection and handling of bioanalytical blood samples will be provided by Lilly. The actual start and end date and time of LY3415244 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 plasma samples will be measured using validated assay methodology in a laboratory designated by Lilly.

The remaining sample collected for PK testing may be pooled and used for exploratory metabolism or bioanalytical assay validation work as deemed appropriate.

9.6. Pharmacodynamics

Pharmacodynamic samples will be collected as shown in Appendix 4 to assess target engagement and activity for LY3415244. Potential pharmacodynamic markers may include measuring soluble markers (sPD-L1 and sTIM-3) in serum and immune cell subsets characterization and distribution. Tumor tissue, plasma, serum, and whole blood may be used for additional exploratory PD work 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 immunogenicity testing will be collected as shown in Appendix 4 to determine antibody production against LY3415244. Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of LY3415244. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of LY3415244.

In the event of a drug hypersensitivity event (immediate or non-immediate), additional samples will be collected as close to the onset of the event as possible and at 4 and 12 to 16 weeks after the event. Instructions for the collection and handling of blood samples will be provided by Lilly. The actual date and time (24-hour clock time) of each sampling should 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 LY3415244. 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 LY3415244 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 LY3415244 or after LY3415244 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 LY3415244, mechanism of action of LY3415244, the variable response to study drug(s), immune function, and pathways associated with cancer, including solid tumors and 4 expansion cohorts (NSCLC, urothelial carcinoma, mesothelioma, and melanoma). 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 Phase 1a and Phase 1b (all cohorts):

- a newly obtained core or excisional pre-treatment biopsy of a tumor lesion **and**
- a tumor tissue sample from a newly obtained 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 4 core-needle biopsies or a surgical biopsy is required, unless medically contraindicated and discussed with Lilly CRP/CRS. Optimally, biopsies should be taken from the same lesion and from areas not previously irradiated. Biopsies should not be taken from areas that have been previously irradiated, unless the previously irradiated area has progressed.

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

For patients participating in Phase 1a and 1b (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 for meaningful clinical data; paired biopsies are planned to be tested from baseline over time for changes in molecular markers to document any potential immunomodulatory activity of treatment with LY3415244 and should be performed if clinically feasible. A minimum paired sample size of 19 in total is expected to provide adequate precision to estimate the immune response. Samples will be examined for biomarkers as described in Section 9.8, including but not limited to, TIM-3 and 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 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 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. 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 LY3415244 or after LY3415244 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
- 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 LY3415244 or after LY3415244 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 LY3415244, thereby identifying and confirming the RP2D of LY3415244 to be administered as monotherapy to patients with solid tumors. The secondary objective is to evaluate PK and any observed evidence of clinical efficacy.

In Phase 1a, the total sample size will be determined by the incidence of DLTs.

With at least 3 patients treated at the RP2D in the dose-escalation phase and additional patients treated at the RP2D in Phase 1b, a total of at least 20 patients can provide adequate precision for the estimated incidence rate of the following quantities of interest: (1) patients having a specified AE or (2) patients showing a response (PR/CR) to treatment. With a total sample size of 20, the 95% confidence interval (CI) is approximately equal to the observed incidence rate ±12% to 24%. Example point estimates of incidence rates and corresponding 2-sided 95% CIs are summarized in Table JZDA.10.1. The values are provided as a reference for estimation rather than a basis of any decision criteria. The RP2D may be revised based on the safety data obtained in the expansion phase (Iasonos and O'Quigley 2013).

Table JZDA.10.1. Estimated Incidence Rate and 2-Sided 95% Confidence Interval

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

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

a 95% Clopper-Pearson interval for binomial distribution.

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 population: will include all enrolled patients from whom a valid assay result (according to laboratory guideline) has been obtained.

Biomarker population: 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 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 LY3415244 will be evaluated for safety and toxicity. AE terms and severity grades will be assigned by the investigator using CTCAE Version 4.0.

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 in Phase 1a
- 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 in Phase 1a and by tumor type and treatment regimen in Phase 1b
- 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 4.0 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 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 1 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-escalation treatment arm and by expansion 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, and OS (as an exploratory objective), will be summarized by Kaplan and Meier (1958) method by dose-escalation treatment arm and expansion. Presentations of antitumor activity may include patients enrolled in the dose-escalation phase 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 to demonstrate that the study population represents the target patient population considered for regulatory approval.

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

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 delays, and dose intensity will be summarized for the enrolled/safety population.

LY3415244 will be administered at the investigator site, therefore treatment compliance is assured.

10.3.3.5. Pharmacokinetic/Pharmacodynamic Analyses

PK parameter estimates for LY3415244 therapy will be calculated by population PK analysis methods using nonlinear mixed effects modeling. 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 Lilly global PK/PD management. In addition, selected PK parameters (based on actual sampling times), including C_{max}, time of C_{max} , and AUC may be calculated by noncompartmental analysis methods and/or model simulations. As an exploratory analysis, PK parameter estimates for C_{min} at steady state following repeated dose may be evaluated.

Pharmacokinetic/pharmacodynamic analyses will be conducted to explore exposure-response relationships between LY3415244 concentrations in systemic circulation and various pharmacodynamic measures, such as selected safety outcomes, receptor occupancy, and biomarkers.

10.3.3.6. Biomarker Analyses

Biomarkers related to treatment, immune functioning, mechanism of action of study drugs, and/or cancer will be collected and reported. In addition, the relationship between biomarkers and clinical outcome will be assessed. Biomarker relationships by tumor type, changes in biomarker levels at baseline and over time, and differences among dose levels or exposure will be explored as possible. The pharmacodynamic effect from all patients undergoing pharmacodynamic assessments will be explored (Section 10.3.3.5).

10.3.3.7. Immunogenicity Analysis

The frequency and percentage of patients with preexisting ADA, ADA at any time point postbaseline, and with treatment-emergent ADA positivity (TE ADA+) to LY3415244 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 PD response including safety and efficacy to LY3415244 may be assessed.

10.3.4. Interim Analyses

In the Phase 1a dose-finding portion of the study, 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 analysis will be performed after all patients in Phase 1a have completed the DLT evaluation period. The Lilly study team will evaluate the data from the interim safety and PK/PD analyses before opening the dose expansion cohorts in Phase 1b. In these interim analyses, early antitumor activity may also be explored.

An expansion-specific safety and efficacy interim analysis will be conducted approximately 24 weeks (6 months) after the LPET for each of the expansion cohorts. These interim analyses may be combined if they are expected to occur within approximately a month of each other. Interim analyses may also be combined with any prespecified safety review or reporting (that is, Trial Level Safety Reviews, Development Safety Update Reviews, or IB update reviews). The expansion-specific safety and efficacy primary analyses will be conducted approximately 52 weeks (12 months) after LPET for each of the expansion(s).

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

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 PD biomarkers. All data defined in the protocol will continue to be collected from patients on treatment after data-cutoff date and results will 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
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-2wk}	area under the concentration versus time profiles of a 2-week dosing interval
BOR	best overall response
C_{avg}	2-week average concentration
C_{max}	maximum plasma concentration
C_{min}	trough concentration
CI	confidence interval
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
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
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
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
EGFR	epidermal growth factor receptor
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
ELISA	enzyme-linked immunosorbent assay
Enter	Patients entered in the study are those who have signed the informed consent form directly or through their legally acceptable representatives.
Gal-9	galectin-9
GCP	good clinical practice
G-CSF	granulocyte colony stimulating factors
GFR	glomerular filtration rate

highly effective methods 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 injectable o implantable • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • 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
IFN-γ	interferon gamma
IgG	immunoglobulin G
interim analysis	An analysis of clinical study data that is conducted before the final reporting database is authorized for datalock.
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
Kd	equilibrium dissociation constant
Kras	Kirsten rat sarcoma
LOQ	limit of quantification
LPET	last patient enters/starts study treatment
mAb	monoclonal antibody
MABEL	minimum anticipated biological effect level
MPM	malignant pleural mesothelioma
MTD	maximum tolerated dose
mTPI-2	modified toxicity probability interval-2
NK cells	natural killer cells
NOAEL	no-observed-adverse-effect-level
NSCLC	non-small cell lung cancer
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
PAD	pharmacologically active dose
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
PK/PD	pharmacokinetic/pharmacodynamic

PR	partial response
PtdSer	phosphatidylserine
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
RO%	receptor occupancy
RP2D	recommended Phase 2 dose
SAP	Statistical Analysis Plan
SAE	serious adverse event
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
sPD-L1	soluble programmed death ligand 1
SOC	system organ class
sTIM-3	Soluble T-cell immunoglobulin and mucin-domain-containing molecule-3
SUSAR	suspected unexpected serious adverse reactions
$T_{1/2}$	terminal half life
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.
TILs	tumor-infiltrating lymphocytes
TTR	Time-to-response

Appendix 2. Clinical Laboratory Tests

Hematology – local laboratory

- Leukocytes (WBC)
- Neutrophils
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils
- Erythrocytes (RBC)
- Hemoglobin (HGB)
- Hematocrit (HCT)
- Platelets (PLT)
- Erythrocyte sedimentation rate (ESR)

Coagulation – local laboratory

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

Clinical chemistry – local and central laboratory

Serum concentrations of:

- Alanine aminotransferase (ALT)
- Albumin
- Alpha-fetoprotein (AFP; required only for patients with HCC)
- Alkaline phosphatase
- Aspartate aminotransferase (AST)
- Amylase[b]
- Bicarbonate
- Bilirubin, direct
- Bilirubin, total
- Blood urea nitrogen (BUN) or blood urea
- C-reactive protein
- Calcium
- Chloride
- Creatinine
- Creatine kinase (CK)[b]
- Gamma glutamyl transferase (GGT)[b]
- Glucose, random
- Lactate dehydrogenase (LDH)[b]
- Lipase[b]
- Magnesium
- Phosphorus
- Potassium
- Sodium
- Total protein
- TSH or free T4

Hepatitis panels – local laboratory

- Hepatitis B surface antigen (HBsAg)
- Hepatitis B core antibody (anti-HBc)
- If either HBsAg or anti-HBc positive, need to include HBV DNA (Exception: HBV DNA is required for patients with HCC)
- Hepatitis C antibody (anti-HCV)
- Hepatitis C RNA (HCV RNA)[c]

HIV test – local 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

Clinical Laboratory Tests

Abbreviations: DNA = deoxyribonucleic acid; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; 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.

[b] Performed centrally only, unless local laboratory is clinically indicated.

[c] Hepatitis C RNA will only be triggered when anti-HCV testing is positive.

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.

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

It is essential that the exact infusion start and stop times (actual clock readings) are recorded. The exact time of collection of each venous blood sample will be based on the clock used to record infusion times. Preferred time windows for each sample collection are provided in the tables in this appendix.

While best efforts should be made to draw the blood samples within the time windows provided, it is more important to ensure that the 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 the ACTUAL date and time of blood sample collection on the Requisition Form AFTER drawing the sample (that is, do not record the planned time of collection) and to record the ACTUAL infusion 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.

Phase 1a and 1b: Pharmacokinetic, Pharmacodynamic, Immunogenicity, Biomarker, Pharmacogenomic, and ECG Collection Time Points (All Cohorts)

Cycle/Day	Study Day	Sample Time (Relative to START of LY3415244 Infusion)	PK[a, b]	PD sTIM-3/ sPD-L1[a, b]	IG[a]	Whole Blood (PGx)	Biomarker Collection				ECG
							Plasma	Whole Blood[c]	Serum	Tissue	
Baseline		**≤28 days prior to C1D1** • **Mandatory fresh tumor tissue collection** • **ECG:** perform a single ECG to determine patient eligibility								X	X
Baseline		**≤7 days prior to C1D1**						X			
C1D1	1	**0 hour predose** • **PK, PD, IG, and biomarkers:** collect samples ≤2 hours prior to start of LY3415244 infusion.[b] • **ECGs:** perform triplicate ECGs at 3 time points, 5 to 15 minutes apart. Each ECG will be collected at 1-minute intervals.	X	X	X	X	X	X	X		X[d]
C1D1	1	**2 hours post START of LY3415244 infusion** • **PK/PD and biomarkers:** collect sample after LY3415244 infusion is completed.	X	X				X	X		X[d]
C1D1	1	**4 hours post START of LY3415244 infusion** • **PK/PD and biomarkers:** collect sample after LY3415244 infusion is completed.	X	X				X	X		X[d]

Phase 1a and 1b: Pharmacokinetic, Pharmacodynamic, Immunogenicity, Biomarker, Pharmacogenomic, and ECG Collection Time Points (All Cohorts)

Cycle/Day	Study Day	Sample Time (Relative to START of LY3415244 Infusion)	PK[a, b]	PD sTIM-3/ sPD-L1[a, b]	IG[a]	Whole Blood (PGx)	Biomarker Collection				ECG
							Plasma	Whole Blood[c]	Serum	Tissue	
C1D2	2	**<u>24 hours post START of LY3415244 infusion</u>** • **PK/PD and biomarkers:** collect sample. • **ECGs:** perform triplicate ECG immediately before the PK sample	X	X				X	X		X[d]
C1D4	4	**<u>72 hours post START of LY3415244 infusion</u>** • **PK/PD:** collect sample.	X	X							
C1D6	6	**<u>120 hours post START of LY3415244 infusion</u>** • **PK/PD:** collect sample.	X	X							
C1D8	8	**<u>168 hours post START of LY3415244 infusion</u>** • **PK/PD and biomarkers:** collect sample.	X	X			X	X	X		
C1D15	15	**<u>0 hour predose</u>** • **PK, PD, IG, and biomarkers:** collect samples ≤2 hours prior to start of LY3415244 infusion • **ECGs:** Perform triplicate ECGs: o Immediately prior to the start of the LY3415244 infusion. o After LY3415244 infusion is completed but before the blood draw for the PK sample	X	X	X			X	X		X[d]

Phase 1a and 1b: Pharmacokinetic, Pharmacodynamic, Immunogenicity, Biomarker, Pharmacogenomic, and ECG Collection Time Points (All Cohorts)

Cycle/Day	Study Day	Sample Time (Relative to START of LY3415244 Infusion)	PK[a, b]	PD sTIM-3/ sPD-L1[a, b]	IG[a]	Whole Blood (PGx)	Biomarker Collection				ECG
							Plasma	Whole Blood[c]	Serum	Tissue	
C1D15	15	**2 hours post start of LY3415244 infusion** • **PK/PD:** collect sample after LY3415244 infusion is completed.	X	X							
C1D15	15	**4 hours post start of LY3415244 infusion** • **PK/PD:** collect sample after LY3415244 infusion is completed.	X	X							
C1D16	16	**24 hours post start of LY3415244 infusion** • **PK/PD:** collect sample.	X	X							
C1D18	18	**72 hours post start of LY3415244 infusion** • **PK/PD:** collect sample. • **ECGs:** perform triplicate ECG immediately before the PK sample	X	X							X[d]
C1D20	20	**120 hours post start of LY3415244 infusion** • **PK/PD:** collect sample.	X	X							
C1D22	22	**168 hours post start of LY3415244 infusion** • **PK/PD and biomarkers:** collect sample.	X	X				X	X		

Phase 1a and 1b: Pharmacokinetic, Pharmacodynamic, Immunogenicity, Biomarker, Pharmacogenomic, and ECG Collection Time Points (All Cohorts)

Cycle/Day	Study Day	Sample Time (Relative to START of LY3415244 Infusion)	PK[a, b]	PD sTIM-3/ sPD-L1[a, b]	IG[a]	Whole Blood (PGx)	Biomarker Collection				ECG
							Plasma	Whole Blood[c]	Serum	Tissue	
C2D1	29	**0 hour predose** • **PK, PD, IG, and biomarkers:** collect samples ≤2 hours prior to start of LY3415244 infusion • **Mandatory tumor tissue collection:** collect within 3 days prior C2D1	X	X	X		X	X	X	X	
C2D15	43	**0 hour predose** • **Biomarkers:** collect samples ≤2 hours prior to start of LY3415244 infusion						X	X		
C2D15; then, Q2W	43, 57, 71, etc.	**0 hour predose** • **PK/PD:** collect samples ≤2 hours prior to start of LY3415244 infusion	X	X							
C3D1	57	**0 hour predose** • **IG, Biomarkers:** collect samples ≤2 hours prior to start of LY3415244 infusion. • **ECGs:** perform triplicate ECG at the following time points: o Prior to start of LY3415244 infusion o At the end of the LY3415244 infusion			X		X	X	X		X[d]
C4D1; then Q3 cycles	85, 169, 253, etc.	**0 hour predose** • **IG:** collect samples ≤ 2 hours prior to start of LY3415244			X						

Phase 1a and 1b: Pharmacokinetic, Pharmacodynamic, Immunogenicity, Biomarker, Pharmacogenomic, and ECG Collection Time Points (All Cohorts)

Cycle/Day	Study Day	Sample Time (Relative to START of LY3415244 Infusion)	PK[a, b]	PD sTIM-3/ sPD-L1[a, b]	IG[a]	Whole Blood (PGx)	Biomarker Collection				ECG
							Plasma	Whole Blood[c]	Serum	Tissue	
When/if any DLT or DLT equivalent occurs		**Anytime**	X	X	X						
Last LY3415244 dose (if known)		**0 hour predose** • **PK, PD, IG, and biomarkers:** collect samples ≤2 hours prior to start of LY3415244 infusion	X	X	X						
30 days post last LY3415244 dose		**Anytime** • **PK/PD, IG, and Biomarkers:** collect at any time	X	X	X		X				X[d]
60 days post last LY3415244 dose		**Anytime**	X	X	X						
90 days post last LY3415244 dose		**Anytime**	X	X							
Disease Progression		**Anytime** • **Biomarkers**: anytime	X	X			X			Tissue (optional)	

Phase 1a and 1b: Pharmacokinetic, Pharmacodynamic, Immunogenicity, Biomarker, Pharmacogenomic, and ECG Collection Time Points (All Cohorts)

Abbreviations: ADA = antidrug antibody; C = Cycle; D = Day; DLT = dose-limiting toxicity; ECG = electrocardiogram; IG = immunogenicity; IRR = infusion-related reaction; PD = pharmacodynamics; PGx = pharmacogenomics; PK = pharmacokinetics; Q = every; sPD-L1 = soluble programmed death ligand 1; sTIM-3 = soluble T-cell immunoglobulin and mucin-domain-containing molecule-3; W = week.

[a] In the event of an IRR, blood samples will be collected for both PK, and IG 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. As part of the IG analysis following IRR, exploratory hypersensitivity samples may be analyzed for markers of basophil/mast cell activation (e.g., tryptase), immune complex formation (e.g., C3 levels) and cytokine release (e.g., IL-6) as appropriate for the clinical presentation. If treatment-emergent ADAs are identified in the follow-up period, the patient will continue to be followed until ADA levels return to 2-fold above baseline (60-day posttreatment sample, every 3 months over the first year and then yearly thereafter until return to 2-fold above baseline unless deemed clinically unnecessary after 1 year), provided the patient has not been lost to follow up or has withdrawn consent. Since LY3415244 plasma concentration is expected to be below the detection limit of the PK assay, no PK sample will be collected beyond 6 months after the last dose of LY3415244.

[b] The 2-, 4-, 24-, 72-, 120-, and 168-hour samples are **relative to the START** of the corresponding dosing event. These samples must be collected after completion of the infusion. Allowable sampling window for pre-dose C1D1 is -8 hours. Allowable sampling windows for 2-, 4-, 24-, 72-, 120-, and 168-hour are ±30 minutes, ±60 minutes, ±8 hours, ±24 hours, ± 24 hours, and ± 48 hours, respectively. If LY3415244 infusion need to be increased up to 2 hours the allowable sampling windows for the 2-hour sample is increased to +60 minutes. Samples at 30, 60, and 90 days post last LY3415244 dose have allowable sampling windows of ±7 days. However, it is essential that the exact infusion start and stop times (actual clock readings) are recorded.

[c] For exploratory research, including but not limited to immunophenotyping.

[d] Triplicate ECGs should be conducted immediately before the PK sample and after the patient has been supine for 5 minutes; collect at a minimum of 1-minute intervals, with all 3 replicate ECGs completed within 5 to 15 minutes.

Appendix 5. 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[a]:**
Aspartate aminotransferase (AST)	Anti-nuclear antibody
Gamma-glutamyl transferase (GGT)	Anti-smooth muscle antibody
Creatine phosphokinase (CPK)	Anti actin antibody

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

[a] Assayed by Lilly-designated laboratory.

[b] Neutrophils reported manually and by automated differential hematology instruments include both segmented and band forms.

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

Appendix 6. Creatinine Clearance Formula

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

For serum creatinine concentration in mg/dL:

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

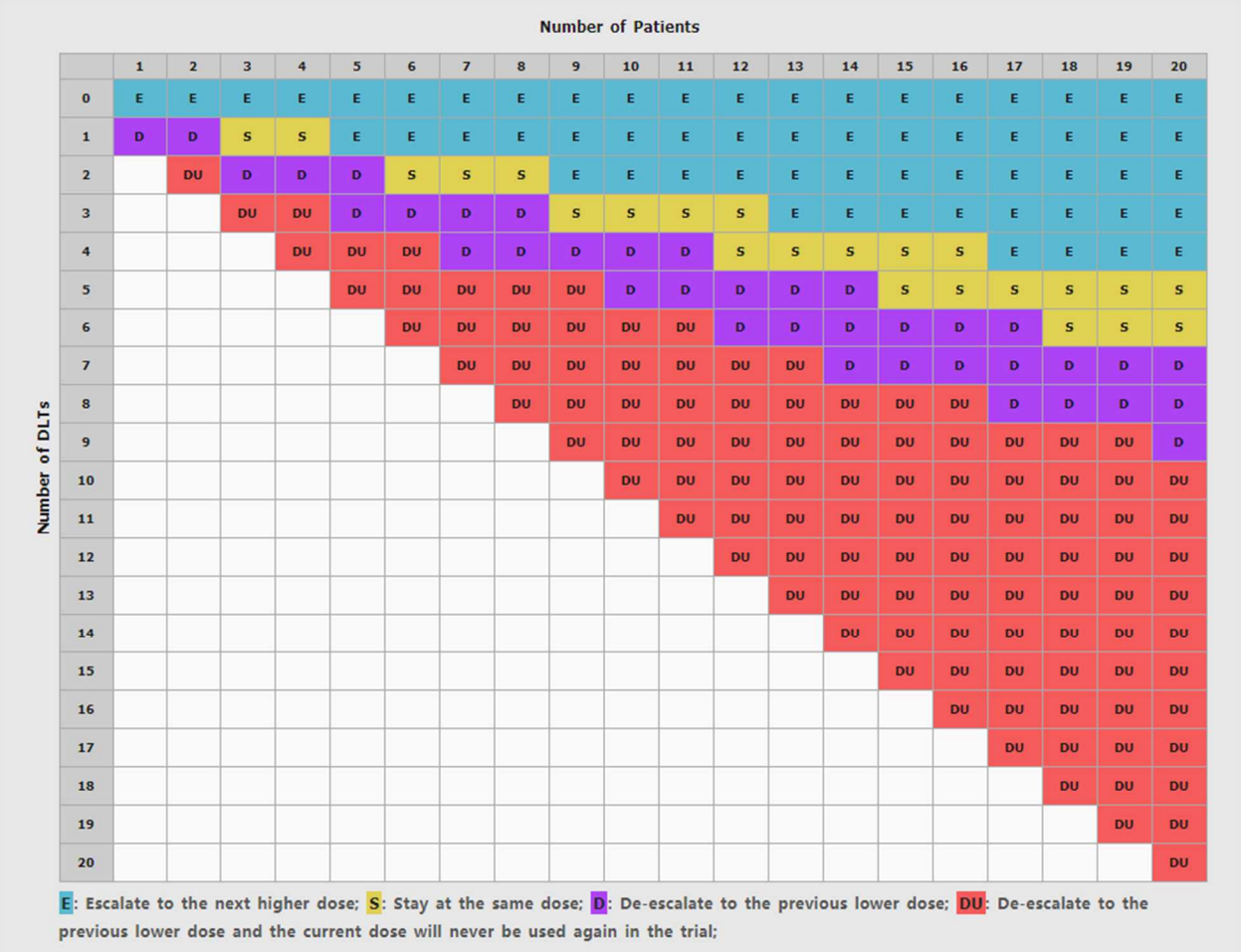
For serum creatinine concentration in μmol/L:

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

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

Reference: Cockcroft and Gault 1976.

Appendix 7. Dose-Finding Spreadsheet of the Modified Toxicity Probability Interval 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 [WWW].

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 8. 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 9. Protocol Amendment J1C-MC-JZDA(a) Summary

Overview

Protocol J1C-MC-JZDA, A Phase 1a/1b Study of LY3415244, a Bispecific Antibody in Patients with Advanced Solid Tumors has been amended. The new protocol is indicated by Amendment (a) 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:

- Section 1. – Updated number of patients; updated table to reflect additional dose levels; clarified how RP2D is determined and the circumstances under which it may be modified
- Section 2. – Table JZDA.2.1. clarified that instructions apply only for cycle-related procedures; increased postinfusion observation to 4 hours, per FDA request; included modified RECIST guidelines to instructions for tumor imaging/assessment of mesothelioma patients; Table JZDA.2.3. updated continued access follow-up to 90 days in footnote a
- Section 3.3. – "in vivo" to "in vitro"
- Section 4. – Table JZDA.4.1. updated to include AUC and PK
- Section 5.1. – Clarified how RP2D is determined and the circumstances under which it may be modified; Figure JZDA.5.1. updated to reflect additional dose levels
- Section 5.1.1. – Clarified dose escalation phase for each cohor in the study design; corrected typo ("PLoQK" to "PK"); clarified the timing of full PK review; updated reference and clarified how RP2D is determined, per PMDA request
- Section 5.2. – Updated cohorts and number of patients to reflect new study design
- CCI [redacted]
- Section 6.1. – Updated hematologic tests to include aPTT in lieu of PT and PTT in criterion [9]; updated discontinuation period for biologic agents to at least 21 days in criterion [11]; updated requirement for duration of effective contraceptive use during study treatment in criterion [13]
- Section 6.2. – Added examples of pulmonary toxicity in criterion [17], per PMDA request; updated examples of clinically significant ECG abnormalities in criterion [17]; clarified breastfeeding exclusion criteria in criterion [20], per PMDA request
- Section 6.4. – Clarified when an additional laboratory test is needed
- Section 7.1. – Updated Table JZDA.7.1. to reflect additional dose levels
- Section 7.2.2.2. – Updated definition of DLT, per FDA request; updated hematologic toxicity in Table JZDA.7.2. per PMDA request
- Section 7.2.2.2.1. – Provided additional justification for Grade 3 or greater toxicities that are to not be considered DLT, per FDA request

- Section 7.4. – Updated postinfusion observation period to 4 hours; corrected table referenced in this section; updated Table JZDA.7.3.; included additional examples of local guidelines
- Section 7.6.1.1. – Included review of adverse events from non-evaluable patients, per PMDA request
- Section 7.7. – Updated "Table JZDA.7.7." to "Table JZDA.7.5."
- Section 9.1. – Elaborated on pleural measurement requirements
- Section 9.1.1.2. – Provided examples of situations requiring urgent medical intervention, per FDA request
- Section 9.1.1.3. – Additional section to outline criteria required to receive treatment during confirmatory scan, per FDA request
- Section 9.4.1. – Clarified on ECG data analyses
- Section 9.4.2. – Clarification on Phase 1b safety stopping rule
- Section 9.4.2.1. – Clarified types of hepatic safety data to be collected
- Section 9.8.1. – Included statistical justification for biomarker sample size
- Section 10.3.4. – Addressed need for exploring antitumor activity in interim analyses
- Section 11. – Updated references list
- Appendix 2. – Removed PTT from coagulation tests; corrected footnote reference for lipase; updated "T4" to "free T4" for consistency
- Appendix 4. – Removed infusion parameters from data to be recorded; updated table to clarify data to be collected on the respective study days; added footnote to ECG for "30 days post last LY3415244 dose" to indicate need for triplicate
- Appendix 8. – Addition to define woman of childbearing potential, per PMDA request
- Minor editorial changes were incorporated that may not be included in this summary

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of double underscore.

Section 1. Synopsis

Number of Patients:

Approximately ~~15-21~~27 to 30 patients will be enrolled in the Phase 1a portion of the study; approximately 80 patients will be enrolled in the Phase 1b portion of the study.

Treatment Arms and Duration:

Phase 1a (dose escalation): Patients will receive LY3415244 monotherapy, as shown in the following table:

	Cohort	Dose of LY3415244	Route	Dosing Schedule
Phase 1a: Dose Escalation	A1	3 mg ~~(C1D1 only)~~ ~~10 mg (C1D15 and subsequent doses)~~	IV	D1 and D15 of each 28-day cycle (Q2W)
	A2	10 mg		
	A3	30 mg		
	~~A2~~A4	30 mg (C1D1 only) 70 mg (C1D15 and subsequent doses)		
	~~A3~~A5	200 mg		
	~~A4~~A6	600 mg		
	~~A5~~A7	1000 mg		
	~~A6~~A8	Optional, TBD[a]		

Abbreviations: C = cycle; D = day; IV = intravenously; Q2W = every 2 weeks; PK/PD = pharmacokinetic/pharmacodynamic; RP2D = recommended Phase 2 dose; TBD = to be determined.

a Enrollment of Cohort ~~A6~~A8 is optional. It will be initiated if PK/PD analyses suggest that another dose level may be appropriate. The dose will not exceed 1500 mg.

Patients may continue to receive study treatment for a maximum of 12 months or until a criterion for discontinuation is met.

Phase 1b (dose expansion): Patients in each of 4 expansion cohorts will receive the recommended Phase 2 dose (RP2D) of LY3415244 intravenously at a schedule to be determined at Phase 1a, until a criterion for discontinuation is met.

~~The combined data from Phase 1a and Phase 1b will be analyzed to confirm or modify the RP2D.~~The data from Phase 1a will determine the RP2D but the RP2D dose may be modified in Phase 1b if supported by additional safety and/or PK/PD data.

Section 2. Schedule of Activities

Table JZDA.2.1. Baseline and On-Study Treatment Schedule of Activities

	Baseline (Day Relative to C1D1)		Cycle 1		Cycle 2		Cycle 3		Cycle 4-n		Instructions: Perform all cycle-related procedures on the specified day (±3 days), unless stated otherwise in this schedule of activities. See Section 7 regarding administration of study treatment.
	≤28	≤7	D1	D15	D1	D15	D1	D15	D1	D15	
…	…	…	…	…	…	…	…	…	…	…	…

Vital signs	X		X	X	X	X	X	X	X	X	**Measure vital signs (temperature, blood pressure, pulse rate, and respiration rate) as follows (±5 minutes):**
											• **In Cycles 1 through 3:**
											  • up to 15 minutes prior to each LY3415244 infusion
											  • every 15 minutes during each LY3415244 infusion
											  • at the end of each LY3415244 infusion
											
											A ~~1~~4-hour postinfusion observation period is required after the end of each LY3415244 infusion in Cycles 1 through 3.
											  • every 30 minutes during the ~~1~~4-hour postinfusion 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 LY3415244 infusion
											  • at least once during each LY3415244 infusion
											at the end of each LY3415244 infusion

Baseline and On-Study Treatment Schedule of Activities

	Baseline (Day Relative to C1D1)		Cycle 1		Cycle 2		Cycle 3		Cycle 4-n		Instructions: Perform all cycle-related procedures on the specified day (±3 days), unless stated otherwise in this schedule of activities. See Section 7 regarding administration of study treatment.
	≤28	≤7	D1	D15	D1	D15	D1	D15	D1	D15	
…	…	…	…	…	…	…	…	…	…		…
Tumor imaging/ assessment	X						X		See Note		• Perform locally according to RECIST 1.1, with the addition of modified RECIST for mesothelioma patients, 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 Q6-12W.
…	…	…	…	…	…	…	…	…	…	…	…
Administer LY3415244			X	X	X	X	X	X	X	X	LY3415244 will be administered as an IV infusion over approximately 60 minutes, depending on dose level (doses ≤70 mg may require bolus IV injection administration over 5 to 10 minutes). In Cycles 1 to 3, the LY3415244 infusion will be followed by a ~~1~~4-hour observation period.

Table JZDA.2.3. Continued Access Schedule of Activities

…

Abbreviations: ADAs = antidrug antibodies; AE = adverse event; D = day; IG = immunogenicity; IRR = infusion-related reaction; PK = pharmacokinetics; Q = every; W = week.

[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~~90 days. No follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

CCI

[redacted]

Table JZDA.4.1. Objectives and Endpoints

...

Abbreviations: AUC = area under time-concentration 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; PFS = progression-free survival; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TEADA = Treatment-emergent anti-drug antibodies; TTR = time-to-response.

Section 5.1. Overall Design

...

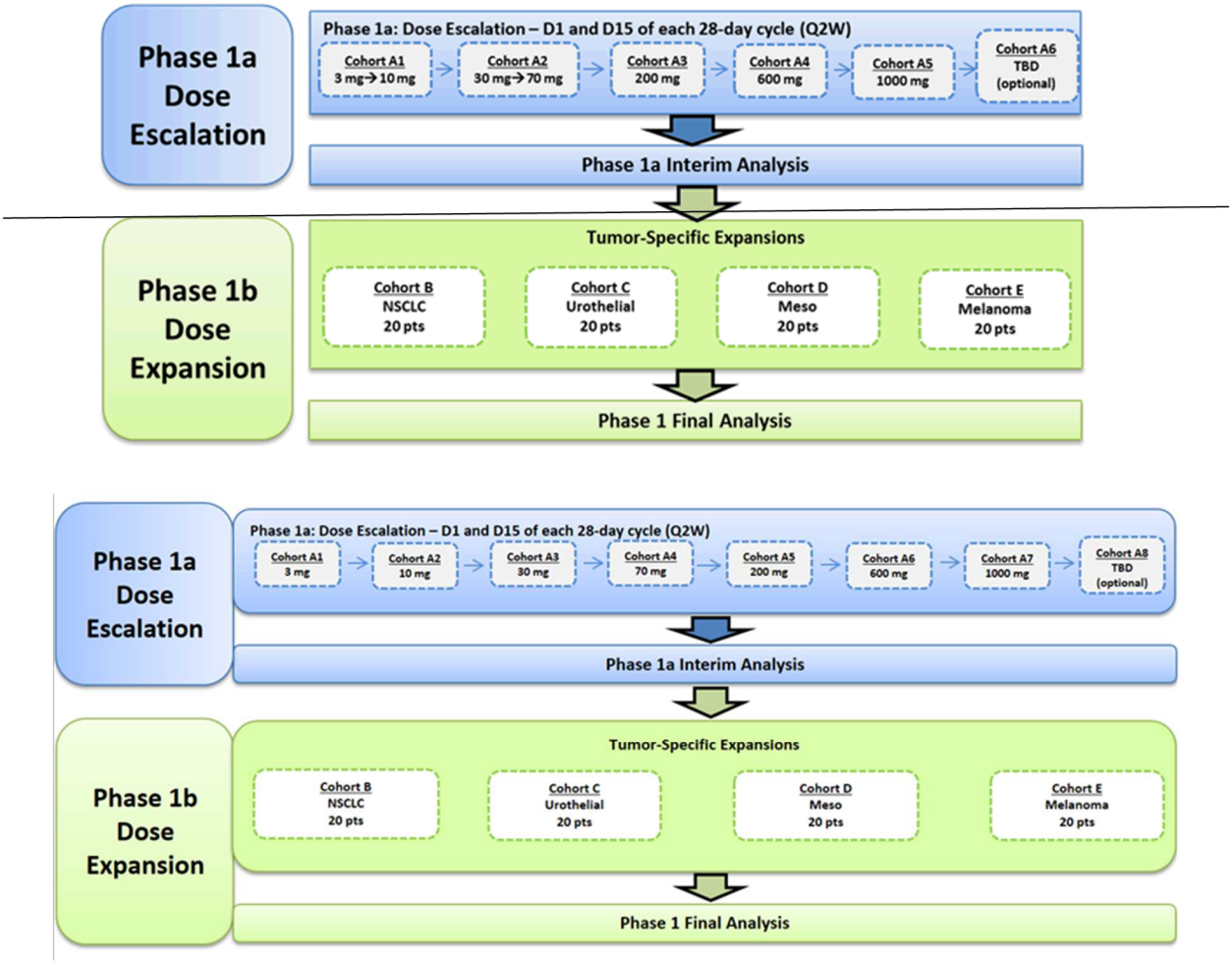
Phase 1a (dose escalation) will assess the safety and tolerability of LY3415244, administered as monotherapy in patients with advanced solid tumors. The RP2D to be tested in Phase 1b will be identified in Phase 1a, as described in Section 7.2.2. Late toxicities of available data up to 90 days will be considered for RP2D determination. Dose escalation of LY3415244 will be driven by a mTPI-2 method (Guo et al. 2016 [WWW]; see Section 7.2.2.1).

Phase 1b (dose expansion) will assess the safety and tolerability of LY3415244, administered as monotherapy in 4 expansion cohorts of patients with selected advanced solid tumor types of non-small cell lung cancer (NSCLC), urothelial cancer, mesothelioma, and melanoma.

Patients in both phases will receive study treatment for a maximum of 12 months (see Section 8.1).

The data from Phase1 a will determine the RP2D but the RP2D dose may be modified in Phase 1b if supported by additional safety and/or PK/PD data. ~~The combined data from Phase 1a and Phase 1b will be analyzed to confirm or modify the RP2D.~~ For the primary objective of establishing safety, patients will be followed for at least 24 weeks after the last patient is enrolled. For the secondary objective of progression-free survival (PFS) and the tertiary objective of overall survival (OS), patients will be followed until death or until study completion (defined in Section 5.3), whichever occurs first.

Figure JZDA.5.1 illustrates the study design.



Abbreviations: D = day; Meso = mesothelioma; mg = milligrams; NSCLC = non-small-cell lung cancer; pts = patients; Q = every; TBD = to be determined; W = week.
Note: Cohort ~~A6~~A8 is optional and may be explored at a dose not exceeding 1500 mg of LY3415244.

Figure JZDA.5.1. Illustration of study design.

Section 5.1.1. Dose Escalation Phase

~~The first patient will be enrolled in~~ Patients in Cohorts A1, A2, A3, A4, A5, A6, A7, and A8, respectively, will receive doses of 3 mg, 10 mg, 70 mg, 200 mg, 600 mg, 1000 mg, and a dose not exceeding 1500 mg according to an every-2-weeks (Q2W) dosing regimen, provided safety is established in the preceding cohorts ~~and treated according to an every-2-weeks (Q2W) dosing regimen~~ (see Table JZDA 7.1). ~~Patients in Cohort A1 will receive a 3-mg dose on Cycle 1 Day 1 (C1D1); the dose will increase to 10 mg beginning at Cycle 1 Day 15 (C1D15). However, if any~~

~~of the 3 patients in Cohort A1 experiences a clinically significant Grade ≥2 AE that is possibly related to study drug, all patients enrolled to Cohort A1 will remain on the 3 mg dose (unless they have already escalated to the 10 mg dose). If per the modified toxicity probability interval 2 (mTPI 2) method, the 3 mg dose level is cleared, a 10 mg dose level will be initiated and there will be no further intra-patient dosing (that is, the 30- and 70 mg dose levels will be explored in separate 30 mg and 70 mg cohorts, rather than an intra-patient dose escalation cohort).~~

After the first patient in Cohort A1 receives the first dose of LY3415244, there will be a delay of 1 week to allow for safety observation before the second and third patients receive LY3415244. There will be no additional delays for subsequent patients.

~~Patients in Cohort A2 will receive a 30 mg dose on C1D1; the dose will increase to 70 mg beginning at C1D15. However, if any of the patients in Cohort A2 experiences a clinically significant Grade ≥2 AE that is possibly related to study drug, patients enrolled to Cohort A2 will remain on the 30 mg dose (unless they have already escalated to the 70 mg dose). If per the mTPI 2 method, the 30 mg dose level is cleared, the 70 mg dose level would then be explored in a separate cohort.~~

CCI

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A 1-cycle (28 days) dose-limiting toxicity (DLT) observation period will apply to all cohorts in Phase 1a.

Section 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 LY3415244 RP2D.

- **Phase 1a:** Total enrollment will be determined by the incidence of DLTs.
  - Cohorts A1 through ~~A6~~A8: approximately ~~21~~27 patients (minimum of 3 patients per cohort) will be enrolled.

CCI [redacted]

...

CCI [redacted]

[redacted]

...

CCI [redacted]

Section 6.1. Inclusion Criteria

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

…

[9] Have adequate organ function as defined in the table below:

System	Laboratory Value
Hematologic	
…	…
~~PT or PTT~~ aPTT	≤1.5 × ULN

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; ULN = upper limit of normal; ~~PT = prothrombin time; PTT= activated partial thromboplastin time;~~ T4 = thyroxine; TSH= thyroid-stimulating hormone

…

[11] Have discontinued previous treatments for cancer and recovered from the acute effects of therapy. Patients must have discontinued from previous treatments, as shown in the table below:

Previous Treatment	Length of Time Prior to First Dose of Study Treatment
…	…
Biologic agents (including immunotherapy)	≥~~14~~21 days

…

[13] Men with partners of childbearing potential or women with childbearing potential must agree to use a highly effective contraceptive method during study treatment and for at least ~~15 weeks~~6 months following the last dose of study drug (eg, intrauterine device, birth control pills, or barrier method). If condoms are used as a barrier contraceptive, a spermicidal agent should be added as double barrier protection.

Section 6.2. Exclusion Criteria

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

…

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

…

i. evidence of (i) interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity (for example, interstitial lung disease or radiation pneumonitis); (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 including 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 ECG abnormalities that, in the judgment of the investigator, are clinically significant (for example, ~~symptomatic or sustained atrial or ventricular arrhythmias; second or third degree atrioventricular block; bundle branch blocks; ventricular hypertrophy~~ arrthythmias requiring treatment; recent myocardial infarction within the last 3 months; or mean QTc ≥470 ms calculated using Fridericia's correction and confirmed by triplicate ECG)

…

[20] Are pregnant, ~~breastfeeding,~~ or planning to become pregnant during the study or within 6 months ~~after completing the study~~following the last dose of LY3415244. Plan to be breastfeeding from C1D1 of study or within 6 months following the last dose of LY3415244.

Section 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~~ an additional laboratory test must be repeated again to confirm eligibility.

Section 7.1. Treatment Administered

LY3415244 will be administered as an IV infusion over approximately 60 minutes, depending on dose level (doses ≤70 mg may require bolus IV infusion). In Cycles 1 through 3, the LY3415244 infusion will be followed by a ~~1~~4-hour observation period.

Table JZDA 7.1 shows the treatment regimen.

Table JZDA.7.1. Treatment Regimen

	Cohort	Dose of LY3415244	Route	Dosing Schedule
Phase 1a: Dose Escalation	A1	3 mg ~~(C1D1 only)~~ ~~10 mg (C1D15 and subsequent doses)~~	IV	D1 and D15 of each 28-day cycle (Q2W)
	A2	10 mg		
	~~A2~~A3	30 mg ~~(C1D1 only)~~ ~~70 mg (C1D15 and subsequent doses)~~		
	A4	70 mg		
	~~A3~~A5	200 mg		
	~~A4~~A6	600 mg		
	~~A5~~A7	1000 mg		
	~~A6~~A8	Optional: TBD[a]		

Abbreviations: C = cycle; D = day; IV = intravenously; mg = milligrams; Q2W = every 2 weeks; RP2D = recommended Phase 2 dose; TBD = to be determined.

a Enrollment of Cohort ~~A6~~A8 is optional. It will be initiated if Cohort ~~A5~~A7 is tolerated and PK/PD analyses suggest that another dose may be appropriate. The dose will not exceed 1500 mg.

Section 7.2.2.2. Dose-Limiting Toxicity Determination

~~A DLT is defined as any of the events listed in Table JZDA.7.2, if both of the following criteria are met:~~

- ~~the event occurs during the DLT observation period (Cycle 1) in Phase 1a, and~~
- ~~the event is clinically significant and definitely, probably, or possibly related to LY3415244, in the opinion of the investigator.~~

A DLT is defined as any of the events listed in Table JZDA.7.2, if the event occurs during the DLT observation period (Cycle 1) in Phase 1a, and toxicity that is not clearly and directly related to the primary disease or another etiology.

All AEs of Grade 3 or higher that occur during the DLT observation period will be included in the DLT definition except for toxicities with a clear, alternative explanation, including the exceptions listed in Section 7.2.2.2.1.

Patients who experience a DLT in Cycle 1 will be discontinued from study treatment.

Table JZDA.7.2. 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 7.2.2.2.1.

Section 7.2.2.2.1. Events That Are Not Considered to Be DLTs

The following events listed in this section will not be considered to be DLTs:

- ~~Toxicity~~ Adverse event that is clearly and directly related to the primary disease or to another etiology
- Known class effects that have been observed with immunotherapy:
    - Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency), if both the following criteria are met:
        - the disorder is manageable with or without systemic corticosteroid therapy and/or hormone replacement therapy, and
        - the patient is asymptomatic
    - Grade 3 inflammatory reaction attributed to a local antitumor response (such as, inflammatory reaction in the lymph nodes or at sites of metastatic disease)
    - Any grade vitiligo or alopecia
    - Grade 3 or 4 lymphopenia

- First occurrence of Grade 3 infusion-related reaction (IRR) during infusion of LY3415244, 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.

- 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 with treatment

  In order to exclude potential detection of electrolyte abnormalities that cannot be associated with clinical signs of symptoms, or laboratory test error.
- ~~Grade 3 or 4 lymphopenia~~
- In order to exclude potential detection of electrolyte abnormalities that cannot be associated with clinical signs of symptoms, or laboratory test error. Isolated Grade 3 electrolyte abnormalities meeting both of the following criteria:
    - ~~is~~ not associated with clinical signs or symptoms, and
    - ~~is~~ reversed with appropriate maximal medical intervention within 2 days

It should be recognized that for patients who have received prior immune therapy, including check point 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. ~~Potential DLTs recognized to be irAEs will not be evaluable for the purposes of dose selection.~~

Section 7.4. Dose Modification

…

A ~~1~~4-hour observation period is required after the administration of LY3415244 in Cycles 1 to 3. During observation period, patients treated with LY3415244 should be closely monitored for

signs and symptoms indicative of an infusion-related reaction by medical staff from the start of the infusion until ~~1 hour~~4 hours after the end of the infusion, in an area where emergency medical resuscitation equipment and other agents (epinephrine prednisolone equivalents, etc.) are available. LY3415244 infusion-related reactions will be defined according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 definition of IRRs.

Table ~~JZDA.7.4~~JZDA.7.3 presents instructions for management of infusion-related reactions associated with LY3415244.

Table JZDA.7.3. Management of Infusion-Related Reactions

Grade	Management	
…	…	…
3 or 4		Immediately and permanently discontinue study treatment. Patients who experience a Grade 3 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 LY3415244 infusion with diphenhydramine (or other antihistamine), acetaminophen (or other antipyretic), steroids etc., at the discretion of treating physician. If symptoms reappear, immediately and permanently discontinue study treatment.

Table JZDA.7.4 presents guidance for irAE management (including use of corticosteroids) and criteria for dose delays and discontinuations if the patient experiences a potential irAE considered at least possibly related to LY3415244.

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. Guidelines used by ~~L~~local standards such as, but not limited to Haanen and colleagues (2017), Puzanov and colleagues (2017), or Brahmer and colleagues (2018), ~~may~~ supersede the guidelines provided in Table JZDA.7.4 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.

Section 7.6.1.1. DLT-Evaluable Patients in Phase 1a

…

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. Adverse events from DLT non-evaluable patients will also be reviewed throughout the dose escalation process in Phase 1a.

Section 7.7 Concomitant Therapy

Table JZDA.~~7.7~~7.5 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 postdiscontinuation 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.

Table JZDA.~~7.7~~7.5. Concomitant Medication Guidelines

Section 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. Modified RECIST will be applied for patients with pleural mesothelioma whereby tumor thickness (perpendicular to chest wall or mediastinum) would be measured at 2 positions on 3 separate levels on transverse cuts of CT scan (Byrne 2004).

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

For Study JZDA, 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 (see Section 9.1.1.3).

"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, rapid disease progression or threat to vital organs or critical anatomical sites, such as central nervous system metastasis, respiratory failure due to tumor compression, or spinal cord compression).

Section 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

Section 9.4.1. Other Safety Measures

…

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.~~

Section 9.4.2. Safety Monitoring

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

For Phase 1a, safety data will be reviewed on a cohort by cohort basis. For Phase 1b, a safety review will be performed when every 10 patients have been treated for approximately 1 cycle for the first 20 patients enrolled into Phase 1b across all expansion cohorts, then every 3 months after the last patient enters study treatment (LPET) for 1 year, and then at least once a year afterward. The purpose of this Phase 1b safety review is to evaluate the safety and tolerability for each expansion cohort and determine if a dose-limiting equivalent toxicity (DLET) has been observed. For the first 20 patients enrolled into Phase1b, based on mTPI-2 method, if 7 or more DLETs are observed, accrual will be temporarily paused, and the available data from Phase 1a and 1b will be analyzed to potentially modify the RP2D, or the study; considerations for stopping recruitment should be given after discussion with investigator and sponsor.

Section 9.4.2.1. Special Hepatic Safety Data Collection

Hepatic data, such as lab tests ~~should be collected~~ (see Appendix 5), liver related signs and symptoms, results from hepatic monitoring procedures, and liver biopsy assessment if available, should be collected in the event that a patient meets one of the following conditions during the course of the study:

Section 9.8.1. Tissue Samples for Biomarker Research

…

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 for meaningful clinical data; paired biopsies are planned to be tested from baseline over time for changes in molecular markers to document any potential immunomodulatory activity of treatment with LY3415244 and should be performed if clinically feasible. A minimum paired sample size of 19 in total is expected to provide adequate precision to estimate the immune response. Samples will be examined for biomarkers as described in Section 9.8, including but not limited to, TIM-3 and PD-L1 expression by immunohistochemistry.

Section 10.3.4. Interim Analyses

…

An interim ~~analyses~~analysis will be performed after all patients in Phase 1a have completed the DLT evaluation period. The Lilly study team will evaluate the data from the interim safety and PK/PD analyses before opening the dose expansion cohorts in Phase 1b. In these interim analyses, early antitumor activity may also be explored.

Section 11. References

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Appendix 2. Clinical Laboratory Tests

Coagulation – local laboratory	
Activated partial thromboplastin time (aPTT) ~~or partial thromboplastin time (PTT)~~	
International normalized ratio (INR) or prothrombin time (PT)	
Clinical chemistry – local and central laboratory	
Serum concentrations of:	
• Alanine aminotransferase (ALT) • Albumin • Alpha-fetoprotein (AFP; required only for patients with HCC) • Alkaline phosphatase • Aspartate aminotransferase (AST) • Amylase[b] • Bicarbonate • Bilirubin, direct • Bilirubin, total • Blood urea nitrogen (BUN) or blood urea • C-reactive protein • Calcium	• Chloride • Creatinine • Creatine kinase (CK)[b] • Gamma glutamyl transferase (GGT)[b] • Glucose, random • Lactate dehydrogenase (LDH)[b] • ~~Lipase~~[e] Lipase[b] • Magnesium • Phosphorus • Potassium • Sodium • Total protein • TSH or free T4

Appendix 4. Sampling Schedule

It is essential that the exact infusion start and stop times (actual clock readings)~~, as well as infusion parameters (such as, type of infusion pump, flow rate settings)~~ are recorded. The exact time of collection of each venous blood sample will be based on the clock used to record infusion times. Preferred time windows for each sample collection are provided in the tables in this appendix.

…

Phase 1a and 1b: Pharmacokinetic, Pharmacodynamic, Immunogenicity, Biomarker, Pharmacogenomic, and ECG Collection Time Points (All Cohorts)

Cycle/Day	Study Day	Sample Time (Relative to START of LY3415244 Infusion)	PK[a, b]	PD sTIM-3/ sPD-L1[a, b]	IG[a]	Whole Blood (PGx)	Biomarker Collection				ECG
							Plasma	Whole Blood[c]	Serum	Tissue	
…	…	…	…	…	…	…	…	…	…	…	…
C1D2	2	**24 hours post START of LY3415244 infusion** • **PK/PD and biomarkers:** collect sample. • **ECGs:** perform triplicate ECG immediately before the PK sample	X	X				X	X		X[d]
C1D4	4	**72 hours post START of LY3415244 infusion** • **PK/PD:** collect sample.	X	X							
C1D6	6	**120 hours post START of LY3415244 infusion** • **PK/PD:** collect sample.	X	X							
C1D8	8	**168 hours post START of LY3415244 infusion** • **PK/PD and biomarkers:** collect sample.	X	X			X	X	X		
C1D15	15	**0 hour predose** • **PK, PD, IG, and biomarkers:** collect samples ≤2 hours prior to start of LY3415244 infusion • **ECGs:** Perform triplicate ECGs: o Immediately prior to the start of the LY3415244 infusion. o After LY3415244 infusion is completed but before the blood draw for the PK sample	X	X	X			X	X		X[d]

Phase 1a and 1b: Pharmacokinetic, Pharmacodynamic, Immunogenicity, Biomarker, Pharmacogenomic, and ECG Collection Time Points (All Cohorts)

Cycle/Day	Study Day	Sample Time (Relative to START of LY3415244 Infusion)	PK[a, b]	PD sTIM-3/ sPD-L1[a, b]	IG[a]	Whole Blood (PGx)	Biomarker Collection				ECG
							Plasma	Whole Blood[c]	Serum	Tissue	
C1D15	15	**2 hours post start of LY3415244 infusion** • **PK/PD:** collect sample after LY3415244 infusion is completed. • ~~**ECGs: Perform triplicate ECGs: Immediately prior to the start of the LY3415244 infusion.**~~ • ~~**After LY3415244 infusion is completed but before the blood draw for the PK sample**~~	X	X							~~X~~[d]
…	…	…	…	…	…						
C1D16	16	**24 hours post start of LY3415244 infusion** • **PK/PD:** collect sample.	X	X							
C1D18	18	**72 hours post start of LY3415244 infusion** • **PK/PD:** collect sample. • **ECGs:** perform triplicate ECG immediately before the PK sample	X	X							X[d]
C1D20	20	**120 hours post start of LY3415244 infusion** • **PK/PD:** collect sample.	X	X							
C1D22	22	**168 hours post start of LY3415244 infusion** • **PK/PD and biomarkers:** collect sample.	X	X				X	X		

Phase 1a and 1b: Pharmacokinetic, Pharmacodynamic, Immunogenicity, Biomarker, Pharmacogenomic, and ECG Collection Time Points (All Cohorts)

Cycle/Day	Study Day	Sample Time (Relative to START of LY3415244 Infusion)	PK[a, b]	PD sTIM-3/ sPD-L1[a, b]	IG[a]	Whole Blood (PGx)	Biomarker Collection				ECG
							Plasma	Whole Blood[c]	Serum	Tissue	
…	…	…	…		…	…	…	…	…	…	…
C4D1; then Q3 cycles	85, ~~106,~~ 169, ~~127,~~ 253, etc.	**0 hour predose** • **IG:** collect samples ≤ 2 hours prior to start of LY3415244 ~~infusion~~			X						
…	…	…	…	…	…	…					
30 days post last LY341524 4 dose		**Anytime** • **PK/PD and Biomarkers:** collect at any time	X	X	X		X				X[d]

Abbreviations: ADA = antidrug antibody; C = Cycle; D = Day; DLT = dose-limiting toxicity; ECG = electrocardiogram; IG = immunogenicity; IRR = infusion-related reaction; PD = pharmacodynamics; PGx = pharmacogenomics; PK = pharmacokinetics; Q = every; sPD-L1 = soluble programmed death ligand 1; sTIM-3 = soluble T-cell immunoglobulin and mucin-domain-containing molecule-3; W = week.

a …

b The 2-, 4-, 24-, 72-, 120-, and 168-hour samples are **relative to the START** of the corresponding dosing event. These samples must be collected after completion of the infusion. Allowable sampling windows for 2-, 4-, 24-, 72-, 120-, and 168-hour are ±30 minutes, ±60 minutes, ±8 hours, ± ~~2~~24 hours, ± 24 hours, and ± ~~24~~48 hours, respectively. Samples at 30, 60, and 90 days post last LY3415244 dose have allowable sampling windows of ±7 days. However, it is essential that the exact infusion start and stop times (actual clock readings)~~, as well as infusion parameters (such as, type of infusion pump, flow rate settings)~~ are recorded.

c …

d Triplicate ECGs should be conducted after the patient has been supine for 5 minutes; collect at a minimum of 1-minute intervals, with all 3 replicate ECGs completed within 5 to 15 minutes.

Appendix 8. 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 J1C-MC-JZDA(b) Summary

Overview

Protocol J1C-MC-JZDA, A Phase 1a/1b Study of LY3415244, a Bispecific Antibody in Patients with 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:

- Section 1. – Added clarification in the Rationale section
- Section 2. – Removed redundant vital signs from the "Physical examination" instructions in Table JZDA.2.1
- Section 5.2. – Clarified that during the Phase 1a DLT assessment period, a maximum of 10 patients per dose, may be enrolled
- CCI
- Section 6.1. – Clarified language in criterion [4]; deleted thyroid restriction in criterion [9] in order to allow patients with manageable thyroid stimulating hormone in the study; and clarified language in criterion [13] regarding effective contraceptive methods of birth control, per Belgium competent authority request
- Section 6.4. – Clarified instructions for repeat laboratory tests during screening
- Section 7.4. – Updated dose modification guidelines and AE management in Table JZDA.7.4 for Endocrine and Hepatobiliary SOCs
- Section 9.8.1. – Added text to clarify that biopsies should not be taken from areas that have been previously irradiated, unless the previously irradiated area has progressed
- Appendix 1. – Added text for clarification for highly effective methods of contraception
- Appendix 4. – Clarified sampling schedule for IG at "C2D15; then, Q2W"; "C3D1"; and "30 days post last LY3415244 dose" and clarified sampling windows for PK and pharmacodynamics sample collection in footnote "b" and timing of ECGs in footnote "d"
- Minor editorial changes were incorporated that may not be included in this summary

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of double underscore.

Section 1. Synopsis

Rationale:

T-cell immunoglobulin and mucin-domain-containing molecule-3 (TIM-3), a co-inhibitory molecule, is expressed on T cells during activation and has been identified as a cell surface marker for "exhausted" T cells following chronic exposure to antigen (Wherry 2011) and marks the most exhausted or dysfunctional populations of T cells in the tumor microenvironment and during chronic viral infection. TIM-3 is often co-expressed with PD-1 and cytotoxic T-lymphocyte antigen 4 on tumor-antigen-specific T cells in cancer patients. Blocking TIM-3 provides the opportunity to enhance antitumor T-cell immunity, much like targeting the PD-1 axis, and provides the opportunity to combine anti-TIM-3 therapy with clinically validated checkpoint inhibitor antibodies such as PD-1 or PD-L1.

Section 2. Schedule of Activities

Table JZDA.2.1. Baseline and On-Study Treatment Schedule of Activities

	Baseline (Day Relative to C1D1)		Cycle 1		Cycle 2		Cycle 3		Cycle 4–n		Instructions: Perform all cycle-related procedures on the specified day (±3 days), unless stated otherwise in this schedule of activities. See Section 7 regarding administration of study treatment.
	≤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 throughout the study
Physical examination	X		X		X		X		X		• At baseline, perform full examination including recent medical history, height~~,~~ and weight ~~and vital signs (temperature, blood pressure, pulse rate, and respiration rate)~~ • Thereafter, perform a focused examination, including weight and vital signs • For vital sign measurements, see additional instructions below

Section 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 LY3415244 RP2D.

- **Phase 1a:** Total enrollment will be determined by the incidence of DLTs.
  - Cohorts A1 through A8: approximately 27 patients (minimum of 3 patients per cohort) will be enrolled. During Phase 1a DLT assessment period, a maximum of 10 patients per dose level may be enrolled.

CCI [redacted]

Section 6.1 Inclusion Criteria

[4] Patients with mesothelioma are not required to have received prior anti-PD-1 or anti-PD-L1 therapy. If the patient has received prior anti-PD-1 or anti-PD-L1 therapy, then inclusion criteria [2]a through [2]d and [3]a and [3]b would apply. Additionally, patients must have:

a. confirmed unresectable or medically inoperable malignant ~~pleural~~ mesothelioma ~~(MPM) subtype~~ and progressive disease (PD) after at least one prior systemic treatment with a platinum-based doublet (both cisplatin and carboplatin are allowed) for unresectable MPM. All prior cytotoxic toxicities must have resolved to Grade ≤2 prior to registration.

Section 6.1 Inclusion Criteria

[9] Have adequate organ function as defined in the table below:

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 (see Appendix 6)	≤1.5 × ULN OR ≥50 mL/min
~~**Thyroid**~~	
~~TSH or free T4~~	~~Within normal limits~~

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; aPTT= activated partial thromboplastin time; AST = aspartate aminotransferase; ULN = upper limit of normal; ~~T4 = thyroxine; TSH = thyroid stimulating hormone~~

Section 6.1 Inclusion Criteria

[13] Men with partners of childbearing potential or women with childbearing potential must agree to use a highly effective contraceptive method~~s~~ of birth control (Appendix 1) during study treatment and for at least 6 months following the last dose of study drug. ~~(eg, intrauterine device, birth control pills, or barrier method). If condoms are used as a barrier contraceptive, a spermicidal agent should be added as double barrier protection.~~

Section 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, and. ~~If~~ the ~~results of a~~ repeated laboratory test must meet the eligibility criteria~~, an additional laboratory test must be repeated again to confirm eligibility~~.

Section 7.4 Dose Modification

Table JZDA.7.4 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, and begin medical management as needed~~
			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

SOC	Toxicity	CTCAE Grade and/or Symptoms[a]		Treatment Plan[b]
		Grade	Symptoms	
Hepatobiliary	Transaminitis, elevated bilirubin	2	• AST or ALT between ~~2.5~~3 × ULN and 5 × ULN, or • TB between 1.5 × ULN and 3 × ULN	• Withhold study treatment and administer prednisone 1-2 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 2-4 mg/kg/day • If the event continues for >3 days despite corticosteroids, add a nonsteroidal immunosuppressive agent[c]

Section 9.8.1 Tissue Samples for Biomarker Research

An attempt to obtain 4 core-needle biopsies or a surgical biopsy is required, unless medically contraindicated and discussed with Lilly CRP/CRS. Optimally, biopsies should be taken from the same lesion and from areas not previously irradiated. Biopsies should not be taken from areas that have been previously irradiated, unless the previously irradiated area has progressed.

Appendix 1 Abbreviations and Definitions

highly effective methods of contraception

Methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation :
  - oral
  - injectable
  - implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner (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.)

~~combined oral contraceptive pill and mini-pill, NuvaRing®, implantable contraceptives, injectable contraceptives (such as Depo-Provera®), intrauterine device (such as Mirena® and ParaGard®), contraceptive patch for women <90 Kg (<198 pounds), total abstinence, or vasectomy.~~

~~Also see the definition of effective method of contraception.~~

Appendix 4 Sampling Schedule

Phase 1a and 1b: Pharmacokinetic, Pharmacodynamic, Immunogenicity, Biomarker, Pharmacogenomic, and ECG Collection Time Points (All Cohorts)

Cycle/Day	Study Day	Sample Time (Relative to START of LY3415244 Infusion)	PK[a, b]	PD sTIM-3/ sPD-L1[a, b]	IG[a]	Whole Blood (PGx)	Biomarker Collection				ECG
							Plasma	Whole Blood[c]	Serum	Tissue	
C2D15; then, Q2W	43, 57, 71, etc.	**0 hour predose** • **PK/PD~~, IG~~:** collect samples ≤2 hours prior to start of LY3415244 infusion	X	X							
C3D1	57	**0 hour predose** • **IG Biomarkers:** collect samples ≤2 hours prior to start of LY3415244 infusion. • **ECGs:** perform triplicate ECG at the following time points: o Prior to start of LY3415244 infusion o At the end of the LY3415244 infusion			X		X	X	X		X[d]

Cycle/Day	Study Day	Sample Time (Relative to START of LY3415244 Infusion)	PK[a, b]	PD sTIM-3/ sPD-L1[a, b]	IG[a]	Whole Blood (PGx)	Biomarker Collection				ECG
							Plasma	Whole Blood[c]	Serum	Tissue	
30 days post last LY341524 4 dose		**Anytime** • **PK, PD, IG, and biomarkers:** collect at any time	X	X	X		X				X[d]

b The 2-, 4-, 24-, 72-, 120-, and 168-hour samples are **relative to the START** of the corresponding dosing event. These samples must be collected after completion of the infusion. Allowable sampling window for pre-dose C1D1 is -8 hours. Allowable sampling windows for 2-, 4-, 24-, 72-, 120-, and 168-hour are ±30 minutes, ±60 minutes, ±8 hours, ±24 hours, ± 24 hours, and ± 48 hours, respectively. If LY3415244 infusion need to be increased up to 2 hours the allowable sampling windows for the 2-hour sample is increased to +60 minutes. Samples at 30, 60, and 90 days post last LY3415244 dose have allowable sampling windows of ±7 days. However, it is essential that the exact infusion start and stop times (actual clock readings) are recorded.

d Triplicate ECGs should be conducted immediately before the PK sample and after the patient has been supine for 5 minutes; collect at a minimum of 1-minute intervals, with all 3 replicate ECGs completed within 5 to 15 minutes.

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