Protocol: J1Q-MC-JZIA(b)

A Phase 1a/1b Study of LY3435151 Administered to Patients With Advanced Solid Tumors

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Title Page

Protocol Title: A Phase 1a/1b Study of LY3435151 Administered to Patients with Advanced Solid Tumors

Protocol Number: J1Q-MC-JZIA

Amendment Number: (b)

Compound Number: LY3435151

Study Phase: Phase 1a/Phase1b

Short Title: A Study of LY3435151 in Patients with Solid Tumors

Acronym: JZIA

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana USA 46285

Regulatory Agency Identifier Number(s)

IND: 144218

Approval Date: Protocol Electronically Signed and Approved by Lilly: 21-Jun-2019 GMT.
Protocol Amendment (a) Electronically Signed and Approved by Lilly: 09-Aug-2019 GMT.
Protocol Amendment (b) Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 28-Jan-2020 GMT

Protocol Amendment Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Amendment (a)	09-Aug-2019
Protocol J1Q-MC-JZIA	21-Jun-2019

Amendment (b)

Overall Rationale for the Amendment:

The purpose of this amendment is to add updated informative language for pembrolizumab, as well as to provide additional clarity for sites and investigators.

Section # and Name	Description of Change	Brief Rationale
Throughout	Addition of pembrolizumab-specific language	Language added to meet pembrolizumab language requirements
Section 1.1 Synopsis; Section 3 Objectives and Endpoints	Revision of Phase 1b C1 and D1 objectives	Clarification
Section 1.3 Schedule of Activities	Baseline radiologic imaging notes updated; revised concomitant medication notes	Additional instructions provided in notes
Section 1.3.1 Sampling Schedules for Pharmacokinetics, Biomarkers, and Safety	Removal of stool sample at V801 in Phase 1b schedule	Editorial error
Section 1.3.1 Sampling Schedules for Pharmacokinetics, Biomarkers, and Safety	C1D2 and C1D4 samples added; footnote added to Hematology CBC	Additional samples added to study; footnote added for sampling flexibility
Section 1.3.1 Sampling Schedules for Pharmacokinetics, Biomarkers, and Safety	Addition of ECGs at C2D1 1h post-dose and C3D1 1h post-dose for Phases 1a and 1b	Additional testing added to study
Section 1.3.1 Sampling Schedules for Pharmacokinetics, Biomarkers, and Safety	Revised footnotes for sampling schedules	Clarification
Section 4.1.1 Dose Escalation Phase	Revision of patient enrollment for Cohort A and Cohort B1	Clarification for Cohort A, correction for Cohort B1

Section # and Name	Description of Change	Brief Rationale
Section 4.1.1.2 Dose-Limiting Toxicity Determination	Added "immune-related" to Grade 3 endocrine disorder DLT exception	Clarification
Section 4.1.2 Dose Expansion Phase	Additional language and instructions added for Cohorts C1,C2, and D3	Language added to provide details on Cohorts C1 and C2 enrollment and randomization; Instructions added to confirm Cohort D3 patients are not eligible for any approved IO therapeutic drug treatment
Section 4.3 Justification for Dose	Addition of language for dose justification for Cohort A1	Clarification
Section 5.1 Inclusion Criteria	Revised criterion 2a, 2b	Language revised to remove redundancy and clarify requirements
Section 5.1 Inclusion Criteria	Added requirement for recovery from radiation toxicities	Language added to clarify requirements
Section 6.1 Study Intervention(s) Administered	Added source for determining infusion duration and order of administration	Information was missing and needed clarification
Section 6.5 Concomitant Therapy	Hormone therapy added to list of prohibited on-study therapies	Hormone therapy will not be permitted on study
Section 6.5 Concomitant Therapy	Revised language surrounding concomitant medication recording	Language revised for accuracy
Section 6.6 Dose Modification	Removal of language regarding resuming study treatment; revision of IRR management table	Clarification; management table revised to align with pembrolizumab language
Section 7.1 Discontinuation of Study Intervention	Clarified continuing treatment criteria and included need for new ICF if continuing treatment	Language revised for accuracy
Section 8.1.1 iRECIST for Immune-Based Therapies	Added upper limit to progression by iRECIST time window	Clarification
Section 8.2.1.1 Immunogenicity Assessment	Clarified that additional blood and urine samples will be collected in the event of drug hypersensitivity reactions	Clarification

Section # and Name	Description of Change	Brief Rationale
Section 8.3.7 Events of Clinical Interest	Added section defining which events will be monitored	Based on regulatory feedback
Section 8.8 Biomarkers	Added whole blood would also be collected	Editorial error
Section 8.8.1 Tumor Tissue Samples for Detection of TILs	Clarifying statement on testing added	Clarified that TIL testing does not replace any companion diagnostic testing required for IO therapy eligibility determination
Section 9.4.1 General Statistical Considerations	Revised description of analysis set for efficacy and safety analyses	Language revised for clarity
Section 10.2 Appendix 2: Clinical Laboratory Tests	Removed duplicated direct bilirubin test; added T3 and free T3 test; changed FT4 to T4; footnotes revised	Editorial error; tests added per regulatory feedback; footnotes revised for clarity
Throughout protocol	Minor formatting and editorial changes	Minor, therefore not detailed

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 1a/1b Study of LY3435151 Administered to Patients with Advanced Solid Tumors

Short Title: A Study of LY3435151 in Patients with Solid Tumors

Rationale: Study J1Q-MC-JZIA (JZIA) is designed to investigate the safety and tolerability of LY3435151 when administered alone and in combination with pembrolizumab in patients with advanced cancers.

T cells play a central role in immune response to tumors. However, tumors have adopted multiple mechanisms to evade host immune surveillance. One of the key mechanisms is the up-regulation of immune suppressive co-inhibitory molecules (immune checkpoint molecules) on the tumor cells. CD226 is a stimulatory receptor expressed by T cells that has been shown to play a critical role in the activation and differentiation of T cells leading to antitumor response in preclinical models. Upregulation of a high-affinity co-inhibitory receptor (TIGIT) on T cells in the tumor microenvironment can sequester the ligands on tumor cells (CD155 and CD112), thereby leading to a reduced/loss of stimulatory signaling through the CD226 pathway. LY3435151 is a monoclonal antibody that is a CD226 agonist that potentially bypasses TIGIT suppression or tumor loss of CD226 ligands. Study JZIA will evaluate the impact of LY3435151 on clinical response, and will assess multiple markers of T cell activation, expansion, and phenotypes in tumors to evaluate the impact of a CD226 agonist on tumor immunity.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• **Ph1a Dose Escalation (Part A & Part B):** To assess the safety and tolerability of LY3435151, thereby identifying the RP2D, administered as monotherapy and in combination with pembrolizumab, in patients with advanced solid tumors of the following types: TNBC, gastric adenocarcinoma, HNSCC, squamous cervical carcinoma, high grade serous ovarian carcinoma, HCC, UPS, and LMS.	• DLTs • Safety (including, but not limited to): TEAEs, SAEs, deaths, and clinical laboratory abnormalities per CTCAE (version 5.0)

Objectives	Endpoints
• **Ph1b Dose Expansion (Part C & Part D):** To assess the safety and tolerability of LY3435151: o administered as monotherapy (Part C), must be PD-1/PD-L1 antagonist naïve: C1: TNBC (not eligible for IO therapies) C2: Gastric adenocarcinoma administered in combination with pembrolizumab (Part D), must be PD-1/PD-L1 antagonist naive: D1: TNBC (not eligible for IO therapies) D2: Gastric adenocarcinoma D3: TIL selected cohort with the following tumor types: HNSCC, squamous cervical carcinoma, high grade serous ovarian carcinoma, HCC, UPS, and LMS.	• Safety endpoints, including but not limited to the following: o TEAEs, SAEs • Clinical laboratory tests, vital signs, and physical examinations
Secondary	
• To assess the PK of LY3435151, administered as monotherapy and in combination with pembrolizumab, in patients with solid tumors	• Serum concentration of LY3435151 alone and when administered in combination with pembrolizumab
• To document any antitumor activity per RECIST 1.1 observed with LY3435151, when administered as monotherapy or in combination with pembrolizumab, in patients with solid tumors	• ORR • DCR • DoR • TTR • PFS

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; DCR = disease control rate; DLT = dose-limiting toxicity; DoR = duration of response; HCC = hepatocellular carcinoma; HNSCC = head and neck squamous cell carcinoma; IO = immuno-oncology; LMS = leiomyosarcoma; ORR = overall response rate; PFS = progression-free survival; Ph = Phase; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended phase 2 dose; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TIL = tumor-infiltrating lymphocyte; TNBC = triple-negative breast cancer; TTR = time to response; UPS = undifferentiated pleomorphic sarcoma.

Overall Design:

Study JZIA is a Phase 1a/1b, multicenter, open-label dose-escalation study followed by a randomized dose-expansion study of LY3435151 as monotherapy and in combination with pembrolizumab in patients with the following cancers: triple-negative breast cancer (TNBC), gastric adenocarcinoma (including gastroesophageal junction adenocarcinoma), head and neck

squamous cell carcinoma (HNSCC), squamous cervical carcinoma, high-grade serous ovarian carcinoma, hepatocellular carcinoma (HCC), undifferentiated pleomorphic sarcoma (UPS), and leiomyosarcoma (LMS).

Disclosure Statement: This is a sequential treatment study with 13 cohorts with no masking.

Number of Participants:

Approximately 170 patients with advanced solid tumors will be enrolled in this study.

- **Phase 1a:** Total enrollment will be determined by the incidence of dose-limiting toxicities (DLTs).
  - Monotherapy dose escalation (Part A): approximately 18 to 22 patients will be enrolled. An additional 12 patients in total may be enrolled at 2 selected dose levels to further inform safety, pharmacokinetics (PK), and pharmacodynamics (PD).
  - Combination dose escalation (Part B): approximately 6 to 8 patients will be enrolled.

- **Phase 1b:** Approximately 126 patients will be enrolled into Phase 1b in this study.
  - A randomization design will be applied to TNBC (C1 and D1) and gastric adenocarcinoma (including gastroesophageal junction) (C2 and D2) cohorts. For each of the 2 tumor types:
    - Stage 1: approximately 16 patients will be initially enrolled and randomized with 1:1 ratio to monotherapy dose expansion (Part C) or combination dose expansion (Part D)
    - Stage 2: additional approximately 32 patients will be enrolled to combination dose expansion (Part D). An interim data review will be performed based on safety, efficacy, and PK/PD data from the first 20 enrolled patients in combination dose expansion (including patients from both Stage 1 and Stage 2).
  - Tumor-infiltrating lymphocyte (TIL) selected cohort with multiple tumor types in combination dose expansion (D3): approximately 30 patients will be enrolled.

Intervention Groups and Duration:

Patients enrolled in this Phase 1a/1b study will receive LY3435151 monotherapy or in combination with pembrolizumab, as shown in the following table. The planned duration of treatment is not fixed; participants will remain on study until disease progression or unacceptable toxicity occurs; duration of pembrolizumab treatment will be fixed at up to 2 years. If participants are discontinued from pembrolizumab, they will be allowed to continue on LY3435151 treatment if receiving ongoing clinical benefit. Likewise, if patients are discontinued from LY3435151 treatment, they will be allowed to continue on pembrolizumab if receiving ongoing clinical benefit for up to 2 years.

Study Intervention Groups and Duration

	Phase/Part	Study Drug(s) (Route of Administration)	Cohort / Dose Level	***Proposed*** Doses	Dose Schedule
Dose-Escalation Phase	**Monotherapy/ Part A**	LY3435151 (IV)	A1: *DL 1*	10 mg	D1 of each 21-day cycle (Q3W)
			A2: *DL2*	30 mg	
			A3: *DL 3*	100 mg	
			A4: *DL 4*	300 mg	
			A5: *DL 5*	900 mg	
			A6: *DL 6*	1800 mg	
	Combination/ Part B	LY3435151 (IV)	B1: *DL 1*	*TBD* [a,b]	
			B2: *DL 2*	*TBD* [a]	
		Pembrolizumab (IV)	B1/B2	*200 mg*	
Dose-Expansion Phase	**Monotherapy/ Part C**	LY3435151 (IV)	C1/C2: *Monotherapy RP2D*	*TBD* [a]	
	Combination/ Part D	LY3435151 (IV)	D1/D2: *Combination RP2D*	*TBD* [a]	
		Pembrolizumab (IV)	D1/D2	*200 mg*	

Abbreviations: D = day; DL = dose level; IV = intravenous; RP2D = recommended phase 2 dose; Q3W = every 3 weeks; TBD = to be determined.

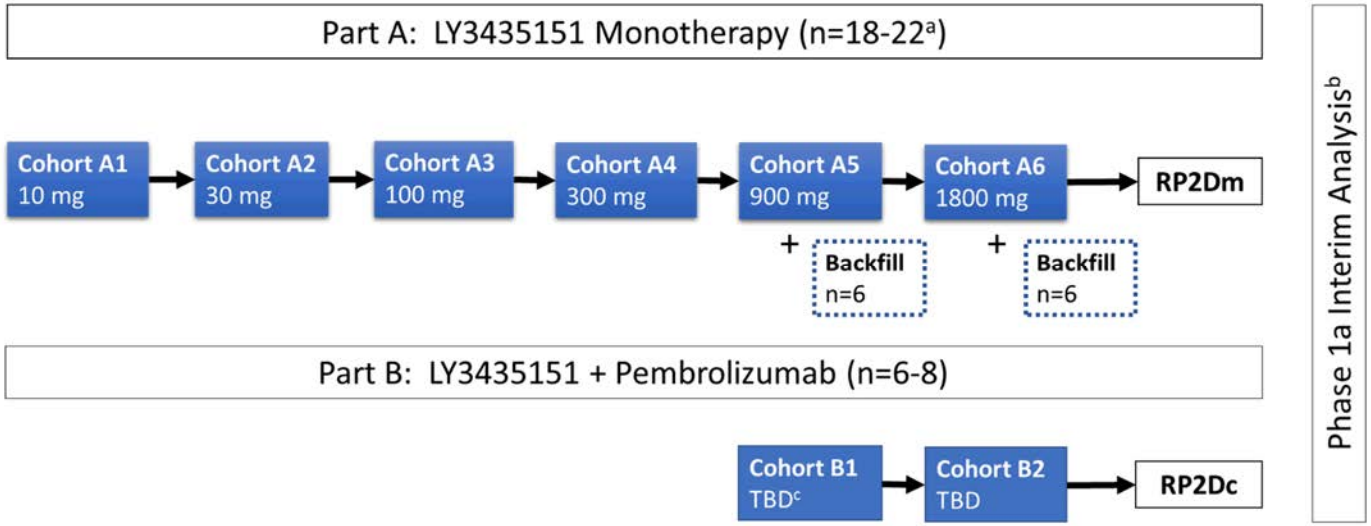
[a] Not to exceed maximum tolerated dose in dose escalation.

[b] LY3435151 dosing in combination will be 1 dose level below the tolerated monotherapy dose level.

Data Monitoring Committee: No

1.2. Schema

1.2.1. Phase 1a: Dose Escalation Schema



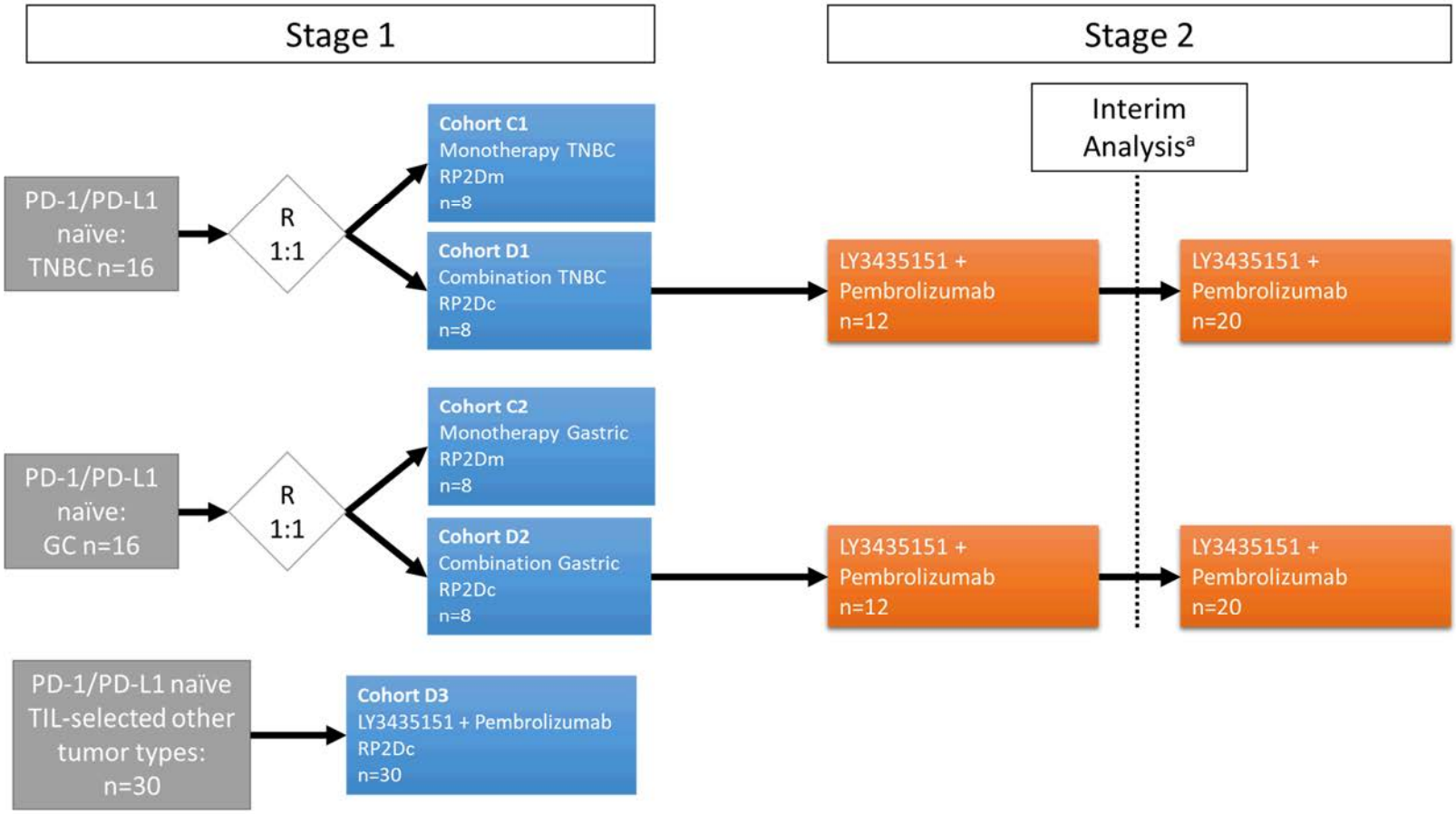
Abbreviations: n = number of participants; RP2Dc = combination recommended Phase 2 dose; RP2Dm = monotherapy recommended Phase 2 dose; TBD = to be determined.

[a] May include backfill participants as described in Section 4.1.1.

[b] Refer to Section 9.5 for details of interim analyses.

[c] LY3435151 dosing in combination will begin 1 dose level below the tolerated monotherapy dose level.

1.2.2. Phase 1b: Dose Expansion Schema



Abbreviations: GC = gastric carcinoma; n = number of participants; IO = immuno-oncology; R = randomization; RP2Dc = combination recommended Phase 2 dose; RP2Dm = monotherapy recommended Phase 2 dose; TIL = tumor-infiltrating lymphocyte; TNBC = triple negative breast cancer.

[a] Refer to Section 9.5 for details of interim analyses.

1.3. Schedule of Activities (SoA)

Schedule of Baseline Activities

Relative Day Prior to C1D1	≤28	≤14	≤7	Instructions
Procedure				
Informed consent	X			ICF must be signed before any protocol-specific procedures are performed.
Inclusion/exclusion evaluation	X			
Physical examination		X		
Height/weight and vital signs		X		Vital signs include temperature, pulse rate, pulse oximetry, respiratory rate, and blood pressure.
ECOG performance status		X		
Medical history		X		Including assessment of preexisting conditions, historical illnesses, substance usage (such as alcohol and tobacco), and other relevant habit assessments.
Cancer treatment history		X		
Concomitant medication	X			Record prior and concurrent medication/cancer treatments, includes 28 days prior to initiation of study treatments
AE collection / CTCAE grading	X			CTCAE version 5.0
Radiologic imaging	X			Baseline radiological tumor assessment per RECIST 1.1 should be done. Radiologic assessments obtained previously as part of routine clinical care up to 28 days before treatment may be used as the baseline assessment. Baseline imaging should include at minimum chest/abdomen/pelvis while follow up scans can be focused on target region of interest.
Tumor Biopsy	X			Mandatory pre-treatment biopsy. No intervening treatment between biopsy and study treatment initiation. See Section 8.8.
Archival tissue sample	X			An archival tumor sample may be requested if available and permitted by local regulations. See Section 8.8.
ECG			X	Single local ECG
ECHO		See Notes		Perform locally as clinically indicated to assess eligibility (optional) per exclusion criteria 14.j.i (See Section 5.2).
Hematology		X		See Appendix 2.
Coagulation		X		See Appendix 2.
Clinical Chemistry		X		See Appendix 2.
Urinalysis		X		See Appendix 2.
Serum pregnancy test			X	Applies to women of childbearing potential only. See Appendix 2.

Thyroid function			X	See Appendix 2.

Abbreviations: AE = adverse event; C1D1 = Cycle 1 Day 1; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; ICF = informed consent form; RECIST = Response Evaluation Criteria in Solid Tumors.

Schedule of On-Treatment Activities

Procedure	All Treatment Periods (Cycle = 21 days)							Notes
	Cycle 1 (± 3 days)			Cycle 2 (± 3 days)			Cycle 3-n (± 3 days)	
Relative Day within Dosing Cycle	**1**	**8**	**15**	**1**	**8**	**15**	**1**	
Physical exam	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	**Measure vital signs (weight, temperature, blood pressure, pulse rate, oxygen saturation, and respiration rate) as follows (±5 minutes):** • **In Cycles 1 and 2:** o Up to 15 minutes prior to each LY3435151 infusion o Every 15 minutes during each LY3435151 infusion o at the end of each LY3435151 infusion • A 4-hour observation period from the end of LY3435151 administration will occur in Cycles 1 and 2. o every 30 (±5) minutes for the first hour and 60 (±5) minutes thereafter during the 4-hour observation period • **In Cycle 3 and beyond, if the patient has not experienced an infusion-related reaction or other infusion-related AE:** o up to 15 minutes prior to each LY3435151 infusion o at least once during each LY3435151 infusion o at the end of each LY3435151 infusion
ECOG performance status	X			X			X	Complete before treatment initiation. May be completed up to 3 days before the scheduled day.
PK sampling	See Section 1.3.1 for time points							
Exploratory blood sample for biomarkers	See Section 1.3.1 for time points							Additional samples may be collected if clinically indicated.
ECG	See Section 1.3.1 for time points							Central triplicate ECGs.
ECHO	See Notes							Perform as clinically indicated

Procedure	All Treatment Periods (Cycle = 21 days)							Notes
	Cycle 1 (± 3 days)			Cycle 2 (± 3 days)			Cycle 3-n (± 3 days)	
Relative Day within Dosing Cycle	**1**	**8**	**15**	**1**	**8**	**15**	**1**	
Whole blood pharmacogenomics	X							Collect once. Sample can be collected at any time if not collected on C1D1.
Hematology	X	X	X	X	X	X	X	See Appendix 2. If baseline laboratory tests were performed ≤3 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. See Section 1.3.1 for additional time points in Cycle 1.
Clinical chemistry	X	X	X	X	X	X	X	See Appendix 2. If baseline laboratory tests were performed ≤3 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.
Thyroid function				X			See Notes	Starting C2D1 and every other cycle thereafter (eg, C4D1, C6D1). See Appendix 2.
Urinalysis	X			X			X	See Appendix 2. If baseline laboratory tests were performed ≤3 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

Procedure	All Treatment Periods (Cycle = 21 days)							Notes
	Cycle 1 (± 3 days)			Cycle 2 (± 3 days)			Cycle 3-n (± 3 days)	
Relative Day within Dosing Cycle	**1**	**8**	**15**	**1**	**8**	**15**	**1**	
								C1D1.
Serum or urine pregnancy test	X			X			X	See Section 8.3.4 and Appendix 2. If baseline laboratory tests were performed ≤3 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.
Coagulation	See Notes							Collect as clinically indicated
Stool sample	See Section 1.3.1							Refer to Section 1.3.1 for sample collection time points
Plasma sample	See Section 1.3.1							Refer to Section 1.3.1 for sample collection time points
On-treatment tumor biopsy				X				Mandatory on-treatment biopsy on C2D1 for all patients except during dose escalation Cohorts A1, A2, and A3. See Section 8.8.
Optional tumor biopsy	See Notes							An optional tumor biopsy may be performed, if clinically feasible, after disease progression or at additional study time points, if warranted and agreed upon by the investigator and Lilly.
Radiologic imaging	See Notes							Scans will be performed and reviewed locally; done every 6 weeks ± 7 days from Cycle 1 Day 1 for 36 weeks. Afterwards, perform every 9 weeks ±7 days. The same method of assessment and technique used at baseline should be used for each consecutive assessment thereafter. RECIST 1.1/iRECIST should be used for all tumors.
AE Collection / CTCAE Grading	See Notes							CTCAE version 5.0. Evaluated at each visit and continuously throughout study. See Section 8.3 for more information about adverse events and adverse event collection.
Concomitant Medication Notation	See Notes							Evaluated at each visit and throughout study. Refer to Section 6.5 for more information about concomitant medications.
Administer LY3435151	X			X			X	Administer Q3W per Section 6.1. May be administered up to 3 days prior to scheduled visit.
Administer pembrolizumab	X			X			X	For Dose Escalation Part B and Dose Expansion Part D, administer Q3W per Section 6.1. May be administered up to 3 days prior to scheduled visit.

Abbreviations: AE = adverse event; C = Cycle; CTCAE = Common Terminology Criteria for Adverse Events; D = Day; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; iRECIST = immuno-Response Evaluation Criteria in Solid Tumors; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors; Q3W = every 3 weeks.

Post-Treatment Follow-Up Schedule of Activities

	Short-Term Follow-Up[a]			Long-Term Follow-Up[b]	Comments
Visit	**801**	**802**	**803**	**804-X**	
Relative Day within Cycle	30-Day Follow-Up ± 5 days	60-Day Follow-Up ± 7 days	90-Day Follow-Up ± 7 days	(90 ± 14 Days)	
Physical exam	X				
Vital signs	X				Including weight, temperature, pulse rate, pulse oximetry, blood pressure, respiratory rate
ECOG performance status	X				
Radiologic imaging	X			X	Only for patients who discontinue study treatment without objectively measured progressive disease, continue to evaluate tumor response according to planned standard of care tumor assessment schedule until patient has objective disease progression or study completion.
Adverse events collection/CTCAE grading	X			X	CTCAE version 5.0. Collect AEs for 30 days following cessation of study treatment and SAEs for 90 days or 30 days following cessation of study treatment if the participant initiates new anticancer treatment, whichever comes first. **Note**: All pregnancies and exposure during breastfeeding must be reported, from time of treatment through 120 days following cessation of treatment, or 30 days following cessation of treatment.
Concomitant medication	X				All concomitant medications received up to 30 days after the last dose of study treatment should be recorded. Concomitant medications administered 30, 60, and 90 days after the last dose of study treatment should be recorded for SAEs and events of clinical interest.
Optional tumor biopsy	X				An optional tumor biopsy may be performed, if clinically feasible, after disease progression or at additional study time points, if warranted and agreed upon by the

	Short-Term Follow-Up[a]			Long-Term Follow-Up[b]	Comments
Visit	**801**	**802**	**803**	**804-X**	
Relative Day within Cycle	30-Day Follow-Up ± 5 days	60-Day Follow-Up ± 7 days	90-Day Follow-Up ± 7 days	(90 ± 14 Days)	
					investigator and Lilly.
Hematology	X				See Appendix 2.
Clinical chemistry	X				See Appendix 2.
Coagulation	X				PT or INR and aPTT should be collected at the mandatory Safety Follow-Up Visit after discontinuation of study therapy.
Thyroid function	X				See Appendix 2.
Collection of post-study-treatment anticancer therapy information	X	X	X	X	Discontinuation from study must occur prior to introduction of the new agent.
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)
Serum or urine pregnancy test	X	X	X	See instructions	Perform pregnancy test for women of childbearing potential. See Section 8.3.4 and Appendix 2. Pregnancy test required at 120 days after study discontinuation per Section 8.3.4 or 30 days following cessation of study treatment if the participant initiates new anticancer therapy.

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; CTCAE = Common Terminology Criteria for Adverse Events; ECOG = Eastern Cooperative Oncology Group; INR = international normalized ratio; PT = prothrombin time; SAE = serious adverse event.

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

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

Continued Access Schedule of Activities

	Continued Access Treatment	Continued Access Follow-up Visits[a]			
		30-Day Follow-Up	60-Day Follow-Up	90-Day Follow-Up	Notes
Visit	**501-5XX**	**901**	**902**	**903**	
Procedure					
AE collection	X	X	X	X	Per CTCAE version 5.0. Collect AEs for 30 days following cessation of study treatment and SAEs for 90 days or 30 days following cessation of study treatment if the participant initiates new anticancer treatment, whichever comes first. As part of AE/SAE collection, monitor vital signs and perform standard laboratory tests (hematology, chemistry, urinalysis, and pregnancy testing) at the same frequency as the study treatment period. All laboratory tests during the continued access period will be performed in the local laboratories only. 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 (eg, tryptase), immune complex formation (eg, C3 levels) and cytokine release (eg, IL-6) as appropriate for the clinical presentation.
Administer study intervention	X				See Section 6.1 for study intervention administration details and guidelines.

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; IG = immunoglobulin; IL = interleukin; IRR = infusion-related reaction; PK = pharmacokinetics; SAE = serious adverse event.

[a] Continued access follow-up begins when the patient and the investigator agree that the patient will no longer continue treatment in the continued access period and lasts approximately 30 days

1.3.1. Sampling Schedules for Pharmacokinetics and Biomarkers and Safety

Schedule for Phase 1a

Sampling Day	Time Relative to End of LY3435151 Infusion	PK Collection	ECG	Serum Cytokines and Exploratory Biomarkers	Whole blood for Flow Profile [d]	Immunogenicity Sample	Plasma Sample for Exploratory Biomarkers	Stool Sample for Microbiota Analysis[g]	Hematology CBC (local testing)[e]
Baseline ≤7 days prior C1D1			X				X	X	
Cycle 1 Day 1	predose[h]	X	X [c]	X	X	X			
Cycle 1 Day 1	1hr ± 15mn	X	X [c]						
Cycle 1 Day 1	3hr ± 30mn	X							X
Cycle 1 Day 2	24hr ± 4hr	X	X [c]	X					X
Cycle 1 Day 4	72hr ± 24hr	X		X					X
Cycle 1 Day 8	168hr ± 24hr	X				X			
Cycle 1 Day 15	336hr ± 24hr	X							
Cycle 2 Day 1	predose [h]	X		X	X	X			
Cycle 2 Day 1	1hr ± 15mn	X	X [c]						
Cycle 2 Day 1	3hr ± 30mn	X							
Cycle 3 Day 1	predose[h]	X		X	X	X	X	X	

Sampling Day	Time Relative to End of LY3435151 Infusion	PK Collection	ECG	Serum Cytokines and Exploratory Biomarkers	Whole blood for Flow Profile [d]	Immunogenicity Sample	Plasma Sample for Exploratory Biomarkers	Stool Sample for Microbiota Analysis[g]	Hematology CBC (local testing)[e]
Cycle 3 Day 1	1hr ± 15mn	X	X [c]						
Cycle 4 Day 1	predose[h]	X							
Cycle 5-n Day 1	predose[h]	X				See footnote[b]			
If IRR, at onset, resolution and 30 days following IRR[a]		X				X			
When/if any DLT or DLT equivalent occurs		X							
EOT[f]		X		X		X	X	X	
V801		X		X		X	X		
V802		X				X			
V803		X		X		X			

Abbreviations: C = Cycle; CBC = complete blood count; D = Day; DLT = dose-limiting toxicity; ECG = electrocardiogram; EOT = end of treatment; hr = hours; IL = interleukin; IRR = infusion-related reaction; mn = minutes; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetics; V = Visit.

[a] Exploratory hypersensitivity immunogenicity and PK samples may be analyzed for markers of basophil/mast cell activation (eg, tryptase), immune complex formation (eg, C3 levels) and cytokine release (eg, IL-6) as appropriate for the clinical presentation.

[b] Immunogenicity sample will be collected every fourth cycle from C1 (eg, C5D1, C9D1)

[c] Central triplicate ECGs

[d] Not applicable for Cohort A1

[e] See Section 1.3 for more hematology sample time points.

[f] End of Treatment (EOT) is the same as study treatment discontinuation, which happens when the subject and the investigator agree that the subject will no longer continue study treatment.

[g] may be collected ±3 days of scheduled time point

[h] predose samples should be collected prior to LY3435151 dosing and, if applicable, pembrolizumab dosing

Schedule for Phase 1b

Sampling Day	Time Relative to End of Infusion	PK Collection	ECG	Serum Cytokines and Exploratory Biomarkers	Whole Blood for Flow Profile	Immunogenicity Sample	Plasma Sample for Exploratory Biomarkers	Stool Sample for Microbiota Analysis[e]
Baseline ≤ 7 days prior C1D1			X				X	X
Cycle 1 Day 1	predose[f]	X	X [c]	X	X	X		
Cycle 1 Day 1	1hr ± 15mn	X	X [c]					
Cycle 2 Day 1	predose[f]	X		X	X	X		
Cycle 2 Day 1	1hr ± 15mn	X	X [c]					
Cycle 3 Day 1	predose[f]	X		X	X	X	X	X
Cycle 3 Day 1	1hr ± 15mn	X	X [c]					
Cycle 4 Day 1	predose[f]	X		X				
Cycle 5-n Day 1	predose[f]	X				See footnote[b]		
If IRR, at onset, resolution, and 30 days following IRR[a]		X				X		
When/if any DLT equivalent occurs		X						
EOT[d]				X			X	X
V801		X		X		X	X	

Sampling Day	Time Relative to End of Infusion	PK Collection	ECG	Serum Cytokines and Exploratory Biomarkers	Whole Blood for Flow Profile	Immunogenicity Sample	Plasma Sample for Exploratory Biomarkers	Stool Sample for Microbiota Analysis[e]
V802		X				X		
V803		X				X		

Abbreviations: C = Cycle; D = Day; DLT = dose-limiting toxicity; ECG = electrocardiogram; EOT = end of treatment; hr = hours; IL = interleukin; IRR = infusion-related reaction; mn = minutes; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetics; V =Visit.

[a] Exploratory hypersensitivity immunogenicity and PK samples may be analyzed for markers of basophil/mast cell activation (eg, tryptase), immune complex formation (eg, C3 levels) and cytokine release (eg, IL-6) as appropriate for the clinical presentation.

[b] Immunogenicity sample will be collected every fourth cycle from C1 (eg, C5D1, C9D1)

[c] Central triplicate ECGs

[d] End of Treatment (EOT) is the same as study treatment discontinuation, which happens when the subject and the investigator agree that the subject will no longer continue study treatment.

[e] may be collected ±3 days of scheduled time point

[f] predose samples should be collected prior to LY3435151 dosing and, if applicable, pembrolizumab dosing

2. Introduction

2.1. Study Rationale

Recent clinical success revealed the potential for potent antitumor activity in a variety of solid tumors by targeting T-lymphocyte inhibitory pathways using monoclonal antibodies that block inhibitory receptors on the surface of T cells. The anti-cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) antibody ipilimumab was approved by the US Food and Drug Administration (FDA) and the European Medicines Agency for the treatment of patients with advanced melanoma in 2011 (EMA 2019; FDA 2019). Blockade of the programmed cell death protein 1 (PD-1) or programmed death-ligand 1 (PD-L1) pathway demonstrated durable responses in 30% to 35% of patients with advanced melanoma (Topalian et al. 2012; Hamid et al. 2013), which led to FDA approval of pembrolizumab and nivolumab in 2014 and European Commission approval of pembrolizumab in 2015. Despite remarkable clinical activity of PD-1/PD-L1 inhibitors demonstrated in several clinical studies in patients with a wide variety of malignancies, there are limitations to their efficacy and many patients do not respond to these therapies. For example, only 10-40% unselected patients of various solid tumors (including non-small cell lung cancer, urothelial carcinoma, classic Hodgkin lymphoma, head and neck squamous cell carcinoma [HNSCC], renal cell carcinoma, Merkel cell carcinoma, hepatocellular carcinoma [HCC], and gastric carcinomas) show clinical response to anti-PD-1/PD-L1 monotherapy, and some initially responding patients eventually developed resistance and disease progression (Zou et al. 2016; Kim et al. 2017).

During checkpoint blockade with anti-CTLA-4 and anti-PD-1/PD-L1 inhibitors, multiple other checkpoint inhibitors may become coordinately upregulated. The compensatory upregulation of these alternative checkpoint receptors, such as LAG-3, TIGIT, TIM-3, CD160, and VISTA axes, have been demonstrated in preclinical models (Syn et al. 2017) including head and neck cancer (Shayan et al. 2017), metastatic ovarian cancer (Huang et al. 2017), metastatic melanoma (Benci et al. 2016), lung adenocarcinoma (Koyama et al. 2016), and prostate cancer (Gao et al. 2017). This could be a result of interferon signaling and activation of various pathways in tumor-infiltrating lymphocytes (TILs), which can negatively regulate T cell activity and eventually lead to treatment failure (Syn et al. 2017). Inhibition of these molecules alone or in combination may increase the frequency of objective responses and achieve efficacy in cancer types that have thus far been largely refractory to CTLA-4 and/or PD-1 blockade. Many clinical trials are currently underway to test antibodies against these inhibitory pathways, both as monotherapy and combination therapy strategies (Sharma et al. 2017).

CD226 is a co-stimulatory receptor, expressed on T, NK, platelets, DC, monocytes, and other immune cells. Ligands of CD226, PVR (CD155) and PVRL2 (CD112), are shared with the co-inhibitory receptors TIGIT and CD96. Activation of CD226 leads to proliferation, differentiation and cytokine production in NK (innate) and T (adaptive) cells in primary human cells. Anti-CD226 antagonist antibodies have shown to completely block the efficacy of anti-PD-L1 combination therapy in syngeneic mouse tumor models demonstrating the role of CD226 in antitumor immunity (Johnston et al. 2014). We propose to include a combination of CD226 agonist with PD-1 antagonist (pembrolizumab) including subjects that are not eligible for approved therapy, including those with no PD-L1 expression as measured by

immunohistochemistry (IHC). The potential benefit could be induced by CD226 agonist modulation of the TIL state or changes to the tumor environment and PD-L1 expression to increase the likelihood of response to pembrolizumab that is not induced by pembrolizumab alone. This may be in addition to the predicted additive effect of CD226 agonist with PD-1 antagonist in those patients that express PD-L1 and do not respond to pembrolizumab due to additional resistance mechanisms as discussed.

Combinations of anti-TIGIT antibodies with a clinically validated checkpoint inhibitor such as PD-1 or PD-L1 antibodies are also being actively investigated for treatment of many other types of cancers as monotherapy and in combinations (Solomon and Garrido-Laguna 2018).

In addition, in order to appropriately select patients who are more likely to benefit from PD-1/L1 inhibitors, various biomarkers have been investigated to predict clinical responses (Kim et al. 2017), such as CD8+ T cells in the tumor microenvironment (Tumeh et al. 2014), high tumor mutational loads (Rizvi et al. 2015), neoantigen heterogeneity (McGranahan et al. 2016), and PD-L1 expression in the tumor microenvironment (Tumeh et al. 2014). Among these suggested biomarkers, PD-L1 expression in pretreatment tumor samples has been most extensively studied and confirmed to be correlated with better clinical outcome in various malignancies (Powles et al. 2014; Borghaei et al. 2015; Chow et al. 2016; Daud et al. 2016). Recently, TILs have become the focus of many studies. As reported in recent literature, increased levels of TILs in women receiving neoadjuvant chemotherapy were associated with increased complete response (CR) rate and survival benefit in both triple-negative breast cancer (TNBC) and human epidermal growth factor receptor 2 (HER2)-positive breast cancers (Denkert et al. 2017). In another study, researchers assessed TILs and PD-L1 expression as prescreening enrichment biomarkers to identify patients with better clinical benefit from checkpoint inhibitors. The response rate in patients with TILs ≥7% was 32% versus 9% in patients with TILs <7% (Fisher's exact test $p = 0.06$) (Martin-Liberal et al. 2018). Therefore, quantifying TILs may help select patients for immunotherapy in early clinical trials from an otherwise unselected population (Teng et al. 2015).

The predicted mechanism of action of LY3435151 suggests that it will primarily act within the tumor environment where TILs are inhibited as described above by either sequestration of CD226 ligand or loss of the ligand's expression on tumor cells. While CD226 is frequently expressed on CD8+ TILs, not all tumors have TILs. As a result, TIL-negative tumors may not demonstrate a clinical response. The presence of TILs is therefore potentially essential for the drug effect in tumors. Based on this hypothesis, Study J1Q-MC-JZIA (JZIA) will:

1) Select solid tumors associated with TIL positivity.
2) Evaluate the presence of TILs prior to therapy to determine the impact of TIL presence and quantity on drug response.
3) Limit treatment to patients that are found to have pre-existing TILs upon analysis of the pre-treatment biopsy (Cohort D3 only).

The combined approach of selecting patients likely to have pre-existing TILs or using TIL selection based on pre-treatment biopsies will potentially increase the probability of observing a response in this study.

Study JZIA is a multicenter, open-label dose-escalation followed by a randomized dose-expansion study designed to investigate the safety and tolerability of LY3435151 when administered as monotherapy and in combination with pembrolizumab for the treatment of patients with advanced solid tumors associated with TIL positivity:

- TNBC (Stanton et al. 2016)
- Gastric adenocarcinoma (including gastroesophageal junction adenocarcinoma) (Steele et al. 2018)
- HNSCC (Steele et al. 2018)
- Squamous cervical carcinoma (Enwere et al. 2017)
- High-grade serous ovarian carcinoma (Stumpf et al. 2009)
- HCC (Xiao-Yan Cai et al. 2006)
- Undifferentiated pleomorphic sarcoma (UPS) and leiomyosarcoma (LMS; Pollack et al. 2017)

2.2. Background

LY3435151 is a fully human immunoglobulin-G1 antibody with Fc effector-null mutations, targeting the CD226 receptor. The activity of LY3435151 has been tested and confirmed in a variety of biological assays, including in vitro T cell functional assays. In tumor models with humanized mice, LY3435151 has shown similar to superior antitumor efficacy compared to anti-PD-L1 monotherapy.

The biological properties of antibody LY3435151 were characterized both in vitro and in vivo in nonclinical pharmacology studies, as described as follows:

- Binds human and cynomolgus monkey CD226 proteins with similar affinity
- Demonstrates no apparent binding to Fcγ receptors or immune effector function
- Displays agonist functional activity and stimulates T cell activation in vitro
- Demonstrates no apparent platelet activation in vitro
- Shows potent antitumor efficacy in humanized mouse models in vivo

As detailed in the Investigator's Brochure (IB), overall preclinical safety data support the proposed LY3435151 starting dose and dose escalation design of Study JZIA. Further details regarding the dosing rationale of LY3435151 for Study JZIA with supporting preclinical data may be found in Section 4.3.

Refer to the IB for detailed information pertaining to nonclinical efficacy, safety, and pharmacokinetics (PK).

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

refer to the IB. Refer to the IB/approved labeling for detailed background information on MK-3475.

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

2.3. Benefit/Risk Assessment

More information about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated adverse events (AEs) of LY3435151 are to be found in the IB.

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

Section 2.1 provides the rationale for the expected benefit, supporting the investigation of LY3435151 in combination with pembrolizumab. Pre-clinical data suggest that some of PD-1 signaling works through cross-talk with the CD226 signaling pathway. Therefore, the benefit of combining CD226 agonist with PD-1 blockade may be stronger activation of tumor-specific cytotoxic T-cells. This would potentially create better anti-tumor immune responses with combination therapy compared to anti-PD-1 blockade alone. Likewise, the same mechanism has the potential to make toxicities, such as irAEs, more frequent or more severe.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• **Ph1a Dose Escalation (Part A & Part B):** To assess the safety and tolerability of LY3435151, thereby identifying the RP2D, administered as monotherapy and in combination with pembrolizumab, in patients with advanced solid tumors of the following types: TNBC, gastric adenocarcinoma, HNSCC, squamous cervical carcinoma, high grade serous ovarian carcinoma, HCC, UPS, and LMS.	• DLTs • Safety (including, but not limited to): TEAEs, SAEs, deaths, and clinical laboratory abnormalities per CTCAE (version 5.0)
• **Ph1b Dose Expansion (Part C & Part D):** To assess the safety and tolerability of LY3435151: o administered as monotherapy (Part C), all patients must be PD-1/PD-L1 antagonist naïve: C1: TNBC(not eligible for IO therapies) C2: gastric adenocarcinoma o administered in combination with pembrolizumab (Part D), all patients must be PD-1/PD-L1 antagonist naïve: D1: TNBC (not eligible for IO therapies) D2: Gastric adenocarcinoma D3: TIL selected cohort with the following tumor types: HNSCC, squamous cervical carcinoma, high grade serous ovarian carcinoma, HCC, UPS, and LMS.	• Safety endpoints, including but not limited to the following: o TEAEs, SAEs • Clinical laboratory tests, vital signs, and physical examinations

Secondary	
• To assess the PK of LY3435151, administered as monotherapy and in combination with pembrolizumab, in patients with solid tumors	• Serum concentration of LY3435151 alone and when administered in combination with pembrolizumab
• To document any antitumor activity per RECIST v1.1 observed with LY3435151, when administered as monotherapy or in combination with pembrolizumab, in patients with solid tumors	• ORR • DCR • DoR • TTR • PFS
Tertiary/Exploratory	
• To assess the relationship between biomarkers, dose/exposure, and clinical outcomes, particularly in relation to tumor TIL levels	• Results of biomarker assessments • Clinical outcomes data
• To document any antitumor activity per RECIST v1.1 observed with LY3435151 when administered as monotherapy or in combination with pembrolizumab to patients with solid tumors associated with TIL positivity	• OS
• To document antitumor activity based on iRECIST observed with LY3435151 when administered as monotherapy or in combination with pembrolizumab to patients with solid tumors associated with high TIL positivity.	• iORR • iPFS • iDoR

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; DCR = disease control rate; DLT = dose-limiting toxicity; DoR = duration of response; HCC = hepatocellular carcinoma; HNSCC = head and neck squamous cell carcinoma; iDoR = duration of response per iRECIST; IO = immuno-oncology; iORR = overall response rate per iRECIST; iPFS = progression-free survival per iRECIST; iRECIST= immuno-Response Criteria in Solid Tumors; LMS = leiomyosarcoma; ORR = overall response rate; OS = overall survival; Ph = Phase; PFS = progression-free survival; PK = pharmacokinetics; RECIST = Response Criteria in Solid Tumors; RP2D = recommended phase 2 dose; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TIL = tumor-infiltrating lymphocyte; TNBC = triple-negative breast cancer; TTR = time to response; UPS = undifferentiated pleomorphic sarcoma.

4. Study Design

4.1. Overall Design

Study JZIA is a Phase 1a/1b, multicenter, open-label dose-escalation study followed by a randomized dose-expansion study of LY3435151 as monotherapy and in combination with pembrolizumab in patients with advanced solid tumors.

Section 1.2.1 contains the study schema for Phase 1a and Section 1.2.2 contains the study schema for Phase 1b.

4.1.1. Dose Escalation Phase

Phase 1a (dose escalation) will assess the safety and tolerability of LY3435151 to identify a monotherapy recommended phase 2 dose (RP2D) and a combination RP2D in patients with solid tumors associated with TIL positivity:

- TNBC
- Gastric adenocarcinoma (including gastroesophageal junction)
- HNSCC
- Squamous cervical carcinoma
- High-grade serous ovarian carcinoma
- HCC
- UPS and LMS.

Patients enrolled in Part A (Cohorts A1 through A6) will receive LY3435151 monotherapy. Patients enrolled in Part B (Cohorts B1 and B2) will receive LY3435151 and pembrolizumab.

The RP2D will be determined based on the number of observed dose-limiting toxicities (DLTs) and PK/pharmacodynamic (PD) data, and may be below the maximum tolerated dose (MTD), which may not necessarily be reached during the dose escalations. The dose-escalation phase will employ a modified toxicity probability interval (mTPI-2) method and starting with Cohort A2 will enroll at least three evaluable patients per cohort. Treatment cycles will consist of 21 days. A 2-cycle DLT observation will apply to all cohorts in Phase 1a. Refer to Section 4.1.1.1 for additional details on the dose escalation method.

A minimum of 1 patient will be enrolled in Cohort A1 and will receive a 10-mg dose. If the 10-mg dose level DLT period is cleared, Cohort A2 (30-mg dose level) will be initiated.

If a patient in Cohort A1 experiences a DLT, additional patients will be enrolled into Cohort A1 following the mTPI-2 method. Based on the mTPI-2 method, at least additional 4 patients will need to be enrolled and experience no DLT during the DLT observing period before escalating to the next dose level (Cohort A2).

After the first patient in Cohort A2 receives the first dose of LY3435151, there will be a delay of 1 week before the second patient receives LY3435151 to allow for safety observation. In all subsequent cohorts, the first patient in each dose level will be observed for at least 24 hours before treatment of additional patients; no additional delays are required for subsequent patients.

Patients in Cohorts A2, A3, A4, A5, and A6 will receive proposed doses of 30 mg, 100 mg, 300 mg, 900 mg, and 1800 mg, respectively, provided safety is established in the preceding cohorts. Once the DLT period of 42 days is completed for respective dose levels within Cohorts A1 to A6, 2 selected cohorts can be expanded with an additional 6 patients each to further inform safety, PK, and PD. For example, additional patients at dose level 5 (900 mg Q3W) may be enrolled in parallel with Cohort A6 after Cohort A5 has cleared the DLT period.

In the Combination Dose Escalation (Part B), 2 dose levels will be explored. Dose level 1 in Part B will be decided based on, but not limited to, the safety and PK/PD data from monotherapy expansion cohorts. The dose of pembrolizumab will remain constant. Once enrollment to dose level 1 in Part B begins, dose escalation will occur in parallel for both Part A and Part B. However, enrollment in a Part B cohort can begin only after all previous dose level cohorts in monotherapy and combination dose escalation (as applicable) are complete, as determined by Eli Lilly and Company (Lilly). For example, if dose level 5 900 mg Q3W is decided as the starting dose level for Part B, Cohort B1 will only begin after the safety of dose level 6 in monotherapy dose escalation is cleared, and Cohort B2 may begin only after both Cohort A6 and Cohort B1 are complete.

If safety data from Part A indicate that de-escalation of the LY3435151 dose is warranted, no additional patients will be enrolled in Treatment Part A or Treatment Part B at dose levels higher than the de-escalated dose.

Lilly and the investigators will hold a meeting to review safety and available PK/PD results after completion of the DLT period for each cohort to ensure it is safe to continue with the next dose-escalation cohort.

4.1.1.1. Dose Escalation Method

Dose escalation of LY3435151 will be driven by an mTPI-2 method taking into consideration available safety, PK, and PD data from previous dose levels for Cohorts A2 through A6. A minimum of 3 evaluable patients will be enrolled in Cohorts A2 through A6.

Similar to the 3+3 design, the mTPI-2 method incorporates prespecified escalation rules. However, 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.

Following a discussion between the Lilly clinical research physician/clinical research scientist (CRP/CRS) and the investigators, a more conservative dose selection may be applied to the next cohort (for instance, if PK/PD 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 or be de-escalated to a lower level, or escalation may cease. In the mTPI-2, the cohort size is not fixed. However, each cohort from Cohort A2 through A6 will contain a minimum of 3 evaluable patients, unless the escalation rules dictate that the dose should be de-escalated (“D” or “DU”). Doses can be escalated, de-escalated, and re-escalated. If the dose

decision was "DU," the dose cannot be re-escalated to that level. This study is designed to identify a dose level with a dose-limiting target toxicity rate of 30%. The mTPI-2 method considers an equivalence interval around the target toxicity rate. For this study, the equivalence interval is elicited to be (25%, 35%), indicating that any values between 25% and 35% can be considered as accepted toxicity rates for MTD. The final MTD will be the dose for which the estimated toxicity rate is the closest to the target toxicity rate of 30% and less than 35%. The resulting mTPI-2 decision rules for any cohort size up to 20, and a hypothetical example for DLT determination after all patients complete DLT evaluations, are provided in Appendix 6.

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/PD results (for example, maximum concentration [C_{max}], area under the concentration-time curve [AUC], PD results) will be used as secondary/supporting data for dose escalation.

Intermediate and/or higher dose schedules of administrations, as well as alternative schedules, 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.

4.1.1.2. Dose-Limiting Toxicity Determination

A DLT is defined as any of the events listed in the table below if the event occurs during the DLT observation period (2 Cycles/42 days for Cohorts A1-A6 and B1-B2) in Phase 1a, and toxicity that is not clearly and directly related to the primary disease or another etiology.

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

Dose-Limiting Toxicities of Study Treatment

Hematologic Toxicity
• Grade 3 thrombocytopenia associated with clinically significant bleeding and /or requiring platelet transfusion or Grade 4 thrombocytopenia of any duration • Grade ≥3 febrile neutropenia and/or neutropenia requiring G-CSF • Grade ≥4 neutropenia lasting >7 days • Grade ≥3 anemia requiring a blood transfusion • Other Grade 4 toxicity lasting >7 days, excluding toxicities listed below and Grade 3 endocrine irAEs that can managed by steroids or hormone replacement therapy

Nonhematologic Toxicity – Nonlaboratory
• Grade 4 AE (unless stated otherwise below)
• Any Grade ≥3 colitis or noninfectious pneumonitis irrespective of duration • Any other Grade 3 AE, excluding toxicities listed below • Grade ≥3 toxicity lasting >7 days despite optimal supportive care • Other Grade 2 irAE, excluding colitis or pneumonitis, that:

○ does not downgrade to Grade 1 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
Nonhematologic Toxicity – Laboratory/Investigations
• Grade 3 or 4 laboratory value if: ○ Medical intervention or hospitalization is required to treat the patient, or ○ The abnormality persists for >7 days (excluding amylase and lipase) • ALT or AST: ○ >8 × ULN ○ ≥2-fold above the patient's baseline value that lasts >7 days, if the patient has HCC or liver metastasis and had ALT or AST >3.0 × ULN at baseline ○ ≥3 × ULN with concomitant bilirubin >2 × ULN, in the absence of cholestasis • Total bilirubin >3 × ULN • Grade ≥3 amylase or lipase that is associated with symptoms or clinical manifestations of pancreatitis
Other Hematologic or Nonhematologic Toxicity
• Grade 5 toxicity (that is, death) • Grade ≥3 electrolyte abnormality that lasts >72 hours unless the patient has clinical symptoms, in which case all Grade ≥3 electrolyte abnormality regardless of duration should count as a DLT. • Treatment delay of >14 days due to an adverse event during Cycle 1 or Cycle 2. • 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 and 2.

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRP/CRS = clinical research physician/clinical research scientist; DLT = dose-limiting toxicity; G-CSF = granulocyte colony-stimulating grown factor; HCC = hepatocellular carcinoma; irAE = immune-related adverse event; ULN = upper limit of normal.

Potential DLTs that are AEs that are reasonably anticipated AEs for concomitant medication should be reviewed by the treating investigator and Lilly CRP/CRS before final determination as a DLT. Review and discussion may include additional participating investigators. Such review may determine that confounding factors render the case to be not evaluable for the purposes of dose selection. Adverse events from such non-evaluable patients will also be reviewed throughout the dose escalation process in Phase 1a.

The definition excludes the following events:

- Toxicity that is clearly and directly related to the primary disease or to another etiology is excluded from this definition
  - Immune-related Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the patient is asymptomatic

- Grade 3 inflammatory reaction attributed to a local antitumor response (such as inflammatory reaction in the lymph nodes or at sites of metastatic disease)
- Any grade vitiligo or alopecia
- First occurrence of Grade 3 infusion-related reaction (IRR) during infusion of LY3435151, if all of the following criteria are met:
  - the patient did not receive corticosteroid prophylaxis,
  - the Grade 3 IRR resolves within 6 hours with appropriate clinical management, and
  - if symptoms reappear, the event would be considered a DLT
- Grade 3 or 4 neutropenia meeting both of the following criteria:
  - is not associated with fever or systemic infection, and
  - improves by at least 1 grade within 7 days
- Grade 3 or 4 lymphopenia
- Grade 3 nausea or vomiting < 72 hours with adequate antiemetic and other supportive care
- Grade 3 fatigue < 1 week
- ≥ Grade 3 electrolyte abnormality that lasts <72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions
- ≥ Grade 3 amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis

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

4.1.1.3. DLT-Equivalent Toxicities

A DLT-equivalent toxicity (ET) is an AE that meets the DLT criteria as defined above and occurs in any cycle other than the DLT assessment period for cohorts in Phase 1a (42 days for Cohorts A1-A6 and B1-B2) and occurs in any cycle for cohorts in Phase 1b. In addition to the DLT assessment period, available safety data beyond the DLT assessment period may also be taken into consideration prior to a decision to advance to the next dose level or the determination of the RP2D.

For individuals experiencing a DLT-ET, dose modifications can be made as outlined in Section 6.6. If cumulative incidence of DLT-ET is 30% at any point during study, re-evaluation of dose will occur.

4.1.1.4. Determination of Recommended Phase 2 Dose

The RP2D will be chosen following discussion between the Lilly CRP/CRS and the investigators based on consideration of the totality of the data during interim analyses and upon completion of

Phase 1a (not inclusive of the backfill cohorts), including but not limited to LY3435151 dose adjustments, AEs, chronic intolerance, PK/PD data, and irAEs. All available data will be used including AEs in the short term (90 day) follow-up period. If LY3435151 has an acceptable clinical safety profile and shows sufficient activity, additional studies and/or cohorts may be added to determine a safe dose alone or in combination with other anticancer therapies. Tumor-infiltrating lymphocyte level and other biomarkers will be evaluated and may influence enrichment strategies for subsequent studies and/or cohorts.

4.1.2. Dose Expansion Phase

For both Part A and Part B, after all patients in the dose-escalation phase have completed the DLT observation period or discontinued, an interim safety and PK/PD analysis will be conducted before opening the dose expansions. Monotherapy Cohorts (C1 and C2) can start accruing patients as soon as the Part A RP2Dm decision has been made.

In the dose expansion phase 1b, a 2-stage design with randomization will be implemented to determine the treatment for patients with immune-oncology (IO) naïve TNBC and gastric adenocarcinoma. Within each tumor type of IO naïve TNBC and gastric in the dose expansion phase, Stage 1 will enroll 16 patients to be randomized with 1:1 ratio to receive either LY3435151 monotherapy (Cohort C1 or C2) or LY3435151 and pembrolizumab combination therapy (Cohort D1 or D2). Randomization will begin after the RP2Dc has been selected and continue only until 8 patients have accrued into the C1 and C2 cohorts. At Stage 2, approximately another 32 patients in each tumor type (to a total of at least 40 patients) will be enrolled to receive LY3435151 in combination with pembrolizumab (Cohort D1 or D2). An interim data review will be performed based on safety, efficacy, and PK/PD data from the first 20 enrolled patients in combination dose expansion (including patients from both Stage 1 and Stage 2) for each tumor types of IO naïve TNBC and gastric adenocarcinoma.

Approximately 30 patients with other IO naïve tumor types will be selected for enrollment based on TIL positivity and will receive LY3435151 in combination with pembrolizumab (Cohort D3). Patients in this cohort should be tested for all biomarkers or companion diagnostic tests required to confirm that the patient is not eligible for any approved IO therapeutic drug treatment prior to being screened for eligibility to receive LY3435151 in combination with pembrolizumab based on TIL positivity.

4.2. Scientific Rationale for Study Design

The overall rationale for the study design is described in the Introduction section under Study Rationale (Section 2.1) and in the Statistical Considerations section (Section 9). Dose selection details can be found below.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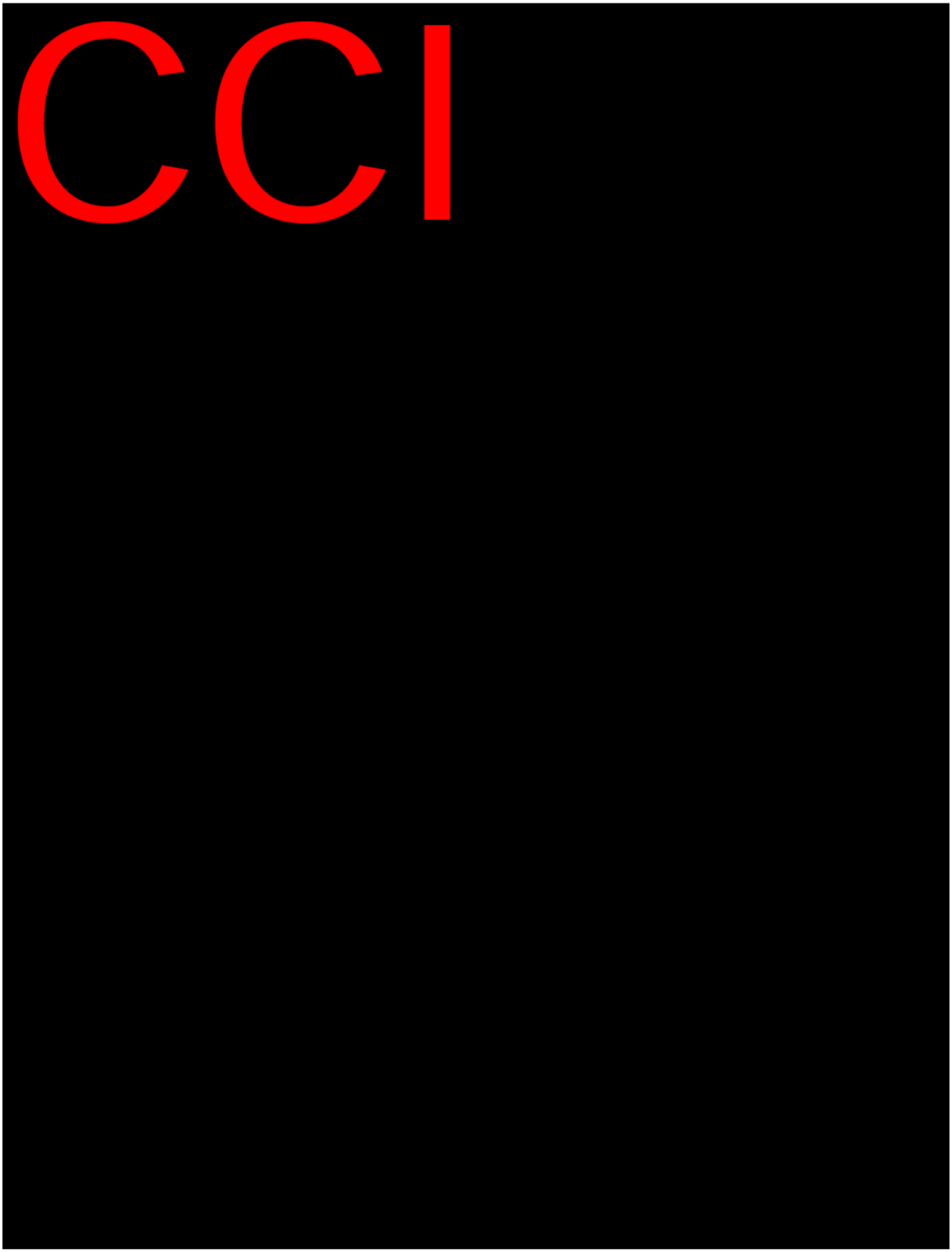
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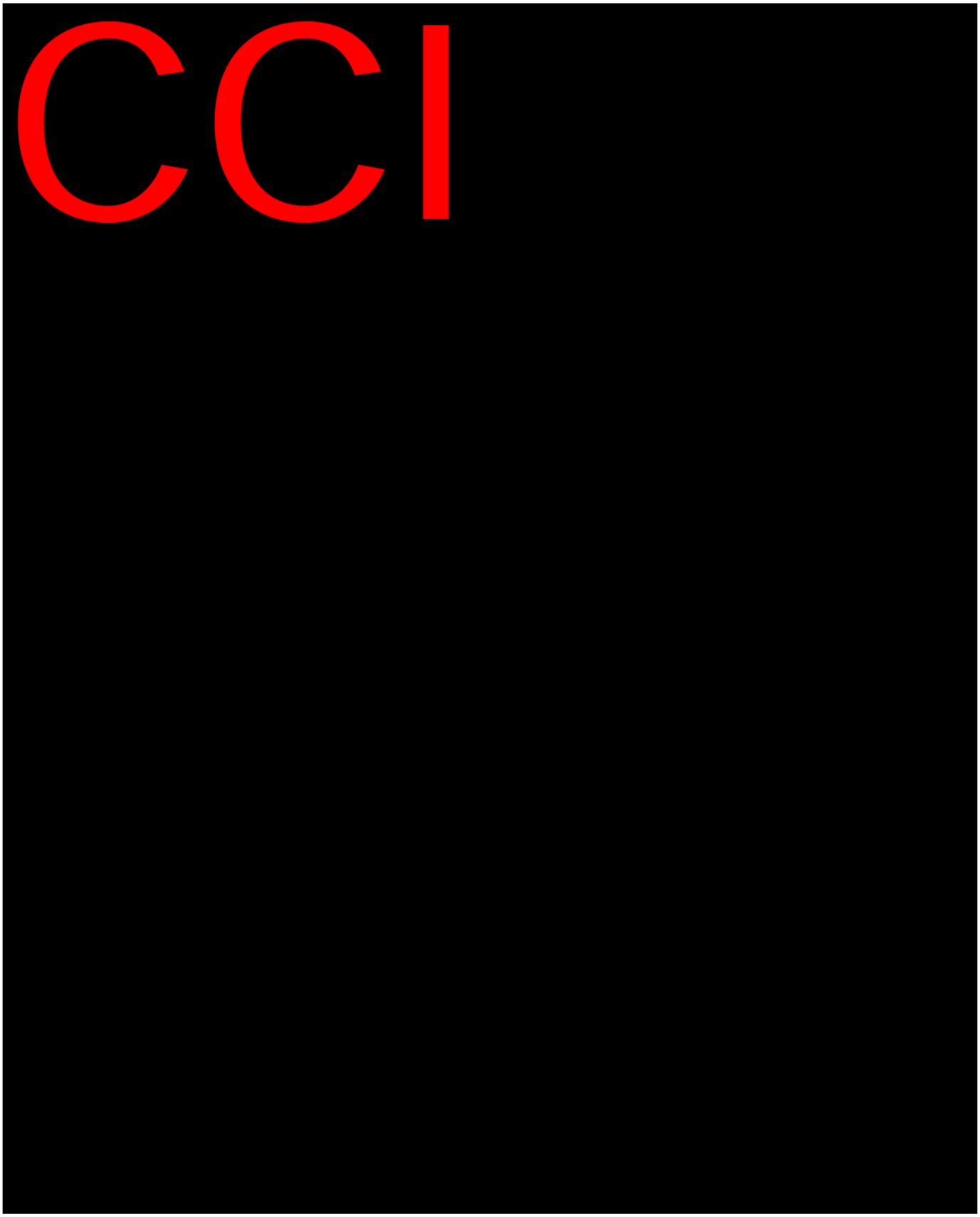
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4.4. End of Study Definition

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

5. Study Population

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

5.1. Inclusion Criteria

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

Age

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

Type of Participant and Disease Characteristics

2. Participants who have histological or cytological evidence of a diagnosis of a solid tumor that is advanced and/or metastatic.
   a. Part A and B Dose-Escalation Phase:
      - The patient must have histological or cytologically proven TNBC, gastric adenocarcinoma (including gastroesophageal junction), HNSCC, cervical carcinoma, high-grade serous ovarian carcinoma, HCC, UPS, or LMS.
      - The patient must be, in the judgment of the investigator, an appropriate candidate for experimental therapy and should have progressed through or is intolerant to therapies known to confer clinical benefit (including prior IO therapies).
   b. Part C (1 and 2) and Part D Expansion Phase (IO naïve TNBC and gastric carcinoma):
      - The patient must be, in the judgment of the investigator, an appropriate candidate for experimental therapy and should have progressed through or is intolerant to therapies known to confer clinical benefit (including IO therapies).
      - Patients with a cancer that is eligible for IO therapy based on a companion diagnostic test must have testing performed and be determined to be not eligible.
      - Gastric carcinoma patients who are microsatellite instability-high or Epstein-Barr Virus-positive will be excluded
        - Gastric carcinoma patients that have HER2 amplification should have received prior anti-HER2 therapy.
      - All patients must be PD-1/PD-L1 antagonist naïve. Patients that were not eligible for pembrolizumab based on PD-L1 expression status will be eligible for inclusion as discussed in Section 2.1.
      - Patients must have histological or cytologically proven:
        i. Cohort C1 and D1: recurrent/metastatic, unresectable TNBC and not eligible for approved IO therapies.
        ii. Cohort C2 and D2: recurrent/metastatic, unresectable gastric adenocarcinoma (including gastroesophageal junction)

iii. Cohort D3: recurrent/metastatic, unresectable HNSCC, squamous cervical carcinoma, high-grade serous ovarian carcinoma, HCC, UPS, or LMS, that are associated with TIL positivity.
- Screening for TILs is required (threshold to be determined by the sponsor).

3. Have at least 1 measurable lesion assessable using standard techniques by Response Evaluation Criteria in Solid Tumors Version (RECIST) 1.1 (Eisenhauer et al. 2009). Use of positron emission tomography scans and ultrasounds for diagnostic purposes is not permitted.
4. Are able and willing to provide the protocol required biopsies from a newly obtained core, endoscopic, or excisional pre-treatment biopsy of a tumor lesion and a newly obtained core, endoscopic, or excisional biopsy collected during the study treatment period (see Section 8.8).
5. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Oken et al. 1982).
6. Have discontinued all previous treatments for cancer for at least 14 days and recovered from the acute effects of therapy. Patients must have discontinued from previous treatments, as shown below:

Previous Treatment	**Length of Time Prior to First Dose of Study Treatment**
Cytotoxic therapies or targeted agents that are small-molecule inhibitors	≥14 days
Mitomycin-C or nitrosoureas	≥42 days
Biologic agents (for example, antibodies such as anti-PD-1 or anti-PD-L1)	≥14 days
Radiotherapy	≥28 days if greater than 30% of bone marrow is irradiated or ≥7 days if less than 30% of bone marrow is irradiated. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis.
Limited field radiotherapy for palliative intent	≥14 days
Major surgery, excluding biopsy	Patients with recent major surgery must have recovered, in the opinion of the investigator, from the toxicity and/or complications from the intervention before starting therapy.

Abbreviations: PD-1 = programmed death-1; PD-L1 = programmed death-ligand 1.

7. For Phase 1a, prior anti-PD-1 or anti-PD-L1 therapy or other immunotherapy is allowed as long as the following criteria are met:

a. did not experience a Grade 4 immune-related toxicity or any immune-related toxicity that led to permanent discontinuation of prior anti-PD-1, anti-PD-L1, or other immunotherapy

b. did not experience a less than or equal to Grade 3 irAE that has not recovered to Grade 1 after use of high-dose corticosteroids that occurred during prior immunotherapy

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

c. did not experience any of the following irAEs during prior anti-PD-1, anti-PD-L1, or other immunotherapy:

   i. any grade ocular irAE

   ii. serious neurologic irAE, Guillain-Barre, Myasthenia Gravis, encephalitis

   iii. serious cardiovascular irAE, such as myocarditis

d. did not require immunosuppressive agents, other than corticosteroids for the management of an AE; or does not currently require maintenance doses of > to 10 mg prednisone/prednisolone (or equivalent) per day for irAE

8. Have adequate organ function, as defined below:

System	Laboratory Value
Hematologic	
ANC	≥1.5 × 10^9 cells/L
Platelets	≥150 × 10^9 cells/L
Hemoglobin	≥9 g/dL
PT/INR or 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 5)	≤1.5 × ULN OR ≥50 mL/min

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; PT/INR = prothrombin time-international normalized ratio; ULN = upper limit of normal.

9. Are able and willing to make themselves available for the duration of the study and are willing to follow study procedures.
10. Have an estimated life expectancy of ≥12 weeks, in the judgment of the investigator.

Sex

11. Men with partners of childbearing potential or women with childbearing potential (WOCBP) must agree to use a highly effective contraceptive method of birth control (Appendix 3) during study treatment and for at least 6 months following the last dose of study drug.
12. Women of childbearing potential must have a negative serum pregnancy test documented within 7 days prior to initiation of treatment (see Appendix 3).

Informed Consent

13. Have given written informed consent/assent prior to any study-specific procedures.

5.2. Exclusion Criteria

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

Medical Conditions

14. Have a serious concomitant systemic disorder that, in the opinion of the investigator, would compromise the patient's ability to adhere to the protocol, such as the following:
    a. human immunodeficiency virus (HIV)-positive patients (HIV 1 and/or 2; screening not required) are excluded unless they are well-controlled on highly active antiretroviral therapy with:
        i. No evidence of acquired immunodeficiency syndrome-defining opportunistic infections within the last 2 years, and
        ii. CD4 count > 350 cells/μl
    b. active or uncontrolled clinically relevant hepatitis B virus or hepatitis C virus infection. Patients with stable and chronic viral hepatitis are eligible.
        i. Not more than one of the following: viral hepatitis, nonalcoholic steatohepatitis, and alcohol induced hepatitis.
    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 CRP/CRS, may affect the interpretation of results. Patients with carcinoma in situ of any origin and patients with prior malignancies who are in remission and whose likelihood of recurrence is very low (such as basal cell carcinoma), as judged by the Lilly CRP/CRS, are eligible for this study
    f. active 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. Patients at risk of vascular AEs, such as those with a history of angiitis, arteritis, or hypersensitivity vasculitis as an AE to medication, for example, are not eligible

Note: This criterion does not apply to patients with: (i) vitiligo, alopecia, or type I diabetes mellitus; (ii) residual hypothyroidism due to an autoimmune condition requiring only hormone replacement; or (iii) psoriasis not requiring chronic systemic immunosuppressive treatment within the past 2 years, not expected to recur in the absence of an external trigger

g. use of escalating or chronic supraphysiologic doses of corticosteroids or immunosuppressive agents (such as exceeding 10 mg/day of prednisone or equivalent). Use of topical, ophthalmic, inhaled, and intranasal corticosteroids is permitted

Note: This criterion does not apply to patients with: (i) controlled 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; (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 electrocardiogram (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; recent myocardial infarction; or mean corrected QT interval [QTc] ≥470 ms calculated using Fridericia's correction and confirmed by triplicate ECG)

15. Have symptomatic central nervous system (CNS) malignancy or metastasis (screening not required). Patients with treated CNS metastases are eligible for this study if they are not currently receiving corticosteroids and/or anticonvulsants to treat

CNS metastases, and their disease is asymptomatic and radiographically stable for at least 30 days.

16. Have unresolved toxicities from prior anticancer therapy, including irAE, that have not resolved to the baseline levels prior to starting the prior anticancer therapy.
17. Have received a live vaccine within 30 days before the first dose of study treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines are live attenuated vaccines and are not allowed.
18. Are pregnant, breastfeeding, or planning to become pregnant during the study or within 6 months of the last dose of study intervention. Plan to be breastfeeding from Cycle 1 Day 1 of study or within 6 months of the last dose of study intervention.
19. Have a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study, or is not in the best interest of the patient to participate, in the opinion of the treating investigator
20. Have current or history of allergy or hypersensitivity to study drug components
21. Have previously received a CD226 agonist.
22. Have experienced a venous thromboembolic event (deep vein thrombosis [DVT]/pulmonary embolism [PE]) within 12 weeks of screening
23. Have a history of recurrent (≥2) venous thromboembolic event (DVT/PE).
24. Have a history of significant bleeding disorders or history of bleeding that required medical intervention to stop or prevent bleeding or known platelet dysfunction.
25. Require chronic granulocyte colony-stimulating factor (G-CSF) use to prevent neutropenia prior to Cycle 1 Day 1 of study.
26. For Parts B and D only: have severe hypersensitivity to pembrolizumab and/or any of its excipients.
27. Have had an allogenic tissue/solid organ transplant.

Prior/Concurrent Clinical Study Experience

28. Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study
29. Have participated, within the last 30 days, in a clinical study involving an investigational product. If the previous investigational product has a long half-life, 5 half-lives or 30 days, whichever is longer, should have passed

5.3. Lifestyle Considerations

There are no specific lifestyle restrictions required by this study.

5.4. Screen Failures

Screen failures are defined as participants who consent/assent to participate in the clinical study but are not subsequently enrolled. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Individuals may be rescreened up to 2 times. The interval between rescreening should be ≥2 weeks. Each time rescreening is performed, the individual and/or the individual's legally acceptable representative, parent(s), or legal guardian (when applicable) must sign a new ICF and will be assigned a new identification number. Repeating of laboratory tests during the screening period or repeating screening tests to comply with the protocol-designated screening period does not constitute rescreening.

6. Study Intervention

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

6.1. Study Intervention(s) Administered

All enrolled patients will receive LY3435151 administered as an IV infusion. Refer to the Pharmacy Manual for additional details regarding LY3435151 infusion duration. For patients enrolled in a combination cohort (Phase 1a or Phase 1b, Part B or Part D), pembrolizumab will be administered as an IV infusion over approximately 30 minutes prior to the LY3435151 infusion.

The table below shows the treatment regimens for Phase 1a/1b. Doses will be administered at approximately the same times on each day.

Pembrolizumab will be administered using IV infusion on Day 1 of each 3-week treatment cycle after all procedures and assessments have been completed. LY3435151 will be administered 30 to 60 minutes post administration of pembrolizumab.

Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes (-5 min/+10 min).

Study Intervention Groups and Duration

	Phase/Part	Study Drug(s) (Route of Administration)	Cohort / Dose Level	***Proposed*** Doses	Dose Schedule
Dose-Escalation Phase	**Monotherapy/ Part A**	LY3435151 (IV)	A1: *DL 1*	10 mg	D1 of each 21-day cycle (Q3W)
			A2: *DL2*	30 mg	
			A3: *DL 3*	100 mg	
			A4: *DL 4*	300 mg	
			A5: *DL 5*	900 mg	
			A6: *DL 6*	1800 mg	
	Combination/ Part B	LY3435151 (IV)	B1: *DL 1*	*TBD* [a,b]	
			B2: *DL 2*	*TBD* [a]	
		Pembrolizumab (IV)	B1/B2	200 mg	

	Phase/Part	Study Drug(s) (Route of Administration)	Cohort / Dose Level	***Proposed*** Doses	Dose Schedule
Dose-Expansion Phase	**Monotherapy/ Part C**	LY3435151 (IV)	C1/C2: *Monotherapy RP2D*	*TBD* [a]	D1 of each 21-day cycle (Q3W)
	Combination/ Part D	LY3435151 (IV)	D1/D2: *Combination RP2D*	*TBD* [a]	
		Pembrolizumab (IV)	D1/D2	200 mg	

Abbreviations: D = Day; DL = dose level; IV = intravenous; RP2D = recommended phase 2 dose; Q3W = every 3 weeks; TBD = to be determined.

[a] Not to exceed maximum tolerated dose in dose escalation.

[b] LY3435151 dosing in combination will be 1 dose level below the tolerated monotherapy dose level

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

6.2. Preparation/Handling/Storage/Accountability

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

5. Investigators should consult the study drug information provided in the Pharmacy Manual or label for the specific administration information (including warnings, precautions, contraindications, adverse reactions, and dose modifications).

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study. The Phase 1b dose expansion part will implement a randomization design to mitigate the selection bias in allocating patients with TNBC or gastric adenocarcinoma to either monotherapy dose expansion (Part C) or combination therapy dose expansion (Part D) for the first 16 patients enrolled into the TNBC or into the gastric cohorts.

6.4. Study Intervention Compliance

Participant compliance with study intervention will be assessed at each visit. Study intervention is administered intravenously only at the investigational sites by the authorized study site personnel. As a result, treatment compliance is ensured. Deviation(s) from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF).

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, antibiotics, prebiotics, synbiotics, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

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

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

The Lilly CRP/CRS should be contacted if there are any questions regarding concomitant or prior therapy. No other chemotherapy, hormone therapy, immunotherapy, herbal supplements and/or herbal drugs intended to treat cancer, or experimental drugs will be permitted while the patients are in this study.

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

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol

- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy

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

  Note: Inhaled steroids are allowed for management of asthma.

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

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

All concomitant medications received within 28 days prior to the first dose of study treatment and up to 30 days after the last dose of study treatment should be recorded. Concomitant medications administered 30, 60, and 90 days after the last dose of study treatment should be recorded for SAEs and events of clinical interest.

6.5.1. Palliative Medicine and Supportive Care

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

Palliative radiation therapy is permitted after discussion with and agreement of the Lilly CRP/CRS or designee for irradiating small areas of painful metastases that cannot be managed adequately using systemic or local analgesics. Such areas must not be an identified target lesion and must not constitute progressive disease or meet RECIST/immuno-Response Evaluation Criteria in Solid Tumors (iRECIST) criteria for progressive disease. Any symptomatic deterioration or clinical disease progression requiring, in the opinion of the investigator, other forms of specific antitumor systemic therapy will be cause for discontinuation of study therapy.

In addition, any disease progression requiring other forms of specific antitumor therapy will also necessitate early discontinuation from the study. Appropriate documentation for all forms of

premedications, supportive care, and concomitant medications must be captured on the case report form (CRF). Replacement hormonal therapy initiated before study entry will be allowed.

Patients should receive full supportive care. Hematopoietic growth factors (eg, G-CSFs) may be administered according to institutional guidelines and the local Package Insert, except in the DLT observation period. Hematopoietic growth factors will be allowed in the DLT observation period if a patient experiences neutropenia that is declared an AE. Administration of G-CSFs prior to first occurrence of neutropenia is prohibited. Blood product transfusions are permitted throughout the study.

Prophylactic antibiotic treatment should be consistent with American Society of Clinical Oncology (ASCO) guidelines (Flowers et al. 2013).

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) with adherence to the local Package Insert. All concomitant medications should be recorded throughout the patient's participation in the study.

6.6. Dose Modification

Dose reductions are not allowed in this study.

No dose modification for either LY3435151 or pembrolizumab (delays or omissions greater than 14 days) is allowed during the DLT observation period (42 days for Cohorts A1-A6 and B1-B2). Starting at Cycle 3, dose delays will be permitted. See Section 7 for discontinuation criteria.

After the DLT observation period, doses of the LY3435151 or pembrolizumab may be delayed, omitted, or discontinued to manage specific AEs or other toxicities. 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 treatments and apply the dose modification guidelines. Investigators are encouraged to consult Lilly for additional guidance.

A cycle is defined as an interval of 21 days as shown in the SoA (Section 1.3). 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.

Starting at Cycle 3, if a patient requires a cycle delay for any safety reasons other than those above, study treatment should be resumed within 21 days, if possible and appropriate. In rare circumstances, a cycle delay of >21 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. Longer delays may be allowed for irAEs, as described in Section 6.6.1. 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.

A 4-hour observation period from the end of LY3435151 administration will occur in Cycles 1 and 2. During the observation period, patients treated with LY3435151 should be closely monitored for signs and symptoms indicative of an IRR by medical staff from the start of the infusion, in an area where emergency medical resuscitation equipment and other agents (eg, epinephrine, prednisolone, or equivalents) are available. LY3435151 IRRs will be defined according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 definition of IRRs.

The table below presents instructions for management of infusion-related reactions associated with LY3435151, pembrolizumab, or combination therapy.

Management of Infusion-Related Reactions

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	• Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	• **Stop Infusion.** • Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr. to 50 mL/hr.). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5 h (± 30 minutes) prior to infusion of LY3435151 or pembrolizumab with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500 to 1000 mg PO (or equivalent dose of analgesic).

Grades 3 or 4 **Grade 3:** Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilator support indicated	• **Stop Infusion.** • Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the CTCAE v5.0 at http://ctep.cancer.gov		

If an IRR is clearly attributable to only one of the drugs, then the patient may continue to receive the other drug after consultation with the sponsor.

6.6.1. Dose Modification and Toxicity Management for Immune-Related AEs Associated with LY3435151, Pembrolizumab, or Combination Therapy

An irAE may be defined as an AE consistent with an immune-mediated chronic inflammatory reaction associated with drug exposure. These irAEs may occur shortly after the first dose or several months after the last dose of drug and may affect more than 1 body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data of immune checkpoint inhibitors, most irAEs are reversible and can be managed with interruptions of therapy, administration of corticosteroids, and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, and skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue therapy and administer corticosteroids. Dose modification and toxicity management guidelines for potential irAEs are provided in the following table.

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

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Study treatment must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab or LY3435151 treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If study treatment has been withheld, study treatment may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity grade (CTCAE V5.0)	Action with study treatment	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AST or ALT elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 - 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3, 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 – 2 mg/kg or equivalent)	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		

injury			followed by taper	
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

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

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

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

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

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

NOTE: The frequency or severity of known potential immune-related adverse events with pembrolizumab may be increased in combination with LY3435151. Therefore, particularly close monitoring for irAEs should be standard. For all irAEs of grade 2 or above, would consider specialist consultation and/or additional work-up including labs and biopsy to confirm diagnosis. For certain toxicities of more serious clinical consequence, such as myocarditis, neurologic, or ophthalmologic irAE, consider withholding therapy for grade 2 toxicities and early hospitalization for close monitoring for grade 3 toxicities. For any grade 2 or greater suspected irAE, please consult with Lilly CRS/CRP.

6.6.2. Dose Modification of Pembrolizumab

No dose reductions of pembrolizumab are permitted, but the dose may be withheld or discontinued for toxicity management. Guidelines for management of IRRs are located in Section 6.6 and for irAEs in Section 6.6.1.

6.6.3. Other allowed dose interruption for pembrolizumab

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

6.7. Intervention after the End of the Study

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

6.7.1. Treatment after Study Completion

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

6.7.1.1. Continued Access

Participants who are still on study intervention at the time of study completion may continue to receive study intervention if they are experiencing clinical benefit and no undue risks. The continued access period will apply to this study only if at least 1 participant is still receiving study intervention 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.

The continued access period will begin after study completion and ends at End of Study. The participant's continued access to study treatment will end when a criterion for discontinuation is met (Section 7). Continued access follow-up will begin when the participant and the investigator agree to discontinue study treatment. Follow-up procedures will be performed as shown in the SoA (Section 1.3).

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

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

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

Possible reasons leading to permanent discontinuation of investigational product:

- **Participant Decision**
  - the participant or the participant's designee (for example, parents or legal guardian) requests to discontinue investigational product.

If a clinically significant finding is identified (including but not limited to changes from baseline in QTc using Fridericia's formula after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

In addition, participants will be discontinued from the investigational product in the following circumstances:

- the patient becomes pregnant during the study
- the patient is significantly noncompliant with study procedures and/or treatment
- 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 patient requires a dose delay of >21 days, excepted as described in Section 6.6.
- disease progression. Disease progression should be confirmed per iRECIST by the site 4 to 8 weeks after site-assessed first radiologic evidence of progressive disease in clinically stable participants. Participants, who have unconfirmed disease progression (iPUD) may continue on treatment at the discretion of the investigator until progression per iRECIST criteria is confirmed by the site. Patients continuing treatment in these circumstances must provide additional informed consent to continue therapy. A separate ICF will be created for this purpose. Any participant deemed clinically unstable should be discontinued from study treatment at first radiologic evidence of progressive disease and is not required to have repeat tumor imaging for confirmation of progressive disease by iRECIST.
- unacceptable toxicity
- the patient experiences a DLT or a DLT-equivalent toxicity
- occurrence of a venous thromboembolic event (DVT/PE) during the study
- the investigator decides that the patient should be discontinued from study treatment
- the patient experiences any of the following abnormal hepatic parameters, with the exception of patients who have existing liver metastases and elevated liver enzymes (>2×ULN) at baseline:
  - ALT or AST >8×ULN
  - ALT or AST >5×ULN for more than 1 week

  - ALT or AST >3×ULN and (TBL >2×ULN or INR >1.5)
  - ALT or AST >3×ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia
- Pembrolizumab will be discontinued after completion of approximately 2 years of treatment with pembrolizumab (completion of 35 treatments with pembrolizumab)

  Note: The number of treatments is calculated starting with the first dose of pembrolizumab in Study JZIA.

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

7.2. Participant Discontinuation/Withdrawal from the Study

Participants will be discontinued in the following circumstances:

- enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- patient decision
  - the patient or the patient's designee requests to be withdrawn from the study
- the patient becomes pregnant during the study. See Section 8.3 regarding regulatory reporting requirements on fetal outcome.

Participants discontinuing from the study prematurely for any reason should complete AE and other safety follow-up per Section 1.3 (Schedule of Activities), Section 8.3 (Adverse Events and Serious Adverse Events), and Section 8.2 (Safety Assessments).

Participants who withdraw their consent from the study and request to discard their genetic and biomarker samples will have their samples destroyed. Analysis results that are available before the consent withdrawal may be published in articles or other disclosures without an identifiable individual patient information.

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, then the patient should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the patient to continue on study treatment. If the investigator and the sponsor CRP/CRS agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP/CRS to allow the inadvertently enrolled participant to continue in the study with or without

treatment with investigational product. Safety follow up is as outlined in Section 1.3 (Schedule of Activities), Section 8.3 (Adverse Events and Serious Adverse Events), and Section 8.2 (Safety Assessments) of the protocol.

7.3. Lost to Follow-Up

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

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

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

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.7.2.

8. Study Assessments and Procedures

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

8.1. Efficacy Assessments

Tumor assessments will be performed for each patient at the times shown in the SoA (Section 1.3).

Response Evaluation Criteria in Solid Tumors v1.1 (Eisenhauer et al. 2009) and iRECIST (Seymour et al. 2017) will be applied as the primary criteria for assessment of tumor response and date of tumor progression. The method of tumor assessment used at baseline must be used consistently throughout the study. Local tumor imaging (investigator assessment with site radiological reading) will be used. See Section 8.1.1 for detailed information regarding iRECIST for immune-based therapies.

Computed tomography (CT) scans, including spiral CT, are the preferred methods of measurement (CT scan thickness recommended to be ≤5 mm); however, magnetic resonance imaging is also acceptable in certain situations, such as when body scans are indicated or if there is a concern about radiation exposure associated with CT. Intravenous and oral contrast are required unless medically contraindicated.

See Section 9.4.3 for definitions of the efficacy endpoints.

8.1.1. iRECIST for Immune-Based Therapies

Rationale of Using iRECIST after First Radiologic PD by RECIST 1.1

The response to immunotherapy may differ from the typical responses observed with cytotoxic chemotherapy, including the following (Wolchock et al. 2009; Nishino et al. 2013):

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

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

After initial disease progression defined by RECIST 1.1, iRECIST guidelines will be applied in the following tumor assessments. In iRECIST, any new lesions are categorized as measurable or non-measurable. Up to 5 lesions total (up to 2 per organ) can be selected as new lesion-target (NL-T). All other new lesions will be followed as new lesion-non-target (NL-NT). The NL-T sum of diameters will be calculated and recorded separately from the sum of diameters for target lesions identified at baseline.

Tumor response by iRECIST will be classified as confirmed progression (iCPD), or unconfirmed progression (iUPD), or stable disease or response (iSD/iPR/iCR) at all subsequent imaging. The initial tumor scan showing disease progression by RECIST 1.1 will be assigned as unconfirmed progression (iUPD) for overall response.

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

- For target lesions: any further increase in the previously identified target lesion sum of diameters by 5mm or more after iUPD.
- For non-target lesions: any further increase in the size of previously identified non-target lesion iUPD (the increase doesn't need to meet RECIST 1.1 criteria for unequivocal progression)
- For new lesions:
    - an increase in the NL-T previously identified as iUPD and increase ≥5mm in sum of diameter OR
    - any increase for NL-NT OR
    - any appearance of additional new lesions

The overall response remains iUPD, IF

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

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

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

Imaging and Treatment Guideline for Patients Who Have Radiologic Evidence of Progressive Disease by RECIST 1.1

If a patient is clinically stable at the first radiologic PD by RECIST 1.1, the patient should not be discontinued from the study until progression is confirmed no less than 4 weeks and no more than 8 weeks later by iRECIST. The continuation of treatment after initial radiologic PD takes into consideration the observation that some patients may experience transient tumor flare or pseudoprogression with immunotherapy, but could have disease response later. Patients who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor assessment will resume at the next scheduled imaging time point, if clinically stable. Patients will be discontinued from study treatment if disease progression is confirmed by iRECIST (Seymour et al. 2017).

If a patient is clinically unstable, the patient should be discontinued from the study treatment at the first radiological PD by RECIST 1.1. The repeat tumor imaging for confirmation of PD by iRECIST is not required.

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

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

Imaging and Treatment Guideline for Patients who have First Radiologic PD by RECIST 1.1

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of progressive disease by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD by iRECIST	May continue study treatment while waiting for confirmatory scan by iRECIST	Not required; Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST	No additional imaging required	Discontinue treatment	No additional imaging required	Not applicable
Repeat tumor imaging shows iUPD by iRECIST	Repeat imaging at 4 to 8 weeks to confirm PD by iRECIST. May occur at next regularly scheduled imaging visit	Continue treatment at the investigator's discretion	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only	Discontinue treatment.
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per Investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study treatment at the Investigator's discretion.	Continue regularly scheduled imaging assessments.	Discontinue treatment

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

8.1.2. Criteria Required to Receive Treatment during Confirmatory Scan Period

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

- absence of clinically significant deterioration
- 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

8.2. Safety Assessments

For each patient, ECGs, vital signs, laboratory tests, and other tests should be collected as shown in the SoA (Section 1.3). Results from any clinical laboratory test analyzed by a central laboratory (refer to Appendix 2) will be provided to investigative sites by Lilly or its designee.

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

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

Serious adverse events will [redacted] as soon as they are reported. Cumulative SAEs, reasonably anticipated SAEs, and relevant literature will be reviewed at least quarterly by [redacted]. Safety findings (including new preclinical data), will be reviewed by a broader group ([redacted]) on a regular basis. Serious safety findings can be escalated to an independent internal safety review committee.

8.2.1. Clinical Safety Laboratory Assessments

- Lilly or its designee will provide the investigator with the results of safety laboratory tests analyzed by a central vendor, if a central vendor is used for the clinical trial.
- See Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or until the completion of Visit 801 after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

If there is an abnormal laboratory value or abnormal value for any other diagnostic or screening test (for example, blood pressure increased or neutrophils decreased) and it is known to be related to a disease diagnosis (for example, hypertension or neutropenia) this should be reported in the CRF as an AE. Do not enter the test abnormality, enter the disease diagnosis or categorical term. If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (for example, SAE or AE or dose modification), then the event(s) must be reported in the CRF as AE(s).

8.2.1.1. Immunogenicity Assessment

Where local regulations and ethical review boards (ERBs) allow, blood samples for immunogenicity testing will be collected to determine antibody production against LY3435151 as specified in the SoA (Section 1.3).

At the visits and times specified in the SoA (Section 1.3), venous blood samples will be collected to determine antibody production against the investigational product. To interpret the results of immunogenicity, a venous blood PK sample will be collected at the same time points to determine the plasma concentrations of LY3435151. All samples for immunogenicity will be taken pre-dose. In the event of drug hypersensitivity reactions (immediate or non-immediate), additional blood and urine samples will be collected as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event to evaluate antidrug antibodies (ADA), PK, and additional exploratory biomarkers of hypersensitivity, which could include tryptase, complement levels, and cytokine measurements. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

Treatment-emergent antidrug antibodies (TE-ADA) are defined in Section 9.4.6.

Immunogenicity will be assessed by a validated assay designed to detect ADA in the presence of the investigational product at a laboratory approved by the sponsor. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the investigational product.

Samples will be retained for a maximum of 15 years after the last patient visit, or for a shorter period if local regulations and ERBs allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to LY3435151. Any samples remaining after 15 years will be destroyed.

8.2.1.2. Hepatic Safety Monitoring

If a study participant experiences elevated alanine aminotransferase (ALT) ≥3 × upper limit of normal (ULN), alkaline phosphatase (ALP) ≥2 × ULN, or elevated total bilirubin (TBL) ≥2 × ULN, liver testing (Appendix 4) should be repeated within 3 to 5 days including ALT, aspartate aminotransferase (AST), ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator and in consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels.

Hepatic data should be collected in the event that 1 (or more) of the following conditions is met for the patient during the course of the study:

- elevation of serum ALT level to ≥10 × ULN
- patients without liver tumors or liver metastasis: ALT ≥5 × ULN and total bilirubin ≥2 × ULN
- patients with liver tumors or liver metastasis: ALT ≥8 × ULN and total bilirubin ≥2 × ULN

- discontinuation from study treatment due to a hepatic event or abnormality of liver test results
- occurrence of a hepatic event considered to be an SAE

8.2.1.3. Venous Thromboembolic Event Assessment

If a patient develops clinical features of a DVT or PE, appropriate local laboratory tests and imaging should be performed as necessary for the diagnosis of the event. For confirmed cases, additional laboratory testing is recommended. Selected tests may be obtained in the event of a confirmed venous thromboembolic event and may be required in follow-up with patients in consultation with Lilly, its designee, or the Lilly designated medical monitor.

8.3. Adverse Events and Serious Adverse Events

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

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

Investigators must document their review of each laboratory safety report.

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

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

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

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

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

The investigator answers yes/no when making this assessment.

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

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

Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent 1 of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

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

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

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

Serious adverse events, including death, caused by disease progression should not be reported unless the investigator deems them to be possibly related to LY3435151, pembrolizumab, or the combination of LY3435151 and pembrolizumab.

Suspected Unexpected Serious Adverse Reactions

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

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

Although all AEs after signing the ICF are recorded by the site in the CRF/electronic data entry, SAE reporting to Lilly begins after the patient has signed the ICF and has received study drug. However, if an SAE occurs after signing the ICF, but prior to receiving LY3435151, it needs to be reported ONLY if it is considered reasonably possibly related to study procedures.

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

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

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

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

Refer to the SoA (Section 1.3) for the timing of AE/SAE collection.

8.3.2. Follow-up of AEs and SAEs

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

8.3.3. Regulatory Reporting Requirements for SAEs

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

8.3.4. Pregnancy

- Additional requirements for pregnancy testing during and after study intervention are located in Appendix 3.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.
- All pregnancies and exposure during breastfeeding, from the time of treatment through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.

8.3.5. Cardiovascular and Death Events

Not applicable.

8.3.6. Complaint Handling

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

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

8.3.7. Events of Clinical Interest

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

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 8.4 – Treatment of Overdose, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3× the ULN and an elevated total bilirubin lab value that is greater than or equal to 2× the ULN and, at the same time, an alkaline phosphatase lab value that is less than 2× the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

8.4. Treatment of Overdose

There is no known antidote to LY3435151 overdose. In case of overdose, the patient should receive supportive measures.

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

No specific information is available on the treatment of overdose of pembrolizumab and/or LY3435151. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

8.5. Pharmacokinetics

At the visits and times specified in the SoA (Section 1.3), venous blood samples will be collected to determine the serum concentrations of LY3435151.

A maximum of 3 samples may be removed or collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor. Concentrations of LY3435151 will be assayed using a validated enzyme-linked immunosorbent assay method.

Bioanalytical samples collected to measure LY3435151 concentration will be retained for a maximum of 1 year following last patient visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses such as additional metabolism or exploratory analyses including bioanalytical assay validation or cross-validation exercises.

8.6. Pharmacodynamics

See Section 8.8 for PD samples to be collected in this study.

8.7. Genetics

8.7.1. Whole Blood Sample for Pharmacogenetic Research

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

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to LY3435151 and to investigate genetic variants thought to play a role in cancer. Samples may also be used to determine the somatic or germline origin of identified genetic alterations in tumor samples. Assessment of variable response may include evaluation of AEs or differences in efficacy.

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

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last participant visit for the study, or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3435151 or after LY3435151 becomes commercially available.

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

8.8. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, PD, mechanism of action, variability of participant response (including safety), and clinical outcome as well as broader mechanisms pertaining to tumor-immune response as well as tumor pathogenesis. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including deoxyribonucleic acid, ribonucleic acid (RNA), proteins, lipids, and other cellular elements.

Plasma, serum, whole blood, stool, and tumor tissue samples for biomarker research will be collected at the times specified in the SoA (Section 1.3) where local regulations allow. A

maximum of 5 samples may be drawn, collected, or removed at additional time points during the study if warranted and agreed upon by the investigator and Lilly. If these additional samples are requested, they will be used to further investigate biomarkers that may explain treatment response and resistance mechanisms.

Samples will be used for research on the drug target, disease process, variable response to LY3435151, pathways associated with cancer, mechanism of action of LY3435151, and/or used to develop research methods or to validate diagnostic tools or assay(s) related to cancer.

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

- a newly obtained core, excisional, or endoscopic pre-treatment biopsy of a tumor lesion from primary or metastatic site **and**
- a tumor tissue sample from a newly obtained core, excisional, or endoscopic biopsy specimen collected during the study treatment period as shown in the SoA (Section 1.3)

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

- 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.
- 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, as indicated in the SoA [Section 1.3].)

For patients requiring a fresh biopsy, the participant must be willing to undergo baseline and on-study biopsies (as applicable) that should not put participants at undue risk greater than that which comes with a core biopsy (ie, a procedure to obtain biopsy should have a serious/severe complication risk no greater than 2%).

Newly acquired tumor biopsies are requested because they provide the most current biomarker characteristics of the tumor compared with biopsies taken at the time of diagnosis (tumor characteristics may shift during subsequent lines of treatment). Pre- and on-treatment assessments are critical to evaluate changes in molecular markers over time and to document any potential immunomodulatory activity of treatment with LY3435151 and should be performed if clinically feasible. Samples may be examined for biomarkers of immune microenvironment changes including by immunohistochemistry and RNA expression analysis.

The tissue samples should be obtained using an appropriate method. Tumor tissue should be submitted as a newly acquired endoscopic core needle (minimum 18 gauge) or surgical biopsy. Cytological or fine-needle aspiration specimens are not acceptable. An attempt to obtain up to 4

core-needle biopsies, surgical biopsy, or endoscopic biopsy is required, unless medically contraindicated or unsafe and discussed with the Lilly CRP/CRS. Optimally, biopsies should be taken from the same metastatic lesion and from areas not previously irradiated (except if the patient had progressed after radiation). Fresh tumor biopsies are planned to be evaluated with the isolation of TILs locally for subsequent analysis. The isolation of TILs needs to be performed immediately post-biopsy locally on-site. The single-cell preparation may be characterized by flow cytometry, additional analysis to be determined, or cryopreservation as discussed with the sponsor. Cores should be allocated: 2 for formalin fixation and 2 for fresh TIL isolation. When 4 cores are not feasible, the first 2 cores should be fixed in formalin. Fresh TIL isolation will be optional for Cohorts A1, A2, and A3 in the dose escalation. Formalin fixed tissue will be used for immunohistochemistry, RNA analysis, and additional analysis as feasible. See the Laboratory Manual for details regarding sample handling. If additional tumor biopsies are collected as part of clinical care, they should be submitted, along with pathology reports, for further analysis. When a biopsy is submitted, due diligence should be used to ensure that tumor specimens (not a normal adjacent or a tumor margin sample) are provided and that the tumor sample contains tumor cells prior to shipment to the central laboratory. If a biopsy does not contain adequate tissue for analysis, the patient may be replaced. Lilly may replace up to 10% of total patients if unable to submit an adequate tumor sample. The pathology report accompanying archival tissue will also be requested. The pathology report must be coded with the patient number. Personal identifiers, including the patient's name and initials, must be removed from the institutional pathology report prior to submission. Lilly has a right to retain a portion of the submitted tissue. Archival blocks will be sectioned and returned to the study site. Slides and tissue samples collected on-study will not be returned.

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

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last participant visit for the study, or for a shorter period if local regulations and ERBs impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3435151 or after LY3435151 becomes commercially available.

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

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

8.8.1. Tumor Tissue Samples for Detection of TILs

Documented evidence of the presence of TILs from either a local laboratory or Study JZIA central laboratory test result will be used to meet study eligibility criteria into Cohort D3 of

Phase 1b. This testing does not replace any companion diagnostic test that would be required to determine eligibility for an IO therapy approved for the patient's indication.

8.9. Medical Resource Utilization and Health Economics

Medical resource utilization parameters and health economics will not be evaluated in this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

In the dose escalation phase (Part A and Part B), the hypothesis is that there is a tolerable dose level for LY3435151 in both monotherapy and in combination with pembrolizumab.

In the dose expansion phase (Part C and Part D), the objective is to evaluate the safety and tolerability, as well as preliminary antitumor activity, of LY3435151 in both monotherapy and in combination with pembrolizumab in the pre-specified tumor types. No formal hypothesis testing will be performed to demonstrate any statistically significant improvement in objective response rate. Therefore, specification of alternative hypotheses on the overall response rate (ORR) does not apply.

9.2. Sample Size Determination

The primary objective of this study is to assess the safety and tolerability of LY3435151, thereby identifying and confirming the RP2D of LY3435151, to be administered as monotherapy and in combination with pembrolizumab, in patients with solid tumors associated with high TIL positivity. The secondary objective is to evaluate PK and any observed evidence of clinical efficacy.

With at least 3 patients treated at the RP2D in the dose-escalation phase and additional patients treated at the RP2D in the dose-expansion phase, 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 (partial response [PR]/CR) to treatment.

In the dose-expansion phase for both TNBC and gastric adenocarcinoma, approximately n=16 patients in each of these 2 tumor types will be randomized with 1:1 ratio to receive LY3435151 as monotherapy or in combination with pembrolizumab (Stage 1). The sample size of n=16 in each tumor type is required to evaluate the PK/PD and safety data between monotherapy and combination therapy. Following the randomization stage, approximately additional 32 patients in each of the 2 tumor types will be enrolled to receive LY3435151 in combination with pembrolizumab (Stage 2). At each interim analysis for TNBC and gastric adenocarcinoma, clinical data from approximately 20 patients in combination dose expansion (8 from Stage 1 and 12 from Stage 2) will be available to evaluate the antitumor activity of the combination therapy. If the interim results suggest continuation of enrollment for the evaluated tumor type in TNBC and gastric adenocarcinoma, additional patients will be enrolled to receive combination therapy until approximately 32 patients in Stage 2 to achieve a total of approximately n=40 patients for the evaluation of antitumor activity of combination therapy in the corresponding tumor type.

In the dose-expansion phase for other tumor types associated with TIL positivity, the sample size of N=30 in combination therapy provides data to evaluate the safety and PK/PD profile, and to potentially assess the antitumor activity of LY3435151 in combination with pembrolizumab in tumor types other than TNBC and gastric adenocarcinoma.

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

Estimated Incidence Rate and 2-Sided 95% CI

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

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

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

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign informed consent
Biomarker	All enrolled patients from whom a valid assay result has been obtained
Pharmacokinetic	All enrolled patients who have received ≥1 full dose of LY3435151 and have baseline and ≥1 postbaseline evaluable PK sample
Safety	All enrolled patients who have received ≥1 dose of study treatment, regardless of their eligibility for the study. The safety population will be used for all dosing/exposure and safety analyses.
DLT-evaluable	All treated patients who have completed 2 cycles (6 weeks) of treatment (having taken at least 75% of the planned doses of LY3435151) or have discontinued treatment due to a DLT.

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

9.4. Statistical Analyses

9.4.1. General Statistical Considerations

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

The efficacy and safety analyses will be conducted on the full analysis set. This set includes all data from all participants receiving at least 1 dose of the investigational product according to the treatment the participants were assigned and actually received.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated.

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

9.4.2. Treatment Group Comparability

9.4.2.1. Participant Disposition

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

9.4.2.2. Participant Characteristics

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

9.4.2.3. Concomitant Therapy

A summary of prior and concomitant medications will be reported.

9.4.2.4. Treatment Compliance

The number of cycles received, dose omissions, dose delays, and dose intensity will be summarized for all treated patients by treatment cohort.

9.4.3. Efficacy Analyses

9.4.3.1. Primary Analyses

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

9.4.3.2. Secondary Analyses

The **disease control rate**, defined as the proportion of patients who achieved a CR or PR or stable disease (SD) out of all patients treated, will also be summarized. Best response is determined from a sequence of responses assessed. Two objective status determinations of CR before progression are required for a best response of CR. Two determinations of PR or better

before progression, but not qualifying for a CR, are required for a best response of PR. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval not less than 6 weeks ±7 days measured from study entry.

The **duration of response** is defined as the time from the date measurement criteria for CR or PR (whichever is first recorded) are first met until the first date that disease is recurrent or objective progression is observed, per RECIST 1.1 criteria, or the date of death from any cause in the absence of objectively determined disease progression or recurrence. Duration of SD will be calculated only for patients with best response of SD. It is measured from the date of start of treatment to the date of first progression of disease or the date of death due to any cause, whichever is earlier. For each patient who is not known to have died or to have had a progression of disease as of the data inclusion cut-off date, duration of SD will be censored at the date of last objective response assessment prior to the date of any subsequent systemic anticancer therapy.

Change in tumor size (CTS) will be assessed in each patient with measurable disease using radiographic imaging. Tumor size is the sum of the tumor measurements for target lesions at each tumor evaluation. Change in tumor size is defined as the percent CTS from the baseline evaluation to the post-dose evaluation at each assessment. Other definitions of CTS may be explored (including specific time points and AUC formulations).

Progression-free survival (PFS) is defined as the time from the date of start of treatment to the first date of the observed clinical or radiologically documented progressive disease or death due to any cause, whichever occurs first. For patients who are not known to have died or progressed as of the data inclusion cut-off date, PFS time will be censored at the date of the last objective progression-free disease assessment prior to the date of any subsequent systematic anticancer therapy.

PFS Event/Censoring Scheme

Situation[a]	Event/Censor	Date of Event or Censor
Tumor progression or death	Event	Earliest date of progressive disease or death
No tumor progression and no death	Censored	Date of last adequate tumor assessment per RECIST 1.1, or date of first dose (whichever is later)[b]
Unless		
No baseline radiologic tumor assessment available	Censored	Date of first dose
No adequate postbaseline tumor assessment available and death reported after 2 scan intervals following the first dose[b, c]	Censored	Date of first dose
Tumor progression or death documented immediately after 2 or more scan intervals following last adequate tumor assessment or randomization (whichever is later)[b,c]	Censored	Date of last adequate tumor assessment, per RECIST 1.1, or date of first dose (whichever is later)[b]
New therapeutic anticancer treatment started prior to tumor progression or death	Censored	Date of last adequate radiological assessment prior to new therapeutic anticancer therapy[b]

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

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

[b] Adequate tumor assessment per RECIST 1.1 refers to an assessment with one of the following responses: CR, PR, SD, or PD.

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

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

9.4.3.3. Tertiary/Exploratory Analyses

Overall survival, as well as the efficacy parameters based on iRECIST, will also be analyzed as the exploratory objectives. Details on the exploratory efficacy parameters are discussed in the SAP.

9.4.4. Safety Analyses

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

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

Safety analyses will include summaries of the following:

- DLTs at each dose level in Part A and Part B;
- AEs, including severity and possible relationship to study drug;
- DLT-equivalent AEs, including severity and possible relationship to study drug;
- SAEs, including possible relationship to study drug;
- AEs leading to dose delays or omissions;
- discontinuations from study treatment due to AEs or death;
- treatment-emergent abnormal changes in laboratory values;
- treatment-emergent abnormal changes in vital signs and ECGs.

9.4.5. Pharmacokinetic/Pharmacodynamic Analyses

Selected PK descriptors for LY3435151 (based on actual sampling times), including C_{max}, approximate time of C_{max}, and AUC will be calculated by noncompartmental analysis methods and/or model simulations. As an exploratory analysis, PK descriptor estimates for trough concentrations at steady state following repeated dose may be evaluated.

In addition, PK parameter estimates for LY3435151 as a single agent and in combination will be calculated by population PK analysis methods using NONMEM, data allowing. The version of any software used for the analysis will be documented, and the program will meet the Lilly requirements of software validation. It is possible that other validated, equivalent PK software programs may be used if appropriate, warranted, and approved by Global PK/PD management.

Pharmacokinetic/pharmacodynamic analyses may be conducted to explore exposure-response relationships between LY3435151 concentrations in systemic circulation and various PD measures as second step if dose-response relationship is positively assessed.

9.4.6. Evaluation of Immunogenicity

The frequency and percentage of participants with preexisting ADA and with TE-ADA+ to LY3435151 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 TE-ADA+ participants, the distribution of maximum titers will be described. The frequency of neutralizing antibodies will also be tabulated in TE-ADA+ patients if assessed.

The relationship between the presence of antibodies to LY3435151 and the PK parameters and PD response, including safety and efficacy, to LY3435151 may be assessed.

9.4.7. Other Analyses

9.4.7.1. Biomarker Analyses

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

9.5. Interim Analyses

Because this is a dose-finding study, safety and PK/PD data (if available) will be reviewed on a cohort-by cohort basis during the study, until the MTDs (or the highest dose levels if MTDs are not reached) are determined for each treatment part. The purpose of these cohort-by-cohort reviews is to evaluate the safety data at each dose level and determine if a DLT has been observed that would suggest the MTD has been met or exceeded. After all patients who are deemed evaluable for the assessment of dose levels complete the DLT observation period or the MTD is determined, an interim safety and PK analysis will be conducted for planning next studies.

For the dose-expansion phase, when the clinical efficacy data and PK/PD data of approximately the first 20 participants are available in each combination dose-expansion cohort of TNBC and gastric adenocarcinoma (Cohort D1 and Cohort D2), an interim data review including but not limited to safety, efficacy, and PK/PD will be conducted within each cohort. If the results of the data review for a particular cohort under combination therapy warrant a positive benefit-risk-profile, additional patients will be enrolled to the corresponding tumor type in the combination dose expansion (Cohort D1 or Cohort D2) until approximately 40 patients are enrolled.

It is planned that enrollment can continue while interim analyses are conducted, but the sponsor may decide to pause the enrollment, if necessary. Other interim analyses may be conducted if deemed appropriate by the sponsor. The interim analyses may be combined with any pre-specified safety review or annual reporting (eg, an update to the IB or Development Safety Update Review).

If it is deemed that enough data are obtained to assess the primary objective and the secondary objectives, a CSR might be created before the last patient visit. In this case, all data until the data cut-off 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 the data cut-off date. These data may be reported separately and the analyses on all patients including these data may not be performed.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

10.1.2. Informed Consent Process

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

Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and is kept on file.

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

10.1.3. Data Protection

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

10.1.4. Dissemination of Clinical Study Data

Dissemination of study data will be performed according to all applicable Lilly and international policies.

10.1.5. Data Quality Assurance

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

- provide instructional material to the study sites, as appropriate
- provide sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and verify data reported to detect potential errors

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

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

Data Capture System

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

An electronic data capture (EDC) system 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-party. 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 results will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

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

10.1.6. Source Documents

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

10.1.7. Study and Site Closure

10.1.7.1. Discontinuation of the Study

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

10.1.7.2. Discontinuation of Study Sites

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

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed below will be performed as indicated in the table below.
- If a local sample is required, it is important that the sample for central analysis is obtained at the same time (if applicable). If there is an abnormal laboratory value or abnormal value for any other diagnostic or screening test (e.g., blood pressure increased, neutrophils decreased, etc.) and it is known to be related to a diagnosis (e.g., hypertension, neutropenia, etc.), this should be entered into the CRF. Do not enter the test abnormality, enter the diagnosis or categorical term.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations and any clinically significant abnormalities recorded in the AE eCRF.

Investigators must document their review of each laboratory safety report. Enrollment and treatment decisions may be based upon local laboratory results. Discrepancies between local and central laboratory results will not be considered a protocol deviation.

Clinical Laboratory Tests

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

Urinalysis[c]
Blood
Glucose
Ketones
pH
Protein
Specific gravity
Urine leukocyte esterase[e]

Thyroid function[a,b]
Thyroid-stimulating hormone (TSH)
Thyroxine (T4)
Triiodothyronine (T3)
Free Triiodothyronine (FT3)

Exploratory Hypersensitivity and Immunogenicity Testing[a, b, f]
Anti-LY3435151 antibodies (immunogenicity)
Tryptase
Drug-specific IgE
Basophil activation test
Complements
Cytokine panel
N-methylhistamine

Clinical Chemistry[a,b]
Serum Concentrations of:
Alanine aminotransferase (ALT)
Albumin
Alkaline phosphatase
Aspartate aminotransferase (AST)
Bilirubin, direct
Bilirubin, total
Blood urea nitrogen (BUN) or blood urea
Calcium
Creatine Kinase
Creatinine
Glucose (random)
Magnesium
Phosphorous
Potassium
Total Protein
Sodium

Pregnancy Test[c,d]
Serum or urine pregnancy test

Coagulation[c]
PT/INR
aPTT

Abbreviations: aPTT = activated partial thromboplastin time; CRF = case report form; IgE = immunoglobulin E; INR = international normalized ratio; PT/INR = prothrombin time-international normalized ratio; RBC = red blood cells; WBC = white blood cells.

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

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

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

c Local or investigator-designated laboratory.

[d] For female patients of childbearing potential.

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

[f] Basophil activation test will be performed if a drug-specific IgE assay is unavailable.

[g] When available, include mean platelet volume, platelet distribution width, and reticulated platelets.

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

Definitions:

Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:

    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

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

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

3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement >40 mIU/mL is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Vasectomized partner • *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)*
Highly Effective Methods[b] That Are User Dependent
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] o oral o intravaginal o transdermal o injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] o oral o injectable
• 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 intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c) Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction)

Collection of Pregnancy Information

Male participants with partners who become pregnant

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

Female participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor, as described in Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention and be withdrawn from the study.

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

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

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	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	
ALT	**Anti-nuclear antibody[a]**
AST	**Alkaline Phosphatase Isoenzymes[a]**
GGT	**Anti-smooth muscle antibody (or anti-actin antibody)[a]**
CPK	

Abbreviations: ALT = alanine aminotransferase; AST = aspirate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

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

b Reflex/confirmation dependent on regulatory requirements and/or testing availability.

10.5. Appendix 5: Creatinine Clearance Formula

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

Patients aged ≥18 years

Cockcroft-Gault prediction of CrCl from serum creatinine (1976)

For serum creatinine concentration in mg/dL:

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

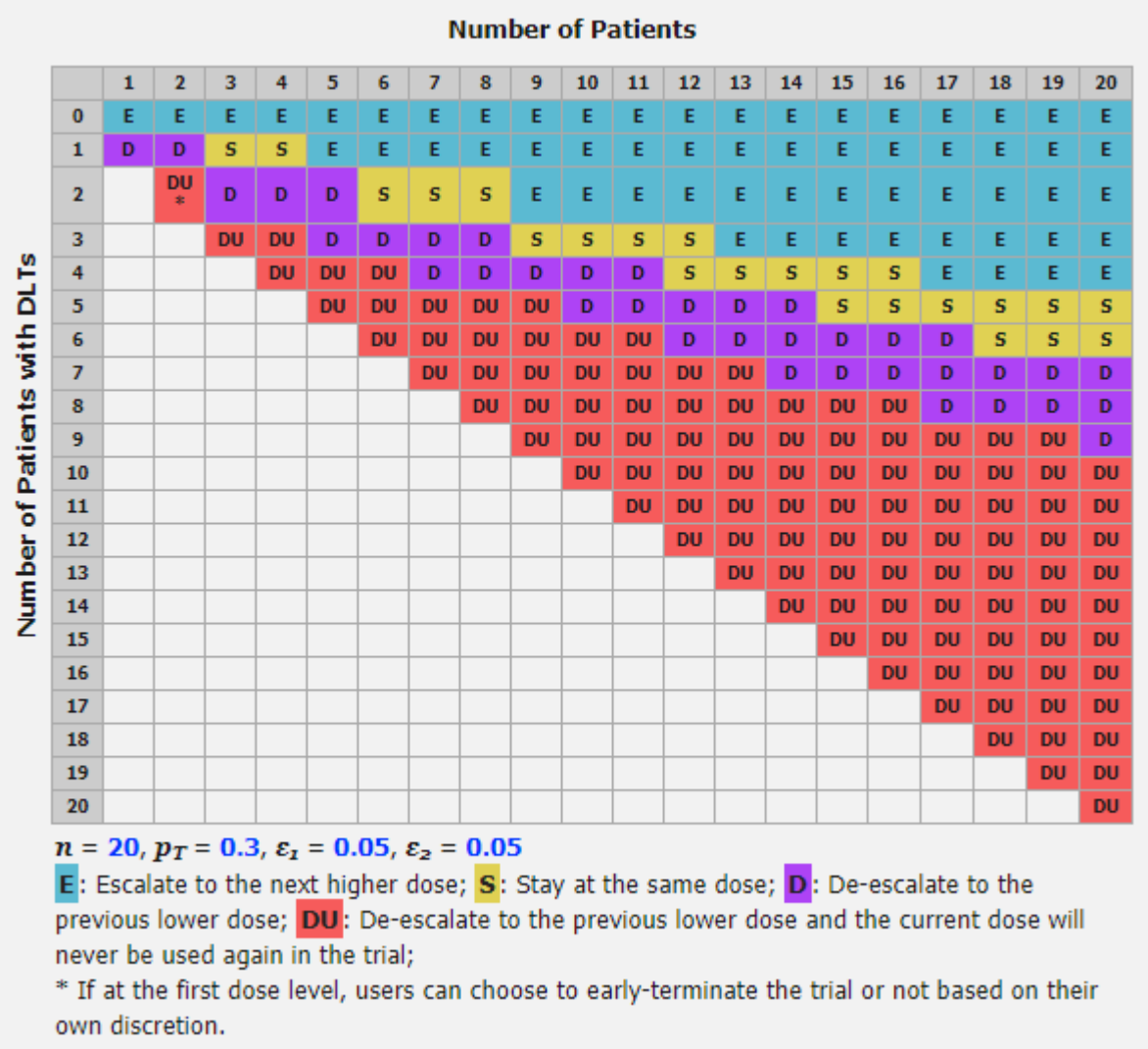
For serum creatinine concentration in μmol/L:

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

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

Source: Cockcroft and Gault 1976.

10.6. Appendix 6: Dose-Finding Algorithm 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

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

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

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

The number of patients dosed at a given 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 will never be used again in the trial (see "DU" at column 7, row 5).

The final MTD will be determined when all patients complete DLT evaluation. A hypothetical example for the MTD determination is shown below for illustration (based on the pre-specified parameters, number of DLTs, and number of DLT-evaluable patients).

p_T = 0.3, ε_1 = 0.05, ε_2 = 0.05, n_{dose} = 6, Dose level 5 is the MTD

Dose level	1	2	3	4	5	6
# of Toxicities	0	0	0	1	0	2
# of Patients Treated	1	3	3	6	3	3

10.7. Appendix 7: Abbreviations

Term	Definition
ADA	antidrug antibody(ies)
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BED	biological effect dose
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum concentration
CNS	central nervous system
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CRP/CRS	clinical research physician/clinical research scientist: Individual responsible for the medical conduct of the study. Responsibilities of the CRP/CRS may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CSR	clinical study report
CT	computed tomography
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CTS	change in tumor size
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate

DLT	dose-limiting toxicity
DVT	deep vein thrombosis
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
ET	equivalent toxicity
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
FT3	Free triiodothyronine
FT4	Free thyroxine
GCP	good clinical practice
G-CSF	granulocyte colony-stimulating factor
GLP	Good Laboratory Practice
GPS	Global Patient Safety
HCC	hepatocellular carcinoma
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
iCPD	confirmed progression per iRECIST
iCR	complete response per iRECIST
IEC	Independent Ethics Committee
Informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IO	immuno-oncology
IP	intraperitoneal(ly)
iPR	partial response per iRECIST
irAE	immune-related adverse event
IRB	institutional review board
iRECIST	immuno-Response Evaluation Criteria in Solid Tumors
IRR	infusion-related reaction
iSD	stable disease per iRECIST
iUPD	unconfirmed progression per iRECIST
IV	intravenous(ly)
LMS	leiomyosarcoma
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
mTPI-2	modified toxicity probability interval
NL-NT	new lesion-non-target
NL-T	new lesion-target
ORR	overall response rate
PD	pharmacodynamic(s)
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PE	pulmonary embolism
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
Q3W	every 3 weeks
QTc	corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid

RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SD	stable disease
SoA	Schedule of Activities
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reaction
T3	triiodothyronine
TBL	total bilirubin
TE-ADA	treatment-emergent antidrug antibody(ies)
TIL	tumor-infiltrating lymphocyte
TNBC	triple-negative breast cancer
TTR	time to response
ULN	upper limit of normal
UPS	undifferentiated pleomorphic sarcoma
WOCBP	woman/women of childbearing potential

10.8. Appendix 8: Protocol Amendment History

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

Amendment (a)

Overall Rationale for the Amendment:

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

Section # and Name	Description of Change	Brief Rationale
Section 1.1. Synopsis	Replaced "anti-PD-1/L1" with "Pembrolizumab"; Added in pembrolizumab dose	Based on FDA feedback
Section 1.2.1. Phase 1a: Dose Escalation Schema	Replaced "PD-1/L1 Combination" with "Pembrolizumab" for Part B of the study schema	Based on FDA feedback
Section 1.3. Schedule of Activities	Changed "Single local ECG" to "Central triplicate ECGs" for on-treatment activities	Updated to be in line with common Lilly practice
Section 1.3. Schedule of Activities	Addition of plasma and stool sample collection information	Clarification
Section 1.3. Schedule of Activities	Addition of "Pregnancy Test" to Post-Treatment Schedule of Activities	Based on pembrolizumab specific language
Section 1.3. Schedule of Activities	Changed "PBMC" to "Whole Blood for Flow Profile"	Clarification
Section 2.3. Benefit/Risk Assessment	Addition of language regarding pembrolizumab benefit/risk information	Based on FDA feedback
Section 4.1.1.2. Dose-Limiting Toxicity Determination	DLT table modified	Based on FDA feedback
Section 4.1.1.4. Determination of Recommended	Addition of text regarding the use of data in the 90-day follow-up period.	Based on FDA feedback

Section # and Name	Description of Change	Brief Rationale
Phase 2 Dose		
Section 4.3. Justification for Dose	Addition of language regarding dose of pembrolizumab in parts B and D of the study.	Based on FDA feedback
Section 5.1. Inclusion Criteria	Modification of inclusion criteria [2] and [8]	Based on FDA feedback
Section 6.1. Study Intervention(s) Administered	Replaced "anti-PD-1/L1" with "Pembrolizumab"; Added in footnote regarding combination dose levels	Based on FDA feedback
Section 6.6. Dose Modification	Addition of language regarding dose delays and omissions	Based on FDA feedback
Section 6.6.2. Dose Modifications of Pembrolizumab	Addition of language regarding dose modifications for pembrolizumab	Based on FDA feedback
Section 7.1. Discontinuation of Study Intervention	Addition of language regarding the discontinuation of pembrolizumab; Addition of bullet point regarding abnormal hepatic parameters; Addition of language for patients who will continue study treatment beyond radiographic progression	Based on FDA feedback
Appendix 2: Clinical Laboratory Tests	Added Creatine Kinase to Clinical Laboratory Tests	Based on PMDA feedback
Throughout protocol	Addition of pembrolizumab-specific language	Based on pembrolizumab specific language
Throughout protocol	Minor formatting and editorial changes	Minor, therefore not detailed

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