Statistical Analysis Plan: J1Q-MC-JZIA(b)

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

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Approval Date: 04-Oct-2019

1. Statistical Analysis Plan: J1Q-MC-JZIA: A Phase 1a/1b Study of LY3435151 Administered to Patients with Advanced Solid Tumors

LY3435151 Solid Tumors

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 ([GC] 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).

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[Protocol J1Q-MC-JZIA]
[Phase 1a/1b]

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

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3. Revision History

Statistical Analysis Plan (SAP) Version 1 was approved prior to first patient visit.

4. Study Objectives

4.1. Primary Objective

- **Phase 1a Dose Escalation (Part A & Part B):** to assess the safety and tolerability of LY3435151, thereby identifying the recommended Phase 2 dose (RP2D), administered as monotherapy and in combination with pembrolizumab, in patients with advanced solid tumors of the following types: triple-negative breast cancer (TNBC), gastric adenocarcinoma (GC), 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).
- **Phase 1b Dose Expansion (Part C & Part D):** to assess the safety and tolerability of LY3435151:
    - administered as monotherapy (Part C), all patients must be programmed death-1 (PD-1) /programmed death-ligand 1 (PD-L1) antagonist naïve:
        - C1: TNBC (not eligible for atezolizumab-containing therapies)
        - C2: GC (including gastroesophageal junction)
    - administered in combination with pembrolizumab (Part D), all patients must be PD-1/PD-L1 antagonist naïve:
        - D1: TNBC (not eligible for atezolizumab-containing therapies)
        - D2: GC (including gastroesophageal junction)
        - D3: tumor-infiltrating lymphocyte (TIL)-selected cohort with the following tumor types: HNSCC, squamous cervical carcinoma, high-grade serous ovarian carcinoma, HCC, UPS, and LMS

4.2. Secondary Objectives

- to assess the pharmacokinetics (PK) of LY3435151, administered as monotherapy and in combination with pembrolizumab, in patients with solid tumors
- to document any antitumor activity per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 observed with LY3435151, when administered as monotherapy or in combination with pembrolizumab, in patients with solid tumors

4.3. Exploratory Objectives

- to assess the relationship between biomarkers, dose/exposure, and clinical outcomes, particularly in relation to tumor TIL levels
- to document survival status observed with LY3435151 when administered as monotherapy or in combination with pembrolizumab to patients with solid tumors associated with TIL positivity

- to document antitumor activity based on immuno-RECIST (iRECIST) observed with LY3435151 when administered as monotherapy or in combination with pembrolizumab to patients with solid tumors associated with high TIL positivity

5. A Priori Statistical Methods

5.1. Summary of Study 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.

5.1.1. Dose Escalation Phase

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

- TNBC
- GC (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-2 (mTPI-2) method and, starting with Cohort A2, will enroll at least 3 evaluable patients per cohort. Treatment cycles will consist of 21 days. A 2-cycle DLT observation period (42 days) will apply to all cohorts in Phase 1a.

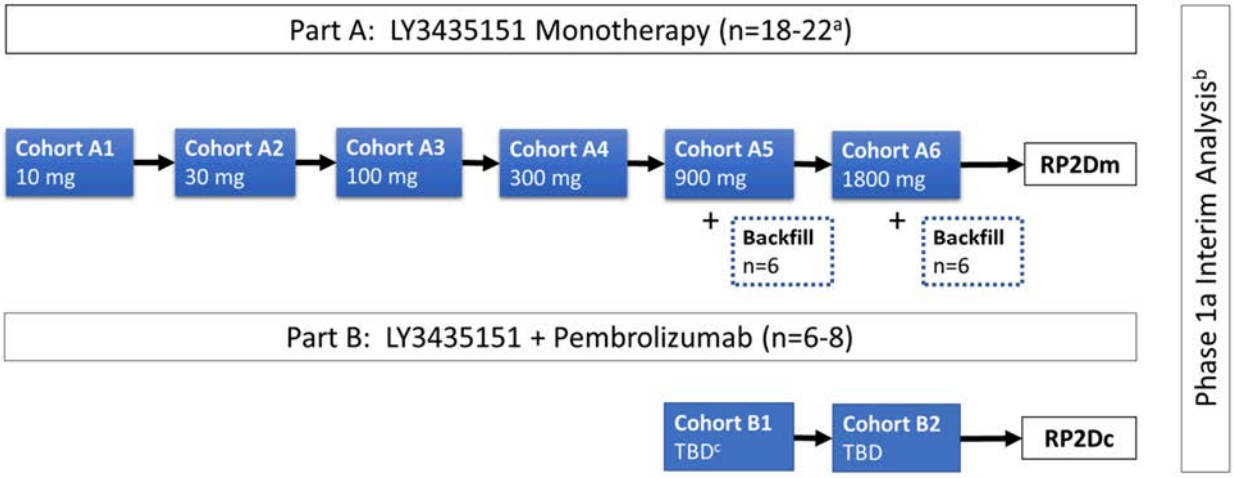
One patient will be enrolled in Cohort A1 and will receive a 10-mg dose on Cycle 1 Day 1. If the 10-mg dose level DLT period is cleared, Cohort A2 (30-mg dose level) will be initiated. If the patient in Cohort A1 experiences a DLT, additional patients will be enrolled into Cohort A1 following the mTPI-2 method. Based on the mTPI-2 method, at least 4 additional patients will need to be enrolled and experience no DLTs 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 for every 3 weeks (Q3W) 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 Period (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 5 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 Part A or Part B at dose levels higher than the de-escalated dose.



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.

[b] Refer to Section 5.8 of Interim Analyses.

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

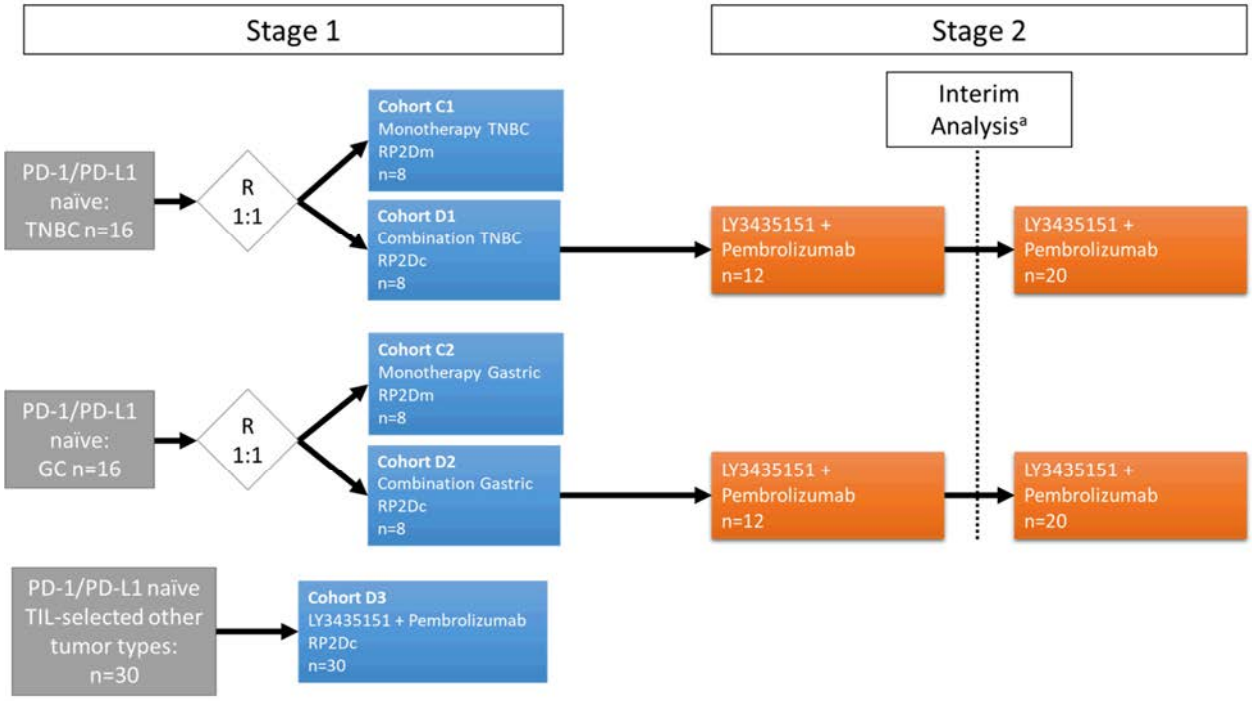
Figure JZIA.1. JZIA Study Design Scheme – Dose Escalation

5.1.2. 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. That is, the randomized Dose Expansion Cohort will begin after the completion of both Dose Escalation Part A and Dose Escalation Part B.

In Dose Expansion Phase 1b, a 2-stage design with randomization will be implemented to determine the treatment for patients with immuno-oncology (IO) naïve TNBC and GC. Within each tumor type of IO-naïve TNBC and GC 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). At Stage 2, approximately 32 additional patients in each tumor type 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 the combination dose expansion (including 8 patients from Stage 1 and the first 12 patients from Stage 2) for each of the 2 tumor types of IO-naïve TNBC and GC. When the interim analysis in Stage 2 is performed for each tumor type, enrollment might still continue to enroll additional 20 patients, unless the totality of evidence suggests otherwise.

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).



Abbreviations: GC = gastric adenocarcinoma; n = number of participants; 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 5.8 of Interim Analyses.

Figure JZIA.2. JZIA Study Design Schema – Dose Expansion

5.2. Determination of Sample Size

5.2.1. 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 prespecified 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.

5.2.2. 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]/complete response[CR]) to treatment

In the dose expansion phase for both TNBC and GC, approximately 16 patients in each of these 2 tumor types will be randomized with a 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 determined in order to minimize the patients receiving monotherapy but still provide sufficient precisionto evaluate the PK/PD and safety data between monotherapy and combination therapy. Following the randomization stage, approximately 32 additional 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 GC, clinical data from approximately 20 patients in the 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 GC, an additional 20 patients will be enrolled to receive combination therapy in Stage 2 in the corresponding tumor type. Therefore, a total of approximately 40 patients will be enrolled in each tumor type for the evaluation of antitumor activity of combination therapy.

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. The sample size of n=30 also allows to potentially assess the antitumor activity of LY3435151 in combination with pembrolizumab in tumor types other than TNBC and GC.

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).

Table JZIA.5.1. Estimated Incidence Rate and 2-Sided 95% Confidence Interval

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

5.3. Handling of Dropouts or Missing Data

Rules for handling dropouts or missing data are listed by type of analysis alphabetically. Unless otherwise specified, observed data will be used and missing data will not be imputed or carried forward.

General rules for imputing dates related to adverse events (AEs) or concomitant therapy:

- Onset date of an AE or start date of a concomitant therapy:
  - if only the day is missing, the date will be set to:
    - the first day of the month that the event occurred, if the onset yearh-month (yyyy-mm) is after the yyyy-mm of first study treatment
    - the day of the first study treatment, if the onset yyyy-mm is the same as yyyy-mm of the first study treatment
  - if both the day and month are missing, the complete date will be set to:
    - January 1 of the year of onset, if the onset year is after the year of the first study treatment
    - the date of the first dose, if the onset year is the same as the year of the first study treatment
- Resolution date of an AE or end date of a concomitant therapy:
  - If only the day is missing, the date will be set to the last day of the month of the occurrence, or to the date of death if the patient died in the same month.
  - If both the day and month are missing, the date will be set to 31 December of the year of occurrence.

If a date is completely missing, then the AE will be considered treatment emergent. In case of additional therapies, the therapy will be considered concomitant.

General rule for imputing other dates: If a date variable is needed for an analysis, use the following general rule to impute the incomplete date:

- If the date has no missing year and month but the day is missing, then assign Day 1 to the day.
- If the date has no missing year, but has missing month, then assign January to the month.

However, after imputation, check if the imputed date is logically consistent with other relevant date variable(s) and make the appropriate correction if necessary. For example, if a visit start date was 10 May 2019 and a tumor assessment date was xx May 2019 (missing day) but it was known that it occurred after that visit, then after imputation, the tumor assessment date became 01 May 2019. In this case, the imputed tumor assessment date should be compared to the visit start date and then corrected to be the visit start date, 10 May 2019.

5.4. Statistical Analyses

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

Unless otherwise specified, the statistical summaries on Phase 1a will be performed by dose levels for Part A and Part B, respectively. For dose expansion phase, the analyses will be performed on patients by treatment arms (monotherapy and combination therapy) for each tumor type of TNBC and GC, and on all patients in the TIL-selected cohort D3.

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.

5.4.1. Analysis Population

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
Intent-to-Treat	All patients who are randomized (enrolled) to study treatment. Patients will be grouped according to randomized treatment. This ITT population will be used for all baseline and efficacy analyses.
Safety	All randomized (enrolled) patients who have received ≥1 dose of LY3435151, regardless of their eligibility for the study. Patients will be grouped according to treatment received in Cycle 1. 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; ITT = intent-to-treat; PK = pharmacokinetics.

5.4.2. Patient Disposition

All patient discontinuation data collected on the electronic case report form will be listed, including the extent of the patient's participation in the study. If known, a reason for discontinuation from treatment and from the study will be listed and summarized. All patients entered in the study will be included in the summary and listing.

All significant protocol deviations will be listed by predetermined categories.

5.4.3. Demographics and Baseline Characteristics

5.4.3.1. Demographics and Disease Characteristics

Patient demographic and baseline characteristics will be summarized and listed for all enrolled patients. At a minimum, sex, age, race, basis for initial diagnosis, initial pathological diagnosis, stage at initial diagnosis, baseline Eastern Cooperative Oncology Group performance status, height, and weight will be summarized. For some subsets of patients, intermediate and study entry pathological diagnosis data will also be listed.

5.4.3.2. Historical Illnesses and Prior Therapies

Historical illnesses are events in the past that ended before the date informed consent is signed. Historical illnesses (coded according to the Medical Dictionary for Regulatory Activities [MedDRA]) will be listed for all enrolled patients.

Prior therapies, including systemic therapy, radiotherapy, and surgeries will be listed for all enrolled patients. Prior radiotherapy and systemic therapy will be summarized by the number of patients with at least 1 of each type of treatment, as well by reason for regimen (for example,

palliative, curative, etc.). Additionally, the number of regimens of prior systemic therapy and, where available, the reason for prior regimens will be summarized.

5.4.4. Concomitant Therapy

Concomitant medications will be summarized and listed for the safety population.

5.4.5. Postdiscontinuation Therapy

The numbers and percentages of patients reporting postdiscontinuation therapies will be provided overall, by type of therapy (surgery, radiotherapy, or systemic therapy), and by drug name.

5.4.6. Exposure

The following exposure-related variables will be reported using summary by phase and treatment group:

- exposure: duration of treatment, number of cycles received, number of patients completing ≥1 cycle, ≥2 cycles, …, x cycles, mean, and standard deviation
- reasons for dose modification (delays, omissions, and reductions, scheduling conflict, and AE summarized by preferred term [PT])
- dose intensity: weekly dose intensity and relative dose intensity

Details of study drug administration will be included in patient listings.

5.4.7. Safety Analyses

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

Safety measureas that will be used in the study include AEs, DLT (defined in protocol) in dose escalation phase, clinical laboratory test results and vital signs. The MedDRA Version 22.0 (or higher) will be used when reporting AEs by MedDRA terms. A treatment-emergent adverse event (TEAE) is defined as an event that first occurred or worsened in severity between the first dose of study treatment and 30 days after the last dose of study treatment and related serious AEs (SAEs) reported beyond 30 days after the last dose of study treatment. Immune-related adverse event (irAE) is also indicated in the database and will be summarized in the safety analysis.

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 the study drug
- DLT-equivalent AEs, including severity and possible relationship to the study drug
- SAEs, summarized by PT and repeated for events deemed by the investigator to be possibly related to study treatment

- irAEs, summarized by PT and repeated for events leading to dose delays or omissions, for events leading to discontinuations from study treatment, and for events leading to death
- AEs leading to dose delays or omissions, summarized by PT
- AEs leading to discontinuations from study treatment, summarized by PT and repeated for events deemed by the investigator to be possibly related to study treatment
- AEs leading to death, summarized by PT and repeated for events deemed by the investigator to be possibly related to study treatment
- reasons for deaths, summarized for all deaths, deaths on therapy, and deaths within 30 days of treatment discontinuation
- treatment-emergent abnormal changes in laboratory values
- treatment-emergent abnormal changes in vital signs and electrocardiograms
- Listings of all AEs, TEAEs, SAEs, and deaths will also be provided.
- Listings of all laboratory data will be provided with a flag for values outside of the laboratory normal. Abnormal results will be listed separately for all enrolled patients.

5.4.8. Efficacy Analyses

The antitumor activity of LY3435151 in combination with pembrolizumab will be assessed based on RECIST 1.1 and iRECIST, respectively.

The Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the curves, median time, and 95% CI of time-to-event parameters such as overall survival (OS), progression-free survival (PFS), and duration of response (DoR) based on RECIST 1.1; iPFS ("i" indicates immune responses assigned using iRECIST) and iDoR based on iRECIST for each arm. Overall response rate (ORR based on RECIST 1.1 and iORR based on iRECIST), with corresponding 95% exact CI, will be summarized for each arm. The details of the efficacy paramters are described below.

5.4.8.1. Primary Efficacy Analyses

The **ORR** 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. Per RECIST 1.1 criteria, ORR for the single arm treatment within each tumor type will be calculated by confirmed best responses. Therefore, best overall response will be determined from a sequence of response assessments. 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.

5.4.8.2. Secondary Efficacy Analyses

The **disease control rate (DCR)**, defined as the proportion of patients who achieved a CR or PR or stable disease (SD) out of all patients treated, will also be summarized. Per RECIST 1.1 criteria, DCR for the single arm treatment within each tumor type will be calculated by confirmed best responses. See above for the details on the calculation of best responses with confirmation.

The **DoR** is defined as the time from the date measurement criteria for CR or PR (whichever is first recorded) are first met until the first date of objective progression is observed, per RECIST 1.1 criteria, or the date of death. If a responder is not known to have died or have objective progression, then the patient will be censored at the date of last evaluable tumor assessment.

Progression-free survival 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. See Table JZIA.5.2 for details.

Table JZIA.5.2. Progression-Free Survival 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; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

[a] Symptomatic deterioration (that is, 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 1 of the following responses: CR, PR, SD, or progressive disease.

[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.

5.4.8.3. Exploratory Efficacy Analyses

Overall survival, as well as the efficacy parameters based on iRECIST, will also be analyzed as the exploratory objectives.

The efficacy parameters based on iRECIST will also be analyzed as the exploratory objective.

Overall response rate (iORR) is measured by the percentage of patients who achieved a iCR or iPR as their best overall response (iBOR) out of all treated patients (safety population). The

iBOR is defined as the best response across all time point assessments based on RECIST 1.1 and iRECIST.

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

Table JZIA.5.3. Progression-Free Survival (iPFS) Event/Censoring Scheme

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

No adequate postbaseline tumor assessment available and death reported after 2 scan intervals following the first dose[b,c]	Censored	Date of randomization (first dose for single-arm study)

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

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

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

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

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

5.5. Pharmacokinetic/Pharmacodynamic Analyses

Selected PK descriptors for LY3435151 (based on actual sampling times), including maximum concentration under the area versus time curve ($C_{max)}$, approximate time of C_{max}, and area under the concentration versus time curve (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 a repeated dose may be evaluated.

In addition, PK parameter estimates for LY3435151 as a single agent and in combination may 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/PD 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.

5.6. Evaluation of Immunogenicity

The frequency and percentage of participants with preexisting antidrug antibodies (ADAs) and with treatment-emergent ADA positive (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 ADAs to LY3435151 and the PK parameters and PD response, including safety and efficacy, to LY3435151 may be assessed.

5.7. Biomarker Analyses

Single-marker and/or multimarker statistical analysis may be performed to explore the association between biomarkers, dose/exposure, and clinical outcomes. Details will be described in a separate Biomarker SAP.

5.8. 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 GC (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 prespecified safety review or annual reporting (for example, an update to the Investigative Brochure 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.

6. References

Iasonos A, O'Quigley J. Design considerations for dose-expansion cohorts in phase I trials. *J Clin Oncol.* 2013;31(31):4014-4021.

Kaplan EL, Meier P. Nonparametric estimation of incomplete observations. *J Am Stat Assoc*. 1958;53:457-481.

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