Protocol I5F-MC-JSCC (c)

A Phase 1a/1b Trial Investigating the CSF-1R Inhibitor LY3022855 in Combination with Durvalumab (MEDI4736) or Tremelimumab in Patients with Advanced Solid Tumors

NCT02718911

Approval Date: 02-Feb-2018

1. Protocol I5F-MC-JSCC(c)

A Phase 1a/1b Trial Investigating the CSF-1R Inhibitor LY3022855 in Combination with Durvalumab (MEDI4736) or Tremelimumab in Patients with Advanced Solid Tumors

Confidential Information

LY3022855

This Phase 1a/1b study is a multicenter, nonrandomized, open-label, dose-escalation study followed by dose expansion (disease-specific expansion cohorts) of intravenous (I.V.) LY3022855 in combination with I.V. durvalumab (MEDI4736) or I.V. tremelimumab in patients with advanced cancer.

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Protocol Electronically Signed and Approved by Lilly on 26 February 2016
Amendment (a) Electronically Signed and Approved by Lilly on 31 May 2016
Amendment (b) Electronically Signed and Approved by Lilly on 01 August 2017
Amendment (c) Electronically Signed and Approved by Lilly on approval date provided below

Approval Date: 02-Feb-2018 GMT

2. Synopsis

Protocol Title:

A Phase 1a/1b Trial Investigating the CSF-1R Inhibitor LY3022855 in Combination with Durvalumab (MEDI4736) or Tremelimumab in Patients with Advanced Solid Tumors

Rationale:

Checkpoint inhibitors of programmed cell death-1 protein (PD-1)/programmed cell death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) pathways have demonstrated proven, clinically meaningful improvement in survival for patients with various tumor types. Preclinical data demonstrate significant interplay between the innate and adaptive immune systems. Targeting colony-stimulating factor 1 (CSF-1) receptor (CSF-1R) may lead to disruption of the immunosuppressive effects of innate immune cells expressing CSF-1R. Combining a checkpoint inhibitor with an inhibitor of the CSF-1 pathway may potentiate the antitumor response. This trial will investigate the effects of CSF-1R inhibition using LY3022855 (anti-CSF-1R monoclonal antibody) in combination with durvalumab (MEDI4736, anti-PD-L1 monoclonal antibody) or tremelimumab (anti-CTLA-4 monoclonal antibody) in patients with advanced cancers.

Objectives:

The primary objectives of this study are:

- To characterize the safety profile and tolerability of each combination, LY3022855 with durvalumab (MEDI4736), and LY3022855 with tremelimumab, in the treatment of patients with advanced solid tumors.
- To define a recommended Phase 2 dose (RP2D) for LY3022855 with durvalumab combination, in the treatment of patients with advanced solid tumors.

The secondary objectives of this study are:

- To document the antitumor activity of each combination, LY3022855 with durvalumab, and LY3022855 with tremelimumab, in the treatment of patients with advanced solid tumors.
- To assess the development of antibodies against LY3022855, durvalumab, and tremelimumab (immunogenicity).
- To characterize the single-dose and multiple-dose pharmacokinetics (PK) of LY3022855 in combination with either durvalumab or tremelimumab, and the single-dose and multiple-dose PK of durvalumab and tremelimumab, each in combination with LY3022855.

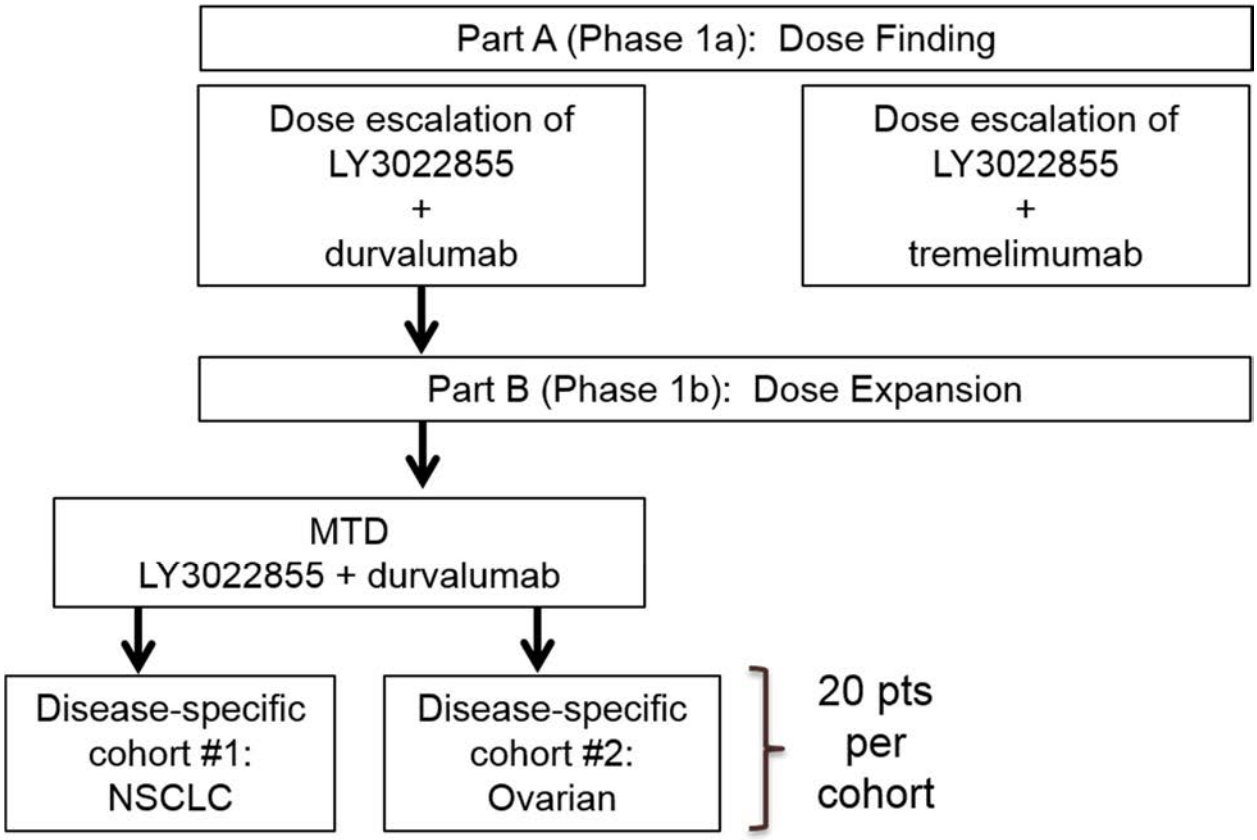
Overall Design:

Study I5F-MC-JSCC is a Phase 1a/1b, open-label, nonrandomized, dose-escalation (Part A for both durvalumab or tremelimumab), followed by dose-expansion (Part B) study of intravenous (I.V.) LY3022855 in combination with only I.V. durvalumab, in patients with advanced solid tumors. A cycle is defined as 28 days (4 weeks). Eligible patients will receive treatment as follows:

- LY3022855 (once weekly [QW] OR once on Days 1, 8, and 15 of each cycle OR once every 2 weeks [Q2W]), in combination with:
    - durvalumab Q2W
      OR
    - tremelimumab once every 4 weeks (Q4W); after 6 doses, tremelimumab once every 12 weeks (Q12W) until discontinuation from study treatment

The following description applies to each combination therapy:

During Part A, patients will be enrolled in a 3+3 design. In the LY3022855-plus-durvalumab regimen, LY3022855 will be administered at increasing dose levels, as tolerated; durvalumab will be administered at a fixed dose. In the LY3022855-plus-tremelimumab regimen, both LY3022855 and tremelimumab will be administered at increasing dose levels, as tolerated. In the event dose-limiting toxicities (DLTs) prevent further dose escalation (LY3022855 [in both combinations] and tremelimumab only), additional dosages between the highest dose tested and the previously identified safe dosage may be explored after further discussion among the investigators, sponsor, and collaborator. Once a maximum tolerated dose (MTD) has been identified for LY3022855-plus-durvalumab, enrollment to the 2 disease-specific expansion cohorts in part B of the study consisting of 20 patients each will begin for ovarian cancer and non-small cell lung cancer (NSCLC). Patients in Part B will be treated at the MTD for the LY3022855-plus-durvalumab combination. Upon completion of Part B, which is intended to confirm tolerability of a combination dose, the RP2D will be declared/defined.



Abbreviations: MTD = maximum tolerated dose; NSCLC = non-small cell lung cancer; pts = patients.
Note for Part A: Only LY3022855 (in both combinations) and tremelimumab, but not durvalumab, are dose escalated.

JSCC study design.

Number of Patients:

Planned Number of Patients	**Part A (Phase 1a, dose escalation)**	**Part B (Phase 1b, disease-specific expansion)**
Enrolled[a]	Up to 78	Approximately 20 per cohort (2 cohorts)
Evaluable[b]	Up to 78 Note: Nonevaluable patients will be replaced to ensure enough patients are enrolled in Part A.	Not applicable Note: The concept of "evaluable" (and, thus, replacement of patients) does not apply to patients in Part B.

a Patients who are enrolled in the trial are those who have been assigned to a treatment and have received at least one dose of study treatment. The assumption is that every patient who is enrolled in Part A is evaluable.

b Patients in Part A who receive all doses of study treatment for Cycle 1 (DLT-evaluation period) will be considered evaluable for the assessment of a dose level, provided it can be documented whether the patient did or did not experience a DLT within 28 days of Cycle 1, Day 1.

Treatment Arms and Duration:

For both Parts A and B, the planned duration of treatment is not fixed; patients will remain on study until they fulfill one of the criteria for study discontinuation.

Part A (Dose Escalation) Dose Regimens for the LY3022855-plus-Durvalumab Combination, by Cohort

	LY3022855		Durvalumab	
Cohort	**Dose (mg)**	**Frequency**	**Dose (mg)**	**Frequency**
D1a	25	QW	750	Q2W
D1b[a]	25	Days 1, 8, and 15 of each cycle	750	Q2W
D1c	25	Q2W	750	Q2W
D2a	50	QW	750	Q2W
D2b[a]	50	Days 1, 8, and 15 of each cycle	750	Q2W
D2c	50	Q2W	750	Q2W
D3a	75	QW	750	Q2W
D3b[a]	75	Days 1, 8, and 15 of each cycle	750	Q2W
D3c	75	Q2W	750	Q2W
D4a	100	QW	750	Q2W
D4b[a]	100	Days 1, 8, and 15 of each cycle	750	Q2W
D4c	100	Q2W	750	Q2W

Abbreviations: QW = weekly; Q2W = every 2 weeks.

Note: A cycle is defined as 28 days (4 weeks). QW refers to dosing on Days 1, 8, 15, and 22 of each cycle; Q2W refers to dosing on Days 1 and 15 of each cycle.

[a] Enrollment to the D*n*b cohort will occur only if ≥2 DLTs are observed after Cycle 1, Day 21 of the corresponding D*n*a cohort.

Part A (Dose Escalation) Dose Regimens for the LY3022855-plus-Tremelimumab Combination, by Cohort

	LY3022855		Tremelimumab	
Cohort	Dose (mg)	Frequency	Dose (mg)	Frequency[a]
T1a	50	QW	75	Q4W
T1b[b]	50	Days 1, 8, and 15 of each cycle	75	Q4W
T1c	50	Q2W	75	Q4W
T2a	100	QW	75	Q4W
T2b[b]	100	Days 1, 8, and 15 of each cycle	75	Q4W
T2c	75	Q2W	75	Q4W
T3a	100	QW	225	Q4W
T3b[b]	100	Days 1, 8, and 15 of each cycle	225	Q4W
T3c	100	Q2W	225	Q4W
T3d	75	QW	225	Q4W
T4a	100	QW	750	Q4W
T4b	100	Q2W	750	Q4W
T4c	100	Days 1, 8, 15 of each cycle	750	Q4W
T4d	75	QW	750	Q4W

Abbreviations: QW = weekly; Q2W = every 2 weeks; Q4W = every 4 weeks.

Note: A cycle is defined as 28 days (4 weeks). QW refers to dosing on Days 1, 8, 15, and 22 of each cycle; Q2W refers to dosing on Days 1 and 15 of each cycle; Q4W refers to dosing on Day 1 of each cycle.

[a] After 6 doses, tremelimumab to be dosed once every 12 weeks until discontinuation.

[b] Enrollment to the T*n*b cohort will occur only if ≥2 DLTs are observed after Cycle 1, Day 21 of the corresponding T*n*a cohort.

Treatment for Part B (Disease-Specific Dose Expansion Cohorts): LY3022855 plus Durvalumab

Patients in Part B will be treated at the MTD identified for LY3022855 in combination with durvalumab in Part A, unless otherwise specified by the sponsor.

Key Study Definitions

enter: Patients who are entered in the trial are those who have signed the informed consent form directly or through their legally acceptable representatives.

enroll: Patients who are enrolled in the trial are those who have been assigned to a treatment and have received at least 1 dose of study treatment.

interim analysis: An analysis of clinical study data that is conducted before the final reporting database is authorized for data lock.

study completion: This study will be considered complete when the primary and secondary objectives have been met.

continued access period: The period between study completion and end of trial during which patients on study treatment who continue to experience clinical benefit and no undue risks may continue to receive study treatment until one of the criteria for discontinuation is met.

end of trial: End of trial is the date of the last visit or last scheduled procedure for the last patient.

Notable Statistical Methods:

The analyses for this study will be descriptive; no p values will be calculated. Data analyses will be provided by cohort and treatment, whenever appropriate. For continuous variables, summary statistics will include the number of patients, mean, median, standard deviation, minimum, and maximum. Categorical endpoints will be summarized using the number of patients and percentages. Missing data will not be imputed.

Tumor response data, according to RECIST 1.1, will be tabulated by cohorts. Particularly, the antitumor effect will be summarized by best overall response, including the overall response rate (ORR) and disease control rate (DCR; complete response [CR]+ partial response [PR]+ stable disease [SD]).

3. Table of Contents

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4. Abbreviations and Definitions

Term	Definition
9H10	anti-murine CTLA-4 antibody
ADA	antidrug antibody
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AESI	adverse event of special interest
ALK	anaplastic lymphoma receptor tyrosine kinase (gene)
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
$AUC_{(0\text{-}tlast)}$	area under the plasma concentration-time curve from time zero to last measurable plasma concentration
$AUC_{(0\text{-}\infty)}$	area under the plasma concentration-time curve from time zero to infinity
audit	A systematic and independent examination of the study-related activities and documents to determine whether the evaluated study-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
BRAF	B-Raf proto-oncogene, serine/threonine kinase (gene)
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase (Attachment 1 and Attachment 3 only)
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	maximum plasma concentration
CNS	central nervous system
collection database	A computer database where clinical trial data are entered and validated.

complaint	Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety, effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
continued access period	The period between study completion and end of trial during which patients on study treatment who continue to experience clinical benefit and no undue risks may continue to receive study treatment until one of the criteria for discontinuation is met.
CR	complete response
CRP	clinical research physician
CRS	clinical research scientist
CS7	anti-murine CSF-1R antibody
CSF-1	colony-stimulating factor 1
CSF-1R	colony-stimulating factor 1 receptor
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events; also referred to as NCI-CTCAE
CTLA-4	cytotoxic T-lymphocyte associated protein 4
DCR	disease control rate
DCSI	development core safety information (portion of an investigator's brochure [IB])
DLET	dose-limiting equivalent toxicity
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
durvalumab	MEDI4736; a PD-L1 monoclonal antibody
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDTA	disodium edetate dihydrate
EGFR	epidermal growth factor receptor (gene)

end of trial	End of trial is the date of the last visit or last scheduled procedure for the last patient.
enroll	Patients who are enrolled in the trial are those who have been assigned to a treatment and have received at least one dose of study treatment.
enter	Patients who are entered in the trial are those who have signed the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board; see also IRB
EudraCT	European Union Drug Regulating Authorities Clinical Trials
GCP	good clinical practice
G-CSF	granulocyte colony-stimulating factor
GFR	glomerular filtration rate
GM-CSF	granulocyte macrophage colony-stimulating factor
GnRH	gonadotropin-releasing hormone
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IgG	immunoglobulin G
IgG1	immunoglobulin G, subclass 1
IgG1κ	immunoglobulin G1 kappa subclass
IgG2	immunoglobulin G, subclass 2
IgM	immunoglobulin M
IL-34	interleukin 34
ILD	interstitial lung disease
informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form (ICF).

interim analysis	An analysis of clinical study data that is conducted before the final reporting database is authorized for data lock.
irAE	immune-related adverse event
IRB	institutional review board; see also ERB
IRR	infusion-related reaction
I.V.	intravenous(ly)
LDH	lactate dehydrogenase
Lilly Safety System	Global safety database that tracks and reports serious adverse and spontaneous events occurring while using a drug/drug delivery system.
LVEF	left ventricular ejection fraction
LY3022855	anti-CSF-1R monoclonal antibody
MEDI4736	durvalumab; anti-PD-L1 monoclonal antibody
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition (scan)
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
open-label	A study in which there are no restrictions on knowledge of treatment allocation, therefore the investigator and the study participants are aware of the drug therapy received during the study.
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease (Attachment 7 only)
PD-1	programmed cell death-1 protein
PD-L1	programmed cell death-ligand 1
PFS	progression-free survival
PK	pharmacokinetic(s)
PK/PD	pharmacokinetic/pharmacodynamic

PR	partial response
QW	weekly
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
Q12W	every 12 weeks
Q28D	every 28 days
Q90D	every 90 days
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's Correction Formula
RECIST	Response Evaluation Criteria in Solid Tumors
reporting database	A point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.
re-screen	to screen a patient who was previously declared a screen failure for the same study
RP2D	recommended Phase 2 dose
SAE	serious adverse event
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical trial.
screen failure	A patient who does not meet one or more criteria required for participation in a trial
SD	stable disease
sPD-L1	soluble PD-L1 (programmed cell death-ligand 1)
study completion	This study will be considered complete when the primary and secondary objectives have been met.
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TAM	tumor-associated macrophage
TNF	tumor necrosis factor

TPO	third-party organization
tremelimumab	anti-CTLA-4 monoclonal antibody
ULN	upper limit of normal
V/F	apparent volume of distribution
w/v	weight per volume

A Phase 1a/1b Trial Investigating the CSF-1R Inhibitor LY3022855 in Combination with Durvalumab (MEDI4736) or Tremelimumab in Patients with Advanced Solid Tumors

5. Introduction

5.1. Rationale and Justification for the Study

Checkpoint inhibitors of programmed cell death-1 protein (PD-1)/programmed cell death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) pathways have demonstrated proven, clinically meaningful improvement in survival for patients with various tumor types. Preclinical data demonstrate significant interplay between the innate and adaptive immune systems. Targeting colony-stimulating factor 1 (CSF-1) receptor (CSF-1R) may lead to disruption of the immunosuppressive effects of innate immune cells expressing CSF-1R. Combining a checkpoint inhibitor with an inhibitor of the CSF-1 pathway may potentiate the antitumor response. This trial will investigate the effects of CSF-1R inhibition using LY3022855 (anti-CSF-1R monoclonal antibody) in combination with durvalumab (MEDI4736, anti-PD-L1 monoclonal antibody) or tremelimumab (anti-CTLA-4 monoclonal antibody) in patients with advanced cancers.

The sponsor, monitor, and investigators will perform this study in compliance with the protocol, good clinical practice (GCP) and International Conference on Harmonisation (ICH) guidelines, and applicable regulatory requirements.

5.1.1. Summary of the Rationale for Amendment (a)

Amendment (a) was created to incorporate a protocol synopsis. The following changes were also included in this amendment:

- Revised an error in Exclusion Criterion #31 regarding left ventricular ejection fraction (LVEF).
- Added Exclusion Criterion #32 to exclude patients with known ROS1 mutation in NSCLC, as a result of newly approved therapies for this patient population.
- Deleted the temperature range (23°C to 27°C) for preparation and infusion of LY3022855. The instructions to do this at room temperature are sufficient.
- Revised the permissible electrocardiogram (ECG) window prior to the start of the LY3022855 infusion from 1 hour to 2 hours to accommodate clinical sites.
- Other minor changes and revisions throughout the protocol to ensure clarity, internal consistency, and correct sentence structure and grammar.

5.1.2. Summary of the Rationale for Amendment (b)

Amendment (b) was created to incorporate the following changes:

- Modification of enrollment criteria in terms of prior treatment to reflect the changing landscape of cancer therapies.

- Dosing modification and toxicity management guidelines for immune-mediated, infusion-related, and non-immune-mediated reactions included under Table JSCC.5, Table JSCC.6, and Table JSCC.7 have been moved to Attachment 7 with no content changes.
- Cohort #3 (LY3022855 in combination with durvalumab in patients with melanoma), Cohort #4 (LY3022855 in combination with tremelimumab in patients with mesothelioma), and Cohort #5 (LY3022855 in combination with tremelimumab in patients with melanoma) from Part B of the study was removed. These changes were made for strategic reasons, and not for any identified safety concerns. The dose escalation of LY3022855 in combination with tremelimunab in Part A of the study will be completed, should this combination be developed in the future.
- Adverse events of special interest (AESIs) observed with durvalumab or tremelimumab were modified in Section 7.2.4.1.1 and Attachment 8 for consistency with durvalumab investigator's brochure (IB) and tremelimumab IB.
- Dose-limiting toxicity (DLT) criteria (creatine kinase[CK] elevation >8×upper limit of normal [ULN]) for CK was added for consistency with the toxicity management and dose modification guidelines listed in Attachment 7 of I5F-MC-JSCC (JSCC) protocol, non-immune-mediated reactions. These guidelines recommend different management for CK elevations that are > 8X ULN compared to CK elevations that are ≤ 8X ULN.
- Modification of DLT criteria to allow flexibility to continue dosing with Grade ≥2 elevations of aspartate aminotransferase (AST), CK, amylase, and lipase in certain situations as described in Section 7.2.2.1 based on the following rationale:

The key toxicological findings attributed to LY3022855 administration in preclinical studies included reversible mild-to-moderate increases in serum transaminases (AST and alanine aminotransferase [ALT]) and target organ effects in liver (Kupffer cell hypertrophy/hyperplasia). No histological changes in the liver were noted to correlate with the transaminase increases, nor were any changes noted in liver functional parameters (that is, alkaline phosphatase, bilirubin, or coagulation). Therefore, based on the small magnitude of the elevations and their limited impact to the overall health of the animal, the increases in ALT and AST were not considered adverse. The effect on Kupffer cells, specialized macrophages in the liver that play an important role in the clearance of several serum enzymes, including AST and CK, was regarded as immunomodulatory and was possibly associated with elevations in circulating CSF-1 levels.

In clinical studies of LY3022855 monotherapy, increases in serum AST and CK levels (mostly Grades 1 and 2) were noted in 19 and 17 patients, respectively, who received LY3022855 (of the total 64 patients) as of 28 January 2017. The majority of these patients experienced elevations in both enzymes and received 1.25 mg/kg Q2W, 2.5 mg/kg QW, 100 mg QW, or 150 mg QW of LY3022855. One case of a dose-limiting adverse event (AE) of Grade 4 rhabdomyolysis leading to Grade 4 acute renal failure was reported in a patient treated with LY3022855 1.25 mg/kg QW. The patient recovered from the events following discontinuation of study treatment. One of the 3 patients administered the dose of 150 mg QW experienced a Grade 3 CK elevation with associated elevated levels of serum and urine myoglobin. Although no similar observations were noted in additional 3 patients, the dose of 100 mg QW was selected as the recommended Phase 2

dose for LY3022855 due to potential safety issues related to the QW dosing of 150 mg as evidenced by the laboratory abnormalities induced by LY3022855. None of the patients with increased levels of AST experienced clinical symptoms suggestive of hepatic toxicity, nor were elevations of bilirubin noted at the time of the AST elevations. Among all patients with AST and CK elevations, only 1 patient who received the dose of 2.5 mg/kg QW of LY3022855 was discontinued from the study due to drug-related increases in CK (Grade 3), AST (Grade 3), and lactate dehydrogenase (LDH; Grade 1).

Comparatively, preclinical and clinical studies on CSF-1R–targeted monoclonal antibodies have shown asymptomatic increases in short-lived enzymes, such as LDH, CK, and AST (Cassier et al. 2015; Zhou et al. 2015). These increases in the levels of serum enzymes can be the result of decreases in Kupffer cells, depletion of which is consistent with the expected pharmacologic effect of CSF-1R pathway inhibition on Kupffer cells (Radi et al. 2011).

In clinical studies of LY3022855 monotherapy, increases in serum amylase and lipase (mostly Grades 1 and 2) were noted in 4 and 9 patients, respectively, who received single-agent LY3022855 (of the total of 64 patients) as of 28 January 2017 . These patients were treated with 1.25 mg/kg QW, 1.25 mg/kg Q2W, 100 mg QW, or 150 mg QW of LY3022855. One of these patients who was treated with LY3022855 1.25 mg/kg QW developed mild-to-moderate increases in amylase and lipase levels and was ultimately diagnosed with Grade 3 pancreatitis, determined to be dose-limiting. The patient recovered from pancreatitis following study treatment interruption but was subsequently removed from study due to the event. There were no other cases of pancreatitis reported with administration of a single-agent LY3022855 as of 28 January 2017.

These data suggest that elevations of serum levels of enzymes AST, CK, amylase, and lipase, are not necessarily indicative of end organ damage, thus, supporting modification of the DLT criteria in this protocol to allow flexibility to continue dosing with Grade ≥2 elevations of AST, CK, amylase, and lipase in certain situations as described in Section 7.2.2.1.

5.1.3. Summary of the Rationale for Amendment (c)

Amendment (c) was created to incorporate the following changes:

- Dose modification and toxicity management guidelines for durvalumab was updated per new guidance from AstraZeneca.
- Added clarification about testing for mutations in *EGFR* or *ALK* genes for patients in Part B (NSCLC cohort only).
- Updated information about tumor biopsy samples to make it consistent across sections.
- Updated treatment delay criteria to provide consistency across the protocol.

5.2. Objectives

5.2.1. Primary Objectives

The primary objectives of the study are:

- To characterize the safety profile and tolerability of each combination, LY3022855 with durvalumab (MEDI4736), and LY3022855 with tremelimumab, in the treatment of patients with advanced solid tumors.
- To define a recommended Phase 2 dose (RP2D) for LY3022855 with durvalumab, in the treatment of patients with advanced solid tumors.

5.2.2. Secondary Objectives

The secondary objectives of this study are:

- To document the antitumor activity of each combination, LY3022855 with durvalumab, and LY3022855 with tremelimumab, in the treatment of patients with advanced solid tumors.
- To assess the development of antibodies against LY3022855, durvalumab, and tremelimumab (immunogenicity).
- To characterize the single-dose and multiple-dose pharmacokinetics (PK) of LY3022855 in combination with either durvalumab or tremelimumab, and the single-dose and multiple-dose PK of durvalumab and tremelimumab, each in combination with LY3022855.

5.2.3. Exploratory Objectives

- To explore the effects of the combination of LY3022855 with durvalumab or tremelimumab in the treatment of patients with advanced solid tumors on changes in immune cell subset frequency and activation.
- To explore the pharmacodynamic profile of each combination, LY3022855 with durvalumab, and LY3022855 with tremelimumab, in the treatment of patients with advanced solid tumors.
- To explore cellular and molecular markers potentially associated with safety and antitumor and biological activity of the combination of LY3022855 with durvalumab or tremelimumab, in the treatment of patients with advanced solid tumors.

5.3. General Introduction to LY3022855, Durvalumab, and Tremelimumab

LY3022855 is a recombinant human monoclonal antibody of the immunoglobulin G (IgG), subclass 1 (IgG1) targeting CSF-1R. LY3022855 was originally identified from a screen of hybridoma candidates generated following immunization of MEDAREX HuMAb™ human IgG-transgenic mice with soluble human CSF-1R and NIH-3T3 cells stably expressing CSF-1R. The antibody comprises 2 identical gamma (γ) heavy chains and 2 identical kappa (κ) light chains. LY3022855 was selected for having high affinity binding to CSF-1R and its ability to block the binding of CSF-1 and interleukin 34 (IL-34) to CSF-1R. The LY3022855 heavy and light chain antibody genes were then engineered into a suitable vector for expression in Chinese hamster ovary cells. Subcloning techniques were used to generate a stable clone expressing high levels of LY3022855 for manufacturing purposes. The nonclinical and clinical experience is fully described in the current version of the LY3022855 investigator's brochure (IB). It is expected that treatment with LY3022855 will mitigate the immunosuppressive effects of cells expressing CSF-1R and lead to increased activation of the human immune system.

Durvalumab (MEDI4736), a human monoclonal antibody of the immunoglobulin G1 kappa (IgG1κ) subclass, inhibits binding of PD-L1 and is being developed for use in the treatment of cancer. As durvalumab is an engineered monoclonal antibody, it does not induce antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity. The proposed mechanism of action for durvalumab is interference of the interaction of PD-L1 with PD-1. Durvalumab is composed of 2 identical heavy chains and 2 identical light chains, with an overall molecular weight of approximately 149 kDa. Durvalumab contains a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to complement protein C1q and the fragment crystallizable gamma (Fcγ) receptors involved in triggering effector function. Durvalumab has high affinity and specificity for PD-L1. Recently reported data demonstrated clinical activity with an acceptable safety profile across a range of tumors including squamous cell carcinoma of the head and neck, pancreatic, gastric, and non-small cell lung cancers (NSCLC), hepatocellular carcinoma, and melanoma (Lutzky et al. 2014; Segal et al. 2014; Rizvi et al. 2015; Segal et al. 2015). The nonclinical and clinical experience is fully described in the current version of the durvalumab IB. It is expected that treatment with an anti-PD-L1 antibody, such as durvalumab, will lead to increased activation of the human immune system, increasing antitumor activity in patients with solid tumors.

Tremelimumab is an IgG2 kappa isotype monoclonal antibody directed against CTLA-4, also known as CD152 (cluster of differentiation 152). This immunomodulatory therapy is being developed by AstraZeneca for use in the treatment of cancer.

Binding of CTLA-4 to its target ligands (B7-1 and B7-2) provides a negative regulatory signal, which limits T cell activation. Anti-CTLA-4 inhibitors antagonize the binding of CTLA-4 to B7 ligands and enhance human T cell activation as demonstrated by increased cytokine (interleukin 2 [IL-2] and interferon [IFN] gamma) production in vitro in whole blood or peripheral blood mononuclear cell (PBMC) cultures (Tarhini and Kirkwood 2008). In addition, blockade of CTLA-4 binding to B7 by anti-CTLA-4 antibodies results in markedly enhanced T cell activation and antitumor activity in animal models, including killing of established murine solid tumors and induction of protective antitumor immunity. Therefore, it is expected that treatment with an anti-CTLA-4 antibody, such as tremelimumab, will lead to increased activation of the human immune system, increasing antitumor activity in patients with solid tumors.

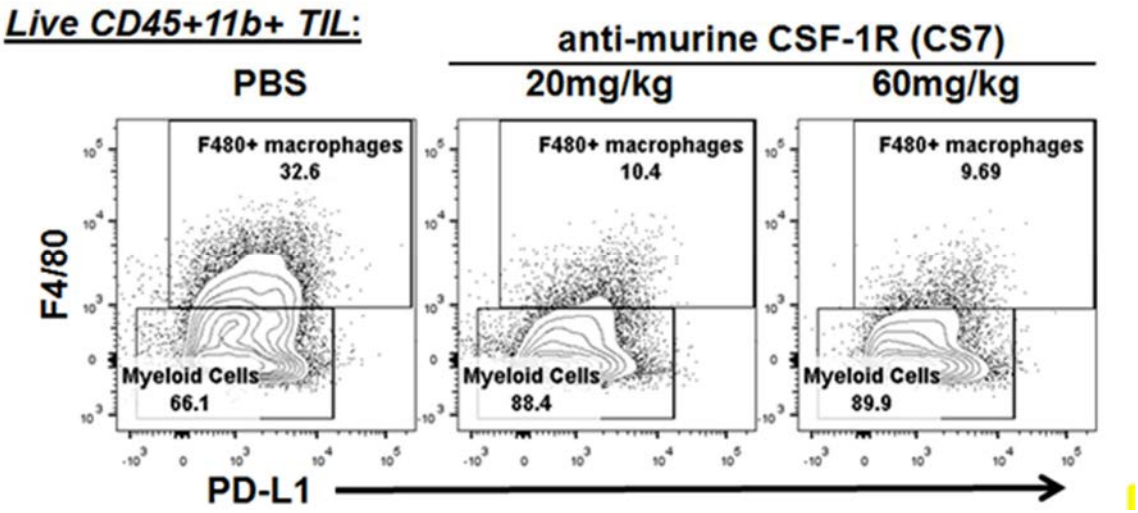
An extensive program of nonclinical and clinical studies has been conducted for tremelimumab both as monotherapy and combination therapy with conventional anticancer agents to support various cancer indications using different dose schedules.

The nonclinical and clinical experience is fully described in the current version of the tremelimumab IB.

Interactions between the innate and adaptive immune systems are critical for normal immune function and in the tumor microenvironment. For example, high numbers of tumor-associated macrophages (TAMs) inversely correlate with infiltration by CD8+ T cells. Targeting TAMs with antibodies directed against CSF-1R have been shown to significantly decrease macrophage infiltration of tumors (Figure JSCC.1). Additionally, anti-CSF-1R treatment that limits

associated macrophages enhances CD8+ T cell infiltration, leading to decreases in tumor burden (DeNardo et al. 2011). Moreover, in a syngeneic breast cancer model, depletion of CD8+ T cells rendered treatment with CSF-1R inhibition less efficacious, indicating interplay between macrophage activity and T cell infiltration.

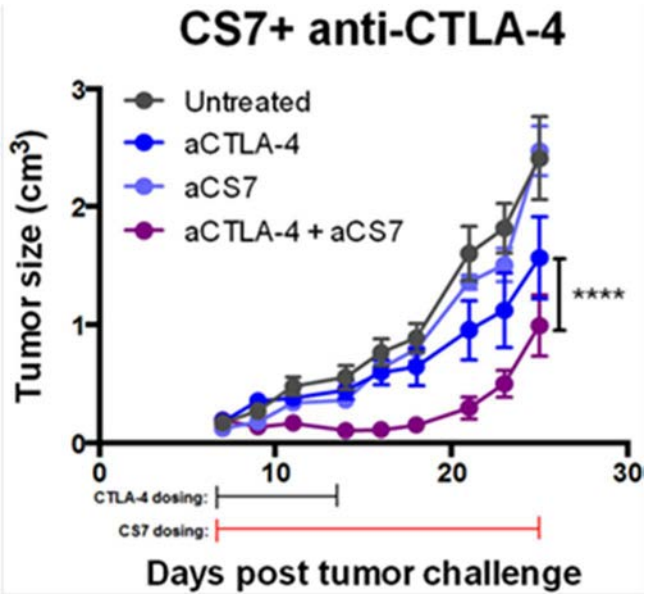
Checkpoint inhibitors of PD-1/PD-L1 and CTLA-4 pathways have demonstrated clinically meaningful improvements in survival for patients with various tumor types. Preclinical studies with CSF-1R-blocking monoclonal antibodies in combination with PD-L1- or CTLA-4-blocking monoclonal antibodies have demonstrated additive effects. Figure JSCC.2 demonstrates additive effects of CSF-1R and CTLA-4 inhibition; Figure JSCC.3 demonstrates additive effects of CSF-1R and PD-L1 inhibition. Given the immunomodulatory effects of the PD-1/PD-L1, CTLA-4, and CSF-1R inhibitors, the incidence of immune-related adverse events (irAEs) as additive effects (that is, in the combinations) may be greater than that observed with the individual agents. This trial will investigate the effects of CSF-1R inhibition using LY3022855 in combination with durvalumab or tremelimumab in patients with advanced cancers.



Abbreviations: CS7 = anti-murine CSF-1R antibody; CSF-1R = colony-stimulating factor 1 receptor; FACS = fluorescence-activated cell sorting (also referred to as flow cytometry); PBS = phosphate-buffered saline; PD-L1 = programmed cell death-ligand 1; TIL = tumor-infiltrating lymphocytes.

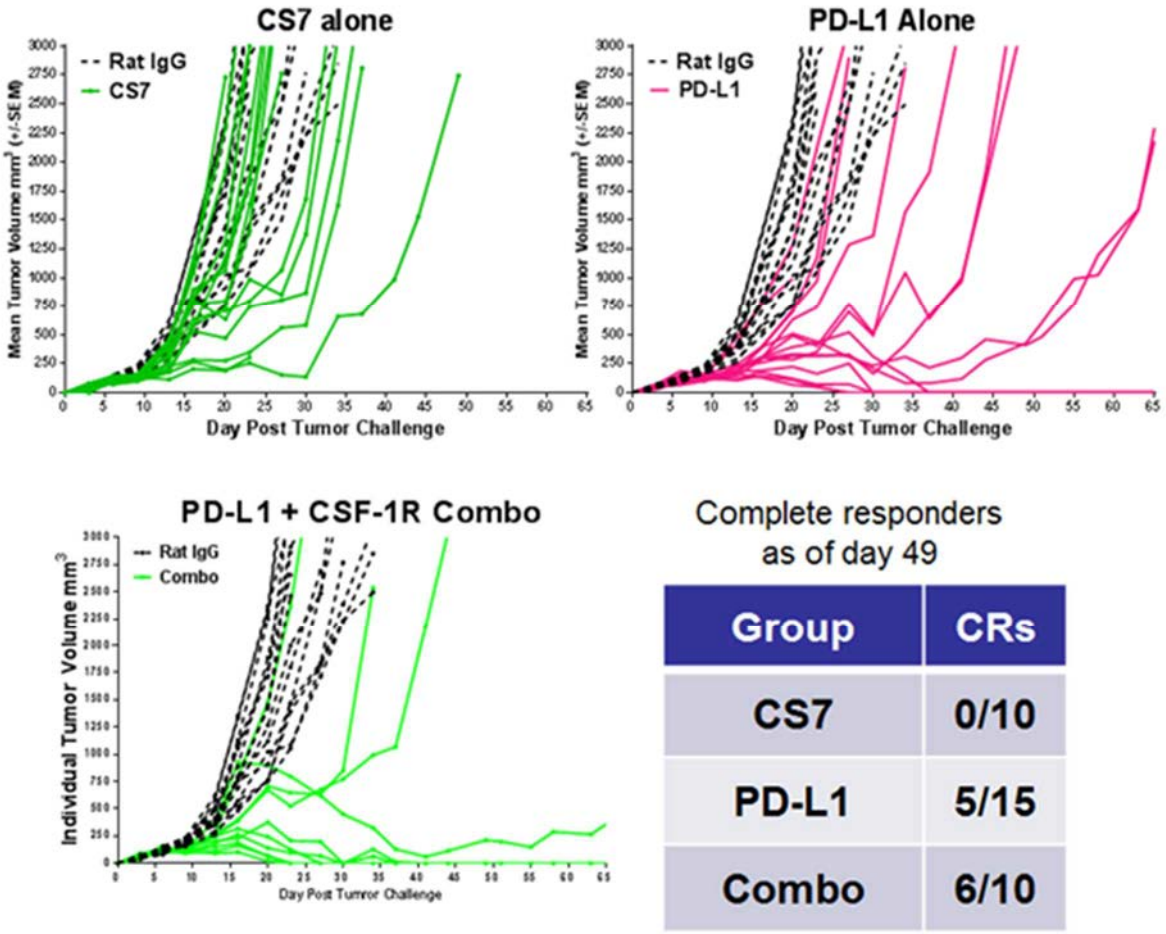
Treatment of murine MC38 tumors with anti-murine CSF-1R antibody (CS7) results in reduction of tumor-infiltrating macrophages. MC38 colon tumors were treated for 1 week with 3 doses of CS7, and then tumors were isolated and examined for the presence of CD45+, CD11b+, CD11cNeg F4/80+ macrophages. Representative FACS plots demonstrate an average of approximately 60% reduction in intra-tumor macrophages when treated with either dose of CS7.

Figure JSCC.1. Treatment of murine MC38 tumors with anti-murine CSF-1R antibody (CS7).



Abbreviations: CS7 = anti-murine CSF-1R antibody; CSF-1R = colony-stimulating factor 1 receptor; CTLA-4 = cytotoxic T-lymphocyte associated protein 4.
Combination therapy of anti-murine CSF-1R (CS7) and CTLA-4 (9H10) antibodies results in superior antitumor activity against 4T1 tumors. Established murine 4T1 triple-negative breast tumors were allowed to grow for 7 days before being treated for 1 week with 9H10 or CS7 alone or in combination, followed by 2 weeks of continued CS7 alone or after combination therapy. Combination therapy resulted in dramatically reduced tumor growth, which was significantly different from 9H10 or CS7 monotherapy. Average growth curves are shown.

Figure JSCC.2. Combination therapy of anti-murine CSF-1R (CS7) and CTLA-4 (9H10) antibodies.



Complete responders as of day 49

Group	CRs
CS7	0/10
PD-L1	5/15
Combo	6/10

Abbreviations: combo = combination; CR = complete response; CS7 = anti-murine CSF-1R antibody; CSF-1R = colony-stimulating factor 1 receptor; PD-L1 = programmed cell death-ligand 1.

Combination therapy of anti-murine CSF-1R (CS7) and PD-L1 antibodies results in superior regression of CT26 (colon cancer) tumors. Established murine CT26 tumors were allowed to grow for 6 days before being treated for 3 weeks with anti-PD-L1 or CS7 alone or in combination. Combination therapy resulted in an enhanced response and doubling of complete tumor regressions, which was significantly different from PD-L1 or CS7 monotherapy. Individual tumor growth curves are shown compared with control (black dashed line) for CS7 (top left), PD-L1 (top right), and the combination (bottom). CR rates at Day 49 are shown in the table.

Figure JSCC.3. Combination therapy of anti-murine CSF-1R (CS7) and PD-L1 antibodies.

Refer to Section 5.4, as well as the respective IBs, for further details regarding the study drugs.

More information about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated adverse events (AEs) of LY3022855 may be found in the LY3022855 IB. Information on AEs expected to be related to the investigational product LY3022855 may be found in Section 7 (Development Core Safety Information [DCSI]) of the LY3022855 IB. Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate, periodically during the course of the study, may be found in Section 6 (Effects in Humans) of the LY3022855 IB.

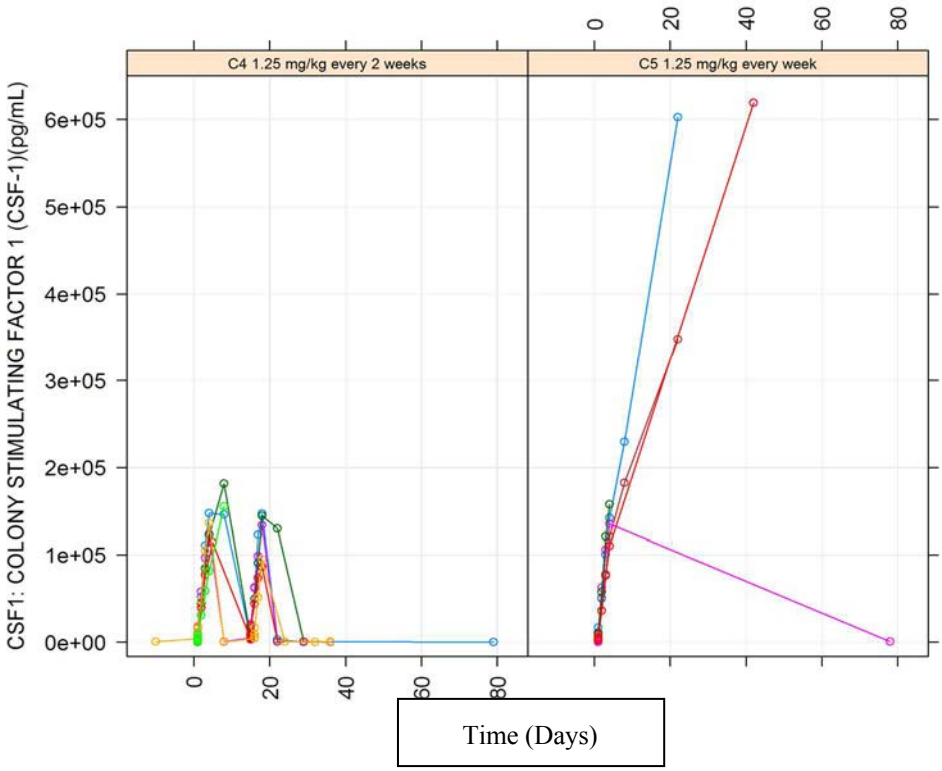
5.4. Rationale for Selection of Dose

5.4.1. LY3022855

Clinical experience with LY3022855 comprises 43 patients (as of 28 Jan 2016) who received the following doses intravenously (I.V.): 2.5 mg/kg weekly (QW) (n=6), 0.3 mg/kg QW (n=4), 0.6 mg/kg QW (n=3), 1.25 mg/kg every 2 weeks (Q2W) (n=20), 1.25 mg/kg QW (n=5), and 1 mg/kg on Weeks 1, 2, 4, and 5 of every 6-week cycle (n=5) in 2 ongoing Lilly-sponsored Phase 1 studies (I5F-IE-JSCA [JSCA] and I5F-MC-JSCB [JSCB]). At the first human dose studied, 2.5 mg/kg QW, which was also the highest dose administered, laboratory abnormalities were noted in 5 patients (Grade 2-3 creatine kinase or Grade 2-3 aspartate aminotransferase [AST] elevations) but were not classified as dose-limiting toxicities (DLTs) due to the lack of clinical signs or symptoms of organ toxicity. Because of these laboratory abnormalities, the study protocol was amended and dose escalation was restarted at a lower dose, 0.3 mg/kg QW. Three dose-limiting toxicities (DLTs) have been observed in Study JSCA: an event of left ventricular dysfunction in Cohort 4 (1.25 mg/kg Q2W) and separate events of pancreatitis and rhabdomyolysis in Cohort 5 (1.25 mg/kg QW). Upon further review, the patient with the DLT of left ventricular dysfunction had a baseline LVEF of 35%, which obfuscated the relationship between LY3022855 and the DLT event; therefore, the patient was considered to be a suboptimal candidate for study participation. No DLTs have occurred at the other dose levels.

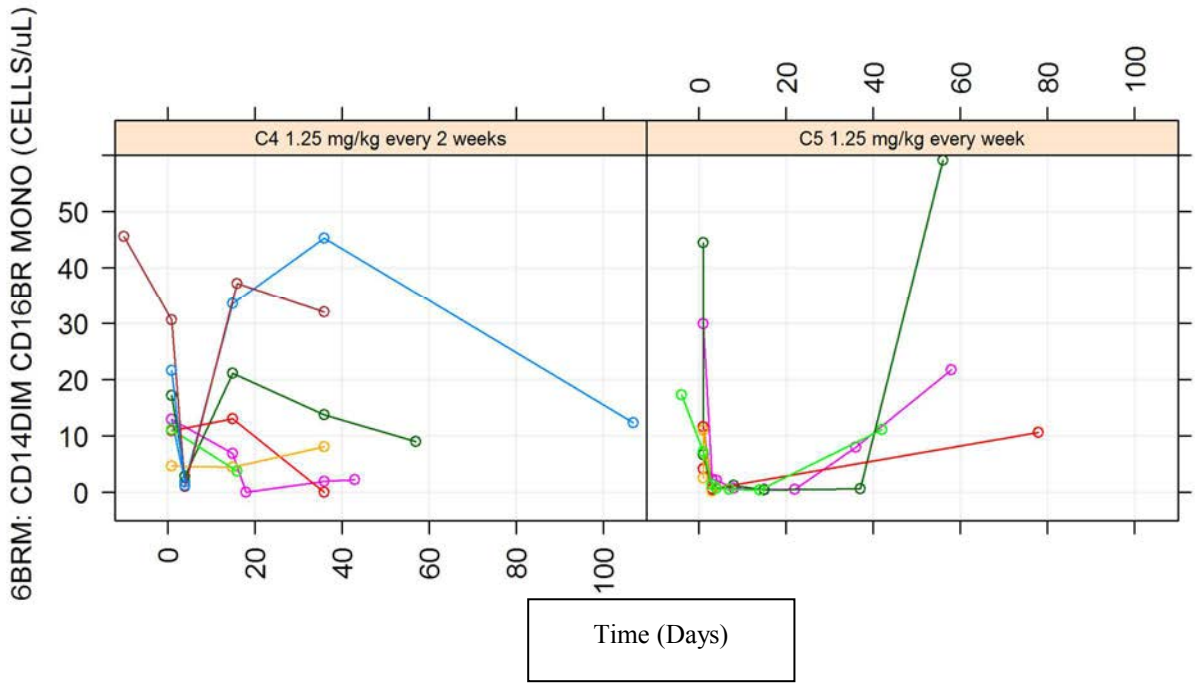
In addition, elevated CK, AST, and LDH levels were observed in patients treated with LY3022855 at 2.5 mg/kg QW (JSCA), as previously stated, and at 1.25 mg/kg Q2W (JSCB). However, enzyme levels decreased to Grade <2 upon discontinuation of LY3022855, indicating that these effects were reversible.

In addition to safety, the pharmacodynamics of the biomarkers, plasma CSF-1, and circulating $CD14^{Dim}CD16^{Bright}$ mononuclear cells were also evaluated in Study I5F-IE-JSCA (JSCA) (Figure JSCC.4 and Figure JSCC.5, respectively). While there were minimal changes observed at the 0.3-mg/kg and 0.6-mg/kg QW dose levels, CSF-1 levels were substantially increased with 1.25-mg/kg and 2.5-mg/kg doses (in a dose-dependent manner), as well as suppression of circulating $CD14^{Dim}CD16^{Bright}$ mononuclear cells, indicating sustained target engagement. Furthermore, these biomarker responses were maintained throughout the dosing interval by increasing the frequency of dosing from 1.25 mg/kg Q2W to 1.25 mg/kg QW.



Abbreviations: CSF-1 = colony-stimulating factor 1; I.V. = intravenous(ly).
Each line represents the profile of a single patient. Weekly I.V. dosing results in sustained elevation of CSF-1, an indicator of target engagement, for the duration of the dosing period. In contrast, dosing every 2 weeks allows CSF-1 levels to return to baseline, indicating reduced target engagement with a more intermittent dosing schedule.

Figure JSCC.4. Profile review of circulating CSF-1 levels in response to LY3022855 treatment.



Abbreviations: FACS = fluorescence-activated cell sorting (also referred to as flow cytometry); I.V. = intravenous(ly).
Each line represents the profile of a single patient. FACS analyses revealed weekly I.V. dosing rapidly and continuously suppressed circulating $CD14^{DIM}CD16^{BR}$ cells, in contrast to biweekly dosing, which resulted in an initial decrease but rapid increase to baseline levels prior to the next dose of LY3022855.

Figure JSCC.5. Profile review of circulating CD14DIM CD16BR MONO (cells/µL) in response to LY3022855 treatment.

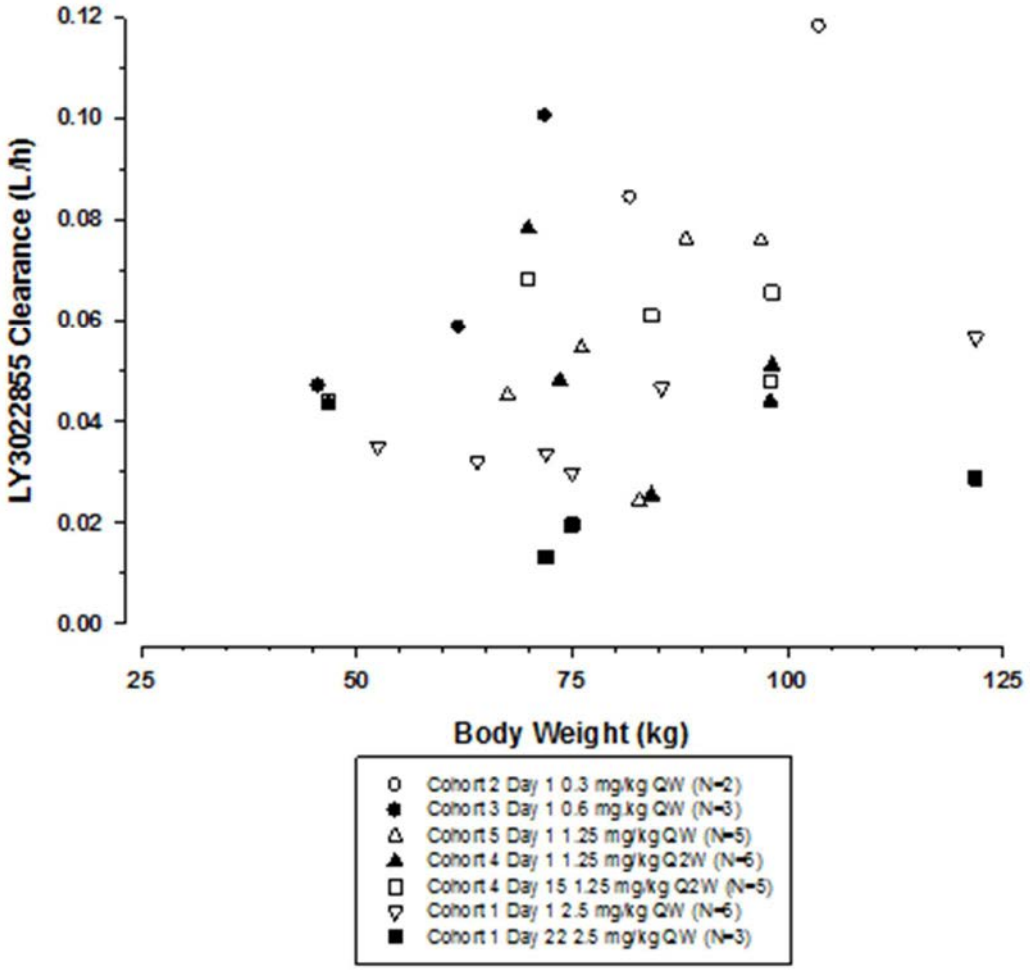
Preliminary analyses of the PK data obtained in Study JSCA reveal a lack of correlation between body weight and clearance of LY3022855 (Figure JSCC.6). The protocol for Study JSCA has, therefore, been amended (as Version 7.0) to investigate the use of non-weight-based dosing in the LY3022855 dose escalation, starting initially with 100 mg QW.

Therefore, based on the available clinical PK, pharmacodynamic, and safety data collected for LY3022855 in Study JSCA and Study JSCB, and considering the lack of clinical experience with LY3022855 in combination with other drug treatments, dose escalation of LY3022855 will commence at an initial dose level of 25 mg QW (approximately equivalent to a 0.3-mg/kg QW dose in a 75-kg patient) when in combination with durvalumab. This LY3022855 dose was not associated with any DLTs in the JSCA monotherapy dose-escalation trial and is approximately one fourth of the currently recommended Phase 2 dose of LY3022855 (1.25 mg/kg Q2W). Because the planned dose of durvalumab is equal to the dose being used in Phase 3 studies and because there is no planned dose escalation of durvalumab, a slightly lower LY3022855 starting dose was selected for the combination with durvalumab, compared with that selected for the combination with tremelimumab. Dose escalation of LY3022855 in combination with

durvalumab will proceed in 25-mg increments, up to a planned maximum of 100 mg QW (approximately equivalent to a 1.25-mg/kg QW dose in a 75-kg patient).

Dose escalation of LY3022855 when in combination with tremelimumab will commence at an initial dose level of 50 mg QW (approximately equivalent to a 0.6-mg/kg QW dose in a 75-kg patient). This LY3022855 dose was not associated with any DLTs in the JSCA monotherapy dose-escalation trial and is approximately one half of the currently recommended Phase 2 dose of LY3022855 (1.25 mg/kg Q2W). Because the planned starting dose of tremelimumab is approximately one tenth of the dose being used in Phase 3 studies and because there is a planned dose escalation for tremelimumab, a slightly higher LY3022855 starting dose was selected for the combination with tremelimumab, compared with that selected for the combination with durvalumab. Dose escalation of LY3022855 in combination with tremelimumab will proceed as a single 50-mg increment, up to a planned maximum of 100 mg QW (approximately equivalent to a 1.25-mg/kg QW dose in a 75-kg patient).

Furthermore, in the case where unacceptable toxicity is observed for the continuous dosing schedule (that is, once per week), the impact of either a reduced dose or a reduced dosing intensity (that is, a weeklong break in treatment) on patient safety will be evaluated.



Abbreviations: PK = pharmacokinetic(s); QW = weekly; Q2W = every 2 weeks.
Exploratory graphical analysis of the PK of LY3022855 samples obtained in Study JSCA indicates no clear relationship between body weight and drug clearance.

Figure JSCC.6. Relationship between body weight and clearance of LY3022855: Reported body weight versus LY3022855 drug clearance (as determined using noncompartmental analysis) for eligible patient data from Study JSCA.

5.4.2. Durvalumab

As of May 2015, approximately 1279 patients have received I.V. durvalumab monotherapy, the majority of which were enrolled on studies CD-ON-MEDI4736-1108 (n=694) and D4191C00003/ATLANTIC (n=303).

Following dose escalation of durvalumab in the first-human-dose study, Study CD-ON-MEDI4736-1108 in patients with advanced solid tumors, 10 mg/kg Q2W was selected for dose expansion. This was the highest dose level administered in the dose-escalation phase of the study (with respect to total cycle dose). Treatment-related Grade 3 or higher AEs were reported in 378 patients (54.5%) who received 10 mg/kg Q2W and were manageable by general treatment guidelines described in the durvalumab study protocols. The safety profile of durvalumab observed in Study CD-ON-MEDI4736-1108 is consistent with that observed in Study D4191C00003/ATLANTIC. In combination studies with tremelimumab, dabrafenib, or gefitinib, durvalumab is dosed at 10 mg/kg Q2W or 20 mg/kg every 4 weeks (Q4W) in the dose-expansion phases of each ongoing investigational trial.

Near-complete target saturation is expected with durvalumab ≥3 mg/kg Q2W, as indicated by suppression of the biomarker for PD-L1 target engagement, sPD-L1 (soluble PD-L1).

A population PK model was developed for durvalumab using monotherapy data from a Phase 1 study (Study CD-ON-MEDI4736-1108; N=292; doses=0.1 to 10 mg/kg Q2W or 15 mg/kg every 3 weeks [Q3W]; solid tumors). Population PK analysis indicated only minor impact of body weight on PK of durvalumab (coefficient of ≤0.5). The impact of body weight-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median, and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body weight of approximately 75 kg). A total of 1000 patients were simulated using body weight distribution of 40 to 120 kg. Simulation results demonstrate that body weight-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-subject variability with fixed dosing regimen.

Similar findings have been reported by others (Ng et al. 2006, Wang et al. 2009, Zhang et al. 2012, Narwal et al. 2013). Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies. In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-subject variability in pharmacokinetic/pharmacodynamic (PK/PD) parameters (Zhang et al. 2012).

A fixed-dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar PK exposure and variability, it was considered feasible to switch to fixed-dosing regimens.

The observed PK exposures of durvalumab in the presence of tremelimumab, dabrafenib, or gefitinib were consistent with respective monotherapy durvalumab exposure data, indicating no

PK interaction between these agents. The PK interaction between the combination of interest for this trial, LY3022855 and durvalumab, has not yet been clinically evaluated.

Therefore, based on the available clinical PK, pharmacodynamic, and safety data collected for durvalumab monotherapy and combination therapy with tremelimumab, this combination trial will commence enrollment at a dose of 750 mg of durvalumab Q2W (equivalent to a 10-mg/kg Q2W dose in a 75-kg patient).

5.4.3. Tremelimumab

As of November 2014, approximately 973 patients have received I.V. tremelimumab monotherapy.

Following an initial multiple-dose escalation of tremelimumab (3, 6, 10 mg/kg every 28 days [Q28D]) in a Phase 1/2 study (Study A3671002), patients were subsequently enrolled to evaluate the antitumor activity of 2 alternative dosing regimens: 10 mg/kg I.V. Q28D versus 15 mg/kg I.V. every 90 days (Q90D). Among patients treated with 10 mg/kg Q28D or 15 mg/kg Q90D, the median durations of objective response were 553 days and 722 days, respectively. Treatment-related SAEs occurred in 25.0% of patients treated with 10 mg/kg Q28D and in 8.9% of patients treated with 15 mg/kg Q90D. The results of this study led to a decision to proceed with the dosing regimen of 15 mg/kg Q90D in subsequent studies initiated by Pfizer Inc (previous sponsor).

However, subsequent retrospective exposure-response analyses suggested that the 15-mg/kg Q90D schedule could result in underexposure to tremelimumab. An intensified schedule of tremelimumab is now under evaluation whereby patients receive 10 mg/kg Q28D for 6 doses, followed by 15 mg/kg Q90D until treatment discontinuation (Calabrò et al. 2015).

In the ongoing combination study with durvalumab and tremelimumab (Study D4190C00006), the dose level selected for tremelimumab in the dose-expansion phase is 1 mg/kg Q4W. Doses higher than 1 mg/kg Q4W (that is, 3 mg/kg Q4W and 10 mg/kg Q4W) in combination with durvalumab at 10, 15, or 20 mg/kg Q4W were associated with increased incidence of AEs.

A population PK model was developed for tremelimumab using data from Phase 1 through Phase 3 studies (N=654; 0.01-15-mg/kg doses Q4W or Q90D; metastatic melanoma) (Wang et al. 2014). The population PK model indicated minor impact of body weight on PK of tremelimumab (coefficient of $\leq$0.5). The weight-based (1 mg/kg Q4W) and fixed-dosing (75 mg Q4W; based on median body weight of approximately 75 kg) regimens were compared using predicted PK concentrations (5th, median, and 95th percentiles) using the population PK model in a simulated population of 1000 patients with body weight distribution of 40 to 120 kg. Similar to durvalumab, simulations indicated that both body weight-based and fixed-dosing regimens of tremelimumab yield similar median steady-state PK concentrations with slightly less between-subject variability with the fixed-dosing regimen.

Therefore, based on the available clinical PK and safety data collected for tremelimumab in monotherapy and in combination with durvalumab, this combination trial will commence enrollment at a dose of 75 mg of tremelimumab Q4W (equivalent to a 1-mg/kg Q4W dose in a

75-kg patient) for the first 6 doses, followed by dosing on an every-12-week (Q12W) schedule, starting 4 weeks after Dose 6 (Week 25), until treatment discontinuation. This starting dose is 10-fold lower than the currently recommended dose of tremelimumab monotherapy, and was selected to allow for an increased margin of safety, since the combination of LY3022855 and tremelimumab has not yet been studied in patients.

It is intended that the dose escalation of tremelimumab could reach 750 mg Q4W for the first 6 doses, followed by dosing on a Q12W schedule (approximately equivalent to a 3-mg/kg Q4W dose in a 75-kg patient). This planned dose level is the currently recommended Phase 2 dose (RP2D) of tremelimumab for the monotherapy (10 mg/kg Q4W).

6. Investigational Plan

6.1. Study Population

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened. Individuals may be re-screened one time, if agreed upon by the investigator and the sponsor. The interval between screenings should be at least 1 week. When re-screening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number. Repeating of laboratory tests during the screening period does not constitute re-screening; laboratory tests may not be repeated more than twice during the screening period in order to meet eligibility criteria.

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

6.1.1. Inclusion Criteria

Patients may be included in the study if they meet all of the following criteria during screening prior to first dose of study drug.

(Note: If a specific cohort is not indicated for a criterion, the criterion applies to all patients.)

[1] Must have histological or cytological evidence of a diagnosis of cancer that is not amenable to curative therapy.

[2] Part B (all cohorts): Must have a type of malignancy that is being studied, as listed in the following:

[a] LY3022855 and durvalumab (MEDI4736) combination cohorts

[i] NSCLC that has relapsed or is refractory (definitions below) to immune checkpoint inhibitor therapy and has progressed through no more than 3 lines of therapy (one line must have been a platinum-containing regimen).

- Relapsed: Following initial clinical benefit (that is, complete response [CR], partial response [PR], or stable disease [SD] on any scan), patients must have documented radiographic disease progression while receiving therapy with an immune checkpoint inhibitor.
- Refractory: Patients must have documented radiographic disease progression ≤16 weeks after the start of treatment with an immune checkpoint inhibitor, with no evidence of clinical benefit (that is, CR, PR, or SD on any scan) while receiving therapy.

a. Patients must not have a known activating mutation of the *EGFR* or *ALK* gene. If a site uses algorithmic testing that has eliminated the possibility of *EGFR* or *ALK* gene mutations, no specific testing for mutations in these genes is required.

b. Patients could have received only one prior immune checkpoint therapy (anti-PD-1/PD-L1 or anti-CTLA-4, or a single regimen combining anti-PD-1/PD-L1 with an anti-CTLA-4).

[ii] Ovarian cancer (epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer) that has been treated with no more than 3 lines of therapy (with or without platinum).

[3] Part A (all cohorts) and Part B (ovarian cancer cohort only): Must be willing to undergo pretreatment and on-treatment core needle or excisional tumor biopsies. For patient in NSCLC Part B cohort, if newly obtained samples cannot be obtained such as in cases of inaccessibility or patient safety concern, an archived tumor sample will be requested if not restricted by local regulations. The archived tumor sample must follow most recent systemic treatment. If no archived specimen since the most recent systemic treatment is available, and a new biopsy is not medically feasible, the patient should not be enrolled in the clinical trial.

[4] [a] Part A (all cohorts): Have the presence of measurable and/or nonmeasurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (Eisenhauer et al. 2009).

[b] Part B (both cohorts): Have the presence of measurable disease as defined by the RECIST 1.1 (Eisenhauer et al. 2009).

[5] Are ≥18 years of age.

[6] (Patient or legal representative) Have given written informed consent and any locally required authorization (for example, Health Insurance Portability and Accountability Act [HIPAA] in the United States or the European Union [EU] Data Privacy Directive) prior to performing any protocol-related procedures, including screening evaluations.

[7] Have adequate normal organ and marrow function, including the following:

System	Laboratory Value
Hematologic	
ANC	≥1.5 × 10^9/L (≥1500/mm^3)
Platelet count	≥100 × 10^9/L (≥100,000/mm^3)
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L (red blood cell transfusions are not allowed within 7 days prior to screening hematology profile)
Renal	
Creatinine OR Measured or calculated creatinine clearance[a] (see Attachment 6)	≤1.5 × institutional ULN OR ≥60 mL/min
Hepatic	
Total bilirubin	≤1.5 × institutional ULN
AST and ALT	≤2.5 × institutional ULN OR ≤5 × institutional ULN for patients with liver metastases
Coagulation	
INR or PT	INR ≤1.5 × institutional ULN or PT ≤5 seconds above institutional ULN
PTT or aPTT	PTT or aPTT ≤5 seconds above institutional ULN
Thyroid	
TSH OR free T4	TSH OR free T4 within the normal limits.

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; GFR = glomerular filtration rate; INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time; T4 = thyroxine; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

[a] GFR should be estimated via the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation (Levey et al. 2009).

[8] Have a performance status of ≤1 on the Eastern Cooperative Oncology Group (ECOG) scale (refer to Attachment 5).

[9] Have discontinued previous treatments for cancer and recovered from the acute effects of therapy.

At the discretion of the investigator, patients with hormone-refractory prostate cancer who are stable on gonadotropin-releasing hormone (GnRH) agonist therapy or maintenance prednisone, and patients with breast cancer who are stable on antiestrogen therapy (for example, an aromatase inhibitor) may have that treatment continued while they are enrolled.

[10] Are reliable and willing to make themselves available for the duration of the study and are willing and able to comply with the protocol for the duration of the study, including undergoing treatment, scheduled visits and examinations (including follow-up), and attempted pretreatment and on-treatment tumor biopsies (Part A – all cohorts and Part B – ovarian cancer cohort only).

[11] Have an estimated life expectancy, in the judgment of the investigator, of at least 12 weeks.

[12] Male patients:

[a] who are sterile (including vasectomy)

or

[b] who are not sterile and agree to use 2 acceptable methods of effective contraception* during the study, starting at screening, for at least 6 months following last dose of study drug(s); and agree not to donate sperm during the study and for at least 6 months following last dose of study drug

[13] Female patients:

[a] are women not of childbearing potential due to surgical sterilization (at least 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy or tubal ligation) confirmed by medical history, or postmenopausal by history. Postmenopausal women include women with either:

[i] ≥60 years of age and spontaneous amenorrhea for at least 12 months, not induced by a medical condition such as anorexia nervosa and not taking medications during the amenorrhea that induced the amenorrhea (for example, oral contraceptives, hormones, GnRH, antiestrogens, selective estrogen receptor modulators [SERMs], or chemotherapy)

or

[ii] spontaneous amenorrhea for 6 to 12 months and a follicle-stimulating hormone (FSH) level greater than 40 mIU/mL

[b] are women of childbearing potential who test negative for pregnancy within 7 days prior to enrollment based on a urine or serum pregnancy test and agree to use 2 acceptable methods of effective contraception* during the study, starting at screening, and for 6 months following the last dose of the study drug(s) and also must not be breastfeeding.

* Acceptable methods of effective contraception include the following, where 2 methods must be used

- Barrier methods
    - Male condom plus spermicide
    - Cap plus spermicide
    - Diaphragm plus spermicide
- Intrauterine device methods
    - Copper T
    - Progesterone T (also considered to be a hormonal method)
    - Levonorgestrel-releasing intrauterine system (for example, Mirena®)
- Hormonal methods
    - Implants
    - Hormonal shot or injection
    - Combined pill
    - Minipill
    - Patch

Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.

6.1.2. Exclusion Criteria

Potential study patients may not be included in the study if any of the following apply during screening.

[14] Have received treatment with an investigational product or nonapproved use of a drug or device (other than the study drug used in this study) within 28 days prior to the initial dose of study drug, or are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

[15] Have been involved in the planning and/or conduct of the study (applies both to sponsor staff and/or to staff at the study site) or have an immediate family member (for example, spouse, parent/legal guardian, sibling, or child) who is investigational site or sponsor staff directly involved with this trial, unless prospective institutional review board (IRB) approval (by chair or designee) is obtained, allowing exception to this criterion for a specific patient.

[16] Have previously been enrolled in the present study.

[17] Have had any of the following anticancer therapies prior to enrollment:

[a] small molecule therapy or chemotherapy within 14 days.

[b] radiation therapy within 14 days.

[c] monoclonal antibody treatment within 28 days.

[18] Are currently receiving or have had prior use of immunosuppressive medication within 28 days before the first dose of study drug, with the exception of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.

[19] Have had major surgery within 28 days prior to enrollment.

[20] Have a serious preexisting medical condition, including, but not limited to, the following:

[a] Known human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS)-related illness (baseline screening required within 28 days prior to enrollment).

[b] History of immunodeficiency (primary and secondary).

[c] Active or prior documented autoimmune disease within the past 24 months. NOTE: Patients with vitiligo, Graves disease, or psoriasis not requiring systemic treatment (within the past 24 months) are not excluded.

[d] Active or prior documented inflammatory bowel disease (for example, Crohn's disease, ulcerative colitis).

[e] Uncontrolled intercurrent illness, including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses including any patient known to have evidence of acute or chronic hepatitis B or hepatitis C.

[f] History of allogeneic organ transplant.

[g] Known history of tuberculosis.

[h] Active non-infectious pneumonitis requiring treatment with steroids, or history of interstitial lung disease (ILD).

[i] Active or uncontrolled clinically serious infection.

[j] Known psychiatric or substance abuse disorders, or social situations that would either limit compliance with study requirements or compromise the ability of the patient to give written informed consent.

[21] 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 greater than 10 mg per day of prednisone or equivalent, and their disease is asymptomatic and radiographically stable for at least 60 days.

[22] Have a second primary malignancy that, in the judgment of the investigator and sponsor, may affect the interpretation of results.

[23] Have mean QT interval corrected for heart rate (QTc) ≥470 milliseconds calculated from one baseline electrocardiogram (ECG) using Fridericia's Correction Formula (QTcF) and confirmed with 2 additional baseline ECGs.

[24] Have known hypersensitivity to LY3022855, durvalumab, or tremelimumab, or to any combination or excipient.

[25] Have received live attenuated vaccination within 30 days prior to study entry.

[26] Have any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results.

[27] Have known muscle damage due to a primary, traumatic, or other muscle disease or a creatine kinase greater than normal limits.

[28] Have had any prior Grade ≥3 irAE† while receiving any previous immunotherapy agent, have any unresolved irAE Grade >1, or any irAE that led to the permanent discontinuation of prior immunotherapy.

[29] Have experienced a Grade ≥3 AE or a neurologic or ocular AE of any grade while receiving prior immunotherapy. Patients with an endocrine AE Grade ≤2 are permitted to enroll if they are stably maintained on appropriate replacement therapy and are asymptomatic.

[30] Have required the use of additional immunosuppression other than corticosteroids for the management of an AE, have experienced recurrence of an AE if re-challenged, and currently require a maintenance dose of >10 mg prednisone or equivalent per day.

[31] Have left ventricular ejection fraction (LVEF) <50%.

[32] Have known *ROS1* mutation in NSCLC (baseline screening not required).

† Immune-related AEs: pneumonitis or ILD; diarrhea or enterocolitis; hepatitis (elevated liver function test); nephritis or renal dysfunction (elevated serum creatinine); rash (excluding bullous skin formations); endocrinopathy (for example, hyperthyroidism, hypothyroidism, hypopituitarism, adrenal insufficiency); immune-mediated neurotoxicity (including but not limited to limbic encephalitis, autonomic neuropathy, excluding myasthenia gravis and Guillain-Barre); immune-mediated peripheral neuromotor syndromes, such as Guillain-Barre and myasthenia gravis.

6.1.3. Lifestyle Restrictions

Patients should not donate blood while participating in this study until after 4 to 5 times the half-life of study treatment(s) (that is, 6 months after the last dose).

6.2. Summary of Study Design

Study I5F-MC-JSCC is a multicenter, nonrandomized, open-label, dose-escalation (Part A), followed by dose-expansion (Part B) Phase 1a/1b study of LY3022855 in combination with durvalumab or tremelimumab (Part A) or durvalumab only (Part B), in patients with advanced solid malignancies. A cycle is defined as 28 days (4 weeks). Eligible patients will receive treatment as follows:

- LY3022855 (once weekly [QW] OR once on Days 1, 8, and 15 of each cycle OR once every 2 weeks [Q2W]), in combination with:
  - durvalumab Q2W (Parts A and B)
    OR
  - tremelimumab once every 4 weeks (Q4W); after 6 doses, tremelimumab once every 12 weeks (Q12W) until discontinuation (Part A only)

The study will be conducted in 2 parts:

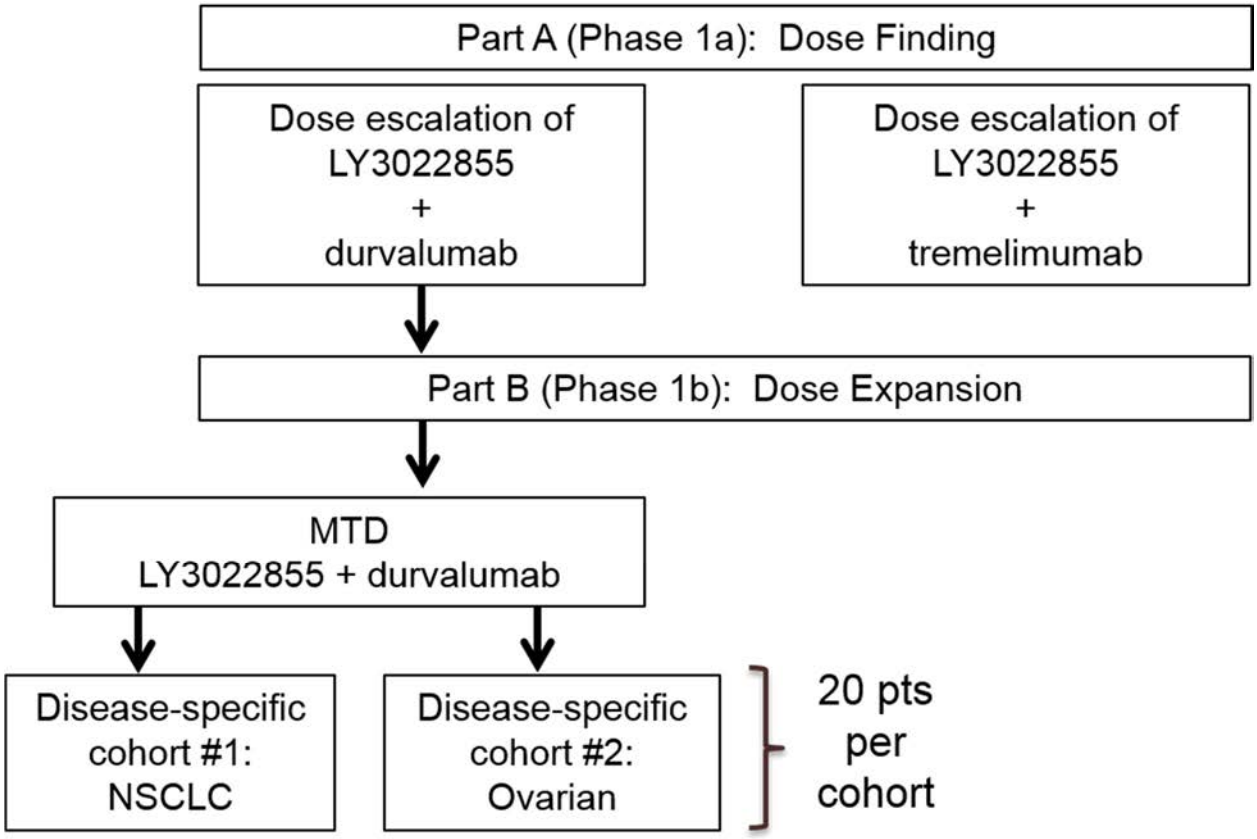
- Part A – Phase 1a, dose escalation
- Part B – Phase 1b, disease-specific expansion

The following description applies to each combination therapy.

During Part A, patients will be enrolled in a 3+3 design. In the LY3022855-plus-durvalumab regimen, LY3022855 will be administered at increasing dose levels, as tolerated; durvalumab will be administered at a fixed dose. In the LY3022855-plus-tremelimumab regimen, both LY3022855 and tremelimumab will be administered at increasing dose levels, as tolerated. In the event DLTs prevent further dose escalation (LY3022855 [in both combinations] and tremelimumab only), additional dosages between the highest dose tested and the previously identified safe dosage may be explored after further discussion among the investigators, sponsor, and collaborator. Once a maximum tolerated dose (MTD) has been identified for the LY3022855-plus-durvalumab combination, enrollment to Part B (2 disease-specific expansion cohorts of 20 patients per cohort) will begin. The NSCLC cohort will consist of a minimum of 10 patients with disease refractory to checkpoint therapy and a minimum of 6 patients with disease relapsed on prior checkpoint therapy. Patients in Part B will be treated at the MTD for LY3022855-plus-durvalumab combination. Upon completion of Part B, which is intended to confirm tolerability of a combination dose, the RP2D will be declared/defined.

All patients enrolled to all cohorts of Part A or to the ovarian cancer cohort (only) of Part B will undergo mandatory attempted pretreatment and on-treatment (6-8 weeks after starting study treatment) tumor core needle or excisional biopsies.

Figure JSCC.7 presents the overall study design. Figure JSCC.8 presents the schema for an individual patient with regard to timing of tumor tissue biopsies.



Abbreviations: MTD = maximum tolerated dose; NSCLC = non-small cell lung cancer; pts = patients.
Note for Part A: Only LY3022855 (in both combinations) and tremelimumab, but not durvalumab, are dose escalated.

Figure JSCC.7. JSCC study design.

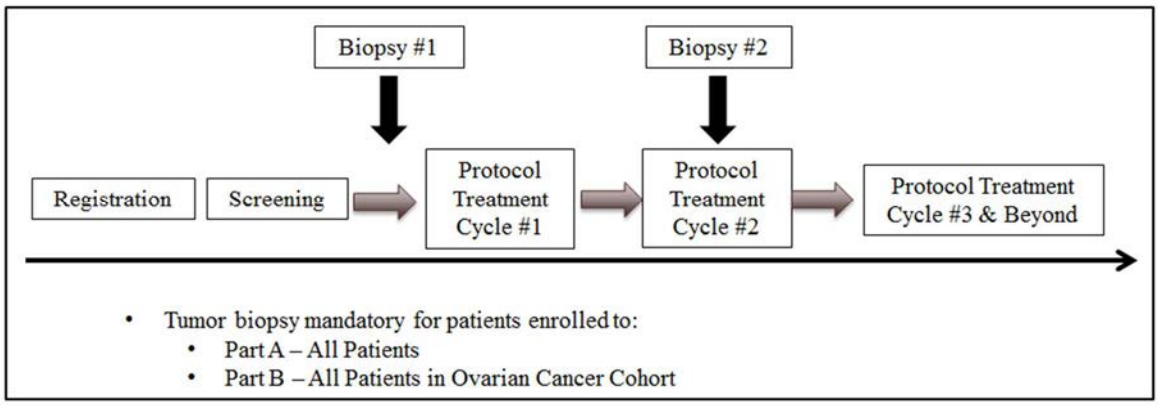


Figure JSCC.8. Schema for an individual patient with regard to timing of tumor tissue biopsies.

To characterize the safety profile and tolerability and to define the RP2D of the combinations of LY3022855 with durvalumab or tremelimumab, an adequate sample size is required. The actual sample size in Part A depends on the incidence of DLTs and is estimated to be up to approximately 78 patients; refer to Section 10.1 for additional details.

In Part A, after all patients who are deemed evaluable for the assessment of dose levels complete the DLT-evaluation period or the MTD is determined, an interim safety and PK analysis may be conducted for each combination for planning next studies. After completion of enrollment to Part B, if it is deemed that enough data are obtained to assess the primary and secondary objectives, a clinical study report may be written before the last patient visit for the study.

The planned duration of treatment is not fixed; patients will remain on study until they fulfill one of the criteria for study discontinuation (Section 6.3).

Refer to Attachment 1 for the Study Schedule.

6.2.1. Study Completion and End of Trial

This study will be considered complete (that is, the scientific evaluation will be complete [study completion]) when the primary and secondary study objectives have been met. "End of trial" refers to the date of the last visit or last scheduled procedure for the last patient.

The end of trial occurs after study completion and after the last patient has discontinued study treatment and completed any applicable continued access follow-up.

6.2.2. Continued Access Period

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

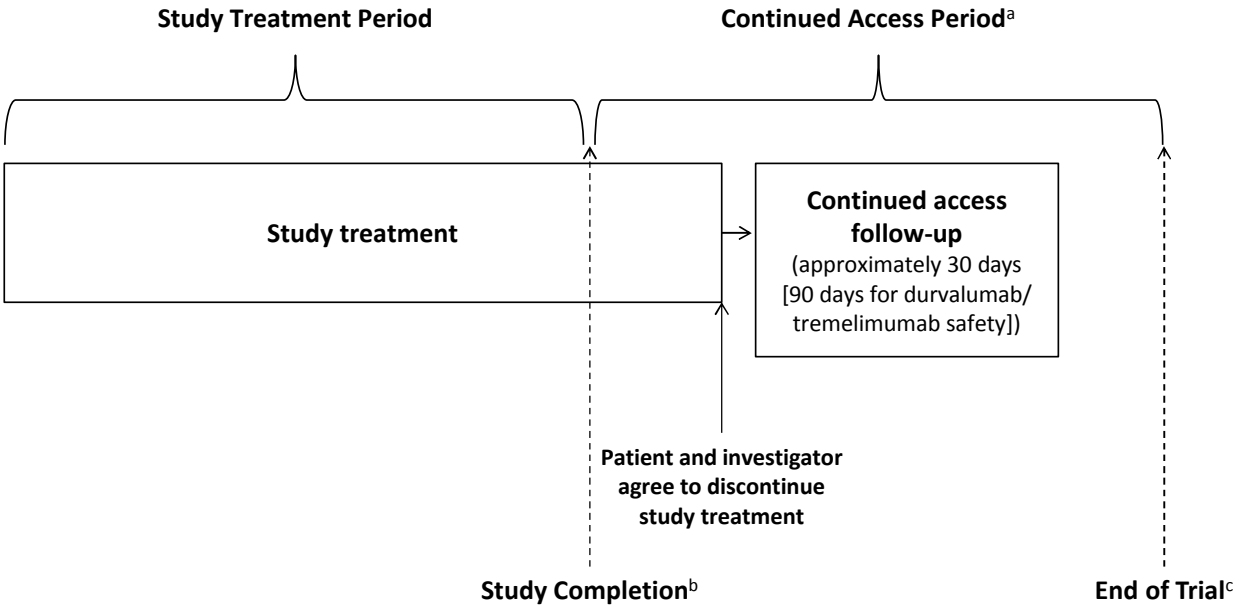
Continued access will apply to this study only if at least one patient is still on study treatment when study completion occurs. Lilly (the sponsor) will notify investigators when the continued access period begins.

The sponsor may allow patients to enroll in an LY3022855 “rollover” protocol to provide long-term continued access for patients enrolled in this study.

Patients must sign a new ICF before continued access is provided.

The patient's continued access to study treatment (Visits 501-5XX) will end when the patient and investigator agree that the patient will no longer continue to receive study treatment. Continued access follow-up (Visits 901 [30-day] and 902 [90-day, only for durvalumab and tremelimumab safety]) will begin the day after the patient and the investigator agree that the patient will no longer continue to receive study treatment. Continued access follow-up for Visit 901 lasts approximately 30 days (±7 days); Visit 902 occurs 90 days (±7 days) after the patient and investigator agree that the patient will no longer continue to receive study treatment. Follow-up procedures will be performed as shown in the Continued Access Schedule in Attachment 1.

Figure JSCC.9 presents the sequence of study periods, including continued access.



[a] Lilly will notify sites when the continued access period begins and ends.
[b] Primary and secondary objectives have been met. Lilly will notify sites when study completion occurs.
[c] End of trial occurs at the last visit or last scheduled procedure for the last patient.

Figure JSCC.9. Continued access diagram.

Patients who are in short-term follow-up (Visit 801 [30-day] or Visit 802 [90-day]) when the continued access period begins will continue in short-term follow-up until the 30-Day/90-Day Follow-Up visit is completed.

6.3. Discontinuations

The reason for and date of discontinuation will be collected for all patients. The date of discontinuation from study treatment is to be reported on the electronic case report form (eCRF). Patients who discontinue will have follow-up procedures performed as shown in the Study Schedule (Attachment 1).

If a patient withdraws informed consent, he or she must not be contacted unless he or she has explicitly provided permission and consent. Lilly may continue to use previously collected medical research data prior to the withdrawal consistent with the original authorization.

Refer to Section 7.6.1 for conditions under which patients may be replaced.

6.3.1. Discontinuation of Patients Inadvertently Enrolled

If the sponsor or the investigator site identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, a discussion must occur between the sponsor's clinical research physician (CRP)/clinical research scientist (CRS) and the investigator to determine if the patient may continue in the study. If both agree that it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor's CRP/CRS to allow the inadvertently enrolled patient to continue in the study with or without study treatment.

6.3.2. Discontinuation of Patients from Study and/or Study Treatment

Patients who are discontinued from the study treatment will have follow-up procedures performed as shown in the Study Schedule (Attachment 1).

Patients will be permanently discontinued from the study and/or from the study treatment in the following circumstances:

- Enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.
- Investigator/Physician Decision
    - The investigator/physician decides that the patient should be discontinued from the study or study drug(s).
    - 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 the study drug(s) occurs prior to introduction of the other agent.
- Patient Decision
    - The patient or the patient's designee (for example, parents or legal guardian) requests to be discontinued from the study or study drug. No follow-up procedures will be performed for patients who withdraw informed consent, unless he or she has explicitly provided permission and consent.
- Sponsor Decision
    - Lilly, in consultation with the collaborator, stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.
- The patient experiences a Grade ≥3 infusion reaction.
- The patient has radiographic evidence of progressive disease or significant symptomatic disease deterioration characterized as progression of disease, in the opinion of investigator, in the absence of radiographic evidence of progressive disease.

Exceptions for continuing study treatment beyond confirmed radiographic progression may be made on a case-by-case basis for patients who are believed to be clinically benefiting from study treatment, and the investigator and the sponsor agree that continuing study treatment is in the patient's best interest.

- The patient experiences unacceptable toxicity (for example, an AE that, in the opinion of the investigator or the sponsor, contraindicates further dosing).
- The patient is noncompliant with study procedures and/or treatment (Section 7.6).
- The patient becomes pregnant or intends to become pregnant during the study.
- The patient begins treatment with alternative anticancer therapy, including another investigational agent.
- The administration of study drug is delayed for more than 28 days.
    - For the patients treated with the LY3022855-plus-tremelimumab combination, a delay of up to 28 days between doses is allowed for Cycles 1 through 6, and up to 60 days between doses for Cycles 7 and beyond.

6.3.3. Patients Lost to Follow-Up

A patient would be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

6.3.4. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, the investigator, or the ethical review board (ERB) of the study site judges discontinuation of study site participation necessary for any scientific, medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

6.3.5. Discontinuation of the Study

The study will be discontinued if Lilly, while considering the rights, safety, and well-being of the patient(s), judges discontinuation of the study necessary for any scientific, medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

7. Treatment

7.1. Materials and Supplies

Clinical study materials will be labeled according to the country's regulatory requirements.

7.1.1. LY3022855

LY3022855 Injection for infusion is supplied at 5 mg/mL strength as a solution dosage, in glass vials with an elastomeric closure. Each vial of LY3022855 Injection for infusion contains 20 mL of the drug product (100 mg/20-mL vial). Vials of LY3022855 Injection for infusion should be stored refrigerated at 2°C to 8°C. The drug product is formulated to contain the active LY3022855 in 10mM histidine, 100mM glycine, 100mM arginine, and 0.01% polysorbate 80 at pH 6.0. LY3022855 is a clear or slightly opalescent and colorless or slightly yellow liquid without visible particles. LY3022855 will be administered as an I.V. infusion. The dose is prepared and infused at room temperature. LY3022855 will be diluted in normal saline to a final volume of 250 mL. Lilly instructions regarding dilution requirements should be followed.

7.1.2. Durvalumab

Durvalumab (MEDI4736) will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26mM histidine/histidine hydrochloride, 275mM trehalose dihydrate, and 0.02% (weight/volume [w/v]) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10 mL.

Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Durvalumab must be used within the individually assigned expiry date on the label.

The following applies to the preparation of durvalumab doses for administration with an I.V. bag. The dose for administration must be prepared by the investigator's or the site's designated investigational product manager using aseptic technique. Total time from needle puncture of the durvalumab vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature

If in-use storage time exceeds these limits, a new dose must be prepared from new vials. Infusion solutions must be allowed to equilibrate to room temperature prior to commencement of administration.

Refer to Attachment 9 for the durvalumab dose volume calculation.

7.1.3. Tremelimumab

Tremelimumab will be supplied by AstraZeneca as a 20-mg/mL solution for infusion after dilution. The solution contains 20 mg/mL of tremelimumab, 20mM histidine/histidine hydrochloride, 222mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, and 0.27mM disodium edetate dihydrate (EDTA); it has a pH of 5.5. The nominal fill volume is 20 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Tremelimumab must be used within the individually assigned expiry date on the label.

The following applies to the preparation of tremelimumab doses for administration with an I.V. bag. The dose of tremelimumab for administration must be prepared by the investigator's or the site's designated investigational product manager using aseptic technique. Total time from needle puncture of the tremelimumab vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature

It is recommended that the prepared final I.V. bag be stored in the dark at 2ºC to 8°C (36°F to 46°F) until needed. If storage time exceeds these limits, a new dose must be prepared from new vials. The refrigerated infusion solutions in the prepared final I.V. bag should be equilibrated at room temperature for about 2 hours prior to administration. Tremelimumab does not contain preservatives and any unused portion must be discarded.

No incompatibilities between tremelimumab and polyvinylchloride or polyolefin I.V. bags have been observed.

Refer to Attachment 9 for the tremelimumab dose volume calculation.

7.2. Study Drug Administration

The investigator or designee is responsible for:

- explaining the correct use of the investigational agent(s) and planned duration of each individual's treatment to the site personnel
- verifying that instructions are followed properly
- maintaining accurate records of study drug dispensation, and collection, and returning or destroying all unused medication to Lilly or its designee at the end of the study.

Patients will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the study drug(s) so that the situation can be assessed.

7.2.1. Dosing Schedule

Refer to Section 7.2.2 for Part A (dose escalation) dose regimens for each combination, by cohort. Refer to Section 7.2.3 for Part B (disease-specific expansion) dose regimens for LY3022855-plus-durvalumab, by cohort.

For each combination regimen, LY3022855 will be administered first, followed by a 30-minute observation period. After the observation period, durvalumab or tremelimumab will be administered. In this study, a cycle is defined as 4 weeks (28 days); Day 1 of a cycle is based on the administration of LY3022855 (rather than durvalumab or tremelimumab). A delay of study treatment due to holiday, weekend, bad weather, or other unforeseen circumstances will be permitted for a maximum of 3 days and not counted as a protocol deviation.

7.2.1.1. LY3022855

Eligible patients will receive LY3022855 as an I.V. infusion administered over a minimum duration of 30 minutes and a maximum duration of 4 hours, based on the known safety and stability of the prepared drug. The infusion rate should not exceed 25 mg/minute. Suggested infusion times are as follows:

- 90 minutes for the first infusion; if no infusion-related reaction (IRR) is observed, decrease the infusion time to 60 minutes for the second infusion
- 60 minutes for the second infusion; if no IRR is observed, decrease the infusion time to 30 minutes for the third infusion
- 30 minutes for the third and subsequent infusions

If, at any time, a patient experiences an IRR, the infusion time should not be decreased. Premedication is not recommended to be administered prior to the first infusion of LY3022855. However, if the patient experiences a Grade 1 or 2 IRR, premedication must be provided prior to any subsequent doses of LY3022855. The choice of premedication is to be made after discussion and agreement between the investigator and sponsor. In such cases (Grade 1 or 2 IRRs), administration of steroids should be avoided, if possible. If an IRR Grade $\leq$2 occurs during or after LY3022855 administration and the patient's condition allows it, treatment with durvalumab or tremelimumab will proceed as planned. Patients experiencing an IRR Grade $\geq$3 will be permanently discontinued from study treatment.

LY3022855 may be administered up to 3 days AFTER the scheduled dosing date and up to 4 days BEFORE the next scheduled dosing date to accommodate for patient vacations, holidays, inclement weather or other unforeseen circumstances. If, at any time, a dose is to be administered beyond the 3-day window, that dose is to be skipped. A maximum of 28 days between administered doses is allowed for delays due to adverse events.

7.2.1.2. Durvalumab

Patients are to receive durvalumab I.V. on Days 1 and 15 of every cycle. Durvalumab may be administered up to 3 days AFTER the scheduled dosing date. If, at any time, a dose is administered beyond the 3-day window, that dose is considered a dose delay. A maximum delay of 28 days between administered doses is allowed (for dose delay in case of immune-related AE

please refer to Section 7.2.4.1). Note that a maximum of 12 months/26 doses of durvalumab treatment is permitted.

Refer to Attachment 9 for the durvalumab dose volume calculation.

Durvalumab will be administered at room temperature (approximately 25°C) by controlled infusion via an infusion pump into a peripheral or central vein. Following preparation of durvalumab, the entire contents of the I.V. bag should be administered as an I.V. infusion over approximately 60 minutes (±5 minutes), using a 0.2- or 0.22-µm in-line filter. Less than 55 minutes is considered a deviation.

The I.V. line will be flushed with a volume of I.V. solution (0.9% [w/v] saline) equal to the priming volume of the infusion set used after the contents of the I.V. bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

A 1-hour observation period is required after the first infusion of durvalumab. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the investigator's discretion (suggested 30 minutes after each durvalumab infusion).

Patients will be monitored during and after the infusion with assessment of vital signs at the times specified in this study protocol.

In the event of a Grade ≤2 IRR, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. For patients with a Grade ≤2 IRR, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (for example, diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the IRR is Grade ≥3 in severity, study drug will be permanently discontinued.

7.2.1.3. Tremelimumab

Patients are to receive tremelimumab I.V. on Day 1 of every cycle for the first 6 doses (Cycles 1-6). Starting with Cycle 7 (4 weeks after Dose 6 [Week 25]), tremelimumab will be dosed once every 3 cycles (12 weeks), that is, on Day 1 of Cycles 7, 10, 13, and so on, until disease progression.

Tremelimumab may be administered up to 3 days AFTER the scheduled dosing date. If, at any time, a dose is administered beyond the 3-day window, that dose is considered a dose delay. A delay of up to 28 days between administered doses is allowed for Cycles 1 through 6, and up to 60 days between doses for Cycles 7 and beyond.

Refer to Attachment 9 for the tremelimumab dose volume calculation.

Tremelimumab will be administered at room temperature (approximately 25°C) by controlled infusion via an infusion pump into a peripheral or central vein. Following preparation of tremelimumab, the entire contents of the I.V. bag should be administered as an I.V. infusion over

approximately 60 minutes (±5 minutes), using a 0.2- or 0.22-µm in-line filter. Less than 55 minutes is considered a deviation.

The I.V. line will be flushed with a volume of 0.9% (w/v) saline equal to the priming volume of the infusion set used after the contents of the I.V. bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

In the event that either preparation time or infusion time exceeds the time limits presented in this section, a new dose must be prepared from new vials. Tremelimumab does not contain preservatives, and any unused portion must be discarded.

A 1-hour observation period is required after the first infusion of tremelimumab. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the investigator's discretion (suggested 30 minutes after each tremelimumab infusion).

Patients will be monitored during and after the infusion with assessment of vital signs at the times specified in this study protocol.

In the event of a Grade ≤2 IRR, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. For patients with a Grade ≤2 IRR, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (for example, diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the IRR is Grade ≥3 in severity, study drug will be permanently discontinued.

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if necessary.

7.2.2. Part A: Dose Escalation (Phase 1a)

By nature of being a dose-escalation study, data will be evaluated on an ongoing basis until the MTD is determined. Safety data, in particular AEs, will be the primary criteria for the dose escalation. No dose escalation can occur without prior discussion and agreement between the investigator, the Lilly study team, and the collaborator; the decision will be documented in writing.

Based on the ongoing safety reviews, modifications to the dose-escalation strategy or other design elements may be made via protocol amendment to ensure patient safety. No intrapatient dose escalation is permitted for any patient. Dose escalation may be ceased at any time based on available safety and PK behavior.

In Part A, study drugs for the LY3022855-plus-durvalumab and LY3022855-plus-tremelimumab combinations may be administered at the dose regimens shown in Table JSCC.1 and

Table JSCC.2, respectively. Refer to Section 7.2.2.2 for further details on the planned dose-escalation method, proceeding from Cohorts D1a and T1a.

Table JSCC.1. Part A (Dose Escalation) Dose Regimens for the LY3022855-plus-Durvalumab Combination, by Cohort

Cohort	LY3022855		Durvalumab	
	Dose (mg)	Frequency	Dose (mg)	Frequency
D1a	25	QW	750	Q2W
D1b[a]	25	Days 1, 8, and 15 of each cycle	750	Q2W
D1c	25	Q2W	750	Q2W
D2a	50	QW	750	Q2W
D2b[a]	50	Days 1, 8, and 15 of each cycle	750	Q2W
D2c	50	Q2W	750	Q2W
D3a	75	QW	750	Q2W
D3b[a]	75	Days 1, 8, and 15 of each cycle	750	Q2W
D3c	75	Q2W	750	Q2W
D4a	100	QW	750	Q2W
D4b[a]	100	Days 1, 8, and 15 of each cycle	750	Q2W
D4c	100	Q2W	750	Q2W

Abbreviations: QW = weekly; Q2W = every 2 weeks.

Note: A cycle is defined as 28 days (4 weeks). QW refers to dosing on Days 1, 8, 15, and 22 of each cycle; Q2W refers to dosing on Days 1 and 15 of each cycle.

[a] Enrollment to the D*n*b cohort will occur only if ≥2 DLTs are observed after Cycle 1, Day 21 of the corresponding D*n*a cohort.

Table JSCC.2. Part A (Dose Escalation) Dose Regimens for the LY3022855-plus-Tremelimumab Combination, by Cohort

Cohort	LY3022855		Tremelimumab	
	Dose (mg)	Frequency	Dose (mg)	Frequency[a]
T1a	50	QW	75	Q4W
T1b[b]	50	Days 1, 8, and 15 of each cycle	75	Q4W
T1c	50	Q2W	75	Q4W
T2a	100	QW	75	Q4W
T2b[b]	100	Days 1, 8, and 15 of each cycle	75	Q4W
T2c	75	Q2W	75	Q4W
T3a	100	QW	225	Q4W
T3b[b]	100	Days 1, 8, and 15 of each cycle	225	Q4W
T3c	100	Q2W	225	Q4W
T3d	75	QW	225	Q4W
T4a	100	QW	750	Q4W
T4b	100	Q2W	750	Q4W
T4c	100	Days 1, 8, 15 of each cycle	750	Q4W
T4d	75	QW	750	Q4W

Abbreviations: QW = weekly; Q2W = every 2 weeks; Q4W = every 4 weeks.

Note: A cycle is defined as 28 days (4 weeks). QW refers to dosing on Days 1, 8, 15, and 22 of each cycle; Q2W refers to dosing on Days 1 and 15 of each cycle; Q4W refers to dosing on Day 1 of each cycle.

[a] After 6 doses, tremelimumab to be dosed once every 12 weeks until discontinuation.

[b] Enrollment to the T*n*b cohort will occur only if ≥2 DLTs are observed after Cycle 1, Day 21 of the corresponding T*n*a cohort.

7.2.2.1. Dose-Limiting Toxicity Determination and Maximum Tolerated Dose Definition

Dose-limiting toxicity is defined as an AE that is at least possibly related to the study drug(s) and that occurs during Cycle 1 (the DLT-evaluation period) and does not improve to the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0 (CTEP 2009) Grade ≤2 (unless stated otherwise), despite medical management, including steroids (if applicable). Toxicity that is clearly and directly related to the primary disease or to another etiology is excluded from this definition. The following are considered DLTs, unless noted otherwise:

- Grade 4 neutropenia lasting ≥7 days
- Grade 3 or 4 neutropenia complicated by fever or infection of any duration
- Any Grade 4 thrombocytopenia
- Any Grade 3 thrombocytopenia complicated by hemorrhage
- Any Grade 3 or 4 anemia

- Grade 3 or 4 nonhematologic toxicity, including:
  - any Grade 4 irAE
  - any Grade 3 or 4 colitis
  - any Grade 3 or 4 noninfectious pneumonitis irrespective of duration
  - any Grade 3 irAE, excluding colitis or pneumonitis, that does not downgrade to Grade 2 within 3 days after onset of the event despite optimal medical management including systemic corticosteroids or does not downgrade to Grade ≤1 or baseline within 14 days
  - any Grade 3 or 4 non-irAE except as noted for transaminases, bilirubin, lipase, or amylase below
  - any liver transaminase elevation >8 × institutional ULN or total bilirubin (TB) >5 × institutional ULN
  - creatine kinase elevation >8 × ULN
- Any Grade 2 pneumonitis that does not resolve to Grade ≤1 within 3 days of the initiation of maximal supportive care

The DLT definition excludes the following conditions:

- Grade 3 fatigue lasting ≤7 days
- 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 (for example, inflammatory reaction at sites of metastatic disease, lymph nodes, etc)
- Concurrent vitiligo or alopecia of any AE grade
- Grade 3 IRR (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management
- Grade 3 or 4 neutropenia that is not associated with fever or systemic infection that improves by at least 1 grade within 3 days. Grade 3 or 4 febrile neutropenia will be a DLT regardless of duration or reversibility
- Grade 3 or 4 lymphopenia
- Grade 3 thrombocytopenia that is not associated with clinically significant bleeding that requires medical intervention, and improves by at least 1 grade within 3 days
- Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days

- Isolated asymptomatic Grade 3 elevation of amylase or lipase without evidence of end organ damage.
- Asymptomatic Grade 3 CK level (5-10 × ULN: CTCAE v4.0) that is not associated with elevated serum or urinary myoglobins and no evidence of rhabdomyolysis or myositis.
- Asymptomatic Grade 3 AST induction that is accompanied by Grade ≤1 ALT and Grade ≤1 TB and no change of ALT or TB from baseline levels.

Adverse events meeting DLT criteria that occur beyond Cycle 1 are defined as dose-limiting equivalent toxicities (DLETs). If a patient is believed to be benefitting from study treatment, patients who experience a DLT may continue to receive study treatment upon agreement of the investigator, sponsor, and collaborator.

For the purpose of this study, the MTD is defined as the highest tested dose that has less than 33% probability of causing a DLT. The MTD will be determined as shown in Table JSCC.3 and Table JSCC.4.

7.2.2.2. Dose-Escalation Method

Three to 6 patients will be enrolled to Cohort 1a (that is, Cohort D1a or T1a; refer to Table JSCC.1 and Table JSCC.2 for LY3022855-plus-durvalumab and LY3022855-plus-tremelimumab combinations, respectively). If none of the first 3 patients or 1 of 6 patients in Cohort 1a experiences a DLT event, enrollment to the next "a" cohort will proceed (that is, to Cohort 2a, and so on). However, if 1 of 3 patients in any cohort (that is, at any dose level) experiences a DLT, up to 3 additional patients will be enrolled at that dose level. If a DLT is observed in ≥2 of a maximum of 6 patients in Cohorts 1a, 2a, 3a, or 4a, concurrent enrollment of 3 to 6 patients to each of the respective "b", "c", and "d" cohorts (as applicable) will occur and no higher dosages will be explored. For example, if no DLTs are noted in Cohort 1a, enrollment to Cohort 2a will occur; however, if 2 patients in Cohort 2a experience DLTs, enrollment to Cohorts 2b and 2c will occur concurrently and no higher dosages will be studied. An exception to this method is that enrollment to D*n*b/T*n*b cohorts will occur only if ≥2 DLTs are observed after Cycle 1, Day 21 of the corresponding D*n*a/T*n*a cohorts. All patients will be assigned to treatment cohorts by the sponsor, with patients assigned sequentially to the "b", "c", and "d" cohorts.

The MTD identified for each combination therapy in Part A will then be the dosage used (confirmed) in Part B (Phase 1b/disease-specific expansion). However, if each of the "b", "c", and "d" cohorts (as applicable) in Part A are observed to have a probability of causing a DLT that is lower than 33%, the sponsor (in consultation with the collaborator) will select the dosage to be used in Part B, based on clinical or correlative study results.

Table JSCC.3. MTD Determination for the Combination of LY3022855 plus Durvalumab

Cohort	Number of Patients Who Experience a DLT (in Cycle 1)		
	0 of 3	1 of 6	≥2
D1a	Enroll to D2a	Enroll to D2a	Enroll to D1b and D1c
D1b	MTD is D1b	MTD is D1b	Not defined
D1c	MTD is D1c	MTD is D1c	Not defined
D2a	Enroll to D3a	Enroll to D3a	Enroll to D2b and D2c
D2b	MTD is D2b	MTD is D2b	MTD is D1a
D2c	MTD is D2c	MTD is D2c	MTD is D1a
D3a	Enroll to D4a	Enroll to D4a	Enroll to D3b and D3c
D3b	MTD is D3b	MTD is D3b	MTD is D2a
D3c	MTD is D3c	MTD is D3c	MTD is D2a
D4a	MTD is D4a	MTD is D4a	Enroll to D4b and D4c
D4b	MTD is D4b	MTD is D4b	MTD is D3a
D4c	MTD is D4c	MTD is D4c	MTD is D3a

Abbreviations: DLT = dose-limiting toxicity; MTD = maximum tolerated dose.

7.2.3. Part B: Disease-Specific Expansion (Phase 1b)

Once the MTD for LY3022855-plus-durvalumab combination has been identified, enrollment to Part B (disease-specific expansion) will begin and will include 2 expansion cohorts (refer to Section 6.1.1, Inclusion Criterion [2]). Patients in these expansion cohorts will be treated at the MTD identified for LY3022855-plus-durvalumab combination in Part A, unless otherwise specified by the sponsor. If patients are treated at a dose other than the MTD, the dosage chosen will not exceed the MTD exposure.

Additional cohorts of patients with alternative tumor histologies may be added if clinical activity is observed during Part A. In the event of DLTs (Section 7.2.2.1) or DLETs occurring in 33% or more of patients in Part B (with a minimum enrollment of 6 patients) within a tumor-specific expansion cohort, investigators and the sponsor study team will assess the nature and severity of these toxicities. No additional patients will be accrued until this safety review is completed and a decision is made either to continue at the current dose or to de-escalate the dose and define a new dose for the expansion phase.

7.2.4. Dose Adjustments, Interruptions, and Delays

No dose reductions (of any study drug) are permitted during this study.

Dosing interruptions of study drugs are permitted for reasons not related to study treatment (for example, minor surgery, unrelated medical events, patient vacation, and/or holidays). The reason for interruption should be documented on the case report form (eCRF).

In addition, doses of study drug(s) may need to be delayed to manage specific AEs or other toxicities. Refer to Section 7.2.4.1 for implementation of dose delays due to AEs.

All dose modifications should be documented, including the approach taken and a clear rationale for the need for modification.

7.2.4.1. Dose Delays for Adverse Events

Study treatment may be held for a maximum of 28 days; see exception for an immune-related AE below. If appropriate, and in the opinion of the investigator and upon agreement with the sponsor, study treatment may resume upon resolution of clinically significant AEs to baseline or improvement to Grade <2. If AEs, see exception for an immune-related AE, do not resolve to baseline or improve to Grade <2 within 28 days following the last administered dose, study treatment should be permanently discontinued and the patient should be discontinued from the trial. If treatment is held, the day of treatment should continue as if no drug interruption has occurred. For example, if study drug is held on D6 of a cycle and AEs have resolved by D10 (4 days later), the study drugs should be resumed per the original schedule, If the original schedule results in a study drug being held for >28 days, the study drug may not be resumed. One or both study drugs may be held, resumed, or discontinued.

If the AE is an immune related AE as outlined in Attachment 7, and if the treatment management guidelines outlined in Attachment 7 are followed and documented in the patient's medical record, treatment may be held for >28 days to allow taper of high dose steroids. Treatment may resume in this setting only upon resolution of immune AEs to baseline or improvement to Grade <2, and only if deemed clinically appropriate by the treating physician and agreed to by the sponsor. If steroids cannot be tapered as outlined in Attachment 7, and/or AEs do not resolve to < Grade 2, the patient may not be resumed on study treatment.

For the purposes of documentation, the investigator must assess if the toxicity is considered at least possibly related to study treatment (that is, the combination regimen) and if the AE is considered to be immune related. Investigators are encouraged to consult the sponsor for additional guidance.

For AEs that are considered at least possibly related to study treatment, the following dose adjustment guidance may be applied:

- Treat each of the toxicities with maximum supportive care (including holding the study drug[s] suspected of causing the toxicity where required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of study drugs along with appropriate continuing supportive care.
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

In addition, there are certain circumstances in which study drugs should be permanently discontinued (refer to Attachment 7).

Following the first dose of study drugs, subsequent administration of study drugs can be modified based on toxicities observed (refer to Attachment 7).

7.2.4.1.1. Specific Adverse Events

Adverse events of special interest (AESIs) observed with durvalumab and/or tremelimumab include colitis; pneumonitis; alanine aminotransferase (ALT)/AST increases; hepatitis/hepatotoxicity; neuropathy/neuromuscular toxicity (that is, events of encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis); endocrinopathy (that is, events of hypophysitis, adrenal insufficiency, hyperthyroidism, and hypothyroidism; type 1 diabetes mellitus); dermatitis; nephritis; and pancreatitis (or labs suggestive of pancreatitis-increased serum lipase or serum amylase); other inflammatory responses that are rare with a potential immune-mediated etiology include, but are not limited to, myocarditis, pericarditis, myositis/polymyositis, and uveitis. Refer to Attachment 8 for details about and management of AESIs.

Guidelines for the management of immune-mediated, infusion-related, and non-immune-related AEs are shown in Attachment 7.

Adverse events (both nonserious and serious) associated with study drugs may represent an immune-related etiology, which may be based on the mechanism of action of study drugs leading to T cell activation and proliferation. These irAEs may occur shortly after the first dose or several months after the last dose of treatment. Potential irAEs include immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies. Patients should be monitored for signs and symptoms of irAEs. In the absence of an alternative etiology (for example, infection or progressive disease), signs or symptoms of enterocolitis, dermatitis, pneumonitis, hepatitis, myocarditis, myopathy/polymyopathy and endocrinopathy should be considered immune related. Refer to Attachment 7 for supportive care guidelines for immune-mediated reactions, including use of corticosteroids.

Based on observations from clinical trials with LY3022855, patients receiving study treatment should be closely monitored for signs of hepatic function impairment (for example, increases in transaminases, lactate dehydrogenase [LDH], bilirubin, coagulation disorders) and creatine kinase increases.

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if necessary. Refer to Attachment 7 for management of infusion-related AEs.

7.3. Method of Assignment to Treatment

7.3.1. Part A: Dose Escalation (Phase 1a)

A patient who meets all criteria for enrollment will be assigned (by the sponsor) to receive study treatment. Before each patient's enrollment into the study, an eligibility check must be conducted between the investigational site and the Lilly clinical research personnel to confirm that each patient meets all enrollment criteria. Upon confirmation of eligibility, the sponsor will confirm the dose and identification number assignment and cohort for each patient.

If investigators have eligible patients who have consented concurrently, more than 3 patients may be assigned to a particular dose level provided that accrual has not ceased due to excessive toxicity. This enrollment procedure is allowed because of the advanced disease state of this patient population and the screening involved in defining eligibility. Assigning more than 3 patients to a particular dose level should be approved by the sponsor following discussions with the investigators.

7.3.2. Part B: Disease-Specific Expansion (Phase 1b)

A patient who meets all criteria for enrollment will be assigned (by the sponsor) to a treatment cohort, based on the patient's diagnosis at baseline.

7.4. Blinding

This is an open-label study.

7.5. Concomitant Therapy

All concomitant medications should be recorded throughout the patient's participation in the study. The principal investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (final study visit). Appropriate documentation for all forms of premedications, supportive care, and concomitant medications, including herbal preparations, must be captured on the case report form (eCRF).

7.5.1. Excluded Concomitant Therapy

Other than the study treatment to which the patient is assigned (Section 7.2) and any required contraceptive (Section 6.1.1), no other chemotherapy, immunotherapy, cancer-related biologic or hormone therapy, herbal preparation intended to treat cancer, or experimental drugs will be permitted while the patient is on this study. Palliative radiotherapy may be allowed after consultation with the sponsor. Disease progression requiring other forms of antitumor therapy will necessitate discontinuation of the study treatment.

The following are also not permitted during the study:

- Immunosuppressive medications including, but not limited to systemic corticosteroids at doses not exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor (TNF)-α blockers.
    - Use of immunosuppressive medications for the management of investigational product-related AEs or in patients with contrast allergies is permitted.
    - Use of inhaled and intranasal corticosteroids is permitted.
    - A temporary period of steroids will be permitted for different indications, at the discretion of the principal investigator (for example, chronic obstructive pulmonary disease, radiation, nausea, etc).
- Live attenuated vaccines within 30 days of Cycle 1, Day 1 dosing (that is, 30 days prior to the first dose of study treatment, during study treatment, and for 30 days postdiscontinuation of study treatment).
    - Inactivated vaccines, such as the injectable influenza vaccine, are permitted.

7.5.2. Permitted Concomitant Therapy

Concurrent use of hormones for noncancer-related conditions (insulin for diabetes, hormone replacement therapy) is permitted.

Patients should receive concomitant medications or treatments deemed necessary by the investigator to provide adequate prophylactic or supportive care, including acetaminophen or diphenhydramine, antibiotics, nutritional support, growth factor support (except granulocyte colony-stimulating factor [G-CSF] or granulocyte macrophage colony-stimulating factor [GM-CSF]), or therapy for correction of metabolic disorders, optimal symptom control, and pain management. If clinically indicated at any time during the study, erythropoietin and transfusions (packed red blood cells, whole blood, platelets, or plasma) may be used according to American Society of Clinical Oncology (ASCO) guidelines (Rizzo et al. 2010).

Refer to Section 7.2.1.1 for information regarding premedication for IRRs.

7.6. Treatment Compliance

Study treatment will be administered I.V. at the investigational site, under the direction of the investigator. As a result, a patient's compliance with study drug administration is ensured. Patients should attend scheduled clinic visits and must comply with study criteria under their control. Deviation(s) from the prescribed dosage regimen should be recorded on the eCRF.

7.6.1. Evaluable Patients

Patients in Part A who receive all doses of study treatment for Cycle 1 (DLT-evaluation period) will be considered evaluable for the assessment of a dose level, provided it can be documented whether the patient did or did not experience a DLT within 28 days of Cycle 1, Day 1.

Conversely, any patient in Part A who is discontinued from the study before completing one cycle of study treatment will be deemed nonevaluable for assessment of a dose level, unless they experience a DLT prior to withdrawal. Nonevaluable patients may be replaced to ensure that enough patients complete one cycle of therapy at each dose level for Part A, unless accrual to that cohort has stopped due to a DLT.

Patients who are not evaluable for PK but who complete one cycle of therapy may be replaced upon consultation with the investigator(s) and the sponsor's CRP/CRS to ensure adequate PK data, unless accrual to that cohort has stopped due to a DLT.

Note that the concept of "evaluable" (and, thus, replacement of patients) does not apply to patients in Part B.

8. Safety, Pharmacokinetic, Pharmacodynamic, and Efficacy Data Collection

8.1. Safety Evaluations

The safety and tolerability of LY3022855, durvalumab, and tremelimumab have been assessed in nonclinical toxicology studies, clinical studies, and the results from these studies are detailed in the IBs. This Phase 1a/1b study contains detailed safety monitoring that will permit initial characterization of the safety profile of the combination of LY3022855 plus durvalumab or LY3022855 plus tremelimumab. Study procedures and their timing, including collection of blood samples, are described in the Study Schedule (Attachment 1).

Standard laboratory tests, including chemistry, hematology, coagulation, and urinalysis panels, will be performed. A urine or serum pregnancy test (based on institutional standards) will be administered if applicable. Other clinical laboratory tests will also be collected. Attachment 2 lists the specific tests that will be performed for this study.

8.1.1. Safety Data Collection and Review

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

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

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to study treatment or the study, or that caused the patient to discontinue study treatment before completing the study. The patient should be followed until the event is resolved, the event is no longer considered drug related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up. Frequency of AE and SAE follow-up evaluation is left to the discretion of the investigator.

The timing of all safety evaluations is shown in the Study Schedule (Attachment 1).
Table JSCC.4 presents a summary of AE and SAE reporting guidelines. Table JSCC.4 also shows which database or system is used to store AE and SAE data.

8.1.2. Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent. A clinical study AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which 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 medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Any clinically significant findings from labs, vital signs measurements, and so on that occur should also be reported to Lilly or its designee as an AE. Lack of drug effect is not an AE in clinical studies because the purpose of the clinical study is to establish drug effect.

The investigator, monitor, and sponsor will review the collected data regularly for evidence of AEs. All patients will be assessed routinely for AEs as outlined in the study schedule. All AEs observed will be graded using CTCAE v4.0.

The NCI-CTCAE v4.0 will serve as the reference document for choosing appropriate terminology for, and grading the severity of, all AEs and other symptoms. All AEs observed will be graded using CTCAE v4.0. Any minor version of CTCAE v4.0 (for example, version 4.03) may be used for this study. Minor CTCAE v4.0 updates from the NCI will not necessitate a protocol amendment. For AEs without matching terminology within the NCI-CTCAE v4.0 criteria, the investigator will be responsible for selecting the appropriate system organ class and assessing severity grade based on the intensity of the event. Note that both CTCAE term (actual or coded) and severity grade must be selected by study site personnel and collected on the eCRF. This collection is in addition to verbatim text used to describe the AE.

In addition to collecting the AE verbatim, the CTCAE term, and the CTCAE severity grade, AE verbatim text will also be mapped by the sponsor or designee to corresponding terminology within the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

For all enrolled patients, study site personnel will record the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. While the patient is on study, site personnel will record any change in these preexisting condition(s) and the occurrence and nature of any AEs. In addition, all AEs related to protocol procedures are reported to Lilly or designee.

If a patient's treatment is discontinued as a result of an AE, study site personnel must clearly report to Lilly or its designee via eCRF the circumstances and data leading to discontinuation of treatment.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure and study drug via eCRF.

The investigator decides whether he or she interprets the observed AEs as either related to disease, to the study medication, study procedure, or other concomitant treatment or pathologies. To assess the relationship of the AE to the study drug, the following terminologies are defined:

- **Related**: a direct cause and effect relationship between the study treatment and the AE is likely.
- **Possibly related**: a cause and effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible.
- **Unrelated**: without question, the AE is definitely not associated with the study treatment.

As per Lilly's standard operating procedures, all "related" and "possibly related" AEs and SAEs will be defined as related to study drug.

8.1.2.1. Serious Adverse Events

An SAE is any AE during this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization (except for study drug administration)
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious adverse events due to disease progression, including death, should not be reported unless the investigator deems them to be possibly related to the study drug.

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.

If an investigator becomes aware of SAEs occurring after the patient's participation in the trial has ended, and the investigator believes that the SAE is related to a protocol procedure or study drug, the investigator should report the SAEs to the sponsor and the SAEs will be entered in the Lilly Safety System.

Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate periodically during the course of the trial may be found in the IB.

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

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

8.1.2.2. Adverse Event and Serious Adverse Event Reporting

Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System.

8.1.2.2.1. Prior to Administration of Study Drug(s)

During screening, all AEs and SAEs (regardless of relatedness to protocol procedures) are collected (by the site, in the source document) after the patient has signed the ICF. For patients who do not enroll in the trial (that is, have not received at least one dose of study drug[s]), only AEs and SAEs related to protocol procedures are required to be collected (captured on the eCRF, and, in the case of an SAE, on the SAE form).

8.1.2.2.2. While on Study Treatment

All AEs and SAEs, regardless of relatedness to study drug(s), or protocol procedures, occurring while the patient is receiving study drug must be collected (captured on the eCRF; in the case of an SAE, also on the SAE form) and reported to Lilly or its designee. A patient is considered to be receiving study drug (that is, "on study treatment") from the date of the first dose of study drug until the date the patient and investigator agree that the patient will no longer continue to receive study treatment.

8.1.2.2.3. During the 30-Day and 90-Day Follow-Up Visits

All AEs and SAEs, regardless of relatedness to study drug(s) or protocol procedures, occurring during the 30-Day and 90-Day Follow-Up visits (Visits 801 and 802) must be collected (captured on the eCRF; in the case of an SAE, also on the SAE form) and reported to Lilly or its designee. The 30-Day Follow-Up visit (Visit 801) begins the day after the patient and investigator agree that the patient will no longer continue to receive study treatment. The duration of this follow-up visit is 30 days (±7 days). At the end of the 30-Day Follow-Up visit, the patient will be required to have specific safety assessments (Attachment 1). If it is deemed to be in the best interest of the patient to start a new anticancer treatment prior to the scheduled end of the follow-up visit, the duration of the visit may be shortened. In this case, the follow-up assessments should be completed prior to the initiation of the new therapy.

The 90-Day Follow-Up visit (Visit 802, only for durvalumab and tremelimumab safety) occurs 90 days (±7 days) after the patient and investigator agree that the patient will no longer continue to receive study treatment. Refer to Attachment 1 for specific safety assessments to be conducted during the 90-Day Follow-Up visit.

Following the safety assessments that mark the end of the follow-up visits (30-Day Follow-Up visit [Visit 801], for LY3022855, durvalumab, and tremelimumab safety, and 90-Day Follow-Up visit [Visit 802], only for durvalumab and tremelimumab safety), the patient will be discontinued from the study, unless there is an ongoing AE or SAE that is possibly related to study drug. In this instance, the patient should continue to be followed by extending the duration of the follow-up visit until the event is resolved, the event is no longer considered to be drug related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up.

After the follow-up visits (30-Day Follow-Up visit [Visit 801], for LY3022855, durvalumab, and tremelimumab safety, and 90-Day Follow-Up visit [Visit 802], only for durvalumab and tremelimumab safety), AEs are not required to be reported unless the investigator feels the AEs were related to either study drug or a protocol procedure. If an investigator becomes aware of an SAE believed to be related to protocol procedures or study drug (at this point, the patient is no longer on the study), the investigator should report the SAE to the sponsor, and the SAE will be entered in the Lilly Safety System.

Refer to Table JSCC.4 for AE and SAE reporting guidelines during continued access and Section 6.2.2 for additional details on continued access, including the Continued Access Treatment Period (Visits 501-5XX) and Continued Access Follow-Up (Visits 901 and 902).

8.1.2.3. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are not listed in the DCSI or in the IB and that the investigator identifies as related to study drug or procedure. The United States 21 CFR 312.32, the 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 recording and expedited reporting of SUSARs that are consistent with global regulatory regulations and the associated detailed guidances.

8.1.2.4. Summary of AE/SAE Reporting Guidelines

The AE and SAE reporting guidelines are summarized in Table JSCC.4; recommendations for reporting SAEs are presented in Attachment 4.

Table JSCC.4. AE and SAE Reporting Guidelines for Study JSCC

Timing	Types of AEs/SAEs Reported	Collection Database	Lilly Safety System
Prestudy (during screening, prior to administration of study drug[s]) Starts at the signing of informed consent and ends just before the first dose of study drug.	Preexisting conditions	X	
	AEs related to protocol procedures	X	
	SAEs related to protocol procedures	X	X
On study treatment Starts the day of the first dose of study drug and ends the day the patient and investigator agree that the patient will no longer continue to receive study treatment.	All AEs	X	
	All SAEs, regardless of relatedness	X	X
30-Day Follow-Up (Visit 801) Starts the day after the patient and investigator agree that the patient will no longer continue to receive study treatment and ends when end-of-study safety assessments are completed. This visit will be extended as needed to follow any ongoing AEs at least possibly related to study drug(s) or protocol procedures.	All AEs	X	
	All SAEs, regardless of relatedness	X	X
90-Day Follow-Up (Visit 802) (only for durvalumab and tremelimumab safety) Occurs 90 days (±7 days) after the patient and investigator agree that the patient will no longer continue to receive study treatment. This visit will be extended as needed to follow any ongoing AEs at least possibly related to study drug(s) or protocol procedures.	All AEs	X	
	All SAEs, regardless of relatedness	X	X

Timing	Types of AEs/SAEs Reported	Collection Database	Lilly Safety System
Continued Access Treatment Period (Visits 501-5XX) Starts at the first study visit after study completion has occurred and ends when the patient and investigator agree that the patient will no longer continue to receive study treatment; applies only to patients who have not met discontinuation criteria.	All AEs	X	
	All SAEs, regardless of relatedness	X	X
Continued Access Follow-Up (Visits 901 and 902) Visit 901: Starts the day after the patient and investigator agree that the patient will no longer continue to receive study treatment and ends when end-of-study safety assessments are completed. Visit 902 (only for durvalumab and tremelimumab safety): Occurs 90 days (±7 days) after the patient and investigator agree that the patient will no longer continue to receive study treatment.	All AEs	X	
	All SAEs, regardless of relatedness	X	X
Patient no longer on study	All SAEs related to protocol procedures or study drug that the investigator becomes aware of		X

Abbreviations: AEs = adverse events; SAEs = serious adverse events.

8.1.2.5. Pregnancy, including Maternal and Paternal Exposure

Although generally not an AE, cases of pregnancy that occur during maternal or paternal exposures to study drugs and through 180 days after the decision is made to discontinue study treatment should be reported as SAEs, within 24 hours. Additionally, congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective terminations without complications should not be handled as AEs.

Patients who become pregnant during the study period must immediately discontinue study treatment but will not be discontinued (withdrawn) from the study.

Data on fetal outcome, including spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality occurring from the date of the first dose of study drug through 180 days after the decision is made to discontinue study treatment should be followed up and documented even if the patient was discontinued (withdrawn) from the study.

Pregnancy itself, or pregnancy of a patient's partner, is regarded as an AE only if an investigator considers that study treatment may have interfered with the effectiveness of a contraceptive medication.

The sponsor will endeavor to collect follow-up information on such pregnancies, provided the partner of the study patient provides consent.

Male patients must refrain from sperm donation from screening through 180 days after the decision is made to discontinue study treatment.

8.1.3. Overdose

An overdose is defined as an occurrence in which a patient receives a higher dose of study drug than the dose that patient was assigned, as specified in this protocol.

Any overdose of LY3022855, durvalumab, or tremelimumab, with or without associated AEs/SAEs, is required to be reported immediately to the sponsor. If the overdose results in an AE, the AE must also be recorded as an AE. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious (for example, death or hospitalization), the event is serious and must be recorded and reported as an SAE.

There is currently no specific treatment in the event of an overdose of LY3022855, durvalumab, and/or tremelimumab.

The investigator will use clinical judgment to treat any overdose.

8.1.4. Other Safety Measures

8.1.4.1. Electrocardiogram

For each patient, a local 12-lead digital ECG will be collected according to the Study Schedule (Attachment 1). Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

At Screening, a triplicate ECG will be obtained, on which QTcF must be <470 milliseconds (calculated from one ECG using Fridericia's Correction Formula and confirmed with 2 additional ECGs). Thereafter, single ECGs will be obtained. In case of clinically significant ECG abnormalities, including a QTcF value >470 milliseconds, 2 additional 12-lead ECGs should be obtained over a brief period (for example, 30 minutes) to confirm the finding.

Electrocardiograms may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs (more replicates) than expected at a particular time point is allowed to ensure high-quality records.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, to determine whether the patient meets entry criteria at the relevant visit(s) and for immediate patient management, should any clinically relevant findings be identified.

If a clinically significant quantitative or qualitative change from baseline is identified after enrollment, the investigator will assess the patient for symptoms (for example, palpitations, near syncope, syncope) to determine whether the patient can continue in the study. The investigator

or qualified designee is responsible for determining if any change in patient management is needed and must document his/her review of the ECG printed at the time of evaluation.

8.1.4.2. Multigated Acquisition Scan or Echocardiogram

At Screening, a multigated acquisition (MUGA) scan or an echocardiogram will be performed for each patient as an eligibility assessment of LVEF (Section 6.1.2). An LVEF evaluation will also be made at additional time points during the study, as clinically indicated. Refer to the Study Schedule (Attachment 1) for details about the timing of this assessment.

8.1.5. Safety Monitoring

The Lilly CRP/CRS will monitor safety data throughout the course of the study.

Representatives from Lilly Global Patient Safety will specifically monitor SAEs. Lilly will review SAEs within time frames mandated by company standard operating procedures.

- If a study patient experiences elevated ALT ≥5 × ULN and elevated TB ≥2 × ULN, clinical and laboratory monitoring should be initiated by the investigator.
- For patients entering the study with ALT ≥3 × ULN, monitoring should be triggered at ALT ≥2 × baseline.

Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP/CRS regarding collection of specific recommended clinical information and follow-up laboratory tests (see Attachment 3).

Refer to Attachment 8 for details about AESIs.

Refer to Attachment 7 for additional details on Toxicology management guidelines.

8.1.6. Complaint Handling

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

Complaints related to concomitant drugs are reported directly to the manufacturers of those drugs in accordance with the package insert.

The investigator or his/her designee is responsible for handling the following aspects of the complaint process in accordance with the instructions provided for this study:

- recording a complete description of the complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- faxing the completed complaint form within 24 hours to Lilly or its designee.

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

8.2. Sample Collection and Testing

Attachment 1 lists the schedule for sample collections in this study, including those for PK, pharmacodynamics, and immunogenicity.

Attachment 2 lists the clinical laboratory tests that will be performed for this study.

8.2.1. Samples for Study Qualification and Health Monitoring

Blood, tissue, and urine samples will be collected to determine whether patients meet inclusion/exclusion criteria.

Standard laboratory tests, including hematology and urinalysis panels, will be performed and analyzed by a local laboratory. Chemistry panels will be performed and analyzed centrally. Enrollment decisions may be based upon chemistry results performed at a local laboratory; however, a sample must be sent to the central laboratory. These central chemistry laboratory results will be used for subsequent safety analyses. In the event of minor discrepancies between local and central laboratory results, the investigator may use the local results for treatment decisions, and the central laboratory results will remain part of the safety database. Discrepancies between local and central results that may have an impact on treatment decisions will not be considered protocol violations.

Investigators must document their review of each laboratory safety report.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, however, it is acceptable to retain samples to batch the tests run, or to retain the samples until the end of the study to confirm that the results are valid. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

8.2.2. Samples for Drug Concentration Measurements (Pharmacokinetics)

At the visits and times specified in the Study Schedule (Attachment 1), venous blood samples will be collected to determine the serum concentrations of LY3022855, durvalumab, and tremelimumab (depending on treatment received). A maximum of 5 samples may be drawn at additional time points during the study if warranted and agreed upon between both the investigator and the 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.

These samples will be analyzed at a laboratory designated by the sponsor. Serum concentrations of LY3022855 will be assayed using a validated enzyme-linked immunosorbent assay (ELISA) method.

The PK samples will be stored at a facility designated by the sponsor.

The remaining plasma from the samples collected for PK may be pooled and used for exploratory metabolism work as deemed appropriate.

Bioanalytical samples collected to measure investigational product concentration and metabolism and/or protein binding, will be retained for a maximum of 2 years following last patient visit for the study.

8.2.3. Samples for Pharmacogenetics

There is growing evidence that genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion, the mechanism of action of the drug, the disease etiology, and/or the molecular subtype of the disease being treated. Therefore, where local regulations and ERBs allow, a blood sample will be collected for pharmacogenetic analysis.

In the event of an unexpected AE or the observation of unusual response, the pharmacogenetic biomarker samples may be genotyped and analysis may be performed to evaluate a genetic association with response to study drug(s). These investigations may be limited to a focused candidate gene study or, if appropriate, genome-wide analysis may be performed to identify regions of the genome associated with the variability observed in drug response. The pharmacogenetic biomarker samples will be used only for investigations related to disease and drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis.

The samples will be coded with the patient number and stored at a facility selected by the sponsor for up to a maximum of 15 years after the last patient visit for the study. The samples and any data generated from them can be linked back to the patient only by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the study drugs.

Samples will be destroyed according to a process consistent with local regulation.

8.2.4. Samples for Pharmacodynamic and Tailoring Biomarkers

Collection of samples for other biomarker research is also part of this study. Blood and tissue samples will be collected.

Required samples for biomarker research to be collected from all patients in this study are the following:

- blood samples (plasma, whole blood, and serum) (refer to Sections 8.2.3 and 8.2.4.1).
- pretreatment and on-treatment (6-8 weeks after starting study treatment) tumor tissue (newly biopsied) (all cohorts of Part A and the ovarian cancer cohort only of Part B) (refer to Section 8.2.4.2). If clinically feasible, the biopsies should be taken from the same lesion.
- an archived tumor sample (following the most recent systemic treatment), if not restricted by local regulations (Part B NSCLC cohort only).

Optional samples for biomarker research that should be collected from patients in the study where possible are the following:

- on-treatment tumor tissue (Part B NSCLC cohort only).

Samples may be stored at a facility selected by the sponsor for up to a maximum of 15 years after the last patient visit for the study.

Sample collection including blood (whole blood, serum, and plasma) and tumor tissue will occur at specified time points as indicated in Attachment 1. These samples are also described in the following sections.

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 trial. 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 the following sections.

8.2.4.1. Blood Samples

Pharmacodynamic assessments are planned to be tested from baseline over time for changes in biomarkers that may include, but not be limited to, circulating levels of CSF-1, sPD-L1, IL-34, and monocyte markers.

In addition, blood samples (EDTA plasma, whole blood, and serum) will be collected and may be used for research on the drug targets, disease process, immune functioning, pathways associated with cancer, mechanisms of action of LY3022855, durvalumab, and tremelimumab, and/or research methods or in validating diagnostic tools or assay(s) related to cancer. The analyses of these samples may include, but are not limited to, testing at baseline and changes over time in immune cell subsets, cytokines, metabolites, and molecular markers to document the immunomodulatory activity of treatment in patients with LY3022855 in combination with durvalumab or tremelimumab. These biomarkers may be compared with observed clinical outcomes to study drug(s). Blood will be collected at times specified in Attachment 1.

Samples may be stored at a facility selected by the sponsor for up to a maximum of 15 years after the last patient visit for the study.

8.2.4.2. Tumor Tissue Samples

Tissue collection will be required for biomarker research and enrollment into the study for patients in Part A (all cohorts) and Part B. For patients enrolled in Part A (all cohorts) and Part B (ovarian cancer cohort only) of the study, tissue will be required for PD-L1 biomarker and other exploratory analysis from a newly obtained core or excisional biopsy of a tumor lesion (should be taken only after study eligibility is confirmed) or from a recent biopsy defined by ≤3 years since last documented progression of disease. For the NSCLC cohort, archived tissue should be submitted form a recent biopsy defined by ≤3 years old and this biopsy follows the most recent systemic therapy. If such an archived biopsy sample is not available, a new biopsy must be obtained for the patient to be eligible to participate in study. For all cohorts, new archived tissue will be obtained only if not restricted by local regulations.

In addition, an on-treatment biopsy is required if any accessible lesions remain for Part A (all cohorts) and Part B (ovarian cancer cohort only). If clinically feasible, the biopsies should be taken from the same lesion. For patients enrolled to NSCLC cohort of Part B, the on-treatment biopsy is optional.

Sites must confirm the availability of adequate tumor tissue for the new biopsy from the site's pathology laboratory or adequate archived tumor tissue. Pretreatment formalin-fixed paraffin-embedded (FFPE) tumor tissue should be submitted in a whole block.

In addition to the biopsies and biomarker samples discussed in Sections 8.2.4.1 and 8.2.4.2, patients may be asked to undergo collection of an additional biopsy specimen and blood sample after treatment with study drug(s) has been initiated, including potentially after disease progression. 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.

Details for the handling and shipping of the tumor tissue will be provided by the sponsor in a separate document. The tissue samples will be obtained using appropriate method. Tumor tissue should be submitted as a newly acquired excisional or core needle (minimum 18 gauge) biopsy in formalin. A minimum of 3-4 core biopsies, using an 18-gauge core needle, is recommended during each biopsy procedure. Cytological or fine-needle aspiration specimens and decalcified bone are not acceptable. Due diligence should be used to ensure that tumor specimen (not normal adjacent or tumor margins) is provided. Pathology reports accompanying the tissue may also be requested.

Tissue samples will be examined for biomarkers that may include, but are not limited to the drug targets, disease process, immune cells/immune functioning within the disease state, and cancer-related conditions, pathways associated with cancer and study drugs, mechanisms of action of LY3022855, durvalumab or tremelimumab, and/or research methods or in validating diagnostic tools or assays.

Tumor samples may also be analyzed to explore potential gene signature(s) associated with response or resistance to LY3022855 in combination therapy. In addition, sequencing of deoxyribonucleic acid (DNA) and/or immunohistochemistry may be performed on these tissue samples to evaluate expansion in clonal T cell populations and changes in immune cell infiltration, activation, modulation, and microenvironment, and changes in stromal and tumor biology in response to study treatment. The results of this analysis may be correlated with clinical outcome data.

The samples will be coded with the patient number and stored at a facility selected by the sponsor for up to a maximum of 15 years after the last patient visit for the study. The samples and any data generated from them can be linked back to the patient only by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the study drug.

Samples will be destroyed according to a process consistent with local regulation.

8.2.5. Samples for Immunogenicity Research

Blood samples for immunogenicity testing will be collected to determine antibody production against study drug(s). Immunogenicity will be assessed by a validated assay designed to detect antidrug antibodies (ADAs) in the presence of study drug(s). Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of study drug(s).

Samples may be stored at a facility selected by the sponsor for up to a maximum of 15 years following last patient visit for the study, to enable further analysis of immune responses to study drug(s). The duration allows the sponsor to respond to regulatory requests related to study drug(s).

8.3. Efficacy Evaluations

A secondary objective of the study is to document any antitumor activity. Refer to Attachment 1 for details regarding the timing of specific efficacy measures.

Each patient will be assessed by one or more of the following radiographic tests for tumor measurement:

- Computed tomography (CT) scan
- Magnetic resonance imaging (MRI).

Each patient's full extent of disease will also be assessed with:

- Tumor measurement by RECIST 1.1 (Eisenhauer et al. 2009)
- Evaluation of tumor markers, if indicated
- Evaluation of performance status (refer to the ECOG scale, Attachment 5).

In rare circumstances, historical radiographic examinations for RECIST criteria that are performed more than 28 days prior to the first dose may be used, but this decision must be discussed with the sponsor and documented in writing.

To confirm objective responses, all lesions should be radiographically assessed, and the same radiographic method used for the initial response determination should be repeated at least 8 weeks following the initial observation of an objective response, using the sample method that was used at baseline. If a patient is discontinued from the study, repeat radiographic assessments may be omitted if clear clinical signs of progressive disease (symptomatic deterioration) are present. At the conclusion of the study, radiographic images may be requested for central review.

8.4. Procedure/Sampling Compliance

Every attempt will be made to enroll patients who have the ability to understand and comply with instructions. Noncompliant patients may be discontinued from the study.

The collection times of safety assessments, PK and pharmacodynamic samples, and efficacy measurements are given as targets, to be achieved within reasonable limits. The scheduled time points may be subject to minor alterations; however, the actual collection time must be correctly recorded on the eCRF.

The scheduled collection times may be modified by the sponsor based on analysis of the safety and PK information obtained during the study. Any major modifications that might affect the conduct of the study, patient safety, and/or data integrity will be detailed in a protocol amendment.

9. Data Management Methods

9.1. Data Quality Assurance

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

- Provide instructional material to the study sites, as appropriate.
- Sponsor start-up training to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the eCRFs, 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/email, telephone, and/or fax.
- Review and evaluate eCRF data and/or use standard computer edits to detect errors in data collection.
- Conduct a quality review of the database.

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

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable IRB/ERBs with direct access to the original source documents.

9.2. Data Capture Systems

9.2.1. Case Report Form

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

Electronic case report form (eCRF) data will be encoded and stored in a clinical trial database. For data handled by a data management third-party organization (TPO), eCRF data and some or all data that are related will be managed and stored electronically in the TPO system. Subsequent to the final database lock, validated data will be transferred to the Lilly data warehouse, using standard Lilly file transfer processes.

For data handled by the sponsor internally, eCRF data and some or all data that are related will be managed by the sponsor and stored electronically in the sponsor's system.

9.2.2. Ancillary Data

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

Bioanalytical data will be stored electronically in the bioanalytical laboratory's database. 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. Data Analyses

10.1. General Considerations

Up to approximately 118 patients (78 [Part A] + 40 [Part B]) may be enrolled in this multicenter, nonrandomized, open-label Phase 1a/1b study of LY3022855.

The sample size for Part A will be determined primarily by the incidence of DLTs prior to establishing the MTDs in Part A. The anticipated sample size for Part A ranges from approximately 12 to 36 patients in the combination of LY3022855 plus durvalumab, and approximately 12 to 42 patients in the combination of LY3022855 plus tremelimumab. Nonevaluable patients, as defined in Section 7.6.1, will be replaced to ensure enough patients are enrolled in Part A.

In each cohort of Part B, approximately 20 patients will be enrolled. The sample size of Part B has been selected to allow adequate assessment of safety and tolerability of LY3022855 in combination with durvalumab at the recommended dose level and can provide adequate precision for the estimated incidence rate of the following quantities of interest: (1) patients having a specified AE, or (2) patients showing a response (PR/CR) to treatment. Example point estimates of incidence rates and corresponding 2-sided 95% confidence intervals (CIs) are summarized in Table JSCC.5. 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 Part B (Iasonos and O'Quigley 2013).

Table JSCC.5. Estimated Incidence Rate and 2-Sided 95% CI

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

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

[a] 95% Clopper-Pearson interval for binomial distribution with sample size of 20.

Safety and efficacy analyses will be conducted on all patients who have received at least one dose of the study treatment(s), regardless of whether they are deemed evaluable for the assessment of a dose level. Statistical analysis of this study will be the responsibility of Eli Lilly and Company.

The interpretation of the study results will be the responsibility of the investigator with the sponsor's CRP/CRS, PK scientist and statistician. The sponsor's CRP/CRS and statistician will also be responsible for the appropriate conduct of an internal review for both the final study report and any study-related material to be authorized by Lilly for publication. The analyses for this study will be descriptive; no p values will be calculated. Data analyses will be provided by cohort and treatment, whenever appropriate. For continuous variables, summary statistics will include number of patients, mean, median, standard deviation, minimum, and maximum. Categorical endpoints will be summarized using number of patients and percentages. Missing data will not be imputed.

Exploratory analyses of the data not described in Sections 10.2 through 10.9 will be conducted as deemed appropriate.

A detailed description of data analyses will be provided in a separate statistical analysis plan document for this study.

10.2. Patient Disposition

All patient discontinuations will be documented, and the extent of each patient's participation in the study will be reported. If known, a reason for their discontinuation will be given.

10.3. Patient Characteristics

Patient characteristics will include a summary and listing of the following:

- patient demographics
- baseline disease characteristics
- prior disease-related therapies
- concomitant medications.

Other patient characteristics will be summarized as deemed appropriate.

10.4. Safety Analyses

All patients who receive at least one dose of study drug(s) will be evaluated for safety and toxicity. Adverse event terms and severity grades will be assigned by the investigator using CTCAE, v4.0.

Safety analyses will include summaries of the following:

- AEs, including severity and possible relationship to study drug
- dose adjustments
- laboratory values
- vital signs
- DLTs at each dose level
- ECG readings
- LVEF evaluation.

10.4.1. Immunogenicity Analyses

Immunogenicity data will be summarized, and correlation to drug level (each drug), activity, and safety will be assessed, as appropriate, respectively. The measures that will be analyzed include baseline presence and level of ADA, treatment-emergent ADA, levels of neutralizing ADA, and incidence and levels of ADA related to IRRs.

10.5. Pharmacokinetic Analyses

Pharmacokinetic analyses will be conducted on patients who have received at least one dose of the study drug and have had samples collected. Pharmacokinetic parameter estimates for LY3022855, durvalumab, and tremelimumab will be calculated by standard noncompartmental methods of analysis. The primary parameters for analysis will be maximum concentration (C_{max}) and area under the plasma concentration-time curve (AUC; AUC from time zero to last measurable plasma concentration [$AUC_{0\text{-}tlast}$] and AUC from time zero to infinity [$AUC_{0\text{-}\infty}$]) of each of the study drugs. Other noncompartmental parameters, such as time of half-life ($t_{1/2}$), apparent clearance (CL/F), and apparent volume of distribution (V/F) for each study drug may be reported. Additional exploratory analyses will be performed if warranted by data and other validated PK software programs (for example, NONMEM) may be used if appropriate and approved by Global Pharmacokinetic management. The version of any software used for the analysis will be documented and the program will meet the Lilly requirements of software validation.

Pharmacokinetic parameter estimates will be evaluated to delineate the effects of dose proportionality, target-mediated drug disposition, and drug accumulation. Log-transformed C_{max} and AUC estimates will be assessed to estimate ratios of geometric means and the corresponding 90% CIs. The potential effect of durvalumab-mediated PD-L1 inhibition and/or tremelimumab-mediated CTLA-4 inhibition on the exposure of LY3022855, and the effect of LY3022855-mediated CSF-1R inhibition on the exposure of tremelimumab and/or durvalumab will be assessed using historical monotherapy exposure data for each of the 3 study drugs.

10.6. Pharmacodynamic Analyses

Characterized profiles of available longitudinal biomarkers for estimable patients will be created and analyzed. Pattern recognition analysis may be applied for the pharmacodynamic biomarkers that indicate the evidence of drug engagement. Those include, but are not limited to, circulating levels of CSF-1, IL-34, and monocyte markers.

10.7. Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic/pharmacodynamic analyses for LY3022855 may be conducted as deemed necessary by Global PK/PD management. These analyses may include, but are not limited to, establishing relationships (or lack of) between exposure and pharmacodynamic biomarkers that were explored or confirmed in pharmacodynamic analyses (refer to Section 10.6).

10.8. Efficacy

Tumor response data, according to RECIST 1.1 (Eisenhauer et al. 2009), will be tabulated by cohorts. Particularly, the antitumor effect will be summarized by best overall response, including the overall response rate (ORR) and disease control rate (DCR; CR+PR+SD). A patient is considered to have a tumor response if they achieve a confirmed CR or PR. The ORR is estimated by the proportion of enrolled patients who have a best overall response of confirmed CR or PR. The DCR is estimated by the proportion of enrolled patients who have a best overall response of confirmed CR, confirmed PR, or stable disease. A 95% exact CI will be constructed to determine the level of precision of the ORR and DCR. Time-to-event variables such as progression-free survival (PFS), time to response, duration of response, and overall survival (OS) will be tabulated if appropriate. The Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the survival curves, medians, and survival rates at specified time points, if applicable.

Upon completion of each Part B cohort, an analysis of safety, PK, pharmacodynamics, biomarkers, and efficacy may occur, once all patients have completed 4 cycles of study therapy or discontinued from the study.

Any cohort-specific analyses may be combined if they are expected to occur within approximately a month, and the analyses may also be combined with the ongoing trial-level safety review or annual safety review for annual safety update reporting.

10.9. Tailoring Biomarker Analyses

If applicable, efficacy measures may be summarized descriptively within subgroups of patients. Exploratory analyses may be applied to correlate the baseline biomarkers with clinical outcome. If applicable, a subset of potential predictive biomarkers associating with interpretable clinical benefit may be further examined with biological evidence.

10.10. Interim Analyses

Because this is a dose-finding study, data will be reviewed on a cohort-by-cohort basis during the study, until the MTDs are determined for each combination. 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 MTD has been met or exceeded. The investigators and the Lilly study team will make the determination regarding dose escalation based upon their review of the safety and tolerability data as described in this protocol.

Safety and/or PK data will be reviewed during the study if needed for dose escalation, modifications to the dose-escalation strategy, or other design elements.

In Part A, after all patients who are deemed evaluable for the assessment of dose levels complete the DLT-evaluation period or the MTD is determined, an interim safety and PK analysis may be conducted for each combination for planning next studies.

If it is deemed that enough data are obtained to assess the primary and secondary objectives, a clinical study report may be written before the last patient visit for the study. In this case, all data until the data cutoff date will be used for the analysis of safety, efficacy, PK, and pharmacodynamic biomarkers. After the data cutoff date, all data defined in the protocol will continue to be collected from patients on treatment, to be listed and summarized in an updated clinical study report. However, summary tables containing the data collected after the data cutoff date will not be created; these data may be reported separately and the analyses on all patients, including these data, may not necessarily be performed.

11. Informed Consent, Ethical Review, and Regulatory Considerations

11.1. Informed Consent

The investigator is responsible for ensuring that the patient understands the potential risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the study in a timely manner.

The ICF will be used to explain the potential risks and benefits of study participation to the patient in simple terms before the patient is entered into the study and to document that the patient is satisfied with his or her understanding of the potential risks and benefits of participating in the study and desires to participate in the study.

The investigator is ultimately responsible for ensuring that informed consent is given by each patient or legal representative before the study is started. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of study drug.

In this protocol, the term "informed consent" includes all consent and assent given by patients or their legal representatives.

11.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are used at investigative sites(s). All ICFs must be compliant with the ICH guideline on GCP.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). The ERB(s) will review the protocol as required.

The study site's ERB(s) should be provided with the following:

- the current IB or package labeling and updates during the course of the study
- ICF
- relevant curricula vitae.

11.3. Regulatory Considerations

This study will be conducted in accordance with:

1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines

2) the ICH GCP Guideline [E6]

3) applicable laws and regulations.

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

Some of the obligations of the sponsor will be assigned to a TPO.

An identification code assigned to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting AEs and/or other study-related data.

11.3.1. Investigator Information

Site-specific contact information may be provided in a separate document.

11.3.2. Protocol Signatures

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

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

11.3.3. Final Report Signature

The final report coordinating investigator or designee will sign the clinical study report 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.

The investigator with the most analyzable patients will serve as the final report coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the final report coordinating investigator.

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

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Attachment 1. Protocol JSCC Study Schedule

Assessments are to be performed at the times stipulated in the schedule and as clinically required in the management of the patient.

Screening/Baseline Assessments (Visit 0)

Relative Day Prior to Day 1 of Cycle 1	≤28	≤14	≤7	Comments
Written informed consent/assignment of patient identification number	X			ICF signed (prior to performance of any protocol-specific tests/procedures).
Review of eligibility criteria	X			
Medical history		X		
Physical examination		X		Full physical examination, including assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, GI, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems.
Vital signs		X		BP, temperature, RR, and PR. Includes height (at baseline only) and weight.
ECOG performance status		X		
ECG (local)		X		Triplicate ECG will be obtained, on which QTcF must be <470 ms (calculated from one ECG using Fridericia's Correction Formula and confirmed with 2 additional ECGs).
HIV screening (local)	X			Per institutional standards. If done within 28 days prior to Cycle 1, Day 1, as part of standard of care, does not need to be repeated prior to the start of Cycle 1.
Hematology (local)		X		Refer to Attachment 2.
Serum chemistry (central)		X		Refer to Attachment 2.
Urinalysis (local)		X		Refer to Attachment 2.
Coagulation (local)		X		Refer to Attachment 2. Obtain prior to tumor biopsy.
Thyroid function (central)		X		Refer to Attachment 2. Free T3 and free T4 will be measured only if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
Pancreas function (central)		X		Refer to Attachment 2.
LVEF evaluation	X			Echocardiogram or MUGA scan.
Radiographic tumor assessment (CT/MRI)	X			If done within 28 d prior to Cycle 1, Day 1, as part of standard of care, does not need to be repeated prior to the start of Cycle 1.
Tumor measurement (palpable or visible)		X		
CTCAE v4.0 grading (preexisting conditions)		X		To be reported only after study eligibility is confirmed. Refer to Section 8.1.2.4 for reporting guidelines.
Concomitant medications		X		

Relative Day Prior to Day 1 of Cycle 1	≤28	≤14	≤7	Comments
Tumor markers (local)		X		As clinically indicated. For example, CEA in patients with colorectal cancer or CA125 in patients with ovarian cancer.
Tumor tissue biopsy		X		For Part A (all cohorts) and Part B (ovarian cancer cohort only): A newly obtained core or excisional biopsy of a tumor should be taken only after study eligibility is confirmed. For the NSCLC cohort in Part B a newly obtained core or excisional biopsy should be obtained if an archived tumor sample following the most recent systemic therapy is not available. Refer to the laboratory manual.
Archived tumor tissue	X			An archived tumor sample following most recent systemic treatment if not restricted by local regulations will be requested from all patients in Part B NSCLC cohort. If such an archived biopsy sample is not available, a new biopsy must be obtained for the patient to be eligible to participate in study. Refer to the laboratory manual.
Whole blood for biomarkers			X	Refer to the laboratory manual.
Pregnancy test (local)			X	Applies only to women of childbearing potential. Urine hCG or serum β-hCG is acceptable.

Abbreviations: AE = adverse event; BP = blood pressure; CA125 = cancer antigen 125; CEA = carcinoembryonic antigen; CT = computed tomography (scan); CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; GI = gastrointestinal; hCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; ICF = informed consent form; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition (scan); PR = pulse rate; QTcF = QT interval corrected for heart rate using Fridericia's Correction Formula; RR = respiration rate; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; v4.0 = Version 4.0 of CTCAE.

On-Study Treatment and Post-Treatment (Follow-Up) Assessments for Combination Therapy: LY3022855 plus Durvalumab

Note that a maximum of 12 months/26 doses of durvalumab treatment is permitted; last infusion at Week 50.

Screening procedures performed for safety within 72 hours prior to Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.

Rows with *italicized* font indicate that there is no planned assessment for the time frame shown on the page.

LY3022855 plus Durvalumab Assessment (central or local laboratory indicated, if applicable)	**Cycle 1 (Visit 1)**						**Comments** Except for the Cycle 1, Day 1 visit, allowable windows are ±3 days, unless otherwise indicated. On dosing days, all assessments to be performed preinfusion, unless stated otherwise.
Relative day within a 28-day cycle:	**1**	**2**	**3**	**8**	**15**	**22**	
Physical examination	X			X	X	X	Targeted physical examination (on the basis of clinical observations and symptomatology).
Vital signs	X			X	X	X	BP, temperature, RR, PR, and weight. Vital signs (BP, RR, and PR only) to be measured around infusions as follows (allowable window ±10 min): Around each LY3022855 infusion: prior to, during (midway through), at the end, and 30 min after the end. Around each durvalumab infusion (based on a 60-min infusion): within 30 min prior to, during (approx. 30 min after start of infusion), and at the end (approx. 60 min after start of infusion). 1-h Observation period after durvalumab infusion: at 30 and 60 min after the end of the infusion (90 and 120 min after start of infusion) for the first durvalumab infusion only, and for subsequent infusions as clinically indicated. If the durvalumab infusion exceeds 60 min, monitoring of BP and PR should occur per the preceding principles or more frequently if clinically indicated.
ECOG performance status	X						
Pregnancy test (local)							*Every 12 wk (±7 d) after the first dose of study drug or according to local regulations or as clinically indicated, whichever is more frequent. Urine hCG or serum β-hCG.*
ECG (local)	X						Single ECG. Obtain ECGs before any associated blood draws. On dosing days, ECG should be taken within 2 h prior to the start of the LY3022855 infusion and at least one time point 0-3 h after the durvalumab infusion. Additional ECGs to be obtained as clinically indicated.

LY3022855 plus Durvalumab Assessment (central or local laboratory indicated, if applicable)	**Cycle 1 (Visit 1)**						**Comments** Except for the Cycle 1, Day 1 visit, allowable windows are ±3 days, unless otherwise indicated. On dosing days, all assessments to be performed preinfusion, unless stated otherwise.
Relative day within a 28-day cycle:	**1**	**2**	**3**	**8**	**15**	**22**	
Hematology (local)	X		X	X	X	X	Refer to Attachment 2.
Serum chemistry (local) - safety labs for dosing	X			X	X	X	Refer to Attachment 2. Results must be available and reviewed before administering study drug.
Serum chemistry (central)	X	X		X	X	X	Refer to Attachment 2.
Urinalysis (local)	X						Refer to Attachment 2. To be performed at Screening, at C1D1, and every 4 wk thereafter. Additional assessments as clinically indicated. Results need not be available before administering study drug.
Coagulation (local)							*Refer to Attachment 2. As clinically indicated.*
Thyroid function (central)	X						Refer to Attachment 2. Free T3 and free T4 will be measured only if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
Pancreas function (central)							*Refer to Attachment 2.*
Tumor markers (local)							
Pharmacogenetic sample	X						Refer to the laboratory manual. Collect once. Sample can be collected at any time, if not collected on C1D1.

LY3022855 plus Durvalumab Assessment (central or local laboratory indicated, if applicable)	**Cycle 1 (Visit 1)**							**Comments** Except for the Cycle 1, Day 1 visit, allowable windows are ±3 days, unless otherwise indicated. On dosing days, all assessments to be performed preinfusion, unless stated otherwise.
Relative day within a 28-day cycle:	**1**		**2**	**3**	**8**	**15**	**22**	
Immunogenicity	X						X	If at any time a patient experiences an IRR, attempt to obtain a blood sample for immunogenicity analysis as close to the onset of the event as possible, at the resolution of the event, and 30 d following the event. A portion of the sample taken for immunogenicity testing may be used for PK analysis.
Myoglobin (local)					X			Refer to Attachment 2. If serum CK Grade ≥2, test for serum and urine myoglobin.
CTCAE v4.0 grading	X				X	X	X	Throughout study as needed. Refer to Section 8.1.1 for reporting guidelines.
Concomitant medications	X				X	X	X	Throughout study as needed.
LY3022855 administration	Refer to Table JSCC.1 for dose frequency during Part A.							For LY3022855 and durvalumab: Part A doses: Refer to Table JSCC.1. Part B doses and dose frequencies to be determined; refer to Section 7.2.2.2 for information.
Durvalumab administration	X					X		
Pharmacokinetics								
LY3022855 (predose on dosing days, unless noted otherwise)	X	X 2 h post-EOI C1D1 (±1 h)	X 24 h post-EOI C1D1 (±4 h)	X 48 h post-EOI C1D1 (±4 h)	X	X	X	The date and the time of all samples must be clearly and accurately recorded. EOI = end of infusion
Durvalumab (predose on dosing days, unless noted otherwise)	X	X Simultaneously with LY PK sample	X Simultaneously with LY PK sample	X Simultaneously with LY PK sample	X	X	X	
Pharmacodynamics and tailoring								
Serum	X	X Simultaneously with LY PK sample	X Simultaneously with LY PK sample	X Simultaneously with LY PK sample	X	X	X	Serum storage for correlative studies.
Plasma	X							Plasma storage for correlative studies.
Whole blood	X		X			X		Gene expression analysis and other exploratory research.
Flow cytometry								
Immunophenotyping #1	X				X	X	X	CD14 and CD16.
Immunophenotyping #2	X				X	X	X	TBNK & T cell subset/activation panels.
Immunophenotyping #3	X							MDSC panel.
Isoenzymes (central)								*Refer to Attachment 2. Obtain at additional time points, as clinically indicated.*

LY3022855 plus Durvalumab Assessment (central or local laboratory indicated, if applicable)	**Cycle 1 (Visit 1)**						**Comments** Except for the Cycle 1, Day 1 visit, allowable windows are ±3 days, unless otherwise indicated. On dosing days, all assessments to be performed preinfusion, unless stated otherwise.
Relative day within a 28-day cycle:	**1**	**2**	**3**	**8**	**15**	**22**	
LVEF evaluation							*Echocardiogram or MUGA scan. Obtain at additional time points, as clinically indicated.*
Radiographic tumor assessment (CT/MRI)							*Perform every 8 wk (±7 d), starting on Cycle 2, Day 22.*
Tumor measurement (palpable or visible)							
Tumor biopsy							*For Part A (all cohorts) and Part B (ovarian cancer cohort only): An on-treatment tumor core needle or excisional biopsy to be performed 6-8 wk after starting study treatment.*

LY3022855 plus Durvalumab Assessment (central or local laboratory indicated, if applicable)	**Cycle 2 (Visit 2)**						**Comments** Except for the Cycle 1, Day 1 visit, allowable windows are ±3 days, unless otherwise indicated. On dosing days, all assessments to be performed preinfusion, unless stated otherwise.
Relative day within a 28-day cycle:	**1**	**8**	**9**	**10**	**15**	**22**	
Physical examination	X	X			X	X	Targeted physical examination (on the basis of clinical observations and symptomatology).
Vital signs	X	X			X	X	BP, temperature, RR, PR, and weight. Vital signs (BP, RR, and PR only) to be measured around infusions as follows (allowable window ±10 min): Around each LY3022855 infusion: prior to, during (midway through), at the end, and 30 min after the end. Around each durvalumab infusion (based on a 60-min infusion): within 30 min prior to, during (approx. 30 min after start of infusion), and at the end (approx. 60 min after start of infusion). 1-h Observation period after durvalumab infusion: at 30 and 60 min after the end of the infusion (90 and 120 min after start of infusion) as clinically indicated. If the durvalumab infusion exceeds 60 min, monitoring of BP and PR should occur per the preceding principles or more frequently if clinically indicated.
ECOG performance status	X						
Pregnancy test (local)							*Every 12 wk (±7 d) after the first dose of study drug or according to local regulations or as clinically indicated, whichever is more frequent. Urine hCG or serum β-hCG.*
ECG (local)	X						Single ECG. Obtain ECGs before any associated blood draws. ECG should be taken within 2 h prior to the start of the LY3022855 infusion and at least one time point 0-3 h after the durvalumab infusion. Additional ECGs to be obtained as clinically indicated.
Hematology (local)	X	X			X	X	Refer to Attachment 2.
Serum chemistry (local) - safety labs for dosing	X	X			X	X	Refer to Attachment 2. Results must be available and reviewed before administering study drug.
Serum chemistry (central)	X	X			X	X	Refer to Attachment 2.
Urinalysis (local)	X						Refer to Attachment 2. To be performed at Screening, at C1D1, and every 4 wk thereafter. Additional assessments as clinically indicated. Results need not be available before administering study drug.
Coagulation (local)	X						Refer to Attachment 2. Obtain prior to tumor biopsy. Additional assessments as clinically indicated.

LY3022855 plus Durvalumab Assessment (central or local laboratory indicated, if applicable)	**Cycle 2 (Visit 2)**						**Comments** Except for the Cycle 1, Day 1 visit, allowable windows are ±3 days, unless otherwise indicated. On dosing days, all assessments to be performed preinfusion, unless stated otherwise.
Relative day within a 28-day cycle:	**1**	**8**	**9**	**10**	**15**	**22**	
Thyroid function (central)	X						Refer to Attachment 2. Free T3 and free T4 will be measured only if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
Pancreas function (central)	X						Refer to Attachment 2.
Tumor markers (local)	X						If clinically indicated.
Pharmacogenetic sample							*Refer to the laboratory manual. Collect once. Sample can be collected at any time, if not collected on C1D1.*
Immunogenicity		X					If at any time a patient experiences an IRR, attempts to obtain a blood sample for immunogenicity analysis as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. A portion of the sample taken for immunogenicity testing may be used for PK analysis.
Myoglobin (local)	X	X			X	X	Refer to Attachment 2. If serum CK Grade ≥2, test for serum and urine myoglobin.
CTCAE v4.0 grading	X	X			X	X	Throughout study as needed. Refer to Section 8.1.1 for reporting guidelines.
Concomitant medications	X	X			X	X	Throughout study as needed.
LY3022855 administration	Refer to Table JSCC.1 for dose frequency during Part A.						For LY3022855 and durvalumab: Part A doses: Refer to Table JSCC.1. Part B doses and dose frequencies to be determined; refer to Section 7.2.2.2 for information.
Durvalumab administration	X				X		
Pharmacokinetics							
LY3022855 (predose on dosing days, unless noted otherwise)	X	X	X 2 h post-EOI C2D8 (±1 h)	X 24 h post-EOI C2D8 (±4 h)	X 48 h post-EOI C2D8 (±4 h)	X		The date and the time of all samples must be clearly and accurately recorded. EOI = end of infusion
Durvalumab (predose on dosing days, unless noted otherwise)	X	X	X Simultaneously with LY PK sample	X Simultaneously with LY PK sample	X Simultaneously with LY PK sample	X		
Pharmacodynamics and tailoring							
Serum	X	X	X Simultaneously with LY PK sample	X Simultaneously with LY PK sample	X Simultaneously with LY PK sample	X		Serum storage for correlative studies.
Plasma		X						Plasma storage for correlative studies.
Whole blood	X				X			Gene expression analysis and other exploratory research.
Flow cytometry							
Immunophenotyping #1	X	X			X			CD14, CD16.
Immunophenotyping #2	X	X			X			TBNK & T cell subset/activation panels.
Immunophenotyping #3	X							MDSC panel.

LY3022855 plus Durvalumab Assessment (central or local laboratory indicated, if applicable)	**Cycle 2 (Visit 2)**						**Comments** Except for the Cycle 1, Day 1 visit, allowable windows are ±3 days, unless otherwise indicated. On dosing days, all assessments to be performed preinfusion, unless stated otherwise.
Relative day within a 28-day cycle:	**1**	**8**	**9**	**10**	**15**	**22**	
Isoenzymes (central)	X						Refer to Attachment 2. Obtain at additional time points, as clinically indicated.
LVEF evaluation						X	Echocardiogram or MUGA scan. Obtain at additional time points, as clinically indicated.
Radiographic tumor assessment (CT/MRI)						X	Perform every 8 wk (±7 d), starting on Cycle 2, Day 22.
Tumor measurement (palpable or visible)						X	
Tumor biopsy		X					For Part A (all cohorts) and Part B (ovarian cancer cohort only): An on-treatment tumor core needle or excisional biopsy to be performed 6-8 wk after starting study treatment; that is, at Cycle 2, between Days 8 and 22. For Part B (NSCLC cohort) an optional on-treatment tumor tissue should be collected from patients in the study where possible.

LY3022855 plus Durvalumab Assessment (central or local laboratory indicated, if applicable)	**Cycle 3 (Visit 3)**				**Cycle 4 (Visit 4)**				**Cycle 5 (Visit 5)**				**Comments** Except for the Cycle 1, Day 1 visit, allowable windows are ±3 days, unless otherwise indicated. On dosing days, all assessments to be performed preinfusion, unless stated otherwise.
Relative day within a 28-day cycle:	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	
Physical examination	X				X				X				Targeted physical examination (on the basis of clinical observations and symptomatology).
Vital signs	X				X				X				BP, temperature, RR, PR, and weight. Vital signs (BP, RR, and PR only) to be measured around infusions as follows (allowable window ±10 min): Around each LY3022855 infusion: prior to, during (midway through), at the end, and 30 min after the end. Around each durvalumab infusion (based on a 60-min infusion): within 30 min prior to, during (approx. 30 min after start of infusion), and at the end (approx. 60 min after start of infusion). 1-h Observation period after durvalumab infusion: at 30 and 60 min after the end of the infusion (90 and 120 min after start of infusion) for the first durvalumab infusion only, and for subsequent infusions as clinically indicated. If the durvalumab infusion exceeds 60 min, monitoring of BP and PR should occur per the preceding principles or more frequently if clinically indicated.
ECOG performance status	X				X				X				
Pregnancy test (local)					X								Every 12 wk (±7 d) after the first dose of study drug or according to local regulations or as clinically indicated, whichever is more frequent. Urine hCG or serum β-hCG.
ECG (local)													*Additional ECGs to be obtained as clinically indicated.*
Hematology (local)	X	X	X	X	X	X	X	X	X		X		Refer to Attachment 2.
Serum chemistry (local) - safety labs for dosing	X	X	X	X	X	X	X	X	X		X		Refer to Attachment 2. Results must be available and reviewed before administering study drug.
Serum chemistry (central)	X	X	X	X	X	X	X	X	X		X		Refer to Attachment 2.
Urinalysis (local)	X				X				X				Refer to Attachment 2. To be performed at Screening, at C1D1, and every 4 wk thereafter. Additional assessments as clinically indicated. Results need not be available before administering study drug.

LY3022855 plus Durvalumab Assessment (central or local laboratory indicated, if applicable)	**Cycle 3 (Visit 3)**				**Cycle 4 (Visit 4)**				**Cycle 5 (Visit 5)**				**Comments** Except for the Cycle 1, Day 1 visit, allowable windows are ±3 days, unless otherwise indicated. On dosing days, all assessments to be performed preinfusion, unless stated otherwise.
Relative day within a 28-day cycle:	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	
Coagulation (local)													*Refer to Attachment 2. As clinically indicated.*
Thyroid function (central)	X				X				X				Refer to Attachment 2. Free T3 and free T4 will be measured only if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
Pancreas function (central)	X				X								Refer to Attachment 2.
Tumor markers (local)	X				X				X				If applicable.
Pharmacogenetic sample													*Refer to the laboratory manual. Collect once. Sample can be collected at any time, if not collected on C1D1.*
Immunogenicity	X												If at any time a patient experiences an IRR, attempts to obtain a blood sample for immunogenicity analysis as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. A portion of the sample taken for immunogenicity testing may be used for PK analysis.
Myoglobin (local)	X												Refer to Attachment 2. If serum CK Grade ≥2, test for serum and urine myoglobin.
CTCAE v4.0 grading	X	X	X	X	X	X	X	X	X	X	X	X	Throughout study as needed. Refer to Section 8.1.1 for reporting guidelines.
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	Throughout study as needed.
LY3022855 administration	Refer to Table JSCC.1 for dose frequency during Part A.												For LY3022855 and durvalumab: Part A doses: Refer to Table JSCC.1. Part B doses and dose frequencies to be determined; refer to Section 7.2.2.2 for information.
Durvalumab administration	X		X		X		X		X		X		
Pharmacokinetics													
LY3022855 (predose on dosing days, unless noted otherwise)	X				X								The date and the time of all samples must be clearly and accurately recorded.
Durvalumab (predose on dosing days, unless noted otherwise)	X				X								
Pharmacodynamics and tailoring													
Serum	X				X								Serum storage for correlative studies.
Plasma													*Plasma storage for correlative studies.*
Flow cytometry													
Immunophenotyping #1	X				X								CD14, CD16.
Immunophenotyping #2	X				X								TBNK & T cell subset/activation panels.
Immunophenotyping #3	X												MDSC panel.

LY3022855 plus Durvalumab Assessment (central or local laboratory indicated, if applicable)	**Cycle 3 (Visit 3)**				**Cycle 4 (Visit 4)**				**Cycle 5 (Visit 5)**				**Comments** Except for the Cycle 1, Day 1 visit, allowable windows are ±3 days, unless otherwise indicated. On dosing days, all assessments to be performed preinfusion, unless stated otherwise.
Relative day within a 28-day cycle:	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	
Isoenzymes (central)													*Refer to Attachment 2. Obtain at additional time points, as clinically indicated.*
LVEF evaluation													*Echocardiogram or MUGA scan. Obtain at additional time points, as clinically indicated.*
Radiographic tumor assessment (CT/MRI)								X					Perform every 8 wk (±7 d), starting on Cycle 2, Day 22.
Tumor measurement (palpable or visible)								X					
Tumor biopsy													*For Part A (all cohorts) and Part B (ovarian cancer cohort only): An on-treatment tumor core needle or excisional biopsy to be performed 6-8 wk after starting study treatment.*

LY3022855 plus Durvalumab Assessment (central or local laboratory indicated, if applicable)	**Cycle 6-n (Visit 6-n)**				**Short-Term Follow-Up[a] (Visits 801 and 802)**		**Comments** Except for the Cycle 1, Day 1 visit, allowable windows are ±3 days, unless otherwise indicated. On dosing days, all assessments to be performed preinfusion, unless stated otherwise.
Relative day within a 28-day cycle:	**1**	**8**	**15**	**22**	**30-Day (±7 d)**	**90-Day* (±7 d)**	*90-Day Follow-Up visit is only for durvalumab safety.
Physical examination	X				X		Targeted physical examination (on the basis of clinical observations and symptomatology).
Vital signs	X				X		BP, temperature, RR, PR, and weight. Vital signs (BP, RR, and PR only) to be measured around infusions as follows (allowable window ±10 min): Around each LY3022855 infusion: prior to, during (midway through), at the end, and 30 min after the end. Around each durvalumab infusion (based on a 60-min infusion): within 30 min prior to, during (approx. 30 min after start of infusion), and at the end (approx. 60 min after start of infusion). 1-h Observation period after durvalumab infusion: at 30 and 60 min after the end of the infusion (90 and 120 min after start of infusion) for the first durvalumab infusion only, and for subsequent infusions as clinically indicated. If the durvalumab infusion exceeds 60 min, monitoring of BP and PR should occur per the preceding principles or more frequently if clinically indicated.
ECOG performance status	X				X	X*	*Performed at 90-day follow-up only for patients who discontinue study treatment due to toxicity, in the absence of confirmed disease progression.
Pregnancy test (local)					X		Every 12 wk (±7 d) after the first dose of study drug or according to local regulations or as clinically indicated, whichever is more frequent. Urine hCG or serum β-hCG.
ECG (local)					X		Single ECG. Obtain ECGs before any associated blood draws. Additional ECGs to be obtained as clinically indicated.
Hematology (local)	X		X		X	X	Refer to Attachment 2.
Serum chemistry (local) - safety labs for dosing	X		X				Refer to Attachment 2. Results must be available and reviewed before administering study drug.
Serum chemistry (central)	X		X		X	X	Refer to Attachment 2.
Urinalysis (local)	X				X		Refer to Attachment 2. To be performed at Screening, at C1D1, and every 4 wk thereafter. Additional assessments as clinically indicated. Results need not be available before administering study drug.
Coagulation (local)							*Refer to Attachment 2. As clinically indicated.*
Thyroid function (central)	X				X		Refer to Attachment 2. Free T3 and free T4 will be measured only if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
Pancreas function (central)					X		Refer to Attachment 2. Only if amylase and lipase were previously elevated above normal limits.
Tumor markers (local)	X						If applicable.
Pharmacogenetic sample							*Refer to the laboratory manual. Collect once. Sample can be collected at any time, if not collected on C1D1.*

LY3022855 plus Durvalumab Assessment (central or local laboratory indicated, if applicable)	**Cycle 6-n (Visit 6-n)**				**Short-Term Follow-Up[a] (Visits 801 and 802)**		**Comments** Except for the Cycle 1, Day 1 visit, allowable windows are ±3 days, unless otherwise indicated. On dosing days, all assessments to be performed preinfusion, unless stated otherwise.
Relative day within a 28-day cycle:	**1**	**8**	**15**	**22**	**30-Day (±7 d)**	**90-Day* (±7 d)**	*90-Day Follow-Up visit is only for durvalumab safety.
Immunogenicity	X				X	X	If at any time a patient experiences an IRR, attempts to obtain a blood sample for immunogenicity analysis as close to the onset of the event as possible, at the resolution of the event, and 30 d following the event. A portion of the sample taken for immunogenicity testing may be used for PK analysis. To be drawn every 6 mo following Cycle 6.
Myoglobin (local)	X						Refer to Attachment 2. If serum CK ≥ Grade 2, test for serum and urine myoglobin.
CTCAE v4.0 grading	X	X	X	X	X		Throughout study as needed. Refer to Section 8.1.1 for reporting guidelines.
Concomitant medications	X	X	X	X	X		Throughout study as needed.
LY3022855 administration	Refer to Table JSCC.1 for dose frequency during Part A.						For LY3022855 and durvalumab: Part A doses: Refer to Table JSCC.1. Part B doses and dose frequencies to be determined; refer to Section 7.2.2.2 for information.
Durvalumab administration	X		X				
Pharmacokinetics							
LY3022855					X		The date and the time of all samples must be clearly and accurately recorded.
Durvalumab					X		
Pharmacodynamics and tailoring							
Serum					X		Serum storage for correlative studies.
Plasma					X		Plasma storage for correlative studies.
Whole blood					X		Exploratory research.
Flow cytometry							
Immunophenotyping #1							*CD14, CD16.*
Immunophenotyping #2							TBNK & *T cell subset/activation panels.*
Immunophenotyping #3							*MDSC panel.*
Isoenzymes (central)							*Refer to Attachment 2. Obtain at additional time points, as clinically indicated.*
LVEF evaluation							*Echocardiogram or MUGA scan. Obtain at additional time points, as clinically indicated.*
Radiographic tumor assessment (CT/MRI)				X	X		Perform every 8 wk (±7 d), starting on Cycle 2, Day 22, then every 12 wk (±7 d) for patients who achieve disease control after 12 mo of study treatment and after Week 48 for patients who discontinue durvalumab due to toxicity or symptomatic deterioration. For patients who continue on durvalumab post-confirmed progression at the investigator's discretion (after consultation with the sponsor), tumor assessments should be performed until durvalumab is stopped.
Tumor measurement (palpable or visible)				X	X		
Tumor biopsy							*For Part A (all cohorts) and Part B (ovarian cancer cohort only): An on-treatment tumor core needle or excisional biopsy to be performed 6-8 wk after starting study treatment.*

Abbreviations: AE = adverse event; BP = blood pressure; CnDn = Cycle n, Day n (for example, C1D1 = Cycle 1, Day 1); CK = creatine kinase; CT = computed tomography (scan); CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; hCG = human chorionic gonadotropin; IRR = infusion-related reaction; LVEF = left ventricular ejection fraction; LY = LY3022855; MDSC = myeloid-derived suppressor cell; MRI = magnetic resonance imaging; MUGA = multigated acquisition (scan); NCI = National Cancer Institute; PK = pharmacokinetic(s); PR = pulse rate; RR = respiration rate; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; v4.0 = Version 4.0 of NCI-CTCAE.

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

Continued Access Schedule for Combination Therapy: LY3022855 plus Durvalumab

Visit	Continued Access Treatment Period 501-5XX	Continued Access Follow-Up[a] 901 (30 d)and 902* (90 d) (±7 d)	*90-Day Follow-Up visit (Visit 902) is only for durvalumab safety.
Procedure[b]			**Instructions**
AE collection	X	X	CTCAE v4.0. Refer to Section 8.1.1 for reporting guidelines.
Pharmacokinetics and immunogenicity		X	If a patient experiences an IRR, collect blood samples for PK and immunogenicity analysis at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 days after the IRR.
Administer LY3022855 and durvalumab	X		Refer to Table JSCC.1 for dose frequency of LY3022855 during Part A. For LY3022855 and durvalumab: Part A doses: Refer to Table JSCC.1. Part B doses and dose frequencies to be determined; refer to Section 7.2.2.2 for information.

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; IRR = infusion-related reaction; v4.0 = Version 4.0 of CTCAE.

[a] Continued access follow-up Visit 901 begins 1 day after the patient and the investigator agree that the patient will no longer continue treatment in the continued access period and lasts approximately 30 days. Visit 902 occurs 90 days (±7 days) after the patient and the investigator agree that the patient will no longer continue treatment in the continued access period. No follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

[b] Efficacy assessments will be done at the investigator's discretion based on the standard of care.

On-Study Treatment and Post-Treatment (Follow-Up) Assessments for Combination Therapy: LY3022855 plus Tremelimumab

Tremelimumab once every 4 weeks; after 6 doses, tremelimumab once every 12 weeks until discontinuation.

Screening procedures performed within 72 hours prior to Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.

Rows with *italicized* font indicate that there is no planned assessment for the time frame shown on the page.

LY3022855 plus Tremelimumab Assessment (central or local laboratory indicated, if applicable)	**Cycle 1 (Visit 1)**						**Comments** Except for the Cycle 1, Day 1 visit, allowable windows are ±3 days, unless otherwise indicated. On dosing days, all assessments to be performed preinfusion, unless stated otherwise.
Relative day within a 28-day cycle:	**1**	**2**	**3**	**8**	**15**	**22**	
Physical examination	X			X	X	X	Targeted physical examination (on the basis of clinical observations and symptomatology).
Vital signs	X			X	X	X	BP, temperature, RR, PR, and weight. Vital signs (BP, RR, and PR only) to be measured around infusions as follows (allowable window ±10 min): Around each LY3022855 infusion: prior to, during (midway through), at the end, and 30 min after the end. Around each tremelimumab infusion (based on a 60-min infusion): within 30 min prior to, during (approx. 30 min after start of infusion), and at the end (approx. 60 min after start of infusion). 1-h Observation period after tremelimumab infusion: at 30 and 60 min after the end of the infusion (90 and 120 min after start of infusion) for the first tremelimumab infusion only, and for subsequent infusions as clinically indicated. If the tremelimumab infusion exceeds 60 min, monitoring of BP and PR should occur per the preceding principles or more frequently if clinically indicated.
ECOG performance status	X						
Pregnancy test (local)							*Every 12 wk (±7 d) after the first dose of study drug or according to local regulations or as clinically indicated, whichever is more frequent. Urine hCG or serum β-hCG.*

LY3022855 plus Tremelimumab Assessment (central or local laboratory indicated, if applicable)	**Cycle 1 (Visit 1)**						**Comments** Except for the Cycle 1, Day 1 visit, allowable windows are ±3 days, unless otherwise indicated. On dosing days, all assessments to be performed preinfusion, unless stated otherwise.
Relative day within a 28-day cycle:	**1**	**2**	**3**	**8**	**15**	**22**	
ECG (local)	X						Single ECG. Obtain ECGs before any associated blood draws. ECG should be taken within 2 h prior to the start of the LY3022855 infusion and at least one time point 0-3 h after the tremelimumab infusion. Additional ECGs to be obtained as clinically indicated.
Hematology (local)	X		X	X	X	X	Refer to Attachment 2.
Serum chemistry (local) - safety labs for dosing	X			X	X	X	Refer to Attachment 2. Results must be available and reviewed before administering study drug.
Serum chemistry (central)	X	X		X	X	X	Refer to Attachment 2.
Urinalysis (local)	X						Refer to Attachment 2. To be performed at Screening, at C1D1, and every 4 wk thereafter. Additional assessments as clinically indicated. Results need not be available before administering study drug.
Coagulation (local)							*Refer to Attachment 2. As clinically indicated.*
Thyroid function tests (central)	X						Refer to Attachment 2. Free T3 and free T4 will be measured only if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
Pancreas function (central)							*Refer to Attachment 2.*
Tumor markers (local)							
Pharmacogenetic sample	X						Refer to the laboratory manual. Collect once. Sample can be collected at any time, if not collected on C1D1.
Immunogenicity	X					X	If at any time a patient experiences an IRR, attempts to obtain a blood sample for immunogenicity analysis as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. A portion of the sample taken for immunogenicity testing may be used for PK analysis.

LY3022855 plus Tremelimumab Assessment (central or local laboratory indicated, if applicable)	**Cycle 1 (Visit 1)**						**Comments** Except for the Cycle 1, Day 1 visit, allowable windows are ±3 days, unless otherwise indicated. On dosing days, all assessments to be performed preinfusion, unless stated otherwise.
Relative day within a 28-day cycle:	**1**	**2**	**3**	**8**	**15**	**22**	
Myoglobin (local)	X				X		Refer to Attachment 2. If serum CK Grade ≥ 2, test for serum and urine myoglobin.
CTCAE v4.0 grading	X			X	X	X	Throughout study as needed. Refer to Section 8.1.1 for reporting guidelines.
Concomitant medications	X			X	X	X	Throughout study as needed.
LY3022855 administration	Refer to Table JSCC.2 for dose frequency during Part A.						For LY3022855 and tremelimumab: Part A doses: Refer to Table JSCC.2.
Tremelimumab administration	X						
Pharmacokinetics							
LY3022855 (predose on dosing days, unless noted otherwise)	X	X 2 h post-EOI C1D1 (±1 h)	X 24 h post-EOI C1D1 (±4 h)	X 48 h post-EOI C1D1 (±4 h)	X	X	X	The date and the time of all samples must be clearly and accurately recorded. EOI = end of infusion
Tremelimumab (predose on dosing days, unless noted otherwise)	X	X Simultaneously with LY PK sample	X Simultaneously with LY PK sample	X Simultaneously with LY PK sample	X	X	X	
Pharmacodynamics and tailoring							
Serum	X	X Simultaneously with LY PK sample	X Simultaneously with LY PK sample	X Simultaneously with LY PK sample	X	X	X	Serum storage for correlative studies.
Plasma	X							Plasma storage for correlative studies.
Whole blood	X	X			X			Gene expression analysis and other exploratory research.
Flow cytometry							
Immunophenotyping #1	X			X	X	X	CD14, CD16.
Immunophenotyping #2	X			X	X	X	TBNK & T cell subset/activation panels
Immunophenotyping #3	X						MDSC panel.
Isoenzymes (central)							*Refer to Attachment 2. Obtain at additional time points, as clinically indicated.*
LVEF evaluation							*Echocardiogram or MUGA scan. Obtain at additional time points, as clinically indicated.*

LY3022855 plus Tremelimumab Assessment (central or local laboratory indicated, if applicable)	**Cycle 1 (Visit 1)**						**Comments** Except for the Cycle 1, Day 1 visit, allowable windows are ±3 days, unless otherwise indicated. On dosing days, all assessments to be performed preinfusion, unless stated otherwise.
Relative day within a 28-day cycle:	**1**	**2**	**3**	**8**	**15**	**22**	
Radiographic tumor assessment (CT/MRI)							*Perform every 8 wk (±7 d), starting on Cycle 2, Day 22.*
Tumor measurement (palpable or visible)							
Tumor biopsy							*For Part A (all cohorts) and Part B (ovarian cancer cohort only): An on-treatment tumor core needle or excisional biopsy to be performed 6-8 wk after starting study treatment.*

LY3022855 plus Tremelimumab Assessment (central or local laboratory indicated, if applicable)	**Cycle 2 (Visit 2)**						**Comments** Except for the Cycle 1, Day 1 visit, allowable windows are ±3 days, unless otherwise indicated. On dosing days, all assessments to be performed preinfusion, unless stated otherwise.
Relative day within a 28-day cycle:	**1**	**8**	**9**	**10**	**15**	**22**	
Physical examination	X	X			X	X	Targeted physical examination (on the basis of clinical observations and symptomatology).
Vital signs	X	X			X	X	BP, temperature, RR, PR, and weight. Vital signs (BP, RR, and PR only) to be measured around infusions as follows (allowable window ±10 min): Around each LY3022855 infusion: prior to, during (midway through), at the end, and 30 min after the end. Around each tremelimumab infusion (based on a 60-min infusion): within 30 min prior to, during (approx. 30 min after start of infusion), and at the end (approx. 60 min after start of infusion). 1-h Observation period after tremelimumab infusion: at 30 and 60 min after the end of the infusion (90 and 120 min after start of infusion) for the first tremelimumab infusion only, and for subsequent infusions as clinically indicated. If the tremelimumab infusion exceeds 60 min, monitoring of BP and PR should occur per the preceding principles or more frequently if clinically indicated.
ECOG performance status	X						
Pregnancy test (local)							*Every 12 wk (±7 d) after the first dose of study drug or according to local regulations or as clinically indicated, whichever is more frequent. Urine hCG or serum β-hCG.*
ECG (local)	X						Single ECG. Obtain ECGs before any associated blood draws. ECG should be taken within 2 h prior to the start of the LY3022855 infusion and at least one time point 0-3 h after the tremelimumab infusion. Additional ECGs to be obtained as clinically indicated.
Hematology (local)	X	X			X	X	Refer to Attachment 2.
Serum chemistry (local) - safety labs for dosing	X	X			X	X	Refer to Attachment 2. Results must be available and reviewed before administering study drug.
Serum chemistry (central)	X	X			X	X	Refer to Attachment 2.

LY3022855 plus Tremelimumab Assessment (central or local laboratory indicated, if applicable)	**Cycle 2 (Visit 2)**						**Comments** Except for the Cycle 1, Day 1 visit, allowable windows are ±3 days, unless otherwise indicated. On dosing days, all assessments to be performed preinfusion, unless stated otherwise.
Relative day within a 28-day cycle:	**1**	**8**	**9**	**10**	**15**	**22**	
Urinalysis (local)	X						Refer to Attachment 2. To be performed at Screening, at C1D1, and every 4 wk thereafter. Additional assessments as clinically indicated. Results need not be available before administering study drug.
Coagulation (local)	X						Refer to Attachment 2. Obtain prior to tumor biopsy. Additional assessments as clinically indicated.
Thyroid function (central)	X						Refer to Attachment 2. Free T3 and free T4 will be measured only if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
Pancreas function (central)	X						Refer to Attachment 2.
Tumor markers (local)	X						If applicable.
Pharmacogenetic sample							*Refer to the laboratory manual. Collect once. Sample can be collected at any time, if not collected on C1D1.*
Immunogenicity		X					If at any time a patient experiences an IRR, attempts to obtain a blood sample for immunogenicity analysis as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. A portion of the sample taken for immunogenicity testing may be used for PK analysis.
Myoglobin (local)	X	X			X	X	Refer to Attachment 2. If serum CK Grade ≥2, test for serum and urine myoglobin.
CTCAE v4.0 grading	X	X			X	X	Throughout study as needed. Refer to Section 8.1.1 for reporting guidelines.
Concomitant medications	X	X			X	X	Throughout study as needed.
LY3022855 administration	Refer to Table JSCC.2 for dose frequency during Part A.						For LY3022855 and tremelimumab: Part A doses: Refer to Table JSCC.2.
Tremelimumab administration	X						
Pharmacokinetics							
LY3022855 (predose on dosing days, unless noted otherwise)	X	X	X 2 h post-EOI C2D8 (±1 h)	X 24 h post-EOI C2D8 (±4 h)	X 48 h post-EOI C2D8 (±4 h)	X	The date and the time of all samples must be clearly and accurately recorded. EOI = end of infusion
Tremelimumab (predose on dosing days, unless noted otherwise)	X	X	X Simultaneously with LY PK sample	X Simultaneously with LY PK sample	X Simultaneously with LY PK sample	X	

LY3022855 plus Tremelimumab Assessment (central or local laboratory indicated, if applicable)	**Cycle 2 (Visit 2)**						**Comments** Except for the Cycle 1, Day 1 visit, allowable windows are ±3 days, unless otherwise indicated. On dosing days, all assessments to be performed preinfusion, unless stated otherwise.
Relative day within a 28-day cycle:	**1**	**8**	**9**	**10**	**15**	**22**	
Pharmacodynamics and tailoring							
Serum	X	X	X Simultaneously with LY PK sample	X Simultaneously with LY PK sample	X Simultaneously with LY PK sample	X	Serum storage for correlative studies.
Plasma		X					Plasma storage for correlative studies.
Whole blood	X				X		Gene expression analysis and other exploratory research.
Flow cytometry							
Immunophenotyping #1	X	X			X		CD14, CD16.
Immunophenotyping #2	X	X			X		TBNK & T cell subset/activation panels.
Immunophenotyping #3	X						MDSC panel.
Isoenzymes (central)	X						Refer to Attachment 2. Obtain at additional time points, as clinically indicated.
LVEF evaluation						X	Echocardiogram or MUGA scan. Obtain at additional time points, as clinically indicated.
Radiographic tumor assessment (CT/MRI)						X	Perform every 8 wk (±7 d), starting on Cycle 2, Day 22.
Tumor measurement (palpable or visible)						X	
Tumor biopsy		X					For Part A (all cohorts) and Part B (ovarian cancer cohort only): An on-treatment tumor core needle or excisional biopsy to be performed 6-8 wk after starting study treatment; that is, at Cycle 2, between Days 8 and 22.

LY3022855 plus Tremelimumab Assessment (central or local laboratory indicated, if applicable)	**Cycle 3 (Visit 3)**				**Cycle 4 (Visit 4)**				**Cycle 5 (Visit 5)**				**Comments** Except for the Cycle 1, Day 1 visit, allowable windows are ±3 days, unless otherwise indicated. On dosing days, all assessments to be performed preinfusion, unless stated otherwise.
Relative day within a 28-day cycle:	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	
Physical examination	X				X				X				Targeted physical examination (on the basis of clinical observations and symptomatology).
Vital signs	X				X				X				BP, temperature, RR, PR, and weight. Vital signs (BP, RR, and PR only) to be measured around infusions as follows (allowable window ±10 min): Around each LY3022855 infusion: prior to, during (midway through), at the end, and 30 min after the end. Around each tremelimumab infusion (based on a 60-min infusion): within 30 min prior to, during (approx. 30 min after start of infusion), and at the end (approx. 60 min after start of infusion). 1-h Observation period after tremelimumab infusion: at 30 and 60 min after the end of the infusion (90 and 120 min after start of infusion) for the first tremelimumab infusion only, and for subsequent infusions as clinically indicated. If the tremelimumab infusion exceeds 60 min, monitoring of BP and PR should occur per the preceding principles or more frequently if clinically indicated.
ECOG performance status	X				X				X				
Pregnancy test (local)					X								Every 12 wk (±7 d) after the first dose of study drug or according to local regulations or as clinically indicated, whichever is more frequent. Urine hCG or serum β-hCG.
ECG (local)													*Additional ECGs to be obtained as clinically indicated.*
Hematology (local)	X	X	X	X	X	X	X	X	X		X		Refer to Attachment 2.
Serum chemistry (local) - safety labs for dosing	X	X	X	X	X	X	X	X	X		X		Refer to Attachment 2. Results must be available and reviewed before administering study drug.

LY3022855 plus Tremelimumab Assessment (central or local laboratory indicated, if applicable)	**Cycle 3 (Visit 3)**				**Cycle 4 (Visit 4)**				**Cycle 5 (Visit 5)**				**Comments** Except for the Cycle 1, Day 1 visit, allowable windows are ±3 days, unless otherwise indicated. On dosing days, all assessments to be performed preinfusion, unless stated otherwise.
Relative day within a 28-day cycle:	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	
Serum chemistry (central)	X	X	X	X	X	X	X	X	X		X		Refer to Attachment 2.
Urinalysis (local)	X				X				X				Refer to Attachment 2. To be performed at Screening, at C1D1, and every 4 wk thereafter. Additional assessments as clinically indicated. Results need not be available before administering study drug.
Coagulation (local)													*Refer to Attachment 2. As clinically indicated.*
Thyroid function (central)	X				X				X				Refer to Attachment 2. Free T3 and free T4 will be measured only if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
Pancreas function (central)	X				X								Refer to Attachment 2.
Tumor markers (local)	X				X				X				If applicable.
Pharmacogenetic sample													*Refer to the laboratory manual. Collect once. Sample can be collected at any time, if not collected on C1D1.*
Immunogenicity	X												If at any time a patient experiences an IRR, attempts to obtain a blood sample for immunogenicity analysis as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. A portion of the sample taken for immunogenicity testing may be used for PK analysis.
Myoglobin (local)	X												Refer to Attachment 2. If serum CK Grade ≥2, test for serum and urine myoglobin.
CTCAE v4.0 grading	X	X	X	X	X	X	X	X	X	X	X	X	Throughout study as needed. Refer to Section 8.1.1 for reporting guidelines.
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	Throughout study as needed.
LY3022855 administration	Refer to Table JSCC.2 for dose frequency during Part A.												For LY3022855 and tremelimumab: Part A doses: Refer to Table JSCC.2.
Tremelimumab administration	X				X				X				

LY3022855 plus Tremelimumab Assessment (central or local laboratory indicated, if applicable)	**Cycle 3 (Visit 3)**				**Cycle 4 (Visit 4)**				**Cycle 5 (Visit 5)**				**Comments** Except for the Cycle 1, Day 1 visit, allowable windows are ±3 days, unless otherwise indicated. On dosing days, all assessments to be performed preinfusion, unless stated otherwise.
Relative day within a 28-day cycle:	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	
Pharmacokinetics													
LY3022855 (predose on dosing days, unless noted otherwise)	X				X								The date and the time of all samples must be clearly and accurately recorded.
Tremelimumab (predose on dosing days, unless noted otherwise)	X				X								
Pharmacodynamics and tailoring													
Serum	X				X								Serum storage for correlative studies.
Plasma													*Plasma storage for correlative studies.*
Flow cytometry													
Immunophenotyping #1	X				X								CD14, CD16.
Immunophenotyping #2	X				X								TBNK & T cell subset/activation panels.
Immunophenotyping #3	X												MDSC panel.
Isoenzymes (central)													*Refer to Attachment 2. Obtain at additional time points, as clinically indicated.*
LVEF evaluation													*Echocardiogram or MUGA scan. Obtain at additional time points, as clinically indicated.*
Radiographic tumor assessment (CT/MRI)								X					Perform every 8 wk (±7 d), starting Cycle 2, Day 22.
Tumor measurement (palpable or visible)								X					
Tumor biopsy													*For Part A (all cohorts) and Part B (ovarian cancer cohort only): An on-treatment tumor core needle or excisional biopsy to be performed 6-8 wk after starting study treatment.*

LY3022855 plus Tremelimumab Assessment (central or local laboratory indicated, if applicable)	**Cycle 6 (Visit 6)**				**Cycle 7-n (Visit 7-n)**				**Short-Term Follow-Up[a] (Visits 801 and 802)**		**Comments** Except for the Cycle 1, Day 1 visit, allowable windows are ±3 days, unless otherwise indicated. On dosing days, all assessments to be performed preinfusion, unless stated otherwise.
Relative day within a 28-day cycle:	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**30-Day (±7 d)**	**90-Day* ±7 d)**	*90-Day Follow-Up visit is only for tremelimumab safety.
Physical examination	X				X				X		Targeted physical examination (on the basis of clinical observations and symptomatology).
Vital signs	X				X				X		BP, temperature, RR, PR, and weight. Vital signs (BP, RR, and PR only) to be measured around infusions as follows (allowable window ±10 min): Around each LY3022855 infusion: prior to, during (midway through), at the end, and 30 min after the end. Around each tremelimumab infusion (based on a 60-min infusion): within 30 min prior to, during (approx. 30 min after start of infusion), and at the end (approx. 60 min after start of infusion). 1-h Observation period after tremelimumab infusion: at 30 and 60 min after the end of the infusion (90 and 120 min after start of infusion) for the first tremelimumab infusion only, and for subsequent infusions as clinically indicated. If the tremelimumab infusion exceeds 60 min, monitoring of BP and PR should occur per the preceding principles or more frequently if clinically indicated.
ECOG performance status	X				X				X	X*	*Performed at 90-day follow-up, only for patients who discontinue study treatment due to toxicity, in the absence of confirmed disease progression.
Pregnancy test (local)									X		Every 12 wk (±7 d) after the first dose of study drug or according to local regulations or as clinically indicated, whichever is more frequent. Urine hCG or serum β-hCG.
ECG (local)									X		Single ECG. Obtain ECGs before any associated blood draws. Additional ECGs to be obtained as clinically indicated.
Hematology (local)	X		X		X		X		X	X	Refer to Attachment 2.
Serum chemistry (local) - safety labs for dosing	X		X		X		X				Refer to Attachment 2. Results must be available and reviewed before administering study drug.
Serum chemistry (central)	X		X		X		X		X	X	Refer to Attachment 2.

LY3022855 plus Tremelimumab Assessment (central or local laboratory indicated, if applicable)	**Cycle 6 (Visit 6)**				**Cycle 7-n (Visit 7-n)**				**Short-Term Follow-Up[a] (Visits 801 and 802)**		**Comments** Except for the Cycle 1, Day 1 visit, allowable windows are ±3 days, unless otherwise indicated. On dosing days, all assessments to be performed preinfusion, unless stated otherwise.
Relative day within a 28-day cycle:	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**30-Day (±7 d)**	**90-Day* ±7 d)**	*90-Day Follow-Up visit is only for tremelimumab safety.
Urinalysis (local)	X				X				X		Refer to Attachment 2. To be performed at Screening, at C1D1, and every 4 wk thereafter. Additional assessments as clinically indicated. Results need not be available before administering study drug.
Coagulation (local)											*Refer to Attachment 2. As clinically indicated.*
Thyroid function (central)	X				X				X		Refer to Attachment 2. Free T3 and free T4 will be measured only if TSH is abnormal or if there is clinical suspicion of an adverse event related to the endocrine system.
Pancreas function (central)									X		Refer to Attachment 2. Only if amylase and lipase previously noted to be elevated above normal limits.
Tumor markers (local)	X				X						If applicable.
Pharmacogenetic sample											*Refer to the laboratory manual. Collect once. Sample can be collected at any time, if not collected on C1D1.*
Immunogenicity	X								X	X	If at any time a patient experiences an IRR, attempts to obtain a blood sample for immunogenicity analysis as close to the onset of the event as possible, at the resolution of the event, and 30 d following the event. A portion of the sample taken for immunogenicity testing may be used for PK analysis. To be drawn every 6 mo following Cycle 6.
Myoglobin (local)	X										Refer to Attachment 2. If serum CK Grade ≥2, test for serum and urine myoglobin.
CTCAE v4.0 grading	X	X	X	X	X	X	X	X	X		Throughout study as needed. Refer to Section 8.1.1 for reporting guidelines.
Concomitant medications	X	X	X	X	X	X	X	X	X		Throughout study as needed.
LY3022855 administration	Refer to Table JSCC.2 for dose frequency during Part A.										For LY3022855 and tremelimumab: Part A doses: Refer to Table JSCC.2. Tremelimumab note: Starting at C7 (that is, after 6 doses), tremelimumab is to be administered once every 12 wk.
Tremelimumab administration	X				X						
Pharmacokinetics											
LY3022855									X		The date and the time of all samples must be clearly and accurately recorded.
Tremelimumab									X		
Pharmacodynamics and tailoring											

LY3022855 plus Tremelimumab Assessment (central or local laboratory indicated, if applicable)	**Cycle 6 (Visit 6)**				**Cycle 7-n (Visit 7-n)**				**Short-Term Follow-Up[a] (Visits 801 and 802)**		**Comments** Except for the Cycle 1, Day 1 visit, allowable windows are ±3 days, unless otherwise indicated. On dosing days, all assessments to be performed preinfusion, unless stated otherwise.
Relative day within a 28-day cycle:	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**30-Day (±7 d)**	**90-Day* ±7 d)**	*90-Day Follow-Up visit is only for tremelimumab safety.
Serum									X		Serum storage for correlative studies.
Plasma									X		Plasma storage for correlative studies.
Whole blood									X		Exploratory research.
Flow cytometry											
Immunophenotyping #1											*CD14, CD16.*
Immunophenotyping #2											*TBNK & T cell subset / activation panels.*
Immunophenotyping #3											*MDSC panel.*
Isoenzymes (central)											*Refer to Attachment 2. Obtain at additional time points, as clinically indicated.*
LVEF evaluation											*Echocardiogram or MUGA scan. Obtain at additional time points, as clinically indicated.*
Radiographic tumor assessment (CT/MRI)				X				X	X		Perform every 8 wk (±7 d), starting on Cycle 2, Day 22, then every 12 wk (±7 d) for patients who achieve disease control after 12 mo of study treatment and after Week 48 for patients who discontinue tremelimumab due to toxicity or symptomatic deterioration. For patients who continue on tremelimumab post-confirmed progression at the investigator's discretion (after consultation with the sponsor), tumor assessments should be performed until tremelimumab is stopped.
Tumor measurement (palpable or visible)				X				X	X		
Tumor biopsy											*For Part A (all cohorts) and Part B (ovarian cancer cohort only): An on-treatment tumor core needle or excisional biopsy to be performed 6-8 wk after starting study treatment.*

Abbreviations: AE = adverse event; BP = blood pressure; CnDn = Cycle n, Day n (for example, C1D1 = Cycle 1, Day 1); CK = creatine kinase; CT = computed tomography (scan); CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; hCG = human chorionic gonadotropin; IRR = infusion-related reaction; LVEF = left ventricular ejection fraction; LY = LY3022855; MDSC = myeloid-derived suppressor cell; MRI = magnetic resonance imaging; MUGA = multigated acquisition (scan); NCI = National Cancer Institute; PK = pharmacokinetic(s); PR = pulse rate; RR = respiration rate; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; v4.0 = Version 4.0 of NCI-CTCAE.

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

Continued Access Schedule for Combination Therapy: LY3022855 plus Tremelimumab

Visit	Continued Access Treatment Period 501-5XX	Continued Access Follow-Up[a] 901 (30 d) and 902* (90 d) (±7 d)	*90-Day Follow-Up visit (Visit 902) is only for tremelimumab safety.
Procedure[b]			**Instructions**
AE collection	X	X	CTCAE v4.0. Refer to Section 8.1.1 for reporting guidelines.
Pharmacokinetics and immunogenicity		X	If a patient experiences an IRR, collect blood samples for PK and immunogenicity analysis at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 days after the IRR.
Administer LY3022855 and tremelimumab	X		Refer to Table JSCC.2 for dose frequency of LY3022855 during Part A. For LY3022855 and tremelimumab: Part A doses: Refer to Table JSCC.2. If the patient has reached Cycle 7 or beyond in the main study, prior to the start of the Continued Access period, the patient will continue to receive tremelimumab in the Continued Access period according to their most recent dosing in the main study; continue dosing every 3 cycles.

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; IRR = infusion-related reaction.

[a] Continued access follow-up Visit 901 begins 1 day after the patient and the investigator agree that the patient will no longer continue treatment in the continued access period and lasts approximately 30 days. Visit 902 occurs 90 days (±7 days) after the patient and the investigator agree that the patient will no longer continue treatment in the continued access period. No follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

[b] Efficacy assessments will be done at the investigator's discretion based on the standard of care.

Attachment 2. Protocol JSCC Clinical Laboratory Tests

Clinical Laboratory Tests - Assayed by Local Laboratory (local or investigator-designated laboratory)

Hematology

- Hemoglobin
- Hematocrit
- Erythrocyte count (RBC)
- Leukocytes (WBC)
- Neutrophils
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils
- Platelets
- Mean corpuscular hemoglobin
- Mean corpuscular hemoglobin concentration
- Mean corpuscular volume

Coagulation

- aPTT
- PT, INR

Urinalysis[a]

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

Serum Chemistry

- Sodium
- Potassium
- Chloride
- Bicarbonate
- Total bilirubin
- Alkaline phosphatase
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Albumin
- Total protein
- Blood urea nitrogen
- Creatinine
- Glucose, random
- Creatine kinase

Serum or Urine Pregnancy Test (females only)

Myoglobin

- Serum myoglobin
- Urine myoglobin

Serologies

- HIV screening

Clinical Laboratory Tests - Assayed by Central Laboratory [b] (sponsor-designated laboratory)

Serum Chemistry

- Sodium
- Magnesium
- Potassium
- Calcium
- Chloride
- Bicarbonate
- Total bilirubin[c]
- Alkaline phosphatase
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Gamma-glutamyl transpeptidase (GGT)[d]
- Albumin
- Total protein
- Blood urea nitrogen
- Creatinine
- Uric acid
- Glucose, random
- Creatine kinase

Thyroid Function

- Thyroid-stimulating hormone
- Free T3
- Free T4

Isoenzymes

- Alkaline phosphatase isoenzymes
- Total creatine kinase
- Creatine kinase isoenzymes
- Total LDH
- LDH isoenzymes

Pancreas Function

- Amylase
- Lipase

Abbreviations: aPTT = activated partial thromboplastin time; HIV = human immunodeficiency virus; INR = international normalized ratio; LDH = lactate dehydrogenase; PT = prothrombin time; T3 = triiodothyronine; T4 = thyroxine; ULN = upper limit of normal.

[a] Microscopy should be used as appropriate to investigate WBCs and use the high power field for RBCs.

[b] Results will be confirmed by the central laboratory at the time of initial testing.

[c] If total bilirubin $\geq 2 \times$ ULN (and no evidence of Gilbert's syndrome), fractionate into direct and indirect bilirubin.

[d] At baseline and as clinically indicated.

Attachment 3. Protocol JSCC Hepatic Monitoring Tests for Treatment Emergent Abnormality

Selected tests may be obtained in the event of a treatment emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly CRP/CRS.

Hepatic Monitoring Tests

Hepatic Chemistry[a]	**Hepatic Serologies**[a,b]
Total bilirubin	Hepatitis A antibody, total
Direct bilirubin	Hepatitis A antibody, IgM
Alkaline phosphatase	Hepatitis B surface antigen
ALT	Hepatitis B surface antibody
AST	Hepatitis B core antibody
GGT	Hepatitis B virus
CK	Hepatitis C virus
	Hepatitis C antibody
Haptoglobin[a]	Hepatitis E antibody, IgG
	Hepatitis E antibody, IgM
Hepatic Coagulation[a]	
PT, INR	**Anti-actin antibody**
	Anti-nuclear antibody[a]
	Anti-smooth muscle antibody[a]

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; CRP = clinical research physician; CRS = clinical research scientist; GGT = gamma-glutamyl transferase (also known as gamma-glutamyl transpeptidase); Ig = immunoglobulin; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; PT = prothrombin time.

[a] Assayed by Lilly-designated or local laboratory.

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

Attachment 4. Protocol JSCC Recommendations for Reporting Serious Adverse Events

Recommendations for Reporting Serious Adverse Events

When contacting Lilly to report an SAE, please have the following information available:

Patient Demographics

- patient identification (number), sex, date of birth, origin, height, and weight

Study Identification

- full trial protocol number, investigator's name, investigator's number

Study Drug

- drug code or drug name, unit dose, total daily dose, frequency, route, start dose, cycle details, start date and last dose date (if applicable)

Adverse Event

- description, date of onset, severity, treatment (including hospitalization), action taken with respect to study drug, clinical significance, test and procedure results (if applicable)

Relationship to Study Drug and Protocol Procedures

Concomitant Drug Therapy

- indication, total daily dose, duration of treatment, start date, action taken

In Case of Death

- cause, autopsy finding (if available), date, relationship to study drug and protocol procedures.

Attachment 5. Protocol JSCC ECOG Performance Status

Eastern Cooperative Oncology Group (ECOG) Performance Status

Activity Status	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out performance of a light or sedentary nature, for example, light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken et al. 1982.

Attachment 6. Protocol JSCC Creatinine Clearance Formula

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation (2009) is based on the same 4 variables as the Modification of Diet in Renal Disease (MDRD) Study equation, but uses a 2-slope spline to model the relationship between estimated glomerular filtration rate (GFR) and serum creatinine, and a different relationship for age, sex, and race. The equation was reported to perform better and with less bias than the MDRD Study equation, especially in patients with higher GFR. This results in reduced misclassification of CKD. As of November 2009, very few clinical laboratories report the estimated GFR using the CKD-EPI creatinine equation. In the future, other GFR estimating equations may outperform CKD-EPI.

The CKD-EPI creatinine equation is as follows:

GFR = 141 X min(SCr/κ, 1)$^{\alpha}$ X max(SCr/κ, 1)$^{-1.209}$ X 0.993^{Age} X 1.018 [if female**] X 1.0159 [**if black**]**

κ = 0.7 if female
κ = 0.9 if male

α = -0.329 if female
α = -0.411 if male

min = the minimum of **SCr/κ or 1**
max = the maximum of **SCr/κ or 1**

SCr = serum creatinine **(mg/dL)**

Source: Levey et al. 2009.

Attachment 7. Protocol JSCC Toxicity Management Guidelines

Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non Immune-Mediated Reactions (Combination Therapy with LY3022855 and Durvalumab or LY3022855 and Tremelimumab)

General Considerations

Dose Modifications		Toxicity Management
Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03. In addition to the criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions: • Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) **within 12 weeks** after last dose of study drug/study regimen • Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing		It is recommended that management of immune-mediated adverse events (imAEs) follows the guidelines presented in this table: – It is possible that events with an inflammatory or immune-mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines. – Whether specific immune-mediated events (and/or laboratory indicators of such events) are noted in these guidelines or not, patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) to a possible immune-mediated event. In the absence of a clear alternative etiology, all such events should be managed as if they were immune related. General recommendations follow. – Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events. – For persistent (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Some events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – should implement high-dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation. – If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [eg, up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (>28 days of taper). – More potent immunosuppressives such as TNF inhibitors (eg, infliximab) (also refer to the individual sections of the imAEs for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the
Grade 1	No dose modification	
Grade 2	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per Investigator or treating physician's clinical judgement. 3. Doses of prednisone are at ≤10 mg/day or equivalent.	
Grade 3	Depending on the individual toxicity, study drug/study regimen	

Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non Immune-Mediated Reactions (Combination Therapy with LY3022855 and Durvalumab or LY3022855 and Tremelimumab)

General Considerations

Dose Modifications	Toxicity Management
may be permanently discontinued. Please refer to guidelines below. **Grade 4** Permanently discontinue study drug/study regimen. Note: For Grade ≥3 asymptomatic amylase or lipase levels, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed. Note: Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines. Similarly, consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper. Note: There are some exceptions to permanent discontinuation of study drug for Grade 4 events (i.e., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus).	guidelines – when these events are not responding to systemic steroids. – With long-term steroid and other immunosuppressive use, consider need for Pneumocystis jirovecii pneumonia (PJP, formerly known as Pneumocystis carinii pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring. – Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (eg, inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit/risk analysis for that patient.

Abbreviations: AE = Adverse event; CTC = Common Toxicity Criteria; CTCAE = Common Terminology Criteria for Adverse Events; imAE = immune-mediated adverse event; IV = intravenous; NCI = National Cancer Institute; PO = By mouth.

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high- resolution CT scan.
	Grade 1 (asymptomatic, clinical or diagnostic observations only; intervention not indicated)	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1 (radiographic changes only):** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated. – Consider Pulmonary and Infectious disease consult.
	Grade 2 (symptomatic; medical intervention indicated; limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	**For Grade 2 (mild to moderate new symptoms):** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (eg, prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated. – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started – If still no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of

			cancer-related infections [Category 2B recommendation])[a] – Consider pulmonary and infectious disease consult. – Consider, as necessary, discussing with study physician.
	Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [eg, tracheostomy or intubation])	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):** – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious disease consult; consider, as necessary, discussing with study physician. – Hospitalize the patient. – Supportive care (eg, oxygen). – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks' dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Diarrhea/Colitis	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, or infections), including testing for clostridium difficile toxin, etc. – Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade event. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.

	Grade 1 (Diarrhea: stool frequency of <4 over baseline per day) (Colitis: asymptomatic; clinical or diagnostic observations only)	No dose modifications.	**For Grade 1:** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.
	Grade 2 (Diarrhea: stool frequency of 4 to 6 over baseline per day) (Colitis: abdominal pain; mucus or blood in stool)	Hold study drug/study regimen until resolution to Grade ≤1 • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide and/or budesonide. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg once every 2 weeks[a]. **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Consider, as necessary, discussing with study physician if no resolution to Grade ≤1 in 3 to 4 days. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (Grade 3 diarrhea: stool frequency of ≥7 over baseline per day; Grade 4 diarrhea:	**Grade 3** Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days; study drug/study	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – Urgent GI consult and imaging and/or colonoscopy as appropriate.

	life-threatening consequences) (Grade 3 colitis: severe abdominal pain, change in bowel habits, medical intervention indicated, peritoneal signs; Grade 4 colitis: life-threatening consequences, urgent intervention indicated)	regimen can be resumed after completion of steroid taper. **Grade 4** Permanently discontinue study drug/study regimen.	– If still no improvement within 3 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (eg infliximab at 5 mg/kg once every 2 weeks). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis.	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (eg, viral hepatitis, disease progression, concomitant medications).
	Grade 1 (AST or ALT >ULN and ≤3.0×ULN and/or TB > ULN and ≤1.5×ULN)	• No dose modifications. • If it worsens, then treat as Grade 2 event.	**For Grade 1:** – Continue LFT monitoring per protocol.
	Grade 2 (AST or ALT >3.0×ULN and ≤5.0×ULN and/or TB >1.5×ULN and ≤3.0×ULN)	• Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1 or baseline, resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Regular and frequent checking of LFTs (eg, every 1 to 2 days) until elevations of these are improving or resolved. – If no resolution to Grade ≤1 in 1 to 2 days, consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and start prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to

		For asymptomatic Grade 2 AST (only if accompanied by Grade ≤ 1 ALT and Grade ≤ 1 TB and no change of ALT or TB from baseline levels):	4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (ie, mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
		• Continue dosing with both LY3022855 and durvalumab or tremelimumab	– Monitor LFTs frequently (eg, every 1 to 2 days or as clinically indicated). – Consider hepatic consult – No steroids required
	Grade 3 or 4 (Grade 3: AST or ALT >5.0×ULN and ≤20.0×ULN and/or TB >3.0×ULN and ≤10.0×ULN) (Grade 4: AST or ALT >20×ULN and/or TB >10×ULN)	**For Grade 3:** For elevations in transaminases ≤8 × ULN, or elevations in bilirubin ≤5 × ULN: • Hold study drug/study regimen dose until resolution to Grade ≤1 or baseline • Resume study drug/study regimen if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days **For asymptomatic Grade 3 AST up to ≤8 × ULN (only if accompanied by Grade ≤ 1 ALT and Grade ≤ 1 TB and no change of ALT or TB from**	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If still no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (ie, mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Perform hepatology consult, abdominal workup, and imaging as appropriate. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

		baseline levels) • Hold LY3022855, and continue dosing with durvalumab or tremelimumab. • If AST downgrades to Grade ≤2, after holding LY3022855, resume dosing with LY3022855 and durvalumab or tremelimumab. • If Grade 3 AST recurs after resumption of dosing with both agents, hold LY3022855 dosing. Continue dosing durvalumab or tremelimumab. Resume treatment with the combination of LY3022855 and durvalumab or tremelimumab if AST remains asymptomatic and downgrades to Grade ≤2. For elevations in transaminases >8 × ULN or elevations in bilirubin >5 × ULN, discontinue study drug/study regimen. Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (ie, elevated alkaline P04) and in the absence of any alternative cause.[b] **For Grade 4:** Permanently discontinue study drug/study regimen.	– Monitor LFTs frequently (eg, every 1 to 2 days or as clinically indicated). – Evaluate for alternative etiologies (eg, viral hepatitis, disease progression, concomitant medications, history of alcohol intake). – Promptly seek hepatic consult as necessary. – No steroids required.

Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade**	**General Guidance**	**For Any Grade:** – Consult with nephrologist. – Monitor for signs and symptoms that may be related to changes in renal function (eg, routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria). – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression or infections). – Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.
	Grade 1 (Serum creatinine > 1 to 1.5 × baseline; > ULN to 1.5 × ULN)	No dose modifications.	**For Grade 1:** – Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.
	Grade 2 (serum creatinine >1.5 to 3.0 × baseline; >1.5 to 3.0 × ULN)	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

			– When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4 (Grade 3: serum creatinine >3.0 × baseline; >3.0 to 6.0 × ULN; Grade 4: serum creatinine >6.0 × ULN)	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Carefully monitor serum creatinine on daily basis. – Consult nephrologist and consider renal biopsy if clinically indicated. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Rash (excluding bullous skin formations)	**Any Grade** (refer to NCI CTCAE v 4.03 for definition of severity/grade depending on type of skin rash)	**General Guidance**	**For Any Grade:** – Monitor for signs and symptoms of dermatitis (rash and pruritus). – IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED.**
	Grade 1	No dose modifications.	**For Grade 1:** – Consider symptomatic treatment, including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream).
	Grade 2	For persistent (>1 to 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid	**For Grade 2:** – Obtain dermatology consult. – Consider symptomatic treatment, including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream). – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing with study physician and promptly start systemic

		taper.	steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs.
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen until resolution to Grade ≤1 or baseline. If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to Grade ≤1 or baseline within 30 days, then permanently discontinue study drug/study regimen. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Consult dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – Consider, as necessary, discussing with study physician.
Endocrinopathy (eg, hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased also included in this section)	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – Consider consulting an endocrinologist for endocrine events. – Consider, as necessary, discussing with study physician. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression including brain metastases, or infections). – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (eg, blood glucose and ketone levels, HbA1c). – For modest asymptomatic elevations in serum amylase and

			lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – If a patient experiences an AE that is thought to be possibly of autoimmune nature (eg, thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.
	Grade 1	No dose modifications.	**For Grade 1 (including those with asymptomatic TSH elevation):** – Monitor patient with appropriate endocrine function tests. – For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5 × LLN, or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
	Grade 2	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until patient is clinically stable. • If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (eg, adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating	**For Grade 2 (including those with symptomatic endocrinopathy):** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short-term corticosteroids (eg, 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (eg, hydrocortisone, sex hormones). – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

		physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	– For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
	Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgment. 3. Doses of prednisone are ≤10 mg/day or equivalent.	**For Grade 3 or 4:** Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. – For all patients with abnormal endocrine workup, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (e.g., hydrocortisone, sex hormones). – For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Neurotoxicity (to include but not be limited to limbic encephalitis and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	**Any Grade** (depending on the type of neurotoxicity, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	General Guidance	**For Any Grade:** – Patients should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes, or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (eg, electromyogram and nerve conduction investigations). – Perform symptomatic treatment with neurological consult as appropriate.

	Grade 1	No dose modifications.	**For Grade 1:** – See "Any Grade" recommendations above.
	Grade 2	For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1. For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or 4. Study drug/study regimen can be resumed once event improves to Grade ≤1 and after completion of steroid taper.	**For Grade 2:** – Consider, as necessary, discussing with the study physician. – Obtain neurology consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin or duloxetine). – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If no improvement within 3 to 5 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (eg, IV IG).
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Consider, as necessary, discussing with study physician. – Obtain neurology consult. – Consider hospitalization. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (eg, IV IG). – Once stable, gradually taper steroids over ≥28 days.
Peripheral neuromotor syndromes (such as Guillain-Barre and	**Any Grade**	**General Guidance**	**For Any Grade:** – The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result

myasthenia gravis)			in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. – Patients should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult. – Neurophysiologic diagnostic testing (eg, electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation. – It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 1	No dose modifications.	**For Grade 1:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult.
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	**For Grade 2:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient

			worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** – Consider, as necessary, discussing with study physician. – Recommend hospitalization. – Monitor symptoms and obtain neurological consult. *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. o If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective.

			○ Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Myocarditis	**Any Grade**	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade:** – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider, as necessary, discussing with the study physician. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (eg, pulmonary embolism, congestive heart failure, malignant pericardial effusion). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – Initial workup should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory workup as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, or infections)
	Grade 1 (asymptomatic with laboratory (e.g., BNP) or cardiac imaging abnormalities)	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic workup for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.	**For Grade 1 (no definitive findings):** - Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory workup as clinically indicated. - Consider using steroids if clinical suspicion is high.
	Grade 2, 3, or 4 (Grade 2: Symptoms with mild to moderate	- If Grade 2,- hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to	**For Grades 2 to 4:** – Monitor symptoms daily, hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac

	activity or exertion) (Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated) (Grade 4: Life-threatening consequences; urgent intervention indicated [eg, continuous IV therapy or mechanical hemodynamic support])	reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently discontinue study drug/study regimen. If Grade 3-4, permanently discontinue study drug/study regimen.	biopsy. – Supportive care (eg, oxygen). – If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Myositis/Polymyositis ("Poly/myositis")	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the study physician. – Initial workup should include clinical evaluation, creatine

			kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory workup as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider barium swallow for evaluation of dysphagia or dysphonia. Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, or infections).
	Grade 1 (mild pain)	- No dose modifications.	**For Grade 1:** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the study physician.
	Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	Hold study drug/study regimen dose until resolution to Grade ≤1. - Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 2:** – Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If clinical course is *not* rapidly progressive, start systemic steroids (eg, prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 3 to 5 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-

			PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (pain associated with severe weakness; limiting self-care ADLs)	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4:** - Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** – Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult, and complete full evaluation. – Consider, as necessary, discussing with the study physician. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Consider whether patient may require IV IG, plasmapheresis. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

[a] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD.
[b] FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.

Abbreviations: AChE = Acetylcholine esterase; ADL = Activities of daily living; AE = Adverse event; ALP = Alkaline phosphatase test; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; BUN = Blood urea nitrogen; CT = Computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; HbA1C = glycated haemoglobin; ILD = Interstitial lung disease; imAE = immune-mediated adverse event; IG = Immunoglobulin; IV = Intravenous; GI = Gastrointestinal; LFT = Liver function tests; LLN = Lower limit of normal; MRI = Magnetic resonance imaging; NCI = National Cancer Institute; NCCN = National Comprehensive Cancer Network; PJP = Pneumocystis jirovecii pneumonia (formerly known as Pneumocystis carinii pneumonia); PO = By mouth; T3 = Triiodothyronine; T4 = Thyroxine; TB = Total bilirubin; TNF = Tumor necrosis factor; TSH = Thyroid-stimulating hormone; ULN = Upper limit of normal.

Infusion-Related Reactions

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Any Grade	General Guidance	**For Any Grade:** – Manage per institutional standard at the discretion of investigator. – Monitor patients for signs and symptoms of infusion-related reactions (eg, fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (eg, generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	**For Grade 1:** The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. **For Grade 2:** The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. Subsequent infusions may be given at 50% of the initial infusion rate.	**For Grade 1 or 2:** – Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. – Consider premedication per institutional standard prior to subsequent doses. – Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 3 or 4	**For Grade 3 or 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Manage severe infusion-related reactions per institutional standards (eg, IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; IM = intramuscular; IV = intravenous; NCI = National Cancer Institute.

Non-Immune-Mediated Reactions

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (ie, events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. **For asymptomatic Grade 2 creatine kinase levels:**	Treat accordingly, as per institutional standard.
	• Hold treatment with both study agents. Perform diagnostic evaluation If results show no evidence of end organ damage, including myositis and rhabdomyolysis, resume treatment with both agents.	• Perform diagnostic evaluation (serum and urine myoglobin, BUN and creatinine) Continue to monitor CK, serum and urine myoglobin, BUN and creatinine **Weekly** until creatine kinase levels return to ≤ **Grade 1** or as clinically indicated.
Grade 3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen. **For asymptomatic Grade 3 creatine kinase levels:**	Treat accordingly, as per institutional standard.
	Hold treatment with both LY3022855 and durvalumab or tremelimumab. Perform diagnostic evaluation. • For Grade 3 elevations in CK ≤ 8X ULN with a diagnostic evaluation showing NO evidence of end organ damage including myositis or rhabdomyolysis, resume treatment with both agents. • For Grade 3 elevations in CK > 8X ULN with a diagnostic evaluation showing NO evidence of end organ damage including myositis or rhabdomyolysis, , hold LY3022855 and resume durvalumab or	• Perform diagnostic evaluation (serum and urine myoglobin, BUN and creatinine). • Continue to monitor CK, serum and urine myoglobin, BUN and creatinine Weekly until CK levels return to ≤ Grade 1 or as clinically indicated. • Treat accordingly as per institutional standard, perform a full diagnostic evaluation and if there is any evidence of potential immune-mediated end organ damage, follow the guidelines for irAE management contained in this attachment.

Non-Immune-Mediated Reactions

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	tremelimumab after discussion with sponsor. If CK decreases to ≤ 8x ULN after holding LY3022855, resume treatment with LY3022855 and durvalumab or tremelimumab. o If CK remains >8X ULN after holding LY3022855, permanently discontinue both LY3022855 and durvalumab or tremelimumab and discuss additional treatment measures with sponsor. In case of myositis or rhabdomyolysis, permanently discontinue treatment with both study agents.	• Continue to monitor CK, serum and urine myoglobin, BUN and creatinine weekly until CK levels return to ≤ Grade 1 or baseline.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.).	Treat accordingly, as per institutional standard.

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician."
Abbreviations: AE = Adverse event; BUN = elevated serum blood urea nitrogen; CK = creatinine; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute.

Attachment 8. Protocol JSCC Durvalumab and Tremelimumab AESIs

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the investigational product and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or nonserious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

AESIs for durvalumab and tremelimumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An immune-related adverse event (irAE) is defined as an adverse event (AE) that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

If the investigator has any questions in regards to an AE being an irAE, the investigator should promptly contact the study physician.

AESIs observed with durvalumab and tremelimumab include:

- Diarrhea / Colitis
- Pneumonitis / ILD (interstitial lung disease)
- ALT/AST increases / hepatitis / hepatotoxicity
- Neuropathy / neuromuscular toxicity (i.e. events of encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis)
- Endocrinopathy (i.e. events of hypophysitis, hypopituitarism, adrenal insufficiency, diabetes insipidus, type I diabetes mellitus and hyper- and hypothyroidism)
- Rash / Dermatitis
- Nephritis / Blood creatinine increases
- Pancreatitis (or labs suggestive of pancreatitis - increased serum lipase, increased serum amylase)
- Other inflammatory responses that are rare with a potential immune-mediated etiology include, but are not limited to, myocarditis, pericarditis, myositis/polymyositis, and uveitis.

Further information on these risks (eg, presenting symptoms) can be found in the current version of the durvalumab and tremelimumab IBs. For durvalumab and tremelimumab, AESIs will comprise the following:

Pneumonitis

AEs of pneumonitis are also of interest, as pneumonitis has been observed with use of anti-PD-1 mAbs (but not with anti-PD-L1 mAbs). Initial work-up should include a high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended.

Guidelines for the management of patients with immune-mediated events including pneumonitis are outlined in Section 7.2.4.

Infusion reactions

AEs of infusion reactions (also known as infusion-related reactions [IRRs]) are of special interest and are defined, for the purpose of this protocol, as all AEs occurring from the start of investigational product infusion up to 48 hours after the infusion start time. For all infusion reactions, if they qualify as SAEs, they should be reported as SAEs as described in Section 8.1.2.1.

Hypersensitivity reactions

Hypersensitivity reactions as well as IRRs have been reported with anti-PD-L1 and anti-PD-1 therapy (Brahmer et al. 2012). As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of mAbs can be caused by various mechanisms, including acute anaphylactic (IgE-mediated) and anaphylactoid reactions against the mAbs and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting, and unresponsiveness.

Guidelines for management of patients with hypersensitivity (including anaphylactic reaction) and IRRs are outlined in Section 7.2.4.

Hepatic function abnormalities (hepatotoxicity)

Hepatic function abnormality is defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in total bilirubin to be greater than 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (for example, cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product.

Guidelines for management of patients with hepatic function abnormality are outlined in Section 7.2.4.

Gastrointestinal disorders

Diarrhea/colitis is the most commonly observed treatment-emergent SAE when tremelimumab is used as monotherapy. In rare cases, colon perforation may occur that requires surgery (colectomy) or can lead to a fatal outcome if not properly managed.

Guidelines on management of diarrhea and colitis in patients receiving study treatment are provided in Section 7.2.4.

Endocrine disorders

Immune-mediated endocrinopathies include hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism. Guidelines for the management of patients with immune-mediated endocrine events are provided in Section 7.2.4.

Pancreatic disorders

Immune-mediated pancreatitis includes autoimmune pancreatitis, and lipase and amylase elevation. Guidelines for the management of patients with immune-mediated pancreatic disorders are provided in Section 7.2.4.

Neurotoxicity

Immune-mediated nervous system events include encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis. Guidelines for the management of patients with immune-mediated neurotoxic events are provided in Section 7.2.4.

Nephritis

Consult with Nephrologist. Monitor for signs and symptoms that may be related to changes in renal function (eg, routine urinalysis, elevated serum blood urea nitrogen [BUN] and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc).

Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, infections, etc).

Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2), in order to prevent potential progression to higher grade event.

Guidelines for the management of patients with immune-mediated neurotoxic events are provided in Section 7.2.4.

Immune-related adverse events

Based on the mechanism of action of durvalumab and tremelimumab leading to T cell activation and proliferation, there is a possibility of observing irAEs during the conduct of this study. Potential irAEs may be similar to those seen with the use of ipilimumab, BMS-936558 (anti-PD-1 mAb), and BMS-936559 (anti-PD-L1 mAb) and may include immune-mediated enterocolitis, dermatitis, hepatitis (hepatotoxicity), pneumonitis, and endocrinopathies (Hodi et al. 2010, Brahmer et al. 2012, Topalian et al. 2012). These AEs are inflammatory in nature and can affect any organ. With anti-PD-L1 and anti-CTLA-4 combination therapy, the occurrence of overlapping or increasing cumulative toxicities that include irAEs could potentially occur at higher frequencies than with either durvalumab or tremelimumab monotherapy. Patients should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (for example, infection or PD), an immune-related etiology should be considered for signs or symptoms of enterocolitis, dermatitis, pneumonitis, hepatitis, and endocrinopathy. In addition to the dose modification guidelines provided in Section 7.2.4, it is recommended that irAEs are managed according to the general treatment guidelines outlined for ipilimumab (Weber et al. 2012). These guidelines recommend the following:

- Patients should be evaluated to identify any alternative etiology.
- In the absence of a clear alternative etiology, all events of an inflammatory nature should be considered immune related.
- Symptomatic and topical therapy should be considered for low-grade events.
- Systemic corticosteroids should be considered for a persistent low-grade event or for a severe event.
- More potent immunosuppressives should be considered for events not responding to systemic steroids (for example, infliximab or mycophenolate).

If the investigator has any questions in regards to an AE being an irAE, the investigator should immediately contact the study physician.

Myocarditis

A variety of clinical presentations, diagnostic evidence (laboratory, imaging, histopathology), and resulting diagnoses have been described in cases of myocarditis in the literature for other immune checkpoint inhibitors, including heart failure, brady- and tachyarrhythmias, and acute coronary syndrome-like presentations without evidence of ischemia. Investigators should be aware of such rare, but severe immune-mediated adverse events including myocarditis with its presenting signs/symptoms (eg, decreased ejection fraction, arrhythmias, in particular occurrences of atrioventricular block).

Investigators should adhere to the Toxicity Management Guidelines by performing a thorough evaluation to rule out alternative etiologies and initiating prompt treatment with steroids and modification of study drug/dose regimen depending on the severity of the event.

Guidelines for the management of patients with myocarditis are provided in Attachment 7.

Myositis/Polymyositis

Investigators should adhere to the Toxicity Management Guidelines by performing a thorough evaluation to rule out alternative etiologies and initiating prompt treatment with steroids and modification of study drug/dose regimen depending on the severity of the event. Guidelines for the management of patients with myositis/polymyositis are provided in Attachment 7.

Attachment 9. Protocol JSCC Durvalumab and Tremelimumab Dose Volume Calculations

Durvalumab Dose Volume Calculation

For durvalumab flat dosing:

1. Cohort dose: X g

2. Dose to be added into infusion bag:

Dose (mL) = X g × 1000 / 50 (mg/mL)

where 50 mg/mL is durvalumab nominal concentration.

The corresponding volume of durvalumab should be rounded to the nearest tenth mL (0.1 mL).

3. The theoretical number of vials required for dose preparation is the next greatest whole number of vials from the following formula:

Number of vials = Dose (mL) / 10.0 (mL/vial)

Example:

1. Cohort dose: 1.5 g

2. Dose to be added into infusion bag:

Dose (mL) = 1.5 g ×1000 / 50 (mg/mL) = 30.0 mL

3. The theoretical number of vials required for dose preparation:

Number of vials = 30.0 (mL) / 10.0 (mL/vial) = 3 vials

Tremelimumab Dose Volume Calculation

For tremelimumab flat dosing:

1. Cohort dose: X mg

2. Dose to be added into infusion bag:

Dose (mL) = X mg / 20 (mg/mL)

where 20 mg/mL is tremelimumab nominal concentration

The corresponding volume of tremelimumab should be rounded to the nearest tenth mL (0.1 mL).

3. The theoretical number of vials required for dose preparation is the next greatest whole number of vials from the following formula:

Number of vials = Dose (mL) / 20 (mL/vial)

Example:

1. Cohort dose: 75 mg

2. Dose to be added into infusion bag:

Dose (mL) = 75 mg / 20 (mg/mL) = 3.8 mL

3. The theoretical number of vials required for dose preparation:

Number of vials = 3.8 (mL) / 20 (mL/vial) = 1 vial

Attachment 10. Protocol JSCC Protocol Amendment I5F-MC-JSCC(c) Summary
A Phase 1a/1b Trial Investigating the CSF-1R Inhibitor LY3022855 in Combination with Durvalumab (MEDI4736) or Tremelimumab in Patients with Advanced Solid Tumors

Overview

Protocol I5F-MC-JSCC, A Phase 1a/1b Trial Investigating the CSF-1R Inhibitor LY3022855 in Combination with Durvalumab (MEDI4736) or Tremelimumab in Patients with Advanced Solid Tumors, has been amended. The new protocol is indicated by Amendment (c) and will be used to conduct the study in place of any preceding version of the protocol.

Amendment (c) was created to incorporate the following changes:

- Dose modification and toxicity management guidelines for durvalumab was updated per new guidance from AstraZeneca.
- Clarification about testing for mutations in *EGFR* or *ALK* genes for patients in Part B (NSCLC cohort) was added.
- Updated information about tumor biopsy samples to make it consistent across sections.
- Updated treatment delay criteria to provide consistency across the protocol.

Revised Protocol Sections

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

The numbering system used for inclusion and exclusion criteria provides a unique number for each criterion and allows for efficiency in data collection.

In case an amendment to the protocol adds a criterion, that criterion will receive the next available number, regardless of whether it is an inclusion or exclusion criterion.

5.1.3. Summary of the Rationale for Amendment (c)

Amendment (c) was created to incorporate the following changes:

- Dose modification and toxicity management guidelines for durvalumab was updated per new guidance from AstraZeneca.
- Added clarification about testing for mutations in *EGFR* or *ALK* genes for patients in Part B (NSCLC cohort only).
- Updated information about tumor biopsy samples to make it consistent across sections.
- Updated treatment delay criteria to provide consistency across the protocol.

6.1.1 Inclusion Criteria

Patients may be included in the study if they meet all of the following criteria during screening prior to first dose of study drug.

(Note: If a specific cohort is not indicated for a criterion, the criterion applies to all patients.)

[1] Must have histological or cytological evidence of a diagnosis of cancer that is not amenable to curative therapy.

[2] Part B (all cohorts): Must have a type of malignancy that is being studied, as listed in the following:

[a] LY3022855 and durvalumab (MEDI4736) combination cohorts

[i] NSCLC that has relapsed or is refractory (definitions below) to immune checkpoint inhibitor therapy and has progressed through no more than 3 lines of therapy (one line must have been a platinum-containing regimen).

- Relapsed: Following initial clinical benefit (that is, complete response [CR], partial response [PR], or stable disease [SD] on any scan), patients must have documented radiographic disease progression while receiving therapy with an immune checkpoint inhibitor.

- Refractory: Patients must have documented radiographic disease progression ≤16 weeks after the start of treatment with an immune checkpoint inhibitor, with no evidence of clinical benefit (that is, CR, PR, or SD on any scan) while receiving therapy.

a. Patients must not have a known activating mutation of the *EGFR* or *ALK* gene. If a site uses algorithmic testing that has eliminated the possibility of EGFR or ALK gene mutations, no specific testing for mutations in these genes is required.

b. Patients could have received only one prior immune checkpoint therapy (anti-PD-1/PD-L1 or anti-CTLA-4, or a single regimen combining anti-PD-1/PD-L1 with an anti-CTLA-4).

[ii] Ovarian cancer (epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer) that has been treated with no more than 3 lines of therapy (with or without platinum).

[3] Part A (all cohorts) and Part B (ovarian cancer cohort only): Must be willing to undergo pretreatment and on-treatment core needle or excisional tumor biopsies. For patient in NSCLC Part B cohort, if newly obtained samples cannot be obtained such as in cases of inaccessibility or patient safety concern, an archived tumor sample will be requested if not restricted by local regulations. The archived tumor sample must follow most recent systemic treatment. If no archived specimen since the most recent systemic treatment is available, and a new biopsy is not medically feasible, the patient should not be enrolled in the clinical trial.~~(Note: An archived tumor sample will be requested, if not restricted by local regulations, for each patient in NSCLC Part B cohort).~~

7.2.1.1. LY3022855

Eligible patients will receive LY3022855 as an I.V. infusion administered over a minimum duration of 30 minutes and a maximum duration of 4 hours, based on the known safety and stability of the prepared drug. The infusion rate should not exceed 25 mg/minute. Suggested infusion times are as follows:

- 90 minutes for the first infusion; if no infusion-related reaction (IRR) is observed, decrease the infusion time to 60 minutes for the second infusion
- 60 minutes for the second infusion; if no IRR is observed, decrease the infusion time to 30 minutes for the third infusion
- 30 minutes for the third and subsequent infusions

If, at any time, a patient experiences an IRR, the infusion time should not be decreased. Premedication is not recommended to be administered prior to the first infusion of LY3022855. However, if the patient experiences a Grade 1 or 2 IRR, premedication must be provided prior to any subsequent doses of LY3022855. The choice of premedication is to be made after discussion and agreement between the investigator and sponsor. In such cases (Grade 1 or 2

IRRs), administration of steroids should be avoided, if possible. If an IRR Grade ≤2 occurs during or after LY3022855 administration and the patient's condition allows it, treatment with durvalumab or tremelimumab will proceed as planned. Patients experiencing an IRR Grade ≥3 will be permanently discontinued from study treatment.

LY3022855 may be administered up to 3 days AFTER the scheduled dosing date and up to 4 days BEFORE the next scheduled dosing date to accommodate for patient vacations, holidays, inclement weather or other unforeseen circumstances. If, at any time, a dose is to be administered beyond the 3-day window, that dose is to be skipped. A maximum of 28 days between administered doses is allowed for delays due to adverse events.

7.2.1.2. Durvalumab

Patients are to receive durvalumab I.V. on Days 1 and 15 of every cycle. Durvalumab may be administered up to 3 days AFTER the scheduled dosing date. If, at any time, a dose is administered beyond the 3-day window, that dose is considered a dose delay. A maximum delay of 28 days between administered doses is allowed (for dose delay in case of immune-related AE please refer to Section 7.2.4.1). Note that a maximum of 12 months/26 doses of durvalumab treatment is permitted.

7.2.1.3. Tremelimumab

Patients are to receive tremelimumab I.V. on Day 1 of every cycle for the first 6 doses (Cycles 1-6). Starting with Cycle 7 (4 weeks after Dose 6 [Week 25]), tremelimumab will be dosed once every 3 cycles (12 weeks), that is, on Day 1 of Cycles 7, 10, 13, and so on, until disease progression.

Tremelimumab may be administered up to 3 days AFTER the scheduled dosing date. If, at any time, a dose is administered beyond the 3-day window, that dose is considered a dose delay. A delay of up to 28 days between administered doses is allowed for Cycles 1 through 6, and up to 60 days between doses for Cycles 7 and beyond.

7.2.4.1. Dose Delays for Adverse Events

Study treatment may be held for a maximum of 28 days; see exception for an immune-related AE below. If appropriate, and in the opinion of the investigator and upon agreement with the sponsor, study treatment may resume upon resolution of clinically significant AEs to baseline or improvement to Grade <2. If AEs do not resolve to baseline or improve to Grade <2 within 28 days following the last administered dose, study treatment should be permanently discontinued and the patient should be discontinued from the trial. If treatment is held, the day of treatment should continue as if no drug interruption has occurred. For example, if study drug is held on D6 of a cycle and AEs have resolved by D10 (4 days later), the study drugs should be resumed per the original schedule, If the original schedule results in a study drug being held for >28 days, the study drug may not be resumed. One or both study drugs may be held, resumed, or discontinued.

If the AE is an immune related AE as outlined in Attachment 7 and if the treatment management guidelines outlined in Attachment 7 are followed and documented in the patient's medical record, treatment may be held for >28 days to allow taper of high dose steroids. Treatment may resume in this setting only upon resolution of immune AEs to baseline or improvement to Grade <2, and only if deemed clinically appropriate by the treating physician and agreed to by the sponsor. If steroids cannot be tapered as outlined in Attachment 7, and/or AEs do not resolve to < Grade 2, the patient may not be resumed on study treatment.

For the purposes of documentation, the investigator must assess if the toxicity is considered at least possibly related to study treatment (that is, the combination regimen) and if the AE is considered to be immune related. Investigators are encouraged to consult the sponsor for additional guidance.

For AEs that are considered at least possibly related to study treatment, the following dose adjustment guidance may be applied:

- Treat each of the toxicities with maximum supportive care (including holding the study drug[s] suspected of causing the toxicity where required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of study drugs along with appropriate continuing supportive care.
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

In addition, there are certain circumstances in which study drugs should be permanently discontinued (refer to Attachment 7).

Following the first dose of study drugs, subsequent administration of study drugs can be modified based on toxicities observed (refer to Attachment 7).

7.2.4.1.1. Specific Adverse Events

Adverse events of special interest (AESIs) observed with durvalumab and/or tremelimumab include colitis; pneumonitis; alanine aminotransferase (ALT)/AST increases; hepatitis/hepatotoxicity; neuropathy/neuromuscular toxicity (that is, events of encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis); endocrinopathy (that is, events of hypophysitis, adrenal insufficiency, hyperthyroidism, and hypothyroidism; type 1 diabetes mellitus); dermatitis; nephritis; and pancreatitis (or labs suggestive of pancreatitis-increased serum lipase or serum amylase); other inflammatory responses that are rare with a potential immune-mediated etiology include, but are not limited to, myocarditis, pericarditis, myositis/polymyositis, and uveitis. Refer to Attachment 8 for details about and management of AESIs.

Guidelines for the management of immune-mediated, infusion-related, and non-immune-related AEs are shown in Attachment 7.

Adverse events (both nonserious and serious) associated with study drugs may represent an immune-related etiology, which may be based on the mechanism of action of study drugs leading to T cell activation and proliferation. These irAEs may occur shortly after the first dose or several months after the last dose of treatment. Potential irAEs include immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies. Patients should be monitored for signs and symptoms of irAEs. In the absence of an alternative etiology (for example, infection or progressive disease), signs or symptoms of enterocolitis, dermatitis, pneumonitis, hepatitis, myocarditis, myopathy/polymyopathy, and endocrinopathy should be considered immune related. Refer to Attachment 7 for supportive care guidelines for immune-mediated reactions, including use of corticosteroids.

8.2.4.2. Tumor Tissue Samples

Tissue collection will be required for biomarker research and enrollment into the study for patients in Part A (all cohorts) and Part B ~~(ovarian cancer cohort only)~~. For patients enrolled in Part A (all cohorts) and Part B (ovarian cancer cohort only) of the study, tissue will be required for PD-L1 biomarker and other exploratory analysis from a newly obtained core or excisional biopsy of a tumor lesion (should be taken only after study eligibility is confirmed) or from a recent biopsy defined by ≤3 years since last documented progression of disease ~~will be required~~. For the NSCLC cohort, archived tissue should be submitted form a recent biopsy defined by ≤3 years old and this biopsy follows the most recent systemic therapy. If such an archived biopsy sample is not available, a new biopsy must be obtained for the patient to be eligible to participate in study. For all cohorts, new archived tissue will be obtained only if not restricted by local regulations.

In addition, an on-treatment~~study~~ biopsy is required if any accessible lesions remain for Part A (all cohorts) and Part B (ovarian cancer cohort only). If clinically feasible, the biopsies should be taken from the same lesion. ~~Pretreatment and/or on-treatment tumor tissue biopsies are optional for all Part B cohorts, except the ovarian cancer cohort, for which these biopsies are mandatory. Sites should confirm the availability of adequate tumor tissue with the site's pathology laboratory.~~ For patients enrolled to NSCLC cohort of Part B, the on-treatment biopsy is optional~~for whom newly obtained samples cannot be obtained such as in cases of inaccessibility or patient safety concern, an archived specimen following most recent systemic treatment should be submitted if not restricted by local regulations~~.

Sites must confirm the availability of adequate tumor tissue for the new biopsy from the site's pathology laboratory or adequate archived tumor tissue. Pretreatment formalin-fixed paraffin-embedded (FFPE) tumor tissue should be submitted in a whole block.

Attachment 1. Protocol JSCC Study Schedule

Assessments are to be performed at the times stipulated in the schedule and as clinically required in the management of the patient.

Screening/Baseline Assessments (Visit 0)

Relative Day Prior to Day 1 of Cycle 1	≤28	≤14	≤7	Comments
Written informed consent/assignment of patient identification number	X			ICF signed (prior to performance of any protocol-specific tests/procedures).
Review of eligibility criteria	X			
Medical history		X		
Physical examination		X		Full physical examination, including assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, GI, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems.
Vital signs		X		BP, temperature, RR, and PR. Includes height (at baseline only) and weight.
ECOG performance status		X		
ECG (local)		X		Triplicate ECG will be obtained, on which QTcF must be <470 ms (calculated from one ECG using Fridericia's Correction Formula and confirmed with 2 additional ECGs).
HIV screening (local)	X			Per institutional standards. If done within 28 days prior to Cycle 1, Day 1, as part of standard of care, does not need to be repeated prior to the start of Cycle 1.
Hematology (local)		X		Refer to Attachment 2.
Serum chemistry (central)		X		Refer to Attachment 2.
Urinalysis (local)		X		Refer to Attachment 2.
Coagulation (local)		X		Refer to Attachment 2. Obtain prior to tumor biopsy.
Thyroid function (central)		X		Refer to Attachment 2. Free T3 and free T4 will be measured only if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
Pancreas function (central)		X		Refer to Attachment 2.
LVEF evaluation	X			Echocardiogram or MUGA scan.
Radiographic tumor assessment (CT/MRI)	X			If done within 28 d prior to Cycle 1, Day 1, as part of standard of care, does not need to be repeated prior to the start of Cycle 1.
Tumor measurement (palpable or visible)		X		
CTCAE v4.0 grading (preexisting conditions)		X		To be reported only after study eligibility is confirmed. Refer to Section 8.1.2.4 for reporting guidelines.
Concomitant medications		X		
Tumor markers (local)		X		As clinically indicated. For example, CEA in patients with colorectal cancer or CA125 in patients with ovarian cancer.

Relative Day Prior to Day 1 of Cycle 1	≤28	≤14	≤7	Comments
Tumor tissue biopsy		X		For Part A (all cohorts) and Part B (ovarian cancer cohort only): A newly obtained core or excisional biopsy of a tumor should be taken only after study eligibility is confirmed. For the NSCLC cohort in Part B a newly obtained core or excisional biopsy should be obtained if an archived tumor sample following the most recent systemic therapy is not available. Refer to the laboratory manual.
Archived tumor tissue	X			An archived tumor sample following most recent systemic treatment if not restricted by local regulations will be requested from all patients in Part B NSCLC cohort. If such an archived biopsy sample is not available, a new biopsy must be obtained for the patient to be eligible to participate in study. Refer to the laboratory manual.
Whole blood for biomarkers			X	Refer to the laboratory manual.
Pregnancy test (local)			X	Applies only to women of childbearing potential. Urine hCG or serum β-hCG is acceptable.

Abbreviations: AE = adverse event; BP = blood pressure; CA125 = cancer antigen 125; CEA = carcinoembryonic antigen; CT = computed tomography (scan); CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; GI = gastrointestinal; hCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; ICF = informed consent form; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition (scan); PR = pulse rate; QTcF = QT interval corrected for heart rate using Fridericia's Correction Formula; RR = respiration rate; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; v4.0 = Version 4.0 of CTCAE.

On-Study Treatment and Post-Treatment (Follow-Up) Assessments for Combination Therapy: LY3022855 plus Durvalumab

Note that a maximum of 12 months/26 doses of durvalumab treatment is permitted; last infusion at Week 50.

Screening procedures performed for safety within 72 hours prior to Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.

Rows with *italicized* font indicate that there is no planned assessment for the time frame shown on the page.

LY3022855 plus Durvalumab Assessment (central or local laboratory indicated, if applicable)	**Cycle 1 (Visit 1)**						**Comments** Except for the Cycle 1, Day 1 visit, allowable windows are ±3 days, unless otherwise indicated. On dosing days, all assessments to be performed preinfusion, unless stated otherwise.
Relative day within a 28-day cycle:	**1**	**2**	**3**	**8**	**15**	**22**	
Physical examination	X			X	X	X	Targeted physical examination (on the basis of clinical observations and symptomatology).
Vital signs	X			X	X	X	BP, temperature, RR, PR, and weight. Vital signs (BP, RR, and PR only) to be measured around infusions as follows (allowable window ±10 min): Around each LY3022855 infusion: prior to, during (midway through), at the end, and 30 min after the end. Around each durvalumab infusion (based on a 60-min infusion): within 30 min prior to, during (approx. 30 min after start of infusion), and at the end (approx. 60 min after start of infusion). 1-h Observation period after durvalumab infusion: at 30 and 60 min after the end of the infusion (90 and 120 min after start of infusion) for the first durvalumab infusion only, and for subsequent infusions as clinically indicated. If the durvalumab infusion exceeds 60 min, monitoring of BP and PR should occur per the preceding principles or more frequently if clinically indicated.
ECOG performance status	X						
Pregnancy test (local)							*Every 12 wk (±7 d) after the first dose of study drug or according to local regulations or as clinically indicated, whichever is more frequent. Urine hCG or serum β-hCG.*
ECG (local)	X						Single ECG. Obtain ECGs before any associated blood draws. On dosing days, ECG should be taken within 2 h prior to the start of the LY3022855 infusion and at least one time point 0-3 h after the durvalumab infusion. Additional ECGs to be obtained as clinically indicated.

LY3022855 plus Durvalumab Assessment (central or local laboratory indicated, if applicable)	**Cycle 1 (Visit 1)**						**Comments** Except for the Cycle 1, Day 1 visit, allowable windows are ±3 days, unless otherwise indicated. On dosing days, all assessments to be performed preinfusion, unless stated otherwise.
Relative day within a 28-day cycle:	**1**	**2**	**3**	**8**	**15**	**22**	
Hematology (local)	X		X	X	X	X	Refer to Attachment 2.
Serum chemistry (local) - safety labs for dosing	X			X	X	X	Refer to Attachment 2. Results must be available and reviewed before administering study drug.
Serum chemistry (central)	X	X		X	X	X	Refer to Attachment 2.
Urinalysis (local)	X						Refer to Attachment 2. To be performed at Screening, at C1D1, and every 4 wk thereafter. Additional assessments as clinically indicated. Results need not be available before administering study drug.
Coagulation (local)							*Refer to Attachment 2. As clinically indicated.*
Thyroid function (central)	X						Refer to Attachment 2. Free T3 and free T4 will be measured only if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
Pancreas function (central)							*Refer to Attachment 2.*
Tumor markers (local)							
Pharmacogenetic sample	X						Refer to the laboratory manual. Collect once. Sample can be collected at any time, if not collected on C1D1.

LY3022855 plus Durvalumab Assessment (central or local laboratory indicated, if applicable)	**Cycle 1 (Visit 1)**							**Comments** Except for the Cycle 1, Day 1 visit, allowable windows are ±3 days, unless otherwise indicated. On dosing days, all assessments to be performed preinfusion, unless stated otherwise.
Relative day within a 28-day cycle:	**1**		**2**	**3**	**8**	**15**	**22**	
Immunogenicity	X						X	If at any time a patient experiences an IRR, attempt to obtain a blood sample for immunogenicity analysis as close to the onset of the event as possible, at the resolution of the event, and 30 d following the event. A portion of the sample taken for immunogenicity testing may be used for PK analysis.
Myoglobin (local)					X			Refer to Attachment 2. If serum CK Grade ≥2, test for serum and urine myoglobin.
CTCAE v4.0 grading	X				X	X	X	Throughout study as needed. Refer to Section 8.1.1 for reporting guidelines.
Concomitant medications	X				X	X	X	Throughout study as needed.
LY3022855 administration	Refer to Table JSCC.1 for dose frequency during Part A.							For LY3022855 and durvalumab: Part A doses: Refer to Table JSCC.1. Part B doses and dose frequencies to be determined; refer to Section 7.2.2.2 for information.
Durvalumab administration	X					X		
Pharmacokinetics								
LY3022855 (predose on dosing days, unless noted otherwise)	X	X 2 h post-EOI C1D1 (±1 h)	X 24 h post-EOI C1D1 (±4 h)	X 48 h post-EOI C1D1 (±4 h)	X	X	X	The date and the time of all samples must be clearly and accurately recorded. EOI = end of infusion
Durvalumab (predose on dosing days, unless noted otherwise)	X	X Simultaneously with LY PK sample	X Simultaneously with LY PK sample	X Simultaneously with LY PK sample	X	X	X	
Pharmacodynamics and tailoring								
Serum	X	X Simultaneously with LY PK sample	X Simultaneously with LY PK sample	X Simultaneously with LY PK sample	X	X	X	Serum storage for correlative studies.
Plasma	X							Plasma storage for correlative studies.
Whole blood	X		X			X		Gene expression analysis and other exploratory research.
Flow cytometry								
Immunophenotyping #1	X				X	X	X	CD14 and CD16.
Immunophenotyping #2	X				X	X	X	TBNK & T cell subset/activation panels.
Immunophenotyping #3	X							MDSC panel.
Isoenzymes (central)								*Refer to Attachment 2. Obtain at additional time points, as clinically indicated.*

LY3022855 plus Durvalumab Assessment (central or local laboratory indicated, if applicable)	**Cycle 1 (Visit 1)**						**Comments** Except for the Cycle 1, Day 1 visit, allowable windows are ±3 days, unless otherwise indicated. On dosing days, all assessments to be performed preinfusion, unless stated otherwise.
Relative day within a 28-day cycle:	**1**	**2**	**3**	**8**	**15**	**22**	
LVEF evaluation							*Echocardiogram or MUGA scan. Obtain at additional time points, as clinically indicated.*
Radiographic tumor assessment (CT/MRI)							*Perform every 8 wk (±7 d), starting on Cycle 2, Day 22.*
Tumor measurement (palpable or visible)							
Tumor biopsy							*For Part A (all cohorts) and Part B (ovarian cancer cohort only): An on-treatment tumor core needle or excisional biopsy to be performed 6-8 wk after starting study treatment.*

LY3022855 plus Durvalumab Assessment (central or local laboratory indicated, if applicable)	**Cycle 2 (Visit 2)**						**Comments** Except for the Cycle 1, Day 1 visit, allowable windows are ±3 days, unless otherwise indicated. On dosing days, all assessments to be performed preinfusion, unless stated otherwise.
Relative day within a 28-day cycle:	**1**	**8**	**9**	**10**	**15**	**22**	
Physical examination	X	X			X	X	Targeted physical examination (on the basis of clinical observations and symptomatology).
Vital signs	X	X			X	X	BP, temperature, RR, PR, and weight. Vital signs (BP, RR, and PR only) to be measured around infusions as follows (allowable window ±10 min): Around each LY3022855 infusion: prior to, during (midway through), at the end, and 30 min after the end. Around each durvalumab infusion (based on a 60-min infusion): within 30 min prior to, during (approx. 30 min after start of infusion), and at the end (approx. 60 min after start of infusion). 1-h Observation period after durvalumab infusion: at 30 and 60 min after the end of the infusion (90 and 120 min after start of infusion) as clinically indicated. If the durvalumab infusion exceeds 60 min, monitoring of BP and PR should occur per the preceding principles or more frequently if clinically indicated.
ECOG performance status	X						
Pregnancy test (local)							*Every 12 wk (±7 d) after the first dose of study drug or according to local regulations or as clinically indicated, whichever is more frequent. Urine hCG or serum β-hCG.*
ECG (local)	X						Single ECG. Obtain ECGs before any associated blood draws. ECG should be taken within 2 h prior to the start of the LY3022855 infusion and at least one time point 0-3 h after the durvalumab infusion. Additional ECGs to be obtained as clinically indicated.
Hematology (local)	X	X			X	X	Refer to Attachment 2.
Serum chemistry (local) - safety labs for dosing	X	X			X	X	Refer to Attachment 2. Results must be available and reviewed before administering study drug.
Serum chemistry (central)	X	X			X	X	Refer to Attachment 2.
Urinalysis (local)	X						Refer to Attachment 2. To be performed at Screening, at C1D1, and every 4 wk thereafter. Additional assessments as clinically indicated. Results need not be available before administering study drug.
Coagulation (local)	X						Refer to Attachment 2. Obtain prior to tumor biopsy. Additional assessments as clinically indicated.

LY3022855 plus Durvalumab Assessment (central or local laboratory indicated, if applicable)	**Cycle 2 (Visit 2)**						**Comments** Except for the Cycle 1, Day 1 visit, allowable windows are ±3 days, unless otherwise indicated. On dosing days, all assessments to be performed preinfusion, unless stated otherwise.
Relative day within a 28-day cycle:	**1**	**8**	**9**	**10**	**15**	**22**	
Thyroid function (central)	X						Refer to Attachment 2. Free T3 and free T4 will be measured only if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
Pancreas function (central)	X						Refer to Attachment 2.
Tumor markers (local)	X						If clinically indicated.
Pharmacogenetic sample							*Refer to the laboratory manual. Collect once. Sample can be collected at any time, if not collected on C1D1.*
Immunogenicity		X					If at any time a patient experiences an IRR, attempts to obtain a blood sample for immunogenicity analysis as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. A portion of the sample taken for immunogenicity testing may be used for PK analysis.
Myoglobin (local)	X	X			X	X	Refer to Attachment 2. If serum CK Grade ≥2, test for serum and urine myoglobin.
CTCAE v4.0 grading	X	X			X	X	Throughout study as needed. Refer to Section 8.1.1 for reporting guidelines.
Concomitant medications	X	X			X	X	Throughout study as needed.
LY3022855 administration	Refer to Table JSCC.1 for dose frequency during Part A.						For LY3022855 and durvalumab: Part A doses: Refer to Table JSCC.1. Part B doses and dose frequencies to be determined; refer to Section 7.2.2.2 for information.
Durvalumab administration	X				X		
Pharmacokinetics							
LY3022855 (predose on dosing days, unless noted otherwise)	X	X	X 2 h post-EOI C2D8 (±1 h)	X 24 h post-EOI C2D8 (±4 h)	X 48 h post-EOI C2D8 (±4 h)	X		The date and the time of all samples must be clearly and accurately recorded. EOI = end of infusion
Durvalumab (predose on dosing days, unless noted otherwise)	X	X	X Simultaneously with LY PK sample	X Simultaneously with LY PK sample	X Simultaneously with LY PK sample	X		
Pharmacodynamics and tailoring							
Serum	X	X	X Simultaneously with LY PK sample	X Simultaneously with LY PK sample	X Simultaneously with LY PK sample	X		Serum storage for correlative studies.
Plasma		X						Plasma storage for correlative studies.
Whole blood	X				X			Gene expression analysis and other exploratory research.
Flow cytometry							
Immunophenotyping #1	X	X			X			CD14, CD16.
Immunophenotyping #2	X	X			X			TBNK & T cell subset/activation panels.
Immunophenotyping #3	X							MDSC panel.

LY3022855 plus Durvalumab Assessment (central or local laboratory indicated, if applicable)	**Cycle 2 (Visit 2)**						**Comments** Except for the Cycle 1, Day 1 visit, allowable windows are ±3 days, unless otherwise indicated. On dosing days, all assessments to be performed preinfusion, unless stated otherwise.
Relative day within a 28-day cycle:	**1**	**8**	**9**	**10**	**15**	**22**	
Isoenzymes (central)	X						Refer to Attachment 2. Obtain at additional time points, as clinically indicated.
LVEF evaluation						X	Echocardiogram or MUGA scan. Obtain at additional time points, as clinically indicated.
Radiographic tumor assessment (CT/MRI)						X	Perform every 8 wk (±7 d), starting on Cycle 2, Day 22.
Tumor measurement (palpable or visible)						X	
Tumor biopsy		X					For Part A (all cohorts) and Part B (ovarian cancer cohort only): An on-treatment tumor core needle or excisional biopsy to be performed 6-8 wk after starting study treatment; that is, at Cycle 2, between Days 8 and 22. For Part B (NSCLC cohort) an optional on-treatment tumor tissue should be collected from patients in the study where possible.

Attachment 7. Protocol JSCC Toxicity Management Guidelines

Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non Immune-Mediated Reactions (Combination Therapy with LY3022855 and Durvalumab or LY3022855 and Tremelimumab)

General Considerations

Dose Modifications		Toxicity Management
Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03. In addition to the criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions: • Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) **within 12 weeks** after last dose of study drug/study regimen • Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing		It is recommended that management of ~~irAEs~~immune-mediated adverse events (imAEs) follows the guidelines presented in this table: – It is possible that events with an inflammatory or immune-mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines. – Whether specific immune-mediated events (and/or laboratory indicators of such events) are noted in these guidelines or not, patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, concomitant medications, and infections)~~.~~ to a possible immune-mediated event. In the absence of a clear alternative etiology, all such events should be ~~considered potentially~~managed as if they were immune related. General recommendations follow. – Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events. – For persistent (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Some events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – should implement high-dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation. – If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [eg, up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (>28 days of taper). – More potent immunosuppressives such as TNF inhibitors (eg, infliximab) (also refer to the individual sections of the ~~irAE~~imAEs for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when these events are not responding to systemic steroids. – With long-term steroid and other immunosuppressive use, consider need for
Grade 1	No dose modification	
Grade 2	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 4. The event stabilizes and is controlled. 5. The patient is clinically stable as per Investigator or treating physician's clinical judgement. 6. Doses of prednisone are at ≤10 mg/day or equivalent.	
Grade 3	Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below.	

Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non Immune-Mediated Reactions (Combination Therapy with LY3022855 and Durvalumab or LY3022855 and Tremelimumab)

General Considerations

Dose Modifications	Toxicity Management
Grade 4 Permanently discontinue study drug/study regimen. Note: For Grade ≥3 asymptomatic amylase or lipase levels, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed. Note: Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines. Similarly, consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper. Note: There are some exceptions to permanent discontinuation of study drug for Grade 4 events (i.e., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus).	Pneumocystis jirovecii pneumonia (PJP, formerly known as Pneumocystis carinii pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring. – Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (eg, inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit/risk analysis for that patient.

Abbreviations: AE = Adverse event; CTC = Common Toxicity Criteria; CTCAE = Common Terminology Criteria for Adverse Events; ~~irAE =~~ imAE = immune-~~related~~mediated adverse event; IV = intravenous; NCI = National Cancer Institute; PO = By mouth.

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
~~**Myositis**~~ **Pneumonitis/Interstitial Lung Disease (ILD)**	~~**Any Grade**~~ ~~**Grade 3 or higher**~~ **Any Grade**	~~**General Guidance**~~ ~~Permanently discontinue study drug/study regimen~~ **General Guidance**	~~**For Any Grade:**~~ ~~– Check urine or serum myoglobin or hold if serum or myoglobin are positive.~~ **For Any Grade:** – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high- resolution CT scan.
	Grade 1 (asymptomatic, clinical or diagnostic observations only; intervention not indicated)	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1 (radiographic changes only):** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated. – Consider Pulmonary and Infectious disease consult.
	Grade 2 (symptomatic; medical intervention indicated; limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	**For Grade 2 (mild to moderate new symptoms):** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (eg, prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated. – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started – If still no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for

			general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-~~PCP~~PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])[a] – Consider pulmonary and infectious disease consult. – Consider, as necessary, discussing with study physician.
	Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [eg, tracheostomy or intubation])	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):** – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious disease consult; consider, as necessary, discussing with study physician. – Hospitalize the patient. – Supportive care (eg, oxygen). – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks' dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient~~s~~ is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-~~PCP~~PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Diarrhea/~~Enterocolitis~~Colitis	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, or infections), including testing for clostridium difficile toxin, etc. – Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential

			progression to higher grade event. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
	Grade 1 (Diarrhea: stool frequency of <4 over baseline per day) (Colitis: asymptomatic; clinical or diagnostic observations only)	No dose modifications.	**For Grade 1:** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.
	Grade 2 (Diarrhea: stool frequency of 4 to 6 over baseline per day) (Colitis: abdominal pain; mucus or blood in stool)	Hold study drug/study regimen until resolution to Grade ≤1 • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide and/or budesonide. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg once every 2 weeks[a]. **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – ~~Consult~~Consider, as necessary, discussing with study physician if no resolution to Grade ≤1 in 3 to 4 days. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-~~PCP~~PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (Grade 3 diarrhea:	**Grade 3** Permanently discontinue study	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone 2 to

	stool frequency of ≥7 over baseline per day; Grade 4 diarrhea: life-threatening consequences) (Grade 3 colitis: severe abdominal pain, change in bowel habits, medical intervention indicated, peritoneal signs; Grade 4 colitis: life-threatening consequences, urgent intervention indicated)	drug/study regimen. for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days; study drug/study regimen can be resumed after completion of steroid taper. **Grade 4** Permanently discontinue study drug/study regimen.	4 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – Urgent GI consult and imaging and/or colonoscopy as appropriate. – If still no improvement within 3 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (eg infliximab at 5 mg/kg once every 2 weeks). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCPPJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis.	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (eg, viral hepatitis, disease progression, concomitant medications). – For isolated AST elevations see below.
	Grade 1 (AST or ALT > to ULN and ≤3 × .0×ULN and/or TB > to ULN and ≤1.5 × ×ULN)	• No dose modifications. • If it worsens, then treat as Grade 2 event.	**For Grade 1:** – Continue LFT monitoring per protocol.
	Grade 2 (AST or ALT >3 to .0×ULN and ≤5 × .0×ULN and/or	• Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1 or	**For Grade 2:** – Regular and frequent checking of LFTs (eg, every 1 to 2 days) until elevations of these are improving or resolved. – If no resolution to Grade ≤1 in 1 to 2 days, discussconsider, as necessary, discussing with study physician.

	TB >1.5~~ to ~~×ULN and ≤3.0~~ × ~~×ULN)	baseline, resume study drug/study regimen after completion of steroid taper. **For asymptomatic Grade 2 AST (only if accompanied by Grade ≤ 1 ALT and Grade ≤ 1 TB and no change of ALT or TB from baseline levels):**	– If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and start prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-~~PCP~~PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
		• Continue dosing with both LY3022855 and durvalumab or tremelimumab	– Monitor LFTs frequently (eg, every 1 to 2 days or as clinically indicated). – Consider hepatic consult – No steroids required
	Grade 3 or 4 (Grade 3: AST or ALT >5~~ to ~~~~ 20 × ~~.0×ULN and ≤20.0×ULN and/or TB >3.0~~ to ~~×ULN and ≤10~~ × ~~.0×ULN) (Grade 4: AST or ALT >20×ULN and/or TB >10×ULN)	**For Grade 3:** For elevations in transaminases ≤8 × ULN, or elevations in bilirubin ≤5 × ULN: • Hold study drug/study regimen dose until resolution to Grade ≤1 or baseline • Resume study drug/study regimen if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If still no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (i.e., mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Perform hepatology consult, abdominal workup, and imaging as appropriate. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-~~PCP~~PJP treatment (refer to current NCCN guidelines for

		do not downgrade to Grade ≤1 or baseline within 14 days **For asymptomatic Grade 3 AST up to ≤8 × ULN (only if accompanied by Grade ≤ 1 ALT and Grade ≤ 1 TB and no change of ALT or TB from baseline levels)**	treatment of cancer-related infections [Category 2B recommendation]).[a]
		• Hold LY3022855, and continue dosing with durvalumab or tremelimumab. • If AST downgrades to Grade ≤2, after holding LY3022855, resume dosing with LY3022855 and durvalumab or tremelimumab. • If Grade 3 AST recurs after resumption of dosing with both agents, hold LY3022855 dosing. Continue dosing durvalumab or tremelimumab. Resume treatment with the combination of LY3022855 and durvalumab or tremelimumab if AST remains asymptomatic and downgrades to Grade ≤2. For elevations in transaminases >8 × ULN or elevations in bilirubin >5 × ULN, discontinue ~~LY3022855 and durvalumab or tremelimumab~~ study drug/study regimen. Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without	– Monitor LFTs frequently (eg, every 1 to 2 days or as clinically indicated). – Evaluate for alternative etiologies (eg, viral hepatitis, disease progression, concomitant medications, history of alcohol intake). – Promptly seek hepatic consult as necessary. – No steroids required.

		initial findings of cholestasis (ie, elevated alkaline P04) and in the absence of any alternative cause.[b] **For Grade 4:** Permanently discontinue ~~LY3022855 and durvalumab or tremelimumab~~study drug/study regimen.	
Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade**	**General Guidance**	**For Any Grade:** – Consult with nephrologist. – Monitor for signs and symptoms that may be related to changes in renal function (eg, routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria). – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression or infections). – Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.
	Grade 1 (Serum creatinine > 1 to 1.5 × baseline; > ULN to 1.5 × ULN)	No dose modifications.	**For Grade 1:** – Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.
	Grade 2 (serum creatinine >1.5 to 3.0 × baseline; >1.5 to 3.0 × ULN)	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity improves to Grade ≤1 or baseline, then resume study	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically

		drug/study regimen after completion of steroid taper.	indicated. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-~~PCP~~PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4 (Grade 3: serum creatinine >3.0 × baseline; >3.0 to 6.0 × ULN; Grade 4: serum creatinine >6.0 × ULN)	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Carefully monitor serum creatinine on daily basis. – Consult nephrologist and consider renal biopsy if clinically indicated. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-~~PCP~~PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Rash (excluding bullous skin formations)	**Any Grade** (refer to NCI CTCAE v 4.03 for definition of severity/grade depending on type of skin rash)	**General Guidance**	**For Any Grade:** – Monitor for signs and symptoms of dermatitis (rash and pruritus). – IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED.**
	Grade 1	No dose modifications.	**For Grade 1:** – Consider symptomatic treatment, including oral antipruritics (eg,

			diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream).
	Grade 2	For persistent (>1 to 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper.	**For Grade 2:** – Obtain dermatology consult. – Consider symptomatic treatment, including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream). – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, ~~discuss~~consider, as necessary, discussing with study physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs.
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen until resolution to Grade ≤1 or baseline. If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to Grade ≤1 or baseline within 30 days, then permanently discontinue study drug/study regimen. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Consult dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-~~PCP~~PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – ~~Discuss~~Consider, as necessary, discussing with study physician.
Endocrinopathy (eg, hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus,	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE	**General Guidance**	**For Any Grade:** – ~~Consult~~Consider consulting an endocrinologist for endocrine events. – Consider, as necessary, discussing with study physician. – Monitor patients for signs and symptoms of endocrinopathies.

hypophysitis, hypopituitarism, and adrenal insufficiency~~)~~; exocrine event of amylase/lipase increased also included in this section)	v4.03 for defining the CTC grade/severity)		Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression including brain metastases, or infections). – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine ~~labs depending on suspected endocrinopathy.~~and related labs (eg, blood glucose and ketone levels, HbA1c). – For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – If a patient experiences an AE that is thought to be possibly of autoimmune nature (eg, thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.
	Grade 1	No dose modifications.	**For Grade 1 (including those with asymptomatic TSH elevation):** – Monitor patient with appropriate endocrine function tests. – For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5 × LLN, or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider ~~endocrinology consult.~~consultation of an endocrinologist.
	Grade 2	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until patient is clinically stable. • If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be	**For Grade 2 (including those with symptomatic endocrinopathy):** ~~– Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids.~~ ~~– Initiate hormone replacement as needed for management.~~ – ~~Evaluate~~Consult endocrinologist to guide evaluation of endocrine function~~,~~ and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary

		resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (eg, adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	scan. – For all patients with abnormal endocrine work up, except ~~for~~ those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short-term corticosteroids (eg, 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (~~eg, levothyroxine,~~eg, hydrocortisone, ~~or~~ sex hormones). – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once ~~the patient is~~patients on steroids are improving, gradually taper ~~steroids~~ immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-~~PCP~~PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
	Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled.	**For Grade 3 or 4:** ~~– Consult endocrinologist.~~ – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. ~~–~~ For all patients with abnormal endocrine work up, except those with isolated hypothyroidism ~~may be treated with replacement therapy without treatment interruption and without corticosteroids.~~ ~~–~~ or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent – ~~Administer~~, as well as relevant hormone replacement ~~therapy as necessary.~~ (eg, hydrocortisone, sex hormones). – For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid

		2. The patient is clinically stable as per investigator or treating physician's clinical judgment. 3. Doses of prednisone are ≤10 mg/day or equivalent.	activity. – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once ~~the patient is~~patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-~~PCP~~PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] ~~Discuss with study physician.~~
Neurotoxicity (to include but not be limited to limbic encephalitis and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	**Any Grade** (depending on the type of neurotoxicity, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	General Guidance	**For Any Grade:** – Patients should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes, or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (eg, electromyogram and nerve conduction investigations). – Perform symptomatic treatment with neurological consult as appropriate.
	Grade 1	No dose modifications.	**For Grade 1:** – See "Any Grade" recommendations above.
	Grade 2	For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1. For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1. If toxicity worsens, then treat as	**For Grade 2:** – ~~Discuss~~Consider, as necessary, discussing with the study physician. – Obtain neurology consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin or duloxetine). – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If no improvement within 3 to 5 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (eg,

		Grade 3 or 4. Study drug/study regimen can be resumed once event improves to Grade ≤1 and after completion of steroid taper.	IV IG).
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 ~~irAE~~imAE does not resolve to Grade ≤1 within 30 days. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – ~~Discuss~~Consider, as necessary, discussing with study physician. – Obtain neurology consult. – Consider hospitalization. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (eg, IV IG). – Once stable, gradually taper steroids over ≥28 days.
Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	**Any Grade**	**General Guidance**	**For Any Grade:** – The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. – Patients should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult. – Neurophysiologic diagnostic testing (eg, electromyogram and nerve conduction investigations, and “repetitive stimulation” if

			myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation. – It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 1	No dose modifications.	**For Grade 1:** – ~~Discuss~~Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult ~~unless the symptoms are very minor and stable.~~.
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	**For Grade 2:** – ~~Discuss~~Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis.

			GUILLAIN-BARRE: o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 ~~irAE~~imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** – ~~Discuss~~Consider, as necessary, discussing with study physician. – Recommend hospitalization. – Monitor symptoms and obtain neurological consult. *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. o If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Myocarditis	**Any Grade**	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade:** – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider, as necessary, discussing with the study physician. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung

			toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (eg, pulmonary embolism, congestive heart failure, malignant pericardial effusion). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – Initial workup should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory workup as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, or infections)
	Grade 1 (asymptomatic with laboratory (e.g., BNP) or cardiac imaging abnormalities)	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic workup for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.	**For Grade 1 (no definitive findings):** - Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory workup as clinically indicated. - Consider using steroids if clinical suspicion is high.
	Grade 2, 3 or 4 (Grade 2: Symptoms with mild to moderate activity or exertion) (Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated) (Grade 4: Life-	- If Grade 2, hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently discontinue study drug/study regimen. If Grade 3-4, permanently discontinue study drug/study regimen.	**For Grades 2 to 4:** – Monitor symptoms daily, hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (eg, oxygen). – If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of

	threatening consequences; urgent intervention indicated [eg, continuous IV therapy or mechanical hemodynamic support])		cancer-related infections [Category 2B recommendation]).[a]
Myositis/Polymyositis ("Poly/myositis")	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the study physician. – Initial workup should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory workup as indicated, including a number of possible rheumatological/antibody tests (ie, consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider barium swallow for evaluation of dysphagia or dysphonia. Patients should be thoroughly evaluated to rule out any alternative etiology

			(eg, disease progression, other medications, or infections).
	Grade 1 (mild pain)	- No dose modifications.	**For Grade 1:** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the study physician.
	Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	Hold study drug/study regimen dose until resolution to Grade ≤1. - Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 2:** – Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If clinical course is *not* rapidly progressive, start systemic steroids (eg, prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 3 to 5 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (pain associated with severe weakness; limiting self-care ADLs)	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory	**For Grade 3 or 4 (severe or life-threatening events):** – Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult, and complete full evaluation. – Consider, as necessary, discussing with the study physician. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of

		insufficiency. **For Grade 4:** - Permanently discontinue study drug/study regimen.	immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Consider whether patient may require IV IG, plasmapheresis. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

[a] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD.
[b] FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.

Abbreviations: AChE = Acetylcholine esterase; ADL = Activities of daily living; AE = Adverse event; ALP = Alkaline phosphatase test; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; BUN = Blood urea nitrogen; CT = Computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; HbA1C = glycated haemoglobin; ILD = Interstitial lung disease; ~~irAE =~~ imAE = immune-~~related~~mediated adverse event; IG = Immunoglobulin; IV = Intravenous; GI = Gastrointestinal; LFT = Liver function tests; LLN = Lower limit of normal; MRI = Magnetic resonance imaging; NCI = National Cancer Institute; NCCN = National Comprehensive Cancer Network; ~~PCP ;~~PJP = Pneumocystis jirovecii pneumonia (formerly known as Pneumocystis carinii pneumonia); PO = By mouth; T3 = Triiodothyronine; T4 = Thyroxine; TB = Total bilirubin; TNF = Tumor necrosis factor; TSH = Thyroid-stimulating hormone; ULN = Upper limit of normal.

Infusion-Related Reactions

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Any Grade	General Guidance	**For Any Grade:** – Manage per institutional standard at the discretion of investigator. – Monitor patients for signs and symptoms of infusion-related reactions (eg, fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (eg, generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	**For Grade 1:** The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. **For Grade 2:** The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. Subsequent infusions may be given at 50% of the initial infusion rate.	**For Grade 1 or 2:** – Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. – Consider premedication per institutional standard prior to subsequent doses. – Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 3 or 4	**For Grade 3 or 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Manage severe infusion-related reactions per institutional standards (eg, IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; IM = intramuscular; IV = intravenous; NCI = National Cancer Institute.

Non-Immune-Mediated Reactions

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (ie, events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. **For asymptomatic Grade 2 creatine kinase levels:**	Treat accordingly, as per institutional standard.
	• Hold treatment with both study agents. Perform diagnostic evaluation If results show no evidence of end organ damage, including myositis and rhabdomyolysis, resume treatment with both agents.	1. Perform diagnostic evaluation (serum and urine myoglobin, BUN and creatinine) Continue to monitor CK, serum and urine myoglobin, BUN and creatinine **Weekly** until creatine kinase levels return to ≤ **Grade 1** or as clinically indicated.
Grade 3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen. **For asymptomatic Grade 3 creatine kinase levels:**	Treat accordingly, as per institutional standard.
	Hold treatment with both LY3022855 and durvalumab or tremelimumab. Perform diagnostic evaluation. • For Grade 3 elevations in CK ≤ 8X ULN with a diagnostic evaluation showing NO evidence of end organ damage including myositis or rhabdomyolysis, resume treatment with both agents. • For Grade 3 elevations in CK > 8X ULN with a diagnostic evaluation showing NO evidence of end organ damage including myositis or rhabdomyolysis, , hold LY3022855 and resume durvalumab or	• Perform diagnostic evaluation (serum and urine myoglobin, BUN and creatinine). • Continue to monitor CK, serum and urine myoglobin, BUN and creatinine Weekly until CK levels return to ≤ Grade 1 or as clinically indicated. • Treat accordingly as per institutional standard, perform a full diagnostic evaluation and if there is any evidence of potential immune-mediated end organ damage, follow the guidelines for irAE management contained in this attachment.

Non-Immune-Mediated Reactions

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	tremelimumab after discussion with sponsor. If CK decreases to ≤ 8x ULN after holding LY3022855, resume treatment with LY3022855 and durvalumab or tremelimumab. o If CK remains >8X ULN after holding LY3022855, permanently discontinue both LY3022855 and durvalumab or tremelimumab and discuss additional treatment measures with sponsor. In case of myositis or rhabdomyolysis, permanently discontinue treatment with both study agents.	• Continue to monitor CK, serum and urine myoglobin, BUN and creatinine weekly until CK levels return to ≤ Grade 1 or baseline.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.).	Treat accordingly, as per institutional standard.

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician."
Abbreviations: AE = Adverse event; BUN = elevated serum blood urea nitrogen; CK = creatinine; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute.

Attachment 8. Protocol JSCC Durvalumab and Tremelimumab AESIs

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the investigational product and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or nonserious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

AESIs for durvalumab and tremelimumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An immune-related adverse event (irAE) is defined as an adverse event (AE) that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

If the investigator has any questions in regards to an AE being an irAE, the investigator should promptly contact the study physician.

AESIs observed with durvalumab and tremelimumab include:

- Diarrhea / Colitis
- Pneumonitis / ILD (interstitial lung disease)
- ALT/AST increases / hepatitis / hepatotoxicity
- Neuropathy / neuromuscular toxicity (i.e. events of encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis)
- Endocrinopathy (i.e. events of hypophysitis, hypopituitarism, adrenal insufficiency, diabetes insipidus, type I diabetes mellitus and hyper- and hypothyroidism)
- Rash / Dermatitis
- Nephritis / Blood creatinine increases
- Pancreatitis (or labs suggestive of pancreatitis - increased serum lipase, increased serum amylase)
- Other inflammatory responses that are rare with a potential immune-mediated etiology include, but are not limited to, myocarditis, pericarditis, myositis/polymyositis, and uveitis.

Further information on these risks (eg, presenting symptoms) can be found in the current version of the durvalumab and tremelimumab IBs. For durvalumab and tremelimumab, AESIs will comprise the following:

Pneumonitis

AEs of pneumonitis are also of interest, as pneumonitis has been observed with use of anti-PD-1 mAbs (but not with anti-PD-L1 mAbs). Initial work-up should include a high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended.

Guidelines for the management of patients with immune-mediated events including pneumonitis are outlined in Section 7.2.4.

Infusion reactions

AEs of infusion reactions (also known as infusion-related reactions [IRRs]) are of special interest and are defined, for the purpose of this protocol, as all AEs occurring from the start of investigational product infusion up to 48 hours after the infusion start time. For all infusion reactions, if they qualify as SAEs, they should be reported as SAEs as described in Section 8.1.2.1.

Hypersensitivity reactions

Hypersensitivity reactions as well as IRRs have been reported with anti-PD-L1 and anti-PD-1 therapy (Brahmer et al. 2012). As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of mAbs can be caused by various mechanisms, including acute anaphylactic (IgE-mediated) and anaphylactoid reactions against the mAbs and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting, and unresponsiveness.

Guidelines for management of patients with hypersensitivity (including anaphylactic reaction) and IRRs are outlined in Section 7.2.4.

Hepatic function abnormalities (hepatotoxicity)

Hepatic function abnormality is defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in total bilirubin to be greater than 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (for example, cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product.

Guidelines for management of patients with hepatic function abnormality are outlined in Section 7.2.4.

Gastrointestinal disorders

Diarrhea/colitis is the most commonly observed treatment-emergent SAE when tremelimumab is used as monotherapy. In rare cases, colon perforation may occur that requires surgery (colectomy) or can lead to a fatal outcome if not properly managed.

Guidelines on management of diarrhea and colitis in patients receiving study treatment are provided in Section 7.2.4.

Endocrine disorders

Immune-mediated endocrinopathies include hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism. Guidelines for the management of patients with immune-mediated endocrine events are provided in Section 7.2.4.

Pancreatic disorders

Immune-mediated pancreatitis includes autoimmune pancreatitis, and lipase and amylase elevation. Guidelines for the management of patients with immune-mediated pancreatic disorders are provided in Section 7.2.4.

Neurotoxicity

Immune-mediated nervous system events include encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis. Guidelines for the management of patients with immune-mediated neurotoxic events are provided in Section 7.2.4.

Nephritis

Consult with Nephrologist. Monitor for signs and symptoms that may be related to changes in renal function (eg, routine urinalysis, elevated serum blood urea nitrogen [BUN] and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc).

Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, infections, etc).

Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2), in order to prevent potential progression to higher grade event.

Guidelines for the management of patients with immune-mediated neurotoxic events are provided in Section 7.2.4.

Immune-related adverse events

Based on the mechanism of action of durvalumab and tremelimumab leading to T cell activation and proliferation, there is a possibility of observing irAEs during the conduct of this study. Potential irAEs may be similar to those seen with the use of ipilimumab, BMS-936558 (anti-PD-1 mAb), and BMS-936559 (anti-PD-L1 mAb) and may include immune-mediated enterocolitis, dermatitis, hepatitis (hepatotoxicity), pneumonitis, and endocrinopathies (Hodi et al. 2010, Brahmer et al. 2012, Topalian et al. 2012). These AEs are inflammatory in nature and can affect any organ. With anti-PD-L1 and anti-CTLA-4 combination therapy, the occurrence of overlapping or increasing cumulative toxicities that include irAEs could potentially occur at higher frequencies than with either durvalumab or tremelimumab monotherapy. Patients should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (for example, infection or PD), an immune-related etiology should be considered for signs or symptoms of enterocolitis, dermatitis, pneumonitis, hepatitis, and endocrinopathy. In addition to the dose modification guidelines provided in Section 7.2.4, it is recommended that irAEs are managed according to the general treatment guidelines outlined for ipilimumab (Weber et al. 2012). These guidelines recommend the following:

- Patients should be evaluated to identify any alternative etiology.
- In the absence of a clear alternative etiology, all events of an inflammatory nature should be considered immune related.
- Symptomatic and topical therapy should be considered for low-grade events.
- Systemic corticosteroids should be considered for a persistent low-grade event or for a severe event.
- More potent immunosuppressives should be considered for events not responding to systemic steroids (for example, infliximab or mycophenolate).

If the investigator has any questions in regards to an AE being an irAE, the investigator should immediately contact the study physician.

Myocarditis

A variety of clinical presentations, diagnostic evidence (laboratory, imaging, histopathology), and resulting diagnoses have been described in cases of myocarditis in the literature for other immune checkpoint inhibitors, including heart failure, brady- and tachyarrhythmias, and acute coronary syndrome-like presentations without evidence of ischemia. Investigators should be aware of such rare, but severe immune-mediated adverse events including myocarditis with its presenting signs/symptoms (eg, decreased ejection fraction, arrhythmias, in particular occurrences of atrioventricular block).

Investigators should adhere to the Toxicity Management Guidelines by performing a thorough evaluation to rule out alternative etiologies and initiating prompt treatment with steroids and modification of study drug/dose regimen depending on the severity of the event.

Guidelines for the management of patients with myocarditis are provided in Attachment 7.

Myositis/Polymyositis

Investigators should adhere to the Toxicity Management Guidelines by performing a thorough evaluation to rule out alternative etiologies and initiating prompt treatment with steroids and modification of study drug/dose regimen depending on the severity of the event. Guidelines for the management of patients with myositis/polymyositis are provided in Attachment 7.

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